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Social isolation, C-reactive protein, and coronary heart disease mortality among community-dwelling adults

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Abstract

Social isolation confers increased risk for coronary heart disease (CHD) events and mortality. In two recent studies, low levels of social integration among older adults were related to higher levels of C-reactive protein (CRP), a marker of inflammation, suggesting a possible biological link between social isolation and CHD. The current study examined relationships among social isolation, CRP, and 15-year CHD death in a community sample of US adults aged 40 years and older without a prior history of myocardial infarction. A nested case-cohort study was conducted from a parent cohort of community-dwelling adults from the southeastern New England region of the United States (N = 2,321) who were interviewed in 1989 and 1990. CRP levels were measured from stored sera provided by the nested case-cohort (n = 370), which included all cases of CHD death observed through 2005 (n = 48), and a random sample of non-cases. We found that the most socially isolated individuals had two-and-a-half times the odds of elevated CRP levels compared to the most socially integrated. In separate logistic regression models, both social isolation and CRP predicted later CHD death. The most socially isolated continued to have more than twice the odds of CHD death compared to the most socially integrated in a model adjusting for CRP and more traditional CHD risk factors. The current findings support social isolation as an independent risk factor of both high levels of CRP and CHD death in middle-aged adults without a prior history of myocardial infarction. Prospective study of inflammatory pathways related to social isolation and mortality are needed to fully delineate whether and how CRP or other inflammatory markers contribute to mechanisms linking social isolation to CVD health.

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Keywords

USA; social isolation; social integration; social support; inflammation; C-reactive protein; coronary heart disease; mortality

INTRODUCTION

Social relationships play a significant role in cardiovascular disease (CVD) incidence, progression and mortality (Rozanski, Blumenthal, & Kaplan, 1999; Strike & Steptoe, 2004). Social isolation, defined as having few close relationships or social ties in the community, confers risk for all-cause and CVD mortality after adjustment for multiple behavioral, psychological, social, and biological CVD risk factors (Berkman, Glass, Brissette, & Seeman, 2000; House, 2001; House, Landis, & Umberson, 1988). Social isolation predicts one-year mortality after acute myocardial infarction as strongly as classic CVD risk factors (Mookadam & Arthur, 2004). A handful of studies (Eng, Rimm, Fitzmaurice, & Kawachi, 2002; House, Robbins, & Metzner, 1982; Kaplan et al., 1988; Kawachi et al., 1996; Orth-Gomer, Rosengren, & Wilhelmsen, 1993) also show that among individuals without established CHD, risk for CHD-specific mortality is highest among the socially isolated compared to those more socially integrated (see Lett et al. (2005) for review). As CHD remains the leading cause of death in the United States and accounts for 30% of deaths globally, identifying risk factors and clarifying their role in CHD is a priority for prevention efforts (Lloyd-Jones et al., 2010).

More recent evidence for the role of inflammation in CHD development and progression has led to examination of inflammatory markers that may be implicated in potential pathways linking social integration to cardiovascular health. In two cross-sectional epidemiological studies, C-reactive protein (CRP), an inflammatory marker shown to predict CHD (Pearson et al., 2003), was more likely to be elevated among the socially isolated relative to individuals at the highest levels of social integration after controlling for a host of mortality risk factors (Ford, Loucks, & Berkman, 2006; Loucks, Berkman, Gruenewald, & Seeman, 2006). A third study did not find strong associations between social isolation and CRP (Loucks, Sullivan et al., 2006), though in this study social isolation was more strongly related to the inflammatory marker, interleukin-6. CRP may be a particularly useful measure in determining biological contributions to the link between social isolation and CHD link due to its clinical utility: CRP is inexpensively and reliably measured and there are recommended clinical cut-offs for CRP levels that identify those most at risk for a CHD event (Pearson et al., 2003). The association between social isolation and concurrent CRP levels on the one hand, and longer-term CHD mortality risk on the other, suggests an important role for CRP in the link between social integration and CHD. Earlier studies relating social isolation to increased risk for CHD mortality indicate weak or no cross-sectional associations among social isolation and more established biological risk factors like cholesterol and blood pressure (Eng et al., 2002; Kawachi et al., 1996; Orth-Gomer et al., 1993). None has included CRP; thus, whether CRP can explain the relationship between social isolation and CHD death is unknown. Further examination of the associations among social isolation, CRP, and CHD events is necessary to inform mechanistic models that include plausible biological pathways linking social relationships to cardiovascular health. Such models are needed to further inform clinical interventions and public health strategies aimed at preventing CHD (Mookadam & Arthur, 2004).

