EDITOR'S CHOICE

Family history of premature coronary heart disease and risk prediction in the EPIC-Norfolk prospective population study

Suthesh Sivapalaratnam,[1] S Matthijs Boekholdt,[1,2] Mieke D Trip,[1,2] Manjinder S Sandhu,[3,4] Robert Luben,[3] John J P Kastelein,[1] Nicholas J Wareham,[5] Kay-Tee Khaw[3]

[1]Department of Vascular Medicine, Academic Medical Center, Amsterdam, The Netherlands
[2]Department of Cardiology, Academic Medical Center, Amsterdam, The Netherlands
[3]Department of Public Health and Primary Care, University of Cambridge, Cambridge, UK
[4]Department of Genetic Epidemiology, Wellcome Trust Sanger Institute, Hinxton, UK
[5]Medical Research Council Epidemiology Unit, Cambridge, UK

Correspondence to
Dr S M Boekholdt, Department of Cardiology, Academic Medical Center, PO Box 22660, 1100 DD Amsterdam, The Netherlands;
s.m.boekholdt@amc.uva.nl

Accepted 21 September 2010
Published Online First 20 October 2010

ABSTRACT

Objective The value of a family history for coronary heart disease (CHD) in addition to established cardiovascular risk factors in predicting an individual's risk of CHD is unclear. In the European Prospective Investigation of Cancer (EPIC)-Norfolk cohort, the authors tested whether adding family history of premature CHD in first-degree relatives improves risk prediction compared with the Framingham risk score (FRS) alone.

Methods and results This study comprised 10 288 men and 12 553 women aged 40—79 years participating in the EPIC-Norfolk cohort who were followed for a mean of 10.9±2.1 years (mean±SD). The authors computed the FRS as well as a modified score taking into account family history of premature CHD. A family history of CHD was indeed associated with an increased risk of future CHD, independent of established risk factors (FRS-adjusted HR of 1.74 (95% CI 1.56 to 1.95) for family history of premature CHD). However, adding family history of CHD to the FRS resulted in a negative net reclassification of 2%. In the subgroup of individuals estimated to be at intermediate risk, family history of premature CHD resulted in an increase in net reclassification of 2%. The sensitivity increased with 0.4%, and the specificity decreased 0.8%.

Conclusion Although family history of CHD was an independent risk factor of future CHD, its use did not improve classification of individuals into clinically relevant risk categories based on the FRS. Among study participants at intermediate risk of CHD, adding family history of premature CHD resulted in, at best, a modest improvement in reclassification of individuals into a more accurate risk category.

INTRODUCTION

Coronary heart disease (CHD) is the leading cause of morbidity and mortality worldwide. Well-established risk factors include age, sex, smoking, hypertension, diabetes mellitus, obesity and dyslipidaemia. In addition, several prospective studies have shown that a family history of CHD is a risk factor independent of these traditional risk factors.[1 2] Depending on the definition used, family history confers an relative risk (RR) for CHD that ranges from twice to 12 times that in the general population.[3]

There is conflicting evidence as to whether family history of CHD provides added value on top of established risk factors in predicting cardiovascular risk. According to the Adult Treatment Panel III (ATP III) guidelines, family history does not improve risk prediction sufficiently to be included in risk models.[3] However, several risk scoring algorithms including Reynolds, PROCAM and QRISK do incorporate a family history of CHD, and ASSIGN does incorporate a family history of all CVD, but not CHD only.[4–7] Interestingly, the frequently used Framingham Risk Score (FRS) does not take family history for CHD into account, but an analysis in the Framingham Offspring cohort concluded that sibling and parental CHD should be incorporated into risk-prediction algorithms.[8]

In the prospective European Prospective Investigation of Cancer (EPIC)-Norfolk cohort, we tested the hypothesis that addition of family history of premature CHD in first-degree relatives improves risk prediction compared with the Framingham risk score algorithm alone.

