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# Family History and Improving Health

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## Preface

The Agency for Healthcare Research and Quality (AHRQ), through its Evidence-Based Practice Centers (EPCs), sponsors the development of evidence reports and technology assessments to assist public- and private-sector organizations in their efforts to improve the quality of health care in the United States. The reports and assessments provide organizations with comprehensive, science-based information on common, costly medical conditions and new health care technologies. The EPCs systematically review the relevant scientific literature on topics assigned to them by AHRQ and conduct additional analyses when appropriate prior to developing their reports and assessments.

To bring the broadest range of experts into the development of evidence reports and health technology assessments, AHRQ encourages the EPCs to form partnerships and enter into collaborations with other medical and research organizations. The EPCs work with these partner organizations to ensure that the evidence reports and technology assessments they produce will become building blocks for health care quality improvement projects throughout the Nation. The reports undergo peer review prior to their release.

AHRQ expects that the EPC evidence reports and technology assessments will inform individual health plans, providers, and purchasers as well as the health care system as a whole by providing important information to help improve health care quality.

We welcome comments on this evidence report. They may be sent by mail to the Task Order Officer named below at: Agency for Healthcare Research and Quality, 540 Gaither Road, Rockville, MD 20850, or by e-mail to epc@ahrq.gov.


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# Structured Abstract

**Objectives:** This systematic review aimed to evaluate, within unselected populations: Question 1 (Q1) key elements of family history (FH) which usefully predict subsequent disease; Question 2 (Q2) the accuracy of reporting FH; Question 3 (Q3) the impact of FH-based risk information on the uptake of preventive interventions; Question 4 (Q4) the potential for harms associated with collecting cancer FH; Question 5 (Q5) factors that facilitate or hinder the collection of family history; and, Question 6 (Q6) future directions.

**Data Sources**: MEDLINE®, EMBASE®, CINAHL®, Cochrane Controlled Trial Register® (CCTR) ®, and PsycINFO were searched from 1995 to March 2, 2009 inclusive.

**Review Methods:** Standard systematic review methodology was employed. Eligibility criteria varied by question, but overall, specified studies reported in English, excluded qualitative designs, and limited populations to those unselected for pre-existing risk (except for Q2). Study designs and outcomes varied by research question.

**Results:** One hundred and thirty-seven publications were eligible in total for this review. *Q1: Key elements of FH:* Eighty-nine studies were eligible for this question of which 59 reported FH and data on subsequent or current disease in subjects. The varied definitions of positive FH were consistently associated with elevated relative risks, but their value in predicting future risk or detecting current disease was difficult to assess without considering further information on other risk factors or the available preventive interventions. *Q2: Accuracy of FH Reporting.* Thirty-seven studies evaluated accuracy and showed relatively high specificity and low sensitivity across all disease categories. Q3: *Uptake of preventive interventions.* Two studies evaluated the impact of FH-based risk and the evidence was insufficient to establish any effect on change in clinical preventive behavior or uptake of interventions. *Q4: Harms of FH taking.* Three studies evaluated the impact of FH-based risk information on psychological outcomes and indicated no evidence of significant harm.*Q5: Factors affecting FH collection:* The evidence base for addressing Q5 is heterogeneous and limited to six studies exploring the association between various factors and family history reporting, documentation and discussion.

**Conclusions:** Our review indicates: (Q1) Many FH definitions showed low discriminatory accuracy in predicting disease risk in individuals but further research is warranted; (Q2) accuracy of reporting is higher for relatives without, than those affected by, a given disease; (Q3) there is insufficient evidence to assess the effect of FH-based risk assessment on preventive behaviors; (Q4) there is limited evidence to assess whether the provision of FH-based personalized risk assessment results in adverse outcomes; (Q5) there is little evidence on factors affecting FH reporting and collection in primary care.

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Appendixes and Evidence Tables for this report are provided electronically at http://www.ahrq.gov/downloads/pub/evidence/pdf/famhistimprov/famhimp.pdf.

# Executive Summary

## Background

Family history (FH) represents the integration of shared genomic and environmental risk factors.[1] First degree relatives (1DRs) share half their genomic information (roughly one copy of 30-50,000 genes), and also behaviors, lifestyles, beliefs, culture, and physical environment, so their disease experience may offer a clue to shared susceptibilities. This suggests that a ‘low tech’ clinical approach–family history–might be a practical and useful way to target interventions and disease prevention efforts to those most at risk. There is empirical evidence to support the common observation that a positive FH confers an extra risk for many diseases: for example, detailed meta-analyses have convincingly demonstrated the association between having one or more 1DRs and risk of a number of common, complex disorders. However, appreciation that there is a link between FH and disease risk needs to be matched by evidence-based approaches to capturing and using such information in different clinical contexts.

This systematic review attempts to address five key issues relevant to the practical value of systematically collecting FH information in primary care practice; what are the most useful elements of FH for assessing disease risk; can we be confident that individuals report FH for common diseases sufficiently and accurately; does systematic collection and use of FH information lead to positive health outcomes, and are there associated harms; what factors promote or hinder collecting and using FH information?

The focus of this review is FH collection within the primary care context, where unselected populations present the full range of disease risks, where primary care practitioners undertake the activity, and where the goal is chronic disease risk assessment and prevention as an end in itself.

### Scope and Purpose of the Systematic Review

This systematic review addresses five research questions (Q) relating to routine use of FH information in risk assessment for complex disorders, as follows:

- Q1. What are the key elements of a family history in a primary care setting for the purposes of risk assessment for common diseases?
- Q2. What is the accuracy of the family history, and under what conditions does the accuracy vary?
- Q3. What is the direct evidence that routinely getting a family history will improve health outcomes for the patient and/or family?
- Q4. What is the direct evidence that routinely getting a family history will result in adverse outcomes for the patient and/or family?
- Q5. What are the factors that encourage or discourage obtaining and using a family history?

Research recommendations from each of these five questions were to be drawn together to answer Q6 in the conclusion.

- Q6. What are future research directions for assessing the value of family history for common diseases in the primary care setting?

# Methods

The five key research questions required interrogation across different domains of primary research literature. Therefore, standard systematic review methodology was employed, but eligibility criteria varied between questions. For all questions, these criteria were guided by discussion with the technical expert panel and partners.

Bibliographic databases searched for this review included: MEDLINE®, EMBASE®, CINAHL®, Cochrane Controlled Trial Register (CCTR)®, and PsycINFO. Years searched were 1995 to March 2, 2009 inclusive.

Eligibility criteria included English studies evaluating collection of FH for all diseases, with the exception of Q1 where we limited studies to those evaluating primary cancers (breast, colorectal, ovarian, prostate, and lung), cardiovascular diseases, mental health disorders, diabetes, asthma, and atopy. Interventions were defined as a structured/systematic collection of FH (Q1, 2, 3, and 4) or as correlates or factors facilitating or hindering the collection of FH (Q5). Populations were limited to those unselected for risk and typical for primary care settings with the exception of Q2. Study designs varied by research question; we excluded case control studies for Q1, observational studies for Q3 and Q4, and qualitative studies for all questions. The outcomes also varied with each research question and included disease incidence, metrics of accuracy, uptake of recommended preventive interventions, harms (e.g., psychological distress), and quality of FH collection.

For research Q1, the analysis was aimed at comparing the discriminatory accuracy of different definitions of 'positive' FH, which might be used in routine clinical practice. Recognizing that the time and resources available for FH taking in these settings may be very limited, we developed a categorization of FH definitions to reflect the 'complexity' of the task (category A to E). It is important to note that this initial attempt at categorization is based on a notion of 'likely effort required', not on any *a priori* notion of the information value of the pedigree itself. Our rationale is that the FH definition which balances 'adequate' predictive validity with least effort (lowest category) might be the most likely to be useful in routine primary care settings.

# Results

The search yielded 32,444 unique citations. During three levels of title and abstract screening, 31,190 articles were excluded. A total of 1,254 citations proceeded to full text screening. After the final eligibility screening, 137 publications were eligible for data extraction.

## Question 1. What are the Key Elements of a Family History in a Primary Care Setting for the Purposes of Risk Assessment for Common Diseases?

Sixty-one reports of 59 studies were identified which met the eligibility criteria, reported FH definitions, and presented data which could be analyzed.[2-62] In addition, one paper[63] did not present data which could be included in the main analysis, but was descriptively summarized because the data were directly relevant to the research question. A further 17 papers[64-80] were eligible but did not define FH, and 10 papers[81-90] did not report interpretable data. These are excluded from the results below. No studies addressing lung cancer or ovarian cancer were identified.

## Breast Cancer

Two longitudinal,[3,4] and two cross-sectional,[5,6] studies were included. Four definitions of 'positive FH' based on affected relatives were examined in five analyses. For the longitudinal analyses, the range of sensitivities was 0.06-0.26, and specificities 0.86- 0.95. The range of positive predictive values (PPVs) was 0.01-0.05, and negative predictive values (NPVs) 0.98-0.99, for breast cancer prevalences up to 2.5 percent in the study samples. For the cross-sectional analyses, the sensitivities were 0.05 and 0.15, with corresponding specificities of 0.97 and 0.90. The PPVs were 0.01 and 0.09 and NPVs were 0.99 and 0.95, for prevalences of 0.7 and 5.4 percent, respectively.

Only a few discrete FH definitions were available for comparison, and there were too few data points to examine the area under the curve (AUC) from summary receiver operator characteristics (SROC) curves. The most sensitive FH marker for risk of future breast cancer appeared to be 'at least one affected 1DR'. Conclusions regarding FH definitions used in a cross-sectional (prevalence screening) approach are not possible because an insufficient number of studies were available with a range of definitions, although the rationale for FH in prevalence screening where other modalities exist is unclear.

## Colorectal Cancer

One longitudinal analysis (based on two separate cohort studies),[7] and two cross-sectional studies,[8,9] were included. Four definitions of 'positive FH' were examined in multiple analyses, all focusing on 1DRs. The interpretation of the longitudinal analyses is limited because only one criterion for positive FH was used, (i.e., at least one affected 1DR). Sensitivities of 0.13 and 0.14 were obtained for the male and female cohorts with a specificity of 0.92 for both. For both cohorts, the PPVs were 0.02 and the NPVs 0.99, for underlying colorectal cancer frequency in these two cohorts of approximately 1 percent. For the cross-sectional analyses, the range of sensitivities was 0.00 to 0.20, and specificities 0.88 to 1.00. The range of PPVs was 0.00 to 0.07 and NPVs of 0.96 or higher, for overall colorectal cancer prevalences ranging from <1 to 4.5 percent. The AUC for cross-sectional studies for category C FH definitions was 0.64.(based on one study).

The results suggest that a simple definition of 'positive FH' (≥1 1DR) is the most sensitive for prediction, but if the underlying disease prevalence was similar to those populations studied, only 2 percent of people fulfilling this definition would actually go on to develop colorectal cancer (CRC) in the subsequent 16-20 years. The cross-sectional studies produced a range of sensitivities with similarly low PPVs for detecting current disease. The findings provide no definitive evidence of the superiority of one definition over any other for predicting future risk of colorectal cancer or assessing the likelihood of current disease.

## Prostate Cancer

Four longitudinal,[10-13] and two cross-sectional,[14,15] studies were included. Ten discrete definitions of 'positive FH' were examined. For the longitudinal analyses, the range of sensitivities was 0.00-0.21, and specificities 0.88-1.00. Omitting one study using mortality as the outcome, the range of PPVs was 0.11-0.26, and NPVs 0.92-1.00, for prostate cancer prevalences up to 8.7 percent. For the cross-sectional analyses, range of sensitivities was 0.01-0.26 and specificities 0.91-1.00. The PPVs were 0.02-0.14 and NPVs 0.96-0.98, for prostate cancer prevalences up to 8.7 percent.

The majority of definitions available for analysis were based on 1DRs and, for longitudinal studies, the overall AUC for category B FH definitions was 0.51 and for category, C was 0.93. This suggests a step up in the overall accuracy of classification of future risk of prostate cancer when FH of 1DRs generally is taken into account compared with specifically parental or sibling history. It was not possible to calculate this metric for cross-sectional studies. The utility of using FH to predict risk of future prostate cancer or detect current disease depends on which of sensitivity, specificity, and overall classification accuracy would be prioritized in routine practice.

## Coronary Heart Disease

Five longitudinal,[16-20] and three cross-sectional,[21-23] studies were included. Seventeen discrete definitions of ‘positive FH’ were analyzed. For the longitudinal analyses, the range of sensitivities was 0.03-0.51 and specificities 0.66-0.98. The range of PPVs was 0-0.13 and NPVs 0.66-0.98, for coronary heart disease (CHD) prevalences up to 10.4 percent. For the cross-sectional analyses, the range of sensitivities was 0.07-0.70 and specificities 0.53-0.98. The range of PPVs was 0.08-0.31, and NPVs 0.83-0.98, for CHD prevalences up to 20.7 percent.

Generally speaking, the highest sensitivities for prediction of future CHD risk were observed for the FH definition, ‘at least one affected parent’, although these also had lower specificities than other FH definitions. For category B FH definitions, the AUC was 0.57. For the assessment of possible current disease, the definition ‘at least one affected 1DR’ had a sensitivity of 70 percent, but it was derived from a single study in which the knowledge of disease status may have influenced awareness of FH. The findings are not sufficiently definitive to indicate a specific FH definition as the most efficient for screening or prediction of future CHD, but provide the foundation for considering how to approach such analyses.

## Stroke

Three longitudinal studies[24-26] were included, allowing examination of three separate definitions of ‘positive FH’, all relating to parental illness. The range of sensitivities was 0.05-0.33, and specificities 0.71-0.98. The range of PPVs was 0.0.02-0.08 and NPVs 0.96-0.98, for prevalences of stroke up to 3.9 percent. There were no cross-sectional studies.

Many of the analyses were derived from one study,[25] and do not provide definitive evidence for the utility of any particular FH definition for predicting the risk of stroke in the future. The AUC for these category B FH definitions was 0.43.

## Diabetes

Five longitudinal,[27-31] and 12 cross-sectional,[32-43] studies were included, along with the findings of a cross-sectional study[63] designed to examine different FH definitions but which did not have analyzable data. Twenty different definitions of ‘positive FH’ were analyzed.

For the longitudinal analyses, the range of sensitivities was 0.02-0.47, and specificities 0.79-1.0. The range of PPVs was 0.02-0.38, and NPVs 0.86-0.99, for underlying diabetes prevalences up to 16.2 percent. For the cross-sectional analyses, the range of sensitivities was 0.02-0.83 and specificities 0.44-0.99, for prevalences up to 17.4 percent. One cross-sectional study[63] reported the results of applying a three-level, FH-based, risk stratification system to representative U.S. adult survey data, where the overall diabetes prevalence was approximately 6.6 percent. Three FH definitions were applied, with sensitivities of 0.19-0.48 and specificities of 0.70-0.94. PPVs were 0.05-0.15 and NPVs were 0.95-0.98.

Overall, category C FH definitions for prediction of future disease risk (≥1 affected 1DR) had an AUC 0.43. The cross-sectional analyses examined a wide range of definitions, but many were assessed within the same study. Some of the highest sensitivities in the review were observed for the cross-sectional diabetes data, although the expected trade-off with specificity was also noted. The AUC figures for category B, C, and D FH definitions were similar (0.69, 0.71, and 0.64, respectively) suggesting no useful step up in discriminatory accuracy with extension of FH enquiry beyond 1DRs.. If the findings were replicated in further studies, they might suggest utility in using simple FH markers in preliminary triaging for diabetes screening.

## Asthma and Atopic Disease

Sixteen studies (17 publications) were included, four longitudinal,[44-46,48] eleven cross-sectional,[2,49-58] and one[59] which was treated as cross-sectional, presenting a followup analysis of a random sample of another eligible study.[58] Four studies[45,46,48,57] were relevant to atopic disease alone, ten[2,49,51-56,58,59] to asthma alone, and two[44,52] presented analyses for both asthma and atopic disease. Ten separate definitions of 'positive FH' were analyzed.

For the longitudinal analyses of atopy, the range of sensitivities was 0.15-0.64, and specificities 0.44-0.91. The range of PPVs was 0.25-0.46 and NPVs 0.7-0.84, for atopy prevalences up to 38.6 percent. For the cross-sectional analyses of atopy, the range of sensitivities was 0.23-0.48, and specificities 0.56-0.83. The range of PPVs was 0.28-0.52 and NPVs 0.68-0.74, for atopic disease prevalences up to 36.2 percent.

For the longitudinal asthma analyses, the range of sensitivities was 0.18-0.69 and specificities 0.43-0.91. The range of PPVs was 0.17-0.25 and NPVs 0.86-0.89, for an asthma prevalence of 14.8 percent. For the cross-sectional analyses, the range of sensitivities was 0.04-0.76 and specificities 0.46-0.99. For the childhood studies only, the range of PPVs was 0.08-0.51 and NPVs 0.82-0.92, for asthma prevalence up to 19.8 percent. For the two adult studies, the PPVs were 0.07, 0.13, and NPVs 0.96 and 0.98, respectively, for prevalences of asthma of 3.1 and 5.5 percent.

The longitudinal and cross-sectional atopy studies did not have sufficient independent data to undertake an AUC analysis. The longitudinal asthma analyses also focused on early childhood onset, and were all based on a single study. There seemed to be a clear increase in sensitivity with looser definition of FH, and a concomitant reduction in specificity, but the discriminatory accuracy was poor (AUC of 0.56). For the cross-sectional studies, category B FH definitions had AUCs of 0.73 (father had asthma) to 0.78 (mother had asthma) and category C definitions had an AUC of 0.67, suggesting that identifying disease in one parent provides maximum predictive information. For both disease outcomes (asthma and atopy), the cross-sectional studies were potentially subject to differential reporting of FH according to awareness of disease status.

## Mental Illness

One longitudinal,[60] and one cross-sectional,[62] study were included. Both examined outcomes to 26 years of age, and presented data on prediction of major depressive disorder (MDD); one study[60] also examined the mood disorder as an outcome condition, considered a more appropriate measure in childhood and adolescence. The longitudinal study[60] followed up the third generation of a family study in which the grandparents of the participants formed the inception cohort. Four definitions of ‘positive FH’ were examined.

For the longitudinal analyses of MDD, the range of sensitivities was 0.72-0.83 and specificities 0.40-0.59; for mood disorder, the range of sensitivities was 0.73-0.83 and specificities 0.42-0.63. The range of PPVs for MDD was 0.14-0.18 and NPVs 0.92-0.95; for mood disorder, the corresponding metrics were 0.24-0.31 and 0.89-0.92. The overall prevalence of MDD for this study was 11.2 percent, and of mood disorder was 18.6 percent. A relatively high proportion of participants met at least one of the definitions for positive FH (44.1-62.7 percent), reflecting the constitution of the original cohort.

The cross-sectional analyses produced sensitivities of 0.12 and 0.24 and specificities of 0.85 and 0.96, respectively. The PPVs were 0.33 and 0.45, and NPVs were 0.79 and 0.78, respectively, for a prevalence of MDD of 23.2 percent.

For prediction of MDD and mood disorders up to early adulthood, all three FH definitions produced sensitivities at the high end of the range observed in this review. They were derived from a single study and their applicability to routine primary care practice is unclear. For the cross-sectional study, only two FH definitions were examined, and no definitive conclusions can be drawn regarding the utility of either for screening for underlying MDD. It was not possible to calculate AUC for any of this data.

# Question 2. What is the Accuracy of the Family History, and Under What Conditions Does the Accuracy Vary?

A total of 37 publications evaluated the accuracy of reporting FH and were eligible for data extraction. There were 16 studies that evaluated accuracy of reporting cancer FH. These studies recruited probands with breast cancer,[91-94] colorectal cancer,[95-97] prostate cancer,[98,99] ovarian cancer,[100] mixed cancers (breast, ovarian, colorectal),[101,102] Ewing’s Sarcoma,[103] lymphoma,[104] melanoma,[105] and unspecified cancer.[106] Subjects were recruited predominately from specialized settings or cancer registries, which would suggest high risk of spectrum and selection bias. Twelve studies evaluated accuracy in persons with mental health disorders that included persons with Schizophrenia,[107-109] persons with dementia or depression,[110-113] and mixed disorders.[114-117] Nine studies evaluated other diseases that included Parkinson’s disease,[118-120] diabetes,[121-124] hypertension,[121,123,125-127] and other cardiovascular disease.[123-125,128] One study collected family history but reported only on the accuracy of informant age of onset rather than accuracy of disease status in the relatives; as such the results were not extracted for our research question.[118]

The methods for FH collection varied across studies as did the questions or tools used to collect FH. Some used highly standardized instruments and others used dichotomous probing (presence or absence of disease in any relative). Methods used to verify relatives’ disease status were primarily multimodal (medical records, disease or death registry, contact with relative) and relatives for whom verification could not be obtained were excluded from analyses.

Most studies probed the accuracy of reporting the same disease as that within the proband/informant, but some studies probed a variety of disease outcomes, for example any cancer or any mental health disorder. Overall, specificity across all disease types and with varying modes of FH collection was consistently high. Sensitivities were lower and generally more variable depending on the disease outcome. Some of the mental health disorders showed the lowest sensitivities, breast cancer, and cardiovascular disease showed the highest values.

Several studies evaluated predictors of accuracy in reporting FH. Factors related to the proband/informant includes age, gender, disease status, education level, race, marital status, type of disease, setting, and insurance status. Predictive factors associated with the relatives include, degree of relation, type of 1DR, disease subgroup, age, gender, and time since diagnosis. No clear trend emerged with age, gender, or education level of the informants and their impact on accuracy. No clear pattern across diseases emerges with the exception that there was a consistent trend towards increased accuracy of reporting relating to 1DRs compared to 2DRs or 3DRs; however, the majority of studies evaluated only 1DRs. Overall, these 37 studies had a high risk of spectrum bias (populations highly selected and not reflective of primary care), verification bias (different methods used inconsistently), and masking bias which may cause an overestimation of accuracy.

## Question 3. What is the Direct Evidence That Routinely Getting a Family History Will Improve Health Outcomes for the Patient and/or Family?

We selected studies that identified the impact on health related outcomes of systematic collection of FH in a typical, non-selected primary care/general population. Only two studies were identified after full text review.[129,130] Both studies were uncontrolled before-after designs and focused on breast cancer risk assessment, including FH collection, as the target intervention. In both studies, there was limited improvement in the clinically relevant process measure of mammography screening. In one study[129] mammography screening improved from 76 to 93 percent, however, the matched sample was small (n=29) and the change in screening did not reach statistical significance (p=0.057). There was no differentiation of the improvement in breast screening habits between the different risk strata. In the second study there was also limited improvement in adherence to mammography in all women (p=0.796) and for each age group (40-49; >=50 years old). Further, in women with high breast cancer risk (relative risk >=1.7) the adherence fell from 81 percent (17/21) to 71 percent (15/21), although this did not reach statistical significance (p<0.317). Both studies also demonstrated improvements in adherence to other process measures: breast self exam (BSE) and clinical breast exam (CBE). Both studies were at risk of selection bias sufficient to affect the interpretation of the results.

## Question 4. What is the Direct Evidence That Routinely Getting a Family History Will Result in Adverse Outcomes for the Patient and/or Family?

Three studies met all eligibility criteria.[131-133] These comprised a randomized controlled trial [133]and two uncontrolled before after studies.[131,132] Each of studies recruited patients from single

British primary care office network with the number of respondents recruited varying and response rates of 19, 29, and 64 percent respectively. The proportion of recruited patients completing survey items at all time points was 91, 89, and 76 percent respectively. These studies suggest that structured FH collection and feedback of familial risk information had no deleterious psychological effects on patients at 6 to 12 weeks after FH intervention. One study[131] further identified the relationship between breast cancer familial risk status and psychological impact. As well as having no deleterious psychological effect in any of the risk groups, for women who were at or just above average risk, the FH risk assessment may have led to appropriate reductions in perceived risk.

## Question 5. What are the Factors That Encourage or Discourage Obtaining and Using a Family History?

Six studies were identified, four of which were undertaken in primary care offices.[134-137] The other two studies' populations were derived from patients being screened in the general population.[138,139] Four studies were cross-sectional.[135,136,138,139] The remaining two studies were a direct observational study[137] and a prospective cohort study with a baseline cross-sectional survey.[134] Factors associated with FH collection or discussion were the primary outcomes of interest of three studies.[136,137,139] These data were retrieved in the other three studies from sub analyses presented in these publications.[134,135,138] Two studies only recruited female patients.[136,138] The identified outcomes of interest were: FH documented in medical records;[134,136] FH discussed by doctor, either confirmed by direct observation[137] or patient survey;[135,138] and self reported FH.[136,139] Women appeared to be better informants than men were and younger physicians were more enthusiastic about discussing FH. There were disparities in FH collection and reporting in underserved groups, specifically non-white ethic groups,[136,139] those with lower educational status,[139] and those on state health insurance.[137]

The evidence base for addressing Q5 is heterogeneous and limited to six studies exploring the association between various factors and FH reporting, documentation and discussion. In most studies the nature of the FH discussed or reported was not clearly identified, often just reported as dichotomous variables. Representativeness of these surveys is also limited by response bias and recall bias. Collectively, these issues limit the generalizability of the study findings, hence caution should be observed in applying this information to clinical situations in primary care.

## Discussion and Conclusions

This review was designed to inform a broad range of questions which ultimately address the clinical value of using FH in chronic disease risk assessment and prevention. The findings from studies reviewed in Q1, Q2, and Q5 should inform the nature and content of future FH tools, which should be developed according to the context in which the tools are being applied. A tool used for an initial general FH screening enquiry, such as during a new patient intake visit or routine physical examination, would generally be less focused than one developed for a specific purpose, such as identifying possible familial risk in a woman concerned because of a breast cancer diagnosis in a sibling. The starting point should be clarifying the minimal FH dataset necessary for each purpose, taking account of the evidence for accuracy, recall, and relevance of each piece of information.

1. Very few studies were designed to address Q1 directly, and the metrics reported usually related to strength of association between FH and disease incidence or prevalence rather than discriminatory ability when applied to individual patients. Our analyses were based largely on a re-examination of data generated for other research purposes. In most cases, positive FH, however defined, had no more than modest ability to correctly classify future risk of complex disorders in individuals. This is logical, because, by definition, they are not high penetrance single gene disorders. The required level of predictive accuracy depends on the purpose of the FH assessment, and the benefits, risks, and costs of decisions made based on the risk assessment. In principle, the definition of 'positive FH' which combines adequate predictive accuracy with the least effort to obtain it would be most suited to busy primary care settings.

Recommendations for direction of future research:

- Further clarification of the purpose of FH taking in primary care settings is required, so that future assessments of the utility of FH are based on an appreciation of the level of predictive accuracy that is required for the specific situation.
- The evidence base requires studies designed explicitly for the purpose of examining the predictive ability of different 'minimum' FH definitions. This requires adequately powered, longitudinally designed studies in which detailed, extensive, clearly defined and documented FH components comprise the 'exposures', in which participants are followed up for a period which is clinically meaningful, in which adequate measures are taken to control bias, and in which the primary metrics relate to individual risk prediction.
- FH items should be formally examined alongside other recommended or readily accessible risk factors, in order to identify the extent to which they provide (or need to provide) useful independent and/or incremental discriminatory ability.

2. The accuracy of self reported FH has implications for the correct risk assessment and management of patients. Accurate reporting of the absence of disease (specificity) appears to be more common than accurate reporting of presence of disease (sensitivity) across different disease areas. Estimates of sensitivity show greater variation and the magnitude varies with different diseases. Although, there is limited evidence, accuracy of recall and reporting may be influenced by both patient and informant (relative) factors, and by the method used to collect FH. Accuracy of FH reporting may also be dependent on the method of collection, which is related to the disease area however, further evaluation is needed.

Recommendations for direction of future research:

- Future studies in accuracy should be undertaken in populations reflective of the primary care setting and representative of the spectrum of disease risk.
- Future studies should endeavor to better characterize the attributes of the informant/proband and especially the relatives; the potential of these factors to influence the accuracy of reporting should be consistently evaluated. Future evaluation should be undertaken in the areas of asthma and atopy, affective mental health disorders, cardiovascular diseases, and diabetes.

3. Within primary care populations, there is very limited evidence to support or refute the effect on risk-reducing behavior changes of taking a FH and using it to personalize risk of developing respective conditions.

Recommendations for future research:

- Well designed trials are required that compare the impact of FH-based, personalized risk advice with standard of care on risk reducing behaviors in populations at different risk levels (including population risk). The outcomes of interest need to be clinically relevant, either leading to improved mortality or morbidity or surrogate measures with strong evidence of links to improved health outcomes. Concurrent qualitative studies should also be considered.
- Proposed trials should be based on evidence from systematic reviews to ensure that prescribed risk-reducing behaviors are evidence-based.

4. In primary care populations, there is very limited information to evaluate direct harm incurred from the routine practice of taking FH and using it to personalize risk information.

Recommendations for future research:

- Trials of FH taking as an intervention should include capture of data to examine the full range of potential impacts on individuals of FH collection and implementation strategies based on familial risk identification, both negative and positive. Concurrent qualitative studies should also be considered. Baseline data on psychological status should be captured so that this can formally be adapted for use in outcome analyses. To enable appropriate evaluation of psychological harm, context-specific measures need to be developed and validated.

5. In order to assess the content validity of systematic FH tools we need to know not only the factors that affect the recall of FH (Q2) but also those factors that affect the collection and use of FH. Thus far, there is limited information on collection and discussion of FH in primary care, with no factors identified that are associated with the use of the FH. There is some suggestion that populations from underserved communities are less likely to report and have the opportunity to discuss FH, but the level of evidence is weak.

Recommendations for future research:

- Further research is required to clarify the most important patient and practitioner factors that may affect the collection and use of FH. This likely requires the development of theoretical frameworks to guide appropriate design, and to ensure that methodologies adequately address the many potential biases and interactions between factors which may be encountered. The most important studies are those that address factors directly relevant to primary care practice, including highlighting patient factors which promote inequity in the application of effective interventions
- Where inequities are identified, interventions should be designed to ameliorate these factors in future trials and service provision. Such research could include analyses of national population and practitioner survey databases.
- While research should focus on clinically relevant outcomes, it should also include process evaluations to identify factors that affect the successful implementation of the FH interventions.

# Evidence Report

# Chapter 1. Introduction

## Background

According to the Centers for Disease Control and Prevention, almost half of Americans live with at least one chronic condition, and chronic diseases account for 70 percent of all deaths in the United States, one third of potential years of life lost before 65, and three quarters of medical care costs.[140] Although the role of important risk factors such tobacco, nutrition, and physical activity are well known, there are many unknown factors that contribute to risk and which prevent completely accurate individualized risk assessment across a range of diseases. Nevertheless, it is possible that a traditional, 'low tech' approach to risk assessment–family history–might be practical and useful for widespread application, to assist in identifying particular risks carried by individuals, in order to target interventions and efforts on disease prevention. Family history (FH) represents the integration of shared genomic and environmental risk factors.[1] First degree relatives (1DRs) share half their genomic information (roughly one copy of 30-50,000 genes), and so their disease experience may offer a clue to shared susceptibilities, even in the absence of a complete understanding of the molecular etiology of a given condition. While FH assessment is a core approach in clinical genetics, FH may offer much more than the possibility of identifying relatively rare inherited diseases which follow a Mendelian inheritance pattern. Approached as a 'black box' FH may provide information on the influence of genetic variants which, *collectively*, act to increase or decrease disease susceptibility, and on other familial factors which alter risk (such as shared behaviors and lifestyles).

Family history may therefore be a cost effective way of tapping into 'integrated' disease risk information.[141] For most common chronic diseases, the impact of a positive FH has been recognized. For example, a population-based study in Utah observed that 14 percent of families accounted for 72 percent of the premature coronary heart disease (CHD) in the state, and 11 percent of families accounted for 86 percent of premature cerebrovascular disease;[142] in another study 30 percent of middle-aged British men who report a FH of CHD experience a 71 percent excess risk of CHD themselves over 10 years.[143] Further, we are aware of the individual roles of obesity and FH in predicting the development of diabetes, but in combination, the predictive value increases from around 20 to 40 percent.

Support for this approach also comes from a detailed meta-analysis,[144] in which the association between having one or more 1DRs and risk of a number of common, complex disorders was convincingly demonstrated.

However, there are important issues that need to be addressed regarding the overall utility of using FH information in primary care settings. The first issue relates to the capture of FH information in itself. For FH information to be useful, there should be some confidence that patients are able to report it accurately and consistently. This has been addressed for some cancers in a previous review.[145] Secondly, there should be evidence that health professionals in primary care can capture such information accurately. Previous reviews[145,146] have examined FH tools and demonstrated that the systematic use of a FH tool improves accuracy and completeness

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Appendixes and Evidence Tables for this report are provided electronically at http://www.ahrq.gov/downloads/pub/evidence/pdf/famhistimprov/famhimp.pdf.

of information capture. It appears that the crucial issue is use of a tool, rather than its specific format, although further research may clarify whether any particular attributes (such as patient-completed versus professional-completed, or electronic versus paper) offer specific advantages for use in particular settings. An important issue which needs to be addressed is the 'minimum FH dataset' necessary for application in primary care settings for chronic disease risk prediction.[147-151] It is important to bear in mind that primary care practitioners face constraints in relation to capturing FH information,[152] and cannot necessarily replicate the practice of genetics specialists in completing detailed, three generational pedigrees.

A broader, but crucial question is that of the overall benefits and harms of capturing FH information. Like any health care intervention, FH-based risk assessment carries resource implications and opportunity costs. Thus, its impact on health outcomes, both beneficial and harmful, should be assessed objectively in order to promote evidence-informed practice and policy.

## Overall Evaluation Approach

In approaching these questions, we have borrowed from a range of evaluative frameworks including: methods developed in diagnostic and screening test research (applied to assessing individual FH items for their predictive validity, and for the assessment of accuracy of FH reporting): methods for the assessment of the effectiveness and safety of clinical interventions (applied to FH taking as a deliberate clinical intervention); and classical epidemiological methods (applied to the assessment of factors which promote or hinder FH taking as a routine clinical activity).

## Scope and Purpose of the Systematic Review

This systematic review addresses six research questions relating to the analytic validity, the clinical validity, and the clinical utility of routinely using FH information in risk assessment for complex disorders, as follows.

1. What are the key elements of a family history in a primary care setting for the purposes of risk assessment for common diseases?
2. What is the accuracy of the family history, and under what conditions does the accuracy vary?
3. What is the direct evidence that routinely getting a family history will improve health outcomes for the patient and/or family?
4. What is the direct evidence that routinely getting a family history will result in adverse outcomes for the patient and/or family?
5. What are the factors that encourage or discourage obtaining and using a family history?
6. What are future research directions for assessing the value of family history for common diseases in the primary care setting?

Regarding research question 1, the specific disease categories of interest were:

- breast, ovarian, colorectal, prostate, and lung cancers
- cardiovascular and heart disease
- stroke
- diabetes

- asthma and allergies (atopic disease)
- major depression and mood disorders

in addition, key elements for consideration were information relating to:

- ancestry
- number of affected or unaffected relatives
- lineage
- age of onset
- sex or gender
- relationship (first degree, second degree)

Question 6 is addressed by drawing together the evidence from questions 1 to 5 and therefore is not evaluated separately. The focus of this review is on using FH in primary care contexts, and as an intervention mainly for chronic disease risk assessment in large population groups, not assessment of rare genetic disorders in high risk groups. This has driven the eligibility criteria for studies towards:

- study populations with the range of disease risk seen in primary care and general settings
- study settings where primary care providers such as family physicians, internists, nurse practitioners, and obstetricians are taking family histories and assessing risk
- family history taking as an intervention carried out by primary care practitioners and directed primarily towards chronic disease risk assessment and prevention as an end in itself
- chronic disease prevention interventions evaluated in primary care or general populations with an inherent range of disease risks, but *not* selected because of special high risk (genetic or otherwise)

The focus on study populations “unselected” for high risk implies groups of participants, which represent a full range of risks, potentially from very low to very high, by definition with clustering around an “average” value. These populations reflect the context of professional and patient decision-making in primary care - patients with a wide range of risks are encountered, but most are neither particularly high nor particularly low risk. This situation is distinguished from that where patients and their providers already have reason to suspect high disease risk, as such populations are more homogenous and are designed to *exclude* individuals who are likely to be average and low risk. While findings from ‘unselected’ populations may possibly be applicable to high risk groups, the converse cannot be assumed.

Family history taking is a health care intervention and its evaluation requires as much attention to potential bias as any other intervention. An important potential confounder in assessing this intervention is pre-existing awareness of family illness. Living with a serious disease within a family can influence risk perceptions and health behaviors,[153,154] quite independently of any intervention by a health professional. This means that the effect of FH taking as a deliberate clinical activity can only be meaningfully assessed using well-designed studies that can address confounding and bias. Family history taking is also an inherently complex intervention and needs to be separated from other activities, such as genetic testing.

# Chapter 2. Methods

## Analytic Framework

The analytic framework is a schematic representation of the strategy for showing the relationships between the primary exposure, which is the collection of family history (FH), and the outcomes of interest for each research question (Q). Figure 1 shows the inter-relationships among the six research questions being addressed in this systematic review.

The framework shows the logical connection between the research questions, commencing with the accuracy of clients reporting their family history (FH) (Q2). If we consider a key purpose for collecting family history, as a test to screen or identifying clients who might be at an altered risk for developing the same disease, then the selection of the optimal items that will comprise a comprehensive FH should be considered; evaluation of the evidence for those items that are most predictive of subsequent disease development is sought in (Q1). Evaluation of the evidence for the impact of collecting FH is addressed in the third research question (Q3). The potential for harmful outcomes as a result of collecting FH will also be addressed (Q4).

The context in which FH is collected and factors that may facilitate or hinder its collection also have bearing on the validity of collecting FH (Q5). These contextual factors (Q5) and those related to accuracy of reporting (Q2) may influence the optimal selection of items to be included within a set constituting adequate FH collection for risk assessment in a primary care setting (Q1). Following the systematic collection of FH in a population representative of primary care, the uptake of prevention, screening, and other interventions are important outcomes of benefit that may result. The strength of the evidence from studies addressing Q1 through Q5 will inform future directions for assessing the value of FH on common chronic diseases in the primary care setting (Q6).

### Search Strategy

Bibliographic databases searched for this review included: MEDLINE®, EMBASE®, CINAHL®, Cochrane Controlled Trials Register (CCTR)®, and PsycINFO. Years searched were 1995 to March 2, 2009 inclusive. Our broad based search was not restricted by disease type, and yielded a very large number of titles and abstracts; as such, we limited the search to 1995 forward. Detailed search strategies are listed in Appendix A. We reviewed a limited number of grey literature sites, including NCPEQ and the Center for Disease Control (CDC). In addition, we retrieved and evaluated references from eligible studies that were not captured in our search. Hand searching was not undertaken.

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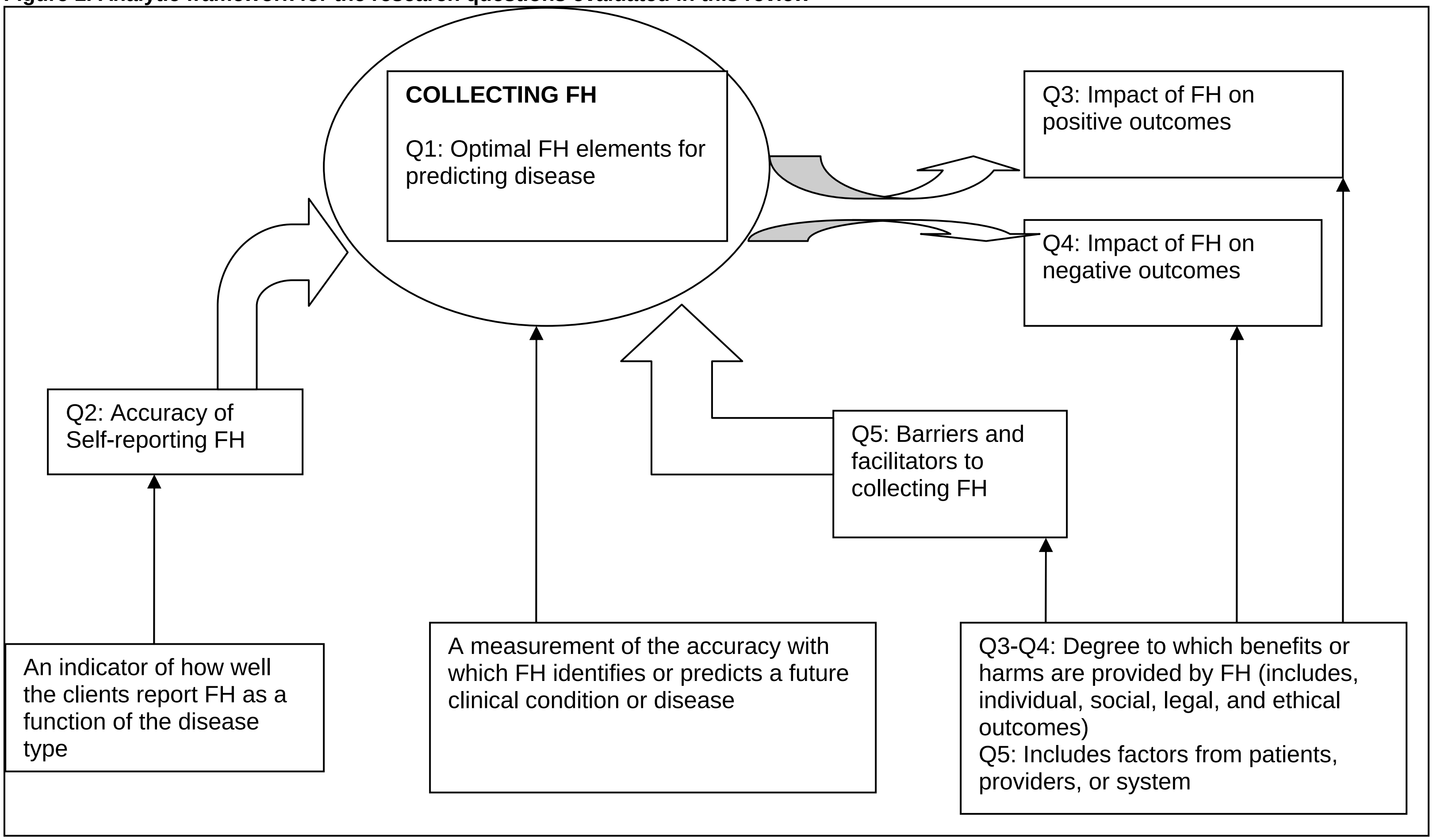
Appendixes and Evidence Tables for this report are provided electronically at http://www.ahrq.gov/downloads/pub/evidence/pdf/famhistimprov/famhimp.pdf.

**Figure 1. Analytic framework for the research questions evaluated in this review**




Abbreviations: FH=family history; Q=question

## Eligibility Criteria

A list of eligibility criteria was determined and standardized forms were developed in Systematic Review Software (SRS, 3.0, TrialStat Corporation, Ottawa, Ontario Canada) and Microsoft Excel for the purposes of this systematic review.

**Publication Year, Type, and Language**

*Inclusion*

Language: Only English language studies were eligible for all research questions.

Publication Date: 1995 to March 2, 2009.

*Exclusion*

Publications that were editorials, letters, conference papers, comments, opinions, or abstract only

## Eligibility Criteria for Research Q1

**Population Subjects**

*Inclusion*

- General population in non-specialist setting
- Primary care patients in non-specialist setting
- Participants in organized screening programs not based on FH

*Exclusion*

- Patients undergoing or having completed genetic testing, whether positive or negative
- Participants selected because of higher than average risk of disease
- None of the disease groups of interest

**Intervention**

*Inclusion*

- Family history collection – any modality
- We delimited this research question based on the disease categories suggested by the OMAR Conference Planning Committee and in consultation with the Technical Expert Panel (TEP). These included
  - Cardiovascular diseases (including stroke and inherited childhood heart conditions)
  - Diabetes
  - Cancer (lung, breast, colorectal, ovarian, prostate)
  - Allergy and atopy (limited to asthma specifically, and atopic disease as a group)
  - Mental health disorders (major depression, mood disorders)

*Exclusion*

- Medical history without FH collection
- Family history collection about diseases other than those specified in the inclusion criteria

**Comparator/Study Design**

*Inclusion*

Any quantitative, analytic design, in which the association between one or more FH items (considered 'exposure') is examined in relation to current disease or future disease risk. With the exceptions of atopy, allergy and mental illness studies, associations were restricted to FH and outcome of the same condition (e.g., association of FH of colorectal cancer and incidence of colorectal cancer but not FH of lung cancer and incidence of colorectal cancer)

*Exclusion*

- Case control studies
- Case reports
- Qualitative designs

**Outcome**

*Inclusion*

- Prevalence or incidence of one of the disease conditions specified by the OMAR committee and the TEP (cardiovascular including stroke and inherited childhood heart conditions, diabetes, cancer, allergy and atopy and mental health disorders)
- Outcomes were restricted to clinically evident or routinely ascertainable disease outcomes. Table 1 details the specific outcomes within each disease category

*Exclusion*

- Outcomes for diseases other than those listed in Table 1
- Pre-disease or outcomes
- Research-based outcomes not in routine clinical use

**Table 1. List of included and excluded outcomes for Question 1 by major disease categories**

| DISEASE CATEGORY | INCLUDE | EXCLUDE |
|---|---|---|
| Coronary artery disease (CAD) (synonyms: ischemic heart disease, coronary heart disease) | • Angina<br>• (Acute) Myocardial infarction (AMI, MI)<br>• Revascularization (CABG, angioplasty)<br>• Heart failure secondary to CAD<br>• CAD death<br>• CAD (not otherwise specified) | • Coronary artery calcification<br>• Intimal media thickness<br>• Hypertension<br>• Aneurysm<br>• Peripheral vascular disease<br>• Valvular heart disease |
| Stroke (synonym: cerebrovascular accident) | • Clinically apparent stroke | • Transient ischemic attack<br>• Subarachnoid hemorrhage not otherwise specified<br>• Convulsions (not otherwise specified)<br>• Dementia (not otherwise specified) |
| Childhood/inherited /congenital heart disease | • Hypertrophic obstructive cardiomyopathy<br>• Long QT syndrome | |
| Depression and mood disorders | • Depression<br>• Bipolar affective disorder (also known as manic/depressive psychosis)<br>• Schizophrenia<br>• Anxiety related disorders | • Other psychiatric conditions |
| Diabetes | • Type 1 diabetes<br>• Type 2 diabetes<br>• Gestational diabetes | • Impaired fasting glucose alone<br>• Impaired glucose tolerance alone<br>• Metabolic syndrome |

**Table 1. List of included and excluded outcomes for Question 1 by major disease categories (continued)**

| DISEASE CATEGORY | INCLUDE | EXCLUDE |
|---|---|---|
| Allergy and Asthma | • Asthma<br>• Atopic disease examined as an overall category (defined in reports as 'atopic disease' either as a general class of conditions or as a composite including at least two of atopic asthma/wheeze, allergic dermatitis, specific food intolerance, allergic rhinitis/sinusitis) | • Food intolerance alone<br>• Eczema alone<br>• Allergic rhinitis/sinusitis alone |
| Cancer | • Breast cancer<br>• Ovarian cancer<br>• Colorectal cancer<br>• Prostate cancer<br>• Lung cancer | • Other cancers |

Abbreviations: CABG=coronary artery bypass graft; CAD=coronary artery disease; AMI=acute myocardial infarction; MI-myocardial infarction; QT interval=time between start of Q wave and end of the T Wave in the hearts' electrical system

## Eligibility Criteria for Research Q2

**Population**

*Inclusion*

- General population
- Primary care patients
- Primary care providers (including family physicians, general internists, obstetricians, gynecologists, nurses, nurse practitioners, physicians assistants, nutritionists, and behavioralists)
- Patients from specialized disease centers

*Exclusion*

- Patients recruited that had genetic testing completed, whether positive or negative

**Intervention**

*Inclusion*

- Index Test: FH collected in any modality
- Reference Standard (verification of disease status in relatives) to include any of the following:
    - Death registries
    - Disease registries
    - Medical records
    - Direct contact with relatives
    - Confirmation by relatives' physicians
    - Verification from research databases only if medical records were contained within them

*Exclusion*

- Index Test: Collection of medical history without FH

- Reference Standard
  - Verification of disease status in relatives that does not include the methods listed above
  - Studies where patient report of FH was the reference standard and the focus of the study was to compare differences with documentation in medical charts

**Study Design**

*Inclusion*

- Any quantitative design, comparative or non-comparative

*Exclusion*

- Case report

**Outcomes**

*Inclusion*

- Metrics of study accuracy
  - Sensitivity
  - Specificity
  - Positive predictive value
  - Negative predictive value
- Measures of completeness of FH collection
- Percent Agreement/Kappa as a measure of accuracy

*Exclusion*

- Studies where only true positives were reported, with no additional information to calculate sensitivity or specificity
- Studies that did not report any outcomes listed above
- Studies that evaluated test-retest reliability alone

## Eligibility Criteria for Research Q3

Consistent with the intent of the question, evidence of the highest methodological quality (direct evidence) was sought. Only studies where the intervention (systematic collection or use of FH) was contrasted to a comparator that did not use FH were sought. The comparator could be between groups (for example, usual care) or within groups (before and after intervention).

**Population**

*Inclusion*

- General population in non-specialist setting
- Primary care patients in non-specialist setting
- Primary care providers (including family physicians, general internists, obstetricians, gynecologists, nurses, nurse practitioners, physician assistants, nutritionists, and behavioralists)
- Participants in organized screening programs not based on FH

*Exclusion*

- Studies where the practitioner is specialist (e.g., geneticist, cancer surgeon, oncologist, cardiologist)
- Patients recruited on the basis of genetic testing whether results were positive or negative

**Intervention**

*Inclusion*

- Collection or use of FH collected in a systematic manner; can be in isolation or part of a multiplicative risk assessment

*Exclusion*

- Collection of FH is not part of the intervention (e.g., patients selected on the basis of increased risk including FH for another intervention)
- Family history is used as a selection criteria for study, not as an intervention

**Comparator/Study Design**

*Inclusion*

Primary studies of the following study designs

- Randomized controlled trials
- Non-randomized controlled trials
- Uncontrolled before-after studies

Comparators:

- No between group comparator
- Comparator group with no intervention
- Comparator group receiving preventive advice without provision of FH-based information

*Exclusion*

- Cohort studies
- Case-control studies
- Case series and case reports

**Outcomes**

*Inclusion*

- Disease-specific mortality
- Disease-specific morbidity
- Uptake of behavior or screening as a result of taking a FH and informing the subject of their risk

*Exclusion*

None of the outcomes listed above

## Eligibility Criteria for Research Q4

Consistent with the intent of the question, evidence of the highest methodological quality (direct evidence) was sought. Only studies where the intervention (systematic collection or use of FH) was contrasted to a comparator that did not use FH were sought. The comparator could be between groups (for example, usual care) or within groups (before and after intervention).

**Population**

*Inclusion*

- General population in non-specialist setting
- Primary care patients in non-specialist setting
- Primary care providers (including family physicians, general internists, obstetricians, gynecologists, nurses, nurse practitioners, physicians assistants, nutritionists, and behavioralists)
- Participants in organized screening programs not based on FH

*Exclusion*

- Studies where the practitioner is specialist (e.g., geneticist, cancer surgeon, oncologist, cardiologist)
- Patients recruited on the basis of genetic testing whether results were positive or negative

**Intervention**

*Inclusion*

- Collection or use of FH collected in a systematic manner; can be in isolation or part of a multiplicative risk assessment

*Exclusion*

- Collection of FH is not part of the intervention. e.g., patients selected on basis of increased risk including FH for another intervention
- Family history is used as a selection criteria for study, NOT intervention

**Comparator/Study Design**

*Inclusion*

Primary studies of the following study designs

- Randomized controlled trials
- Non-randomized controlled trials
- Uncontrolled before-after studies (non-controlled trials)

Comparators

- No comparator group
- Comparator group with no intervention
- Comparator group with intervention not based on FH collection or FH-based preventive advice

*Exclusion*

- Cohort studies
- Case-control studies
- Case series and case reports

**Outcome**

*Inclusion*

- Quality of life
- Family functioning
- Social functioning
- Psychological distress e.g., worry, anxiety, depression, inaccurate risk perception
- Related to the FH collection and /or use only, not to the resulting intervention

*Exclusion*

- Outcomes not listed above

## Eligibility Criteria for Research Q5

**Population**

*Inclusion*

- General population in non-specialist setting
- Primary care patients in non-specialist setting
- Primary care providers (including family physicians, general internists, obstetricians, gynecologists, nurses, nurse practitioners, physician assistants, nutritionists, and behavioralists)
- Participants in organized screening programs not based on FH

*Exclusion*

- Studies where the practitioner is a specialist (e.g., geneticist, cancer surgeon, oncologist, cardiologist)
- Patients recruited with genetic testing complete, whether positive or negative

**Intervention**

*Inclusion*

Factors (independent variables) that positively OR negatively affect either the collection and/or use of FH, or the extent and quality of FH collected or used.

Factors can be patient-specific, practitioner-specific, and setting-specific. These include:

- Psychosocial
- Socio-demographic (e.g., ethnicity; gender)
- Financial
- Relationship of patient with healthcare provider (e.g., new provider/established provider)

*Exclusion*

- None

**Comparator/Study Design**

*Inclusion*

- Any quantitative design, comparative or non-comparative

*Exclusion*

- Any qualitative study design

**Outcome**

*Inclusion*

Self reported FH by patient or measure of FH collection or use. Metric to assess FH collection or use include:

- Attributes that determine if FH reported (either yes/no or extent of FH)
- Attributes that determine if FH discussed (either yes/no or extent of FH)
- Attributes that determine if FH used (either yes/no or extent of FH)

*Exclusion*

None

## Study Selection

A team of study assistants was trained to apply the eligibility criteria for screening the title and abstract lists and the full text papers. All levels of screening were done in web-based Systematic Review Software (SRS) (TrialStat Corporation, Ottawa, Ontario Canada). Standardized forms and a training manual explaining the criteria were developed and reviewed with the screeners (Appendix B). For the title and abstract phase, two reviewers evaluated each citation for eligibility. Articles were retrieved if either one of the reviewers judged it as meeting eligibility criteria or if there was insufficient information to determine eligibility. For screening of full text articles, two screeners came to consensus on the identification, selection, and abstraction of information. Disagreements that could not be resolved by consensus were resolved by one of our McMaster research team members.

## Data Extraction

Appropriate data collection forms were developed for use in SRS (Appendix B). All eligible studies from full text screening were abstracted onto a data form according to predetermined criteria. One data extractor transferred the data onto these forms, and another checked the answers for accuracy before they were entered into SRS. Data entries were verified by the investigators responsible for summarizing the different report results sections.

## Quality Assessment

Given the diversity of research questions and eligible study designs, we considered the assessment of quality separately for each research question. For Q1, the large number of studies were grouped by study design and disease types, which served in part, to stratify studies by similar risk for biases. The study designs for the eligible studies of Q1 were classified as longitudinal and cross sectional. Cohort studies where FH was assessed at the same point as disease outcome was ascertained were considered cross sectional studies. For quality assessment we selected questions on method of sampling, and participation rates for the cross sectional studies; we evaluated method of disease outcome ascertainment, method of family history ascertainment, and an accounting of withdrawals for all study designs (see Appendix B forms for the specification of the criteria).

For Q2, the Quality Assessment of Diagnostic Accuracy Assessment (QUADAS) was selected and all but four items within the 14 criteria were applicable for the "index test" of collecting FH. Appendix B details the criteria and the method of standardizing responses. Criteria from items 3, 4, 12, and 13 of the QUADAS were not applicable to collecting FH from informants and verifying the diseases in relatives. In applying these QUADAS items, we assumed that the index test (FH collection) and the reference test were equivalent across studies. Appendix B shows the modifications and interpretation of the QUADAS for this question.

There were two different designs among studies eligible for research Q3 and Q4; for the randomized clinical trials, the Jadad scale[155] was used to evaluate internal validity. For the before after study design no formal scale was available, critical appraisal was undertaken for the risk of selection and outcome biases. For eligible cross sectional studies for research Q5, selection bias (method of sampling) and response bias were evaluated.

# Summarizing our Findings: Descriptive and Analytic Approaches

A qualitative descriptive approach was used to summarize study characteristics and outcomes for all research questions. Multiple publications on the same study cohort were grouped together and treated as a single study with the most current data reported for presentation of summary results. Standardized summary tables explaining important study population and population characteristics, as well as study results, were created.

Meta-analysis was not appropriate for any of the research questions. It was not undertaken for Q1 because of significant clinical heterogeneity across studies, and because many observations were compared within studies, therefore the studies were not completely independent. Similarly, it was not undertaken in Q2 because of significant clinical heterogeneity across studies, too few studies for some disease categories, or insufficient data (no measures of variance). There were an insufficient number of studies in Q3 and Q4 for meta-analysis. Clinical and methodological heterogeneity was significant for eligible studies in Q5.

For research Q1, the purpose of the analysis was to compare the discriminatory accuracy of specific FH items and definitions of 'positive' FH which might be used in routine clinical practice. The ideal method would have been a meta-regression analysis to assess the contribution of the different variables of interest (ancestry, lineage, age of onset, etc) to overall discriminatory accuracy. However, no studies were identified which permitted such an analysis. In order to address the research question, therefore, a simpler, alternative approach was developed. For each study, all definitions of 'positive FH' which were associated with analyzable data (see below) were recorded and, within disease condition, similar FH definitions (e.g., 'mother', 'father', 'at least one 1DR', etc.,) were grouped for comparison. We approached the definitions from a pragmatic clinical perspective, rather than epidemiological perspective so that in studies with multiple definitions we combined data from mutually exclusive categories into inclusive categories. For example, the category 'affected mother' included data from the categories 'mother only' and 'both parents'. Thus, the category "affected mother" should generally be taken to mean, "affected mother, whether or not the father also affected.

We extracted the actual numbers of true and false positive and negative results (TP, FP, TN, and FN) according to these definitions, or estimated these numbers based on reported proportions. We calculated sensitivities, and specificities with the accompanying 95 percent confidence intervals (CI).

Recognizing the primary care context for the review, in which the time and resources available for FH taking may be very limited, we developed a categorization of FH definitions to reflect the 'complexity' of the task (Table 2). It is important to note that this initial attempt at categorization is based on a notion of 'likely effort required', not on any *a priori* notion of the information value of the pedigree itself. We suggest that the FH definition that combines 'adequate' predictive validity with least effort (lowest category) might be the most likely to be useful in routine primary care settings.

Summary receiver operator characteristic (SROC) curves were estimated to assess the effect on accuracy of different FH definitions within each major disease group. The SROC curve mimics the receiver operator characteristic (ROC) curve and is a way to measure the diagnostic accuracy across different studies. We estimated the area under the curve (AUC) and the index Q* and their standard errors. The value of Q* indicates overall accuracy by finding where sensitivity and specificity are equal. Since Q* is defined by the point where sensitivity and specificity are equal, Q* may not address the clinical usefulness of the test when sensitivity and specificity are not equally important in practice. Note that a minimum of three studies with the same FH definition would be required for this computation. Statistical analyses were carried out using Stata/SE 8.0 for Windows (Stata Corporation) or MetaDiSc.[156] Additionally, data points entered into the analyses had to be independent; as such, we selected the most inclusive FH definition within each family history category (Table 2). For example, data from a single study reporting values for greater than or equal to one parent, mother, and father would not be independent; the data from greater than one parent was selected to include in the SROC analyses.

**Table 2. Notional classification of family history items and definition of a positive family history**

| Category | General approach to FH collection | "Positive" FH | Example | Workload |
|---|---|---|---|---|
| **A** | Ask the most general question to identify one affected family member whose relationship does not need to be specified | One single relative affected by condition, relationship irrelevant | *Does anyone in your family have the condition?* | • Enquiry stops if patient recalls one affected relative<br>• Workload very low if approached as simple screening question<br>• Workload higher if approached by systematically working through pedigree to ascertain relatives' status |
| **B** | Ask about 1-2 specific family members, and no others. | One or two defined relatives affected by condition | *Do either of your parents have the condition?*<br>*Does your brother have the condition?*<br>*Did your mother have this condition? If so, do you also have a sister with it?* | • Enquiry stops when affected/unaffected status of no more than 2 specified relatives is clarified<br>• Workload potentially very low |
| **C** | Ask about close family only | One or more first degree relatives (not pre-specified further) affected by condition | *Does any member of your immediate family have the condition?*<br>*Have any of your parents, brothers or sisters been affected by this condition?* | • Enquiry stops when the minimum number of specified affected relatives is reached OR unaffected status of all first degree relatives clarified<br>• Workload depends on number of siblings and children, but enquiry limited by number of first degree relatives |
| **D** | Be ready to go beyond close family but do not consider lineage | One or more first and/or second, and/or [possibly] third degree relatives (but not pre-specified further) affected by condition | *Have any of your immediate or broader family (aunts, uncles, grandparents, etc.) have the condition?* | • Enquiry stops when minimum number of specified affected relatives is reached OR unaffected status of all relatives of interest is clarified<br>• Workload depends on number of relatives in close and extended family and how far FH criteria extend beyond first degree |

Abbreviations: FH=family history

**Table 2. Notional classification of family history items and definition of a positive family history (continued)**

| Category | General approach to FH collection | "Positive" FH | Example | Workload |
|---|---|---|---|---|
| **E** | Follow specific guidelines which define relevant FH history in a more complex manner or which go beyond affected relatives | More complex combination of numbers, degree of relationship, and/or lineage of relatives affected by condition, and/or considerations such as consanguinity | *Have at least two immediate relatives from the same side of the family (i.e., excluding both parents but including one parent and a brother or sister or two of your brothers and sisters) been diagnosed with the condition?*<br>*If not, has one immediate relative and at least two of your aunts, uncles, grandmother, grandfather, nieces or nephews (on the same side of the family) been diagnosed with the condition? If not, have at least three of your aunts, uncles, grandmother, grandfather, nieces, and/or nephews (on the same side of the family) been diagnosed with the condition?* | • Enquiry stops when the criteria for positive FH are met OR the unaffected status of relatives of interest is clarified.<br>• Workload variable, depends on complexity of criteria and number of relatives potentially of interest |

# Peer Review Process

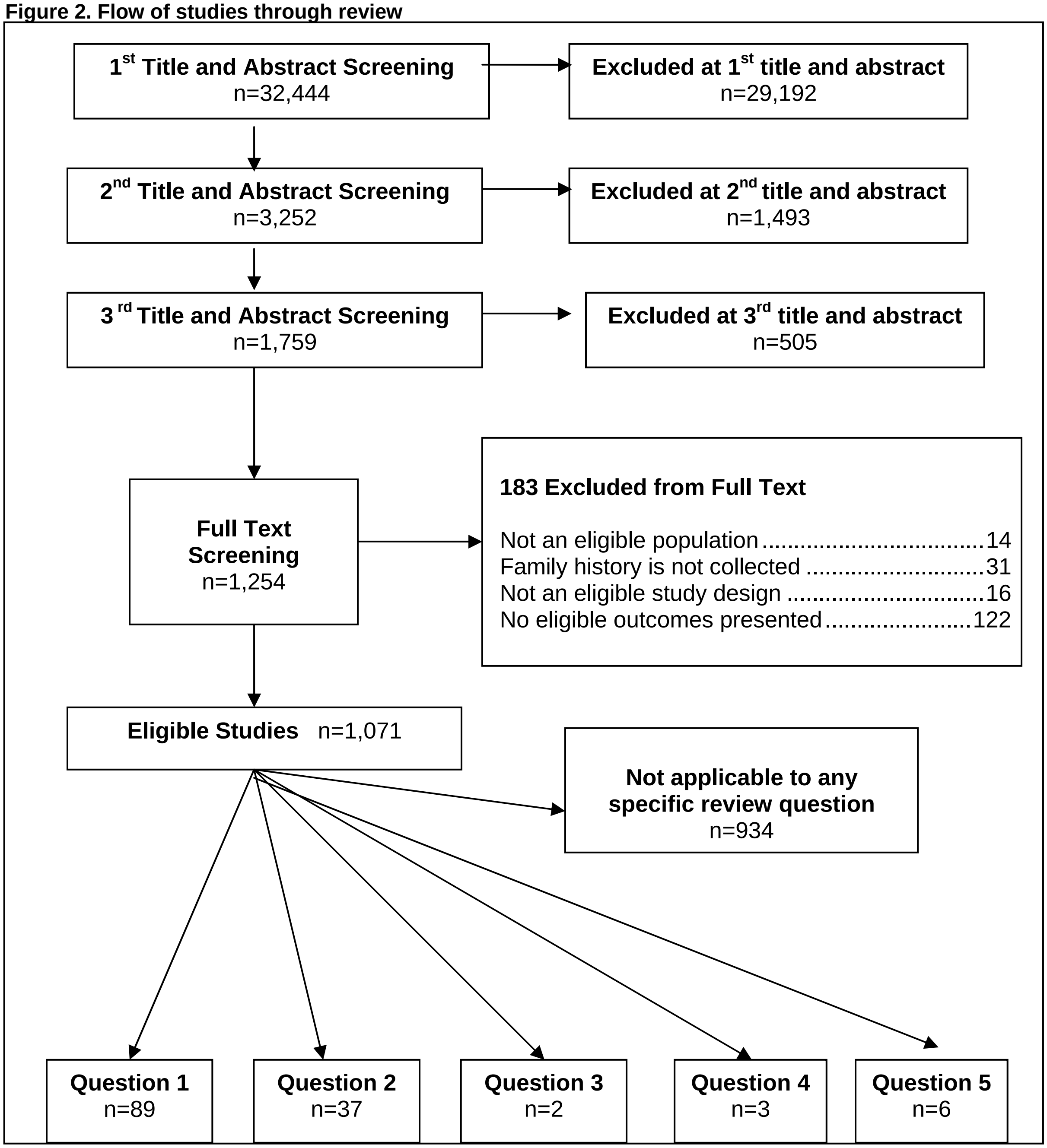
The partner organization, TOO, research team, and members of the TEP identified potential peer reviewers. The MU-EPC compiled a list of these reviewers, all of whom were approved by the AHRQ prior to the circulation of the draft report.

A draft version of this report was circulated to 10 peer reviewers (see Appendix E). The reviewers represented clinicians and expert in family medicine/primary care, cancer, cardiovascular disease, diabetes, asthma, genetics, and family history. The reviewers were provided with a standardized form to solicit feedback on the methods of the review, the presentation of the information and the interpretation of the results. Where possible, comments and suggestions were incorporated.

# Chapter 3. Results

Figure 2 details the flow of studies and the final subset for reviewing. The search yielded 32,444 unique citations. During three levels of title and abstract screening, 31,190 articles were excluded. A total of 1,254 citations proceeded to full text screening. After the final eligibility screening, 137 publications were eligible for data extraction.

**Figure 2. Flow of studies through review**




Appendixes and Evidence Tables for this report are provided electronically at http://www.ahrq.gov/downloads/pub/evidence/pdf/famhistimprov/famhimp.pdf.

# Question 1. What are the Key Elements of a Family History in a Primary Care Setting for the Purposes of Risk Assessment for Common Diseases?

## Introduction

Sixty-one reports of 59 studies were identified that met the eligibility criteria, reported family history (FH) definitions, and presented data which could be analyzed.[2-62] In addition, one paper[63] did not present data which could be included in the main analysis, but was descriptively summarized because the data were directly relevant to the research question. A further 17 papers[64-80] were eligible but did not define FH, and 10 papers[81-90] did not report interpretable data. These are excluded from the results below.

