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THE USE OF HIGH SENSITIVITY C-REACTIVE PROTEIN IN CLINICAL PRACTICE

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SUMMARY

Measurement of the inflammatory biomarker high sensitivity C-reaction protein (hsCRP) has been proposed for assessment of risk for cardiovascular disease (CVD). It remains unclear which patient populations would benefit from and should be targeted for hsCRP testing. Current data indicate that hsCRP levels are independently associated with risk of CVD, including both coronary events and stroke, in various asymptomatic populations; add predictive power to current coronary risk scores for some intermediate risk individuals; and are associated with clinical outcomes in high risk individuals treated with statin therapy. HsCRP levels are also associated with incident diabetes and CVD outcomes in patients with the metabolic syndrome. There is a growing body of evidence to support recommendations for measurement of hsCRP in selected asymptomatic individuals deemed to be at intermediate risk of CVD according to traditional risk factor assessment and who do not already warrant treatment with chronic aspirin and statin therapy, and selected secondary CVD prevention patients for further risk stratification in combination with LDL cholesterol.

Keywords

coronary disease; diabetes mellitus; prevention; risk factors; stroke

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COMPETING INTERESTS K Musunuru has declared an association with Alnylam Pharmaceuticals. TJ Gluckman has declared associations with the following companies: Sanofi-Aventis, Pfizer and Merck. MH Davidson has declared associations with diaDexus. See the article online for full details of the relationships. The other authors declared no competing interests.

[Aus: to appear online: Dr. Musunuru has served as a consultant for Alnylam Pharmaceuticals within the last year. Dr. Gluckman has received honoraria from Sanofi-Aventis and Pfizer and has served as a consultant for Merck within the last year. Dr. Davidson has received honoraria from and served as a consultant for diaDexus within the last year. We declare no conflicts of interest pertaining to this topic.]

REVIEW CRITERIA We performed a comprehensive review of peer-reviewed publications that were identified through searches of MEDLINE and the Cochrane Database from January 1990 through December 2007 using the search term “C-reactive protein”, in combination with one of the following: “heart disease”, “stroke”, “hypertension”, “metabolic syndrome” and “stroke”. Bibliographies from these references were also reviewed, and additional studies were identified by experts. Initially identified papers were English language, with the subject of the paper being the clinical risk prediction of cardiovascular disease or diabetes mellitus. All studies were considered in our analysis. In analyzing the association of C-reactive protein (whether high-sensitivity or not) with cardiovascular disease (coronary heart disease or stroke) or diabetes in asymptomatic populations, we selected studies that used multivariate adjustment for at least four traditional cardiovascular disease or diabetes risk factors. We excluded studies in which the populations had significant prevalence of comorbidities (>10% with, e.g., systolic heart failure, diabetes). In studies that included both men and women, when separate data were available for each sex we considered them separately rather than as a single population. When multiple publications reporting data from the same cohort were available, we chose the most recent publication.

INTRODUCTION

More than 800,000 individuals suffer a myocardial infarction annually in the US, and another 700,000 experience a stroke.¹ Of these events, nearly half occur in patients with no overt evidence of hyperlipidemia and 15% to 20% occur in patients with none of the major traditional risk factors.^{2,3} At the opposite end of the spectrum, a disproportionate number of events occur in individuals with a history of myocardial infarction, indicating the high level of risk for recurrent events in these patients.

Although half of women and two-thirds of men in the US are affected by cardiovascular disease (CVD) after the age of 40,^{1,4} only a small proportion of asymptomatic adults (<1% of women and approximately 5% of men) are classified as at 'high risk' for CVD using contemporary risk scores. This discrepancy has been coined the 'detection gap'.⁵ In the US, 10% of asymptomatic women (~7 million) and 40% of asymptomatic men (~26 million) are considered to be at intermediate risk.^{5,6} As the level of risk determines the intensity of preventive interventions, there is a clear need for better risk assessment in asymptomatic individuals, particularly those at intermediate risk.

The National Cholesterol Education Program Adult Treatment Panel (NCEP ATP) III guidelines⁷ provide a global risk score for 'hard' coronary heart disease (CHD) events (myocardial infarction and death caused by coronary heart disease), and the 1998 Framingham risk score equation estimates total CHD events (myocardial infarction, cardiac death, coronary insufficiency);^{8,9} a 10-year absolute risk of a hard coronary event less than 10% is considered to be low risk, 10-20% is intermediate risk, and greater than 20% is high risk.⁷ It has been proposed that the intermediate risk category be extended to include individuals who have a 10-year absolute risk between 5% and 20%. Proponents of this change argue that this lower cut-off identifies a group of individuals, especially women, who could gain more benefit from aspirin and more aggressive lipid-lowering therapy and lifestyle modification than those with 10-year absolute risk of less than 5%.^{5,10} Increasingly, the intermediate risk category is being further divided into 'low' and 'high' subgroups (i.e. 5-<10% and ≥ 10 -<20%).

Numerous biomarkers have been proposed for improving CVD risk prediction. A biomarker is felt to be useful if the following criteria are met: it adds to clinical knowledge; it provides risk information that is independent of established predictors; it is easy to measure and interpret in a primary care setting; it is accurate, reproducible and internationally standardized; and it has a favorable cost-benefit ratio.¹¹ Screening biomarkers should also improve patient management, particularly through more accurate risk classification and guidance in choice of therapy.¹¹ C-reactive protein (CRP) is an easily measured and widely investigated biomarker of inflammation. The link between inflammation and atherosclerosis is well established; inflammation is a key element of the atherosclerotic process, contributing to all of its stages (initiation, growth, and plaque rupture).¹²⁻¹⁴ Thus, it would not be surprising if serum levels of inflammatory markers such as CRP improve prediction of CHD and stroke risk in at least some patient populations.

Although a number of Reviews related to the high-sensitivity CRP test (hsCRP) have been published in recent years, no review has comprehensively addressed the relevance of hsCRP in a variety of scenarios encountered in clinical practice—primary prevention of CVD, stroke and diabetes mellitus, and secondary prevention of CVD. We summarize the available data and assess whether they support proposed guidelines for clinical hsCRP measurement. We will consider CRP as a means to improve risk stratification and enable a better match between therapy and level of risk, not as a therapeutic target in its own right. Data are lacking as to whether CRP reduction *per se* reduces cardiovascular risk independent of other modifiable risk factors.

PUBLISHED DATA

Primary prevention

In 2003, the Centers for Disease Control and Prevention (CDC) and the AHA issued recommendations regarding the use of inflammatory biomarkers for CVD detection, prevention and treatment.¹⁵ At the time, the body of evidence regarding the clinical use of hsCRP measurements was modest, and most recommendations were given an ACC/AHA class II level of support, indicating that the weight of evidence was favorable but that more data was needed before general consensus could be reached.

