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C-Reactive Protein as a Risk Factor for Coronary Heart Disease: A Systematic Review and Meta-analyses for the U.S. Preventive Services Task Force

David I. Buckley, MD, MPH; Rongwei Fu, PhD; Michele Freeman, MPH; Kevin Rogers, MD; and Mark Helfand, MD, MPH

Background: C-reactive protein (CRP) may help to refine global risk assessment for coronary heart disease (CHD), particularly among persons who are at intermediate risk on the basis of traditional risk factors alone.

Purpose: To assist the U.S. Preventive Services Task Force (USPSTF) in determining whether CRP should be incorporated into guidelines for CHD risk assessment.

Data Sources: MEDLINE search of English-language articles (1966 to November 2007), supplemented by reference lists of reviews, pertinent studies, editorials, and Web sites and by expert suggestions.

Study Selection: Prospective cohort, case–cohort, and nested case–control studies relevant to the independent predictive ability of CRP when used in intermediate-risk persons.

Data Extraction: Included studies were reviewed according to predefined criteria, and the quality of each study was rated.

Data Synthesis: The validity of the body of evidence and the net benefit or harm of using CRP for CHD risk assessment were evaluated. The combined magnitude of effect was determined by meta-analysis. The body of evidence is of good quality, consistency, and applicability. For good studies that adjusted for all Framingham risk variables, the summary estimate of relative risk for incident CHD was 1.58 (95% CI, 1.37 to 1.83) for CRP levels greater than 3.0 mg/L compared with levels less than 1.0 mg/L. Analyses from 4 large cohorts were consistent in finding evidence that including CRP improves risk stratification among initially intermediate-risk persons. C-reactive protein has desirable test characteristics, and good data exist on the prevalence of elevated CRP levels in intermediate-risk persons. Limited evidence links changes in CRP level to primary prevention of CHD events.

Limitations: Study methods for measuring Framingham risk variables and other covariates varied. Ethnic and racial minority populations were poorly represented in most studies, limiting generalizability. Few studies directly assessed the effect of CRP on risk reclassification in intermediate-risk persons.

Conclusion: Strong evidence indicates that CRP is associated with CHD events. Moderate, consistent evidence suggests that adding CRP to risk prediction models among initially intermediate-risk persons improves risk stratification. However, sufficient evidence that reducing CRP levels prevents CHD events is lacking.

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For author affiliations, see end of text.

In the United States, cardiovascular disease accounts for nearly 40% of all deaths each year (1). The factors that make up the Framingham risk score (age, sex, blood pressure, serum total cholesterol or low-density lipoprotein cholesterol level, high-density lipoprotein cholesterol level, cigarette smoking, and diabetes) account for most of the excess risk for incident coronary heart disease (CHD) (2, 3). However, these factors do not explain all of the excess risk (4, 5), and approximately 40% of CHD deaths occur in persons with cholesterol levels that are lower than the population average (6). Several lines of evidence (7, 8) have implicated chronic inflammation in CHD, and inflammatory markers have received much attention as new or emerging risk factors that could account for some of the unexplained variability in CHD risk.

C-reactive protein (CRP) is a sensitive, nonspecific systemic marker of inflammation (9). Although it is unknown whether CRP is involved in CHD pathogenesis (10, 11), elevated serum CRP levels are associated with traditional cardiovascular risk factors and obesity (12, 13). In 2002, an expert panel recommended against routine use of CRP in risk assessment for primary prevention of CHD but supported CRP measurement in persons with a 10-year CHD risk of 10% to 20%. It noted that the benefits of this strategy "remain uncertain" and recommended further research into the implications of using CRP in risk categorization for therapeutic risk reduction in patients (14).

The potential clinical benefit of new risk factors for refining global risk assessment is thought to be greatest for persons who are classified as intermediate-risk when stratified by using conventional risk factors (15). In the Framingham risk scoring system, intermediate-risk persons are those with a 10% to 20% risk for coronary death or nonfatal myocardial infarction ("hard CHD events") over 10 years. Further stratification by using new markers might reclassify some intermediate-risk persons as low-risk (10-year risk <10%) and others as high-risk (10-year risk >20%). This would permit more aggressive risk reduction

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therapy in persons reclassified as high-risk and may consequently reduce incident CHD events (16).

Several previous meta-analyses (17–19) have assessed the possible independent predictive ability of CRP level for incident CHD risk. In 1998, a meta-analysis of 5 long-term, population-based prospective cohort studies and 2 cohorts of patients with preexisting CHD (17) calculated a risk ratio for coronary events of 1.7 (95% CI, 1.4 to 2.1) for CRP levels in the top tertile versus the bottom tertile. An update of this meta-analysis in 2000 (18) included 7 additional studies. The combined risk ratio for the 11 population-based prospective cohort studies of persons without preexisting CHD was 2.0 (CI, 1.6 to 2.5). Another update in 2004 (19) included 11 new studies as well as the 11 previous cohorts. The combined odds ratio for all 22 studies was 1.58 (CI, 1.48 to 1.69).

These 3 meta-analyses, however, lacked a systematic assessment of the characteristics and quality of study design and execution. In particular, they did not systematically assess the degree of adjustment for standard measures of CHD risk (such as the Framingham risk score). Although the first 2 meta-analyses reported the degree of adjustment for potential confounders in each of the included studies, they did not specify how many or which standard coronary risk factors were adjusted for. Furthermore, these meta-analyses did not use the degree of adjustment as a basis for quality rating or inclusion. The most recent meta-analysis (19) did not rate quality or degree of adjustment for potential confounders. In addition, because the investigators used broad inclusion criteria, the studies in these meta-analyses do not necessarily represent the intermediate-risk population.

We conducted a systematic review and meta-analyses of epidemiologic studies to help the U.S. Preventive Services Task Force (USPSTF) determine whether CRP level should be incorporated into guidelines for coronary and cardiovascular risk assessment in primary care. Our review addresses the question of whether elevated CRP levels are independently predictive of incident CHD events, specifically among intermediate-risk persons. Our approach incorporated elements previously used by the USPSTF (20) and several domains of the approach developed by the Grading of Recommendations, Assessment, Development, and Evaluation workgroup (21).

Methods

Data Sources and Searches

We searched MEDLINE for original epidemiologic studies published between 1966 and November 2007. Our search strategy included the terms *cardiovascular diseases*, *C-reactive protein*, *inflammation*, and *biological markers* and was limited to articles published in English. We obtained additional articles from recent systematic reviews; reference lists of pertinent studies, reviews, editorials, and Web sites; and consultations with experts.