METHODS

Study population and data acquisition

EPIC-Norfolk is a prospective cohort study among men and women aged 40—79 years recruited from general practices in the Norfolk region, UK. The EPIC-Norfolk study was approved by the Norfolk Local Research Ethics Committee and complies with the Declaration of Helsinki. Participants gave written consent. Full details of the population are reported elsewhere.[9] In brief, between 1993 and 1997, 25 639 individuals underwent a baseline health examination (anthropometry, blood pressure, non-fasting lipid levels) and completed a general health questionnaire (history of disease, including diabetes, heart attack and stroke, medication use and smoking habits). In addition, they were asked about family history for heart attack in first-degree relatives. The study cohort was similar to UK population samples with regard to many characteristics, including anthropometry, blood pressure and lipids, but with a lower proportion of smokers.[9]

All EPIC-Norfolk participants were flagged for death certification at the Office for National Statistics, and vital status was obtained for the entire cohort. Participants admitted to a hospital were identified by their National Health Service number. Hospitals were linked to the East Norfolk Health Authority database, which identifies all hospital contacts throughout England and Wales for Norfolk residents. Participants were identified as having a CHD event (eg, unstable angina, stable

angina and myocardial infarction) during follow-up if CHD was the underlying cause of a hospital admission or death. Previous validation studies in this cohort indicate a high specificity of such case ascertainment.[10]

In our analysis, those participants of the EPIC-Norfolk cohort who did not report a heart attack or stroke at baseline were included. We report the results of follow-up to 30 April 2009, a mean of 10.9±2.1 years.

Statistical analysis

Baseline characteristics were compared between people with and without a family history of premature CHD. A Student t test was used for continuous variables (age, body mass index, waist circumference, waist/hip ratio, systolic and diastolic blood pressure, total cholesterol, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol) a χ^2 test was used for categorical variables (sex, smoking status, diabetes mellitus). Because triglycerides and the FRS were not normally distributed, these parameters were log-transformed. The log-transformed variables were normally distributed and were compared using a Student t test.

The Framingham risk score was calculated using a previously reported algorithm, which takes into account age, sex, total cholesterol, HDL cholesterol, systolic and diastolic blood pressure, smoking and the presence of diabetes. Since the FRS overestimates CHD risk in Europeans, and more specifically in the EPIC-Norfolk study population, we recalibrated the FRS as previously described.[11]

Study participants were divided into three categories according to family history of CHD in a first-degree relative: negative family history, positive family history of premature CHD defined as CHD in a first-degree male relative <55 and female relative <65 years of age and a family history above these cut-offs. For all Cox proportional regression model (Cox regression) analyses, the reference group consisted of participants with a negative family history. Cox regression was used to calculate hazard ratios (HRs) and corresponding 95% CI (95% CI) for the risk of future CHD in each category. For each of these categories, the unadjusted, sex-, age- and FRS-adjusted HRs were calculated. Similar analyses were performed for participants with positive premature family history of CHD only among siblings and only among parents. Men and women with both parental and sibling CHD were excluded from these analyses.

We quantified whether using a family history of premature CHD in addition to the FRS resulted in improved classification of study participants into low-, intermediate- and high-risk categories, as previously described.[12] Reclassification of study participants who did and did not develop CHD during follow-up was analysed separately. Any 'upward' movement in categories for study participants who did develop a CHD event implies improved classification, and any 'downward' movement indicates worse reclassification. The interpretation is opposite for those who did not develop a CHD event.[12] Improvement in reclassification was estimated by taking the sum of differences in proportions of individuals reclassified upward minus the proportion reclassified downward for individuals who developed events and the proportion of individuals moving downward minus the proportion moving upward for those who did not develop events. Using this method, the overall reclassification sum is the net reclassification improvement. This approach was used in the entire study sample, and in addition only in the group estimated to be at intermediate risk by the FRS, also known as the clinical net reclassification improvement.

Finally, we calculated sensitivity defined as the ability to 'classify as high risk someone who subsequently develops CHD' and specificity as the ability to 'classify as low risk someone who does not subsequently develop CHD.'

Analyses were performed using SPSS (version 15.0).

