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Screening for Intermediate Risk Factors for Coronary Heart Disease: Systematic Evidence Synthesis

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The information in this report is intended to help clinicians, employers, policymakers, and others make informed decisions about the provision of health care services. This report is intended as a reference and not as a substitute for clinical judgment.

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Structured Abstract

Objectives: In the United States, coronary heart disease and cardiovascular disease account for nearly 40% of deaths each year. An individual's estimated risk for coronary heart disease events, often based on factors incorporated into the Framingham risk score, guides the intensity of risk reduction interventions. We conducted a systematic review of epidemiologic studies to help the U.S. Preventive Services Task Force determine which, if any, of 9 additional risk factors should be considered for incorporation into guidelines for coronary and cardiovascular risk assessment in primary care.

Data Sources: We conducted multiple searches of MEDLINE (1966 to March 2006) for epidemiologic studies relevant to the independent predictive ability of the risk factor when used in intermediate-risk individuals. We obtained additional articles from recent systematic reviews, reference lists of pertinent studies, reviews, editorials, websites, and by consulting experts.

Review Methods: We rated the validity and applicability of each included study and characterized several dimensions of the body of evidence for each risk factor. For applicability, we assessed whether the study was drawn from the general population or a demographic subset of asymptomatic adults; whether it included or focused on intermediate-risk individuals (those who have a 10% - 20% 10-year risk of coronary heart disease events); and the measurement of the Framingham and emerging risk factors and of endpoints. We conducted several meta-analyses of the ability of each of the risk factors to predict major coronary heart disease events independently of Framingham risk factors in intermediate-risk subjects.

Results: Results of the literature review are summarized in the Tables. There are no definitive data from randomized trials on how use of any of these factors in risk assessment would affect cardiac morbidity and mortality. We used a mathematical model to assess the potential impact of using a test for C-reactive protein in intermediate-risk individuals. Under the assumption that those reclassified as high risk (>20% 10-year risk) would have a 30% reduction in the 10-year risk of coronary heart disease events, the main finding was that, use of C-reactive protein could reclassify enough intermediate-risk men to have a major impact.

Conclusion: Several emerging risk factors provided independent information about coronary heart disease risk, but for most there were limitations in the evidence base. Across all of the criteria listed in the table, C-reactive and electron beam computed tomography scan had the strongest evidence for an independent effect in intermediate-risk individuals, and both reclassify some individuals as high-risk. However, data on electron beam computed tomography are relatively sparse, the technique is more expensive, and its potential harms require more investigation. Periodontal disease, carotid intima media thickness, homocysteine, and lipoprotein(a) probably provide independent information about coronary heart disease risk, but data about their prevalence and impact when added to Framingham risk score in intermediate-risk individuals are limited.

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I. INTRODUCTION

In the United States, coronary heart disease (CHD) and cardiovascular disease (CVD) account for nearly 40% of all deaths each year.[1] Several risk factors for CHD and CVD, such as tobacco use, elevated low-density lipoprotein cholesterol (LDL-C), hypertension, hypercoagulable states, and obesity, are modifiable. Identifying individuals at risk, encouraging therapeutic lifestyle changes, and, when appropriate, initiating drug treatment to reduce LDL-C, are highly effective measures to reduce an individual's risk of coronary events and stroke.

An individual's risk for CHD events (or sometimes CVD events) guides the intensity of LDL-C lowering and other interventions. For this reason, assessing an individual's risk plays an important role in initiating measures to modify risk. Several risk stratification systems are available for this purpose. The Adult Treatment Panel III (ATP III) of the National Cholesterol Education Program (NCEP) algorithm, which is the most widely used system, categorizes individuals into 3 risk categories (see *Table 1*).[2, 3] This system uses the Framingham risk scoring system to stratify individuals who do not have established CHD, diabetes, or noncardiac vascular disease.

The sex-specific Framingham risk functions predict an individual's 10-year risk of risk of developing "hard CHD events," that is, the combined risk of myocardial infarction (MI) or death from coronary disease.[4] The functions were derived from 2439 white men and 2812 white women, 30 to 74 years of age, in either the original Framingham cohort or the Framingham Offspring Study.

When used with the ATP III algorithm, the sex-specific Framingham risk functions takes into account age, blood pressure, the serum total cholesterol level, the high-density lipoprotein cholesterol (HDL-C) level, and cigarette smoking. Otherwise, the Framingham risk score includes these factors plus diabetes. The Framingham score does not take into account family history, obesity, triglycerides, small LDL particles, lipoprotein(a) (Lp[a]), coagulation factors, homocysteine, or the metabolic syndrome. Of these excluded factors, the best-established is a family history of coronary disease in first-degree relatives, which was a relatively strong, independent predictor of CHD events in the Framingham Offspring Study.[5] The metabolic syndrome is a common constellation of findings associated with a higher risk of developing diabetes. It may also be an independent predictor of stroke.[6]

The Framingham risk functions also do not take race or ethnicity into account, but have been validated in many populations. The risk functions perform well in black men and women,[7] but overestimate the risk of CHD events in Japanese-American and Hispanic men, Native American women, and in Chinese men and women.[8]

TABLE 1. ATP-III RISK CATEGORIES

- Established CHD and CHD equivalents. *Any of the following:*
  - established CHD
  - diabetes
  - established noncardiac vascular disease—peripheral arterial disease, abdominal aortic aneurysm, carotid artery disease (symptomatic, e.g., transient ischemic attack or stroke of carotid origin, or >50 percent stenosis on angiography or ultrasound)
  - a 10-year risk of CHD events ≥20% using Framingham scoring
- Multiple (2+) risk factors that modify LDL goals (cigarette smoking, hypertension, HDL <40 mg/dL, family history of premature CHD, age ≥45 in men, ≥55 in women)
- 0-1 Risk Factors

Framingham risk factors account for most of the excess risk for CHD morbidity and mortality among individuals who have not had a previous cardiovascular event or diagnosis.[4, 9] However, 10-20% of individuals with CHD have no identified risk factors and miss the opportunity for primary prevention.[10, 11] Approximately 40% of CHD deaths occur in patients with cholesterol levels lower than the population average.[10]

The potential impact of new risk factors is greatest for individuals who are classified as intermediate-risk using the Framingham risk functions. In an analysis of National Health and Nutrition Examination Survey (NHANES) data, men older than age 45 years who had two elevated risk factors or one elevated risk factor and four or more borderline risk factors, and women older than age 55 years who had at least three elevated risk factors, were most likely to be classified as intermediate-risk.[12]

Epidemiologists and biologists have tried to identify new risk factors, particularly modifiable risk factors that could explain some of the variability in CHD risk that is not explained by traditional risk factors. Over 100 potential risk factors have been proposed.[13] Many of these candidates have been evaluated in epidemiologic studies, and some are now widely used in primary care practice. Two broad classes of factors—inflammatory markers and markers of atherosclerotic burden—have received the most attention.

An American Heart Association (AHA) conference, Prevention Conference V, held in 1998, assessed inflammatory markers as well as markers of atherosclerotic burden. The conferees examined several potential clinical uses for inflammatory markers, two of which are relevant to primary prevention: (1) prediction of a first cardiovascular event in all individuals who do not have known CVD (that is, primary prevention), and (2) "to augment risk assessment in the identification of persons who should be considered for lipid-lowering, antiplatelet, or other cardioprotective drug therapies." With respect to the latter, the conferees posed the question of whether individuals who have an elevated baseline risk based on their Framingham risk score could benefit by further stratification using a novel risk factor. The potential effect of further stratification might include reclassifying some individuals as lower risk and others as high-risk,

permitting more aggressive treatment and encouragement of lifestyle changes toward the latter group.

Inflammatory Markers

Several lines of evidence have implicated chronic inflammation in the etiology of CHD.[14] With respect to inflammatory markers, the Prevention Conference V concluded that

> "…many of these markers (including inflammatory markers) are not yet considered applicable for routine risk assessment because of: (1) lack of measurement standardization, (2) lack of consistency in epidemiological findings from prospective studies with endpoints, and (3) lack of evidence that the novel marker adds to risk prediction over and above that already achievable through the use of established risk factors."[15]

In 2002, the Centers for Disease Control and Prevention (CDC) and the AHA co-sponsored a conference and workshop on several laboratory-based inflammatory markers: adhesion molecules, cytokines, fibrinogen, high-sensitivity C-reactive protein (hsCRP), serum, amyloid A, and the white blood cell (WBC) count.[16] The workshop participants concluded that, of the tests studied, the hsCRP test had the most desirable characteristics. Assays for some markers, such as cytokines, were not sufficiently standardized for clinical use, and other markers that had reliable, commercially available assays, such as the WBC count, were not as predictive or had not been demonstrated to be an independent predictor of CVD events. The conference recommended that, when hsCRP is used, it should be "measured twice, either fasting or nonfasting, with the average expressed in mg/L, in metabolically stable patients," and that results should be categorized as low, average, or high corresponding to approximate tertiles of values (<1.0, 1.0 to 3.0, and >3.0 mg/L, respectively.)

The workshop participants recommended against routine use of hsCRP in conjunction with risk assessment for all primary prevention individuals, but supported measurement of hsCRP in individuals who had a 10-year CHD risk in the range of 10% to 20%. They noted, however, that the benefits of this strategy "remain uncertain," and recommended that randomized trials should be performed "to test whether risk categorization by hsCRP leads to: (1) therapeutic risk reductions in additional patients who are not currently identified, or (2) a reduction in the number of patients in need of treatment by identifying low-risk groups that heretofore had been recommended for further diagnostic testing or aggressive interventions."

Markers of Atherosclerotic Burden

With respect to markers of atherosclerotic burden, Prevention Conference V endorsed the selective, physician-directed use of electron beam computed tomography (EBCT) scan for risk prediction in some intermediate-risk patients for whom the results might be useful in

reclassifying the patient as high-risk[17] as did an American College of Cardiology (ACC)/AHA conference.[18]

ATP-III, which was also published in 2002, evaluated a broader range of emerging risk factors.[19] ATP-III used the following criteria to assess the potential benefit of each factor:

- Significant predictive power that is independent of the other major risk factors
- A relatively high prevalence in the target population (justifying routine measurement in risk assessment)
- Laboratory or clinical measurement must be widely available, well standardized, inexpensive, have
accepted population-reference values, and be relatively stable biologically
- Preferably, but not necessarily, modification of the risk factor in clinical trials will have shown reduction in risk.

ATP-III examined several lipid-related potential risk factors (triglycerides, lipoprotein remnants, lipoprotein (a), small LDL particles, HDL subspecies, apolipoproteins, total cholesterol/HDL ratio) and the following nonlipid factors: homocysteine; fibrinogen and other prothrombotic factors; hsCRP; impaired fasting glucose; ankle-brachial index; exercise electrocardiogram testing; cardiac sonography to measure carotid intima-media thickening (IMT); and EBCT, spiral computed tomography, and other imaging tests for coronary calcification. In general, ATP-III endorsed the findings of Prevention Conference V and the ACC/AHA conferences. ATP III concluded that homocysteine, hsCRP, carotid IMT, and EBCT can be useful in certain circumstances, but did not recommend incorporating any emerging risk factors into risk assessment in *all* individuals in primary prevention risk assessment. ATP III also found that measurement of fasting glucose, waist circumference, and triglycerides are useful in the context of diagnosing the metabolic syndrome.

The 2004 update to ATP III lists the presence of a hsCRP>3 mg/L or coronary calcification>75th percentile for a person's age and sex among several factors that favor use of an LDL-lowering agent in persons who have a 10-year risk of 10% to 20% and LDL-C level of 100 to 129 mg/dL.[3]

Scope and Key Questions

We conducted a systematic review of epidemiologic studies of certain emerging risk factors (*Table 2*) to help the US Preventive Services Task Force (USPSTF) determine which, if any, factors should be incorporated into guidelines for coronary and cardiovascular risk assessment in primary care. The USPSTF selected all but one of the risk factors examined in this report. After a preliminary literature review, the authors of the report added one factor, periodontal disease.

TABLE 2. EMERGING RISK FACTORS

Risk factors addressed in this report:

Ankle-brachial index
C-reactive protein
Carotid intima media thickness
Electron beam computed tomography
Fasting glucose
Homocysteine
Lipoprotein(a)
Periodontal disease
White blood cell count

Some potential risk factors not addressed in this report:

Angiotensin-converting enzyme genotype
ApoE genotype
Apolipoproteins A1 and B
Cystatin C
D-dimer
Electrocardiogram findings
Exercise treadmill testing
Factors V, VII, and VIII
Fibrinogen
Fibrinopeptide A
Heart rate
High-density lipoprotein subtypes
Infectious agents: Cytomegalovirus, Chlamydia pneumonia, Helicobacter pylori, Herpes viruses
Insulin resistance
Interleukins (e.g., IL-6)
Lipoprotein-associated phospholipase A(2)
Metabolic syndrome
Microalbuminuria
Oxidized LDL
PAI-1 genotype
Physical inactivity
Plasminogen activator inhibitor 1 (PAI-1)
Platelet activity
Platelet aggregation
Platelet size and volume
Prothrombin fragment 1 + 2
Pulse pressure
Remnant lipoproteins
Serum amyloid A
Soluble CD40 ligand
Tissue-plasminogen activator
Vascular and cellular adhesion molecules
von Willebrand factor antigen
Waist-to-hip ratio

The analytic framework for this report is depicted in *Figure 1*. The population of interest for this review consists of asymptomatic adults who are identified as being "intermediate risk" after calculating the Framingham risk score. This target population excludes individuals with

diabetes, coronary disease, peripheral vascular disease, and other individuals who have a predicted 10-year risk of "hard" coronary artery disease (CAD) events greater than 20%. *Figure 1* shows that, after testing with one of the "emerging" risk factors, some intermediate-risk individuals are reclassified as "high-risk" (>20% risk of hard CAD events over 10 years) or "low-risk" (<10% risk over 10 years.) As a result of reclassification to high-risk, these individuals would be managed with more aggressive risk factor modification which could result in an improved risk profile and in greater reductions in the incidence of CAD than they would be expected to have if they were managed as intermediate-risk patients.

The USPSTF selected the following Key Questions for this report (*Figure 1*):

1. Compared with Framingham risk factors alone, does risk stratification of asymptomatic adults using novel risk markers (*Table 2*) lead to reduced incidence of cardiovascular events (myocardial infarction, angina, sudden death, cerebrovascular accident), coronary heart disease events, or overall mortality?
2. What novel risk markers accurately predict cardiovascular events independent of Framingham risk factors? What is the added predictive value of novel risk markers?
   a) What is the prevalence of these risk markers among intermediate-risk and low-risk individuals?
   b) At what frequency does application of these novel risk markers significantly change the 10-year risk of cardiovascular events based on traditional risk factors alone (e.g., from intermediate risk [10-20%] to high risk [>20%] or to low risk [<10%])?
3. What are the harms of risk assessment?
4. a) In groups identified as high-risk (>20% 10-year risk) by novel risk markers, does aggressive risk factor modification (treatment to lower blood pressure and lipid targets or more intense counseling) lead to improved intermediate outcomes (e.g., reduction in lipid levels; reduction in blood pressure; increased physical activity; healthy dietary changes, etc.)?
   b) Does improvement in intermediate outcomes lead to reduced incidence of cardiovascular events (myocardial infarction, angina, sudden death, cerebrovascular accident), cardiovascular disease-specific mortality, overall mortality?
5. What are the harms of aggressive risk factor modification?
6. What are the costs associated with risk factor assessment and aggressive risk factor modification?

The key questions reflect the USPSTF's goal of comparing the strength of evidence and the magnitude of effect of the emerging risk factors. No previous USPSTF decision has called for a similar comparison of a large number of alternatives, and none have focused primarily on refining an existing risk assessment tool. For this reason, the methods section describes in detail our approach to comparing the quality of evidence and magnitude of potential effect for the candidate risk factors.

II. METHODS

Evaluation Framework

At the outset, USPSTF members met with the investigators to determine how the report findings would be used in making recommendations for risk assessment in primary care. These discussions centered on what information about an emerging risk factor would be considered to be sufficient to recommend its use in intermediate-risk individuals in primary care practice.

Based on input from USPSTF members, and review of previously developed frameworks for evaluating the evidence and impact of a new prognostic test[16] or diagnostic test[20], we developed an approach for evaluating and comparing each candidate risk factor. In this report, we

- Describe the strength and consistency of evidence that each risk factor provides independent prognostic information when used in addition to the Framingham scoring in intermediate-risk individuals.
- Assess the impact of using the risk factor on reclassification of individuals from intermediate to high risk and to low-risk.
- Estimate the potential impact of adding the risk factor on morbidity and mortality due to coronary disease and stroke.

The overall evaluation scheme is shown in *Figure 2* and discussed in detail below.
The potential impact of a novel risk factor depends on: 1) its predictive ability, 2) its prevalence in the target population, 3) the number of intermediate-risk individuals who are reclassified as high-risk when the risk factor is applied, 4) the net benefit (benefits minus harms) that would accrue to these high-risk individuals if they were managed according to guidelines for high-risk patients. We addressed these features of each test sequentially, for example, if predictive ability had not been well established we did not proceed to evaluate prevalence and clinical impact.

Literature Search and Strategy

For each risk factor listed in *Table 2*, we conducted multiple searches of MEDLINE (1966 to March 2006). We focused searches on identifying epidemiologic studies relevant to the independent predictive ability of the risk factor when used in intermediate-risk individuals (*Appendix I*). We obtained additional articles from recent systematic reviews, reference lists of pertinent studies, reviews, editorials, websites, and by consulting experts.

Eligibility Criteria

We reviewed abstracts and full-text articles identified by the searches for relevance (*Appendix II*). Eligible articles had English-language abstracts and provided primary data relevant to the

key questions. We excluded studies conducted exclusively in adults with previously diagnosed coronary disease or coronary disease equivalent (e.g., diabetes). Studies were included if they reported, at minimum, outcomes of coronary deaths and non-fatal MIs. Only prospective cohort studies (including those based on a cohort included in a randomized trial) and nested case-control studies were considered for assessing the predictive value of the novel risk factors.

We listed the cohorts represented among included studies and grouped publications by cohort. When more than one paper was published using data from a single cohort, we analyzed the findings for the cohort study rather than the nested case control study, or from the analysis with the highest validity and applicability to the study questions based on our quality ratings. For each cohort, we reviewed included and excluded publications to determine whether a particular risk factor had been measured. Then we determined whether published studies reported results in a manner that would allow us to determine the odds ratio for the novel risk factor among patients who did not have known CVD or diabetes and were intermediate-risk. When it was clear that a risk factor had been measured, but the independent contribution of the risk factor for predicting CHD events in the target population could not be determined, we contacted authors for more information that would enable us to include the cohort in the review.

Approach to Assessing the Strength of Evidence

The overall strength of evidence is a function of the validity and applicability of individual studies as well as several dimensions of a *body* of studies.

The validity of individual studies

The validity assessment evaluates the extent to which one can be confident that a study's estimate of effect is correct. Investigators rated the validity of evidence of each study using criteria specific to cohort and nested case-control studies (*Appendix III*).[21] These criteria were applied previously to large bodies of observational studies of hormone replacement therapy[22] and of vitamins and the long-term risk of cardiovascular events.[23]

Applicability of individual studies

Investigators assessed the applicability of each study's sample, risk assessment, and outcome measures to the targets for this review. In rating the applicability of each study, investigators assessed the following study characteristics:

1) Study Sample. Ideally, the study sample was drawn from the general population or a demographic subset of asymptomatic adults who would be classified as "intermediate risk" in the ATP-III risk stratification scheme. Samples that included patients with known CHD or diabetes were acceptable if multivariate analyses adjusted for these characteristics or the results for the target population could be extracted from the study. A poor rating for Framingham Risk Factor assessment (next item) would reduce the likelihood that the study sample was representative of intermediate-risk individuals. Inclusion of additional risk factors (e.g., family history, triglyceride level) did not reduce the applicability rating.

2) Framingham Risk Factor measurement. Many studies used risk stratification schemes that were not identical to the components of the Framingham score; for example, some studies used the patient's report of whether they had a history of hypercholesterolemia as a proxy for an actual total cholesterol level, while others had components (e.g., triglyceride level, family history) that were not included in the Framingham risk scoring model. Investigators compared the actual measures used for each component of the risk assessment method and coefficients from the study's prediction model to the gold standard of the measurements and model coefficients used in developing the Framingham risk score.[4]
3) Emerging Risk Factor measurement and categories. Clinical, radiologic and laboratory test methods varied among studies. Some of this variation reflected improvement over time in assay or radiologic methods (for example, higher-sensitivity assays or higher-resolution radiographs). We recorded the methods used to measure the emerging risk factor and to define abnormal results. For many of these tests, a gold standard definition of abnormality has not been defined, and studies used a variety of quantiles (tertiles, quintiles, deciles) to make statistical comparisons.
4) Outcomes (Events). Studies used a variety of measures of the incidence of coronary or cardiovascular events. For the purpose of this review, the ideal measure included fatal and nonfatal MI and death due to coronary disease ("hard CHD" events.) When possible, we analyzed results for these events, but we also analyzed studies in which these events could not be separated out from broader measures that included other coronary events, such as unstable angina and percutaneous coronary intervention; and measures that included hard CHD events plus stroke ("major cardiovascular events", CVD).

Strength of evidence for a body of studies

Judgments about the validity or strength of evidence for a body of studies require consideration of study design, limitations of quality within a given design, consistency and applicability of the evidence. By a "body" of studies, we mean all evidence that addressed a specific question. For example, a body of evidence might include 10 cohort studies and 5 nested case-control studies addressing the predictive ability of CRP in intermediate-risk subjects. In rating the strength of a body of studies, investigators considered:

- The aggregate validity and applicability of the body of studies.
- The number and range of studies. A higher number of independent cohorts and a wider range of study circumstances compared with other risk factors would improve the rating.
- The consistency of results, that is, the similarity of effect across studies and, if applicable, across study designs. Evidence of consistency related to a dose response relationship, or the use of various cut-offs for an elevated test result, would also strengthen confidence in the validity of the body of literature.
- The precision of the results.
- The risk of reporting bias.
- The likelihood that there is a flaw common to most or all of the studies in a body of evidence. This criterion protects against the circumstance in which consistency of results reflects a consistent bias or flaw in study design. For example, failure of most or all

studies to address a known potential confounder, or failure of some studies to adjust for a confounder that was important in other studies, would weaken confidence in the validity of the body of evidence.

Approach to Assessing the Magnitude of Benefit

As noted above, the predictive ability of a risk factor, its prevalence, and the number of people who are reclassified as high risk affect the outcome of interest, that is, the reduction in the incidence of "hard CHD" events that would occur when the risk factor is applied.

Predictive ability

We reviewed population-based, epidemiologic studies that assess the ability of the risk factor to predict major CHD events independently of Framingham risk factors in intermediate-risk subjects (Key Question 2).

For each risk factor that had consistent, fair-to-good-quality evidence, we conducted a meta-analysis of epidemiologic studies to determine the combined estimate of association between various risk factors and CHD events after controlling for Framingham risk factors. Estimates of risk ratio (relative risk [RR], hazard ratio [HR] or odds ratio [OR]) were obtained from a model with adjustment of Framingham risk factors from each study. Since different studies reported risk ratios on the basis of different cutoff levels including median, tertiles, quartiles or quintiles etc., or as increase in risk for a given increase in the risk factor, we standardized the risk ratio of each risk factor in the following ways to provide clinically relevant and easily interpretable results. For CRP, we adopted cutoff points proposed by CDC/AHA[16] (Low < 1.0mg/L; Average 1.0 - 3.0 mg/L; High > 3.0 mg/L) with group of < 1.0 mg/L as reference. When studies categorized CRP concentrations using other cutoff points, we calculated risk ratios using 1.0 and 3.0 mg/L as cutoff points by assuming that CRP is log-normally distributed[24] and there is a log-linear association of CHD risk over mid-range of log-CRP concentrations.[24] Distribution parameters of CRP were estimated from published information from each study. For coronary artery calcium (CAC) score, we standardized the results into 4 CAC score categories (0 as reference, 1-100, 101-401, and > 400). These or similar categories have been used in several studies,[25-27] and represent a simple categorization of the range of CAC scores encountered in clinical practice. The risk ratios based on these four categories were calculated from the published estimates assuming a log-linear relationship between CHD risk and log-CAC score[28] or age- and sex-adjusted percentiles (CS% score).[29] The median CAC score and the median CS% score in each of these categories was estimated using published cross-sectional data[29] and we matched the age and gender distribution for each study. For homocysteine, many studies reported risk ratios per unit increase in homocysteine concentration, and we standardized the estimates to be risk ratios of a 5μmol increase, as well as risk ratio of top quintile vs. bottom = quintile assuming a log-normal distribution of homocysteine (since most studies reported a right-skewed distribution of homocysteine), and log-linear relationship between CHD risk and homocysteine concentrations.

Heterogeneity was assessed by standard χ^2 tests. The risk ratios were combined by using a random effects model to account for variation among studies. When there is no variation among studies, the random effects model yields the same results as a fixed effects model. Study level variables such as degree of adjustment (the number of Framingham variables adjusted, the number of non-Framingham variables adjusted), mean duration of the study, study design (cohort vs. nested case-control), outcome measures (hard CHD events vs. hard plus other CHD or CVD events), quality rating, and for CAC score, minimum area of calcification, slice thickness and risk factors measured or by questionnaire, etc., were investigated either by using a random effects meta-regression or by sensitivity analysis. Publication bias was checked using funnel plots and Egger's linear regression method[30] and adjusted using the "trim and fill" method[31] when necessary.

Prevalence

Even if a risk factor has been shown to provide independent information, its usefulness in screening cannot be reliably assessed unless there are reliable estimates of its prevalence in the target population. For risk factors that had statistically significant and independent predictive ability, we assessed the prevalence of the risk factor in the intermediate-risk population, with particular attention to the availability and reliability of estimates of prevalence among demographic subgroups. When available, we also used nationally representative data to estimate prevalence. We considered lack of data about prevalence in the target population (intermediate-risk adults) to be a serious limitation. For tests that lacked such information, we did not proceed to subsequent steps in examining the magnitude of benefit.

Other considerations

If meta-analysis of the population-based studies indicated that use of the test is able to improve overall prediction beyond that of traditional risk factors, we examined several other characteristics that affect its actual impact in practice, including:[16]

(1) the ability to standardize the assay and to control the variability of the measurement
(2) the presence of population norms to guide interpretation of results
(3) the costs, burden, and harms of using the test

Among risk factors that had similar predictive ability and prevalence, differences in cost, convenience, technical characteristics such as intra-assay or inter-observer reliability, and harms could affect the acceptability and cost-effectiveness of testing intermediate-risk individuals. We examined evidence about these characteristics to choose candidate risk factors for further analysis.

Number of reclassified individuals

For risk factors that had at least fair-quality data about prevalence in intermediate-risk individuals from the general population, we extracted information about the number of intermediate-risk individuals reclassified as high-risk or low-risk by using the novel risk factor when it was available in published studies.

Net benefit

At present, no randomized controlled trials have assessed whether risk stratification of intermediate risk patients using a novel risk factor, and more aggressive risk factor modification of patients identified as high-risk on the basis of a novel risk factor, improves outcomes (Key Questions 1 and 4b.) There are also no data from adequately powered controlled trials that would permit a direct measurement of the benefits or harms of treatment decisions arising from use of a novel risk factor in intermediate-risk patients (Key Questions 4a and 5).

A body of evidence, however, indirectly supports the view that the benefits of aggressive risk factor management with lipid-lowering therapy depends on overall risk, even when low density lipoprotein levels are not elevated.[19] If the benefits of aggressive risk factor management are more related to overall risk than to the specific contributing risk factors, correctly classifying more high-risk patients would be expected to be beneficial. Therefore, after consultation with USPSTF members, we chose to estimate the net benefit to reclassified individuals by assuming that they have a net benefit similar to those of high-risk and very-high-risk subjects in major lipid-lowering trials.

This approach provides an estimate of the *upper bound* of potential benefit rather than the *expected* or *likely* benefit. Moreover, the validity of this assumption is likely to differ for different risk factors or categories of risk factors. For example, the validity of this assumption might be different for inflammatory markers, such as hsCRP or periodontal disease, than for markers of atherosclerosis such as coronary calcification or ankle-brachial index; or lipid-related markers such as triglyceride or Lp(a) levels.

The literature review and meta-analyses described above resulted in information about the strength of evidence, prevalence, and adjusted odds for predicting the 10-year risk of CHD events for each risk factor. We tabulated this information, adding in information about reliability and cost, to select risk factors for further analysis of the number of individuals who would be reclassified by using the risk factor to further stratify intermediate-risk subjects. To be selected for additional analysis, the risk factor had to have at least fair strength of evidence; there also had to be reliable information about the prevalence of the risk factor among intermediate-risk individuals in the adult population (or in a defined demographic subgroup of the general population); and our estimate of the adjusted odds ratio for the 10-year risk of hard CHD events had to be statistically significant and relatively high compared with others.

Modeling Potential Benefits of Risk Factor Testing

For one risk factor, high sensitivity C-reactive protein (hsCRP), the availability of data from the NHANES 1999-2002 survey allowed us to construct a model to estimate the potential benefit of testing and treatment in individuals with no prior history of CHD who were representative of the US population. The choice of hsCRP was also desirable because the estimate of the adjusted odds ratio for the 10-year risk of hard CHD events from our meta-analysis was statistically significant and relatively high compared with other risk factors. As such, the potential benefit of testing and treatment based on hsCRP would likely represent an upper bound of the potential benefit from using other risk factors to improve CHD risk prediction.

Direct evidence showing that CRP testing reduces future risk of CHD events is not presently available. To estimate the potential benefit of CRP testing, we developed a model that predicts the impact of using CRP measurements to reclassify individuals in an intermediate risk category, defined as a 10%-20% 10-year risk of "hard" CHD events (fatal or non-fatal MIs) based on traditional Framingham risk factors 10-20% CHD 10-year risk category to a high-risk category, defined as >20% 10-year risk of hard CHD events. The clinical endpoint for the potential benefit of CRP testing in the model was the number of hard CHD events averted through more aggressive risk-reduction therapy for those individuals shifted into the high-risk category. For example, based on NCEP/ATP III recommendations, a 10-year CHD risk >20% in an asymptomatic person is considered to be a CHD-equivalent.[2] These individuals may benefit from more aggressive treatment with statin drugs to lower LDL. Based on recent trial data, we assumed the efficacy of aggressive risk-reduction therapy for high-risk individuals to be a 30% in the 10-year risk for future hard CHD.[3]

We also assumed 100% patient adherence with aggressive risk-reduction therapy. We believe this is optimistic, however. For example, a study of statin usage in a usual-care setting, based on review of an health maintenance organization's (HMO) electronic pharmacy dispensing records, found adherence with statin prescriptions based on refills to be 80% at 6 months, and 74%, 65%, and 61% at 1, 2, and 3 years, respectively.[32] We also assumed that treatment would have no adverse effects. Altogether, we chose these assumptions to provide a best-case scenario for the potential benefits of CRP testing.

Our model did not consider individuals who were already in the high-risk category, assuming these individuals would already be treated according to ATP III recommendations. Based on recommendations of the NCEP/ATP III panel, asymptomatic persons with a 10-year CHD risk >20% based on multiple risk factors are at similar risk for CHD events as those with established CHD. Such individuals can be classified as having a CHD risk equivalent that already indicates the need for more intensive risk-reduction therapy.[2] Although adjusting for CRP-associated risk in some for those with low hsCRP measurements will reclassify some of these individuals from the high-risk to the intermediate-risk category, we are not aware of data that would support less aggressive risk-reduction therapy in these individuals. We also did not model outcomes for individuals reclassified from the intermediate-risk category to the low-risk (<10% 10-year CHD risk) category. Such patients may already be treated with blood pressure lowering medication, or following life-style recommendations to modify CHD risk factors, that would be appropriate to continue in any case.

To estimate the impact of using hsCRP measurement in intermediate-risk individuals, we used data collected in the NHANES from 1999 through 2002. NHANES 1999-2002 used a multistage, stratified sampling design to ensure that the participants were a representative sample of the US population. Full details of the NHANES study design and the datasets used are available online.[33]

We extracted information from the NHANES 1999-2002 data for men and women age 40 to 79 years with no history of CHD or CHD equivalents (history of angina, stroke, congestive heart failure, diabetes). We selected men and women 40 to 79 years old as the age most relevant to primary CHD prevention efforts. Those selected also had to have complete information the traditional Framingham risk factors needed to calculate 10-year CHD risk using the NCEP/ATP-

III risk 10-year CHD risk prediction tool.[34] These included age, sex, total cholesterol, HDL, systolic blood pressure, current smoking status, and whether the participant was currently taking medication for hypertension. Complete data on hsCRP measurements were also available for those participants selected for our study.

To predict the additional 10-year risk associated with CRP elevation, we modified the ATP-III risk equation by incorporating the OR from our meta-analysis of published studies. In our meta-analysis of good quality studies that adjusted for all Framingham risk factors, the combined risk ratio for men was 1.27 (95% CI, 0.99, 1.63) for hsCRP 1.0-3.0 mg/L compared to hsCRP < 1.0 mg/L, and 1.59 (95% CI, 1.06, 2.40) for hsCRP >3.0 mg/L compared to hsCRP < 1.0 mg/L. For women, the combined risk ratio was 1.24 (95% CI, 1.01, 1.52) for hsCRP 1.0-3.0 mg/L compared to hsCRP < 1.0mg/L, and 1.81 (95% CI, 1.42, 2.31) for hsCRP >3.0 mg/L compared to hsCRP < 1.0mg/L. We used these risk ratios for hsCRP to modify the estimated 10-year risk for first incident CHD events for each individual in the NHANES dataset, resulting in a revised set of estimates of 10-year CHD risk. The 10-year risk was modified for each sex separately.

Since these risk ratios are combined estimates based on odds ratios and hazard ratios, we considered two different approaches to modify the 10-year risk. We denote the estimated 10-year risk for first hard CHD events from step 1 as P_{FH}, and the modified 10-year risk as $P_{FH+hsCRP}$. First, we assumed that the relationship between P_{FH} and $P_{FH+hsCRP}$ could be expressed by a logit equation:

$$\log\left(\frac{p_{FH+hsCRP}}{1-p_{FH+hsCRP}}\right) = \log\left(\frac{p_{FH}}{1-p_{FH}}\right) + \beta_1 * hsCRP_1 + \beta_2 * hsCRP_2 \qquad (1)$$

where $hsCRP_1$ and $hsCRP_2$ are two dummy variables with value 1 and 0. When $hsCRP_1 = 1$, it means the individual was categorized into group hsCRP 1.0-3.0 mg/L, and $hsCRP_1 = 0$ means otherwise. Similarly $hsCRP_2 = 1$ means the individual has a hsCRP level >3.0 mg/L and $hsCRP_2 = 0$ means otherwise. Coefficients β_1 and β_2 were calculated based on the combined estimates of risk ratios from meta-analysis. For men, $\beta_1 = \log(1.27) = 0.24$, $\beta_2 = \log(1.59) = 0.46$; for women, $\beta_1 = \log(1.24) = 0.22$, $\beta_2 = \log(1.81) = 0.59$. For those individuals with CRP of 1.0-3.0 mg/L or >3.0 mg/L, the modified 10-year risk was calculated based on (1).

To calculate the 10-year risk of those individuals with CRP < 1.0 mg/L, we made an additional assumption that total number of sex-specific incident hard CHD events predicted for 10 years based on Framingham risk factors would remain constant after adjusting for risk associated with hsCRP; in other words, applying hsCRP did not alter the overall risk of CHD events, but only redistributed the existing risk. Therefore, for those individuals with CRP < 1.0 mg/L, the modified 10-year risk was calculated as follows:

$$\log\left(\frac{p_{FH+hsCRP}}{1-p_{FH+hsCRP}}\right) = \log\left(\frac{p_{FH}}{1-p_{FH}}\right) + \beta_0 \qquad (2)$$

where β_0 is estimated for each sex based on the assumption that total number of predicted 10-year events remains constant after adjusting for hsCRP.An alternative approach is to treat the combined estimates of risk ratios as hazard ratios and obtain the modified 10-year risk based on a

Cox regression model. NCEP/ATP III equation is a formula to calculate cumulative risk based on Cox regression. Adding hsCRP terms to NCEP/ATP III equation, we have

$$p_{FH+hsCRP} = 1 - s_0(t)^{\exp(\boldsymbol{x}\boldsymbol{\beta}_{FH} + \beta_1 * hsCRP_1 + \beta_2 * hsCRP_2)} \qquad (3)$$

where vector $\boldsymbol{\beta}_{\mathrm{FH}}$ represents coefficients for Framingham risk factors in NCEP/ATP III risk equation, $\boldsymbol{x}$ is a vector to represent the collection of Framingham risk factors, and $s_0(t)$ is the baseline 10-year risk. For $hsCRP_1$ and $hsCRP_2$, they have the same meaning as in (1) and coefficients β_1 and β_2 have same values as in (1). To calculate the modified 10-year risk of those individuals with CRP < 1.0 mg/L based on Cox regression, we used

$$p_{FH+hsCRP} = 1 - s_0(t)^{\exp(\boldsymbol{x}\boldsymbol{\beta}_{FH} + \beta_0)}. \qquad (4)$$

Again β_0 is estimated for each sex based on the assumption that total number of predicted 10-year events remains constant after adjusting for hsCRP.

The approach of using logit equation ((1) and (2)) could be considered as directly adjusting the 10-year ATP III risk using hsCRP, and equations (3) and (4) could be considered as recalculating the 10-year risk by adding information from hsCRP. For both approaches, we assumed that adding hsCRP does not affect the coefficients of Framingham risk factors in NCEP/ATP III equation thus our estimates on the modified 10-year risk are likely to be an upper bound in terms of magnitude of the effects of hsCRP. The two approaches yield similar results and for simplicity, we only presented results from first approach using logit equation.

We then used the revised estimates of individuals' 10-year risk for incident hard CHD events (after adjustment for hsCRP) to examine the potential impact of using hsCRP on CHD risk prediction. The 10-year risk for CHD events and number of expected CHD events, before adjustment for CRP, were calculated using the NCEP/ATP III risk prediction equation based on Framingham risk factors. We calculated the 10-year risk for CHD events and the number of expected CHD events after adjustment for CRP using the modified risk prediction equation incorporating CRP-associated risk estimates from the meta-analysis.

The clinical endpoint used in the model was the number of CHD events averted over 10 years. To calculate the impact of testing intermediate-risk individuals on incident coronary events, we assumed that individuals reclassified from the intermediate-risk to high-risk category after adjusting for CRP-associated risk would receive aggressive risk-reduction, with an additional *net* efficacy, taking compliance into account, of 30% in reducing the risk of future CHD events compared with the therapy they would have received if classified as intermediate-risk patients.

Statistical analysis

Analysis of logit equation approach was performed by using the Microsoft Excel Solver utility (Microsoft, Inc, Redmond, WA). , and the alternative approach using Cox regression was conducted by using SAS 9.1 (SAS institute Inc., Cary, NC, USA). When calculating population means for Framingham risk factors, CRP, predicted 10-year risk and population proportions for

each risk group (low, intermediate or high), we used the combined 1999 to 2002 4-year final examination weights from NHANES data. Calculations of standard errors and 95% confidence intervals (CI) incorporated stratification and sampling unit data from the NHANES datasets to account for the complex sampling design used in the study. Population estimates were age-adjusted by the direct method using population age-distribution estimates for the year 2000.[35] All data analyses were performed using the JK-1 jackknife replication procedure in WESVAR® 4.2 statistical software (Westvar, Rockville, MD). To check the reliability of our analyses, we also analyzed the population distributions for Framingham risk factors and demographic variables (*Table 1* and *Table 2*), and population distributions of CHD risk before and after adjusting for CRP (*Table 3*) using the Taylor series linearization method in SUDAAN Version 8 software (RTI, Research Triangle Park, NC) and found nearly identical results.