Toward this end, we examined the association of social integration and CRP in a sample of adults without clinically-manifest CVD, and the association of social integration and risk for CHD mortality over a 15-year period in these adults. We hypothesized that social isolation

would be cross-sectionally associated with increased CRP levels, and prospectively associated with increased risk for CHD death. If CRP indeed varied as a function of social isolation, and predicted CHD mortality, we also examined whether CRP confounded – and thus, potentially mediated -- the association between social isolation and CHD death.

METHOD

Overview

We performed a case-cohort study nested within a community-based sample of 2,321 adults from the southeastern New England region in the United States. A case-cohort study is an epidemiologic design similar to a case-control study, except that the control group is chosen without regard to the outcome (i.e., a random sample of the base population). This strategy averts the financial cost of analyzing frozen sera from a full cohort and allows both cross sectional and longitudinal analyses of the data. During a household interview, participants provided a serum sample and responded to a series of questions assessing health, psychosocial, demographic, and behavioral information. Sera were frozen per standard protocol and not thawed for analysis until the present study. Death information was obtained from the United States Centers for Disease Control and Prevention (CDC) National Death Index (NDI) through December 2005. In depth description of the nested case-cohort study and the parent cohort from which case and control participants were sampled has been published elsewhere (Eaton et al., 2008; Gramling et al., 2008).

Participants

All participants were enrolled during the post-intervention period of the Pawtucket Heart Health Program (PHHP), a controlled community intervention designed to lower prevalence of CVD risk factors (Carleton, Lasater, & Assaf, 1995) Three thousand fifty adults between the ages of 40 and 75 years, including adults in the intervention community and a comparison community, completed household interviews in the years immediately following the PHHP intervention (1989–1990). All participants were recruited via a rigorous population-based sampling strategy described by Kish (1968) and Demming (1960). Among these participants, 2,321 (76%) reported never having a myocardial infarction and provided sera for frozen storage. For the current study, a random 14% of this base population, selected without regard to subsequent mortality, constitutes the sub-cohort (n = 327) under study. This sub-cohort included both adults who died of CHD during follow-up (n = 8) and adults who did not die of CHD during follow-up (n = 319). Sera was analyzed for all non-cases in the random sub-cohort, and for all 48 cases of CHD death identified in the base population through 2005, which constituted the full case-cohort sample (n = 370) for the current study.

Measures

Social Integration—The PHHP survey included items assessing four types of social connections previously used to index social integration and shown to have predictive validity (Berkman & Syme, 1979; Eng et al., 2002; Ford et al., 2006; Loucks, Berkman, Gruenewald, & Seeman, 2005; Loucks, Berkman et al., 2006): (a) current marital status (coded currently married = 1 and not currently married = 0), (b) degree of contact with close friends and relatives, (c) religious affiliation, and (d) participation in community groups. Degree of contact with friends and family was determined from the question, “How many close friends and relatives do you usually talk with or see once per week?” Zero, 1 and 2 contacts were coded as 0, and more than 2 were coded as 1. Participants were also asked to list churches, clubs, associations, societies or unions of which they were a member. Religious affiliation was coded 0 if respondents did not indicate membership in a church or religious group, or 1 if a church/religious group membership was listed. Participation in

community or religious groups was determined based on the number of group meetings attended in the past 3 months, assessed by the question, "How many times in the past three months have you attended a meeting (or worship service) or participated in a group project in any of these?" No attendance at group meetings was coded as 0, and attending at least one group meeting was coded as 1. To calculate a social integration index, scores on each of the four indicators were summed (Berkman & Syme, 1979; Eng et al., 2002; Ford et al., 2006; Loucks et al., 2005; Loucks, Berkman et al., 2006), and summed scores of 0 and 1 were considered the lowest level of social integration (that is, more social isolated), while scores of 2, 3, and 4 (most socially integrated) indicated increasing levels of social integration.