## Note on Interpretation of Results

Data are presented below for both longitudinal and cross sectional analyses. The most common approach to assessing the contribution of FH to disease risk is to measure strength of association (i.e., how many times higher the incidence or prevalence of the disorder is in people with the FH than people without). The metrics used can include relative risk (RR), odds ratio (OR), hazard ratio (HR) and others. These do not provide an estimate of individual probability of disease. For this systematic review, FH is approached as if it was a ‘test’, and predictive accuracy metrics are used to judge performance. In this situation, each FH definition is considered to be a different ‘calibration point’ (the cutoff for ‘positive’ or ‘negative’ result) for the ‘FH test’. The longitudinal analyses provide an estimate of how well different FH definitions *predict* the occurrence of future disease in individual study participants. The cross sectional analyses provide an estimate of how well different FH definitions discriminate between individuals who *currently* have and do not have the disease of interest. Longitudinal studies examine prediction of future cases, while cross sectional studies examine current disease. Four metrics are used to assess the performance of different FH definitions:

- Sensitivity – provides an estimate of the *proportion of future or current cases* which are correctly identified by the particular ‘positive’ FH definition
- Specificity – provides an estimate of the *proportion of individuals destined to be disease-free* who are correctly identified by *not meeting* the particular FH definition
- Positive predictive value (PPV) – indicates the *proportion of individuals who meet the particular FH definition* who will actually develop or currently have the disease
- Negative predictive value (NPV) – indicates the *proportion of individuals who do not meet the particular FH definition* who will remain disease free or do not currently have the disease.

PPV and NPV are influenced by the underlying prevalence of the disease in the population studied – the higher the prevalence, the higher the PPV and the lower the NPV, and vice versa. Sensitivity and specificity are not influenced by disease prevalence. The final metric, area under the summary receiver operator characteristics (SROC) curve and area under the curve (AUC), provides an overall assessment of accuracy of classification. Note that the SROC curve could only be computed if a minimum of three studies had the same FH definition. An AUC of 1.0

indicates a perfectly calibrated test – 100 percent of individuals are correctly classified as affected or unaffected. An AUC of 0.5 indicates that the test as calibrated correctly classifies fifty percent of individuals into affected and unaffected and therefore is no better than chance. An AUC of less than 0.5 suggests the test is worse than chance. The 'ideal' calibration of a test (i.e., the 'best' FH definition) depends on whether the goal is to prioritize sensitivity (lowest possible chance of missing real cases), specificity (lowest possible chance of false positives), or overall accuracy of classification (the highest AUC).

## Breast Cancer

Four studies were included (see Webtable 1, Appendix C), two with a longitudinal design,[3,4] and two cross sectional.[5,6] Two studies were conducted in the U.S.,[3,6] one in Canada,[4] and one in the United Arab Emirates.[5] Sample sizes ranged from 1,445 to 115,460. The longest followup periods for the longitudinal studies were 12 months[4] and 8 years.[3] Please see Webtables 2 and 3 for the methods used to ascertain FH and breast cancer, and the diagnostic criteria used to define the latter.

**Family history.** Four definitions of 'positive FH' based on affected relatives were examined in five analyses, all focusing on first degree relatives (1DRs) in some combination. They all fell into Category C or E (see Table 2, Chapter 2); in addition, one study examined parental consanguinity. Three of the studies reported the strength of association between positive FH (i.e., affected relatives) and breast cancer risk in terms of relative risk or odds ratio. Depending on the FH definition used, these ranged from 1.37 to 2.83. A relative risk of 0.66 for the association between parent consanguinity and breast cancer was reported[5] but the data in this report were not examined for a FH of affected relatives. These data are presented for each FH definition in Webtable 4, Appendix C.

**Predictive accuracy.** Figures 3 to 6 present sensitivity and specificity data for these FH definitions.

For the longitudinal analyses, the range of sensitivities was 0.06-0.26, and specificities 0.86-0.95. The range of positive predictive values (PPVs) was 0.01-0.05, and negative predictive values (NPVs) 0.98-0.99, for breast cancer prevalences up to 2.5 percent in the study samples.

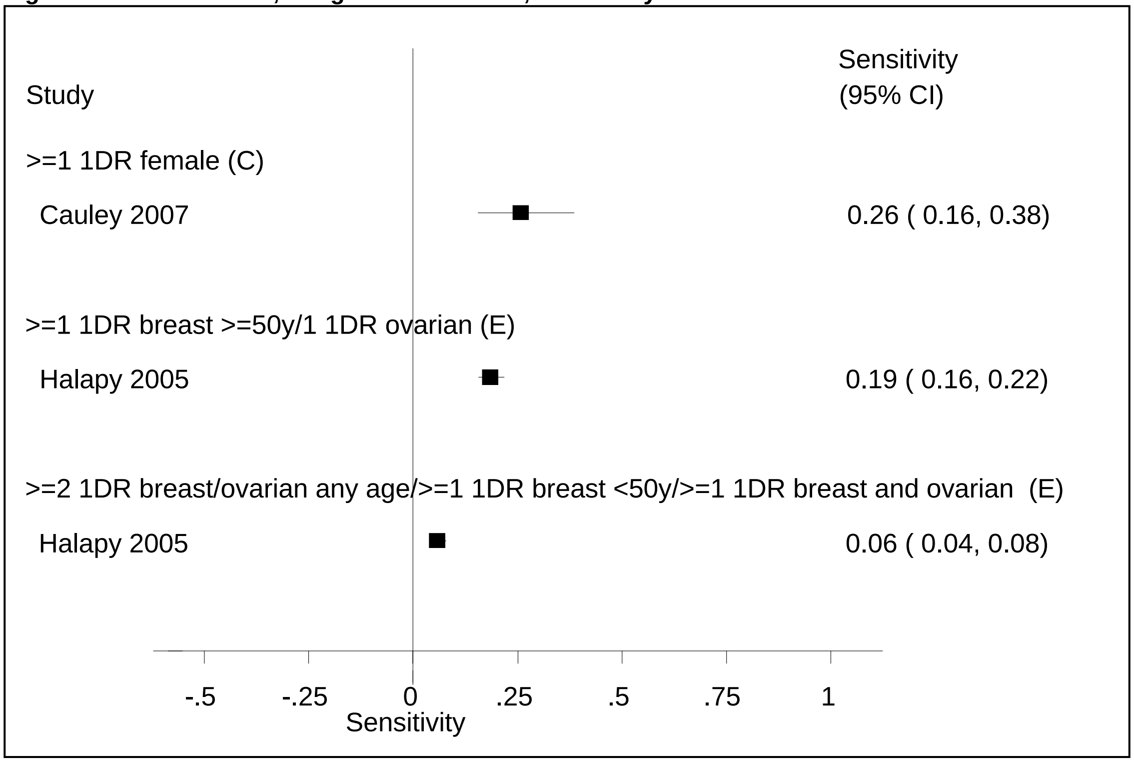
For the cross-sectional analyses, the sensitivities were 0.05 and 0.15, with corresponding specificities of 0.97 and 0.90. The PPVs were 0.01 and 0.09 and NPVs were 0.99 and 0.95, for prevalences of 0.7 and 5.4 percent, respectively. It was not possible to calculate AUC.

**Conclusion.** These analyses were limited by the very few discrete FH definitions available for comparison, and the heterogeneity of the studies in terms of underlying disease frequency in the study samples, length of followup, method of disease ascertainment, and other factors.

With the exception of the parental consanguinity analysis, the definitions of positive FH used in these studies were consistently associated with elevated relative risks (Webtable 4), (i.e., a positive FH of cancer in relatives), at a population level. However defined, it was also a risk factor for future breast cancer incidence (in longitudinal studies) and was positively associated with the presence of current breast cancer (in cross-sectional studies). Within the analyses examined, the most sensitive FH marker for future breast cancer appeared to be 'at least one affected 1DR': this is a 'low complexity' approach to FH (see Table 2). In the single longitudinal study which used it, this definition correctly identified 26 percent of women who went on to develop breast cancer within 4-8 years (with a false positive rates of 12 percent).[3] The proportion of participants with a positive FH defined thus who actually developed breast cancer within 4-8 years was 5 percent. PPV is dependent on underlying disease frequency, which was 2.5 percent. Thus, it can be tentatively concluded that a simple definition of positive FH, based on one 1DR (assumed female) with breast cancer, appeared to be associated with the highest sensitivity for future breast cancer risk within 4-8 years, but that, as always, the predictive ability in practice depends on the breast cancer prevalence in the patient population to whom it was being applied. These observations need to be replicated in further studies which also clarify the contribution of FH information to overall risk prediction based on other established risk factors. Conclusions regarding FH definitions used in a cross-sectional (prevalence screening) approach are not possible because insufficient analyses were available with a range of definitions. However, there would not appear to be a rationale for breast cancer screening triage on the basis of FH in the context of widespread access to effective alternative screening technologies.

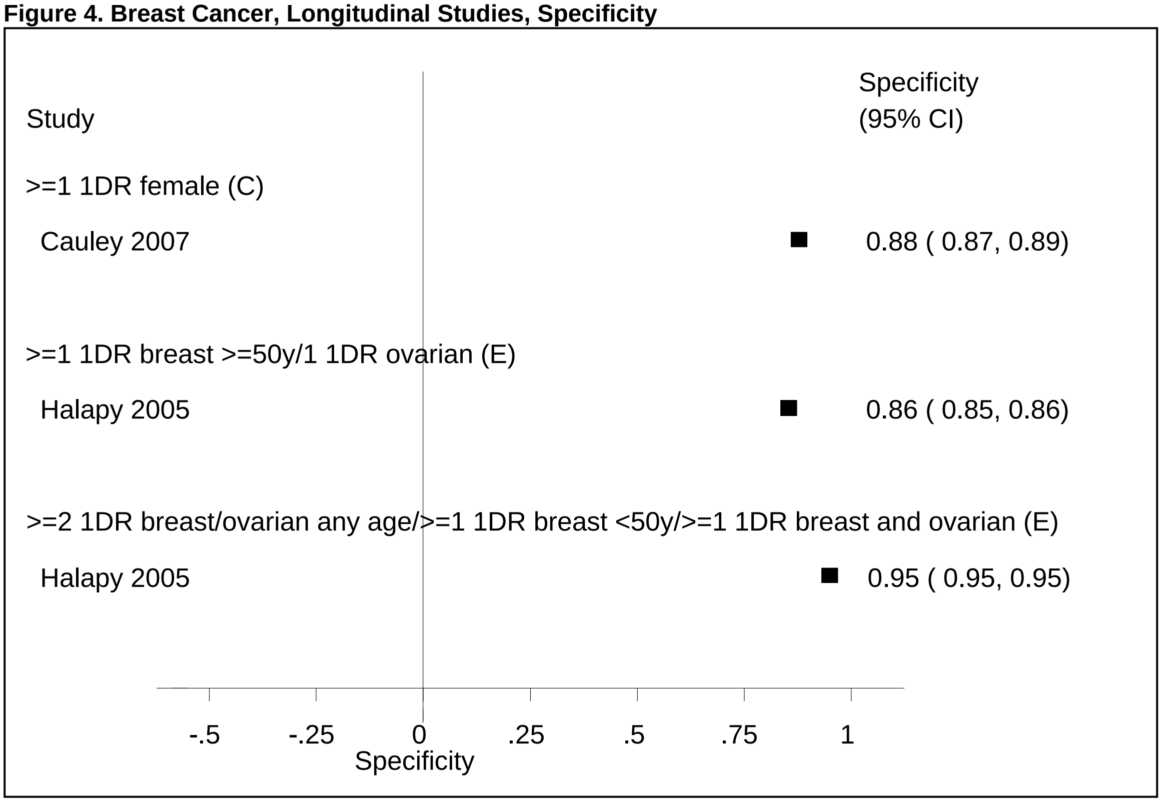
**Quality assessment.** The two longitudinal studies and one of the cross-sectional studies[6] scored highly on all or most quality assessment items despite that fact that two of the published reports[4,6] did not indicate clearly that the same method of FH ascertainment had been applied to all participants. Overall, these studies were judged to be at low risk of significant bias. One cross-sectional study[5] scored less well across almost all items because of incomplete reporting, making it difficult to judge the likelihood of important bias. See Webtable 5, Appendix C.

**Figure 3. Breast Cancer, Longitudinal Studies, Sensitivity**



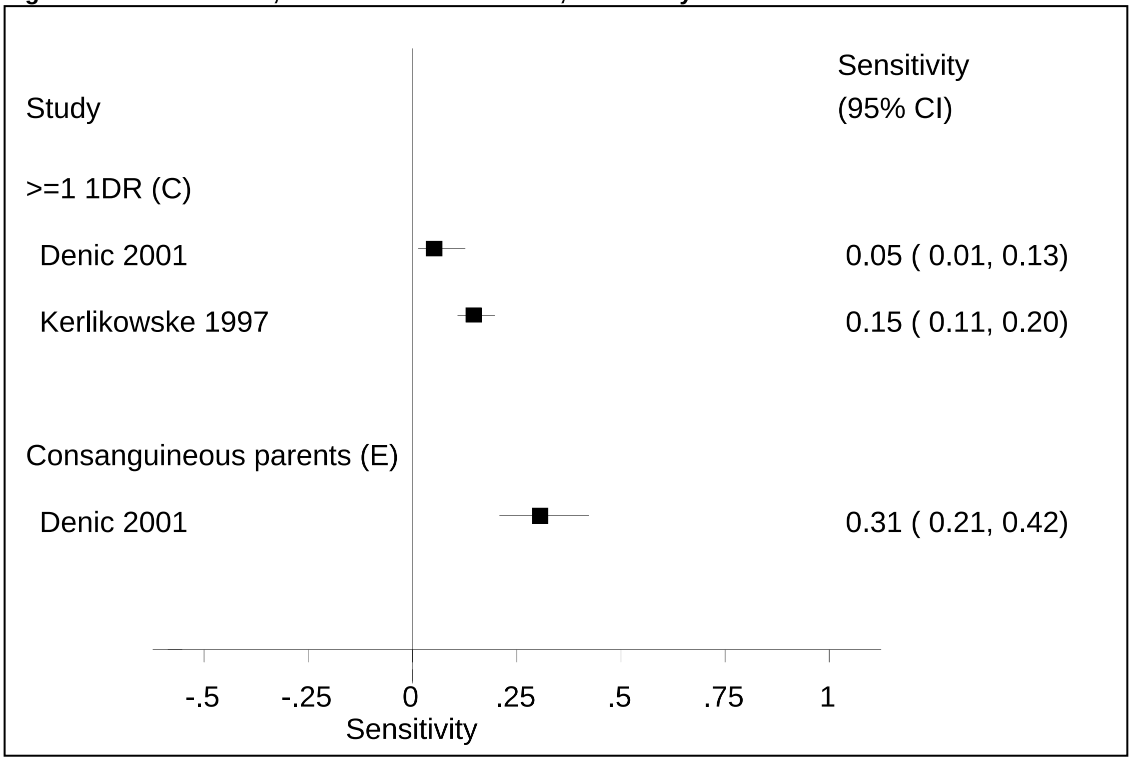

Abbreviations: 1DR=first degree relative; CI=confidence interval

**Figure 4. Breast Cancer, Longitudinal Studies, Specificity**



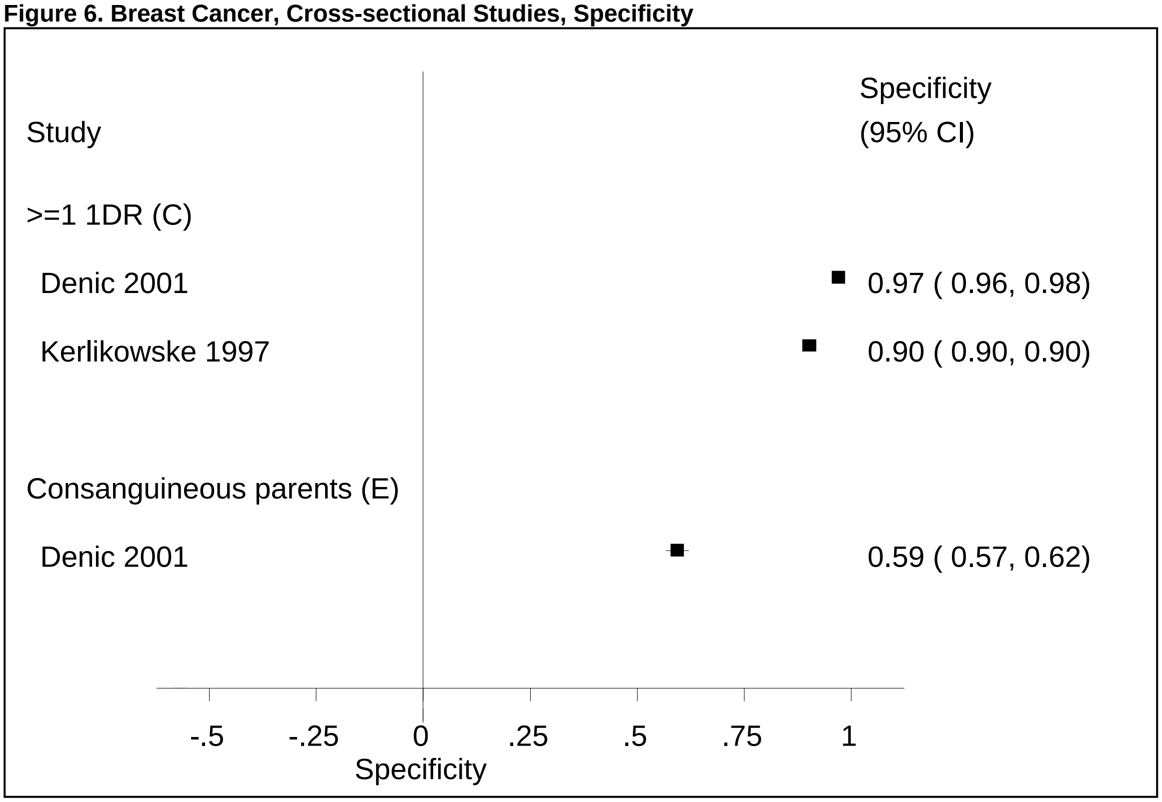

Abbreviations: 1DR=first degree relative; CI=confidence interval

**Figure 5. Breast Cancer, Cross-sectional Studies, Sensitivity**




Abbreviations: 1DR=first degree relative; CI=confidence interval

**Figure 6. Breast Cancer, Cross-sectional Studies, Specificity**




Abbreviations: 1DR=first degree relative; CI=confidence interval

## Colorectal Cancer

Three studies were included in the colorectal cancer (CRC) analysis (see Webtable 1, Appendix C), one longitudinal (with data derived from two separate original cohort studies, one with male, and the other with female participants),[7] and two cross-sectional.[8,9] One was conducted in a U.S. population[7] one in the U.K,[8] and one in several Asian cities.[9] Samples sizes ranged from 860 to 134,365. The followup periods reported in the longitudinal study were 14 years for the female cohort and 20 years for the male cohort.[7] Please see Webtables 6 and 7, in Appendix C for the methods used to ascertain FH and CRC, and the diagnostic criteria employed for the latter.

**Family history.** Four definitions of 'positive FH' were examined, all focusing on 1DRs and all in Category C (Table 2). One study[8] examined multiple definitions within the same dataset and reported analyses by gender, and by age of onset of cancer. All three publications reported the strength of association between positive FH and colorectal cancer risk in terms of RR or OR. Depending on the FH definition used, and the outcome (all disease or premature disease) of these ranged from 1.33 to 5.29. The data by specific FH definition are presented in Webtable 4, Appendix C.

**Predictive accuracy.** Figures 7 through 10 present sensitivity and specificity data for these FH definitions.

The interpretation of the longitudinal analyses is limited because only one criterion for positive FH is used, (>=1 1DR). Sensitivities of 0.13 and 0.14 were obtained for the male and female cohorts with a specificity of 0.92 for both. For both cohorts, the PPVs were 0.02 and the NPVs 0.99, for underlying colorectal cancer prevalence of around 1 percent.

For the cross-sectional analyses, the range of sensitivities was 0.00 to 0.20, and specificities 0.88 to 1.00. The range of PPVs was 0.00 to 0.07 and NPVs of 0.96 or higher, for overall CRC prevalences ranging from <1 to 4.5 percent. It was not possible to calculate AUC for either the longitudinal or cross-sectional data. The AUC for category C FH definition was 0.64.

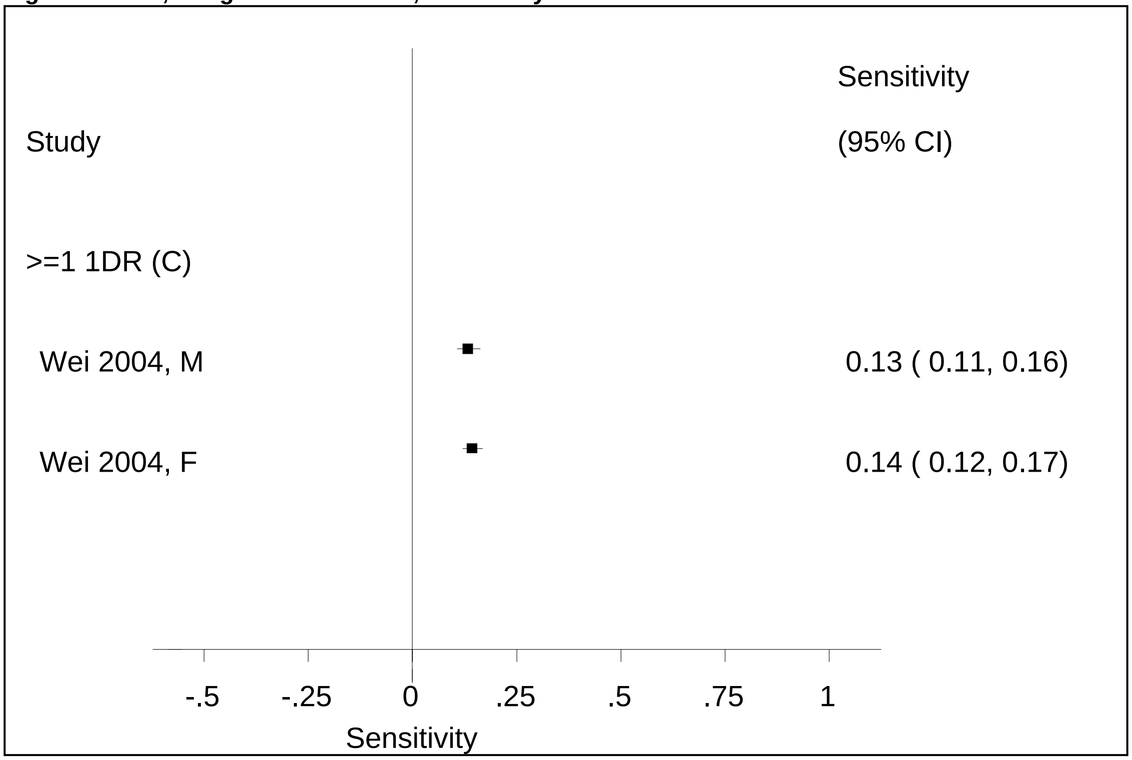
**Conclusion.** These analyses were limited by the relatively few discrete FH definitions available for comparison. The two longitudinal analyses reported in a single report appeared to be fairly homogeneous in terms of participant characteristics, albeit one examined males and one examined females. The results suggest that a simple definition of 'positive FH' (>=1 1DR) was associated with an ability to correctly identify around 13-14 percent of cases of CRC arising in the subsequent 16-20 years, with a false positive rate of about 8 percent. However, a PPV of 0.02 would imply that 98 percent of the 'FH positive' individuals would be wrongly classified (would not develop CRC). It is likely that some of the latter avoided cancer through screening and the removal of pre-malignant lesions (thus the FH 'test' was not strictly 'wrong'). However, the larger the proportion of the population meeting the FH criterion (around 8 percent in this study), the higher the chance of unnecessary clinical intervention.

In relation to the two cross-sectional studies, a wide range of sensitivities and specificities were observed, due in part to the multiple analyses performed within one dataset,[8] making it difficult to discern any pattern across definitions of different complexity. Irrespective of this, the highest PPV was 0.07, suggesting rather low ability of any FH definition to indicate the presence of prevalent CRC.

While these analyses do not, in themselves, suggest the utility of any particular positive FH definition in relation to prediction of or screening for CRC, they are also not sufficient to rule out the possibility of using FH to usefully augment existing predictive or screening strategies.

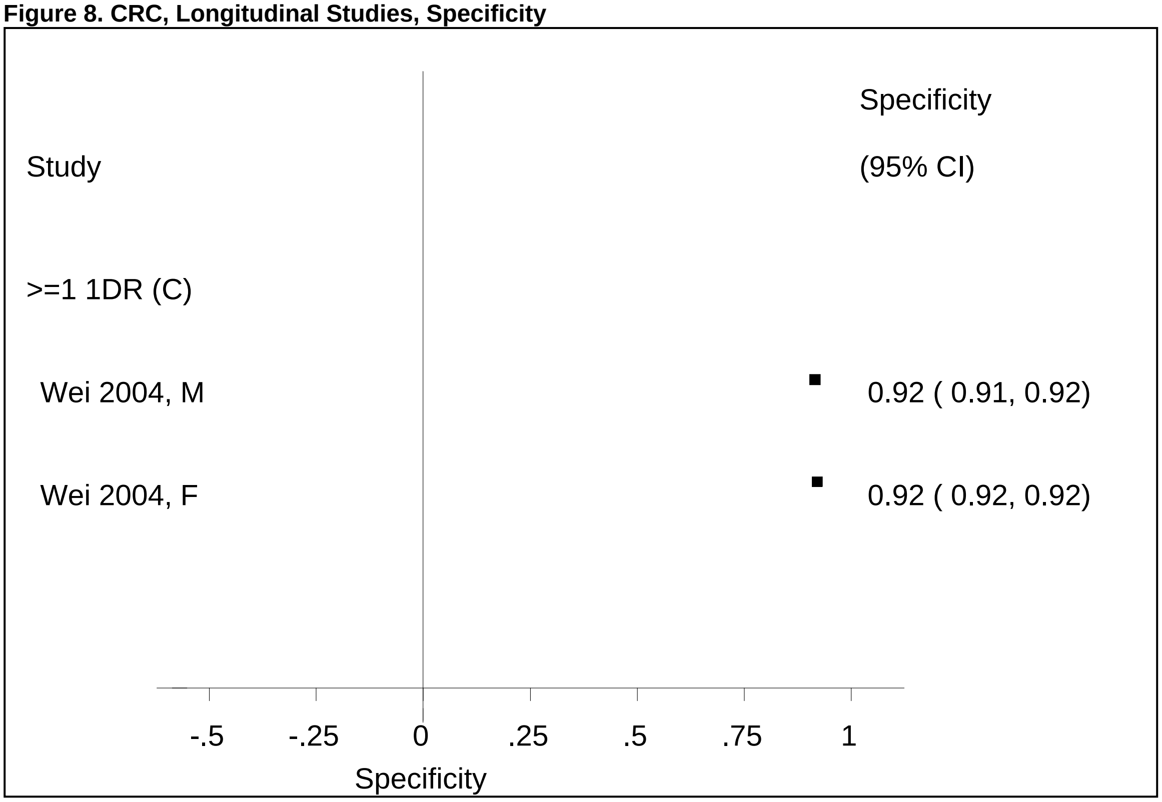
**Quality assessment.** All three studies scored highly in relation to uniform methods of ascertaining FH (exposure) and colorectal cancer (outcome). For two studies,[7,8] it was possible that knowledge of disease status may have influenced ascertainment of FH, and for all three it was possible that knowledge of FH may have influenced ascertainment of colorectal cancer. The possibility of selection bias through attrition or low response rates could not be ruled out for all three studies. See Webtable 5, Appendix C.

**Figure 7. CRC, Longitudinal Studies, Sensitivity**



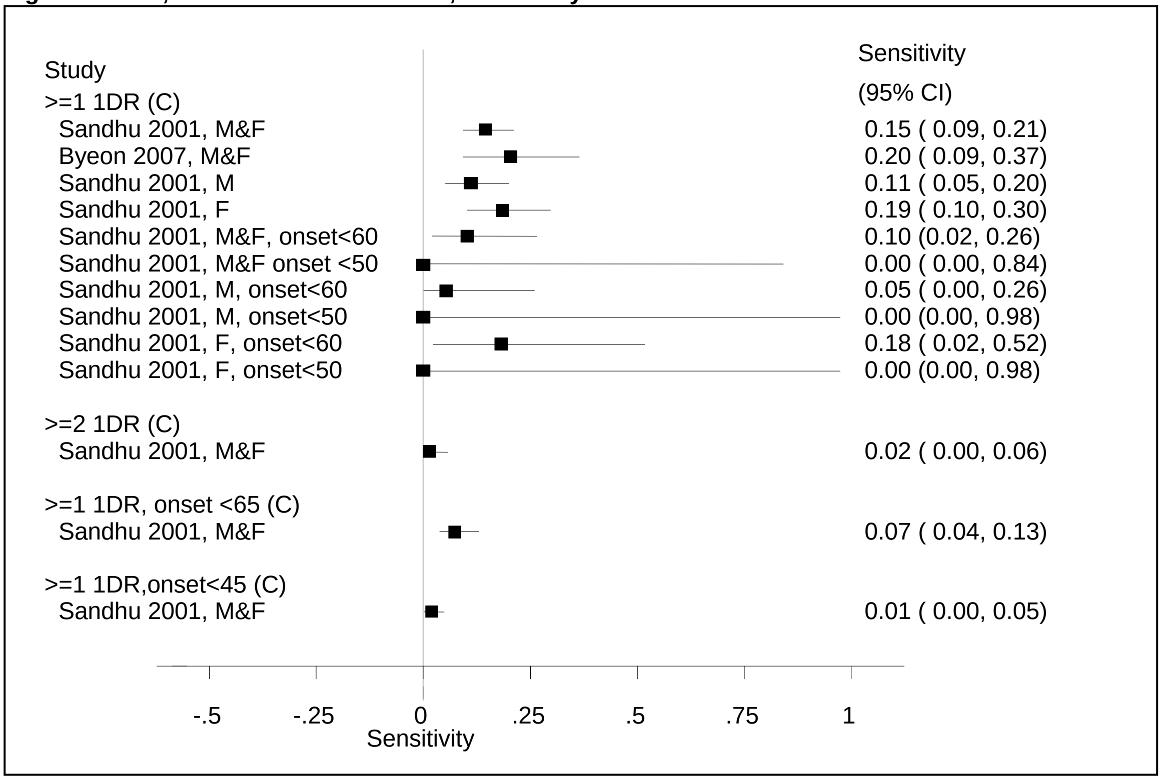

Abbreviations: 1DR=first degree relative; CI=confidence interval; CRC=colorectal cancer; F=female; M=male

**Figure 8. CRC, Longitudinal Studies, Specificity**



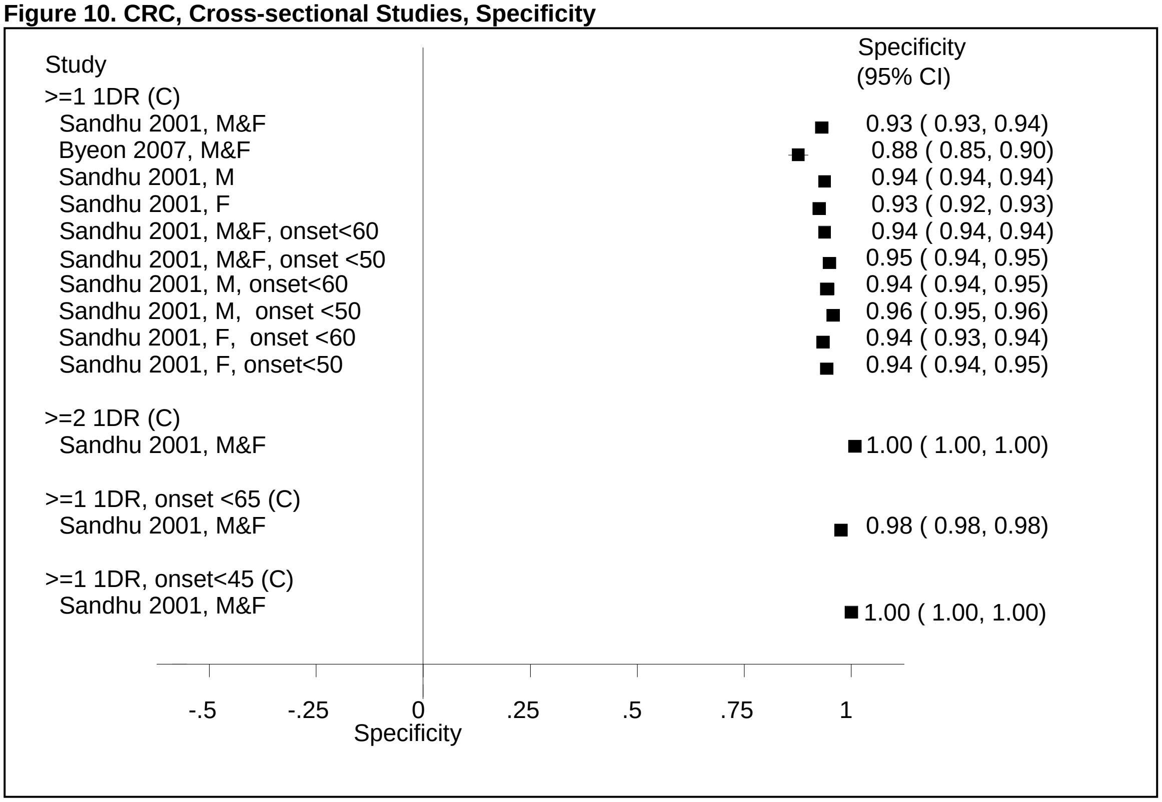

Abbreviations: 1DR=first degree relative; CI=confidence interval; CRC=colorectal cancer; F=female; M=male

**Figure 9. CRC, Cross-sectional Studies, Sensitivity**




Abbreviations: 1DR=first degree relative; CI=confidence interval; CRC=colorectal cancer; F=female; M=male

**Figure 10. CRC, Cross-sectional Studies, Specificity**




Abbreviations: 1DR=first degree relative; CI=confidence interval; CRC=colorectal cancer; F=female; M=male

## Prostate Cancer

The prostate cancer analysis was based on six studies (see Webtable 1, Appendix C), four longitudinal[10-13] and two cross-sectional.[14,15] One study[15] reported an analysis of participants in a prospective cohort study, but FH was ascertained at a late stage in the study therefore it was treated as a cross-sectional analysis. Four were conducted in U.S. populations,[10,12,13,15] and two in Finnish populations.[11,14] The average followup periods for the longitudinal studies ranged from 6.8 to 18 years. Please see Webtables 8 and 9, in Appendix C for the methods used to ascertain FH and prostate cancer, and the diagnostic criteria used.

**Family history.** Ten discrete definitions of 'positive FH' were examined, with at least one falling in each of the categories A-E (Table 2). All studies reported the strength of association between positive FH and prostate cancer risk in terms of RR or OR. Depending on the FH definition used, these ranged from 0.97 to 6.5. The data by specific definition are presented in Webtable 4, Appendix C.

**Predictive accuracy.** Figures 11 through 14 present the sensitivity and specificity data for the various FH definitions used in these analyses. For the longitudinal analyses, the range of sensitivities was 0.00-0.21, and specificities 0.88-1.00. Excluding one study using mortality as the outcome, the range of PPVs was 0.11-0.26, and NPVs 0.92-0.95, for prostate cancer prevalences up to 8.7 percent. The AUC for category B FH definitions was 0.51 and for category C FH definitions was 0.93.

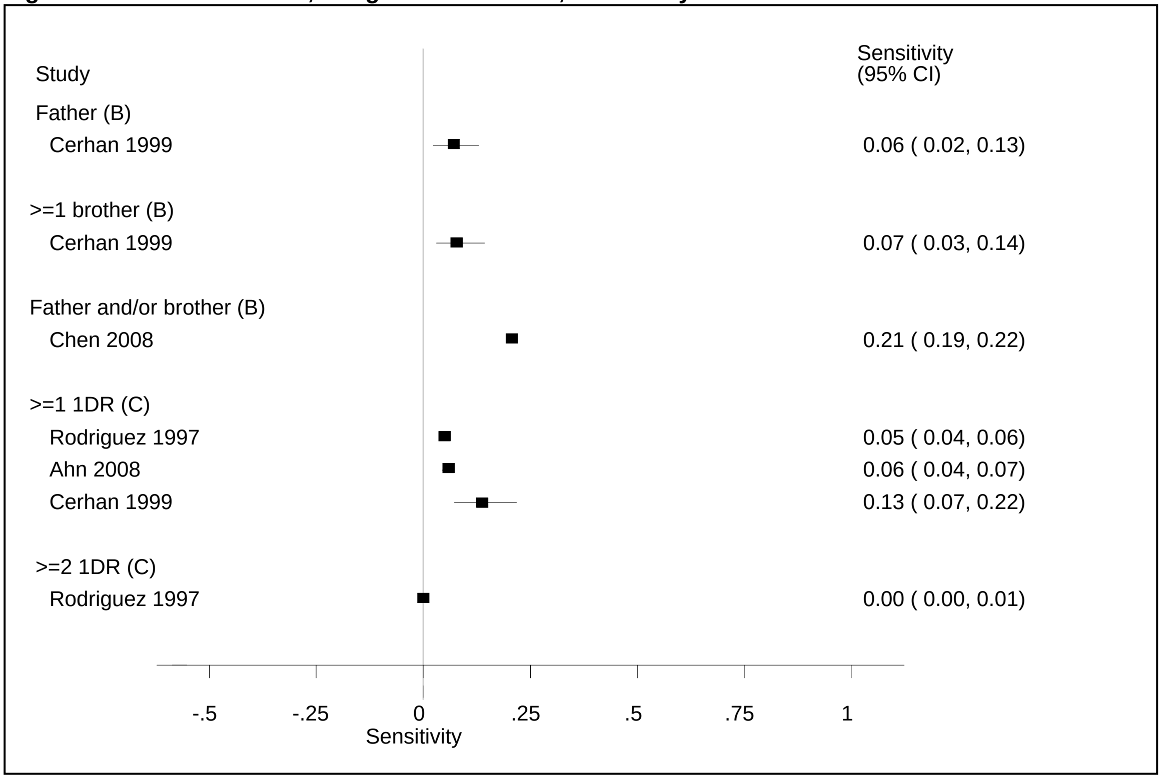
For the cross-sectional analyses, range of sensitivities was 0.01-0.26 and specificities 0.91-1.00. The PPVs were 0.02-0.14 and NPVs 0.96-0.98, for prostate cancer prevalences up to 8.7 percent. The AUC could not be calculated.

**Conclusion.** A range of definitions of positive FH were examined in these studies, in both predictive and screening contexts. Almost all of the definitions of FH used were associated with positive risk of future disease incidence or current disease presence. However, the definitions examined here appeared, overall, no better than chance in predicting future presence or absence of prostate cancer in the participants studied.

Regarding FH as an approach to identify individuals who may currently be affected (cross-sectional studies), the sensitivities and PPVs were uniformly low. The highest sensitivity was 26 percent for presence of cancer and the highest PPV 14 percent in a study where many participants were already aware of their cancer diagnosis. Further studies to clarify the information gained from FH information (and specific definitions) might be warranted if it added value when used in conjunction with other screening strategies.

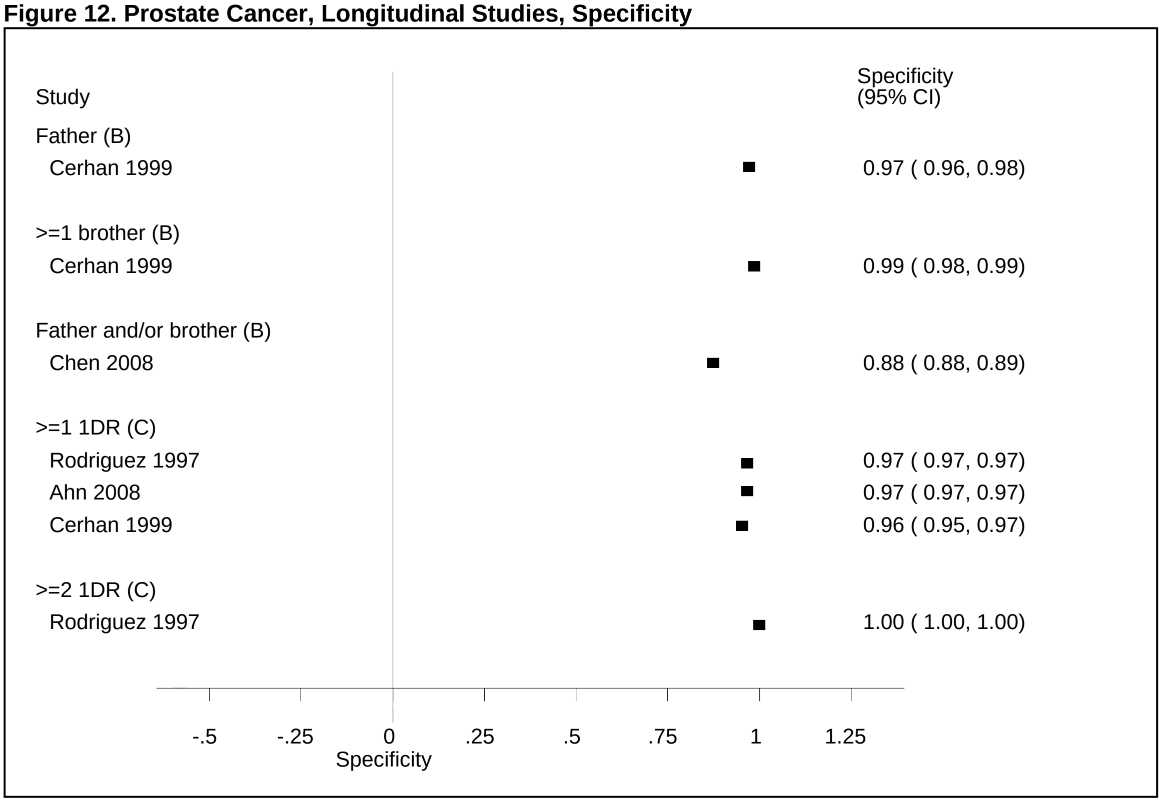
**Quality assessment.** In general, the longitudinal studies scored high on quality assessment items, with the exception of one[13] in which key methodological details were not reported. For the two cross-sectional studies, the possibility that knowledge of FH influenced ascertainment of prostate cancer outcomes could not be ruled out, and both were possibly subject to selection bias through low response rates. See Webtable 5, Appendix C.

**Figure 11. Prostate Cancer, Longitudinal Studies, Sensitivity**



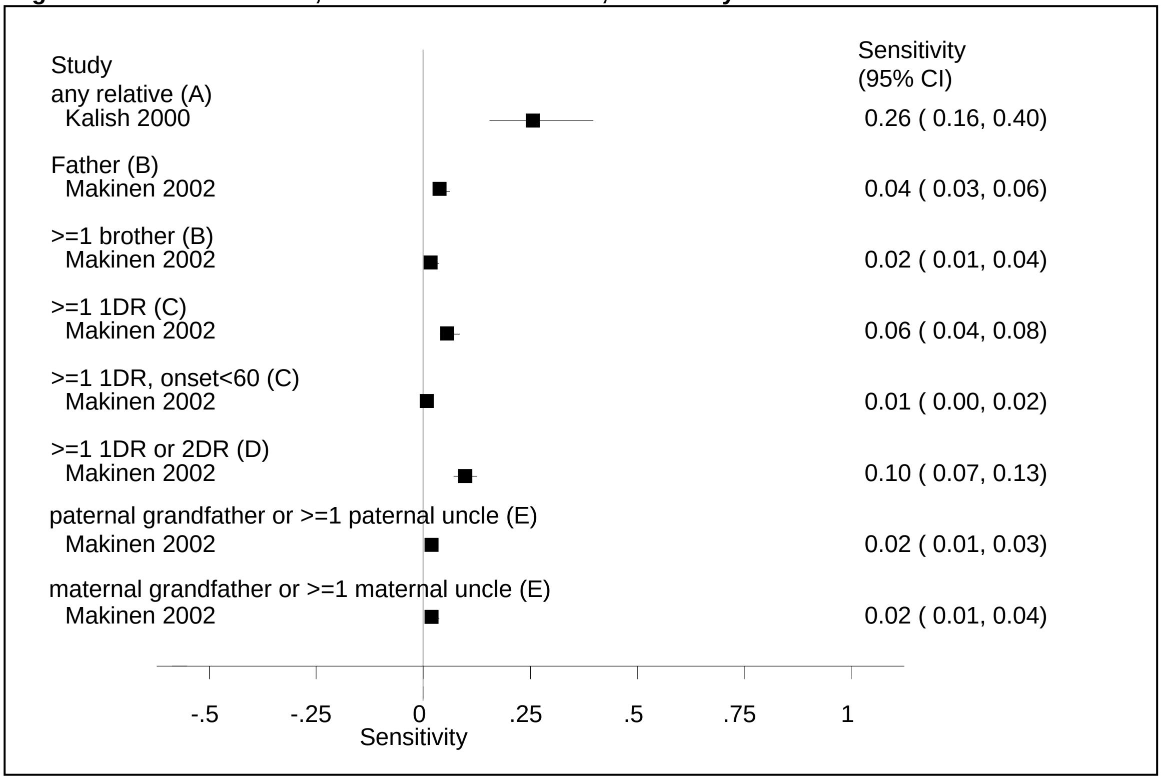

Abbreviations: 1DR=first degree relative; CI=confidence interval

**Figure 12. Prostate Cancer, Longitudinal Studies, Specificity**



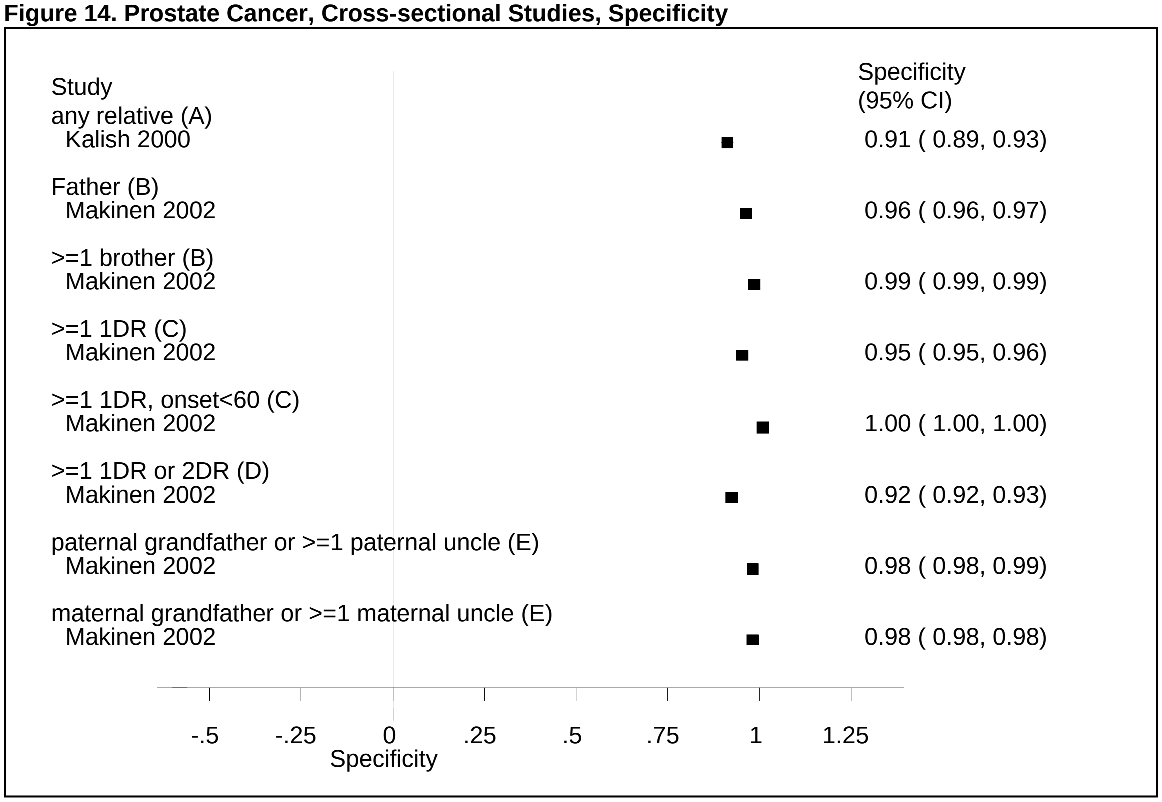

Abbreviations: 1DR=first degree relative; CI=confidence interval

**Figure 13. Prostate Cancer, Cross-sectional Studies, Sensitivity**




Abbreviations: 1DR=first degree relative; CI=confidence interval

**Figure 14. Prostate Cancer, Cross-sectional Studies, Specificity**




Abbreviations: 1DR=first degree relative; 2DR=second degree relative; CI=confidence interval

## Coronary Heart Disease

Eight studies were included in the coronary heart disease (CHD) analysis (see Webtable 10, Appendix C), five longitudinal[16-20] and three cross-sectional.[21-23] Four were conducted in U.S. populations,[16,20,22,23] (one in American Filipina women[23]) and one each in Pakistan,[21] Sweden,[17] Finland,[18] and Denmark.[19] One of the longitudinal studies[16] reported analyses based on two individual cohort studies, one in men and one in women. The average followup periods for the longitudinal studies ranged from 6.2 to 19.6 years. Please see Webtables 11 and 12 in Appendix C for the methods used to ascertain FH and coronary heart disease, and the various definitions and diagnostic criteria used.

**Family history.** Seventeen discrete definitions of 'positive FH' were analyzed, with at least one in each of the categories B-E. All studies except one[20] reported the strength of association between positive FH and coronary heart disease risk in terms of RR or OR. Depending on the FH definition used, these ranged from 0.93 to 6.2. The data by specific definition are presented in Webtable 4, Appendix C.

**Predictive accuracy.** Figures 15 through 18 present the sensitivity and specificity data for these definitions of FH. For the longitudinal analyses, the range of sensitivities was 0.03-0.51 and specificities 0.66-0.98. The range of PPVs was 0-0.13 and NPVs 0.66-0.98, for CHD prevalences up to 10.4 percent. The definitions were all category B and the AUC for this category was 0.58.

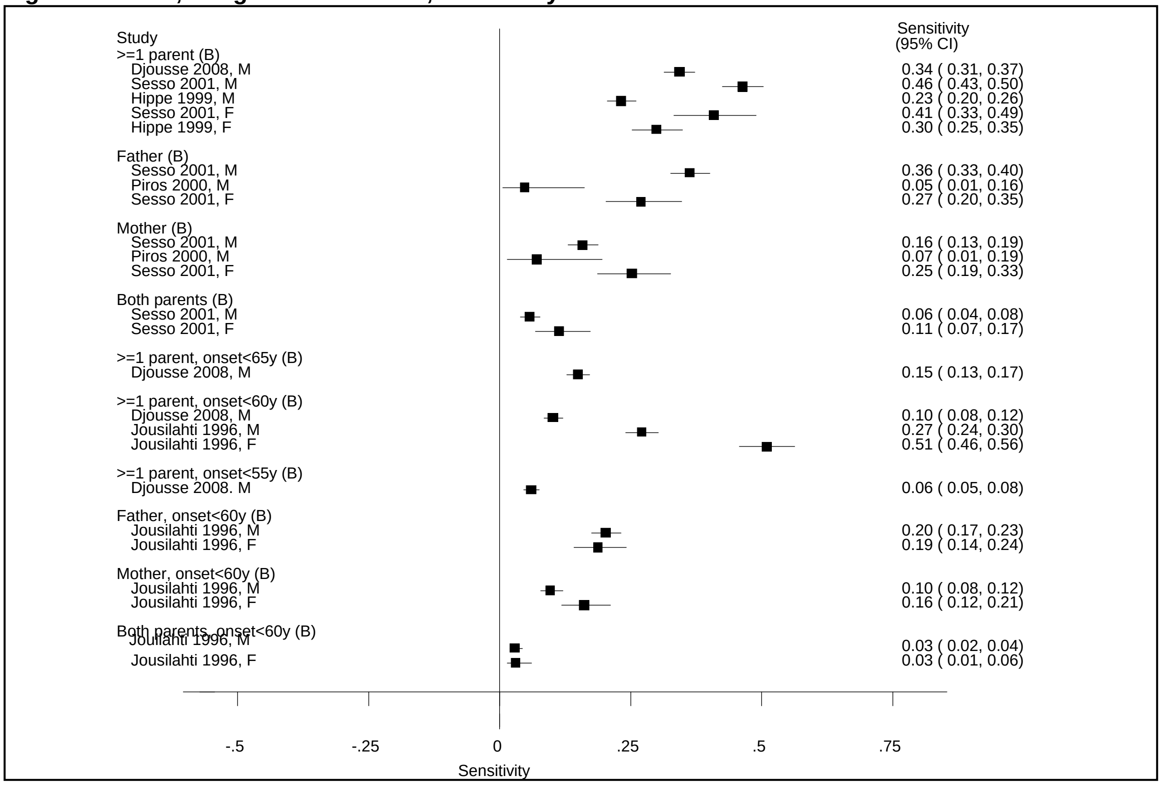
For the cross-sectional analyses, the range of sensitivities was 0.07-0.70 and specificities 0.53-0.98. The range of PPVs was 0.08-0.31, and NPVs 0.83-0.98, for CHD prevalences up to 20.7 percent. The AUC could not be estimated for cross-sectional studies.

**Conclusion.** The longitudinal analyses suggest an association between broadness and narrowness of a minimum FH definition and sensitivity and specificity although these simple definitions as a whole classified the future CHD risk correctly for only 58 percent of participants. The PPVs were almost all below 10 percent. This means that, if practice populations are similar to those analyzed here, at least 90 percent of individuals meeting any of the FH definitions would be incorrectly classified as high risk for developing CHD. The highest disease prevalence in the cohorts studied was around 10 percent, but in some analyses, more than a third of the participants met the FH definition. Generally, similar PPVs were obtained for the definitions examined in the cross-sectional studies, although the analyses were dominated by a single study.[22]

Overall, the value of the most highly predictive FH definitions needs to be assessed in the light of the predictive ability of other established factors such as blood pressure, lipid profiles, or anthropometric measures, and in the context of the risks and costs of available interventions to reduce risk, to determine whether it is likely to add significant information value in routine clinical settings. The underlying prevalence of disease in the patient population is an important factor which needs to be taken into account.

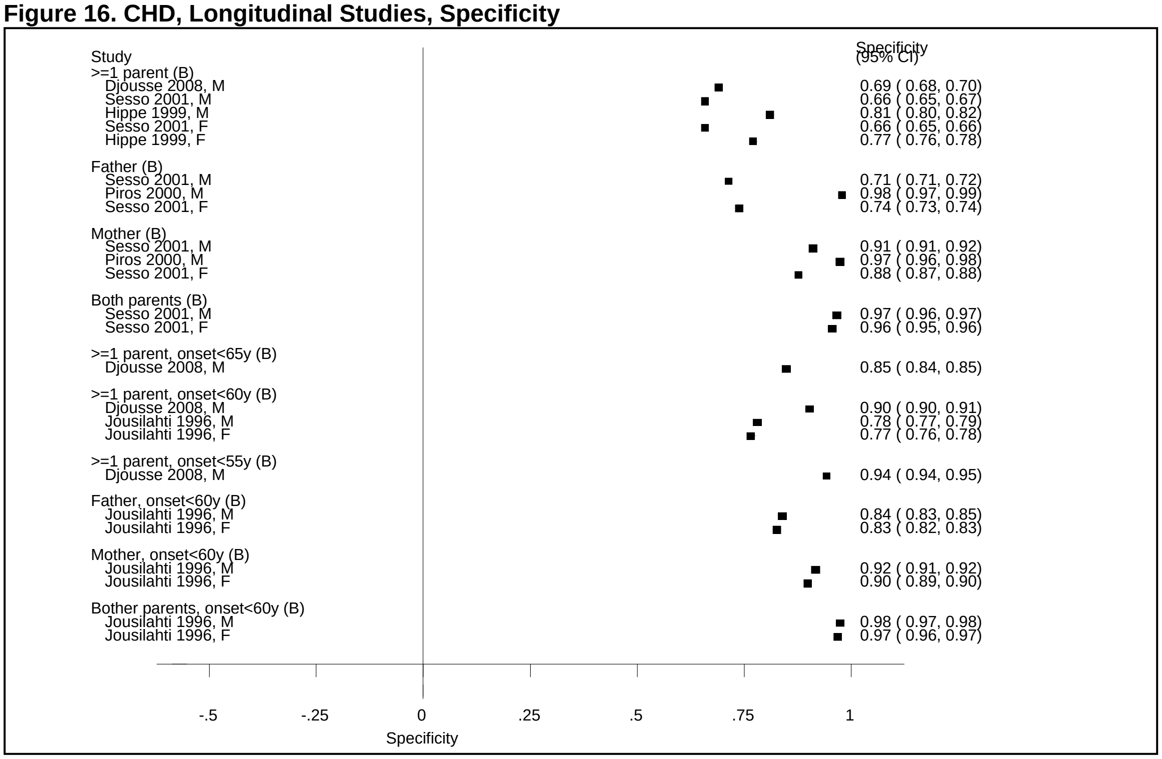
**Quality assessment.** The five longitudinal studies generally scored fairly high on quality assessment items, with the exception of one[17] where inadequate reporting made it impossible to assess four of the six items. For all three cross-sectional studies, the possibility of awareness of FH status influencing reporting of presence or absence of coronary heart disease, and vice versa, could not be ruled out. Also, sample selection bias could not be excluded because of non-probability sampling methods[21,23] and/or sub-optimal response rates. See Webtable 13, Appendix C.

**Figure 15. CHD, Longitudinal Studies, Sensitivity**



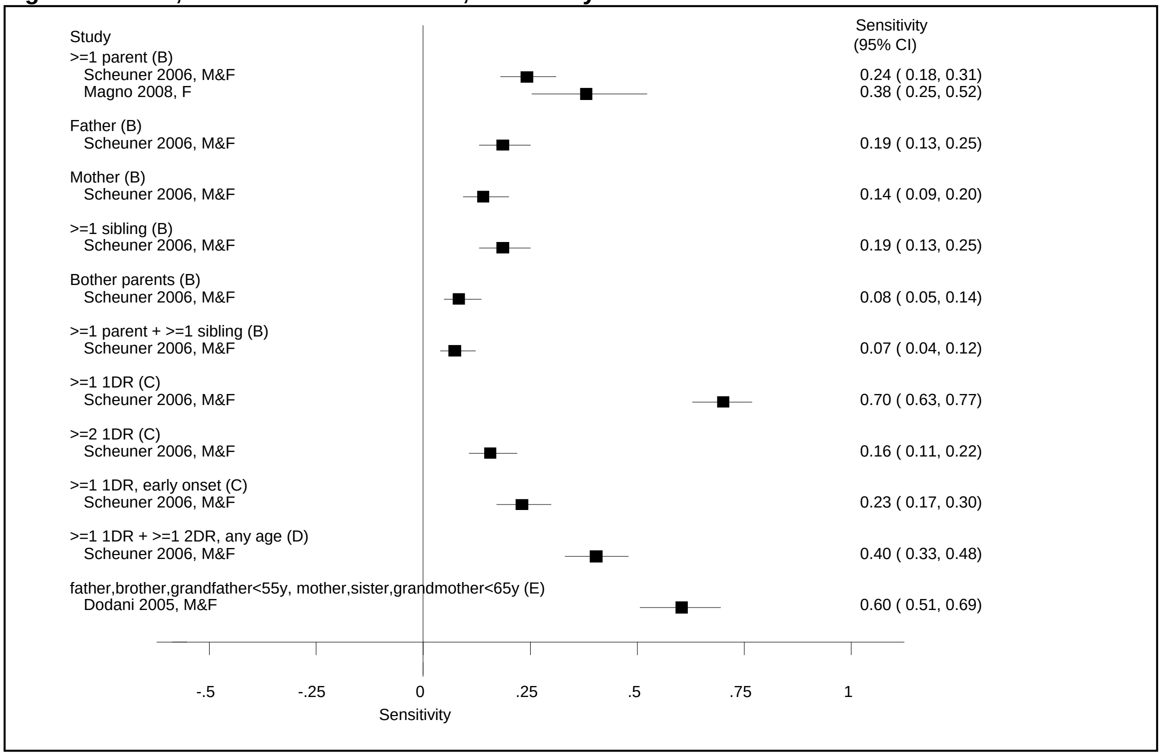

Abbreviations: CHD=coronary heart disease; CI=confidence interval; F=female; M=male

**Figure 16. CHD, Longitudinal Studies, Specificity**



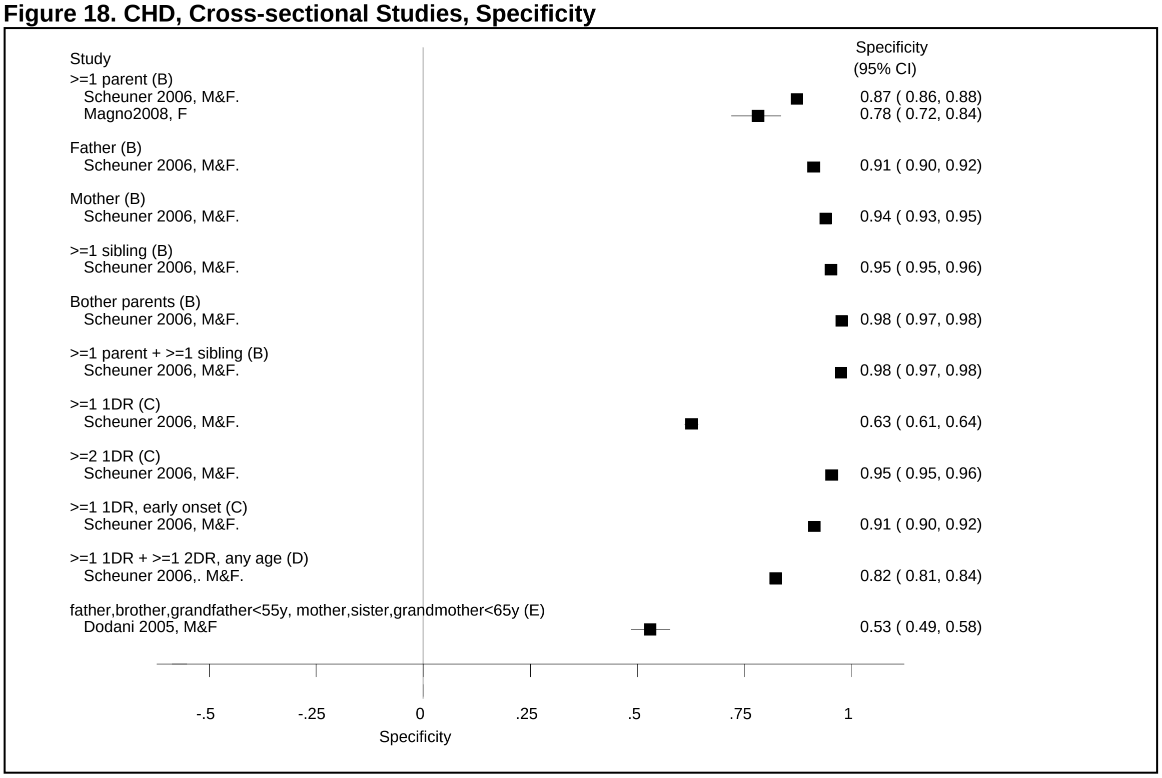

Abbreviations: CHD=coronary heart disease; CI=confidence interval; F=female; M=male

**Figure 17. CHD, Cross-sectional Studies, Sensitivity**




Abbreviations: 1DR=first degree relative; 2DR=second degree relative; CHD=coronary heart disease; CI=confidence interval F=female; M=male

**Figure 18. CHD, Cross-sectional Studies, Specificity**




Abbreviations: 1DR=first degree relative; 2DR=second degree relative; CHD=coronary heart disease; CI=confidence interval; F=female; M=male

## Stroke

Three studies were included (see Webtable 10, Appendix C) in the stroke analysis, all longitudinal in design.[24-26] One was conducted in a U.S. population,[24] one in Finland,[25] and one in Japan.[26] The average followup periods ranged from 5 to 19 years, and analyses focused on clinically apparent stroke only. Please see Webtable 14 for the methods used to ascertain FH and stroke outcomes, and the diagnostic criteria used.

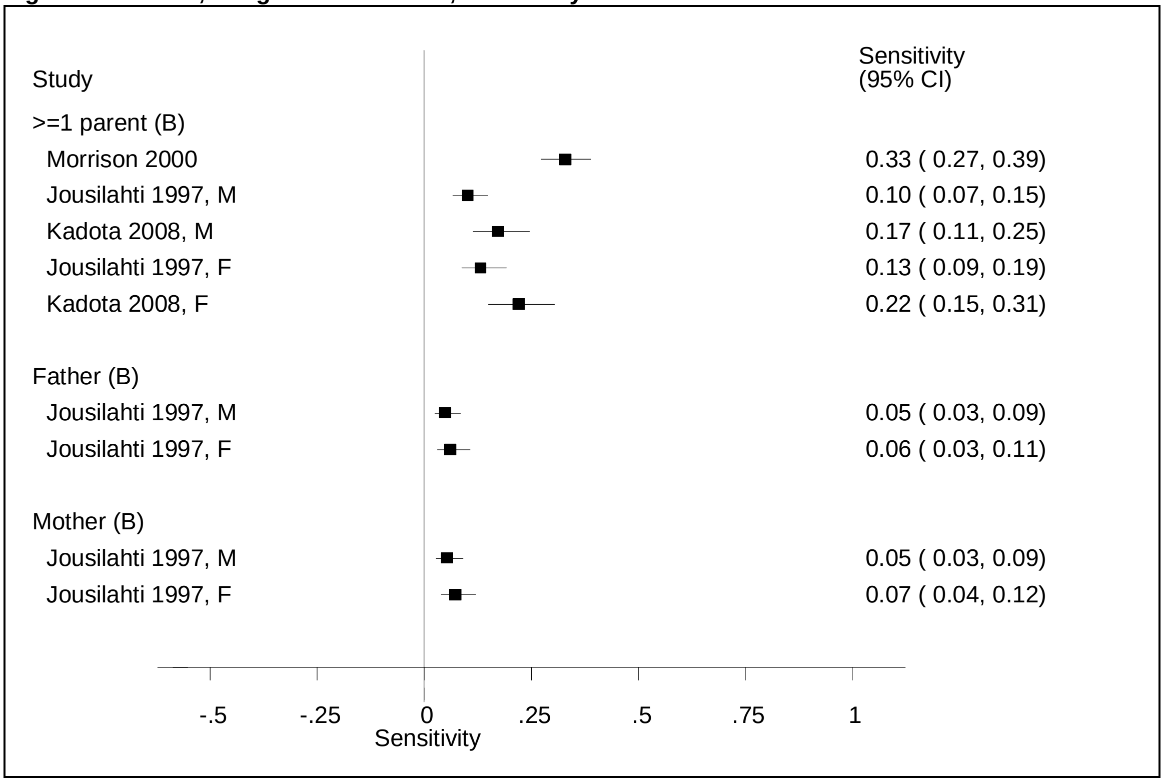
**Family history.** Three separate definitions of 'positive FH' were examined, all relating to parental illness and all in category B (Table 2). All three studies reported the strength of association between positive FH and stroke risk in terms of relative risk. Depending on the FH definition used, these RRs ranged from 0.73 to 2.17. The data by specific definition are presented in Webtable 4, Appendix C.