RESULTS

In total, 2798 out of the 25 639 EPIC-Norfolk study participants were excluded because they reported CHD or stroke at baseline, leaving 22 841 individuals for the current analysis (10 288 men and 12 553 women). During follow-up 2752 participants (12.0%) experienced a CHD event. In table 1, baseline characteristics and the calculated FRS are presented for the study participants classified according to whether they developed CHD during follow-up and whether or not they had a family history of premature CHD. Among individuals who did not experience CHD during follow-up, systolic and diastolic blood pressure, total cholesterol, LDL cholesterol and triglycerides were higher in individuals with a positive family history of CHD. The mean

Table 1 Baseline characteristics

	No coronary heart disease during follow-up (n=20089)			Coronary heart disease during follow-up (n=2752)		
	Negative n=14866	Positive n=5223	p Value	Negative n=1907	Positive n=845	p Value
Age (years)	57±9	59±9	<0.001	65±8	65±7	0.03
Male sex	42.1 (6257)	42.4 (2217)	0.65	66.6 (1271)	64.3 (543)	0.22
Body mass index (kg/m^2)	26.1±3.8	26.2±3.8	0.40	27.1±3.9	27.0±3.8	0.40
Waist circumference (cm)	87±12	87±12	0.33	94±12	93±11	0.16
Waist/hip ratio	0.85±0.09	0.85±0.09	0.36	0.90±0.09	0.90±0.08	0.33
Current smoking	11.7 (1735)	10.2 (535)	0.02	13.7 (261)	12.3 (104)	0.5
Diabetes mellitus	1.4 (211)	1.6 (83)	0.38	6.2 (119)	6.0 (51)	0.84
Systolic blood pressure (mm Hg)	134±18	136±18	<0.001	142±19	141±19	0.18
Diastolic blood pressure, (mm Hg)	82±11	83±11	<0.001	85±12	84±12	0.02
Total cholesterol (mmol/l)	6.1±1.1	6.2±1.1	<0.001	6.4±1.2	6.4±1.1	0.82
Low-density lipoprotein cholesterol (mmol/l)	3.9±1.0	4.0±1.0	<0.001	4.2±1.0	4.2±1.0	0.62
High-density lipoprotein cholesterol (mmol/l)	1.4±0.4	1.4±0.4	0.60	1.3±0.4	1.3±0.4	0.80
Triglycerides (mmol/l)	1.5 (1.0 to 2.1)	1.5 (1.1 to 2.1)	<0.001	1.8 (1.3 to 2.5)	1.8 (1.3 to 2.5)	0.20
Framingham Risk Score	17.1 (3.0 to 23.8)	18.6 (4.3 to 26.4)	<0.001	31.8 (16.4 to 42.1)	33.0 (16.2 to 44.3)	0.19

Data are presented as a percentage (number), mean±SD or median (IQR).

Table 2 RR for future coronary heart disease according to status of coronary heart disease

	Family history		
	None	Premature	Non-premature
Any first-degree relative			
Cases/total	1526/14585	381/2188	845/6068
Unadjusted	1	1.74 (1.55 to 1.95)	1.36 (1.25 to 1.48)
Adjusted for sex and age	1	1.91 (1.71 to 2.14)	1.29 (1.18 to 1.40)
Adjusted for Framingham Risk Score	1	1.74 (1.56 to 1.95)	1.30 (1.20 to 1.41)
Parental history			
Cases/total	1995/16691	165/1146	592/5004
Unadjusted	1	1.22 (1.04 to 1.43)	0.99 (0.90 to 1.09)
Adjusted for sex and age	1	1.61 (1.38 to 1.89)	1.10 (1.01 to 1.21)
Adjusted for Framingham Risk Score	1	1.43 (1.22 to 1.68)	1.05 (0.96 to 1.15)
Sibling history			
Cases/total	2515/21681	87/490	150/670
Unadjusted	1	1.58 (1.27 to 1.95)	2.04 (1.73 to 2.40)
Adjusted for sex and age	1	1.44 (1.17 to 1.79)	1.18 (1.00 to 1.40)
Adjusted for Framingham Risk Score	1	1.43 (1.15 to 1.77)	1.47 (1.25 to 1.74)

Premature is defined as <55 years in men and <65 years in women. Non-premature is defined as ≥55 years in men and ≥65 in women.