CRP Measure—C-reactive protein (CRP) concentration was determined using an immunoturbidimetric assay on a Hitachi 917 analyzer (Roche Diagnostics - Indianapolis, IN), using reagents and calibrators from Denka Seiken (Niigata, Japan). The assay has a sensitivity of 0.03 mg/L. Inter-assay variability at concentrations of 0.91, 3.07, and 13.38 mg/L were 2.81, 1.61, and 1.1%, respectively. Assays were conducted in the Clinical and Epidemiological Research Laboratory, which is part of the Department of Laboratory Medicine at Children's Hospital, Boston, MA. Prior epidemiologic research has verified the validity of these samples (Eaton et al., 2008). Elevated CRP was defined as a CRP concentration > 3.0 mg/L based on American Heart Association (AHA) and CDC recommendations for identifying patients at high risk for CHD (Pearson et al., 2003).

Case Definition and Selection—We obtained the date of death and underlying cause of death by linking personal identifiers (first name, middle initial, last name, sex, exact day/month/year of birth) for each participant to the CDC's National Death Index (NDI) for the years 1989–2005. Linkage and cause of death were established using NDI-standardized protocols. Cases were those participants whose primary or contributing cause of death was CHD, as identified by International Classification of Disease (ICD) 9 codes (410–414.9) or ICD 10 codes (21.9–69.4), depending on the date of death.

Potential Confounders—Several variables were considered for potential confounding given their well-established associations with CHD risk: age, gender, community (intervention vs. comparison), education level, income, diabetes mellitus, antidepressant use, regular physical exercise, body mass index (BMI), and Framingham risk category. Participants reported on multiple demographics (age, gender, education level, income), the presence of chronic conditions (including diabetes), current medication use (including anti-depressants), and current smoking status. Physical activity was assessed by the question, "At least once a week, do you engage in any regular physical activity such as a brisk walk, jogging, bicycling, etc., long enough to work up a sweat?" Height and weight were measured in light clothing without shoes and body mass index (BMI: kg/m^2) was calculated. Blood pressure was measured in the rested, sitting position following a uniform protocol. Total and HDL cholesterol were measured prior to freezing sera for storage. In order to minimize the likelihood of overspecified models and maximize power for analyses, we reduced the number of covariates considered by assigning individuals to Framingham risk categories of low, moderate-to-high, or very high risk for CVD using the Framingham point score (FPS). The FPS profile is based on age, gender, smoking status, cholesterol level, and hypertension status (National Institutes of Health, 2001).

Statistical Analyses—To evaluate the cross-sectional association between social isolation and CRP, we limited analyses to the sub-cohort only, because this is a random sample of the parent cohort representing the source population from which cases arise and is not biased by outcome (i.e., CHD death). To evaluate whether CRP potentially mediated the

social isolation-CHD mortality association, we used the full case-cohort sample as is intended for these longitudinal analyses.

Characteristics of non-cases and cases of CHD death were compared with t-tests for continuous variables and chi-square tests for categorical variables. The social integration variable (that is, a score of 1, 2, 3, or 4) was coded as indicator terms for analyses. Unadjusted and adjusted logistic regression models were used to determine associations between social integration level and elevated CRP in the random sub-cohort. Binomial linear regression was attempted to derive prevalence odds ratios as odds ratios are not always a good approximation of risk (Spiegelman & Hertzmark, 2005). However, models did not converge and our interest in examining associations rather than evaluating relative risk supported a logistic regression approach. We also examined whether social integration was associated with CRP levels (i.e., as a continuous variable) using linear regression. Using the full case-cohort sample, unadjusted and adjusted logistic models were used to determine whether social integration related to subsequent CHD mortality. Finally, we examined whether the association between social integration and CHD death was reduced when models included CRP, which would suggest a potential mediating role of CRP in the social integration and CHD death relationship. Models were adjusted for age and for additional covariates selected using the change-in-estimate method (Greenland, 1989). Provided the inclusion of a potential confounder changed the estimated OR for social integration by approximately 10%, the covariate that produced the greatest change in the OR was retained in the regression model. Model building continued until the estimated ORs were not modified by inclusion of additional confounders.

The institutional research review boards at Memorial Hospital of Rhode Island and the University of Rochester School of Medicine and Dentistry approved this study.

RESULTS

Descriptive statistics for demographics, health status and behavior variables, Framingham CVD risk category, degree of social integration and CRP levels for the random sub-cohort, and for CHD death cases (n = 48) versus non-cases (n =322) for the full case-cohort, are shown in Table 1.

