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

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Abstract

Introduction—Single measurements of elevated high-sensitivity C-reactive protein (hs-CRP) are associated with increased risk of diabetes, cardiovascular disease (CVD) and mortality. Large increases or sustained elevations in hs-CRP may be associated with even greater risk of these outcomes.

Objective—To characterize the association of six-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 (1990-92) and 4 (1996-98). 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 following visit 4.

Results—Compared to persons with sustained low/moderate hs-CRP, those with increased or sustained elevated hs-CRP had an increased risk of incident diabetes (HRs [95% CIs]: 1.56 [1.38,

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DISCLOSURES

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1.76] and 1.39 [1.25, 1.56], respectively), whereas those with decreased hs-CRP did not. Persons with sustained elevated hs-CRP had an increased risk of coronary heart disease, ischemic stroke, heart failure and mortality (HRs [95% CIs]: 1.51 [1.23- 1.85]; 1.70 [1.32-2.20]; 1.60 [1.35, 1.89]; 1.52 (1.37, 1.69), respectively) compared to 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 six-year period were associated with a subsequent increased risk of diabetes; and persons with sustained elevations in hs-CRP were at the highest risk of CVD and mortality. Two measurements of hs-CRP are better than one for characterizing risk and large increases are particularly prognostic.

Keywords

C-reactive protein; cardiovascular disease; diabetes mellitus; epidemiology; mortality

High-sensitivity C-reactive protein (hs-CRP) is a non-specific marker of inflammation that is commonly used for cardiovascular disease (CVD) risk stratification. Hs-CRP is an acute-phase reactant produced in the liver, and is secreted into the bloodstream in response to the presence of pro-inflammatory 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 [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 to 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 six-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 four field centers in the United States: Forsyth County, North Carolina; Jackson, Mississippi; suburban Minneapolis, Minnesota; and Washington County, Maryland.²⁹ Participants were invited to return for four follow-up examinations during 1990-92, 1993-95, 1996-98 and 2011-13 (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 (1990-92 and 1996-98, respectively) and had hs-CRP measures available at each of these visits. Because of small numbers, non-white and non-black participants were excluded, as well as black participants from either the Minneapolis or Washington County field centers. Additionally, participants were excluded if they were missing visit 2 or visit 4 covariates (**Figure 1**).

Measurement of high-sensitivity C-reactive protein

Visit 2 hs-CRP was measured during 2011-13 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 to 428.9) in any position for diagnosis using the International Classification of Diseases, 9th Revision (ICD-9) or death due to heart failure based on a 428 ICD-9 code or an ICD, 10th Revision 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, gender, race/ethnicity, years of education attained, cigarette smoking status, alcohol consumption, and physical activity level (as measured using the Baecke sport index³⁴). Use of cholesterol-lowering and antihypertensive medications was obtained via self-report and an inventory of medications that were brought to each visit. Body mass index (BMI) was calculated from measured height and weight. Diastolic and systolic blood pressure was measured using a random zero sphygmomanometer, and was recorded as the mean of the 2nd and 3rd measurements at visit 2, and as the mean of 1st and 2nd measurements at visit 4 (since only two measurements were taken at this visit). Total cholesterol and high-density lipoprotein cholesterol (HDL-c) were measured at Baylor College of Medicine (Houston, TX) from plasma using the Roche Cobas Bio (Roche Diagnostics, Indianapolis, IN) at visit 2 and the Roche Hitachi 911 (Roche Diagnostics, Indianapolis, IN) at visit 4. Total cholesterol was measured using an enzymatic method and HDL-c was measured using a precipitation method.³⁰

Statistical Analysis

First, we categorized hs-CRP at visits 2 and 4 as low/moderate (<3 mg/L) versus elevated (≥ 3 mg/L), based on established clinical cut-points.⁵ Second, we created a four-level variable as follows: sustained low/moderate (hs-CRP <3 mg/L at both visits 2 and 4); 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 2 and 4).

We calculated the proportion of participants in each of the 4 categories of change in hs-CRP from visit 2 to visit 4. We compared demographic and clinical characteristics across categories of hs-CRP change. We used Cox proportional hazards regression models to assess the association of visit 2 hs-CRP, visit 4 hs-CRP, and hs-CRP change with each of the following incident outcomes, individually: diabetes, CHD, fatal CHD, ischemic stroke, heart failure and mortality (18 separate models). We modeled visit 2 hs-CRP and visit 4 hs-CRP as binary variables, and change in hs-CRP as a 4-level variable (as described above). We began follow-up at the date of the visit 4 examination and administratively censored participants on December 31, 2011. All models were adjusted for the following visit 4 covariates as continuous variables, unless otherwise specified: age, gender (male, female), race-center (Minneapolis whites, Jackson blacks, Washington County whites, Forsyth blacks and Forsyth whites), education level attained (high school, high school or college, high school; measured at visit 1), cigarette smoking (current, former, never), alcohol consumption (current, former, never), physical activity level (measured at visit 1), prevalent CVD (yes, no), prevalent diabetes (yes, no), use of cholesterol-lowering medication (yes, no), use of

antihypertensive medication (yes, no), BMI, systolic blood pressure, total cholesterol, and HDL-c. The proportional hazards assumption was assessed using log-log plots of the survival function, and by testing the statistical significance of the interaction of hs-CRP with the natural log of time in each fully adjusted Cox model. The interaction was statistically significant for models of incident diabetes, so we conducted additional analyses for incident diabetes censoring participants at 5 years.

