

History of Unemployment Predicts Future Elevations in C-Reactive Protein among Male Participants in the Coronary Artery Risk Development in Young Adults (CARDIA) Study

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Abstract

Background Unemployment is associated with risk of future morbidity and premature mortality.

Purpose To examine whether unemployment history predicts future C-reactive protein (CRP) levels in male participants in the Coronary Artery Risk Development in Young Adults (CARDIA) Study.

Methods Unemployment, body mass index (BMI), and health behaviors were measured at 7, 10, and 15 years post-recruitment. CRP was measured at Years 7 and 15.

Results Having a history of unemployment at Year 10 was associated with higher CRP at Year 15, independent of age, race, BMI, Year 7 CRP, Year 15 unemployment, and average income across Years 10–15. Poor health practices and depressive symptoms explained 22% of the association, but Year 10 unemployment history remained a significant predictor. Findings did not differ across age, race, education, or income.

Conclusions Discrete episodes of unemployment may have long-term implications for future CRP levels.

Keywords Unemployment · C-reactive protein · Socioeconomic status · Health behaviors

Introduction

Research supports a link between individual unemployment and future premature morbidity and mortality. Age adjusted all-cause mortality is substantially higher among individuals with a history of unemployment relative to persons who never have been unemployed (see [1]). For example, among individuals aged 15–47 years who were included in the Swedish twin registry, unemployment in 1973 predicted increased mortality risk 10 and 24 years later relative both to employed persons in the general population and to their employed twin siblings [2, 3]. Associations were independent of age, smoking status, alcohol consumption, and pre-existing chronic illness.

Much of the longitudinal evidence supporting an association between unemployment and future morbidity has focused on psychological symptoms and self-reported health [4]. In a Swedish study examining long-term effects of unemployment among school leavers, experiencing at least 6 months of unemployment between ages 16 and 21 was associated with more smoking, greater psychological symptoms, and among men, greater physical symptoms at age 30 [5]. Similarly, in a study based on data from the Health and Retirement Survey, U.S. workers aged 50 and older who suffered involuntary job loss reported more depressive symptoms and worse physical functioning up to 2 years later [6]. A subsequent follow-up of this study demonstrated a link between unemployment and verifiable physical disease in that workers with a history of unemployment were at increased risk of experiencing a

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clinical cardiovascular event up to 10 years later relative to those who remained employed, even after controlling for relevant risk factors [7]. Additional evidence to support unemployment as an antecedent of future morbidity is offered by census studies conducted in Denmark and the United Kingdom that have found unemployment to predict incident of cancer, particularly of the respiratory tract (see [8]). Among two cohorts of Danish persons aged 20–64 in 1970 and 1986, respectively, unemployment predicted an increased risk of cancer morbidity and mortality 5 years later [9]. Examination of smoking trends indicated that the elevated risk was explained only partially by increased smoking rates [9].

Taken together, these findings suggest a link between unemployment and future morbidity and mortality. Previous studies do not, however, elucidate the mechanism by which being unemployed might lead to poor health. Although unemployment is associated with an increased likelihood of engaging in poor health behaviors [10], health behaviors alone do not explain the excess morbidity and mortality among the unemployed. As unemployment likely leads to reductions in socioeconomic status (SES), one commonsense explanation for the link between unemployment and poor health outcomes is that unemployment is a proxy for SES, in particular income, and that financial hardship may be what is truly driving the association. Studies that have controlled for SES, however, continually show associations between unemployment and health to be independent of socioeconomic disadvantage [11], even when specifically controlling for income [7].

In addition to potential material deprivation brought about by joblessness, psychosocial correlates of unemployment, such as reduced social support [12], loss of self-esteem, and increased depressed affect [13, 14] may contribute to increased stress among the unemployed. The experience of such stress may account for some of the health risk associated with being unemployed that is not explained by other behavioral and environmental factors. Stress is thought to influence pathogenic processes that underlie the development of manifest clinical disease [15]. Chronic systemic inflammation, as indicated by moderately elevated proinflammatory biomarker concentrations, may constitute one such process. Adrenergic activation subsequent to psychological stress has been shown to influence physiologic processes relevant to the elaboration of the inflammatory response [16, 17]. Both acute laboratory stressors [18] and self-reported stress in natural environments [19] have been linked to increased levels of the acute phase reactant, C-reactive protein (CRP). Proinflammatory cytokine concentrations in healthy adults also have been found to increase with increasing severity of depressive symptoms [20].