Social Integration Level and Elevated CRP in the Random Sub-Cohort

In the unadjusted models, those at the lowest level of social integration had more than twice the odds of elevated CRP concentrations relative to those at the highest level of social integration (OR = 2.32; 95% CI = 1.16–4.66; Table 2). This association was not changed by adjustment for age, BMI, or income (OR = 2.69; 95% CI = 1.26–5.75). Moderate levels of social integration were not associated with elevated CRP compared to the most socially integrated adults (Table 2). Similar associations were evident from linear regression analyses using continuous CRP levels, where those at the lowest level of social integration had significantly higher CRP levels (M = 10.83 pg/mL, SD = 2.27) compared to those at the highest levels of social integration (M = 4.00 pg/mL, SD = 1.40; B = 6.50; p = .008). Again, CRP levels did not differ between those at the moderate (low-moderate: M = 3.28 pg/mL, SD = 1.67; high-moderate: M = 4.88 pg/mL, SD = 1.51) and highest levels of social integration, and these associations withstood adjustment for age, BMI, and income.

Social Integration Level and CHD Mortality in the Full Case-Cohort

A tenth (9.7%) of the most socially integrated individuals died of CHD while more than a fifth (22%) of the least socially integrated individuals died of CHD during the fifteen years of follow-up. In the unadjusted model, those at the lowest level of social integration had

more than twice the odds of CHD death compared to those at the highest level of social integration (OR = 2.63; 95% CI = 1.14–6.10; Table 3, Model 1). This association was not changed by adjustment for age, gender or Framingham risk score (OR = 2.52; 95% CI = 1.02–6.17).

Social Integration Level, CRP, and CHD Mortality

As expected, elevated CRP was a significant predictor of CHD death (OR = 2.22; 95% CI = 1.20–4.09). However, elevated CRP did not attenuate the association between social integration and CHD mortality (Table 3, Model 2). Those at the lowest level of social integration continued to have greater odds of dying from CHD-related causes (OR = 2.40; 95% CI = 1.03–5.64) compared to those at the highest level of social integration. After adjustment for age, gender, and Framingham risk category, the association between low social integration and greater risk for CHD death remained (OR = 2.66; 95% CI = 1.03–6.85; Table 3, Model 3). Moderate levels of social integration were not associated with higher CHD death (Table 3). The association between social integration and CHD risk was very similar when we included CRP levels as a continuous predictor in models (in lieu of categorical elevated CRP; final adjusted OR = 2.59; 95% CI = 1.00–6.69).

To examine whether any single component of the social integration index was contributing more strongly to outcomes, we estimated the association between each component of the index and CRP and CHD mortality. Religious affiliation and voluntary group participation showed an association with CHD mortality in unadjusted models; however, for all components, all CIs included 1.0 in final adjusted models (Table 4).

DISCUSSION

These findings lend further support for the biological strain of social isolation and extend the literature in important ways. Among individuals without a prior myocardial infarction, the least socially integrated had more than twice the odds of elevated CRP levels. Whereas low social isolation was previously shown to relate to elevated CRP in older adults aged 70 to 79 years (Loucks, Berkman et al., 2006), and only among men 60 years of age and older (average age around 70 years; (Ford et al., 2006)), the current findings suggest this association may emerge in middle-adulthood, as our sample was on average 55 years old. As in prior studies (Eng et al., 2002; House et al., 1982; Kaplan et al., 1988; Kawachi et al., 1996; Orth-Gomer et al., 1993), the least socially integrated were also more likely to die from CHD over a 15-year period than individuals at the highest levels of social integration. We extended these studies of initially CHD-free adults by evaluating CRP as a potential mediator of integration and CHD mortality links. Elevated CRP, however, did not explain the association between social isolation and CHD mortality risk in our sample of adults without prior myocardial infarction. Notably, social isolation carried an independent risk comparable to elevated CRP, and increased the risk of CHD death even after controlling for traditional cardiovascular risk factors. These findings support recent recommendations for screening and intervening for social isolation in post-myocardial infarction patients (Mookadam & Arthur, 2004), and further suggest a similar course for the prevention of CHD and myocardial infarction. As others have noted (House, 2001), prospective associations between social ties and mortality are consistently shown to be nonlinear, and our findings support the same conclusion. While the least socially integrated carried greater risk for both elevated CRP and CHD mortality, we did not find variation across the higher levels of integration. Such nonlinearity suggests that interventions may benefit those who are indeed socially isolated, but that enhancing the social network of non-isolated individuals may not produce great benefit (House, 2001). As others have shown (e.g., Ford, Loucks, & Berkman, 2006), no specific types of social connections appeared to have a substantially greater contribution to associations between the overall index and outcomes.

