Prevalence of High C-Reactive Protein in Persons with Serum Lipid Concentrations within Recommended Values

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Background: C-Reactive protein (CRP) has been shown to be a strong predictor of coronary heart disease (CHD) and is being considered in cardiovascular disease risk assessment. The number of normolipidemic individuals who are eligible for evaluation of CRP in overall CHD risk assessment is not known.

Methods: We analyzed data from the National Health and Nutrition Examination Survey 1999–2000 and computed the prevalence of high CRP (>3 mg/L) among normolipidemic adults. We also computed the prevalence among individuals free of CHD and diabetes. In addition, we examined the prevalence stratified by body mass index.

Results: The prevalence of high CRP among those with lipid concentrations within recommended values ranged from 28.8% to 35.3%, depending on the lipid fraction examined. Exclusion of individuals with CHD or diabetes and those with CRP concentrations >10 mg/L reduced the prevalence range (23.1–27.1%). Prevalence increased with increasing body mass index.

Conclusions: In 2000, ~12 million adults in the United States considered normolipidemic had high CRP concentrations. Additional studies to explore the role of CRP in cardiovascular disease risk assessment are needed.

Coronary heart disease (CHD) is one of the major causes of morbidity and mortality in the United States, causing 1 in every 5 deaths in the year 2000 (1). One approach to reducing the incidence of and mortality from CHD is to identify individuals who are at high risk of developing CHD and administer preventive measures in a timely fashion. The goal is to be able to predict future coronary events so that preventive measures can be implemented.

Several risk assessment algorithms for CHD have been developed. These generally incorporate such risk factors as age, smoking status, blood pressure, and serum lipid concentrations, including LDL-cholesterol (LDL-C), HDL-cholesterol (HDL-C), and total cholesterol (TC) (2, 3). More recently, however, markers of inflammation, including cytokines and adhesion molecules, have been studied for their association with CHD (4). Of these, C-reactive protein (CRP), a nonspecific marker of inflammation, has consistently been shown to be a strong predictor of coronary events (5–8). Consequently, measuring CRP may help in identifying persons at high risk of a future coronary event (9). Of particular interest is the observation that increased concentrations of CRP have been found to predict increased risk of cardiovascular disease in people without overt hyperlipidemia (10, 11). Incorporating the measurement of CRP in clinical practice could have a critical long-term impact, but this requires further exploration in terms of costs and benefits. To better understand the ramifications of using CRP to identify people at high risk of cardiovascular disease, an estimate of the number of people with increased CRP concentrations is needed. We therefore used data from the National Health and Nutrition Examination Survey (NHANES) to study the prevalence of high concentrations of CRP among normolipidemic individuals.

Materials and Methods

A representative sample of the noninstitutionalized US civilian population included in NHANES 1999–2000 was used for this study (12). A stratified multistage sampling design was used, and African-American and Mexican-American participants, those >60 years of age, and those

1 Nonstandard abbreviations: CHD, coronary heart disease; LDL-C and HDL-C, LDL- and HDL-cholesterol, respectively; TC, total cholesterol; CRP, C-reactive protein; and NHANES, National Health and Nutrition Examination Survey.
with low incomes were oversampled. The participants were interviewed by trained interviewers using a computer-assisted personal interview system. The interviews were conducted at each participant’s home, and the participants were requested to attend a mobile examination center. Additional questionnaires were completed, various examinations were conducted, and blood samples were collected at the mobile examination center. Greater details of the collection and processing of blood samples are provided in the NHANES Laboratory/Medical Technologists Procedures Manual (13). Specimens were stored at −20 °C until shipment to the University of Washington for CRP measurement or to the Lipoprotein Analytical Laboratory at Johns Hopkins University for lipid measurements.

The CRP concentrations were measured by latex-enhanced nephelometry on a Behring Nephelometer. Cholesterol was measured by enzymatic assays on a Hitachi 717 Analyzer (Roche Diagnostics) with commercial reagents. Serum control pools were obtained from Solomon Park Research Laboratories.

Information regarding existing medical conditions was collected by questionnaires. Participants were asked, “Has a doctor or other health professional ever told you that you had coronary heart disease?” Similar questions were asked for angina and heart attack (also called myocardial infarction). In addition, the participants were asked, “Have you ever been told by a doctor or other health professional that you have diabetes or sugar diabetes?” Those responding affirmatively were considered to have these conditions. Participants were also asked whether a doctor or other health professional had advised them to take prescribed medicine to lower blood cholesterol and whether they were following that advice. The answers to these questions were used to identify participants currently taking cholesterol-lowering medication.