In addition to being an indicator of ongoing disease activity, chronic inflammation may be a precursor of future

clinical conditions [21, 22]. Inflammation has been implicated in the initiation and development of clinically significant organic pathology including atherosclerosis [23] and type II diabetes mellitus [24, 25]. Results of several epidemiologic studies have indicated that in addition to being a marker of ongoing inflammatory disease activity, CRP may be a precursor of clinical cardiovascular disease [21] and an early marker of future Alzheimer's disease and cognitive decline [22]. Thus an association between unemployment and chronic inflammation may be one route by which having a history of unemployment increases risk of future morbidity and mortality.

Using data from male participants in the Coronary Artery Risk Development in Young Adults (CARDIA) Study, we examined whether having a history of unemployment is related to future chronic inflammation. Specifically, we examined whether participants' reports of current or recent unemployment at either 7 years or 10 years post-enrollment was associated with higher circulating concentrations of the proinflammatory biomarker C-reactive protein (CRP) at 15 years post-enrollment. All analyses controlled for age, race/ethnicity, CRP concentrations at Year 7, body mass index (BMI), household income, and current or recent unemployment reported at Year 15 (i.e., unemployment between Years 7 and 10).

Several features of CARDIA enabled us to expand upon the unemployment and health literature by allowing us to examine potential moderators and mediators of the unemployment-health association. The large size and socioeconomic diversity of the CARDIA sample, as well as the inclusion of a substantial proportion of blacks permitted us to address the question of whether associations between unemployment and CRP differ according to demographic factors such as age, race, educational attainment, and income. Also, CARDIA collected extensive data on health behaviors and psychosocial variables. Thus, we were able to examine (a) the extent to which health behaviors (smoking, alcohol consumption, physical activity) account for the association between unemployment and future CRP, and (b) whether psychosocial stressors such as self-reported chronic burden, lack of social support and social integration, demands and criticisms from close others, and depressive symptoms further contribute to that association.

Although CARDIA collected unemployment and CRP data from participants of both genders, the main analyses for the present report are limited to data from male participants. Women's unemployment histories are complicated by women being more likely than men to engage in voluntary unemployment, especially for the purposes of child-rearing. Moreover, hormonal factors related to the menstrual cycle and/or use of oral contraceptives can influence CRP levels, thus leading to difficulties in data interpretation.

Methods

Design

CARDIA is an ongoing, multi-site prospective study examining a variety of factors thought to be related to the development of heart disease in young adults. In addition to a physical exam at study entry in 1986 (Year 0/baseline), participants were asked to attend follow-up examinations during 1987–1988 (Year 2), 1990–1991 (Year 5), 1992–1993 (Year 7), 1995–1996 (Year 10), and 2000–2001 (Year 15). A majority of the group has been examined at each of the follow-up examinations (90%, 86%, 81%, 79%, and 74%, respectively).

Participants and Recruitment

At baseline, 5,115 black and white adults (46% male), aged 18–30 years, were recruited into CARDIA at four sites: Birmingham, AL, USA; Chicago, IL, USA; Minneapolis, MN, USA; and Oakland, CA, USA. Recruitment was stratified on age (18–24 and 25–30 years), race (black and white), sex, and education (≤ 12 years and >12 years). Participants were recruited by telephone in three of the four localities and by telephone and door-to-door contact in the fourth. The overall response rate ranged from 51–82% (for additional detail see [26, 27]). Site institutional review committee approval and informed consent were obtained. This manuscript has been approved by the CARDIA steering committee. The primary analyses we present include male participants who attended the Year 15 CARDIA exam and had complete data on employment status at Years 7 and 15 ($n=1,117$) or at Years 10 and 15 ($n=1,093$) (see below).

Measures

C-reactive Protein

At Years 7 and 15, blood samples for CRP were collected in 2-mL blue top (citratid) vacutainer tubes and centri-

fuged at 4°C for approximately 20 min. Citrated plasma was promptly separated from cells, transferred to a cryovial, frozen at -70°C , and shipped to the University of Vermont for determination of CRP.