We conducted several sensitivity analyses. First, to assess whether visit 4 hs-CRP was independently associated with each of the outcomes above and beyond past hs-CRP level, we additionally adjusted analyses of visit 4 hs-CRP for visit 2 hs-CRP level, both modeled as binary variables. Second, to assess the effect of proximity of hs-CRP measurement to the timing of events, we conducted the analysis of visit 2 hs-CRP with each of the outcomes beginning follow-up from the date of the visit 2 examination, rather than that of the visit 4 examination. Third, we repeated the main analyses using a cut-point of 2 mg/L to define high levels of hs-CRP. Fourth, we repeated the main analyses excluding persons who had hs-CRP >10 mg/L at either visit 2 or visit 4, since levels in this range may indicate acute infection.³⁵ Fifth, we repeated the main analysis for incident diabetes additionally excluding persons with undiagnosed prevalent diabetes at visit 4 based on fasting glucose levels ≥ 126 mg/dL. Sixth, we conducted analyses of continuous change in hs-CRP from visit 2 to visit 4, by subtracting hs-CRP at visit 2 from hs-CRP at visit 4. To account for potential non-linear associations, we included 4 spline terms in the models, with knots at changes in hs-CRP of -3, 0, and 3 mg/L.

We used Stata version 13.0 (StataCorp, College Station, Texas) to conduct all statistical analyses. This work was supported by the NIH/NHLBI Cardiovascular Epidemiology training grant T32HL007024, and NIH/NIDDK grant R01DK089174. The ARIC Study is carried out as a collaborative study supported by National Heart, Lung, and Blood Institute contracts. The authors are solely responsible for the design and conduct of this study, all study analyses, the drafting and editing of the paper, and its final contents.

RESULTS

The mean age of participants was approximately 57 years at visit 2 and 63 years at visit 4. Nearly half of the study population had sustained low/moderate hs-CRP and 29% had sustained elevated hs-CRP during the 6-year period (**Table 1**). Of the 6,385 persons with low/moderate hs-CRP at visit 2, 76% also had low/moderate hs-CRP at visit 4, 6 years later. Of the 3,775 persons with elevated hs-CRP at visit 2, 77% also had elevated hs-CRP at visit 4. Visit 2 and visit 4 hs-CRP were highly correlated (Spearman's correlation coefficient = 0.69, $P < 0.0001$). Persons with sustained elevated hs-CRP were more likely to be black or female compared to those with sustained low/moderate hs-CRP (31% versus 16% and 71% vs 47%, respectively) (**Table 1**). Persons with increased or sustained elevated hs-CRP were more likely to be obese and to have prevalent hypertension, diabetes and CVD, compared to persons with sustained low/moderate hs-CRP (**Table 1**). Persons with hs-CRP that decreased were more likely to be taking cholesterol-lowering medications at visit 4 (**Table 1**).

The “increased” and “decreased” categories successfully identified participants who experienced substantially large changes in hs-CRP. In fact, persons whose hs-CRP level decreased below or increased above the clinical threshold of 3 mg/L over 6 years experienced greater changes in hs-CRP compared to those with either sustained low/moderate or elevated levels (median changes of -2.7 and 3.1 mg/L in persons with hs-CRP that decreased and increased, respectively; and median changes of 0.0 and 0.4 mg/L in persons with sustained low/moderate and elevated hs-CRP, respectively) (**Table 1**). Median duration of follow-up was 13 years for analyses of incident diabetes, and 14 years for analyses of incident CVD and all-cause mortality.

High hs-CRP (≥ 3 mg/L) measured at either visit 2 or visit 4 was statistically significantly associated with increased risk of incident diabetes, CHD, fatal CHD, stroke and heart failure, as well as all-cause mortality, with hazard ratios (HRs) for the CVD outcomes in the 1.3-2.1 range (**Table 2**). HRs for associations of high hs-CRP at visit 2 and visit 4 with incident diabetes were stronger when analyses were censored at 5 years (1.25 and 1.82, respectively) than when the entire follow-up was included.

Persons with increased or sustained elevated hs-CRP had an increased risk of incident diabetes compared to those with sustained low/moderate hs-CRP (HRs: 1.56 and 1.39, respectively; **eFigure 1, Figure 2 and Table 3**). HRs were stronger in analyses with shorter duration of follow-up (censored at 5 years) (2.06 and 1.79, respectively). Persons who had elevated hs-CRP at either one or both visits had an increased risk of incident CHD compared to those with sustained low/moderate hs-CRP (range of HRs: 1.3-1.5). Persons who had increased or sustained elevated hs-CRP had an increased risk of fatal CHD compared to those with sustained low/moderate hs-CRP, and magnitudes of association were greater than for non-fatal CHD (HRs were 2.0 and 2.2, respectively). Sustained elevated hs-CRP was associated with increased risk of ischemic stroke (HR was 1.7), whereas elevated hs-CRP at only one visit was not. Persons with increased or sustained elevated hs-CRP had a higher risk of incident heart failure compared to those with sustained low/moderate hs-CRP (HRs were 1.4 and 1.6, respectively). Although not statistically significant, there was a suggestion of increased risk of heart failure for those with elevated hs-CRP at visit 2 only. Compared to persons with sustained low/moderate hs-CRP, persons with hs-CRP that decreased had increased risk of mortality, persons with hs-CRP that increased had slightly higher risk of mortality, and those with sustained elevated hs-CRP had the highest risk of mortality (range of HRs 1.2-1.5; **Figure 2 and Table 3**).