Demographic data were also collected by questionnaire and used as follows: age at screening (continuous), gender, and race or ethnicity (white, African-American, Mexican-American, other). Body mass index, defined as body weight in kilograms divided by height (in meters) squared (kg/m²), was categorized into three groups: normal (<25 kg/m²), overweight (25 to <30 kg/m²), and obese (≥30 kg/m²).

**Analysis**

A total of 2188 participants 20 years and older attended the morning clinic and provided fasting blood samples. We limited our analyses to participants with no missing information for age, gender, race/ethnicity, body mass index, and concentrations of CRP, HDL-C, LDL-C, and TC. This gave 1774 participants available for data analyses.

We used the American Heart Association’s recommended values to categorize serum lipid concentrations (14). Participants with serum HDL-C concentrations <400 mg/L and TC concentrations >2000 mg/L were considered at high risk. For LDL-C, participants with serum concentrations ≥1300 mg/L were considered at high risk. We also used a combined category called the “normal lipid profile”, which included participants with all three serum lipid concentrations (HDL-C, LDL-C, and TC) within the recommended intervals. For CRP, serum concentrations >3.0 mg/L were considered high, as recommended by the American Heart Association and the CDC (4).

We computed crude and adjusted prevalence of high CRP for those with recommended concentrations of serum HDL-C, LDL-C, and TC and for those with a normal lipid profile. The prevalence estimates were adjusted for age, sex, and race/ethnicity. The recommendations regarding the serum LDL-C concentration depend on the presence of other risk factors; therefore, we also conducted our analyses by excluding participants with existing CHD and diabetes. Several reports have shown a strong association between obesity and serum concentrations of CRP (15–17); we therefore computed the prevalence of CRP among those with serum lipid concentrations within recommended ranges by categories of body mass index. We used SUDAAN (Software for the Statistical Analysis of Correlated Data) (18) to account for the complex sampling design and to calculate the weighted estimates.

**Results**

The crude prevalence of high CRP concentration among those with an overall normal lipid profile was 28.8% (Table 1). The prevalence of high CRP concentration increased with age and was higher among women and Mexican-American participants. The adjusted prevalence of high CRP value by age, gender, and race/ethnicity is presented in Fig. 1. Adjustment for these factors did not alter the results. When examined by each lipid separately, the prevalence of high CRP concentrations ranged from 31.2% to 35.3% for crude values and from 32.8% to 34.7% after adjustment. Exclusion of individuals with existing CHD and diabetes led to slightly lower estimates. The adjusted prevalence of high CRP among individuals with a normal lipid profile was 28.6%. The range by separate lipid concentrations was 31.8–33.4%.

After we excluded those with heart disease and diabetes, approximately one-fifth (19.7%) of those with normal lipid profiles were obese, approximately one in four persons (25.9%) were overweight, and the remaining 54.4% were within the normal body mass index range (<25 kg/m²). The prevalence of high CRP concentration varied widely by body mass index. Those within the normal body mass index range had a crude prevalence of high CRP ranging from 16.0% (for those with TC within the recommended range) to 20.5% (for those with LDL-C within the recommended range). The prevalence of high CRP concentration increased with increasing body mass index, with prevalences of 31.4–35.1% for overweight people and 52.5–60.9% for obese participants (Table 1).

The possibility exists that CRP concentrations >10
mg/L among normolipidemic individuals may be attributable to other infections or inflammation (4). After we excluded participants with CRP concentrations >10 mg/L, the adjusted prevalence of high CRP (>3 mg/L) was 23.1% among those with a normal lipid profile, but ranged between 25.9% and 27.1% when examined by each lipid separately (Table 2). Similarly, the adjusted prevalences of high CRP among normal, overweight, and obese participants with a normal lipid profile were 14.4%, 31.6%, and 36.0%, respectively.

Earlier studies reported that the use of lipid-lowering drugs may lower serum concentrations of CRP (19, 20). Exclusion of participants who reported current use of prescription medicines for high cholesterol did not change our results (data not shown).

**Discussion**

The data from NHANES 1999–2000 show that approximately one in every four persons 20 years of age and older without CHD and diabetes and with serum lipid concentrations within recommended ranges had a high CRP concentration (>3 mg/L). The prevalence of high CRP concentrations varied with body mass index, and at least one-third of the obese people with lipid concentrations within recommended ranges and without CHD or diabetes had a high CRP concentration.