These findings can further inform interventions, suggesting that the specific type of relationship may be less important than having meaningful social ties, whatever form they take (House, 2001).

As observed in prior research (Eng et al., 2002; Kawachi et al., 1996; Orth-Gomer et al., 1993), social isolation did not relate strongly to more traditional risk factors in our sample, including diabetes mellitus ($\chi^2 = .72$, $p = .70$) or Framingham risk category ($\chi^2 = 2.30$, $p = .17$), but was associated with elevated CRP levels (Ford et al., 2006; Loucks, Berkman et al., 2006). Low social integration might affect CRP levels through poor health behaviors, though health behaviors did not confound the association between social isolation and elevated CRP or CHD death in this study. Chronic stress is associated with higher levels of circulating inflammatory markers, including IL-6 (Kiecolt-Glaser et al., 2003; von Kanel et al., 2006), a stimulator of CRP production, as well as CRP (Marin, Martin, Blackwell, Stetler, & Miller, 2007). Social ties are posited to influence health by providing resources to buffer the physiological effects of stress (Berkman et al., 2000; Cohen, 1988; Cohen, Doyle, Skoner, Rabin, & Gwaltney, 1997), and possibly stress-related CRP increases.

Although elevated CRP could not explain social isolation's relationship to increased risk for CHD death, we cannot rule out the possibility that CRP remains an important causal mechanism. In our sample, social isolation and elevated CRP were associated cross-sectionally, and were both independent predictors of CHD death. Prospective studies are necessary to determine if social isolation is predictive of increases in CRP to elevated levels and, in turn, subsequent CHD death. Unknown, too, are how changes in social integration might co-vary with CRP changes and other markers of inflammation that contribute to cardiovascular disease morbidity and mortality and underscore again the necessity of prospective study.

There remain important questions about the role of CRP in CHD development and progression. Atheromatous plaques that develop decades before a clinical event are a target for inflammation, which, in turn, is marked by elevated CRP (Hingorani, Shah, Casas, Humphries, & Talmud, 2009). In clinical observational research, CRP levels may reflect subclinical disease and associated inflammation, rather than contributing to the development of CHD (Hingorani et al., 2009). The association between social isolation and CRP levels has been found to be stronger for adults older than 60 years of age, especially men (Ford et al., 2006; Loucks, Berkman et al., 2006), raising the possibility that CRP levels reflect subclinical CVD and may not provide additional information about CRP's causal role in pathways linking social isolation to CHD. Alternatively, a lack of social integration might lead to increased inflammation that then speeds up the progression of underlying subclinical CHD to clinically-manifest CHD. Indeed, Ford and colleagues (2006) found that low social integration was also associated with increased hypertension prevalence and higher cholesterol levels relative to those more socially integrated. Although our sample characteristics and smaller sample size precluded any age-stratified analyses (over 65% of the sample was below 60 years of age), we did find overall associations between social isolation and higher CRP levels, and CHD death, among primarily middle-aged adults without prior CHD events. These findings extend the limited literature on social integration and CRP by providing evidence of their association in a pre-clinical disease context. Further prospective study of initially cardiovascular disease-free individuals is necessary to clarify whether inflammatory pathways play a mechanistic role in social isolation's links to CHD mortality.

Limitations of the current study include a substantially Caucasian sample and smaller sample size that precluded examination of potential race and ethnicity or gender differences. Relatively little is known about the moderating role of ethnicity on associations between