Study Selection

We included studies that published original data relevant to measuring the increased risk for incident CHD associated with elevated CRP level. We only considered prospective cohort studies (including those based on a cohort within a randomized trial), case–cohort studies, and nested case–control studies. We only included studies that had a follow-up of 2 years or more, reported the outcomes of coronary death and nonfatal myocardial infarction, and adjusted for a minimum of 5 of the 7 risk factors used in the Framingham risk score. We excluded studies in which no participants were likely to be classified as intermediate-risk by using the Framingham risk score and those conducted exclusively in patients with previously diagnosed coronary disease, coronary disease equivalents (such as diabetes), or medical conditions that may cause premature CHD. We included studies in which some patients had cardiovascular disease at baseline only if the studies adjusted for prevalent disease in their analysis. The full systematic evidence report (22) provides a more detailed description of our study methods.

Data Extraction and Quality Assessment

One investigator reviewed the relevant articles and recorded overlap with the studies included in previous meta-analyses. For our meta-analyses, when multiple articles were published from a single cohort, we included the findings from the analysis with the highest applicability to the study question and the highest validity, on the basis of our quality ratings. In general, we selected cohort studies over nested case–control studies, good-quality studies over fair-quality studies, studies that adjusted for more Framingham risk variables, studies with longer follow-up, and studies that most closely addressed our principal question.

We used standardized forms to abstract data on study design, population, size, CRP measurement, Framingham risk factor measurement, length of follow-up, outcomes, and data analysis. For each study, we recorded how many Framingham risk factors and other confounding factors were included in the model; whether the investigators reported model fit measures, discrimination measures, or model calibration statistics separately for models with and without CRP; and whether the study assessed the degree to which persons were reclassified on the basis of CRP level, overall or in the intermediate-risk group.

Two investigators used the USPSTF criteria (20) to independently assess the quality of each study as good, fair, or poor. These criteria are specific to the study design (cohort or nested case–control) and include such items as appropriate assembly or ascertainment of the cohort or the case patients and control participants, reliability and equal application of measurements, response or follow-up rate, and appropriate adjustment for confounding. Because we sought to evaluate the predictive ability of CRP independent of the Framingham risk factors, we required that a study adjust for all 7 of the Framingham variables to re-

ceive a quality rating of "good," even if the study otherwise had high internal validity. We resolved disagreements regarding quality by discussion, further review, and adjudication by a third reviewer (if necessary).

Data Synthesis and Analysis

The ideal approach to assessing the clinical effect of expanding the Framingham risk score has been debated extensively. Most previous research on the effect of a new risk factor has focused on the c-statistic, a measure of discrimination. The c-statistic, however, may be a poor indicator of the effect of using CRP level to further stratify persons classified as intermediate-risk by the Framingham risk score. For this reason, recent literature (23–26) has emphasized that studies should examine how well assessing CRP level improves risk prediction and further risk stratification among persons initially classified as intermediate-risk.

Most studies provided an overall estimate of the risk associated with high CRP levels, after adjustment for other risk factors, but did not provide specific evidence about the intermediate-risk group. For these studies, we conducted 2 meta-analyses to obtain pooled adjusted risk ratios for the association of hard CHD events and CRP level. The first included all studies that were fair-quality or better, adjusted for at least 5 Framingham risk factors, included at least some participants who were likely to be at intermediate risk, and estimated the risk for CHD associated with CRP level after adjusting for confounders. Because including studies that had methodological flaws or assessed fewer Framingham risk factors could have led to overestimation of the pooled risk ratio, we conducted a second meta-analysis that was restricted to good-quality studies, all of which adjusted for all Framingham risk factors.

Because different studies reported ratios for different cutoff levels (including tertiles, quartiles, or quintiles), or as an increase in risk for a given unit of increase in CRP level, we standardized the risk ratio of CRP level for our meta-analyses to provide clinically relevant and easily interpretable results. We used currently recommended cutoff points (14) for low (<1.0 mg/L), average (1.0 to 3.0 mg/L), and high (>3.0 mg/L), with less than 1.0 mg/L as a reference. When studies used other cutoff points to categorize CRP level, we calculated risk ratios at cutoff points of 1.0 and 3.0 mg/L by assuming a log-normal distribution of CRP level (17, 27) and a log-linear association of CHD risk over the midrange of log-CRP levels (17, 28). We estimated distribution parameters of CRP level from published information from each study. We estimated CIs by using reported SEs for the coefficient of CRP level when studies analyzed CRP level as a continuous variable and by applying the same assumption of a log-linear relationship when studies categorized CRP level by using other cutoff points. We combined the risk ratio estimates by using a random-effects model to incorporate variation among studies into the combined estimate (29). We assessed statistical heterogeneity among the studies by using standard chi-square tests and estimated the magnitude of heterogeneity by using the I^2 statistic (30). We used random-effect meta-regression to examine possible sources of heterogeneity and investigate whether the risk ratio estimates were associated with various study-level characteristics (30). We tested whether the distribution of the effect sizes was symmetric with respect to the precision measure by using funnel plots and the Egger linear regression method (31). We used Stata, version 10.0 (StataCorp, College Station, Texas), to perform the analyses.

Although our meta-analyses addressed whether CRP adds information to the Framingham risk score, they could not assess how well risk ratios derived from the entire population apply to intermediate-risk participants, or how those participants would be reclassified if CRP were used. To examine reclassification, we identified and critically appraised the studies that either compared predictive models that used all Framingham risk factors, with and without CRP levels, or measured the incidence of CHD events among intermediate-risk participants classified by CRP levels.

Role of the Funding Source

The Agency for Healthcare Research and Quality suggested the topic and provided copyright release for this manuscript but did not participate in the literature search, data analysis, or interpretation of the results.

Results

Study Characteristics

Of 1292 abstracts of potentially relevant studies, 37 published studies (8, 18, 19, 23, 28, 32–63) conducted in 24 cohorts met our inclusion criteria (**Appendix Figure**, available at www.annals.org). (**Appendix Tables 1** and **2**, available at www.annals.org, have more information on these studies.) From these, we identified 23 principal articles that represented the most pertinent publication for meta-analysis from each of the 24 cohorts (18, 19, 28, 33, 35, 37, 42–46, 48, 50–52, 54–56, 59–63) (**Table**). All but 1 study (37) explicitly excluded patients with baseline CHD or cardiovascular disease, and this study adjusted for prevalent CHD. All studies measured CRP level by using a high-sensitivity CRP assay.