Results of sensitivity analyses supported our main findings. After adjusting for visit 2 hs-CRP, associations of visit 4 hs-CRP were similar for diabetes, and slightly attenuated for CVD and mortality (HRs for CVD and mortality ranged from 1.4-2.1 before adjustment and 1.25-2.0 after adjustment; **eTable 1**). Associations of visit 2 hs-CRP beginning follow-up at visit 2 were similar to those beginning follow-up at visit 4 (**eTable 1**). In analyses excluding persons with hs-CRP >10 mg/L at either visit, we observed similar results for associations of hs-CRP measured at a single time point and change in hs-CRP with each outcome (**Table 3 and eTable 2**). In analyses that defined elevated versus low/moderate hs-CRP using a cut-point of 2 mg/L, we observed a similar direction of association but generally diminished HRs (**Table 3 and eTable 3**). In analyses of incident diabetes that excluded persons with

undiagnosed prevalent diabetes at visit 4, results were similar and only slightly attenuated (**eTable 4**). Lastly, we found that when analyzed continuously, the association of change in hs-CRP with outcomes was generally U-shaped (**eFigure 2**). These continuous analyses support our main findings, that compared to persons with no or small changes, persons with large increases in hs-CRP had statistically significant increased risk of subsequent diabetes, CHD, heart failure and mortality; and there was evidence that those with large decreases also had an increased risk of CHD, heart failure and mortality (**eFigure 2**).

DISCUSSION

We observed that hs-CRP measured at a single time point was associated with an approximately 40-50% increased risk of diabetes, cardiovascular events and death over nearly 15 years of follow-up. Furthermore, persons with sustained elevations in hs-CRP were at the highest relative risk of CVD and mortality. Large increases in and sustained elevations in hs-CRP that surpassed the 3 mg/L threshold were strongly associated with increased risk of future diabetes. Similarly, the more proximal measure of hs-CRP was a strong predictor of incident diabetes, regardless of hs-CRP measured six years earlier.

In the ARIC sample, 6-year increased hs-CRP and sustained elevated hs-CRP were associated with diabetes development. Obesity is an important cause of diabetes and elevated inflammatory markers. A previous analysis conducted in the ARIC Study and other studies suggest that inflammation may be on the causal pathway between obesity and diabetes.^{1,36} Alternatively, the association of inflammation with diabetes may be mediated by obesity, as reported by a previous study conducted in ARIC.³⁷ However, the mechanism(s) by which inflammation plays a role in the development of diabetes has yet to be fully characterized, although it has been suggested that inflammation is associated with and may even intensify the effects of conditions such as endoplasmic reticulum stress and oxidative stress, which may lead to insulin resistance and β -cell dysfunction.¹

In contrast to our findings for diabetes, any elevation in hs-CRP, whether measured at visit 4 or six years earlier at visit 2, was associated with an increased risk of CHD, heart failure and mortality over nearly 15 years, and although some of the confidence intervals overlapped, there was a suggestion of even higher risk in persons with sustained elevated levels of inflammation. This supports prior evidence that chronically high levels of inflammation may either play an active role in the long-term development of atherosclerosis, or may be a marker of chronic endothelial insult. Interestingly, we only observed an increased risk of ischemic stroke in persons with sustained elevated levels of hs-CRP and not with a single elevated hs-CRP value, which may suggest a more long-term or chronic process involving inflammation in the development of ischemic stroke.

Previous papers have largely used a single measure of hs-CRP to measure inflammation and have not accounted for its inherently time-varying nature and short-term variability (intraclass correlation coefficients ranged from 0.6-0.8 using repeat measurements from a couple of weeks to a few years apart).³⁸⁻⁴⁰ In fact, a joint statement from the Centers for Disease Control and Prevention and the American Heart Association previously recommended using two measurements of hs-CRP about two weeks apart to reduce the

within-person variability and increase stability of measurement values.⁵ An analysis that corrected for regression dilution resulted in stronger associations of hs-CRP with clinical outcomes compared to using only a single measurement.⁷ Therefore, we would expect stronger associations of hs-CRP with outcomes if combining multiple measurements.

As described previously, the categorical analysis of change in hs-CRP captured persons with large changes in hs-CRP that most likely reflect true biological changes in inflammation. Due to the high random variation in hs-CRP,^{38–40} associations of continuous, small changes may not have substantial clinical significance. Indeed, our continuous analyses confirmed that small changes in hs-CRP were associated with small increases in risk, if any, and that large increases in hs-CRP were most strongly associated with future risk of events.

The few previous studies that have assessed the association of change in hs-CRP over several years with risk of diabetes, CVD and mortality have been inconclusive. Increases in hs-CRP and proximally measured elevated hs-CRP have been shown to be associated with increased risk of total mortality^{41–43}. In the Cardiovascular Health All Stars Study of adults with a mean age of 85 years, increase in hs-CRP over 9 years was not associated with increased risk of CVD.⁴² This study differed from ours in that there were fewer participants (N=597) and likely less power to detect moderate associations. The participants in CHS were also much older (mean age of 85 years) than the participants in our study; different risk relationships might be expected in an older population with a higher prevalence of cardiovascular risk factors and co-morbidities. This previous study also assessed a doubling of hs-CRP rather than changes in clinical categories. In the Whitehall II Study of middle-aged adults, hs-CRP was higher over 15 years of follow-up in both persons who died of CVD and persons who developed diabetes compared to those who did not. There was a suggestion that among persons who died from CVD, past trajectories of hs-CRP had increased more steeply compared to those who were still alive; whereas among persons who developed diabetes, past trajectories of hs-CRP increased more slowly compared to those who did not.⁴⁴ Their conclusions that increases in hs-CRP were not associated with diabetes are different from what we report. In fact, the Whitehall investigators found that persons who developed diabetes had higher hs-CRP at baseline, but that past trajectories of hs-CRP in persons with and without diabetes actually converged over time. It should be noted that the Whitehall study included only persons who had complete follow-up data available (in contrast to traditional survival analysis methods involving censoring). It is plausible that some of the persons at highest risk of diabetes died from cardiovascular disease or other causes and were possibly more likely to be lost to follow-up and not included in the study, contributing to survival bias in these data and discrepancies between the findings from Whitehall and other studies.

