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Social Isolation and Adult Mortality: The Role of Chronic Inflammation and Sex Differences

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Abstract

The health and survival benefits of social embeddedness have been widely documented across social species, but the underlying biophysiological mechanisms have not been elucidated in the general population. We assessed the process by which social isolation increases the risk for all-cause and chronic disease mortality through proinflammatory mechanisms. Using the 18-year mortality follow-up data (n = 6,729) from the National Health and Nutrition Examination Survey (1988–2006) on Social Network Index and multiple markers of chronic inflammation, we conducted survival analyses and found evidence that supports the mediation role of chronic inflammation in the link between social isolation and mortality. A high-risk fibrinogen level and cumulative inflammation burden may be particularly important in this link. There are notable sex differences in the mortality effects of social isolation in that they are greater for men and can be attributed in part to their heightened inflammatory responses.

Keywords

cancer, chronic inflammation, heart disease, mortality, sex differences

Social relationships have long been believed to be beneficial for optimal social and physical functioning and survival. Dating back to Durkheim's ([1897] 1951) classical work linking social context with the risk for suicide, a large body of literature has shown that engagement with social life through network ties can protect us against illness, enhance coping with stress and illness, and improve illness outcomes, whereas social isolation and alienation can do the opposite and increase mortality (House, Landis, and Umberson 1988). Recent studies of model animals have also demonstrated that social isolation and hypervigilance increase the incidence of mammary tumors, accelerate aging, and shorten the life span in female rats (McClintock et al. 2005).

Although various social, psychological, and behavioral processes linking social relationships to morbidity and mortality have been well studied (Smith and Christakis 2007; Thoits 2011; Umberson, Crosnoe, and Reczek 2010), biophysiological mechanisms underlying these links are just beginning to be elucidated. A recent call by Berkman

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et al. (2000) for greater consideration of biological pathways through which social ties affect health emphasizes physiological stress responses. The role of the innate immune reflex, particularly chronic inflammation induced by tissue damage or invading pathogens, in the development of chronic diseases and mortality has been increasingly recognized (Finch 2007). Whether or how inflammatory responses to life challenges may mediate the connections between social relationship deficits and risk for mortality is largely unknown.

Studies of the health benefits of social relations suggest potential links between social ties and inflammation in the context of two leading causes of death, cardiovascular and malignant diseases (Penwell and Larkin 2010). Because the results of these studies are mixed and vary by specific biomarkers and samples used, it remains to be determined whether and how social embeddedness, or the lack thereof, affects disease progression and mortality through its influence on the inflammatory responses. Research also suggests sex differences in the prevalence of inflammation (Yang and Kozloski 2011), in the effects of social integration on mortality (Berkman, Vaccarino, and Seeman 1993), and in the associations of social isolation with inflammation (Ford, Loucks, and Berkman 2006). These differences may further complicate the understanding of the mortality consequence of social relationship deficits in human populations. Because social relations encompass many different conceptualizations and measures, such as social integration, social networks, and social support, it is usually difficult to include all in one empirical study. Our study focuses on the lack of social integration (social isolation) because it was most frequently examined in previous research and can contribute to the broader understanding of social relationships and health.

Using a nationally representative population-based mortality follow-up study, we extend previous research to test the hypothesis that social isolation leads to all-cause and chronic disease mortality by elevating chronic inflammation. We address additional gaps in the literature by testing hypotheses that there are significant sex differences and age variations in this relationship. We improve the measurement of inflammation by assessing multiple markers to more comprehensively evaluate the specific biological pathways linking social isolation and mortality. By establishing the initial evidence for the linkages between a general indicator of social relationships, major markers of immune function, and disease-specific mortality, this study provides the basis for future investigations of more intricate processes whereby the biophysiological mechanism may further mediate or interact with other social, psychological, and behavioral mechanisms connecting social relationships and health.

BACKGROUND

Social Isolation, Disease Etiology, and Mortality

Humans, like other social species, are wired for social connection. As posited by Umberson et al. (2010), "without social ties, distress emerges and health fails." The health impact of social relationships has been shown in numerous empirical studies of diverse populations. The structural dimension or quantity of social relationships as measured by the Berkman-Syme Social Network Index (SNI), which sums the number of social ties (marriage and contacts with family and friends) and participation in social organizations (religious attendance and volunteering), may be of particular importance to health and survival. Furthermore, social isolation or the absence of social contacts and social participation, rather than the specificity of spheres of interaction, matters for general susceptibility to disease and mortality (Berkman and Syme 1979; Stringhini et al. 2012). A large and increasing body of research has found that social isolation is significantly associated with specific disease etiology such as coronary heart disease (CHD) (Orth-Gomér, Rosengren, and Wilhelmsen 1993), depression (Cacioppo and Hawkley 2003), and memory loss (Ertel, Glymour, and Berkman 2008), as well as decreased general health status in older adults (Cornwell and Waite 2009), overall mortality (House et al. 1988; Musick, Herzog, and House 1999; Seeman et al. 1987; Strawbridge et al. 1997), and mortality from heart disease (Eng et al. 2002; Stringhini et al. 2012) and other causes (Hummer et al. 1999).