III. RESULTS

Literature Search Results

Searches yielded 4,088 citations (*Appendix IV*), from which we identified relevant analyses of emerging risk factors from 64 cohorts (*Table 3*). CRP, homocysteine, and lipoprotein(a) were evaluated in many of the cohorts. Conversely, EBCT, IMT, and periodontal disease were studied in the fewest settings and in few, if any, of the best-known and largest cohorts used in cardiovascular epidemiology.

The analyses summarized in *Table 3* vary substantially with respect to validity and applicability. The strongest evaluations were those in cohorts that had been followed for 10 years or more and that had complete evaluations for traditional risk factors prior to initiation of treatment for hyperlipidemia or hypertension. Most evaluations were weaker in that subjects were followed for less time or had incomplete evaluations that did not measure all relevant Framingham risk factors at the time of inception.

TABLE 3. COHORTS IN WHICH CHD NOVEL RISK FACTORS WERE STUDIED

Cohort*†	# RFs	CIMT	CRP	EBCT	FG	Hcy	Lp(a)	PD	WBC
Adult Health Study, a subset of 100,000 residents in Hiroshima or Nagasaki as of 1950	1								÷
Atherosclerosis Risk in Communities (ARIC)	6	+	+		Ø	÷	+		÷
British Regional Heart Study (BRHS)	3		+			÷			+
British United Provident Association (BUPA)	1					+			
British Women's Heart and Health Study	1		÷						
Bruneck Study	1						÷		
Caerphilly Study and Speedwell Study	4		Ø÷		Ø	÷			+
California, USA (Wong, 2000[92])	1			+					
Camerano study group	1				Ø				
Cardiovascular Health Study	1	+							
Chicago, IL, USA (Kondos, 2003[94])	1			+					
Dallas, TX, USA (LaMonte, 2005[97])	1			+					
Dental longitudinal study, VA	1							+	
East and West Finland Study	1				Ø				
Edinburgh Artery Study	1						Ø		
FINRISK '92 Hemostasis Study	1						Ø		
Framingham/Framingham Offspring Study	5		÷		+	+	+		÷
France (Blacher, 2002[116])	1					+			
Goteburg, Sweden (Ohlson, 1986[57])	1				Ø				
Gothenburg, Sweden (Zylberstein, 2004[141]; Rosengren, 1990[162])	2					+	+		
Gottingen Risk Incidence and Prevalence Study (GRIPS)	1						+		
Health Professionals Follow-up Study (HPFS)	3		+				Ø	+	

Cohort*†	# RFs	CIMT	CRP	EBCT	FG	Hcy	Lp(a)	PD	WBC
Helsinki Aging Study	1							+	
Helsinki Heart Study	2						÷		÷
Helsinki Policemen Study	1				Ø				
Hoorn	1					+			
Hordaland Homocysteine Study	1					+			
Italy (Belcaro, 1996[83])	1	+							
Kaiser Permanente	1		÷						
Kuopio Ischemic Heart Disease Risk Factor Study	2	+				Ø			
Lipid Research Clinics Coronary Primary Prevention Trial	1						+		
Malmo, Sweden (Lind, 2003[126])	1					÷			
Mini Finland Health Survey	1							Ø	
Mobile Clinic Health Exam Survey, Finland	1					Ø			
Monitoring of trends and determinants in cardiovascular disease study (MONICA)	4		+		Ø	÷	+		
Monitoring Project on CVD Risk Factors	1					Ø			
Multiple risk factor intervention trial (MRFIT)	4		÷			Ø	Ø		÷
Nashville, TN, USA (Raggi, 2001[29])	1			+					
NHANES I	2							+	Ø
North Karelia Project	1					Ø			
Northern Manhattan Study	1					÷			
Nurses' Health Study (NHS)	3		÷			+		+‡	
Nutrition Canada Study	1							÷	
Olmsted County, MN, USA (Nguyen, 1997[173])	1						+		
Paris Prospective Study I and II	1								÷
Physicians Health Study (PHS)	4		+			+	Ø	Ø	
Prospective Army Coronary Calcium Project	1			+					
Prospective Cardiovascular Munster Study (PROCAM)	1						+		
Prospective Epidemiological Study of Myocardial Infarction (PRIME)	2		+				÷		
Quebec Cardiovascular Study	2		Ø				÷		
Reykjavik Study	1		+						
Rotterdam Study	4	+	÷	+		÷			
Second Northwick Park Heart Study	1						+		
South Bay Heart Watch	2		÷	+					
St. Francis Heart Study – population 1	1			+					
St. Francis Heart Study – population 2	1			+					
Stanford Five-City Project	1						÷		
Tromso Health Study	1					+			
Vantaa Study	1				Ø				
Vasterbotten Intervention Program (VIP)	2					÷	+		
Women's Health Initiative Observational Study (WHI-OS)	1		+						

Cohort*†	# RFs	CIMT	CRP	EBCT	FG	Hcy	Lp(a)	PD	WBC
Women's Health Study (WHS)	3		+			÷	+		
Worksite Hypertension Program	1				÷				
Zutphen Study (Dutch portion of 7 Countries Study)	2					÷			÷

#RFs=number of emerging risk factors per cohort among publications that met inclusion criteria.
Note: No studies of ankle-brachial index (ABI) met the inclusion criteria.
*Some cohorts contained sub-cohorts by gender or region.
†Please see evidence tables for references, as they vary per risk factor
‡ Combined with Health Professional Follow-up Study cohort.

"+" indicates that the risk factor was significantly predictive of CHD.
"÷" indicates a positive association that was not statistically significant.
"Ø" indicates a null finding.
Abbreviations: CIMT=carotid intima media thickness, CRP=C-reactive protein, EBCT=electron beam computed tomography, Hcy=homocysteine, FG=fasting glucose, Lp(a)=lipoprotein(a), PD=periodontal disease, WBC=white blood cell count.

Key Question 1. Impact of Using Novel Risk Markers

We found no direct evidence from randomized trials that stratification of asymptomatic adults using novel risk markers leads to reduced incidence of CHD events compared with the use of Framingham risk factors alone.

Key Question 2. Prediction of CHD Events

What novel risk markers accurately predict cardiovascular events independent of Framingham risk factors? What is the added predictive value of novel risk markers? When data were available, this section also addresses KQ 2b, "At what frequency does application of these novel risk markers significantly change the 10-year risk of cardiovascular events based on traditional risk factors alone?"

Ankle-brachial index

The ankle-brachial index (ABI) is an indicator of peripheral arterial disease (PAD) – atherosclerotic disease involving large arteries of the lower extremity. The ABI is determined by measuring the systolic blood pressure at the ankle, based on palpation or ultrasound measurement of the dorsalis pedis pulse, and dividing this by the systolic blood pressure measured in the arm. An ABI < 0.9 is the cutoff point commonly used to indicate possible significant compromise of lower extremity arterial blood flow. In the Framingham cohort, the principal risk factors for CAD events, i.e., hyperlipidemia, hypertension, and smoking, were found to be equally good as predictors of incident PAD.[36]

We found no evidence that ABI independently predicts the risk of CHD events (fatal and nonfatal MI) in individuals who have no history of CHD and do not have symptomatic PAD. We reviewed 514 abstracts and evaluated 18 potentially relevant papers in detail. All papers

were excluded with the most common reason being inclusion of subjects in the study who had CAD, based on electrocardiogram (ECG) findings, self-reported angina, coronary angiography or a history of stroke. Other reasons for exclusion were: 1) CAD events were not reported as an endpoint, 2) subjects included persons with symptomatic PAD, 3) statistical analyses did not include adjustment for Framingham risk factors, 4) the study was a cross-sectional analysis of prevalent, rather than incident disease, based on baseline study data, and 5) ABI was used as a covariate in an analysis of another candidate CVD risk factor to adjust for the presence of subclinical disease.

White blood cell count

Elevated WBC count is an indicator of cellular response to inflammation. An advantage of the white blood cell count as a potential screening tool for CHD is the availability of a standardized, reproducible assay. A disadvantage is that an elevated WBC count may not be a specific indicator for CHD. Sources other than an atherosclerotic coronary artery, such as atherosclerosis in other arteries, as well as systemic inflammation and local infections (e.g., gingivitis, prostatitis, bronchitis, urinary tract infections, or gastric inflammation) may result in elevated WBC levels.[16] A high WBC count has been strongly associated with smoking, an established risk factor for CHD, as well as other CHD risk factors including hypertension and low HDL cholesterol.[37, 38]

A meta-analysis published in 1998 compared the results of 19 prospective cohort studies of WBC count and CHD.[24] Fourteen studies were population-based, and 5 studies were conducted in patients with preexisting CHD. Most studies adjusted for smoking, blood pressure, and obesity, and several also adjusted for fibrinogen. To limit the potential of publication bias and inadequate adjustment for potential confounders among small studies, the meta-analysis combined data from 7 large studies that each involved more than 400 cases and adjusted at a minimum for age, gender, and smoking. The combined RR comparing the top third of WBC count (mean 8.4 x 1000/mm^3) with the bottom third (5.6 x 1000/mm3) was 1.4 (95% CI 1.3-1.5), and there was no significant heterogeneity between studies. The result was similar to the overall risk ratio in all 19 studies (1.5, 95% CI 1.4-1.6). These analyses cannot be compared directly with the findings of the current review, however, because they included subjects with preexisting vascular disease, as well as studies that we rated poor in quality.[39, 40]

In our review, the literature search for WBC count yielded 245 citations, from which we identified 10 cohort studies reported in 11 publications[39-49] and one nested case-control study[50] that examined the WBC count as a predictor of CHD events (*Evidence Table 1*). Two studies that adjusted for all Framingham risk factors was rated good-quality,[42, 49], while 5 were rated fair, [45-48, 50] and 3 were rated poor-quality [39, 40, 44] Five studies were limited by incomplete adjustment for diabetes and other FRFs.[44-47, 50] Other limitations include small sample size and limited duration of followup.[46]

The evidence that WBC count independently predicts CHD events was inconclusive. Among the fair and good-quality studies, WBC emerged as an independent predictor of CHD adjusting for smoking and other risk factors in some reports[43, 45, 47, 48, 50] but not in others.[41, 42, 46, 48, 49]

The relationship between WBC count and CHD events also varied with the timing of the assessment of endpoints. For example, an older, fair-quality cohort study reported conflicting results in analyses conducted at different time points. After a median follow-up of 13.9 years, one analysis of the NHANES cohort reported significantly elevated CHD risk associated with WBC among white men (RR 1.31, 95%CI 1.07-1.61) and women (HR 1.31, 95%CI 1.05-1.63), comparing a WBC count of >8.1 with <6.6 x 1000/mm3.[43] The analysis adjusted for age, smoking, blood pressure, total cholesterol, and history of diabetes. Among blacks in the study, a statistically significant increase in CHD incidence was detected at age 45-64, adjusted for age, sex, and smoking: RR 2.05, 95% CI 1.01-4.17. A significant association among blacks did not occur at age 65-74, however, a subsequent analysis of the cohort after 18 years of follow-up found no association: HR 1.01 (95% CI 0.85-1.20) comparing the highest to the lowest tertile of WBC count and adjusting for age, race, gender, smoking, blood pressure, total cholesterol, and diabetes.[49] Analyses of another good-quality cohort study at separate time points found no association between total WBC count and CHD risk, adjusted for race and all Framingham risk factors after 5 and 10 years of follow-up, respectively.[41, 42]

Fasting glucose

In 1997, the American Diabetes Association (ADA) published criteria that rely primarily on fasting glucose (FG) values for the diagnosis and classification of diabetes mellitus. The 1997 ADA criteria defined a new class of glucose disturbance called impaired fasting glucose (IFG) that refers to a metabolic stage intermediate between normal glucose homeostasis and diabetes.[51] This stage included individuals with FG levels $\geq$110 mg/dL but < 126 mg/dL. A FG concentration of 109 mg/dL was chosen as the upper limit of normal because above this level, acute phase insulin secretion is lost in response to intravenous administration of glucose and is associated with a progressively greater risk of developing micro- and macrovascular complications.[51] The ADA subsequently redefined the range for IFG as 100-125 mg/dL.[52]

A fair-quality systematic review[53] included six studies of FG, published between 1979-1996.[54-59] From the combined data, the study determined that a FG of 110 mg/dL was associated with a relative risk of cardiovascular events of 1.33 (95% CI 1.06-1.67) compared with the reference FG of 75 mg/dL. However, only two[57, 59] of the studies in the meta-regression analyzed the incidence of fatal and non-fatal CHD events. The remaining studies analyzed mortality only and did not meet the inclusion criteria for the current report.

For our review, the literature search for FG yielded 147 citations, from which we identified 8 cohort studies (representing 10 cohorts), including 2 that occurred in the previous review (*Evidence Table 2*).[57-64] The mean duration of follow-up ranged from 3 to 17 years. The mean age at baseline ranged from 47 to 68 years. Five studies excluded subjects with diabetes based on medical history[58, 60, 63] or based on a FG level greater than 126 mg/dL.[57, 61] Two studies included subjects with a history of diabetes but analyzed them separately.[59, 62] Subjects with baseline CVD or CHD were excluded in all studies but one[59] that adjusted for baseline CHD as a confounder. Hard CHD events were the outcome of interest in all studies but two that additionally included soft CHD (angina, intermittent claudication) and other CVD outcomes (stroke, transient ischemic attack).[60, 63]

The cohort studies ranged in size from 445 to 13,446 subjects. The categorization of FG values varied among studies. Two studies defined impaired FG using the 1997 ADA criteria of 110-125 mg/dL.[60, 64] One study analyzed FG dichotomously at a threshold of 103 mg/dL.[57] Another study analyzed two thresholds of FG separately: 103 mg/dL and 110 mg/dL.[61] Other studies assessed FG in continuous increments[63, 64] or in groups of increasing FG.[58, 62] Overall, FG did not appear to be a strong independent predictor of incident CHD after adjustment for traditional Framingham risk factors. The 2 best-quality cohort studies [62, 63] had mixed results. One found a weak association between FG and CHD after 4 years of follow-up, reporting a hazard ratio of 1.088 per 13 mg/dL increase in FG (95%CI 1.02-1.16) adjusted for Framingham risk score.[63] The other study found no association with increasing FG after 4-7 years of follow-up.[62]

Two studies were rated good-quality[62, 63], 6 were rated fair-quality,[53, 58-61, 64] and 1 was rated poor-quality.[57] Limitations of studies include small numbers of cases relative to the number of adjusting variables or fasting glucose categories[60] and incomplete adjustment for Framingham risk factors.[57, 59]

Among fair-quality studies, no significant increased risk of CHD comparing FG 110-125 with < 110 mg/dL was found after 6 years of follow-up,[60] and no trend with increasing FG appeared after 3-7 years followup[59, 62] or after 9.5 years.[58] A poor-quality study that adjusted only for age and gender similarly found no association comparing FG 103-125 with $\leq$103 mg/dL after 17 years of follow-up.[57] A fair-quality study among people with hypertension reported an adverse synergistic interaction between glucose and total cholesterol (TC) that magnified CHD risk associated with TC. Among subjects with FG >103 mg/dL in this study, the adjusted hazard ratio was 2.46 (95% CI 1.26-4.77) comparing TC 200-259 with <200 mg/dL. Among subjects with FG <103 mg/dL, the adjusted HR was 0.89 (0.61-1.29).[61]

Periodontal disease

Some estimates indicate that approximately 75% of adults in the US have periodontal disease and of those, approximately 20-30% have severe forms.[65-67] Periodontal disease is associated with measures of chronic inflammation such as elevated fibrinogen and CRP levels [68-70]. The common measures of periodontal disease in our review include bone loss, pockets, inflammation/gingivitis, and tooth loss or self report of tooth loss or periodontal disease.

We reviewed 126 abstracts and identified 9 studies conducted in 7 cohorts[71-78] The studies were conducted in North America and Finland, and included from 175 to 170,000 men and women (*Evidence Table 3*). Follow-up ranged between 5 and 21 years. Periodontal disease was defined (and diagnosed) differently among the studies. Some studies employed dental examinations and radiographs and others relied on self report. Cardiovascular and CHD outcomes also were defined differently among the studies. Although our focus in this review is on CHD outcomes, we analyzed studies that used a broader range of endpoints. Three studies were rated good-quality[73, 74, 76] and 5 were fair-quality.[71, 72, 75, 77, 78] Periodontal disease based on either self report or dental examinations was evaluated in 6 studies.[71-74, 77, 78] Five studies showed increased risk of CHD in association with baseline periodontal disease[71-73, 75, 77] and 2 showed no association[74, 78] although one study found an increased risk that was not statistically significant (RR 1.5) among women.[78] When these studies were combined in meta-analysis, the summary estimate of

risk ratio was 1.24 (95% CI 1.01-1.51) for any CHD or CVD event as shown in *Figure 3*. In subgroup analyses, the association with CHD was increased with female gender, longer follow-up times, and in studies based on dental exam rather than self-report (*Figure 4*).

Gingivitis as a measure of periodontal disease was evaluated in 2 studies [73, 77] and both showed or suggested elevated rates of CHD death among individuals with baseline gingivitis. When combined in meta-analysis the summary estimate was 1.35 (95% CI 0.79-2.30). Bone loss was an important risk factor for subsequent CHD with 2 studies showing statistically significant relative risks from 1.36-1.90.[72, 76]

Four studies[71, 73, 76, 77] including the Health Professional Follow-up, Nutrition Canada and the NHANES-1 studies, found that tooth loss made an independent contribution to the prediction of CHD events; one fair quality study suggested increased risk but was not statistically significant.[71] When these 4 studies were combined in meta-analysis, the summary estimate for all CHD/CVD events was 1.41 (95% CI 1.22-1.63) indicating a 41% increased risk of CHD or CVD events among individuals with 0-10 teeth at baseline.(*Figure 3*)

Carotid intima media thickness

Several simple non-invasive measures of non-cardiac atherosclerosis have been investigated as risk factors or predictors of CVD. Carotid IMT, as measured by carotid ultrasound, has been shown to be associated with traditional CVD risk factors[41, 79] and is a marker of systemic atherosclerosis as assessed from pathology. Carotid IMT is also a predictor of stroke [80-82] and has strong correlations with CHD risk factors.

To assess the value of carotid IMT as a predictor of coronary events, we identified 6 population-based longitudinal studies in asymptomatic persons followed for the development of CHD (*Evidence Table 4*).[79, 83-87] Two of the studies were from the same cohort.[84, 87] We used the more recent of the two.[87] The reports from 2 of the 5 cohorts had no adjustment for other risk factors and were rated poor-quality.[79, 83] The remaining cohorts included men and women aged 42 or older, ranged between approximately 1,300 to 16,000 individuals, and were conducted in the US[41, 86] and in the Netherlands.[84, 87]

Carotid IMT persisted as an independent risk factor in the 3 cohorts after full or partial adjustment for Framingham risk factors. The relative risks or hazard ratios ranged from 1.19-3.80 for various degrees of carotid IMT (mm) or a composite score of carotid IMT or plaque. In subsequent analysis of data from the Atherosclerosis Risk in Communities (ARIC) cohort, adding carotid IMT scores to a risk prediction equation based on Framingham risk factors slightly improved the prediction of subsequent CHD among healthy adults, particularly men.[41]

Electron beam computed tomography

EBCT can be used to quantify calcification of the coronary arteries into a CAC score. Coronary calcification is known to correlate with atherosclerotic burden.[88-90] Coronary calcification increases with age and, on average, is more extensive in men than women.

A meta-analysis published in 2003 analyzed 4 longitudinal studies[26] of asymptomatic adults. The follow-up periods ranged from 32 to 43 months; during follow-up 39 cardiac deaths and 71 nonfatal infarctions were observed in 3,970 subjects. Three of these studies were conducted in patients who were self-referred or referred by a physician to an EBCT facility.[29, 91, 92] These 3 studies had other flaws: none of them adjusted for the Framingham risk factors, and, in two, outcome assessment was not blinded. The fourth, a population-based prospective cohort study from the South Bay Heart Watch,[28] adjusted statistically for most of the Framingham risk factors and used blinded adjudication of outcomes. All 4 studies found that a high CAC score was associated with a higher risk of CAD events (RRs of 1, 2.1, 4.2, and 7.2 for CAC score categories of 0, 1-100, 101-400, and >400, respectively.) However, the estimates were much lower for the South Bay Heart Watch (RRs 1.0; 1.7, 95%CI 1.1-2.6; 2.3, 95%CI 1.1-4.7; 2.8, 95%CI 1.2-6.8 for CAC score categories of 0, 1-100, 101-400, and >400, respectively) than for the 3 other studies. None of the studies attempted to assess the added predictive value of CAC scores among intermediate-risk individuals.

Our literature search for EBCT yielded 167 citations, from which we identified 9 prospective cohort studies that met inclusion criteria,[29, 91-98] of which all but one[93] met further criteria for meta-analysis (*Figure 5*). We conducted a meta-analysis that included several studies published since 2003, and focused on a subset of studies that used valid methods and were applicable to intermediate-risk individuals in the general population. Specifically, good-quality studies: (a) were population-based, (b) measured risk factors rather than using proxies ascertained by questionnaires, (c) assessed outcomes in a blinded fashion, (e) adjusted for all traditional risk factors (blood pressure, age, sex, smoking, diabetes, and cholesterol). Publications from 3 cohort studies met these criteria.[95, 96, 98] We also compared the relative risk ratios for good-quality studies to those for 4 fair-quality[29, 92, 94, 97] and 1 poor-quality study.[91]

Characteristics of these studies are summarized in *Evidence Table 5*. For the 7 fair or good-quality studies[29, 92, 94-96] combined in a meta-analysis, pooled relative risks (95% CIs) were 2.56 (1.96, 3.35); 5.35 (3.13, 9.16); and 8.01 (4.81, 13.33) for CAC scores of 1-100, 101-400, and >400, respectively (*Figure 5*). Estimates of the effect of CAC scores varied widely. Estimates from the good-quality studies were substantially lower than those for fair-quality and poor-quality studies (*Figure 6*), but were still substantial.

The 3 good-quality, population-based cohort studies also showed increasing adjusted relative risks for hard coronary events as CAC scores increased. One of these, conducted in 1,029 subjects (mean age, 65.7 years) in the South Bay Heart Watch cohort, had an average follow-up of 75 months.[95] The investigators calculated Framingham risk scores and then stratified by CAC scores. In the 10-15% and 16-20% Framingham groups, respectively, 17/257 subjects and 26/383 subjects had a coronary death or MI within 75 months. The raw frequency of events for these combined groups is shown below in *Table 4*. Compared to subjects who had a CAC score of zero, patients who had higher CAC scores had significantly higher risk of having a CHD event. The investigators calculated hazard ratios separately for the 10-15% and 15-20% groups. All hazard ratios were statistically significant for subjects whose baseline 10-year risk was 15-20%. In this group, the HRs (95% CI) for CAC scores of 1-100, 101-300, and >300 were 5.3 (1.1-25.0), 6.2 (1.2-31.8), and 8.9 (1.9-41.8), respectively. For subjects whose baseline 10-year risk was 10-15%, the hazard ratios (95%CIs) were 3.2 (0.6-17.7), 6.2 (1.0-37.0), and 17.6 (3.7-83.0).

Study participants with a baseline Framingham score of 10-15% and CAC scores above 300 had a projected 10-year event rate in the range of a high-risk group, that is, a >20% 10-year risk.

TABLE 4. FREQUENCY OF EVENTS IN FRAMINGHAM 10-20% RISK GROUP BY CAC SCORE

CAC score	Number of events / Number of patients
0	7/195
1-100	12/223
101-300	8/104
>300	16/118

Abbreviation: CAC=coronary artery calcification.

The second good-quality study followed 1795 asymptomatic participants (mean age, 71 years; range, 62 to 85 years) in the Rotterdam Coronary Calcification Study, a sub-study of the Rotterdam study for a mean of 3.3 years.[96] Patients with previous coronary disease were excluded, but 2.8% of subjects had a history of stroke. Unlike most other studies, the authors categorized CAC results into the following 4 categories: 0 to 100, 101 to 400, 401 to 1000, and 1000. Compared to the lowest group, the multivariate-adjusted relative risk for CHD events was 2.7 (95% CI, 1.0 to 7.7) for calcium scores of 101 to 400, 4.1 (95% CI, 1.3 to 11.6) for calcium scores of 401 to 1000, and 8.1 (95% CI, 2.9 to 22.3) for calcium scores >1000. The investigators also computed the additional value of CAC after computing a Framingham risk score. Because they partitioned the subjects into 2 groups—10-year risk > 20% and 10-year risk<20%—the study does not provide an estimate of the additional value of CAC in intermediate-risk individuals. CAC improved prediction in both groups. Compared with the reference category (subjects with a calcium score of 0 to 100 and a 10-year Framingham risk score< 20%), relative risks of CHD were 3.2 for a calcium score of 101 to 1000 and 8.7 for a calcium score>1000.

A third good-quality study, from the Prospective Army Coronary Calcium (PACC) Project, provided information about a younger, lower-risk cohort followed for 3 years.[98] In this sample of 2000 individuals (mean age 43 years), the prevalence of coronary calcium was 22.4% of men and 7.9% of women. Only 9 CHD events were observed; all in men. Coronary calcium was associated with an 11.8-fold increased risk for incident CHD (p=0.002) in a Cox model controlling for the Framingham risk score. This result pertains primarily to low-risk rather than intermediate-risk individuals and was not included in our meta-analysis. Nevertheless, it indicates that CAC measurement may be of particular value in younger individuals who are low-risk by traditional measures.

The Saint Francis Heart Study, a population-based study of 4903 asymptomatic persons age 50 to 70 years (mean age 59), also examined the value of CAC scores when used in addition to the Framingham risk score.[93] The report concerns 4613 participants who completed a follow-up evaluation 4.3 years after inception. Among intermediate-risk individuals, the 2nd and 3rd terciles of CAC scores were associated with approximately 2 times and 5 times higher risk of CHD events, respectively. This finding was presented in a graph without actual numbers or statistical testing. Moreover, as reported in the article, the event rate includes revascularization as an endpoint.[a]

[a] The author agreed to provide the data required to include the study in the meta-analysis.

Several limitations of the evidence regarding EBCT can be noted. First, as shown in *Table 3*, EBCT has been evaluated in fewer of the major epidemiologic cohorts than some other novel risk factors. The reason is that, while stored tissue samples from subjects can be used to test retrospectively for serum tests such as CRP, there is no way to obtain a calcium score retrospectively. For this reason, data on EBCT are relatively sparse; follow-up periods relatively short, compared with those for studies of CRP, homocysteine, and other blood tests; and Framingham risk factors are not measured as completely as they were in the larger, older cohort studies. Moreover, because the test cannot be evaluated in longer-term studies such as Framingham and the Nurses Health Study, most of the studies had too few "hard" CHD events to conduct a complete analysis of risk factors.

The American College of Cardiology Foundation (ACCF) and AHA recently released a report on EBCT and its use in primary prevention of CHD. This report states that CAC scoring may be an appropriate means of risk stratifying those of intermediate-risk as determined by the Framingham risk score. Their study, like ours, identify several key prospective cohort studies that best address the use of CAC scoring by EBCT in an asymptomatic, intermediate-risk population – a group most likely to benefit from more aggressive primary prevention and the population central to our study's question. Greenland, *et. al,* and Vliegenthart *et. al.* had high quality scores in the ACCF/AHA report and in ours and form the primary basis for recommendations. (Taylor *et. al.* also had a high quality rating but observes a low-risk, rather than intermediate-risk cohort.) We concluded, however, that several features of this key literature limit recommending the implementation of CAC scoring by EBCT into clinical practice at this time.

First, self-selection bias likely existed in the Rotterdam Study since only 61% of eligible individuals invited to participate actually formed the study group. The South Bay Heart Watch cohort may also have been self-selected since only 5023 individuals responded to 100,000 letters of invitation.

Second, the cohorts of the Rotterdam Study and the South Bay Heart Watch may not be representative of an intermediate-risk group as determined by the Framingham score. In the Rotterdam Study, the ability of CAC scoring to add predictive value was evaluated in those with a 10-year Framingham risk of >20% or ≤20%. The subset with a Framingham risk ≤20% could include a substantial number of individuals of low-risk, *i.e.,* a 10-year Framingham risk score of ≤10%. Therefore, it is difficult to generalize this study's results to an intermediate-risk population - a group most likely to benefit from improved risk stratification and aggressive primary prevention.

In the South Bay Heart Watch, the annual event rate for the group with a projected 10-year risk of 16-20% was only 1%. That is, the Framingham risk score significantly underestimated risk in this group, possibly due to small sample size. The sparse number of events particularly limited conclusions regarding those deemed high risk by the CAC score (≥300) and intermediate risk by the Framingham score. Eight of 41 patients with a CAC score ≥300 and a Framingham risk score of 11-15% experienced MI or coronary death – a 20% event rate. However, 8 of 77 participants with a CAC score ≥300 and Framingham risk score of 16-20% had MI or coronary death – an 11% event rate. The small number of events and the inability of the Framingham risk

score to differentiate risk in those with a Framingham risk score of 11-15% as compared to 16-20% regardless of CAC score raise concerns about the validity of these findings.

In summary, in two good-quality, applicable, population-based prospective studies, higher CAC scores were associated with a higher risk of CHD events over 2 to 4 years of follow-up. The RRs were large but not statistically significant for CAC scores in the range 101-400 (3.97, 95% CI 0.94 to 16.8) but were statistically significant for the groups with CAC scores of 1-100 (3.46, 95% CI 1.23 to 9.71) and > 400 (6.48, 95% CI 1.48 to 28.5.) Results from a good-quality study in middle-aged men support the conclusion that CAC adds independent information to the Framingham risk score. Older cohort studies appear to overestimate the independent effect of CAC scores. The studies on EBCT were limited by participant self-selection and sparse data on individuals at intermediate risk by the Framingham risk score.

Homocysteine

The role of plasma homocysteine in vascular disease has been studied extensively in the last 4-5 decades.[99] Interest in homocysteine as a causal factor was spurred by the observation that over 50% of children with the genetic disorder homocystinuria die of premature vascular disease,[100, 101] and strategies which reduce homocysteine levels in these children reduce vascular event rates.[101, 102] In addition, in humans, non-human primates, and mammals, elevations of homocysteine are associated with several physiologic abnormalities which might explain increased vascular risk.[103, 104]

In humans, severe elevations of homocysteine may occur because of rare inborn errors of metabolism. Moderate elevations may occur because of less severe genetic mutations associated with enzyme abnormalities in the metabolic pathway involving folate and homocysteine. Elevations of homocysteine also result from inadequate dietary intake of folate and vitamins B6 and B12. In the US, mild elevations occur in 5-30% of the population and epidemiologic studies have shown that over 50 % of US adults are not consuming enough folate to keep their homocysteine levels low.[105-107]

Prior meta-analyses have shown that mild to moderate elevations of homocysteine are associated with a slight increase in CHD risk.[108-110] However, these meta-analyses have been limited by the inclusion of cross-sectional studies, studies conducted among patients with known CHD, and case control studies conducted among survivors of CHD events. Furthermore, because elevated homocysteine levels are also associated with known CHD risk factors, such as hypertension,[108] male sex,[111] renal dysfunction,[112] and smoking,[108] prior meta-analyses are limited by the inclusion of studies with insufficient adjustment for factors that might confound the relationship between CHD and elevated homocysteine levels. Thus, these meta-analyses have provided less than definitive answers to the question of whether elevations of homocysteine might explain a portion of CHD in individuals of average CHD risk based on traditional risk factors. For many of these reasons, as well as a lack of primary prevention studies showing reduced risk of CHD with treatment of elevated homocysteine, screening for elevated homocysteine levels in the general adult population has not been recommended by major health care organizations such as the USPSTF.

For this review, 31 publications of homocysteine were considered for inclusion.[14, 113-141, 258] Of these, 24 cohorts were included (*Evidence Tables 6 & 7*). Some of these were not used in our meta-analysis (*Figure 7*) because either the outcome studies could not be clearly attributed to CHD, or data were included in another publication (see *Evidence Tables 6 & 7* for details). When these studies were combined in a random effects meta-analysis the estimated relative risk for total CHD associated with each 5 µmol/L increase in homocysteine was 1.18 (95% CI 1.10-1.26) for all studies combined and 1.21 (95% CI 1.10-1.32) for studies in which individuals with prevalent CHD were explicitly excluded from the cohort (*Figure 7*). This relationship was similar for men and women. The increase in risk was consistent in all subgroup analyses including evaluations by age, length of follow-up, study quality, gender and type of study. None of the studies attempted to evaluate the impact of homocysteine as an independent risk factor in intermediate-risk subjects.

The good-quality studies adjusted for all or nearly all of the risk factors that make up the Framingham risk score. Study quality did not explain differences observed among the studies. A sensitivity analysis determined that the meta-analytic results were similar when poor studies were included in the model (OR 1.19, 95% CI 1.12 to 1.27).

In women, all studies showed either a statistically significant[14, 124, 141] association between higher homocysteine levels and CHD events or an elevated risk estimate that did not reach statistical significance.[114, 115, 118] When combined in meta-analysis, the estimated relative risk among studies including women for each 5 µmol/L increase in homocysteine was 1.21 (1.06-1.37) (*Figure 8*).

One of the limitations of this review is that the outcomes measured varied by study. In an attempt to determine whether the relationship between homocysteine and subsequent CHD varied by outcome, we stratified the studies by the type of event and showed no difference in findings—that is, all outcomes, including MI, total CHD, and CVD were positively associated with baseline HC levels. The combined estimates for each of these outcomes are shown in *Figure 8*.

Prior evaluations of the homocysteine literature found a disparity in results between case control studies, which have tended to show higher relative risks, and cohort studies, which have shown either no elevation in risk or more moderate risk associated with elevated homocysteine when compared to case control studies. In the current review we evaluated whether study type was associated with a significantly different relative risk as observed in previous meta-analyses. As shown in *Figure 8*, there was no difference between the relative risk estimates for nested case control studies and the cohort studies included in this review.

Finally, to determine whether baseline homocysteine levels are associated with short or long term risk, we stratified the studies included in this review by length of follow-up. Among the studies with follow-up of less than 5 years the summary risk ratio was 1.39 (95% CI 1.20-1.62) and among studies of longer duration (>10 years) the risk ratio was 1.13 (95% CI 1.00-1.28).

Our review shows a relatively consistent association between elevated homocysteine levels and CHD that is independent of traditional risk factors. This association held in all subgroups and in widely varying cohorts. The relationship between higher levels of homocysteine and CHD we

have identified may be due to unrecognized confounding by factors associated with homocysteine and CHD which explain the observed relationship. We have attempted to control for confounding by only including studies of fair or better quality in our meta-analyses but we recognize that it is plausible, even with excellent control of confounding by known CHD risk factors that the observed association between higher homocysteine levels and CHD may be due to unrecognized confounding. One approach to understanding this possibility is reviewing the number of confounders adjusted for in each study and attempting to quantify the potential confounders that were not adjusted for in the included studies multivariable analyses. In our review, we found little evidence of differences in relative risk estimates between studies with many adjustments for confounders compared with fewer adjustments. One of the greatest limitations of observational studies, even of the very best quality, is that they cannot completely adjust for confounders. The possibility of unrecognized confounding is supported by the fact that elevations of homocysteine are associated with other important risk factors for CHD such as hypertension,[142, 143] smoking,[143] microalbuminuria,[144] physical activity,[143] and male sex.[143] While most studies adjusted for traditional risk factors, most did not adjust for renal dysfunction which has been shown to be a confounder in several studies.[145, 146] However, the Framingham analysis[134], as well as the Rotterdam[117] and Gothenburg studies[141] found no change in relative risk estimates when measures of renal function were added to the multivariable models.

There are several limitations of this review. First, we relied on only published data which may be biased towards publishing positive findings. We evaluated this with a funnel plot which did not suggest publication bias. Second, since we only used published data, the outcomes evaluated were not standardized between studies. For example, some studies evaluated only MI as an outcome and others evaluated several CHD outcomes. The similarity between the relative risk estimates identified for each outcome suggests that the outcomes were sufficiently similar to combine in meta-analysis. In addition, we relied on each study's definition of the outcome. Third, studies reported their findings variably making it difficult to identify either a dose response or thresh-hold effect, but relatively easy to identify that in most cohorts, individuals with higher homocysteine levels had worse CHD outcomes when compared to those with lower levels.

Another limitation is that ascertainment of outcomes differed in each study. Some studies relied on population registries and others self-report. We tried to account for this potential source of error in our quality ratings and reduce this problem by only including fair or better quality studies in this review. We believe our quality review would be more likely to miss random error in outcome assessment than systematic error which would result in underestimating the association between homocysteine and CHD. Furthermore, because all included studies were prospective and homocysteine levels measured long before the outcomes occurred, it is very unlikely that bias in assigning the outcome is important in our findings.

There are several strengths of this review. First, we used only data from population-based prospective cohort studies. All individuals had homocysteine levels measured at baseline and were followed forward in time for the development of CHD. While this does not allow us to determine whether homocysteine is a causal risk factor or a marker of risk, it does reduce the problem of determining cause and effect that is associated with cross sectional studies. The population based nature of the cohorts substantially improves generalizability of the findings

which is of great importance when considering public health and prevention guidelines that are applied broadly in a population. Another strength of this review is that we quality rated all of the studies and eliminated those of poor quality (five studies) where the findings could only be viewed as of questionable validity. Even when these findings were included in the review and meta-analysis, the association between homocysteine levels and CHD was similar.

Lipoprotein(a)

The Lp(a) lipoprotein was discovered by Berg in 1963.[147] Lp(a) is a cholesterol-rich plasma lipoprotein particle, the structure and composition of which closely resemble LDL. The distinguishing feature of Lp(a) is the presence of an additional large glycoprotein known as apolipoprotein-a (apo[a]), which is linked by a disulfide bridge to apolipoprotein B-100, the sole protein of LDL. Apo(a) has a high sequence homology (75-90%) with plasminogen[148] and may competitively interfere with plasminogen action in fibrinolysis, promoting development of lipid-rich plaques that are more prone to rupture than more fibrous lesions.[149-152] This suggests that Lp(a) may contribute to the thrombotic and atherogenic aspects of CHD. A plasma Lp(a) threshold of 30 mg/dL has been linked to increased CVD risk in men.[153, 154]

Lp(a) synthesis is under strong genetic control, and the serum Lp(a) concentrations of children aged 7-24 months correlate strongly with their parents' and siblings' serum Lp(a) concentrations.[155] Differences in Lp(a) by nationality and ethnic group have been observed. Median Lp(a) values in Black Americans were approximately 3-fold higher than in White Americans (21.5 vs. 6.1 in Black vs. White men; 23.9 vs. 6.4 in women), and while the distribution of Lp(a) in Whites was highly skewed (median 3.7, mean 6.9), the skewness was much less pronounced in Blacks (median 11.6, mean 13.0).[156] Native American Indians have low concentrations of Lp(a), and only a small percentage (1.7%-7.4%) have Lp(a) >30 mg/dL.[157]

There is little correlation between Lp(a) and traditional CHD risk factors. Increased age was associated with elevated Lp(a) level in some studies.[158-160] Smoking appears to be unrelated to Lp(a) level.[158, 159, 161, 162] The relationship between Lp(a) and LDL cholesterol is inconsistent, even among studies that corrected for the estimated contribution of Lp(a) cholesterol to LDL cholesterol.[158-162] Diabetes, blood pressure, and HDL cholesterol do not appear to be consistently associated with Lp(a) levels.