FRS was also higher in this group. Among individuals who did experience CHD during follow-up, similar differences were not observed.

Table 2 depicts the unadjusted and adjusted HR of incident CHD for individuals with a family history of CHD compared with those without. A subdivision was made according to the age at which the first-degree relative had CHD. Compared with study participants without a family history for CHD, those with a first-degree relative with premature CHD had a FRS-adjusted HR of 1.74 (95% CI 1.56 to 1.95), whereas in those with non-premature CHD, the HR was 1.30 (95% CI 1.20 to 1.41). Lower age cut-off values did not change these results substantially.

Hazards associated with sibling CHD were not influenced by the age of onset in the first-degree relative (table 2). Only premature parental disease was associated with increased risk for CHD (table 2). Results were similar for men and women, and there was no evidence for a statistically significant interaction between sex and family history status (data not shown).

There was an inverse association between the age of onset of CHD in the first-degree relative and the study participant's risk of CHD (figure 1). Reclassification analyses for men and women are summarised in figure 2. The use of family history of premature CHD resulted in 162 individuals being correctly reclassified into a higher-risk category, as compared with the FRS alone. A total of 178 individuals were incorrectly reclassified into a lower-risk category. Similarly, 1197 individuals who did not develop CHD during follow-up were correctly reclassified into a lower category, whereas 1477 individuals were incorrectly reclassified into a higher category. The net effect was incorrect classification in 280 cases. The net reclassification improvement was −2.0%. This indicates that as a result of adding family history of premature CHD to FRS, 2.0% more individuals were moved in an incorrect direction than in a correct direction. Using a similar approach in the subgroup of individuals initially classified as intermediate risk using the FRS, 106 individuals were correctly reclassified into the high-risk category, and 84 were incorrectly reclassified into the low-risk category, whereas 787 individuals were correctly reclassified into the low-risk category, and 536 individuals were incorrectly reclassified into the high-risk category. Thus, in the intermediate-risk group, the use of family history of premature CHD resulted in a slight increase in clinical net reclassification improvement of 2.05%.

Among people who ultimately developed CHD, adding family history of premature CHD to the FRS increased the percentage that was correctly classified at baseline as high risk from 64.7% to 65.1%. Among people who did not develop CHD during follow-up, adding family history of premature CHD to the FRS decreased the percentage correctly classified as low-risk from 46.4% to 45.6%.

DISCUSSION

In the EPIC-Norfolk study, a family history of CHD was an independent risk factor for future CHD. The magnitude of risk was influenced by the age of onset of CHD in the first-degree

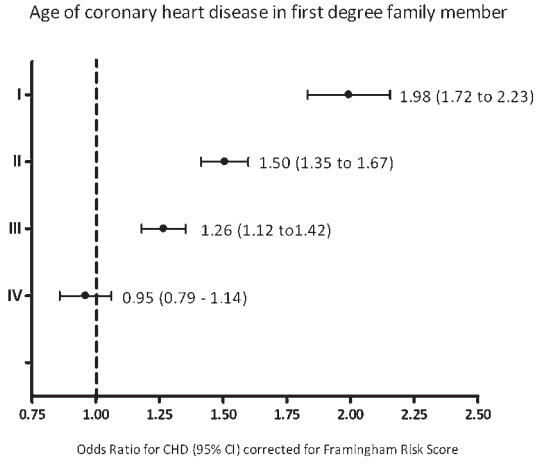

Figure 1 Different categories (I—IV) based on the age of onset of coronary heart disease (CHD) in a first-degree relative, using the following age cut-offs in years: I, <55 in men and <65 in women; II, ≥55 and <65 in men, and ≥65 and <75 in women; III, ≥65 and <75 in men, and ≥75 and <85 in women; IV, ≥75 in men and ≥85 in women. The reference group for the calculated ORs consisted of participants with a negative family history of CHD.