As evidence continues to mount on the survival benefits of social embeddedness, several questions, remain that require additional considerations. First, studies of mortality risk are often restricted to samples homogeneous in geographic areas (e.g., Alameda County, California, Seeman et al. 1987.) and/or sex and socioeconomic status (e.g., male health professionals, Eng et al. 2002.) and hence are difficult to generalize to the overall or disadvantaged population in which deficits in social connectedness and organizational participation may have

more pronounced effects. Second, although the associations of social isolation with all-cause mortality may suggest a general susceptibility to disease, cause-specific associations reflect different physiological mechanisms but have not been well examined. For example, the SNI did not appear to be significantly associated with cancer mortality in an analysis of a sample of highly educated healthy men (Eng et al. 2002). It is unknown whether such differences across causes of death persist in the general population and, if so, why they do. Third, few specific mediating mechanisms have been identified through which social isolation may increase the risk for disease and be conducive to premature deaths. For instance, multivariate analyses have shown significant independent effects of social isolation on CHD incidence after accounting for several cardiovascular risk factors and unhealthy lifestyles and therefore suggest that the effect of social isolation is not mediated by standard CHD risk factors but by other, less well known pathogenic mechanisms (Orth-Gomér et al. 1993).

Social Isolation and Inflammation: Psychosocial, Behavioral, and Physiological Mechanisms

It is increasingly recognized that social connection plays important roles in shaping the physical and mental well-being of individuals through a variety of mechanisms. A vast majority of past social science research featured psychosocial and behavioral processes by which different aspects of social relationships affect health (Smith and Christakis 2007; Thoits 2011; Umberson et al. 2010). It has also been proposed that the detrimental effects of social isolation are exerted via physiological processes (Cacioppo and Hawkley 2003; Seeman et al. 1987). Because little research has simultaneously considered social and biological explanations, we do not know much about how social isolation "gets under the skin" to shape individual risk for mortality. The separate bodies of knowledge, however, should and can be integrated to generate an enriched understanding of the multifaceted interconnections between these processes.

The stress process model, a central tenet in medical sociology, has been frequently brought to bear on the psychosocial mechanisms connecting social relations and mental and physical illnesses (Pearlin et al. 1981). Within this framework, chronic exposures to stress and reduced coping resources associated with social isolation can induce a cascade of immune, neuroendocrine, and cardiovascular changes (Seeman et al. 1987). Lack of social ties and resources signals stressful social circumstances and constitutes chronic distress that may have direct health consequences (Pearlin et al. 1981). Frequent religious attendance and volunteering, on the other hand, have been shown to reduce distress and lower risk for mortality (Hummer et al. 1999; Musick et al. 1999; Strawbridge et al. 1997). There is growing attention to the relationship between social integration and immune function. Laboratory research has long documented that stress has direct physiological effects on multiple regulatory systems through activation of the hypothalamic-pituitary-adrenal (HPA)axis and sympathetic nervous system (SNS), which modulate immune function and inflammatory processes (Seeman et al. 2001; Selye 1956). And it has been suggested that social connections may operate to reduce such effects by dampening physiological arousal or reactivity (Berkman et al. 1993), whereas social isolation is itself a stressor that produces negative reactivity and affect (e.g., anxiety, depression, irritability), promotes chronic elevations in HPA and SNS activation (Cacioppo and Hawkley 2003), downregulates systems of inflammatory genes (Williams et al. 2009), and increases inflammation (Hermes et al. 2006).

Individuals with fewer social connections and organizational participation may also be less able than others to buffer the physiological and health impacts of social life challenges (Smith and Christakis 2007). The stress-buffering functions of social support and personal psychological resources can thus be linked with inflammatory processes in various ways. It has been suggested that socially isolated individuals are deprived of opportunities for emotional support and instrumental coping assistance, which can decrease sense of control and self-esteem (Thoits 2011). Deficiencies in these coping resources may in turn increase physiological arousal and lead to a variety of mental disorders such as anxiety and depression through compromised physiological reactivity to stressors (Taylor and Stanton 2007) and impaired immune function (Southwick and Charney 2012). There is also evidence that links loneliness with less tangible and perceived support in times of stress, lower self-esteem and mastery, increased anxiety, depression, and consequently more frequent activation of the stress response systems and ill health (Cacioppo and Hawkley 2003; Cacioppo et al. 2006).