Thirteen of the 24 cohorts in our review were also included in the 2004 meta-analysis (19). Five of these 13 cohorts were represented by the same article in both our meta-analysis and the previous meta-analysis (18, 19, 46, 48, 54). For the other 8, we used more recent articles (33, 37, 42, 51, 52, 56, 59, 60). We included 1 additional cohort study published in 2002 (28) and studies from 10 new cohorts published after the timeframe of the previous meta-analysis (35, 43–45, 50, 55, 61–63). We excluded studies from 8 cohorts that the previous meta-analysis had included. Most of these were studies in which the participants were or were likely to be at increased risk for CHD (64–69). We excluded 2

Table. **Study Characteristics and Adjusted Estimates of CHD Risk Associated With CRP**

Study, Year (Reference)	Participants, *n*	Follow-up, *y*	Men, %*	Outcome	Framingham Risk Factors, *n*†	Other Adjusted Covariates, *n*	CRP Quantile Analyzed	Effect Size (95% CI)‡	Quality Rating
Cohort studies									
Cushman et al, 2005 (56)	3971	10	54.3	Major CHD events§	7	5	>3.0 vs. <1.0 mg/L 1.0–3.0 vs. <1.0 mg/L	1.45 (1.14–1.86) 1.08 (0.86–1.35)	Good
Koenig et al, 2004 (33)	3435	6.6	100	Major CHD events§	7	0	>3.0 vs. <1.0 mg/L 1.0–3.0 vs. <1.0 mg/L	2.21 (1.49–3.27) 1.44 (0.95–2.17)	Good
St-Pierre et al, 2005 (42)	1982	13	100	Major CHD events§	7	3	Highest vs. lowest quartile	0.98 (0.65–1.49)	Good
Wilson et al, 2005 (43)	4446	8	43.8	Major CHD events§	6	0	>3.0 vs. <1.0 mg/L 1.0–3.0 vs. <1.0 mg/L	1.22 (0.81–1.84) 1.38 (0.88–2.15)	Fair
Park et al, 2002 (28)	967	6.4	90.5	Major CHD events§	5	3	1-unit increase in log scale	1.49 (0.94–2.37)	Fair
Lowe et al, 2004 (37)	3065	7.5	100	Major CHD events§	5	1	Highest vs. lowest quintile	1.72 (1.14–2.58)	Fair
Lawlor et al, 2005 (35)	2723	3.5	0	CHD events‖	6	6	Doubling of CRP level	1.03 (0.94–1.13)	Fair
Mora et al, 2006 (60)	27 742	9.9	0	CVD events¶	7	2	Increasing quintiles	1.22 (0.87–1.71); 1.24 (0.90–1.72); 1.40 (1.02–1.91); 1.68 (1.22–2.29)	Good
Tzoulaki et al, 2007 (63)	923	17	67.1	CVD events¶	6	3	Highest vs. lowest tertile	1.62 (1.11–2.38)	Fair
Nested case–control studies									
Boekholdt et al, 2006 (55)	3272	6	64.1/63.4	Major CHD events§	7	1	Increasing quartiles	0.97 (0.75–1.27); 1.28 (1.00–1.64); 1.66 (1.31–2.12)	Good
Luc et al, 2003 (44)	772	5	100	Major CHD events§	7	1	Increasing tertiles	0.81 (0.47–1.40); 2.16 (1.26–3.72)	Good
Pai et al, 2004 (45): Nurses' Health Study	708	8	0	Major CHD events§	7	5	>3.0 vs. <1.0 mg/L 1.0–3.0 vs. <1.0 mg/L	1.53 (0.89–2.62) 1.17 (0.69–2.00)	Good
Pai et al, 2004 (45): Health Professionals Follow-up Study	794	6	100	Major CHD events§	7	4	>3.0 vs. <1.0 mg/L 1.0–3.0 vs. <1.0 mg/L	1.79 (1.14–2.83) 1.60 (1.09–2.34)	Good
Pradhan et al, 2002 (46)	560	2.9	0	Major CHD events§	7	6	Increasing quartiles	1.4 (0.8–2.8); 1.4 (0.7–2.6); 2.1 (1.1–4.1)	Good
van der Meer et al, 2003 (50)	657	4–8	61.1/40.6	Major CHD events§	7	2	Increasing quartiles	0.9 (0.5–1.7); 1.0 (0.5–1.9); 1.2 (0.6–2.2)	Fair
Danesh et al, 2004 (19)	5933	19.4	72/69	Major CHD events§	6	3	Highest vs. lowest tertile	1.37 (1.17–1.60)	Fair
Danesh et al, 2000 (18)	1149	9.5	100	Major CHD events§	6	2	Highest vs. lowest tertile	2.61 (1.81–3.77)	Fair
Ridker et al, 1997 (48)	492	8	100	Major CHD events§	5	3	Increasing quartiles	1.5 (0.9–2.5); 2.4 (1.5–4.0); 2.6 (1.6–4.4)	Fair
Witherell et al, 2003 (51)	325	5.1	56.2/57.4	Major CHD events§	5	2	Increase of 1 natural log (2.72-fold)	1.3 (1.0–1.7)	Fair
Gram et al, 2000 (54)	391	7–15	74.4/72.9	CHD events‖	6	2	Continuous (log-transformed)	1.14 (0.88–1.47)	Fair
Case–cohort studies									
Pischon et al, 2007 (61)	979	6	75.2/39.5	Major CHD events§	7	0	>3.0 vs. <1.0 mg/L 1.0–3.0 vs. <1.0 mg/L	2.56 (1.51–4.35) 1.88 (1.15–3.07)	Good
Koenig et al, 2006 (59)	1058	11	0	Major CHD events§	7	4	Highest vs. lowest tertile	1.35 (0.64–2.84)	Fair

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Table—Continued

Study, Year (Reference)	Participants, *n*	Follow-up, *y*	Men, %*	Outcome	Framingham Risk Factors, *n*†	Other Adjusted Covariates, *n*	CRP Quantile Analyzed	Effect Size (95% CI)‡	Quality Rating
Ballantyne et al, 2004 (52)	1348	6	67.8/41.1	CHD events‖	7	1	>3.0 vs. <1.0 mg/L 1.0–3.0 vs. <1.0 mg/L	1.72 (1.24–2.39) 1.31 (0.96–1.80)	Good
Tuomisto et al, 2006 (62)	464	9	65.4/60.0	CHD events‖	7	1	Increasing quartiles	1.25 (0.63–2.51); 1.46 (0.73–2.90); 1.90 (0.97–3.74)	Fair