Since 2003, considerable data has been published regarding the use of hsCRP in improving the assessment of cardiovascular risk in primary prevention patients. We found at least 20 prospective studies of distinct cohorts demonstrating that elevated hsCRP levels are associated with elevated risk of future coronary events after adjustment for at least four traditional risk factors, including Framingham risk factors and/or diabetes and obesity (Table 1A and 1B).¹⁶⁻³⁶ This association applied both to men and women across a wide age range (e.g. from middle-aged to elderly). Some studies stratified patients by hsCRP level—less than 1 mg/l, 1-3 mg/l, and greater than 3 mg/l—and showed that these cutoffs correspond with lower, moderate and higher risk groups, respectively, although the risk was fairly linear across a wide range of CRP levels. A small number of studies reported a positive association between hsCRP and coronary event rate but none reached statistical significance after adjustment for at least four other risk factors (Table 1A and 1B).^{25, 27, 37-44} Initial analysis of data from the Framingham Study found that CRP levels did not provide clear incremental value over the Framingham risk score;³⁷ however, the assay used to measure CRP was not high sensitivity. When the analysis was repeated using a high-sensitivity assay, there was a positive correlation between CRP and CVD; after multivariate adjustment hsCRP levels greater than 3 mg/l were significantly associated with increased incident CVD (Table 1A and 1B).²³

Although informative, individual studies are subject to variation and interpreting risk data can be difficult. To date there has been one formal meta-analysis, but there is a clear need for further pooled investigations such as that from the Emerging Risk Factors Collaboration. Meta-analysis of 22 prospective studies found that after adjusting for traditional risk factors individuals in the top tertile of hsCRP levels (>3 mg/l) have a odds ratio of 1.45 for major cardiac events (95% CI 1.25-1.68) compared with those in the lowest tertile (<1 mg/l).³¹ This meta-analysis incorporated studies that individually demonstrate a statistically significant association between hsCRP levels and cardiac events (including many of the studies listed in Table 1A) as well as a number of studies that did not show a statistically significant association (among those listed in Table 1B), suggesting that the overall conclusion of the study was not confounded by publication bias.

CRP versus traditional risk factors: does CRP add incremental value?—

Interestingly, in studies in which traditional risk factors underwent rigorous multivariate analysis to assess the strength of association with CVD risk, the magnitude of the association between incident CVD and hsCRP was comparable with that between CVD and LDL-cholesterol level, systolic blood pressure, or smoking behavior (Table 2). However, even if the association between elevated hsCRP levels and increased CVD risk is similar to that of individual traditional risk factors, the burden is on proponents of hsCRP measurement to demonstrate that the addition of hsCRP measurement to CVD risk prediction strategies has a clinical impact, even if only in limited patient populations. Recent data from the Women's Health Study suggest that adding CRP level to the NCEP ATP III global risk score improves the accuracy of CVD risk assessment in some asymptomatic individuals. In this large prospective cohort study of asymptomatic middle-aged women, the addition of hsCRP to the ATP III global risk score reclassified many intermediate risk individuals as higher or lower

risk; following hsCRP assessment 32% of women with a 5- $<$ 10% 10-year risk of 'hard' coronary events and 42% of women with a 10- $<$ 20% 10-year absolute risk were reclassified into a lower or higher-risk group.⁴⁵

Using the same cohort of women, a more recent study that analyzed 35 cardiovascular risk factors found that hsCRP provided the best prediction model for incident CVD events (myocardial infarction, stroke, revascularization, and CVD-related death) when used along with traditional risk factors (age, cholesterol, blood pressure, smoking and diabetes) and parental history of myocardial infarction before age 60 years.⁴⁶ When this expanded risk algorithm (the Reynolds Risk Score) was validated in a separate group of 8,158 women followed up for 10 years, it provided more accurate risk assessment than did the smaller set of traditional risk factors; 44% of women in intermediate risk categories (5- $<$ 10% and 10- $<$ 20% 10-year risk) were reclassified as higher risk (27%) or lower risk (18%).⁴⁶ It remains to be seen whether the Reynolds Risk Score will yield similar results in more diverse populations. In a cohort of middle-aged asymptomatic men, Koenig *et al.* showed that hsCRP provided incremental information regarding risk beyond that obtained using the Framingham risk score, particularly in those at intermediate risk.⁴⁷ Additional studies show that hsCRP levels provide risk information incremental to the Framingham risk score in elderly men at intermediate risk and elderly women at high risk.^{20, 23}

The c-statistic—The reclassification of intermediate-risk individuals to a different risk category could have important implications for preventive pharmacotherapy in these patients. It remains to be seen, however, whether such reclassification improves patient outcomes. In the absence of long-term, prospective studies, statistical criteria are being used to evaluate the incremental utility of hsCRP measurement. In a 2006 publication from the Framingham Offspring Study, elevated baseline levels of hsCRP were associated with higher overall mortality during 7-year follow-up.⁴⁸ Despite the higher mortality, the c-statistic (derived from the receiver-operator curve [ROC] whereby a value of 0.5 signifies a test of no utility and a value of 1.0 signifies a test with perfect discrimination) of the risk prediction model did not change with the addition of hsCRP. Indeed, most studies have not found the inclusion of hsCRP in models to increase the c-statistic significantly.

Whether the c-statistic is more suited to retrospective case-control studies than for prospective risk prediction models and whether criteria other than the c-statistic could be more appropriate for assessing risk models is under debate.⁴⁹⁻⁵¹ Although improvement of the c-statistic is one criterion by which a biomarker can be judged to be 'ideal', relying solely on the c-statistic could be misleading and force the exclusion of clearly useful risk factors—the addition or subtraction of blood pressure and lipid profile individually from a model based on Framingham risk factors does not significantly change the c-statistic.⁵¹ As more risk factors are incorporated into a model it becomes increasingly difficult for a risk factor to increase the c-statistic, even if that risk factor carries as strong an association with the disease in question as the other risk factors.

The optimal set of parameters by which to judge the additive value of a biomarker to risk prediction algorithms is a subject of active investigation. A summary quantitative measure of model fit that compares the proportion of individuals moving up or down in risk categories with the use of a biomarker (net reclassification index [NRI])⁵² has been used to assess whether hsCRP adds information to traditional risk factors. In the Women's Health Study, the NRI using hsCRP was 6%,¹¹³ whereas in the Framingham study, the NRI using hsCRP was 9%.²³ Even if one accepts that the c-statistic is the gold standard by which to assess the utility of hsCRP, most analyses of hsCRP have considered the change in the c-statistic when the test is applied to a population as a whole, rather than just to intermediate-risk patients. In a cohort of middle-aged asymptomatic men, addition of hsCRP to the Framingham risk model improved the c-statistic from 0.735 to 0.750 when calculated for the whole study population—a modest change

that could be interpreted as being of little clinical importance. By contrast, when calculated for just the intermediate-risk individuals with a 10-year CVD risk of 11-14% the c-statistic increased from 0.725 to 0.776, and increased from 0.695 to 0.751 for patients with a 10-year risk of 15-19%—considerable improvements that support hsCRP use in these subgroups.⁴⁷ More analyses of this kind in different cohorts could help determine the appropriateness of the c-statistic in establishing the value of a biomarker.