Modification of health behaviors may further contribute to the health effects of social isolation. Socially isolated individuals, compared to those more socially engaged, are under less normative pressure from and control by network members and are less likely to have access to multiple sources of information to foster healthy behaviors, gain access to health care, or minimize stressful or hazardous situations (Cacioppo and Hawkley 2003). In addition, they may be deficient in personal control that enables individuals to influence their own behaviors through more health enhancing knowledge and preventive behaviors (Umberson et al. 2010). Termed "interpersonal health effects," social engagement can promote or constrain various socially transmissible behaviors among network members such as tobacco and alcohol assumption, diet, weight control, and exercise (Smith and Christakis 2007). And there is evidence that cigarette smoking and obesity are major stimuli that significantly increase the risk for inflammation (Yang and Kozloski 2011). On the other hand, studies of social isolation and health have not found that health behaviors account for most of the variation in health across the continuum of social connectedness (Cacioppos, social network and Hawkley 2003; Seeman 2000).

The growing availability of biomarkers in population-based sample surveys provides new opportunities for assessing the role of physiological factors in the mortality risk of social isolation, which may inform further assessment of the interplay of psychosocial, health behavioral, and physiological factors in shaping health outcomes. Empirical studies along this line are largely confined to inflammatory risk factors for cardiovascular disease. Studies have linked chronic stress and lower SNI to increased production of proinflammatory cytokines such as interlukin-6 (IL-6) (Loucks et al. 2006) that stimulate the production of acute phase proteins such as C-reactive protein (Crp) (Ford et al. 2006; McDade et al. 2006). Studies of fibrinogen, an inflammatory regulator, have shown either a negative association with social networks (Orth-Gomér et al. 1993) or mixed results (Ford et al. 2006). Other studies of much smaller samples have not found consistent links between certain measures of social relations such as loneliness and emotional support and Crp or IL-6 (Hemingway et al. 2003; McDade et al. 2006). As the second leading cause of death, cancer has also attracted increasing attention in recent etiologic research. Although cancer studies are clinically based and restricted to small samples of white women with ovarian and breast cancer, they show similar findings of physiological benefits of social connections (Spiegel 2012; Stringhini et al. 2012). Specifically, social ties and support have been found to be related to reduced levels of IL-6 (Costanzo et al. 2005; Lutgendorf et al. 2000) and some inflammatory cytokines promoting tumor growth (Lutgendorf et al. 2002; Marucha et al. 2005).

In general, these studies did not directly assess mortality outcomes but provide biologic mechanistic evidence largely consistent with observed relationships between social isolation and leading causes of death. Chronic inflammation has been shown in biomedical research to be an important pathogenic mechanism contributing to the incidence and progression of a host of age-related conditions, such as arterial disease, diabetes, and malignancies in both animals and humans (Finch 2007; McClintock et al. 2005; Penwell and Larkin 2010; Yang and Kozloski 2011). Recent studies of population-based samples have further suggested that markers of chronic inflammation such as high Crp and fibrinogen levels and low serum albumin levels are predictive of overall mortality as well as mortality due to circulatory diseases and cancers (Fried et al. 1998; Newman et al. 2009; Yang and Kozloski 2012). Therefore, inflammation can act as an important link between social isolation and mortality.

Sex Differences

Prior research suggests that men with low levels of social integration are more vulnerable to disease and death than women (House et al. 1988). Potential explanations for this finding have emerged from studies showing notable sex differences in the biologic processes influenced by social relationships. Reviews of studies on social networks and support in relation to health have found little evidence of significant sex differences in the prevalence of social networks but suggest sex differences in physiological responses to

disrupted social ties. For example, women appear to react to loss of ties with less psychological distress or physical impairment than men. Some psychosocial mechanisms have been proposed to explain this difference. For instance, when a social loss (e.g., widowhood) is considered normative, it can increase women's abilities to anticipate such a loss, encourage women to substitute other close ties for the lost tie(s), or help them better cope with burdens and rewards of caregiving, which in turn may enhance women's resilience, which is key to health and survival following such loss (Berkman et al. 1993).

Physiological mechanisms may also play important roles (Shumaker and Hill 1991). A large body of animal studies indicates sexual dimorphism in behavioral stress responses (Taylor et al. 2000). That is, men display the classic "fight-or-flight" response to stressors, whereas women react with "tend-and-befriend" responses, characterized by nurturing behaviors that downregulate stress reactivity (tending pattern) and by affiliating with social groups to reduce risk (befriending pattern). A recent study further showed that although social isolation impairs innate inflammatory responses by delaying the shift from macrophage recruitment to scar formation in both male and female rats, isolated female rats produced a more robust response and faster wound healing than isolated male rats (Hermes et al. 2006). And lack of social integration and support has also been related to higher allostatic load, an omnibus measure of the burden of offsetting cumulative biological risks and disorders, with deleterious effects being more pronounced in older men than women (Seeman et al. 2002). These findings may have implications for the sex differences in stress-related disorders and mortality in general human populations.

In our study of a diverse population of Americans, we expect that although both men and women receive stress-reducing benefits from social contact, the same level of social isolation may induce less adverse physiological responses in women than men. To the extent that mortality risks of inflammation may be differentially associated with social ties for women compared with men, we hypothesize that inflammation plays different roles in accounting for the mortality effects of social isolation by sex. In addition, because the greater mortality effects of social isolation were found mainly in older men (e.g., Seeman et al. 2002), we do not know whether these sex differences apply to younger adults. Age variations in sex differences in both inflammation (Yang and Kozloski 2011) and mortality (Yang and Kozloski 2012) can contribute to the complexity of explanations but have not been systematically examined or modeled in population-based studies of social isolation and mortality. We broaden the age range of the study sample to include younger and middle-aged adults to allow the examination of age differences in this link.