CHD = coronary heart disease; CRP = C-reactive protein; CVD = cardiovascular disease.
* Reported as case patients/control participants for case–control studies and case patients/cohort sample for case–cohort studies.
† Number of factors adjusted for in the analysis, from among these 7: age, sex, blood pressure, diabetes mellitus, high-density lipoprotein cholesterol level, total cholesterol or low-density lipoprotein cholesterol level, and smoking.
‡ Multivariate-adjusted hazard ratio for cohort studies or odds ratio for nested case–control studies.
§ Death from CHD or nonfatal myocardial infarction.
‖ Includes major CHD events and other CHD events, such as angina, silent myocardial infarction, coronary revascularization, coronary artery bypass graft, and angioplasty.
¶ Includes CHD events and fatal or nonfatal stroke.

studies from our review because they studied mortality only (70, 71). We rated 10 studies in 11 of the 24 cohorts as good-quality (33, 42, 44–46, 52, 55, 56, 60, 61) and 13 studies in 14 cohorts as fair-quality (18, 19, 28, 35, 37, 43, 48, 50, 51, 54, 59, 62, 63). Baseline CRP level was positively associated with incident CHD events in 23 of the 24 cohorts, with adjusted relative risks that ranged from 0.98 to 2.61.

Meta-analysis of Fair-Quality or Better Studies

Our meta-analysis of the 22 studies (in 23 cohorts) that explicitly excluded baseline CHD yielded a risk ratio of 1.60 (CI, 1.43 to 1.78) for high versus low CRP levels (**Figure 1**) and 1.26 (CI, 1.17 to 1.35) for average versus low CRP levels (**Figure 2**). Including the study that did not explicitly exclude baseline CHD (37) did not appreciably change the combined risk ratio estimates. We found statistically significant heterogeneity of effects among studies at a P value less than 0.100, both for the comparison of high versus low CRP levels ($I^2 = 31.9\%$; $P = 0.072$) and average versus low CRP levels ($I^2 = 44.0\%$; $P = 0.015$). However, the standardized estimates of effect were consistently positive, with a range of 0.98 to 2.75 for high CRP levels and 0.99 to 1.88 for average CRP levels. Furthermore, the positive relationship persisted in analyses of all subgroups at both high and average levels of CRP (**Figure 3**). In subgroup meta-regression analyses, we found no statistically significant differences among categories for any study-level characteristic, including number of Framingham variables and other covariates adjusted, outcome measures (major CHD events vs. major CHD plus other CHD events or cardiovascular events), study design, sex, quality rating, and length of follow-up. We conducted a sensitivity analysis to compare the 17 studies that required standardization of risk ratios with the 6 studies that used recommended cutoffs. The combined risk ratio estimates were similar between the 2 groups of studies. We detected no statistically significant asymmetry when we examined funnel plots or used the Egger linear regression method and no evidence of a tendency for smaller studies to show a larger degree of association.

Meta-analysis of Good-Quality Studies

We also performed a meta-analysis limited to the 10 good-quality studies from 11 cohorts, all of which adjusted for all Framingham risk factors or calculated a Framingham risk score (33, 42, 44–46, 52, 55, 56, 60, 61). The relative risk was 1.58 (CI, 1.37 to 1.83) for high versus low CRP levels (**Figure 1**) and 1.22 (CI, 1.11 to 1.33) for average versus low CRP levels (**Figure 2**). We found no statistically significant heterogeneity of effects among studies in this analysis. We excluded 4 fair-quality studies that used all Framingham risk factors (43, 50, 59, 62). We conducted a sensitivity analysis and found similar results with and without these 4 studies. The relative risk was 1.53 (CI, 1.36 to 1.73) for high versus low CRP levels and 1.20 (CI, 1.12 to 1.29) for average versus low CRP levels.

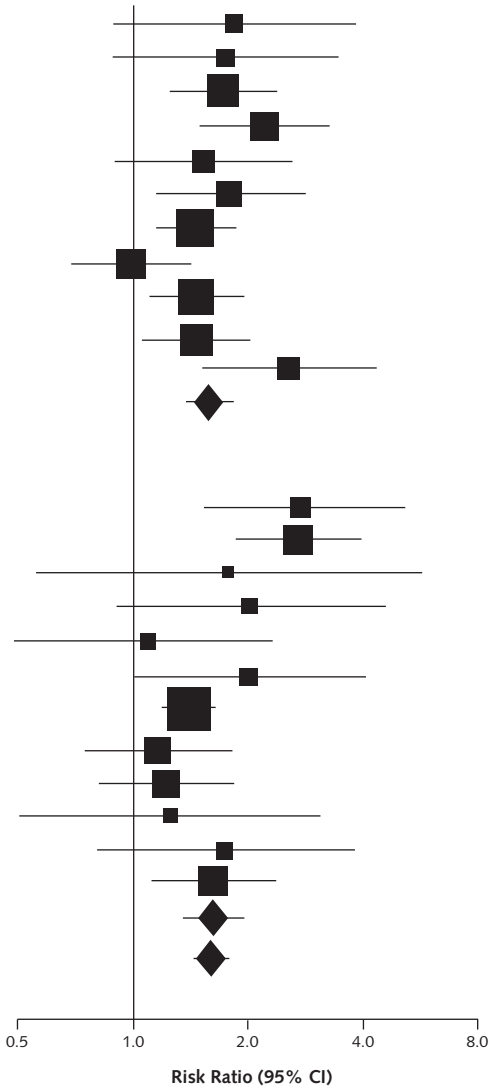
Reclassification of Persons at Intermediate Risk

From a clinical perspective, the most meaningful measure of CRP's value as a marker is its effect on rates of reclassification from intermediate-risk to other risk categories. Recent articles (24–26, 72) have proposed methods of assessing clinical risk reclassification when the goal of analysis is risk prediction. They note that measures of risk reclassification are probably better than the c-statistic for assessing the value of adding a new marker to a prediction model.