CRP was measured using the BNII nephelometer from Dade Behring utilizing a particle-enhanced immunonephelometric assay. The assay range is 0.175–1,100 mg/L, intrassay CVs ranged from 2.3–4.4% and interassay CVs ranged from 2.1–5.7%. Resulting CRP values were \log_{10} -transformed to normalize the distribution.

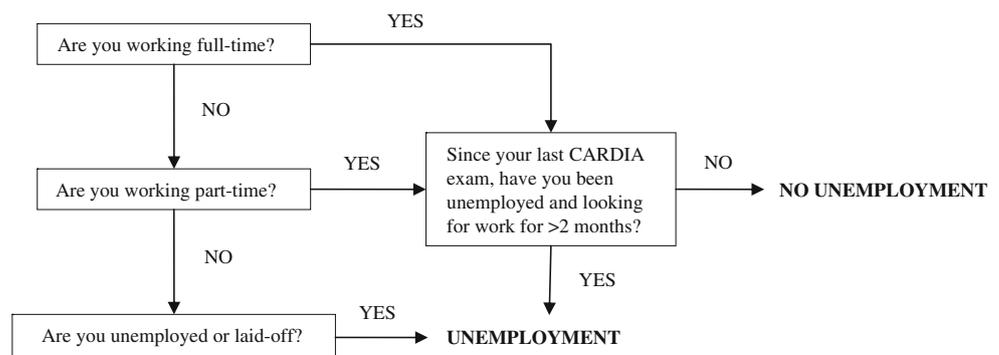
Body Mass Index

BMI (kg/m^2) was computed from participants' height and weight, which were measured at each CARDIA exam. The present analyses include BMI data from Year 15 only.

Employment History

Participants reported on current and recent unemployment at Years 7, 10, and 15. Unemployment during a given exam year was determined based on participants' responses (yes/no) to three items designed to measure current main daily activities and/or responsibilities, (*Are you working full-time? Are you working part-time? Are you unemployed or laid-off?*), a single item that inquired about recent unemployment of 2 months or longer (*Since your last CARDIA exam, have you been unemployed and looking for work for more than two months?*), and a single item that inquired about current student status (*Are you currently attending school or college or graduate school?*). For present purposes, individuals were classified as having a history of unemployment at a given exam if they reported being (a) unemployed/laid-off at the time of the current follow-up exam or (b) unemployed/laid-off for >2 months since the preceding exam, regardless of current employment status. Participants were classified as not having a history of unemployment if they (a) were currently working full-time or part-time and (b) had not been unemployed for >2 months since the preceding exam (see Fig. 1). All

Fig. 1 Algorithm for determining unemployment status



persons who endorsed being students at the time of the exam were excluded from analyses.

From these data, we created three dichotomous unemployment variables (1=any unemployment; 0=no unemployment) to represent participant status during each discrete follow-up period of interest (i.e., post-Year 5 exam up to and including Year 7; post-Year 7 exam up to and including Year 10; post-Year 10 exam up to and including Year 15).

Income

During Years 5–10, participants reported household income using seven categories, ranging from “less than \$5,000” to “\$75,000 or more.” At Year 15 the upper range was expanded to include two additional categories: “\$75,000 to \$99,999” and “\$100,000 or more.” For analytic purposes, income was recoded as the midpoint of each of the nine categories (\$150,000 for the highest category). Recoded income data were adjusted for household size by dividing by the square-root of the number of persons living in the home [28], and for inflation by dividing by the consumer purchasing index relative to 1990, the first year during the CARDIA study that household income data were collected. Aggregate income was computed as the simple mean of the adjusted income scores across Years 7, 10, and 15 when Year 7 unemployment history was examined as the predictor and across Years 10 and 15 when Year 10 unemployment history was examined as the predictor. The resulting aggregate scores were square-root transformed to reduce skewness.

Education

Education was measured at each exam year by highest grade (or year) of regular school completed. Participants selected one code from 01 to 20, with 01 indicating the first year of elementary school and 20 indicating ≥ 4 years of graduate education.