Previous studies used different inflammatory markers such as Crp and IL-6 to test their associations with social isolation or mortality and produced different results. Because they often focused on individual biomarkers of inflammation from small samples, a comprehensive assessment of multiple inflammatory markers is needed. Moreover, each marker reflects different stages of the inflammatory process and hence may bear different relationships to social isolation and to disease-specific mortality.[1] Each marker, however, is also affected by other physiological processes, distinct from inflammation.[2] Therefore, a composite measure of multiple inflammatory markers, which form a single factor, will be more specific than any one alone. And as suggested by the studies of allostatic load (Seeman et al. 2002) and infection burden index (Zajacova, Dowd, and Aiello 2009), the composite measure of inflammation reflects the presence of multiple risk factors and hence the overall burden of inflammation, which has considerable power in accounting for health effects of complex factors such as social relationships.

DATA AND METHODS

Sample and Measures

The data come from the Third National Health and Nutrition Examination Survey (NHANES III) Linked Mortality Study public-use file (1988–2006) (CDC 2006). The NHANES III, conducted by the National Center for Health Statistics between 1988 and 1994, used a multistage stratified sampling design and included a representative cross-sectional sample of the noninstitutionalized U.S. population, with an oversample of older

persons and minorities. Respondents' mortality status was followed up until 2006 (CDC 2006). Mortality information is based on probabilistic matching between NHANES and National Death Index death certificate records. Respondents who were not identified as deceased by the end of the follow-up period were assumed to be alive. In addition to all-cause deaths, we adopted the International Classification of Diseases, 10th Revision, underlying-cause-of-death recode to identify deaths due to circulatory diseases and malignant neoplasms, as indicated in Table 1. We restricted analyses to these two causes because they account for the vast majority of deaths and have strong correlations with inflammation, and deaths from other causes are too few to allow reliable estimations of death rates.

The study sample consists of 9,350 respondents aged 40 years and older who attended both household interviews and clinical examinations in NHANES III and were eligible for mortality follow-up through 2006.[3] We excluded respondents whose Crp values were greater than 10 mg/dL (.1 percent), which indicates acute infection, because our focus is on chronic inflammatory disorders. Because sex differences in inflammatory health can be directly affected by the effects of ovarian steroids (e.g., Crp levels can be elevated in the later stages of pregnancy as well as by the use of hormone replacement therapy), we excluded women who were pregnant (1.8 percent) or receiving female hormone therapy (25.3 percent) in the preliminary analysis. Because we did not find any difference in findings within the female sample or in comparison with the male sample, and because their exclusion would have substantially reduced the sample size and statistical power for the survival analyses, we included them in the final analyses. The final sample consists of 6,729 respondents who had data on all measures used in the analyses and recorded 2,774 total deaths, 1,274 deaths from circulatory diseases, and 602 deaths from cancer for the follow-up period of up to 18 years.

Table 1 presents sample characteristics by sex and age, with weighted descriptive statistics of all covariates in regression analyses. The measure of social isolation is derived from the Berkman-Syme SNI, which summarizes the number of social ties across four domains: marriage, contacts with friends and relatives, religious attendance, and membership in social organizations. Each of these ties is a dichotomous variable indicating the presence or absence of ties on the basis of previous studies using the NHANES III data (e.g., Ford et al. 2006), as shown in the Appendix. The SNI is the sum of the scores for the four dichotomized variables and ranges from 0 to 4. The SNI has been used in recent studies and shows high levels of predictive validity for a variety of health outcomes (e.g., Ford et al. 2006; Loucks et al. 2006). Table 1 shows that 18.6 percent of men and 16.2 percent of women in the sample were socially isolated (SNI = 0 or 1). The majority of the sample fell in the middle to higher end of the SNI range.

We measure chronic inflammation using three inflammatory markers available in the NHANES III: Crp, fibrinogen, and serum albumin. The laboratory measurements and assay procedures for these markers have been described elsewhere (Centers for Disease Control and Prevention 1996). The cut points for high risk for chronic inflammation are shown in Table 1 and were defined by clinical practice or previous studies for Crp and albumin and empirically defined for fibrinogen as the top quartile.[4] On the basis of the dichotomized individual markers, we constructed a summary count index of inflammation burden as the sum of the positive indicators ranging from 0 to 3. The index has been used in previous studies of physiological dysregulation (Yang and Kozloski 2011, 2012). To further confirm that these three variables form a single estimate of risk for chronic inflammation, we used an oblique model in a principal-components analysis (with serum albumin reverse coded). All three inflammatory markers constituted a single factor (56.3 percent of the variance, eigenvalue = 1.69) with loading coefficients (for Crp of .82, fibrinogen of .79, and albumin of .63). Table 1 shows that 15.5 percent of men in the sample had scores of 0 or no high-risk inflammation markers, 64.5 percent had scores of 1, 18.7 percent had scores of 2, and 1.4 percent had scores of 3; the corresponding figures for the female sample show a lower percentage (6.5 percent) of scores of 0 and higher percentages of the high inflammatory scores.