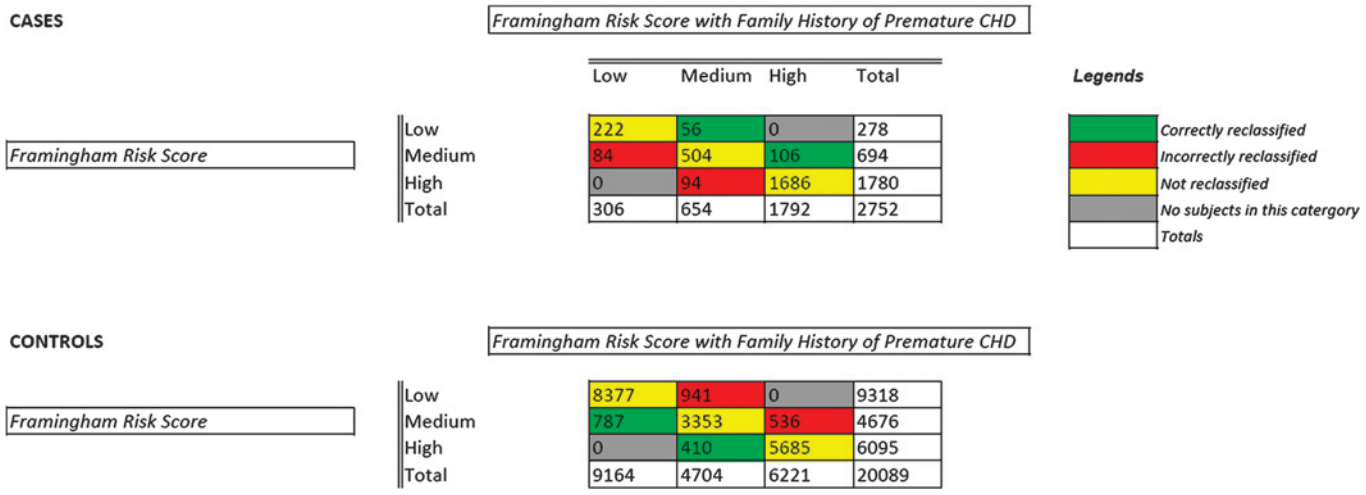

Figure 2 Reclassification based on family history of premature coronary heart disease.

relative and whether the affected individual was a sibling or parent. Only premature parental CHD and any history of sibling CHD were associated with higher HRs. Adding family history of premature CHD to the FRS did not result in an overall increase in net reclassification improvement. There was only a marginal increase in sensitivity and decrease in specificity. In the subgroup of individuals estimated to be at intermediate risk using the FRS, addition of family history of premature CHD resulted in a slight classification improvement of 2%.

Several large cohort studies have reported an association between self-reported family history of CHD with an RR for CHD that ranges from twice to 12 times that of the general population depending on the definition used.[3] Results after adjustment for other variables were not conclusive, with relative risks of CHD estimates still ranging from 0.8 to 2.2.[13–23] Recently developed risk scores, such as the QRISK and the Reynolds risk score, have incorporated family history of CHD in their algorithms. The QRISK risk score was developed using data on more than 1 million non-diabetic individuals from general practice registers in the UK.[5] The QRISK algorithm incorporates family history and social deprivation in addition to the risk factors used in the Framingham score and is reported to calibrate better in the UK population than the older Framingham risk functions formulated by Anderson *et al*.[24] The Reynolds risk score for men was developed in a sample of the Physicians' Health Study II, which included 10 724 initially healthy American non-diabetic men. Addition of hsCRP, diabetes and family history of CHD significantly improved CHD risk prediction compared with a model based on established risk factors. In 8.4% of all study participants and in 15.8% of the subgroup at intermediate Framingham risk, CHD risk prediction improved.[6 12 25] The marginal effect of family history of premature CHD on CHD risk predication in this large cohort of apparently healthy individuals may be due to several reasons. First, a family history of CHD might not have a large impact on an individual's CHD risk, unless it is caused by highly penetrant mutations, which tend to be rare and therefore have limited impact at the population level. Second, in some of these families where a monogenetic disorder resulting in premature CHD, such as familial hypercholesterolaemia, has been identified, treatment might have been started at an early age, thus reducing CHD risk. Third, a large proportion of the impact of family history on CHD risk is mediated by established risk factors, which makes its independent contribution to CHD risk difficult to quantify.[8]

