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Favorable levels of all major cardiovascular risk factors at younger ages and high-sensitivity C-reactive protein 39 years later — The Chicago Healthy Aging Study

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ABSTRACT

Objectives. Examine associations of favorable levels of all cardiovascular disease (CVD) risk factors (RFs) [i.e., low risk (LR)] at younger ages with high sensitivity C-reactive protein (hs-CRP) at older ages.

Methods. There were 1324 participants ages 65–84 years with hs-CRP ≤ 10 mg/L from the Chicago Healthy Aging Study (2007–2010), and CVD RFs assessed at baseline (1967–73) and 39 years later. LR was defined as untreated blood pressure (BP) ≤120/≤80 mm Hg, untreated serum total cholesterol <200 mg/dL, body mass index (BMI) <25 kg/m^2, not smoking, and no diabetes. Hs-CRP was natural log-transformed or dichotomized as *elevated* (≥3 mg/L or ≥2 mg/L) vs. *otherwise*.

Results. With multivariable adjustment, the odds ratios (95% confidence intervals) for follow-up hs-CRP ≥3 mg/in participants with baseline 0 RF, 1 RF and 2+ RFs compared to those with baseline LR were 1.35 (0.89–2.03), 1.61 (1.08–2.40) and 1.69 (1.04–2.75), respectively. There was also a graded, direct association across four categories of RF groups with follow-up hs-CRP levels (β coefficient/P-trend = 0.18/0.014). Associations were mainly due to baseline smoking and BMI, independent of 39-year change in BMI levels. Similar trends were observed in gender-specific analyses.

Conclusions. Favorable levels of all CVD RFs in younger age are associated with lower hs-CRP level in older age.

Introduction

High-sensitivity C-reactive protein (hs-CRP), an acute phase reactant and a marker for systemic inflammation, has been found to be associated with future cardiovascular disease (CVD) events and mortality (Buckley et al., 2009; Kengne et al., 2012; Libby et al., 2002; Ridker, 2003; Ridker et al., 2000; Strandberg and Tilvis, 2000) as well as with single CVD risk factors (RFs), including obesity or body mass index (BMI) (Arena et al., 2006; Ganguli et al., 2011; Ishii et al., 2012; Khoo et al., 2011; Strandberg and Tilvis, 2000; Visser et al., 1999), smoking (Khoo et al., 2011; Strandberg and Tilvis, 2000), blood pressure (Khoo et al., 2011; Lakoski et al., 2005), serum cholesterol (Chiu et al., 2012; Ganguli et al., 2011), and diabetes (Chiu et al., 2012). However, no data are available on the associations between having a favorable level of all CVD RFs (i.e., low risk — LR) at younger ages and hs-CRP levels at older ages.

Many studies have indicated that the benefits of having LR profile include increased longevity (Lloyd-Jones et al., 2006; Stamler et al., 1999), lower morbidity (Lloyd-Jones et al., 2006), better health-related quality of life (Daviglus et al., 2003; Strandberg et al., 2004), and lower heath care costs (Daviglus et al., 2005). Hence, the critical importance of LR concept in overcoming the CVD epidemic has been increasingly recognized (Lloyd-Jones et al., 2010). Establishing the long-term association of LR profile earlier in life and hs-CRP levels later in life will add more evidence on the benefits of LR on subsequent health status and, therefore support efforts to increase the prevalence of LR, in keeping with strategic goals of the American Heart Association for cardiovascular health promotion and disease prevention through 2020 and beyond (Lloyd-Jones et al., 2010).

We examined these associations using data on 962 men and 362 women from the Chicago Healthy Aging Study (CHAS). Participants' risk profiles were ascertained in both young adulthood/early middle age (1967–73) and 39 years later (2007–10). Hs-CRP was assessed at

Abbreviations: CVD, cardiovascular disease; RF, risk factor; hs-CRP, high sensitivity C-reactive protein; LR, low risk; BMI, body mass index; CHA, Chicago Heart Association Detection Project in Industry; CHAS, Chicago Healthy Aging Study; SBP, systolic blood pressure; DBP, diastolic blood pressure; ECG, electrocardiographic; HRT, hormone replacement therapy.

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the 39 year follow-up examination. We hypothesized that LR status at younger/middle ages is associated with lower levels of inflammatory markers of CHD/CVD assessed later in life, and that a graded direct association exists across baseline RF groups – LR to very high risk – with levels of inflammatory markers at follow-up. The long-term associations of individual CVD risk factors and hs-CRP levels at older ages were also examined. In addition, the question of whether the 39-year change in BMI would modify the above associations was investigated.

Methods

The Chicago Healthy Aging Study (CHAS)

CHAS is a study of a subset of participants from the Chicago Heart Association Detection Project in Industry (CHA), a prospective cohort study of 39,665 men and women ages 18–74 in work places throughout the Chicago area in 1967–73, focused on RFs for cardiovascular diseases. Details of the CHA (Stamler et al., 1993; Stamler et al., 1975) and CHAS (Pirzada et al., 2013; Vu et al., 2012) studies have been published. Briefly, there were 11,908 potential CHAS participants based on criteria as follows: CHA survivors, aged 65–84 years during 2007–10, free of major ECG abnormalities or myocardial infarction (MI) at the CHA examination (baseline). We used stratified sampling method to recruit CHAS participants based on their baseline RF profile (LR and not LR). Fifty-nine percent (n = 7090) of names (988 LR and 6102 not LR) were randomly selected for contacting by mail or phone. We successfully contacted 2799 persons during 2007–10, but 1404 persons refused to participate in CHAS, which provided a participation rate of 49.8%. The final CHAS sample included 1395 participants (28% women, 9.3% African American, 19.5% baseline LR). LR participants were oversampled to obtain adequate numbers for between-group comparisons (Vu et al., 2012).