We adjust for additional demographic and socioeconomic factors (race-ethnicity, education, and

Table 1. Sample Characteristics: NHANES III Mortality Follow-Up Study: 1988 to 2006.

	Men			Women		
Variable	All Ages (*n* = 3,082)	40–64 Years (*n* = 1,674)	≥65 Years (*n* = 1,408)	All Ages (*n* = 3,647)	40–64 Years (*n* = 2,039)	≥65 Years (*n* = 1,608)
Number of deaths (death rate/1,000 person-years)						
All causes	1,434 (28.7)	362 (12.2)	1,072 (73.4)	1,340 (24.7)	305 (9.8)	1,035 (55.5)
Circulatory diseases[a]	648 (12.6)	151 (5.0)	497 (34.0)	626 (10.8)	99 (2.9)	527 (27.2)
Malignant neoplasms[b]	346 (7.7)	101 (4.1)	245 (17.7)	256 (5.3)	110 (3.7)	146 (8.4)
Social Network Index						
0 or 1	18.0%	18.6%	16.8%	16.2%	16.6%	15.7%
2	32.4%	33.8%	29.6%	31.2%	30.3%	32.8%
3	33.5%	33.2%	33.9%	37.8%	38.0%	37.6%
4	16.2%	14.3%	19.7%	14.7%	15.2%	13.9%
Chronic inflammation						
C-reactive protein (mg/dL), mean (SD)	.45 (.70)	.40 (.60)	.53 (.84)	.53 (.77)	.52 (.68)	.56 (.89)
<1 (normal)	92.5%	93.6%	90.5%	87.6%	87.5%	87.7%
1–3 (low chronic)	6.0%	5.3%	7.2%	10.6%	11.2%	9.6%
>3 (high chronic)	1.5%	1.1%	2.4%	1.8%	1.3%	2.7%
Plasma fibrinogen (mg/dL), mean (SD)	301.19 (85.00)	289.57 (81.28)	323.44 (87.53)	314.11 (84.17)	307.07 (83.61)	325.15 (83.87)
Serum albumin (µg/mL), mean (SD)	4.16 (.33)	4.20 (.33)	4.08 (.32)	4.03 (.32)	4.06 (.31)	3.99 (.32)
<4.0 (higher risk)	35.0%	29.5%	45.7%	52.0%	48.0%	58.0%
Inflammation burden index mean (SD)	.60 (.71)	.48 (.65)	.81 (.77)	.84 (.74)	.76 (.71)	.97 (.77)
0	15.5%	19.2%	8.3%	6.5%	7.9%	4.3%
1	64.5%	65.7%	62.1%	65.3%	67.6%	61.8%
2	18.7%	14.2%	27.5%	26.6%	23.6%	31.3%
3	1.4%	1.0%	2.2%	1.6%	.9%	2.7%
Demographic and social factors						
Race						
Non-Hispanic white	80.5%	76.8%	87.4%	79.1%	74.2%	86.8%
Non-Hispanic black	8.8%	10.0%	6.7%	10.6%	12.7%	7.2%
Mexican American	4.0%	5.0%	2.1%	3.6%	4.7%	1.8%
Other	6.7%	8.2%	3.8%	6.8%	8.5%	4.2%
Education (years), mean (SD)	11.43 (3.19)	11.93 (3.47)	10.81 (3.65)	11.55 (3.57)	11.76 (3.06)	10.92 (3.33)
≤12	66.7%	62.5%	74.8%	73.5%	71.4%	76.7%
13–15	15.7%	18.0%	11.1%	14.7%	15.0%	14.2%
≥16	17.7%	19.5%	14.1%	11.8%	13.6%	9.1%
Family income ($), mean (SD)	28,239.75 (13,668.33)	30,345.15 (13,329.57)	22,670.83 (14,857.78)	26,104.64 (14,551.03)	28,296.63 (13,918.33)	24,210.91 (13,408.01)

(continued)

Table 1. (continued)