There are several limitations that should be considered in the interpretation of our results. We only had measurements of hs-CRP at two time points, which cannot fully capture trajectories over time. However, requiring either elevation at both time points or movement from one clinically relevant category to another, rather than small changes that could be due to random error (e.g., biological or analytical variability), strengthened our ability to place participants into appropriate categories, and was an attempt to minimize misclassification. As with all observational studies, we may not have been able to fully control for all potential

biases and there remains a possibility of residual confounding. Strengths of our study included the large community-based sample with more than a decade of follow-up for important and rigorously assessed clinical outcomes.

In conclusion, for diabetes risk assessment, the most proximally measured value of hs-CRP may be more important than past measurements. We found that for cardiovascular outcomes and mortality, as expected, two measurements of hs-CRP are better than one for identification of persons at highest risk. Regardless of whether inflammation, and specifically hs-CRP, is in the causal pathway or is simply a marker of the pathogenesis of these outcomes, our results suggest that multiple measurements of hs-CRP may better indicate risk of disease development. Further study of repeated measurements of hs-CRP, in particular hs-CRP measured over a shorter time interval, would be especially useful in persons of intermediate risk, and could potentially inform risk classification and identification of high-risk participants for inclusion in randomized clinical trials or other research studies.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviated

CRP	Diabetes
CVD	Death

REFERENCES

1. Donath MY, Shoelson SE. Type 2 diabetes as an inflammatory disease. *Nat Rev Immunol.* 2011; 11(2):98–107. doi:10.1038/nri2925. [PubMed: 21233852]
2. Hotamisligil GS. Inflammation and metabolic disorders. *Nature.* 2006; 444(7121):860–7. doi: 10.1038/nature05485. [PubMed: 17167474]
3. Montecucco F, Mach F. New evidences for C-reactive protein (CRP) deposits in the arterial intima as a cardiovascular risk factor. *Clin Interv Aging.* 2008; 3(2):341–9. [PubMed: 18686755]
4. De Ferranti SD, Rifai N. C-reactive protein: a nontraditional serum marker of cardiovascular risk. *Cardiovasc Pathol.* 2007; 16(1):14–21. doi:10.1016/j.carpath.2006.04.006. [PubMed: 17218210]

5. Pearson TA, Mensah GA, Alexander RW, et al. Markers of inflammation and cardiovascular disease: application to clinical and public health practice: A statement for healthcare professionals from the Centers for Disease Control and Prevention and the American Heart Association. *Circulation*. 2003; 107(3):499–511. doi:10.1161/01.CIR.0000052939.59093.45. [PubMed: 12551878]
6. Buckley DI, Fu R, Freeman M, Rogers K, Helfand M. 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. *Ann Intern Med*. 2009; 151(7):483–95. [PubMed: 19805771]
7. Danesh J, Collins R, Appleby P, Peto R. Association of fibrinogen, C-reactive protein, albumin, or leukocyte count with coronary heart disease: meta-analyses of prospective studies. *JAMA*. 1998; 279(18):1477–82. [PubMed: 9600484]
8. Oluleye OW, Folsom AR, Nambi V, Lutsey PL, Ballantyne CM. Troponin T, B-type natriuretic peptide, C-reactive protein, and cause-specific mortality. *Ann Epidemiol*. 2013; 23(2):66–73. doi: 10.1016/j.annepidem.2012.11.004. [PubMed: 23228375]
9. Ahmadi-Abhari S, Luben RN, Wareham NJ, Khaw K-T. Seventeen year risk of all-cause and cause-specific mortality associated with C-reactive protein, fibrinogen and leukocyte count in men and women: the EPIC-Norfolk study. *Eur J Epidemiol*. 2013; 28(7):541–50. doi:10.1007/s10654-013-9819-6. [PubMed: 23821244]
10. Dregan A, Charlton J, Chowienzyk P, Gulliford MC. Chronic Inflammatory Disorders and Risk of Type 2 Diabetes Mellitus, Coronary Heart Disease, and Stroke: A Population-Based Cohort Study. *Circulation*. 2014 doi:10.1161/CIRCULATIONAHA.114.009990.
11. Kardys I, Knetsch AM, Bleumink GS, et al. C-reactive protein and risk of heart failure. The Rotterdam Study. *Am Heart J*. 2006; 152(3):514–20. doi:10.1016/j.ahj.2006.02.023. [PubMed: 16923423]
12. Bekwelem W, Lutsey PL, Loehr LR, et al. White blood cell count, C-reactive protein, and incident heart failure in the Atherosclerosis Risk in Communities (ARIC) Study. *Ann Epidemiol*. 2011; 21(10):739–48. doi:10.1016/j.annepidem.2011.06.005. [PubMed: 21784657]
13. Wang X, Bao W, Liu J, et al. Inflammatory markers and risk of type 2 diabetes: a systematic review and meta-analysis. *Diabetes Care*. 2013; 36(1):166–75. doi:10.2337/dc12-0702. [PubMed: 23264288]
14. Duncan BB, Schmidt MI, Pankow JS, et al. Low-grade systemic inflammation and the development of type 2 diabetes: the atherosclerosis risk in communities study. *Diabetes*. 2003; 52(7):1799–805. [PubMed: 12829649]
15. Barzilay JI, Abraham L, Heckbert SR, et al. The relation of markers of inflammation to the development of glucose disorders in the elderly: the Cardiovascular Health Study. *Diabetes*. 2001; 50(10):2384–9. [PubMed: 11574423]
16. Freeman DJ, Norrie J, Caslake MJ, et al. C-reactive protein is an independent predictor of risk for the development of diabetes in the West of Scotland Coronary Prevention Study. *Diabetes*. 2002; 51(5):1596–600. [PubMed: 11978661]
17. Hu FB, Meigs JB, Li TY, Rifai N, Manson JE. Inflammatory markers and risk of developing type 2 diabetes in women. *Diabetes*. 2004; 53(3):693–700. [PubMed: 14988254]
18. Laaksonen DE, Niskanen L, Nyyssönen K, et al. C-reactive protein and the development of the metabolic syndrome and diabetes in middle-aged men. *Diabetologia*. 2004; 47(8):1403–10. doi: 10.1007/s00125-004-1472-x. [PubMed: 15309290]
19. Liu S, Tinker L, Song Y, et al. A prospective study of inflammatory cytokines and diabetes mellitus in a multiethnic cohort of postmenopausal women. *Arch Intern Med*. 2014; 167(15): 1676–85. doi:10.1001/archinte.167.15.1676. [PubMed: 17698692]
20. Pradhan AD, Manson JE, Rifai N, Buring JE, Ridker PM. C-reactive protein, interleukin 6, and risk of developing type 2 diabetes mellitus. *JAMA*. 2001; 286(3):327–34. [PubMed: 11466099]
21. Dehghan A, Kardys I, de Maat MPM, et al. Genetic variation, C-reactive protein levels, and incidence of diabetes. *Diabetes*. 2007; 56(3):872–8. doi:10.2337/db06-0922. [PubMed: 17327459]
22. Ridker PM, Paynter NP, Rifai N, Gaziano JM, Cook NR. C-reactive protein and parental history improve global cardiovascular risk prediction: the Reynolds Risk Score for men. *Circulation*.