Psychosocial Factors

Psychosocial factors were measured using previously published scales. These included depressive symptoms (Center for Epidemiologic Studies Depression [CES-D] Scale) [29], chronic burden (ongoing strains lasting ≥ 6 months in the domains of work, finances, relationships, and health of close others) [30], social network diversity (sum of three dichotomous measures: any close friends, any close relatives, any group memberships) [31], and emotional support and demands/criticisms from family and friends [31]. All psychosocial measures were collected beginning at Year 15, save for depressive symptoms which were also collected at Year 10. Thus, in addition to

examining Year 15 depressive symptoms as a potential mediator we examined aggregate depression, which was computed as the arithmetic average of participants' CES-D scores across Years 10 and 15.

Health Behaviors

Self-reported health behaviors were obtained by interview at each exam. Measures included smoking status (current smoker=1, former or never smoker=0), number of cigarettes smoked per day (zero assigned to non-smokers), drinker status (yes=1, no=0), alcohol consumption (number of drinks consumed per week: one drink=one 12-oz glass, bottle or can of beer, one 5-oz glass of wine, or one 1.5-oz shot of liquor; zero assigned to non-drinkers), and physical activity (all scales documented on CARDIA website [32]). Physical activity scores were computed by multiplying participants' reported frequencies of engagement in thirteen categories of exercise and recreational sport activity by the intensity of the activity (expressed in exercise units; EU). Separate scores were derived for heavy intensity, moderate intensity, and total activity. Additional details on the scoring procedure are available elsewhere [33].

In addition to examining the mediating effects of Year 15 health behaviors, we examined the effects of aggregate health behaviors combined across Years 7, 10, and 15 or across Years 10 and 15. Aggregate smoker status was assigned according to whether participants ever reported being a smoker during their participation in the study. Aggregate number of cigarettes smoked per day was computed as the mean of participants' daily cigarette consumption across the appropriate 2 or 3 years. Similarly, aggregate alcohol consumption was computed as the mean of participants' reported weekly consumption and aggregate physical activity was computed as the mean of participants' total physical activity scores.

Exclusion Criteria

Of the 1,619 male participants who attended the Year 15 exam, 198 were excluded from the present analyses for not having CRP data at Year 7 or Year 15, and an additional 91 because their Year 7 and/or Year 15 CRP concentrations were >10 $\mu\text{g/mL}$, the cut-point at which acute infection or injury might be inferred [34]. Participants also were excluded if they were missing Year 15 income data ($n=18$) or if they could not be classified as either having a history of unemployment or having been consistently employed at the Year 15 follow-up exam ($n=85$). This latter exclusion criterion applied to participants who were missing data on any of the four items used to determine presence or absence of a history of unemployment at

Year 15 or were currently enrolled in school at Year 15 (see *Employment status* above). This criterion also applied to persons who reported having been unemployed for >2 months since the preceding CARDIA exam and had endorsed being enrolled in school at the preceding exam (“recent students”). We adopted this conservative strategy to control for the possibility that recent joblessness was due to attending school full time rather than actual unemployment per se. Application of the above exclusion criteria resulted in a sample of 1,227 participants.

In order to maximize the sample on which we conducted analyses examining unemployment at Years 7 and 10, respectively, as the independent variable we created two subsamples from those participants whose data were eligible for inclusion in the present study based on the above criteria ($n=1,227$). For analyses that examined Year 7 unemployment history as the predictor, additional participants were excluded if they could not be classified as having a history of unemployment or having been consistently employed at Year 7 ($n=110$); for analyses that examined Year 10 unemployment history as the predictor, additional participants were excluded if they could not be classified as having a history of unemployment or having been consistently employed at Year 10 ($n=134$). The resulting subsamples were thus comprised of 1,117 and 1,093 participants, respectively.

Statistical Analyses

The SAS system for Windows (release 9.1, SAS Institute 1995) was used to perform all statistical analyses. Pearson correlations were used to examine univariate associations between variables. Multiple linear regression was used to estimate and test the association of unemployment history with CRP levels. Age, race, Year 7 CRP, Year 15 BMI, aggregate household income across Years 7–15 or Years 10–

15, and current or recent unemployment at Year 15 were included as standard covariates in all analyses. We controlled for Year 15 unemployment such that we might be able to determine whether having been previously unemployed has an independent effect on future CRP above and beyond that of concurrent unemployment.