Variable	Men			Women		
	All Ages (n = 3,082)	40–64 Years (n = 1,674)	≥65 Years (n = 1,408)	All Ages (n = 3,647)	40–64 Years (n = 2,039)	≥65 Years (n = 1,608)
Health behaviors						
Cigarette smoking						
Never	25.8%	26.0%	25.4%	55.6%	51.0%	62.7%
Former	47.2%	40.2%	60.5%	24.0%	21.8%	27.6%
Current	27.1%	33.8%	14.1%	20.4%	27.2%	9.7%
Alcohol use (drinks per day), mean (SD)	.68 (1.46)	.77 (1.55)	.50 (1.25)	.21 (.79)	.24 (.94)	.15 (.45)
None	48.0%	43.0%	57.7%	70.0%	64.1%	79.2%
≤1	33.9%	36.2%	29.4%	24.8%	29.7%	17.1%
1–3	12.4%	14.0%	9.5%	4.6%	5.2%	3.6%
>3	5.7%	6.8%	3.5%	.7%	1.0%	.1%
Physical activity (any)						
None	20.0%	19.3%	21.2%	33.2%	31.5%	35.8%
Body mass index (kg/m^2), mean (SD)	27.35 (4.62)	27.60 (4.77)	26.87 (4.28)	27.56 (6.44)	28.12 (6.94)	26.67 (5.47)
≥30	24.4%	25.9%	21.6%	29.6%	33.4%	23.8%
Morbidity and health status						
Number of chronic conditions,[c] mean (SD)	1.35 (1.46)	1.11 (1.33)	1.81 (1.58)	1.47 (1.43)	1.19 (1.27)	1.91 (1.55)
Self-rated health						
Excellent and very good	40.8%	43.9%	34.9%	39.6%	40.4%	38.3%
Good	36.6%	37.9%	34.2%	34.9%	35.8%	33.6%
Fair	17.7%	14.6%	23.6%	20.2%	19.3%	21.7%
Poor	4.9%	3.6%	7.3%	5.3%	4.5%	6.5%

Note: Descriptive statistics of covariates are weighted to adjust for survey design effects.
[a]International Classification of Diseases, 10th Revision, codes I00 to I78 and I80 to I99, including cardiovascular (coronary, hypertensive, and rheumatic heart diseases) and cerebrovascular diseases.
[b]International Classification of Diseases, 10th Revision, codes C00 to C97, including all cancers, with lung cancer being the most prevalent
[c]Includes 14 self-reported chronic illnesses: angina, arthritis, asthma, bronchitis, diabetes, emphysema, heart attack, heart failure, cancer, stroke, hip fracture, osteoporosis, spine fracture, and wrist fracture.

family income) health behaviors (smoking, alcohol drinking, physical activity, and body mass index), and morbidity and general health status (number of chronic conditions and self-rated health) because they have been shown to be important predictors of adult mortality of all causes (Finch 2007; Fried et al. 1998). The coding and descriptive statistics of these control variables are also included in Table 1. We recoded continuous variables into intervals for the identification of nonlinear effects and more stable estimates of hazard ratios (HRs) in survival analysis.

Analytic Methods

We conducted three sets of multivariate regression analyses to ascertain the role of chronic inflammation in the relationship between the SNI and mortality. First, we estimated Cox proportional-hazards regression models to examine the gross effects of the SNI

on subsequent mortality by cause, including overall mortality and mortality due to circulatory diseases and cancer. We adopted the common practice of censoring survival times at competing causes of death (Allison 2010). We compared results using alternative operationalizations of the SNI, including the continuous scale that represents linear effects, categorical variables that indicate nonlinear effects, and a dichotomous variable capturing a threshold effect. The choice of the best SNI variable is based on both significance tests of regression coefficients and model fit statistics using the Bayesian information criterion. Consistent with earlier studies (Berkman and Syme 1979; Eng et al. 2002), we found a stronger threshold effect with the absence of social ties predicting higher mortality and a better model fit. We present results using the dichotomous variable of social isolation (SNI = 0 or 1) versus socially connected (SNI $\geq$ 2).

Second, we examined the associations between social isolation and inflammation measured by each of the three individual markers and also by the summary inflammation burden index. Specifically, we estimated ordered logistic regression models for Crp, logistic models for fibrinogen and serum albumin, and ordered logistic models for the inflammation burden index. Additional ordinary least squares analyses were conducted to examine the associations of social isolation with log-transformed continuous scales of individual inflammation markers. These results show fewer significant effect coefficients, suggesting a lack of linear relationships with social network ties. We present only results from the categorical regression models that also show better model fit to the data.

Third, we estimated the net effects of social isolation on mortality by adding inflammation variables to the Cox regression models estimated in the first analysis. In all three sets of analyses, we estimated models by sex and age groups and also compared results without and with adjustment of additional covariates. The contribution of inflammation to the association between social isolation and mortality was determined in three ways: (1) by comparisons of significance levels of the social isolation coefficients before and after the inclusion of the inflammation variables, (2) by the percentage attenuation in the social isolation coefficients after inclusion of the inflammation variables and its 95 percent confidence interval (CI) using a bias-corrected accelerated bootstrap method with 1,000 resamplings (see e.g., Stringhini et al. 2012), and (3) by Wald tests of the Cox models without and with inclusion of the inflammation variables (Hosmer and Lemeshow 1999). Statistical analyses were performed using Stata 12.0 and R and were adjusted for survey design effects using sampling weights.