- 2008; 118(22):2243–51. 4p following 2251. doi:10.1161/CIRCULATIONAHA.108.814251. [PubMed: 18997194]
23. Ridker PM, Danielson E, Fonseca FAH, et al. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. *N Engl J Med*. 2008; 359(21):2195–207. doi:10.1056/NEJMoa0807646. [PubMed: 18997196]
 24. Perk J, De Backer G, Gohlke H, et al. European Guidelines on cardiovascular disease prevention in clinical practice (version 2012). The Fifth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by re. *Eur Heart J*. 2012; 33(13):1635–701. doi:10.1093/eurheartj/ehs092. [PubMed: 22555213]
 25. Genest J, Mcpherson R, Frohlich J, et al. 2009 Canadian Cardiovascular Society / Canadian guidelines for the diagnosis and treatment of dyslipidemia and prevention of cardiovascular disease in the adult – 2009 recommendations. *Can J Cardiol*. 2009; 25(10):567–579. [PubMed: 19812802]
 26. Myers GL, Christenson RHM, Cushman M, et al. National Academy of Clinical Biochemistry Laboratory Medicine Practice guidelines: emerging biomarkers for primary prevention of cardiovascular disease. *Clin Chem*. 2009; 55(2):378–84. doi:10.1373/clinchem.2008.115899. [PubMed: 19106185]
 27. Goff DC, Lloyd-Jones DM, Bennett G, et al. 2013 ACC/AHA Guideline on the Assessment of Cardiovascular Risk: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol*. 2013; 63(25) doi:10.1016/j.jacc.2013.11.005.
 28. Wensley F, Gao P, Burgess S, et al. Association between C reactive protein and coronary heart disease: mendelian randomisation analysis based on individual participant data. *BMJ*. 2011; 342:d548. doi:10.1136/bmj.d548. [PubMed: 21325005]
 29. The Atherosclerosis Risk in Communities (ARIC) Study: design and objectives. The ARIC investigators. *Am J Epidemiol*. 1989; 129(4):687–702. [PubMed: 2646917]
 30. Parrinello, CM.; Grams, ME.; Couper, D., et al. American Heart Association Epidemiology and Prevention and Nutrition, Physical Activity and Metabolism 2014 Scientific Sessions. San Francisco, CA: 2014. Calibration of analytes over twenty-five years in the Atherosclerosis Risk in Communities Study.
 31. White AD, Folsom AR, Chambless LE, et al. Community surveillance of coronary heart disease in the Atherosclerosis Risk in Communities (ARIC) Study: methods and initial two years' experience. *J Clin Epidemiol*. 1996; 49(2):223–33. [PubMed: 8606324]
 32. Rosamond WD, Folsom AR, Chambless LE, et al. Stroke Incidence and Survival Among Middle-Aged Adults?: 9-Year Follow-Up of the Atherosclerosis Risk in Communities (ARIC) Cohort. *Stroke*. 1999; 30(4):736–743. doi:10.1161/01.STR.30.4.736. [PubMed: 10187871]
 33. Loehr LR, Rosamond WD, Chang PP, Folsom AR, Chambless LE. Heart failure incidence and survival (from the Atherosclerosis Risk in Communities study). *Am J Cardiol*. 2008; 101(7):1016–22. doi:10.1016/j.amjcard.2007.11.061. [PubMed: 18359324]
 34. Baecke JAH, Burema J, Frijters JER. A short questionnaire for the measurement of habitual physical activity in epidemiological studies. *Am J Clin Nutr*. 1982; 36(5):936–42. [PubMed: 7137077]
 35. Ridker PM. Cardiology Patient Page. C-reactive protein: a simple test to help predict risk of heart attack and stroke. *Circulation*. 2003; 108(12):e81–5. doi:10.1161/01.CIR.0000093381.57779.67. [PubMed: 14504253]
 36. Luft VC, Schmidt MI, Pankow JS, et al. Chronic inflammation role in the obesity-diabetes association: a case-cohort study. *Diabetol Metab Syndr*. 2013; 5(1):31. doi: 10.1186/1758-5996-5-31. [PubMed: 23806173]
 37. Duncan BB, Schmidt MI, Chambless LE, Folsom AR, Carpenter M, Heiss G. Fibrinogen, other putative markers of inflammation, and weight gain in middle-aged adults--the ARIC study. *Atherosclerosis Risk in Communities*. *Obes Res*. 2000; 8(4):279–86. doi:10.1038/oby.2000.33. [PubMed: 10933303]