Twelve cohort studies reported in 18 publications,[41, 163-179] nine nested case-control studies reported in nine publications,[149, 162, 180-186] and two meta-analyses[187, 188] met the inclusion criteria for this review. Thirteen studies included only men,[162, 165, 167, 170, 172, 176, 178, 181-184, 186, 189] six included both men and women,[171, 173-175, 177, 185], and two studies included women only.[164, 179] Subjects' race was 97-100% White in all but one study.[41]

The studies analyzed Lp(a) using various quantitative comparisons, and the results shown compare the highest to the lowest quantile of Lp(a) in each study *(Evidence Table 8)*. Overall, 10 of the studies reported a statistically significant association between Lp(a) and CHD risk: three of five good-quality studies, and seven of 13 fair studies. Six studies dichotomized Lp(a) at various thresholds, of which five studies reported a significant association with CHD risk. Using a threshold of 20 mg/dL, two studies reported elevated RRs of 2.7 (95% CI 1.4-5.2)[178] and 6.76

(95%CI 2.1-21.7).[180] At a threshold of 30 mg/dL, three other studies reported elevated RRs of 2.0 (p=0.0001) in men,[170] 1.9 in men (95%CI 1.2-2.9),[165] and 1.61 in women (95%CI 1.13-2.29).[164]

Three of four studies that compared various levels of Lp(a) with a reference of ≤3 mg/dL reported elevated and statistically significant RRs. These RRs (95% CI) were 7.2 (1.3-39.8) for Lp(a) >13.4 mg/dL,[184] 1.81 (1.02-3.19) for Lp(a) between 15.6 and 34.8 mg/dL,[183] 1.9 (1.1-3.3) for Lp(a) >26.3 mg/dL, [176] 2.08 (95%CI 1.2-3.6) at ≥34.9 mg/dL[183], and 1.47 (95% CI 1.21-1.79) at >44 mg/dL.[179] Four studies that analyzed various continuous increments of Lp(a) reported mixed results. Of two studies that assessed risk per 1-SD increase in Lp(a), one found a positive association (RRs of 1.15 in men, 1.17 in women, p<0.01)[177], and another found no association (RR 0.93, 95% CI 0.73-1.18).[175] A third study found an association of small magnitude: RR 1.0003 per 0.1 mg/dL increase in Lp(a) (p=0.01),[162] and a fourth study found no association per 1-unit increase of Lp(a) on a logarithmic scale.[174] Four other studies categorized Lp(a) in groups that could not be directly compared with other studies, and reported null associations with CHD risk,[167, 172, 173, 186] although one such study detected a statistically significant trend of increasing risk with increasing quintile of Lp(a).[172]

Variation in sample handling and storage methods, and a lack of standardization of commercial assays, present limitations to the direct comparison of Lp(a) studies. A previous meta-analysis found that storage temperature was strongly associated with variability in Lp(a) analysis in a meta-analysis.[187] Much of the inaccuracy of commercial Lp(a) determinations results from the use of techniques sensitive to apo(a) size.[190] A study by Kronenberg concluded that small apo(a) isoforms were more susceptible to degradation than large apo(a) isoforms.[191] The Enzyme-linked immunosorbent assay (ELISA) has been reported to underestimate the concentration of Lp(a) containing small apo(a) isoforms.[192] Studies that compared the ELISA and immunoradiometric assay (IRMA) methods reported conflicting levels of agreement between the two assays.[181, 193]

In the current review, six studies assayed Lp(a) in fresh sera.[164, 165, 171-173, 178] Other studies assayed Lp(a) in samples that were frozen at temperatures ranging from –20C to –130C, for periods ranging from <1 year to 20 years.[162, 167, 170, 174-176, 179-186, 189] Studies quantified Lp(a) using electrophoresis, immunoradiometric assays, or turbimetric assays, and defined categories of Lp(a) in a range of quantitative and qualitative increments. Positive findings were reported in four[164, 165, 173, 178] of six studies that used fresh sera, and in 7[162, 170, 176, 177, 179, 180, 183] of 14 studies that measured Lp(a) in frozen samples. No pattern in effect size emerged among studies that stored frozen sera for increasing lengths of time. Two studies used an immunoturbimetric assay that measured Lp(a) independently of apolipoprotein(a) isoform size in samples that had been frozen in liquid nitrogen (-130 to -180C) for an unspecified duration, and found mixed results.[186, 194] One study was conducted in women enrolled in a trial comparing aspirin, vitamin E, and placebo, and was rated good-quality,[194] while the other was a fair-quality nested case-control study that included only men.[186] Among women, Lp(a) >44 mg/dL was significantly associated with increased CHD risk compared with Lp(a) <3.50 mg/dL (OR 1.47, 95% CI 1.21-1.79), and there was a statistically significant trend with increasing Lp(a) quintile (p<0.001).[194] The analysis adjusted for CRP, current hormone use, and body mass index, and randomized treatment group, in addition to Framingham risk factors, but found a significant interactive effect with

LDL-C. In the study among men, no association or trend emerged.[186] The analysis did not adjust for all Framingham risk factors, specifically TC, LDL, and HDL.

We conducted a meta-analysis of 16 good- and fair-quality studies that excluded subjects with a history of CHD at baseline, and could be combined based on standardized Lp(a) levels and found that Lp(a) $\geq$30 mg/dL was associated with an increased risk ratio of 1.57 (95% CI 1.31-1.88) compared with Lp(a) < 30 mg/dL (*Figure 9*). Two fair-quality studies[178, 180] were excluded from this analysis because the studies used a cut-off of 20 mg/dL, and did not report sufficient data to standardize the risk ratio at 30 mg/dL. A sensitivity analysis that included these additional studies had a similar combined result: 1.65 (95% CI 1.38-1.98). There was significant heterogeneity, however, across studies ($p<0.001$). The pooled estimate was similar among men and women, and tended to be higher in studies with longer follow-up times (*Figure 10*). The heterogeneity was not explained by the other study level variables, such as study design or degree of adjustment for confounders (*Figure 10*). None of the studies assessed whether Lp(a) adds to CHD risk specifically in intermediate-risk subjects.

Two previous meta-analyses of prospective studies of Lp(a) found a positive association between Lp(a) and CHD risk,[187, 188] but they differed from the current report by including studies of apolipoprotein(a), and studies that assessed mortality rather than total incidence. One reported a combined risk ratio of 1.7 (95% CI 1.4 to 1.9) comparing the top third of baseline Lp(a) to the bottom third, did not detect significant heterogeneity among studies, and found similar results when grouping studies by sample storage and assay method.[188] The other meta-analysis reported a combined ratio of 1.40 (95% CI 1.22-1.57) comparing Lp(a) levels in cases vs. controls, found significant heterogeneity ($p<0.001$) among studies, and that lower freezer temperatures correlated with a higher point estimate for the Lp(a) case:control ratio.[187]

C-reactive protein

CRP, a pentameric protein synthesized in the liver, was identified in 1930 in serum from patients with lobar pneumococcal pneumonia.[195] It is a sensitive, nonspecific systemic marker of inflammation and tissue damage that has long been used to monitor inflammation in fever and other conditions. [196] In addition to chronic inflammation, elevated levels of CRP are associated with traditional cardiovascular risk factors and with obesity.[197, 198] Whether CRP is involved in the pathogenesis of CVD is unknown.[199, 200]

The first report of CRP as a predictor of CHD events was published in 1996, from a nested case-control analysis from the Multiple Risk Factor Intervention Trial (MRFIT).[201] In that study, smokers with no known cardiac disease who were in quartile 4 of CRP had 4.3 times (95% CI 1.74-10.8) as high a risk of MI or CHD death than those in the lowest quartile after 13 to 17 years of follow-up.

A 1998 meta-analysis of 5 long-term, population-based prospective cohort studies and 2 cohorts of patients with known coronary disease at baseline calculated an odds ratio for coronary events of 1.7 (95% CI 1.4 to 2.1) for hsCRP levels in the top tercile (>2.4 mg/L) vs. the bottom tercile (<1.4 mg/L).[24] The only criterion for assessing the quality of each cohort study was a prospective design; another criterion, the number of covariates adjusted for in the analysis, was

recorded but not used to select or weight the studies. Two of the 5 population-based cohort studies adjusted only for age, sex, and smoking status.[201, 202] In another, from the Physicians Health Study, individuals in the top two CRP[b] quartiles had 2.5 times as high a risk of MI as individuals in the lowest quartile after adjustment for body-mass index, diabetes, history of hypertension, and parental history of CAD. The investigators did not simultaneously adjust for these factors and serum lipid levels.[203]

An update of this meta-analysis was published in 2000.[204] In this meta-analysis, the pooled OR for 11 population-based prospective cohort studies was 2.0 (95% CI 1.6 to 2.5). All studies found a positive relationship; in seven studies, the odds ratio was less than 2.0, and in five studies it was 2.0 or higher. Of the six studies added to the analysis since 1998, the best and largest was a nested case-control analysis of middle-aged men (506 cases and 1025 controls) randomly selected from general practice registers in each of 24 British towns.[204] Men in the highest tercile of CRP (>2.4 mg/l) were 2.13 (95% CI 1.38 to 3.28) times as likely to have an MI or death from coronary disease as controls after adjustment for age, smoking status, blood pressure, total cholesterol, HDL-C, triglycerides, body mass index, town, and socioeconomic status. An important finding of this study was that adjustment for socioeconomic status reduced the OR from 2.92 (95% CI 2.13 to 4.01) to 2.13 (95% CI 1.38 to 3.28). A second analysis excluding men who had coronary disease at baseline had similar results (OR 2.31, 95% CI 1.42 to 3.76). Another updated meta-analysis was published in 2004.[205] It included 11 new general-population cohort studies and updated information from one of the 11 cohorts included in the previous update. Older and smaller studies tended to report larger odds ratios. The investigators calculated an overall pooled OR for 22 studies of 1.58 (95% CI 1.48 to 1.68) and one derived from the four largest, more recent studies (1.49, 95% CI 1.37 to 1.62.) Both estimates are much lower than the same authors calculated in the 2000 meta-analysis.

These meta-analysis results support the view that, overall, an elevated hsCRP is associated with a higher risk of CHD events. However, the results are not necessarily useful for making a recommendation about the additional contribution hsCRP would make if used to further refine risk stratification in intermediate-risk individuals. Moreover, the investigators did not systematically assess characteristics of the design or execution of the studies, and in the 2004 update, did not rate the quality of adjustment for potential confounders.

Our approach was guided by these considerations. First, we identified 27 papers from 18 cohorts in North America and Europe that recruited asymptomatic individuals or a combination of asymptomatic individuals and patients with known CHD (*Evidence Table 9*). Fourteen papers reported cohort studies,[206-219] and 13 reported either nested case-control[14, 203-205, 220-226] or case-cohort [227, 228] analyses (*Evidence Table 10*). All but two studies [210, 212] excluded patients with known CHD. When multiple studies were published from a single cohort, we restricted our analyses to the highest quality papers that most closely addressed the questions of the review. Of this group of principal studies, all but one adjusted for at least five of the seven Framingham risk factors,[203-205, 207, 209, 210, 212, 216, 218-222, 225-227] and 8 adjusted for all seven factors.[207, 216, 218, 220-222, 225, 227] Of the 17 principal studies, nine were rated good-quality [204, 207, 216, 218-222, 227] and eight were rated fair-quality,[203, 205, 209, 210, 212, 213, 225, 226] seven were in males only,[203, 204, 207, 210, 212, 218, 220] three were in females only,[209, 216, 222] and six were in males and females combined.[205, 213, 219,

[b] The assay had a sensitivity of 0.08 µg per milliliter.

[225-227] One study examined two separate cohorts - one of males only and one of females only - and presented analyses of the cohorts separately and combined.[221]

Higher baseline CRP was associated with incident CHD events in 15 of the 17 studies, with the adjusted RRs ranging from 0.96 to 2.6. In eight studies the association was statistically significant,[203-205, 207, 216, 220, 222, 227] and in eight other studies the association was not statistically significant.[209, 210, 212, 213, 218, 219, 225, 226] In the study of two separate cohorts,[221] CRP was associated with CHD in both cohorts, but was only statistically significant in the cohort of men. Five studies[203, 210, 216, 220, 221] showed a statistically significant dose-response relationship between baseline CRP level and incident CHD.

The studies used a variety of cut-points and categories, including CRP as a continuous variable. In our meta-analysis, we standardized CRP levels to the three CDC/AHA-recommended categories (<1.0 mg/dL; 1.0 to 3.0 mg/dL; and >3.0 mg/L), and estimated the relative risk for incident CHD for each of the higher two categories compared with the lowest category. Analysis of all 15 studies (in 16 cohorts) that explicitly excluded CHD at baseline showed a RR of 1.64 (95% CI, 1.41-1.91) for CRP > 3.0 mg/L vs. CRP < 1.0 mg/L (*Figure 11*), and an RR of 1.27 (95% CI, 1.16-1.40) for CRP between 1.0 mg/L and 3.0 mg/L vs. CRP<1.0 mg/L (*Figure 12*). The relationship between CRP level > 3.0 mg/dL and CHD events persisted in several subgroup analyses (*Figure 13*).

We also performed a meta-analysis limited to the seven good-quality studies from eight cohorts that estimated the relative risk of incident CHD and adjusted for all Framingham risk score factors or calculated a Framingham risk score,[207, 216, 218, 220-222, 227] and obtained similar results. For CRP > 3.0 mg/L vs. < 1.0 mg/L, the RR was 1.66 (95% CI, 1.37-2.02), and for CRP between 1.0 mg/L and 3.0 mg/L vs. CRP < 1.0 mg/L, the RR was 1.22 (95% CI, 1.08-1.38). We excluded from this meta-analysis two fair-quality studies that used all Framingham risk score factors. One of these 2 studies[225] adjusted for all Framingham risk score factors, but excluded a large proportion of cases (23%) due to missing data. The other study[219] excluded sex from the multivariate analysis after finding no difference in the effect of traditional risk factors between men and women. We conducted a sensitivity analysis to compare the combined RR with and without these 2 studies, and found the results to be comparable. For CRP > 3.0 mg/L vs. < 1.0 mg/L, the RR was 1.58 (95% CI, 1.32-1.88), and for CRP between 1.0 mg/L and 3.0 mg/L vs. CRP < 1.0 mg/L, the RR was 1.20 (95% CI, 1.08-1.33).

Five studies [207, 216, 218, 219, 225] included analyses that compared predictive models using all Framingham risk factors with and without CRP. Three of these studies [207, 216, 219] specifically evaluated subjects of intermediate risk when stratified using the 10-year Framingham risk score, and two [207, 219] of the three measured the c-statistic or the area under the receiver operating characteristic curve (AUC). Results were mixed. Two studies that stratified subjects by Framingham risk scores found that CRP improved discrimination specifically among intermediate-risk individuals. [207, 216] In the Monitoring of Trends and Determinants in Cardiovascular Disease (MONICA) cohort, [207] adding CRP to the Framingham risk score significantly improved discrimination among individuals with an initial 10-year risk of 11-19% (*Figure 14*). Among those with serum CRP > 3.0 mg/L, some individuals with an initial 10-year risk of 15-19% were reclassified as high-risk, and no subjects with an initial 10-year risk of 11-

14% were reclassified as high-risk. In an analysis of data from the Women's Health Study, [216] CRP was clearly predictive for incident CVD among subjects with 10-year Framingham risk between 10 and 20%. The risk for CVD events was twice as high for those with CRP between 1.0 and 3.0 mg/L or between 3.0 and 10.0 mg/L when compared with those with CRP less than 1.0 mg/L, although confidence intervals were not reported. The negative study, an analysis from the Framingham cohort, found no improvement in discrimination as measured by the c-statistic, but did not assess the effect of adding CRP on reclassification.[219]

Several studies that examined the performance of adding CRP to traditional CHD risk factors used the change in the c-statistic, or the area under the receiver operating characteristic curve.[207, 218, 219, 225] A risk factor that has a small effect on the c-statistic, however, may be strongly associated with risk in a multiple logistic (or Cox) regression model, and vice versa.[229-231] We considered the RR from multivariate adjusted regression analysis in prospective studies to be a better measure of CRP's value as a marker of risk than tests of discrimination such as the c-statistic. From a clinical perspective, the impact on rates of reclassification from intermediate-risk to other categories of risk is a more meaningful measure of CRP's value as a marker. A recent publication from the Women's Health Study[232] illustrates that the c-statistic does not agree with this measure of clinical utility. The investigators used data from the Women's Health Study to develop a new risk scoring system for non-diabetic women, based on Framingham variables and hsCRP. The calculation of a new risk scoring system permitted comparison of the impact of hsCRP relative to that of traditional risk factors (*Table 5*). In the study, model fit was characterized using the Bayes Information Criterion (BIC), the c-index (a generalization of the c-statistic), and the Hosmer-Lemeshow calibration statistic. The model that included CRP had a lower BIC value (6960.26 with CRP vs. 6969.60 without CRP) and a higher calibration p-value (0.23 vs. 0.039), indicating better model fit. Notably, the c-index did not substantially differ between models with and without CRP (0.815 vs. 0.813). Among those originally classified as intermediate-risk (10% to 20%), 14% were reclassified as low-risk (<10%) and 5% were reclassified as high-risk (>20%). For those reclassified as high-risk, the actual 10-year risk was 19.9%, whereas those who remained intermediate-risk had an actual 10-year risk of 11.5%.

TABLE 5. SCORES FOR FRAMINGHAM RISK FACTORS AND hsCRP

Points	Total cholesterol (mg/dL)	Age (years)	HDL (mg/dL)	Systolic blood pressure (mm Hg) (treated)	hsCRP (mg/L)	Smoking
-2	<160		60+	<120		
0	160-199	45-49	50-59		0.5 to <1	No
1			40-49	120-129	1.0 to <3	
2	200-239	50-54			3.0 to <10	
3	240-279		<40	130-139	10+	
4	280+	55-59				
5				140-159		Yes

Abbreviations: HDL=high density lipoprotein, hsCRP=high sensitivity c-reactive protein.

Key Question 2a. Prevalence of Risk Markers among Intermediate-risk Individuals

We sought accurate information about the prevalence of abnormal results of the risk factors in the intermediate-risk target group. We did not examine prevalence for the ABI, WBC, or glucose level because the evidence supporting them as independent risk factors was indeterminate. Of the remaining risk factors, three - CRP, homocysteine, and LP(a) - were measured along with most Framingham risk factors and sociodemographic information in subsets of the NHANES sample, providing accurate population-based prevalence data for the target group. In addition, the 3 population-based studies of hsCRP that stratified patients by Framingham risk score also provided accurate information about the prevalence of high hsCRP levels in the target population.

Periodontal disease

Estimates of the prevalence of periodontal disease in the general population use varying definitions and, consequently, vary widely.[67] Some estimates indicate that 75% of adults have some periodontal disease and of those, approximately 20-30% have severe forms.[65-67] An analysis from NHANES has shown the prevalence of periodontitis (23%), gingivitis (30%), and healthy periodontum (34%) and found that periodontitis was more common among people with risk factors for CHD and those who are poorer and less educated.[75, 233] In the Nurses Health and Health Professional Follow-up studies, 16% of men and 36% of women had 24 or fewer teeth.[76]

While these population-based sources indicate that periodontal disease is common, no data are available about its prevalence among intermediate-risk individuals. We also did not find reliable data about the prevalence of periodontal disease among Black-Americans and Hispanic-Americans.

Carotid intima media thickness

We did not identify reliable data about the prevalence of high carotid IMT among asymptomatic intermediate-risk individuals.

Electron beam computed tomography

In one of the 4 population-based longitudinal studies, the high-CAC score group included over 17% of intermediate-risk males and over 24% of intermediate-risk females.[93] A cross-sectional study of 8549 asymptomatic individuals without known CHD also reported prevalence of coronary artery calcification scores among Framingham risk groups (*Table 6*).[234, 235]

TABLE 6. PREVALENCE OF CORONARY ARTERY CALCIFICATION (CAC) SCORES BY FRAMINGHAM RISK GROUP

	Males (%)			*Females (%)*		
CAC Score	*Low*	*Inter-mediate*	*High*	*Low*	*Inter-mediate*	*High*
0	48	32	17	63	28	27
1-100	34	37	36	29	36	30
101-400	11	17	29	6	24	15
>400	8	13	28	2	12	13
>75th age-sex Percentile	21	27	31	19	32	40

Key Question 3. Harms of Risk Assessment

We found no specific evidence about the harms of risk assessment with emerging markers.

EBCT for obtaining CAC delivers about 1 mSv of radiation exposure. Though studies included in this report all used EBCT, many centers are now implementing newer MSCT scanners. The newer Multislice CT scanners are being marketed because they offer better temporal resolution and more complete image reconstruction of the cardiac cycle; however, the radiation dose equivalent of these scanners is significantly higher (10-20 mSv). By contrast, the effective dose equivalent associated with coronary angiography is 6 mSv.[236]

A 2003 USPSTF review of screening for coronary disease[237] assessed other potential adverse effects of screening with EBCT as follows:

"Potential adverse effects of screening for asymptomatic coronary artery disease with EBCT include increased false positive test results and labeling. As is the case with electrocardiography and exercise electrocardiography treadmill testing, false-positive EBCT results often cause patients to undergo invasive diagnostic procedures such as coronary angiography, with resultant costs and risk of adverse events. Abnormal test results may also produce considerable anxiety until the test result is determined to be false. Labeling a person as suffering from coronary disease may also have negative consequences. Mixed evidence from hypertension screening suggests that being labeled as having increased risk may be associated with poorer future health." [28]

They also noted that in two studies of people's reactions to a positive EBCT scan, patients were more worried about their health than those with negative results, but the impact of this finding on health and quality of life was unclear.[238, 239]

Key Question 4a. Evidence About Treatment in Groups Identified as High-risk by Novel Risk Markers

Homocysteine

Many trials of folate therapy with or without vitamins B6 and/or B12 have shown that homocysteine can be effectively reduced.[240] In healthy adults, however, a causal relationship between homocysteine and CHD would be greatly supported if treatment studies showed a decrease in CHD risk in association with homocysteine lowering treatment. Early data from treatment trials have not shown reduced CHD with treatment.[240, 241] Notably, recent data from both the Heart Outcomes Prevention Evaluation (HOPE) 2 study[240] and the NORVIT trial[241] showed no benefit in reducing the risk of major cardiovascular events in patients with vascular disease or recurrent CVD after acute MI in spite of reducing homocysteine levels with folic acid treatment. However, all trials to date have been of tertiary prevention and conducted among individuals with prevalent CHD, cerebrovascular disease or diabetes. Whether treatment of elevated homocysteine levels before an individual develops vascular disease will be beneficial is not resolved by these trials of tertiary prevention. Intriguingly, the HOPE study showed a significant decrease in stroke with a relative risk of 0.75 (0.59-0.97) supporting a possible role in modifying vascular disease; this was not shown in the NORVIT trial.

Periodontal disease

Good preventive dental care has multiple benefits, especially on quality of life. Treating periodontal disease has been shown to reduce markers of inflammation such as CRP. However, studies evaluating the effect of preventive dental care or of treatment for periodontal disease on the risk for CHD events have not been conducted.

Electron beam computed tomography and carotid intima media thickness

Lipid lowering therapy has been shown to be associated with slowing of carotid IMT. Conflicting evidence exists regarding the effect of statins on coronary calcification. In a prospective study of 66 asymptomatic patients with a LDL of at least 130, cerivastatin appeared to slow the increase in coronary calcification, though this finding was not statistically significant. This cohort had a baseline EBCT scan and then a 2nd scan after a mean interval of 14 months without treatment. A 3rd scan was performed after a mean of 12 months of treatment with cerivastatin. During the treatment phase the median CACS increased from 199 (23-3118) to 234 (21.6–3124) as compared to an increase during the untreated period of 165 (20.1–2239) to 199 (p=0.07).[242]

In a randomized controlled trial, 20 mg of atorvastatin did not reduce coronary calcification after 4 years as compared to no treatment. In the control group, the mean baseline CACS was 563 (25th percentile 183, 75th percentile 671), and the mean CACS at 4 years was 922 (25th percentile 343, 75th percentile 1138). In the treatment group, the baseline CACS was 528 (184, 636) and

the 4-year CAC was 846 (335-1077). The p-value of the difference between the 2 groups was 0.80.[243]

High sensitivity C-reactive protein

Although large randomized trials are lacking, weight loss, exercise training, or both have been associated with reductions in hsCRP and other inflammatory markers in observational (before/after) studies and a few small controlled trials.[244] Intensive treatment with statins reduces both LDL-C and CRP. For example, in the Pravastatin or Atorvastatin Evaluation and Infection Therapy (PROVE-IT) trial, a randomized trial of atorvastatin 80 mg vs. pravastatin 40 mg in patients with a recent MI, statin treatment resulted in decreased CRP levels, which was independently and significantly correlated with the rate of progression of atherosclerosis.[245] A primary prevention study of rosuvastatin for patients who have an elevated hsCRP is in progress.

Key Question 6. Reliability, Availability of Population Norms, and Cost

The reliability, availability of population norms, and cost can also affect the choice of a new test for routine use in risk assessment. While most of the candidate tests are reliable and inexpensive, there are some exceptions.

Periodontal examination

Assessment of periodontal disease is part of the physical examination. Some studies used self report (e.g., How many teeth do you have? Have you ever been told you had periodontal disease?) as a proxy for periodontal examination. The self-reported number of teeth is a highly accurate measure in the general population.[66] Questions regarding a history of periodontal disease with bone loss are less accurate; among dentists, these questions have a positive predictive value of 0.76 and a negative predictive value of 0.74. The accuracy when asked in primary care is not clear. A periodontal examination requires skill with dental instruments and x-rays to assess for bone loss, depth of pockets, probe depth, gingival inflammation, number of teeth, plaque status and attachment loss. Most studies combined these assessments into scales such as the Periodontal Treatment Need System, the Russell PD Index, and others. The reliability of this examination in primary care has not been assessed.

Electron beam computed tomography

Inter-observer reliability

CAC scores from a given scan assessed by different readers are highly correlated with over 90% inter-observer agreement and correlation coefficients of 0.99.[246-248]

Interscan variation

There is statistically significant variation between two scans performed with close temporal proximity on a given patient. In a study by Yoon, 951 asymptomatic, self-referred patients underwent two consecutive EBCT scans and had coronary calcium scores computed.[248] The mean absolute difference between scans one and two was 19.3 +/- 70. Of 951 subjects, 354 (37%) had identical scores on scans one and two; and 314 (88.7%) of these individuals had coronary calcium scores of zero. In those with no coronary calcification on one of their two scans, the largest difference in coronary calcium score was four in women and nine in men.

The clinical significance of this interscan variation depends on the magnitude of the coronary calcium score and the threshold defining high risk. For example, if the threshold to treat were a coronary calcium score of 100 and a patient's initial scan showed a coronary calcium score of zero, the score from a second scan would be unlikely to approach 100.

Scanner and patient variability

In a study by Nelson, calibration "phantoms" with known concentrations of calcium hydroxyapatite were used to explore variation between different types of EBCT scanners and to examine the effects of certain patient characteristics on coronary calcium scores independent of the actual burden of coronary calcification.[249] Statistically significant variation was found among CAC scores obtained by different EBCT scanners. Likewise, certain patient characteristics, particularly body mass index, were observed to affect quantification of coronary calcium by EBCT.

Nelson's group developed a formula to calibrate EBCT scanners to correct for this variation. Standardizing scores in this fashion changed the actual Agatston score category (0, 1-10, 11-100, 101-400, 401-1000,>1000) in only 3.5% of the study participants. This finding suggests that variation in unadjusted coronary calcium scores due to scanner type or patient characteristics have little clinical impact at the population level but may have a clinically significant effect on an given patient's management if their CACS were near a treatment threshold.[249]

Cost

The cost of an EBCT scan to yield a CAC score is $400-500 per scan.[26]

Lipoprotein(a)

Studies vary in sample handling and storage methods, which have not been standardized, and commercial assays are aimed at research laboratories rather than clinical laboratories. A meta-analysis found that storage temperature was strongly associated with variability in Lp(a) analysis.[187] Much of the inaccuracy of commercial Lp(a) determinations results from the use of techniques sensitive to apoliprotein(a) size.[190] A study by Kronenberg concluded that small apoliprotein(a) isoforms were more susceptible to degradation than large apoliprotein(a) isoforms.[191] The ELISA assay has been reported to underestimate the concentration of Lp(a)

containing small apolipoprotein(a) isoforms.[192] Studies that compared the ELISA and IRMA assay methods reported conflicting levels of agreement between the two assays.[181, 193]

Summary of Evidence About Emerging Risk Factors

Table 7 below summarizes the findings and quality of evidence on the nine risk factors addressed in this review, by key question. *Table 8* characterizes the evidence for each risk factor according to the evaluation framework described above, in Methods. Several emerging risk factors provided independent information about CHD risk, but for most there were limitations in the evidence base. Across all of the criteria listed in *Table 8*, hsCRP and EBCT had the strongest evidence for an independent effect in intermediate-risk individuals, and both reclassify some individuals as high-risk. However, data on EBCT are relatively sparse, it is more expensive, and its potential harms require more investigation. Periodontal disease, carotid IMT, homocysteine, and lp(a) probably provide independent information about CHD risk, but data about their prevalence and impact when added to Framingham risk score in intermediate-risk individuals is limited.

TABLE 7. SUMMARY OF SYSTEMATIC EVIDENCE REVIEW

KQ#	Key Question	Level and Type of Evidence	Quality of Evidence	Comments
1	Compared with Framingham risk factors alone, does risk stratification of asymptomatic adults using novel risk markers (*Table 2*) lead to reduced incidence of cardiovascular events (myocardial infarction, angina, sudden death, cerebrovascular accident), coronary heart disease events, or overall mortality?	None	Not applicable	There is no direct evidence that using a novel risk factor in screening leads to reduced incidence of cardiovascular events.
2	What novel risk markers accurately predict cardiovascular events independent of Framingham risk factors? What is the added predictive value of novel risk markers?	Cohort and nested case control studies	Good-fair for CRP Fair for: Hcy, PD, Lp(a), WBC, FG, carotid IMT Poor for EBCT No evidence for ABI	In large population-based studies that adjusted for all Framingham risk score variables, CRP had a pooled RR of 1.66 (95%CI: 1.37, 2.02) for CRP >3.0 mg/L compared to CRP <1.0 mg/L. Some risk factors (Hcy, PD, Lp[a]) appear to be independently associated with incident CHD, but studies did not clearly establish applicability to the intermediate-risk population. For other risk factors, the results were inconsistent or the association was weak (WBC, FG), or the studies had more serious flaws (WBC, IMT). EBCT studies used unconventional measures for Framingham risk score factors and had self-selected subjects.

2a	What is the prevalence of these risk markers among intermediate-risk and low-risk individuals?	Population-based studies including NHANES	Good for: Hcy, Lp(a), and CRP Fair for: periodontal disease, EBCT Poor for: carotid IMT Not assessed for ABI, WBC, FG.	Reliable prevalence data are available from NHANES for Hcy, Lp(a), and CRP. Limited data on periodontal disease indicators are available in NHANES. Prevalence data for EBCT are limited by uncertain applicability to the general population. Prevalence was not assessed for ABI, WBC, and FG due to lack of evidence of an independent association.
2b	At what frequency does application of these novel risk markers significantly change the 10 year risk of cardiovascular events based on traditional risk factors alone? (e.g., from intermediate risk [10-20%] to high risk [>20%] or to low risk [<10%])	Cohort and nested case control studies for CRP, combined with prevalence data from NHANES	Good for CRP Not applicable for other risk factors	In a prediction model based on good-quality cohort studies, about 31% of men and 6% of women were classified as intermediate-risk of CHD before adjustment for CRP, and about 11% of men and 6% of women originally in the intermediate risk group were reclassified to the high risk category after adjustment for CRP. We did not conduct similar analyses for other novel risk factors due to lack of evidence of an independent association, or uncertain applicability to the target population.
3	What are the harms of risk assessment?	None	Not applicable	We found no direct evidence regarding the harms of risk assessment. One study noted that potential adverse effects of screening with EBCT include increased false positive test results, leading to overuse of invasive diagnostic procedures, but provided no specific data. EBCT for CAC delivers about 1 mSv of radiation exposure, but EBCT scanners have been largely replaced by Multidector CT scanners that deliver 10 times more radiation than EBCT, or 2-4 times more than coronary angiography.
4a	In groups identified as high-risk (>20% 10-year risk) by novel risk markers, does aggressive risk factor modification (treatment to lower blood pressure and lipid targets or more intense counseling) lead to improved intermediate outcomes (e.g., reduction in lipid levels; reduction in blood pressure; increased physical activity; healthy dietary changes, etc.)?	See comments	See comments	There is strong evidence (not addressed in this review) that aggressive risk factor modification improves intermediate outcomes among groups identified as high risk using traditional risk factors alone. It is plausible that aggressive risk factor modification would have a similar effect in individuals identified as high-risk by a combination of traditional and novel risk factors, but we did not find treatment studies conducted in such a group.
4b	In groups identified as high-risk (>20% 10-year risk) by novel risk markers, does aggressive risk factor modification lead to reduced incidence of cardiovascular events (myocardial infarction, angina, sudden death, cerebrovascular accident), cardiovascular disease-specific mortality, overall mortality?	None	Not applicable	We found no trials of aggressive risk factor modification in patients who were classified as high-risk because of novel risk factors, who would otherwise have been treated as intermediate-risk.

5	What are the harms of aggressive risk factor modification?	See comments	See comments	The adverse effects of risk factor modification are described in other USPSTF reports (e.g., Screening for Dyslipidemia in Adults; Screening for Dyslipidemia in Children and Adolescents; Screening and Treatment of Obesity in Adults) and in smoking cessation guidelines. These are available at: http://www.ahrq.gov/clinic/uspstf/uspstopics.htm
6	What are the costs associated with risk factor assessment and aggressive risk factor modification?	None	Not applicable	Most of the tests are inexpensive. In one EBCT study, the cost of an EBCT scan to yield a CAC score was $400-500 per scan. There has been no adequate evaluation of costs associated with additional procedures generated from use of tests for novel risk factors.

Abbreviations: ABI=ankle brachial index, CAC=coronary artery calcium; CRP=C-reactive protein; EBCT=electron beam computed tomography; FG=fasting glucose; FRF=Framingham risk factors; Hcy=homocysteine; IMT=intima media thickness; Lp(a)=lipoprotein(a), NHANES=National Health and Nutrition Examination Survey, PD=periodontal disease, RR=relative risk, USPSTF=United States Preventive Services Task Force, WBC=white blood cell count.

TABLE 8. ASSESSMENT OF THE STRENGTH OF EVIDENCE AND MAGNITUDE OF BENEFIT

Validity of evidence						*Net benefit or harm*				
Evidence on independent effect after controlling for Framingham factors						**Magnitude of effect ***	**Prevalence**	**Other considerations**		
Number of cohorts	Study design	Limitations (aggregate quality)	Consistency	Applicability (intermediate-risk individuals in the general population)	Other †	Adjusted relative risk (95% CI)	Prevalence in intermediate-risk individuals in the general population	Reliability, population norms, and cost	Treatment effects?	Harms
Ankle-brachial index										
0	Cohort	Serious limitations ‡	No important inconsistency	Significant uncertainty ‡	None	Not assessed	Not assessed	Not assessed		
C-reactive protein										
18	Cohort & Nested Case-Control	Some limitations	No important inconsistency	Good	+Dose-response	1.64 (1.41-1.91) for >3.0 v. <1.0	Good (NHANES) and others	Reliable; Inexpensive	See note §	Low or none
Carotid intima media thickness										
5	Cohort	Some limitations	No important inconsistency	Some uncertainty ‖	Sparse data	1.19 to 3.8	Poor Evidence	Not assessed	Unclear (for cardiac effects)	Unclear
Electron beam computed tomography										
9 ‖	Cohort	Serious limitations ¶	No important inconsistency	Significant uncertainty (patients, outcome measure) ‖	Sparse data	2.56 (1.96, 3.35) for 1-100 v. 0 5.35 (3.13, 9.16) for 101-400 v. 0 8.01 (4.81, 13.33) for >400 v. 0	Fair Evidence	Relatively low reliability; No norms for general population; Expensive	Conflicting evidence	Significant potential harms
Fasting glucose										
10	Cohort	Some limitations	Some inconsistency	Some uncertainty ‖	Weak or absent association	None or small	Not assessed	Not assessed		

TABLE 8. ASSESSMENT OF THE STRENGTH OF EVIDENCE AND MAGNITUDE OF BENEFIT

Validity of evidence						*Net benefit or harm*				
Evidence on independent effect after controlling for Framingham factors						**Magnitude of effect ***	**Prevalence**	**Other considerations**		
Number of cohorts	Study design	Limitations (aggregate quality)	Consistency	Applicability (intermediate - risk individuals in the general population)	Other †	Adjusted relative risk (95% CI)	Prevalence in intermediate-risk individuals in the general population	Reliability, population norms, and cost	Treatment effects?	Harms
Homocysteine										
24	Cohort & Nested Case-Control	Some limitations	Some inconsistency	Significant uncertainty‖	None	1.18 (1.10-1.26) all studies & 1.21 (1.10-1.32) CHD explicitly excluded, per 5 µmol increase	Good (NHANES)	Reliable; inexpensive	Folate decreases serum levels but effect on CHD unknown	Low or none
Lipoprotein(a)										
21	Cohort & Nested Case-Control	Some limitations	No important inconsistency	Significant uncertainty (patients, outcome measure)	None	1.57 (1.31-1.88) for 30+ v. <30 mg/dL	Good (NHANES)	Low reliability; No standard commercial assay	Unclear	Low or none
Periodontal disease										
7	Cohort	Some limitations	No important inconsistency	Some uncertainty‖	None	1.24 (1.01-1.51)	Fair Evidence	Uncertain reliability; Inexpensive	Unclear	Unclear
White blood cell count										
10	Cohort & Nested Case-Control	Some limitations	Inconsistent results	Some uncertainty‖	Plausible confounders	1.01 to 2.10	Not assessed	Reliable; Inexpensive	No evidence	Low or none

*Table 8 shows a single risk ratio with 95% confidence interval if we conducted a meta-analysis for the risk factor. A range of point estimates indicates the highest and lowest risk ratios reported among studies that were not combined in meta-analysis.

†Negative factors include: imprecise or sparse data; high risk of reporting bias; effect of plausible residual confounding; a weak or absent association. Positive factors include: a strong or very strong association; evidence of a dose-response gradient.