RESULTS

Analysis 1: Social Isolation and Mortality

The mortality analysis using Cox regression models summarized in Table 2 shows strong detrimental effects of social isolation on overall mortality for both sexes. In Model 1 for the all-age samples adjusting for age and race-ethnicity, the HRs are estimated to be 1.84 (95 percent CI = 1.51–2.25) and 1.83 (95 percent CI = 1.53–2.19) for men and women, respectively, indicating vastly elevated risks of death (>80 percent) for those who were socially isolated. The HRs from Model 1 by age groups show that the mortality effects of social isolation are significant for both middle and older age groups but larger for older adults, particularly older men (HR = 2.03, $p < .001$).

The results for cause-specific mortality are similar to those for overall mortality in direction but vary in magnitude. Although the effects of social isolation on circulatory disease mortality are not statistically significant for middle-aged adults, they are strong and highly significant for older adults and larger in older men. Less significant effects are found for cancer mortality for women and older men. However, the large effect of social isolation for middle-aged men (HR = 1.91, $p < .05$) is noteworthy. Model 2 shows that adjusting for other covariates such as socioeconomic status, health behaviors, morbidity, and general health status reduced some of these effects. The independent effects of social isolation, however, remain, and the pattern of sex and age variations in these effects largely holds.

Analysis 2: Social Isolation and Inflammation

Next, we assessed associations between social isolation and each of the three inflammation markers as

Table 2. Effects of Social Isolation on Mortality by Cause.

	All Cause			Circulatory Diseases			Cancer		
	All Ages	40–64 Years	≥65 Years	All Ages	40–64 Years	≥65 Years	All Ages	40–64 Years	≥65 Years
Men									
Model 1[a]: HR	1.84***	1.56*	2.03***	1.78***	1.26	2.08***	1.62*	1.91*	1.37
(95% CI)	(1.51–2.25)	(1.08–2.25)	(1.60–2.58)	(1.34–2.37)	(.71–2.21)	(1.51–2.87)	(1.10–2.38)	(1.02–3.60)	(.88–2.14)
Model 2[b]: HR	1.53***	1.19	1.78***	1.56**	1.04	1.94***	1.30	1.31	1.23
(95% CI)	(1.26–1.87)	(.82–1.73)	(1.42–2.23)	(1.16–2.10)	(.58–1.87)	(1.40–2.69)	(.87–1.95)	(.69–2.48)	(.78–1.95)
Women									
Model 1[a]: HR	1.83***	1.65**	1.91***	1.75***	1.24	1.91***	1.08	1.10	1.02
(95% CI)	(1.53–2.19)	(1.14–2.39)	(1.55–2.34)	(1.35–2.29)	(.63–2.43)	(1.43–2.54)	(.70–1.67)	(.57–2.07)	(.58–1.81)
Model 2[b]: HR	1.45***	1.25	1.57***	1.47**	1.10	1.64**	.86	.75	.90
(95% CI)	(1.20–1.75)	(.84–1.87)	(1.27–1.93)	(1.11–1.95)	(.54–2.26)	(1.20–2.22)	(.55–1.34)	(.39–1.47)	(.51–1.61)

[a]Controls for age (for all-ages sample) and race-ethnicity.
[b]Controls for age (for all-ages sample), race-ethnicity, education, family income, smoking, drinking, physical activity, BMI, chronic conditions, and self-rated health.
*$p < .05$, **$p < .01$, and ***$p < .001$ (two-tailed tests).

well as the inflammation burden index (presented in Table 3). Social isolation is related to more inflammation as measured by Crp, fibrinogen, and the inflammation index. We also find that sex and age variations in these associations are consistent with our expectation. Overall, the associations are more pronounced for men than women. For the total male sample, adjusting for age and race, Model 1 shows 58 percent higher odds of having elevated Crp for those who were socially isolated (95 percent CI = 1.02–2.46) and 94 percent higher odds of being at the highest quartile of fibrinogen (95 percent CI = 1.44–2.62). The odds ratios (ORs) are also large and significant for older men in the fibrinogen model. For the total female sample, adjusting for age and race, Model 1 reports only slightly elevated Crp risks for the socially isolated that are not statistically significant but 38 percent higher odds of being at the high-risk level of fibrinogen, which is significant. The ORs estimated for the high-risk (i.e., low) level of serum albumin are generally small. The lack of statistical significance for these estimates, however, likely reflects the low specificity of serum albumin as an inflammation marker. The results for the three individual markers are most significant for fibrinogen. A higher inflammation burden is related to social isolation for both men and women, but the association is statistically significant only for men, particularly older men (Model 1: OR = 1.74, $p < .01$). Adjusting for additional covariates as mentioned above reduced the ORs in Model 1, but the positive ORs remain significant in Model 2 for men in the older age group for fibrinogen (OR = 1.88, $p < .01$) and the inflammation burden index (OR = 1.59, $p < .05$).

