Six-year change in high-sensitivity C-reactive protein and risk of diabetes, cardiovascular disease, and mortality

Christina M. Parrinello, MPH, [a] **Pamela L. Lutsey, PhD, MPH,** [b] **Christie M. Ballantyne, MD,** [c] **Aaron R. Folsom, MD, MPH,** [b] **James S. Pankow, PhD, MPH,** [b] **and Elizabeth Selvin, PhD, MPH** [a,d] ***Baltimore, MD; Minneapolis, MN; and Houston, TX***

Background Single measurements of elevated high-sensitivity C-reactive protein (hs-CRP) are associated with increased risk of diabetes, cardiovascular disease, and mortality. Large increases or sustained elevations in hs-CRP may be associated with even greater risk of these outcomes. The objective of this study was to characterize the association of 6-year change in hs-CRP with incident diabetes, incident cardiovascular events (heart disease, stroke, and heart failure), and mortality.

Methods We included 10,160 ARIC participants with hs-CRP measured at visits 2 (1990-1992) and 4 (1996-1998). Change in hs-CRP was categorized as sustained low/moderate (<3 mg/L at both visits), decreased (≥3 mg/L at visit 2 and <3 mg/L at visit 4), increased (<3 mg/L at visit 2 and ≥3 mg/L at visit 4), and sustained elevated (≥3 mg/L at both visits). Cox proportional hazards models were used to assess the association of 6-year change in hs-CRP with incident diabetes, cardiovascular events, and death during ~15 years after visit 4.

Results Compared with persons with sustained low/moderate hs-CRP, those with increased or sustained elevated hs-CRP had an increased risk of incident diabetes (hazard ratios [95% CIs] 1.56 [1.38-1.76] and 1.39 [1.25-1.56], respectively), whereas those with deceased hs-CRP did not. Persons with sustained elevated hs-CRP had an increased risk of coronary heart disease, ischemic stroke, heart failure, and mortality (hazard ratios [95% CIs] 1.51 [1.23-1.85], 1.70 [1.32-2.20], 1.60 [1.35-1.89], and 1.52 [1.37-1.69], respectively) compared with those with sustained low/moderate hs-CRP. Associations for sustained elevated hs-CRP were greater than for those with increased hs-CRP over 6 years.

Conclusions Large increases or sustained elevations in hs-CRP over a 6-year period were associated with a subsequent increased risk of diabetes, and persons with sustained elevations in hs-CRP were at the highest risk for cardiovascular disease and mortality. Two measurements of hs-CRP are better than one for characterizing risk, and large increases are particularly prognostic. (Am Heart J 2015;170:380-389.e4.)

High-sensitivity C-reactive protein (hs-CRP) is a nonspecific marker of inflammation that is commonly used for cardiovascular disease (CVD) risk stratification. High-sensitivity CRP is an acute-phase reactant produced in the liver and is secreted into the bloodstream in response to the presence of proinflammatory cytokines. Inflammation has been implicated in the development of insulin resistance, diabetes,[1,2] and atherosclerosis,[3-5] and high hs-CRP measured at a single time point has been widely studied and associated with CVD (including coronary heart disease

From the [a]*Department of Epidemiology and the Welch Center for Prevention, Epidemiology and Clinical Research, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD,* [b]*Division of Epidemiology and Community Health, University of Minnesota School of Public Health, Minneapolis, MN,* [c]*Section of Cardiovascular Research, Baylor College of Medicine and Houston Methodist DeBakey Heart and Vascular Center, Houston, TX, and* [d]*Division of General Internal Medicine, Department of Medicine, Johns Hopkins University, Baltimore, MD.*

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Reprint requests: Elizabeth Selvin, PhD, MPH, Department of Epidemiology and the Welch Center for Prevention, Epidemiology and Clinical Research, Johns Hopkins Bloomberg School of Public Health, 2024 E. Monument, Suite 2-600, Baltimore, MD 21287.

E-mail: eselvin@jhu.edu

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[CHD], stroke, and heart failure),[6–12] incident diabetes,[10,13–21] and all-cause mortality.[8,9] Furthermore, hs-CRP has been shown to improve cardiovascular risk prediction.[22] Randomized clinical trials have shown that the use of statins in individuals with elevated hs-CRP was associated with a reduction in hs-CRP and a decreased risk of vascular events.[23] This evidence forms the basis of various guidelines, including those from the American College of Cardiology/American Heart Association, the European Society of Cardiology, and the Canadian Cardiovascular Society, that recommend considering use of hs-CRP to inform treatment decisions, mainly for persons at intermediate risk.[24–27] Although hs-CRP may not necessarily be in the causal pathway,[28] these guidelines acknowledge its role as an established marker of future risk of CVD.