Five studies (23, 33, 40, 43, 56) included an analysis that compared predictive models that used all Framingham risk factors, with and without CRP level, specifically among participants whose 10-year Framingham risk score categorized them as intermediate-risk. Three of the 5 (23, 33, 43) measured the c-statistic or the area under the receiver-operating characteristic curve. Only 1 study (23) used statistical analyses to compare the calibration of prediction models with and without CRP level. Using data from the Women's Health

Figure 1. **Risk ratio for coronary heart disease associated with C-reactive protein level >3.0 versus <1.0 mg/L.**

Study, Year (Reference)	Participants, *n**	Risk Ratio (95% CI)
Good-quality studies		
Pradhan et al, 2002 (46)	560	1.83 (0.88–3.82)
Luc et al, 2003 (44)	772	1.75 (0.88–3.47)
Ballantyne et al, 2004 (52)	1348	1.72 (1.24–2.39)
Koenig et al, 2004 (33)	3435	2.21 (1.49–3.27)
Pai et al, 2004 (women) (45)	708	1.53 (0.89–2.62)
Pai et al, 2004 (men) (45)	794	1.79 (1.14–2.83)
Cushman et al, 2005 (56)	3971	1.45 (1.14–1.86)
St-Pierre et al, 2005 (42)	1982	0.98 (0.68–1.42)
Boekholdt et al, 2006 (55)	3272	1.46 (1.10–1.95)
Mora et al, 2006 (60)	27 742	1.46 (1.05–2.02)
Pischon et al, 2007 (61)	979	2.56 (1.51–4.35)
Combined		1.58 (1.37–1.83)
Fair-quality studies		
Ridker et al, 1997 (48)	492	2.75 (1.52–5.16)
Danesh et al, 2000 (18)	1149	2.70 (1.85–3.96)
Gram et al, 2000 (54)	391	1.78 (0.55–5.74)
Park et al, 2002 (28)	967	2.02 (0.90–4.60)
van der Meer et al, 2003 (50)	657	1.09 (0.48–2.32)
Witherell et al, 2003 (51)	325	2.00 (1.00–4.06)
Danesh et al, 2004 (19)	5933	1.40 (1.18–1.64)
Lawlor et al, 2005 (35)	2723	1.15 (0.74–1.81)
Wilson et al, 2005 (43)	4466	1.22 (0.81–1.84)
Koenig et al, 2006 (59)	1058	1.25 (0.50–3.10)
Tuomisto et al, 2006 (62)	464	1.74 (0.80–3.81)
Tzoulaki et al, 2007 (63)	923	1.62 (1.11– 2.38)
Combined		1.62 (1.34–1.95)
All studies combined		1.60 (1.43–1.78)
Test for heterogeneity: $Q = 32.32$, $I^2 = 31.9\%$; $P = 0.072$		



* Number of participants included in the analysis.

Study, Cook and colleagues (23) demonstrated that although measures of discrimination did not substantially differ between models with and without CRP level, a model that included CRP level had better fit, as measured by the Hosmer–Lemeshow calibration statistic. In that analysis, 14% of participants originally classified as intermediate-risk (10% to 20%) were reclassified as low-risk (<10%) and 5% were reclassified as high-risk (>20%). The actual 10-year risk was 19.9% for those reclassified as high-risk and 11.5% for those who remained intermediate-risk.

The other 4 studies used less rigorous analyses to assess the effect of CRP level on risk classification and did not measure calibration, with mixed results. Three studies (33, 40, 56) found that assessing CRP improved risk stratification specifically among intermediate-risk participants. In the Monitoring of Trends and Determinants in Cardiovascular Disease study (33), assessing CRP level in addition to the Framingham risk factors resulted in improved risk classification among participants with an initial 10-year risk of 11% to 19%. Among participants with a CRP level greater than 3.0 mg/L, some with an initial 10-year risk of 15% to 19% were reclassified as high-risk, whereas no participants with an initial 10-year risk of 11% to 14% were reclassified as high-risk. In an analysis of data from the Women's Health Study (40), CRP level was clearly predictive of incident cardiovascular disease among participants with 10-year Framingham risk scores between 10% and 20%. The risk for cardiovascular events was twice as high for those with CRP levels between 1.0 and 3.0 mg/L or

between 3.0 and 10.0 mg/L than for those with levels less than 1.0 mg/L, although CIs were not reported. Similarly, in an analysis from the Cardiovascular Health Study, CRP level added to risk prediction among men at intermediate risk (56). Among men with a 10-year Framingham risk score between 10% and 20%, the observed 10-year incidence of CHD was 32% for those with CRP levels greater than 3.0 mg/L, compared with between 15% and 16% for those with CRP levels between 1.0 and 3.0 mg/L or less than 1.0 mg/L (56). In that cohort, however, CRP level did not add to risk prediction among intermediate-risk women. The negative study (43), an analysis from the Framingham cohort, estimated the 10-year risk for incident cardiovascular disease by tertile of CRP level among participants previously stratified as having a 10-year Framingham risk score between 10% and 20%. Tertile cut-points were 0.81 mg/L and 3.78 mg/L. The estimated 10-year risk did not significantly differ among the 3 CRP tertiles, and all 3 subgroups based on CRP level had an estimated 10-year risk in the intermediate range.

Discussion

The body of evidence that CRP level is independently associated with incident CHD is strong, with a risk ratio of 1.58 (CI, 1.37 to 1.83). Our search and systematic selection identified 23 studies of appropriate design from 24 cohorts. The aggregate quality of these studies is good to fair, and the body of evidence has no important inconsistency. We found no indication that the data from included studies were imprecise or sparse and no indication of high risk for reporting bias. We also noted some evidence of a

Figure 2. **Risk ratio for coronary heart disease associated with C-reactive protein level 1.0 to 3.0 versus <1.0 mg/L.**