‡ No studies were eligible because of: (1) inclusion of subjects with known coronary artery disease or symptomatic peripheral vascular disease, or (2) coronary heart disease events were not reported as an endpoint.
§Weight reduction, statins, and other interventions reduce c-reactive protein. Evidence linking c-reactive protein changes to coronary heart disease events is limited.
‖ Studies did not establish applicability of results to intermediate-risk individuals.
¶ Most studies had self-selected patients. Not evaluated in the major population-based cohorts. Use of self-report for Framingham risk factors could inflate estimates of the contribution of coronary artery calcification score. Results given are for two population-based, good-quality cohort studies.

Abbreviations: CHD=coronary heart disease, NHANES=National Health and Nutrition Examination Survey.

Key Questions 2b, 4, and 5. Predicting the Potential Impact of Testing on Reclassification and Coronary Events

Direct evidence of the impact of testing for CRP on CHD events is not presently available. To examine the potential impact of CRP testing, we developed a model to estimate the impact of using a CRP test to stratify individuals classified as intermediate-risk based on the NCEP/ATP III risk equation. The methods we used to develop this model are described in detail above (II. Methods).

We extracted data for 5,335 survey participants, age 40 to 79 years, from the combined NHANES 1999-2000 and NHANES 2001-2002 datasets. Of these, 2,665 were men (weighted population n, 51,691,227), and 2,670 were women (weighted population n, 57,329,733). Population weights were age-adjusted using the reference population from year 2000 census data. We excluded 258 males (weighted n, 3,972,053) and 158 women (weighted n, 2,772,778) with prior cardiovascular events or CHD-equivalents (angina, stroke, congestive heart failure, diabetes). We also excluded 900 participants with incomplete data, including 622 who did not have complete Framingham risk factor data, and 278 who did not have hsCRP data.

The remaining 4,019 participants consisted of 1,949 men (weighted n, 39,055,881) and women and 2,070 women (weighted n, 45,382,856). The weighted mean age of men was 53.7 years and 55.2 years for women. Among both men and women, about 77 % were White-American, 9% were Black-Americans, and 11% were Hispanic-Americans, with other racial and ethnic groups accounting for the remaining 3%. Altogether the included participants represented 78% of the standard age-adjusted reference population of 109 million individuals aged 40-79 years based on year 2000 census estimates.

Risk Distribution (RD) Table 11 describes the characteristics of the 1,949 included men classified into three CRP categories, hsCRP< 1.0 mg/L, hsCRP 1.0-3.0 mg/L, and hsCRP >3.0 mg/L. Men with elevated hsCRP tended to be older, had higher total cholesterol and lower HDL cholesterol, higher systolic blood pressure, were more likely to be treated for hypertension, and are more likely to smoke. Among men, between 13.3% and 16.5% were also taking medication to lower cholesterol, a non-significant difference, although the intensity of treatment might have varied across categories. This could impact the 10-year risk of CHD events, however, cholesterol treatment is not incorporated in the ATP III risk prediction equation. As expected, based on the higher burden of traditional Framingham CHD risk factors, the baseline risk of expected CHD events at 10 years significantly increases as hsCRP increases. *RD Table 12* shows similar patterns of characteristics for 2,070 women across each hsCRP category, except that the prevalence of smoking in women is relatively the same across categories.

RD Tables 11 and 12 also show the distribution of hsCRP values by race and ethnicity. Black American men had a significantly higher prevalence of hsCRP > 3 mg/L than Hispanic American men. A higher prevalence of elevated hsCRP (> 3 mg/L) was seen in both Black American and Hispanic American women compared to White American women. There were too few survey participants to reliably estimate prevalence for other racial or ethnic groups (e.g., Asian Americans, Native Americans).

CRP might be used in two different ways to improve risk stratification and primary prevention in the general population. One approach would be to obtain serum hsCRP levels on all individuals. This approach might be preferred if a large proportion of individuals in each category would be reclassified by adding hsCRP to initial screening. *RD Table 13* shows how, using this strategy, the proportion of individuals classified as low (predicted 10-year risk of events <10%), intermediate (10-20%), or high risk (> 20%) changes when hsCRP is included in the risk prediction equation. The clinical endpoint used in the model was the number of CHD events averted over 10 years. Overall, the proportion of men classified as high risk increased from 9.1 (8.1, 10) to 10.8 (CI 9.5, 12.0), and the proportion of women classified as high risk increased from 0.7 (0.0, 1.1) to 1.0 (0.0, 3.0). The pattern of changes in the low-risk and intermediate-risk groups was inconsistent across age, sex, and racial subgroups.

A second strategy is to use hsCRP to further stratify intermediate-risk individuals, but not to test individuals who are initially classified as low-risk or high-risk. Before adjustment for hsCRP, 30.7% of men (n, 737; weighted n, 11,981,854) and 7.0% of women (n, 168; weighted n, 3,196,119) were classified as intermediate-risk for CHD events (*RD Table 13*). *RD Table 14* shows the impact of testing for hsCRP in this group. CRP testing in men with intensive risk-reduction therapy of those reclassified from the intermediate to the high-risk category could potentially avert 47.8 CHD events over 10 years per 1,000 events in men age 40 to 79. We assumed that individuals reclassified from the intermediate-risk to high-risk category after adjusting for CRP-associated risk would receive aggressive risk-reduction therapy, with an efficacy of 30% in reducing the risk of future CHD events, and assumed 100% patient adherence with treatment.

In a sensitivity analysis using the lower and upper confidence intervals for the combined risk ratio from the meta-analysis, the estimated number of CHD events averted ranged from 19.2 per 1000 events to 78.5 per 1000 events in men age 40 to 79 years. Too few women age 40 to 49 years were reclassified to the higher risk group to reliably predict any potential of benefit of CRP testing. Among women (weighted n) from the NHANES 1999-2002 study classified in the intermediate (10-20%) risk category based on traditional Framingham risk factors, only 10 women were reclassified to the high risk group after adjustment for CRP-associated risk. *RD Table 15* shows the characteristics of men who were reclassified from the intermediate risk to the high risk group compared to those remaining in the intermediate risk group after adjustment for CRP. Men in the higher risk group were older, had higher total weighted mean total cholesterol, higher weighted mean systolic blood pressure, and tended to be more likely to take cholesterol and blood-pressure lowering medications.

To place these findings in perspective, we applied the same model to examine a hypothetical blood pressure reduction strategy. Among 737 men and 186 women in the intermediate risk category, based on Framingham risk factors only, 128 men and 45 women had systolic blood pressures > 140 mm Hg (Stage 1 hypertension) and were not taking hypertension medications. The weighted mean systolic blood pressure in these individuals was 151.6 for men (95% CI, 146.8 to 156.4), and 163.7 for women (95% CI, 159.6 to 167.9). We assumed a 10-year risk reduction for CHD events of 21% (95% CI, 8% to 31%), based on a meta-analysis of clinical trials comparing low-dose diuretics with placebo for hypertension treatment.[250] Among all ages, assuming 100% patient adherence, hypertension therapy in this group could potentially avert 31.9 (95% CI, 12.2 to 47.1) CHD events at 10 years per 1000 men and 27.5 (95% CI, 10.5 to

40.6) CHD events at 10 years per 1000 women. Because there is strong evidence for the benefit of blood pressure screening and treatment as a primary prevention strategy for CVD,[251] this strategy would be appropriate for all patients with untreated hypertension in the intermediate risk group.

Summary

We found that elevated CRP is significantly associated with elevated levels of other CHD risk factors, as has been reported previously for the NHANES population.[198] This may explain our finding that incorporating the increased risk for CHD associated with CRP might have little impact in improving global risk assessment for CHD in the US. These findings substantiate those of previous studies that conclude that obtaining CRP measurements as a part of routine CHD risk factor assessment for all individuals may not improve global assessment of CVD risk in the population.[198, 219]

An important issue, however, is whether selected individuals could potentially benefit from improved CHD risk stratification based on CRP measurement. The 2003 consensus statement from a joint committee of the AHA and the CDC recommended that CRP measurements may be considered as another risk factor in guiding therapy specifically for those individuals with a 10-20% 10-year CHD risk based on traditional risk factors.[16] Soon afterwards, an updated meta-analysis of epidemiologic studies of CRP found that earlier estimates of its predictive ability were inflated, leading to reconsideration of the consensus conference's recommendations.[205]

Our analysis suggests that, using estimates of relative risk based on recent epidemiologic studies that had more complete adjustment for confounders, CRP measurement may be useful in this context for men. We found that that adding hsCRP testing for men with intermediate 10-20% 10-year CHD risk could potentially avert 47.8 hard CHD events (fatal or non-fatal MIs) over 10 years in men.

There were too few women in the intermediate risk group who were reclassified into the high risk group to reliably predict potential CHD events averted. We think this is largely explained by the finding that over 90% of women in this large population-based survey fall into the low risk category (< 10% 10-year CHD risk) based on traditional Framingham risk factors alone. It is conceivable that among women age 70-79 years, of whom 30.6% fall into the intermediate risk category, some could potentially benefit from reclassification based on elevated CRP measurements, however there are too few women in the NHANES 1999-2002 data to assess this.

This study is useful because it examines the burden of CHD risk and first CHD events that may relate to elevated CRP among NHANES 1999-2002 participants, a well-studied cross-sectional survey population representative of the US adult population. Studies of CRP in specific populations are useful in assessing the relative risk associated with this biomarker of inflammation.[204, 207, 217, 252] Our model builds on previous studies using NHANES III survey data to study the population distribution of CHD risk in US adults,[253] and to assess the public health impact of treatment for borderline levels of traditional CHD risk factors based on the attributed risk of first CHD events related these.[12] An earlier, unpublished model we developed using CRP data from the NHANES III survey, that did not use the presently available hsCRP assay, found similar results to the model presented here.

A particular strength of this study is that we are able to focus attention on specific segments of the larger population that may receive the most benefit from CRP measurement. While our findings should be examined further in prospective, population-based studies, they indicate that CRP measurement could play an important role in improving the prediction of CHD risk in a large segment of the US male population. Our model would also be applicable to understanding the potential benefits of other novel risk factors. For example, we also had sufficient information from our evidence review to model potential benefits for homocysteine testing, however, this data was not available in the NHANES 1999-2002 data set.

The clinical utility of measuring CRP, however, arises from the potential benefit of treatment for those identified with elevated with CRP. It is presently not clear that any treatments are effective in reducing excess CHD risk that may attributable to elevated CRP. It has also been proposed that knowledge about elevated CRP levels may be useful in encouraging therapeutic lifestyle change in some individuals.[223, 252] Conversely, a low CRP level could provide false reassurance that lifestyle change is not needed. Finally, if a lower CRP level leads to lower estimated risk of first CHD events in relation to assessment with traditional risk factors, there is presently no evidence supporting a less aggressive approach to medical management than recommended by NCEP/ATP III guidelines.

This study has several limitations. We used several "best-case" assumptions about the effectiveness of treatment. The first is that individuals reclassified as high-risk by a high CRP level would benefit as much from aggressive treatment as other high-risk individuals. The second is that we applied the risk reduction in CHD events from aggressive risk reduction management, observed in controlled trials over 2 to 5 years, to the entire 10-year risk of events. This assumption could be wrong if the benefits of aggressive treatment dissipate 5 to 10 years after initiation. Third, we assumed that the relative risk reduction from trials of statin therapy reflects the balance of benefits and harms in the population that would be identified by a CRP. In fact, many of these trials are selected for characteristics associated with a lower rate of adverse events and a higher compliance rate than would be observed in the general population.

There are other factors that influence the potential benefits of CRP testing that our model does not account for. For example, about 1 in 5 men who were reclassified from the intermediate risk to the high risk group (*RD Table 15*) were already taking cholesterol lowering medication. A comparison of serum lipoprotein levels in adults over 20 years of age between the NHANES III data (1988-1994) and more recent NHANES 1999-2002 data showed a significant decrease in LDL cholesterol levels, but no change in HDL cholesterol levels.[254] This change was observed despite a significant increase in the prevalence of obesity and minimal changes in total dietary cholesterol. Over this same time, however, there was a significant increase in the proportion of US adults taking cholesterol lowering medications from 3.4% in 1988-1994 to 9.3% in 1999-2002. Present NCEP/ATP III treatment recommendations classify individuals into a number of different subgroups based on CHD risk factors and LDL cholesterol levels.[3] The NCEP/ATP III risk prediction equation does not consider cholesterol treatment. If men reclassified from the intermediate to the high risk group were already receiving treatment of elevated cholesterol, then the incremental benefit of aggressive risk-reduction therapy could be lower than that predicted by our model.

We also found that a significant number of first CHD events might be averted in both men and women by applying accepted primary prevention strategies such as blood pressure screening and treatment. About 17% of men and 24% of women falling into the intermediate risk category had at least Stage I hypertension (systolic blood pressure >140), but were not taking blood pressure lowering medication. Among men in particular, this would be expected to lower the overall risk of 10-year CHD events in the intermediate risk category. As a result, there would likely be fewer men reclassified as high risk after adjustment for CRP. Tobacco cessation counseling and treatment is another effective and cost-effective CHD primary prevention strategy that would lead to a significantly fewer first CHD events over 10 years, but has yet to be fully integrated into most clinical practices.[255-257]

We applied the NCEP/ATP III risk prediction equation, based on Framingham risk calculations, to predict CHD risk in a multi-racial, multi-ethnic population. We choose this approach in order to study risk distributions in participants who were more representative of the broader US population rather than limit our study to whites only. The Framingham CHD prediction algorithm has been validated and appears reasonably accurate in other racial/ethnic groups, excepting Hispanic men in whom the Framingham risk prediction scores overestimate CHD risk.[7] In our study, we did not find that Hispanic men had a significantly higher estimated 10-year CHD risk than other racial/ethnic groups, and excluding Hispanic men did not change the distribution of CHD risk before and after CRP adjustment in the remainder of the study population. Adjustment for CRP-related risk also did not change the distribution of CHD risk among Hispanic men.

While our findings should be examined further in prospective, population-based studies, our analysis indicates that CRP measurement could play an important role in improving the prediction of CHD risk in a large segment of the US male population with 10-20% 10-year risk of first CHD events.

IV. DISCUSSION

Future Research Recommendations

Table 9 summarizes future research recommendations from this review.

TABLE 9. SUMMARY OF FUTURE RESEARCH RECOMMENDATIONS

Risk factor	Research recommendations
Ankle-brachial index	None.
Carotid intima media thickness	Epidemiologic cohorts that have measured carotid IMT should measure the impact of carotid IMT on prediction of CHD events among intermediate-risk individuals and on reclassification of these individuals. It is highly plausible that intervention directed toward modification of traditional risk factors in individuals with increased carotid IMT might reduce the risk of subsequent CHD. Randomized controlled trials are needed to evaluate this hypothesis.
C-reactive protein	Trials of aggressive risk factor modification in asymptomatic patients who have elevated CRP levels are underway. Additional information from cohort studies in racial and ethnic minority populations is needed.
Electron beam computed tomography	Better studies of the accuracy of different protocols for EBCT scanning and methods for CAC scoring are needed. A broader range of cohort studies are needed to define the prevalence and impact of CAC scoring by EBCT in the general population. Clinical trials of aggressive versus less aggressive risk factor modification for individuals who have high CAC scores are unlikely to be acceptable ethically. For this reason, trials should compare a comprehensive risk assessment and follow-up strategies that do and don't include EBCT testing.
Fasting glucose	None.
Homocysteine	Although homocysteine is well-studied, most research to date has focused on whether elevated homocysteine is a causal factor, rather than simply a marker of elevated CHD risk. Epidemiologic cohorts could measure the impact of elevated homocysteine levels on prediction of CHD events among intermediate-risk individuals and on reclassification of these individuals.
Lipoprotein(a)	Additional epidemiologic research is needed in racial and ethnic minority groups. Additional development of reliable, stable assays is needed before clinical applications are practical.
Periodontal disease	The weight of currently existing evidence suggests that there may be an important link between periodontal disease and CHD. Additional longitudinal studies with standardized measures of periodontal disease and careful adjustment for socioeconomic status as well as for traditional CHD risk factors would be useful. To definitively link CHD and periodontal disease etiologically will require randomized controlled trials in which individuals are randomized to treatment versus no treatment of periodontal disease and followed carefully for CHD outcomes. However, a short-term trial may not definitively answer the etiologic question as it is highly plausible that long term exposure to

Risk factor	Research recommendations
	periodontal disease might be more predictive of subsequent CHD. Thus, the best intervention trial would be one that began in early childhood rather than adult life.
White blood cell count	None.

Abbreviations: CAC=coronary artery calcification, CHD=coronary heart disease, CRP=c-reactive protein, EBCT=electron beam computed tomography, IMT=intima media thickness.

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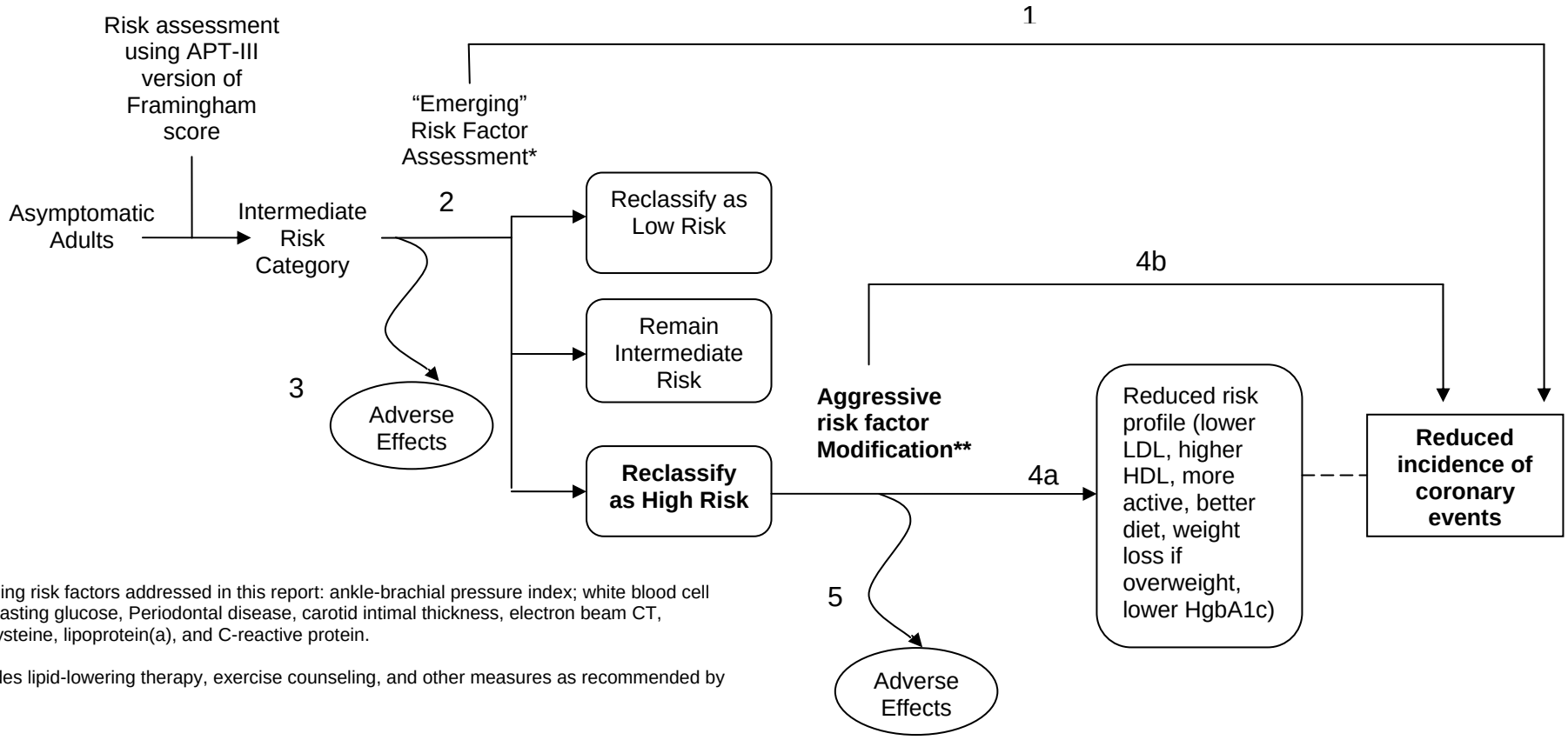
FIGURE 1. ANALYTIC FRAMEWORK AND KEY QUESTIONS



*Emerging risk factors addressed in this report: ankle-brachial pressure index; white blood cell count; fasting glucose, Periodontal disease, carotid intimal thickness, electron beam CT, homocysteine, lipoprotein(a), and C-reactive protein.

**Includes lipid-lowering therapy, exercise counseling, and other measures as recommended by NCEP

KEY QUESTIONS

1. Compared with Framingham risk factors alone, does risk stratification of asymptomatic adults using novel risk markers lead to reduced incidence of cardiovascular events (myocardial infarction, angina, sudden death, cerebrovascular accident), coronary heart disease events, or overall mortality?
2. What novel risk markers accurately predict cardiovascular events independent of Framingham risk factors? What is the added predictive value of novel risk markers?
   a) What is the prevalence of these risk markers among intermediate-risk and low-risk individuals?
   b) At what frequency does application of these novel risk markers significantly change the 10 year risk of cardiovascular events based on traditional risk factors alone? (e.g., from intermediate risk [10-20%] to high risk [>20%] or to low risk [<10%])
3. What are the harms of risk assessment?
4. a) In groups identified as high-risk (>20% 10-year risk) by novel risk markers, does aggressive risk factor modification (treatment to lower blood pressure and lipid targets or more intense counseling) lead to improved intermediate outcomes (e.g., reduction in lipid levels; reduction in blood pressure; increased physical activity; healthy dietary changes etc)?
   b) Does improvement in intermediate outcomes lead to reduced incidence of cardiovascular events (myocardial infarction, angina, sudden death, cerebrovascular accident), cardiovascular disease-specific mortality, overall mortality?
5. What are the harms of aggressive risk factor modification?
6. What are the costs associated with risk factor assessment and aggressive risk factor modification?

FIGURE 2. SEQUENTIAL EVALUATION SCHEME FOR EACH RISK FACTOR

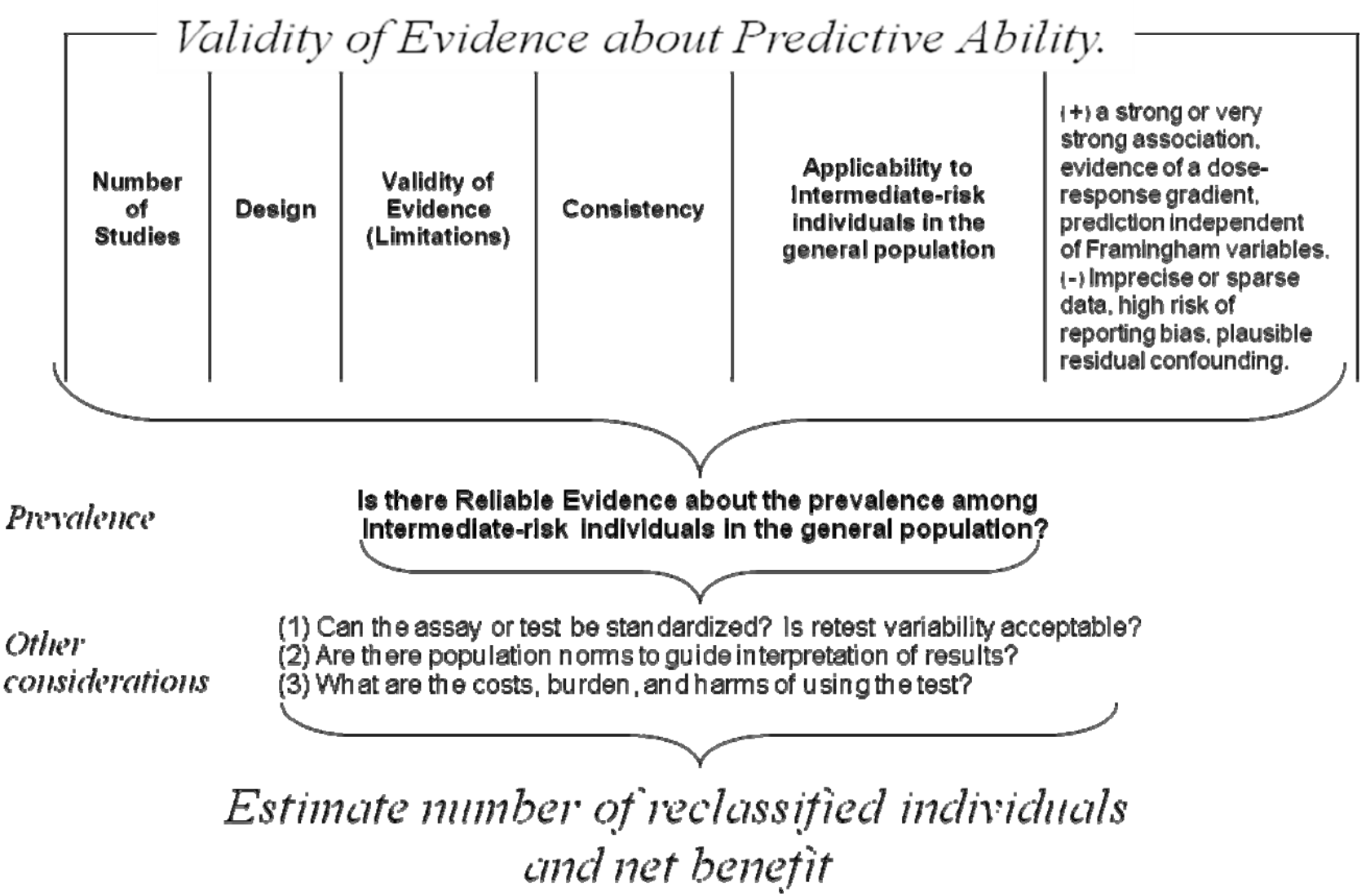
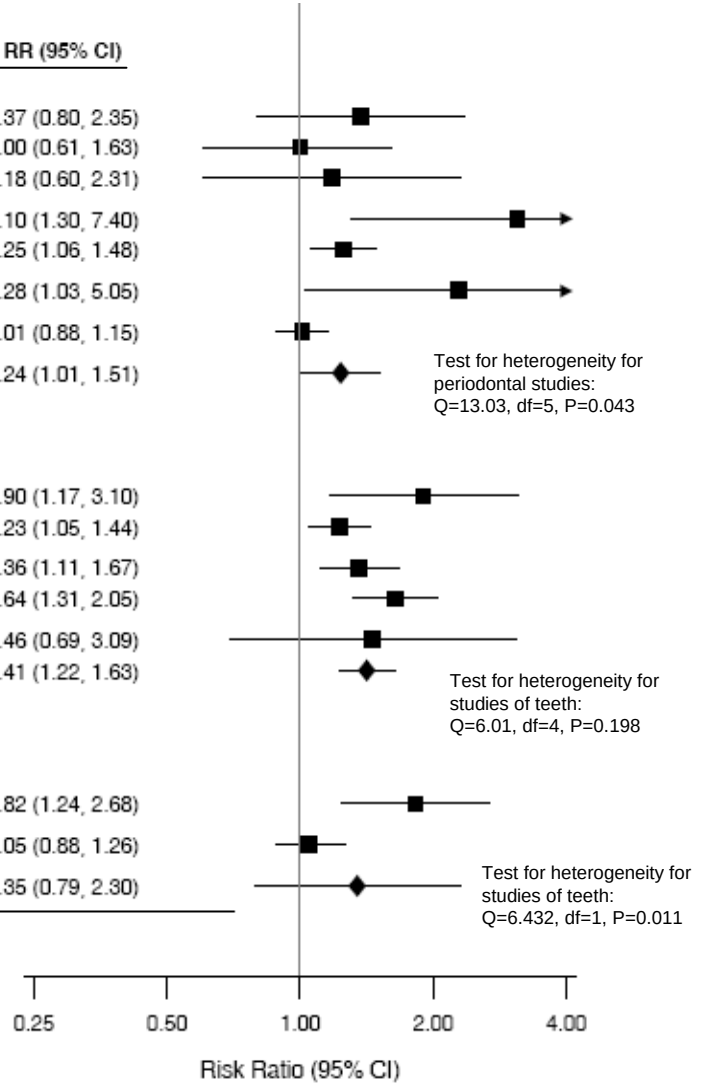


FIGURE 3. STUDY CHARACTERISTICS AND RISK RATIOS OF CHD ASSOCIATED WITH DIFFERENT CATEGORIES OF PERIODONTAL DISEASE

	Outcome	Number of Subjects*	Risk Factor Measurement	Quality	Gender	Followup (in yrs)	RR (95% CI)
Risk Factor = Periodontitis							
Morrison, 1999	CHD Death	2297	Dental exam	Fair	B	21	1.37 (0.80, 2.35)
Tuominen, 2003 (M)	CHD Death	2518	Dental exam	Fair	M	12	1.00 (0.61, 1.63)
Tuominen, 2003 (F)	CHD Death	2392	Dental exam	Fair	F	12	1.18 (0.60, 2.31)
Beck, 1996	CHD Events	1221	Dental Exam	Fair	M**	18	3.10 (1.30, 7.40)
DeStefano, 1993	CHD Events	5041	Dental Exam	Good	B	14	1.25 (1.06, 1.48)
Ajwani, 2003	CVD Death	175	Dental Exam	Fair	B**	5	2.28 (1.03, 5.05)
Howell, 2001	CVD Events	22037	Self report	Fair	M	12	1.01 (0.88, 1.15)
Periodontitis Studies Combined							1.24 (1.01, 1.51)
Risk Factor = 0-10 teeth							
Morrison, 1999	CHD Death	3330	Dental exam	Fair	B	21	1.90 (1.17, 3.10)
DeStefano, 1993	CHD Events	5398	Dental Exam	Good	B	14	1.23 (1.05, 1.44)
Hung, 2004 (M)	CHD Events	41407	Self report	Good	M	12	1.36 (1.11, 1.67)
Hung, 2004 (F)	CHD Events	58974	Self report	Good	F**	20	1.64 (1.31, 2.05)
Ajwani, 2003	CVD Death	175	Dental Exam	Fair	B**	5	1.46 (0.69, 3.09)
Studies of 0-10 Teeth Combined							1.41 (1.22, 1.63)
Risk Factor = Gingivitis							
Morrison, 1999	CHD Death	3921	Dental exam	Fair	B	21	1.82 (1.24, 2.68)
DeStefano, 1993	CHD Events	5537	Dental Exam	Good	B	14	1.05 (0.88, 1.26)
Gingivitis Studies Combined							1.35 (0.79, 2.30)



*Number of subjects included in the analysis
Abbreviations: B=both genders, F=female, M=male.

FIGURE 4. RISK RATIOS OF CHD ASSOCIATED WITH PERIODONTAL DISEASE, BY SELECTED CHARACTERISTICS

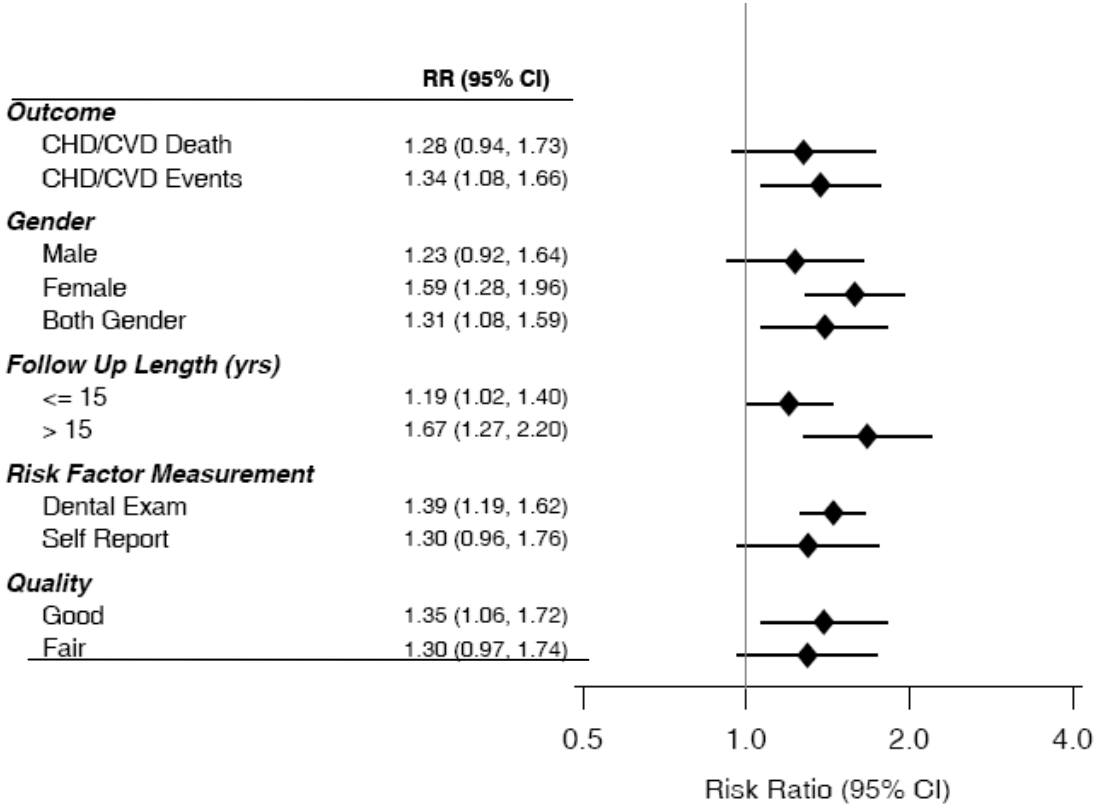
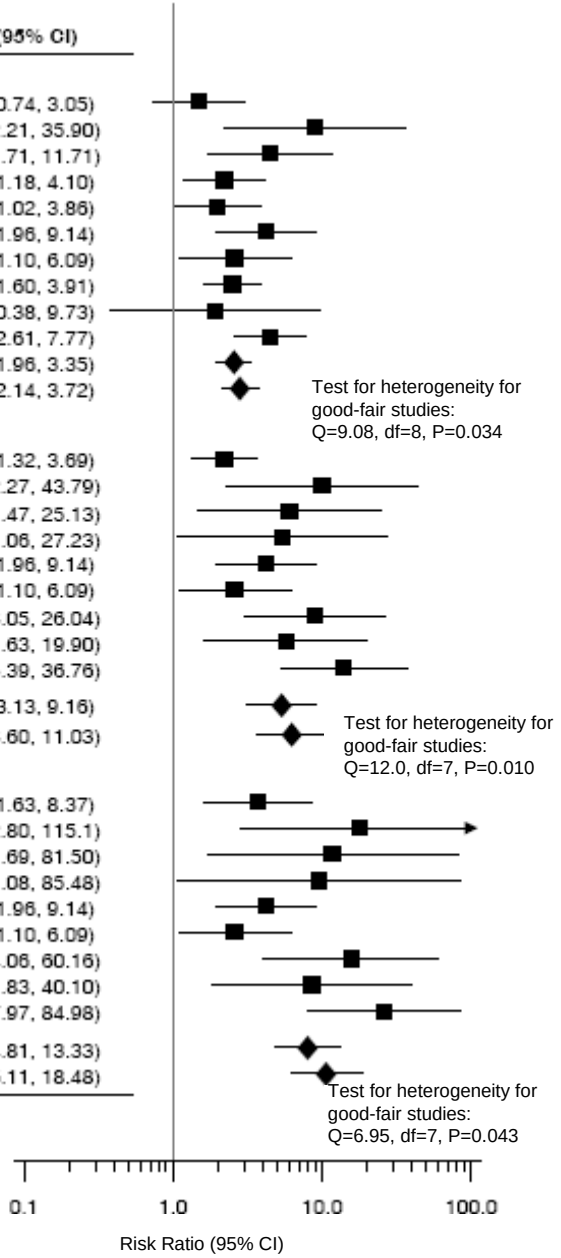


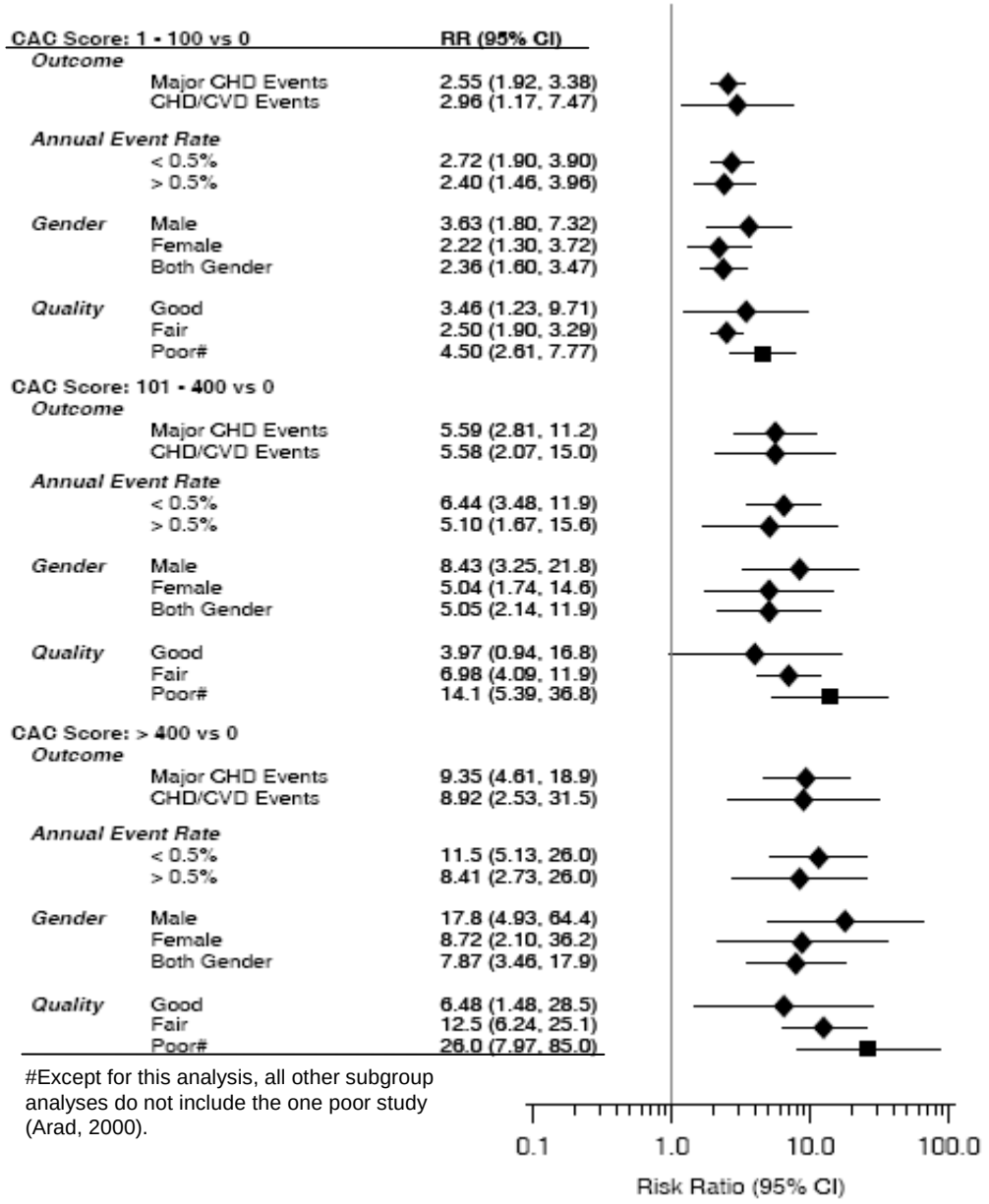
FIGURE 5. STUDY CHARACTERISTICS AND RISK RATIO OF CHD ASSOCIATED WITH CORONARY ARTERY CALCIUM (CAC) SCORE CATEGORIES

	Quality	Outcome	Number of Subjects*	%Male	Followup (in yrs)	Annual*** Event Rates	Measurement of Risk Factors	RR (95% CI)
CAC Score: 1 - 100 vs 0								
Greenland, 2004	Good	Major CHD Events	1029	90	6.3	0.82%	Measured	1.50 (0.74, 3.05)
Taylor, 2005	Good	CHD Events	1627	100	3.0	0.18%	Measured	8.91 (2.21, 35.90)
Vliegenthart, 2005	Good	Major CHD Events	1795	42.5	3.3	0.70%	Measured	4.47 (1.71, 11.71)
Kondos, 2003 (Male)	Fair	Major CHD Events	4151	100	3.1	0.40%	PT history**	2.20 (1.18, 4.10)
Kondos, 2003 (Female)	Fair	CHD Events	1484	0	3.1	0.10%	PT history	1.99 (1.02, 3.86)
LaMonte, 2005 (Male)	Fair	Major CHD Events	6835	100	3.5	0.26%	PT history	4.23 (1.96, 9.14)
LaMonte, 2005 (Female)	Fair	Major CHD Events	3911	0	3.5	0.14%	PT history	2.59 (1.10, 6.09)
Raggi, 2001	Fair	Major CHD Events	676	51	2.7	1.60%	PT history	2.50 (1.60, 3.91)
Wong, 2000	Fair	CVD Events	926	79	3.3	0.30%	PT history	1.92 (0.38, 9.73)
Arad, 2000	Poor	CHD Events	1172	71	3.6	0.20%	PT history	4.50 (2.61, 7.77)
Fair-Good Studies Combined								2.56 (1.96, 3.35)
All Studies Combined								2.82 (2.14, 3.72)
CAC Score: 101 - 400 vs 0								
Greenland, 2004	Good	Major CHD Events	1029	90	6.3	0.82%	Measured	2.21 (1.32, 3.69)
Vliegenthart, 2005	Good	Major CHD Events	1795	42.5	3.3	0.70%	Measured	9.97 (2.27, 43.79)
Kondos, 2003 (Male)	Fair	Major CHD Events	4151	100	3.1	0.40%	Measured	6.07 (1.47, 25.13)
Kondos, 2003 (Female)	Fair	CHD Events	1484	0	3.1	0.10%	PT history	5.39 (1.06, 27.23)
LaMonte, 2005 (Male)	Fair	Major CHD Events	6835	100	3.5	0.26%	PT history	4.23 (1.96, 9.14)
LaMonte, 2005 (Female)	Fair	Major CHD Events	3911	0	3.5	0.14%	PT history	2.59 (1.10, 6.09)
Raggi, 2001	Fair	Major CHD Events	676	51	2.7	1.60%	PT history	8.91 (3.05, 26.04)
Wong, 2000	Fair	CVD Events	926	79	3.3	0.30%	PT history	5.70 (1.63, 19.90)
Arad, 2000	Poor	CHD Events	1172	71	3.6	0.20%	PT history	14.1 (5.39, 36.76)
Fair-Good Studies Combined								5.35 (3.13, 9.16)
All Studies Combined								6.30 (3.60, 11.03)
CAC Score: > 400 vs 0								
Greenland, 2004	Good	Major CHD Events	1029	90	6.3	0.82%	Measured	3.70 (1.63, 8.37)
Vliegenthart, 2005	Good	Major CHD Events	1795	42.5	3.3	0.70%	Measured	18.0 (2.80, 115.1)
Kondos, 2003 (Male)	Fair	Major CHD Events	4151	100	3.1	0.40%	Measured	11.7 (1.69, 81.50)
Kondos, 2003 (Female)	Fair	CHD Events	1484	0	3.1	0.10%	PT history	9.65 (1.08, 85.48)
LaMonte, 2005 (Male)	Fair	Major CHD Events	6835	100	3.5	0.26%	PT history	4.23 (1.96, 9.14)
LaMonte, 2005 (Female)	Fair	Major CHD Events	3911	0	3.5	0.14%	PT history	2.59 (1.10, 6.09)
Raggi, 2001	Fair	Major CHD Events	676	51	2.7	1.60%	PT history	15.6 (4.06, 60.16)
Wong, 2000	Fair	CVD Events	926	79	3.3	0.30%	PT history	8.57 (1.83, 40.10)
Arad, 2000	Poor	CHD Events	1172	71	3.6	0.20%	PT history	26.0 (7.97, 84.98)
Fair-Good Studies Combined								8.01 (4.81, 13.33)
All Studies Combined								10.6 (6.11, 18.48)



*Number of subjects included in the analysis
**__Abbreviations__: PT=patient.
***Annual rate of major CHD events for the entire cohort.