Although hs-CRP is a well-studied and well-known inflammatory biomarker, there are sparse data regarding its longitudinal associations with outcomes in the general population. It is unclear whether changes in hs-CRP or sustained elevations in hs-CRP have added clinical value compared with a single measurement, although we would expect multiple measurements to lead to improved reliability and therefore result in stronger associations with outcomes. The objective of this study was to characterize the association of 6-year change in hs-CRP (particularly, large increases) and sustained elevations, with incident diabetes, incident cardiovascular events (heart disease, stroke, and heart failure), and mortality during a maximum of 16 years of follow-up in a community-based sample.

Methods

Study population

The Atherosclerosis Risk in Communities (ARIC) study is a community-based cohort of 15,792 participants who were originally recruited from 1987 to 1989 from 4 field centers in the United States: Forsyth County, NC; Jackson, MS; suburban Minneapolis, MN; and Washington County, MD.[29] Participants were invited to return for 4 follow-up examinations in 1990 to 1992, 1993 to 1995, 1996 to 1998, and 2011 to 2013 (response rates were 93%, 86%, 80%, and 65%, respectively). All procedures were approved by an institutional review board at each site, and written informed consent was provided by all study participants.

The main analyses for this study were restricted to participants who had attended both visits 2 and 4 (1990-1992 and 1996-1998, respectively) and had hs-CRP measures available at each of these visits. Because of small numbers, nonwhite and nonblack participants were excluded, as well as black participants from either the Minneapolis or Washington County field centers. In addition, participants were excluded if they were missing visit 2 or visit 4 covariates (Figure 1).

Measurement of hs-CRP

Visit 2 hs-CRP was measured in 2011 to 2013 at the University of Minnesota (Minneapolis, MN) from serum stored at −70°C using an immunoturbidimetric assay on the Roche Modular P chemistry analyzer (Roche Diagnostics, Indianapolis, IN). Visit 4 hs-CRP was measured in 2010 at Baylor College of Medicine (Houston, TX) from plasma stored at −70°C using a nephelometric method on the Siemens Dade Behring BN II analyzer (Siemens Healthcare Diagnostics, Deerfield, IL). The coefficient of variation for visit 2 and visit 4 hs-CRP, after excluding outliers, was 7.0% and 6.5%, respectively. We conducted a laboratory calibration study to evaluate possible differences in the hs-CRP measurements between laboratories, specimen type, assay method, instrument, and time of measurement, and found that the differences in hs-CRP were not large enough to warrant calibration.[30]

Outcome definitions

Cardiovascular events and all-cause mortality were ascertained via continuous surveillance of hospitalizations and death certificates, annual telephone follow-up with the participant or a proxy, and linkage with the National Death Index. *Incident CHD* was defined as a first occurrence of either adjudicated hospitalization for definite/probable myocardial infarction or death due to CHD.[31] *Fatal CHD* was defined as the subset of incident CHD events that were confirmed to be definite fatal CHD events. *Incident stroke* was defined as a first occurrence of adjudicated hospitalization or death due to definite/probable ischemic stroke.[32] *Incident heart failure* was defined as a first occurrence of either hospitalization with a discharge code of 428 (428.0-428.9) in any position for diagnosis using the *International Classification of Diseases, Ninth Revision* (*ICD-9*) or death due to heart failure based on a 428 *ICD-9* code or an *ICD-10* code of 150.[33] For analyses of incident CVD, we excluded participants with prevalent CVD at visit 4 (based on self-reported CVD history or events occurring up to and including the visit 4 date) (Figure 1).

Incident diabetes was defined as the first occurrence of self-reported physician diagnosis of diabetes or use of glucose-lowering medication, based on responses to annual telephone calls to all participants. Participants were administratively censored on the date of their last response to the annual telephone follow-up if they had not reported having diabetes up to and including that date. For analyses of incident diabetes, we excluded participants with prevalent diabetes at visit 4 (defined by self-reported physician diagnosis or glucose-lowering medication use) (Figure 1).

Additional covariates

The following variables were self-reported by participants: age, sex, race/ethnicity, years of education