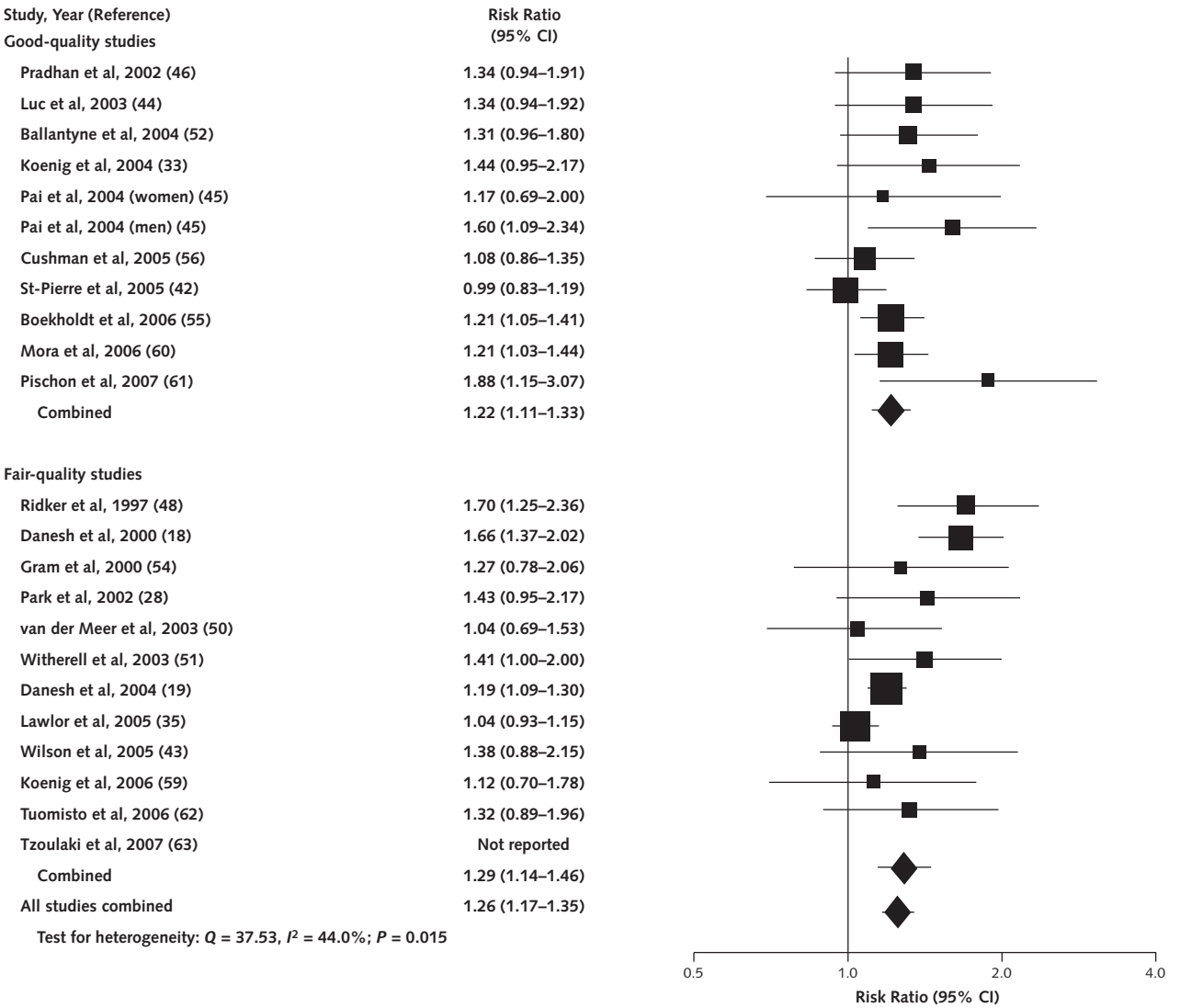
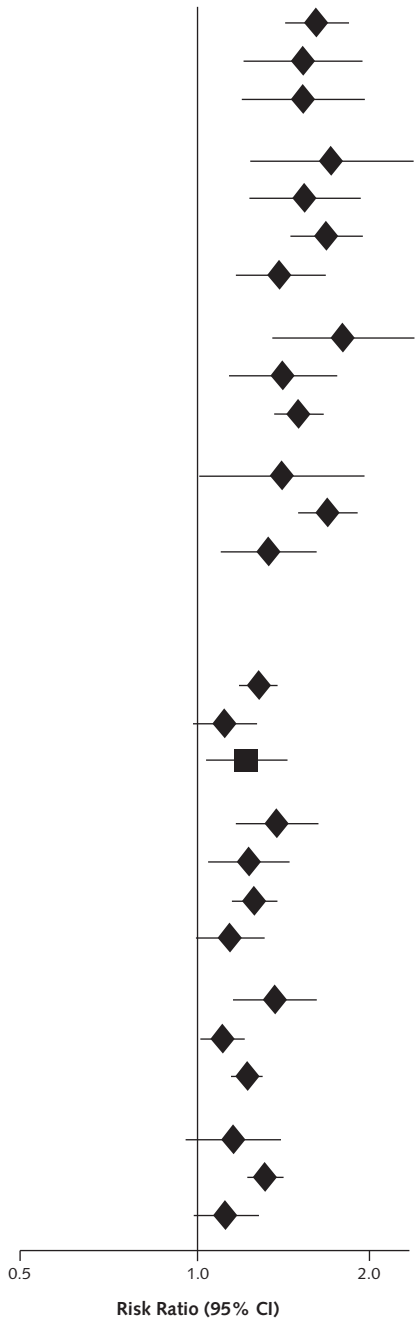


Figure 3. **Analyses of all subgroups at high (>3.0 mg/L) and average (1.0 to 3.0 mg/L) CRP levels.**

Subgroup Characteristic	Cohorts, *n**	Risk Ratio (95% CI)
CRP level >3.0 mg/L vs. <1.0 mg/L		
Outcome		
Major CHD events	18	1.61 (1.41–1.84)
CHD events	4	1.53 (1.20–1.96)
CVD events	2	1.53 (1.19–1.96)
Number of risk factors adjusted for		
4–6 Framingham†, <3 other	5	1.72 (1.23–2.39)
4–6 Framingham†, ≥3 other	5	1.54 (1.23–1.93)
All 7 Framingham†, <3 other	8	1.68 (1.45–1.95)
All 7 Framingham†, ≥3 other	6	1.39 (1.16–1.67)
Sex		
Male	7	1.80 (1.35–2.40)
Female	5	1.41 (1.13–1.75)
Both	12	1.50 (1.36–1.66)
Follow-up length		
<5 y	3	1.40 (1.00–1.96)
5–10 y	17	1.69 (1.50–1.90)
>10 y	4	1.33 (1.10–1.61)
CRP level 1.0–3.0 mg/L vs. <1.0 mg/L		
Outcome		
Major CHD events	18	1.28 (1.18–1.38)
CHD events	4	1.11 (0.98–1.27)
CVD events	1	1.22 (1.03–1.44)
Number of risk factors adjusted for		
4–6 Framingham†, <3 other	5	1.38 (1.16–1.63)
4–6 Framingham†, ≥3 other	4	1.23 (1.04–1.44)
All 7 Framingham†, <3 other	8	1.25 (1.15–1.37)
All 7 Framingham†, ≥3 other	6	1.14 (0.99–1.31)
Sex		
Male	7	1.36 (1.15–1.62)
Female	5	1.10 (1.01–1.20)
Both	11	1.22 (1.14–1.30)
Follow-up length		
<5 y	3	1.15 (0.95–1.39)
5–10 y	17	1.31 (1.22–1.41)
>10 y	3	1.12 (0.98–1.27)



CHD = coronary heart disease; CRP = C-reactive protein; CVD = cardiovascular disease.
* Number of cohorts included in the analysis.
† Framingham risk factors are based on reference 2.

dose–response gradient. These criteria support the conclusion of a strong body of evidence.