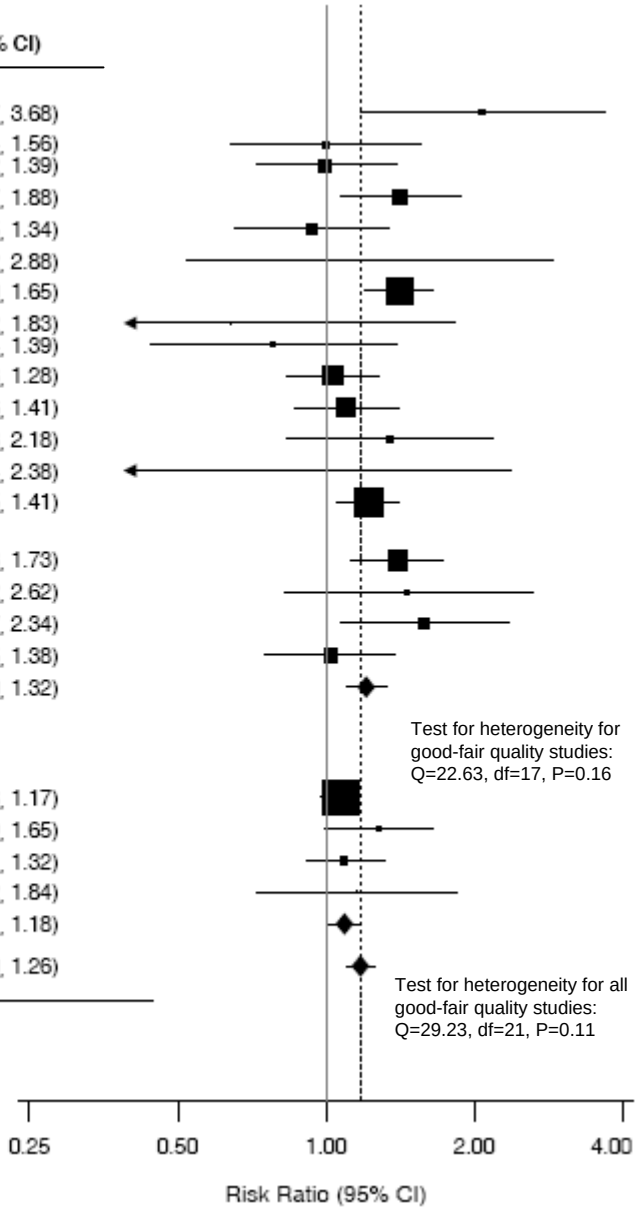
FIGURE 6. SUBGROUP ANALYSIS OF RISK RATIO OF CHD ASSOCIATED WITH CORONARY ARTERY CALCIUM (CAC) SCORE CATEGORIES



#Except for this analysis, all other subgroup analyses do not include the one poor study (Arad, 2000).

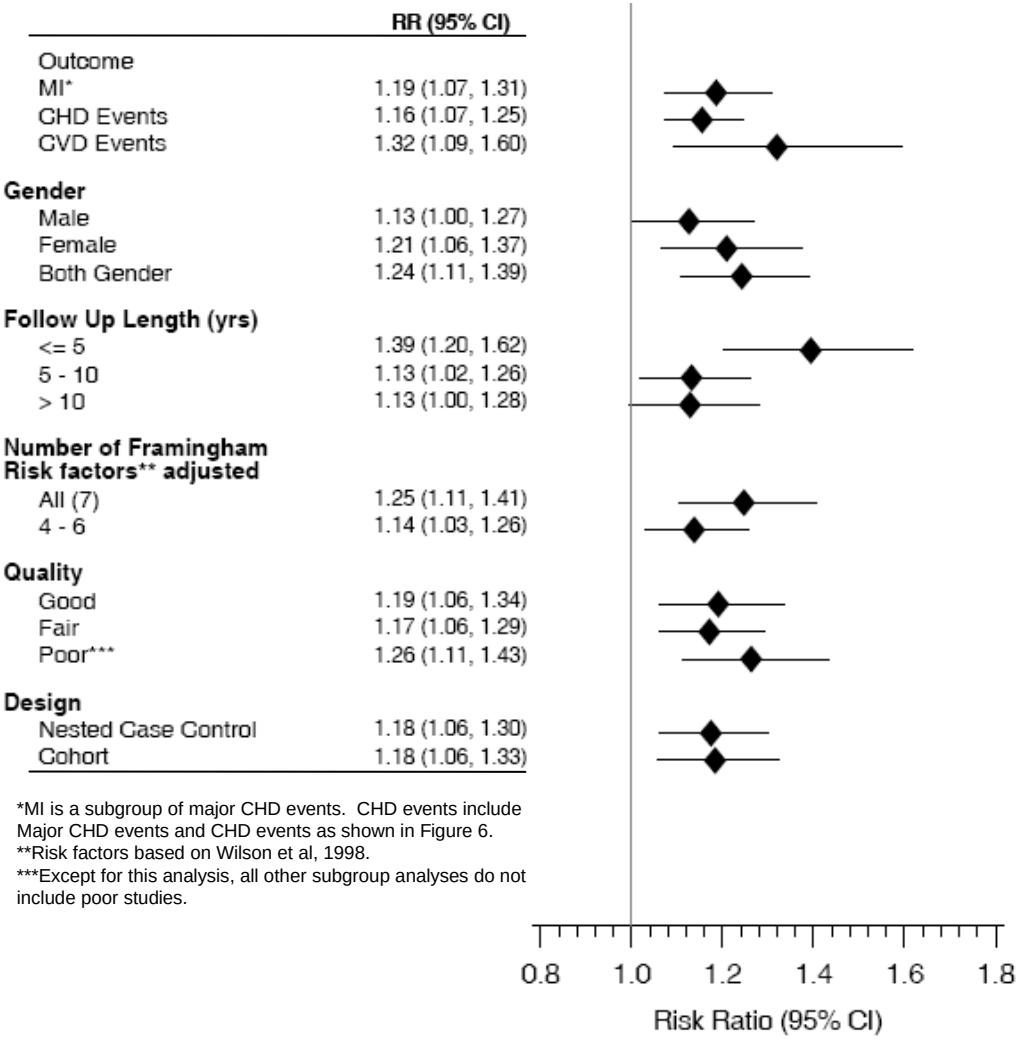
FIGURE 7. STUDY CHARACTERISTICS AND RISK RATIO OF CHD ASSOCIATED WITH EVERY 5 µmol INCREASE OF HOMOCYSTEINE

	Outcome*	Number of Subjects**	Design	Quality	Gender	Followup (in yrs)	RR (95% CI)
Baseline CHD/CVD Explicitly Excluded							
Stampfer, 1992	CHD Events	542	NCC	Good	M	7	2.08 (1.17, 3.68)
Alfthan, 1994	CHD Events	460	NCC***	Fair	F M	9	1.00 (0.64, 1.56) 1.00 (0.72, 1.39)
Arnesen, 1995	CHD Events	600	NCC	Fair	B	4	1.41 (1.07, 1.88)
Evans, 1997	CHD Events	732	NCC	Good	M***	14	0.94 (0.65, 1.34)
Folsom, 1998	CHD Events	769	NCC	Good	B	3	1.22 (0.52, 2.88)
Wald, 1998	CHD Events	1335	NCC	Fair	M	8.7	1.41 (1.20, 1.65)
Knekt, 2001	CHD Events	1020	NCC	Good Fair	F M	13	0.64 (0.22, 1.83) 0.78 (0.44, 1.39)
de Bree, 2003	CHD Events	939	NCC	Good	B	10.3	1.03 (0.83, 1.28)
Lind, 2003	CHD Events	482	NCC	Fair	M	17	1.10 (0.86, 1.41)
Shai, 2004	CHD Events	695	NCC	Good	F***	8	1.35 (0.83, 2.18)
Voutilainen, 2004	CHD Events	1229	Cohort	Fair	M	7.8	0.89 (0.34, 2.38)
Zylberstein, 2004	CHD Events	1368	Cohort	Fair	F	24	1.22 (1.05, 1.41)
Bostom, 1999	CVD Events	1933	Cohort	Good	B	11.5	1.40 (1.13, 1.73)
Ridker, 2000	CVD Events	366	NCC	Good	F	3	1.46 (0.82, 2.62)
Vollset, 2001 (65-67 yrs)	CVD Events	4766	Cohort	Fair	B	4.1	1.58 (1.07, 2.34)
Nurk, 2002 (40-42 yrs)	CVD Events	12288	Cohort	Fair	B	5.3	1.02 (0.75, 1.38)
Combined							1.21 (1.10, 1.32)
Baseline CHD/CVD Not Explicitly excluded							
Stehower, 1998	CHD Events	878	Cohort	Fair	M	9	1.07 (0.98, 1.17)
Bots, 1999	CHD Events	757	NCC	Good	B	2.7	1.28 (0.99, 1.65)
Fallon, 2001	CHD Events	1560	NCC	Good	M	10	1.09 (0.91, 1.32)
Sacco, 2004	CHD Events	2939	Cohort	Good	B	4	1.15 (0.72, 1.84)
Combined							1.09 (1.01, 1.18)
All Studies Combined							1.18 (1.10, 1.26)



*For CHD events, all studies included "hard" CHD events except for 2 studies: Folsom, 1998 and Stampfer, 1992.
**Number of subjects included in the analysis.
***__Abbreviations__: B=both genders, F=female, M=male, NCC=nested case control study design.

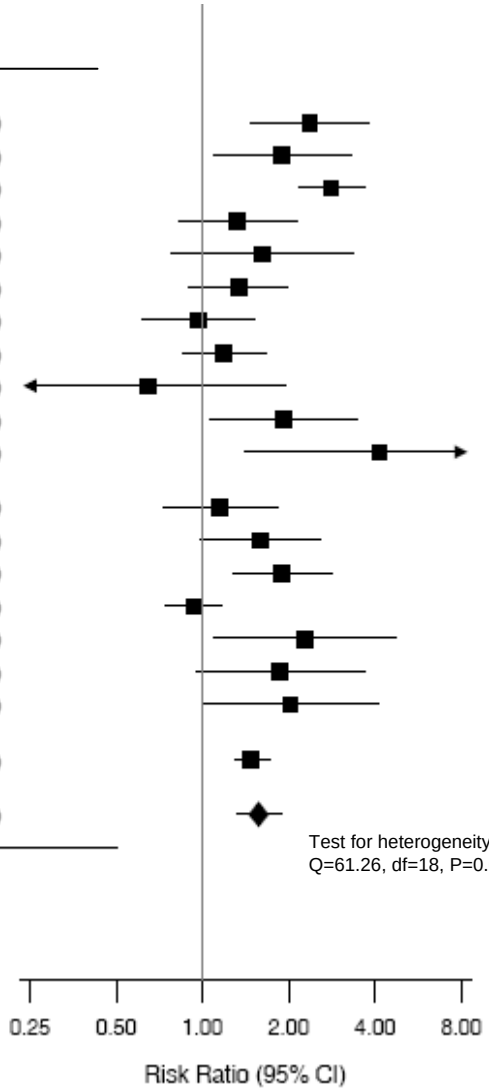
FIGURE 8. RISK RATIO OF CHD ASSOCIATED WITH EVERY 5 µmol/L INCREASE OF HOMOCYSTEINE, BY SELECTED CHARACTERISTICS



*MI is a subgroup of major CHD events. CHD events include Major CHD events and CHD events as shown in Figure 6.
**Risk factors based on Wilson et al, 1998.
***Except for this analysis, all other subgroup analyses do not include poor studies.

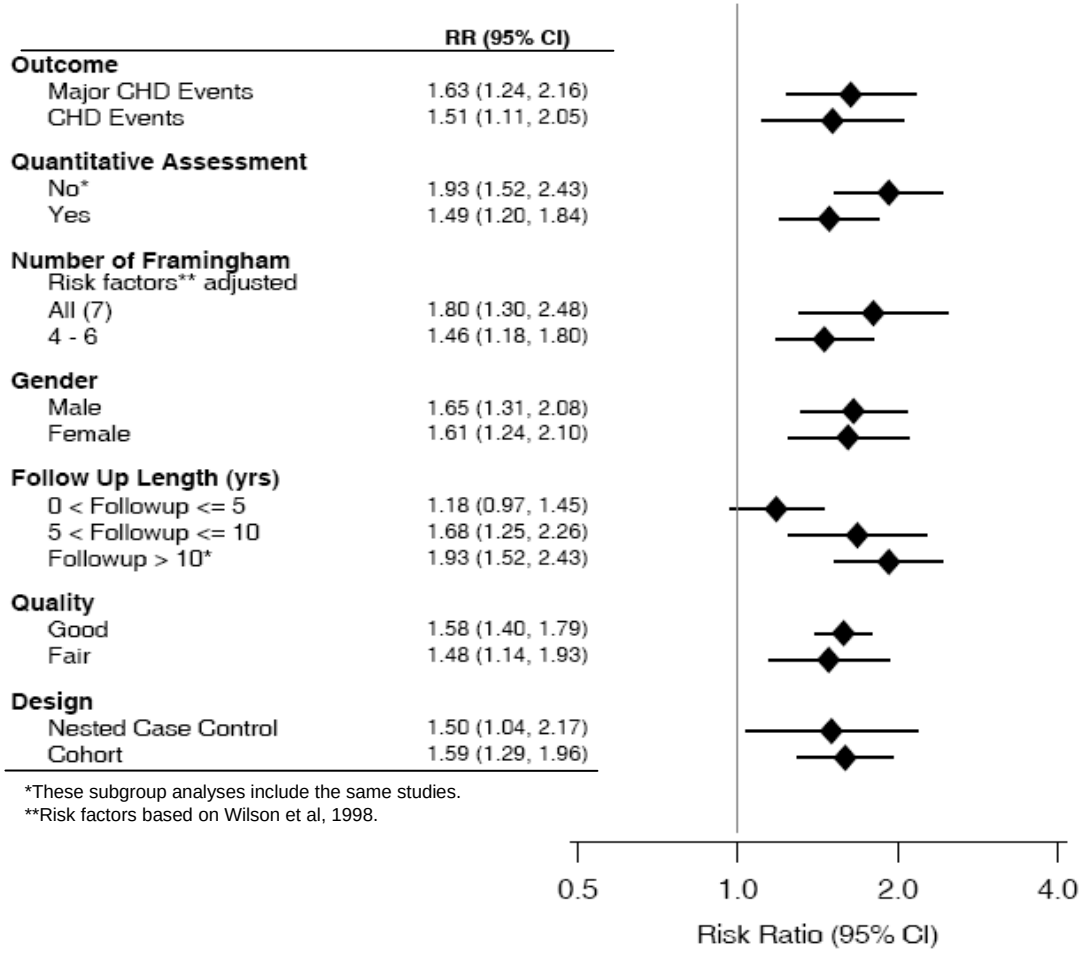
FIGURE 9. STUDY CHARACTERISTICS AND RISK RATIO OF CHD ASSOCIATED WITH LIPOPROTEIN(a) (>=30 vs <30 mg/dL)

	Outcome	Number of Subjects*	Study Design	Quantitative Assessment	Quality	Gender	Followup (in yrs)	RR (95% CI)
Baseline CHD/CVD Explicitly Excluded								
Bostom, 1994	Major CHD Events	3103	Cohort	No***	Good	F**	12	2.37 (1.48, 3.80)
Bostom, 1996	Major CHD Events	2191	Cohort	No***	Good	M**	15.4	1.90 (1.10, 3.29)
Cremer, 1997	Major CHD Events	5639	Cohort	Yes	Fair	M	10	2.82 (2.16, 3.68)
Jauihiainen, 1991	Major CHD Events	268	NCC**	Yes	Fair	M	5	1.32 (0.82, 2.13)
Luc, 2002	Major CHD Events	9133	Cohort	Yes	Good	M	5	1.62 (0.78, 3.38)
Pischon, 2005	Major CHD Events	739	NCC	Yes	Fair	M	6	1.34 (0.90, 1.99)
Price, 2001	Major CHD Events	783	Cohort	Yes	Fair	F	5	0.97 (0.62, 1.52)
Price, 2001	Major CHD Events	809	Cohort	Yes	Fair	M	5	1.19 (0.85, 1.67)
Ridker, 1993	Major CHD Events	592	NCC	Yes	Fair	M	5	0.65 (0.22, 1.94)
Schaefer, 1994	Major CHD Events	623	NCC	Yes	Fair	M	8.5	1.92 (1.06, 3.47)
Rosengren, 1990	Major CHD Events	135	NCC	Yes	Fair	M	6	4.17 (1.41, 12.3)
Cantin, 1998	CHD Events	2156	Cohort	Yes	Fair	M	5	1.15 (0.73, 1.82)
Nguyen, 1997	CHD Events	4967	Cohort	No***	Fair	M	13.9	1.60 (0.99, 2.58)
Nguyen, 1997	CHD Events	4969	Cohort	No***	Fair	F	14.1	1.90 (1.27, 2.84)
Salomaa, 2002	CHD Events	2240	Cohort	Yes	Fair	B**	6.6	0.93 (0.74, 1.16)
Seed, 2001	CHD Events	2616	Cohort	Yes	Fair	M	6	2.27 (1.09, 4.71)
Sharrett, 2001	CHD Events	5432	Cohort	Yes	Good	M	10	1.87 (0.95, 3.69)
Sharrett, 2001	CHD Events	6907	Cohort	Yes	Good	F	10	2.03 (1.00, 4.11)
Suk Danik, 2006	CVD Events	27791	Cohort	Yes	Good	F	10	1.48 (1.29, 1.71)
Combined								1.57 (1.31, 1.88)



*Number of subjects included in the analysis
****Abbreviations**: B=both genders, F=female, M=male.
***In these studies, Lipoprotein(a) is detected by electrophoresis band. The presence of a band is closely related with >= 30 mg/dL.

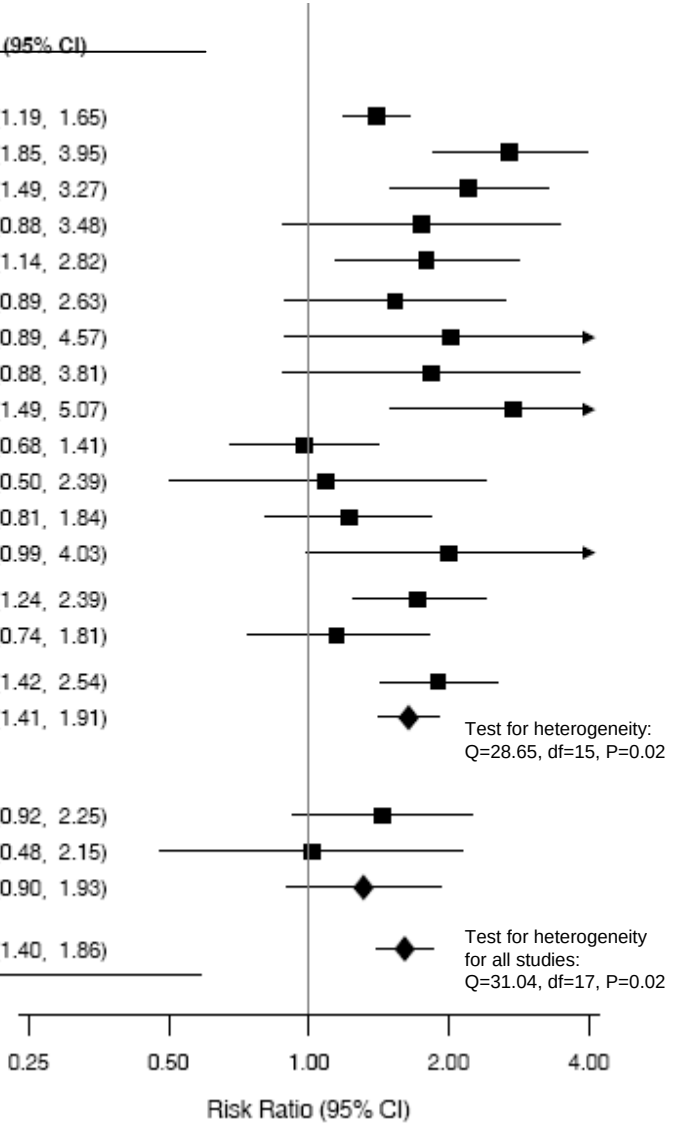
FIGURE 10. RISK RATIO OF CHD ASSOCIATED WITH LIPOPROTEIN(a) (>=30 vs <30 mg/dL), BY SELECTED CHARACTERISTICS



*These subgroup analyses include the same studies.
**Risk factors based on Wilson et al, 1998.

FIGURE 11. STUDY CHARACTERISTICS AND RISK RATIO OF CHD ASSOCIATED WITH C-REACTIVE PROTEIN (>3.0 mg/L vs mg/L)

	Outcome	Number of Subjects*	Study Design	Quality	Gender	Followup (in yrs)	RR (95% CI)
Baseline CHD/CVD Explicitly Excluded							
Danesh, 2004	Major CHD Events	5933	NCC**	Fair	B	19.5	1.40 (1.19, 1.65)
Danesh, 2000	Major CHD Events	1149	NCC	Good	M**	9.5	2.70 (1.85, 3.95)
Koenig, 2004	Major CHD Events	3435	Cohort	Good	M	6.6	2.21 (1.49, 3.27)
Luc, 2003	Major CHD Events	772	NCC	Good	M	5	1.75 (0.88, 3.48)
Pai, 2004	Major CHD Events	794	NCC	Good	M	8	1.79 (1.14, 2.82)
Pai, 2004	Major CHD Events	708	NCC	Good	F**	8	1.53 (0.89, 2.63)
Park, 2002	Major CHD Events	967	Cohort	Fair	B**	6.4	2.02 (0.89, 4.57)
Pradhan, 2002	Major CHD Events	560	NCC	Good	F	2.9	1.83 (0.88, 3.81)
Ridker, 1997	Major CHD Events	492	NCC	Fair	M	8	2.75 (1.49, 5.07)
St-Pierre, 2005	Major CHD Events	1982	Cohort	Good	M	13	0.98 (0.68, 1.41)
van der Meer, 2003	Major CHD Events	657	NCC	Fair	B	4-8	1.09 (0.50, 2.39)
Wilson, 2005	Major CHD Events	4446	Cohort	Good	B	8	1.22 (0.81, 1.84)
Witherell, 2003	Major CHD Events	325	NCC	Fair	B	5.1	2.00 (0.99, 4.03)
Ballantyne, 2004	CHD events	1348	CC**	Good	B	6	1.72 (1.24, 2.39)
Lawlor, 2005	CHD events	2723	Cohort	Fair	F	3.5	1.15 (0.74, 1.81)
Ridker, 2004	CVD Events	15745	Cohort	Good	F	9	1.90 (1.42, 2.54)
Combined							1.64 (1.41, 1.91)
Baseline CHD/CVD Not Explicitly excluded							
Lowe, 2001	Major CHD Events	1595	Cohort	Fair	M	6.25	1.44 (0.92, 2.25)
Mendall, 2000	Major CHD Events	1395	Cohort	Fair	M	13.7	1.02 (0.48, 2.15)
Combined							1.32 (0.90, 1.93)
All Studies Combined							1.61 (1.40, 1.86)



*Number of subjects included in the analysis.
****Abbreviations**: B=both genders, CC=case control, F=female, M=male, NCC=nested case control study design.

FIGURE 12. RISK RATIO OF CHD ASSOCIAED WITH C-REACTIVE PROTEIN (1.0 – 3.0 mg/L vs <1.0 mg/L)

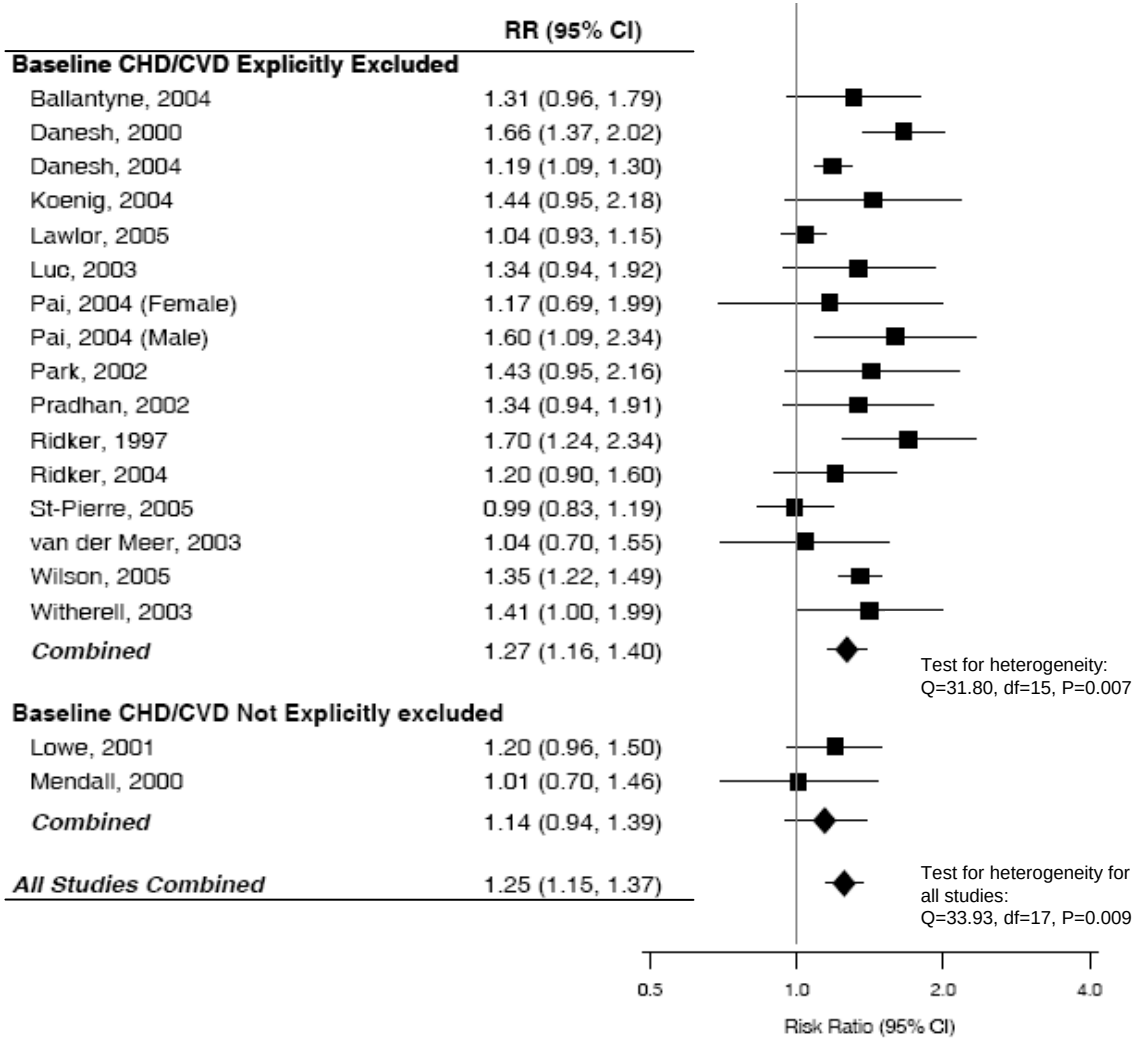
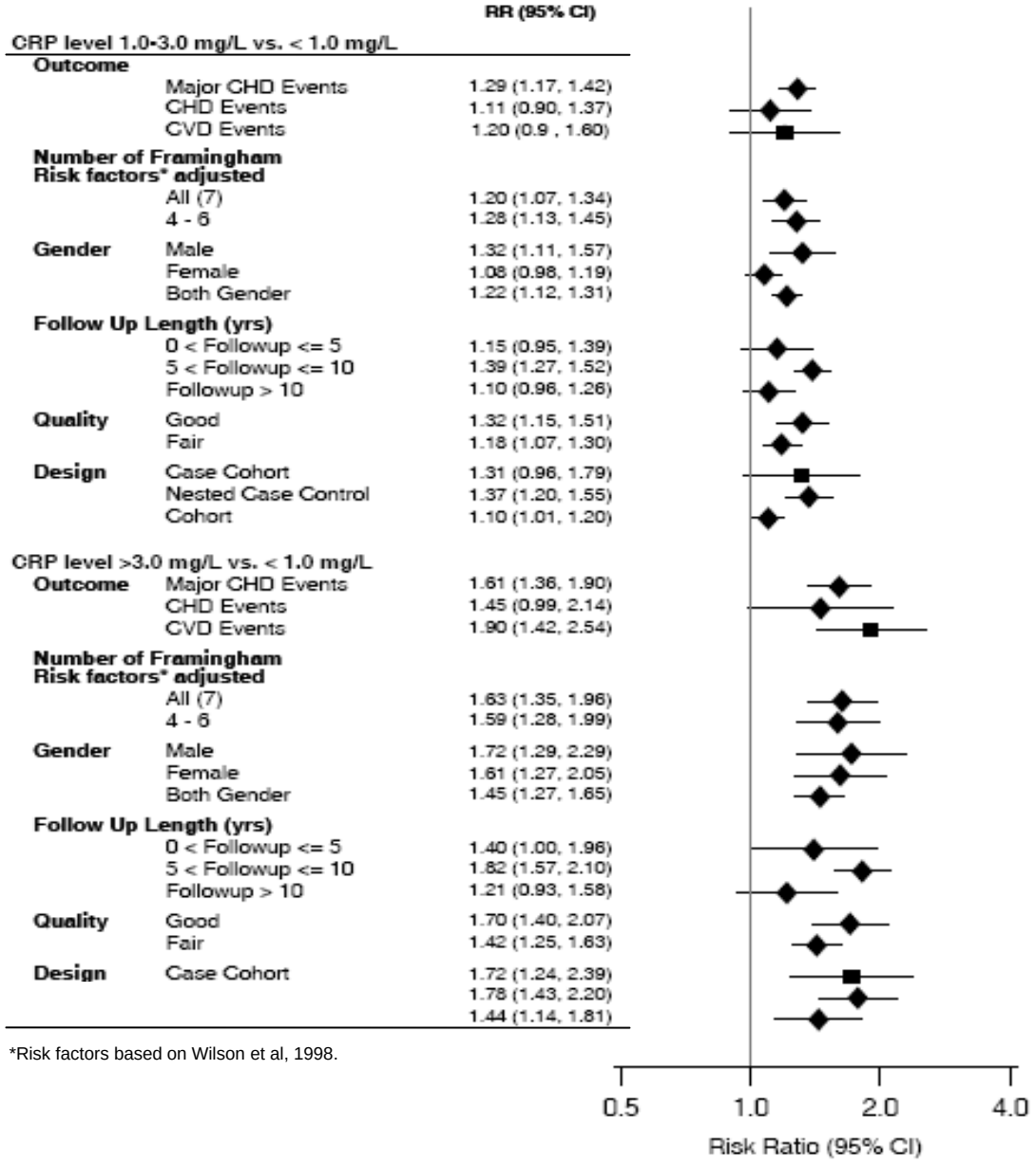


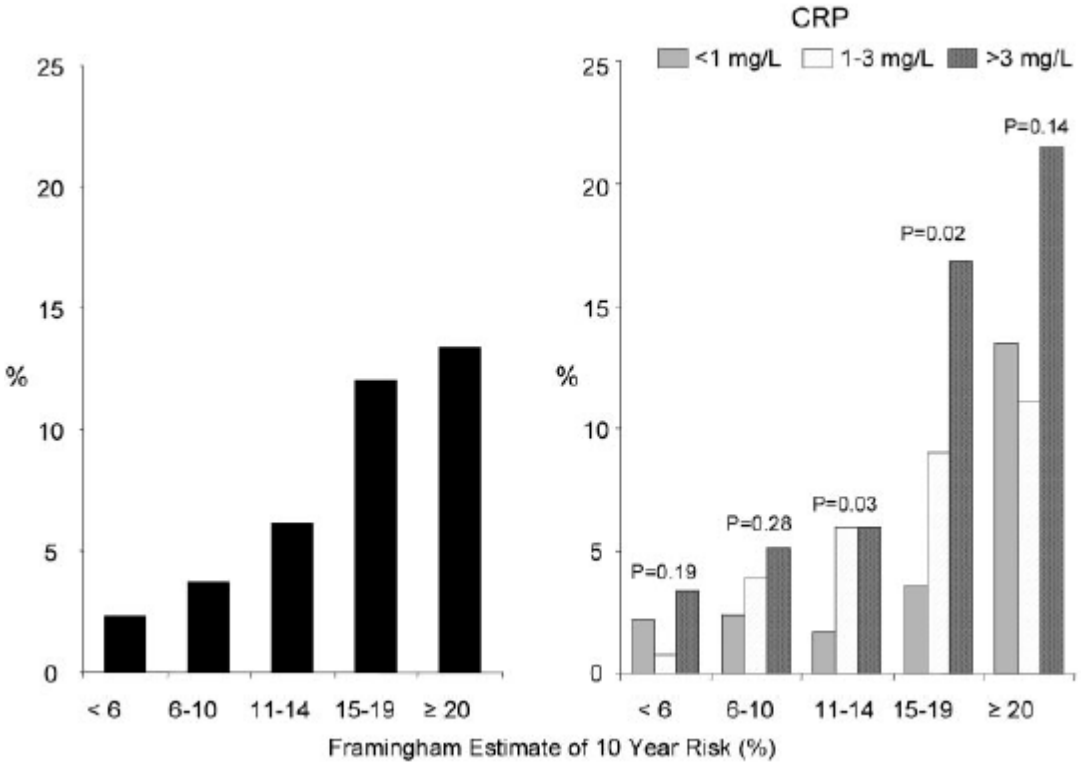
FIGURE 13. RISK RATIO OF CHD ASSOCIATED WITH C-REACTIVE PROTEIN, BY SELECTED CHARACTERISTICS



*Risk factors based on Wilson et al, 1998.

FIGURE 14. OCCURANCE OF A FIRST CORONARY EVENT WITHIN 10 YEARS, ESTIMATED BY COX PROPORTIONAL HAZARDS MODELS IN PERCENTAGES.

Left, Percentage estimated by a model with Framingham Risk Score (FRS) (5 categories) adjusted for survey. Right, Percentage estimated for each of 5 FRS categories by a model with CRP (3 categories) adjusted for FRS (continuous) and survey. Probability values indicate significance status of CRP in the Cox model. MONICA/KORA Augsburg Cohort Study, 1984 to 1998. From Circulation, March 23, 2004, page 1352.[207]



APPENDIX I. SEARCH STRATEGIES

Search Terms: Appropriate terms were selected in conjunction with a medical research librarian and experts in the field, and individual search strategies were created to retrieve the literature pertaining to novel risk factors for intermediate risk of coronary heart failure.