Results

Sample Characteristics

Sample characteristics are displayed in Table 1. As indicated by the table, subsamples with complete data at Years 7 and 15 and at Years 10 and 15 were nearly identical. Relative to the 1,618 male participants who attended the Year 15 exam, the present subsamples included proportionally fewer blacks (38% vs. 44%), but did not differ from the larger population on age, Year 15 BMI, or Year 15 income or education. Median Year 15 educational attainment was comparable to that of the U.S. male population aged 35–45 in the year 2000 wherein 54% of census respondents reported having completed at least some college [35]. Median Year 15 income was somewhat higher than that of the 2000 U.S. population of a similar age range (1999 median household income, ages 35–45: \$50,654) [36].

Correlations of Independent and Dependent Variables with the Standard Covariates

Pearson correlation coefficients describing univariate associations of Year 7 and 10 unemployment history and Year 15 CRP with each of the standard covariates are displayed in Table 2. Having an unemployment history at Year 7 or Year 10 was positively associated with reporting

Table 1 Sample characteristics^a

Descriptive variable	Subsample with complete data at Years 7 and 15 ($n=1,117$)	Subsample with complete data at Years 10 and 15 ($n=1,093$)
Mean age at Year 0 (years)	25.24 (3.40)	25.15 (3.45)
% Black	37.87% (423)	38.15% (417)
Mean BMI at Year 15 (kg/m^2)	28.03 (4.86)	28.08 (4.93)
Median Year 15 educational attainment (years)	15.0 (7.0–20.0)	15.0 (7.0–20.0)
Median Year 15 household income (thousands \$US, unadjusted)	62.50 (2.50–150.00)	62.50 (2.50–150.00)
% Reporting a history of unemployment since previous exam		
Year 15 (2000–2001)	17.19% (192)	16.93% (185)
Year 10 (1995–1996)	15.86% (161)	16.01% (175)
Year 7 (1992–1993)	19.79% (221)	19.11% (194)
Median Year 7 CRP ($\mu\text{g}/\text{mL}$)	0.81 (.15–9.98)	0.82 (.15–9.98)
Median Year 15 CRP ($\mu\text{g}/\text{mL}$)	1.02 (.15–9.77)	1.01 (.15–9.77)

^aData expressed as mean (SD), median (range), % (n)

Table 2 Pearson correlation coefficients describing univariate associations between independent and dependent variables with each of the standard covariates

Covariate	<i>n</i> =1,117		<i>n</i> =1,093	
	Year 7 history	Year 15 CRP	Year 10 history	Year 15 CRP
Year 7 CRP (log ₁₀ [μg/mL])	0.04	0.59***	0.07*	0.60***
Age (years)	-0.06†	<0.01	-0.08**	-0.01
Race (0=white, 1=black)	0.19***	0.16***	0.15***	0.16***
Year 15 BMI (log ₁₀ [kg/m ²])	-0.07*	0.43***	-0.03	0.45***
Year 15 current/recent unemployment (0=no, 1=yes)	0.33***	0.09**	0.36***	0.11***
Aggregate household income ([$\$US$] ^{1/2})	-0.39***	-0.11***	-0.32***	-0.13***

Coefficients are presented for the *n*=1,117 (complete Year 7 and Year 15 data) and *n*=1,093 (complete Year 10 and Year 15 data) samples, respectively

†*p*<0.01; **p*<0.05; ***p*<0.01; ****p*<0.001

current or recent unemployment at Year 15 and with having a lower aggregate income across Years 7–15 and Years 10–15, respectively. Blacks and younger persons were more likely to report a history of unemployment at Years 7 and 10 than were whites and older persons.

As expected, Year 15 CRP concentrations were strongly and positively associated with CRP concentrations at Year 7. Likewise, Year 15 CRP increased with increasing Year 15 BMI. Year 15 CRP concentrations also were higher among blacks relative to whites, and among persons who reported current or recent unemployment at Year 15 relative to those who did not. CRP was negatively associated with aggregate income across Years 7–15 and Years 10–15, respectively.