social isolation and CHD (Lett et al., 2005). Loucks and colleagues found social isolation and elevated CRP concentration associations to be strongest for older men relative to women (Ford et al., 2006; Loucks, Berkman et al., 2006). Our sample was predominantly female, reflecting the higher proportion of females in the parent cohort from which the random sub-cohort was drawn (Carleton et al., 1995). Given the age-related increase in proportion of females in the population, it is also likely that the age range (40–75 years) and distribution in the case-cohort sample (27.6% were 65 years of age or older) contributed to the higher proportion of females. It is unclear whether the association between social isolation and CHD is stronger for men versus women (Lett et al., 2005). Larger studies assessing degree of social integration, CRP, and CHD death are needed to clarify the potential moderating effects of race and ethnicity, gender and other sociodemographic characteristics. Though our sample included fewer participants and cases than prior epidemiological studies reporting associations between social isolation and CRP (Ford et al., 2006; Loucks, Berkman et al., 2006; Loucks, Sullivan et al., 2006), or social isolation and CHD death in initially CHD-free individuals (Eng et al., 2002; House et al., 1982; Kaplan et al., 1988; Kawachi et al., 1996; Orth-Gomer et al., 1993), our sample had a slightly lower proportion of socially isolated individuals (14.1%) compared to studies using similar indexing approaches (for example, 15.5% (Loucks, Sullivan et al., 2006)). More recently, loneliness was associated with incident coronary heart disease among women (Thurston & Kubzansky, 2009), and functional aspects of social support (for example, perceived emotional support) are predictive as well (Lett et al., 2005), underscoring a need for further elaboration of the relative or synergistic effects of structural and functional aspects of social connections. An additional limitation is the reliance on names and birthdates to identify dates of death, which may have resulted in more missed deaths in comparison to more reliable identifiers, such as social security numbers. For example, some deaths may have been missed due to name changes resulting from marriage that may have in turn increased the individual's social integration. In this case, missed deaths could have led to an overestimation of social integration's protective effects. Finally, we assessed a single marker of systemic inflammation. Future research should include a more comprehensive assessment of systemic inflammation markers. As noted previously, one study found levels of IL-6, but not CRP, to be strongly associated with social integration level (Loucks, Sullivan et al., 2006). Given that inflammation has more recently been implicated in a host of diseases and conditions, including diabetes, chronic pain, and depression (Kiecolt-Glaser et al., 2003; Maier & Watkins, 2003; Miller, Maletic, & Raison, 2009; Papanicolaou, Wilder, Manolagas, & Chrousos, 1998), the association found here between social isolation and elevated CRP strongly suggests additional clinical outcomes should be assessed.

Our findings add to the emerging literature investigating the inflammatory pathways linking social isolation and cardiovascular health. Additional studies are needed to determine the longitudinal contribution of inflammation to social isolation's influences on CHD. Clarifying these pathways is crucial to the development of prevention efforts aimed at reducing the incidence and progression of CHD.

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TABLE 1

Characteristics of the Random Sub-Cohort and for CHD Death Cases and Non-Cases for Full Case-Cohort

Variable	Random Sub-Cohort (*n* = 327)	Full Case-Cohort		
		CHD Death Cases (*n* = 48)	Non-Cases (*n* = 322)	*p*
Age [mean (SD)]	55.5 (9.8)	62.7 (9.6)	55.5 (9.9)	<.001
Female, No. (%)	200 (61.2)	19 (39.6)	199 (61.8)	.004
Intervention community, No. (%)	149 (45.2)	22 (45.8)	143 (44.4)	.88
Education, No. (%)				
Less than high school	151 (46.2)	27 (56.3)	148 (46.0)	.18
High school graduate or GED	101 (30.9)	12 (25.0)	99 (30.7)	
Some college	43 (13.1)	7 (14.6)	43 (13.4)	
College graduate	32 (9.8)	2 (4.2)	32 (9.9)	
At or below median per capita income, No. (%)[a]	146 (49.7)	24 (58.5)	145 (49.8)	.32
Antidepressant use, No. (%)	38 (11.6)	6 (12.5)	37 (11.5)	.81
Diabetes mellitus, No. (%)	32 (9.8)	12 (25.0)	29 (9.0)	.003
Body Mass Index [mean (SD)]	28.0 (5.6)	28.7 (4.5)	27.9 (5.6)	.34
Regular physical activity, No. (%)	77 (23.5)	12 (25.0)	77 (23.9)	.86
Framingham risk category, No. (%)				
Low CVD risk	149 (45.6)	6 (12.5)	149 (46.3)	<.001
Moderate-high CVD risk	108 (33.0)	18 (37.5)	108 (33.5)	
Very high CVD risk	70 (21.4)	24 (50.0)	65 (20.2)	
Social integration level, No. (%)				
Level 1 (socially isolated)	45 (14.1)	13 (27.1)	46 (14.3)	.04[b]
Level 2	68 (21.7)	8 (16.7)	68 (21.1)	
Level 3	86 (26.6)	14 (29.2)	87 (27.0)	
Level 4 (most socially integrated)	120 (37.6)	13 (27.1)	121 (37.6)	
CRP (mg/L) [mean(SD)][c]	4.35 (9.2)	6.59 (8.8)	4.35 (9.3)	.12
Elevated CRP, No. (%)	110 (33.6)	52.1	32.9	.01

CHD = coronary heart disease; SD = standard deviation; CVD = cardiovascular disease

[a] Median per capita household income = $9,166.67 per year.