**Predictive accuracy.** Figures 19 and 20 present the sensitivity and specificity data for the FH definitions in these studies. The range of sensitivities was 0.05-0.33, and specificities 0.71-0.98. The range of PPVs were 0.02-0.08 and NPVs 0.96-0.98, for prevalences of stroke up to 3.9 percent. The AUC for these category B FH definitions was 0.43.

**Conclusion.** The FH definitions available for analysis were restricted to parental FH only, and many of the data were derived from a single study[25] which focused on stroke before the age of 60. The data support a negative association between strictness of FH and magnitude of sensitivity. However, the PPVs suggest that using any of these FH definitions in isolation from knowledge of other risk factors, could lead to over 90 percent of 'FH positive' individuals being wrongly identified as being at higher risk. This is due to the overall low frequency of stroke in the study populations over the time periods studied.

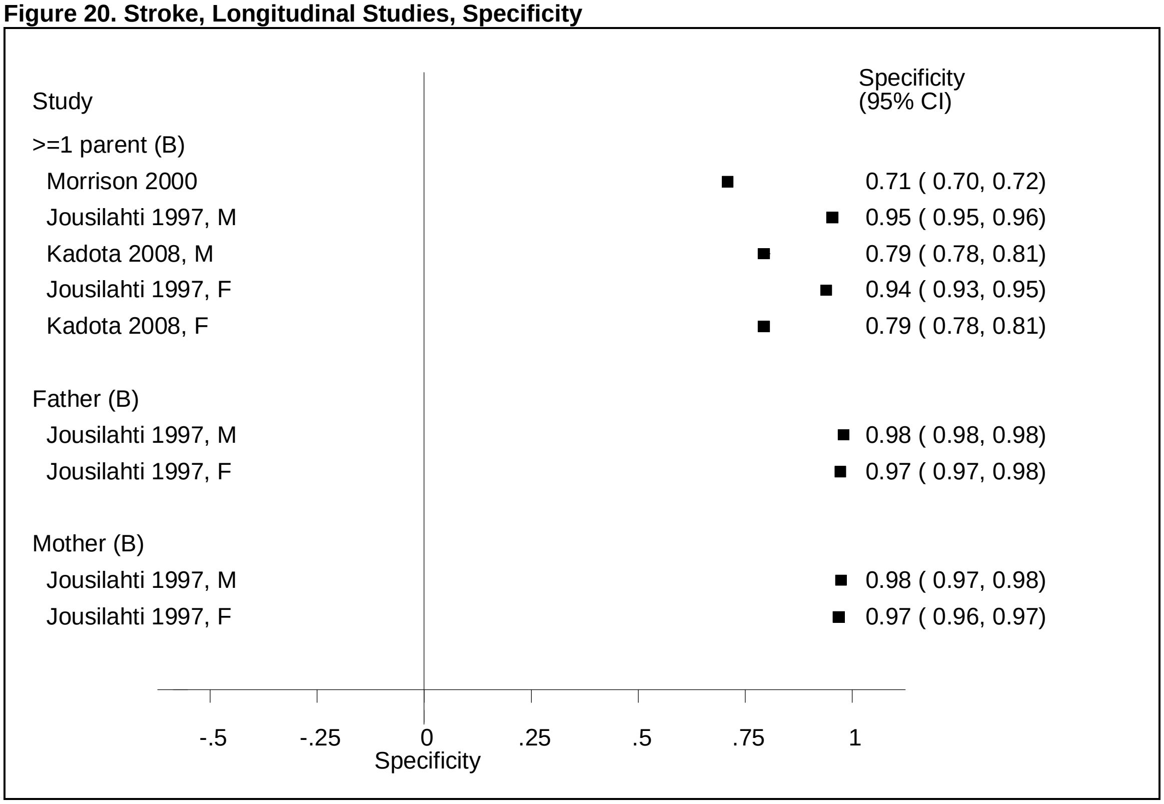
**Quality assessment.** Two[25,26] scored highly on all or almost all quality assessment items. The assessment of the third[24] was limited by lack of reporting in relation to four of six quality criteria. The possibility of awareness of FH influencing ascertainment of stroke outcome could not be ruled out, and it was not clear whether the same method of FH collection was applied to all participants. The rate of attrition over several years of followup was unclear. See Webtable 13, Appendix C.

**Figure 19. Stroke, Longitudinal Studies, Sensitivity**




Abbreviations: CI=confidence interval; F=female; M=male

**Figure 20. Stroke, Longitudinal Studies, Specificity**




Abbreviations: CI=confidence interval; F=female; M=male

## Diabetes

Seventeen studies were included in this analysis (see Webtable 15, Appendix C). Five were longitudinal[27-31] and 12 were cross-sectional.[32-43] In addition, the findings of a cross-sectional study[63] designed expressly to examine different FH definitions are included, although the data were not presented in a way which permitted their inclusion in the calculations below.

Five studies were conducted in U.S. populations,[29,31,33,37,40] including one in Japanese Americans[29] and one in native Alaskans.[33] Two studies were conducted in Norwegian populations,[27,38] and two in the Netherlands.[28,41] Single studies were conducted in the United Kingdom,[30] India,[32] Pakistan,[42] Nigeria,[34] Israel,[35] Jordan,[43] Greece,[36] and Sweden.[39] The average followup periods for the longitudinal studies ranged from 5 to 22 years, except for one study which examined disease risk in offspring (mean offspring age 54 years) of the original Framingham cohort.[31] Sample sizes ranged from 454 to 64,498. Please see Webtable 15 in Appendix C for the methods used to ascertain FH and diabetes, and the diagnostic criteria used.

**Family history.** Twenty different definitions of 'positive FH' were analyzed, in categories B-E (Table 2). All studies except one[42] reported the strength of association between positive FH and diabetes risk for at least one definition in terms of relative risk, odds ratio, or similar metric. Depending on the FH definition used, these ranged from 1.53 to 14.83. The data by specific definition are presented in Webtable 4, Appendix C.

**Predictive accuracy.** Figures 21 through 24 present the sensitivity and specificity data for these definitions of FH. For the longitudinal analyses, the range of sensitivities was 0.02-0.47, and specificities 0.79-1.0. The range of PPVs was 0.02-0.38, and NPVs 0.86-0.99, for underlying diabetes prevalences up to 16.2 percent. (Webtable 16) The AUC for category C was 0.43.

For the cross-sectional analyses, (Webtable 17) the range of sensitivities was 0.02-0.83 and specificities 0.44-0.99, for prevalences up to 17.4 percent. The AUC figures for category B, C, and D definitions were 0.69, 0.71, and 0.64, respectively.

A further paper[63] reported the results of applying a three-level, FH-based, risk stratification system to representative U.S. adult survey data. The definitions for the risk strata are summarized in Table 3. The overall prevalence of diabetes in the survey population was 6.6 to 6.7 percent, and ORs of 2.8 and 7.5 were obtained for the moderate and high definitions respectively. The FH definitions used for the stratification system are presented in Table 3 while the sensitivities, specificities, and predictive values for the increased (moderate plus high) and high risk categories obtained in this analysis are presented in Table 4.

**Table 3. Three-level risk stratification system[63]**

| Stratum | Definition |
|---|---|
| High | ≥ 2 parents and/or siblings with diabetes<br>or<br>≥ 1 parent or sibling and 2 grandparents with diabetes from the same lineage |
| Moderate | One 1DR and one 2DR with diabetes<br>or<br>One 1DR with diabetes<br>or<br>Two 2DRs with diabetes from the same lineage |
| Average | No more than one 2DR with diabetes |

Abbreviations: 1DR=first degree relative; 2DR=second degree relative

**Table 4. Discriminatory accuracy metrics associated with risk stratification system[63]**

| Risk level | Sensitivity | Specificity | PPV | NPV |
|---|---|---|---|---|
| All adults (20-85) | | | | |
| High | 0.19 | 0.94 | 0.10 | 0.97 |
| Moderate + high | 0.48 | 0.73 | 0.05 | 0.98 |
| Older adults (45-85) | | | | |
| High | 0.21 | 0.93 | 0.15 | 0.95 |
| Moderate + high | 0.46 | 0.70 | 0.08 | 0.96 |

Abbreviations: NPV=negative predictive value; PPV=positive predictive value

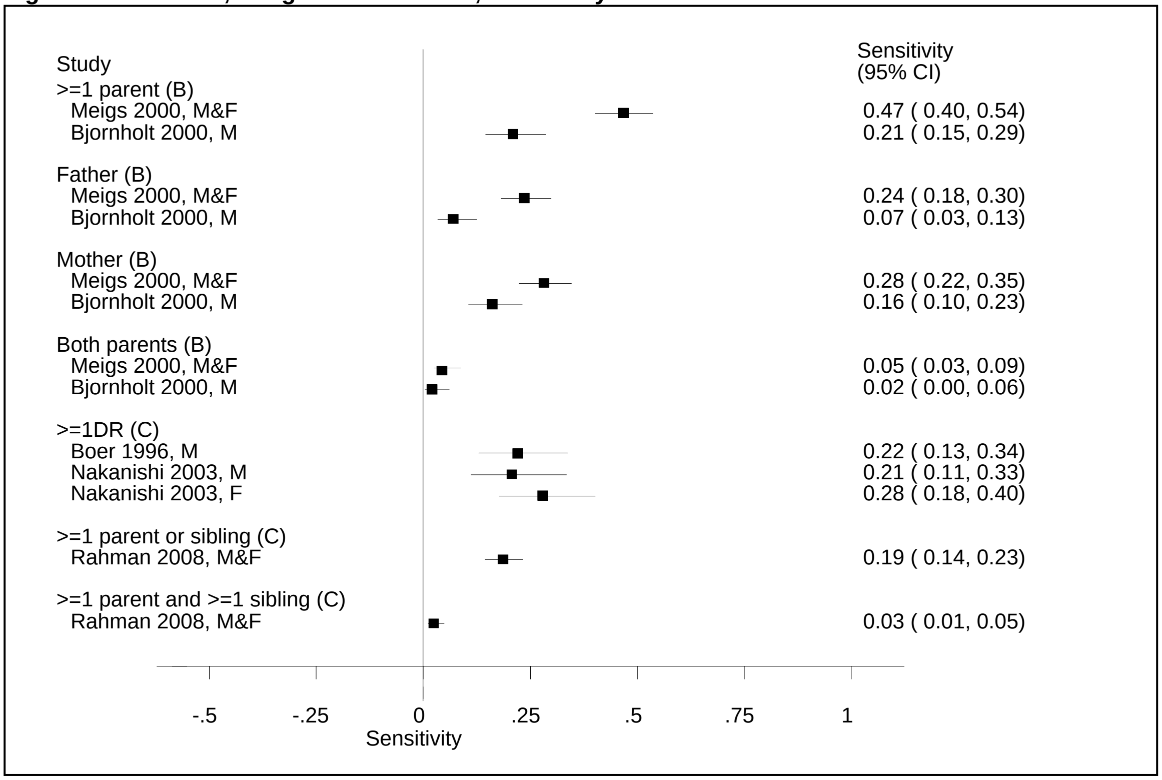
**Conclusion.** A large range of FH definitions were examined in these studies, ranging from very simple to very complex. Almost all indicated a positive association between FH and risk of diabetes. The studies were very heterogeneous in terms of how diabetes was defined, the underlying diabetes risk in the population, length of followup, and other characteristics. Taken overall, the analyses suggest that using FH to predict future risk of diabetes may have some utility, and that category B definitions (specifying 1-2 affected relatives) achieve higher overall discriminatory accuracy than category C definitions. However, the relationship between diabetes prevalence and PPV should be taken into account.

FH may be a useful factor to take into account in triaging individuals for diabetes screening (i.e., screening for undetected prevalent disease). The AUC figures suggest that no further discriminatory accuracy is obtained by going beyond simple FH definitions, (i.e., limited enquiry about 1DRs only). If these findings were replicated, it is possible that meeting a simple FH criterion might be sufficient to merit a second stage screening test such as fasting glucose, where health care resource constraints present limits to universal screening using clinical tests. Again, the underlying prevalence of diabetes in the population should be taken into account as this affects the predictive value of any FH definition.

**Quality assessment.** The longitudinal studies generally scored highly on quality assessment items. For one,[30] it was possible that ascertainment of diabetes may not have been blinded to FH status, and in two studies[28,31] this was not adequately reported. One longitudinal study had more than 20 percent attrition over 4 years;[28] the participants were elderly men, the attrition is likely to have reflected mortality, and a higher rate of diabetes incidence in those lost cannot be excluded.

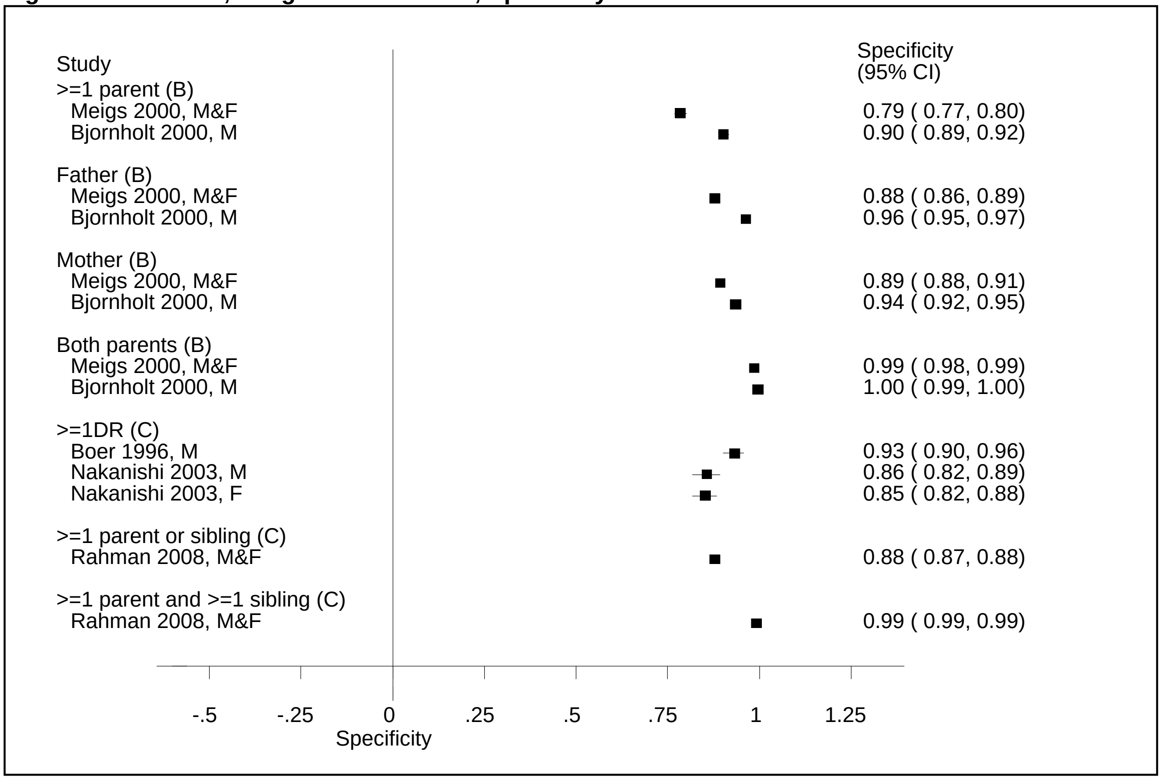
Two other longitudinal studies failed to report data on attrition.[27,29] Almost all of the cross-sectional studies were subject to possible exposure information bias, in that awareness of disease status may have influenced FH reporting. Similarly, many cross-sectional studies included self-report of diabetes in their outcome definition, which was not independent of awareness of FH status. These issues appeared to have been appropriately controlled for, in only one cross-sectional study.[39] The other major quality issue in the cross-sectional studies was the possibility of selection bias, through definite or possible non-probability sampling,[36,39] and definite or possible sub-optimal participation rates (all but two studies[32,38]). See Webtable 18, Appendix C.

**Figure 21. Diabetes, Longitudinal Studies, Sensitivity**



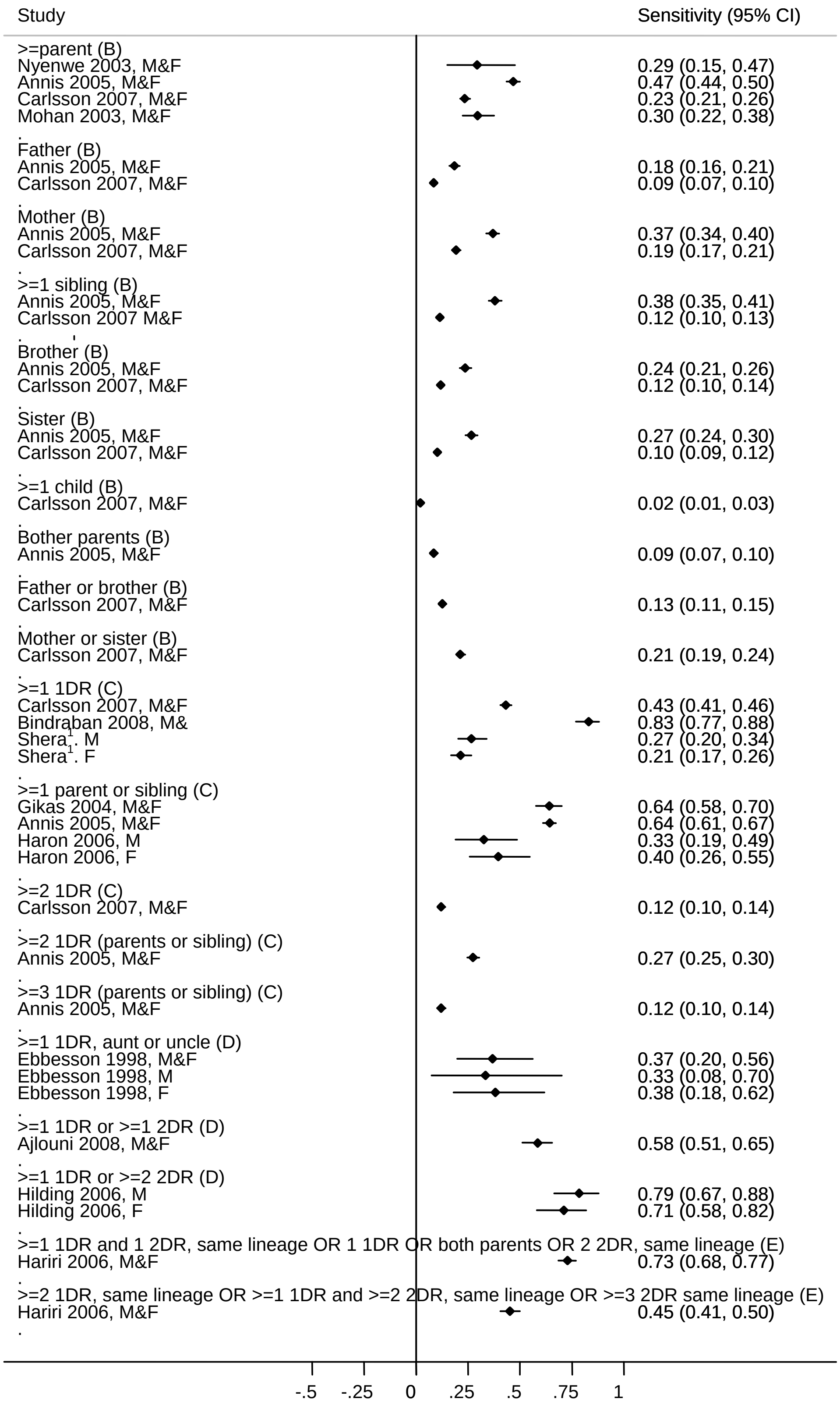

Abbreviations: 1DR=first degree relative; CI=confidence interval; F=female; M=male

**Figure 22. Diabetes, Longitudinal Studies, Specificity**



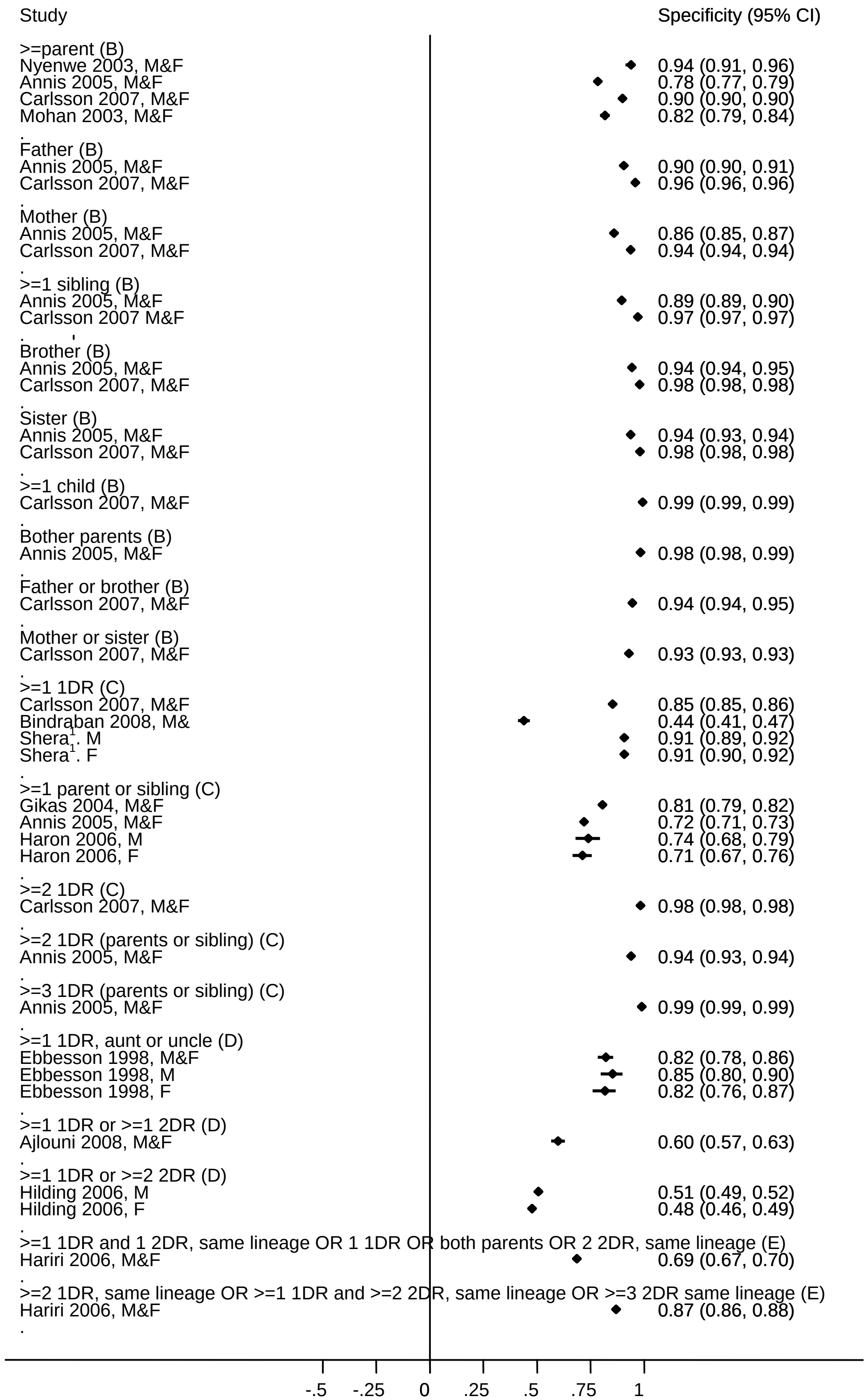

Abbreviations: 1DR=first degree relative; CI=confidence interval; F=female; M=male

**Figure 23. Diabetes, Cross-sectional Studies, Sensitivity**




Abbreviations: 1DR=first degree relative; 2DR=second degree relative; CI=confidence interval;

**Figure 24. Diabetes, Cross-sectional Studies, Specificity**




Abbreviations: 1DR=first degree relative; 2DR=second degree relative; CI=confidence

## Asthma and Atopic Disease

The asthma and atopic disease analysis was based on 17 publications but only 16 studies are presented, four longitudinal,[44-46,48] eleven cross-sectional.[2,49-58] One of the cross-sectional studies[59] presented a followup analysis of a random sample of an initial cross-sectional analysis[58] and was treated as cross-sectional (see Webtable 19, Appendix C); the data for these two studies were evaluated separately. Six studies[44-46,48,52,57] analyzed data relating to atopic disease in general, of which two[44,52] also included separate analyses for asthma. The remaining ten studies [2,49,51-56,58,59] presented data relating to asthma alone.

Three were conducted in U.S. populations,[49,52,54] two in Germany,[45,46] two in Brazil (including two reports of the same cohort),[48,58,59] and one each in Qatar,[51] Turkey,[55] Japan,[56] Poland,[57] Sweden,[53] Norway,[2] Spain,[50] and the United Kingdom.[44]

The four longitudinal studies all followed birth cohorts, one to 12 months,[48] two to 2 years,[44,45] and one to four years.[44]

Most of the cross-sectional analyses focused predominantly on children and young adults (up to 20 years of age), with only two conducted in adult populations, examining asthma only.[2,53] By definition, all of the asthma studies examined FH of asthma; one of the longitudinal studies[44] also examined FH of atopy as a risk factor for asthma, so for completeness these data were included in this report. Please see Webtables 20 through 23 in Appendix C for the methods used to ascertain FH and the outcomes of asthma and atopy, and the diagnostic criteria employed.

**Family history.** Ten separate definitions of 'positive FH' were employed, in categories B-D (Table 2). For the studies of atopy outcome, relative risks/odds ratios ranged from 0.52 to 11.2. For the studies of asthma outcome, relative risks/odds ratios from 1.06 to 12.15 were observed. The data by specific definition are presented in Webtable 4, Appendix C.

**Predictive accuracy.** Figures 25 through 32 present the sensitivity and specificity data for these definitions of FH, for the outcomes atopy and asthma separately. For the longitudinal analyses of atopy, the range of sensitivities was 0.15-0.64, and specificities 0.44-0.91. The range of PPVs was 0.25-0.46 and NPVs 0.7-0.84, for atopy prevalences up to 38.6 percent. The AUC could not be estimated.

For the cross-sectional analyses of atopy, the range of sensitivities was 0.23-0.48, and specificities 0.56-0.83. The range of PPVs was 0.28-0.52 and NPVs 0.68-0.74, for atopic disease prevalences up to 36.2 percent. The data did not permit calculation of AUC figures.

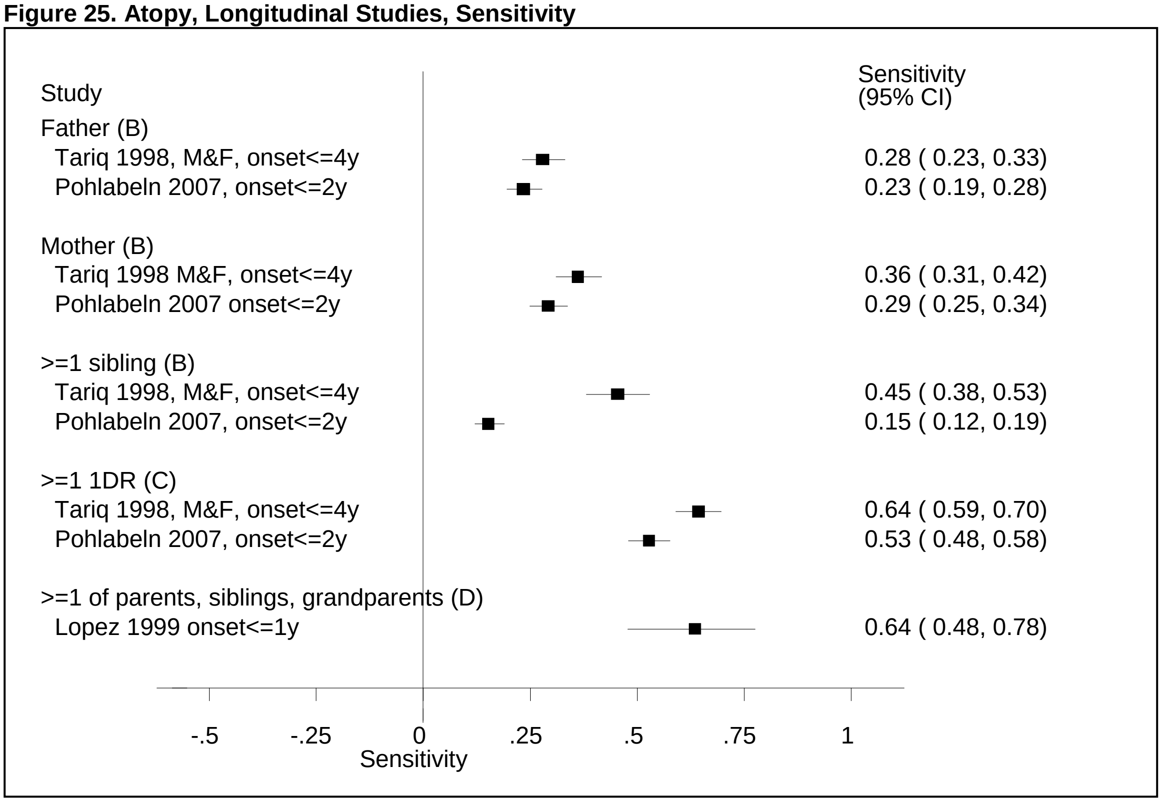
For the longitudinal asthma analyses, the range of sensitivities was 0.18-0.69 and specificities 0.43-0.91. The range of PPVs was 0.17-0.25 and NPVs 0.86-0.89, for an asthma prevalence of 15.9 percent. The AUC values could not be estimated. For the cross-analyses, the range of sensitivities was 0.04-0.76 and specificities 0.46-0.99. For the childhood studies only, the range of PPVs was 0.08-0.51 and NPVs 0.82-0.94, for asthma prevalence up to 19.8 percent. For the two adult studies, the PPVs were 0.07 and 0.13 and NPVs 0.96 and 0.98, respectively, for prevalences of asthma of 3.1 and 5.5 percent. The AUC values for category B and C definitions were 0.73 (father positive) and 0.77 (mother positive) and 0.66, respectively.

**Conclusion.** With the exception of two studies, all of the asthma and atopy analyses examined prediction of disease in children and young people. Positive FH definitions were almost entirely based on affected 1DRs only. The clinical utility of using any FH definition to predict future risk onset of asthma or atopic disease in infants or children depends on the availability of preventive interventions, although there may be educational benefits for parents with respect to early recognition of symptoms in susceptible children. The utility of choosing of

FH definition as a screening tool for current allergy or asthma depends on the availability, cost, and risks of other screening or diagnostic modalities.

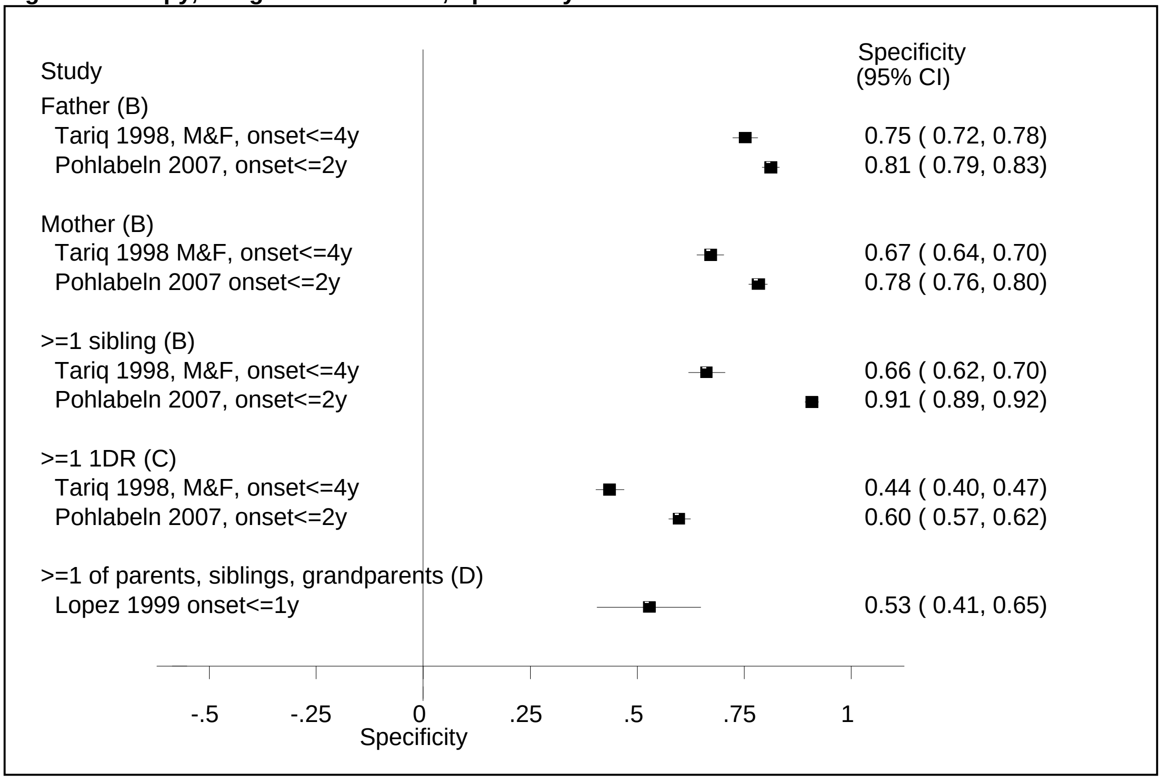
**Quality assessment.** Three of the four longitudinal studies scored well across four of the six quality assessment items, the fourth[46] meeting three criteria. The issues of concern consistent across all four were the possibility of ascertainment of atopy or asthma outcome being influenced by awareness of FH status, and the possibility for differences in method of capture of FH information.[46,48] Followup rates were suboptimal for one study,[45] and not adequately reported in another.[46] An issue across all the cross-sectional studies was the possibility of awareness of FH influencing disease definition or ascertainment, and/or awareness of disease status influencing FH reporting. In all, except four reports of three independent studies,[51,55,58,59] the possibility of selection bias through non-probability sampling and/or sub-optimal participation rates could not be dismissed. See Webtable 24, Appendix C.

**Figure 25. Atopy, Longitudinal Studies, Sensitivity**



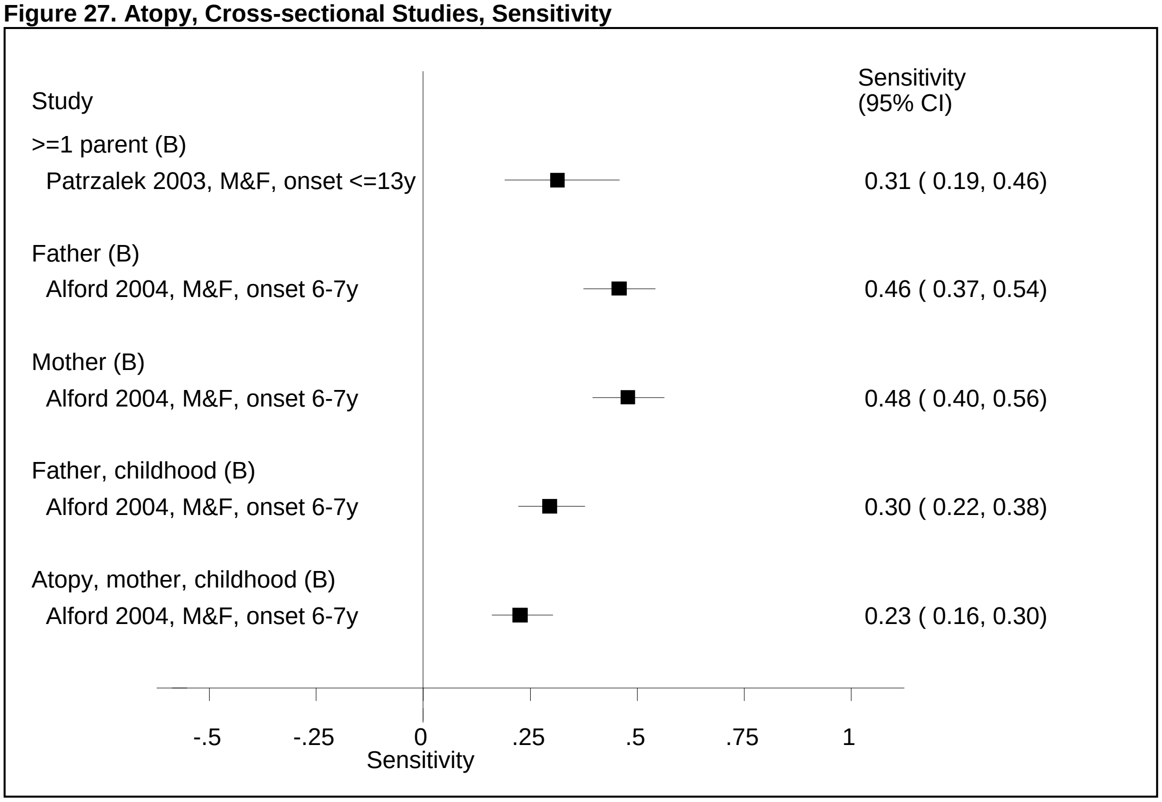

Abbreviations: 1DR=first degree relative; CI=confidence interval; F=female; M=male; y=years

**Figure 26. Atopy, Longitudinal Studies, Specificity**



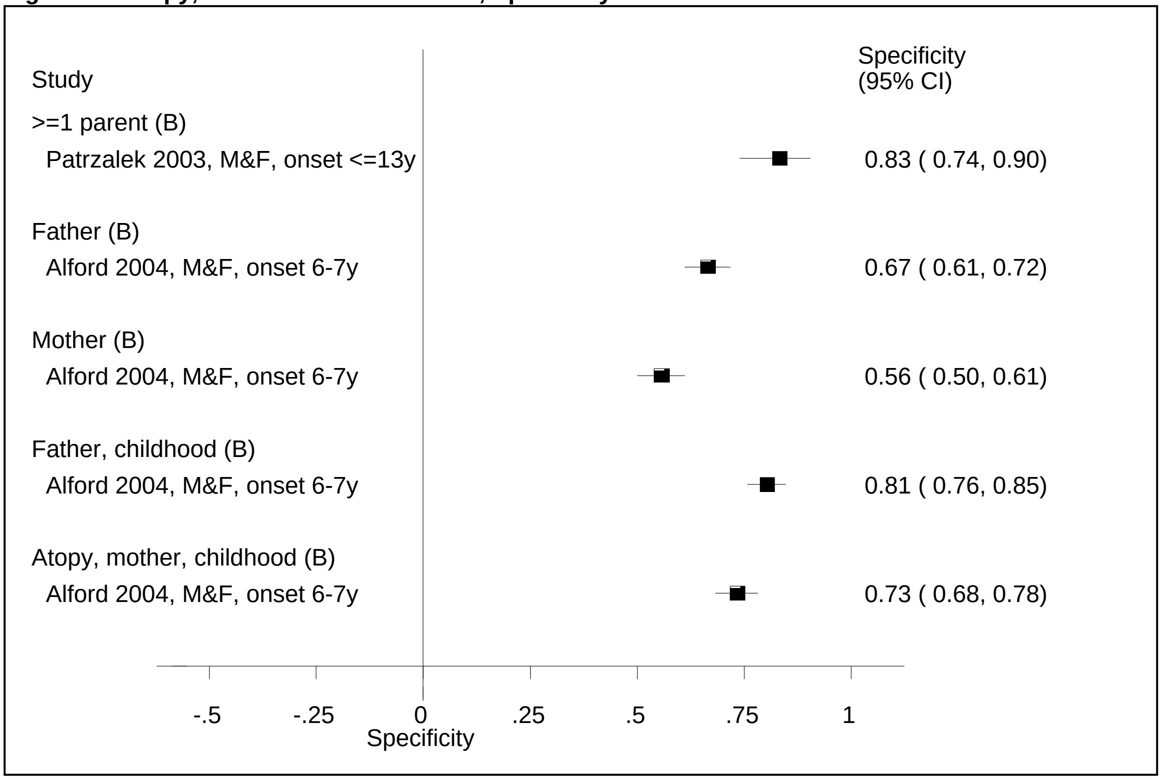

Abbreviations: 1DR=first degree relative; CI=confidence interval; F=female; M=male; y=years

**Figure 27. Atopy, Cross-sectional Studies, Sensitivity**



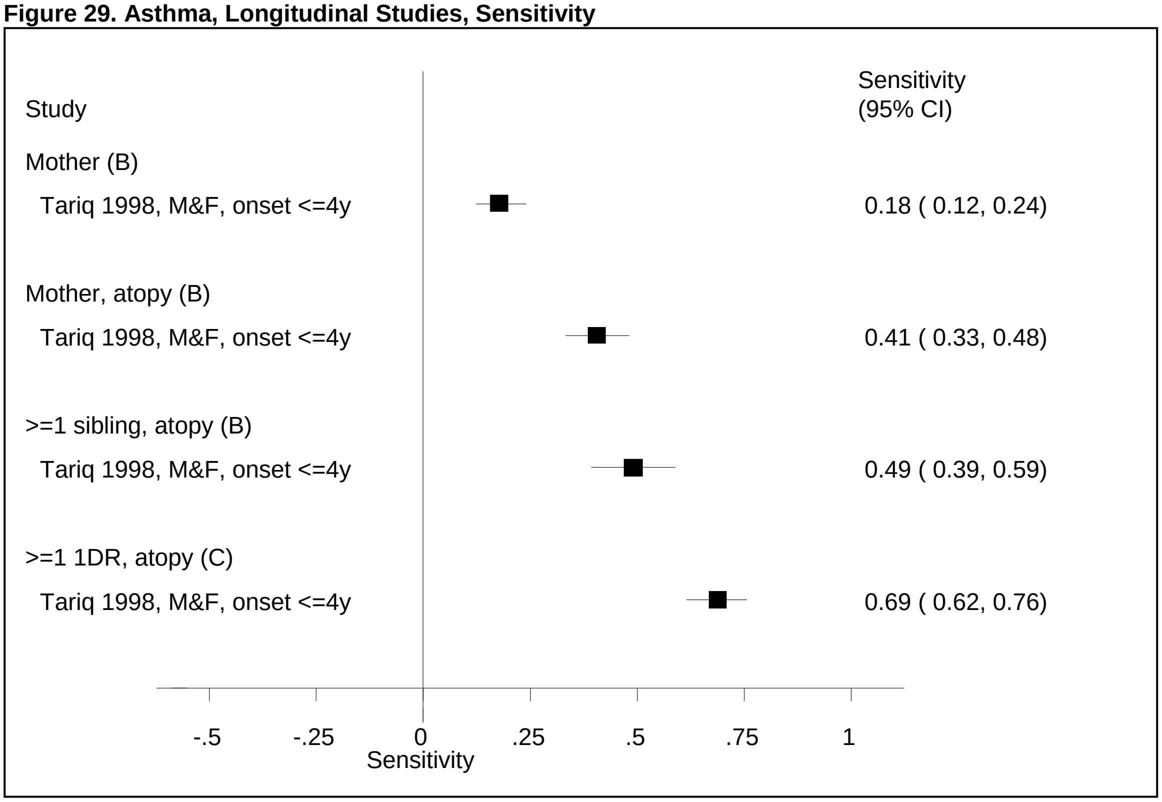

Abbreviations: CI=confidence interval; F=female; M=male; y=years

**Figure 28. Atopy, Cross-sectional Studies, Specificity**



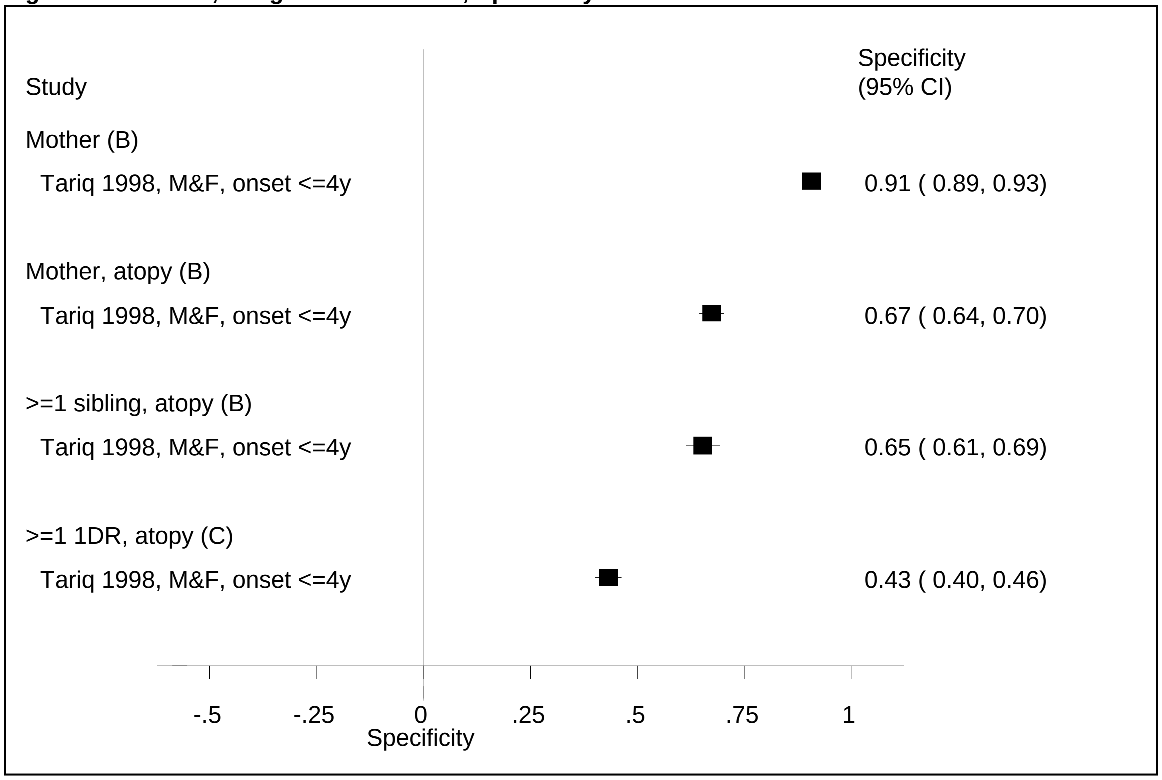

Abbreviations: CI=confidence interval; F=female; M=male; y=years

**Figure 29. Asthma, Longitudinal Studies, Sensitivity**



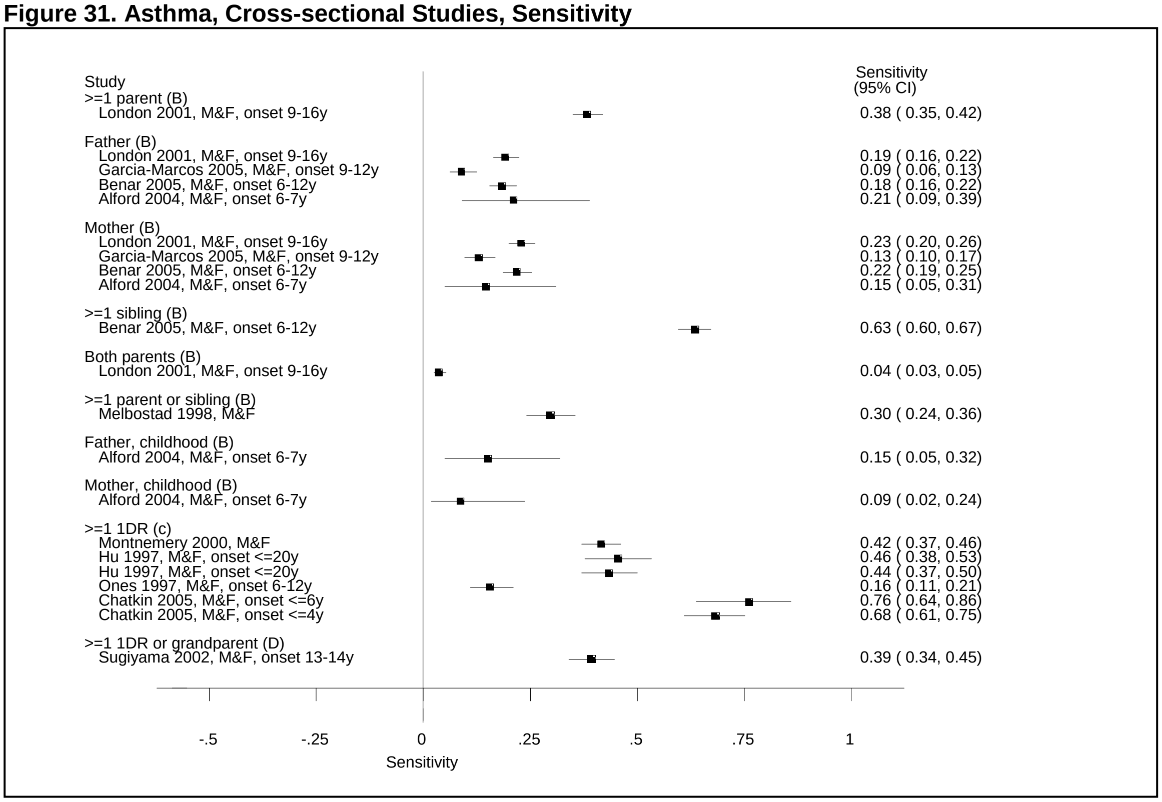

Abbreviations: CI=confidence interval; 1DR=first degree relative; F=female; M=male; y=years

**Figure 30. Asthma, Longitudinal Studies, Specificity**



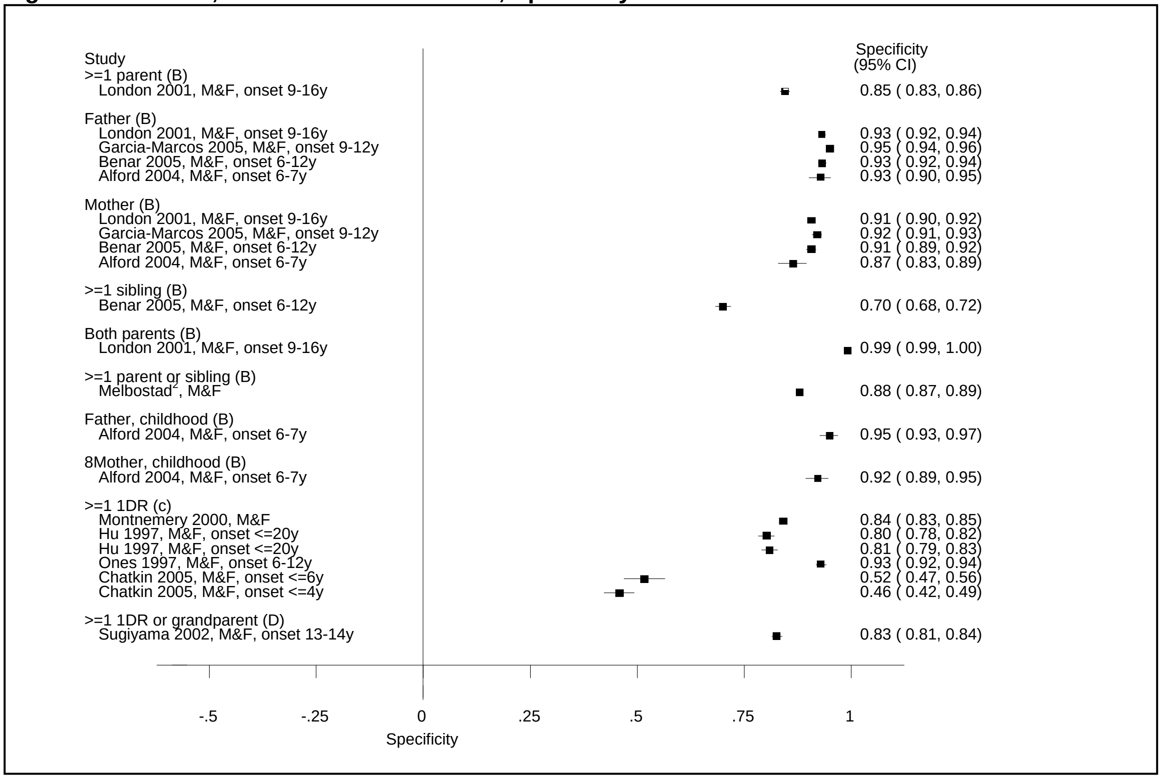

Abbreviations: CI=confidence interval; 1DR=first degree relative; F=female; M=male; y=years

**Figure 31. Asthma, Cross-sectional Studies, Sensitivity**




Abbreviations: 1DR=first degree relative; CI=confidence interval; F=female; M=male; y=years

**Figure 32. Asthma, Cross-sectional Studies, Specificity**




Abbreviations: 1DR=first degree relative; CI=confidence interval; F=female; M=male; y=years

## Mental Illness

Two papers contributed to the analysis of mental illness, (see Webtable 25, Appendix C) one longitudinal,[60] and one cross-sectional.[62] Both presented data on prediction of major depressive disorder (MDD) and one[60] also examined any mood disorder as an outcome condition, considered a more appropriate measure in childhood and adolescence. Both examined outcomes according to DSM-IV criteria, to 26 years of age and were conducted in U.S. populations.

The longitudinal study[60] followed up the third generation of a family study in which the grandparents of the participants formed the inception cohort. The second study[62] was based on a single-age cohort followed from childhood to age 26, which was treated as a cross-sectional analysis because the FH was ascertained at the followup point. Please see Webtables 26 through 28 in Appendix C for the methods used to ascertain FH and the outcomes of MDD and mood disorder, and the specifics of the diagnostic criteria used.

**Family history.** Four definitions of ‘positive FH’ were examined, all in category B (Table 2). For the analyses of MDD outcome, relative risks/odds ratios ranged from 1.84 to 2.9. For the analysis of mood disorder outcome, a single relative risk of 2.8 was reported. The data by specific definition are presented in Webtable 4, Appendix C, along with data on disease frequency and predictive values.

Parental plus grandparental MDD was associated with a  the relative risk of 2.80 for any mood disorder, and 2.33 for MDD in the third generation.[60] Odds ratios of 1.84 and 2.88 were found for the association between parental depression and sibling depression, respectively, in the cross-sectional study.[62]

**Predictive accuracy.** Figures 33 through 38 present the sensitivity and specificity data for these studies, for the outcomes MDD and mood disorder, respectively. For the longitudinal analyses, the range of sensitivities was 0.72-0.83 and specificities 0.40-0.59; for any mood disorder, the range of sensitivities was 0.73-0.83 and specificities 0.42-0.63. The range of PPVs for MDD was 0.14-0.18 and NPVs 0.92-0.95; for mood disorder, the corresponding values were 0.24-0.31 and 0.89-0.93. The overall prevalence of MDD for this study was 11.2 percent, and for any mood disorder was 18.6 percent. A relatively high proportion of participants met at least one of the definitions for positive FH (44.1-62.7 percent), reflecting the constitution of the original cohort.

The cross-sectional analyses produced sensitivities of 0.12 and 0.24 and specificities of 0.85 and 0.96, respectively. The PPVs were 0.33 and 0.45, and NPVs were 0.79 and 0.78, respectively, for a prevalence of MDD of 23.2 percent.

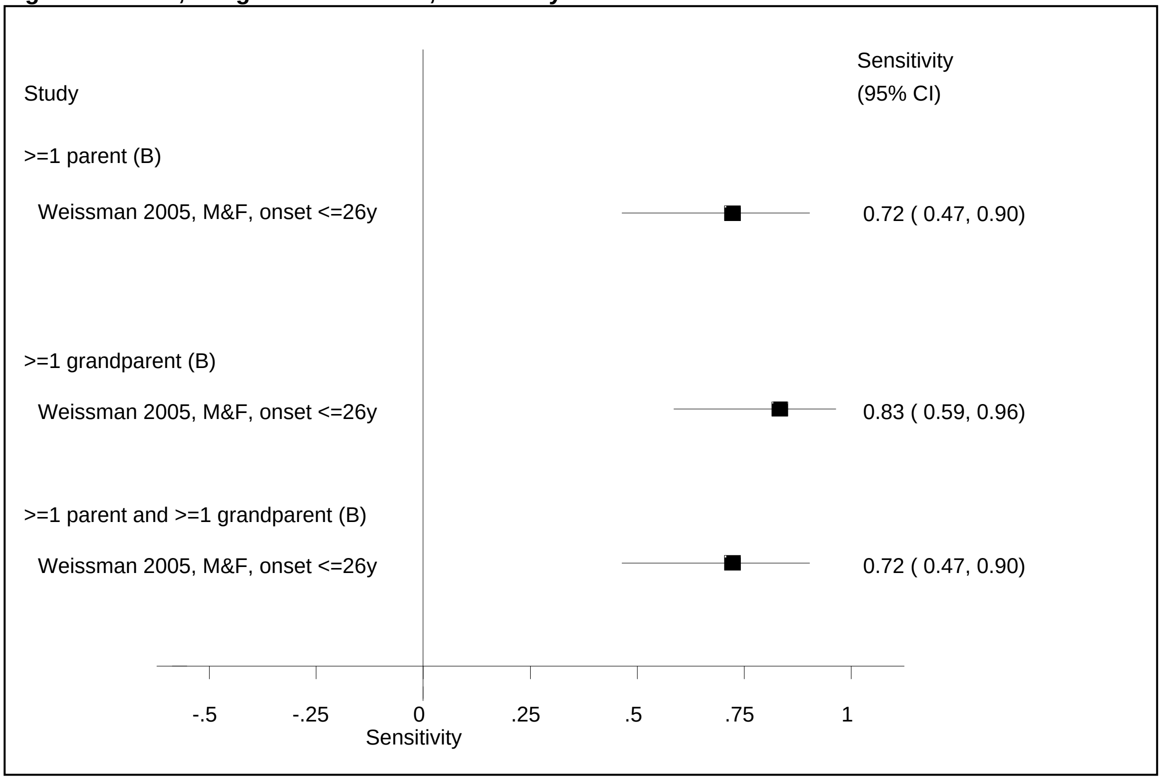
It was not possible to calculate AUC values for any of the mental illness analyses.

**Conclusion.** The analyses were limited to two studies only, both of which had higher than expected frequency of MDD or mood disorder. In one this was a result of study design,[60] and in the other this may reflect participant selection bias.[62] On the face of it, the findings of the longitudinal study appear to suggest that FH definitions based on parents could predict around three fourths of cases of major depression or mood disorder in offspring up to the age of 25, although the false positive rate is rather high at 50 percent or more. The clinical utility of PPVs of around 15 percent for MDD and 25-30 percent for mood disorder depends on the possibility of preventive intervention in childhood or adolescence, and the more general net benefits of being aware of an individual’s susceptibility. Whether this level of predictive validity would be obtained in lower prevalence populations is questionable, and lower NPVs could be associated with stigmatization and unnecessary clinical intervention. The uncommon design of this study (three generation cohort) means that the findings cannot automatically be extrapolated to general populations, and the ascertainment of FH was not typical of a primary care consultation, where patient self-reporting would likely be less accurate and less complete. In contrast, the cross-sectional study was initially established as a population-based study although fewer than half of the original participants were included in the analysis considered here. The prevalence of major depression was high (almost a quarter of the study group); like the other study, the method of assessing FH was likely more complete and detailed than would be obtained in a primary care consultation based on patient self-reporting. For the two FH definitions examined in this study, it is not possible to draw conclusions regarding the value of using FH alone to screen for presence of major depression.

Taking all of these issues into account, it is difficult to extrapolate the findings to typical primary care settings. If similar predictive values were obtained in studies conducted in less selected populations and with more typical data collection procedures, parental history of depression might offer useful information relating to identifying youth and young adults at risk.

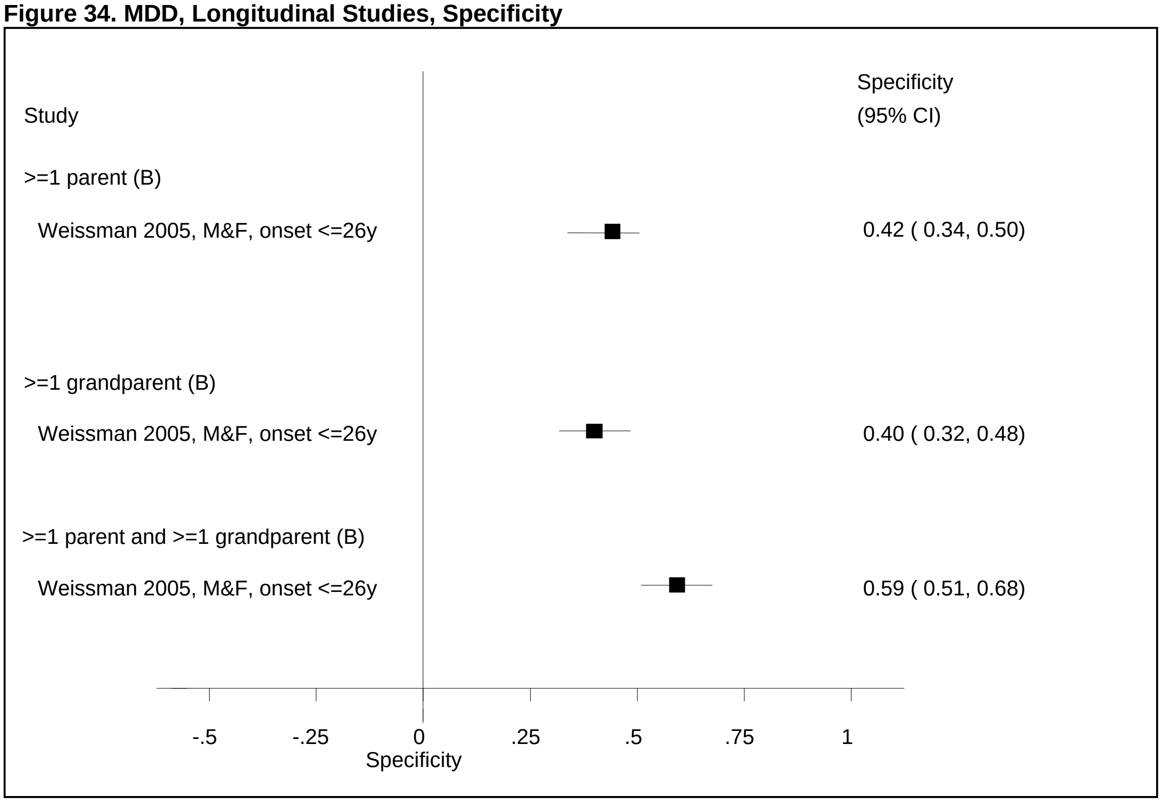
**Quality assessment.** The longitudinal study[60] scored high across all quality assessment criteria, likely reflecting its unusual prospective multi-generational design. The cross-sectional study[62] (which was in fact a cross-sectional analysis of an original prospective cohort study) was assessed as being potentially prone to bias in relation to independence of assessment of FH and disease outcome, and selection bias through sub-optimal participation rate at the point the analysis was performed. See Webtable 29, Appendix C.