Previous meta-analyses (17–19) have found an association between CRP level and incident CHD. These meta-analyses were limited by their lack of a systematic basis for judging the validity of the evidence they used, and applicability to the target population and question of interest may be limited. Our systematic review and

meta-analyses included more recent and updated studies, excluded studies of predominantly high-risk or low-risk populations, systematically rated the quality of all studies, and qualitatively appraised findings that are directly applicable to intermediate-risk patients.

The clinical implications of the association of CRP level with CHD events are less clear, because the pooled risk ratio does not necessarily measure the usefulness of CRP level in reclassifying intermediate-risk persons. The underlying studies did not directly assess whether the risk ratio for the overall sample applied to the intermediate-risk subgroup (for example, by looking for an interaction between the Framingham risk score and CRP levels). The strength of evidence from studies that attempted to measure the effect of using CRP level to improve risk classification among persons initially classified as intermediate-risk is moderate. Among intermediate-risk persons, subgroups with high CRP levels generally had a higher risk for coronary events than did those with average or low CRP levels.

In addition to multivariate regression analyses in prospective studies, many investigators (72–75) have advocated the use of other statistical methods to assess the incremental value of adding CRP level to global risk assessment. Several studies in our review (23, 33, 40, 42, 43, 50, 56, 58) compared predictive models that used all Framingham risk factors with and without a CRP level. Most of these used the change in the c-statistic or the area under the receiver-operating characteristic curve to compare the performance after adding CRP level. However, a marker can have a small effect on the c-statistic, a measure of discrimination, but be strongly related to risk as assessed in a multiple logistic or Cox regression model, or vice versa (76–78). Recent articles (24–26, 72) have discussed the limitations of the c-statistic and proposed methods of assessing clinical risk reclassification when risk prediction is the goal of analysis.

Relatively few studies have evaluated the effect of adding CRP level to reclassify initially intermediate-risk persons. Four studies in our review (33, 40, 43, 56) assessed differences in CHD risk among subgroups of intermediate-risk participants who were stratified by CRP level. Three of the 4 studies (33, 40, 56) found that those with higher CRP levels were at higher risk for CHD. However, their results are imprecise and their estimates are group averages, so they do not show how many persons would be reclassified as high-risk. A fifth study (23) calculated the risk reclassification when CRP level was added to a predictive model that included all Framingham risk score variables and found that the model with CRP level had better calibration to observed risk. In the negative study (43), researchers of the Framingham cohort concluded that CRP level does not seem to be beneficial for CHD risk assessment, particularly because adding CRP level to the risk model did not improve c-statistic results. Recently, these researchers reported a good-quality analysis of Framingham data (79) in which they calculated the risk reclassification of individual study participants when CRP level was added to traditional risk factors; including CRP level improved risk assessment by appropriately reclassifying a statistically significant percentage of incident CHD cases and noncases into higher or lower risk categories.

Although the types of analyses differed, 4 large, good-quality cohort studies are consistent in finding that assessing CRP level improves CHD risk stratification (23, 33, 40, 56, 79). These consistent findings provide moderately strong evidence that adding CRP level to risk models in intermediate-risk patients improves the identification of those at higher risk for incident CHD. However, additional research is needed to assess the effect of CRP level on risk reclassification of initially intermediate-risk persons and to statistically evaluate the calibration of prediction models to observed risk (26).

Establishing the independent predictive ability of a new risk factor is necessary but not sufficient for assessing its potential usefulness in screening for CHD risk. Other criteria must be considered, such as the prevalence of the factor in the target population, the reliability and cost of the test, potential harms of testing, and the effect that treatment for the risk factor has on modifying risk (80). C-reactive protein level favorably satisfies most of these criteria. National survey data suggest a prevalence of high CRP level of at least 20% to 25% among intermediate-risk persons (13, 81). Inexpensive, precise, high-sensitivity CRP serum assays are available (82, 83). Although considerable within-patient variation among CRP measurements has been reported (84), the reliability of 2 or 3 serial measurements is similar to that of a total cholesterol assay (84, 85). Weight loss, exercise, and smoking cessation can reduce serum CRP levels (86, 87), and lowering CRP levels with statin therapy in patients with acute coronary syndrome can lower their risk for recurrent myocardial infarction or coronary death (88). The viability of CRP as a new factor in global risk assessment for incident CHD is limited by sparse evidence that directly links therapeutic changes in CRP level to primary prevention of CHD events.

Results were recently published for JUPITER (Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin), a good-quality randomized, controlled trial of rosuvastatin for primary prevention of cardiovascular events in 17 802 men and women with elevated (>2 mg/L) CRP levels, low-density lipoprotein cholesterol levels less than 3.4 mmol/L (<130 mg/dL) (median, 2.8 mmol/L [108 mg/dL]), and no other indication (such as diabetes) for statin therapy (89). Of 8901 participants who received 20 mg of rosuvastatin daily, 83 experienced first cardiovascular events (myocardial infarction, stroke, or death from cardiovascular causes) during the study period (median, 1.9 years), compared with 157 of 8901 participants in the placebo group, for a hazard ratio of 0.53 (CI, 0.40 to 0.69). By 1 year of follow-up, the median low-density lipoprotein cholesterol level was un-

changed in participants receiving placebo and 1.4 mmol/L (55 mg/dL) in participants assigned to receive rosuvastatin. Rosuvastatin was also associated with an increased risk for physician-reported diabetes (3.0% vs. 2.4%).

Current guidelines recommend aggressive therapy only for high-risk patients, such as those with a Framingham risk score greater than 20%, diabetes, or known cardiovascular disease. Because approximately half of the patients in JUPITER had a Framingham risk score greater than 10%, these results provide evidence that 1 form of intensive risk reduction—aggressive lipid-lowering therapy—produces benefit for a population that includes intermediate-risk persons.

The implications of JUPITER for screening are less clear. JUPITER did not evaluate whether intermediate-risk patients who are reclassified as high-risk by using CRP level would benefit from treatment compared with intermediate-risk patients who are not reclassified. For example, the risk reduction from rosuvastatin therapy may have been as great in intermediate-risk participants who had CRP levels closer to the population average. The study also did not directly test whether lowering CRP levels reduced cardiac risk. Finally, JUPITER did not report rates of coronary events separately for low-risk and intermediate-risk persons. To fully understand the balance of benefits and harms associated with any particular form of intensive risk reduction intended for patients classified according to CRP levels, we also need to know the numbers needed to treat and the harms for different risk category subgroups. The length of follow-up was inadequate to fully evaluate the potential harms of aggressive statin therapy (90). When the trial was terminated, only 1076 (1 in 18) participants had 4 years of follow-up, and 2705 had 3 years of follow-up.