In summary, hsCRP assessment in asymptomatic individuals seems most useful for those that are at intermediate risk based on traditional risk factors (e.g. ATP III global risk score of 5-20%) and who do not already warrant chronic treatment with aspirin and statin therapy. In individuals at very low risk, even a doubling or tripling of risk (e.g. from 1% to 3%) would not change their risk classification and should not greatly change physician or patient behavior as the absolute CVD risk remains low. Conversely, high-risk individuals are candidates for chronic aspirin and lipid-lowering therapy regardless of their hsCRP level. Among individuals at intermediate risk, however, reclassification to a higher or lower CVD risk category on the basis of hsCRP levels could influence decisions on whether to use more-aggressive or less-aggressive preventive strategies.

There are substantially more data now supporting the measurement of hsCRP in select asymptomatic patients than there were in 2003, when the CDC and AHA guidelines were published. Nevertheless, more data are needed to establish the utility of hsCRP in creating improved risk prediction strategies—such as the Reynolds Risk Score—and validation of those strategies in intermediate-risk individuals in numerous cohorts.

Stroke and hypertension

In numerous prospective studies, elevated hsCRP levels have correlated with an increased risk of stroke, even after adjusting for multiple traditional risk factors (Table 3).^{21, 24, 30, 34, 53-57} Although as with coronary events there are some studies that fail to demonstrate a statistically significant association.^{39, 55, 57-60} Considering these studies together, the relative risk associated with elevated hsCRP levels is comparable to the relative risk of other established risk factors for stroke, with as much as a three-fold increase in risk in high-CRP strata compared to low-CRP strata. As a result of this strong association, consideration can be given towards the measurement of hsCRP for the primary prevention of stroke in individuals with other risk factors for stroke who would not otherwise receive preventive therapy. Data are, however, lacking on what proportions of individuals would be appropriately reclassified as being of higher or lower risk for stroke following incorporation of hsCRP.

Among individuals with blood pressure above desired goals as specified by the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) guidelines, the concomitant finding of elevated hsCRP should encourage the use of antihypertensive therapy and more-aggressive lifestyle modification. However, it is reasonable that all patients with hypertension and other risk factors for stroke should be counseled to undertake lifestyle modification. In conclusion, there are not yet specific data to support hsCRP measurement in addition to traditional strategies for stroke risk prediction.

The metabolic syndrome and diabetes mellitus

In individuals with the metabolic syndrome, elevated hsCRP levels correlated with both an increased risk of developing non-insulin-dependent diabetes and the development of both diabetes and CVD.⁶¹⁻⁷⁷ Multiple prospective cohort studies have confirmed hsCRP to be associated with incident non-insulin-dependent diabetes independent of other risk factors such as obesity, particularly in women (Table 4).⁶¹⁻⁷³ In addition, CRP levels are associated with

CVD risk among those with the metabolic syndrome and appear to differentiate individuals at high risk for both incident diabetes mellitus and CVD events from those at low risk.

Among individuals already diagnosed with diabetes, hsCRP levels can further stratify cardiovascular risk,^{72, 74, 75} underscoring the pathophysiologic link between insulin resistance, inflammation and CVD.^{66, 76, 77} As noted for stroke risk factors, it is important to recommend more aggressive lifestyle modification to all individuals meeting criteria for the metabolic syndrome, regardless of whether they have elevated CRP levels.

Lifestyle interventions

Weight reduction, smoking cessation and exercise are recommended for patients at risk for CVD or diabetes, and these interventions have been shown to lower hsCRP levels.^{78-82, 111, 112} It should be noted, however, that data are lacking as to whether hsCRP reduction *per se* reduces cardiovascular risk independent of other modifiable risk factors. Lifestyle interventions should emphasize both increasing physical activity and dietary interventions that help the patient obtain and maintain an ideal body weight. In a large study of asymptomatic adult women and adjusted for cardiovascular risk factors, the relative risks for having hsCRP level greater than 3 mg/l were 1.3 for inactive, normal weight women, 2.7 for active, overweight women, 3.1 for inactive, overweight women, 8.3 for active, obese women, 9.9 for those who were inactive and obese.⁸¹ In a comprehensive review of 40 observational studies and 12 randomized clinical trials, most of which were in healthy individuals, both lower fitness and higher fatness contributed to raised inflammation and hsCRP levels. Baseline levels of hsCRP may be important in the overall changes observed with intervention studies, with the greatest changes seen in those individuals with high baseline levels and, in some studies, no changes seen in individuals with low baseline levels.⁸³

Statin therapy

Many studies have shown that statin therapy lowers hsCRP levels, with relatively little correlation between the degree of LDL-cholesterol reduction and hsCRP reduction in individual patients.⁸⁴⁻⁸⁷ These data are consistent with laboratory studies demonstrating that statins have anti-inflammatory as well as lipid-lowering effects.⁸⁸⁻⁹⁰ As statins seem to be somewhat unique in this regard compared with other classes of lipid-lowering agents, they should be used preferentially over other lipid-lowering agents in the hypercholesterolemic patient with elevated hsCRP. A greater degree of CVD event reduction with statin therapy occurs in hypercholesterolemic patients with an elevated level of hsCRP than those with similar cholesterol levels and low levels of hsCRP;^{16, 86, 87, 91} however, whether CRP is raised or not, all hypercholesterolemic patients should receive lipid-lowering therapy. Whether statins prevent CVD events in individuals who have elevated hsCRP levels without hyperlipidemia was the subject of a large-scale clinical trial (Justification for the Use of Statins in Primary Prevention: an Intervention Trial Evaluating Rosuvastatin [JUPITER]) that was recently stopped early due to overwhelming benefit of rosuvastatin therapy in reducing adverse clinical outcomes.⁹² Until the results of JUPITER are published, statin therapy cannot be routinely recommended to patients with low levels of LDL-cholesterol and high levels of hsCRP; however, it is nonetheless reasonable to encourage substantial lifestyle changes (i.e. exercise, weight loss and complete smoking cessation) if not already undertaken. Of note, other agents, including metformin, thiazolidinediones, insulin, angiotensin-receptor blockers, and combinations of agents, such as ezetimibe-statin combination therapy, are known to lower hsCRP levels, but their optimum roles in primary prevention remain to be determined.

Secondary prevention

A number of studies have demonstrated the prognostic utility of hsCRP in patients with acute coronary syndromes,⁹³⁻⁹⁸ even when troponin is undetectable.⁹⁷ When such high-risk

patients receive statin therapy, the best long-term clinical outcomes occur among those that achieve very low levels of LDL cholesterol (<1.8 mmol/l [70 mg/dl]) and hsCRP (<2 mg/l). In the Pravastatin or Atorvastatin Evaluation and Infection Therapy - Thrombolysis in Myocardial Infarction 22 (PROVE IT - TIMI 22) and Aggrastat to Zocor (A to Z) trials, in terms of reduction of coronary events and improvement in survival, achievement of low CRP levels was as significant as reaching low LDL-cholesterol levels.^{87, 96} Furthermore, better outcomes were seen in individuals with both low LDL-cholesterol and low CRP levels than in those with low LDL-C and high hsCRP levels.