38. DeGoma EM, French B, Dunbar RL, Allison M a, Mohler ER, Budoff MJ. Intraindividual variability of C-reactive protein: the Multi-Ethnic Study of Atherosclerosis. *Atherosclerosis*. 2012; 224(1):274–9. doi:10.1016/j.atherosclerosis.2012.07.017. [PubMed: 22846611]
39. Bower JK, Lazo M, Juraschek SP, Selvin E. Within-person variability in high-sensitivity C-reactive protein. *Arch Intern Med*. 2012; 172(19):1519–21. doi:10.1001/archinternmed.2012.3712. [PubMed: 22945505]
40. Wu S, Li Y, Jin C, et al. Intra-individual variability of high-sensitivity C-reactive protein in Chinese general population. *Int J Cardiol*. 2012; 157(1):75–9. doi:10.1016/j.ijcard.2010.12.019. [PubMed: 21215477]
41. Kizer JR, Arnold AM, Jenny NS, et al. Longitudinal changes in adiponectin and inflammatory markers and relation to survival in the oldest old: the Cardiovascular Health Study All Stars study. *J Gerontol A Biol Sci Med Sci*. 2011; 66(10):1100–7. doi:10.1093/gerona/glr098. [PubMed: 21659339]
42. Jenny NS, French B, Arnold AM, et al. Long-term assessment of inflammation and healthy aging in late life: the Cardiovascular Health Study All Stars. *J Gerontol A Biol Sci Med Sci*. 2012; 67(9): 970–6. doi:10.1093/gerona/glr261. [PubMed: 22367431]
43. Alley DE, Crimmins E, Bandeen-Roche K, Guralnik J, Ferrucci L. Three-year change in inflammatory markers in elderly people and mortality: the Invecchiare in Chianti study. *J Am Geriatr Soc*. 2007; 55(11):1801–7. doi:10.1111/j.1532-5415.2007.01390.x. [PubMed: 17727645]
44. Tabák AG, Kivimäki M, Brunner EJ, et al. Changes in C-reactive protein levels before type 2 diabetes and cardiovascular death: the Whitehall II study. *Eur J Endocrinol*. 2010; 163(1):89–95. doi:10.1530/EJE-10-0277. [PubMed: 20573938]

Figure 1.
Exclusion criteria for study population

Figure 2.

Association of six-year change or sustained elevation in high-sensitivity C-reactive protein with incident diabetes, incident cardiovascular events and all-cause mortality

Cox proportional hazards models were adjusted for the following covariates: age, gender, race-center, education level, alcohol consumption, smoking status, physical activity (Baecke sport activity index), systolic blood pressure, blood pressure-lowering medication, cholesterol-lowering medication, HDL cholesterol, total cholesterol, body mass index, prevalent diabetes (for analyses of non-diabetes outcomes), prevalent CVD (for analyses of non-CVD outcomes). All covariates were visit 4 values, except for physical activity and education, which were measured at visit 1.

Table 1

Study population* characteristics by six-year change in and sustained levels of high-sensitivity C-reactive protein

	Sustained Low/Moderate (<3 mg/L at both visits) (N=4,859, 47.8%)		Decreased (>3 to <3 mg/L) (N=869, 8.6%)		Increased (<3 to >3 mg/L) (N=1,526, 15.0%)		Sustained Elevated (>3 mg/L at both visits) (N=2,906, 28.6%)	
	Mean (SD) or%	Mean (SD) or%	Mean (SD) or%	Mean (SD) or %	Mean (SD) or%	Mean (SD) or%	Mean (SD) or%	Mean (SD) or%
	Visit 2 (1990-92)	Visit 4 (1996-98)	Visit 2 (1990-92)	Visit 4 (1996-98)	Visit 2 (1990-92)	Visit 4 (1996-98)	Visit 2 (1990-92)	Visit 4 (1996-98)
Age, years	56.6 (5.7)	62.6 (5.7)	57.6 (5.8)	63.6 (5.8)	56.5 (5.6)	62.6 (5.6)	56.7 (5.6)	62.7 (5.6)
Male	53.3%	--	46.3%	--	38.3%	--	28.6%	--
Black	16.0%	--	20.4%	--	18.9%	--	30.6%	--
Field center								
Minneapolis, MN	31.2%	--	28.9%	--	31.5%	--	22.9%	--
Jackson, MS	14.4%	--	17.8%	--	16.5%	--	27.3%	--
Washington County, MD	28.3%	--	30.0%	--	27.6%	--	25.7%	--
Forsyth, NC	26.1%	--	23.3%	--	24.4%	--	24.1%	--
Education								
<High school	15.1%	--	20.0%	--	17.0%	--	24.1%	--
High school or college	41.8%	--	42.7%	--	44.2%	--	43.1%	--
>College	43.1%	--	37.3%	--	38.8%	--	32.8%	--
Sport index	2.6 (0.81)	--	2.5 (0.76)	--	2.5 (0.80)	--	2.3 (0.74)	--
Alcohol consumption								
Current	62.6%	55.3%	57.6%	46.6%	61.5%	52.2%	51.2%	40.9%
Former	17.5%	26.6%	20.9%	32.9%	17.5%	28.4%	22.5%	33.9%
Never	19.9%	18.1%	21.5%	20.5%	21.0%	19.4%	26.3%	25.2%
Smoking status								
Current	15.8%	12.1%	20.6%	15.4%	22.2%	15.9%	23.4%	17.5%
Former	41.4%	45.7%	40.3%	45.2%	36.8%	43.1%	34.3%	40.0%
Never	42.8%	42.2%	39.1%	39.4%	41.0%	41.0%	42.3%	42.5%
Body mass index								
<25 kg/m ²	41.0%	33.0%	25.6%	24.4%	33.8%	23.7%	15.4%	13.7%
25-30 kg/m ²	42.5%	44.7%	41.0%	40.6%	42.6%	39.9%	36.1%	31.1%
30 kg/m ²	16.5%	22.3%	33.4%	35.0%	23.6%	36.4%	48.5%	55.2%
Hypertension†	25.0%	38.8%	40.0%	51.4%	30.8%	46.4%	44.9%	60.0%
HDL-c, mg/dL	50.6 (17.0)	50.7 (16.7)	46.9 (16.3)	48.8 (16.2)	51.4 (17.0)	49.8 (17.2)	49.3 (16.0)	49.0 (15.6)
Total cholesterol, mg/dL	207.7 (37.2)	199.6 (35.4)	211.5 (41.7)	201.9 (40.2)	209.9 (38.3)	202.6 (37.7)	211.5 (39.5)	202.3 (38.6)
Cholesterol-lowering medication	6.3%	14.4%	6.6%	20.5%	6.2%	11.8%	6.2%	14.1%
Prevalent diabetes	4.3%	6.9%	9.4%	15.8%	4.6%	8.5%	11.8%	18.8%
Prevalent CVD	6.3%	10.2%	11.3%	17.5%	7.4%	12.7%	12.5%	18.4%
hs-CRP, mg/L‡	1.1 (0.6-1.7)	1.1 (0.7-1.7)	4.4 (3.5-6.4)	1.9 (1.3-2.4)	1.9 (1.3-2.5)	4.9 (3.8-6.8)	6.4 (4.4-10.2)	7.1 (4.8-9.7)