MEDLINE

Ankle Brachial Index

1 exp cohort studies/
2 exp Cardiovascular Diseases/
3 1 and 2
4 (ankle brachial blood pressure or ankle brachial pressure or ankle brachial index).mp.
5 abi.mp.
6 exp Blood Pressure/
7 ankle.mp. or exp ANKLE/
8 4 or 5
9 6 and 7
10 8 or 9
11 3 and 10
12 limit 11 to english language

C-reactive Protein

1 exp cohort studies/
2 exp Cardiovascular Diseases/
3 1 and 2
4 exp C-Reactive Protein/
5 exp Inflammation/ and exp Biological Markers/
6 3 and 5
7 3 and 4
8 6 or 7

Carotid Intima-media Thickness

1 exp cohort studies/
2 exp Cardiovascular Diseases/
3 1 and 2
4 exp tunica intima/ or exp tunica media/
5 exp carotid arteries/
6 4 and 5
7 3 and 6
8 ((Intima-media thick$ or imt) adj5 carotid).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
9 3 and 8
10 (carotid adj3 thick$).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
11 3 and 10
12 7 or 9 or 11

Electron Beam Tomography

1 exp cohort studies/
2 exp Cardiovascular Diseases/
3 1 and 2
4 (electron beam computed tomograph$ or ebct).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
5 3 and 4
6 exp Tomography, X-Ray Computed/
7 electron beam$.mp.
8 6 and 7
9 3 and 8
10 5 or 9

Homocysteine

1 exp cohort studies/
2 exp Cardiovascular Diseases/
3 1 and 2
4 exp HOMOCYSTEINE/ or homocysteine$.mp. or hyperhomocysteinem$.mp. or Cystathionine beta-Synthase.mp.
5 3 and 4

Impaired Fasting Glucose

1 exp cohort studies/
2 exp Cardiovascular Diseases/
3 1 and 2
4 exp Fasting/ and exp Blood Glucose/
5 3 and 4
6 exp Glucose Intolerance/ or exp Glucose Tolerance Test/
7 3 and 6
8 (fasting glucose adj3 (impair$ or lower$)).mp. [mp=title, original title, abstract, name of substance, mesh subject heading]
9 3 and 8
10 5 or 9

Lipoprotein(a)

1 exp cohort studies/
2 exp cardiovascular diseases/
3 1 and 2
4 small dense ldl.mp.
5 small dense low density lipoprot$.mp.
6 (oxidiz$ adj1 (ldl or low density lipoprot$)).mp.
7 apolipoprotein$.mp.
8 exp Apolipoproteins/
9 triglyceride rich lipoprotein$.mp.
10 lipoprotein a.mp. or exp "Lipoprotein(a)"/
11 (lpa or "lp(a)").mp.

12 (lipoprot$ adj3 remnant$).mp.
13 ((high density lipoprot$ or hdl) adj subfraction$).mp.
14 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13
15 3 and 14

Periodontal Disease

1 exp cohort studies/
2 exp Cardiovascular Diseases/
3 1 and 2
4 exp Periodontal Diseases/
5 3 and 4

White Blood Cell Count

1 exp Cardiovascular Diseases/
2 exp cohort studies/
3 1 and 2
4 exp C-Reactive Protein/
5 exp inflammation/ and exp Biological markers/
6 4 or 5
7 6 and 3
8 exp leukocyte count/
9 8 and 3
10 9 not 7
11 8 and 1

APPENDIX II. INCLUSION/EXCLUSION CRITERIA

All risk factors used the below inclusion/exclusion criteria to determine included studies:

Include

- Minimum outcomes: coronary deaths & non-fatal myocardial infarction
- Appropriate measures of Framingham variables (Age, sex, LDL, HDL, total cholesterol, diabetes, smoking status, hypertension)
- & at least one novel risk factor
- Cohort, nested case-control, cardiovascular trial follow-up study (or systematic review or meta-analysis of these study types) that measures a novel risk factor and estimates its predictive value after adjusting for Framingham variables

Exclude

- No data
- Population or sub-population with known coronary disease or coronary disease equivalent (e.g., diabetes)
- Does not include minimum outcomes
- Does not measure Framingham variables appropriately
- Wrong study design/article format

APPENDIX III. US PREVENTIVE SERVICES TASK FORCE QUALITY RATING CRITERIA*

Diagnostic Accuracy Studies

Criteria

- Screening test relevant, available for primary care, adequately described
- Study uses a credible reference standard, performed regardless of test results
- Reference standard interpreted independently of screening test
- Handles indeterminate results in a reasonable manner
- Spectrum of patients included in study
- Sample size
- Administration of reliable screening test

Definition of ratings based on above criteria

Good: Evaluates relevant available screening test; uses a credible reference standard; interprets reference standard independently of screening test; reliability of test assessed; has few or handles indeterminate results in a reasonable manner; includes large number (more than 100) broad-spectrum patients with and without disease.

Fair: Evaluates relevant available screening test; uses reasonable although not best standard; interprets reference standard independent of screening test; moderate sample size (50 to 100 subjects) and a "medium" spectrum of patients.

Poor: Has important limitations such as: uses inappropriate reference standard; screening test improperly administered; biased ascertainment of reference standard; very small sample size of very narrow selected spectrum of patients.

Randomized Controlled Trials (RCTs) and Cohort Studies

Criteria

- Initial assembly of comparable groups**:** RCTs—adequate randomization, including concealment and whether potential confounders were distributed equally among groups; cohort studies—consideration of potential confounders with either restriction or measurement for adjustment in the analysis; consideration of inception cohorts
- Maintenance of comparable groups (includes attrition, cross-overs, adherence, contamination)
- Important differential loss to follow-up or overall high loss to follow-up
- Measurements: equal, reliable, and valid (includes masking of outcome assessment)
- Clear definition of interventions
- Important outcomes considered
- Analysis: adjustment for potential confounders for cohort studies, or intention-to-treat analysis for RCTs (i.e. analysis in which all participants in a trial are analyzed according to the intervention to which they were allocated, regardless of whether or not they completed the intervention)

APPENDIX III. US PREVENTIVE SERVICES TASK FORCE QUALITY RATING CRITERIA* (CONTINUED)

Definition of ratings based on above criteria

Good: Meets all criteria: Comparable groups are assembled initially and maintained throughout the study (follow-up at least 80 percent); reliable and valid measurement instruments are used and applied equally to the groups; interventions are spelled out clearly; important outcomes are considered; and appropriate attention to confounders in analysis.

Fair: Studies will be graded "fair" if any or all of the following problems occur, without the important limitations noted in the "poor" category below: Generally comparable groups are assembled initially but some question remains whether some (although not major) differences occurred in follow-up; measurement instruments are acceptable (although not the best) and generally applied equally; some but not all important outcomes are considered; and some but not all potential confounders are accounted for.

Poor: Studies will be graded "poor" if any of the following major limitations exists: Groups assembled initially are not close to being comparable or maintained throughout the study; unreliable or invalid measurement instruments are used or not applied at all equally among groups (including not masking outcome assessment); and key confounders are given little or no attention.

Case Control Studies

Criteria

- Accurate ascertainment of cases
- Nonbiased selection of cases/controls with exclusion criteria applied equally to both
- Response rate
- Diagnostic testing procedures applied equally to each group
- Measurement of exposure accurate and applied equally to each group
- Appropriate attention to potential confounding variable

Definition of ratings based on above criteria

Good: Appropriate ascertainment of cases and nonbiased selection of case and control participants; exclusion criteria applied equally to cases and controls; response rate equal to or greater than 80 percent; diagnostic procedures and measurements accurate and applied equally to cases and controls; and appropriate attention to confounding variables.

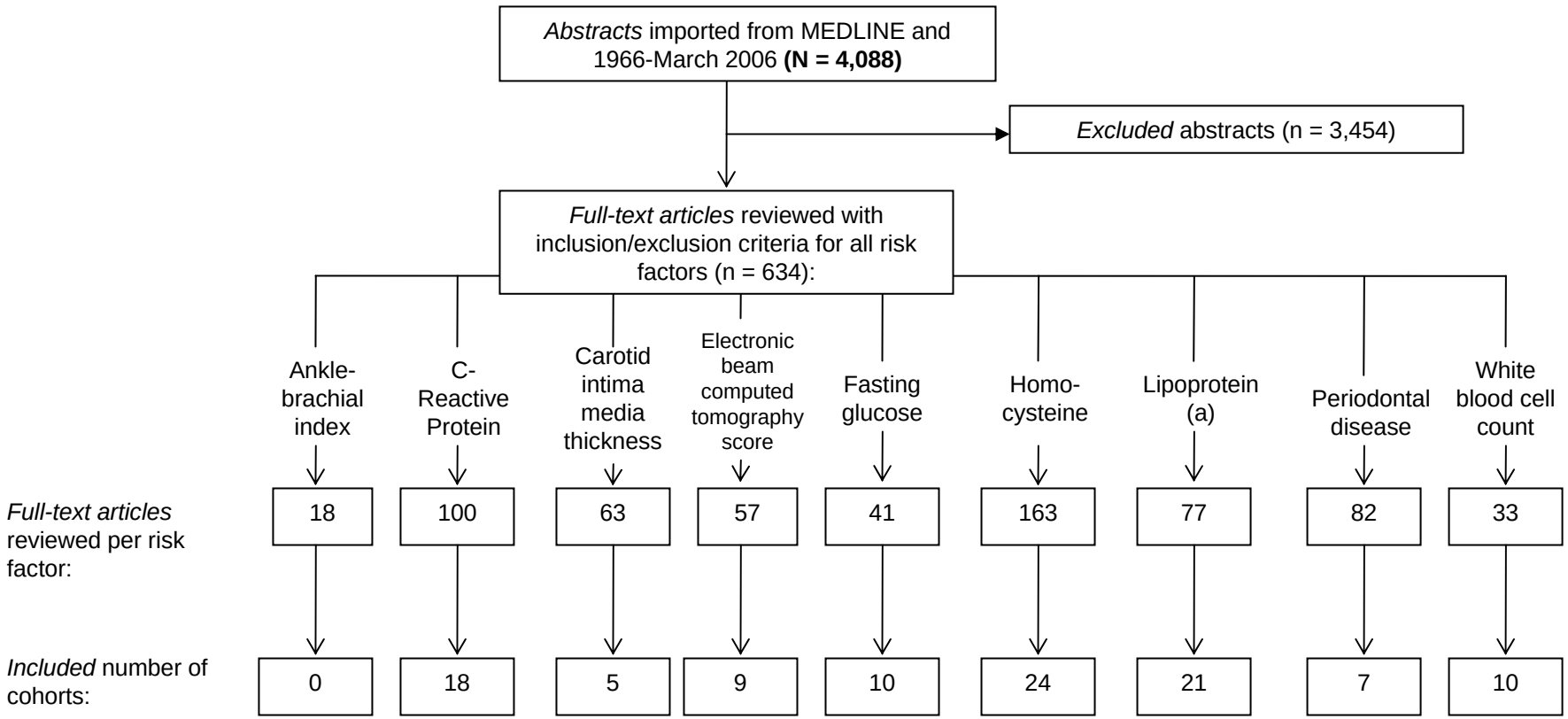
Fair: Recent, relevant, without major apparent selection or diagnostic work-up bias but with response rate less than 80 percent or attention to some but not all important confounding variables.

Poor: Major selection or diagnostic work-up biases, response rates less than 50 percent, or inattention to confounding variables.

*__Reference:__

Harris RP, Helfand M, Woolf SH, et al. Current methods of the US Preventive Services Task Force: a review of the process. *Am J Prev Med.* 2001:20(3S); 21-35.

APPENDIX IV. SEARCH AND SELECTION OF LITERATURE



EVIDENCE TABLE 1. WHITE BLOOD CELL COUNT AS A RISK FACTOR FOR CORONARY HEART DISEASE

Author, year	Parent study	N enrolled	N incident cases	% Male	N cases in full model	Duration of follow-up	Age range or mean	Excluded baseline CHD	Excluded baseline DM
Cohort studies									
Folsom, 1997[42]	ARIC	14,477	348	43.50%	289	5 years	45-64	Yes	No
Gillum, 1993[43] Wheeler, 2004[49]	NHANES I	6,196	1,401	47%	1163 (whites); 238 (blacks) 914 in Wheeler 2004	Range 6.8 to 16.4 years, median 13.9 years; median 18.3 in Wheeler 2004	Gillum 1993: 25-74; Wheeler 2004: mean 48.1	Yes	No
Kannel, 1992[44]	Framingham Offspring Study	2,794	197	49.90%	NR	12 years	30-59	Yes	No

EVIDENCE TABLE 1. WHITE BLOOD CELL COUNT AS A RISK FACTOR FOR CORONARY HEART DISEASE

Author, year	Framingham RFs: age, BP, TC or LDL, DM, Gender, HDL, Smoking	Additional Non-FRFs in analysis	Type of categorization	RR (95%CI)	Quality rating
Cohort studies					
Folsom, 1997[42]	Age, BP, TC or LDL, DM, gender, HDL, smoking	ARIC field center, use of antihypertensives, waist-to-hip ratio, and sport index.	Categorized, x1000/mm3: <0.31 5.1-6.5 >6.5 Result compares highest to lowest 3rd	Men: 1.13 (95%CI 0.98-1.31) Women: 1.45 (95%CI 0.86-2.44)	Good
Gillum, 1993[43] Wheeler, 2004[49]	Age, BP, TC or LDL, DM, gender, smoking Not for HDL	Pulse rate, hemoglobin concentration, BMI, education	Categorized, x1000/mm3: <6.6 6.6-8.1 >8.1	(Whites only) Men: RR (95%CI) <6.6 1.00 (reference) 6.6-8.1 0.94 (0.76-1.15) >8.1 1.31 (1.07-1.61) Women: <6.6 1.00 (reference) 6.6-8.1 1.26 (1.03-1.55) >8.1 1.31 (1.05-1.63) Wheeler, 2004: lowest 3rd: 1.00 (reference) middle 3rd: 1.07 (0.92-1.26) highest 3rd: 1.01 (0.85-1.20)	Fair
Kannel, 1992[44]	Age, gender, smoking Not for BP, TC/LDL, HDL, or DM	NR	Dichotomized; Compares <=6.0 to >6.0 x1000/mm3	Men / Women Nonsmokers: 2.1 (p<0.01) / 1.2 (p=ns) Smokers: 1.3 (p=ns) / 1.6	Poor

EVIDENCE TABLE 1. WHITE BLOOD CELL COUNT AS A RISK FACTOR FOR CORONARY HEART DISEASE

Author, year	Parent study	N enrolled	N incident cases	% Male	N cases in full model	Duration of follow-up	Age range or mean	Excluded baseline CHD	Excluded baseline DM
Olivares, 1993[39]	Paris Prospective Study II	2,856	24 major events	100%	2782	5.5 years	Per cohort: 42.1, 44.3	Yes	No
Phillips, 1992[45]	British Regional Heart Study; MRFIT 1 and 2	28,181 combined	1,768	100%	1,768	6-12 years, mean per study: BRHS: 8.0 MRFIT 1: 7.0 MRFIT 2: 12.0	Mean 46-50	MRFIT1,2: Yes BRHS: No	MRFIT1,2: Yes BRHS: No
Prentice, 1982[46]	Adult Health Study, a subset of 100,000 residents in Hiroshima or Nagasaki as of 1950	16,290	154	38%	62	2 years	74% < 45	Yes	No
Sweetnam, 1997[47]	Caerphilly and Speedwell Collaborative Heart Disease Studies	4,615	565	100%	NR	9-10 years	45-63	No	NR (See Bainton D)

EVIDENCE TABLE 1. WHITE BLOOD CELL COUNT AS A RISK FACTOR FOR CORONARY HEART DISEASE

Author, year	Framingham RFs: age, BP, TC or LDL, DM, Gender, HDL, Smoking	Additional Non-FRFs in analysis	Type of categorization	RR (95%CI)	Quality rating
Olivares, 1993[39]	Age, smoking status, gender; did not adjust for TC, HDL, BP, or diabetes.	NR	Continuous per 1,000 cells/mm3	RR for total WBC in 1,000 cells/mm3: 1.04 (95%CI 0.95-1.14), p-value = 0.40	Poor
Phillips, 1992[45]	MRFIT1,2: age, BP, TC or LDL, DM, gender, smoking Not for HDL BRHS: age, BP, TC or LDL, gender, smoking Not for DM or HDL	NR	Continuous per 2000/mm3 increase	BRHS: 1.32 (1.18, 1.47), p<0.0001 MRFIT 1: 1.15 (1.07, 1.23), p=0.0001 MRFIT 2: 1.14 (1.05, 1.25), p=0.003	Fair
Prentice, 1982[46]	Sex, age, smoking, TC, BP. Not for DM or HDL	NR	Continuous hundred/mm3	RR 1.54 (p=0.58) adjusted for age, sex, smoking, BP and TC, but the number of cases was limited (N =62). RR adjusted for age, sex, and BP was similar between never smokers & current smokers: 3.00 (p=0.38, ns) v. 2.09 (p=0.4, ns)	Fair
Sweetnam, 1997[47]	Age, BP, TC or LDL, gender, smoking Not for DM or HDL	Preexistent IHD BMI	Quintiles; result compares highest to lowest quintile	OR = 2.10 (95%CI 1.51-2.92).	Fair

EVIDENCE TABLE 1. WHITE BLOOD CELL COUNT AS A RISK FACTOR FOR CORONARY HEART DISEASE

Author, year	Parent study	N enrolled	N incident cases	% Male	N cases in full model	Duration of follow-up	Age range or mean	Excluded baseline CHD	Excluded baseline DM
Weijenberg, 1996[48]	Zutphen Study (Dutch portion of 7 Countries Study)	884	NR	100%	NR	5 years	64-84	No	No
Zalokar, 1981[40]	Paris Prospective Study I	7206	104	100%	NR	6.5 years	43-53	Yes	No

EVIDENCE TABLE 1. WHITE BLOOD CELL COUNT AS A RISK FACTOR FOR CORONARY HEART DISEASE

Author, year	Framingham RFs: age, BP, TC or LDL, DM, Gender, HDL, Smoking	Additional Non-FRFs in analysis	Type of categorization	RR (95%CI)	Quality rating
Weijenberg, 1996[48]	Age, BP, TC or LDL, DM, gender, HDL, smoking	BMI, serum albumin, Hct,	Continuous per 1000/mm3 increase	RR 1.14 (95%CI 0.98-1.32)	Fair
Zalokar, 1981[40]	Adjusted only for gender and smoking in men aged 43-53. Did not adjust for BP, TC/LDL, HDL, DM.	NR	<6000-7799/mm3 >7800/mm3	Incidence per 1000 person-years (95%CI), by #cigarettes per day/WBC count: 1-9/<6000-7799: 0.8 (0.0-4.6) 1-9/7800+: 0.0 (0.0-16.2) 10-19/<6000-7799: 1.7 (0.5-4.0) 10-19/7800+: 7.6 (3.7-13.5) 20-24/<6000-7799: 4.8 (2.8-7.7) 20-24/7800+: 9.1 (5.3-14.6) 25+/<6000-7799: 3.7 (1.2-8.6) 25+/7800+: 6.1 (2.9-15.1)	Poor

EVIDENCE TABLE 1. WHITE BLOOD CELL COUNT AS A RISK FACTOR FOR CORONARY HEART DISEASE

Author, year	Parent study	N enrolled	N incident cases	% Male	N cases in full model	Duration of follow-up	Age range or mean	Excluded baseline CHD	Excluded baseline DM
Nested case-control studies									
Manttari, 1992[50]	Helsinki Heart Study	140 cases 280 controls	N/A	100%	140	5 years	40-55	Yes	No

EVIDENCE TABLE 1. WHITE BLOOD CELL COUNT AS A RISK FACTOR FOR CORONARY HEART DISEASE

Author, year	Framingham RFs: age, BP, TC or LDL, DM, Gender, HDL, Smoking	Additional Non-FRFs in analysis	Type of categorization	RR (95%CI)	Quality rating
Nested case-control studies					
Manttari, 1992[50]	Age, TC or LDL, gender, smoking Not for BP, DM or HDL	Physical activity, alcohol, BMI	Categorized, x1000/mm3: <5.2 5.2-6.7 >6.7	Nonsmokers: WBC < 5.2: 1.00 (reference) WBC 5.2-6.7: 1.11 (0.54-2.24) WBC > 6.7: 1.86 (0.81-4.28) Smokers: WBC < 5.2: 1.58 (0.64-3.90) WBC 5.2-6.7: 2.62 (1.62-6.70) WBC > 6.7: 3.07 (2.23-8.19)	Fair

Abbreviations:

ARIC=Atherosclerosis risk in communities, BMI=Body mass index, BP=Blood pressure, BRHS=British Regional Heart Study, CHD=Coronary heart disease, CI=Confidence interval, DBP=Diastolic blood pressure, DM=Diabetes mellitus, ECG=Electrocardiogram, Hct=Hematocrit, HDL=High density lipoprotein, IHD=Ischemic heart disease, LDL=Low density lipoprotein, MI=Myocardial infarction, MRFIT=Multiple Risk Factor Intervention Trial, NA=Not applicable, NHANES=National Health and Nutrition Examination Survey, NOS=Not otherwise specified, NR=Not reported, OR=Odds ratio, RR=Relative risk, SBP=Systolic blood pressure, TC=Total cholesterol, WBC=White blood cell

EVIDENCE TABLE 2. IMPAIRED FASTING GLUCOSE AS A RISK FACTOR FOR CORONARY HEART DISEASE

Study	N enrolled	N events	Duration of follow-up	Age range or mean (years)	% Men	Additional (Non-FRF) variables adjusted in analysis	Excluded DM Hx	Excluded baseline CVD/CHD
Antonicelli, 2001[60] Camerano study group	455	73	Follow-up visits were every 3 years; median followup 6 years	68.3	46	Blood pressure medication, triglycerides	Yes	Yes
Cohen, 2004[61] Worksite Hypertension Program	6672	NR	Mean 5.6 +- 4.5 years (range 0.5-21.7 years)	51.8	63.8	Ethnicity, left-ventricular hypertrophy, prior BP treatment, interaction of TC and FG	Yes	Yes

EVIDENCE TABLE 2. IMPAIRED FASTING GLUCOSE AS A RISK FACTOR FOR CORONARY HEART DISEASE

Study	Degree of adjustment for Framingham variables	Type of categorization	HR (95%CI) by FG level	Quality rating
Antonicelli, 2001[60] Camerano study group	Age, BP, TC or LDL, DM, Gender, Smoking Not for HDL	1) Dichotomized: >=126 vs. <126 mg/dL 2) 110-126 vs. <110 mg/dL (results not shown)	<126 mg/dL: 1.0 (reference) >=126 mg/dL: 2.01 (1.07-3.76), p=0.03 FG 110-126 mg/dL had no significant increased risk of CHD compared with FG < 110 mg/dL (results not shown)	Fair
Cohen, 2004[61] Worksite Hypertension Program	Age, BP, TC or LDL, DM, Gender, Smoking Not for HDL	Dichotomized: using 2 cutoffs, 103 and 110 mg/dL	Elevated FG magnifies the relative risk of CHD associated with TC in non-diabetic hypertensive patients. FG >103 mg/dL: TC 200-259 was 2.46 (1.26-4.77) compared with TC <200, p=0.008. Results were similar but less significant using FG 110 mg/dL as the cutoff: 2.70 (1.09-6.67), p=0.031 FG <103 mg/dL: TC 200-259 was 0.89 (0.61-1.29) compared with TC <200, p=ns	Fair

EVIDENCE TABLE 2. IMPAIRED FASTING GLUCOSE AS A RISK FACTOR FOR CORONARY HEART DISEASE

Study	N enrolled	N events	Duration of follow-up	Age range or mean (years)	% Men	Additional (Non-FRF) variables adjusted in analysis	Excluded DM Hx	Excluded baseline CVD/CHD
Folsom, 1997[62] ARIC	13,446	305	4-7 years, with followup in 1990-1992 and 1993-1995	45-64	NR (~50)	ARIC study center, ethanol consumption, education, sports index, hormone replacement, BMI, waist-to-hip ratio, fibrinogen, triglycerides, antihypertensive medication use	No; analyzed separately	Yes
Meigs, 2002[63] Framingham Offspring Study	3,370	118	4 years	54	46	None	Yes	Yes
Ohlson, 1986[57] Goteburg, Sweden	832	106	17 years	50	100	None	Yes	Yes

EVIDENCE TABLE 2. IMPAIRED FASTING GLUCOSE AS A RISK FACTOR FOR CORONARY HEART DISEASE

Study	Degree of adjustment for Framingham variables	Type of categorization	HR (95%CI) by FG level	Quality rating
Folsom, 1997[62] ARIC	Age, BP, TC or LDL, DM, HDL, Gender, Smoking	Categorized in 5 groups, in mg/dL: 1) <91 2) 91-97 3) >97-102 4) >102-115 5) >115-140	Among people without diabetes, fasting glucose was not independently associated with CHD incidence. Adjusted RR (95%CI) each FG category: Women: 1) <91: 1.00 (reference) 2) 91-97: 0.92 (0.45-1.89) 3) >97-102: 0.81 (0.35-1.87) 4) >102-115: 0.76 (0.36-1.63) 5) >115-140: 0.53 (0.18-1.55) Men: 1) <91: 1.00 (reference) 2) 91-97: 0.92 (0.56-1.50) 3) >97-102: 0.50 (0.28-0.89) 4) >102-115: 0.66 (0.40-1.07) 5) >115-140: 1.08 (0.62-1.90)	Good
Meigs, 2002[63] Framingham Offspring Study	Age, BP, TC or LDL, DM, HDL, Gender, Smoking	Continuous per 13 mg/dL increase	FPG, per 0.7 mmol/L (13 mg/dL) increase: 1.088 (95% CI 1.02-1.16) P=0.008 When included in the same prediction model, 2-h postchallenge hyperglycemia remained a significant risk factor for CVD, whereas fasting plasma glucose had a weak protective effect of borderline significance.	Good
Ohlson, 1986[57] Goteburg, Sweden	Age, DM Not for BP, TC or LDL, HDL, Smoking	Dichotomized: >103 vs. <=103 mg/dL	No trend in CHD risk by quintile or decile of FBG. FBG >103 vs. <=103 mg/dL: 1.3 (0.7-3.3) (5.7 mmol/L = 103 mg/dL)	Poor

EVIDENCE TABLE 2. IMPAIRED FASTING GLUCOSE AS A RISK FACTOR FOR CORONARY HEART DISEASE

Study	N enrolled	N events	Duration of follow-up	Age range or mean (years)	% Men	Additional (Non-FRF) variables adjusted in analysis	Excluded DM Hx	Excluded baseline CVD/CHD
Pyorala, 1985[58] Helsinki Policemen Study	982	63	9.5 years	47.4	100	Physical activity, BMI, TG	Yes	Yes
Qiao, 2002[64] 5 cohorts from the DECODE study: Helsinki Policemen Study, Vantaa Study, FIN-MONICA study (2 regions), East and West Finland Study	6766	380	7-10 years; mean 8 years	55	58	BMI	No; analyzed separately	Yes
Yarnell, 1994[59] Caerphilly and Speedwell Studies	4860 (4349 in analysis)	405	Caerphilly: 61 months Speedwell: mean 38 months	45-59	100	Triglyceride; pre-existing IHD	No; analyzed separately	No; adjusted as confounder

EVIDENCE TABLE 2. IMPAIRED FASTING GLUCOSE AS A RISK FACTOR FOR CORONARY HEART DISEASE

Study	Degree of adjustment for Framingham variables	Type of categorization	HR (95%CI) by FG level	Quality rating
Pyorala, 1985[58] Helsinki Policemen Study	Age, BP, TC or LDL, DM, Gender, Smoking	Quintiles, not otherwise specified	OR = 1.118 (p=ns)	Fair
Qiao, 2002[64] 5 cohorts from the DECODE study: Helsinki Policemen Study, Vantaa Study, FIN-MONICA study (2 regions), East and West Finland Study	Age, BP, TC or LDL, DM, Gender, Smoking Not for HDL	Continuous per one standard deviation in natural-log transformed FG	2-h glucose tolerance test was a stronger predictor of CHD than fasting glucose. Hazard ratio (95% CI) for CHD corresponding to one standard deviation increase in natural-log transformed fasting glucose v. 2-h OGTT: 1.05 (0.94-1.17) v. 1.17 (1.05-1.30)	Fair
Yarnell, 1994[59] Caerphilly and Speedwell Studies	Age, BP, DM, Gender, Smoking Not for TC or LDL, HDL	Categorized in 5 groups, in increments of 18 mg/dL: 1) <=85 2) 86- 3) 104- 4) 122- 5) >=140	No trend in CHD risk with increasing FG. OR (95%CI) by FPG: <=4.7 (<=85): 1.0 (reference) 4.8- (86-): 0.9 (0.6-1.2) 5.8- (104-): 1.1 (0.6-2.1) 6.8- (122-): 2.9 (1.2-6.6), p<0.05) >=7.8 (>=140): 1.4 (0.5-3.9)	Fair

Abbreviations:

ARIC=Atherosclerosis risk in communities, BMI=Body mass index, BP=Blood pressure, CHD=Coronary heart disease, CI=Confidence interval, CVD=Cardiovascular disease, DBP=Diastolic blood pressure, DM=Diabetes mellitus, FG or FBG= Fasting (blood) glucose, FPG=Fasting plasma glucose, HDL=High density lipoprotein, HR=Hazard ratio, Hx=History, IHD=Ischemic heart disease, LDL=Low density lipoprotein, MI=Myocardial infarction, Non-FRF=Non Framingham risk factor, NR=Not reported, OGTT=Oral glucose tolerance test, OR=Odds ratio, RR=Relative risk, SBP=Systolic blood pressure, TC=Total cholesterol, TG=Triglycerides

EVIDENCE TABLE 3. PERIODONTAL DISEASE AS A RISK FACTOR FOR CORONARY HEART DISEASE

Author, year, title	Parent study	N Enrolled	Duration Follow-Up	Outcomes	Demographics	Measurement of Dental Disease
Ajwani, 2003[71]	Helsinki Aging Study	175	5 years	Mortality, CVD mortality	175 men and women aged 75-85 with at least 2 teeth; prevalent CHD included	Dental exam
Beck, 1996[72]	Dental Longitudinal Study VA	1,221	18 years; 6 exams	Total CHD (MI, CHD death, angina), stroke	1094 community dwelling, men ages 21-81, all veterans, free of unknown chronic illnesses, with dental examinations and complete datasets	Radiographic and dental exams
DeStefano, 1993[73] *(Updated in Hujoel, 2001[233])*	NHANESI	9,760	14 years	CHD mortality, total mortality, CHD admission	Men and women aged 25-74 years without known CHD	Dental exam
Howell, 2001[74]	PHS	22,037	12 years	Stroke, all CVD, CV death, non-fatal MI	22037 male physicians aged 40-84 without stroke, MI, TIA, or cancer, providing dental information	Self report

EVIDENCE TABLE 3. PERIODONTAL DISEASE AS A RISK FACTOR FOR CORONARY HEART DISEASE

Author, year, title	Variables Adjsuted for	Exposure	Results	Quality rating
Ajwani, 2003[71]	Age, sex, TC, HDL, BP, smoking, BMI, prevalent CHD, social class	Periodontal disease Tooth loss	CV mortality PD Baseline: 2.28 (1.03-5.05) Partially edentulous: 1.46 (0.69-3.10)	Fair
Beck, 1996[72]	Age, BMI, smoking, sBP, dBP, TC, family history, CHD, EtOH	Periodontal disease Bone loss	Total CHD hi vs. low bone loss: 1.5 (1.04-2.14) - adjusted: age, smoking, sBP, NIDDM pockets >3mm: 3.1 (1.3-7.40) - adjusted: age, BMI, sBP, TC ≥ half of teeth with pockets >3mm: 2.0 (1.13-3.70) - adjusted: age, BMI, sBP, TC mean bone loss (continuous): 1.4 (1.10-1.86) Fatal CHD hi vs. low bone loss: 1.9 (1.10-3.43) - adjusted: age, smoking, sBP, Type 2 DM	Fair
DeStefano, 1993[73] *(Updated in Hujoel, 2001[233])*	Age, sex, race, education, marital status, sBP, TC, BMI, DM, activity, EtOH, poverty index, smoking	Number of decayed teeth, periodontal classification, periodontal index, oral hygiene index	CHD deaths or admissions: Periodontitis 1.25 (1.06-1.48) Men ≤ 50: 1.72 Gingivitis 1.05 (0.88-1.26) Oral hygiene index (per unit) 1.12 (1.06-1.20) Periodontal index (per unit) 1.04 (1.01-1.08) Edentulous 1.23 (1.05-1.44)	Good
Howell, 2001[74]	Age, sex, smoking, DM, BP, BMI, exercise, alcohol	Tooth loss Periodontal disease	Baseline periodontal disease/tooth loss during follow-up: Non-fatal MI: 1.01 (0.82-1.24)/ 1.01 (0.87-1.17) Non-fatal stroke: 1.01 (0.81-1.27)/ 1.07 (0.91-1.27) CV death: 1.0 (0.79-1.26)/ 0.61 (0.51-0.73) All CV: 1.01 (0.88-1.15)/ 0.92 (0.83-1.01)	Fair

EVIDENCE TABLE 3. PERIODONTAL DISEASE AS A RISK FACTOR FOR CORONARY HEART DISEASE

Author, year, title	Parent study	N Enrolled	Duration Follow-Up	Outcomes	Demographics	Measurement of Dental Disease
Hujoel, 2000[75]	NHANES I	8,032	4 follow-up exams, 1975-1992	CHD death, hospitalization, or revascularization	8032 general US population, dentate, age 25-70 without CHD	Dental exam
Hujoel, 2001[231] *(Update of DeStefano, 1993[73])*	NHANESI, NHEFS	11,348	4 follow-up exams, 17 years	- 1st occurrence - CHD mortality - CHD revascularization - non-fatal MI	4027 males and females, NHANES, ages 55-74 with either periodontitis (n=1857) or edentulous (n=2170)	Dental exam
Hung, 2004[76]	Health Professional Follow-up Study, NHS	51,529 males & 121,700 females	Women $\leq$20 years; men $\leq$12 years	CHD including fatal CHD, SCD without other likely cause, non-fatal MI	Health professionals; 41,407 men ages 40-75; 58,974 women ages 30-55; healthy at baseline; provided dental data	Self report

EVIDENCE TABLE 3. PERIODONTAL DISEASE AS A RISK FACTOR FOR CORONARY HEART DISEASE

Author, year, title	Variables Adjsuted for	Exposure	Results	Quality rating
Hujoel, 2000[75]	Demographics, SES, DM, smoking, alcohol, dBP, sBP cholesterol, mental illness, activity, BMI	Periodontitis, gingivitis	PD category / CHD events / CHD death Periodontitis: 1.14 (0.96-1.36) / 1.20 (0.90-1.61) Gingivitis: 1.05 (0.88-1.26) / 1.17 (0.84-1.61)	Good
Hujoel, 2001[231] *(Update of DeStefano, 1993[73])*	Age, sex, TC, BP, DM, smoking, BMI, exercise, alcohol use	Russell Periodontal index	Comparing edentulous to periodontal infections, adjusted for confounders, RR for CHD event 1.02(0.86-1.21)	Fair
Hung, 2004[76]	Age, sex, TC, smoking, DM, BP, BMI, exercise, alcohol, FMH, MVI, Vit E, menopausal, HRT use	History of periodontal disease Number of teeth lost History of bone loss	Men Baseline # teeth / CHD events / CHD death 25-32: 1.0 / 1.0 17-24: 1.10 (0.95-1.26) / 1.26 (1.01-1.57) 11-16: 1.35 (1.06-1.72) / 1.19 (0.79-1.80) 0-10: 1.36 (1.11-1.67) / 1.79 (1.34-2.40) CHD events / CHD death incidence tooth loss: 0.86 (0-72-1.04) / 0.69 (0.48-1.01) cumulative tooth loss: 0.94 (0.82-1.09) / 1.03 (0.80-1.33) Women Baseline # teeth / CHD events / CHD death 25-32: 1.0 / 1.0 17-24: 1.14 (0.92-1.42) / 1.02 (0.66-1.55) 11-16: 1.34 (0.97-1.87) / 1.07 (0.56-2.05) 0-10: 1.64 (1.31-2.05) / 1.65 (1.11-2.46)	Good

EVIDENCE TABLE 3. PERIODONTAL DISEASE AS A RISK FACTOR FOR CORONARY HEART DISEASE

Author, year, title	Parent study	N Enrolled	Duration Follow-Up	Outcomes	Demographics	Measurement of Dental Disease
Morrison, 1999[77]	Nutrition Canada Survey	16,090 of which 3670 were excluded	≤ 21 years	Mortality, CHD mortality	4248 males and 5083 females ages 35-84 without CHD or cerebrovascular disease	Dental exam
Tuominen, 2003[78]	Mini Finland Health Survey	3,091 men, 3,436 women	12 years	CHD death	Ages 30-69; representative of Finnish population	Dental exam

EVIDENCE TABLE 3. PERIODONTAL DISEASE AS A RISK FACTOR FOR CORONARY HEART DISEASE

Author, year, title	Variables Adjsuted for	Exposure	Results	Quality rating
Morrison, 1999[77]	Age, sex, TC, smoking, DM, HTN, province	Edentulousness, periodontitis, gingivitis	Fatal CHD None: 1.0 Mild gingivitis: 1.54 (0.89-2.67) Severe gingivitis: 2.15 (1.25-3.72) Periodonitis: 1.37 (0.80-2.35) Endentulous: 1.9 (1.17-3.10)	Fair
Tuominen, 2003[78]	Age, sex, TC, smoking, DM, BP	Edentulousness, periodontal treatment need system, frequency of dental attendance	For all parameters no association. Periodontal pockets: Men RR (95% CI) / Women RR (95% CI) None 1.0 / 1.0 4-6mm 1.0 (0.6-1.6) / 0.9 (0.3-2.1) > 6mm 1.0 (0.6-1.6) / 1.5 (0.6-3.8)	Fair

Abbreviations

ASA/B=Aspirin, BMI=Body mass index, BP=Blood pressure, CHD=Coronary heart disease, CV=Cardiovascular, CVD=Cardiovascular disease, DM=Diabetes mellitus, FMH=Family history, HDL=High density lipoprotein, HO=History of, HRT=Hormone replacement therapy, HTN=Hypertension, LDL=Low density lipoprotein, M=Measured, MI=Myocardial Infarction, MVI=Multivitamin, NHANES I=National Health and Nutrition Examination Survey-I, NHEFS=NHANES I Epidemiological Follow-up Study, NHS=Nurses Health Study, NR=Not reported, PD=Periodontal disease, RCT=Randomized controlled trial, RR=Relative risk, SCD=Sudden cardiac death, TC=Total cholesterol