Similar results have also been found in individuals with stable coronary artery disease, and those who achieve low hsCRP levels on statin therapy have reduced risk of stroke⁹⁹ and regression of atherosclerosis on intravascular ultrasonography.⁸⁶ These data indicate that achieving low levels of hsCRP after initiation of statin therapy could be an important therapeutic goal along with very low levels of LDL-cholesterol. It seems reasonable to consider hsCRP measurement in patients with a history of CVD who have achieved LDL-cholesterol goals on low or moderate statin therapy—the finding of a high hsCRP level could help guide decisions to further intensify statin therapy, although this strategy remains to be formally validated in a prospective trial.

PRACTICAL CONSIDERATIONS

Testing

CRP cutoffs of less than 1 mg/l, 1-3 mg/l, and greater than 3 mg/l are commonly used for cardiovascular risk discrimination and correspond to approximate tertile risk values in Caucasian populations.⁸⁴ These same levels also discriminate risk of incident diabetes and vascular events among those with the metabolic syndrome.

Limited information is available regarding the utility of these hsCRP tertile levels in minority populations,⁸⁴ although evidence indicates that hsCRP levels are often higher in African Americans than in Caucasian and Asian Americans.^{100, 101} Of note, rates of CVD are also raised in African Americans compared with Caucasians.¹ The effect of different treatment strategies across different ethnic groups based on hsCRP risk stratification is currently unknown.

The relationship between hsCRP and CVD risk is linear across the full range of CRP levels. An alternative system that divides hsCRP levels into five categories (<0.5 mg/l, 0.5-1.0 mg/l, 1.0-3.0 mg/l, 3.0-5.0 mg/l, and >5.0 mg/l) could provide further discrimination,¹⁰⁰ much in the same manner that five categories are currently recommended for stratification of blood pressure and lipids.¹⁰² The use of tertiles of hsCRP for risk stratification is consistent with risk discrimination in major population studies but could lead to confusion and inconvenience if applied in clinical practice. For primary prevention, therefore, the more conservative recommendation is that high hsCRP levels be defined as 3 mg/l or greater, which readily identifies a group that has substantially increased risk compared with those individuals who have hsCRP below 1 mg/l. For secondary prevention, levels of 2 mg/l or greater are consistent with higher risk in patients with established coronary disease and ongoing treatment with statins.¹⁰³

Individuals with CRP levels that are consistently greater than 10 mg/l are at particularly high risk for developing CVD.^{100, 102} CRP levels greater than 10 mg/l should not be viewed, therefore, as uninformative; patients with an hsCRP level in this range should undergo repeat assessment at a later date to see if the level remains elevated, which would suggest increased long-term vascular risk and perhaps warrant treatment.^{100, 102-104}

Whereas most epidemiologic studies have relied on single hsCRP measurements per patient, in practice the clinical value of hsCRP could be improved if individuals with an initially high value undergo repeat assessment at least a month later. As hsCRP levels are not affected by intraindividual circadian variation or recent food ingestion, a blood sample for determination of hsCRP level can be obtained at any time of the day, and a fasting sample is not required.⁷⁴ Variation in hsCRP levels is comparable to that seen in cholesterol measurements.⁷⁴ It remains unclear whether there is significant seasonal variation in hsCRP levels and how this might affect vascular risk.^{105, 106} As patients in the midst of an acute phase response can have transiently elevated hsCRP levels, repeat testing is recommended for all values in excess of 5 mg/l. If the second blood sample yields a reduced hsCRP level, then the second value should be used in the assessment of CVD risk. When persistently high hsCRP values are obtained, vascular risk seems to be high regardless of the cause of the underlying inflammation.^{100, 102-104}

Although older assays are capable of detecting high levels of CRP during the acute phase response, these assays are not sensitive enough to detect the low levels of inflammation needed for vascular risk prediction. As many hospital-based and outpatient laboratories offer CRP testing to assess the presence systemic inflammatory states (i.e. collagen vascular disease, rheumatologic conditions, endocarditis) and hsCRP testing for cardiovascular evaluation, physicians need to specify an 'hsCRP' test when they seek information concerning vascular risk. Multiple commercial assays for hsCRP are available and have been standardized to provide consistent clinical information in inpatient and outpatient settings.⁷⁴ A comprehensive program for standardization of commercial hsCRP assays was completed in 2003, so that all hsCRP results are now reported in mg/l.

Specificity for CVD

It is important to note that CRP is a marker of general inflammation and therefore could highlight the presence of chronic inflammatory conditions other than atherosclerosis. Case-control and retrospective studies have found associations between cancer and elevated hsCRP levels, however, prospective studies have not confirmed this association.¹⁰⁷ Elevated hsCRP levels in cancer patients most likely reflect prevalent disease rather than being a marker of future risk.¹⁰⁷ Of note, hsCRP was shown to predict all-cause mortality in two recent studies.^{108, 109} In both studies CVD was the most common cause of death underlying all-cause mortality, as it is in the general population, accounting for >60% of adult deaths. Even in light of the possibility that CRP is not specific to vascular mortality but may also predict nonvascular mortality, in intermediate-risk patients with multiple CVD risk factors elevated CRP should be regarded as a clear signal of CVD risk and can guide therapy specifically intended to reduce vascular mortality, e.g., statin therapy.

Cost-effectiveness

Cost-effectiveness is an important consideration when assessing new biomarkers as screening all patients has severe cost implications. A 2003 cost-effectiveness analysis examined the incremental cost-effectiveness of hsCRP screening followed by targeted statin therapy for individuals with elevated levels, compared with dietary counseling alone, for the primary prevention of cardiovascular events among patients with low or normal LDL cholesterol levels.¹¹⁰ The investigators found that using hsCRP screening to target statin therapy for the primary prevention of CVD among individuals without overt hyperlipidemia was a cost-effective option—US\$48,100 per quality-adjusted life-year (QALY) for 58-year-old men and \$94,400 per QALY for 58-year-old women. In some scenarios, hsCRP was even cost-saving. Their results varied by level of baseline cardiovascular risk and the cost and efficacy of statin therapy in patients with high hsCRP levels. In light of the early termination of the JUPITER trial, the efficacy of statins might be much higher in asymptomatic individuals than originally expected.

In the primary prevention setting, a screening strategy that always requires lipids to be measured before hsCRP evaluation would probably not be cost-effective. In a patient known to have a Framingham risk estimate of 5-20% on the basis of prior evaluations (i.e. intermediate risk) and who is not receiving aspirin and/or statin therapy, concomitant hsCRP measurement at the time of lipid evaluation may be appropriate. As the cost of hsCRP is low, this approach may be more efficient and more cost-effective than using a second physician visit and additional phlebotomy after lipid results have been obtained.