**Figure 33. MDD, Longitudinal Studies, Sensitivity**



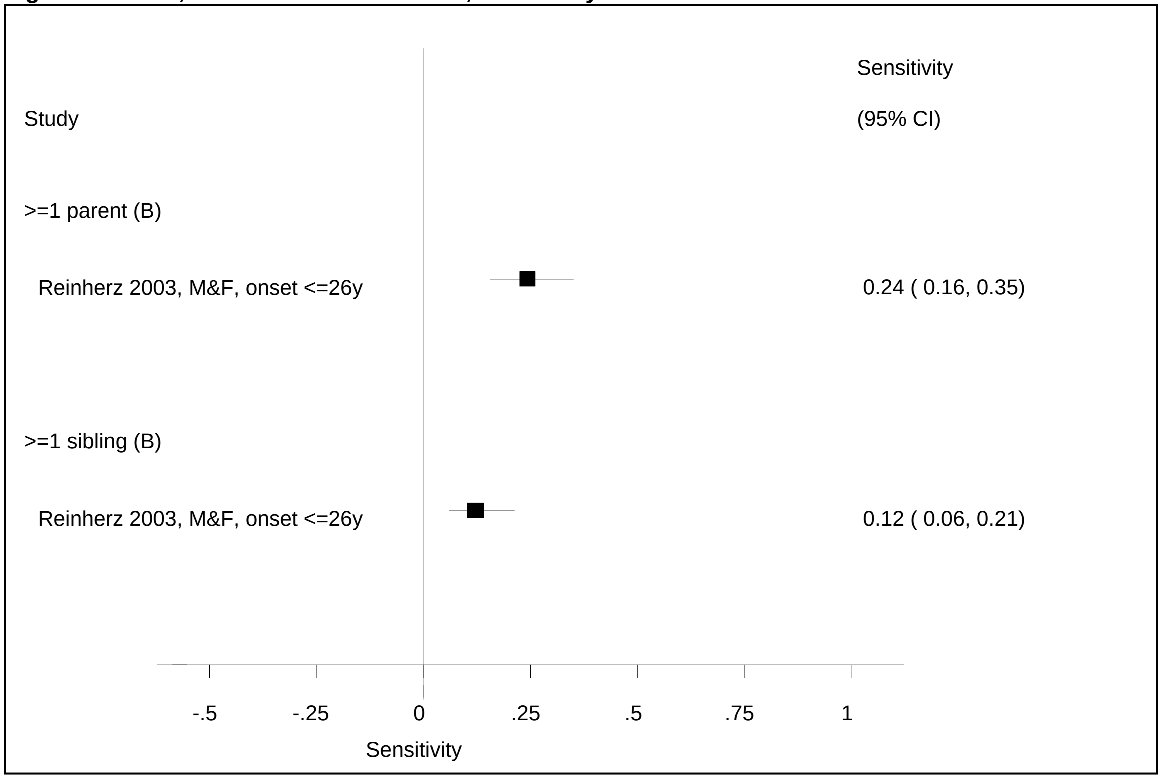

Abbreviations: CI=confidence interval; F=female; M=male; MDD=major depressive disorder; y=years

**Figure 34. MDD, Longitudinal Studies, Specificity**



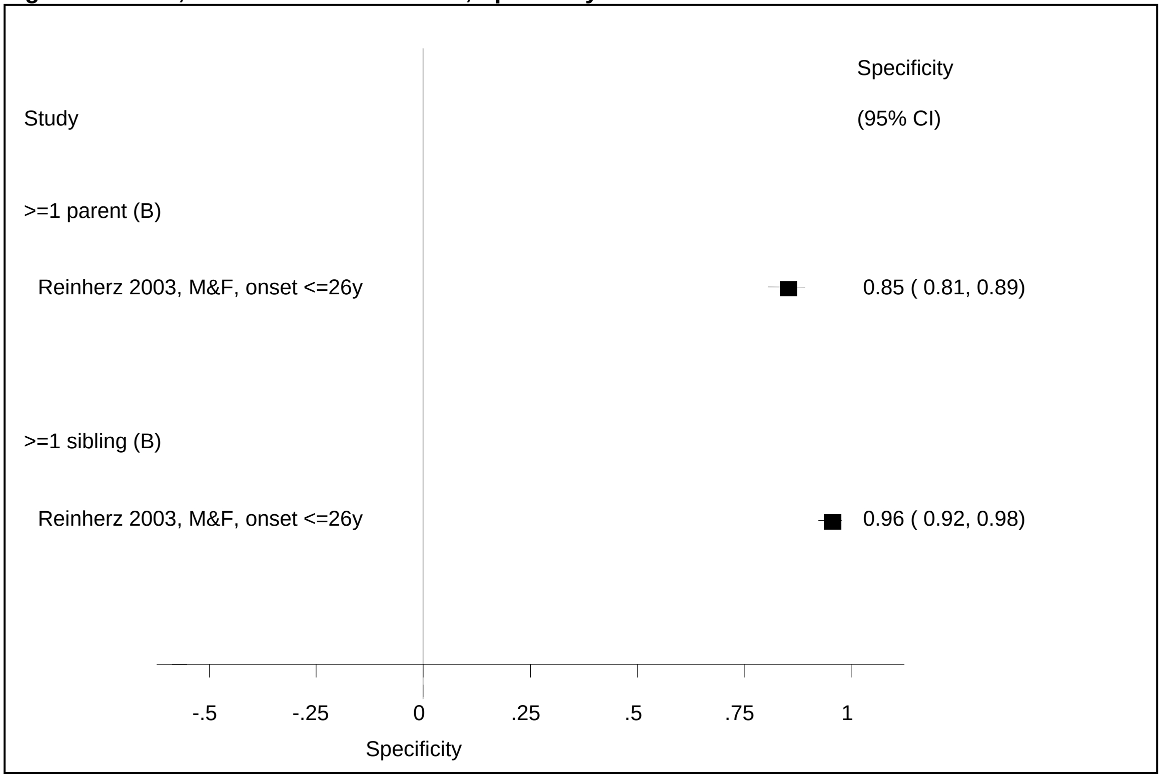

Abbreviations: CI=confidence interval; F=female; M=male; MDD=major depressive disorder; y=years

**Figure 35. MDD, Cross-sectional Studies, Sensitivity**



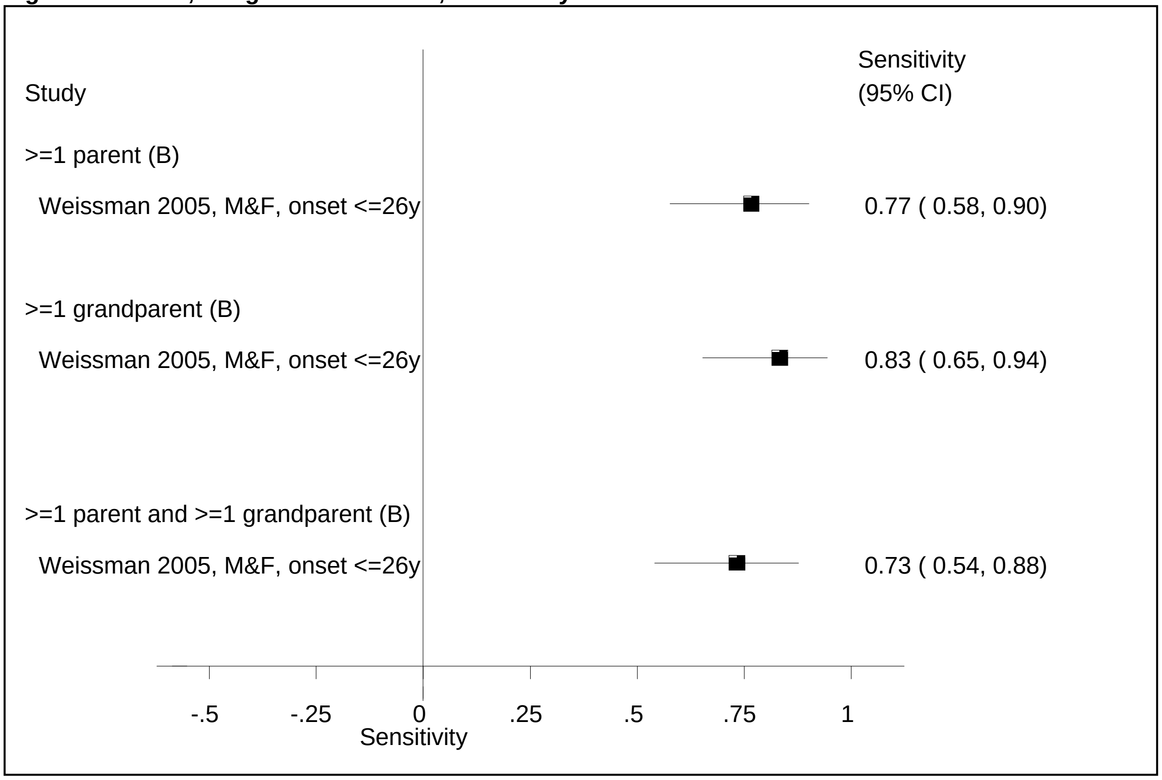

Abbreviations: CI=confidence interval; F=female; M=male; MDD=major depressive disorder; y=years

**Figure 36. MDD, Cross-sectional Studies, Specificity**



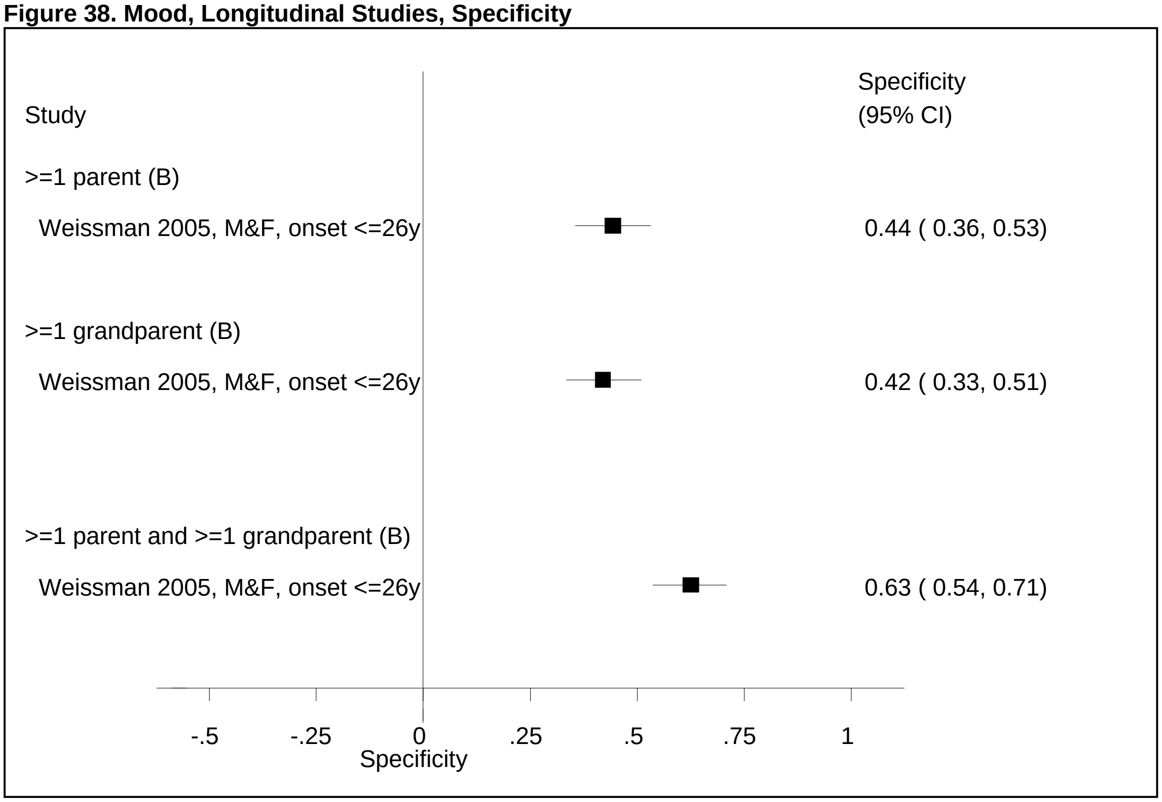

Abbreviations: CI=confidence interval; F=female; M=male; MDD=major depressive disorder; y=years

**Figure 37. Mood, Longitudinal Studies, Sensitivity**




Abbreviations: CI=confidence interval; F=female; M=male; y=years

**Figure 38. Mood, Longitudinal Studies, Specificity**




Abbreviations: CI=confidence interval; F=female; M=male; y=years

# Question 2: What is the Accuracy of the Family History, and Under What Conditions Does the Accuracy Vary?

## General Approach to Evaluating Accuracy

Accuracy of a test (in this case reporting of FH) represents the proportion of all test results that are true (both positive and negative outcomes). If individuals reporting FH were 100 percent accurate, they would correctly identify all relatives with the disease and all those without the disease. A number of metrics may be used to convey accuracy and from these, sensitivity and specificity are not influenced by the underlying prevalence of the characteristic of interest in the population (in this case, a positive FH). We therefore aimed to present sensitivity and specificity where this is reported in, or could be calculated from, eligible papers as the metric reflecting accuracy of self-reporting. Where this was not available, we reported other metrics of accuracy such as percent agreement.

In this systematic review, we considered "reporting of FH by the informant" as the "index test", and required that there be comparison to a "gold standard" (representing the real or true disease state). We use the term informant to reflect that in some instances the person reporting family history may be a proxy respondent who knows the individual for whom family history is being evaluated. In this context, sensitivity indicates how accurate informants are at identifying relatives who truly have the disease. If reporting is highly sensitive, only a few relatives with the disease will be reported as disease-free. Conversely, if reporting is highly specific, only a few relatives who are truly disease-free are misreported as having cancer. It is likely that accuracy of reporting one's FH will be influenced by factors relating to both the informant and the relatives; the method of capturing the FH data is also an important consideration.

As there is no clear "gold standard" against which the accuracy of self-reporting of FH is evaluated, we decided to accept the following reference standards for the presence or absence of disease in the 1DRs and 2DRs, or higher, of the informant: 1) the relative's medical record, 2) confirmation of status by the relative's physician, 3) death certificate, 4) disease registry, and 5) direct confirmation by the relative in question. Not all research databases that contain medical records were eligible as sources of verification for this review as we excluded studies that did not provide complete accuracy information including those databases that provided information on the number of true positives only. Data from these studies would not assist us in understanding the true accuracy of respondents providing their FH.

A total of 37 publications evaluated the accuracy of reporting FH, were eligible for data extraction, and reported data separately for spouses and genetic relatives. The majority of papers (n=16) evaluated accuracy of reporting cancer FH, in persons who had cancer (breast, ovarian, colorectal, prostate, lymphoma, melanoma, Ewing's or mixed cancers) or who were being screened for cancer. There were 12 studies that evaluated accuracy of reporting FH for mental health disorders and these included persons with mood disorders, mixed disorders, and schizophrenia. The remaining studies evaluated persons with Parkinson's disease (n=2), persons with cardiovascular/hypertension related problems (n=3) or persons with diabetes (n=2) and two studies[123,124] with populations from longitudinal cohorts that had mixed diseases (diabetes, hypertension, cardiovascular disease, and asthma).

## Accuracy of Self-reporting of Cancer FH

**Population.** A total of 16 studies evaluated accuracy of reporting cancer FH. These studies recruited informants (probands) with breast cancer,[91-94] colorectal cancer,[95-97] prostate cancer,[98,99] ovarian cancer,[100] mixed cancers (breast, ovarian, colorectal),[101,102] Ewing's Sarcoma,[103] lymphoma,[104] melanoma,[105] and unspecified cancer.[106]

Nine studies were case series in design and seven were case control studies for probands with breast,[91] colorectal,[95-97] ovarian,[100] and prostate[98] cancers, and lymphoma.[104] In the case-referent studies, controls were derived from a range of sources including: the general population (age-matched),[91,100,104] informants' spouses and general practice rosters,[97] patients who had undergone colonoscopy but were free of polyps,[96] and healthcare administration databases.[95,98] The case series studies, all collected FH from subjects with cancer who were recruited from specialized clinics or registries. One study[103] evaluated a sample of deceased relatives of the probands; the challenges and potential errors of death certification and registries were the focus of this paper.

**Method of family history collection in informants/probands.** The methods of cancer FH collection varied. Six studies used face to face interviews,[91,95,97,99,103,106] six used mailed surveys,[92,94,96,98,102,105] three used telephone interviews,[93,101,104] and one study did not report the mode of collection.[103] Generally, the specific type of FH questions were not specified, but probed information predominately related to degree of the relative.

**Method of disease verification in informants/relative.** The methods used to verify relatives' cancer status were primarily multimodal and included: review of medical records (including cancer registry) and death registry;[92,94,103,106] face to face interview or postal survey of relatives;[101] postal survey alone;[96,105] and contact with physician of deceased relative.[99] Three studies[91,98,102] used medical records alone, and five studies used linkage with cancer registry alone.[93,95,97,100,104]

Disease status was verified in both affected and unaffected relatives in all but five studies.[91,94,99,102,105]

**Study outcomes.** Some studies examined only specific cancer family histories, while others examined all cancers of interest. Four studies[95,97,100,104] examined reporting of any type of cancer in relatives while the remaining studies examined cancers that matched that of the probands. Tables 5 to 9 show the findings according to the cancer reported in the relatives; we show the major cancers identified in (Q1) which include breast, ovarian, colorectal, and prostate (other cancers were reported much less frequently). We also include the three studies evaluating lymphoma,[104] melanoma,[105] and unspecified cancers.[106]

In general, specificity across all cancer types and with varying modes of collection was consistently high (Tables 5 to 9). For reporting of breast cancer FH, specificities of 91 to 100 percent were reported; for colon cancer, 91 to 99 percent; for ovarian cancer, 96 to 100 percent; for prostate cancer, 93 to 99 percent. For lymphoma in relatives, rates were equally high. Two studies using population controls and samples from large registries[100,104] showed that specificities were not altered by the type of cancer reported in relatives; sensitivities were higher for cancers at more common sites (for example breast and lung) and lower for less common sites (such as leukemia, and lymphoma). The sensitivity varied by the cancer of interest; for reporting of relatives with breast cancer, the range was 72 to 95 percent (Tables 5 to 9); for colon cancer, 33 to 90 percent; for ovarian cancer, 42 to 83 percent; and, for prostate cancer, 47 to 79 percent. From the limited data, it was not possible to draw definitive conclusions about the effects of either the method of collecting cancer FH, or the method of verification of relatives' reported status, on sensitivity.

There were five case control studies[95,97,98,100,104] that allowed direct comparison of reporting accuracy between affected and unaffected informants. In general, there were not significant differences between cases and controls with regards to specificity. However, controls reported lower sensitivities in lymphoma for 1DR with hematopoietic cancer,[104] and ovarian cancers (sample size very low for this cancer).[95] In contrast, higher sensitivities were reported in controls of relatives with colorectal cancer.[95,97]

Predictors of accuracy in cancer FH were not consistently evaluated across all the studies probing accuracy of self reported cancer FH. Factors related to informants that have been evaluated in eligible studies include age, gender, education level, and race, and marital status, type of cancer, setting, and insurance status. Factors associated with relatives include, degree of relation, type of 1DR, age, gender, cancer site/type, and time since diagnosis. We summarize the factors most frequently evaluated.

Eight studies[91,95-97,100-102,104] evaluated the age of the informant as a predictor of accuracy with mixed results. Four studies showed that younger age (<50 and 50-59) was associated with higher specificity,[104] or that accuracy increased overall with younger age[95,100,101] while one[96] showed decreased accuracy with younger age and three found no age effect.[91,97,102] No clear trend emerges, and the type of cancer does not seem to be a factor. It was also difficult to compare across studies as the manner in which age intervals were categorized was not consistent.

Six studies[95-97,101,102,104] examined an association between the informant's gender and accuracy, and no general trend was observed. One study[95] suggested higher accuracy in reporting relatives with ovarian cancer by women than men. Another study[101] suggested lower specificity of reporting relatives' cancers by men compared to women.

Six studies[95-97,101,102,104] evaluated the effect of education level using a variety of categorizations; none showed any effect with the exception of two studies. These studies showed that for subjects with ovarian cancer and longer education (>10 years) had decreased sensitivities[100] for reporting all types combined and breast cancer alone and those with college versus high school education had increased accuracy in subjects with breast cancer genetic syndromes.[94]

Four studies[93,94,97,102] examined associations between accuracy and the degree of relative whose status was being reported. There was a consistent trend towards increased accuracy of reporting relating to 1DR compared to 2DRs or 3DRs. One study[97] noted challenges in confirming the true status of 2DRs and that fewer 2DRs and 3DRs were identified overall, suggesting the potential for reporting and confirmation biases. Two studies[100,104] showed that the type of 1DR (for example parent versus sibling) did not affect the high specificity rates and did not differ for controls or cases; the sensitivities were slightly lower for daughters and sisters of controls only.[100]

**Quality and risk of bias in studies.** Webfigure 1, Appendix C details the nine individual items used to evaluate risk of bias. We summarize the three primary flaws observed within this group of studies. The risk of spectrum bias was high, given that seven of the studies were case control in design (indicating the presence of spectrum bias as not representative of range of persons within primary care) and the remaining populations had cancer and were recruited from specialized settings. For example, one study[92] involving informants affected by breast cancer was restricted to those aged under 40 years, one third of whom were affected by bilateral breast cancer, and were referred to a tertiary level oncology center. Although there are some challenges in characterizing the spectrum of patients with cancer, some studies included very high risk or atypical cancer patients, particularly for breast cancer, rather than patients with all levels of risk for cancer.

Partial or differential biases may lead to overestimation of accuracy.[157] The disease status was verified in both affected and unaffected relatives in all but five studies[91,94,99,102,105] suggesting that partial verification bias was limited. However, even in the studies that adequately attempted to evaluate the status of unaffected relatives, many subjects with incomplete data (due to linkage problems, or difficulty ascertaining confirmation) were excluded from the analyses. For some studies, up to 31 percent[92] of relatives could not have their disease status verified. Another study[103] showed that 11 percent of death certificates were inconclusive and that up to 24 percent of certificates for deceased relatives could not be located.[103] Reported difficulties included, errors in medical records or pathology reports,[92,103] death of relative prior to registry formation or other form of record keeping,[92] emigration of relatives, incorrect addresses for relatives or contact information for hospitals, refusal of access to death certificate information or destruction of files,[102] and inability to secure consent from the relatives in question.[102]

Blinding those verifying cancer status in relatives to the status of the informant was less of an issue in these cancer accuracy studies. For some studies the use of record linkage strategies was independent of the status of the relatives.[100,104] Lack of blinding could lead to differential interpretation particularly where the information contained in medical charts is ambiguous. Bias due to lack of blinding might be less likely to have occurred in studies where verification was based on cancer or hospital registries, and where the diagnoses would have been checked through a separate process. However, there are other errors associated with linking databases that can lead to misclassification of disease status. Overall, blinding of data collectors to the status of the relative or the informant was not undertaken in the majority of studies, suggesting a high risk of masking bias.

**Summary.** There were 16 studies evaluating accuracy of reporting cancer FH. These studies recruited probands with breast cancer,[91-94] colorectal cancer,[95-97] prostate cancer,[98,99] ovarian cancer,[100] mixed cancers (breast, ovarian, colorectal),[101,102] Ewing's Sarcoma,[103] lymphoma,[104] melanoma,[105] and unspecified cancer.[106] Subjects were recruited predominately from specialized settings or cancer registries which would suggest a high risk of spectrum and selection bias.

The methods of cancer FH collection varied as did the questions or tools used to collect FH. Similarly, the methods used to verify relatives' cancer status were primarily multimodal and relatives for whom verification could not be obtained were excluded from analyses.

Some studies examined only specific cancer family histories, while others examined all cancers of interest. Overall, specificity across all cancer types and with varying modes of collection was consistently high (>90 percent); sensitivities were lower and generally more variable (40 to 90 percent) depending on the cancer types. Two large studies using data linkages to registries[100,104] showed that specificities were not altered by the type of cancer reported in relatives; that sensitivities were higher for cancers at more common sites and lower for less common sites. Five case control studies showed no significant differences between cases and controls with regards to specificity although controls reported lower sensitivities in lymphoma,[104] and in colorectal cancer.[95,97]

Predictors of accuracy in cancer FH were not consistently evaluated across all studies. Factors that have been evaluated in eligible studies include informant age, gender, education level, and race, and marital status, type of cancer, setting, and insurance status. Factors associated with relatives include, degree of relation, type of 1DR, age, gender, cancer site/type, and time since diagnosis. No clear trend emerges with age, gender, or education level of the informants and the impact on accuracy. There was a consistent trend towards increased accuracy of reporting relating to 1DR compared to 2DRs or 3DRs.

Overall, these 16 studies are at high risk of spectrum and verification biases, which may cause an overestimation of accuracy (see Webfigure 1, Appendix C).

**Table 5. Accuracy of self-reporting of FH for cancer in studies that verified the status for breast cancer in relatives**

| Study | Population/ Design/ Sample Size | Index Test (FH) Reference Standard | Accuracy | |
|---|---|---|---|---|
| **Breast Cancer in Relatives (Affected and Unaffected)** | | | | |
| | | | **Sensitivity(95%) a/a+c; value[ ]** | **Specificity(95%) d/ b+d; value [ ]** |
| Anton-Culver[93] 1996 U.S. | Consecutive case series (n=359): female breast cancer probands from either a population based or cancer registry | **Index Test:** Telephone interview (1DRs and 2DRs)<br><br>**Reference Standard:** Cancer registry | 54/60; [0.90] (0.79-0.96) | 364/369; [0.98] (0.97-1.00) |
| Chang[104] 2006 Sweden | Cases (n=1508): lymphoma cancer probands from cancer registries, hospitals, and clinics;<br>Controls (n=1229): randomly sampled from the population | **Index Test:** Telephone interview (1DR)<br><br>**Reference Standard:** Cancer registry | Cases: [0.73] (0.70-0.75)<br><br>Controls: [0.72] (0.69-0.74) | Cases: [0.99] (0.98-0.99)<br><br>Controls: [0.99] (0.98-1.00) |
| Kerber[95] 1997 U.S. | Cases (n=125): colon cancer probands from DARCC study health administration database<br>Controls (n=206): population based from DARCC health administration database | **Index Test:** Personal interview (1DR and 2DR)<br><br>**Reference Standard:** Utah population health database; Cancer registry | Cases: 11/13; [0.85] (0.55-0.98)<br>κ=0.73 (0.55-0.90)<br><br>Controls: 18/22; [0.82] (CI NR)^<br>κ=0.58 (0.44-0.71) | Cases: 107/112; [0.95] (0.90-0.98)<br><br>Controls: 167/184; [0.91] (CI NR)^ |

Abbreviations: 1DR=first degree relative; 2DR=second degree relative; 3DR=third degree relative; 4DR=fourth degree relative; 5DR=fifth degree relative; BC=breast cancer; CI=confidence interval; DARCC= Diet, Activity and Reproduction in Colon Cancer; FH=family history; GRIS=Genetics Registry System; HBOCS=hereditary breast-ovarian cancer syndrome; LFS=Li-Fraumeni Syndrome; n=number of subjects; NR=not reported; y=years

**Table 5. Accuracy of self-reporting of FH for cancer in studies that verified the status for breast cancer in relatives (continued)**

| Study | Population/ Design/ Sample Size | Index Test (FH) Reference Standard | Accuracy | |
|---|---|---|---|---|
| **Breast Cancer in Relatives (Affected and Unaffected)** | | | | |
| | | | **Sensitivity(95%) a/a+c; value[ ]** | **Specificity(95%) d/ b+d; value [ ]** |
| Soegaard[100]<br>2008<br>Denmark | Cases (n=579 ): female ovarian cancer probands recruited from gynecological departments;<br>Controls (n=1,564): Population based from civil registry | **Index Test:**<br>Personal interview (1DR)<br><br>**Reference Standard**:<br>Cancer registry | Case [0.89] (0.81-0.97);<br>$\kappa$=0.85 (0.79-0.92)<br><br>Control [0.94] (0.90-0.98);<br>$\kappa$=0.89 (0.85-0.93) | Case [0.99] (0.99-1.00)<br><br>Control [1.00] (0.99-1.00) |
| Ziogas[101]<br>2003<br>U.S. | Probands with breast (n=670), ovarian (n=123) and colorectal (n=318 both male and female) cancer from clinic based family registries | **Index Test:**<br>Telephone interview (1DR, 2DR, 3DR) followed by mailed GRIS pedigree<br><br>**Reference Standard:**<br>1) Medical records or<br>2) Self-reporting from relatives or<br>3) Death certificates of deceased relatives | 188/197; [0.95] (0.91-0.98) | 850/873; [0.97] (0.96-0.98) |
| **Breast Cancer in Relatives (Affected only)** | | | | |
| Ereola[92]<br>2000<br>Finland | Probands (n=NR) with breast cancer:<br>a) diagnosed when <40 y<br>b) patients with bilateral disease, c) unselected for age and laterality | **Index Test:**<br>Mailed questionnaire<br><br>**Reference Standard:**<br>1) Genealogy confirmed by church parish registries<br>2) Hospital records<br>3) Cancer registry | % Cases Reported % Cases Reported Correctly<br><br>1DR 100 95<br>2DR 99 96<br>3DR 61 94<br>4DR 23 100<br>5DR 17 100<br>Total 87 95 | |
| King[99]<br>2002<br>U.S. | Probands with prostate cancer (n=143) from the cancer centers | **Index Test:**<br>Interview<br><br>**Reference Standard**:<br>Medical records and death certificates | Accuracy rates:<br>Documented (%); 97.6%<br>Accurate (%) – 95.0% | |

**Table 5. Accuracy of self-reporting of FH for cancer in studies that verified the status for breast cancer in relatives (continued)**

| Study | Population/ Design/ Sample Size | Index Test (FH) Reference Standard | Accuracy | |
|---|---|---|---|---|
| | | | **Sensitivity(95%) a/a+c; value[ ]** | **Specificity(95%) d/ b+d; value [ ]** |
| **Breast Cancer in Relatives (Affected only)** | | | | |
| Parent[91]<br>1995<br>Canada | Cases (n=414): probands with breast cancer enrolled in study on study on nutritional factors in breast cancer<br>Controls (n=429): population based | **Index Test:**<br>Personal interview (1DR).<br><br>**Reference Standard**:<br>Medical records | Mean error in reported age minus confirmed age of diagnosis<br>Cases: 0.24 yrs (95% CI, -0.60-1.08)<br>Controls : -0.03 yrs (95% CI, -0.88=0.82)<br><br>Some data to suggest that more errors in reporting of age of diagnosis are associated with >70 yrs of respondent, and >10 yrs since diagnosis of the relative | |
| Schneider[94]<br>2004<br>U.S. | Two series of subjects undergoing genetic testing for having a relative with a) LFS (n=32), or b) HBOCS (n=52) Some of the HBOCS had breast cancer | **Index Test:**<br>Self-reporting questionnaire (up to 4 generations)<br><br>**Reference Standard:**<br>1) Medical records or 2) death certificates | Accuracy of any cancer diagnoses HBOCS cohort=78%<br>Accuracy of any cancer diagnoses by LFS cohort=52%<br>Accuracy of breast cancer report=96%<br>Accuracy of ovarian cancer report=74%<br>Accuracy of other LFS related cancers=55% | |
| Sijmons[102]<br>2000<br>Netherlands | Retrospective analysis of tumor reports from counselees on 120 families in a medical genetics clinic | **Index Test:**<br>Self-reporting questionnaire followed by interview<br><br>**Reference Standard:**<br>1) Medical records<br>2) Contact with relatives | Accuracy rate for cancer:<br>Breast 93%<br>Colorectal 89%<br>Ovarian 71%<br>Other 63%<br>All types 78% | |

**Table 6. Accuracy of self-reporting of FH for cancer in studies that verified the status for colorectal cancer in relatives**

| Study | Population/ Design/ Sample size | Index Test (FH) Reference Standard | Accuracy | |
|---|---|---|---|---|
| **Colorectal Cancer in Relatives (Affected and Unaffected)** | | | | |
| | | | **Sensitivity(95%) a/a+c; value[ ]** | **Specificity(95%) d/ b+d; value [ ]** |
| Aitken[96] 1995 Australia | Cases (n=74): probands with colorectal cancer<br>Controls (n=163): Recruited from primary care setting who had undergone colonoscopy | **Index Test:**<br>Mailed survey (1DR)<br><br>**Reference Standard:**<br>1) Medical record<br>2) Death certificates | 70/81; [0.86] (0.77-0.93) | 219/239; [0.92] (0.87-0.95) |
| Chang[104] 2006 Sweden | Cases (n=1,508): lymphoma cancer probands from cancer registries, hospitals, and clinics;<br>Controls (n=1,229): randomly sampled from the population | **Index Test:**<br>Telephone interview (1DR)<br><br>**Reference Standard:**<br>Cancer registry | In any 1DRs:<br>Cases: [0.48] (0.46-0.51)<br>Controls: [0.53] (0.50-0.55) | In any 1DRs:<br>Cases: [0.99] (0.99-1.00)<br>Controls: [0.99] (0.99-1.00) |
| Kerber[95] 1997 U.S. | Cases (n=125): colon cancer probands from DARCC study health administration database<br>Controls (n=206): population based from DARCC health administration database | **Index Test:**<br>Personal interview (1DR and 2DR)<br><br>**Reference Standard:**<br>Utah population health database; Cancer registry | Cases:<br>11/17; [0.65] (0.38-0.86)<br>Controls:<br>13/16; [0.81] (CI NR)^ | Cases:<br>98/108; [0.91] (0.84-0.95)<br>Controls:<br>178/190; [0.94] (CI NR)^ |

Abbreviations: 1DR=first degree relative; 2DR=second degree relative; 3DR=third degree relative; BC=breast cancer; CI=confidence interval; DARCC= Diet, Activity and Reproduction in Colon Cancer; FH=family history; GRIS=genetics registry system; HBOCS=hereditary breast-ovarian cancer syndrome; LFS=Li-Fraumeni Syndrome; n=number of subjects; NR=not reported

**Table 6. Accuracy of self-reporting of FH for cancer in studies that verified the status for colorectal cancer in relatives (continued)**

| Study | Population/ Design/ Sample size | Index Test (FH) Reference Standard | Accuracy | |
|---|---|---|---|---|
| **Colorectal Cancer in Relatives (Affected and Unaffected)** | | | | |
| | | | **Sensitivity(95%) a/a+c; value[ ]** | **Specificity(95%) d/ b+d; value [ ]** |
| Mitchell[97] 2004 U.K. | Cases (n=199) probands with colorectal cancer Controls (n=133): recruited from general practice lists in the same county and some spouses of probands | **Index Test:** Personal interview by genetics nurse (1DR, 2DR, 3DR)<br><br>**Reference Standard**: Cancer registry | Cases:<br>30/53; [0.57] (0.43-0.69)<br>1DRs [0.57] (0.43-0.69)<br>2DRs [0.271] (0.17-0.41)<br>Controls:<br>1DRs [0.53] (0.31-0.74)<br>2DRs [0.33] (0.19-0.51) | Cases:<br>1256/1269; [0.99] (0.98-0.99)<br>1DRs [0.99] (0.98-0.99)<br>2DRs [0.97] (0.99-0.99)<br>Controls:<br>1DRs [0.99] (0.98-0.99)<br>2DRs [0.99] (0.99-0.99) |
| Soegaard[100] 2008 Denmark | Cases (n=579): female ovarian cancer probands recruited from gynecological departments; Controls (n=1,564): population based from civil registry | **Index Test:** Personal interview (1DR)<br><br>**Reference Standard**: Cancer registry | Cases:<br>[0.70] (0.54-0.86);<br>κ=0.68 (0.55-0.82)<br>Controls:<br>[0.69] (0.59-0.80);<br>κ=0.69 (0.60-0.78) | Cases:<br>[0.99] (0.99-1.00)<br><br>Controls:<br>[1.00] (0.99-1.00) |
| Ziogas[101] 2003 U.S. | Probands with breast (n=670), ovarian (n=123) and colorectal (n=318 both male and female) cancer from clinic based family registries | **Index Test:** Telephone interview (1DR, 2DR, 3DR) followed by mailed GRIS pedigree<br><br>**Reference Standard:**<br>1) Medical records or<br>2) Self-reporting from relatives or<br>3) Death certificates of deceased relatives | 174/194; [0.90] (0.84-0.93) | 1454/1498; [0.97] (0.96-0.98) |

**Table 6. Accuracy of self-reporting of FH for cancer in studies that verified the status for colorectal cancer in relatives (continued)**

| Study | Population/ Design/ Sample size | Index Test (FH) Reference Standard | Accuracy | |
|---|---|---|---|---|
| **Colorectal Cancer in Relatives (Affected only)** | | | | |
| | | | **Sensitivity(95%) a/a+c; value[ ]** | **Specificity(95%) d/ b+d; value [ ]** |
| King[99]<br>2002<br>U.S. | Probands with prostate cancer (n=143) from the cancer center | **Index Test:**<br>Interview<br><br>**Reference Standard**:<br>Medical records and death certificates | Accuracy rates for colon cancer<br>Documented (%) 88.9%<br>Accurate (%) – 91.7% | |

**Table 7. Accuracy of self-reporting of FH for cancer in studies that verified the status for ovarian cancer in relatives**

| Study | Population/ Design/ Sample size | Index Test (FH) Reference Standard | Accuracy | |
|---|---|---|---|---|
| **Ovarian Cancer in Relatives (Affected and Unaffected)** | | | | |
| | | | **Sensitivity(95%) a/a+c; value[ ]** | **Specificity(95%) d/ b+d; value [ ]** |
| Kerber[95]<br>1997<br>U.S. | Cases (n=125): colon cancer probands from DARCC study health administration database<br>Controls (n=206): population based from DARCC health administration database | **Index Test:**<br>Personal interview (1DR and 2DR)<br><br>**Reference Standard:**<br>Utah population health database; Cancer registry | Cases:<br>2/3; [0.67] (0.09-0.99)<br><br>Controls:<br>1/5; [0.50] (CI NR) | Cases:<br>117/122; [0.96] (0.91-0.99)<br><br>Controls:<br>201/204;[0.98] (CI NR) |
| Soegaard[100]<br>2008<br>Denmark | Cases (n=579): female ovarian cancer probands recruited from gynecological departments;<br>Controls (n=1,564): population based from civil registry | **Index Test:**<br>Personal interview (1DR)<br><br>**Reference Standard**:<br>Cancer registry | Cases:<br>[0.44] (0.27-0.61);<br>$\kappa$ = 0.57 (0.40-0.73)<br>Controls:<br>[0.42] (0.25-.59);<br>$\kappa$ = 0.47 (0.31-0.63) | Cases:<br>[1.00] (1.00-1.00)<br><br>Controls:<br>[1.00] (1.00-1.00) |
| Ziogas[101]<br>2003<br>U.S. | Probands with breast (n=670), ovarian (n=123) and colorectal (n=318 both male and female) cancer from clinic based family registries | **Index Test:**<br>Telephone interview (1DR, 2DR, 3DR) followed by mailed GRIS pedigree<br><br>**Reference Standard:**<br>1) Medical records or<br>2) Self-reporting from relatives or<br>3) Death certificates of deceased relatives | 35/42; [0.83] (0.69-0.93) | 1017/1028; [0.99] (0.98-0.99) |

Abbreviations: 1DR=first degree relative; 2DR=second degree relative; 3DR=third degree relative; BC=breast cancer; CI=confidence interval; DARCC= Diet, Activity and Reproduction in Colon Cancer; FH=family history; GRIS=genetics registry system; HBOCS=hereditary breast-ovarian cancer syndrome; LFS=Li-Fraumeni Syndrome; n=number of subjects; NR=not reported

**Table 7. Accuracy of self-reporting of FH for cancer in studies that verified the status for ovarian cancer in relatives (continued)**

| Study | Population/ Design/ Sample size | Index Test (FH) Reference Standard | Accuracy | |
|---|---|---|---|---|
| | | | **Sensitivity(95%) a/a+c; value[ ]** | **Specificity(95%) d/ b+d; value [ ]** |
| **Ovarian Cancer in Relatives (Affected Only)** | | | | |
| King[99]<br>2002<br>U.S. | Probands with prostate cancer (n=143) from the cancer center | **Index Test:** Interview<br><br>**Reference Standard**: Medical records and death certificates | Accuracy rates for ovarian cancer:<br>Documented (%); Accurate (%) – 100.0%; 50.0% | |

**Table 8. Accuracy of self-reporting of FH for cancer in studies that verified the status for prostate cancer in relatives**

| Study | Population/ Design/ Sample size | Index Test (FH) Reference Standard | Accuracy | |
|---|---|---|---|---|
| **Prostate Cancer in Relatives (Affected and Unaffected)** | | | | |
| | | | **Sensitivity(95%) a/a+c; value[ ]** | **Specificity(95%) d/ b+d; value [ ]** |
| Chang[104] 2006 Sweden | Cases (n=1,508): lymphoma cancer probands from cancer registries, hospitals, and clinics; Controls (n=1,229): randomly sampled from the population | **Index Test:** Telephone interview (1DR) **Reference Standard:** Cancer registry | In any 1DRs: Cases: [0.47] (0.44-0.49) Controls: [0.60] (0.57-0.63) | In any 1DRs: Cases: [0.99] (0.98-0.99) Controls: [0.99] (0.99-1.00) |
| Kerber[95] 1997 U.S. | Cases (n=125): colon cancer probands from DARCC study health administration database Controls (n=206): population based from DARCC health administration database | **Index Test:** Personal interview (1DR and 2DR) **Reference Standard:** Utah population health database; Cancer registry | Cases: 11/16; [0.69] (0.41-0.89) Controls: 21/30; [0.7] | Cases: 101/109; [0.93] (0.86-0.97) Controls 166/176; [0.94] |
| Ziogas[101] 2003 U.S. | Probands with breast (n=670), ovarian (n=123) and colorectal (n=318 both male and female) cancer from clinic based family registries. | **Index Test:** Telephone interview (1DR, 2DR, 3DR) followed by mailed GRIS pedigree **Reference Standard:** 1) Medical records or 2) Self-reporting from relatives or 3) Death certificates of deceased relatives | Cases: 46/58; [0.79] (0.67-089) | Cases: 557/564; [0.99] (0.98-0.99) |

Abbreviations: 1DR=first degree relative; 2DR=second degree relative; BC=breast cancer; CI=confidence interval; DARCC= Diet, Activity and Reproduction in Colon Cancer; FH=family history; GRIS=genetics registry system; HBOCS=hereditary breast-ovarian cancer syndrome; LFS=Li-Fraumeni Syndrome; n=number of subjects; NR=not reported; y=years

**Table 8. Accuracy of self-reporting of FH for cancer in studies that verified the status for prostate cancer in relatives (continued)**

| Study | Population/ Design/ Sample size | Index Test (FH) Reference Standard | Accuracy | |
|---|---|---|---|---|
| | | | **Sensitivity(95%) a/a+c; value[ ]** | **Specificity(95%) d/ b+d; value [ ]** |
| **Prostate Cancer in Relatives (Affected only)** | | | | |
| Zhu[98]<br>1999<br>U.S. | Cases: Probands (n=181) with prostate cancer<br>Controls (n=297): enrolled in Group Health Cooperative | **Index Test:**<br>Self-reporting data<br><br>**Reference Standard:**<br>Medical records, death certificate | Cancer in Brothers<br>Cases 40-64y: $\kappa$ = 0.85 (0.65-1.00)<br>65-69y: $\kappa$ = 0.39 (0.14-0.65)<br>Controls 40-64y: $\kappa$ = 0.52 (0.16-0.88)<br>65-69y: $\kappa$ = 0.60 (0.31-0.88)<br><br>Cancer in Fathers<br>Cases: 40-64y: $\kappa$ = 0.76 (-0.55-0.98)<br>65-69y: $\kappa$ = 0.70 (0.45-0.94)<br>Controls:40-64y: $\kappa$ = 0.24 (-0.15-0.62)<br>65-69y: $\kappa$ = 0.51 (0.20-0.82) | |
| King[99]<br>2002<br>U.S. | Probands with prostate cancer (n=143) from the cancer center | **Index Test:**<br>Interview<br><br>**Reference Standard**:<br>Medical records and death certificates | Accuracy rates for prostate cancer: Documented (%); Accurate (%) – 69.0%; 86.2% | |

**Table 9. Accuracy of self-reporting of FH for cancer in studies that verified the status for other cancers in relatives**

| Study | Population/ Design/ Sample size | Index Test (FH) Reference Standard | Accuracy | |
|---|---|---|---|---|
| **Other Cancer in Relatives (Affected and Unaffected)** | | | | |
| | | | **Sensitivity(95%) a/a+c; value[ ]** | **Specificity(95%) d/ b+d; value [ ]** |
| Chang[104] 2006 Sweden | Cases (n=1,508): lymphoma cancer probands from cancer registries, hospitals, and clinics; Controls (n=1,229): randomly sampled from the population | **Index Test:** Telephone interview (1DR)<br><br>**Reference Standard:** Cancer registry | Hematopoietic system cancer Cases: [0.60] (0.57-0.62) Controls: [0.38] (0.35-0.40)<br><br>Any cancer in any 1DRs: Cases: [0.85] (0.83-0.87) Controls: [0.80] (0.83-0.87) | Hematopoietic system cancer Cases: [0.98] (0.97-0.99) Controls: [0.99] (0.98-0.99)<br><br>Any cancer in any 1DRs Cases: [0.89] (0.87-0.91) Controls: [0.92] (0.90-0.94) |
| Mussio[106] 1998 Switzerland and Italy | Probands (n=193) with cancer (type not specified) recruited from two different sites from population-based cancer registries | **Index Test:** Standardized Questionnaire interview<br><br>**Reference Standard:** 1) Medical records 2) Cancer registry | Mixed cancers by study group:<br><br>Study A: [0.85] Study B: [0.74] Study A+B: [0.82] | Mixed Cancers by study group:<br><br>Study A: [0.97] Study B: [0.97] Study A+B: [0.97] |
| **Other Cancer in Relatives (Affected Relatives Only)** | | | | |
| Aitken[105] 1996 Australia | Participants of the Queensland Familial Melanoma Project (913 cases) | **Index Test:** FH questionnaire<br><br>**Reference Standard:** Medical records | Medical confirmation of melanoma as the diagnosis was obtained for 623/1040 (59.9%; 95% CI: 56.9-62.9%).<br>A false positive reporting rate by cases of 40.1% | |
| Novakovic[103] 1996 U.S. | Deceased relatives of probands (n=122) with Ewing's sarcomas | **Index Test:** Questionnaire<br><br>**Reference Standard:** Medical records and death certificates | % Agreement between self-reporting and death certificate 52% (63/122) dead relatives<br>1DR or proxy spouse: 58%<br>2DR: 48%<br><br>% Disagreement between self-reporting and death certificate:<br>13% (16/122) dead relatives<br>1DR 12%<br>2DR 14 | |

Abbreviations: 1DR=first degree relative; 2DR=second degree relative; FH=family history; cancer syndrome; n=number of subjects

## Accuracy of Self-Report of Mental Health Disorder FH

There are unique challenges when evaluating accuracy of reporting FH in persons with mental illnesses. Traditionally, FH is sought from the proband or control subject (index test) and verification of the FH is sought by contact with the relative (reference standard). However, in mental health disorders this is not the typical approach for collecting or verifying FH, where informants (usually relatives) are sought to establish FH. In general, this raises the problem of disentangling accuracy of medical history versus accuracy of reporting FH as the index test.

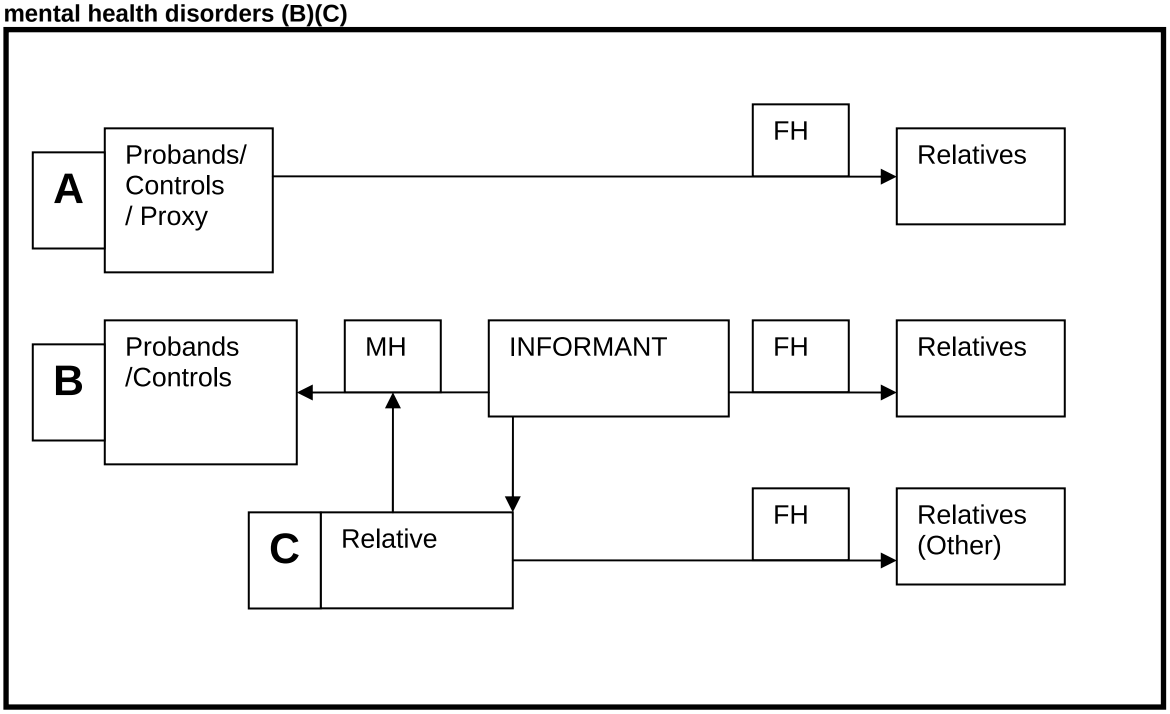
Most mental health illnesses are diagnosed primarily using clinical criteria, necessitating confirmation of the presence of symptoms or behaviors in the individuals being assessed. In some situations where a genetic link is presumed, the diagnosis is substantiated by a positive FH (i.e., bipolar disorders). The person who is suspected to have the mental illness may not have sufficient insight into their condition to report the presence of these diagnostic symptoms; similarly, it is not clear if they can identify the presence of these symptoms in relatives. This is particularly the case when there is cognitive impairment (e.g., dementia) or the patient is in an acute phase of the mental health illness (e.g., manic phase of bipolar disorder). Informants who have health information about the proband, their relatives, or both are often sought as an adjunct to establishing a probable diagnosis. There is the added conundrum that if the relatives also have a mental illness, verification of their own or the probands' disease status is potentially problematic, the relatives themselves may not be aware that they also may have a mental illness.

Figure 39 shows a schematic of the manner in which FH (index test) is collected in studies evaluating persons with mental health disorders. Scenario A represents the typical pathway to collect FH where persons who have the disease (probands) or who do not (controls) are queried directly about the disease status of their relatives. In this case the index test is based on information from the probands or control; in an ideal situation the proxy (who is usually a relative) is typically not included in the subsequent verification of the their own disease status (as a relative).

Scenario B represents the standard approach in which FH (index test) is collected within families of probands with mental health disorders. The figure shows that the proband is very often not directly solicited for information about the disease status of relatives, but rather to indicate who might be a possible informant or relative to contact for further information. Scenario B represents the idealized situation where the informants provide assistance in establishing the presence of symptoms and behaviors (rather than presence or absence of disease) that would assist in "diagnosing" the mental health disorder in both the proband (medical history (MH)) and the relatives. Establishing a positive or negative FH is typically not determined by the informant; rather their report on the presence of symptoms is then used to establish a diagnosis for several mental health disorders. Note that scenario B assumes that the informant is different from the relatives. Scenario C represents the typical situation in mental health accuracy studies where relatives are informants with regards to their own disease status (or presence of key symptoms) and that of other relatives. Thus, the dilemma here is that informants, who are usually relatives, are present in both the index test (reporting symptoms or FH) and in verifying the disease status (reference test). The fundamental difference between the index and reference tests is the differing methods used to solicit information about the symptoms or disease status. Additionally, it is difficult to disentangle the "medical history" of the relative in the index test, versus the FH.

Essentially evaluation of accuracy in families with mental health disorders becomes a comparison of methods specific to accuracy of reporting of the informant, rather than the proband/proxy. As such, the accuracy within these studies represents the accuracy between two methods of collecting family and medical history from relatives or informants. Although the primary interest of this systematic review is on accuracy of reporting by the proband rather than the informant and on FH rather than medical history, we recognize that this may not be the norm within this clinical area. We alert the reader to this difference and where possible we attempt to present data that most likely reflects accuracy of FH rather than MH.

**Figure 39. A schematic representation of collecting FH (Index test) in typical manner (A) and in persons with mental health disorders (B)(C)**




Abbreviations: FH=family history; MH=medical history

**General study characteristics.** Our systematic review identified 12 studies that evaluated the accuracy of collecting FH in persons with mental health disorders. One study collected FH but reported only on the accuracy of informant age of onset rather than accuracy of disease status in the relatives; as such, the results were not extracted for our research question.[118]

We grouped the remaining 11 studies based on the primary diagnosis of the probands; in the majority of studies, the subjects who were queried about FH were the relatives (predominately 1DR) of the probands. The disease outcomes for these studies were not restricted to those of the probands alone, but tended to include a variety of mental health disorders. Within studies evaluating mental health disorders, we include a series of studies with a mixed population of elderly with both dementia and depression.

There were three studies that evaluated relatives of persons with schizophrenia;[107-109] three studies (four publications) that evaluated relatives of, or persons with, dementia and depression;[110-113] and, four studies that evaluated relatives of persons with mixed disorders including depression and anxiety,[114,115] personality disorders alone,[117] and combined schizophrenia and bipolar affective disorders.[116] We have grouped the presentation of the results according to these mental health disorder classifications.

## Schizophrenia and Related Disorders

**Population.** Three studies[107-109] evaluated relatives (and some informants) of subjects with predominately schizophrenia related disorders. Although two of these studies[108,109] included relatives of controls subjects, the results were not stratified by cases and controls; all three studies were therefore case series in design. The informants in each study were based on the FH reported by 1DRs although, with the exception of one study,[107] the characteristics of these relatives were poorly described.

**Method of FH collection in informants/probands.** All three studies used a standardized instrument to collect FH (Family History Research Diagnostic Criteria, FH-RDC) and included additional standardized diagnostic questions specific to symptoms for schizophrenia and related subtype disorders (Table 10).

**Method of verification in informants/relatives.** All three studies used multiple strategies (termed best estimate diagnosis (BED)) that included direct interview (including FH and diagnostic criteria), medical records when available, and diagnosis by one or more expert clinicians.

**Study outcomes.** All studies evaluated FH for schizophrenia and related subtype disorders; one study[109] included history of bipolar related disorders and additional categories such as alcohol abuse. Table 10 details the accuracy outcomes for these studies; the presentation of results is limited to those of primary schizophrenia and bipolar disorders (accuracy outcomes for all subtypes is not shown). Overall, these three studies show consistently high specificity and poorer sensitivity. The sensitivity rates for schizophrenia were moderate (72 to 68 percent) in two studies,[107,109] but very low in another study (25 percent).[108] Related subtypes of schizophrenia, for example schizoaffective or atypical psychosis, had lower sensitivities (varying from 0 to 55 percent across studies); this suggests that the diagnostic subtype may be a factor affecting the estimates of sensitivity. The sensitivity estimate for bipolar disorders was low (25 percent) compared to schizophrenia (68 percent) in the same study.[109]

One study[109] evaluated factors likely to affect the false positive rate, including subject (person for whom disease status was given), and attributes such as, previous hospitalization, female gender, and older age. For the informant (person who reported FH) the diagnosis of an affective disorder increased false positives. These findings suggest that difficulties in informant perceptions of psychiatric behaviors account for the inaccuracies. Another study[107] found no significant association between the type of 1DR and estimates of accuracy.

**Quality and risk of bias in studies.** All three studies were at high risk for *spectrum bias*, as the informants were predominately relatives of the probands who were recruited from specialized clinics. In all studies, it was difficult to ascertain which relatives (or informants) refused or were unable to participate in the study, suggesting high risk of *selection bias*. With the exception of one study,[109] there was also a high risk of partial verification bias as it was not clear why some informants did not receive the reference standard test. Similarly, no attempts were made to seek verification of disease status in relatives who were deceased or who could not participate in direct interview.[107-109] In two studies[107,108] it is likely that FH collection (index test) may have been included in the BED (reporting unclear) suggesting the potential for incorporation bias. Only one study stated explicitly that the diagnosticians were masked to both the status of the relative and the proband prior to undertaking the reference test.[109] However, masking to the proband status is likely to have minimal impact given that the informants were the subjects of these studies.

**Summary.** Three case series studies[107-109] evaluated relatives of subjects with predominately schizophrenia related disorders and bipolar disorder.[109] The majority of the sample of informants was 1DRs of the probands, with some inclusion of control relatives; however, results were not stratified for cases and controls. All studies used a standardized test (FH-RDC) to collect FH from informants and similarly used standardized psychiatric diagnostic tests to establish disease within the relatives. Overall, these three studies show consistently high specificity and poorer sensitivity; sensitivity varied with the diagnostic subgrouping. The single study[109] that evaluated schizophrenia and bipolar disorders showed lower sensitivities for the later diagnostic group. All three studies were at high risk for selection and verification biases likely leading to overestimation of accuracy.

## Dementia and Depression

**Population.** Four case series studies[110-113] by the same primary author evaluated geriatric subjects with dementia and depression. One of these studies[110] collected FH of 1DRs and their spouses and combined information in the context of informant pairs (eliminating true familial relationship); as such the results of this study do not reflect accuracy of true FH and the data are not presented here. The studies evaluated relatives of patients with Alzheimer's dementia, major depression, or both disorders; one study[111] included data from the probands' accuracy of medical history as well. Controls subjects and their relatives were recruited in all three studies from the general population; the proportion of these varied with each study and not all results were stratified for this group. The informants in all studies were predominately 1DRs, but small numbers of spouses, 2DRs, and other relatives were also included. The method of recruiting the relatives was not well described and information on those relatives refusing participation was not reported.

**Method of FH collection in informants/probands.** FH was collected in all studies using the FH-RDC instrument and included the use of other diagnostic screening instruments (see Table 10).

**Method of disease verification in informants/relatives.** Status of the index subjects was determined using standardized psychiatric instruments to diagnose dementia and depression.

**Study outcomes.** The studies evaluating this geriatric group showed that probands/controls and informants (predominately 1DR) are more accurate in identifying which relatives do not have dementia and depression (specificity range from 74 to 99 percent). All studies showed a difference in sensitivities for diagnosing dementia (21 to 23 percent) compared to depression (34 to 46 percent) (Table 10); sensitivity of anxiety disorders was lowest across all studies (7 or 8 percent).

One study[111] estimated accuracy of probands and controls using two different forms of interview with the reference standard being the psychiatric criteria interview; similarly, they probed relatives using these two different methods. Their findings suggest that probands/controls have higher sensitivity in reporting dementia FH (82 percent) than do their relatives (23 percent); this difference did not hold for diagnosing depression in family members (sensitivity 46 versus 42 percent). It is difficult to interpret these findings given that so little information other than age and gender was provided about probands and controls; it is not clear how the cognitive status of the probands may have influenced these results. Two studies[112,113] showed some differences in sensitivity for relatives of probands (38 percent) compared to relatives of controls (12 versus 16 percent) when diagnosing any psychiatric disorder; specificities were higher (93 to 97 percent) and did not differ markedly for this psychiatric outcome.

**Quality and risk of bias in studies.** All the studies evaluating relatives and probands with dementia and depression were at high risk of spectrum and selection bias; no information about relatives that did not participate was provided. A single study[111] was not found to be at risk for either type of verification bias (partial or differential) or masking bias. The timing of the index and reference standard tests was not clearly specified in any study. Given the limited number of studies, there is a high risk for bias leading to overestimation of accuracy within this group of studies.

**Summary.** Four case series studies[110-113] by the same primary author evaluated geriatric subjects with dementia, major depression, or both; one study presented informant pair data not consistent with FH accuracy and was not extracted.[110] All studies used a standardized test (FH-RDC) to collect FH in informants and similarly used standardized diagnostic psychiatric tests to establish disease within the relatives. All studies within this patient group would suggest that probands and informants are better at identifying relatives that do not have depression or dementia. However, these studies are at high risk of bias, and the results should be interpreted with caution.

## Other Disorders of Mental Health

**Population.** There were four additional studies that collected FH from populations with affective or anxiety and depression disorders,[114,115] personality disorders,[117] and persons with bipolar affective disorder, major depression, schizoaffective  substance abuse, and substance addictions.[116] This later study was grouped within the category of mixed disorders rather than schizophrenia, as these represented a very small proportion of subjects and the outcome of this study was any anxiety disorder. All studies were case series in design; however, three studies included healthy subjects and their relatives.[114,116,117] At least two informants were sought per index subjects in most studies.[114,116,117] In general, it was difficult to disentangle which of the informants were relatives (sharing genetic material) and which were not.

**Method of FH collection in informants/probands.** FH was collected in all studies using standardized instruments (Table 10).

**Method of disease verification in informants/relatives.** In all studies, confirmation of disease status was obtained using BED by independent clinicians.

**Study outcomes.** Table 10 shows the specific disease outcomes. We have reported those with the highest specificity or frequency of diagnoses. The presentation of results in these studies is confounded by the use of informant pairs, which may include information from or about spouses of probands or spouses of their relatives.

A single study[117] evaluated the degree of agreement (kappa) between the proband self-reporting versus their relative's direct reports; this study showed very low agreement (ranging from -0.1 to 0.21) suggesting that probands and relatives provide different perspectives on the presence of a variety of personality disorders. Another study[114] showed widely varying estimates of sensitivity (from 23.6 to 52.5 percent) depending on the type of anxiety disorder; specificity varied from 68 to 89.2 percent. Accuracy of both proband self-reporting and relative self-reporting for mental disorders showed higher sensitivities and lower specificities overall; no consistent effect of age and gender or type of relative on accuracy was found.

Similar results were shown in a study that evaluated anxiety disorders in probands with predominately affective disorders; low sensitivities (6 to 19 percent) and higher specificities (97 to 99 percent) were observed.[116] This study also showed some effects of female index subject on accuracy for some anxiety disorders, suggesting some over-reporting and lower accuracy overall. A final study[115] showed lower sensitivities and higher specificities when reporting FH of anxiety disorders; however the magnitude of the estimates for anxiety disorder sensitivities were almost triple those reported in another study.[116] The authors conclude that the FH tool used is not adequate for specialty settings, but suggest that it may be appropriate as a screen in primary care settings.[115]

**Quality and risk of bias in studies.** Webfigure 2, Appendix C details QUADAS ratings for these studies. All the studies had high risk of spectrum bias, as the subjects would not be typical within a primary care setting. As with most studies in the mental health area, it is difficult to determine which of the relatives did not have their disease status verified suggesting high risk of bias for both partial and differential verification. Masking of the clinicians who determined the BED was not an issue in these studies.

**Summary.** There were four additional studies that collected FH from populations with affective or anxiety and depression disorders,[114,115] personality disorders,[117] and persons with bipolar, major depression, schizoaffective substance abuse, and substance addictions.[116] FH was collected in a structured and standardized manner; BED was used in all studies to determine the status of the relatives. In general, probands and relatives were more accurate in reporting who did not have affective or anxiety related disorders; sensitivities for major depression and any psychiatric disorder were higher than those for anxiety disorders and levels of agreement were very low for personality disorders. As a group, these studies represent a broad group of mental health illnesses, and still show a consistent trend with respect to accuracy. However, all these studies are at high risk for spectrum and differential biases.

**Table 10. Accuracy of self-reporting of FH for relatives with mental health illnesses**

| Study | Population/ Design/ Sample Size | Index Test (FH) Reference Standard | Accuracy | |
|---|---|---|---|---|
| **Schizophrenia in Relatives (Affected and Unaffected)** | | | | |
| | | | **Sensitivity(95%) a/a+c; value[ ]** | **Specificity(95%) d/ b+d; value [ ]** |
| Fogelson[108]<br>2004<br>U.S. | Case series of probands (n=117) with adult onset schizophrenia recruited from inpatients public psychiatric hospitals and adult psychiatry outpatients. | **Index Test:**<br>Structured FH (FH_RDC) Interview of at least two informants about 1DR<br><br>**Reference Standard:**<br>BED:<br>Structured FH face to face interview (based on NIMH Relative Psychiatric History), plus DC (DIS, PSE) on 1DR, plus medical records (when available) | Schizophrenia: 2/8; [0.25]<br><br>Any psychotic disorder: 8/18; [0.44]<br><br>Schizoid personality disorder: 2/6; [0.33] | Schizophrenia: 246/247; [0.99]<br><br>Any psychotic disorder: 237/237; [1.0]<br><br>Schizoid personality disorder: 244/244; [1.0] |
| Li[107]<br>1997<br>U.S. | Case series of probands (n=48) with schizophrenia related disorders recruited from specialized schizophrenia center | **Index Test:**<br>Structured FH (FH-RDC) and DC (SRD, SRP) telephone interview (1DR)<br><br>**Reference Standard:**<br>SFS method: Face to face interviews using the SADS and SIDP-R lifetime version on 1DR. Diagnosis made by consensus | Psychotic SRD:13/18 [0.72]<br><br>Chronic Schizophrenia: 9/13; [0.69]<br><br>Psychotic SRD and SRP: 31/56; [0.55] | Psychotic SRD:18/18; [1.0]<br><br>Chronic Schizophrenia: 182/183; [0.99]<br><br>Psychotic SRD and SRP: 129/140; [0.92] |
| Roy[109]<br>1996<br>Ireland | Case series of probands (n=402) with schizophrenia, or major affective disorder recruited from rural registry Controls (n=150) recruited from county electoral registry. IDR were the focus of this study | **Index Test:**<br>Structured FH (FH-RDC) from >1 informant about 1DR<br><br>**Reference Standard:**<br>BED: Structured interview (SSPD, DSM-III-R), medical records, and FH information (two diagnosticians made final diagnosis) | Schizophrenia: [0.68]<br><br>Schizoaffective disorder: [0.23]<br><br>Bipolar disorder: [0.25]<br><br>Unipolar depression: [0.26] | Schizophrenia: [0.994]<br><br>Schizoaffective disorder: [0.997]<br><br>Bipolar disorder: [0.993]<br><br>Unipolar depression: [0.958] |

Abbreviations: 1DR=first degree relative; BED=best estimate diagnosis; CIDI=Composite International Diagnostic Interview; DAT=Dementia of the Alzheimer type; DC=diagnostic criteria; DIGS=diagnostic interview for genetic studies; DIS=diagnostic interview schedule; DSM=Diagnostic and Statistical Manual; Dx=diagnosis; EPQ=Eysenck personality questionnaire; FH=family history; FHE=family history for epidemiologic studies; FHIPD=family history interview for personality disorders; FH-RDC=family history research diagnostic criteria; GAD=general anxiety disorder; K-SADS-E=Schedule for affective disorders and Schizophrenia suitable for children and adolescents - episode; MMSE=Mini-mental state examination; n=number of subjects; NIMH=National Institute of Mental Health; OCD=Obsessive compulsive disorder; PD=Parkinson's disease; PDE=personality disorder examination; pts=patients; PSE=present state exam; SAD-LA=Schedule for affective disorders and Schizophrenia lifetime anxiety version; SADS=Schedule of affective disorders and Schizophrenia; SCID-NP=Structured clinical interview, non–patient version; SE=standard error; SIDAM=structured interview for the diagnosis of Dementia of the Alzheimer type, Multi-infarct Dementia and Dementias of other etiology; SRD=Schizophrenia related disorder; SRP=Schizophrenia related personality disorder
^ =for controls

**Table 10. Accuracy of self-reporting of FH for relatives with mental health illnesses (continued)**

| Study | Population/ Design/ Sample Size | Index Test (FH) Reference Standard | Accuracy | |
|---|---|---|---|---|
| **Depression and Dementia in Relatives (Affected and Unaffected)** | | | | |
| | | | **Sensitivity(95%) a/a+c; value[ ]** | **Specificity(95%) d/ b+d; value [ ]** |
| Heun[112] 1996 Germany | Case series of probands >60 years with depression or Alzheimer's Dementia (n=100) Controls (n=40) from general population. | **Index Test:** Interviews FH (FH-RDC) plus DC (Dementia Risk Questionnaire, Dementia Questionnaire)<br><br>**Reference Standard:** Interviews that included: CIDI, MMSE, and SIDAM) | Dementia: 5/24; [0.208] Depressive disorders: 12/30; [0.400] Anxiety disorders: 3/45; [0.067]<br><br>Any psychiatric disorders: All relatives: 31/100; [0.310] Probands relatives: 28/74; [0.378] Controls Relatives: 3/26; [0.115] | Dementia: 263/266; [0.989] Depressive disorders: 250/260; [0.962] Anxiety disorders: 243/245; [0.992]<br><br>Any psychiatric disorders: All relatives: 179/190; [0.942] Probands Relatives: 118/127 [0.929] Controls Relatives: 61/63; [0.968] |
| Heun[111] 1998 1998 [110] Germany | Case series with probands >60 years of age with DAT and geriatric depression (n=75) | **Index Test:** Interview using the FH-RDC and DC (Dementia Risk questionnaire and Dementia Questionnaire)<br><br>**Reference Standard:** Face to face interviews with DC (CIDI, SIDAM) | Diagnosis of dementia by FH information: Index subjects as informants: 23/28; [0.82]<br><br>Relatives of pts and controls: 5/22; [0.23] p<0.001(t-test; d.f.=247)<br><br>Diagnosis of depression by FH information: Index subjects as informants: 12/26; [0.46]<br><br>Relatives of pts and controls: 5/12; [0.42] | Diagnosis of dementia by FH information: Index subjects as informants: 43/47; [0.92]<br><br>Relatives of pts and controls: 167/173; [0.97]<br><br>Diagnosis of depression by FH information: Index subjects as informants: 36/49; [0.74]<br><br>Relatives of pts and controls: 177/183; [0.97] p<0.001(t-test; d.f.=247) |

Table 10. Accuracy of self-reporting of FH for relatives with mental health illnesses (continued)

| Study | Population/ Design/ Sample Size | Index Test (FH) Reference Standard | Accuracy | |
|---|---|---|---|---|
| **Mixed Mental Health Disorders in Relatives (Affected and Unaffected)** | | | | |
| | | | **Sensitivity(95%) a/a+c; value[ ]** | **Specificity(95%) d/ b+d; value [ ]** |
| Lish[115]<br>1995<br>U.S. | Informants (n=77) and relatives (n=239) selected from participants in regional survey, or from specialty university clinics for persons with anxiety and depression | **Index Test:**<br>FH Screen for Epidemiologic Studies (FHE) – interview of history and pedigree collection<br><br>**Reference Standard:**<br>BED: Direct interview using the SADS-lifetime anxiety version for adults or the K-SADS-E for children | Informants reporting on: selves; adult relatives; minors<br>Major depression/ dysthymia: [0.674]; [0.352]; [0.000]<br><br>Any affective disorder: [0.674]; [0.364]; [0.000]<br><br>Any anxiety disorder: [0.905]; [0.522]; [0.000]<br><br>Any FHE diagnosis: [0.887]; [0.622]; [0.364] | Informants reporting on: selves; adult relatives; minors<br>Major depression/ dysthymia: [0.750]; [0.849]; [0.973]<br><br>Any affective disorder: [0.750]; [0.848]; [0.973]<br><br>Any anxiety disorder: [0.686]; [0.818]; [0.918]<br><br>Any FHE diagnosis: [0.733]; [0.718]; [0.735] |
| Rougemont-Buecking[116]<br>2008<br>Switzerland | Case series evaluating informants (n=1,625) and index subject pairs (siblings, parents, an adult offspring, or spouse). Probands (n=621) included both inpatients and outpatients with psychiatric disorders. Controls (n=105) from an orthopaedic ward were also recruited | **Index Test:**<br>Structured personal interview using the FH-RDC and DC (1DR and spouses)<br><br>**Reference Standard:**<br>Interview-derived diagnoses using the DC that included the DIGS, GAD, SAD-LA, OCD. | Any anxiety disorder: [0.185]<br>Panic disorder: [0.136]<br>Social phobia: [0.119]<br>GAD: [0.111]<br>OCD: [0.059] | Any anxiety disorder: [0.948]<br>Panic disorder: [0.991]<br>Social phobia: [0.981]<br>GAD: [0.974]<br>OCD: [0.992] |

**Table 10. Accuracy of self-reporting of FH for relatives with mental health illnesses (continued)**

| Study | Population/ Design/ Sample Size | Index Test (FH) Reference Standard | Accuracy | |
|---|---|---|---|---|
| **Mixed Mental Health Disorders in Relatives (Affected and Unaffected) continued** | | | | |
| | | | **Sensitivity(95%) a/a+c; value[ ]** | **Specificity(95%) d/ b+d; value [ ]** |
| Weissman[114]<br>2000<br>U.S. | Case series with probands and informants with childhood diagnosis of depression (n=199) or anxiety (n=65)<br>Healthy controls (n=175); from these a total of 289 were included in this study | **Index Test:**<br>Brief FH screen (1DR)<br><br>**Reference Standard:**<br>BED based on independent and blind direct interviews using the SAD-LA | Proband reports on Relatives<br>Any diagnosis<br>[52.5] (SE 3.8)<br>Any depression<br>[37.9] (SE 4.6)<br>Major depression<br>[37.9] (SE 5.4)<br>Any anxiety<br>[23.6] (SE 5.4) | Proband reports on Relatives<br>Any diagnosis<br>[68.0] (SE 4.5)<br>Any depression<br>[85.1] (SE 2.8)<br>Major depression<br>[81.2] (SE 2.8)<br>Any anxiety<br>[89.2] (SE 2.2) |
| Ferro[117]<br>1997<br>U.S. | Case series with probands (n=224) with a variety of personality disorders; 1DR relatives were also interviewed. | **Index Test:**<br>FH<br>interview for personality disorders (FHIPD) (IDR)<br><br>**Reference Standard:**<br>Structured interview using the PDE, SCID-NP, and the EPQ | Concordance measured by kappa between PDE and FHIPD, by disorder:<br><br>Paranoid: 0.10<br>Schizoid: 0.19<br>Schizotypal: -0.01<br>Antisocial: 0.28<br>Borderline: 0.15<br>Histrionic: 0.04<br>Narcissistic: 0.07<br>Avoidant: 0.21<br>Dependent: 0.05<br>Obsessive-compulsive: 0.11<br>Passive-aggressive: 0.10<br>Self-defeating: 0.04 | |

## Accuracy of Self-reporting of Parkinson's Disease FH

**Population.** Two studies evaluated incident cases of Parkinson's disease[120] from a population-based sample, and cases from a Parkinson and movement disorder clinic.[119] One was a true case control study[120] and the other, which did not stratify by proband disease status,[119] is classified as a case series. Controls were recruited from communities and matched for demographic factors such as age, gender, or ethnicity.[119,120] Parkinson's disease in probands was determined using the Unified Parkinson's Disease Rating scale and the Mini Mental Health Status (MMSE) in one study[119] and established clinical diagnostic questions in the other study.[120] One study[120] did provide some information on the median duration of Parkinson's Disease, (mean 8 years with a range from 0 to 24 years) while the other did not specify the characteristics of cases.[119]

Both studies allowed for proxy informants when cases or controls were deceased or unable to complete the interview. One study[119] detailed the proxy participants and showed that only 36 percent of cases (50 percent for controls) were able to directly respond to the interview. The proxy respondents included predominately offspring (cases 58 percent, controls 49 percent) and spouses (nieces/stepchildren, relatives-in-law) (cases 33 percent, controls 22 percent).