	Sustained Low/Moderate (<3 mg/L at both visits) (N=4,859, 47.8%)		Decreased (>3 to <3 mg/L) (N=869, 8.6%)		Increased (<3 to >3 mg/L) (N=1,526, 15.0%)		Sustained Elevated (>3 mg/L at both visits) (N=2,906, 28.6%)	
	Mean (SD) or%	Mean (SD) or%	Mean (SD) or%	Mean (SD) or %	Mean (SD) or%	Mean (SD) or%	Mean (SD) or%	Mean (SD) or%
	Visit 2 (1990-92)	Visit 4 (1996-98)	Visit 2 (1990-92)	Visit 4 (1996-98)	Visit 2 (1990-92)	Visit 4 (1996-98)	Visit 2 (1990-92)	Visit 4 (1996-98)
Change in hs-CRP, mg/L [‡]	--	0.0 (−0.4, 0.4)	--	−2.7 (−4.9, −1.7)	--	3.1 (1.9, 5.3)	--	0.4 (−2.1, 2.7)

* The study population presented here is the population used for the analyses using all-cause mortality as the endpoint, N=10,160; all covariates presented are from visit 2, except for education level and the Baecke sport index, and field center, which was obtained at visit 1

[†] Hypertension was defined as diastolic ≥ 90 mmHg or systolic ≥ 140 mmHg or self-reported blood pressure-lowering medication

[‡] Median and interquartile range presented

Table 2

Association of hs-CRP measured at visit 2 (1990-92) or visit 4 (1996-98) with incident diabetes, incident cardiovascular events and all-cause mortality that occurred from 1996-98 through 2011

	Visit 2 hs-CRP		Visit 4 hs-CRP	
	Events/Total N (%)	HR (95% CI)	Events/Total N (%)	HR (95% CI)
Diabetes				
3 mg/L	890/2,976 (30%)	1.13 (1.03, 1.24)	1,122/3,617 (31%)	1.44 (1.31, 1.58)
<3 mg/L	1,211/5,772 (21%)	1 (Reference)	979/5,131 (19%)	1 (Reference)
CHD				
3 mg/L	276/3,086 (9%)	1.31 (1.11, 1.55)	321/3,702 (9%)	1.40 (1.18, 1.65)
<3 mg/L	361/5,697 (6%)	1 (Reference)	316/5,081 (6%)	1 (Reference)
Fatal CHD				
3 mg/L	69/3,086 (2%)	1.47 (1.04, 2.08)	88/3,702 (2%)	2.09 (1.46, 2.99)
<3 mg/L	77/5,697 (1%)	1 (Reference)	58/5,081 (1%)	1 (Reference)
Ischemic stroke				
3 mg/L	174/3,086 (6%)	1.50 (1.20, 1.87)	190/3,702 (5%)	1.43 (1.14, 1.79)
<3 mg/L	192/5,697 (3%)	1 (Reference)	176/5,081 (3%)	1 (Reference)
Heart failure				
3 mg/L	468/3,086 (15%)	1.35 (1.18, 1.56)	529/3,702 (14%)	1.46 (1.26, 1.68)
<3 mg/L	470/5,697 (8%)	1 (Reference)	409/5,081 (8%)	1 (Reference)
Mortality				
3 mg/L	1,100/3,775 (29%)	1.32 (1.21, 1.44)	1,227/4,432 (28%)	1.39 (1.27, 1.52)
<3 mg/L	1,283/6,385 (20%)	1 (Reference)	1,156/5,728 (20%)	1 (Reference)

Abbreviations: CHD, coronary heart disease; CI, confidence interval; HR, hazard ratio

Cox proportional hazards models were adjusted for the following covariates: age, gender, race-center, education level, alcohol consumption, smoking status, physical activity (Baecke sport activity index), systolic blood pressure, blood pressure-lowering medication, cholesterol-lowering medication, HDL cholesterol, total cholesterol, body mass index, prevalent diabetes (for analyses of non-diabetes outcomes), prevalent CVD (for analyses of non-CVD outcomes). All covariates were visit 4 values, except for physical activity and education, which were measured at visit 1.