CONCLUSIONS

CRP levels when assessed by the high-sensitivity assay are associated with CVD in multiple patient groups and add predictive power to traditional risk scores for some intermediate-risk individuals. CRP data could also assist with targeting of lifestyle modification and pharmacologic preventive therapies. The available data support selective use of hsCRP measurement to improve risk prediction in the primary prevention setting in individuals at intermediate CVD risk according to traditional risk scores and who do not already warrant chronic aspirin and statin therapy. Data supporting the selective use of hsCRP levels to guide treatment in secondary prevention patients not already on maximal statin therapy is currently limited. In both contexts, further validation studies will be needed before these strategies are universally endorsed.

Biography

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Table 1A

Association of C-reactive protein with coronary heart disease in primary prevention populations; studies that show a significant association after multivariate adjustment ($P < 0.05$).

Study	Ref	Population	Adjusted for	Endpoint	Comparison	RR or OR (95% confidence interval)
AFCAPS/TexCAPS	16	Men, women	Age, sex, smoking, HTN, parental history of CAD, lipid levels	MI, CHD death, UA	Quartiles (per one-quartile increase)	1.17 (1.03-1.33)
ARIC	17	Men, women	Age, sex, race, smoking, HTN, DM, LDL, HDL	Incident CHD	Tertiles (3 vs. 1)	1.72 (1.24-2.39)
BRHS	18	Men	Age, town, smoking, BP, TC, HDL, TG, BMI, occupation, housing tenure, marital status, car ownership, childhood socioeconomic factors	MI, CHD death	Tertiles (3 vs. 1)	2.13 (1.38-3.28)
Caerphilly + Speedwell	19	Men	Age, area, smoking, BMI, DBP, TC, evidence of ischemia at baseline	MI, CHD death	Quintiles (5 vs. 1)	1.72 (1.14-2.58)
CHS	20	Men, women > age 65	Age, sex, race, field center, HTN, DM, smoking, BMI, waist circumference, TC, HDL, aspirin use	MI, CHD death	CRP > 3.0 mg/L vs. < 1.0 mg/L	1.45 (1.14-1.86)
Edinburgh	21	Men, women	Age, sex, subclinical disease (ABI), pack-years smoking, DM, BMI, TC/HDL ratio, physical activity	MI, stroke, revascularization	Tertiles (3 vs. 1)	1.62 (1.11-2.38)
EPIC-Norfolk	22	Men, women	Age, sex, smoking, DM, BMI, SBP, LDL, HDL	CAD	Quartiles (4 vs. 1)	1.66 (1.31-2.12)
FHS (high-sensitivity CRP assay)	23	Men, women	Age, sex, smoking, TC/HDL ratio, DM, SBP, use of antihypertensives	CVD	CRP > 3.0 mg/L vs. < 1.0 mg/L	1.74 (1.15-2.63)
Honolulu	24	Men	Age, smoking, alcohol, TC, HTN, DM, BMI, physical activity index	MI	Quartiles (4 vs. 1)	1.6 (1.1-2.2)
HPFUS	25	Men	Age, smoking, month of blood sampling, parental history of CHD, alcohol, physical activity, TC/HDL ratio, BMI, DM, HTN	MI, CHD death	Quintiles (5 vs. 1)	2.55 (1.40-4.65)
Kuopio	26	Men	Age, year of exam, smoking, LDL, HDL, SBP, use of antihypertensives, diet, fasting insulin, fasting glucose, waist girth, exercise, alcohol, socioeconomic status	CVD death	Tertiles (3 vs. 1)	1.71 (1.16-2.54)
MONICA-Augsburg	27	Men	Age, survey, BMI, smoking, alcohol, physical activity, SBP, TC/HDL ratio, parental history of MI, history of DM	MI, CHD death	Tertiles (3 vs. 1)	1.89 (1.28-2.77)

Study	Ref	Population	Adjusted for	Endpoint	Comparison	RR or OR (95% confidence interval)
PHS	28	Men	Age, BMI, DM, history of HTN, family history of CAD	MI	Quartiles (4 vs. 1)	2.6 (1.6-4.4)
PRIME	29	Men	Age, smoking, DM, HTN, LDL, HDL, TG	MI, CHD death	Tertiles (3 vs. 1)	2.16 (1.26-3.72)
PROSPER	30	Men, women > age 70	Age, sex, randomized treatment, country, current and past smoking, SBP, DBP, use of antihypertensives, LDL, HDL, TG, DM, BMI	MI, CHD death, stroke	Tertiles (3 vs. 1)	1.51 (1.17-1.95)
Reykjavik	31	Men, women	Age, sex, year of enrollment, smoking, SBP, TC, TG, BMI, FEV ₁ , DM, socioeconomic status	MI, CHD death	Tertiles (3 vs. 1)	1.45 (1.25-1.68)
SOF	32	Women > age 65	Age, HTN, LDL, HDL, DM, smoking, BMI, estrogen use, education level, clinical site	CVD death	Quartiles (4 vs. 1)	8.0 (2.2-29)
WHI	33	Women	Age, ethnicity, smoking, length of follow-up, TC/HDL ratio, BMI, history of HTN, family history of premature CAD, DM, exercise frequency, alcohol, use of HRT	MI, CHD death	Quartiles (4 vs. 1)	2.1 (1.1-4.1)
WHS	34	Women	Age, smoking, DM, BP, use of HRT	MI, ischemic stroke, coronary revascularization, CVD death	Quintiles (5 vs. 1)	2.3 (1.6-3.4)
WOSCOP	35	Men	Age, statin treatment, DM, HTN, angina, BMI, SBP, TC, LDL, HDL, TG	MI, CHD death, revascularization	Quintiles (5 vs. 1)	1.49 (1.00-2.22)

Table 1B

Association of C-reactive protein with coronary heart disease in primary prevention populations; studies that do not show a significant association after multivariate adjustment ($P > 0.05$)