Lagged Associations of Unemployment at Years 7 and 10 with Year 15 CRP

As hypothesized, results of univariate analyses revealed positive associations between unemployment history at Years 7 and 10 with CRP concentrations at Year 15 ($r=0.06$, $p<0.06$ and $r=0.12$, $p<0.001$, respectively). When examined with multivariate analyses that included the standard covariates described above, the association between Year 7 unemployment and Year 15 CRP was completely nullified ($b=0.01$, $SE=0.03$, $p=0.70$), whereas the association between Year 10 unemployment and Year 15 CRP remained robust ($b=0.07$, $SE=0.03$, $p<0.02$). Thus, among the present sample of adult men, having a history of unemployment between the Year 7 and Year 10 follow-up exams is associated with higher circulating CRP 5–8 years later, irrespective of age, race, Year 7 CRP, Year 15 BMI, average income across Years 10 and 15, and current or recent unemployment at Year 15. Results of analyses examining Year 10 unemployment history as the predictor were similar, albeit slightly weaker, when “recent students” were included in the analyses ($n=1,123$, $p<0.03$). Because

examinations of unemployment history at Years 7 and 10, respectively, were conducted in slightly different samples, we re-ran the above analyses limiting the sample to only those men who had complete data at Years 7, 10, and 15 ($n=1,015$). Comparable results were obtained insofar as Year 10 unemployment history emerged as an independent predictor of Year 15 CRP ($p<0.04$), whereas Year 7 history did not ($p>0.60$).

To rule out the possibility that inflammation at Year 7 influenced subsequent unemployment, we examined the data in two ways. First, we conducted an analysis of variance examining the association of Year 7 CRP with change in unemployment between Years 7 and 10. Unemployment change was operationalized as a three-level categorical variable indicating whether individuals (a) went from having a history of unemployment at Year 7 to no history at Year 10; (b) went from being consistently employed at Year 7 to having a history of unemployment at Year 10; or (c) experienced no change in unemployment history. Results indicated no relation between Year 7 CRP and change in unemployment ($F(2, 1,012)=0.37$, $p=0.69$). Second, we conducted a logistic regression wherein we examined whether Year 7 CRP predicted Year 10 unemployment history, controlling for age, race, Year 7 unemployment history, and Year 10 education. The association between Year 7 CRP and Year 10 unemployment history was not significant ($b=0.32$, $SE=0.24$, $p=0.18$). Given the results of these analyses, it is unlikely that conditions related to elevated CRP at Year 7 influenced whether participants became unemployed during the succeeding 3 years.

Moderation of Year 10 Unemployment History Effect by Sociodemographic factors

We explored whether the association of Year 10 unemployment history with Year 15 CRP was moderated by age, race, Year 15 education, or Year 15 income. In separate

models that included the standard covariates, we examined the main effects of Year 10 unemployment history, each potential moderator (age, race, Year 15 education, or Year 15 income), and the interaction of Year 10 unemployment with each potential moderator. None of the above demographic factors moderated the association of aggregate unemployment with CRP (all cross-product p values >0.73 ; data not shown). Thus, the association of Year 10 unemployment history with Year 15 CRP was consistent across age, race, education, and income.

Mediation by Health Behaviors

We examined whether the association between reporting a history of unemployment at Year 10 and having higher circulating CRP at Year 15 might be accounted for by poor health behaviors (smoking, excessive alcohol consumption, low physical activity) among the men who had been unemployed. Because Year 15 and aggregate health behaviors were strongly intercorrelated ($r=0.88-0.93$, $p<0.001$), we report results only from those analyses that examined aggregate health behaviors as potential mediators. For present purposes, health behaviors that correlated significantly with Year 15 CRP ($p<0.05$) were examined as potential mediators. These included: ever smoker status ($r=0.08$), average number of cigarettes smoked per day aggregated across Years 10 and 15 ($r=0.12$), and aggregate physical activity ($r=-0.09$), all p values <0.01 . Potential mediators were examined in separate models that included controls for age, race, Year 7 CRP, Year 15 BMI, current or recent unemployment at Year 15, and aggregate income across Years 10 and 15.

Results from mediation analyses are displayed in Table 3. When examined individually, ever smoker status, greater average number of cigarettes smoked per day and lower aggregate physical activity across the Year 10 and 15 follow-up exams each accounted for some of the association of Year 10 unemployment history with Year 15 CRP. Simultaneous inclusion of all health behavior variables into the same model reduced the association between Year 10 unemployment and Year 15 CRP by approximately 20%.

Neither when examined singly nor in aggregate did any of the health behaviors significantly reduce the association of Year 10 unemployment with Year 15 CRP. In all cases, Year 10 unemployment remained an independent predictor of Year 15 CRP. Analyses examining Year 15 health behaviors as potential mediators yielded similar results (data not shown).