EVIDENCE TABLE 4. CAROTID INTIMA-MEDIA THICKNESS AS A RISK FACTOR FOR CORONARY HEART DISEASE

Author, year, title	Parent study	N enrolled	Duration follow-up	Outcomes	Variables adjusted for in analysis
Belcaro, 1996[83]	Italy	2,322 randomly selected	6 years	CV events: those requiring hospital admission	None
Chambless, 2003[41]	ARIC	15,792 - original 12,841	5.2 years	CHD "events" MI-definite or possible CHD death ELG MI Coronary revascularization	Age Sex Race HDL TC BP
O'Leary,1999[86]	Cardiovascular Health Study	5888 enrolled, then 1389 excluded due to presence of CV disease, leaving 4476 for study	median 6.2 years	Incident MI and/or stroke	sBP dBP Age Sex Atrial fibrillation DM Smoking
Salonen, 1991[79]	Kuopio	1,288 men aged 42-60	1 month - 2.5 years	CHD events	None

EVIDENCE TABLE 4. CAROTID INTIMA-MEDIA THICKNESS AS A RISK FACTOR FOR CORONARY HEART DISEASE

Author, year, title	Demographics	Results	Quality rating
Belcaro, 1996[83]	Ages 30-70; no prevalent CVD	Univariate analysis: Subjects with lower US score had lower event rates	Poor
Chambless, 2003[41]	No baseline CVD, DM, HTN, or hyperlipidemia	Women Men Tertile 3/1: 3.76 (1.68-8.43) 2.02 (1.32-3.09) >95th/less 2.42 (1.45-4.04) 1.36 (0.84-2.18) >1mm 2.62 (1.55-4.46) 1.20 (0.81-1.77) 0.19mm continuous 1.42 (1.24-1.64) 1.18 (1.06-1.32)	Good
O'Leary,1999[86]	Median age 72, 32% men, 15.2% African American	Composite score: Maximal CCA and ICA IMT (by quintile) 1: 1.0 2: 1.58 (0.89-2.81) 3: 2.20 (1.28-3.78) 4: 2.45 (1.44-4.19) 5: 3.61 (2.13-6.11) per 1 SD 1.36 (1.23-1.52) P trend < 0.001	Fair
Salonen, 1991[79]	Ages (n) NR aged 42: 277 aged 48: 299 aged 54: 365 aged 60: 347	IMT (MM) 2.14 (1.08-4.26) Small plaques in common carotid 4.15 (1.51-11.47) Large "stenotic" plaques 6.71 (1.33-33.91)	Poor

EVIDENCE TABLE 4. CAROTID INTIMA-MEDIA THICKNESS AS A RISK FACTOR FOR CORONARY HEART DISEASE

Author, year, title	Parent study	N enrolled	Duration follow-up	Outcomes	Variables adjusted for in analysis
Van der Meer, 2004[87]	Rotterdam	6389	Until January 2000	Incident MI	Age Sex TC HDL BP DM BMI Smoking ASA BP meds Lipid meds

EVIDENCE TABLE 4. CAROTID INTIMA-MEDIA THICKNESS AS A RISK FACTOR FOR CORONARY HEART DISEASE

Author, year, title	Demographics	Results				Quality rating
Van der Meer, 2004[87]	Mean age 69.3 10% with DM 22% smokers 62% women	IMT:	Continuous(ISD)	1.28(1.14-1.44)		Good
				Women	Men	
		Mild	1.19(0.75-1.89)	1.15(0.46-2.89)	1.30(0.71-2.38)	
		Mod	1.24(0.81-1.88)	2.98(1.35-6.59)	1.14(0.62-2.10)	
		Severe	1.74(1.19-2.56)	3.80(1.64-8.79)	2.24(1.22-4.11)	

Abbreviations

ASA=Aspirin, BMI=Body mass index, BP=Blood pressure, CCA=Common carotid artery, CHD=Coronary heart disease, CVD=Cardiovascular disease, dBP=Diastolic blood pressure, DM=Diabetes mellitus, HDL=High density lipoprotein, ICA=Internal carotid artery, IMT=Intima-media thickness, MI=Myocardial Infarction, sBP=Systolic blood pressure, SD=Standard deviation, TC=Total cholesterol

EVIDENCE TABLE 5. ELECTRON BEAM COMPUTED TOMOGRAPHY SCORE AS A RISK FACTOR FOR CORONARY HEART DISEASE

Author, title, year	Source of cohort	Mean age (±SD)	Percent female	Observed annual hard event rate for entire cohort	Observed hard events / total no. of study participants	Mean length of follow-up (years)
Arad et al, 2000[91]	self-referred	53±11	29%	0.40%	18 / 1177	3.6
Arad et al, 2005[93]	population-based	59±6	35%	‡0.20%	40 / 4613	4.3
Greenland, 2004[95]	population-based	65.7±7.8	10%	0.94%,# 0.97%	17 / 257,# 26 / 383	7¶
Kondos, 2003[94]	self-referred	50±9 for men; 54±9 women	26%	0.4% (M) 0.1% (W)	52 / 4151 (M) 6 / 1484 (F)	3.1

EVIDENCE TABLE 5. ELECTRON BEAM COMPUTED TOMOGRAPHY SCORE AS A RISK FACTOR FOR CORONARY HEART DISEASE

Author, title, year	Observed hard events per number of participants in highest CACS interval	Observed annual hard event rate for highest CACS interval	CACS groups for corresponding RR and OR	RR* (CI)	OR*(CI)
Arad et al, 2000[91]	not reported	N.A.	>80 160 600	NR	14.3 (4.9-42.3) 19.7 (6.9-56.4) 20.2 (7.3-55.8)
Arad et al, 2005[93]	63 / 450 (CACS ≥400)	3.3%§	□	NR	NR
Greenland, 2004[95]	8 / 41# 8 / 77 (CACS>300)	2.8%# 1.5% (CACS>300)	0 1-100 101-300 >300	1, 3.4 (0.7-17.7)# 3.2 (0.7-17.7)), 5.3 (1.1-25.0) 6.2 (1.0-37.0), 6.2 (1.2-31.8) 17.6 (3.7-83.0), 8.9 (1.9-41.8)	NR
Kondos, 2003[94]	24 / 1034 (M) 3 / 390 (F) (CAC>75th%)**	0.7% (M) 0.3% (F) (CAC>75th%)**	0 1-3.8 4-30 31-169 170-7000	1*** 1.76 (0.39-7.88) 2.84(0.73-11.11) 5.61 (1.57-20.06) 7.24 (2.01-26.15)	NR

EVIDENCE TABLE 5. ELECTRON BEAM COMPUTED TOMOGRAPHY SCORE AS A RISK FACTOR FOR CORONARY HEART DISEASE

Author, title, year	†Risk factors adjusted (italics=measured)	Endpoint for which RR's or OR's are calculated	Slice thickness	Minimum area of calcification	Quality rating
Arad et al, 2000[91]	age, htn, elevated TC, DM, smoking, family history	hard and soft coronary events	3 mm	0.93 mm2	Poor
Arad et al, 2005[93]	*age, gender, family history, LDL, HDL, smoking, blood pressure, DM, CRP*	hard and soft coronary events	3 mm	NR	Fair
Greenland, 2004[95]	Framingham risk score	hard coronary events	6 mm	NR	Good
Kondos, 2003[94]	age, smoking, htn, hypercholesterolemia, DM	hard coronary events	3 mm	1 mm2	Fair

EVIDENCE TABLE 5. ELECTRON BEAM COMPUTED TOMOGRAPHY SCORE AS A RISK FACTOR FOR CORONARY HEART DISEASE

Author, title, year	Source of cohort	Mean age (±SD)	Percent female	Observed annual hard event rate for entire cohort	Observed hard events / total no. of study participants	Mean length of follow-up (years)
LaMonte, 2005[97]	self and physician referred	54+/-10	36%	males 0.26% females 0.14%	males 62 / 6835 females 19 / 3911	3.5+/-1.4
Raggi, 2001[29]	physician-referred	52±16 - those without events; 55±8 - those with events	49%	1.60%	30 / 676	2.9
Taylor, 2005[98]	population-based	males - 42.9+/-2.8 females 42.8+/-2.7	18%	males 0.18% females 0%	males 9 / 1627 females 0 / 356	3+/-1.4
Vliegenthart, 2005[96]	population-based	71±5	58%	0.70%	40 / 1795	3.3

EVIDENCE TABLE 5. ELECTRON BEAM COMPUTED TOMOGRAPHY SCORE AS A RISK FACTOR FOR CORONARY HEART DISEASE

Author, title, year	Observed hard events per number of participants in highest CACS interval	Observed annual hard event rate for highest CACS interval	CACS groups for corresponding RR and OR	RR* (CI)	OR*(CI)
LaMonte, 2005[97]	males 34 / 1380 (CACS>249, 20% males) females 7 / 376 (CACS>112, 10% females)	males 0.7% (CAC>249) females 0.5% (CACS>112)	Men 0 1-38 39-249 >249 Women 0 1-16 17-112 >113	Men 1.0 3.3 (0.8-13.4) 10.2 (3-35.4) 17.7 (5.1-61.8) Women 1.0 2.2 (0.5-10.1) 3.9 (1.0-15.2) 7.2 (0.8-12.5)	NR
Raggi, 2001[29]	29 / 357 (CACS>0)	2.8% (CACS>0)	Increase in age-sex specific CACS decile	NR	1.03 (1.02-1.05)
Taylor, 2005[98]	7 / 124 (CACS>44, 7% males)	1.9% (CACS>44)	1-9 10-44 >44	4.32 (1.10-16.97) per increasing in tertile for those with CACS>0	NR
Vliegenthart, 2005[96]	14/196 (CACS >1000)	2.2% (CACS>1000)	0-100 101-400 401-1000 >1000	1 2.7 (1.0-7.7) 4.1 (1.4-11.6) 8.1 (2.9-22.3)	NR

EVIDENCE TABLE 5. ELECTRON BEAM COMPUTED TOMOGRAPHY SCORE AS A RISK FACTOR FOR CORONARY HEART DISEASE

Author, title, year	†Risk factors adjusted (italics=measured)	Endpoint for which RR's or OR's are calculated	Slice thickness	Minimum area of calcification	Quality rating
LaMonte, 2005[97]	age, sex by stratification, htn and hypercholesterolemia and DM and smoking (y/n)	hard coronary events	3 mm	NR	Fair
Raggi, 2001[29]	age, sex, smoking, htn, DM, and hypercholesterolemia	hard and soft coronary events and stroke	3 mm	1.03 mm2	Fair
Taylor, 2005[98]	Framingham risk score	hard coronary events and unstable angina	3 mm	NR	Good
Vliegenthart, 2005[96]	age, sex, *BMI, blood pressure ,TC* , *HDL* , smoking, DM, family history	hard coronary events	3 mm	0.65 mm2	Good

EVIDENCE TABLE 5. ELECTRON BEAM COMPUTED TOMOGRAPHY SCORE AS A RISK FACTOR FOR CORONARY HEART DISEASE

Author, title, year	Source of cohort	Mean age (±SD)	Percent female	Observed annual hard event rate for entire cohort	Observed hard events / total no. of study participants	Mean length of follow-up (years)
Wong, 2000[92]	self- and physician-referred	54±10	21%	0.30%	6 / 926	3.3

EVIDENCE TABLE 5. ELECTRON BEAM COMPUTED TOMOGRAPHY SCORE AS A RISK FACTOR FOR CORONARY HEART DISEASE

Author, title, year	Observed hard events per number of participants in highest CACS interval	Observed annual hard event rate for highest CACS interval	CACS groups for corresponding RR and OR	RR* (CI)	OR*(CI)
Wong, 2000[92]	1 / 122 (CACS>271)	0.2% (CACS>271)	1-15 16-80 81-270 >270	O.72 (p>0.05) 3.29 (p>0.05) 4.5 (p<0.05) 8.8 (p<0.001)	NR

EVIDENCE TABLE 5. ELECTRON BEAM COMPUTED TOMOGRAPHY SCORE AS A RISK FACTOR FOR CORONARY HEART DISEASE

Author, title, year	†Risk factors adjusted (italics=measured)	Endpoint for which RR's or OR's are calculated	Slice thickness	Minimum area of calcification	Quality rating
Wong, 2000[92]	age, gender, htn, hypercholesterolemia, DM, smoking	hard coronary events	3 mm	0.51 mm2	Fair

* adjusted

† Risk factors that were measured, rather than obtained by history, are in itallics.

‡ rate is for 4613 study participants of whom 1293 had risk factors measured and were included in multivariate analysis

§ event rate includes coronary death, nonfatal MI, CABG, and PTCA. Event rate for this combined outcome for entire cohort was 2.6%

 Framingham risk calculated in manuscript text. For intermediate-risk group (10-year risk 10-20%), observed coronary event rates (hard and soft) were greater than 2% per year for those with CAC scores in the highest 3rd tertile (actual CAC score not reported).

¶ median rather than mean

data for Framingham risk groups 10-15% and 16-20%, respectively. Referent for RR's is Framingham risk 0-9% and CAC score <300.

** CACS greater than 75th age-sex percentile

*** RR's are for males. RR's for females were not statistically significant.

ABBREVIATIONS: CACS = coronary artery calcium score; CS% = calcium score percentile; DM = diabetes mellitus; M=male, F=female; MI = myocardial infarction; OR= odds ratio; RR=relative risk

EVIDENCE TABLE 6. COHORT STUDIES OF HOMOCYSTEINE AS A RISK FACTOR FOR CORONARY HEART DISEASE

Author, year, title	Parent study	N enrolled	Duration follow-up	Variables adjusted for	Quality rating
Bostom, 1999[134]	Framingham	1933, mean age 71, males and females	10 years	Sex, age, DM, smoking, sBP, TC, LDL	Good
Nurk, 2002[135] *(See Vollset below)*	Hordaland Homocysteine Study	17361 men and women	Mean 5.3 years	Sex, age, smoking, DM, Cholesterol, BMI, sBP, HTN	Fair
Sacco, 2004[136]	Northern Manhattan Study	2939 men & women aged >=40, mean age 69 Excluded prevalent stroke.	Mean 5 years	Age, race, sex, education, HTN, DM, cardiac disease, HDL < 40, alcohol, smoking, renal insufficiency, B12 deficiency	Good
Stehouwer, 1998[137]	Zutphen Elderly Study, 7 countries studied	878 men aged 64-84, baseline CHD included Mean age 71	9+ years	Age, BMI, BP, HDL, TC, DM, smoking	Fair
Ubbink, 1998[138]	Caerphilly in South Wales	2398 mean age 50-64	5 years	Age, social class, sex, smoking, prevalent CHD, DM, BMI, HDL, TC, dBP	Fair
Vollset, 2001[139] *(See Nurk above)*	Hordaland	4766 men and women aged 65-67 of high and low CVD risk (prevalent CHD included)	4.1 years	TC, sBP, dBP, smoking, BMI, physical activity, age, sex, baseline CVD risk status	Fair
Voutilainen, 2004[140]	Kuopio	2,682 men recruited; 1,229 eligible No baseline CHD ages	7 years, 8 months	Age, exam year, sBP, smoking, BMI, LDL, HDL	Fair
Zylberstein, 2004[141]	24 year follow-up of the population study of women in Gotenburg without baseline myocardial infarction	1368 women aged 38-60	24 years	Age, smoking, BMI W/H ratio, TG, chol, BP, (coffee, creatinine, B-12, dietary folate) added to 3rd model	Fair

Abbreviations: AMI=acute myocardial infarction, BMI=body mass index, BP=blood pressure, CAD=coronary artery disease.

EVIDENCE TABLE 7. NESTED CASE CONTROL STUDIES OF HOMOCYSTEINE AS A RISK FACTOR FOR CORONARY HEART DISEASE

Author, year, title	Parent study	Enrolled N cases, N controls	Demographics	Duration of follow-up	List variables adjusted for	Quality rating
Albert, 2002[113]	Physicians Health Study	CA 97 CO 192	22,071 male physicians aged 40-84 without CVD	9 years	Age, smoking, length of follow-up, HTN, DM, BMI, FMH, alcohol use, exercise	Fair
Alfthan, 1994[114]	North Karelia	CA 92 men, 99 women CO 141 men, 128 women	12,055 men and women ages 30-64 from 2 Finnish provinces without CVD	9 years	Age, sex, TC sBP, smoking	Fair
Arnesen, 1995[115]	Tromso Health Study	CA 122 CO 478	~22,000 men and women aged 12-61	4 years	Survey date, age, sex, hours since last meal, TC, HDL, BP, DM, TG, smoking, angina	Fair
Blacher, 2002[116]	France	CA 110 CO 154	215 men, 49 women mean age 65 15 with prior CHD	Mean 14 years	Age, sex, BP, CRP, DM, prevalent CHD	Poor
Bots, 1999[117]	Rotterdam	CA 224 CO 533	Men and women age ≥ 55 ~24% of cases and 6.5% of controls with prior MI	2.7 years mean	Age, sex, TC, HDL, BP, DM, smoking, prevalent CHD or stroke	Good
Chasan-Taber, 1996[258]	Physicians Health Study	CA 333 CO 333	14,916 male physicians ages 40-84 without CHD	7.5	DM, angina, age, smoking, ASA use, HTN, quetelets, TC, HDL	Good
de Bree, 2003[118]	Monitoring Project on CVD RF	CA 170 CO 749	Men and women ages 20-59 Prevalent CHD excluded	8-13.4 years (mean 10.3 years)	Age, sex, TC, HDL, BP, smoking, creatinine, study center	Good

EVIDENCE TABLE 7. NESTED CASE CONTROL STUDIES OF HOMOCYSTEINE AS A RISK FACTOR FOR CORONARY HEART DISEASE

Author, year, title	Parent study	Enrolled N cases, N controls	Demographics	Duration of follow-up	List variables adjusted for	Quality rating
Evans, 1997[119]	MRFIT	CA 240 CO 472	12,866 Caucasian men aged 35-57 at moderately high risk	11-17 years	Age, smoking, clinic, race, HDL, LDL, smoking, TG, dBP	Good
Fallon, 2001[120]	Caerphilly	CA 312 CO 1248	Men aged 45-59 South Wales 29.8% of cases with ECG ischemia	10 years	Age, TC, HDL, smoking, TG, BMI, alcohol use, BP, fibrinogen prevalent CHD, DM, creatinine	Good
Folsom, 1998[121]	ARIC	CA 232 CO 537	Population -based, ages 45-64 Prevalent stroke, CHD, and TIA excluded men and women	Median 3.1 years	Age, sex, TC, HDL, BP, DM, smoking, race, center	Good
Hoogeveen, 2000[122]	Hoorn	CA 171 CO 640	Men and women aged 50-75 Prevalent CHD included	5 years	Age, sex, TC, BP, DM, smoking, HbAIC, albumin	Fair
Hultdin, 2004[123]	MONICA, VIP	CA 50 CO 56	89 men 17 women Age 53 Not clearly stated but appears prevalent MI excluded	8.4 years	Age, sex, creatinine albumin	Poor
Knekt, 2001[125]	Mobile clinic health exam survey Finland 1973-1976	With CHD CA 166 CO 311 Without CHD CA 272 CO 524	3471 men aged 45-64 884 (25%) with prior CHD	13 years	Age, sex, TC, BP, DM, smoking, alcohol use, BMI	Fair

EVIDENCE TABLE 7. NESTED CASE CONTROL STUDIES OF HOMOCYSTEINE AS A RISK FACTOR FOR CORONARY HEART DISEASE

Author, year, title	Parent study	Enrolled N cases, N controls	Demographics	Duration of follow-up	List variables adjusted for	Quality rating
Knekt, 2001 [124]	Mobile clinic health exam	Baseline CHD CA 74 CO 147 No CHD at Baseline CA 75 CO 149	3479 women aged 45-64 757 (22%) with prior CHD	13 years	Age, sex, TC, BP, DM, smoking, BMI	Good
Lind, 2003 [126]	Malmo	CA 241 CO 241	Men mean age 48 Prevalent CVD excluded	17 years	Age, sex, TC, BP, DM, smoking	Fair
Ridker, 1999[127] *(see Ridker 2000 below)*	Women' s Health Study	CA 122 CO 244	Women, mean age 59, enrolled in trial, post-menopausal, no prevalent CVD	3 years	Age, sex, TC, BP, BMI, exercise, family history	Good
Ridker, 2000[14]	Women' s Health Study	CA 122 CO 244	Womens Health Study Mean age 59.3 Post-menopausal No prevalent CVD	3 years	Age, sex, TC, HDL, BP, DM, smoking, BMI, ASA, vitamin E, family history, CVD, CRP, Lp(a)	Good
Shai, 2004[128]	Nurses Health Study	CA 237 CO 458	U.S. nurses ages 30-55 at inception, n=32826. Excluded prevalent CHD.	8 years	age, smoking, hours fasting, year Hcy, BMI, parental MI<age 60, HTN, DM, HRT, alcohol, activity, HDL, TC, CRP	Good
Stampfer, 1992[129]	Physicians Health Study	CA 271 CO 271	U.S. male physicians aged 40-84 (mean 58.9) Prior MI, CVA, TIA, Cancer excluded	5 years	Age, sex, TC, HDL, BP, DM, ASA, angina, BMI, smoking	Good

EVIDENCE TABLE 7. NESTED CASE CONTROL STUDIES OF HOMOCYSTEINE AS A RISK FACTOR FOR CORONARY HEART DISEASE

Author, year, title	Parent study	Enrolled N cases, N controls	Demographics	Duration of follow-up	List variables adjusted for	Quality rating
Verhoef, 1997[130]	Physicians Health Study	CA 149 CO 149	U.S. male physicians aged 40-84 (mean 58.9) Prior MI, CVA, TIA, Cancer excluded	9 years	TC, HDL, BP, DM, BMI, alcohol use, ASA	Good
Voutilainen, 2000[131]	Kuopio Ischemic Heart Disease Risk Factor Study	CA 163 CO 163	Men, median age 53 without prevalent CHD	8.9 years	Exam year, urinary nicotine	Poor
Wald, 1998[132]	British United Provident Association (BUPA)	CA 229 CO 1126	Men, median age 53, without prevalent CHD	8.7 years	Age, sex, BP, Apoprotein B	Poor
Whincup, 1999[133]	British regional heart study	CA 386 CO 454	7735 men aged 40-59 (mean ~52) Prevalent CHD included 44% CA 26% CO	12.8 years	Age, TC, HDL, BP, DM, smoking, BMI, exercise, alcohol use, FEV, creatinine, urate	Poor

Abbreviations:
ARIC=Atherosclerosis Risk in Communities Trial, ASA=acetylsalicylic acid, BMI=body mass index, CA=cases , CHD=coronary heart disease, CO=controls , CRP=c-reactive protein, CVD=cardiovascular disease, DM=diabetes mellitus, HTN=hypertension, ECG=electrocariogram, FEV=forced expiratory volume, Lp(a)=lipoprotein(a), MI=myocardial infarction, MONICA=Monitoring of Trends and Determinants in Cardiovascular Disease Study, MRFIT=Multiple risk factor intervention trial, RF=risk factor, sBP=systolic blood pressure,TC=total cholesterol, TG=triglycerides, TIA=transient ischemic attack, VIP=Vasterbotten Intervention Program.

EVIDENCE TABLE 8. LIPOPROTEIN(A) AS A RISK FACTOR FOR CORONARY HEART DISEASE

Author, year Cohort	Study design	N enrolled	Duration of follow-up	FRFs in model	Sample storage	Assay method
Bostom, 1994[164] & 1996[165] Framingham & Offspring	Cohort	3103 women; 2191 men	Median 15.4 years	Age, BP, TC/LDL, Diabetes, Gender, HDL, Smoking, BMI	Fresh	Electrophoresis; ELISA
Cantin, 1998[167] Quebec Cardiovascular Study	Cohort	2156 men	5 years	Age, BP, TC/LDL, Gender, HDL, Smoking; did not adjust for diabetes	Frozen 7 years at -80C	ELISA
Cremer, 1997[170] GRIPS	Cohort	5639 men	10 years	Age, BP, TC/LDL, Diabetes, Gender, HDL, Smoking, EtOH, physical activity, family hx of MI, apo B, apo AI, fibrinogen, uric acid	Frozen 9 years at -90C	ELISA
Dahlen, 1998[180 &] Thogersen, 2004[184] MONICA & VIP	NCC	62 cases 124 controls 100% male	NR	Age, BP, TC/LDL, Gender, Smoking, BMI; did not adjust for Diabetes and HDL	Frozen 9 years at -80C	ELISA
Evans 2001[149] MRFIT	NCC	246 cases 490 controls for Lp(a) analysis; 246 controls for apo(a) isoform 100% male	Up to 20 years	Age, Diabetes, Gender, Smoking, apo(a) size; did not adjust for BP, TC/LDL and HDL. (Model not reported adjusted for all FRFs +CRP: null finding)	Frozen 20 years at -50 to 70C	ELISA
Jauhiainen, 1991[181] Helsinki Heart Study	NCC	138 cases 130 controls 100% male	5 years	Age, TC/LDL, Gender, HCL, Smoking, did not adjust for BP abd Diabetes	Frozen 7 years at -20C	ELISA

EVIDENCE TABLE 8. LIPOPROTEIN(A) AS A RISK FACTOR FOR CORONARY HEART DISEASE

Author, year Cohort	Type of categorization	RR	RR.LB	RR.UB	Study quality	Significant association?
Bostom, 1994[164] & 1996[165] Framingham & Offspring	Dichotomous: band presence vs. absence Band presence generally correlates to Lp(a) levels of >30 mg/dL.	Men: 1.9 Women: 1.61	Men: 1.2 Women: 1.13	Men: 2.9 Women: 2.29	Good	Y
Cantin, 1998[167] Quebec Cardiovascular Study	Tertiles, mg/dL: <11.0 11.0-33.0 >33.0	1.16	0.73	1.85	Fair	N
Cremer, 1997[170] GRIPS	Dichotomous: <30 v. >=30 mg/dL	2.0 (p=0.0001)	NR	NR	Fair	Y
Dahlen, 1998[180 &] Thogersen, 2004[184] MONICA & VIP	Dichotomous: <20 v. >=20 mg/dL; Categorized: <=30 mg/L 30-65 mg/L 65-134 mg/L >134 mg/L	Dichot: 6.76 Categ: 7.21	Dichot: 2.11 Categ: 1.31	Dichot: 21.68 Categ: 39.8	Fair	Y
Evans 2001[149] MRFIT	Quartiles, mg/dL: 0.1-1.2 1.3-3.4 3.5-9.2 9.3-83.3 Results are for nonfatal MI among smokers	0.99	0.95	1.03	Fair	N
Jauhiainen, 1991[181] Helsinki Heart Study	Dichotomous: <28 v. >=28 mg/dL	1.32	0.77	2	Fair	N

EVIDENCE TABLE 8. LIPOPROTEIN(A) AS A RISK FACTOR FOR CORONARY HEART DISEASE

Author, year Cohort	Study design	N enrolled	Duration of follow-up	FRFs in model	Sample storage	Assay method
Kronenberg, 1999[191] Bruneck Study	Cohort	421 men 498 women	5 years	Analysis stratified by high and low molecular weight apo(a).	NR	ELISA
Luc, 2002[172] PRIME	Cohort	9133 men	5 years	Age, BP, TC/LDL, Diabetes, Gender, HDL, Smoking, TG	Fresh	Immunoassay
Nguyen, 1997[173]	Cohort	4967 men; 4969 women	14.1 years in women, 13.9 years in men	Age, BP, TC/LDL, Diabetes, Gender, TG; did not adjust for HDL and smoking	Fresh	Electrophoresis
Pischon, 2005[186] Health Professionals Follow-up Study	NCC	243 cases 496 controls 100% male	6 years	Age, gender, history of hypertension, diabetes, smoking; did not adjust for TC, LDL, HDL.	Frozen in liquid nitrogen at -130C, duration not reported.	Immunoturbi-metric method
Price, 2001[174] Edinburgh Artery Study	Cohort	809 men; 783 women	5 years	Age, BP, TC/LDL, Gender, HDL, Smoking, BMI, fibrinogen; did not adjust for diabetes	Frozen 7 years at -50C	ELISA
Ridker, 1993[182] Physicians' Health Study	NCC	296 cases 296 controls 100% male	60.2 months	Age, BP, TC/LDL, Gender, HDL, Smoking, Randomized Rx, BMI, family hx of MI	Frozen 5 years (mean follow-up) at -80C	ELISA
Rosengren, 1990[162]	NCC	26 cases 109 controls 100% male	6 years	Age, BP, TC/LDL, Gender, Smoking, BMI, maternal hx of MI; did not adjust for diabetes and HDL	Frozen 6 years at -70C	NR

EVIDENCE TABLE 8. LIPOPROTEIN(A) AS A RISK FACTOR FOR CORONARY HEART DISEASE

Author, year Cohort	Type of categorization	RR	RR.LB	RR.UB	Study quality	Significant association?
Kronenberg, 1999[191] Bruneck Study	Lp(a) cutoff of 32 mg/dL. Referent group: HMW apo(a), low Lp(a).	HMW apo(a), high Lp(a): 1.0 LMW apo(a), high Lp(a): 3.4	HMW apo(a), high Lp(a): 0.2 LMW apo(a), high Lp(a): 1.7	HMW apo(a), high Lp(a): 4.6 LMW apo(a), high Lp(a): 6.5	Fair	N
Luc, 2002[172] PRIME	Quartiles, mg/dL: <21 21-66 66-210 >210	1.42	0.88	2.27	Good	N
Nguyen, 1997[173]	Categorized: Band presence in 4 groups of increasing amount (qualitative assessment)	Men: 1.6 Women: 1.9	Men: 1.0 Women: 1.3	Men: 2.6 Women: 2.9	Fair	Y
Pischon, 2005[186] Health Professionals Follow-up Study	Quintiles, median values per quintile (mg/dL): 1) 2.00 (reference) 2) 6.50 3) 11.60 4) 23.80 5) 67.35	1.59 P for trend = 0.11	0.95	2.65	Fair	N
Price, 2001[174] Edinburgh Artery Study	Continuous: one-unit increase of lp(a) on a logarithmic scale	1.06	0.91	1.24	Fair	N
Ridker, 1993[182] Physicians' Health Study	Quintiles, mg/dL: <=3 3.1-7.3 7.4-13.3 13.4-27.9 28-116	0.83	0.36	1.89	Fair	N
Rosengren, 1990[162]	Continuous per 0.1 mg/dL increase	1.0031 (p=0.010)	NR	NR	Fair	Y

EVIDENCE TABLE 8. LIPOPROTEIN(A) AS A RISK FACTOR FOR CORONARY HEART DISEASE

Author, year Cohort	Study design	N enrolled	Duration of follow-up	FRFs in model	Sample storage	Assay method
Salomaa, 2002[175] FINRISK	Cohort	986 men and 1254 women without baseline CHD	Mean 79 months	Age, BP, TC/LDL, Diabetes, Gender, Smoking; did not adjust for HDL	Frozen 8 months at -70C	Immunoradio-metric assay
Schaefer, 1994[183] Lipid Research Clinics - Coronary Primary Prevention Trial	NCC	233 cases 390 controls 100% male	7-10 years till 1983	Age, BP, TC/LDL, Diabetes, Gender HDL, Smoking, BMI	Frozen 18 years at -80C	ELISA
Seed, 2001[176] 2nd Northwick Park Heart Study	Cohort	3,052 men; 2,616 analyzed (free of CHD at baseline and with Lp(a) levels)	Mean 6 years	Age, BP, TC/LDL, Diabetes, Gender, Smoking; did not adjust for HDL	Frozen 1 year at -80C	ELISA
Sharrett, 2001[177] ARIC	Cohort	5432 men; 6907 women	10 years	Age, BP, TC/LDL, Diabetes, Gender, HDL, Smoking	Frozen 6 weeks at -70C	ELISA
Suk Danik, 2006[179] Women's Health Study	Cohort	27791 women	10 years	Age, BP, TC/LDL, Diabetes, Gender, HDL, Smoking. Model also adjusted for body mass index, current hormone therapy use, CRP, and treatment group (vit E, aspirin, or placebo)	Frozen at -150- to -180C, duration NR	Immunoturbi-metric method
Von Eckardstein, 2001[178] PROCAM	Cohort	820 men	10 years	Age, BP, TC/LDL, Diabetes, Gender HDL, Smoking, Angina, TG, family history of MI	Fresh	Electro-immunoassay

EVIDENCE TABLE 8. LIPOPROTEIN(A) AS A RISK FACTOR FOR CORONARY HEART DISEASE

Author, year Cohort	Type of categorization	RR	RR.LB	RR.UB	Study quality	Significant association?
Salomaa, 2002[175] FINRISK	Continuous per 1-SD increase	0.93	0.73	1.18	Fair	N
Schaefer, 1994[183] Lipid Research Clinics - Coronary Primary Prevention Trial	Quintiles, mg/dL: <=3.0 3.1-7.2 7.3-15.5 15.6-34.8 34.9-119.8	2.08	1.19	3.63	Fair	Y
Seed, 2001[176] 2nd Northwick Park Heart Study	Categorized, mg/dL: <2.9 2.9-26.3 >26.3 mg/dL	1.9	1.1	3.3	Fair	Y
Sharrett, 2001[177] ARIC	Continuous per 1-SD increase	Men: 1.15 (p<0.01) Women: 1.17 (p<0.01)	NR	NR	Good	Y
Suk Danik, 2006[179] Women's Health Study	Quintiles, median (range, mg/dL) in each: 1) 1.90 (0.10-3.40) 2) 5.40 (3.50-7.50) 3) 10.60 (7.60-15.30) 4) 24.30 (15.40-43.90) 5) 65.50 (44.00-239.60)	Women: 1.47	1.21	1.79	Good	Y
Von Eckardstein, 2001[178] PROCAM	Dichotomous: <20 v. >=20 mg/dL	2.7	1.4	5.2	Fair	Y

EVIDENCE TABLE 8. LIPOPROTEIN(A) AS A RISK FACTOR FOR CORONARY HEART DISEASE

Author, year Cohort	Study design	N enrolled	Duration of follow-up	FRFs in model	Sample storage	Assay method
Wild, 1997[185] Stanford Five-City Project	NCC	134 cases 134 controls 32.8% female	Cross-sectional population surveys were conducted every 2 years from 1979 to 1986, in 1989-1990	TC only. Did not exclude subjects with diabetes, and did not adjust for diabetes.	Frozen at -70C >5 years	ELISA

EVIDENCE TABLE 8. LIPOPROTEIN(A) AS A RISK FACTOR FOR CORONARY HEART DISEASE

Author, year Cohort	Type of categorization	RR	RR.LB	RR.UB	Study quality	Significant association?
Wild, 1997[185] Stanford Five-City Project	Odds are calculated for 3-quintile difference in log Lp(a), and 1-mmol/L unit difference for the cholesterol levels.	Men: 1.44 Women: 1.38	Men: 1.04 Women: 0.52	Men: 1.98 Women: 3.66	Fair	Yes, in men but not in women

Abbreviations:

Apo(a)=Apolipoprotein(a), apo AI=apolipoprotein A-1, apo B=apolipoprotein B, ARIC=Atherosclerosis Risk in Communities, BMI=body mass index, BP=blood pressure, CHD=coronary heart disease, CRP=c-reactive protein, ELISA=enzyme-linked immunosorbent assay, EtOH= Alcohol use, FRF=Framingham risk factor, GRIPS=Goettingen Risk Incidence and Prevalence Study, HDL=High density lipoprotein, Hx=History, LP(a)=Lipoprotein(a), MI=Myocardial infarction, MONICA=Monitoring of Trends and Determinants in Cardiovascular Disease, NCC=Nested case control, NR=Not reported, PROCAM=Prospective Cardiovascular Muenster Study, RR=Relative risk (LB=lower bound, UB=upper bound), Rx=Treatment, SD=Standard deviation, TC=Total cholesterol, TG=Triglycerides.