FHS (non-high sens. assay)	37	Men, women	Age, sex, smoking, TC/HDL ratio, DM, SBP, use of antihypertensives	MI, CHD death	CRP > 3.0 mg/L vs. < 3.0 mg/L	1.22 (0.81-1.84)
MONICA-Augsburg	27	Women	Age, survey, BMI, smoking, alcohol, physical activity, SBP, TC/HDL ratio, parental history of MI, history of DM	MI, CHD death	Tertiles (3 vs. 1)	1.35 (0.64-2.84)
MRFIT	38	Men	Age, cigarettes smoked, DBP, HDL, LDL, TG	MI, CHD death	Quartiles (4 vs. 1)	1.54 (0.96-2.50)
Health ABC	39	Men, women > age 70	Age, sex, race, smoking, DM, HTN, BMI, HDL, TG, albumin	Incident CHD	Tertiles (3 vs. 1)	1.20 (0.83-1.75)
Hoorn	40	Men, women	Age, sex, impaired glucose tolerance, DM, HTN, smoking, TC, HDL, TG, IHD, PAD, obesity	CVD death	Tertiles (3 vs. 1)	1.32 (0.52-3.35)
Iowa 65+	41	Men, women > age 65	Age, sex, prevalent CVD, smoking, DM, BMI	CVD death	Quartiles (4 vs. 1)	1.8 (0.9-3.6)
NHS	25	Women	Age, smoking, month of blood sampling, fasting status, parental history of CHD, alcohol, physical activity, TC/HDL ratio, BMI, DM, HTN, use of HRT	MI, CHD death	Quintiles (5 vs. 1)	1.61 (0.84-3.07)
Quebec	42	Men	Age, smoking, history of DM, SBP, medication use at baseline, BMI, LDL, HDL, TC/HDL ratio	MI, CHD death, angina, coronary insufficiency	Halves (2 vs. 1)	1.1 (0.7-1.6)
Rotterdam	43	Men, women > age 55	Age, sex, current smoking, BMI, HTN, DM, family history of early MI, TC, HDL	MI	Quartiles (4 vs. 1)	1.2 (0.6-2.2)
SMILE	44	Men	Age, smoking, alcohol, DM, obesity, SBP, DBP, TC, HDL, TG	MI	Quintiles (5 vs. 1)	1.4 (0.9-2.1)

Studies: AFCAPS/TexCAPS, Air Force/Texas Coronary Atherosclerosis Prevention Study; ARIC, Atherosclerosis Risk in Communities; BRHS, British Regional Heart Study; Caerphilly Heart Study; CHS, Cardiovascular Health Study; Edinburgh, Edinburgh Artery Study; EPIC-Norfolk, European Prospective Investigation into Cancer Norfolk Study; FHS, Framingham Heart Study; Health ABC, Dynamics of Health, Aging and Body Composition Study; Honolulu, Honolulu Heart Study; Hoorn, Hoorn Study; Iowa 65+, Iowa 65+ Rural Health Study; Kuopio, Kuopio Ischaemic Heart Disease Risk Factor Study; HPFUS, Health Professionals Follow Up Study; Leiden, MRFIT, Multiple Risk Factor Intervention Trial; MONICA-Augsburg, Monitoring Cardiovascular Disease Augsburg Cohort Study; NHS, Nurses' Health Study; PHS, Physicians' Health Study; PRIME, PRIME (étude prospective du l'infarctus myocarde) Study; PROSPER, Prospective Study of Pravastatin in the Elderly at Risk; Quebec, Quebec Cardiovascular Study; Reykjavik, Reykjavik Study; Rotterdam, Rotterdam Study; SMILE, Study of Myocardial Infarctions Leiden; SOF, Study of Osteoporotic Fractures; Speedwell, Speedwell Prospective Study; WHI, Women's Health Initiative; WHS, Women's Health Study; WOSCOP, West of Scotland Coronary Protection Study.

Abbreviations: AF, atrial fibrillation; BP, blood pressure; CAD, coronary artery disease; CHD, coronary heart disease; CRP, C-reactive protein; CVD, cardiovascular disease; DBP, diastolic blood pressure; DM, diabetes mellitus; FEV₁, forced expiratory volume in 1 second; HDL, high-density-lipoprotein cholesterol; HRT, hormone replacement therapy; HTN, hypertension; IHD, ischemic heart disease; LDL, low-density-lipoprotein cholesterol; MI, myocardial infarction; OR, odds ratio; RR, risk ratio; SBP, systolic blood pressure; TC, total cholesterol; TG, triglycerides; UA, unstable angina.

Table 2

Magnitude of association between C-reactive protein and coronary heart disease compared with traditional risk factors in primary prevention studies that reported these comparisons

Study	Ref	Adjusted for	Endpoint	Comparison	Risk factor	RR or OR (95% confidence interval)
EPIC-Norfolk	22	Age, sex, smoking, DM, BMI, SBP, LDL, HDL	CAD	Quartiles (4 vs. 1) or yes vs. no	CRP Smoking Diabetes BMI SBP LDL HDL	1.66 (1.31-2.12) 2.13 (1.65-2.75) 4.26 (2.61-6.93) 1.74 (1.36-2.23) 1.56 (1.22-1.99) 1.68 (1.33-2.14) 0.57 (0.44-0.73)
FHS (non-high sens. assay)	37	Age, sex, smoking, TC/HDL ratio, DM, SBP, use of antihypertensives, CRP	MI, CHD death	High vs. low or yes vs. no	CRP Age SBP TC/HDL ratio Diabetes Current smoking Use of antihypertensives	1.22 (0.81-1.84) 1.83 (1.54-2.17) 1.13 (1.04-1.23) 1.20 (1.10-1.30) 2.16 (1.44-3.23) 1.59 (1.08-2.35) 1.21 (0.86-1.73)
Health ABC	39	Age, sex, race	Incident CHD	High vs. low or yes vs. no	CRP Smoking Total cholesterol LDL HDL Hypertension Diabetes BMI	1.33 (0.98-1.80) 1.32 (0.98-1.77) 1.13 (0.76-1.70) 1.07 (0.80-1.44) 1.19 (0.84-1.70) 1.28 (0.95-2.22) 1.90 (1.33-2.70) 1.51 (0.10-2.07)
Reykjavik	31	Age, sex, year of enrollment, smoking, SBP, TC, TG, BMI, FEV ₁ , DM, socioeconomic status	MI, CHD death	Tertiles (3 vs. 1) or yes vs. no	CRP Total cholesterol Current smoking SBP	1.45 (1.25-1.68) 2.35 (2.03-2.74) 1.87 (1.62-2.16) 1.50 (1.30-1.73)
WHS	36	Age, smoking, DM, BP, use of HRT	MI, stroke, coronary revascularization, CVD death	Quintiles (5 vs. 1)	CRP Total cholesterol	2.98 (1.90-4.67) 2.08 (1.45-2.97)

Study	Ref	Adjusted for	Endpoint	Comparison	Risk factor	RR or OR (95% confidence interval)
EPIC-Norfolk ^{22 a}					LDL	1.62 (1.17-2.25)
					Non-HDL	2.51 (1.69-3.72)
					HDL	0.43 (0.30-0.61)
FHS (non-high sens. assay) ^{37 b}					CRP	1.66 (1.31-2.12)
					Smoking	2.13 (1.65-2.75)
					Diabetes	4.26 (2.61-6.93)
					BMI	1.74 (1.36-2.23)
					SBP	1.56 (1.22-1.99)
					LDL	1.68 (1.33-2.14)
					HDL	0.57 (0.44-0.73)
					CRP	1.22 (0.81-1.84)
					Age	1.83 (1.54-2.17)
					SBP	1.13 (1.04-1.23)
Health ABC ^{39 c}					TC/HDL ratio	1.20 (1.10-1.30)
					Diabetes	2.16 (1.44-3.23)
					Current smoking	1.59 (1.08-2.35)
					Use of antihypertensives	1.21 (0.86-1.73)
					CRP	1.33 (0.98-1.80)
					Smoking	1.32 (0.98-1.77)
					Total cholesterol	1.13 (0.76-1.70)
					LDL	1.07 (0.80-1.44)
					HDL	1.19 (0.84-1.70)
					Hypertension	1.28 (0.95-2.22)
Reykjavik ^{31 d}					Diabetes	1.90 (1.33-2.70)
					BMI	1.51 (0.10-2.07)
					CRP	1.45 (1.25-1.68)
					Total cholesterol	2.35 (2.03-2.74)