Other issues may influence guideline recommendations and merit discussion. Cross-sectional studies have found correlations between CRP level and traditional CHD risk factors (91), but the implications for the use of CRP in global risk assessment are not clear. The findings have been interpreted to mean that CRP level may represent a different aspect of risk, with complex interrelationships among CRP level, traditional risk factors, and CHD (91, 92). Others conclude that elevated CRP level is largely attributable to traditional risk factors, and CRP level "may have limited clinical utility as a screening tool" (13). In fact, the causal relationships between CRP level and traditional CHD risk factors are not clear (93). Correlation of CRP level with traditional risk factors does not preclude its potential association with CHD. The findings of many studies, including our meta-analyses, suggest that the degree of correlation between CRP level and traditional risk factors is not so great that CRP loses its independent effect. Although this statistical independence does not establish causality (94), it does support the potential use of CRP level as an adjunct in global risk assessment, particularly for targeted groups—such as intermediate-risk persons.

Our review has limitations. Studies used varying definitions, cutoffs, and methods of measurement for the Framingham risk factors and other cofactors. We accounted for these differences in our quality assessments and standardized our meta-analyses to recommended cut-off values. Because all studies were prospective, the likelihood of differential bias in measurement or reporting within studies is low. However, the net effect of the Framingham variables may vary from that of a calculated Framingham risk score for studies that did not measure each variable as defined for the Framingham risk score. In addition, although we distinguished those studies that completely adjusted for Framingham factors in our quality assessments and subgroup analyses, the inclusion of a nonuniform assortment of additional potential confounders might influence a study's relative risk estimate, with the net effect expected to be a reduction in the magnitude. Minority populations were poorly represented in most studies in our review. Ethnic and racial differences in biomarker levels (95, 96) and applicability of the Framingham risk score (97, 98) may limit the generalizability of our results.

In summary, our systematic review and meta-analyses indicate that CRP level is independently associated with incident CHD. The clinical implication of this finding is less clear, because the pooled risk ratio does not necessarily measure the usefulness of CRP level in reclassifying intermediate-risk persons. Although current evidence on the risk reclassification that would result from adding CRP level to a global risk score is promising, the strength of evidence from the 4 cohorts that attempted to measure the effect of using CRP among intermediate-risk persons is moderate. The viability of CRP as an adjunct to traditional factors is also uncertain because evidence linking changes in CRP level to primary prevention of CHD events is insufficient.

From the Oregon Evidence-based Practice Center, Oregon Health & Science University, and Veterans Affairs Medical Center, Portland, Oregon, and University of Utah Health Sciences Center, Salt Lake City, Utah.

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Requests for Single Reprints: David I. Buckley, MD, MPH, Oregon Health & Science University, Mailcode FM, 3181 Southwest Sam Jackson Park Road, Portland, OR 97239.

Current author addresses and author contributions are available at www.annals.org.

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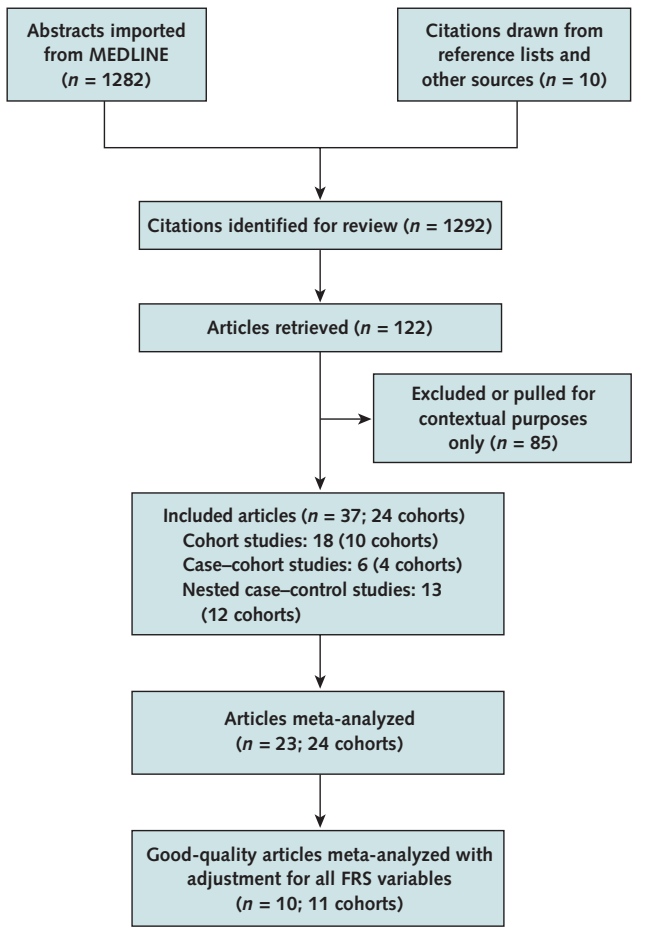
Current Author Addresses: Drs. Buckley, Fu, and Helfand: Oregon Health & Science University, Mailcode FM, 3181 Southwest Sam Jackson Park Road, Portland, OR 97239.
Ms. Freeman: Portland Veterans Affairs Medical Center, 3710 U.S. Veterans Hospital Road, Mailcode RD 71, Portland, OR 97239.
Dr. Rogers: 2150 South Main 511, Salt Lake City, UT 84115.

Author Contributions: Conception and design: D.I. Buckley, K. Rogers, M. Helfand.
Analysis and interpretation of the data: D.I. Buckley, R. Fu, M. Freeman, K. Rogers, M. Helfand.
Drafting of the article: D.I. Buckley, R. Fu, M. Helfand.
Critical revision of the article for important intellectual content: D.I. Buckley, R. Fu, M. Freeman, K. Rogers, M. Helfand.
Final approval of the article: D.I. Buckley, R. Fu, K. Rogers, M. Helfand.
Statistical expertise: R. Fu, M. Helfand.
Obtaining of funding: M. Helfand.
Administrative, technical, or logistic support: M. Freeman, M. Helfand.
Collection and assembly of data: D.I. Buckley, R. Fu, K. Rogers, M. Helfand.

Appendix Figure. **Literature search and selection.**



FRS = Framingham risk score.