**Method of FH collection in informants.** FH reported by the informants was captured using a standardized single question[120] or series of questions that assisted in establishing the presence of symptoms used to diagnose Parkinson's disease (Table 11).[119] Both studies included questions about the composition of families.

**Method of verification in relatives.** Both studies[119,120] evaluated Parkinson's Disease in 1DRs and screened for the presence of disease with diagnostic questions; subsequent to this, relatives that screened positive were invited for neurological examinations or, in the case of deceased relatives, medical records were reviewed. One study[119] also compared informant and relative's self-reporting (stratified by 1DR sibling, parents, or offspring); only a small subgroup of relatives was subsequently selected for verification by neurologist examination and review of medical records. Evaluation in both affected and unaffected relatives was intended in both these studies.

**Study outcomes and direction of findings.** One study,[119] evaluated the accuracy of 1DRs based on methods of diagnosis that varied from liberal (for example, a single symptom), to definite diagnosis (that included presence of several symptoms and confirmation from a specialist). This same study reported the percent agreement between the informants and relatives self-reporting as a function of the diagnostic criteria. The findings showed lower kappa values for liberal diagnosis criteria (0.41, 95 percent CI 0.23-0.59) than for definite diagnostic criteria (0.80, 95 percent CI 0.53-1.00) for any 1DR relative. A similar trend was reported for siblings of the informants. The ranges of degree of agreement were different when offspring were probed, with kappa varying from 0.69 (95 percent CI 0.48-0.89) for definite diagnosis to 0.74 (95 percent CI 0.63-0.85) for liberal criteria. Within this same study, a smaller subsample was selected and verification of disease status in the relatives showed that informants (either cases or controls) were more accurate in identifying relatives who did not have Parkinson's disease.[119] The sensitivity markedly declined as the certainty of disease improved. Although we note that this subgroup of informants and their relatives where characterized by fewer controls, the findings would suggest neither the gender of the informant nor whether they were cases or controls affected this trend. Overall, parents of the informants had better sensitivities than siblings or offspring.

A second study[120] also showed that informants were more accurate in reporting relatives who did not have disease (Table 11). This trend was not different for cases or controls; controls had the lowest sensitivity (45 percent controls versus 68 percent in cases). Nor was this trend affected by the type of interview (proxy or direct), characteristics of the relative (parents or sibling), or the life status (deceased or not). The study findings would suggest that offspring (in comparison to siblings or parents) had lower sensitivities (60 versus 100 percent) and specificities (98 versus 99 percent).

**Quality of studies.** Several areas of potential biases were noted within these two studies. Three biases, selection, verification, and masking, were judged most likely to affect study outcomes and are summarized here; all relevant QUADAS items are detailed in Webfigure 3, Appendix C.

As both studies were case control in original design, they are prone to selection bias (QUADAS item 1). In addition, one study[119] did not specify how a subsample, chosen for purposes of validation, was selected and showed unequal number of controls (only 20 controls and 76 cases). Both studies attempted to evaluate affected and unaffected relatives and as such, risk of partial verification bias was low (QUADAS item 5). Both studies used multiple methods to verify the disease status of the relatives (for example, self-reporting of relative and neurologist examination) and these were clearly described. However, both studies were prone to differential verification bias, as confirmation of deceased or incapacitated relatives' necessitated different reference standard methods (QUADAS item 6). In addition, both studies asked additional questions for those who responded positively to either the presence of Parkinson's Disease[120] or to those who had at least one Parkinson's symptom; informants and relatives who responded no or who had no positive symptoms were assumed to be disease free.

The risk of biasing due to lack of blinding during interpretation of the index or reference tests was not consistent across studies. Although a high proportion of proxy informants (63 percent were 1DR) were used in one study, these 1DRs were excluded from further data collection;[120] the second study did not clarify any exclusions due to participation as proxy informant (QUADAS item 10).[119] The data collectors were not blinded for all methods used to verify the status of the relative in either study (QUADAS item 11).

**Summary.** Two studies evaluated accuracy of reporting in persons with Parkinson's disease.[119,120] Both studies used multimodal strategies for establishing disease status within the 1DRs. One population-based study showed that informants were more accurate at identifying relatives without the disease (specificity); this study also showed that cases were more accurate than controls (68 percent versus 45 percent) in correctly identifying relatives with Parkinson's disease (sensitivity).[120] A second study[119] also showed that informants were more accurate at identifying relatives without Parkinson's disease for the diagnostic certainty categories of "definite/ probable" and "definite". Their findings suggest that the degree of certainty of diagnosing Parkinson's disease, impacts the level of agreement between informants and relatives self-reporting of disease status. This trend in accuracy was not affected by the type of interview, type of 1DR, or the life status of the relative.

Given that there is risk of bias in more than one area within so few studies, we judge that there is high risk of bias affecting the interpretation of the results, likely causing an overestimation of accuracy.

## Accuracy of Self-reporting of Diabetes FH

**Population.** Four studies evaluated the accuracy of reporting FH of diabetes on subjects with diabetes,[122] and hypertension or diabetes[121] and from cohorts with mixed diseases.[123,124] The study designs used included case series,[121] cross-sectional,[122] and longitudinal cohorts.[123,124]

**Method of FH collection in informants/probands.** Face to face interview[121] telephone interview[122] and self-administered questionnaire[123,124] were used to capture FH (Table 11).

**Method of disease verification in informants/relatives.** Disease status of the relatives was verified with clinical assessment,[121] and interview or questionnaire.[121-124]

**Study outcomes and direction of findings.** One study[124] showed differences in sensitivities for parents (87 percent) versus siblings (72 percent); specificities (98 percent) were not altered by type of 1DR. Another study[123] compared accuracy for reporting for mothers and fathers and showed slightly higher sensitivities for mothers (56 versus 65 percent); there were no differences in specificities (97 percent) (Table 11). Another study[121] showed high specificity (98 percent) with lower sensitivity (53 to 61 percent ) for both methods of verification (either interview with the sibling or with clinical data). One study[122] reported only concordance values varying by paternal grandparents (kappa=0.76) and mother (kappa=0.90).

**Quality and risk of bias in studies.** Webfigure 4, Appendix C shows the QUADAS rating for these studies. All studies included subjects with the disease, but two studies[123,124] selected subjects that were representative of primary care and therefore less prone to spectrum bias. Only one study[121] was at risk for differential verification bias as not all records or death certificates were found for all potential subjects. Masking bias was difficult to assess in most studies for the reference standard.

**Summary.** Four studies evaluated the accuracy of reporting FH of diabetes in subjects with diabetes,[122] hypertension or diabetes,[121] and from cohorts with mixed diseases.[123,124] FH was captured in a standardized manner and verification included contact with relatives, self-administered questionnaire, or clinical assessment. Overall, specificities ranged from 97 to 98 percent and sensitivities varied from 53 to 87 percent. When reporting FH of diabetes, subjects are more accurate at identifying relatives that do not have the disease. Quality of these four studies would suggest that the risk of bias was low.

## Accuracy of Self-reporting of Cardiovascular Diseases FH

**Population.** Six studies evaluated healthy students,[126] subjects with hypertension,[125] hypertension or diabetes,[121] definite or probable myocardial infarction (MI),[128] and two studies evaluated probands from longitudinal study cohorts with and without a variety of diseases including stroke, hypertension, MI and diabetes. Three studies were case series in design,[121,125,126] two were longitudinal designs,[123,124] and one case control.[128]

**Method of FH collection in informants/probands.** A variety of methods were used to capture FH (Table 11) but all were well described and standardized.

**Method of disease verification in informants/relatives.** Disease status was verified with medical records,[123,125] death records,[128] clinical assessment,[121,123] records from research database,[123] and interview or questionnaire involving relatives.[121,124,126]

**Study outcomes and direction of findings.** Hypertension: Four studies reported on hypertension within relatives; from these, two studies[123,126] showed sensitivities (0.57–0.60 percent) and specificities (0.90–0.96 percent) for reporting of disease in mothers was higher than those for fathers (sensitivity 0.44-0.74, specificity 0.88-0.89 percent). In contrast another study[126] in undergraduate volunteers showed that reporting paternal hypertension was more sensitive (74 percent) than for maternal disease (60 percent), but specificities were still high (89 to 96 percent) (Table 11). Another study[124] compared accuracy of reporting of hypertension in parents and siblings, and showed lower sensitivities (56 versus 76 percent) but higher specificities (84 versus 91) for siblings. A single study[121] showed the opposite trend with higher sensitivities (90 percent) and lower specificities (55 to 78 percent).

Heart disease: Four studies evaluated accuracy of reporting cardiovascular disease[123,124,128] MI,[123,125] and stroke.[123] One study[125] evaluating concordance with reporting MI, showed better agreement for fathers than mothers (Table 11). Another study[123] showed accuracy of reporting of disease in mothers relative to fathers (Table 11); generally specificities (91 to 98 percent) were higher than sensitivities. Sensitivities were lowest for stroke (42 to 51 percent) and highest for death by heart disease (72 to 81 percent) with variable differences in parental gender due to the disease endpoint. A similar trend with higher specificity was shown in another study[124] and no appreciable differences were observed when reporting on disease in parents or in siblings. In contrast, a case control study[128] showed higher sensitivities (83 to 95 percent) for both cardiac heart disease and all heart disease for both cases and controls; specificities ranged from 59 to 83 percent.

Other factors affecting accuracy: One study evaluated the impact of differing positive family history definitions with broad classification (for example heart attack at any age) or narrower parameters (for example, heart attack <55 years).[123] This study showed that broader definitions of FH increased true positives, and positive predictive values and sensitivities.

Three studies evaluated the impact of proband characteristics, and mixed results were shown. One study[123] showed age of the proband did not impact accuracy. Another study[124] showed that older adults (55 or older) had a greater probability of disagreement, however this varied with the four diseases evaluated. Similarly, there were some variations for the type of relative; for example older probands with cardiovascular disease had greater probability of disagreement with reporting disease in siblings and spouses than in parents. Across all diseases evaluated, no clear trend emerges.

Comparison of cases and controls within one study[128] showed higher sensitivities (85 and 90 percent) for 1DRs; 1DRs of controls tended to have the highest sensitivities (90 and 95 percent). For 2DR relatives, the pattern between sensitivities (76 to 80 percent) and specificities (65 to 80 percent) was less pronounced. In another study probands with disease reported less accurately for all relatives and for all disease types except cardiovascular disease.[124]

In two other studies the presence of a risk factor for a disease[123] or having the disease[128] did not affect estimates of accuracy relative to those that were free of the disease or risk factor.

**Quality and risk of bias in studies.** Webfigure 5, Appendix C shows the QUADAS rating for these studies. Three of the studies[123,124,128] had large population based samples representative of primary care. Relative to these studies, those with smaller sample sizes studies were prone to differential bias. It was difficult to assess the risk of masking bias for the reference standard in most studies. Criteria for subject selection and withdrawals were well described in most studies.

**Summary.** Six studies evaluated accuracy of reporting hypertension,[123-125] hypertension or diabetes,[121] definite or probable MI,[123,128] and stroke[123] in their relatives, predominately 1DR. FH was captured in a standardized manner for all studies and verification included contact with relative (interview or postal questionnaire), or death certificate or medical record. All but one study[128] reporting sensitivity and specificity generally showed lower sensitivities across hypertension and other cardiovascular outcomes.

**Table 11. Accuracy of self-reporting of FH for relatives with other diseases**

| Study | Population/ Design/ Sample Size | Index Test (FH) Reference Standard | Accuracy | |
|---|---|---|---|---|
| **Parkinson's in Relatives (Affected and Unaffected)** | | | | |
| | | | **Sensitivity(95%) a/a+c; value[ ]** | **Specificity(95%) d/ b+d; value [ ]** |
| Elbaz[120]<br>2003<br>U.S. | 1) Cases: probands (n=133) with Parkinson's disease accrued from medical records-linkage system of state county.<br>2) Controls (n=119): from local community<br>3) Proxy informants were primarily 1DR for deceased and incapacitated subjects | **Index Test:** Standardized FH (and DC) telephone interview<br><br>**Reference Standard:** Structured FH (and DC) telephone interview of 1DR followed by clinical examination (positive screen only) | Cases:<br>17/25; [0.68]<br>(0.47-0.85)<br><br>Controls:<br>05/11; [0.45]<br>(0.17-0.77) | Cases:<br>622/630; [0.99]<br>(0.98-0.99)<br><br>Controls:<br>499/500; [1.0]<br>(0.99-1.0) |
| Marder[119]<br>2003<br>U.S. | 1) Cases: probands (n=304) with non-demented PD recruited from specialized centre<br>2) Community controls (n=232)<br>3) Proxy Informants (for 1DR who could not be interviewed or were deceased) | **Index Test:**<br>Personal or telephone interview (1DR)<br>Algorithm to assign level of certainty to the diagnosis<br><br>**Reference Standard**:<br>1) Telephone interview with relatives followed by neurological examination<br>2) Medical record review (for deceased relatives) | By certainty of PD diagnosis (Dx):<br><br>Liberal Dx: 22/22; [1.0]<br><br>Conservative Dx: 21/22; [0.955]<br><br>Definite or probable Dx: 16/22; [0.727]<br><br>Definite Dx: 12/22; [0.545] | By certainty of PD diagnosis (Dx):<br><br>Liberal Dx: 98/104; [0.942]<br><br>Conservative Dx: 100/104; [0.962]<br><br>Definite or probable Dx: 103/104; [0.99]<br><br>Definite Dx: 103/104; [0.99] |

Abbreviations: 1DR=first degree relative; 2DR=second degree relative; CHD=coronary heart disease; CI=confidence interval; DC=detailed family composition; Dx=diagnosis; FH=family history; MI=myocardial infarction; n=number of subjects; PD=Parkinson's Disease; y=years

**Table 11. Accuracy of self-reporting of FH for relatives with other diseases (continued)**

| Study | Population/ Design/ Sample Size | Index Test (FH) Reference Standard | Accuracy | |
|---|---|---|---|---|
| **Diabetes in Relatives (Affected and Unaffected)** | | | | |
| | | | **Sensitivity(95%) a/a+c; value[ ]** | **Specificity(95%) d/ b+d; value [ ]** |
| Bensen[124]<br>1999<br>U.S. | Sample from the NHLBI Family Heart Study (n=3020) selected randomly and non-randomly (oversampled with CHD). Some of the probands had CHD, diabetes, hypertension, and asthma | **Index Test:**<br>Mailed questionnaire including personal history and FH (1DR and spouses)<br><br>**Reference Standard:**<br>Same questionnaire as probands | Diabetes<br><br>Proband vs Parent<br>0.87 (p=0.032)<br>$\kappa$=0.83<br>Proband vs Sibling<br>0.72 (p=0.021)<br>$\kappa$=0.72 | Diabetes<br><br>Proband vs Parent<br>0.98 (p=0.005)<br>$\kappa$=0.83<br>Proband vs Sibling<br>0.98 (p=0.002)<br>$\kappa$=0.72 |
| Murabito[123]<br>2004<br>U.S. | Participants from Framingham Offspring study (males = 791, females 837) Some probands had high blood pressure, diabetes, high cholesterol, heart attack <55 yrs, and stroke < 65 yrs. | **Index Test:**<br>Structured questionnaire including personal history and FH (1DR father and mother separately)<br><br>**Reference Standard:**<br>Research database (original Framingham cohort) that contained medical records of both parents | Diabetes<br><br>Within Fathers<br>56 (50-62)<br><br><br>Within Mothers<br>65 (59-71) | Diabetes<br><br>Within Fathers<br>97 (96-98)<br><br><br>Within Mothers<br>97 (96-98) |
| Bochud[121]<br>2004<br>Switzerland | Case series of families selected from an ongoing national register of hypertension (n=384) and diabetes (n=404) who attended primary health care centers | **Index Test:**<br>Structured questionnaire including personal history and FH (1DR)<br><br>**Reference Standard:**<br>Clinical assessment | Diabetes<br>Sibling report of history: [0.534] (0.433-0.633)<br>Clinical status: [0.614] (0.501-0.719) | Diabetes<br>Sibling report of history: [0.982] (0.971-0.989)<br>Clinical status: [0.978] (0.966-0.986) |
| Karter[122]<br>1999<br>U.S. | Subgroup of African American (and non-Hispanic) participants (n=206) from population (n=43,533) survey study; probands had diabetes and one additional relative affected | **Index Test:** Telephone interview – FH questionnaire (1DR, 2DR)<br><br>**Reference Standard:**<br>Telephone interview with relative to complete pedigree | Overall concordance [$\kappa$]:<br><br>Diabetes in paternal grandfathers: =0.76<br>Diabetes in mother: =0.90 | |

**Table 11. Accuracy of self-reporting of FH for relatives with other diseases (continued)**

| Study | Population/ Design/ Sample Size | Index Test (FH) Reference Standard | Accuracy | |
|---|---|---|---|---|
| | | | **Sensitivity(95 %) a/a+c; value[ ]** | **Specificity(95%) d/ b+d; value [ ]** |
| **Hypertension, Stroke, and Cardiovascular Disease in Relatives (Affected and Unaffected)** | | | | |
| Bochud[121] 2004 Switzerland | Case series of families selected from an ongoing national register of hypertension (n=384) and diabetes (n=404) who attended primary health care centers | **Index Test:** Structured questionnaire including personal history and FH (1DR)<br><br>**Reference Standard:** Clinical assessment | Hypertension<br><br>Sibling report of history: [0.89] (0.864-0.913)<br>Clinical Status: [0.898] (0.866-0.924) | Hypertension<br><br>Sibling report of history: [0.776] (0.732-0.816)<br>Clinical Status: [0.554] (0.514-0.595) |
| Murabito[123] 2004 U.S. | Participants from Framingham Offspring study (males=791, females 837) Some probands had high blood pressure, diabetes, high cholesterol, heart attack <55 yrs, and stroke <65 yrs | **Index Test:** Structured questionnaire including personal history and FH (1DR father and mother separately)<br><br>**Reference Standard:** Research database (original Framingham cohort) that contained medical records of both parents | Hypertension<br><br>Within Fathers [0.44] (41-47)<br><br>Within Mothers [0.57] (54-60)<br><br>High Cholesterol<br><br>Within Fathers [0.19] (17-21)<br><br>Within Mothers [0.18] (16-20) | Hypertension<br><br>Within Fathers [0.88] (86-90)<br><br>Within Mothers [0.90] (88-92)<br><br>High Cholesterol<br><br>Within Fathers [0.92] (90-94)<br><br>Within Mothers [0.95] (93-97) |
| Bensen[124] 1999 U.S. | Sample from the NHLBI Family Heart Study (n=3020) selected randomly and non-randomly (oversampled with CHD). Some of the probands had CHD, diabetes, hypertension, and asthma | **Index Test:** Mailed questionnaire including personal history and FH (1DR and spouses)<br><br>**Reference Standard:** Same questionnaire as probands | Hypertension<br><br>Proband vs Parent<br>0.76 (p=0.021)<br>$\kappa$=0.58<br>Proband vs Sibling<br>0.56 (p=0.013)<br>$\kappa$=0.47 | Hypertension<br><br>Proband vs Parent<br>0.84 (p=0.018)<br>$\kappa$=0.58<br>Proband vs Sibling<br>0.91 (p=0.006)<br>$\kappa$=0.47 |

**Table 11. Accuracy of self-reporting of FH for relatives with other diseases (continued)**

| Study | Population/ Design/ Sample Size | Index Test (FH) Reference Standard | Accuracy | |
|---|---|---|---|---|
| | | | **Sensitivity(95 %) a/a+c; value[ ]** | **Specificity(95%) d/ b+d; value [ ]** |
| **Hypertension, Stroke, and Cardiovascular Disease in Relatives (Affected and Unaffected)** | | | | |
| France[126]<br>1998<br>U.S. | Undergraduate student volunteers (age 19 to 50 y) (n=493) participated in a health survey | **Index Test:** FH questionnaire on parental blood pressure information (1DR)<br><br>**Reference Standard:** FH questionnaires on blood pressure mailed to biological parents; telephone interview | Hypertension<br><br>Maternal history: [0.604]<br>Paternal history: [0.737]<br>Both parents combined: [0.682] | Hypertension<br><br>Maternal history: [0.963]<br>Paternal history: [0.890]<br>Both parents combined: [0.929] |
| Murabito[123]<br>2004<br>U.S. | Participants from Framingham Offspring study (males = 791, females 837) Some probands had high blood pressure, diabetes, high cholesterol, heart attack <55 yrs, and stroke <65 yrs. | **Index Test:** Structured questionnaire including personal history and FH (1DR father and mother separately)<br><br>**Reference Standard:** Research database (original Framingham cohort) that contained medical records of both parents | Heart Attack <55 yr<br><br>Within Fathers 74 (64-84)<br>Within Mothers Too few events<br><br>Death by heart disease<br><br>Within Fathers 81 (77-85)<br>Within Mothers 72 (65-79)<br><br>Stroke <65 yr<br><br>Within Fathers 42 (32-52)<br>Within Mothers 51 (40-62) | Heart Attack <55 yr<br><br>Within Fathers 91 (90-92)<br>Within Mothers Too few events<br><br>Death by heart disease<br><br>Within Fathers 86 (84-88)<br>Within Mothers 91 (90-92)<br><br>Stroke <65 yr<br><br>Within Fathers 96 (95-97)<br>Within Mothers 98 (97-99) |

**Table 11. Accuracy of self-reporting of FH for relatives with other diseases (continued)**

| Study | Population/ Design/ Sample Size | Index Test (FH) Reference Standard | Accuracy | |
|---|---|---|---|---|
| | | | **Sensitivity(95 %) a/a+c; value[ ]** | **Specificity(95%) d/ b+d; value [ ]** |
| **Hypertension, Stroke, and Cardiovascular Disease in Relatives (Affected and Unaffected)** | | | | |
| Silberberg[128] 1998 Australia | Cases: patients (n=432) with CHD enrolled in population study that registered all suspected of coronary event Controls (n=248) population controls from the same region | **Index Test:** Modified FH questionnaire from literature<br><br>**Reference Standard**: Death certificates | CJD reported for 1DRs<br><br>Cases:<br>CHD: [0.85] (0.74-0.92)<br>All heart disease: [0.83] (0.75-0.90)<br>Controls:<br>CHD: [0.95] (0.84-0.99)<br>All heart disease: [0.90] (0.80-0.96)<br><br>Reported for 2DRs<br>Cases:<br>CHD: [0.80] (0.71-0.87)<br>All heart disease: [0.76] (0.69-0.82)<br>Controls:<br>CHD: [0.80] (0.72-0.86)<br>All heart disease: [0.76] (0.70-0.81) | CHD reported for 1DRs<br><br>Cases:<br>CHD: [0.59] (0.49-0.69)<br>All heart disease: [0.70] (0.58-0.80)<br>Controls:<br>CHD: [0.74] (0.65-0.82)<br>All heart disease: [0.83] (0.73-0.90)<br><br>Reported for 2DRs<br>Cases:<br>CHD: [0.68] (0.61-0.75)<br>All heart disease: [0.80] (0.72-0.86)<br>Controls:<br>CHD: [0.65] (0.60-0.71)<br>All heart disease: [0.74] (0.67-0.80) |
| Bensen[124] 1999 U.S. | Sample from the NHLBI Family Heart Study (n=3020) selected randomly and non-randomly (oversampled with CHD). Some of the probands had CHD, diabetes, hypertension, and asthma | **Index Test:** Mailed questionnaire including personal history and FH (1DR and spouses)<br><br>**Reference Standard:** Same questionnaire as probands | CHD<br>Proband vs Parent<br>0.85 (p=0.023)<br>κ=0.76<br>Proband vs Sibling<br>0.81 (p=0.015)<br>κ=0.80 | CHD<br>Proband vs Parent<br>0.93 (p=0.010)<br>κ=0.76<br>Proband vs Sibling<br>0.98 (p=0.002)<br>κ=0.80 |

**Table 11. Accuracy of self-reporting of FH for relatives with other diseases (continued)**

| Study | Population/ Design/ Sample Size | Index Test (FH) Reference Standard | Accuracy | |
|---|---|---|---|---|
| | | | **Sensitivity(95 %) a/a+c; value[ ]** | **Specificity(95%) d/ b+d; value [ ]** |
| **Hypertension, Stroke, and Cardiovascular Disease in Relatives (Affected and Unaffected)** | | | | |
| Klungel[125] 1999 The Netherlands | Probands with hypertension (n=899) subjects from a cross-sectional population-based study (n=36,000) | **Index Test:** Self reported information on cardiovascular diseases with question on FH<br><br>**Reference Standard**: Medial records | **Overall concordance [κ] (95% CI):**<br><br>MI in father: [0.07] (0.04-0.10)<br>MI in mother: [0.05] (0.02-0.07) | |

# Question 3. What is the Direct Evidence That Routinely Getting a Family History Will Improve Health Outcomes for the Patient and/or Family?

## General Approach

We selected studies that identified the impact on health related outcomes of systematic collection of FH in a typical, non-selected primary care/general population.

Appropriate health related outcomes identified from studies included patients' screening intention,[158] uptake of and adherence to screening tests and procedures,[136,158-166] preventative health behavior,[129,130,162] and prophylactic preventive treatment and surgery.[167]

Our focus was on the systematic collection of individual FH information, and communication of personal risk of one or more of the conditions of interest, in populations considered representative of primary care populations. In line with the decision to identify the highest level of evidence, only published intervention studies (RCTs, controlled trials, and uncontrolled before-after studies), where the intervention was the systematic collection of FH and this was compared to current or control clinical practice, were included for this question. Webtable 30 identifies those studies excluded, primarily because the design was not the specified intervention study design.

## Studies Reviewed

Only two studies were identified for data abstraction after full text review of 34 studies.[129,130] Both were uncontrolled before-after studies and focused on breast cancer risk assessment, including FH collection, as the target intervention.

The employer study focused on telephone based risk assessment (including systematic FH collections) in female patients at their place of work. In the study,[129] all 8,900 women employees were sent electronic mail and there was a poster campaign about the breast cancer telephone risk assessment service. Five percent (444) took up the service and 343 completed the telephone survey, with 189 agreeing to divulge their names and addresses, enabling followup. These 189 subjects were sent a followup postal questionnaire at 8 months, achieving a response rate of 72 percent (136). The baseline telephone survey and followup postal survey enquired about the outcome measure of mammography, as well as reporting clinical breast exam (CBE) and breast self exam (BSE).

In the other study[130] participants were recruited, on a walk-in basis, through six community pharmacies and two health promotion events for women aged 18 years or older. Prior to intervention, respondents completed a baseline survey (as indicated in Table 12). The risk factor data (including FH) was input into a breast cancer risk assessment tool. This tool used the Gail model for risk calculation, which requires information on the number of 1DRs with breast cancer. This was followed by a pharmacist consultation to discuss individual breast cancer risk, supplemented by written information. All women, irrespective of risk status, were encouraged by the pharmacist to follow American Cancer Society (ACS) guidelines for BSE, CBE and mammography. As with the employer study, the baseline and followup surveys enquired about adherence to mammography, (together with adherence to CBE and BSE).

## Outcomes

The study findings are summarized in Table 12. In the employer study, based on 12 risk factors (including FH) women were classified as being at low to average, moderately increased, or markedly increased breast cancer risk. All women were advised to perform CBE and regular BSE and mammography.

The original cohort of 343 women had a similar age range to the general U.S. population but a higher proportion reported recent mammography. Further, a high proportion of the 343 women initially recruited had a FH of breast cancer with 10 percent (34) having a 1DR diagnosed with breast cancer before the age of 50. Of the 136 women who completed both telephone survey and followup postal survey, 52 percent (70) reported changing breast screening behavior. There was a statistically significant improvement in the two risk reducing behaviors: Mammography screening improved from 76 to 93 percent but the matched sample was small (29) and the change in screening did not reach statistical significance (p=0.057). There was also improvement in BSE (34 to 62 percent; P<0.001) and CBE (82 to 92 percent: p<0.0137). There was no differentiation of the improvement in breast screening habits between the different risk strata.

The community pharmacy study drew participants from women attending pharmacies and heart health events, and no specific data were presented regarding representativeness. Their analyses indicate that 21 of 140 (15 percent) participants were assigned to the high risk category (≥1.7 percent risk of breast cancer in 5 years), which appears higher than would be expected for an unselected female population in this age group. In addition, the high baseline rates of mammography and CBE compared with published figures for the general population may indicate that this study has limited external validity.

There was limited improvement in adherence to mammography in all women (p=0.796) and each age group (40-49; >= 50 years old). Further, in high breast cancer risk women (with relative risk >=1.7) the adherence fell from 81 percent (17/21) to 71 percent (15/21), although this did not reach statistical significance (p<0.317). Results were also presented for other process measures: the proportion of women performing BSE increased from 31 to 56 percent, while mean BSE performed over 6 months increased from 2.79 to 4.1. Both metrics identified statistically significant changes (p<0.001). Changes in CBE were less dramatic with an increase from 86 to 91 percent (p<0.09). However, in younger women (aged 40-49) the change was slightly more significant with improvement in CBE from 81 to 99 percent (p<0.025).

**Table 12. Description of studies with evidence that routinely getting a FH will improve health outcomes for the patient and/or family**

| Author<br>Year<br>Design<br>Setting | Target Behavior | Population<br>n<br>Followup | FH Collection Component of Intervention | Who Delivered Intervention | Outcome Measures | Findings |
|---|---|---|---|---|---|---|
| Kadison[129]<br>1998<br><br>Before-after<br><br>Two large employers, Boston, MA, U.S. | Screening mammo<br><br>BSE<br><br>Clinical breast exam | Female employees invited by electronic mail<br><br>n=343 recruited<br><br>n=136 followup at 8 months | Telephone-administered survey for 12 Risk factors.<br>1. Number of 1DRs with breast cancer (inc. age of diagnosis); Relatives with bilateral breast cancer.<br>2. Other risk factors:<br>age at menarche, pregnancy history, age and weight at menopause; history of ovarian/uterine cancer; chest radiotherapy | Automated telephone based Breast Cancer Risk Assessment System: real time risk information and option of paper copy of risk assessment and advice | Compl with monthly BSE, CBE by a healthcare practitioner and mammo | Proportions comply with screening<br>**BSE**<br>Pre: 40/119<br>Post: 74/119<br>p<0.001<br>**CBE**<br>Pre: 98/119<br>Post: 110/119<br>p<0.0137<br>**Mammo**<br>Pre: 22/29<br>Post: 27/29<br>(in 6 months following assessment)<br>p<0.0572 |

Abbreviations: 1DR=first degree relative; ACS=American Cancer Society; BSE=breast self exam; CBE=clinical breast exam; Compl=Compliance; FH=family; Mammo=Mammography; n=number of subjects; y=years

**Table 12. Description of studies with evidence that routinely getting a FH will improve health outcomes for the patient and/or family (continued)**

| Author Year Design Setting | Target Behavior | Population n Followup | FH Collection Component of Intervention | Who Delivered Intervention | Outcome Measures | Findings |
|---|---|---|---|---|---|---|
| Giles[130] 2001<br><br>Before-after<br><br>Community pharmacies and health screening event, Richmond, VA, U.S. | Screening mammo<br><br>BSE<br><br>Clinical breast exam | Women ≥18y invited by a walkup basis<br><br>n=188 recruited<br><br>n=140 followup at 6 months | Interviewer-administered survey:<br>1. Number of 1DRs with breast cancer<br>2. Other risk factors:<br>age at menarche,<br>age at first live birth, number of breast biopsies<br>3. Other:<br>history of practicing BSE,<br>formal instruction in BSE,<br>confidence in performing BSE,<br>history of mammography | Community Pharmacist | Adherence with ACS guidelines for BSE, CBE, and mammo | Proportions following ACS guidelines (self-reporting) (% (95% CI*)<br>BSE<br>Pre: 42/137 (31 (23-38))<br>Post: 77/137 (56 (48-64))<br>p<0.001<br>CBE<br>Pre: 121/140 (86 (81-92))<br>Post: 128/140 (91 (87-96))<br>p<0.09<br>Mammo<br>≥50y<br>Pre: 33/44 (75 (62-88))<br>Post: 31/44 (70 (57-84))<br>p<0.48<br>40-49y<br>Pre: 18/32 (56 (39-73))<br>Post: 21/32 (66 (49-82))<br>p<0.257 |

## Quality Assessment of Studies

In the before and after employer study there appears to be selection bias, with recruited participants being younger and having higher breast cancer risk than the U.S. general population, and with higher proportions reporting recent mammography. If it is assumed that the 4 percent (343) of invited patients who participated and completed the baseline survey were more health conscious, then there is also a potential for recall bias. Over the 8 months of the study response rate fell from 77 percent of the 444 participating women completing the baseline telephone survey, to 31 percent (136) at followup. The telephone-based breast risk assessment intervention took place at the same time as a Breast Cancer Awareness Month at one employer, making it difficult to determine whether the improvement in breast screening behavior was a direct consequence of the telephone-based service.

The community pharmacy study was described as a ‘randomized, paired, pre-post study’, which is misleading. In our assessment, it was an uncontrolled pre-post study in which before-after outcomes for individual participants were analyzed as paired data. No control group was used and therefore no random allocation was possible. The potential for bias in this study is high, given that no assessment could be made of the influence of external factors, or placebo or Hawthorne effects. The study indicated an *a priori* sample size calculation; their assumptions about baseline adherence rates may have been erroneous, as they were unusually high at around 70-80 percent for CBE and mammography (also suggesting a possible ceiling effect).

## Conclusion

The evidence base for addressing Q3 is limited to two studies. This was primarily due to restrictions on study design but also, clearly defining the population as representative of primary care excluded the numerous studies in a specialist setting. In both studies, familial breast cancer risk was not considered in isolation but as part of a multifactorial risk assessment tool. It was not possible to disentangle the impact of the FH risk assessment from the other risk factors. In both studies, the interventions did not really resemble the routine, personal interaction, which might occur between a primary care professional and an individual patient. In the employer study, risk assessment was offered to all women employees of two large U.S. organizations. It might be expected that such a recruitment procedure would be representative of the general population, however, the recruited patients were more representative of a high risk population (including high familial risk). Similarly, the recruited patients were different from the general population in other ways: baseline mammography screening levels and the matched data indicated the population already had a high BSE rate. The external validity of the results was also affected by non-response to followup survey and, as acknowledged by authors, the study was underpowered for some of the outcome measures. The low participation rate (5 percent) is a weakness of the study, but it probably represents a realistic situation when an open invitation for risk assessment is offered to the general uninformed population. Both uptake of this service and followup screening would be improved if recommended by the woman’s usual physician. In the community pharmacy study, the subjects were recruited through a local screening campaign, and no data was available on the representativeness of the recruited women. Like the employer study, the proportion of women at high breast cancer risk and the baseline screening behavior was higher than expected for an unselected U.S. population. As well as concerns about the external validity of both studies, they were only able to assess process measures (mammography screening; BSE; CBE), with mammography screening being the only outcome with evidence of improved health outcomes. In both studies, there was limited improvement in mammography screening however, the sample sizes were small. Further, in the community pharmacy study subanalyses suggested those identified at high breast cancer risk adhered less to mammography, however this change was not statistically significant, with high baseline screening rates.

# Question 4. What is the Direct Evidence That Routinely Getting a Family History Will Result in Adverse Outcomes for the Patient and/or Family?

## General Approach

We reviewed published studies, which assessed negative impacts of systematically collecting FH information and providing patients with familial risk information for any medical condition. The focus was on systematic collection of individual FH information, and communication of personal risk of one or more of the conditions of interest, in populations considered representative of primary care populations.

The adverse psychological outcomes of interest identified at full text review included perceived risk,[158,160,162,166,168,169] and perceived vulnerability and worry.[131-133,158,162,168]

In line with our decision to identify the highest level of evidence, only published intervention studies (RCTs, controlled trials, and before-after studies), where intervention was the systematic collection of FH and this was compared to current or control clinical practice, were included for this question. Webtable 30 identifies those studies excluded, primarily because they were not the required intervention study design.

## Studies Reviewed

After reviewing 38 studies at full text, only three studies met all eligibility criteria.[131-133] These studies recruited patients from single British primary care offices with the number of respondents recruited varying from 100 to 666 and response rates of 19, 29, and 64 percent. Descriptions of each study are given in Table 13. A sample size calculation was provided in one of the studies.[133] The proportion of recruited patients completing survey items at all time points was 91, 89, and 76 percent respectively.[131-133]

One paper[133] described a randomized controlled trial (RCT) comparing general anxiety, health status and specific FH measures between control patients receiving a general health check and intervention patients who completed a FH risk assessment with the health check. Outcomes were measured using the self-administered short form (six items) Spielberger State-Trait Inventory (STAI) and the five item Perception of Health Questionnaire at baseline, 1 week, 2 weeks and 3 months after first visit. The 12-item FH concerns measure (adopted from self-administered Psychological Consequences Questionnaire) was also completed at 2 weeks and 3 months. The health check comprised two visits: baseline to record standard health check variables and, in the intervention arm, the self-completed FH questionnaire. Two weeks later the results of the health check and FH questionnaire were reported back to the patient, including recommended action. The 2 week outcome survey was completed immediately after this consultation.

The two other studies[131,132] were both uncontrolled before-after studies with different interventions. One[131] evaluated the psychological impact of collecting cancer FH information through a postal questionnaire distributed to all patients in the 35 to 65 age group, followed by individualized assessment of their genetic risk of CRC and breast cancer (where appropriate). General anxiety and cancer worry were assessed at baseline and 4 to 6 weeks after risk information feedback using the STAI and a multidimensional cancer worry scale, respectively.

The other study[132] assessed the impact of offering a familial risk assessment and counseling clinic to identify genetic and preconceptual issues in patients of child-bearing age (20 to 34). As well as identifying the uptake and acceptability of the clinic, general anxiety was assessed immediately before and after the clinic appointment and 12 weeks later with the short form STAI.

## Outcomes

In the first study[133] 156 patients were randomly assigned to control and intervention groups, with 100 patients attending doctor's office for routine physical examination. Seventy-six completed outcome surveys at all 4 time points. In the intervention group, mean STAI score at baseline was 36.7, rising to 39.4 at 1 week and falling back to 37.1 at 2 weeks; in the control group STAI mean score was similar at baseline but fell at 1 and 2 weeks (to 32.5 and 33.0 respectively). This corresponded to a significantly higher anxiety score for the intervention group at 1 and 2 weeks post clinic visit (p=0.014). The mean scores for the intervention and control groups at 3 months were not significantly different (34.2 and 34.8 respectively). When comparing perception of health scores at different time points, the only significant change between the groups was that a larger proportion of the FH intervention group gave a more pessimistic response between baseline and 1 week post-visit to questions about risk to future health, compared to the control group (26 vs. 7 percent; p=0.025). There was no significant difference between the two groups regarding FH concerns at 2 weeks and 3 months.

The second study[131] analyzed participants in two groups. Lower risk' (those at no more than slightly elevated risk) participants, for whom no followup was necessary, were given feedback by letter only. The outcomes for this group are summarized in Table 14. The STAI at baseline and 4-6 week followup were similar (35.8 and 35.1 respectively), corresponding to no statistically significant difference observed in anxiety. Similarly, most other cancer worry measures identified no statistically significant change following the intervention, with the exception of a small reduction in participants' perception of their own risk (p<0.01).

Of the remaining participants, most were interviewed to clarify details of their FH, which led to further designation into 'higher risk' and 'false positive' groups, the latter comprising patients deemed not actually to be at high risk after further enquiry. For both 'higher risk' and 'false positive' groups, no difference between baseline and followup responses to general anxiety and cancer worries scales was observed. However, both of these groups showed higher baseline cancer risk perception scores compared to the lower risk group (p<0.001 for 'higher risk' group and p=0.003 for 'false positive' group).

In the third study[132] 124 patients attended the primary care office-based genetic clinic, with 121 completing the pre- and post-clinic STAI and 91 returning the 12$^{th}$ week. Eighty-nine patients completed the survey at all 3 time points. Fifty-four percent (67/124) of patients attended clinic due to concerns about possible familial illness, and 35 percent (43) attended for pregnancy planning. In the clinic, a three generation FH was recorded using a standard proforma and risk was assessed by primary care providers (family doctor and health visitor) against regional guidelines, literature, and standard texts. Forty percent (50) of patients had a FH with a genetic component, however only 7 percent (9) required specialist input. Based on all the completed surveys at each time point, the mean STAI score at baseline was 34.8, falling significantly to 30.1 (p<0.001) right after the consultation, returning to initial levels after 12 weeks (33.0). As commented by the authors, a significant proportion of the genetic counseling involved reassuring patients that they were at "low" familial risk. In the study publication, there was no differentiation of anxiety scores between the different risk strata.

**Table 13. Description of studies with evidence that routinely getting a FH will result in adverse outcomes for the patient and/or family**

| Author Year Setting Design | Disease | Population n | Time Points for Analysis | Duration / Nature of Intervention | Who delivered Intervention | Method of FH Collection | Other Intervention |
|---|---|---|---|---|---|---|---|
| Leggatt[131]<br>2000<br>U.K.<br><br>Before - After ucon study | Colorectal/ colon/rectal<br>Breast cancer | Unselected patients aged 35 to 65 years registered at one general practice<br><br>Recruited= 666 (29% response)<br>Completed =604 | Baseline<br>1-1.5 months | N/A<br><br>Postal FH question | Lower risk group: letter from family doctor<br><br>Potential increased risk groups: family doctor and/or Oncologist/ geneticist | Postal cancer FH question | Participants provided with risk information |
| Qureshi[133]<br>2001<br>U.K.<br><br>RCT | Generic covered all conditions identified by respondent | Random selection of patients aged 18-60 registered at one general practice for at least 2 years, and who had not received a health check in that time<br><br>Recruited= 100 (64% response)<br>Completed =76 | Baseline<br><br>1 week<br><br>2 weeks<br><br>3 months | Two consults, two weeks apart (completing FH question and health check in 1st consult) | FH screening question intervention only: self-admin, results reviewed by a clinical geneticist<br><br>Health Check (control + intervention): Researcher results reviewed by a GP | In-office self-admin FH question with prompt sheet of relevant conditions | |

Abbreviations: FH=family history; FHQ=family history questionnaire; GP=general practitioner; Immed=Immediate; N/A=not applicable; question=questionnaire; RCT=randomized controlled trial; ucon study=uncontrolled study

**Table 13. Description of studies with evidence that routinely getting a FH will result in adverse outcomes for the patient and/or family (continued)**

| Author Year Setting Design | Disease | Population | Time Points for Analysis | Duration / Nature of Intervention | Who delivered Intervention | Method of FH Collection | Other Intervention |
|---|---|---|---|---|---|---|---|
| Rose[132] 1999 U.K.<br><br>Before and After uncon study | Generic covered all conditions identified by respondent | Unselected patients aged 20-34 years registered at one general practice, excluding pregnant women<br><br>Recruited= 124 (18.9% response) Completed =91 | Baseline<br><br>Immed post-consult<br><br>12 weeks | 30 minute genetic consult (taking a 3 generation FH and completion of question) | GP and health visitor. the latter had previously worked as a clinical nurse specialist in genetics | Recorded on a pro forma during clinic appt | Participants provided with lessons on pregnancy planning, lifestyle factors, and general information regarding familial risk |

**Table 14. Findings from studies with evidence that routinely getting a FH will result in adverse outcomes for the patient and/or family**

| Author | Measure(s) | Description of Subjects Analyzed | Subjects | Main Findings | Other Findings |
|---|---|---|---|---|---|
| Leggett[131] 2000 U.K. | Anxiety<br><br>Cancer worry scales<br>- perceived own risk of developing cancer<br>-freq. of cancer related thoughts<br>- effect performance daily tasks<br>- effect on mood | "Lower risk" Group | n=568 | No significant change between baseline and followup for both measures | Also no significant change between baseline and followup in other risk groups |
| Qureshi[133] 2001 U.K. | Spielberg State-Trait Anxiety Inventory (STAI) – short form<br><br>Perception of Health<br><br>Psychological Consequences Questionnaire (FH Concern) | All enrolled patients aged 18-60 years in single primary care office completing questionnaires at all 4 time points. | Complete data at all 4 time points<br><br>Control: n=42<br><br>Intervention: n=34 | State Anxiety score (at weeks 1 and 2) higher in the intervention group than control (p=0.014), but did not persist (no significant difference at 3 months) | Perception of health measure: significant result at week 1, the intervention group having a more pessimistic response to the question eliciting pts concerns about future health (p=0.025)<br>FH concern measure: no significant difference at 2 weeks or 3 months |
| Rose[132] 1999 U.K. | Spielberg State-Trait Anxiety Inventory (STAI) – short form | All enrolled patients aged 20-34 years in single primary care office | Complete baseline STAI: 121<br>+12 weeks: n=91 | State Anxiety score fell immediately after the consultation (p<0.001) and rose to pre-clinic levels at 12 weeks | Main lessons learnt by pts during consultation related to pregnancy planning and life-style advice, as well as genetics related topics |

Abbreviations: FH=family history; Freq=frequency; n=number of subjects; p=probability; pts=patients

## Quality Assessment of Studies

Two of the eligible studies were uncontrolled before-after studies,[131,132] while the third study was a RCT.[133] All took place in single primary care offices.

A standardized quality assessment checklist was employed on the study that used a randomized trial design.[133] The modified Jadad scores were 5 out of 8 for this study. Although the randomization procedure was described in the paper, the allocation procedure was not clear. Similarly, criteria for participant inclusion were given, but no exclusion criteria were described. A sample size calculation was reported for the primary outcome measure. Identifying adverse events of the intervention was not scored but the objective of the study was to identify such factors. Further, the study did not report measures to achieve blinding.

No formal quality assessment checklists were employed on the two uncontrolled before-after studies.[131,132] Neither study compared respondents and non-respondents to the familial risk assessment invitation. However, both did attempt to elicit profiles of non-responders in other ways. In one study, respondents were compared to the overall practice population, identifying that more older subjects took up the offer.[131] The other study noted 81 percent of invited subjects did not respond, and a fifth (n=144) of these non-responders were sent a postal survey. One hundred and ten subjects replied with nearly 50 percent stating their reason for non-attendance was inconvenient time or lack of time, while another 40 percent were not motivated or considered assessment irrelevant to them. Nether study reported sample size calculations.

## Conclusion

The evidence base for addressing Q4 is limited to three studies, a randomized controlled trial[133] and two uncontrolled before after studies.[131,132] These suggest that structured FH collection and feedback of familial risk information had no deleterious psychological effects in the medium term (6-12 weeks) on patients who took up the FH intervention. Leggatt further identified the relationship between breast cancer familial risk status and psychological impact. There was no deleterious psychological effect in any of the risk groups, while in women who were at or just above average risk, the FH risk assessment may have led to appropriate reductions in perceived risk.

The most common psychological measure in all three studies was the short form of the STAI. However, the clinical significance of the score remains unclear. The baseline scores in the FH intervention arms did vary between the three studies from 34.8[132] to 36.7.[133] The three studies showed different short term impacts of intervention, in one study,[133] there was a short tem rise in anxiety score while in the second,[132] the score fell and in the third[131] there was no change. Other than Leggatt,[131] the studies did not differentiate the anxiety scores between lower and higher risk groups. In this study, there was no change in the anxiety and cancer worry in both risk groups at 4 and 6 weeks after cancer FH assessment. However, the finding of higher baseline levels of these psychological measures in the groups who went on to have further assessment is difficult to explain and may reflect the effects of having a positive FH in itself, rather than having FH information collected and assessed. Of the three studies only Leggatt et al.,[131] used a validated context-specific measure (cancer worry scale). In another study a context-specific measure was adopted from a validated instrument (PCQ) but it did not demonstrate any significant impact of the FH collection intervention.[133]

# Question 5. What are the Factors That Encourage or Discourage Obtaining and Using a Family History?

## General Approach

Initially there was limited clarity on the breadth and depth of this research question. After extensive review of the diverse literature in this area and a series of discussions with the technical expert panel, we focused the reviewed publications on studies that clearly identified the association between factors that facilitate or inhibit the process of collecting, discussing, and/or using FH. Within the group of studies collecting FH, studies evaluating the association between self reported FH and other factors were separately collated. The process of FH collection, discussion and use can be influenced by attributes of the patient, the health care professional, and the setting in which the FH is identified. In line with the overall scope and purpose of the review, the patients were from populations representative of a primary care setting, while the practitioners would have been primary care providers (as discussed in Chapter 2).

## Studies Reviewed

Of the six studies identified, four were undertaken in primary care offices[134-137] and in the another two studies the population was derived from patients being screened in the general population.[138,139]

Four studies were cross-sectional.[135,136,138,139] The remaining two studies were a direct observational study[137] and a prospective cohort study with a baseline cross-sectional survey.[134] Factors associated with FH collection or discussion were the primary outcomes of interest of three studies.[136,137,139] This relevant data from the other three studies were retrieved from subanalyses presented in these publications.[134,135,138] Two studies only recruited female patients.[136,138]

The cross-sectional surveys recruited between 500 and 149,332 subjects. The direct observational study followed 4454 patient visits and the cohort study surveyed 163 patients.

In Murff et al.,[136] patients with at least one visit to the primary care provider over the previous year were randomly selected from 11 primary care practice sites in the Greater Boston area. As well as medical record review, the consenting patients completed a telephone survey. This survey identified sociodemographic factors and satisfaction with health care. Only 2,858 women were included in the sampling frame for the study. The average age of the women was 47.6. The response rate was 62 percent (1,803) with responders more likely to have had a mammogram performed in the last 5 years. Fletcher et al.,[135] also randomly mailed questionnaires to 6,807 of 31,959 patients aged 35 to 55 years old in a single large multispecialty group practice about FH of colorectal cancer and screening experience. Twenty-eight per cent (1,854) of this sample completed the postal survey, with 19 percent (355) of these respondents reporting a FH of colorectal cancer.

In Karliner et al.,[138] the sample was derived from 14,490 women in the San Francisco area who had had a mammographic screening in the previous 2 years and completed a baseline questionnaire at the time of screening. The questionnaire identified women's familial risk using the Gail model. In the sampling frame, women were randomly sampled according to risk status (although all higher risk minority women were included). Of 2,715 women in the sampling frame, 63 percent (1,700) completed a followup telephone survey. The telephone survey collected information on sociodemographic data, as well as, information on breast cancer risk and screening behavior. Pinsky et al.,[139] also sampled from a large cross-sectional survey of the general population aged 55 to 74 years. The publication reports on the 149,332 subjects who completed the FH section of the baseline survey in a national multi-cancer screening trial. The expected prevalence rates of various cancer types were compared to observed levels for different relatives and gender of respondents. Further, the relationship with various socio-demographic factors was also identified.

In Acheson et al.,[137] researchers directly observed consultations of 138 community family physicians over 2 separate days (4 months apart), with a standardized consultation encounter tool (modified Davis Observation Code). The study was restricted to family physicians practicing in North East Ohio, although the profile of the physicians was representative of physicians throughout the U.S. The observation was supplemented by a review of medical records, physician surveys, and field notes. Full details of the FH information was only extracted from medical records in the latter half of the study.

The study by Volk et al.,[134] also recruited from a single primary care office in Boston. Among 1,098 subjects contacted by mail, 17 percent (189) consented to participate in the study, with 15 percent (163) completing a postal survey that incorporated a structured format to obtain FH information. As well as the survey, consenting subjects agreed to have their electronic medical records scrutinized for FH information and compared to the information collected on the survey.

## Outcomes

In the six studies, the FH outcome was predominantly a dichotomized variable. The outcomes of interest were: FH documented in medical records;[134,136] FH discussed by doctor, either confirmed by direct observation[137] or patient survey;[135,138] and self reported FH.[139,170] The study findings are summarized in Table 15.

**FH recorded in medical records.** Murff et al.,[136] noted a comprehensive cancer FH risk assessment was more likely to be documented in white patients' medical records (84 percent versus 67 percent in non whites), and in patients where English was the first language (94 percent English versus 85 percent), both with p<0.001. When dichotomized by age (less than 40 or 40 years and older) the ethnic difference remained. In the under 40 group, FH of breast cancer interviews occurred in 30 percent of white women, compared to 15 percent of African Americans and 11 percent of Hispanics (p<0.001). No information was presented on provider factors (practitioner and setting).

Volk et al.,[136] identified a different factor in FH collection, the type of conditions identified in electronic health records (EHR) in U.S. primary care practice. Forty-seven percent of EHRs had a FH recorded (93/189). Compared to the postal FH survey, the EHR collected FH of diabetes, breast cancer, CHD, but 90 percent of positive family histories of glaucoma, osteoporosis, and colon cancer were better identified by systematic FH surveys. Compared to EHRs, the survey also identified further FH details on glaucoma, osteoporosis, and diabetes leading to alteration in their familial risk status (94.7, 95.0, and 73.8 percent of positive family histories, respectively, changed risk status).

**FH discussed in consultation.** Acheson[137] identified the FH information discussed in consultations. FH was discussed in 24 percent of consultations. This study differentiated between factors that influenced discussion of FH between newly registered patients at the doctors' office and established patients. Recently appointed physicians (as indicated by being in practice for fewer years) were more likely to discuss FH with established patients (p=0.02). In addition, 25 percent of residency trained practitioners discussed FH with established patients compared to 70 percent of non-residency trained practitioners (p=0.06). There was no association with practitioners who offered prenatal care.

In the case of patient factors: the age, gender, health and marital status were explored for established and new patients. The only significant association was that older established patients were less likely to discuss FH than younger established patients (age 15 to 44, 24.8 percent; 65 years or over, 17.6 percent; p<0.001) Further, patients with Medicare insurance were less likely to be asked about FH.

Family history was discussed in 61 percent of physical examinations with new patients, compared to 44 percent of such checks in established patients. During these checks, female patients were more likely to discuss FH. When FH was discussed this seemed to extend the consultation time and be associated with other problem being addressed in the consultation in both new and established patients.

Kartliner et al.,[138] surveyed women who had attended mammography screening. The study explored multiple factors associated with clinicians discussing cancer FH. Jewish ancestry, education, language of interview, insurance status, previous cancer investigations, and worry or risk perception were not associated with clinicians discussing cancer FH. However there was an association with younger women (p<0.0001), women who had had a routine physical examination in the last year (p=0.0001), and women concerned about breast cancer (p=0.006). In Fletcher et al.,[135] women younger than 50 were less likely to be asked about their FH of colon or rectal cancer with 39.1 percent asked [95 percent CI: 36.1-42.0%] compared to 72.2 percent asked in those 50 years and older [95 percent CI: 70.0-76.4%].

**Factors associated with self-reporting FH.** Pinsky et al.,[139] noted in a cross-sectional survey that male respondents reported less FH of cancer than female respondents. The most common family histories reported were breast (11.8 percent), lung (10.1 percent), colorectal (9.4 percent), and prostate cancer (7.3 percent), with lymphoma (0.6 percent), vaginal (0.1 percent) and testicular cancer (0.4 percent) being less commonly reported. Further, it appeared liver and bone cancers were over-reported while lymphoma, melanoma, bladder cancer, and testicular cancer were under-reported. Minority groups (Black, Asian, Hispanic) reported lower rates of FH compared to the non-Hispanic white group (p<0.01). Respondents with less than 8 years education also had lower rates but this group only represented about 1 percent of the surveyed population.

**Table. 15 Factors associated with improved FH collection and utilization**

| | Factors Associated With Improved FH Collection in Medical Records | Factors Associated With Medical Practitioner Discussing FH | Factors Associated With Improved Self-reporting of FH |
|---|---|---|---|
| ***Patient factors:*** | White (compared to other ethnic groups)[136]<br><br>Certain medical conditions (diabetes, breast cancer, coronary artery disease)[134] | Not on state health insurance[137]<br><br>Patients who worry about breast cancer[138]<br><br>Age: mixed picture, in one study more likely to discuss in younger age group for all conditions,[137] while in another study in older age group for colorectal cancer[135] | Women[139]<br><br>White non-Hispanics (compared to other ethnic groups)[139]<br><br>Higher education status[139]<br><br>Certain common cancers: breast, lung, and colorectal[139] |
| ***Practitioner factors:*** | | Practitioners in same practice for fewer years[137]<br><br>Resident-trained[137] | |
| ***Setting:*** | | Routine physical examination in established patients,[137] particularly women[137,138] | |

Abbreviations: FH=family history

## Quality Assessment of Studies

In three of the identified studies the characteristics of respondents and non-respondents were identified with the respondents being older than non-respondents.[134-136] One study examined other sociodemographic factors, noting respondents were more likely to be Caucasian,[135] while in another survey, respondents had slightly more FH recorded in their medical charts and were more likely to have performed BSE and mammography screening.[136] Of the five studies that used cross-sectional surveys, the response rate was 80 percent or over in three studies, two of which were based in primary care,[134,136] and the other was a population-based survey.[139] Of the remaining two studies, a telephone survey had a 63 percent response rate[138] and a primary care-based postal survey achieved a 27 percent response.[135] In most studies the nature of the FH discussed or reported was not clearly identified, often just reported as dichotomous variables. Only four of the six studies actually took place in primary care offices, and three of these were based in practices within the greater Boston area.[135,136,138] Representativeness of these surveys is also limited by response bias and recall bias, for example Murff et al.,[136] recruited older women and the responders were more likely to have had mammography screening. Collectively, these issues limit the generalizability of the study findings; hence, caution is urged in applying this information to clinical situations in primary care.

## Conclusion

The evidence base for addressing Q5 is heterogeneous and limited to six studies exploring the association between various factors and FH reporting, documentation and discussion. There was a paucity of evidence to help “operationalize” family history collection and use in primary care, for instance, procedures and systems to improve collection. However, there are certain patterns that maybe informative. Routine physical examinations offer an appropriate screening “turnstile” to collect FH. Further, women appeared better informants than men did and recently appointed physicians were more enthusiastic about discussing FH. There are also disparities in FH collection and reporting in underserved groups, specifically non-white ethic groups,[136,139] those with lower educational status,[139] and those on state health insurance.[137] This is probably due to a combination of factors including poor recall by patients and difference in the nature of practitioners’ consultations with different groups. Two studies also briefly considered other pragmatic resource issues: the potential of incorporating the family history in electronic health records[136] and extent to which discussing FH extended consultation time. The opportunity cost of systematically collecting family histories still needs to be explored.

# Chapter 4. Discussion

## Overview

This review was designed to inform a broad range of questions (Q) which ultimately address the clinical value of using family history (FH) in chronic disease risk assessment and prevention in primary care.

The evidence derived from questions (Q) 1, 2, and 5 was designed to inform primary care providers of the most efficient elements of FH information, and approaches to collection, which might be best suited to routine application, given the constraints that are faced such as limited time availability. This draws together the most informative components of an individual's FH for future or current disease risk, the factors, which influence accuracy of reporting, and the factors, which stand in the way of, or promote, the actual collection of FH data. In addition, if primary care providers are to be persuaded that systematically collecting and interpreting FH is a beneficial activity, they need to be provided with the most robust evidence of the benefits of this intervention in improving patients' health outcomes, and any significant adverse effects. The evidence for these issues was derived from questions 3 and 4.

## Q1. What are the Key Elements of a Family History in a Primary Care Setting for the Purposes of Risk Assessment for Common Diseases?

As discussed in Chapter 1, for FH to be useful in chronic disease risk assessment, it is not enough for patients to report, and professionals elicit, FH information accurately: it is necessary to clarify which elements of FH are most useful for disease prediction.[150] In specialist genetics settings, the gold standard, comprehensive, three generation pedigree forms the foundation for identifying specific potential disease inheritance patterns, such as autosomal recessive or X-linked dominant.[171,172] However, in a primary care context, the goal is usually to identify an individual's overall level of familial risk, without necessarily seeking out specific patterns, though this is not precluded. Since, by definition, complex disorders are not likely to display an easily discernable, high penetrance pattern of inheritance, it is reasonable to take a simpler approach in which FH elements (e.g., type of relative, closeness of relationship, gender, age of onset, etc.) are combined and their predictive validity examined empirically. In principle, the FH definition which combines useful predictive power with least effort to obtain is likely to be the one best suited for routine application. Some insight into the 'information value' of different FH definitions might be useful in developing evidence-based, primary care-oriented FH tools,[151] which could then be evaluated against appropriate control interventions for the effect of their use on health outcomes.

A large number of studies were identified that provided data relevant to this question, although they were mostly not designed for the analyses performed here. Only a very few reports were designed to examine different definitions of 'positive FH', and almost all assessed FH as a possible risk factor for disease in classical epidemiological approaches. Many of the cross-

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Appendixes and Evidence Tables for this report are provided electronically at http://www.ahrq.gov/downloads/pub/evidence/pdf/famhistimprov/famhimp.pdf.

sectional studies were potentially subject to information bias, in relation to both exposures and outcomes: it is possible that some participants knew their FH more accurately because they were affected by the condition in question, and vice versa. In almost all studies, the strength of association between FH and disease frequency was assessed at a population level, using relative risks, odds ratios, and related metrics. However, assessing the utility of FH for risk assessment in individual patients requires examination of discriminatory accuracy metrics: sensitivity, specificity, and predictive values. The question is not so much 'how many times more likely" are people with a given FH to develop a disorder compared to those who do not have the FH. Rather, the question is more of the nature, 'What is the chance that, given this FH, this person will go on to develop this disease in the time period of interest?" Even for the most common complex disorders, most people 'at risk' do not actually go on to develop the disease, therefore even large relative risks may actually be associated with very small absolute risks over a 5 or 10 year period.

Even though most studies included did not report predictive metrics, or were not even designed to address Q1, it was still possible to extract sufficient data to begin to explore the issue of interest. We examined FH definitions in longitudinal and cross-sectional studies, appreciating that they provided different insights: the former are designed to address prediction of future disease, and the latter reflect screening for current disease. Although some analyses covered a wide range of FH definitions, we observed that most studies defined FH largely in terms of first degree relatives (1DRs), and only a few drew in information on a broader set of relatives. Very few reports provided a rationale for the specific FH definition, and it was not possible to assess the value of criteria such as age of onset or lineage in any meaningful way.

A pragmatic approach was used in approaching individual FH definitions. For example, rather than separating out mutually exclusive FH categories (e.g., 'affected brother only' versus 'affected brother and sister') for analysis, we combined categories and compared presence of that FH characteristic versus absence of that FH characteristic (e.g., 'affected brother, irrespective of status of other relatives' versus 'no affected brother, irrespective of status of other relatives'). This permitted the assessment of that single FH characteristic ('affected brother' or 'unaffected brother') as if it were the only question that a health professional asked the patient, thus allowing some sense of its predictive ability as a simple screening or triage question in and of itself.

Overall, the discriminatory accuracy was generally modest, for most FH definitions used in isolation. This is not surprising – as noted previously, complex disorders do not have a strong or highly penetrant genetic component, and therefore it would be illogical to expect a very high predictive value for FH, however defined. Also not surprisingly, the most sensitive FH definitions were usually those, which were very loose, (e.g., a minimum of one affected relative, whether or not further specified). From a theoretical perspective, it would be expected that a simple, loose definition such as this would have highest chance of picking up people genuinely at high risk, but would also identify many false positives. The more elements required to define 'positive' FH, the less sensitive and more specific the definition, again to be expected.

Another factor, which needs to be considered, is whether the way in which FH was captured in these studies was reflective of routine clinical practice. For some studies, for example, the multigenerational cohort studies, it is clear that FH ascertainment was in no way typical of primary care practice. However, many of the definitions were simple and probably reflect the types of answers that would be received even if elicited verbally as part of an office consultation. The factors influencing accuracy of reporting were examined as part of Q2.