Study	Risk factor	RR or OR (95% confidence interval)
WHS ^{36 e}	Current smoking	1.87 (1.62-2.16)
	SBP	1.50 (1.30-1.73)
	CRP	2.98 (1.90-4.67)
	Total cholesterol	2.08 (1.45-2.97)
	LDL	1.62 (1.17-2.25)
	Non-HDL	2.51 (1.69-3.72)
	HDL	0.43 (0.30-0.61)

Studies: EPIC-Norfolk, European Prospective Investigation into Cancer Norfolk Study; FHS, Framingham Heart Study; Health ABC, Dynamics of Health, Aging and Body Composition Study; Reykjavik, Reykjavik Study; WHS, Women's Health Study.

Abbreviations: BMI, body mass index; BP, blood pressure; CAD, coronary artery disease; CHD, coronary heart disease; CRP, C-reactive protein; CVD, cardiovascular disease; DM, diabetes mellitus; FEV₁, forced expiratory volume in 1 second; HDL, high-density-lipoprotein cholesterol; HRT, hormone replacement therapy; LDL, low-density-lipoprotein cholesterol; MI, myocardial infarction; OR, odds ratio; RR, risk ratio; SBP, systolic blood pressure; TC, total cholesterol; TG, triglycerides.

Abbreviations: BMI, body mass index; BP, blood pressure; CAD, coronary artery disease; CHD, coronary heart disease; CRP, C-reactive protein; CVD, cardiovascular disease; DM, diabetes mellitus; EPIC-Norfolk, European Prospective Investigation into Cancer Norfolk Study; FEV₁, forced expiratory volume in 1 second; FHS, Framingham Heart Study; Health ABC, Dynamics of Health, Aging and Body Composition Study; HDL, high-density-lipoprotein cholesterol; HRT, hormone replacement therapy; LDL, low-density-lipoprotein cholesterol; MI, myocardial infarction; OR, odds ratio; RR, risk ratio; SBP, systolic blood pressure; TC, total cholesterol; TG, triglycerides; WHS, Women's Health Study.

^a Adjusted for age, sex, smoking, DM, BMI, SBP, LDL, HDL. Endpoint was CAD. Compared quartiles (4 vs. 1) or yes vs. no.

^b Age, sex, smoking, TC/HDL ratio, DM, SBP, use of antihypertensives, CRP. Endpoints were MI and CHD-related death. Compared high vs. low or yes vs. no

^c Age, sex, race. Endpoint was incident CHD. Compared high vs. low or yes vs. no

^d Age, sex, year of enrollment, smoking, SBP, TC, TG, BMI, FEV₁, DM, socioeconomic status. Endpoints were MI and CHD death. Compared tertiles (3 vs. 1) or yes vs. no

^e Age, smoking, DM, BP, use of HRT. Endpoints were MI, stroke, coronary revascularization and CVD death. Compared quintiles (5 vs. 1).

Table 3
Association of C-reactive protein with stroke in primary prevention populations

Study	Ref	Population	Adjusted for	Endpoint	Comparison	RR or OR (95% confidence interval)
Studies that show a significant association after multivariate adjustment ($p < 0.05$)						
ARIC	53	Men, women	Age, sex, race, smoking, LDL, HDL, DM, BMI, SBP, use of antihypertensives	Ischemic stroke	CRP > 3.0 mg/L vs. < 1.0 mg/L	1.97 (1.14-3.39)
CHS	54	Men, women > age 65	Age, sex, race, smoking, DM, HTN, SBP, TC, internal + common carotid IMT	Ischemic stroke	CRP > 3.0 mg/L vs. < 1.0 mg/L	1.45 (1.14-1.86)
Edinburgh	21	Men, women	Age, sex, subclinical disease (ABI), pack-years smoking, DM, BMI, TC/HDL ratio, physical activity, MI, stroke, angina, intermittent claudication	Stroke	Tertiles (3 vs. 1)	2.18 (1.30-3.66)
FHS	55	Women	Age, smoking, TC, HDL, DM, SBP	Ischemic stroke or TIA	Quartiles (4 vs. 1)	2.1 (1.19-3.83)
Hisayama	56	Men, women	Age, sex, smoking, alcohol, SBP, ECG abnormalities, DM, BMI, TC, HDL, physical activity	Ischemic stroke	Quintiles (5 vs. 1)	3.11 (1.04-9.32)
Honolulu	24	Men	Age, smoking, alcohol, TC, HTN, DM, BMI, physical activity index	Thromboembolic stroke	Quartiles (4 vs. 1)	1.6 (1.1-2.4)
NHANES	57	Women	Age, race or ethnicity, smoking, education, SBP, TC, HDL, DM, BMI, physical activity	Stroke	Tertile 3 vs. undetectable CRP	1.82 (1.10-2.99)
PHS	28	Men	Age, HTN, DM, BMI, family history of CAD	Stroke	Quartile (4 vs.1)	1.6 (1.0-3.1)
PROSPER	30	Men, women > age 70	Age, sex, randomized treatment, country, current and past smoking, SBP, DBP, use of antihypertensives, LDL, HDL, TG, DM, BMI, CHD, PAD, stroke, TIA	Stroke	Tertiles (3 vs. 1)	1.37 (1.00-1.86)
WHS	34	Women	Age, smoking, DM, BP, use of HRT	Ischemic stroke	Tertiles (3 vs. 1)	2.0 (1.3-3.1)
Studies that do not show a significant association after multivariate adjustment ($p > 0.05$)						
FHS	55	Men	Age, smoking, TC, HDL, DM, SBP	Ischemic stroke or TIA	Quartiles (4 vs. 1)	1.6 (0.87-3.13)
Health ABC	39	Men, women > age 70	Age, sex, race, smoking, DM, HTN, BMI, HDL, TC, albumin	Stroke	Tertiles (3 vs. 1)	1.41 (0.73-2.71)
Leiden 85+	59	Men, women	Age, sex, current smoking, use of NSAIDs, TC, HTN, DM, previous cardiovascular events	Fatal stroke	CRP 5-10 mg/L vs. < 5 mg/L	2.1 (0.9-5.4)

Study	Ref	Population	Adjusted for	Endpoint	Comparison	RR or OR (95% confidence interval)
NHANES	57	Men	Age, race or ethnicity, smoking, education, SBP, TC, HDL, DM, BMI, physical activity	Stroke	Tertile 3 vs. undetectable CRP	1.62 (0.79-3.32)
Rotterdam	60	Men, women > age 55	Age, sex, SBP, use of antihypertensives, DM, smoking, CHD, AF, LVH, intima-media thickness	Stroke	Quartiles (4 vs. 1)	1.09 (0.84-1.41)

Studies: ARIC, Atherosclerosis Risk in Communities; CHS, Cardiovascular Health Study; Denmark, Frederiksberg University Hospital, Copenhagen, Denmark cohort; Edinburgh, Edinburgh Artery Study; FHS, Framingham Heart Study; Health ABC, Dynamics of Health, Aging and Body Composition Study; Hisayama, Hisayama Study; Honolulu Heart Study; Leiden 85-Plus Study; NHANES, Third National Health and Nutrition Examination Survey; PHS, Physicians' Health Study; PROSPER, Prospective Study of Pravastatin in the Elderly at Risk; Rotterdam, Rotterdam Study; WHS, Women's Health Study.