Mediation by Psychosocial Factors

Several psychosocial factors that may be relevant to health outcomes among unemployed persons also were considered as potential mediators (depressive symptoms, low social support, demands and criticisms from close others, inadequate social integration, chronic burden). Only Year 15 depressive symptoms and average depression across Years 10 and 15 correlated with Year 15 CRP ($r=0.08$, $p<0.01$, both variables). As these two depression measures were strongly correlated ($r=0.81$, $p<0.001$), only average depression symptoms across Years 10 and 15 was examined as a potential mediator. When depression was added to the model, Year 10 unemployment remained an independent predictor of Year 15 CRP ($b=0.07$, $SE=0.03$, $p<0.03$), and the association of unemployment with CRP was reduced by only 6%. This reduction was not significant.

Combined Effect of Health Behaviors and Depression

We examined the extent to which the combination of health behaviors and depression explained the association of Year 10 unemployment with Year 15 CRP by including ever smoker status, average number of cigarettes smoked per day, average physical activity, and average depression simultaneously in the same model. Addition of average depression to the aggregate health behavior model produced little change in the association of Year 10 unemployment history with CRP ($b=0.06$, $SE=0.03$, $p<0.04$; Δ partial $R^2=-22.3\%$). This final model explained approximately 43% of the variance in Year 15 CRP, with Year 10 unemployment history accounting for approximately 0.22% (i.e., 0.51% of the explained variance). Though very small,

Table 3 Change in regression coefficients predicting Year 15 CRP from Year 10 unemployment history after inclusion of health behaviors as potential mediators ($n=1,093$)^a

Health behaviors across Years 10 and 15	Year 10 unemployment history			
	b value	SE	p value	Δ Partial R^2
Ever smoker status	0.068	0.031	<0.03	-7.0%
Average number of cigarettes smoked per day	0.068	0.031	<0.03	-12.2%
Average physical activity	0.069	0.031	<0.03	-9.4%
All aggregate health behaviors	0.065	0.031	<0.04	-19.9%

^a All models control for age, race, Year 7 CRP, Year 15 BMI, Year 15 unemployment, and aggregate income across Years 10 and 15

the percent of CRP variance explained by unemployment history is comparable to that explained by average number of cigarettes smoked per day (0.25% of the total variance; 0.58% of the explained variance), which was the only mediator that remained significant when all examined mediators were included in the model.

Discussion

The present study found that having a history of unemployment at any time during the 3 years following an initial CRP measurement (Year 7) predicted higher levels of CRP 5–8 years later for black and white men aged 33–45 at the time of second CRP measurement. The association of unemployment history with CRP was independent of demographic factors, BMI, initial CRP levels, current or recent unemployment at Year 15, and aggregate household income across Years 10–15. Associations were consistent across blacks and whites, and did not differ according to age, educational attainment, or income. When assessed using a conservative analysis that included multiple control variables, the effect of Year 10 unemployment history on Year 15 CRP levels was small but comparable to the effect on CRP associated with daily cigarette consumption (see “Results”), a known correlate of circulating CRP levels [37]. Given the increased risk of morbidity and premature mortality among persons with a history of unemployment and the extensive evidence linking inflammatory processes with clinical disease, these findings suggest a potential physiologic mechanism whereby the experience of unemployment may influence future health outcomes.

It is possible that poor health behaviors among men who had been unemployed explain some of the increase in CRP associated with having a history of unemployment. In fact, the combined influence of smoker status, alcohol intake, and physical activity accounted for roughly 20% of the association. Depressive affect subsequent to joblessness also might influence the link between unemployment and CRP, as aggregate depression across Years 10 and 15, accounted for 6% the variance in Year 15 CRP attributable to unemployment. Unsurprisingly, there was substantial overlap between the contributions made by health behaviors and depressive symptoms in explaining the association of Year 10 unemployment history with Year 15 CRP.