As part of this review, we developed a notional categorization system (Table 2) to reflect the effort required to obtain the minimum information implied by any given FH definition. We wished to take account of the time constraints under which many primary care practitioners work, and the possible limitations of immediate knowledge, which patients might bring to a consultation. The use of electronic medical records (EMR) might permit the easy assembly of more extensive FH and render the distinctions in the table irrelevant. Also, decision-support systems based on EMRs would facilitate the implementation of FH scoring systems, which represent the next 'step up' in FH assessment, taking into account information on factors such as family size, time at risk, etc.[173] In contrast, a practitioner who may only have time to use a few 'screening questions' might be well served by knowing the absolute minimum level of information that needs to be elicited for a given level of predictive accuracy. While the category A-E framework is not intended to be definitive, we were able to provide some evidence that this type of approach might be useful. For example, for prevalence studies of diabetes, the AUC value for category D showed no improvement in discriminatory accuracy over categories B and C. If these observations are valid, it would indicate that simple, targeted questions about first degree relatives would be as informative as more extensive enquiry for identifying individuals at risk of undiagnosed diabetes. While these analyses can only be regarded as preliminary, they suggest an approach for future research.

Having gained some insight into the performance of specific FH definitions in predictive chronic diseases, the appropriate question is to ask next, is how they perform when considered with information on other risk factors. Depending on the disease in question, a clinician is unlikely to disregard other risk factors and base a risk assessment on FH alone. However, if a positive FH significantly improved the predictive ability of other established factors, then it might make the difference in the choice of preventive interventions, and/or in promoting risk reducing health behaviors. It was beyond the scope of this review to model the incremental predictive value of particular FH definitions combined with other risk factor variables, but this would be a logical extension of this enquiry.

It is impossible to draw an overarching conclusion from the analyses conducted for Q1, and it was not possible to assess the performance of FHs across a range of disorders. The tables detailing predictive value alongside disease prevalence were constructed to permit comparison with different clinical contexts, and to give a sense of the highest likely achievable predictive utility, within the constraints of the data. In considering these data, it is necessary to clarify the underlying prevalence of the condition in the population of interest, whether the purpose is stratification of future disease risk (and the time frame) or triaging for screening for current disease, and the way in which FH information may or may not be combined with other risk factor information for a holistic assessment of an individual patient.

## Q2. What is the Accuracy of the Family History, and Under What Conditions Does the Accuracy Vary?

In order for FH to be of value in clinical decision making, patients must possess, and primary care practitioners be able to ascertain, accurate family health information. Assessing accuracy requires a clear idea of an appropriate gold standard—what patients 'should' know, and what clinicians 'should' be able to obtain. In simple terms, an 'accurate' FH could be considered to be one which is sensitive (disease in relatives is correctly identified) and specific (lack of disease in relatives is correctly identified).

In order to fully explore the question of accuracy of reporting we did not restrict the population to those within a primary care setting as we correctly anticipated that there would be few accuracy studies within this population. In this regard, the majority of studies evaluated subjects with the disease or first degree relatives (1DRs) who are by definition at high risk. Overall, the applicability of these findings from specialized clinical settings to primary care settings may be limited; the high risk of spectrum bias would tend to cause overestimation in accuracy. Although, the attributes of the probands (or informants) were described, those of the relatives (for example, gender or even the relation to the proband) were not, particularly in studies within the mental health area.

Overall, the few rigorous studies, which fully evaluated accuracy consistently, suggested that informants are more accurate in identifying which relatives are free of the disease (specificity) than in identifying relatives who have been affected by cancer (sensitivity). This trend was generally consistent across all disease groups, except heart disease; there was some variation in the rates for sensitivity. For example, in the mental health area, rates of sensitivity were consistently very low (>40) but in cancer FH they were higher (~ 80 percent). Similarly, in those studies that reported sensitivity for both cases and controls, there is variation between the different disease areas; for example, sensitivities in relatives of controls probed for Parkinson's disease were much lower than those observed in assessments of controls in breast cancer studies

Our findings also suggest that FH reporting may be more accurate for 1DRs than second degree or beyond, although few studies examined accuracy in the latter. Similarly, attributes of the informants and relatives have not been consistently evaluated; in those limited studies that did examine this factor, there was no clear pattern in the attributes of the informant or those of the relative that influence accuracy results. The methods used to collect FH and the disease category is likely to account for this inconsistency. We also have little insight into which informant characteristics are associated with more accurate reporting; future evaluations could consider formally examining factors such as sex, age, and cultural background. It is possible that informants affected by cancer may seek out more complete information on their FH after their initial diagnosis, but we were unable to confirm this within this literature.

The accuracy of reporting by probands, members of the population or relatives cannot be completely separated from the performance of tools to gather such data. We observed great variation in methods used to collect FH that ranged from simple dichotomous questions, to more complex standardized tools that had established psychometric properties. In the area of mental health, FH is an important component in establishing the presence of disease, and as such was included in both the index test and the reference standard; that is the FH of the relative (not just medical history) formed part of the case definition of what was also collected in order to establish the presence of the disorder (for example in bipolar disorders). It was challenging to disentangle medical history and FH in some of the studies within mental health; similarly, in this area FH included a broader conceptualization which included relatives such as "spouses". Future evaluation within mental health studies would be strengthened by clarifying these differences.

Most studies evaluating accuracy used a multimodal approach to establishing the presence of disease within the relatives. In part, this was necessitated by the status of the relatives; for example, clinical examination could only be undertaken in relatives that are alive. As such, there will always be a high risk of bias for differential verification irrespective of the different disease categories evaluated. It is impossible to comment on which gold standard is 'best' for judging accuracy, but we recognize that multiple strategies are necessary to capture the status of all relatives.

Future efforts to improve accuracy of reporting would be improved by explicit consideration of whether sensitivity or specificity is the primary goal, which is dependent on the clinical context and purpose of a FH oriented strategy. For example, maximizing sensitivity prioritizes the goal of missing as few 'at risk' family histories as possible, and is consistent with a policy in which the potential benefits from finding potential cases carry more weight than the potential costs and harms of investigating individuals or families with false positive histories. In contrast, maximizing specificity prioritizes avoiding the potential costs and harms of false positives, and is consistent with a policy that directs limited resources towards only identifying individuals or families with the greatest likelihood of being at significant disease risk, at the cost of missing some true positives.

In general, we might expect that the accuracy of FH reporting will improve in future, as current initiatives lead to more awareness on the part of the general public. It is not clear whether this will be countered by the effect that increased population mobility has on people's abilities to keep up to date with the health of more distant family members.

## Q3. What is the Direct Evidence That Routinely Getting a Family History Will Improve Health Outcomes for the Patient and/or Family?

## AND

## Q4. What is the Direct Evidence That Routinely Getting a Family History Will Result in Adverse Outcomes for the Patient and/or Family?

These two research questions were identified as being complementary, and were therefore approached together in this discussion.

While the literature contains many observational studies examining the association between awareness of familial disease risk and patient risk behavior, psychological distress and uptake of services (see Webtable 30 for list of observational studies) they do not identify the temporal sequence from risk awareness to change in relevant outcomes. Thus, they do not provide clear evidence that family history collection and/or risk identification as a deliberate clinical activity in itself leads to changes in health outcomes. As demonstrated in the review, there is very limited information available from such robust intervention studies.

The focus of this review was to inform primary care practice, and we identified few studies conducted in a general population or non-specialist context. This is not surprising, considering that when familial risk assessment is offered to general populations (not specially selected for risk), the response rate is usually low. In the reviewed studies, the FH collection interventions were predominately integrated in multifactorial risk assessment tools particularly in the two studies examining improvements in health outcomes (Q3). Although these studies were not in a primary care office setting, they did approach the general population through respondent-initiated enquiry. These models suggest that the modality of risk assessment may affect the use of this service. Anonymous telephone-based risk assessment services may attract patients already aware of their strong family histories (and/or other risk factors) due to concerns about insurance discrimination. This may be particularly the situation if the assessment is associated with similarly anonymous telephone based genetic counseling. However, in patients unaware of the implications of their FH, in-office assessment followed by their personal physician's recommendation may be the preferred option.

Irrespective of the mode and type of FH assessment, the impact on risk-reducing behavior remains unclear. We identified evidence that suggests that incorporating FH collection into multifactorial risk assessment increased screening rates for breast cancer risk, but direct evidence for other conditions is lacking. Incorporating FH collection into a multifactorial risk assessment tool leads to difficulties in disentangling the effect of the FH intervention from other factors.

When considering the adverse effects of FH collection and risk assessment (Q4), only three small studies were identified. They suggest that FH collection and risk assessment increases general anxiety in the short term, with scores returning to pre-intervention levels by 6 to 12 weeks. While the short term impact of intervention is increased anxiety, the process of reviewing the FH may also reassure the clinic attendees. On the other hand, if individuals are aware that they are at low familial risk, confirmation of status on familial risk assessment would be expected to make no difference to the score. To some extent, these findings mirror those of genetic testing for adult onset disorders, in which the consistent finding is that genetic test results provoke short-term increases in anxiety which return to baseline levels within 1-2 months.[174,175]

However, to fully assess the psychological effect of FH collection and use as an approach to chronic disease risk prediction, validated context-specific tools need to be developed. Further, other than psychological distress, studies of other adverse outcomes were not identified (e.g., reduction in screening behavior).[130]

Finally, it is important to note that, even if FH collection and risk assessment had a positive net effect on risk reducing behavior, this does not provide evidence that the prescribed risk-reducing behavior leads to improved health outcomes.

## Q5. What are the Factors That Encourage or Discourage Obtaining and Using a Family History?

Although 'taking a FH' is a core activity in primary care,[176] little is known about the factors that encourage or inhibit it. We identified only a few studies that addressed this question and they were very heterogeneous and did not provide a clear understanding of the factors that improve the appropriate collection and use of FH information in non-specialist settings, whether for general application in complex disease risk assessment or screening patients with more evident familial disease who require more focused FH collection. In many cases FH collection and use is presented as a dichotomized variable, limiting the interpretation of the data.

Despite the difficulty of synthesizing these studies, some observations are possible. To do so, it is necessary to consider together studies which examined the likelihood that FH was *discussed* with those which examined whether FH was *recorded* in patient records as a proxy for the same underlying activity, (i.e., that FH was collected, recorded, and acted upon). On this basis, there is tentative evidence to support the importance of: 1) patient factors such as gender, age, education, their ethnic group, the nature of their health insurance, 2) provider factors such as younger or older practitioners, whether or not they were residency-trained, 3) the condition of interest (e.g., the FH of some cancers appears more likely to be reviewed than other conditions), and 4) the context, including whether the consultation focuses on a specific disease or not, physical examinations, whether or it is a new patient consultation, whether or not the patient brings specific disease concerns.

There is insufficient evidence on whether organizational factors such as electronic health records, make a meaningful difference to FH capture or recording. In a previous review,[145] we noted that the use of FH tools was associated with more accurate and complete recording of FH information than non-systematic approaches, but it is not clear whether providing such tools in itself promotes their routine use.

## Limitations

The studies reviewed in this report were limited to those published in English; however, the impact of any language bias is offset by the optimal applicability to English speaking countries for which this report was prepared. Given the scope of the research questions, we limited our search from 1995 to March 2009. We acknowledge that the 1995 publication date cutoff may have excluded some studies.[177,178] Similarly, due to restraints of time and resources, grey literature was explored in a limited manner.

In considering the elements of FH which provide most value in predicting risk of disease (Q1), we re-analyzed data for a large number of studies, most of which were not primarily designed to address the goals of this review. We took at face value the definitions of FH as they were described in the source reports, and did not contact authors for confirmation. Neither did we attempt to assess the likely accuracy of FH reporting, nor take into account the method by which it was collected (although this was noted as a descriptive item). We grouped together data from studies that were very heterogeneous, in terms of study population and definitions of disease outcome. While almost all studies indicated that FH information was captured by structured interview or self-completion questionnaire, we cannot consider that these methods necessarily replicate the quality of information that might be obtained by a primary care practitioner in a clinical setting. Finally, the AUC calculations were restricted by the number of data points available. The findings presented should therefore be considered to give an indication only of the possible predictive ability of different FH items, rather than to be a definitive analysis.

In the context of accuracy (Q2), we did not restrict studies according to the manner in which FH was collected and considerable variation in the methods used was observed. Almost universally, studies included the collection of FH based on self-reporting (from either the proband, informant, or relative) and are therefore dependent on the individual respondents' knowledge of their history. This represents a limitation on FH taking in practice rather than a limitation specifically of this systematic review. Additionally, eligible studies evaluating the accuracy of FH reporting did not use the same method to ascertain FH or verify status within all relatives. As such, interpretation of the metrics of accuracy was limited to the methods of FH ascertainment and verification used in these studies. Finally, when evaluating and comparing quality of studies, we assumed the index and reference tests were similar.

In examining the effects of FH taking on behavior (Q3) and adverse effects (Q4), the review was limited to populations and setting applicable to primary care. We acknowledge that systematic FH collation and interpretation in specialist setting may provide evidence relevant to primary care but the scope and pragmatic considerations limited the focus of the review. The emphasis on very specific clinical behavioral outcomes also does not allow for exploration of other effects on the part of patients, such as seeking out more extensive information from family members as a result of having been asked “the first” set of questions on FH. Further exploration of the ethico-legal and social aspects would have added a valuable perspective to the review, but there was limited information in the quantitative literature; it was beyond the scope of this report to examine the extensive and diverse qualitative literature that may have explored these aspects of FH.

In consultation with our TEP and partners, we considered the issue of how different FH tools might relate to the review questions; however, we determined that incorporating a comparison of tools, in addition to the original questions, was not feasible, and altered the already broad focus of the review. FH tools for cancer have been examined in a previous AHRQ systematic review,[145] this review identified several generic FH tools.[179-181] Another systematic review has also examined cancer and generic tools applicable to primary care settings.[146]

## Conclusion

Firstly, we explore the implications of the individual questions.

1. The main analysis drew on data from studies designed to address other primary questions, but yielded some useful quantitative information, which indicates the likely upper limit on predictive utility of different FH definitions for the diseases of interest, where FH is used in isolation as a risk factor. The analysis was constrained by the definitions of FH used in the primary studies, but we developed a notional approach to categorizing FH definitions to assist interpretation of their workload impact in routine clinical settings. In and of themselves, very few of the specific FH items or combinations examined had more than modest ability to predict future disease risk in individuals. In general, the least constrained definitions (e.g., at least one affected 1DR, with no other information required) were generally associated with higher sensitivities and lower specificities. This conclusion is not surprising, since a very high predictive ability based on FH alone would imply a disorder with a strong genetic element and high penetrance. For complex disorders, even modest independent discriminatory ability might provide clinically useful predictive information in combination with other risk indicators readily available to the primary care practitioner.

It is worth noting the importance of considering the complexity of the FH definition itself and its relationship with the type of risk information it conveys. The most complex definitions, particularly those which incorporate lineage (Category E, Table 2, Chapter 2), appeared to be designed to identify Mendelian-type patterns of inheritance.[182] As such, they would therefore be expected to identify rare population subgroups with a “genetic version” of a complex disorder. Such an approach is, by definition, likely to be highly specific and but rather insensitive. In contrast, a positive FH based on a very simple definition might provide a marker which picks out a higher than average ‘familial loading’ for a disorder, but has no need to consider detailed pedigree information. This approach would be characterized by higher sensitivity but lower specificity. The purpose of the FH assessment in primary care (to pick out very high risk subgroups for further genetic assessment or to work out more general familial disease loading) merits further discussion.

Recommendations for direction of future research:

- Further clarification of the purpose of FH taking in primary care settings is required, so that future assessments of the utility of FH are based on an explicit distinction between, for example, disease risk assessment as part of routine preventive care (e.g., the routine physical examination) in which other risk information is taken into account, triage for screening (e.g., selecting people for formal tests of glucose tolerance), or applying genetic referral/testing guidelines in patients who appear to have a prominent familial disease history, in whom genetic disease is suspected.

- The evidence base requires studies designed explicitly for the purpose of examining the predictive ability of combinations of individual FH items. This requires adequately powered, longitudinally designed studies in which detailed, extensive, clearly defined and documented FH components comprise the 'exposures', in which participants are followed up for a period which is clinically meaningful, in which adequate measures are taken to control bias, and in which the primary metrics relate to individual risk prediction.
- FH items should be formally examined alongside other recommended or readily accessible risk factors, in order to identify the extent to which they provide useful independent and/or incremental discriminatory ability.

2. The accuracy of self reported FH has implications for the correct risk assessment and management of patients. Accuracy of FH reporting appears to be dependent on the method of collection, which is related to the disease area. Accurate reporting of the absence of disease (specificity) appears to be greater than accurate reporting of presence of disease (sensitivity) across different disease areas. Estimates of sensitivity show greater variation and the magnitude varies with different diseases. Although, there is limited evidence, accuracy of recall and reporting may be influenced by both patient and informant (relative) factors, and by the method used to collect FH.

Recommendations for direction of future research:

- Future studies in accuracy should be undertaken in populations reflective of the primary care setting and representative of the spectrum of disease risk. Future studies should endeavor to better characterize the attributes of the informant/proband and especially the relatives; the potential of these factors to influence the accuracy of reporting should be consistently evaluated. Future evaluation should be undertaken in the areas of asthma and atopy, affective mental health disorders, cardiovascular diseases, and diabetes.

3. Within primary care populations, there is very limited evidence to support or refute the effect on risk-reducing behavior changes (e.g., lifestyle changes or uptake of recommended clinical interventions) of taking a FH and using it to personalize risk of developing respective conditions.

Recommendations for future research:

- Well-designed trials are required that compare FH-based, personalized risk advice with standard of care on risk reducing behaviors in populations at different risk levels (including population risk). The outcomes of interest need to be clinically relevant, either leading to improved mortality or morbidity or surrogate measures with strong evidence of links to improved health outcomes. Concurrent qualitative studies should also be considered.
- Proposed trials should be based on evidence from systematic reviews to ensure that prescribed risk-reducing behaviors are evidence-based.

4. In primary care populations, there is very limited information to evaluate direct harm incurred from the routine practice of taking FH and using it to personalize risk information.

Recommendations for future research:

- Trials of FH taking as an intervention should include capture of data to examine the full range of potential impacts on individuals of FH collection and implementation strategies based on familial risk identification, both negative and positive. Concurrent qualitative studies should also be considered. Baseline data on psychological status should be captured so that this can formally be adjusted for use in outcome analyses. To enable appropriate evaluation of psychological harm, context-specific measures need to be developed and validated.

5. In order to assess the content validity of systematic FH tools we need to know not only the factors that affect the recall of FH (Q2) but also those factors that affect the collection and use of FH. Thus far, in this population, there is limited information on collection and discussion of FH by the population and practitioners, with no factors identified that are associated with the use of the FH. There is some suggestion that populations from underserved communities are less likely to report and have the opportunity to discuss FH, but the level of evidence is weak.

Recommendations for future research:

- Further research is required to clarify the most important patient and practitioner factors that may affect the collection and use of FH. This likely requires the development of theoretical frameworks to guide appropriate design, and to ensure that methodologies adequately address the many potential biases and interactions between factors, which may be encountered. The most important studies are those which address factors directly relevant to primary care practice, including highlighting patient factors which promote inequity in the application of effective interventions
- Where inequities are identified, interventions should be designed to ameliorate these factors in future trials and service provision. Such research could include analyses of national population and practitioner survey databases.
- While research should focus on clinically relevant outcomes, it should also include process evaluations to identify factors, which affect the successful implementation of the FH interventions.

The findings of this systematic review pose as many questions as they answer, but they do not undermine the general view that FH taking is a worthwhile activity in primary care settings. The evidence base for FH-based assessment and intervention is not well-developed, but absence of evidence is not absence of effect. The few studies that have examined potential harms of FH taking suggest that such concerns may be unfounded, and should not hinder the development of rigorous evaluations of FH taking and FH-based risk interventions. There is consistent evidence from a previous report[145] that FH tools (albeit for cancer) promote higher quality information capture than non-systematic approaches. The findings from this systematic review begin to suggest how to choose FH items to populate tools and emphasize the importance of considering purpose (to what use will FH information be put?) and context (time available, and nature of clinical encounter).

Finally, although this systematic review identified the paucity of relevant evidence for many important issues, the findings do not negate the “extraordinary potential of the FH” in primary care practice.[183] The systematic and often graphical collation of this information (e.g., as genograms) in family-oriented clinical practice may be used for purposes which go beyond specific disease risk assessment, for example to assess the impact of "family health" (broadly defined) on an individual's well-being.[184] Family practice, in particular, is characterized by the continuity of the relationship between, patients, families, and practitioners. Thus, in the real world, FH may be pieced together over time and decision-making may be incremental as more information emerges. A deeper appreciation of the context in which FH is captured, interpreted, and acted upon is important as further FH based interventions are developed and evaluated.

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# Appendix A – Search Strategies Detailed

**<u>Main Review</u>**

## Medline

1. Ambulatory care/
2. ambulatory care.tw.
3. Primary health care/
4. Physicians, family/
5. Family practice/
6. primary health care.tw.
7. primary healthcare.tw.
8. primary care.tw.
9. general practi*.tw.
10. family practic*.tw.
11. (family adj2 (physician? or doctor? or clinic?)).tw.
12. family medical care.tw.
13. gp.ti,ab.
14. Community health services/
15. or/1-14
16. exp Pedigree/
17. limit 16 to humans
18. Medical History Taking/
19. Genetic Predisposition to Disease/
20. anamnesis.ti,ab.
21. ((family or familial) adj3 (histor$ or history-taking or risk$)).ti.
22. (human adj2 pedigree).ti,ab.
23. Family Health/
24. (family history adj3 (taking or collect$ or tool? or questionnaire? or form? or algorith?m or assessment)).ti,ab.
25. (familial history adj3 (taking or collect$ or tool? or questionnaire? or form? or algorith?m or assessment)).ti,ab.
26. (genetic adj2 (risk adj3 (assessment or evaluation))).ti,ab.
27. ((first or second) adj2 degree relative?).ti,ab.
28. ((parental or paternal or maternal) adj2 history).ti.
29. or/17-28
30. (sensitivity or specificity).ti.
31. (accura$ or inaccur$ or valid$ or reliability).ti.
32. under reporting.ti.
33. underreporting.ti.
34. exp "Reproducibility of Results"/
35. completeness.ti.
36. consistency.ti.
37. or/30-36
38. Risk factors.ti.

39. *risk factors/
40. or/38-39
41. family history.tw.
42. 41 and 40
43. exp Stroke/ge, ep, pc, et [Genetics, Epidemiology, Prevention & Control, Etiology]
44. (stroke$ or cerebrovascular$ or cerebral vascular or CVA$).ti.
45. ((cerebral or cerebellar or brainstem or vertebrobasilar) adj5 (infarct$ or isch?emi$ or thrombo$ or apoplexy or emboli$)).ti.
46. ((cerebral or intracerebral or intracranial or parenchymal or brain or intraventricular or brainstem or cerebellar or infratentorial or supratentorial or subarachnoid) adj (haemorrhage or hemorrhage or haematoma or hematoma or bleeding or aneurysm)).ti.
47. or/43-46
48. Asthma/ge, pc, et, ep [Genetics, Prevention & Control, Etiology, Epidemiology]
49. (asthma or atopy or atopic).ti.
50. or/48-49
51. Depression/pc, ep, ge, et [Prevention & Control, Epidemiology, Genetics, Etiology]
52. Depressive Disorder, Major/pc, ep, et, ge [Prevention & Control, Epidemiology, Etiology, Genetics]
53. (involutional adj2 (depress$ or psychos$ or melancholia)).ti.
54. ((major or chronic) adj2 depress$).ti.
55. or/51-54
56. exp Diabetes Mellitus, Type 1/ge, ep, pc, et [Genetics, Epidemiology, Prevention & Control, Etiology]
57. Diabetes Mellitus/et, pc, ge, ep [Etiology, Prevention & Control, Genetics, Epidemiology]
58. exp Diabetes Mellitus, Type 2/ge, ep, pc, et [Genetics, Epidemiology, Prevention & Control, Etiology]
59. (diabetes or diabetic?).ti.
60. or/56-59
61. ((breast or ovar$ or prostate or colon or colorectal or lung) adj3 (cancer$ or neoplasm$ or carcinom$ or tumo?r$)).ti.
62. exp Breast Neoplasms/et, ge, ep, pc [Etiology, Genetics, Epidemiology, Prevention & Control]
63. exp Colorectal Neoplasms/ge, pc, et, ep [Genetics, Prevention & Control, Etiology, Epidemiology]
64. exp Ovarian Neoplasms/et, ge, ep, pc [Etiology, Genetics, Epidemiology, Prevention & Control]
65. exp Prostatic Neoplasms/et, ge, ep, pc [Etiology, Genetics, Epidemiology, Prevention & Control]
66. exp Lung Neoplasms/et, ge, ep, pc [Etiology, Genetics, Epidemiology, Prevention & Control]
67. or/61-66
68. exp Cardiovascular Diseases/pc, ge, ep, et [Prevention & Control, Genetics, Epidemiology, Etiology]
69. chd.ti.

70. thrombo$.ti.
71. ((coronary or heart or cardiovascular) adj2 disease?).ti.
72. or/68-71
73. 60 or 55 or 72 or 50 or 67 or 47
74. 15 or 37 or 73
75. 74 and 29
76. 75 or 42
77. (note or comment or editorial or letter or congresses).pt.
78. 76 not 77
79. animals/ not (humans/ and animals/)
80. 78 not 79
81. limit 80 to english language
82. limit 81 to yr="1995 - 2008"

## EMBASE

1. general practice/ or primary medical care/ or private practice/
2. exp ambulatory care/ or exp primary health care/
3. general practitioner/
4. exp community care/
5. ambulatory care.tw.
6. primary health care.tw.
7. primary healthcare.tw.
8. general practi*.tw.
9. family practi*.tw.
10. primary care.tw.
11. (family adj2 (physician? or doctor? or clinic?)).tw.
12. family medical care.tw.
13. gp.ti,ab.
14. or/1-13
15. "sensitivity and specificity"/
16. exp Validity/
17. exp Reproducibility/
18. (sensitivity or specificity).ti.
19. (accura$ or inaccur$ or valid$ or reliability).ti.
20. under reporting.ti.
21. underreporting.ti.
22. consistency.ti.
23. completeness.ti.
24. or/15-23
25. family history/
26. ((family or familial) adj3 (histor$ or history-taking or risk$)).ti.
27. (human adj2 pedigree).ti,ab.
28. (family history adj3 (taking or collect$ or tool? or questionnaire? or form? or algorith?m or assessment)).ti,ab.
29. (genetic adj2 (risk adj3 (assessment or evaluation))).ti,ab.

30. ((first or second) adj2 degree relative?).ti,ab.
31. ((parental or paternal or maternal) adj2 history).ti.
32. or/25-31
33. *risk factor/
34. risk factor?.ti.
35. or/33-34
36. family history/
37. family history.tw.
38. or/36-37
39. 38 and 35
40. exp Asthma/
41. (asthma* or atopy or atopic).ti.
42. Atopy/
43. or/40-42
44. endogenous depression/ or involutional depression/ or major depression/
45. (involutional adj2 (depress$ or psychos$ or melancholia)).ti.
46. ((major or chronic) adj2 depress$).ti.
47. or/44-46
48. exp Diabetes Mellitus/
49. (diabetes or diabetic?).ti.
50. or/48-49
51. exp Breast Cancer/
52. exp Ovary Cancer/
53. exp Prostate Cancer/
54. exp Colorectal Cancer/
55. exp Lung Cancer/
56. ((breast or ovar$ or prostate or colon or colorectal or lung) adj3 (cancer$ or neoplasm$ or carcinom$ or tumo?r$)).ti.
57. or/51-56
58. exp cardiovascular disease/
59. chd.ti.
60. thrombo$.ti.
61. ((coronary or heart or cardiovascular) adj2 disease?).ti.
62. (stroke$ or cerebrovascular$ or cerebral vascular or CVA$).ti.
63. ((cerebral or cerebellar or brainstem or vertebrobasilar) adj5 (infarct$ or isch?emi$ or thrombo$ or apoplexy or emboli$)).ti.
64. ((cerebral or intracerebral or intracranial or parenchymal or brain or intraventricular or brainstem or cerebellar or infratentorial or supratentorial or subarachnoid) adj (haemorrhage or hemorrhage or haematoma or hematoma or bleeding or aneurysm)).ti.
65. or/58-64
66. 57 or 47 or 65 or 50 or 43
67. 24 or 14 or 66
68. 67 and 32
69. 68 or 39
70. limit 69 to human

71. limit 70 to english language
72. (conference paper or editorial or letter or note or proceeding).pt.
73. 71 not 72
74. limit 73 to yr="1995 - 2008"

## CINAHL

1. Primary Health Care/
2. primary health care.tw.
3. primary healthcare.tw.
4. primary care.tw.
5. Physicians, Family/
6. Family Practice/
7. general practi*.tw.
8. family practic*.tw.
9. (family adj2 (physician? or doctor? or clinic?)).tw.
10. family medical care.tw.
11. gp.ti,ab.
12. (family adj2 (medic* or care)).tw.
13. Community Health Services/
14. or/1-13
15. exp "Reliability and Validity"/
16. "Reproducibility of Results"/
17. (sensitivity or specificity).ti.
18. (accura$ or inaccur$ or valid$ or reliability).ti.
19. under reporting.ti.
20. underreporting.ti.
21. consistency.ti.
22. completeness.ti.
23. or/15-22
24. family history/
25. ((family or familial) adj3 (histor$ or history-taking or risk$)).ti.
26. (human adj2 pedigree).ti,ab.
27. (family history adj3 (taking or collect$ or tool? or questionnaire? or form? or algorith?m or assessment)).ti,ab.
28. (genetic adj2 (risk adj3 (assessment or evaluation))).ti,ab.
29. ((first or second) adj2 degree relative?).ti,ab.
30. ((parental or paternal or maternal) adj2 history).ti.
31. or/24-30
32. Stroke/
33. (stroke$ or cerebrovascular$ or cerebral vascular or CVA$).ti.
34. ((cerebral or cerebellar or brainstem or vertebrobasilar) adj5 (infarct$ or isch?emi$ or thrombo$ or apoplexy or emboli$)).ti.
35. ((cerebral or intracerebral or intracranial or parenchymal or brain or intraventricular or brainstem or cerebellar or infratentorial or supratentorial or subarachnoid) adj

(haemorrhage or hemorrhage or haematoma or hematoma or bleeding or aneurysm)).ti.

36. or/32-35
37. Asthma/
38. (asthma* or atopy or atopic).ti.
39. or/37-38
40. Depression/
41. (involutional adj2 (depress$ or psychos$ or melancholia)).ti.
42. ((major or chronic) adj2 depress$).ti.
43. or/40-42
44. diabetes mellitus/ or diabetes mellitus, insulin-dependent/ or diabetes mellitus, non-insulin-dependent/
45. (diabetes or diabetic?).ti.
46. or/44-45
47. exp Breast Neoplasms/
48. exp Colorectal Neoplasms/
49. exp Ovarian Neoplasms/
50. exp Prostatic Neoplasms/
51. exp Lung Neoplasms/
52. ((breast or ovar$ or prostate or colon or colorectal or lung) adj3 (cancer$ or neoplasm$ or carcinom$ or tumo?r$)).ti.
53. or/47-52
54. exp Cardiovascular Diseases/
55. chd.ti.
56. thrombo$.ti.
57. ((coronary or heart or cardiovascular) adj2 disease?).ti.
58. or/54-57
59. 46 or 43 or 36 or 39 or 53 or 58
60. 14 or 59 or 23
61. 60 and 31
62. limit 61 to english language
63. limit 62 to (abstract or "book review" or commentary or doctoral dissertation or editorial or exam questions or letter or masters thesis or pamphlet)
64. 62 not 63
65. limit 64 to yr="1995 - 2008"

## psycINFO

1. cerebrovascular accidents/
2. (stroke$ or cerebrovascular$ or cerebral vascular or CVA$).ti.
3. ((cerebral or cerebellar or brainstem or vertebrobasilar) adj5 (infarct$ or isch?emi$ or thrombo$ or apoplexy or emboli$)).ti.
4. ((cerebral or intracerebral or intracranial or parenchymal or brain or intraventricular or brainstem or cerebellar or infratentorial or supratentorial or subarachnoid) adj (haemorrhage or hemorrhage or haematoma or hematoma or bleeding or aneurysm)).ti.

5. or/1-4
6. asthma/
7. asthma.ti.
8. exp major depression/
9. (involutional adj2 (depress$ or psychos$ or melancholia)).ti.
10. ((major or chronic or severe) adj2 depress$).ti.
11. or/8-10
12. diabetes mellitus/
13. (diabetes or diabetic?).ti.
14. or/12-13
15. exp Ovaries/
16. exp Colon Disorders/
17. exp Prostate/
18. lung disorders/
19. or/15-18
20. exp Neoplasms/
21. cancer.ti.
22. or/20-21
23. 22 and 19
24. Breast Neoplasms/
25. ((breast or ovar$ or prostate or colon or colorectal or lung) adj3 (cancer$ or neoplasm$ or carcinom$ or tumo?r$)).ti.
26. or/23-25
27. exp cardiovascular disorders/
28. chd.ti.
29. thrombo$.ti.
30. ((coronary or heart or cardiovascular) adj2 disease?).ti.
31. or/27-30
32. 11 or 26 or 31 or 14 or 6 or 7 or 5
33. primary health care/
34. general practitioners/
35. family medicine/
36. family physicians/
37. primary health care.tw.
38. primary healthcare.tw.
39. primary care.tw.
40. family practic*.tw.
41. (family adj2 (physician? or doctor? or clinic?)).tw.
42. general practi*.tw.
43. family medical care.tw.
44. gp.ti,ab.
45. or/33-44
46. exp statistical validity/
47. (sensitivity or specificity).ti.
48. (accura$ or inaccur$ or valid$ or reliability or completeness or consistency).ti.
49. under reporting.ti.

50. underreporting.ti.
51. exp statistical analysis/
52. psychometrics/
53. or/46-52
54. or/46-50
55. at risk populations/ or predisposition/ or "susceptibility (disorders)"/
56. anamnesis.ti,ab.
57. ((family or familial) adj3 (histor$ or history-taking or risk$)).ti.
58. (human adj2 pedigree).ti,ab.
59. (family history adj3 (taking or collect$ or tool? or questionnaire? or form? or algorith?m or assessment)).ti,ab.
60. (familial history adj3 (taking or collect$ or tool? or questionnaire? or form? or algorith?m or assessment)).ti,ab.
61. (genetic adj2 (risk adj3 (assessment or evaluation))).ti,ab.
62. ((first or second) adj2 degree relative?).ti,ab.
63. ((parental or paternal or maternal) adj2 history).ti.
64. or/55-63
65. 53 or 32 or 45
66. 64 and 65
67. limit 66 to human
68. limit 67 to english language
69. limit 68 to (abstract collection or bibliography or "column/opinion" or "comment/reply" or editorial or encyclopedia entry or letter)
70. 68 not 69
71. limit 70 to yr="1995 - 2008"

## CCTR

1. Ambulatory care/
2. ambulatory care.tw.
3. Primary health care/
4. Physicians, family/
5. Family practice/
6. primary health care.tw.
7. primary healthcare.tw.
8. primary care.tw.
9. general practi*.tw.
10. family practic*.tw.
11. (family adj2 (physician? or doctor? or clinic?)).tw.
12. family medical care.tw.
13. gp.ti,ab.
14. Community health services/
15. or/1-14
16. exp Pedigree/
17. limit 16 to humans
18. Medical History Taking/

19. Genetic Predisposition to Disease/
20. anamnesis.ti,ab.
21. ((family or familial) adj3 (histor$ or history-taking or risk$)).ti.
22. (human adj2 pedigree).ti,ab.
23. Family Health/
24. (family history adj3 (taking or collect$ or tool? or questionnaire? or form? or algorith?m or assessment)).ti,ab.
25. (familial history adj3 (taking or collect$ or tool? or questionnaire? or form? or algorith?m or assessment)).ti,ab.
26. (genetic adj2 (risk adj3 (assessment or evaluation))).ti,ab.
27. ((first or second) adj2 degree relative?).ti,ab.
28. ((parental or paternal or maternal) adj2 history).ti.
29. or/17-28
30. (sensitivity or specificity).ti.
31. (accura$ or inaccur$ or valid$ or reliability).ti.
32. under reporting.ti.
33. underreporting.ti.
34. exp "Reproducibility of Results"/
35. completeness.ti.
36. consistency.ti.
37. or/30-36
38. Risk factors.ti.
39. *risk factors/
40. or/38-39
41. family history.tw.
42. 41 and 40
43. exp Cerebrovascular Accident/ge, ep, pc, et [Genetics, Epidemiology, Prevention & Control, Etiology]
44. (stroke$ or cerebrovascular$ or cerebral vascular or CVA$).ti.
45. ((cerebral or cerebellar or brainstem or vertebrobasilar) adj5 (infarct$ or isch?emi$ or thrombo$ or apoplexy or emboli$)).ti.
46. ((cerebral or intracerebral or intracranial or parenchymal or brain or intraventricular or brainstem or cerebellar or infratentorial or supratentorial or subarachnoid) adj (haemorrhage or hemorrhage or haematoma or hematoma or bleeding or aneurysm)).ti.
47. or/43-46
48. Asthma/ge, pc, et, ep [Genetics, Prevention & Control, Etiology, Epidemiology]
49. (asthma or atopy or atopic).ti.
50. or/48-49
51. Depression/pc, ep, ge, et [Prevention & Control, Epidemiology, Genetics, Etiology]
52. Depressive Disorder, Major/pc, ep, et, ge [Prevention & Control, Epidemiology, Etiology, Genetics]
53. (involutional adj2 (depress$ or psychos$ or melancholia)).ti.
54. ((major or chronic) adj2 depress$).ti.
55. or/51-54

56. Diabetes Mellitus/et, pc, ge, ep [Etiology, Prevention & Control, Genetics, Epidemiology]
57. exp Diabetes Mellitus, Type 1/ge, ep, pc, et [Genetics, Epidemiology, Prevention & Control, Etiology]
58. exp Diabetes Mellitus, Type 2/ge, ep, pc, et [Genetics, Epidemiology, Prevention & Control, Etiology]
59. (diabetes or diabetic?).ti.
60. or/56-59
61. ((breast or ovar$ or prostate or colon or colorectal or lung) adj3 (cancer$ or neoplasm$ or carcinom$ or tumo?r$)).ti.
62. exp Breast Neoplasms/et, ge, ep, pc [Etiology, Genetics, Epidemiology, Prevention & Control]
63. exp Colorectal Neoplasms/ge, pc, et, ep [Genetics, Prevention & Control, Etiology, Epidemiology]
64. exp Ovarian Neoplasms/et, ge, ep, pc [Etiology, Genetics, Epidemiology, Prevention & Control]
65. exp Prostatic Neoplasms/et, ge, ep, pc [Etiology, Genetics, Epidemiology, Prevention & Control]
66. exp Lung Neoplasms/et, ge, ep, pc [Etiology, Genetics, Epidemiology, Prevention & Control]
67. or/61-66
68. exp Cardiovascular Diseases/pc, ge, ep, et [Prevention & Control, Genetics, Epidemiology, Etiology]
69. chd.ti.
70. thrombo$.ti.
71. ((coronary or heart or cardiovascular) adj2 disease?).ti.
72. or/68-71
73. 60 or 67 or 55 or 50 or 72 or 47
74. 73 or 15 or 37
75. 29 and 74
76. 75 or 42
77. limit 76 to yr="1995 - 2008"

# Appendix B - Forms

## Level 1 – Title and Abstract Screening

Submit Data

1.

**Is this citation a full report in English of a primary study which focuses on capturing, collecting, collating, analyzing data related to the collection of family history?**

- (•) No
- ( ) Yes/Maybe

Clear Selection

Submit Data

## Level 2 – Title and Abstract Screening

Submit Data

1.

**Does this paper meet the criteria for:**

- [ ] Yes/Maybe for Review Question 1
- [ ] Yes/Maybe for Review Question 2
- [ ] Yes/Maybe for Review Question 3
- [ ] Yes/Maybe for Review Question 4
- [ ] Yes/Maybe for Review Question 5
- [ ] Yes/Maybe for Review Question 6
- [x] None of the Review Questions

Submit Data

## Level 3 – Title and Abstract NQ & BW Screening

Save to finish later | Submit Data

1. **Does this paper meet the criteria for:**

- [ ] Yes/Maybe for Review Question 1
- [ ] Yes/Maybe for Review Question 2
- [ ] Yes/Maybe for Review Question 3
- [ ] Yes/Maybe for Review Question 4
- [ ] Yes/Maybe for Review Question 5
- [ ] Yes/Maybe for Review Question 6
- [ ] None of the Review Questions

2. **Notes**

Enlarge Shrink

Save to finish later | Submit Data

# Level 4 – Full Text Screening

Submit Data

| | TRUE | FALSE | |
|---|---|---|---|
| 1. Population includes general population or primary care patients or primary care providers | ◯ | ◯ | Clear |
| 2. Population includes participants in organized screening programs where inclusion is not based on known family history | ◯ | ◯ | Clear |
| 3. Population is limited to subjects studied by a specialist (i.e. geneticist, oncologist, surgeon etc) | ◯ | ◯ | Clear |
| 4. Population includes healthcare payer or provider | ◯ | ◯ | Clear |
| 5. Population includes NONE of the above populations IF TRUE, STOP HERE - GO TO NEXT PAPER | ◯ | ◯ | Clear |
| 6. Population is recruited with genetic testing complete IF TRUE, STOP HERE - GO TO NEXT PAPER | ◯ | ◯ | Clear |
| 7. Intervention is the collection of a family history using any modality | ◯ | ◯ | Clear |
| 8. Intervention is collection of a family history in a systematic manner | ◯ | ◯ | Clear |
| 9. Intervention is the use of family history, which was collected in a systematic manner, as part of a multiplicative risk assessment | ◯ | ◯ | Clear |
| 10. Family history is used as a selection criteria for the study subjects, not an intervention | ◯ | ◯ | Clear |
| 11. Family history is NONE of the above FH interventions IF TRUE, STOP HERE - GO TO NEXT PAPER | ◯ | ◯ | Clear |
| 12. Study is a primary quantitative design | ◯ | ◯ | Clear |
| 13. Study is an RCT or RT (randomized trial) or CCT (controlled clinical trial) or Before-after study | ◯ | ◯ | Clear |
| 14. Study is NONE of the above (RCT or RT or CCT or other primary quantitative design) IF TRUE, STOP HERE - GO TO NEXT PAPER | ◯ | ◯ | Clear |
| 15. Study is a case report (n = 1) IF TRUE, STOP HERE - GO TO NEXT PAPER | ◯ | ◯ | Clear |
| 16. Outcomes include a measure of a specified pre-disease or disease state (see list in guide) | ◯ | ◯ | Clear |
| 17. Outcomes include prevalence or incidence of the condition of interest in the subject (See list of pre-disease or diseases of interest in guide) | ◯ | ◯ | Clear |
| 18. Outcomes include RR or HR or OR for getting the condition of interest (See list of pre-disease or diseases of interest in guide) | ◯ | ◯ | Clear |
| 19. Results compare family history items to death registries, medical records, direct contact with relatives, confirmation by relatives' physicians or disease registries for verification of the family history report | ◯ | ◯ | Clear |
| 20. Outcomes inlclude validation of family history report by any of sensitivity, specificity, % agreement/Kappa, positive predictive value, negative predictive value, completeness, reliability | ◯ | ◯ | Clear |
| 21. Outcomes include quality of life, family functioning, social functioning, ethical issues, legal issues, social issues, related to the family history collection and/or use | ◯ | ◯ | Clear |
| 22. Outcomes include mortality or morbidity related to the family history collection and/or use | ◯ | ◯ | Clear |
| 23. Outcomes include psychological distress (e.g. worry, anxiety, depression, inaccurate risk perception) related to the famly history colleciton and/or use | ◯ | ◯ | Clear |
| 24. Outcomes include factors that encourage or discourage family history collection or use | ◯ | ◯ | Clear |
| 25. Outcomes include a metric to assess family history collection or use (e.g. uptake of procedure) | ◯ | ◯ | Clear |
| 26. Outcomes include perspectives on family history, for topics including economic, financial and opportunity cost, insurability, discrimination, confidentiality, liability (for economic data analysis, US data is used) | ◯ | ◯ | Clear |
| 27. Outcomes presented include NONE of the above outcomes or results IF TRUE, STOP HERE - GO TO NEXT PAPER | ◯ | ◯ | Clear |

Submit Data

# Review Question 1: QUALITY ASSESSMENT QUESTIONS

## ALL STUDIES

1. Was the same method of ascertainment of disease outcome applied to all participants, regardless of family history?

   a) Yes
   b) No
   c) Unclear

2. Was ascertainment of disease outcome completely blind to participants' family history status?

   a) Yes
   b) No
   c) Unclear

3. Was the same method of ascertainment of family history applied to all participants?

   a) Yes
   b) No
   c) Unclear

4. Was ascertainment of family history status completely blind to disease outcome?

   a) Yes
   b) No
   c) Unclear

## LONGITUDINAL DESIGNS ONLY

5. Were participants with the disease outcome excluded at the start of the study?

   a) Yes
   b) No
   c) Unclear
   e) Not applicable (cross-sectional design)

6. Was there adequate follow up of all participants?

   a) at least 80% follow up
   b) Less than 80% follow up, adequate description of those lost
   c) Less than 80% follow up, inadequate or missing description of those lost
   d) Unclear
   e) Not applicable (cross-sectional design)

## CROSS-SECTIONAL DESIGNS ONLY

7. Was the sampling method representative of the population intended to the study?

   a) Yes (probability sampling)
   b) No (non-probability sampling)
   c) Unclear
   e) Not applicable (longitudinal design)

8. Was the participation rate adequate?

   a) Yes, response rate at least 80%
   b) Response rate less than 80%, adequate description of non-participants
   c) Response rate less than 80%, inadequate or missing description of non-participants
   d) Unclear
   e) Not applicable (longitudinal design)

| Modified Quality Assessment of Diagnostic Accuracy Studies (OUADAS) [1] | |
|---|---|
| **QUADAS ITEM (*Topic/Bias*)** | **Interpretation for Family History OMAR Review** |
| **1)** Was the spectrum of patients' representative of the patients who will receive the test in practice?<br><br>*(Selection)* | We are interpreting this to be representative of the spectrum of patients seen within family practice or primary care, **which should include all levels of severity or disease duration. The population would be representative of those seen in practice where the test is likely to be applied (primary care settings and providers).**<br><br>Note that this criterion speaks more to generalizability than to a true selection bias.<br>We considered issues of generalisability in terms of a) demographic features (prevalence, age, gender, b) disease characteristics (severity and duration), and c) co-morbidities or differential diagnosis. Note method of recruitment and characteristics of those recruited.<br><br>**YES**: Subjects represent spectrum of subjects seen within primary care settings.<br>**NO:** Not that case control studies are considered by QUADAS to be a NO for this item, but we do not consider this to be a fatal flaw. Subjects that appear to represent a limited portion of the spectrum of patients with respect to disease severity, or duration, or risk for positive family history. Our review did not exclude studies that included subjects from specialty clinics or relatives of persons with the disease. As such, these relative may also be considered to be "high risk" for the disease (as the subjects<br>patients may appear to be recruited because of high risk for family history and are scored NO.<br>**UNCLEAR:** Description of participants is partial and there is uncertainty of the severity or duration of the disease. |
| **2)** Were the selection criteria clearly described?<br><br>*(Selection)* | Look for a clear definition of the eligibility criteria (both inclusion and EXCLUSION criteria).<br>Note the criteria used to select BOTH the proband/control and the relatives/ informants.<br><br>**YES:** Appears that sufficient description of the eligibility criteria, the process of recruiting for both the probands/ informants and the relatives.<br>**NO**: All relevant information for selection processes is not reported. The following information may be omitted or poorly described:<br>a) how the probands/ informants were selected (possibly how the proxy informants were selected)<br>b) how the relatives were selected<br>**UNCLEAR**: Only partial information is reported and don't feel you have enough information to score this item. |

| Modified Quality Assessment of Diagnostic Accuracy Studies (OUADAS) [1] | |
|---|---|
| **QUADAS ITEM (*Topic/Bias*)** | **Interpretation for Family History OMAR Review** |
| **3)** Is the reference standard likely to correctly classify the target intervention?<br><br>*(Misclassification)* | The reference standard is the method used to determine the presence or absence of the target condition. The reference standard is therefore an important determinant of the diagnostic accuracy of a test. Estimates of test performance are based on the assumption that the index test is being compared to a reference standard which is 100% sensitive and specific.<br><br>*Not applicable to this systematic review as we limited this review to including studies that used methods of the reference standard that we consider to correctly classify the target condition.* |
| **4)** Is the reference standard and index test short enough to be reasonably sure the target condition did not change between the two tests?<br>*(Misclassification)* | This problem may lead to misclassification bias as the disease may progress to a more advanced stage or there may be spontaneous recover. We do not anticipate that this is the context for family history, whereby the interval within which testing occurs will cause family history to be altered.<br><br>*Not applicable to this systematic review.* |

| Modified Quality Assessment of Diagnostic Accuracy Studies (OUADAS) [1] | |
|---|---|
| **QUADAS ITEM (*Topic/Bias*)** | **Interpretation for Family History OMAR Review** |
| **5)** Did the whole sample or a random selection of the sample receive verification using a reference standard of diagnosis?<br><br>*(Partial Verification bias)* | This item concerns to **partial verification bias** which occurs when not all of the study participants receive the reference standard (in our context, confirmation of the TRUE disease status). This is a form of selection bias. Sometimes the reason only a part of the sample receives the reference standard is because knowledge of the index test results **influence** the decision to perform the reference standard. Please note that in the context of family history, the reference standard can only be applied to the family members or relatives. The probands or informants are in essence the "index test" even though we are interested in the accuracy of the probands/ informants.<br><br>We consider the whole sample to be ALL relatives for which the proband or informant provided information (including "Don't know" status).<br>**YES:** All relatives that the proband identifies/ reports upon represent the whole sample of relatives. As such, some form of verification is attempted for all identified relatives.<br>**NO:** Not all relatives receive verification via the reference standard. As such, we consider partial verification bias to be present in the following situations:<br>1) Knowledge of the index test will determine which relatives are reported to have the disease status. Often **UNAFFECTED relatives** do not have their disease status verified by any method (assume proband/informant report is the truth of the disease status); in this case, the disease status is verified in the **AFFECTED relatives** only. In this situation the outcomes of sensitivity and specificity cannot be computed.<br>2) Relatives for which the proband/ informant indicates "Don't know status" are excluded and do not have their disease status verified (no reference standard testing).<br>3) Relatives that are **DECEASED**; as such they are excluded from having any verification undertaken (no reference standard testing).<br>4) Relatives that are **UNABLE TO PARTICIPATE** in interviews or further clinical testing are excluded from having any verification method (no reference standard testing).<br>**UNCLEAR:** Insufficient information to determine whether partial verification was present. |

| Modified Quality Assessment of Diagnostic Accuracy Studies (OUADAS) [1] | |
|---|---|
| **QUADAS ITEM (*Topic/Bias*)** | **Interpretation for Family History OMAR Review** |
| **6)** Did the patients receive the same reference standard regardless of the index test? *(Differential Verification Bias)* | "**Differential verification bias** occurs when some of the index test results are verified by a <u>different</u> reference standard. This is especially a problem if multimodal types of reference standards are used. For example, differential verification bias usually occurs when relatives who are testing positive (have the disease) based on the proband report "index test receive" a more invasive or extensive reference standard than those with a negative test result.<br><br>In most accuracy studies evaluating the reporting of family history, there is the use of more than one method to verify the disease status of the relative and we have restricted these to interview with relative, medical record, disease or death registry, and contact with the subject physician. Using multi-modal approaches to verification of disease status seems to be necessary for this area of research; relatives may be deceased, live afar, or are incapacitated because of disease or frailty. It is expected that most studies will be unable to use a single reference standard method (for example interview with the relative) for all identified relatives.<br><br>Verification can occur by different methods for different relatives or verification using multiple methods on the SAME relative (and a hierarchy of selection for disease status is used) [See Elbaz 2003[2] In the latter case, some authors state decision rules at which of the multiple tests will be considered to reflect the truth of the disease status of the relative. In the area of mental health disorders, they will often consider "multiple informants" as the "reference" standard" and only include relatives for which there were "verification" reports from more than one informant.<br><br>**YES**: All relatives received the SAME reference standard (for example, all living relatives were interviewed, and all deceased relatives had a proxy informant (for example interview with a spouse of the deceased relative).<br>**NO:** All relatives did NOT receive the same references standard:<br>1) This item can indicate that some of the relatives received a DIFFERENT reference standard. For example, consider the case where:<br>a) UNAFFECTED relatives have their disease status checked with medical records alone rather than interview or disease or death registry<br>b) POSITIVE SCREEN relatives get a physical examination but those screening negative do NOT get a physical examination.<br>c) DECEASED relatives have their disease status checked through medical records or interviews of other relatives (rather than neurological exam received by living relatives).<br>c) From all informants/relatives who were identified and provided some initial information, only those available for **direct interview** are provided with more extensive testing (for example with diagnostic mental health instruments); these relatives/ informants receive more extensive evaluation (i.e. different and additional reference standard tests).<br>**UNCLEAR**: Some information provided but insufficient to determine this item. |

| Modified Quality Assessment of Diagnostic Accuracy Studies (OUADAS) [1] | |
|---|---|
| **QUADAS ITEM (*Topic/Bias*)** | **Interpretation for Family History OMAR Review** |
| **7)** Was the reference standard **independent** of the index test (i.e. the index test did not form part of the reference standard)?<br>*(Incorporation bias)* | "When the result of the index test is used in establishing the final diagnosis, **incorporation bias** may occur. This incorporation will probably increase the amount of agreement between index test results and the outcome of the reference standard, and hence overestimate the various measures of diagnostic accuracy." This item is not applicable in tests that do not **use multiple tests as part of the reference standards**.<br><br>The index test in this systematic review is the reporting of family history by the probands or informants. There are some special situations where informants are unable to provide family history information (for example they are too ill); in these situations, proxy family members are asked to provide the family history. These same family members, who served as proxy informants, may also be asked about their own disease status and may have knowledge of the responses they gave on behalf of the informant. We view this as an issue of **masking bias**, not incorporation bias.<br><br>In the mental health area, family history is often included as part of a list of criteria to determine the disease status of either the proband OR the relative. In addition to inquiring about family history, the verification of the disease is established by asking probands or relatives a checklist of symptoms or other questions related to establishing diagnostic criteria. Thus, in this situation, there is the potential for incorporation bias, as the knowledge of the family history OR details of the presence or absence of symptoms (provided by the informant or proband) may be used to establish the mental health disorder within the relative.<br><br>In some studies evaluating probands with mental health disorders, the authors make it very clear that different instruments were used to collect family history from the probands and from the relatives. In this case, although family history is collected from both the proband/informant and the relative, we are assuming this is NOT incorporation bias. The response of the proband/ informant is independent and is not included in the information collected to establish disease within the relative.<br><br>**YES**: The index test (proband/ informant) reporting of family history is NOT included in the determination of the disease status of the relatives.<br>**NO:** The index test (proband/ informant) reporting of family history is included in the determination of the disease status of the relatives.<br>**UNCLEAR**: Some information provided but insufficient to determine this item. |

| Modified Quality Assessment of Diagnostic Accuracy Studies (OUADAS) [1] | |
|---|---|
| **QUADAS ITEM (*Topic/Bias*)** | **Interpretation for Family History OMAR Review** |
| **8)** Was the execution of the index test described in sufficient detail to permit **replication** of the test? *(Incorporation bias)* | We are looking for sufficient detail for **REPLICATION** of the index test. This should include details of the "questions" used to probe family history, and if possible the degree of relative (for example 1DR, 2DR, etc). Additionally, in studies evaluating probands with mental health disorders, note the sequence when family history was collected. We fully anticipate that there will be differences in the ways in which family history is collected across studies. If reported, evaluate the manner in which "don't know" information was captured and classified.<br><br>NB: We are aware that even if the method is replicable, it may not capture the **quality of the manner** in which FHx was captured; that is the study describes in detail the question used to probe family history, but the question is not well structured and may lead to poor or erroneous responses from the proband/informant. In this case, although the method was "replicable", we do not evaluate this as NO for QUADAS; rather we comment on the nature of the question.<br><br>**YES:** If the manner in which FHx was collected is well specified (for example, standardized questions, or instrument are detailed).<br>**NO:** There is no information about the manner in which FHx was probed (for example the questions asked) or the methods used to collect the information (not clear if a standardized format was used).<br>**UNCLEAR:** Indicate that a standardized instrument was used, but do not know what was probed. Partial information is provided but not enough to score this item. |
| **9)** Was the execution of the reference standard described in sufficient detail to permit its **replication**?<br>(Incorporation bias) | In the case of the reference standard, we are looking for sufficient detail to be able to REPLICATE how disease status was established. In the case where interview of the relative is used as a reference standard, any additional probing (for example questions to establish presence of mental health disorder) should also be described.<br><br>Note that in most studies multi-modal approaches were used to establish the disease status of the relative. As such it is important that the authors describe how 1) deceased versus living relatives had their disease status verified, 2) positive versus negative status relatives (based on index test) had their disease status verified, 3) relatives that were unable to be contacted or participate, and 4) relatives for which no additional information could be obtained. If reported evaluate how "don't know" information was captured and classified.<br><br>**YES:** Indicate the manner in which the disease status was established in relatives (self report, medical chart, linkage with registry, physical examination, etc). Note how missing information or "don't know" (due to inability to get records for example) are handled.<br>**NO:** The information is insufficient to replicate the reference standard.<br>**UNCLEAR**: Indicate methods for some of the multiple sources used to verify the disease status within relatives but insufficient information to score this item. |

| Modified Quality Assessment of Diagnostic Accuracy Studies (OUADAS) [1] | |
|---|---|
| **QUADAS ITEM (*Topic/Bias*)** | **Interpretation for Family History OMAR Review** |
| **10)** Were the index test results **interpreted** without knowledge of the results of the reference standard? *(Blinding)* | We assume this bias to be associated with the collection of data from the researchers and is related to **"review bias" or blinding**. Family history collection from probands/ informants generally precedes contact with relatives for subsequent verification. As such the data collectors would typically not be aware of the true disease status of the relative when collecting family history from the informant.<br><br>However, for some diseases, proxy informants (often relatives) are used when informants are incapacitated or deceased). In the context of this systematic review, bias can occur when the proxy members used to provide family history are also the relatives who are used to verify their own or others disease status. They are **not blind** to their previous report of the disease status of their own health or that of other relatives.<br><br>**YES:** Index test results were interpreted without knowledge of the relatives' disease status. If proxy informants (i.e. relatives) had their disease status verified by means other than interview (for example medical record linkage or clinical assessment), OR the proxy informants who are relatives were **excluded** from the pool of relatives in the analysis, then score YES for this item.<br>**NO:** Index test are not interpreted without knowledge of the reference standard. Also, the potential for masking bias is likely, when the proxy informants (i.e. relatives) were used and then these SAME relatives were then asked to confirm their own or other relatives disease status by interview only.<br>**UNCLEAR:** Partial description is provided but not enough information to score this item. |

| Modified Quality Assessment of Diagnostic Accuracy Studies (OUADAS) [1] | |
|---|---|
| **QUADAS ITEM (*Topic/Bias*)** | **Interpretation for Family History OMAR Review** |
| **11)** Were the reference standard results **interpreted** without knowledge of the index test?<br>*(Blinding)* | We assume this bias to be associated with the collection of data from the researchers and is related to **"review bias" or blinding**. Contact with the relatives is dependent on some minimal information or screening provided by the proband/informant. However, there is the possibility that the **data collectors** who contact the relatives (or check their medical records, etc.) are not blind to the report given by the proband/informant. Specifically, we look for a description specifying the masking of the data collectors of the reference standard.<br><br>In the mental health area, data collectors ask relatives a series of screening questions to determine the presence of a mental health disorder. Subsequently, their responses to these questions are used by an EXTERNAL diagnostician to determine the status of the disease. Although, in some cases it is not clear if the data collector was blind to the report from the index test (proband/informant report), we do accept the external diagnostician as being blind in this case.<br><br>**YES:** Study reports or methods describe blinding of data collectors or diagnostician verifying the disease status of the relative.<br>**NO:** Study reports or methods confirm lack of blinding of the data collector to their disease status base don the informant report of family history.<br>**UNCLEAR**: Blinding for some of the verification methods but not all of the methods is provided or there insufficient information to judge this item. |
| **12)** Were the same clinical data available when test results were interpreted as would be available when the test is used in practice?<br>*(Misclassification)* | QUADAS instructions suggest that if the interpretation of the index test is fully automated and involves no interpretation then this item may not be relevant and can be omitted from the quality assessment tool. However, the interpretation of the family history collection (index test) may require some judgement and depends on what is asked of the proband/informant or relative.<br>Clinical data in the context of family history collection in primary care, could refer to information from direct observation, or access to proxy informants (such as a 1DR who may accompany the proband). It is unlikely that a primary care physician may have access to medical records, disease registries and death registries with information about the status of the **relatives**.<br><br>*In the context of this systematic review, this item will not discriminate between studies; we will omit this item.* |

| Modified Quality Assessment of Diagnostic Accuracy Studies (OUADAS) [1] | |
|---|---|
| **QUADAS ITEM (*Topic/Bias*)** | **Interpretation for Family History OMAR Review** |
| **13)** Were un-interpretable/ intermediate test results reported? *(Misclassification)* | In the context of family history collection it was difficult to define what results were "uninterpretable". We assume that this item is interpreted to apply to disease status classification when the proband/informant (index test) did not know the disease status of the relative. Similarly, the disease status of the relative (reference standard) is not known or cannot be confirmed (for example, medical records may not have been easily obtained, or were inconclusive with regards to the disease status, or self report was unclear).<br><br>In many studies (particularly mental health disorders) many of the relatives were excluded from the analysis and as such this is an issue of partial verification or a case of differential verification.<br><br>*In the context of this systematic review this item could not be disentangled from partial and differential verification bias and was not applicabled* |

| Modified Quality Assessment of Diagnostic Accuracy Studies (OUADAS) [1] | |
|---|---|
| **QUADAS ITEM (*Topic/Bias*)** | **Interpretation for Family History OMAR Review** |
| **14)** Were withdrawals for the study explained? *(Misclassification)* | “This occurs when subjects withdraw from the study **before** the results of either the index test or reference standard test are known. Note that the subjects considered in the context of the review include both the proband/informant sample AND the relatives/proxy sample. If patients differ systematically from those that remain in the analysis, then there is the potential for bias.<br><br>We consider the sample of relatives to be those reported from the probands/ informants during the index test. As such, some studies do not specify the total sample of relatives reported; rather they report the number of relatives/ informants for which data was available.<br><br>Potential subjects recruited can include those that are 1) alive, 2) deceased and a best proxy is found, 3) incapacitated to be interviewed and a best proxy is found,<br>Potential recruited subjects are likely to be excluded if 1) they refuse to participate, or b) a proxy informant is not found.<br>In some studies, subjects were further excluded if there was not a match 9<br><br>**YES**: If all probands/ informants are accounted for in a flow diagram or reporting details; this includes the number of subjects as follows:<br>1) those recruited<br>2) providing consent or refusing consent<br>3) for which a proxy respondent could not be provided<br>4) unable to complete the family history collection (for example due to frailty)<br>5) number not able to contact<br>If all relatives (identified by the proband/ informants/ or registry) are accounted for in a flow diagram or reporting details; this includes the number of subjects as follows:<br>1) ALL relatives identified by the probands/ informants/ registry<br>2) relatives who gave consent or those refusing consent<br>3) unable to complete family history<br>4) for which a proxy informant could not be found<br>5) who were deceased<br>6) could not be contacted<br>7) unable to get verification of disease status<br>**NO**: If all informants who entered the study are not accounted for.<br>**UNCLEAR**: Partial information is provided, but insufficient to judge this criteria. |

Modified QUADAS form

| REF ID# | AUTHOR/ YEAR | |
|---|---|---|
| **QUADAS ITEM** | **RESPONSE** | **COMMENTS** |
| 1) Was the spectrum of patients' representative of the patients who will receive the test in practice? | YES<br>NO<br>UNCLEAR | |
| 2) Were the selection criteria clearly described? | YES<br>NO<br>UNCLEAR | |
| 3) Is the reference standard likely to correctly classify the target intervention? | YES<br>NO<br>UNCLEAR | |
| 4) Is the reference standard and index test short enough to be reasonably sure the target condition did not change between the two tests? | YES<br>NO<br>UNCLEAR | |
| 5) Did the whole sample or a random selection of the sample receive verification using a reference standard of diagnosis? | YES<br>NO<br>UNCLEAR | |
| 6) Did the patients receive the same reference standard regardless of the index test? | YES<br>NO<br>UNCLEAR | |
| 7) Was the reference standard independent of the index test (i.e. the index test did not form part of the reference standard)? | YES<br>NO<br>UNCLEAR | |
| 8) Was the execution of the index test described in sufficient detail to permit replication of the test? | YES<br>NO<br>UNCLEAR | |
| 9. Was the execution of the reference standard described in sufficient detail to permit its replication? | YES<br>NO<br>UNCLEAR | |
| 10) Were the index test results interpreted without knowledge of the results of the reference standard? | YES<br>NO<br>UNCLEAR | |
| 11) Were the reference standard results interpreted without knowledge of the index test? | YES<br>NO<br>UNCLEAR | |
| 12) Were the same clinical data available when test results were interpreted as would be available when the test is used in practice? | YES<br>NO<br>UNCLEAR | |
| 13) Were uninterpretable/ intermediate test results reported? | YES<br>NO<br>UNCLEAR | |
| 14) Were withdrawals for the study explained? | YES<br>NO<br>UNCLEAR | |

# References

Elbaz A, McDonnell SK, Maraganore DM, et al. Validity of family history data on PD: evidence for a family information bias. Neurology 2003;61(1):11-7.