Abbreviations: ABI, ankle-brachial index; AF, atrial fibrillation; BMI, body mass index; BP, blood pressure; CHD, coronary heart disease; CRP, C-reactive protein; DBP, diastolic blood pressure; DM, diabetes mellitus; ECG, electrocardiogram; FEV₁, forced expiratory volume in 1 second; HDL, high-density-lipoprotein cholesterol; HRT, hormone replacement therapy; HTN, hypertension; IMT, intima-media thickness; LDL, low-density-lipoprotein cholesterol; LVH, left ventricular hypertrophy; MI, myocardial infarction; NSAID, nonsteroidal anti-inflammatory drug; OR, odds ratio; PAD, peripheral artery disease; RR, risk ratio; SBP, systolic blood pressure; TC, total cholesterol; TG, triglycerides; TIA, transient ischemic attack.

Table 4
Association of C-reactive protein with diabetes in primary prevention populations

Study	Ref	Population	Adjusted for	Endpoint	Comparison	RR or OR (95% confidence interval)
ARIC	61	Men, women	Age, sex, center, ethnicity, BMI, fasting glucose, fasting insulin, weight/hip ratio, HTN, parental history of DM	Incident DM	Quartiles (4 vs. 1)	1.23 (0.74-2.03)
Australian	62	Men, women	Age, sex, baseline glucose, BMI, smoking, alcohol, urine albumin/creatinine ratio, TC, SBP	Incident DM	Tertiles (3 vs. 1+2)	1.75 (1.19-2.56)
CHS	63	Men, women > age 65	Age, sex, fasting glucose, fasting insulin, BMI, subclinical CVD, use of thiazide diuretics	Incident DM	Quartiles (4 vs. 1)	1.83 (1.24-2.86)
EPIC-Potsdam	64	Men, women	Age, sex, BMI, waist/hip ratio, smoking, alcohol, sporting activities, educational attainment, HgbA1c	Incident DM	Halves (2 vs. 1)	1.9 (1.2-3.2)
Hisayama	65	Women	Age, family history of diabetes, fasting insulin, BMI, smoking, alcohol, physical activity, TC, HDL, TG, SBP	Incident DM	Tertiles (3 vs. 1)	2.25 (1.01-5.01)
Hisayama	65	Men	Age, family history of diabetes, fasting insulin, BMI, smoking, alcohol, physical activity, TC, HDL, TG, SBP	Incident DM	Tertiles (3 vs. 1)	2.63 (1.23-5.65)
IRAS	66	Men, women	Age, sex, clinic site, fasting insulin, smoking	Incident DM	Per 1 SD increase	1.34 (1.11-1.61)
Japanese-American	67	Women	Age, BMI, smoking, FH, BMI, insulin resistance, glucose tolerance testing, HRT	Incident DM	Quartiles (4 vs. 1)	3.11 (1.25-7.75)
Japanese-American	67	Men	Age, BMI, smoking, FH, BMI, insulin resistance, glucose tolerance testing	Incident DM	Quartiles (4 vs. 1)	2.84 (1.09-7.39)
Kuopio	68	Men	Age, fasting insulin, fasting glucose, TG, waist/hip ratio, smoking, alcohol, physical activity, presence of CVD, socioeconomic status, family history of DM, SBP, use of antihypertensives	Incident DM	CRP > 3.0 mg/L vs. < 1.0 mg/L	2.30 (1.04-5.07)
Mexico	69	Women	Age, smoking, alcohol, physical activity	Incident DM	Tertiles (3 vs. 1)	4.1 (2.1-8.0)
Mexico	69	Men	Age, smoking, alcohol, physical activity	Incident DM	Tertiles (3 vs. 1)	0.8 (0.4-2.0)
MONICA-Augsburg	70	Women	Age, survey, BMI, smoking, alcohol, physical activity, TC/HDL ratio, parental history of DM	Incident DM	Tertiles (3 vs. 1)	2.74 (1.47-5.11)
MONICA-Augsburg	70	Men	Age, survey, BMI, smoking, alcohol, physical activity, TC/HDL ratio, parental history of DM	Incident DM	Tertiles (3 vs. 1)	1.09 (0.71-1.66)
NHS	71	Women	Age, race, fasting status, time blood drawn, smoking, alcohol, BMI, physical activity, diet,	Incident DM	Quintiles (5 vs. 1)	4.36 (2.80-6.80)

Study	Ref	Population	Adjusted for	Endpoint	Comparison	RR or OR (95% confidence interval)
WHS	72	Women	family history of DM, menopausal status, HRT Age, fasting status, fasting insulin, BMI, smoking, alcohol, physical activity, family history of DM, HRT	Incident DM	Quartiles (4 vs. 1)	4.3 (1.1-17.1)
WOSCOP	73	Men	Age, fasting glucose, BMI, smoking, alcohol, SBP, HDL, TC, TG, statin therapy, WCC	Incident DM	Quintiles (5 vs. 1)	2.46 (1.20-5.04)

Studies: ARIC, Atherosclerosis Risk in Communities; Australian Aborigine cohort; CHS, Cardiovascular Health Study; EPIC-Norfolk, European Prospective Investigation into Cancer and Nutrition; Hisayama Study; IRAS, Insulin Resistance and Atherosclerosis Study; Japanese-American, Japanese-American cohort; Kuopio, Kuopio Ischaemic Heart Disease Risk Factor Study; Mexico, Mexico City Diabetes Study; MONICA-Augsburg, Monitoring Cardiovascular Disease Augsburg Cohort Study; NHS, Nurses' Health Study; WHS, Women's Health Study; WOSCOP, West of Scotland Coronary Protection Study.

Abbreviations: BMI, body mass index; CRP, C-reactive protein; CVD, cardiovascular disease; DM, diabetes mellitus; HDL, high-density-lipoprotein cholesterol; HgbA1c, hemoglobin A1c; HRT, hormone replacement therapy; HTN, hypertension; HRT, hormone replacement therapy; OR, odds ratio; RR, risk ratio; SBP, systolic blood pressure; SD, standard deviation; TC, total cholesterol; TG, triglycerides; WCC, white cell count.