Higher serum concentrations of CRP have been shown to predict future cardiovascular events in apparently healthy individuals and among both men and women. At

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**Table 1. Prevalence of high CRP concentrations (>3.0 mg/L) among those with serum lipid concentrations within recommended ranges, NHANES 1999–2000.**

<table>
<thead>
<tr>
<th>All participants</th>
<th>Normal LDL-C*</th>
<th>Normal HDL-C*</th>
<th>Normal TC*</th>
<th>Normal lipid profile*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weighted percentage with concentrations within recommended ranges</td>
<td>57.4%</td>
<td>75.5%</td>
<td>50.6%</td>
<td>33.5%</td>
</tr>
<tr>
<td>Median CRP concentrations, mg/L</td>
<td>2.0</td>
<td>2.0</td>
<td>1.7</td>
<td>1.5</td>
</tr>
<tr>
<td>Crude (SE) prevalence of high CRP, %</td>
<td>34.3 (1.9)</td>
<td>35.3 (1.9)</td>
<td>31.2 (2.1)</td>
<td>28.8 (2.5)</td>
</tr>
<tr>
<td>Adjusted (SE)* prevalence of high CRP, %</td>
<td>34.7 (1.9)</td>
<td>34.1 (1.9)</td>
<td>32.8 (2.2)</td>
<td>29.1 (2.6)</td>
</tr>
<tr>
<td>Estimated no. with high CRP</td>
<td>39 614 994</td>
<td>53 556 554</td>
<td>31 725 125</td>
<td>19 404 367</td>
</tr>
</tbody>
</table>

**Persons without CHD and diabetes mellitus**

| Weighted percentage with concentrations within recommended ranges | 56.8% | 77.0% | 50.3% | 34.5% |
| Median CRP concentrations, mg/L | 1.9 | 1.9 | 1.7 | 1.4 |
| Crude (SE) prevalence of high CRP, % | 32.9 (2.0) | 34.3 (2.0) | 29.9 (2.2) | 28.1 (2.7) |
| Adjusted (SE)* prevalence of high CRP, % | 33.4 (1.9) | 33.0 (1.9) | 31.8 (2.3) | 28.6 (2.7) |
| Estimated no. with high CRP | 33 060 702 | 46 546 352 | 26 652 940 | 17 156 960 |

**Stratified by body mass index**

| Normal (<25.0 kg/m²) | | | | |
| Crude (SE) prevalence of high CRP, % | 20.5 (2.4) | 19.8 (2.2) | 16.0 (2.5) | 16.7 (2.8) |
| Adjusted (SE)* prevalence of high CRP, % | 21.5 (2.2) | 19.5 (2.0) | 18.0 (2.6) | 17.9 (2.8) |
| Estimated no. with high CRP | 9 886 302 | 12 525 522 | 6 754 469 | 5 520 589 |

| Overweight (25.1 to <30.0 kg/m²) | | | | |
| Crude (SE) prevalence of high CRP, % | 33.8 (4.0) | 35.1 (3.2) | 31.4 (4.2) | 33.6 (5.6) |
| Adjusted (SE)* prevalence of high CRP, % | 34.9 (4.3) | 34.7 (3.4) | 33.8 (4.4) | 34.5 (5.5) |
| Estimated no. with high CRP | 9 939 317 | 14 163 735 | 8 307 616 | 5 317 662 |

| Obese (≥30 kg/m²) | | | | |
| Crude (SE) prevalence of high CRP, % | 56.1 (4.1) | 60.9 (3.3) | 56.3 (4.5) | 52.5 (6.1) |
| Adjusted (SE)* prevalence of high CRP, % | 54.3 (3.7) | 57.1 (3.4) | 55.3 (4.2) | 49.3 (5.6) |
| Estimated no. with high CRP | 13 435 082 | 19 857 096 | 11 590 855 | 6 318 710 |

*See text; defined according to the American Heart Association (14).

*Adjusted for age, sex, and race or ethnicity.
present, however, serum lipid concentrations are generally used, in addition to other behavioral risk factors, to identify people at high risk of coronary events. Although high cholesterol concentrations do predict future coronary events, many such events occur among normolipidemic individuals who appear to be at low clinical risk. This has led to the evaluation of new cardiovascular disease risk factors to better predict coronary events (21). Discussion about the role of CRP in the primary prevention of cardiovascular events, its comparison with serum lipid concentrations in the prediction of future events, its clinical applications, and the possibility of including CRP testing as a screening tool for cardiovascular disease is ongoing (10, 11, 22, 23).

Our estimates are based on persons 20 years of age and older with no history of diagnosed CHD and diabetes and with a normal serum lipid profile. We used our sample proportions to compute population estimates. According to the 2000 census population of the US, an estimated 177 million people are 20 years of age and older and have no history of diabetes or heart disease. The estimate for the number of people with lipid concentrations within recommended ranges depends on the specific lipid fraction used: HDL-C, LDL-C, or TC. If the overall “normal lipid profile” is used, ~34%, or 61 million people, have a normal lipid profile. Of these, ~28%, or 17.2 million, have high CRP concentrations. This estimate is reduced to ~12.2 million after people with CRP concentrations >10 mg/L are excluded.