N=8,748 for diabetes analyses; N=8,783 for CVD analyses and N=10,160 for mortality analyses

Table 3

Association of six-year change in high-sensitivity C-reactive protein with incident diabetes, incident cardiovascular events and all-cause mortality

	Main analysis		Excluding persons with CRP>10 mg/L at either visit		Using a cut-point of 2 mg/L to define categories	
	Events/Total N (%)	HR (95% CI)	Events/Total N (%)	HR (95% CI)	Events/Total N (%)	HR (95% CI)
Diabetes						
Sustained elevated	730/2,264 (32%)	1.39 (1.25, 1.56)	480/1,488 (32%)	1.40 (1.24, 1.58)	1,089/3,469 (31%)	1.53 (1.37, 1.71)
Increased	392/1,353 (29%)	1.56 (1.38, 1.76)	362/1,249 (29%)	1.53 (1.34, 1.73)	316/1,270 (25%)	1.42 (1.23, 1.63)
Decreased	160/712 (22%)	1.07 (0.90, 1.27)	140/619 (23%)	1.05 (0.87, 1.25)	163/818 (20%)	1.02 (0.85, 1.21)
Sustained low/moderate	819/4,419 (19%)	1 (Reference)	819/4,419 (19%)	1 (Reference)	533/3,191 (17%)	1 (Reference)
CHD						
Sustained elevated	215/2,369 (9%)	1.51 (1.23, 1.85)	220/2,643 (8%)	1.46 (1.16, 1.83)	305/3,548 (9%)	1.36 (1.11, 1.66)
Increased	106/1,333 (8%)	1.43 (1.14, 1.81)	76/1,200 (6%)	1.31 (1.03, 1.68)	86/1,263 (7%)	1.17 (0.90, 1.51)
Decreased	61/717 (9%)	1.34 (1.01, 1.77)	58/772 (8%)	1.24 (0.91, 1.68)	66/832 (8%)	1.16 (0.87, 1.54)
Sustained low/moderate	255/4,364 (6%)	1 (Reference)	180/3,140 (6%)	1 (Reference)	180/3,140 (6%)	1 (Reference)
Fatal CHD						
Sustained elevated	60/2,369 (3%)	2.17 (1.43, 3.30)	62/2,643 (2%)	2.12 (1.34, 3.35)	85/3,548 (2%)	1.86 (1.22, 2.83)
Increased	28/1,333 (2%)	1.98 (1.24, 3.19)	13/1,200 (1%)	1.98 (1.21, 3.23)	14/1,263 (1%)	0.95 (0.51, 1.77)
Decreased	9/717 (1%)	1.02 (0.50, 2.08)	10/772 (1%)	0.84 (0.38, 1.87)	11/832 (1%)	0.89 (0.45, 1.77)
Sustained low/moderate	49/4,364 (1%)	1 (Reference)	36/3,140 (1%)	1 (Reference)	36/3,140 (1%)	1 (Reference)
Ischemic stroke						
Sustained elevated	143/2,369 (6%)	1.70 (1.32, 2.20)	86/1,536 (6%)	1.59 (1.19, 2.13)	194/3,548 (5%)	1.65 (1.26, 2.15)
Increased	47/1,333 (4%)	1.09 (0.78, 1.52)	41/1,230 (3%)	1.03 (0.72, 1.47)	48/1,263 (4%)	1.26 (0.88, 1.79)
Decreased	31/717 (4%)	1.13 (0.76, 1.67)	25/625 (4%)	1.02 (0.67, 1.57)	29/832 (3%)	0.95 (0.63, 1.45)
Sustained low/moderate	145/4,364 (3%)	1 (Reference)	145/4,364 (3%)	1 (Reference)	95/3,140 (3%)	1 (Reference)
Heart failure						
Sustained elevated	386/2,369 (16%)	1.60 (1.35, 1.89)	228/1,536 (15%)	1.54 (1.28, 1.85)	489/3,548 (14%)	1.37 (1.15, 1.63)
Increased	143/1,333 (11%)	1.38 (1.13, 1.68)	128/1,230 (10%)	1.34 (1.09, 1.65)	130/1,263 (10%)	1.37 (1.10, 1.71)
Decreased	82/717 (11%)	1.22 (0.96, 1.56)	68/625 (11%)	1.12 (0.86, 1.46)	100/832 (12%)	1.28 (1.01, 1.62)
Sustained low/moderate	327/4,364 (7%)	1 (Reference)	327/4,364 (7%)	1 (Reference)	219/3,140 (7%)	1 (Reference)
Mortality						
Sustained elevated	864/2,906 (30%)	1.52 (1.37, 1.69)	510/1,848 (28%)	1.42 (1.26, 1.60)	1,209/4,307 (28%)	1.40 (1.26, 1.56)
Increased	363/1,526 (24%)	1.34 (1.18, 1.52)	322/1,401 (23%)	1.31 (1.15, 1.49)	276/1,399 (20%)	1.08 (0.94, 1.24)
Decreased	236/869 (27%)	1.23 (1.06, 1.42)	196/757 (26%)	1.14 (0.98, 1.34)	253/982 (26%)	1.13 (0.97, 1.30)
Sustained low/moderate	920/4,859 (19%)	1 (Reference)	920/4,859 (19%)	1 (Reference)	645/3,472 (19%)	1 (Reference)

For main analyses: N=8,748 for diabetes analyses; N=8,783 for CVD analyses and N=10,160 for mortality analyses

For analyses excluding persons with hs-CRP >10 mg/L at either visit 2 or visit 4: N=7,775 for diabetes analyses, N=7,755 for CVD analyses, N=8,865 for mortality analyses

Cox proportional hazards models were adjusted for the following covariates: age, gender, race-center, education level, alcohol consumption, smoking status, physical activity (Baecke sport activity index), systolic blood pressure, blood pressure-lowering medication, cholesterol-lowering medication, HDL cholesterol, total cholesterol, body mass index, prevalent diabetes (for analyses of non-diabetes outcomes), prevalent CVD (for analyses of non-CVD outcomes). All covariates were visit 4 values, except for physical activity and education, which were measured at visit 1.