EVIDENCE TABLE 9. COHORT STUDIES OF C-REACTIVE PROTEIN AS A RISK FACTOR FOR CORONARY HEART DISEASE

Author, year	Study name	Population/sampling	N in analysis	% Male	Mean age/range (years)	Mean follow-up (years)
Blake, 2003[206]	WHS	Cohort derived from RCT of health professionals/ random	15,215	0	Mean = 54.1	8.1 (median)
Koenig, 2004[207]	MONICA	General community/ random	3,435	100	Incident CHD = 59.2 No incident CHD = 56.2 Range: 45 to 74	6.6
Koenig, 2004[208]	MONICA	General community/ random	934	100	All Subjects = 54.1 Incident CHD = 56.0 No incident CHD = 53.9 Range = 45 to 64	14
Lawlor, 2005[209]	British Women's Heart and Health Study	Community general practitioners' patient registries/ random stratified by town and age	2,723	0	Range = 60 to 79	3.5 (median)
Lowe, 2001[210]	Speedwell	General practitioners' patient panels/ complete	1595	100	Incident CHD = 58.6 No Incident CHD = 57.1 Range: 49 to 67	6.25
Lowe, 2004[211]	1) Caerphilly, and 2) Speedwell	General practitioners' patient panels & General community	3065	100	Range = 49 to 66	1) 8.75 2) 6.25
Mendall, 2000[212]	Caerphilly	General community	1,395	100	Range: 45 to 59	13.7
Park, 2002[213]	South Bay Heart Watch	General community/ respondents to mailing	967	90.5	Incident CHD = 67 No incident CHD = 66 Range: 45 and older	6.4

EVIDENCE TABLE 9. COHORT STUDIES OF C-REACTIVE PROTEIN AS A RISK FACTOR FOR CORONARY HEART DISEASE

	Definitions of Incident CHD Outcomes				
	Non-fatal MI			Deaths	
Author, year	Clinical features	ECG	Cardiac enzymes	Death certificate	Clinical Information
Blake, 2003[206]	1	1	1	1	1
Koenig, 2004[207]	1	1	1	1	1
Koenig, 2004[208]	1	1	1	1	1
Lawlor, 2005[209]	1	1	1	1	1
Lowe, 2001[210]	1	1	1	1	1
Lowe, 2004[211]	1	1	1	1	1
Mendall, 2000[212]	1	1	1	1	1
Park, 2002[213]	1	1	1	1	1

EVIDENCE TABLE 9. COHORT STUDIES OF C-REACTIVE PROTEIN AS A RISK FACTOR FOR CORONARY HEART DISEASE

		Framingham variables adjusted for in analyses							
Author, year	Other CVD Outcomes included in analysis	Age	Sex	Smoking	DM	HTN	HDL	LDL	TC
Blake, 2003[206]	Non-fatal ischemic stroke; coronary revascularization; and combined CV death	1	all female	1	1	1	1	1	0
Koenig, 2004[207]	None	1	all male	1	1	1	1	0	1
Koenig, 2004[208]	None	1	all male	1	1	1	1	0	1
Lawlor, 2005[209]	Angina; CABG; and angioplasty	1	all female	1	1	1	1	0	0
Lowe, 2001[210]	New Q-waves on follow-up ECG in the absence of Q-waves at baseline	1	all male	1	0	1	0	0	1
Lowe, 2004[211]	New Q-waves on follow-up ECG in the absence of Q-waves at baseline	1	all male	1	0	1	0	0	1
Mendall, 2000[212]	New Q-waves on follow-up ECG in the absence of Q-waves at baseline	1	all male	1	0	1	0	0	1
Park, 2002[213]	None	1	0	1	0	1	1	0	0

EVIDENCE TABLE 9. COHORT STUDIES OF C-REACTIVE PROTEIN AS A RISK FACTOR FOR CORONARY HEART DISEASE

Author, year	Other adjusted covariates	Number of Incident CHD events	Type of analysis	Analyzed by
Blake, 2003[206]	1) BMI; 2) Randomized assignment to ASA or Vitamin E	321 combined CV outcomes (97 Non-Fatal MI; 33 CVD deaths; 85 Non-Ischemic stroke; 106 Coronary Revascularization)	Cox proportional hazards regression	Dichotomous (<3mg/L and ≥3mg/L)
Koenig, 2004[207]	None	191	Cox proportional hazards regression	CDC/AHA cutpoints
Koenig, 2004[208]	1) Physical activity; 2) BMI; 3) Alcohol intake; 4) Education	97	Cox proportional hazards regression	Continuous
Lawlor, 2005[209]	1) BMI; 2) ETOH use; 3) exercise; 4) leg length; 5) trunk length; 6) FEV; 7) "Life course SES position"	151 (In the full sample of 3,745)	Cox proportional hazards regression	Continuous
Lowe, 2001[210]	1) BMI; 2) Ischemia at baseline; 3) Sample thawed/unthawed	191	Multiple logistic regression	Quintiles
Lowe, 2004[211]	1) Cohort membership; 2) BMI; 3) evidence of ischemia at baseline	351 (In the full sample of 3213)	Multiple logistic regression	Quintiles
Mendall, 2000[212]	1) Plate; 2) BMI; 3) FEV1; 4) ETOH; 5) Current and father's social class; 6) Fibrinogen	249	Multiple logistic regression	Quintiles
Park, 2002[213]	1) ASA use; 2) BMI; 3) Race	50	Cox regression	Continuous

EVIDENCE TABLE 9. COHORT STUDIES OF C-REACTIVE PROTEIN AS A RISK FACTOR FOR CORONARY HEART DISEASE

	Effect Size (RR, HR, OR) of CRP categories compared with lowest category (95% CI)					
Author, year	2nd	3rd	4th	5th	Effect Size (95% CI) for increase in CRP as continuous variable	Quality rating
Blake, 2003[206]	1.44 (no 95% CI reported, p=0.005)	n/a	n/a	n/a	n/a	Good
Koenig, 2004[207]	1.44 (0.95, 2.17)	2.21 (1.49, 3.27)	n/a	n/a	n/a	Good
Koenig, 2004[208]	n/a	n/a	n/a	n/a	1.28 (1.03, 1.06) [For 1 SD increase in CRP level]	Good
Lawlor, 2005[209]	n/a	n/a	n/a	n/a	1.03 (0.94, 1.13) [For doubling of CRP level]	Fair
Lowe, 2001[210]	nr	nr	nr	1.6 (0.90, 2.83)	n/a	Fair
Lowe, 2004[211]	nr	nr	nr	1.72 (1.14, 2.58)	n/a	Fair
Mendall, 2000[212]	1.11 (0.58, 2.10)	0.92 (0.48, 1.75)	1.14 (0.60, 2.15)	0.96 (0.50, 1.86)	n/a	Fair
Park, 2002[213]	n/a	n/a	n/a	n/a	1.49 (0.94, 2.37) [For 1 unit increase in log scale]	Fair

EVIDENCE TABLE 9. COHORT STUDIES OF C-REACTIVE PROTEIN AS A RISK FACTOR FOR CORONARY HEART DISEASE

Author, year	Study name	Population/sampling	N in analysis	% Male	Mean age/range (years)	Mean follow-up (years)
Pirro, 2001[214]	Quebec Cardiovascular	General community, using electoral lists/ random	2,037	100	Mean = 56.5 Range: 45 to 76	5
Ridker, 2005[215]	WHS	Cohort derived from RCT of health professionals/ random	15,632	0	Mean = 54.4 Range(interquartile): 48 to 59	10
Ridker, 2004[216]	WHS	Cohort derived from RCT of health professionals/ random	15,745	0	Range: 45 and older	9
Ridker, 2002[217]	WHS	Cohort derived from RCT of health professionals/ random	27,939	0	Mean = 54.7 Range: 45 and older	8
St. Pierre, 2005[218]	Quebec Cardiovascular	General community, using electoral lists/ random	1,982	100	All Subjects = 56.5 Incident CHD = 58.7 No Incident CHD = 56.2	13
Wilson, 2005[219]	Framingham (original and second generation offspring cohorts)	General community	4,446	43.8	Men = 57 Women = 59	8

EVIDENCE TABLE 9. COHORT STUDIES OF C-REACTIVE PROTEIN AS A RISK FACTOR FOR CORONARY HEART DISEASE

	Definitions of Incident CHD Outcomes				
	Non-fatal MI			Deaths	
Author, year	Clinical features	ECG	Cardiac enzymes	Death certificate	Clinical Information
Pirro, 2001[214]	1	1	1	1	1
Ridker, 2005[215]	1	1	1	1	1
Ridker, 2004[216]	1	1	1	1	1
Ridker, 2002[217]	1	1	1	1	1
St. Pierre, 2005[218]	1	1	1	1	1
Wilson, 2005[219]	*	*	*	*	*

EVIDENCE TABLE 9. COHORT STUDIES OF C-REACTIVE PROTEIN AS A RISK FACTOR FOR CORONARY HEART DISEASE

		Framingham variables adjusted for in analyses							
Author, year	Other CVD Outcomes included in analysis	Age	Sex	Smoking	DM	HTN	HDL	LDL	TC
Pirro, 2001[214]	Atypical angina and coronary insufficiency	1	all male	1	1	1	1	1	1
Ridker, 2005[215]	Non-fatal ischemic stroke; coronary revascularization; and combined CV death	1	all female	1	1	1	0	0	0
Ridker, 2004[216]	Non-fatal ischemic stroke; coronary revascularization; and combined CV death	1	all female	1	1	1	1	1	0
Ridker, 2002[217]	Non-fatal ischemic stroke; coronary revascularization; and combined CV death	1	all female	1	1	1	0	0	0
St. Pierre, 2005[218]	None	1	all male	1	1	1	1	1	0
Wilson, 2005[219]	None	1	0	1	1	1	1	0	1

EVIDENCE TABLE 9. COHORT STUDIES OF C-REACTIVE PROTEIN AS A RISK FACTOR FOR CORONARY HEART DISEASE

Author, year	Other adjusted covariates	Number of Incident CHD events	Type of analysis	Analyzed by
Pirro, 2001[214]	1) Medication use; 2) BMI; 3) Triglycerides	105 (61 "hard")	Cox proportional hazards regression	Dichotomous (<1.77mg/L and ≥1.77mg/L)
Ridker, 2005[215]	1) BMI; 2) Randomized assignment to ASA or Vitamin E	464 combined CV outcomes (131 MI; 76 "CV deaths")	Cox proportional hazards regression	Quintiles
Ridker, 2004[216]	None	698 combined CV outcomes	Cox proportional hazards regression	CDC/AHA cutpoints
Ridker, 2002[217]	1) Use of HRT; 2) Randomized assignment to ASA or Vitamin E	571 combined CV outcomes (371 CHD; 80 CV death; 158 Ischemic stroke)	Cox proportional hazards regression	Quintiles
St. Pierre, 2005[218]	1) Medication use; 2) BMI; 3) Triglycerides	210	Cox proportional hazards regression	Quartiles
Wilson, 2005[219]	None	160	Cox proportional hazards regression	CDC/AHA cutpoints

EVIDENCE TABLE 9. COHORT STUDIES OF C-REACTIVE PROTEIN AS A RISK FACTOR FOR CORONARY HEART DISEASE

	Effect Size (RR, HR, OR) of CRP categories compared with lowest category (95% CI)					
Author, year	2nd	3rd	4th	5th	Effect Size (95% CI) for increase in CRP as continuous variable	Quality rating
Pirro, 2001[214]	1.1 (0.7, 1.6)	n/a	n/a	n/a	n/a	Fair
Ridker, 2005[215]	1.85 (1.16, 2.96)	1.91 (1.21, 3.03)	2.38 (1.52, 3.72)	2.98 (1.90, 4.67)	n/a	Fair
Ridker, 2004[216]	1.2 (0.9, 1.6)	1.9 (1.4, 2.5)	n/a	n/a	n/a	Good
Ridker, 2002[217]	1.4 (0.9, 2.2)	1.6 (1.1, 2.4)	2.0 (1.3, 3.0)	2.3 (1.6, 3.4)	n/a	Fair
St. Pierre, 2005[218]	nr	nr	0.98 (0.65, 1.49)	n/a	n/a	Good
Wilson, 2005[219]	1.38 (0.88, 2.15)	1.22 (0.81, 1.84)	n/a	n/a	n/a	Fair

Abbreviations: AHA=American Heart Association, ASA=Acetylsalicylic acid, BMI=body mass index, CABG=coronary artery bypass graft, CDC=Centers for Disease Control, CHD=coronary heart disease, CI=confidence interval ,CV or CVD=cardiovascular disease, CRP=c-reactive protein, ECG=echocardiogram, ETOH=alcohol use, FEV=forced expiratory volume, MONICA=Monitoring of trends and determinants in cardiovascular disease study, RCT=randomized controlled trial, SD=standard deviation, SES=socio-economic status, WHS=Women's Health Study.

EVIDENCE TABLE 10. NESTED CASE CONTROL STUDIES OF C REACTIVE PROTEIN AS A RISK FACTOR FOR CORONARY HEART DISEASE

Author, year	Study name	Population/sampling	N in analysis	% Male	Mean age/range (years)
Ballantyne, 2004[227]	ARIC	Community/probability sample	1,348	Case=67.8 Non-case=41.1	Case=58.5 Non-case=56.7
Danesh, 2004[205]	Reykjavik Study	Community/random	5,933	Case=72 Control=69	Case=55.8 (9.3) Control=55.7 (9.1)
Danesh, 2000[204]	British Regional Heart Study	General practitioners' patient registries/random (summary for those with no baseline CHD)	1,149	100	Case=55.2 (5.3) Control=52.2 (5.3)
Folsom, 2002[228]	ARIC	Community/probability sample	1,205	Only reported by cohort quintile	Only reported by cohort quintile.
Luc, 2003[220]	PRIME	Community	772	100	Case=55.3 (2.9) Control=55.2 (2.7)
Pai, 2004[221]	NHS	National sample of registered nurses in U.S.	708	0	Case=60.4 (6.5) Control=60.2 (6.5)

EVIDENCE TABLE 10. NESTED CASE CONTROL STUDIES OF C REACTIVE PROTEIN AS A RISK FACTOR FOR CORONARY HEART DISEASE

		Definitions of Incident CHD Outcomes					
		Non-fatal MI			Deaths		
Author, year	Mean follow-up (years)	Clinical features	ECG	Cardiac enzymes	Death certificate	Clinical Information	Other CVD Outcomes included in analysis
Ballantyne, 2004[227]	Approximately 6.0 (time to event 4.1)	1	1	1	1	1	Silent MI (9.5%); and coronary revasculization (39.0%)
Danesh, 2004[205]	Case=17.5 (8.7) Control=20.6 (8.2)	1	1	1	1	0	None
Danesh, 2000[204]	Case=9.5	1	1	1	1	0	None
Folsom, 2002[228]	3.88	1	1	1	1	1	Silent MI (9.5%); and coronary revasculization (39.0%)
Luc, 2003[220]	5	1	1	1	1	1	Angina pectoris
Pai, 2004[221]	8	1	1	1	1	1	None

EVIDENCE TABLE 10. NESTED CASE CONTROL STUDIES OF C REACTIVE PROTEIN AS A RISK FACTOR FOR CORONARY HEART DISEASE

	Framingham variables adjusted for in analyses									
Author, year	**Age**	**Sex**	**Smoking**	**DM**	**HTN**	**HDL**	**LDL**	**TC**	**Other adjusted covariates**	**Type of analysis**
Ballantyne, 2004[227]	1	1	1	1	1	1	1	0	1) Race	Cox proportional hazards regression
Danesh, 2004[205]	1	1	1	1	1	0	0	1	1) Year of enrollment; 2) Triglycerides; 3) BMI; 4) FEV1	Unmatched stratified logistic regression
Danesh, 2000[204]	1	all male	1	0	1	1	0	1	1) Town; 2) Triglycerides; 3) BMI	Unmatched stratified logistic regression
Folsom, 2002[228]	1	1	1	1	1	1	0	1	1) Race; 2) Use of antihypertensives	Pooled logistic regression
Luc, 2003[220]	1	all male	1	1	1	1	1	0	1) Triglycerides; 2) Time and place of recruitment	Stratified conditional logistic regression
Pai, 2004[221]	1	all female	1	1	1	1	0	1	1) BMI; 2) ETOH intake; 3) Physical activity; 4) Month of sampling; 5) Parental history of CHD before 60 years old; 6) Fasting status; 7) HRT use	Unconditional logistic regression

EVIDENCE TABLE 10. NESTED CASE CONTROL STUDIES OF C REACTIVE PROTEIN AS A RISK FACTOR FOR CORONARY HEART DISEASE

Author, year	Analyzed by	Effect Size (RR, HR, OR) of CRP categories compared with lowest category (95% CI)				Effect Size (95% CI) for increase in CRP as continuous variable	Quality rating
		2nd	3rd	4th	5th		
Ballantyne, 2004[227]	CDC/AHA cutpoints	1.31 (0.96, 1.80)	1.72 (1.24, 2.39)	n/a	n/a	n/a	Good
Danesh, 2004[205]	Tertiles	nr	1.37 (1.17, 1.60)	n/a	n/a	n/a	Fair
Danesh, 2000[204]	Tertiles	nr	2.61 (1.81, 3.77)	n/a	n/a	n/a	Fair
Folsom, 2002[228]	Quintiles	0.8 (0.5, 1.3)	1.6 (1.0, 2.7)	1.9 (1.1, 3.4)	1.5 (0.8, 2.7)	n/a	Fair
Luc, 2003[220]	Tertiles	0.81 (0.47, 1.40)	2.16 (1.26, 3.72)	n/a	n/a	n/a	Good
Pai, 2004[221]	CDC/AHA cutpoints	1.17 (0.69, 2.00)	1.53 (0.89, 2.62)	n/a	n/a	n/a	Good

EVIDENCE TABLE 10. NESTED CASE CONTROL STUDIES OF C REACTIVE PROTEIN AS A RISK FACTOR FOR CORONARY HEART DISEASE

Author, year	Study name	Population/sampling	N in analysis	% Male	Mean age/range (years)
Pai, 2004[221]	HPFS	National sample of male health professionals in U.S.	794	100	Case=65.2 (8.3) Control=65.1 (8.3)
Pradhan, 2002[222]	WHI-OS	Nation-wide, general community, post-menopausal women/random with priority for ethnic minorities	560	0	In full sample of 608: case=69.0 (6.6) control=69.0 (6.6)
Ridker, 2000[14]	WHS	Case and control within RCT of female postmenopausal health professionals	366	0	Case=59.3 Control=59.3
Ridker, 1998[223]	WHS	Case and control within RCT of female postmenopausal health professionals	366	0	Case=59.3 (8.4) Control=59.3 (8.4)
Ridker, 1997[203]	PHS	Case and control within RCT of male health professionals	492	100	Case=58 (8.6) Control=59 (9.1)

EVIDENCE TABLE 10. NESTED CASE CONTROL STUDIES OF C REACTIVE PROTEIN AS A RISK FACTOR FOR CORONARY HEART DISEASE

		Definitions of Incident CHD Outcomes					
		Non-fatal MI			Deaths		
Author, year	Mean follow-up (years)	Clinical features	ECG	Cardiac enzymes	Death certificate	Clinical Information	Other CVD Outcomes included in analysis
Pai, 2004[221]	6	1	1	1	1	1	None
Pradhan, 2002[222]	2.9	1	1	1	1	1	None
Ridker, 2000[14]	3	1	1	1	1	1	Stroke; and coronary revasculation
Ridker, 1998[223]	3	1	1	1	1	1	Stroke; and coronary revasculation
Ridker, 1997[203]	8	1	1	1	1	1	Stroke; and venous thrombosis

EVIDENCE TABLE 10. NESTED CASE CONTROL STUDIES OF C REACTIVE PROTEIN AS A RISK FACTOR FOR CORONARY HEART DISEASE

	Framingham variables adjusted for in analyses									
Author, year	**Age**	**Sex**	**Smoking**	**DM**	**HTN**	**HDL**	**LDL**	**TC**	**Other adjusted covariates**	**Type of analysis**
Pai, 2004[221]	1	all male	1	1	1	1	0	1	1) BMI; 2) ETOH intake; 3) Physical activity; 4) Month of sampling; 5) Parental history of CHD before 60 years old	Unconditional logistic regression
Pradhan, 2002[222]	1	all female	1	1	1	1	0	1	1) BMI; 2) ETOH; 3) Exercise frequency; 4) Follow-up time; 5) Family history of premature CHD; 6) Ethnicity; 7) HRT use	Conditional logistic regression
Ridker, 2000[14]	1	all female	1	1	1	1	0	0	1) BMI; 2) parental history of premature MI	Logistic regression
Ridker, 1998[223]	1	all female	1	1	1	Adjusted for "hypercholester-olemia", unspecified.			1) Random assignment ASA/beta-carotene; 2)BMI; 3) Exercise; 4) Family history of CHD	Logistic regression
Ridker, 1997[203]	1	all male	1	1	1	0	0	0	1) Random assignment ASA/beta-carotene; 2) Time since randomization; 3) BMI; 4) Family history of CHD	Conditional logistic regression

EVIDENCE TABLE 10. NESTED CASE CONTROL STUDIES OF C REACTIVE PROTEIN AS A RISK FACTOR FOR CORONARY HEART DISEASE

Author, year	Analyzed by	Effect Size (RR, HR, OR) of CRP categories compared with lowest category (95% CI) 2nd	3rd	4th	5th	Effect Size (95% CI) for increase in CRP as continuous variable	Quality rating
Pai, 2004[221]	CDC/AHA cutpoints	1.60 (1.09, 2.34)	1.79 (1.14, 2.83)	n/a	n/a	n/a	Good
Pradhan, 2002[222]	Quartiles	1.4 (0.8, 2.8)	1.4 (0.7, 2.6)	2.1 (1.1, 4.1)	n/a	n/a	Good
Ridker, 2000[14]	Quartiles	nr	nr	3.1 (1.1, 8.3)	n/a	n/a	Fair
Ridker, 1998[223]	Quartiles	2.0 (0.8, 4.7)	2.3 (1.0, 5.6)	4.1 (1.7, 9.9)	n/a	n/a	Fair
Ridker, 1997[203]	Quartiles	1.5 (0.9, 2.5)	2.4 (1.5, 4.0)	2.6 (1.6, 4.4)	n/a	n/a	Fair

EVIDENCE TABLE 10. NESTED CASE CONTROL STUDIES OF C REACTIVE PROTEIN AS A RISK FACTOR FOR CORONARY HEART DISEASE

Author, year	Study name	Population/sampling	N in analysis	% Male	Mean age/range (years)
Rifai, 2002[224]	WHS	Case and control within RCT of female postmenopausal health professionals	260	0	Case = 60.4 Control = 60.3
Van der Meer, 2003[225]	Rotterdam Study	Community-based cohort	657	Case = 61.1 Control = 40.6	Case = 70.8 (7.6) Control = 69.2 (8.4)
Witherell, 2003[226]	Kaiser Permanente Medical Care Program (KPMCP)	Subscribers of KPMCP in Northern California	325	Case = 56.2 Control = 57.4	Case = 55.2 (7.5) Range = 40.0 to 68.2

EVIDENCE TABLE 10. NESTED CASE CONTROL STUDIES OF C REACTIVE PROTEIN AS A RISK FACTOR FOR CORONARY HEART DISEASE

		Definitions of Incident CHD Outcomes					
		Non-fatal MI			Deaths		
Author, year	Mean follow-up (years)	Clinical features	ECG	Cardiac enzymes	Death certificate	Clinical Information	Other CVD Outcomes included in analysis
Rifai, 2002[224]	4.8	1	1	1	1	1	Stroke
Van der Meer, 2003[225]	Mean not reported. Range = 4 to 8.	1	1	1	1	1	None
Witherell, 2003[226]	5.1	1	1	1	1	1	None

EVIDENCE TABLE 10. NESTED CASE CONTROL STUDIES OF C REACTIVE PROTEIN AS A RISK FACTOR FOR CORONARY HEART DISEASE

	Framingham variables adjusted for in analyses									
Author, year	**Age**	**Sex**	**Smoking**	**DM**	**HTN**	**HDL**	**LDL**	**TC**	**Other adjusted covariates**	**Type of analysis**
Rifai, 2002[224]	1	all female	1	1	1	Adjusted for "hyperlipidemia", unspecified.			1) Random assignment ASA/beta-carotene; 2)BMI; 3) Exercise; 4) Family history of CHD	Conditional logistic regression
Van der Meer, 2003[225]	1	1	1	1	1	1	0	1	1) Age squared; 2) BMI; 3) Family history of early MI	Logistic regression
Witherell, 2003[226]	1	1	1	0	1	0	0	1	1) interaction between TC and history of HTN; 2) Hx of abnormal ECG; 3) obesity; 4) race; 6) date of serum collection; 7) location of check-up	Logistic regression

EVIDENCE TABLE 10. NESTED CASE CONTROL STUDIES OF C REACTIVE PROTEIN AS A RISK FACTOR FOR CORONARY HEART DISEASE

Author, year	Analyzed by	Effect Size (RR, HR, OR) of CRP categories compared with lowest category (95% CI) 2nd	3rd	4th	5th	Effect Size (95% CI) for increase in CRP as continuous variable	Quality rating
Rifai, 2002[224]	Quartiles	2.9 (1.2, 7.1)	3.4 (1.4, 8.2)	5.6 (2.3, 13.2)	n/a	n/a	Fair
Van der Meer, 2003[225]	Quartiles	0.9 (0.5, 1.7)	1.0 (0.5, 1.9)	1.2 (0.6, 2.2)	n/a	n/a	Fair
Witherell, 2003[226]	Continuous	n/a	n/a	n/a	n/a	1.3 (1.0, 1.7) [For increase in CRP level of 1 natural log (i.e., 2.72-fold)]	Fair

Abbreviations: AHA=American Heart Association, ARIC=Atherosclerosis Risk in Communities Study, ASA=Acetylsalicylic acid, BMI=body mass index, CHD=coronary heart disease, CRP=c-reactive protein, CVD=cardiovascular disease, DM=diabetes mellitus, ECG=electrocardiogram, ETOH=alcohol use, FEV=forced expiratory volume, HPFS=Health Professionals Follow-up Study, HRT=hormone replacement therapy, HTN=hypertension, MI=myocardial infarction, NHS=Nurses Health Study, PRIME=Prospective Epidemiological Study of Myocardial Infarction, RCT=randomized controlled trial, TC=total cholesterol, WHI-OS=Women's Health Initiative Observational Study.

RISK DISTRIBUTION TABLE 11. DISTRIBUTION OF CRP LEVELS AND CLINICAL CHARACTERISTICS FOR 1949 US MEN 40 TO 79 YEARS WITH NO PRIOR HISTORY OF CHD OR CHD EQUIVALENT[†]

	hs-CRP < 1 mg/L n = 536 Weighted n = 11,997,526 (31%) Mean (95% CI)	hs-CRP 1-3 mg/L n = 758 Weighted n =15,140,641 (39%) Mean (95% CI)	hs-CRP > 3 mg/L n =655 Weighted n = 11,917,713 (31%) Mean (95% CI)
Age, years	51.9 (51.3, 52.4)	53.9 (53.4, 54.4)	55.3 (54.2, 56.5)
Total cholesterol, mg/dl	207.9 (206.2, 209.5)	210.9 (205.6, 216.1)	212.6 (208.3, 216.9)
High-density lipoprotein cholesterol, mg/dl	52.2 (51.6, 52.8)	47.0 (44.0, 50.0)	45.2 (44.8, 45.5)
Taking Medication for Cholesterol %	13.3% (12.2%, 14.5%)	16.5% (11.2%, 21.8%)	14.0% (12.3%, 15.7%)
Systolic blood pressure, mm Hg	124.1 (121.1, 127.0)	127.0 (126.1, 127.8)	130.5 (129.7, 131.3)
Taking Medication for Hypertension, %	12.1% (9.7%, 14.4%)	17.2% (14.9%, 19.6%)	26.8% (22.1%, 31.5%)
Current Smoker, %	16.7% (11.4%, 22.0%)	21.7% (15.8%, 27.6%)	31.4% (29.1%, 33.6%)
10 Year Risk of First Hard CHD Event[‡], %	7.3% (6.7%, 7.9%)	9.7% (8.6%, 10.9%)	11.8% (11.1%, 12.6%)
hsCRP Prevalence			
Caucasian American	30.7 (30.1, 31.4)	39.3 (37.6, 41.1)	29.9 (27.5, 32.3)
African American	26.4 (19.8, 32.9)	34.1 (27.8, 40.3)	39.6 (39.2, 39.9)
Hispanic American	30.4 (15.0, 45.8)	41.0 (27.5, 54.4)	28.7 (26.6, 30.7)

[†]Estimates are based on age-adjusted and population-weighted data for individuals selected from the the National Health and Nutrition Examination Survey 1999 to 2002

[‡] Estimated 10-year risk for first CHD event (fatal or nonfatal myocardial infarction) based on the NCEP/ATP III risk prediction equation

Abbreviations:

CHD = coronary heart disease, CI = confidence interval CRP = c-reactive protein.

RISK DISTRIBUTION TABLE 12. DISTRIBUTION OF CRP LEVELS AND CLINICAL CHARACTERISTICS FOR 2070 US WOMEN 40 TO 79 YEARS WITH NO PRIOR HISTORY OF CHD OR CHD EQUIVALENT†

	hs-CRP < 1 mg/L n = 365 Weighted n = 10,050,739(22%) Mean (95% CI)	hs-CRP 1-3 mg/L n = 648 Weighted n = 14,202,955 (31%) Mean (95% CI)	hs-CRP > 3 mg/L n = 1,057 Weighted n = 21,129,161 (47%) Mean (95% CI)
Age, years	51.8 (50.6, 53.0)	56.1 (56.0, 56.3)	56.2 (55.6, 56.7)
Total cholesterol, mg/dl	203.8 (200.2, 207.3)	215.5 (214.3, 216.7)	216.8 (216.5, 217.1)
High-density lipoprotein cholesterol, mg/dl	62.8 (60.0, 65.6)	59.6 (58.6, 60.5)	55.8 (54.5, 57.1)
Taking Medication for Cholesterol %	9.2% (7.8%, 10.7%)	16.5% (15.5%, 17.4%)	15.1% (14.0%, 16.1%)
Systolic blood pressure, mm Hg	122.3 (119.5, 125.2)	128.8 (126.7, 130.9)	132.0 (128.3, 135.7)
Hypertension treatment, %	12.0% (5.2%, 18.8%)	25.0% (19.5%, 30.5%)	32.1% (23.0%, 41.1%)
Current Smoker, %	18.3% (14.8%, 21.9%)	18.6% (18.4%, 18.9%)	17.2% (16.8%, 17.6%)
10 Year Risk of First Hard CHD Event‡, %	2.0% (1.7%, 2.4%)	3.4% (2.9%, 3.9%)	3.9% (3.6%, 4.2%)
Prevalence of hs-CRP			
Caucasian American	23.3 (18.9, 27.7)	31.4 (27.7, 35.1)	45.2 (43.7, 46.8)
African American	15.0 (13.9, 16.1)	30.0 (29.6, 30.3)	55.0 (54.0, 56.0)
Hispanic American	13.5 (6.8, 20.2)	33.4 (26.4, 40.5)	53.1 (52.8, 53.4)

†Estimates are based on age-adjusted and population-weighted data for individuals selected from the the National Health and Nutrition Examination Survey 1999 to 2002

‡ Estimated 10-year risk for first CHD event (fatal or nonfatal myocardial infarction) based on the NCEP/ATP III risk prediction equation

Abbreviations:
CHD = coronary heart disease, CI = confidence interval, CRP = c-reactive protein.

RISK DISTRIBUTION TABLE 13. RISK FOR FIRST HARD CHD EVENT AMONG US ADULTS AGE 40 TO 79 YEARS BEFORE AND AFTER ADJUSTMENT FOR RISK RELATED TO CRP[†]

		10-Year Risk for CHD, % of Weighted Population, (95% CI)					
		Before Adjustment for CRP [§]			After Adjustment for CRP		
	n (weighted n)	<10%	10-20%	>20%	<10%	10-20%	>20%
Men							
40-49	646	87.8	11.1	1.2	86.0	12.6	1.4
	(16,851,595)	(86.5 ,89.0)	(7.8 ,14.3)	(0.0 ,3.2)	(85.6 ,86.4)	(10.2 ,15.1)	(0.0 ,3.5)
50-59	457	67.5	28.1	4.4	64.8	27.9	7.3
	(11,314,783)	(64.4 ,70.5)	(21.6 ,34.7)	(0.8 ,8.0)	(58.7 ,70.8)	(25.3 ,30.5)	(3.4 ,11.2)
60-69	493	15.7	70.8	13.5	23.2	60.2	16.6
	(6,536,782)	(13.9 ,17.6)	(64.5 ,77.1)	(5.4 ,21.6)	(22.0 ,24.5)	(49.8 ,70.6)	(5.8 ,27.5)
70-79	353	1.8	53.0	45.2	3.6	49.1	47.3
	(4,352,720)	(0.0 ,5.2)	(48.8 ,57.2)	(41.1 ,49.2)	(2.2 ,5.1)	(46.2 ,52.0)	(43.6 ,51.0)
Total	1,949	60.3	30.7	9.1	60.1	29.1	10.8
	(39,055,881)	(60.0 ,60.5)	(29.5 ,31.8)	(8.1 ,10.0)	(57.5 ,62.8)	(25.2 ,32.9)	(9.5 ,12.0)
Women							
40-49[‡]	662	99.4	0.5	0.1	99.1	0.8	0.1
	(17,798,619)	(99.2 ,99.5)	(0.4 ,0.6)	(0.0 ,0.3)	(98.8 ,99.5)	(0.2 ,1.3)	(0.0 ,0.3)
50-59[‡]	473	98.1	1.6	0.3	98.0	1.7	0.3
	(12,317,649)	(98.0 ,98.2)	(1.0 ,2.3)	(0.0 ,1.0)	(97.2 ,98.9)	(1.5 ,1.8)	(0.0 ,1.0)
60-69	556	90.5	9.0	0.5	88.5	10.4	1.0
	(8,185,685)	(84.9 ,96.1)	(4.0 ,14.0)	(0.0 ,1.1)	(86.1 ,90.9)	(9.9 ,11.0)	(0.0 ,3.0)
70-79	379	66.3	30.6	3.1	67.7	27.7	4.6
	(7,080,903)	(65.0 ,67.5)	(28.5 ,32.7)	(2.2 ,4.0)	(61.0 ,74.3)	(20.0 ,35.4)	(3.5 ,5.7)
Total	2,070	92.3	7.0	0.7	88.5	10.4	1.0
	(45,382,856)	(84.9 ,96.1)	(4.0 ,14.0)	(0.0 ,1.1)	(86.1 ,90.9)	(9.9 ,11.0)	(0.0 ,3.0)
Race/Ethnicity							
Men							
Caucasian	978	59.8	31	9.2	59.3	29.9	10.8
	(30,460,553)	(58.8 ,60.8)	(30.3 ,31.7)	(8.4 ,9.9)	(59.0 ,59.6)	(28.7 ,31.1)	(9.9 ,11.7)
African American	371	59.7	31.0	9.3	60.6	27.9	11.5
	(3,502,278)	(56.0 ,63.4)	(28.5 ,33.6)	(3.0 ,15.5)	(59.0 ,62.2)	(25.1 ,30.6)	(7.1 ,15.9)
Hispanic	561	66.6	25.0	8.4	64.8	25.0	10.1
	(4,034,941)	(58.9 ,74.3)	(19.6 ,30.5)	(6.0 ,10.7)	(47.6 ,82.0)	(7.8 ,42.2)	(9.8 ,10.5)
Women							
Caucasian	1,012	92.3	7.1	0.6	91.8	7.2	1.0
	(34,562,831)	(91.3 ,93.3)	(6.8 ,7.4)	(0.0 ,1.3)	(91.3 ,92.4)	(6.5 ,7.8)	(0.0 ,2.1)
African American	382	91.2	7.5	1.3	90.2	8.0	1.8
	(4,267,199)	(86.2 ,96.2)	(3.6 ,11.4)	(0.2 ,2.4)	(86.7 ,93.7)	(5.9 ,10.0)	(0.3 ,3.2)
Hispanic	625	93.7	5.4	0.9	92.8	6.2	1.0
	(4,844,679)	(93.5 ,93.9)	(4.5 ,6.3)	(0.0 ,2.0)	(89.0 ,96.6)	(3.2 ,9.2)	(0.2 ,1.9)

[†] Estimates are based on age-adjusted and population-weighted data for individuals from the National Health and Nutrition Examination Survey 1999 to 2002 with no prior history of CHD or CHD equivalent

[§] Estimated 10-year risk for first CHD event (recognized or unrecognized myocardial infarction or coronary death) based on the NCEP/ATP III risk prediction equation

[‡] Estimate unstable due to small sample size.

Abbreviations:

CHD = coronary heart disease, CRP = c-reactive protein.

RISK DISTRIBUTION TABLE 14. DISTRIBUTION OF EXPECTED CHD EVENTS AT 10 YEARS AMONG US ADULT POPULATION 40 TO 79 YEARS OLD WITH 10-20% 10-YEAR RISK BEFORE AND AFTER ADJUSTMENT FOR RISK ASSOCIATED WITH CRP*

		Before Adjustment for CRP			After adjustment for CRP								
		Number at Risk weighted n	10-Year Risk for CHD Events, %	Expected CHD Events,† weighted n	Number at Risk for CHD Events at 10 Years by Risk Category weighted n (% Total)						10-Year Risk for CHD Events, %		
Men	Age, yr	10-20%	10-20%	10-20%	<10%		10-20%		>20%		<10%	10-20%	>20%
	40-49‡	1,863,023	13.8%	257,221	187,343	(10.1%)	1,616,219	(86.8%)	59,462	(3.2%)	8.1%	14.2%	20.9%
	50-59	3,182,698	14.0%	444,077	409,889	(12.9%)	2,415,479	(75.9%)	357,330	(11.2%)	8.9%	13.7%	21.7%
	60-69	4,628,912	14.6%	673,710	703,156	(15.2%)	3,480,548	(75.2%)	445,209	(9.6%)	9.0%	14.7%	21.9%
	70-79	2,307,221	16.1%	371,580	79,811	(3.5%)	1,817,562	(78.8%)	409,848	(17.8%)	9.0%	15.0%	22.2%
	Total	11,981,854	14.6%	1,746,589	1,380,198	(11.5%)	9,329,808	(77.9%)	1,271,849	(10.6%)	8.8%	14.4%	21.9%
Women	Age, yr	10-20%	10-20%	10-20%	<10%		10-20%		>20%		<10%	10-20%	>20%
	40-49‡	93,394	15.7%	14,650			93,394	(100.0%)				15.7%	
	50-59‡	197,679	12.4%	24,474	62,980	(31.9%)	134,699	(68.1%)			8.0%	14.4%	
	60-69‡	736,351	13.7%	100,696	101,060	(13.7%)	582,107	(79.1%)	53,185	(7.2%)	7.7%	14.0%	21.8%
	70-79‡	2,168,696	13.4%	291,120	515,720	(23.8%)	1,514,005	(69.8%)	138,971	(6.4%)	8.7%	14.3%	21.2%
	Total	3,196,119	13.5%	430,939	679,760	(21.3%)	2,324,204	(72.7%)	192,156	(6.0%)	8.5%	14.3%	21.3%

* Estimates are based on age-adjusted and population-weighted data for individuals from the National Health and Nutrition Examination Survey 1999 to 2002 with no prior history of CHD or CHD equivalent

† Estimated 10-year risk for first CHD event (recognized or unrecognized myocardial infarction or coronary death) based on the NCEP/ATP III risk prediction equation

‡ Estimates unstable due to small sample size.

Abbreviations:

CHD = coronary heart disease, CRP = c-reactive protein.

RISK DISTRIBUTION TABLE 14. DISTRIBUTION OF EXPECTED CHD EVENTS AT 10 YEARS AMONG US ADULT POPULATION 40 TO 79 YEARS OLD WITH 10-20% 10-YEAR RISK BEFORE AND AFTER ADJUSTMENT FOR RISK ASSOCIATED WITH CRP*

		After adjustment for CRP						
		Expected CHD Events at 10 years by Risk Category weighted n (% Total)						CHD Events per 1000 Persons Averted with Treatment[§]
Men	Age, yr	<10%		10-20%		>20%		n/1000
	40-49[‡]	15,106	(5.9%)	229,691	(89.3%)	12,424	(4.8%)	14.5
	50-59	36,611	(8.2%)	329,947	(74.3%)	77,519	(17.5%)	52.4
	60-69	63,161	(9.4%)	513,204	(76.2%)	97,346	(14.4%)	43.3
	70-79	7,184	(1.9%)	273,260	(73.5%)	91,136	(24.5%)	73.6
	Total	122,062	(7.0%)	1,346,102	(77.1%)	278,426	(15.9%)	47.8
Women	Age, yr	<10%		10-20%		>20%		n/1000
	40-49[‡]			14,650	(100%)			—
	50-59[‡]	5,030	(20.6%)	19,444	(79.4%)			—
	60-69[‡]	7,780	(7.7%)	81,343	(80.8%)	11,573	(11.5%)	34.5
	70-79[‡]	44,651	(15.3%)	217,060	(74.6%)	29,409	(10.1%)	30.3
	Total	57,461	(13.3%)	332,497	(77.2%)	40,981	(9.5%)	28.5

[§]Based on treatment of individuals with >20% 10-year risk for CHD events after adjustment of CRP assuming 30% reduction in the 10-year risk of CHD events and 100% compliance with treatment.

RISK DISTRIBUTION TABLE 15. CLINICAL CHARACTERISTICS OF US MEN 40 TO 79 YEARS WITH 10-20% 10-YEAR CHD RISK AFTER ADJUSTMENT OF CRP[†]

	10-Year Risk for CHD Events, %	
	10-20%	>20%
n (weighted n)	565 (9,329,808)	93 (1,271,849)
Age, years	60.4 (59.9, 60.9)	64.4 (63.9, 64.8)
Total cholesterol, mg/dl	216.2 (216.2, 216.3)	224.7 (218.8, 230.7)
High-density lipoprotein cholesterol, mg/dl	46.8 (46.1, 47.5)	45.6 (44.0, 47.1)
Taking Medication for Cholesterol %	15.4% (3.1%, 27.6%)	22.3% (19.8%, 24.8%)
Systolic blood pressure, mm Hg	131.4 (130.2, 132.6)	137.2 (136.1, 138.4)
Taking Medication for Hypertension, %	26.1% (20.8%, 31.3%)	36.0% (20.8%, 51.2%)
Current Smoker, %	37.4% (34.9%, 39.9%)	36.0% (16.7%, 55.3%)
10 Year Risk of "Hard" CHD Event[‡], %	14.4% (13.9%, 14.9%)	21.9% (21.8%, 22.0%)

[†]Estimates are based on age-adjusted and population-weighted data for individuals selected from the the National Health and Nutrition Examination Survey 1999 to 2002 with no history of CHD or CHD Equivalent

[‡] Estimated 10-year risk for first CHD event (recognized or unrecognized myocardial infarction or coronary death) based on the NCEP/ATP III risk prediction equation after adjustment for risk related to CRP

Abbreviations:
CHD = coronary heart disease, CRP = c-reactive protein.