In general, comparing CHAS participants and non-participants by baseline LR and non-LR status of 11,908 potential CHAS-eligible CHA participants (aged 65–84 years in 2007–2010 and presumed to be alive based on the last received vital status information from National Death Index and CMS records), those who participated in CHAS were slightly younger, less likely to be Black and male, more educated and slightly healthier with regard to CVD RFs than non-CHAS participants, especially for the non-LR group (results not tabulated).

Data on CVD risk profiles, including systolic/diastolic blood pressure (SBP/DBP), serum total cholesterol, BMI, diabetes, smoking history, medical diagnoses and treatment, ECGs, and demographic characteristics, were collected at both baseline and follow-up. Data on subclinical measures and inflammatory markers were collected at follow-up (Fig. 1).

All examination procedures were performed by trained and certified staff. The study was approved by the Northwestern University Institutional Review Board; signed informed consent was obtained from all participants.

Exclusions

Of 1395 CHAS participants examined at the clinic, 71 were hierarchically excluded for the following reasons: missing data on hs-CRP (n = 3), hs-CRP >10 mg/L (n = 67) due to suggestions that these values may present acute inflammation (Ridker, 2003), and missing covariates at the follow-up examination (n = 1). Thus, the final sample included 1324 CHAS participants. Additionally, because some evidence suggests that CRP elevations above 10 mg/L may present only in very obese persons rather than in those with acute inflammation (Ishii et al., 2012), those with hs-CRP >10 mg/L were included in a sensitivity analysis, with the sample of 1391 participants.

Follow-up hs-CRP measurement

Hs-CRP at follow-up was measured in serum samples by the University of Minnesota Physicians Outreach Laboratories using a latex-particle enhanced immunoturbidimetric assay kit and read on the Roche Modular P Chemistry analyzer (Roche Diagnostics, Indianapolis, IN 46250). Hs-CRP was expressed in milligrams per liter (mg/L) and was dichotomized as ≥3 mg/L (cut point indicating elevated risk for CVD) (Wong and Malik, 2005) or *elevated CRP* vs. *otherwise* (<3 mg/L). Another cut-point of hs-CRP ≥2 mg/L was also used for a sensitivity analysis (Goff et al., 2014).

Definition of baseline risk factor status

Baseline RF status was categorized into 4 groups: 1) *Low risk*: all RFs at favorable levels — SBP/DBP ≤120/≤80 mm Hg and not taking antihypertensive medication; serum total cholesterol <200 mg/dL and not taking lipid-lowering medication; BMI <25 kg/m^2; not smoking; and no diabetes. Not LR participants then were further classified as: 2) 0 RF (but with one or more not favorable levels [i.e., SBP 121–139 mm Hg or DBP 81–89 mm Hg and not taking antihypertensive medication; serum cholesterol 200 — 239 mg/dL and not taking lipid-lowering medication; BMI 25.0–29.9 kg/m^2]); or 3) 1 adverse RF only (1 RF); or 4) 2 or more adverse RFs (2 + RFs) [i.e., SBP >140 or DBP >90 mm Hg or taking antihypertensive medication; serum cholesterol >240 mg/dL or taking lipid-lowering medication; BMI >30 kg/m^2; current smoking; or diabetes].

Data analyses

Descriptive characteristics were compared across the 4 baseline risk categories using the F tests (for continuous variables) or Chi-square tests (for binary variables). Age-sex-race adjusted prevalence of hs-

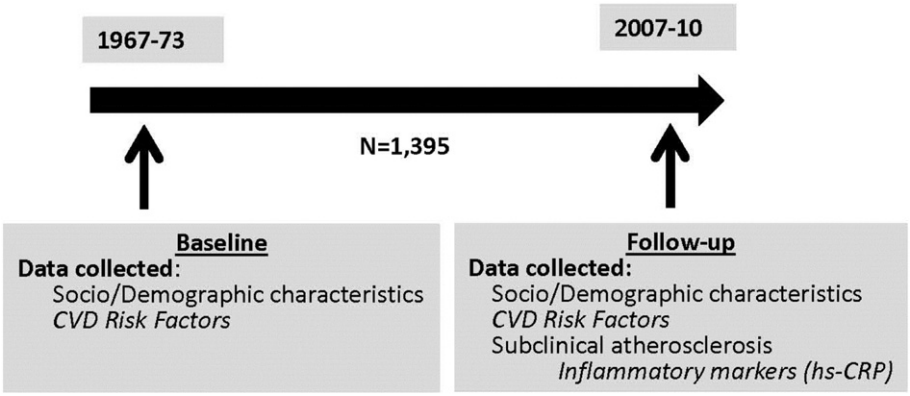

Fig. 1. Chicago Healthy Aging Study.