Whiting PF, Weswood ME, Rutjes AW, et al. Evaluation of QUADAS, a tool for the quality assessment of diagnostic accuracy studies. BMC Med Res Methodol 2006;6:9

**Webtable 1. General data for cancer studies**

| Author Year | Study setting | Study design | n | Sub-groups measured | How/when FH obtained | Definition of outcome | How/when outcome ascertained |
|---|---|---|---|---|---|---|---|
| Ahn 2008 | Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study, cohort of Finnish male smokers | prospective cohort | 19,652 | male smokers and their 1DRs | questionnaire | histologically confirmed prostate cancer | national cancer registry and centralized record reviews |
| Byeon 2007 | Seoul, Korea Asymptomatic adults aged 20 - 90 y | prospective cohort | 860 | all subjects | questionnaire | histologically confirmed colon or rectal cancer, adenoma≥10mm, villous adenoma, or adenoma with high grade dysplasia | screening colonoscopy |
| Cauley 2007 | women with osteoporosis, ≤80 y | analysis of MORE and CORE RCTs | 2,576 | all subjects followed for up to 8 y | self-completion questionnaire | incidence of breast cancer, histological confirmation | screening mammography, CBE |
| Cerhan 1996 | population-based, Iowa, U.S. | prospective cohort | 1,494 | males aged 67.9 ± 9.7 y | questionnaire | ICD oncology code 61.9 | passive followup through state cancer registry |
| Chen 2008 | health professionals in U.S. | cohort | 51,525 | age, clinical stage, Gleason score | questionnaire | histologically confirmed prostate cancer excluding stage T1a | self or proxy report through biennial survey |
| Denic 2001 | married women who are United Arab Emirates nationals, ages 40 to 65 y | cross-sectional | 1,445 | women, ages 40 to 65 y | interview | physician-confirmed breast cancer | self-report confirmed by medical records |

Abbreviations: 1DR=first degree relative; 2DR=second degree relative; CORE=Continuing Outcomes Relevant to Evista; CRC=Colorectal cancer; FH=Family History; ICD-9=International Classification of Diseases-Ninth Edition; MORE=Multiple Outcomes of Raloxifene Evaluation; n=number of subjects; PSA=prostate specific antigen; RCT=randomized controlled trial; y=years

**Webtable 1. General data for cancer studies (continued)**

| Author Year | Study setting | Study design | n | Sub-groups measured | How/when FH obtained | Definition of outcome | How/when outcome ascertained |
|---|---|---|---|---|---|---|---|
| Halapy 2005 | Ontario Breast Screening Program; women in Ontario | retrospective cohort | 115,460 | women aged 50-69y with no personal history of breast cancer or augmentation mammoplasty, and free of acute breast symptoms | interview | histologically confirmed invasive breast cancer | screening mammography, cancer registry |
| Kalish 2000 | Massachusetts Male Aging Study mean age 54.1 ± 8.4 y | prospective cohort | 1,149 | all subjects | questionnaire | prostate cancer, not further specified | PSA screening, medical record search, cancer registries |
| Kerlikowske 1997 | women accrued from a screening mammographic examination at the University of California San Francisco Mobile Mammography Screening Program | cross-sectional | 39,542 | women aged 30 y and older with no history of breast cancer and no previous mastectomies | interview | histologically confirmed invasive breast cancer | screening mammography, physician survey, pathology and radiology databases, SEER data |
| Mäkinen 2002 | Finnish prostate cancer screening trial, Finland, men aged 55 to 67 y | cross-sectional | 20,311 | males aged 55 to 67 y | questionnaire | histologically confirmed prostate cancer | PSA screening |

**Webtable 1. General data for cancer studies (continued)**

| Author Year | Study setting | Study design | n | Sub-groups measured | How/when FH obtained | Definition of outcome | How/when outcome ascertained |
|---|---|---|---|---|---|---|---|
| Rodriguez 1997 | male participants in U.S. Cancer Prevention Study II | prospective cohort | 481,011 | all subjects | questionnaire | ICD-9 code 185 recorded as underlying cause of death | biennial personal inquiry, National Death Index |
| Sandhu 2001 | East Anglian component of the European Prospective Investigation into Cancer, UK, men and women aged 45-74 y | cross-sectional | 30,353 | men and women aged<br>40-79 y<br>40-49 y<br>50-59 y<br>60-69 y<br>70-79 y<br><br>Women aged<br>40-79 y<br>40-49 y<br>50-59 y<br>60-69 y<br>70-79 y<br><br>Men aged<br>40-79 y<br>40-49 y<br>50-59 y<br>60-69 y<br>70-79 y | questionnaire | registered in regional cancer registry with ICD-9 diagnosis codes 153.0-153.9, 154.0, 154.1 | regional cancer registry |
| Wei 2004 | patients from Nurses' Health Study and Health Professionals Followup Study | combined prospective cohort | 134,365 | women<br>men | questionnaire | histologically confirmed colon or rectal cancer | self or proxy report through biennial survey plus National Death Index |

**Webtable 2. Predictive values associated with FH definitions for breast cancer in longitudinal analyses**

| FH category | Specific definition | Age criterion | Lineage criterion | Studies | Disease prevalence in study sample (%) | Prevalence of positive FH in study sample (%) | PPV for study sample | NPV for study sample | Most highly adjusted reported RR or equivalent[1] (max length of FU) |
|---|---|---|---|---|---|---|---|---|---|
| C | ≥1 1DR female | N | N | Cauley | 2.5 | 12.5 | 0.05 | 0.98 | HR 2.83 (4-8y) |
| E | ≥1 1DR breast ≥50 OR 1 1DR ovarian | N | N | Halapy | 0.6 | 14.6 | 0.01 | 0.99 | 1.37 (12 mo) |
| E | ≥2 1DR breast and/or ovarian any age OR ≥1 1DR breast <50 y OR ≥1 1DR both breast and ovarian | Y | N | Halapy | 0.6 | 5.0 | 0.01 | 0.99 | 2.28 (12 mo) |

Abbreviations: 1DR=first degree relative; FH=family history; FU=followup; mo=months; HR=hazard ratio; N=no; NPV=negative predictive value; PPV=positive predictive value; RR=relative risk; y=years; Y=yes

[1] RR=relative risk, metric reported unless otherwise stated

**Webtable 3. Predictive values associated with FH definitions for breast cancer cross-sectional analyses**

| FH category | Specific definition | Age criterion | Lineage criterion | Studies | Disease prevalence in study sample (%) | Prevalence of positive FH in study sample (%) | PPV for study sample | NPV for study sample | Most highly adjusted reported OR or equivalent[1] |
|---|---|---|---|---|---|---|---|---|---|
| C | ≥1 1DR | N | N | Denic | 5.4 | 3.0 | 0.09 | 0.95 | NR |
| | | | | Kerlikowske | 0.7 | 9.9 | 0.01 | 0.99 | 1.7 |
| E | consgs parents | N | N | Denic | 5.4 | 40.1 | 0.04 | 0.94 | 0.66 (RR) |

Abbreviations: 1DR=first degree relative; consg=consanguineous; FH=family history; N=no; NPV=negative predictive value; NR=not reported; OR=odds ratio PPV=positive predictive value; RR=relative risk

[1] OR=odds ratio, metric reported unless otherwise stated

**Webtable 4. OR, HR and RR presented in each report for review question 1**

| Author Year | Family history | Outcome | Confounder adjustment | OR/HR /RR | OR/HR /RR | CI (low) | CI (high) |
|---|---|---|---|---|---|---|---|
| Ajlouni 2008 | diabetes (family history) | diabetes | | OR (multivariate) | 3.09 | 2.69 | 5.68 |
| AhnJ 2008 | prostate cancer (1DR family history) | prostate cancer | age & trial intervention | RR | 1.91 | 1.49 | 2.47 |
| | prostate cancer (1DR family history) | prostate cancer (advanced disease (stage≥3) | age & trial intervention | RR | 4.16 | 2.67 | 6.49 |
| Alford 2004 | asthma (paternal history) | asthma- current (seroatopy) | sex of the study child, parental education, parental smoking, multiple pet ownership, first-born status, and history of disease in other parent. | OR | 8.35 | 1.75 | 39.96 |
| Annis 2005 | diabetes | diabetes (1DR relative) | NR | crude odds ratio | 5 | NR | NR |
| Bener 2005 | asthma (father) | asthma | NR | RR. | 2.3 | 1.9 | 2.7 |
| | asthma (mother) | asthma | NR | RR. | 2.1 | 1.8 | 2.4 |
| Bergmann 1997 | atopy dermatitis (father history) | atopy - early | adjusted | OR | 4.92 | 2.34 | 10.3 |
| Bindraban 2008 | diabetes (1DR relative) | diabetes | NR | OR (multi) | 2.7 | 1.8 | 4.2 |
| Bjornholt 2000 | diabetes type 2 (maternal) | diabetes type 2 | NR | HR | 2.65 | 1.64 | 4.25 |
| | diabetes type 2 (paternal) | diabetes type 2 | NR | HR | 1.79 | 0.78 | 3.61 |
| | diabetes type 2 (both) | diabetes type 2 | NR | HR | 6.89 | 2.18 | 21.7 |

Abbreviations: 1DR=first degree relative; AMI=acute myocardial infarction; B=any family history; BMI=body mass index; BP=blood pressure; CI=confidence interval; CHD=coronary heart disease; CVD=cardiovascular disease; DBP=diastolic blood pressure; F=father's side of family; FH=family history; HDL=high density lipoprotein; HDL-C=high density lipoprotein-cholesterol; HOMA-R=homeostasis model assessment; HR=hazard ratio, HRT=hormone replacement therapy; IGT=impaired glucose tolerance; LADA=latent autoimmune diabetes in adults; LDL=low density lipoprotein; MI=myocardial infarction; multi=multivariate; NGT=normal glucose tolerance; NR=not reported; OR=odds ratio; POR=prevalence odds ratio; RR=relative risk; S=sibling; SBP=systolic blood pressure; SOB=shortness of breath; TG=triglycerides

**Webtable 4. OR, HR and RR presented in each report for review question 1 (continued)**

| Author Year | Family history | Outcome | Confounder adjustment | OR/HR /RR | OR/HR /RR | CI (low) | CI (high) |
|---|---|---|---|---|---|---|---|
| Byeon 2007 | colorectal cancer (FH) | proximal advanced neoplasm without polyps | NR | OR | 6.0 | 1.3 | 26.6 |
| Carlsson 2007 | diabetes(family) | LADA<br>Type2<br>Type1 | age, sex | OR | 3.92<br>4.20<br>2.78 | 2.76<br>3.72<br>1.89 | 5.58<br>4.75<br>4.10 |
| Cauley 2007 | breast cancer (FH) | breast cancer | NR | HR | 2.83 | 1.58 | 5.05 |
| Cerhan 1999 | prostate cancer | prostate cancer (father or brother) | age, alcohol intake, nutrients or food | RR | 3.7 | 1.9 | 7.2 |
| | prostate cancer | prostate cancer (father | age, alcohol intake, nutrients or food | RR | 2.3 | 0.9 | 5.9 |
| | prostate cancer | prostate cancer (brother) | age, alcohol intake, nutrients or food | RR | 6.5 | 2.6 | 16 |
| Chen 2008 | prostate cancer (father & brother) | prostate cancer | ethnicity, BMI, total calories, vigorous activity, cigarette smoking, consumption of tomato sauce, calcium, alpha linolenic acid, fish, red meat | RR | 2.34 | 1.76 | 3.12 |
| Chatkin 2003 | asthma or allergy (family history) | current wheeze | adjusted | RR | 1.85 | 1.42 | 2.42 |
| Chatkin 2005 | asthma (FH) | asthma | smoking during pregnancy and confounding variables? | RR | 2.8 | 1.5 | 5.1 |
| Denic 2001 | breast cancer | breast cancer (consgs) | none | RR | 0.66 | 0.42 | 1.06 |

**Webtable 4. OR, HR and RR presented in each report for review question 1 (continued)**

| Author Year | Family history | Outcome | Confounder adjustment | OR/HR /RR | OR/HR /RR | CI (low) | CI (high) |
|---|---|---|---|---|---|---|---|
| Djousse 2008 | MI (parental history) | heart failure in male physician | mutual adjustment for age (< 45, 45–49, 50–54, 55–59, 60–64, 65 + y), smoking (never, past, and current smokers), body mass index (< 25, 25–29, 30 + kg m–2), exercise (0, ≤ 1, 2–4, 5 + per week), alcohol (< 1, 1–4, 5–7, and 8 + drinks/week), breakfast cereals (≤ 1, 2–6, 7 + servings/week), cereal and history of hypertension, diabetes, left ventricular hypertrophy, atrial fibrillation, aspirin, fruit and vegetable consumption (< 3, 3–4, 5–6, 7–13, 14 + servings/week), and multivitamin use. | HR | 1.32 | 1.02 | 1.72 |
| Dodani 2005 | coronary artery disease (FH) | coronary artery disease | NR | OR | 1.7 | 1.13 | 2.63 |
| Ebbesson 1998 | diabetes | diabetes | age and obesity | OR | 4.4 | 1.8 | 10.7 |
| | diabetes | glucose intolerance | age and obesity | OR | 3.3 | 1.6 | 6.7 |
| Garcia-Marcos 2005 | asthma (maternal & paternal) | atopic wheezing | male gender, mould stains, dog, cat | OR | 2.16 | 1.44 | 3.22 |
| Gikas 2004 | diabetes (FH) | diabetes | age | OR | 6.91 | 5.11 | 9.34 |

**Webtable 4. OR, HR and RR presented in each report for review question 1 (continued)**

| Author Year | Family history | Outcome | Confounder adjustment | OR/HR /RR | OR/HR /RR | CI (low) | CI (high) |
|---|---|---|---|---|---|---|---|
| Gillespie 2006 | allergic disease | wheezing | total number of people in the house, total number of rooms in the house, owning a pet, having a damp, musty smell, dampness or mold in the bedroom, having an open fireplace, maternal smoking, type of flooring in the bedroom | OR | 1.67 | 1.07 | 2.60 |
| | allergic disease | rash | total number of people in the house, total number of rooms in the house, owning a pet, having a damp, musty smell, dampness or mold in the bedroom, having an open fireplace, maternal smoking, type of flooring in the bedroom | OR | 2.10 | 1.22 | 3.61 |
| Granstrom 2008 | breast cancer (mother) | breast cancer | NR | RR | 1.75 | 1.56 | 1.97 |
| Halapy 2005 | breast cancer (strong FH) | breast cancer | age, HRT, prior screen | RR (rate ratio) | 2.14 | 0.91 | 4.99 |
| Hariri 2006 | diabetes (FH) (moderate & high familial risk) | diabetes | all other demographic characteristic | OR | 3.6 | 2.8 | 4.7 |
| Hariri 2006 | diabetes (high FH) | diabetes | demographic variables & BMI | OR | 4.6 | 1.9 | 11.3 |
| Haron 2006 | diabetes (FH) | diabetes | NR | OR | 2.47 | 1.45 | 4.20 |
| Hedlund 2006 | asthma symptom complex (FH) | asthma | socio economic class, occupational exposure to dust, gases or fumes, SOB | OR | 2.9 | 2.2 | 3.7 |
| Hennis 2002 | diabetes (FH) | diabetes | adjusted (confounding variables) | OR | 2.85 | 2.39 | 3.40 |
| Hilding 2006 | diabetes (FH) | diabetes in men | age, BMI, physical activity | OR | 3.1 | 1.7 | 5.6 |
| | diabetes (FH) | diabetes in women | age, BMI, physical activity | OR | 1.7 | 1 | 3 |

**Webtable 4. OR, HR and RR presented in each report for review question 1 (continued)**

| Author Year | Family history | Outcome | Confounder adjustment | OR/HR /RR | OR/HR /RR | CI (low) | CI (high) |
|---|---|---|---|---|---|---|---|
| Hippe 1999 | MI | MI | age, population study of origin, cholesterol BMI, diabetes (women) | RR | 1.42 | 0.12 | 1.79 |
| | MI | MI | age, population study of origin, cholesterol BMI, diabetes (men) | RR | 1.30 | 1.11 | 1.52 |
| Jorgensen 2002 | diabetes (FH) | diabetes (glucose tolerance) | age, sex | OR | 2.46 | 1.33 | 5.55 |
| | diabetes (FH) | diabetes & IGT | age, sex | OR | 3.17 | 1.55 | 6.47 |
| Jousilahti 1996 | premature coronary heart disease (either parent) | AMI | age (men) | RR | 1.61 | 1.36 | 1.89 |
| | premature coronary heart disease (either parent) | AMI | age (women) | RR | 1.85 | 1.40 | 2.43 |
| | premature coronary heart disease (either parent) | AMI | age, study year, cardiovascular risk factors (men) | RR | 1.54 | 1.31 | 1.82 |
| | premature coronary heart disease (either parent) | AMI | age, study year, cardiovascular risk factors (women) | RR | 1.80 | 1.36 | 2.37 |
| | premature coronary heart disease (either parent) | AMI | age, study year, and cardiovascular risk factors, and socioeconomic indicators (men) | RR | 1.55 | 1.31 | 1.83 |
| | premature coronary heart disease (either parent) | AMI | age, study year, and cardiovascular risk factors, and socioeconomic indicators (women) | RR | 1.80 | 1.37 | 2.37 |
| Jousilahti 1997 | stroke | stroke (any type) | age, study year, multifactorial double dagger adjustments | RR (Men) | 1.89 | 1.23 | 2.91 |
| | stroke | stroke (any type) | age, study year, multifactorial double dagger adjustments | RR (women) | 1.80 | 1.17 | 2.75 |
| Kadota 2008 | hypertension (FH) | all stroke | age, systolic BP, blood glucose, total cholesterol, smoking, drinking | HR | 1.36 | 0.96 | 1.93 |
| Kalish 2000 | prostate cancer (F)<br>prostate cancer (S)<br>prostate cancer (B) | prostate cancer | age | RR | 2.59<br>3.87<br>3.29 | 1.27<br>1.74<br>1.82 | 5.29<br>8.57<br>5.9 |

**Webtable 4. OR, HR and RR presented in each report for review question 1 (continued)**

| Author Year | Family history | Outcome | Confounder adjustment | OR/HR /RR | OR/HR /RR | CI (low) | CI (high) |
|---|---|---|---|---|---|---|---|
| Kalyoncu 2001 | atopy (family) | asthma<br>current wheeze<br>seasonal rhinitis | NR | POR | 1.99<br>2.18<br>2.20 | 1.14<br>1.55<br>1.69 | 3.47<br>3.06<br>2.86 |
| Kerlikowske 1997 | breast cancer (1DR relatives (mother, sister or daughter) | ductal carcinoma In situ | NR | OR (30-49 year old) | 2.4 | 1.1 | 4.9 |
| Khan 2002 | NR | NR | NR | NR | NR | NR | NR |
| Kim 2008 | diabetes (family history) | diabetes | NR | RR | 2.12 | 1.49 | 3.00 |
| Krakowiak 2007 | atopy | occupational asthma | NR | OR | 5.9 | 1.76 | 20.00 |
| Kulig 2000 | NR | NR | NR | NR | NR | NR | NR |
| Kurukulaaratchy 2004 | asthma (maternal history) | atopic wheeze | NR | OR | 2.9 | 1.32 | 3.32 |
| | asthma (paternal history) | atopic wheeze | NR | OR | 2.59 | 1.60 | 4.019 |
| Lack 2003 | asthma (maternal) | peanut allergy | NR | OR | 1.55 | 0.72 | 3.32 |
| Levitt 1999 | diabetes (Family history) | diabetes | NR | RR (risk ratio) | 2.31 | 1.42 | 3.77 |
| London 2001 | allergy and asthma combined (parental history) | early-onset persistent asthma | NR | RR | 17.60 | 11 | 28.2 |
| Lopez 1999 | NR | NR | NR | NR | NR | NR | NR |
| Magno 2008 | MI (parental) | CVD | age, exercise, parental history, LDL, HDL, hypertension, microalbuminuria, adiponectin | OR | 2.81 | 1.37 | 5.74 |
| Makinen 2002 | prostate cancer (family history) | prostate –specific antigen | NR | RR (rate ratio) | 1.3 | 0.9 | 1.8 |
| | prostate cancer (1DR relative(s)) | prostate –specific antigen | NR | RR | 1.26 | 0.87 | 1.82 |
| | prostate cancer (father) | prostate –specific antigen | NR | RR | 1.18 | 0.76 | 1.53 |

**Webtable 4. OR, HR and RR presented in each report for review question 1 (continued)**

| Author Year | Family history | Outcome | Confounder adjustment | OR/HR /RR | OR/HR /RR | CI (low) | CI (high) |
|---|---|---|---|---|---|---|---|
| Meigs 2000 | diabetes type 2 (mother)<br>diabetes type 2 (father)<br>diabetes type 2 (both) | diabetes type 2 | age | OR | 3.4<br>3.5<br>6.1 | 2.3<br>2.3<br>2.9 | 4.9<br>5.2<br>13.0 |
| Melbostad 1998 | asthma (parents or sibling) | asthma (started in last 10 years) | NR | OR | 3.1 | 2.3 | 4.9 |
| Montnemery 2000 | asthma | asthma | NR | OR | 3.71 | 3.06 | 4.51 |
| | chronic bronchitis/ emphysema | asthma | NR | OR | 5.19 | 4.09 | 6.60 |
| Morrison 2000 | stroke | subclinical stroke (cerebral infarct) | age, gender, race, multiple stroke risk factors | OR | 1.64 | 1.20 | 2.24 |
| | stroke | subclinical stroke (cerebral infarct) | age, gender, race, | OR | 1.67 | 1.23 | 2.26 |
| Motala 2008 | diabetes | diabetes | NR | OR | 3.5 | ---- | ---- |
| Mohan 2003 | NR | NR | NR | NR | NR | NR | NR |
| Nakanishi 2003 | diabetes type 2 | diabetes type 2 | age, SBP, DBP, TG, HDL-c, NGT, IGT | HR (women) | 1.86 | 1.08 | 3.19 |
| | diabetes type 2 | diabetes type 2 | age, SBP, DBP, TG, HDL-c, NGT, IGT, and BMI | HR (women) | 1.84 | 1.07 | 3.15 |
| | diabetes type 2 | diabetes type 2 | age, SBP, DBP, TG, HDL-c, NGT, IGT, HOMA~R | HR (women) | 1.81 | 1.05 | 3.13 |
| | diabetes type 2 | diabetes type 2 | age, SBP, DBP, TG, HDL-c, NGT, IGT, BMI, and HOMA~R | HR (women) | 1.79 | 1.04 | 3.10 |
| Nyenwe 2003 | diabetes type 2 (FH) | diabetes type 2 | NR | OR | 9.45 | 3.49 | 35.53 |
| Ones 1997 | asthma (1DR relatives) | asthma | NR | OR | 2.49 | 1.66 | 3.73 |
| Ozdemir 2005 | diabetes (FH) | diabetes | NR | OR | 1.20 | 0.56 | 1.20 |
| Park 1995 | asthma (FH) | asthma (Current) | sex, race, education | OR | 3.3 | 2.4 | 4.5 |
| | asthma (FH) | asthma (physician reported) | sex, race, education | OR | 3.1 | 2.4 | 4.3 |
| Patrzalek 2003 | allergy (maternal/paternal) | allergic disease | NR | OR | 11.2 | NR | NR |

**Webtable 4. OR, HR and RR presented in each report for review question 1 (continued)**

| Author Year | Family history | Outcome | Confounder adjustment | OR/HR /RR | OR/HR /RR | CI (low) | CI (high) |
|---|---|---|---|---|---|---|---|
| Piros 2000 | MI (mother or father | MI | NR | RR | 2.45 | 1.30 | 4.62 |
| Pohlabeln 2007 | NR | NR | NR | NR | NR | NR | NR |
| Rahman 2008 | diabetes (parent & sibling) | diabetes | crude | OR | 3.30 | 1.61 | 6.75 |
| Reinherz 2003 | psychiatric disorders (sibling) | depression | NR | OR adjusted | 2.88 | 1.20 | 6.97 |
| Rodriguez 1997 | prostate cancer (≥1DR relatives) | prostate cancer | age at enrolment, race, years of e index, physical activity, intake of vegetables and fat, smoking status at study < vasectomy | RR (rate ratio) | 3.19 | 1.51 | 6.71 |
| | prostate cancer (FH) | prostate cancer | age at enrolment, race, years of e index, physical activity, intake of vegetables and fat, smoking status at study < vasectomy | RR (rate ratio) | 1.60 | 1.31 | 1.97 |
| Sandhu 2001 | colorectal cancer | colorectal cancer | age, smoking | OR (women) | 2.77 | 1.46 | 5.26 |
| | colorectal cancer (one or more 1DR relatives) | colorectal cancer | age, smoking | OR (women) | 2.11 | 1.26 | 3.54 |
| | colorectal cancer (two or more 1DR relatives) | colorectal cancer | age, smoking | OR (women) | 5.29 | 1.63 | 17.17 |
| Saquib 2005 | NR | NR | NR | NR | NR | NR | NR |
| Scheuner 2006 | CHD (1DR relatives) | CHD | age, race, marital status, education, income, self-reported obesity, hypercholesterolemia, hypertension | OR | 3.8 | 2.3 | 6.2 |
| | stroke (1DR relatives) | stroke | age, race, marital status, education, income, self-reported obesity, hypercholesterolemia, hypertension | OR | 1.5 | 1 | 2.3 |

**Webtable 4. OR, HR and RR presented in each report for review question 1 (continued)**

| Author Year | Family history | Outcome | Confounder adjustment | OR/HR /RR | OR/HR /RR | CI (low) | CI (high) |
|---|---|---|---|---|---|---|---|
| Sesso 2001 | MI (parental history maternal and/or parental) | CVD, MI, stroke | age, | RR (women, MI) | 2.86 | 1.73 | 4.73 |
| Shera 2007 | NR | NR | NR | NR | NR | NR | NR |
| Sugimori 1998 | diabetes | diabetes | NR | HR | 1.65 | 1.16 | 2.36 |

**Webtable 5. Quality items for cancer studies for review question 1**

| Author Year | Same outcome ascertain-ment, irrespective of FH (outcome information bias) | Outcome ascertain-ment blind to FH (outcome information bias) | Same FH ascertain-ment, irrespective of disease status (exposure information bias) | FH ascertain-ment blind to disease status (exposure information bias) | Exclusion of cases at inception (cohort) (misclassi-fication) | Adequate followup (cohort) (selection bias) | Representat ive sampling (cross-sectional) (selection bias) | Adequate response rate (cross-sectional) (selection bias) |
|---|---|---|---|---|---|---|---|---|
| **Breast cancer** | | | | | | | | |
| Cauley 2006 | Yes | Yes | Yes | Yes | Yes | At least 80% followup | Not applicable (longitudinal design) | Not applicable (longitudinal design) |
| Halapy 2005 | Yes | Yes | Unclear | Yes | Yes | At least 80% followup | Not applicable (longitudinal design) | Not applicable (longitudinal design) |
| Denic 2001 | Unclear | Unclear | Yes | No | Not applicable (cross sectional design) | Not applicable (cross sectional design) | Unclear | Response rate less than 80%, inadequate or missing description of non-participants |
| Kerlikowske 1997 | Yes | Yes | Unclear | Yes | Not applicable (cross sectional design) | Not applicable (cross sectional design) | Yes (probability sampling) | Yes, response rate at least 80% |

**Webtable 5. Quality items for cancer studies for review question 1 (continued)**

| Author Year | Same outcome ascertain-ment, irrespective of FH (outcome information bias) | Outcome ascertain-ment blind to FH (outcome information bias) | Same FH ascertain-ment, irrespective of disease status (exposure information bias) | FH ascertain-ment blind to disease status (exposure information bias) | Exclusion of cases at inception (cohort) (misclassi-fication) | Adequate followup (cohort) (selection bias) | Representative sampling (cross-sectional) (selection bias) | Adequate response rate (cross-sectional) (selection bias) |
|---|---|---|---|---|---|---|---|---|
| **CRC** | | | | | | | | |
| Byeon 2007 | Yes | Unclear | Yes | Yes | Not applicable (cross sectional design) | Not applicable (cross sectional design) | No (non-probability sampling) | Unclear |
| Sandhu 2001 | Yes | No | Yes | No | Not applicable (cross sectional design) | Not applicable (cross sectional design) | Yes (probability sampling) | Unclear |
| Wei 2004 | Yes | Unclear | Yes | Unclear | Yes | Unclear | Not applicable (longitudinal design) | Not applicable (longitudinal design) |
| **Prostate cancer** | | | | | | | | |
| Ahn 2008 | Yes | Yes | Yes | Yes | Yes | Unclear | Not applicable (longitudinal design) | Not applicable (longitudinal design) |
| Cerhan 1996 | Yes | Yes | No | Yes | Yes | at least 80% followup | Not applicable (longitudinal design) | Not applicable (longitudinal design) |
| Chen 2008 | Yes | Unclear | Yes | Unclear | Unclear | Unclear | Not applicable (longitudinal design) | Not applicable (longitudinal design) |

**Webtable 5. Quality items for cancer studies for review question 1 (continued)**

| Author Year | Same outcome ascertain-ment, irrespective of FH (outcome information bias) | Outcome ascertain-ment blind to FH (outcome information bias) | Same FH ascertain-ment, irrespective of disease status (exposure information bias) | FH ascertain-ment blind to disease status (exposure information bias) | Exclusion of cases at inception (cohort) (misclassi-fication) | Adequate followup (cohort) (selection bias) | Representat ive sampling (cross-sectional) (selection bias) | Adequate response rate (cross-sectional) (selection bias) |
|---|---|---|---|---|---|---|---|---|
| Kalish 2000 | Yes | No | Yes | Yes | Not applicable (cross sectional design) | Not applicable (cross sectional design) | Yes (probability sampling) | Unclear |
| Makinen 2002 | Yes | Unclear | Yes | Yes | Not applicable (cross sectional design) | Not applicable (cross sectional design) | Yes (probability sampling) | Response rate less than 80%, inadequate or missing description of non-participants |
| Rodriguez 1997 | Yes | Unclear | Yes | Yes | Yes | Unclear | Not applicable (longitudinal design) | Not applicable (longitudinal design) |

**Webtable 6. Predictive values associated with FH definitions for colorectal cancer in longitudinal analyses**

| FH category | Specific definition | Age criterion | Lineage criterion | Studies | Disease prevalence in study sample (%) | Prevalence of positive FH in study sample (%) | PPV for study sample | NPV for study sample | Most highly adjusted reported RR or equivalent[1] (max length of FU) |
|---|---|---|---|---|---|---|---|---|---|
| C | ≥1 1DR | N | N | Wei, M | 1.3[1] | 8.5[1] | 0.02[1] | 0.99[2] | colon 1.86 [3]<br>rectum 1.33[3] |
| | | | | Wei, F | 1.0[1] | 7.9[1] | 0.02[1] | 0.99[2] | colon 1.86[3]<br>rectum 1.33[3] |

Abbreviations: 1DR=first degree relative; F=female; FH=family history; FU=followup; M=male; NPV=negative predictive value; N=No; PPV=positive predictive value; RR=relative risk

[1] RR=relative risk, metric reported unless otherwise stated

[2] Colon and rectal cancer outcomes combined

[3] Reported for males and females combined

**Webtable 7. Predictive values associated with FH definitions for colorectal cancer in cross-sectional analyses**

| FH category | Specific definition | Age criterion | Lineage criterion | Studies | Disease prevalence in study sample (%) | Prevalence of positive FH in study sample (%) | PPV for study sample | NPV for study sample | Most highly adjusted reported OR or equivalent[1] |
|---|---|---|---|---|---|---|---|---|---|
| C | ≥1 1DR | N | N | Sandhu, M&F | 0.5 | 6.8 | 0.01 | 1.00 | 2.32 |
| | | | | Byeon, M&F | 4.5 | 12.7 | 0.07 | 0.96 | 3.2 |
| | | | | Sandhu, M | 0.6 | 6.1 | 0.01 | 0.99 | 1.87 |
| | | | | Sandhu, F | 0.4 | 7.4 | 0.01 | 1.00 | 2.77 |
| | | | | Sandhu, M&F, premature(<50) | 0.0 | 5.1 | 0.00 | 1.00 | - |
| | | | | Sandhu, M&F, premature(<60) | 0.2 | 6.1 | 0.00 | 1.00 | 1.75 |
| | | | | Sandhu, M, premature (<60) | 0.3 | 5.6 | 0.00 | 1.00 | - |
| | | | | Sandhu M, premature (<50) | 0.0 | 4.2 | 0.00 | 1.00 | - |
| | | | | SandhuF, premature (<60) | 0.1 | 6.5 | 0.00 | 1.00 | 3.62 |
| | | | | Sandhu, F, premature (<50) | 0.0 | 5.7 | 0.00 | 1.00 | - |
| C | ≥2 1DR | N | N | Sandhu, M&F | 0.5 | 0.3 | 0.03 | 1.00 | 5.29 |
| C | ≥1 1DR, onset <65 | Y | N | Sandhu,M&F | 0.5 | 2.4 | 0.02 | 1.00 | 3.26 |
| C | ≥1 1DR, onset <45 | Y | N | SandhuM&F | 0.5 | 0.3 | 0.02 | 1.00 | 4.93 |

Abbreviations: 1DR=first degree relative; F=female; FH=family history; M=male; N=no; NPV=negative predictive value; NR=not reported; OR=odds ratio PPV=positive predictive value; Y=yes

[1] OR=odds ratio, metric reported unless otherwise stated

**Webtable 8. Predictive values associated with FH definitions for prostate cancer in longitudinal analyses**

| FH category | Specific definition | Age criterion | Lineage criterion | Studies | Disease prevalence in study sample (%) | Prevalence of positive FH in study sample (%) | PPV for study sample | NPV for study sample | Most highly adjusted reported RR or equivalent[1] (max length of FU) |
|---|---|---|---|---|---|---|---|---|---|
| B | father | N | N | Cerhan | 6.5 | 3.0 | 0.13 | 0.94 | 2.3 (6-8 y) |
| B | ≥1 brother | N | N | Cerhan | 6.5 | 1.8 | 0.26 | 0.94 | 6.5 (6-8 y) |
| B | father and/or brother | N | N | Chen | 8.7 | 12.4 | 0.14 | 0.92 | 1.83 (10y) |
| C | ≥1 1DR | N | N | Rodriguez | 0.4 | 3.0 | 0.01 | 1.00 | 1.6 (9 y) |
| | | | | Ahn | 5.7 | 3.0 | 0.11 | 0.95 | 1.91 (12 y) |
| | | | | Cerhan | 6.5 | 4.8 | 0.18 | 0.94 | 3.7 (6-8 y) |
| C | ≥2 1DR | N | N | Rodriguez | 0.4 | 0.1 | 0.03 | 1.00 | 3.19 (9 y) |

Abbreviations: 1DR=first degree relative; FH=family history; FU=followup; NPV=negative predictive value; N=No; PPV=positive predictive value; RR=relative risk; y=years
[1] RR=relative risk, metric reported unless otherwise stated

**Webtable 9. Predictive values associated with FH definitions for prostate cancer in cross-sectional analyses**

| FH category | Specific definition | age criterion | Lineage criterion | Studies | Disease prevalence in study sample (%) | Prevalence of positive FH in study sample (%) | PPV for study sample | NPV for study sample | Most highly adjusted reported OR or equivalent[1] |
|---|---|---|---|---|---|---|---|---|---|
| A | any relative | N | N | Kalish | 5.0 | 9.6 | 0.14 | 0.96 | 3.29 |
| B | Father | N | N | Makinen | 2.4 | 3.5 | 0.03 | 0.98 | 1.18 |
| B | ≥1 brother | N | N | Makinen | 2.4 | 1.3 | 0.04 | 0.98 | 1.57 |
| C | ≥1 1DR | N | N | Makinen | 2.4 | 4.7 | 0.03 | 0.98 | 1.26 |
| C | ≥1 1DR, onset <60 | Y | N | Makinen | 2.4 | 0.4 | 0.03 | 0.98 | 1.40 |
| D | ≥1 1DR or 2DR | N | N | Makinen | 2.4 | 7.7 | 0.03 | 0.98 | 1.27 |
| E | paternal grandfather or ≥1 paternal uncle | N | Y | Makinen | 2.4 | 1.7 | 0.02 | 0.98 | 0.97 |
| E | maternal grandfather or ≥1 maternal uncle | N | Y | Makinen | 2.4 | 1.8 | 0.03 | 0.98 | 1.14 |

Abbreviations: 1DR=first degree relative; FH=family history; N=no; NPV=negative predictive value; NR=not reported; OR=odds ratio PPV=positive predictive value; Y=yes

[1] OR=odds ratio, metric reported unless otherwise stated

**Webtable 10. General data for cardiovascular and stroke studies**

| Author Year | Study setting | Study design | n | Sub-groups measured | How/when FH obtained | Definition of outcome | How/when outcome ascertained |
|---|---|---|---|---|---|---|---|
| Djousse 2008 | association between parental history of MI & incident HF in PHS, U.S. | RCT | 20187 | age | questionnaire | independently validated heart failure | annual survey |
| Dodani 2005 | Aga Khan University Hospital in Karachi, Pakistan recruited Pakistanis >18 y | cross-sectional study | 580 | men and women >18 y; mean age of 46 y with 78.5% male | questionnaire | ≥1 of documented myocardial infarction, angiographically confirmed coronary artery disease, or history of typical angina with positive treadmill test | clinical evaluation |
| Hippe 1999 | Copenhagen Centre for Prospective Population Studies, men and women, age 20 to 93 y | prospective cohort | 24,664 | women<br>men | questionnaire | ICD-8 code 410 | search of national death register and national hospital discharge register |

Abbreviations: 1D=1DR; 1DR=first degree relative; 2DR=second degree relative; AMI=acute myocardial infarction; CAD=coronary artery disease; CHD=congestive heart disease; CVD=cardiovascular disease; FH=family history; FPG=fasting plasma glucose; HDL=high density lipoprotein; HF=heart failure; LDL=low density lipoprotein; MI=myocardial infarction; MRI=magnetic resonance imaging; n=number of subjects; PHS=physician's health study; RCT=Randomized Controlled Study; TIA=transient ischemic attack; U.S.=United States of America; WHO=World Health Organization; y=years

**Webtable 10. General data for cardiovascular and stroke studies (continued)**

| Author Year | Study setting | Study design | n | Sub-groups measured | How/when FH obtained | Definition of outcome | How/when outcome ascertained |
|---|---|---|---|---|---|---|---|
| Jousilahti 1997 | random sample of 25 to 64 y in Finland | cohort | 14,371 | gender<br>type of stroke | questionnaire | fatal or non-fatal stroke coded to ICD-8 432, 433, 436 or ICD-9 431, 432 | national death register, national hospital discharge register |
| Jousilahti 1996 | Finland, males and females, 30 to 59 y | prospective cohort | 15,620 (7,605 males, 8,015 females) | Male<br><br>Female | questionnaire | cause of death coded to ICD-8 410-414 or hospitalizations coded to ICD-8 410-411 | national death register, national hospital discharge register |
| Kadota 2008 | cohort study of the National Survey on Circulatory Disorders, Japan | longitudinal prospective cohort | 8,037 | gender | Survey, not further specified | underlying cause of death coded to ICD-9 430-438, ICD-10 I60-I69 | national death register |
| Magno 2008 | community dwelling Filipino American women aged 40 to 86 y | cross-sectional | 266 | all subjects | questionnaire | hospitalization for CVD episodes or procedures OR ECG abnormalities (Minnesota codes 1.1, 1.2, 1.3, 4.1-4.4, 5.3 or 7.1.1), Rose angina, self-report of physician-diagnosed myocardial infarction | clinical evaluation |

**Webtable 10. General data for cardiovascular and stroke studies (continued)**

| Author Year | Study setting | Study design | n | Sub-groups measured | How/when FH obtained | Definition of outcome | How/when outcome ascertained |
|---|---|---|---|---|---|---|---|
| Morrison 2000 | the Atherosclerosis Risk in Communities Study, Houston, Texas, aged 45 to 64 y | cohort | 15,792 | cerebral MRI on 1931 subjects ≥55 y | interview | clinical ischemic stroke not further specified | review of hospital records, annual survey, death certificates |
| Piros 2000 | railway engine drivers, Sweden, males aged 25-59 y | prospective cohort | 1,409 | males aged 25 to 59 y | Not specified, likely questionnaire | hospital-diagnosed myocardial infarction with ≥2 of typical chest pain, typical enzyme changes, ECG findings OR autopsy evidence OR sudden death with history of ischemic symptoms and no evidence for non-coronary death | hospital-diagnosed MI, national register on diseases |
| Scheuner 2006 | HealthStyles 2003 survey administered to American adults (male and female) with a mean age of 48.8 y | cross-sectional study | 3,956 | stratified random sample of participants from 2003 survey | questionnaire | positive report of doctor-diagnosed CHD | questionnaire responses |
| Sesso 2001 | The Physician's Health Study (PHS) trial in the prevention of CVD and cancer | prospective cohort study | men n=20,515<br><br>Women n=37,985 | U.S. male physicians aged 40-84 y<br><br>female health professionals aged ≥45 y | questionnaire | events meeting WHO criteria for myocardial infarction, confirmed by independent committee | annual survey |

**Webtable 11. Predictive values associated with FH definitions for CHD in longitudinal analyses**

| FH category | Specific definition | Age criterion | Lineage criterion | Studies | Disease prevalence in study sample (%) | Prevalence of positive FH in study sample (%) | PPV for study sample | NPV for study sample | Most highly adjusted reported RR or equivalent[1] (max length of FU) |
|---|---|---|---|---|---|---|---|---|---|
| B | ≥1 parent | N | N | Djousse, M | 5.1 | 31.1 | 0.06 | 0.69 | NR |
| | | | | Sesso, M | 3.2 | 34.5 | 0.04 | 0.66 | NR |
| | | | | Hippe, M | 9.0 | 19.3 | 0.11 | 0.81 | 1.30 (12 y) |
| | | | | Sesso, F | 0.4 | 34.1 | 0.01 | 0.66 | NR |
| | | | | Hippe, F | 4.3 | 23.2 | 0.05 | 0.77 | 1.42 (12 y) |
| B | father | N | N | Sesso, M | 3.2 | 28.8 | 0.04 | 0.71 | 1.58 (13 y) |
| | | | | Piros, M | 3.0 | 2.2 | 0.06 | 0.98 | 4.13 (10 y) |
| | | | | Sesso, F | 0.4 | 26.2 | 0.00 | 0.74 | 0.93 (6 y) |
| B | mother | N | N | Sesso, M | 3.2 | 9.1 | 0.05 | 0.91 | 2.14 (13 y) |
| | | | | Piros, M | 3.0 | 2.7 | 0.08 | 0.97 | 3.55 (10 y) |
| | | | | Sesso, F | 0.4 | 12.3 | 0.01 | 0.88 | 1.76 (6 y) |
| B | both parents | N | N | Sesso, M | 3.2 | 3.5 | 0.05 | 0.97 | 1.98 (13 y) |
| | | | | Sesso, F | 0.4 | 4.4 | 0.01 | 0.96 | 2.49 (6 y) |
| B | ≥1 parent, onset <65y | Y | N | Djousse, M | 5.1 | 15.2 | 0.05 | 0.85 | NR |
| B | ≥1 parent, onset <60y | Y | N | Djousse, M | 5.1 | 9.7 | 0.05 | 0.90 | NR |
| | | | | Jousilahti, M | 10.4 | 22.4 | 0.13 | 0.78 | 1.55 (12 y) |
| | | | | Jousilahti, F | 4.4 | 24.6 | 0.09 | 0.77 | 1.80 (12 y) |
| B | ≥1 parent, onset <55y | Y | N | Djousse, M | 5.1 | 5.7 | 0.05 | 0.94 | 1.32 (20 y)[2] |
| B | father, onset <60y | Y | N | Jousilahti, M | 10.4 | 16.5 | 0.13 | 0.84 | 1.65 (12 y) |
| | | | | Jousilahti, F | 3.2 | 17.4 | 0.03 | 0.83 | 1.58 (12 y) |

Abbreviations: 1DR=first degree relative; CHD=coronary heart disease; F=female; FH=family history; FU=followup; M=male; N=no; NPV=negative predictive value; PPV=positive predictive value; RR=relative risk; y=years; Y=yes

[1] RR=relative risk, metric reported unless otherwise stated

[2] Reference=no family history

**Webtable 11. Predictive values associated with FH definitions for CHD in longitudinal analyses (continued)**

| FH category | Specific definition | Age criterion | Lineage criterion | Studies | Disease prevalence in study sample (%) | Prevalence of positive FH in study sample (%) | PPV for study sample | NPV for study sample | Most highly adjusted reported RR or equivalent[1] (max length of FU) |
|---|---|---|---|---|---|---|---|---|---|
| B | mother, onset<60y | Y | N | Jousilahti, M | 10.4 | 8.5 | 0.12 | 0.92 | 1.34 (12 y) |
| | | | | Jousilahti, F | 3.2 | 10.4 | 0.05 | 0.90 | 2.1 (12 y) |
| B | both parents, onset <60y | Y | N | Jousilahti, M | 10.4 | 2.6 | 0.12 | 0.97 | 1.37 (12 y) |
| | | | | Jousilahti, F | 3.2 | 3.1 | 0.03 | 0.97 | 1.27 (12 y) |

**Webtable 12. Predictive values associated with FH definitions for CHD in cross-sectional analyses**

| FH category | Specific definition | Age criterion | Lineage criterion | Studies | Disease prevalence in study sample (%) | Prevalence of positive FH in study sample (%) | PPV for study sample | NPV for study sample | Most highly adjusted reported OR or equivalent |
|---|---|---|---|---|---|---|---|---|---|
| B | ≥1 parent | N | N | Scheuner, M&F premature | 4.5 | 13.2 | 0.08 | 0.96 | 3.8 |
| | | | | Magno, F | 20.7 | 25.2 | 0.31 | 0.83 | 2.81 |
| B | father | N | N | Scheuner, M&F, premature | 4.5 | 9.3 | 0.09 | 0.96 | NR |
| B | mother | N | N | Scheuner, M&F, premature | 4.5 | 6.3 | 0.10 | 0.96 | NR |
| B | ≥1 sibling | N | N | Scheuner, M&F, premature | 4.5 | 5.3 | 0.16 | 0.96 | 3.1 |
| B | both parents | N | N | Scheuner, M&F, premature | 4.5 | 2.4 | 0.16 | 0.96 | 6.2 |
| B | ≥1 parent + ≥1 sibling | N | N | Scheuner, M&F, premature | 4.5 | 2.6 | 0.13 | 0.96 | 5.0 |
| C | ≥1 1DR | N | N | Scheuner, M&F, premature | 4.5 | 38.8 | 0.08 | 0.98 | 3.8 |
| C | ≥2 1DR | N | N | Scheuner, M&F, premature | 4.5 | 5.1 | 0.14 | 0.96 | 5.1 |
| C | ≥1 1DR, early onset | Y | N | Scheuner, M&F, premature | 4.5 | 9.3 | 0.11 | 0.96 | 5.0 |
| D | ≥1 1DR + ≥1 2DR, any age | N | N | Scheuner, M&F, premature | 4.5 | 18.7 | 0.10 | 0.97 | 4.5 |
| E | fr, br, grfr<55, mr, sis, gmr<65 | Y | N | Dodani, M&F | 19.1 | 49.5 | 0.23 | 0.85 | 1.7 |

Abbreviations: 1DR=first degree relative; 2DR=second degree relative; br=brother; CHD=coronary heart disease; F=female; FH=family history; fr=father; grfr=grandfather; grmr=grandmother; M=male; mr=mother; N=no; NPV=negative predictive value; NR=not reported; OR=odds ratio; PPV=positive predictive value; sis=sister; Y=yes

**Webtable 13. Quality items for CVD and stroke studies for review question 1**

| Author Year | Same outcome ascertain-ment, irrespective of FH (outcome information bias) | Outcome ascertain-ment blind to FH (outcome information bias) | Same FH ascertain-ment, irrespective of disease status (exposure information bias) | FH ascertain-ment blind to disease status (exposure information bias) | Exclusion of cases at inception (cohort) (misclassi-fication) | Adequate followup (cohort) (selection bias) | Representat ive sampling (cross-sectional) (selection bias) | Adequate response rate (cross-sectional) (selection bias) |
|---|---|---|---|---|---|---|---|---|
| **CVD** | | | | | | | | |
| Jousilahti 1996 | Yes | Yes | Yes | Yes | Yes | At least 80% followup | Not applicable (longitudinal design) | Not applicable (longitudinal design) |
| Sesso 2001 | Yes | Unclear | Yes | Yes | Yes | Unclear | Not applicable (longitudinal design) | Not applicable (longitudinal design) |
| Piros 2000 | Yes | Unclear | Unclear | Unclear | Unclear | At least 80% followup | Not applicable (longitudinal design) | Not applicable (longitudinal design) |
| Hippe 1999 | Yes | Yes | Yes | Yes | Yes | Unclear | Not applicable (longitudinal design) | Not applicable (longitudinal design) |
| Djousse 2008 | Yes | Unclear | Yes | Yes | Yes | Unclear | Not applicable (longitudinal design) | Not applicable (longitudinal design) |

Abbreviations: 1DR=first degree relative; CHD=coronary heart disease; F=female; FH=family history; FU=followup; M=male; N=no; NPV=negative predictive value; PPV=positive predictive value; RR=relative risk; y=years; Y=yes

**Webtable 13. Quality items for CVD and stroke studies for review question 1 (continued)**

| Author Year | Same outcome ascertain-ment, irrespective of FH (outcome information bias) | Outcome ascertain-ment blind to FH (outcome information bias) | Same FH ascertain-ment, irrespective of disease status (exposure information bias) | FH ascertain-ment blind to disease status (exposure information bias) | Exclusion of cases at inception (cohort) (misclassi-fication) | Adequate followup (cohort) (selection bias) | Representat ive sampling (cross-sectional) (selection bias) | Adequate response rate (cross-sectional) (selection bias) |
|---|---|---|---|---|---|---|---|---|
| Magno 2008 | Yes | No | Yes | No | Not applicable (cross-sectional design) | Not applicable (cross-sectional design) | No (non-probability sampling) | Unclear |
| Dodani 2005 | Yes | No | Unclear | No | Not applicable (cross sectional design) | Not applicable (cross sectional design) | No (non-probability sampling) | Unclear |
| Scheuner 2006 | Yes | No | Yes | No | Not applicable (cross sectional design) | Not applicable (cross sectional design) | Yes (probability sampling) | Response rate less than 80%, inadequate or missing description of non-participants |
| **Stroke** | | | | | | | | |
| Morrison 2000 | Unclear | Unclear | Unclear | Yes | Yes | Unclear | Not applicable (longitudinal design) | Not applicable (longitudinal design) |
| Jousilahti 1997 | Yes | Yes | Yes | Yes | Yes | Unclear | Not applicable (longitudinal design) | Not applicable (longitudinal design) |
| Kadota 2008 | Yes | Yes | Yes | Yes | Yes | At least 80% followup | Not applicable (longitudinal design) | Not applicable (longitudinal design) |

**Webtable 14. Predictive values associated with FH definitions for stroke in longitudinal analyses**

| FH category | Specific definition | Age criterion | Lineage criterion | Studies | Disease prevalence in study sample (%) | Prevalence of positive FH in study sample (%) | PPV for study sample | NPV for study sample | Most highly adjusted reported RR or equivalent[1] (max length of FU) |
|---|---|---|---|---|---|---|---|---|---|
| B | ≥1 parent | N | N | Morrison | 1.9 | 29.1 | 0.02 | 0.98 | 1.64 (5 y) |
| | | | | Jousilahti, M, premature disease | 3.4 | 4.9 | 0.07 | 0.97 | 1.89 (7-12 y) |
| | | | | Kadota, M | 3.9 | 20.4 | 0.03 | 0.96 | 0.73 (19 y) |
| | | | | Jousilahti, F, premature disease | 2.6 | 6.2 | 0.06 | 0.98 | 1.80 (7-12 y) |
| | | | | Kadota, F | 2.7 | 20.7 | 0.03 | 0.97 | 1.38 (19 y) |
| B | father | N | N | Jousilahti, M, premature disease | 3.4 | 2.1 | 0.08 | 0.97 | 2.17(7-12 y) |
| | | | | Jousilahti, F, premature disease | 2.6 | 2.8 | 0.06 | 0.98 | 2.15 (7-12 y) |
| B | mother | N | N | Jousilahti, M, premature disease | 3.4 | 2.6 | 0.07 | 0.97 | 1.83 (7-12 y) |
| | | | | Jousilahti, F, premature disease | 2.6 | 3.2 | 0.06 | 0.98 | 1.67 (7-12 y) |

Abbreviations: 1DR=first degree relative; F=female; FH=family history; FU=followup; M=male; N=no; NPV=negative predictive value; PPV=positive predictive value; RR=relative risk; y=years

[1] RR=relative risk, metric reported unless otherwise stated

**Webtable 15. General data for diabetes studies**

| Author Year | Study setting | Study design | n | Sub-groups measured | How/when FH obtained | Definition of outcome | How/when outcome ascertained |
|---|---|---|---|---|---|---|---|
| Ajlouni 2008 | study of diabetes and performance risk score in Hindustani Surinamese, African Surinamese, and Dutch aged 35-60, Amsterdam Netherland | cross-sectional | 1,415 | age | interview | clinical evaluation | clinical evaluation |
| Annis 2005 | National Health and Nutrition Examination Survey (NHANES) of the civilian, not institutionalized U.S. population over the age of 20 y | retrospective cohort | 10,283<br><br>10,067 analysed | men and women ³20y | interview | self-report of physician diagnosis | survey |
| Bindraban 2008 | study of Jordanian aged 25 y and above, Jordan | cross-sectional | 1,121 | Gender, age | interview | fasting glucose>7.0mmol/l or self-reported diabetes | clinical evaluation |

Abbreviations: 1DR=first degree relative; 2DR=second degree relative; DM=diabetes mellitus; EPIC=European prospective investigation of cancer; FH=family history; FPG=fasting plasma glucose; GTT=glucose tolerance test; LPG=level of plasma glucose; n=number of subjects; OGTT=oral glucose tolerance test; WHO=World Health Organization; y=years

**Webtable 15. General data for diabetes studies (continued)**

| Author Year | Study setting | Study design | n | Sub-groups measured | How/when FH obtained | Definition of outcome | How/when outcome ascertained |
|---|---|---|---|---|---|---|---|
| Bjornholt 2000 | accruement from a cardiovascular screening survey in Oslo, Norway | prospective followup study | 1,947 | healthy non-diabetic men aged 40 to 59 years with fasting blood glucose levels <110 mg/dl at baseline | questionnaire | diabetes confirmed from ≥2 of: fasting glucose≥120 mg/dl/2-h glucose ≥180mg/dl OR hospital diagnosis of diabetes OR death coded to ICD-9 diabetes codes | clinical evaluation |
| Boer 1996 | Zutphen Elderly Study - a longitudinal study on the risk factors for chronic diseases | cross-sectional study | 468 | men aged 69 to 90 y | interview | fasting glucose≥7.8mmol/l OR 2-h glucose ≥11.1mmol/l or known diabetes | clinical evaluation |
| Carlsson 2007 | Nord-Trøndelag Health Study, Norway | cross-sectional study | 64,498 | men and women >20 y | questionnaire | incompletely described but likely self-report of physician diagnosis | clinical evaluation |
| Ebbesson 1998 | residents of Alaska, U.S. men and women aged ≥25 y | prospective cohort | 391 | men and women aged ≥25 y<br>women only<br>men only | interview | fasting glucose≥7.8 mmol/l or WHO 1985 criteria | clinical evaluation |
| Gikas 2004 | Salamis, Greece, age 20-94y | cross-sectional | 2,805 | all subjects | interview | self-report of doctor diagnosis of diabetes or hypoglycemic therapy | survey |

**Webtable 15. General data for diabetes studies (continued)**

| Author Year | Study setting | Study design | n | Sub-groups measured | How/when FH obtained | Definition of outcome | How/when outcome ascertained |
|---|---|---|---|---|---|---|---|
| Hariri 2006 | National Health and Nutrition Examination Survey, United States population, males and non-pregnant females ≥20 y | cohort study | 3,823 | non-pregnant adults, ≥20 y | interview | self-report of physician diagnosis OR fasting glucose ≥126mg/dl | survey and clinical evaluation |
| Hariri 2006 | HealthStyles 2004 mail survey of health-related attitudes and beliefs | cross-sectional study | 4,345 | U.S. adult population, aged 18 and over | questionnaire | self-report of physician diagnosis of diabetes | survey |
| Haron 2006 | Northern Israeli Circassian men and women, aged 35 y and older | retrospective cohort | 740 | men and women >35y | interview | hypoglycemic therapy OR fasting glucose ≥126mg/dl on two occasions OR 2-hr glucose ≥200mg/dl | clinical evaluation |
| Hilding 2006 | Stockholm Diabetes Prevention Programme, men and women aged 35 to 56 y from the outskirts of Stockholm | cross-sectional study | 7,949 total<br><br>3,128 men and 4,821 women | men and women, aged 35-56y, half with a FH of diabetes | questionnaire | WHO 1998 criteria | clinical evaluation |
| Meigs 2000 | Framingham Offspring Study aged 12 to 58 y at baseline | cohort | 2,527 | all subjects | Original clinical evaluation data from first generation of parent-offspring cohort study | fasting glucose≥7.8mmol/l or self-report of hypoglycemic therapy | clinical evaluation |

**Webtable 15. General data for diabetes studies (continued)**

| Author Year | Study setting | Study design | n | Sub-groups measured | How/when FH obtained | Definition of outcome | How/when outcome ascertained |
|---|---|---|---|---|---|---|---|
| Mohan 2003 | Chennai Urban Population Study, Chennai, India, men and women aged >= 20 | prospective cohort | 1,262 | men and women aged >= 20 y | interview | hypoglycemic therapy OR fasting glucose ≥126mg/dl OR 2-hr glucose ≥200mg/dl | clinical evaluation |
| Nakanishi 2003 | Japanese-Americans, Hawaii and Los Angeles, CA, U.S. | prospective Cohort | 403 men<br><br>557 women | men aged 61.2±1.9 y (FH+); 67.2±1.0 y (FH-)<br><br>women aged 60.7±1.4 y (FH+); 61.9±0.8 y (FH-) | survey, not further specified | 1998 WHO criteria for diabetes on basis of oral GTT | clinical evaluation |
| Nyenwe 2003 | Nigeria, age >40y | cross-sectional | 491 | all subjects | questionnaire | WHO 1999 criteria or self-report of physician diagnosis | clinical evaluation |
| Rahman 2008 | European Prospective Investigation (EPIC) of Cancer-Norfolk, age 40 to 79 y | prospective cohort | 24,495 | all subjects | questionnaire | incompletely described but likely physician diagnosis OR receiving hypogycemic therapy OR elevated non-fasting glucode OR elevated HBA1c | self-report at followup, hospital and family practice registers, death registration, hypogycemic prescription records |
| Shera 2007 | random sample of subjects >24 y in Pakistan | cross-sectional | 5,433 | gender | unclear | fasting glucose >140 mg/dl or 2 h glucose >200 mg/dl | clinical evaluation |

**Webtable 16. Predictive values associated with FH definitions for diabetes in longitudinal analyses**

| FH category | Specific definition | Age criterion | Lineage criterion | Studies | Disease prevalence in study sample (%) | Prevalence of positive FH in study sample (%) | PPV for study sample | NPV for study sample | Most highly adjusted reported RR or equivalent[1] (max length of FU) |
|---|---|---|---|---|---|---|---|---|---|
| B | ≥1 parent | N | N | Meigs, M&F | 8.7 | 23.7 | 0.17 | 0.94 | NR |
| | | | | Bjornholt, M | 7.3 | 10.6 | 0.15 | 0.94 | NR |
| B | father | N | N | Meigs, M&F | 8.7 | 13.2 | 0.16 | 0.92 | 3.5 (20 y) |
| | | | | Bjornholt,M | 7.3 | 3.9 | 0.13 | 0.93 | 1.79 (22 y)[2] |
| B | mother | N | N | Meigs, M&F | 8.7 | 12.1 | 0.20 | 0.93 | 3.4 (20 y) |
| | | | | Bjornholt, M | 7.3 | 7.2 | 0.16 | 0.93 | 2.65 (22 y)[2] |
| B | both parents | N | N | Meigs, M&F | 8.7 | 1.7 | 0.26 | 0.92 | 6.1 (20 y) |
| | | | | Bjornholt,M | 7.3 | 0.5 | 0.30 | 0.93 | 6.89 (22 y)[2] |
| C | ≥1 1DR | N | N | Boer, M | 16.2 | 9.3 | 0.38 | 0.86 | 3.9 (5 y) |
| | | | | Nakanishi, M | 14.4 | 15.1 | 0.20 | 0.87 | 1.56 (7 y) |
| | | | | Nakanishi, F | 12.2 | 16.3 | 0.21 | 0.89 | 1.79 (7 y) |
| C | ≥1 parent or sibling | N | N | Rahman, M&F | 1.3 | 12.2 | 0.02 | 0.99 | 1.53 (5 y) |
| C | ≥1 parent and ≥1 sibling | N | N | Rahman, M&F | 1.3 | 0.8 | 0.04 | 0.99 | 3.30 (5 y) |

Abbreviations: 1DR=first degree relative; FH=family history; FU=followup; N=no; NPV=negative predictive value; NR=not reported; PPV=positive predictive value; RR=relative risk; y=years

[1] RR=relative risk, metric reported unless otherwise stated

[2] Male and female data combined

**Webtable 17. Predictive values associated with FH definitions for diabetes in cross-sectional analyses**

| FH category | Specific definition | Age criterion | Lineage criterion | Studies | Disease prevalence in study sample (%) | Prevalence of positive FH in study sample (%) | PPV for study sample | NPV for study sample | Most highly adjusted reported OR or equivalent[1] |
|---|---|---|---|---|---|---|---|---|---|
| B | ≥1 parent | N | N | Nyenwe, M&F | 6.9 | 7.7 | 0.26 | 0.95 | 9.4 |
| | | | | Annis, M&F | 9.6 | 24.1 | 0.19 | 0.93 | 3.04 (one parent) |
| | | | | Carlsson, M&F | 2.1 | 10.4 | 0.05 | 0.98 | 4.62[2] |
| | | | | Mohan, M&F | 12.0 | 19.7 | 0.18 | 0.89 | 2.05 |
| B | father | N | N | Annis, M&F | 9.6 | 10.4 | 0.17 | 0.91 | NR |
| | | | | Carlsson, M&F | 2.1 | 4.3 | 0.04 | 0.98 | 4.29[2] |
| B | mother | N | N | Annis, M&F | 9.6 | 16.2 | 0.22 | 0.93 | NR |
| | | | | Carlsson, M&F | 2.1 | 6.6 | 0.06 | 0.98 | 5.17[2] |
| B | ≥1 sibling | N | N | Annis, M&F | 9.6 | 13.1 | 0.28 | 0.93 | 3.52 |
| | | | | Carlsson, M&F | 2.1 | 3.1 | 0.08 | 0.98 | 2.92[2] |
| B | brother | N | N | Annis, M&F | 9.6 | 7.5 | 0.30 | 0.92 | NR |
| | | | | Carlsson, M&F | 2.1 | 2.5 | 0.10 | 0.98 | 4.76[2] |
| B | sister | N | N | Annis, M&F | 9.6 | 8.2 | 0.31 | 0.92 | NR |
| | | | | Carlsson, M&F | 2.1 | 2.2 | 0.10 | 0.98 | 4.01[2] |
| B | ≥1 child | N | N | Carlsson, M&F | 2.1 | 0.8 | 0.06 | 0.98 | 2.40[2] |
| B | father or brother | N | N | Carlsson, M&F | 2.1 | 5.7 | 0.05 | 0.98 | 3.58[2] |

Abbreviations: 1DR=first degree relative; 2DR=second degree relative; FH=family history; N=no; NPV=negative predictive value; NR=not reported; PPV=positive predictive value; RR=relative risk; y=years; Y=yes

[1] OR=odds ratio, metric reported unless otherwise stated

[2]Type 2 diabetes

[3]Data for males and females combined

**Webtable 17. Predictive values associated with FH definitions for diabetes in cross-sectional analyses (continued)**

| FH category | Specific definition | Age criterion | Lineage criterion | Studies | Disease prevalence in study sample (%) | Prevalence of positive FH in study sample (%) | PPV for study sample | NPV for study sample | Most highly adjusted reported OR or equivalent[1] |
|---|---|---|---|---|---|---|---|---|---|
| B | mother or sister | N | N | Carlsson, M&F | 2.1 | 7.5 | 0.06 | 0.98 | 4.16[2] |
| C | ≥1 1DR | N | N | Carlsson, M&F | 2.1 | 15.2 | 0.06 | 0.99 | 3.51[2] |
| | | | | Bindraban, M&F | 13.7 | 59.9 | 0.19 | 0.94 | 2.7 |
| | | | | Shera, M | 9.3 | 11.0 | 0.22 | 0.92 | NR |
| | | | | Shera, F | 8.4 | 10.3 | 0.18 | 0.93 | NR |
| C | ≥1 parent or sibling | N | N | Gikas, M&F | 8.7 | 23.3 | 0.24 | 0.96 | 6.91 |
| | | | | Annis, M&F | 9.6 | 31.5 | 0.19 | 0.95 | 3.95 |
| | | | | Haron, M | 14.9 | 27.0 | 0.18 | 0.86 | 2.5[3] |
| | | | | Haron, F | 10.6 | 29.9 | 0.14 | 0.91 | 2.5[3] |
| C | ≥2 1DR | N | N | Carlsson, M&F | 2.1 | 1.9 | 0.13 | 0.98 | 8.33[2] |
| C | ≥2 1DR (parents or sibling) | N | N | Annis, M&F | 9.6 | 8.2 | 0.32 | 0.92 | 5.14 |
| C | ≥3 1DR (parents or sibling) | N | N | Annis, M&F | 9.6 | 2.2 | 0.52 | 0.91 | 14.83 |
| D | ≥1 1DR, aunt or uncle | N | N | Ebbesson, M&F | 6.2 | 19.0 | 0.12 | 0.95 | 4.4 |
| | | | | Ebbesson, M | 4.2 | 15.4 | 0.09 | 0.97 | NR |
| | | | | Ebbesson, F | 8.8 | 20.0 | 0.17 | 0.93 | NR |
| D | ≥1 1DR or ≥1 2DR | N | N | Ajlouni, M&F | 17.4 | 43.4 | 0.23 | 0.87 | 3.09 |
| D | ≥1 1DR or ≥2 2DR | N | N | Hilding, M | 2.3 | 50.1 | 0.04 | 0.99 | 3.1 |
| | | | | Hilding, F | 1.4 | 52.7 | 0.02 | 0.99 | 1.7 |

**Webtable 17. Predictive values associated with FH definitions for diabetes in cross-sectional analyses (continued)**

| FH category | Specific definition | Age criterion | Lineage criterion | Studies | Disease prevalence in study sample (%) | Prevalence of positive FH in study sample (%) | PPV for study sample | NPV for study sample | Most highly adjusted reported OR or equivalent[1] |
|---|---|---|---|---|---|---|---|---|---|
| E | ≥1 1DR and 1 2DR, same lineage OR 1 1DR OR both parents OR 2 2DR, same lineage | N | Y | Hariri, M&F | 10.4 | 35.8 | 0.21 | 0.96 | 3.6 |
| E | ≥2 1DR, same lineage OR ≥11DR and ≥2 2DR, same lineage OR ≥3 2DR same lineage | N | Y | Hariri, M&F | 10.4 | 16.4 | 0.29 | 0.93 | 4.7 |

**Webtable 18. Quality items for diabetes studies for review question 1**

| Author Year | Same outcome ascertain-ment, irrespective of FH (outcome information bias) | Outcome ascertain-ment blind to FH (outcome information bias) | Same FH ascertain-ment, irrespective of disease status (exposure information bias) | FH ascertain-ment blind to disease status (exposure information bias) | Exclusion of cases at inception (cohort) (misclassi-fication) | Adequate followup (cohort) (selection bias) | Representat ive sampling (cross-sectional) (selection bias) | Adequate response rate (cross-sectional) (selection bias) |
|---|---|---|---|---|---|---|---|---|
| **Diabetes** | | | | | | | | |
| Bjornholt 2000 | Yes | Yes | Yes | Yes | Yes | At least 80% followup | Not applicable (longitudinal design) | Not applicable (longitudinal design) |
| Mohan 2003 | Yes | No | Unclear | No | Not applicable (cross-sectional design) | Not applicable (cross-sectional design) | Yes (probability sampling) | Yes, response rate at least 80% |
| Rahman 2008 | Yes | No | Yes | Yes | Yes | At least 80% followup | Not applicable (longitudinal design) | Not applicable (longitudinal design) |
| Sugimori 1998 | Yes | Yes | Unclear | Yes | Yes | Unclear | Not applicable (longitudinal design) | Not applicable (longitudinal design) |
| Meigs 2000 | Yes | Unclear | Yes | Yes | Yes | At least 80% followup | Not applicable (longitudinal design) | Not applicable (longitudinal design) |