[b] *p*-value represents chi-square comparison between distributions of the lowest and highest levels of social integration for CHD cases versus non-cases; full chi-square (including all social integration levels), $p = .10$.

[c] One participant (selected into the random sub-cohort and a non-case) had CRP levels > 14 SD above the mean; this participant was excluded for purposes of describing mean levels of CRP. Excluding this participant from all other analyses did not alter results; findings presented include this participant.

TABLE 2

Elevated CRP in Relation to Social Integration in the Random Sub-Cohort (*n* = 327), OR (95% CI)

	Model 1 OR (95% CI)	Model 2 OR (95% CI)
Social integration		
Level 1 (least socially integrated)	2.32 (1.16–4.66)	2.69 (1.26–5.75)
Level 2	1.00 (0.52–1.85)	0.99 (0.49–2.01)
Level 3	1.16 (0.65–2.10)	1.15 (0.59–2.22)
Level 4 (more socially integrated)	(Referent)	(Referent)
Age (years)		1.04 (1.02–1.07)
Body Mass Index (kg/m2)		1.09 (1.04–1.15)
At or below median per capita income		1.09 (.64–1.88)

OR = odds ratio; CI = confidence interval; CVD = cardiovascular disease. Elevated CRP indicated by CRP levels > 3.0 mg/L.

TABLE 3

15-Year Risk of CHD Mortality in Relation to Social Integration, Elevated CRP, and Traditional Risk Factors in the Full Case Cohort (*n* = 370), OR (95% CI)

	Model 1 OR (95% CI)	Model 2 OR (95% CI)	Model 3 OR (95% CI)
Social integration			
Level 1 (least socially integrated)	2.63 (1.14–6.10)	2.40 (1.03–5.64)	2.66 (1.03–6.85)
Level 2	1.10 (0.43–2.77)	1.09 (0.43–2.79)	.87 (0.32–2.37)
Level 3	1.50 (0.67–3.35)	1.48 (0.66–3.33)	1.83 (0.76–4.42)
Level 4 (most socially integrated)	(Referent)	(Referent)	(Referent)
Elevated CRP		2.06 (1.11–3.84)	1.50 (.76–2.95)
Age (years)			1.07 (1.03–1.11)
Female			0.40 (.19–.83)
Framingham risk category			
Low CVD risk			(Referent)
Moderate-high CVD risk			2.21 (0.80–6.09)
Very high CVD risk			4.00 (1.40–11.45)

OR = odds ratio; CI = confidence interval; CVD = cardiovascular disease. Elevated CRP indicated by CRP levels > 3.0 mg/L.

TABLE 4

Elevated CRP and CHD Mortality in Relation to Components of the Social Integration Index, OR (95% CI)

	Elevated CRP		CHD Mortality		
	Model 1	**Model 2**	**Model 1**	**Model 2**	**Model 3**
Not currently married	1.32 (0.82–2.13)	1.53 (0.90–2.58)	1.08 (0.58–2.02)	1.04 (0.55–1.96)	1.37 (0.68–2.77)
Little to no regular contact with friends and family	1.13 (0.55–2.33)	1.54 (0.70–3.37)	1.36 (0.57–3.25)	1.33 (0.55–3.21)	1.19 (0.46–3.06)
No religious affiliation	1.53 (0.95–2.44)	1.56 (0.93–2.63)	2.07 (1.12–3.82)	1.95 (1.05–3.62)	1.73 (0.89–3.38)
Little to no participation in voluntary community groups	1.45 (0.89–2.36)	1.42 (0.82–2.46)	1.85 (1.01–3.42)	1.80 (0.97–3.36)	1.49 (0.75–2.95)

OR = risk ratio; CI = confidence interval; Elevated CRP indicated by CRP levels > 3.0 mg/L. For elevated CRP, Model 1 OR unadjusted; Model 2 adjusted for age, BMI, and income. For CHD mortality, Model 1 OR unadjusted; Model 2 adjusted for elevated CRP; Model 3 adjusted for elevated CRP, age, gender, and Framingham risk category.