Strengths and limitations

The EPIC-Norfolk population study is larger than most other prospective studies that have been analysed for the association between family of history of CHD and CHD risk. Second, established risk factors were measured directly for all study participants. Thus, measures of lipid levels and biometrics were ascertained directly and not obtained by self-reporting, which is more susceptible to misclassification. A potential limitation of our study is the fact that family history of CHD was self-reported and not validated. Nevertheless, self-reported family history is what is used in usual clinical practice and thus might be of greater practical value. The accuracy of family history may well vary in different population groups. However, in the National Heart, Lung, and Blood Institute Family Heart Study and in the Newcastle Family History Study, self-report of a family history of premature CHD in a first-degree relative was found to be reasonably accurate with sensitivity above 80% and specificity about 90%.[14 26 27]

A potential systemic error was the lack of information on pedigree size. The ability to have a positive family history is dependent on pedigree size. Unfortunately, we could not adjust for the total amount of siblings a study participant had. Finally, CHD events were identified by means of death certification and hospital admission reports, which may have resulted in misclassification. Previous validation in this cohort, however, indicated high specificity of such case ascertainment.[10]

CONCLUSIONS

In this large population-based cohort, we confirm that family history is an independent risk factor for CHD. However, this information did not contribute to improve CHD risk prediction in the entire cohort. Only in the subgroup of individuals at intermediate risk of CHD as estimated by the FRS, did the use of family history of premature CHD result in a modest improvement in reclassification of individuals into a more accurate risk category.

Funding EPIC-Norfolk is supported by programme grants from the Medical Research Council UK and Cancer Research UK.

Competing interests None.

Patient consent Obtained.

Ethics approval Ethics approval was provided by the Norfolk Local Research Ethics Committee.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