What might account for the remaining variance not explained by health behaviors and depression? Increasing evidence suggests a link between chronic psychological stress and elevated markers of inflammation [17, 19, 38, 39]. As suggested by comparative research, chronic stress may promote pro-inflammatory processes via activation of the sympathetic-adrenal medullary system [16]. Alternatively, overstimulation of the hypothalamic-pituitary-adrenal axis by chronic stress may lead to eventual glucocorticoid

resistance and subsequent suppression of anti-inflammatory processes [40]. Because of the importance placed on employment status among men in early and middle adulthood, unemployment may be an especially potent threat to self-esteem. Thus, among this age group the self-esteem-related correlates of unemployment on CRP may overshadow those of the behavioral and psychological correlates examined in this study, such as the life stressors assessed by the chronic burden scale, and lack of social support and integration. Alternatively, it is possible that persons who reported a history of unemployment at Year 10 differ from their consistently employed counterparts on a “third factor” not controlled for in the present study that contributes both to their lack of employability and influences CRP levels.

Despite the positive univariate correlation between Year 7 unemployment history and Year 15 CRP, the association lost significance when the standard covariates were included in the model. At the Year 7 exam, participants were between the ages of 25 and 37. Thus, it is possible that many of these individuals were still at a stage early enough in their careers that temporary periods of unemployment may not be viewed as especially stressful. Alternatively, a substantial number of the persons who were consistently employed between the Year 5 and Year 7 exams may have been somewhat dissatisfied with their jobs. Recent graduates, for example, may have been working at jobs that did not match their post-graduation expectations. Being employed in a position that is not relevant to one’s career plans has been associated with greater psychological distress and worse health behaviors among recent college graduates [41].

There are a few limitations to the present study. First of all, only a single CRP measurement was taken both at Years 7 and 10, thus neglecting intra-individual variability. Block and colleagues reported a reliability coefficient of 0.73 for serum CRP sampled across a 2-week interval, which translates into a 27% attenuation of expected regression coefficients linking a single measure of CRP with other variables of interest [42]. Our large sample size provided us with sufficient power to detect associations even with the reduced reliability and suggests that the small size of the association between unemployment and CRP that we report here likely is an underestimate.

Another limitation is that data were not available regarding the circumstances leading to unemployment. There are broadly two very different reasons that workers become unemployed. The first relates to plant closings/layoff, in which individual selection is minimal. The second relates to discrete job terminations wherein individual selection plays a larger role, either in terms of leaving a job voluntarily or being fired as a consequence of individual actions. We could not distinguish participants based on the self-selective nature of their unemployment

histories. It is possible that men who select out of employment may differ as a group from other men in the sample on factors not addressed by the present study. Another possibility is that men who became unemployed during the follow-up may have done so for health-related reasons, perhaps subsequent to developing manifest or occult inflammatory disease. In this way, active disease processes may have led both to elevated CRP levels and unemployment. Control for Year 7 CRP concentrations, however, should contribute substantially to ruling out the potential for this direction of effects.

Finally, because we limited our analyses to men, it cannot be known whether the reported results generalize to women. In preliminary analyses using CARDIA data from both male and female participants, we found that the association of unemployment history with CRP was apparent in men but not in women (data not shown). As previously discussed, women's unemployment histories are complicated by women being more likely than men to engage in voluntary unemployment. Moreover, hormonal factors related to the menstrual cycle and/or use of oral contraceptives can influence CRP levels, thus leading to difficulties in data interpretation. Given these inherent complications, we opted not to present the data on female CARDIA participants here as they may not accurately reflect the true association of unemployment and CRP among women.

In sum, the present findings suggest that a discrete episode of unemployment may influence CRP levels between 5 and 8 years later. These findings are in agreement with those from previous research reporting lags of 2–10 years between unemployment and measured health outcomes [5–7]. Moreover, given our control for current/recent unemployment at Year 15, which itself was correlated with Year 15 CRP (see Table 2), the present findings suggest an independent delayed effect of acute episodes of past unemployment on future CRP levels. Although the clinical significance of the magnitude of increase is not clear, even modest elevations in circulating CRP are known to indicate existing chronic inflammatory disease and also may reflect pre-morbid disease processes. Thus, the present findings enhance our understanding of unemployment and health risk by suggesting that the stress of unemployment may influence future morbidity and mortality via a mechanism involving chronic inflammation. Additional research is necessary to identify (a) psychological or behavioral mechanisms by which unemployment might influence circulating CRP levels and (b) those individuals who are most vulnerable to physiologic changes subsequent to unemployment.

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