**Webtable 18. Quality items for diabetes studies for review question 1 (continued)**

| Author Year | Same outcome ascertain-ment, irrespective of FH (outcome information bias) | Outcome ascertain-ment blind to FH (outcome information bias) | Same FH ascertain-ment, irrespective of disease status (exposure information bias) | FH ascertain-ment blind to disease status (exposure information bias) | Exclusion of cases at inception (cohort) (misclassi-fication) | Adequate followup (cohort) (selection bias) | Representat ive sampling (cross-sectional) (selection bias) | Adequate response rate (cross-sectional) (selection bias) |
|---|---|---|---|---|---|---|---|---|
| Shera 2006 | Yes | Unclear | Unclear | Unclear | Not applicable (cross sectional design) | Not applicable (cross sectional design) | Yes (probability sampling) | Unclear |
| Bindraban 2008 | Yes | No | Yes | No | Not applicable (cross sectional design) | Not applicable (cross sectional design) | Yes (probability sampling) | Response rate less than 80%, adequate description of non-participants |
| Ajlouni 2008 | Yes | No | Unclear | No | Not applicable (cross sectional design) | Not applicable (cross sectional design) | Yes (probability sampling) | Unclear |
| Boer 1996 | Yes | Unclear | Yes | Yes | Yes | Less than 80% followup, inadequate or missing description of those lost | Not applicable (longitudinal design) | Not applicable (longitudinal design) |
| Nakanishi 2003 | Yes | Yes | Unclear | Yes | Yes | Unclear | Not applicable (longitudinal design) | Not applicable (longitudinal design) |

**Webtable 18. Quality items for diabetes studies for review question 1 (continued)**

| Author Year | Same outcome ascertain-ment, irrespective of FH (outcome information bias) | Outcome ascertain-ment blind to FH (outcome information bias) | Same FH ascertain-ment, irrespective of disease status (exposure information bias) | FH ascertain-ment blind to disease status (exposure information bias) | Exclusion of cases at inception (cohort) (misclassi-fication) | Adequate followup (cohort) (selection bias) | Representat ive sampling (cross-sectional) (selection bias) | Adequate response rate (cross-sectional) (selection bias) |
|---|---|---|---|---|---|---|---|---|
| Hariri 2006 | Yes | No | Yes | No | Not applicable (cross sectional design) | Not applicable (cross sectional design) | Yes (probability sampling) | Response rate less than 80%, inadequate or missing description of non-participants |
| Haron 2006 | Yes | No | Yes | No | Not applicable (cross sectional design) | Not applicable (cross sectional design) | Yes (probability sampling) | Response rate less than 80%, adequate description of non-participants |
| Gikas 2004 | Yes | No | Unclear | No | Not applicable (cross sectional design) | Not applicable (cross sectional design) | No (non-probability sampling) | Yes, response rate at least 80% |
| Hilding 2006 | Yes | Yes | Yes | Yes | Not applicable (cross sectional design) | Not applicable (cross-sectional design) | Unclear | Response rate less than 80%, inadequate or missing description of non |
| Nyenwe 2003 | Yes | No | Unclear | No | Not applicable (cross sectional design) | Not applicable (cross sectional design) | Yes (probability sampling) | Response rate less than 80%, inadequate or missing description of non |

**Webtable 18. Quality items for diabetes studies for review question 1 (continued)**

| Author Year | Same outcome ascertain-ment, irrespective of FH (outcome information bias) | Outcome ascertain-ment blind to FH (outcome information bias) | Same FH ascertain-ment, irrespective of disease status (exposure information bias) | FH ascertain-ment blind to disease status (exposure information bias) | Exclusion of cases at inception (cohort) (misclassi-fication) | Adequate followup (cohort) (selection bias) | Representat ive sampling (cross-sectional) (selection bias) | Adequate response rate (cross-sectional) (selection bias) |
|---|---|---|---|---|---|---|---|---|
| Carlsson 2007 | Unclear | Unclear | Yes | No | Not applicable (cross sectional design) | Not applicable (cross sectional design) | Yes (probability sampling) | Yes, response rate at least 80% |
| Ebbesson 1998 | Yes | No | Unclear | No | Not applicable (cross sectional design) | Not applicable (cross sectional design) | Yes (probability sampling) | Response rate less than 80%, adequate description of non-participants |
| Annis 2005 | Yes | No | Yes | No | Not applicable (cross sectional design) | Not applicable (cross sectional design) | Yes (probability sampling) | Unclear |
| Hariri 2006 | Yes | No | Yes | No | Not applicable (cross sectional design) | Not applicable (cross sectional design) | Yes (probability sampling) | Unclear |

**Webtable 19. General data for asthma studies**

| Author Year | Study setting | Study design | n | Sub-groups measured | How/when FH obtained | Definition of outcome | How/when outcome ascertained |
|---|---|---|---|---|---|---|---|
| Alford 2004 | relationship between parental onset and duration of disease and the risk of paediatric atopic disease in children from birth to 6/7 y old, U.S. | | 835 | childhood and adulthood | maternal interview | asthma: self-report symptoms within previous 12 mo and currently using asthma medication Atopy: positive skin prick test | parental questionnaire plus clinical assessment |
| Bener 2005 | government primary schools in the State of Qatar | cross-sectional study | 3,204 | school children living in urban and semi-urban areas, 51.9% boys and 48.1% girls, with a mean age of 8.92 y | parental interview | ISAAC criteria for self-report of physician diagnosis of asthma OR asthma treatment OR hospital admission | parental questionnaire |
| Bergmann 1997 | evaluation of parental history and cord blood-IgE for the appropriate atopic phenotypes in the infants<br><br>in 6 German obstetric department, Germany | cohort | 1,314 | gender, cord blood IgE, family history (father, mother) | parental questionnaire | self-report of physician diagnosis of atopic disease OR diagnosis on basis of research clinical examination or reported symptomatology OR computer algorithm diagnosis on basis of specific criteria for symptomatology and clinical signs | questionnaire, interview, clinical assessment |

Abbreviations: 1DR=first degree relative; FH=family history; IgE=immunoglobin E; ISAAC=international study of asthma and allergies in childhood; n=number of subjects; y=years; U.S.=United States of America

**Webtable 19. General data for asthma studies (continued)**

| Author Year | Study setting | Study design | n | Sub-groups measured | How/when FH obtained | Definition of outcome | How/when outcome ascertained |
|---|---|---|---|---|---|---|---|
| Chatkin 2003 | children age 4 to 5 y in Brazil | cohort | 981 | all subjects | maternal interview | ISAAC criteria for current asthma | parental interview |
| Chatkin 2005 | male and female children age 6 to 7 y in southern Brazil | cross-sectional | 494 | all subjects | maternal interview | ISAAC criteria for current asthma | parental interview |
| Garcia-Marcos 2005 | evaluation of environmental and family risk factors for atopic and non-atopic wheezing among school children 9-12 y of age (ISAAC phase II), Spain | cross-sectional | 2720 | atopic and non-atopic wheezing | questionnaire | ISAAC criteria for current wheezing | parental questionnaire |
| Hu 1995 | Los Angeles & San Diego California young adults ages 20 to 22 y | cross sectional | 2,041 | all subjects | questionnaire | physician-reported asthma plus one of: asthma medication in previous 12 months or coughing, wheezing, shortness of breath lasting >3 days in previous 12 months | self-report questionnaire |

**Webtable 19. General data for asthma studies (continued)**

| Author Year | Study setting | Study design | n | Sub-groups measured | How/when FH obtained | Definition of outcome | How/when outcome ascertained |
|---|---|---|---|---|---|---|---|
| London 2001 | a schoolbased study of Southern California children | cross-sectional | 5,046 | presence of a sibling, maternal smoking | parents or guardians completed a self-administered questionnaire during the school year | "yes" response to the question, has a doctor ever diagnosed this child as having asthma? | parents or guardians completed a self-administered questionnaire during the school year |
| Lopez 1999 | study of genetic and environmental influences on atopic immune response in term neonates born in women's health care center, Brazil | cohort | 114 | sex, ethnicity | maternal questionnaire | atopic dermatitis according to criteria of Hanifin & Rajka OR wheezing on at least 2 occasions with good response to beta agonist OR history of immediate urticaria, vomiting, diarrhea and or wheezing in response to specific food at least twice. Single manifestations of symptoms indicating probable disease included | parental questionnaire plus clinical assessment |
| Melbostad 1998 | Norway, farmers and spouses | cross-sectional | 8,482 | all subjects Never/ever smoker animal production/no animal production | questionnaire | unclear data analyzed for ''current asthma' | self-report questionnaire plus spirometry |

**Webtable 19. General data for asthma studies (continued)**

| Author Year | Study setting | Study design | n | Sub-groups measured | How/when FH obtained | Definition of outcome | How/when outcome ascertained |
|---|---|---|---|---|---|---|---|
| Montnemery 2000 | study of familial related risk-factors in the development of chronic bronchitis/emphysema in 20-59 y old population Sweden | cross-sectional | 12073 | age, gender | questionnaire | positive response to question, 'have you now, or have you had asthma?' | self-reported |
| Õneş 1997 | Istanbul, Turkey schoolchildren aged 6 to 12 y | cross-sectional | 2,216 | six randomly selected primary schools | parental questionnaire | ISAAC criteria for self-report of physician diagnosis of asthma | parental questionnaire |
| Patrzalek 2003 | children age 0 to 3 y, Warsaw, Poland | prospective cohort | 141 | all subjects | parental questionnaire | atopic dermatitis OR recurrent wheeze OR food allergy, not further defined | parental questionnaire, clinical assessment, IgE |
| Pohlabeln 2007 | relationship between pet ownership at time of birth and prevalence of atopic diseases approximately 2 years later in 5 hospitals in three cities. Germany | Cohort | 3,132 | sex, parental education, study center, family history (maternal & paternal, sibling) | maternal questionnaire | ISAAC criteria for atopic disease | parental questionnaire |

**Webtable 19. General data for asthma studies (continued)**

| Author Year | Study setting | Study design | n | Sub-groups measured | How/when FH obtained | Definition of outcome | How/when outcome ascertained |
|---|---|---|---|---|---|---|---|
| Sugiyama 2002 | Japanese schoolchildren, 13 to 14 y, part of International Study of Asthma and Allergies in Childhood, Phase One | cross-sectional | 4,466 | all subjects with complete data | questionnaire | ISAAC criteria for mild, moderate or severe wheezing | self-report questionnaire |

**Webtable 19. General data for asthma studies (continued)**

| Author Year | Study setting | Study design | n | Sub-groups measured | How/when FH obtained | Definition of outcome | How/when outcome ascertained |
|---|---|---|---|---|---|---|---|
| Tariq 1998 | babies born on the Isle of Wight | prospective cohort | 1,218 | infants at ages 1, 2, and 4 y | interview | asthma: ≥3 episodes of wheeze, each lasting ≥3 days; Atopy: ≥3 separate episodes of wheeze, each lasting at least 3 days or recurrent, scaly, pruritic, erythematous rash in typical distribution lasting >6 weeks OR two of thee nasal symptoms (discharge, blockage, recurrent sneezing) accompanied by eye symptoms OR skin rasj or respiratory or abdominal symptoms within 4 hours of ingestion of particular food on 2 occasions | parental report plus skin prick tests |

**Webtable 20. Predictive values associated with FH definitions for atopic disease in longitudinal analyses**

| FH category | Specific definition | Age criterion | Lineage criterion | Studies | Disease prevalence in study sample (%) | Prevalence of positive FH in study sample (%) | PPV for study sample | NPV for study sample | Most highly adjusted reported RR or equivalent[1] (max length of FU) |
|---|---|---|---|---|---|---|---|---|---|
| B | atopy, both parents | N | N | Bergmann M&F, onset ≤2y | 0.4 | NA | 0.25 | 0.84 | NR |
| B | atopy, father | N | N | Tariq, M&F, onset ≤4y | 26.8 | 25.5 | 0.29 | 0.74 | NR |
| | | | | Pohlabeln onset≤2y | 23.0 | 19.8 | 0.27 | 0.78 | NR |
| B | atopy, mother | N | N | Tariq, M&F onset ≤4y | 26.8 | 33.7 | 0.29 | 0.74 | NR |
| | | | | Pohlabeln onset≤2y | 23.0 | 23.4 | 0.29 | 0.79 | NR |
| B | atopy, ≥1 sibling | N | N | Tariq, M&F, onset ≤4y | 27.3 | 36.9 | 0.34 | 0.76 | 2.2 (4 y) |
| | | | | Pohlabeln onset≤2y | 23.0 | 10.6 | 0.33 | 0.78 | NR |
| C | atopy, ≥1 1DR | N | N | Tariq, M&F, onset ≤4y | 26.8 | 58.5 | 0.29 | 0.77 | 1.6 (4 y) |
| | | | | Pohlabeln onset≤2y | 23.0 | 43.1 | 0.28 | 0.81 | NR |
| D | atopy, ≥1 of parents, siblings, grandparents | N | N | Lopez, onset ≤1y | 38.6 | 53.5 | 0.46 | 0.70 | NR |

Abbreviations: 1DR=first degree relative; FH=family history; FU=followup; N=no; NPV=negative predictive value; NR=not reported; PPV=positive predictive value; RR=relative risk; y=years

[1] RR=relative risk, metric reported unless otherwise stated

**Webtable 21. Predictive values associated with FH definitions for atopic disease cross-sectional analyses**

| FH category | Specific definition | Age criterion | Lineage criterion | Studies | Disease prevalence in study sample (%) | Prevalence of positive FH in study sample (%) | PPV for study sample | NPV for study sample | Most highly adjusted reported OR or equivalent[1] |
|---|---|---|---|---|---|---|---|---|---|
| B | atopy, ≥1 parent | N | N | Patrzalek, M&F, ≤13y | 36.2 | 22.0 | 0.52 | 0.68 | 11.2 |
| B | atopy, father | N | N | Alford, M&F, onset 6-7y | 30.5 | 37.2 | 0.38 | 0.74 | 1.75 |
| B | atopy, father, childhood | Y | N | Alford, M&F, onset 6-7y | 30.5 | 22.6 | 0.40 | 0.72 | 1.02 |
| B | atopy, mother | N | N | Alford, M&F, onset 6-7y | 30.9 | 45.5 | 0.33 | 0.71 | 1.71 |
| B | atopy, mother, childhood | Y | N | Alford, M&F, onset 6-7y | 30.9 | 25.4 | 0.28 | 0.68 | 0.52 |

Abbreviations: 1DR=first degree relative; F=female; FH=family history; FU=followup; M=male; N=no; NPV=negative predictive value; OR=odds ratio; PPV=positive predictive value; y=years; Y=yes

[1] OR=odds ratio, metric reported unless otherwise stated

**Webtable 22. Predictive values associated with FH definitions for asthma in longitudinal analyses**

| FH category | Specific definition | Age criterion | Lineage criterion | Studies | Disease prevalence in study sample (%) | Prevalence of positive FH in study sample (%) | PPV for study sample | NPV for study sample | Most highly adjusted reported RR or equivalent[1] (max length of FU) |
|---|---|---|---|---|---|---|---|---|---|
| B | asthma, mother | N | N | Tariq, M&F, onset ≤4y | 14.9 | 10.4 | 0.25 | 0.86 | 3.0 (4 y) |
| B | atopy, mother | N | N | Tariq, M&F, onset ≤4y | 14.8 | 33.7 | 0.18 | 0.87 | 1.9 (4 y) |
| C | atopy, ≥1 sibling | N | N | Tariq, M&F, onset ≤4y | 15.9 | 36.9 | 0.21 | 0.87 | 2.2 (4 y) |
| C | atopy, ≥1 1DR | N | N | Tariq, M&F, onset ≤4y | 14.8 | 58.5 | 0.17 | 0.89 | 2.0 |

Abbreviations: FH=family history; FU=followup; N=no; NPV=negative predictive value; PPV=positive predictive value; RR=relative risk; y=years

[1] RR = relative risk, metric reported unless otherwise stated

**Webtable 23. Predictive values associated with FH definitions for asthma in cross-sectional analyses**

| FH category | Specific definition | Age criterion | Lineage criterion | Studies | Disease prevalence in study sample (%) | Prevalence of positive FH in study sample (%) | PPV for study sample | NPV for study sample | Most highly adjusted reported OR or equivalent[1] |
|---|---|---|---|---|---|---|---|---|---|
| B | asthma, ≥1 parent | N | N | London, M&F, onset 9-16y | 14.4 | 18.8 | 0.30 | 0.89 | NR |
| B | asthma, father | N | N | London, M&F, onset 9-16y | 14.4 | 8.6 | 0.32 | 0.87 | 4.10 (early)<br>2.72 (late) |
| | | | | Garcia-Marcos, M&F, onset 9-12y | 13.1 | 5.4 | 0.22 | 0.87 | 1.8 (atopic)<br>1.6 (non-atopic) |
| | | | | Bener, M&F, onset 6-12y | 19.8 | 9.0 | 0.40 | 0.82 | 2.3 |
| | | | | Alford, M&F, onset 6-7y | 6.9 | 8.0 | 0.18 | 0.94 | 6.00 |
| B | asthma, father, childhood | Y | N | Alford, M&F, onset 6-7y | 6.9 | 5.7 | 0.19 | 0.94 | 4.39 |

Abbreviations: 1DR=first degree relative; F=female; FH=family history; N=no; NPV=negative predictive value; M=male; mod=moderate; NR=not reported; OR=odds ratio; PPV=positive predictive value; sev=severe; y=years; Y=yes

[1] OR=odds ratio, metric reported unless otherwise stated

**Webtable 23. Predictive values associated with FH definitions for asthma in cross-sectional analyses (continued)**

| FH category | Specific definition | Age criterion | Lineage criterion | Studies | Disease prevalence in study sample (%) | Prevalence of positive FH in study sample (%) | PPV for study sample | NPV for study sample | Most highly adjusted reported OR or equivalent[1] |
|---|---|---|---|---|---|---|---|---|---|
| B | asthma, mother | N | N | London, M&F, onset 9-16y | 14.4 | 11.3 | 0.29 | 0.87 | 4.06 (early)<br>2.91 (late) |
| | | | | Garcia-Marcos, M&F, onset 9-12y | 13.1 | 8.6 | 0.20 | 0.88 | 1.62 (atopic)<br>1.76 (non-atopic) |
| | | | | Bener, M&F, onset 6-12y | 19.8 | 11.8 | 0.37 | 0.82 | 2.1 |
| | | | | Alford, M&F, onset 6-7y | 7.1 | 13.6 | 0.08 | 0.93 | 1.06 |
| B | asthma, mother, childhood | Y | N | Alford, M&F, onset 6-7y | 7.1 | 7.8 | 0.08 | 0.93 | - |
| B | asthma, ≥1 sibling | N | N | Bener, M&F, onset 6-12y | 19.8 | 36.5 | 0.34 | 0.89 | 3.0 |
| B | asthma, both parents | N | N | London, M&F, onset 9-16y | 14.4 | 1.1 | 0.51 | 0.86 | 12.15 (early)<br>5.38 (late) |
| B | ≥1 parent or sibling | N | N | Melbostad, M&F | 3.1 | 12.5 | 0.07 | 0.98 | 2.9 |

**Webtable 23. Predictive values associated with FH definitions for asthma in cross-sectional analyses (continued)**

| FH category | Specific definition | Age criterion | Lineage criterion | Studies | Disease prevalence in study sample (%) | Prevalence of positive FH in study sample (%) | PPV for study sample | NPV for study sample | Most highly adjusted reported OR or equivalent[1] |
|---|---|---|---|---|---|---|---|---|---|
| C | asthma, ≥1 1DR | N | N | Montnemery, M&F | 5.5 | 17.3 | 0.13 | 0.96 | 3.71 |
| | | | | Hu, M&F, onset ≤20y | 8.2 | 21.9 | 0.17 | 0.94 | 3.3 |
| | | | | Hu, M&F, onset ≤20y | 11.8 | 21.9 | 0.24 | 0.91 | 3.1 |
| | | | | Ones, M&F, onset 6-12y | 9.8 | 7.8 | 0.20 | 0.91 | 2.49 |
| | | | | Chatkin, M&F, onset ≤6y | 12.8 | 51.8 | 0.19 | 0.94 | 2.8 |
| | | | | Chatkin, M&F, onset ≤4y | 18.3 | 56.8 | 0.22 | 0.87 | 1.66 |
| D | asthma, ≥1 1DR or grandparent | N | N | Sugiyama, M&F, onset 13-14y | 7.7 | 19.0 | 0.16 | 0.94 | 2.34 (mild)<br>4.39 (mod)<br>3.41 (sev) |

**Webtable 24. Quality items for asthma and atopy studies for review question 1**

| Author Year | Same outcome ascertain-ment, irrespective of FH (outcome information bias) | Outcome ascertain-ment blind to FH (outcome information bias) | Same FH ascertain-ment, irrespective of disease status (exposure information bias) | FH ascertain-ment blind to disease status (exposure information bias) | Exclusion of cases at inception (cohort) (misclassi-fication) | Adequate followup (cohort) (selection bias) | Representat ive sampling (cross-sectional) (selection bias) | Adequate response rate (cross-sectional) (selection bias) |
|---|---|---|---|---|---|---|---|---|
| **Asthma & atopy** | | | | | | | | |
| Tariq 1998 | Yes | No | Yes | Yes | Yes | At least 80% followup | Not applicable (longitudinal design) | Not applicable (longitudinal design) |
| Hu 1997 | Yes | No | Yes | No | Not applicable (cross sectional design) | Not applicable (cross-sectional design) | Unclear | Response rate less than 80%, inadequate or missing description of non |
| Melbostad 1998 | Yes | No | Yes | No | Not applicable (cross sectional design) | Not applicable (cross sectional design) | Yes (probability sampling) | Response rate less than 80%, inadequate or missing description of non |

**Webtable 24. Quality items for asthma and atopy studies for review question 1 (continued)**

| Author Year | Same outcome ascertain-ment, irrespective of FH (outcome information bias) | Outcome ascertain-ment blind to FH (outcome information bias) | Same FH ascertain-ment, irrespective of disease status (exposure information bias) | FH ascertain-ment blind to disease status (exposure information bias) | Exclusion of cases at inception (cohort) (misclassi-fication) | Adequate followup (cohort) (selection bias) | Representative sampling (cross-sectional) (selection bias) | Adequate response rate (cross-sectional) (selection bias) |
|---|---|---|---|---|---|---|---|---|
| Montnemery 2001 | Yes | No | Yes | No | Not applicable (cross sectional design) | Not applicable (cross sectional design) | Yes (probability sampling) | Response rate less than 80%, adequate description of non-participants |
| London 2001 | Yes | No | Yes | No | Not applicable (cross sectional design) | Not applicable (cross sectional design) | Unclear | Response rate less than 80%, inadequate or missing description of non-participants |
| Chatkin 2003 | Yes | Unclear | Yes | Unclear | Not applicable (cross sectional design) | Not applicable (cross sectional design) | Yes (probability sampling) | Yes, response rate at least 80% |
| Chatkin 2005 | Yes | Yes | Yes | No | Not applicable (cross sectional design) | Not applicable (cross sectional design) | Yes (probability sampling) | Yes, response rate at least 80% |
| Sugiyama 2002 | Yes | No | Yes | No | Not applicable (cross sectional design) | Not applicable (cross sectional design) | Yes (probability sampling) | Response rate less than 80%, adequate description of non-participants |

**Webtable 24. Quality items for asthma and atopy studies for review question 1 (continued)**

| Author Year | Same outcome ascertain-ment, irrespective of FH (outcome information bias) | Outcome ascertain-ment blind to FH (outcome information bias) | Same FH ascertain-ment, irrespective of disease status (exposure information bias) | FH ascertain-ment blind to disease status (exposure information bias) | Exclusion of cases at inception (cohort) (misclassi-fication) | Adequate followup (cohort) (selection bias) | Representati ve sampling (cross-sectional) (selection bias) | Adequate response rate (cross-sectional) (selection bias) |
|---|---|---|---|---|---|---|---|---|
| Ones 1997 | Yes | No | Yes | No | Not applicable (cross sectional design) | Not applicable (cross sectional design) | Yes (probability sampling) | Yes, response rate at least 80% |
| Bener 2005 | Yes | No | Yes | No | Not applicable (cross sectional design) | Not applicable (cross sectional design) | Yes (probability sampling) | Yes, response rate at least 80% |
| Garcia-Marcos 2005 | Yes | No | Yes | No | Not applicable (cross sectional design) | Not applicable (cross-sectional design) | Yes (probability sampling) | Response rate less than 80%, inadequate or missing description of non-participants |
| Lopez 1999 | Yes | Unclear | Unclear | Yes | Yes | at least 80% followup | Not applicable (longitudinal design) | Not applicable (longitudinal design) |
| Pohlabeln 2007 | Yes | Unclear | Yes | Yes | Yes | Less than 80% followup, inadequate or missing description of those lost | Not applicable (longitudinal design) | Not applicable (longitudinal design) |

**Webtable 24. Quality items for asthma and atopy studies for review question 1 (continued)**

| Author Year | Same outcome ascertain-ment, irrespective of FH (outcome information bias) | Outcome ascertain-ment blind to FH (outcome information bias) | Same FH ascertain-ment, irrespective of disease status (exposure information bias) | FH ascertain-ment blind to disease status (exposure information bias) | Exclusion of cases at inception (cohort) (misclassi-fication) | Adequate followup (cohort) (selection bias) | Representative sampling (cross-sectional) (selection bias) | Adequate response rate (cross-sectional) (selection bias) |
|---|---|---|---|---|---|---|---|---|
| Alford 2004 | Yes | No | Yes | No | Not applicable (cross-sectional design) | Not applicable (cross-sectional design) | Yes (probability sampling) | Response rate less than 80%, inadequate or missing description of non-participants |
| Bergmann 1997 | Yes | Unclear | Unclear | Yes | Yes | Unclear | Not applicable (longitudinal design) | Not applicable (longitudinal design) |
| Patrzalek 2003 | Unclear | Unclear | Yes | No | Not applicable (cross-sectional design) | Not applicable (cross-sectional design) | Yes (probability sampling) | Unclear |

**Webtable 25. General data for mental health studies**

| Author Year | Study setting | Study design | n | Sub-groups measured | How/when FH obtained | Definition of outcome | How/when outcome ascertained |
|---|---|---|---|---|---|---|---|
| Reinherz 2003 | predominately Caucasian, working-class community in the north eastern U.S., men and women's life course of a single age (5-26 y) | prospective cohort | 354 | men and women, age 18 to 26 | participant and maternal survey, methods not clear | DSM-IV criteria for major depression | diagnostic interviews at three time points |
| Weissman 2005 | 3 - Generation Study U.S. | longitudinal retrospective cohort | 161 | grandchildren of original cohort (generation 3)<br><br>children of original cohort (generation 2) | clinical assessment of generations one and two of three generation cohort study | best estimate diagnosis, DSM-IV criteria for major depressive disorder, mood disorder | diagnostic interviews |

Abbreviations: CIDI=composite international diagnostic interview; DSM III-R=diagnostic and statistical method of mental disorders third edition-revised; DSM IV=diagnostic and statistical method of mental disorders fourth edition; FH=family history; GAS=global assessment scale; MDD=major depressive disorder; n=number of subjects; RCT=randomized controlled study; U.S.=United States of America; y=years

**Webtable 26. Predictive values associated with FH definitions for mood disorders in longitudinal analyses**

| FH category | Specific definition | Age criterion | Lineage criterion | Studies | Disease prevalence in study sample (%) | Prevalence of positive FH in study sample (%) | PPV for study sample | NPV for study sample | Most highly adjusted reported RR or equivalent[1] (max length of FU) |
|---|---|---|---|---|---|---|---|---|---|
| B | MDD, ≥1 parent | N | N | Weissman, M&F, onset ≤26y | 18.6 | 59.6 | 0.24 | 0.89 | NR |
| B | MDD, ≥1 grandparent | N | N | Weissman, M&F, onset ≤26y | 18.6 | 62.7 | 0.25 | 0.92 | NR |
| B | MDD, ≥1 parent and ≥1 grandparent | N | N | Weissman, M&F, onset ≤26y | 18.6 | 44.1 | 0.31 | 0.91 | 2.8 |

Abbreviations: FH=family history; FU=followup; MDD=major depressive disorder; N=no; NPV=negative predictive value; NR=not reported; PPV=positive predictive value; RR=relative risk; y=years

[1] RR=relative risk, metric reported unless otherwise stated

**Webtable 27. Predictive values associated with FH definitions for major depressive disorder in longitudinal analyses**

| FH category | Specific definition | Age criterion | Lineage criterion | Studies | Disease prevalence in study sample (%) | Prevalence of positive FH in study sample (%) | PPV for study sample | NPV for study sample | Most highly adjusted reported RR or equivalent[1] (max length of FU) |
|---|---|---|---|---|---|---|---|---|---|
| B | | | | Weissman, M&F, onset ≤26y | 11.2 | 59.6 | 0.14 | 0.92 | NR |
| B | ≥1 grandparent | N | N | Weissman, M&F, onset ≤26y | 11.2 | 62.7 | 0.15 | 0.95 | NR |
| B | ≥1 parent and ≥1 grandparent | N | N | Weissman, M&F, onset ≤26y | 11.2 | 44.1 | 0.18 | 0.94 | 2.33 |

Abbreviations: F=female; FH=family history; FU=followup; N=no; NPV=negative predictive value; M=male; NR=not reported; PPV=positive predictive value; RR=relative risk; y=years

[1] RR=relative risk, metric reported unless otherwise stated

**Webtable 28. Predictive values associated with FH definitions for major depressive disorder in cross-sectional analyses**

| FH category | Specific definition | Age criterion | Lineage criterion | Studies | Disease prevalence in study sample (%) | Prevalence of positive FH in study sample (%) | PPV for study sample | NPV for study sample | Most highly adjusted reported OR or equivalent[1] |
|---|---|---|---|---|---|---|---|---|---|
| B | ≥1 parent | N | N | Reinherz,M &F, onset ≤26y | 23.2 | 16.9 | 0.33 | 0.79 | 1.84 |
| B | ≥1 sibling | N | N | Reinherz,M &F, onset ≤26y | 23.2 | 6.2 | 0.45 | 0.78 | 2.88 |

Abbreviations: F=female; FH=family history; N=no; NPV=negative predictive value; M=male; OR=odds ratio; PPV=positive predictive value; y=years
[1] OR=odds ratio, metric reported unless otherwise stated

**Webtable 29. Quality items for mental illness studies for review question 1**

| Author Year | Same outcome ascertain-ment, irrespective of FH (outcome information bias) | Outcome ascertain-ment blind to FH (outcome information bias) | Same FH ascertain-ment, irrespective of disease status (exposure information bias) | FH ascertain-ment blind to disease status (exposure information bias) | Exclusion of cases at inception (cohort) (misclassi-fication) | Adequate followup (cohort) (selection bias) | Representat ive sampling (cross-sectional) (selection bias) | Adequate response rate (cross-sectional) (selection bias) |
|---|---|---|---|---|---|---|---|---|
| **Mental illness** | | | | | | | | |
| Weissman 2005 | Yes | Yes | Yes | Yes | Yes | at least 80% followup | Not applicable (longitudinal design) | Not applicable (longitudinal design) |
| Reinherz 2003 | Yes | No | Unclear | Unclear | Not applicable (cross-sectional design) | Not applicable (cross-sectional design) | Yes (probability sampling) | Response rate less than 80%, adequate description of non-participants |

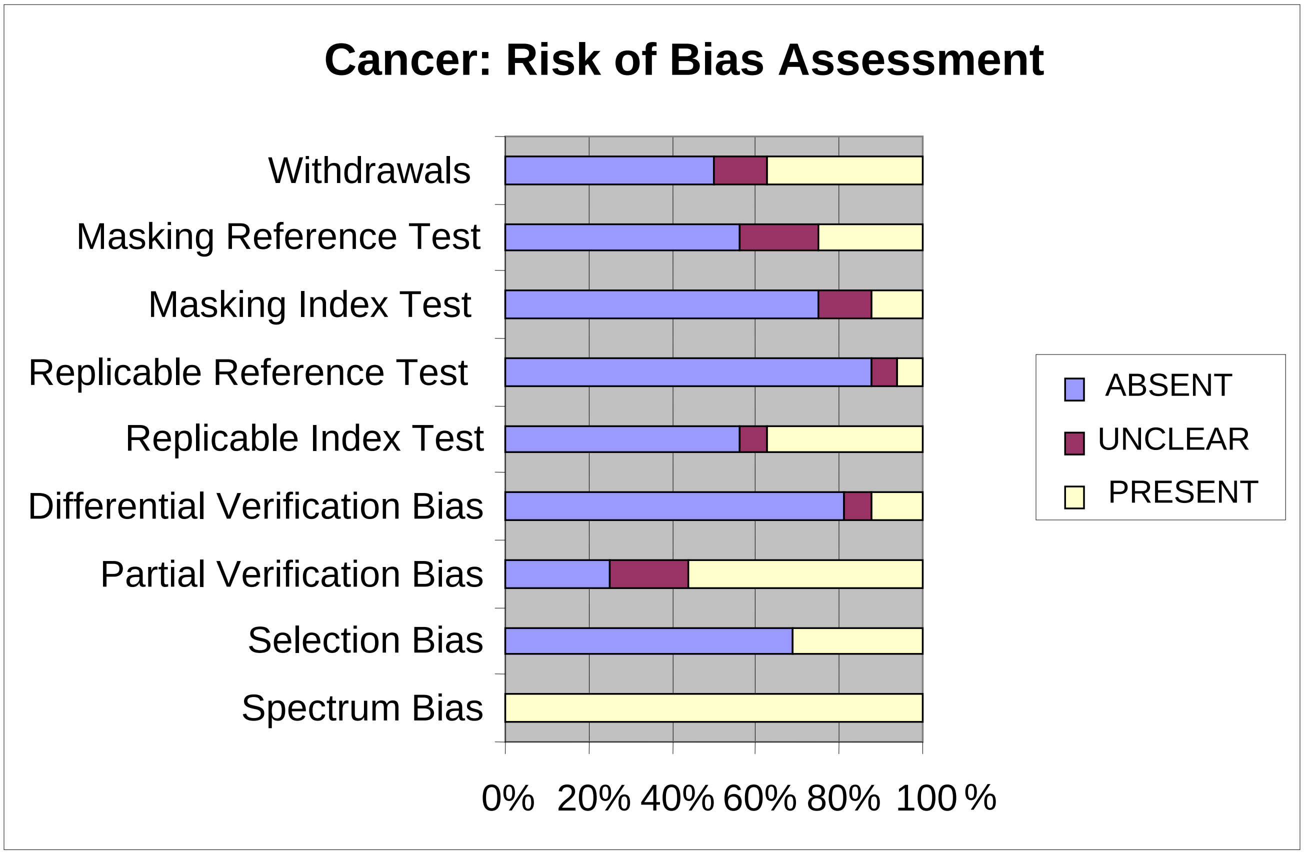
**Webtable 30. Studies excluded from Question 3 and Question 4 because of study design**

| Studies (stratified by design) | Question exclusion |
|---|---|
| ***Case-control*** | |
| Andersen (2002) | Q4 |
| Bloom (2006) | Q3/Q4 |
| Bottorff (2002) | Q4 |
| Cappelli (2001) | Q4 |
| Cappelli (1999) | Q4 |
| Drossaert (1996) | Q3/Q4 |
| Imperiale (2008) | Q3/Q4 |
| Kaikkonen (2006) | Q3/Q4 |
| Meschia (2006) | Q3/Q4 |
| Perez (2001) | Q4 |
| Tung (2004) | Q3/Q4 |
| ***Cohort*** | |
| Calvocoressi (2004) | Q4 |
| Chang (2005) | Q3 |
| Clavel-Chapelon (1999) | Q4 |
| Cobbe (1997) | Q3/Q4 |
| Gil (2003) | Q3/Q4 |
| Phillips (2005) | Q3/Q4 |
| Sellers (1997) | Q3/Q4 |
| Thalib (2004) | Q3/Q4 |
| van Dooren (2005) | Q4 |
| ***Cross-sectional*** | |
| Armstrong (2002) | Q3/Q4 |
| Beebe-Dimmer (2004) | Q3/Q4 |
| Bratt (1997) | Q4 |
| Bunn (2002) | Q3/Q4 |
| Cantor (2002) | Q4 |
| Carney (2006) | Q4 |
| Cohen (2006) | Q3/Q4 |
| Costanza (2005) | Q4 |
| Crepeau (2008) | Q4 |
| Criqui (2007) | Q3/Q4 |
| Davids (2004) | Q3/Q4 |
| Dawson (1997) | Q4 |
| Dotterud (1995) | Q3 |
| Drescher (2000) | Q3/Q4 |
| Easton (1996) | Q3/Q4 |
| Erblich (2000) | Q4 |
| Erblich (2000) | Q4 |
| Finney (2001) | Q3/Q4 |
| Fletcher (2007) | Q3/Q4 |
| Friedman (2004) | Q3/Q4 |
| Gaga (2005) | Q3/Q4 |
| Glanz (1999) | Q4 |
| Harpaz (2004) | Q3/Q4 |
| Hebert-Croteau (1997) | Q4 |
| Higgins (2005) | Q3/Q4 |
| Jacobsen (2004) | Q4 |
| Karliner (2007) | Q3/Q4 |
| Laukkanen (2007) | Q3/Q4 |

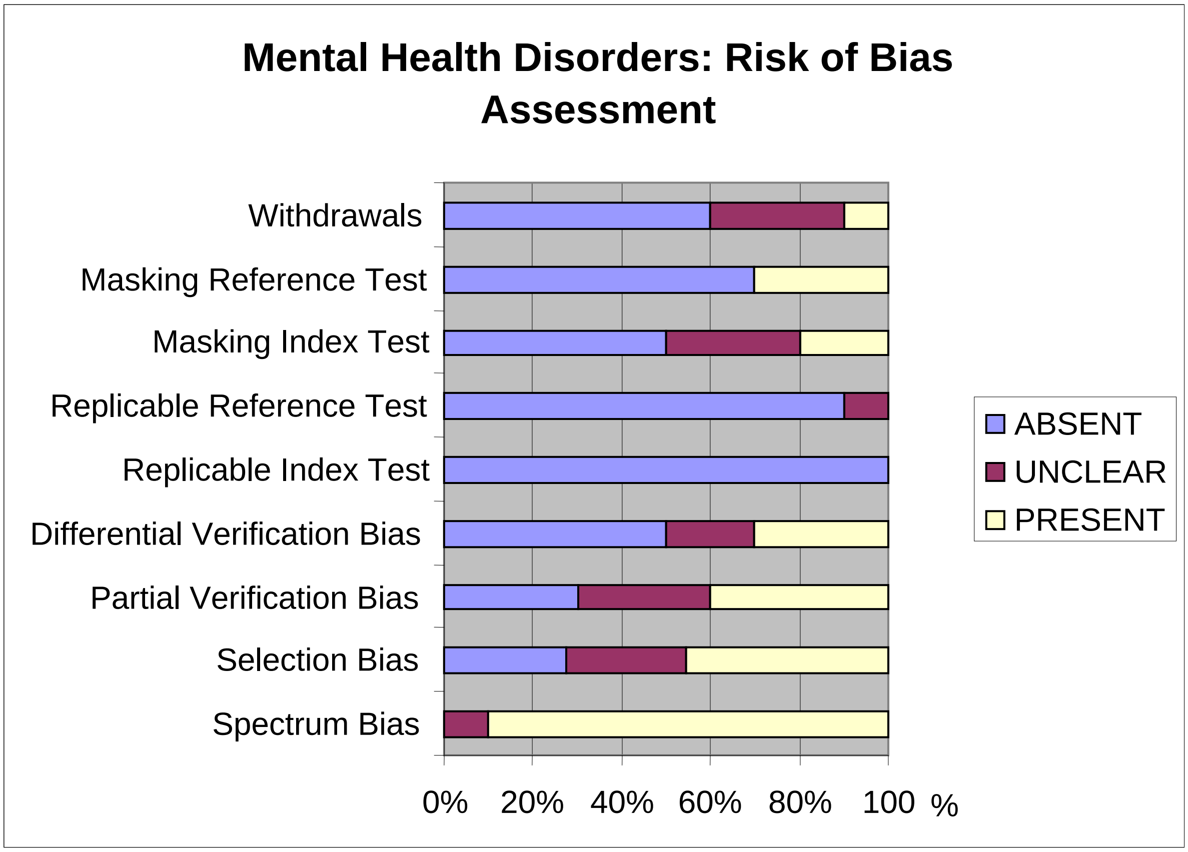
**Webtable 30. Studies excluded from Question 3 and Question 4 because of study design(continued)**

| | |
|---|---|
| Lippert (1999) | Q4 |
| Longacre (2006) | Q4 |
| Lopez-Perez | Q3 |
| MacDonald (2005) | Q4 |
| McCusker (2004) | Q3/Q4 |
| Mellon (2008) | Q4 |
| Murff (2005) | Q3/Q4 |
| Murff (2004) | Q3/Q4 |
| Petersen (1999) | Q3/Q4 |
| Quillin (2006) | Q4 |
| Robb (2004) | Q4 |
| Roncaglioni (2004) | Q4 |
| Rose (1999) | Q3/Q4 |
| Scheuner (2006) | Q3/Q4 |
| Shirakawa (2006) | Q3/Q4 |
| Stark (2006) | Q4 |
| Stoney (1999) | Q4 |
| Tozzi (2008) | Q3/Q4 |
| Van Der Sande (2001) | Q3/Q4 |
| Wang (2006) | Q3 |
| West (2003) | Q3/Q4 |
| Zheng (2006) | Q3/Q4 |

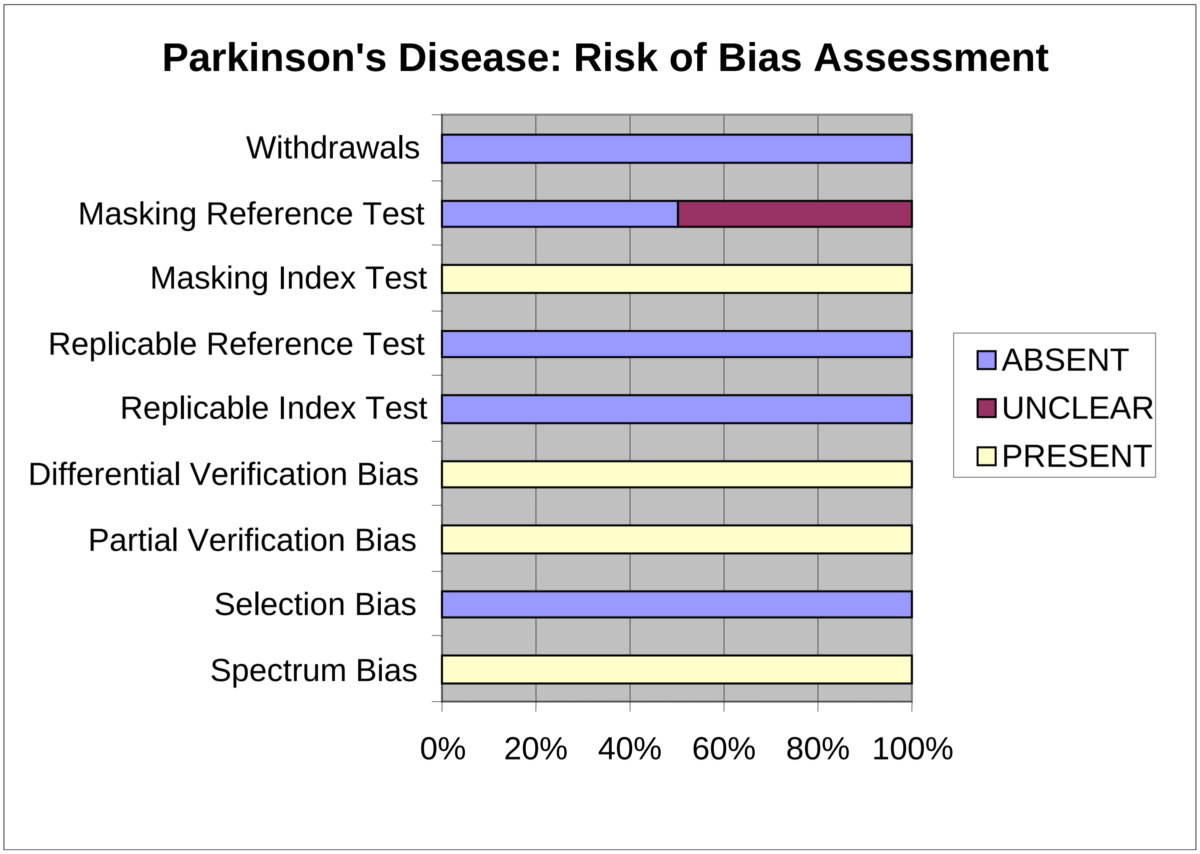
**Webfigure 1. Cancer, risk of bias**



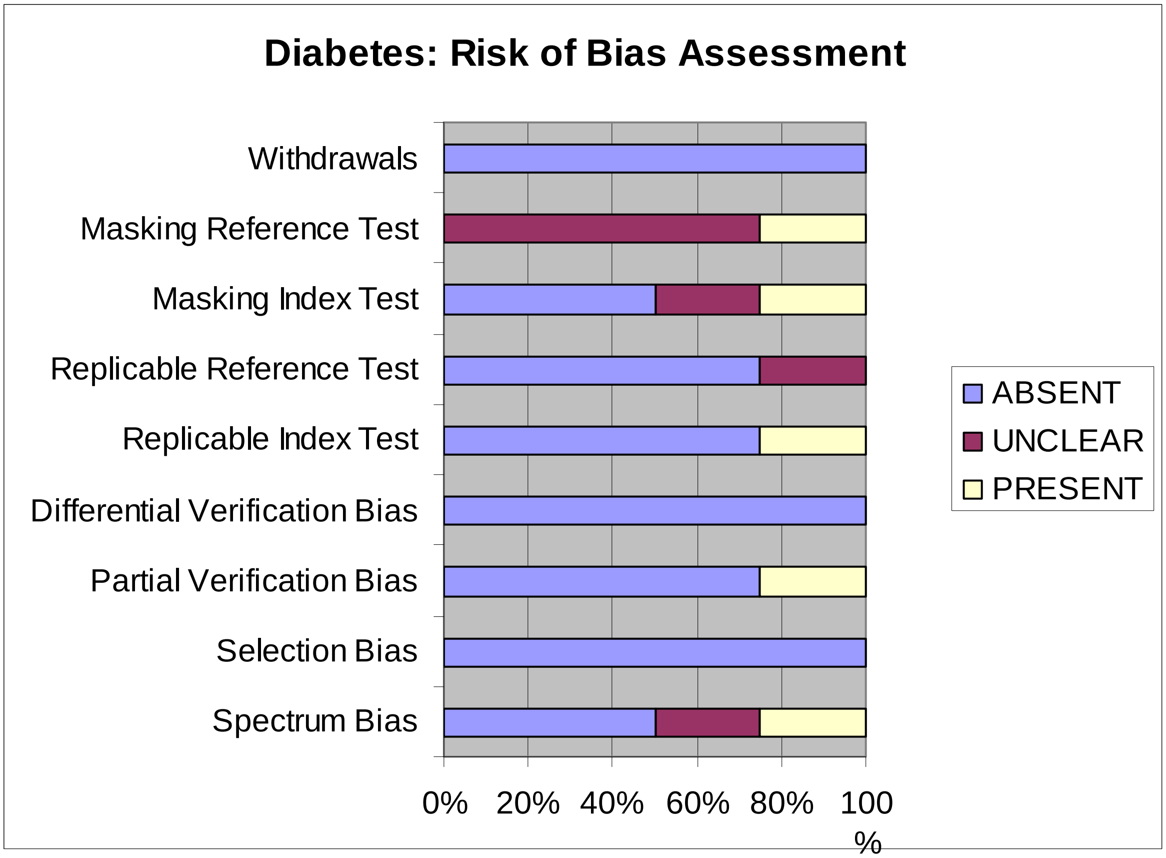
**Webfigure 2. Mental health disorders, risk of bias**



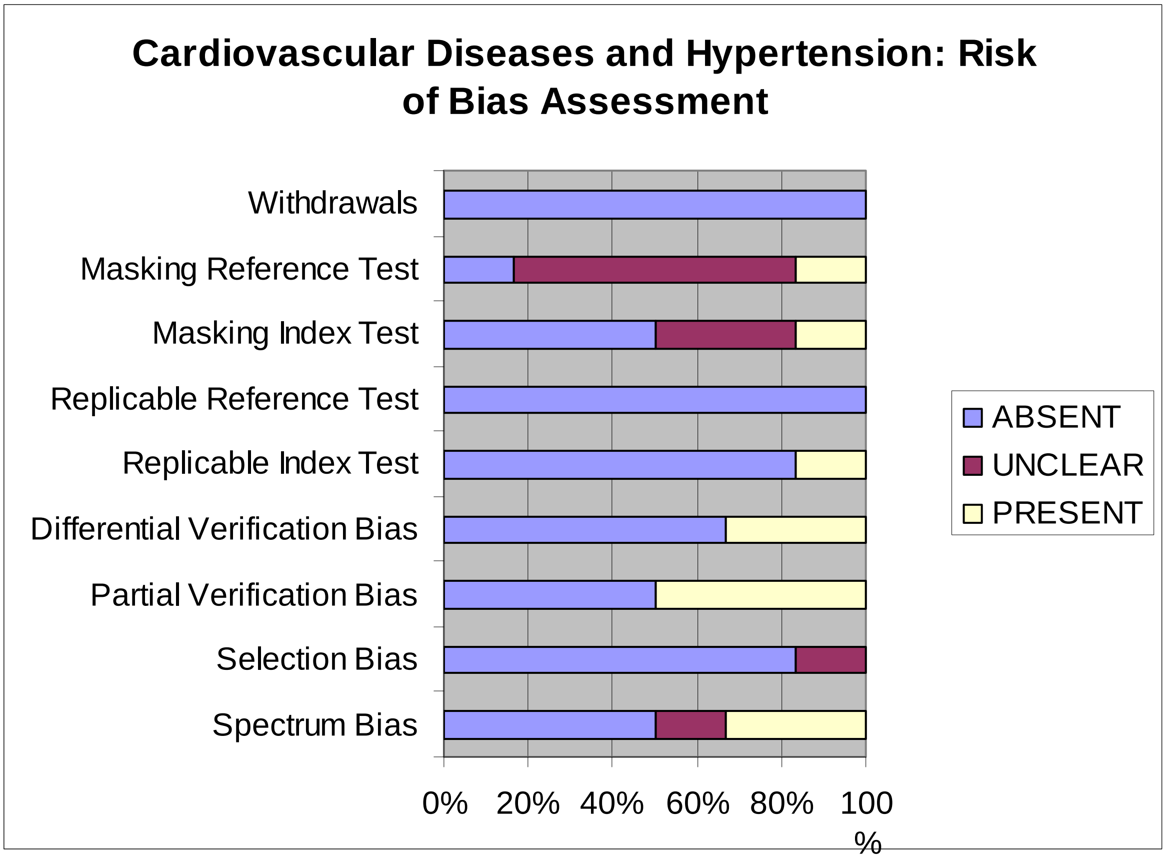
**Webfigure 3. Parkinson's Disease, risk of bias**



**Webfigure 4. Diabetes, risk of bias**



**Webfigure 5. Cardiovascular disease and hypertension, risk of bias**



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# Appendix D – Excluded Studies

EUROASPIRE. A European Society of Cardiology survey of secondary prevention of coronary heart disease: principal results. EUROASPIRE Study Group. European Action on Secondary Prevention through Intervention to Reduce Events. [erratum appears in Eur Heart J 1998 Feb;19(2):356-7]. Eur Heart J 1997 Oct;18(10):1569-82.
Excluded because no eligible outcomes presented

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Excluded because it does not meet all criteria for any one review question, although each of population, intervention and outcome criteria were met for the review questions in aggregate

Aasvee K, Kurvinen E, Sundvall J, et al. Aggregation of lipoprotein and inflammatory parameters in families with a history of premature myocardial infarction: the Tallinn myocardial infarction study. Clin Chem Lab Med 2008;46(11):1602-8.
Excluded because no eligible outcomes presented

Abaitua FR, Martinez JI, Lopez RE, et al. Family history as a predictor for childhood hyperlipidemia. Cardiovasc Risk Factors 1996;6(5):277-83.
Excluded because it does not meet all criteria for any one review question, although each of population, intervention and outcome criteria were met for the review questions in aggregate

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Excluded because it does not meet all criteria for any one review question, although each of population, intervention and outcome criteria were met for the review questions in aggregate

Aberg N, Sundell J, Eriksson B, et al. Prevalence of allergic diseases in schoolchildren in relation to family history, upper respiratory infections, and residential characteristics. Allergy 1996;51(4):232-7.
Excluded because it does not meet all criteria for any one review question, although each of population, intervention and outcome criteria were met for the review questions in aggregate

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Excluded because it does not meet all criteria for any one review question, although each of population, intervention and outcome criteria were met for the review questions in aggregate

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Excluded because it does not meet all criteria for any one review question, although each of population, intervention and outcome criteria were met for the review questions in aggregate

Acton RT, Burst NM, Casebeer L, et al. Knowledge, attitudes, and behaviors of Alabama's primary care physicians regarding cancer genetics. Acad Med 2000 Aug;75(8):850-2.
Excluded because no eligible outcomes presented

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Adamson AJ, Foster E, Butler TJ, et al. Non-diabetic relatives of Type 2 diabetic families: dietary intake contributes to the increased risk of diabetes. Diabet Med 2001 Dec;18(12):984-90.
Excluded because no eligible outcomes presented

Aggarwal AN, Chaudhry K, Chhabra SK, et al. Prevalence and risk factors for bronchial asthma in Indian adults: a multicentre study. Indian J Chest Dis Allied SciI 2006 Jan;48(1):13-22.
Excluded because it does not meet all criteria for any one review question, although each of population, intervention and outcome criteria were met for the review questions in aggregate

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Excluded because it does not meet all criteria for any one review question, although each of population, intervention and outcome criteria were met for the review questions in aggregate

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Excluded because it does not meet all criteria for any one review question, although each of population, intervention and outcome criteria were met for the review questions in aggregate

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Excluded because it does not meet all criteria for any one review question, although each of population, intervention and outcome criteria were met for the review questions in aggregate

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Excluded because it does not meet all criteria for any one review question, although each of population, intervention and outcome criteria were met for the review questions in aggregate

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Excluded because it does not meet all criteria for any one review question, although each of population, intervention and outcome criteria were met for the review questions in aggregate

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Excluded because it does not meet all criteria for any one review question, although each of population, intervention and outcome criteria were met for the review questions in aggregate

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Excluded because it does not meet all criteria for any one review question, although each of population, intervention and outcome criteria were met for the review questions in aggregate

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Excluded because it does not meet all criteria for any one review question, although each of population, intervention and outcome criteria were met for the review questions in aggregate

Al Habsi H, Lim JNW, Chu CE, et al. Factors influencing the referrals in primary care of asymptomatic patients with a family history of cancer. Genet Med 2008;10(10):751-7.
Excluded because it does not meet all criteria for any one review question, although each of population, intervention and outcome criteria were met for the review questions in aggregate

Al Mahroos F, McKeigue PM. High prevalence of diabetes in bahrainis: Associations with ethnicity and raised plasma cholesterol. Diabetes Care 1998;21(6):936-42.
Excluded because it does not meet all criteria for any one review question, although each of population, intervention and outcome criteria were met for the review questions in aggregate

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Excluded because family history not collected

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Excluded because no eligible outcomes presented

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Excluded because it does not meet all criteria for any one review question, although each of population, intervention and outcome criteria were met for the review questions in aggregate

Al Shafaee MA, Al Shukaili S, Rizvi SGA, et al. Knowledge and perceptions of diabetes in a semi-urban Omani population. BMC Public Health 2008;8:249.
Excluded because no eligible outcomes presented

Al Shaibani H, Bu-Alayyan S, Habiba S, et al. Risk factors of breast cancer in Kuwait: Case-control study. Iranian Journal of Medical Sciences 2006;31(2):61-4.
Excluded because it does not meet all criteria for any one review question, although each of population, intervention and outcome criteria were met for the review questions in aggregate

Alberto VO, Harocopos CJ, Patel AA, et al. Family and personal history in colorectal cancer patients: what are we missing? Colorectal Dis 2006 Sep;8(7):612-4.
Excluded because it does not meet all criteria for any one review question, although each of population, intervention and outcome criteria were met for the review questions in aggregate

Aldington S, Pritchard A, Perrin K, et al. Prolonged seated immobility at work is a common risk factor for venous thromboembolism leading to hospital admission. Intern Med J 2008;38(2):133-5.
Excluded because it does not meet all criteria for any one review question, although each of population, intervention and outcome criteria were met for the review questions in aggregate

Allan CL, Flett B, Dean HJ. Quality of life in first nation youth with type 2 diabetes. Matern Child Health J 2008;12(Suppl 1):S103-S109
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Altobelli E, Chiarelli F, Valenti M, et al. Family history and risk of insulin-dependent diabetes mellitus: a population-based case-control study. Acta Diabetol 1998 Apr;35(1):57-60.
Excluded because it does not meet all criteria for any one review question, although each of population, intervention and outcome criteria were met for the review questions in aggregate

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Excluded because it does not meet all criteria for any one review question, although each of population, intervention and outcome criteria were met for the review questions in aggregate

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Andermann AAJ, Watson EK, Lucassen AM, et al. The opinions, expectations and experiences of women with a family history of breast cancer who consult their GP and referred to secondary care. Community Genet 2001;4(4):239-43.
Excluded because it does not meet all criteria for any one review question, although each of population, intervention and outcome criteria were met for the review questions in aggregate

Andersen MR, Peacock S, Nelson J, et al. Worry about ovarian cancer risk and use of ovarian cancer screening by women at risk for ovarian cancer. Gynecol Oncol 2002 Apr;85(1):3-8.
Excluded because it does not meet all criteria for any one review question, although each of population, intervention and outcome criteria were met for the review questions in aggregate

Andersen MR, Bowen D, Yasui Y, et al. Awareness and concern about ovarian cancer among women at risk because of a family history of breast or ovarian cancer. Am J Obstet Gynecol 2003 Oct;189(4 Suppl):S42-S47
Excluded because no eligible outcomes presented

Andersen MR, Smith R, Meischke H, et al. Breast cancer worry and mammography use by women with and without a family history in a population-based sample. Cancer Epidemiol Biomarkers Prev 2003 Apr;12(4):314-20.
Excluded because it does not meet all criteria for any one review question, although each of population, intervention and outcome criteria were met for the review questions in aggregate

Anderson E, Berg J, Black R, et al. Predicting breast cancer risk: Implications of a "weak" family history. Fam Cancer 2008;7(4):361-6.
Excluded because it does not meet all criteria for any one review question, although each of population, intervention and outcome criteria were met for the review questions in aggregate

Anderson WF, Matsuno RK, Sherman ME, et al. Estimating age-specific breast cancer risks: A descriptive tool to identify age interactions. Cancer Causes Control 2007;18(4):439-47.
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Andersson SO, Baron J, Bergstrom R, et al. Lifestyle factors and prostate cancer risk: A case-control study in Sweden. Cancer Epidemiol Biomarkers Prev 1996;5(7):509-13.
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Andresdottir MB, Sigurdsson G, Sigvaldason H, et al. Fifteen percent of myocardial infarctions and coronary revascularizations explained by family history unrelated to conventional risk factors. The Reykjavik Cohort Study. Eur Heart J 2002 Nov;23(21):1655-63.
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Andrieu N, Launoy G, Guillois R, et al. Estimation of the familial relative risk of cancer by site from a French population based family study on colorectal cancer (CCREF study). Gut 2004 Sep;53(9):1322-8.
Excluded because it does not meet all criteria for any one review question, although each of population, intervention and outcome criteria were met for the review questions in aggregate

Aprikian AG, Bazinet M, Plante M, et al. Family history and the risk of prostatic carcinoma in a high risk group of urological patients. J Urol 1995 Aug;154(2:Pt 1):404-6.
Excluded because it does not meet all criteria for any one review question, although each of population, intervention and outcome criteria were met for the review questions in aggregate

Arabia G, Grossardt BR, Geda YE, et al. Increased risk of depressive and anxiety disorders in relatives of patients with Parkinson disease. Arch Gen Psychiatry 2007 Dec;64(12):1385-92.

Excluded because it does not meet all criteria for any one review question, although each of population, intervention and outcome criteria were met for the review questions in aggregate

Arif AA, Venati G, Bordes TF, et al. Correlates of physician visits among children and adolescents in West Texas: Effects of hyperglycemia symptoms. J Rural Health 2004;20(3):296-300.
Excluded because no eligible outcomes presented

Armstrong K, Weber B, Ubel PA, et al. Interest in BRCA1/2 testing in a primary care population. Prev Med 2002;34(6):590-5.
Excluded because it does not meet all criteria for any one review question, although each of population, intervention and outcome criteria were met for the review questions in aggregate

Arsov T, Miladinova D, Spiroski M. Factor V Leiden is associated with higher risk of deep venous thrombosis of large blood vessels. Croat Med J 2006;47(3):433-9.
Excluded because it does not meet all criteria for any one review question, although each of population, intervention and outcome criteria were met for the review questions in aggregate

Ashton KA, Proietto A, Otton G, et al. The influence of the Cyclin D1 870 G>A polymorphism as an endometrial cancer risk factor. BMC Cancer 2008 Sep;8:272.
Excluded because no eligible outcomes presented

Askling J, Dickman PW, Karlen P, et al. Family history as a risk factor for colorectal cancer in inflammatory bowel disease. Gastroenterology 2001 May;120(6):1356-62.
Excluded because it does not meet all criteria for any one review question, although each of population, intervention and outcome criteria were met for the review questions in aggregate

Auranen A, Grenman S, Makinen J, et al. Borderline ovarian tumors in Finland: epidemiology and familial occurrence. Am J Epidemiol 1996 Sep 15;144(6):548-53.
Excluded because it does not meet all criteria for any one review question, although each of population, intervention and outcome criteria were met for the review questions in aggregate

Azadeh S, Moghimi-Dehkordi B, Fatem SR, et al. Colorectal cancer in Iran: an epidemiological study. Asian Pac J Cancer Prev 2008 Jan;9(1):123-6.
Excluded because no eligible outcomes presented

Babaoglu K, Hatun S, Arslanoglu I, et al. Evaluation of glucose intolerance in adolescents relative to adults with type 2 diabetes mellitus. J Pediatr Endocrinol 2006 Nov;19(11):1319-26.
Excluded because it does not meet all criteria for any one review question, although each of population, intervention and outcome criteria were met for the review questions in aggregate

Backlund AB, Perzanowski MS, Platts-Mills T, et al. Asthma during the primary school ages - Prevalence, remission and the impact of allergic sensitization. Allergy 2006;61(5):549-55.
Excluded because it does not meet all criteria for any one review question, although each of population, intervention and outcome criteria were met for the review questions in aggregate

Bai Y, Gao YT, Deng J, et al. Risk of prostate cancer and family history of cancer: a population-based study in China. Prostate Cancer Prostatic Dis 2005;8(1):60-5.
Excluded because it does not meet all criteria for any one review question, although each of population, intervention and outcome criteria were met for the review questions in aggregate

Bajdik CD, Fang R, Band PR, et al. Do work-related breast cancer risks in pre-menopausal women depend on family history? Chronic Dis Can 2004;25(3-4):147-51.
Excluded because it does not meet all criteria for any one review question, although each of population, intervention and outcome criteria were met for the review questions in aggregate

Baldwin RC, Tomenson B. Depression in later life. A comparison of symptoms and risk factors in early and late onset cases. Br J Psychiatry 1995 Nov;167:649-52.
Excluded because it does not meet all criteria for any one review question, although each of population, intervention and outcome criteria were met for the review questions in aggregate

Bank I, van de Poel MH, Coppens M, et al. Absolute annual incidences of first events of venous thromboembolism and arterial vascular events in individuals with elevated FVIII:c. A prospective family cohort study. Thromb Haemost 2007 Nov;98(5):1040-4.
Excluded because it does not meet all criteria for any one review question, although each of population, intervention and outcome criteria were met for the review questions in aggregate

Bankhead C, Emery J, Qureshi N, et al. New developments in genetics-knowledge, attitudes and information needs of practice nurses. Fam Pract 2001 Oct;18(5):475-86.
Excluded because it does not meet all criteria for any one review question, although each of population, intervention and outcome criteria were met for the review questions in aggregate

Bao W, Srinivasan SR, Wattigney WA, et al. The relation of parental cardiovascular disease to risk factors in children and young adults. The Bogalusa Heart Study. Circulation 1995 Jan 15;91(2):365-71.
Excluded because it does not meet all criteria for any one review question, although each of population, intervention and outcome criteria were met for the review questions in aggregate

Bao W, Srinivasan SR, Valdez R, et al. Longitudinal changes in cardiovascular risk from childhood to young

adulthood in offspring of parents with coronary artery disease: The Bogalusa heart study. JAMA 1997;278(21):1749-54.
Excluded because it does not meet all criteria for any one review question, although each of population, intervention and outcome criteria were met for the review questions in aggregate

Barlow-Stewart K, Soo SY, Meiser B, et al. Toward cultural competence in cancer genetic counseling and genetics education: Lessons learned from Chinese-Australians. Genet Med 2006;8(1):24-32.
Excluded because not an eligible study design

Barone B, Rodacki M, Zajdenverg L, et al. Family history of type 2 diabetes is increased in patients with type 1 diabetes. Diabetes Res Clin Practice 2008 Oct;82(1):e1-e4
Excluded because no eligible outcomes presented

Barrison AF, Smith C, Oviedo J, et al. Colorectal cancer screening and familial risk: a survey of internal medicine residents' knowledge and practice patterns. Am J Gastroenterol 2003 Jun;98(6):1410-6.
Excluded because family history not collected

Barth JA, Deckelbaum RJ, Starc TJ, et al. Family history of early cardiovascular disease in children with moderate to severe hypercholesterolemia: relationship to lipoprotein (a) and low-density lipoprotein cholesterol levels. J Lab Clin Med 1999 Mar;133(3):237-44.
Excluded because no eligible outcomes presented

Basit A, Hakeem R, Hydrie MZ, et al. Fatness, lipids, insulin sensitivity, and life style of children from high and low risk families. J Ayub Med Coll Abbottabad 2003 Jul;15(3):6-9.
Excluded because it does not meet all criteria for any one review question, although each of population, intervention and outcome criteria were met for the review questions in aggregate

Basit A, Hakeem R, Hydrie MZI, et al. Relation between family history, obesity and risk for diabetes & heart disease in Pakistani children. Pakistan J Med Sci 2004;20(4):296-302.
Excluded because no eligible outcomes presented

Bastani R, Maxwell AE, Bradford C, et al. Tailored risk notification for women with a family history of breast cancer. Prev Med 1999 Nov;29(5):355-64.
Excluded because not an eligible population

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# Appendix E - Technical Expert Panel and Peer Reviewers

## Task Order Officer

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## Technical Expert Panel

In designing the study questions and methodology at the outset of this report, the EPC consulted several technical and content experts.  Broad expertise and perspectives are sought. Divergent and conflicted opinions are common and perceived as health scientific discourse that results in a thoughtful, relevant systematic review. Therefore, in the end, study questions, design and/or methodologic approaches do not necessarily represent the views of individual technical and content experts.

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## Peer Reviewers

Peer reviewer comments on a preliminary draft of this report were considered by the EPC in preparation of this final report. Synthesis of the scientific literature presented here does not necessarily represent the views of individual reviewers.

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