At least part of the high CRP concentrations may be explained by obesity and obesity-related conditions. On the basis of prevalence estimates among those with a normal lipid profile by body mass index, an estimated 5.5 million people with a body mass index <25 kg/m² have a high CRP concentration. This estimate is reduced to ~4.1 million after the exclusion of people with CRP concentrations >10 mg/L. The population estimates are much higher if examined by each lipid separately. If the prevalence estimates for those with a body mass index <25 kg/m² were applied to all eligible participants, a total of 7.1 million people would be expected to have a high CRP concentration instead of 12.2 million. This difference of 7.1 million people would be expected to have a high CRP concentration. This estimate is reduced to ~4.1 million after the exclusion of people with CRP concentrations >10 mg/L. The population estimates are much higher if examined by each lipid separately. If the prevalence estimates for those with a body mass index <25 kg/m² were applied to all eligible participants, a total of 7.1 million people would be expected to have a high CRP concentration instead of 12.2 million. This difference of 7.1 million people would be expected to have a high CRP concentration instead of 12.2 million. This difference of 7.1 million people would be expected to have a high CRP concentration instead of 12.2 million. This difference of 7.1 million people would be expected to have a high CRP concentration instead of 12.2 million. This difference of 7.1 million people would be expected to have a high CRP concentration instead of 12.2 million. This difference of 7.1 million people would be expected to have a high CRP concentration instead of 12.2 million. This difference of 7.1 million people would be expected to have a high CRP concentration instead of 12.2 million. This difference of 7.1 million people would be expected to have a high CRP concentration instead of 12.2 million. This difference of 7.1 million people would be expected to have a high CRP concentration instead of 12.2 million. This difference of 7.1 million people would be expected to have a high CRP concentration instead of 12.2 million. This difference of 7.1 million people would be expected to have a high CRP concentration instead of 12.2 million. This difference of 7.1 million people would be expected to have a high CRP concentration instead of 12.2 million. This difference of 7.1 million people would be expected to have a high CRP concentration instead of 12.2 million. This difference of 7.1 million people would be expected to have a high CRP concentration instead of 12.2 million. This difference of 7.1 million people would be expected to have a high CRP concentration instead of 12.2 million. This difference of 7.1 million people would be expected to have a high CRP concentration instead of 12.2 million. This difference of 7.1 million people would be expected to have a high CRP concentration instead of 12.2 million. This difference of 7.1 million people would be expected to have a high CRP concentration instead of 12.2 million. This difference of 7.1 million people would be expected to have a high CRP concentration instead of 12.2 million. This difference of 7.1 million people would be expected to have a high CRP concentration instead of 12.2 million. This difference of 7.1 million people would be expected to have a high CRP concentration instead of 12.2 million. This difference of 7.1 million people would be expected to have a high CRP concentration instead of 12.2 million. This difference of 7.1 million people would be expected to have a high CRP concentration instead of 12.2 million. This difference of 7.1 million people would be expected to have a high CRP concentration instead of 12.2 million. This difference of 7.1 million people would be expected to have a high CRP concentration instead of 12.2 million. This difference of 7.1 million people would be expected to have a high CRP concentration instead of 12.2 million. This difference of 7.1 million people would be expected to have a high CRP concentration instead of 12.2 million. This difference of 7.1 million people would be expected to have a high CRP concentration instead of 12.2 million. This difference of 7.1 million people would be expected to have a high CRP concentration instead of 12.2 million. This difference of 7.1 million people would be expected to have a high CRP concentration instead of 12.2 million. This difference of 7.1 million people would be expected to have a high CRP concentra-
uals with increased CRP concentrations and lipid concentrations within recommended ranges can be mitigated in at least two ways. The public health perspective is to promote and encourage behavioral changes that may lead to decreases in CRP concentrations. These include reducing overall obesity and waist circumference (24, 25), cessation of smoking (26), better diet with increased fiber intake (27), and physical activity (28). Behavioral changes in these modifiable risk factors have been shown to lower CRP concentrations and, hence, the risk of coronary events. Alternatively, the clinical approach to reduce serum concentrations of cholesterol and CRP with therapeutic and pharmacologic agents has also been discussed (20).

In conclusion, our results provide important information about the size of the US population with lipid concentrations within recommended ranges who may be eligible for CRP evaluation. Additional studies are needed to further clarify the predictive value of CRP among normolipidemic persons and to establish the cost–benefit ratio of adding the CRP test to the routine assessment of coronary risk as suggested by the American Heart Association (29).

References