1. **Lloyd-Jones DM,** Nam BH, D'Agostino RB Sr, *et al*. Parental cardiovascular disease as a risk factor for cardiovascular disease in middle-aged adults: a prospective study of parents and offspring. *JAMA* 2004;**291**:2204—11.
2. **Murabito JM,** Pencina MJ, Nam BH, *et al*. Sibling cardiovascular disease as a risk factor for cardiovascular disease in middle-aged adults. *JAMA* 2005;**294**:3117—23.
3. **National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III).** Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. *Circulation* 2002;**106**:3143—421.
4. **Assmann G,** Cullen P, Schulte H. Simple scoring scheme for calculating the risk of acute coronary events based on the 10-year follow-up of the prospective cardiovascular Munster (PROCAM) study. *Circulation* 2002;**105**:310—15.
5. **Hippisley-Cox J,** Coupland C, Vinogradova Y, *et al*. Derivation and validation of QRISK, a new cardiovascular disease risk score for the United Kingdom: prospective open cohort study. *BMJ* 2007;**335**:136.
6. **Ridker PM,** Paynter NP, Rifai N, *et al*. C-reactive protein and parental history improve global cardiovascular risk prediction: the Reynolds Risk Score for men. *Circulation* 2008;**118**:2243—51, 4p.
7. **Woodward M,** Brindle P, Tunstall-Pedoe H. Adding social deprivation and family history to cardiovascular risk assessment: the ASSIGN score from the Scottish Heart Health Extended Cohort (SHHEC). *Heart* 2007;**93**:172—6.
8. **Wilson PW,** D'Agostino RB, Levy D, *et al*. Prediction of coronary heart disease using risk factor categories. *Circulation* 1998;**97**:1837—47.
9. **Day N,** Oakes S, Luben R, *et al*. EPIC-Norfolk: study design and characteristics of the cohort. European Prospective Investigation of Cancer. *Br J Cancer* 1999;**80** (Suppl 1):95—103.
10. **Boekholdt SM,** Peters RJ, Day NE, *et al*. Macrophage migration inhibitory factor and the risk of myocardial infarction or death due to coronary artery disease in adults without prior myocardial infarction or stroke: the EPIC-Norfolk Prospective Population study. *Am J Med* 2004;**117**:390—7.
11. **D'Agostino RB Sr,** Grundy S, Sullivan LM, *et al*. Validation of the Framingham coronary heart disease prediction scores: results of a multiple ethnic groups investigation. *JAMA* 2001;**286**:180—7.
12. **Pencina MJ,** D'Agostino RB Sr, D'Agostino RB Jr, *et al*. Evaluating the added predictive ability of a new marker: from area under the ROC curve to reclassification and beyond. *Stat Med* 2008;**27**:157—72.
13. **Barrett-Connor E,** Khaw K. Family history of heart attack as an independent predictor of death due to cardiovascular disease. *Circulation* 1984;**69**:1065—9.
14. **Silberberg JS,** Wlodarczyk J, Fryer J, *et al*. Risk associated with various definitions of family history of coronary heart disease. The Newcastle Family History Study II. *Am J Epidemiol* 1998;**147**:1133—9.
15. **Jousilahti P,** Puska P, Vartiainen E, *et al*. Parental history of premature coronary heart disease: an independent risk factor of myocardial infarction. *J Clin Epidemiol* 1996;**49**:497—503.
16. **Colditz GA,** Stampfer MJ, Willett WC, *et al*. A prospective study of parental history of myocardial infarction and coronary heart disease in women. *Am J Epidemiol* 1986;**123**:48—58.
17. **Colditz GA,** Rimm EB, Giovannucci E, *et al*. A prospective study of parental history of myocardial infarction and coronary artery disease in men. *Am J Cardiol* 1991;**67**:933—8.
18. **Friedlander Y,** Kark JD, Stein Y. Family history of myocardial infarction as an independent risk factor for coronary heart disease. *Br Heart J* 1985;**53**:382—7.
19. **Myers RH,** Kiely DK, Cupples LA, *et al*. Parental history is an independent risk factor for coronary artery disease: the Framingham Study. *Am Heart J* 1990;**120**:963—9.
20. **Phillips AN,** Shaper AG, Pocock SJ, *et al*. Parental death from heart disease and the risk of heart attack. *Eur Heart J* 1988;**9**:243—51.
21. **Sesso HD,** Lee IM, Gaziano JM, *et al*. Maternal and paternal history of myocardial infarction and risk of cardiovascular disease in men and women. *Circulation* 2001;**104**:393—8.
22. **Sholtz RI,** Rosenman RH, Brand RJ. The relationship of reported parental history to the incidence of coronary heart disease in the Western Collaborative Group Study. *Am J Epidemiol* 1975;**102**:350—6.
23. **Thelle DS,** Forde OH. The cardiovascular study in Finnmark county: coronary risk factors and the occurrence of myocardial infarction in first degree relatives and in subjects of different ethnic origin. *Am J Epidemiol* 1979;**110**:708—15.
24. **Anderson KM,** Odell PM, Wilson PW, *et al*. Cardiovascular disease risk profiles. *Am Heart J* 1991;**121**:293—8.
25. **Ridker PM,** Buring JE, Rifai N, *et al*. Development and validation of improved algorithms for the assessment of global cardiovascular risk in women: the Reynolds Risk Score. *JAMA* 2007;**297**:611—19.
26. **Li R,** Bensen JT, Hutchinson RG, *et al*. Family risk score of coronary heart disease (CHD) as a predictor of CHD: the Atherosclerosis Risk in Communities (ARIC) study and the NHLBI family heart study. *Genet Epidemiol* 2000;**18**:236—50.
27. **Silberberg JS,** Wlodarczyk J, Fryer J, *et al*. Correction for biases in a population-based study of family history and coronary heart disease. The Newcastle Family History Study I. *Am J Epidemiol* 1998;**147**:1123—32.