Analysis 3: Social Isolation, Inflammation, and Mortality

We next adjusted for inflammation in Cox regression models reported in Table 2 to further examine its effect on mortality jointly with social isolation. Analyses using the inflammatory burden index showed more significant results and better model fit than those using any of the individual inflammatory markers such as Crp and fibrinogen. Therefore, we focused on the inflammation burden index in the final analysis. Model 1 in Table 4 presents HRs of social isolation and inflammation burden index that adjusts for age and race. Inflammation is highly predictive of mortality in models that simultaneously include social isolation. Having a higher score for the index is associated with drastically increased risks of overall mortality for both sexes, particularly middle-aged men. The same is true for circulatory disease and

Table 3. Social Isolation and Inflammation: Odds Ratio (95% Confidence Interval).

	Crp		Fibrinogen		Serum Albumin		Inflammation Index	
Sex and Age	Model 1[a]	Model 2[b]	Model 1[a]	Model 2[b]	Model 1[a]	Model 2[b]	Model 1[a]	Model 2[b]
Men								
All ages	1.58*	1.29	1.94***	1.68**	1.03	.93	1.47**	1.28
	(1.02–2.46)	(.82–2.04)	(1.44–2.62)	(1.21–2.30)	(.77–1.36)	(.70–1.24)	(1.13–1.92)	(.99–1.67)
Age 40–64 years	1.52	1.22	1.86**	1.56*	.94	.80	1.35	1.12
	(.80–2.92)	(.61–2.44)	(1.21–2.87)	(1.00–2.45)	(.63–1.40)	(.53–1.21)	(.95–1.92)	(.79–1.60)
Age ≥ 65 years	1.67	1.42	2.06***	1.88**	1.19	1.11	1.74**	1.59*
	(.97–2.86)	(.82–2.46)	(1.41–3.03)	(1.27–2.81)	(.81–1.74)	(.75–1.66)	(1.20–2.53)	(1.07–2.34)
Women								
All ages	1.01	.81	1.38*	1.17	.88	.84	1.08	.95
	(.71–1.43)	(.56–1.17)	(1.08–1.78)	(.90–1.53)	(.69–1.13)	(.65–1.08)	(.85–1.39)	(.73–1.23)
Age 40–64 years	1.14	.84	1.44*	1.11	.82	.76	1.04	.85
	(.72–1.80)	(.51–1.38)	(1.01–2.06)	(.75–1.62)	(.58–1.15)	(.53–1.09)	(.74–1.46)	(.60–1.21)
Age ≥ 65 years	.82	.75	1.30	1.21	1.00	.95	1.16	1.07
	(.49–1.36)	(.42–1.35)	(.93–1.83)	(.84–1.73)	(.71–1.40)	(.66–1.37)	(.82–1.65)	(.73–1.56)

[a]Controls for age (for all-ages sample) and race-ethnicity.
[b]Controls for age (for all-ages sample), race-ethnicity, education, family income, smoking, drinking, physical activity, BMI, chronic conditions, and self-rated health.
*$p < .05$, **$p < .01$, and ***$p < .001$ (two-tailed tests).

cancer mortality, but more so for men than women. When social isolation and inflammation are simultaneously considered, the mortality effects of a higher inflammation burden (having two or three markers at high risk) are usually greater than social isolation. The estimated HRs in Model 2 show that further adjustment of control variables eliminated the social isolation effects on overall mortality for the middle-age groups but not the older groups, suggesting that demographic, behavioral, and health factors may be particularly important in explaining why social isolation increases mortality risk for middle-aged adults.

On the basis of results from the above models, we assessed the impact of inflammation on the association between social isolation and mortality. Comparing models without and with adjustment of inflammation, we find that the effects of social isolation are mediated by inflammation to varying degrees by cause of death, sex, and age. Table 5 presents the results of statistical tests of the mediating effects of inflammation for men of selected age groups only, because of the lack of associations for women as shown in Table 2. In general, the inclusion of inflammation reduced the sizes of coefficients of social isolation across all models and eliminated the significance of the coefficients of social isolation in the model of cancer mortality.

Table 5 shows that in Model 1, adjusting for age and race fit to the sample of all men, inflammation burden explained 14 percent (95 percent CI = −27 to −3) of the association of social isolation with all-cause mortality, 12 percent (95 percent CI = −35 to −2) of the association of social isolation with circulatory disease mortality, and 24 percent (95 percent CI = −121 to −3) of the association of social isolation with cancer mortality. Slightly smaller percentage reductions are observed for models fit to age-stratified samples of men. All changes are highly significant as shown by the Wald χ^2 test ($p < .001$). These reductions are substantial compared with those achieved by the adjustment of control variables in Model 2 (Model 1 plus controls), particularly for older men. For all-cause mortality, the percentage reduction in men aged 65 years and older is 11 percent with the addition of inflammation to Model 1, compared with 19 percent with the addition of controls. For circulatory disease mortality, the corresponding percentage reductions are 7 percent and 10 percent. Last, estimates from the full model (Model 2 plus inflammation) suggest that, for men of all

Table 4. Social Isolation, Inflammation, and Mortality: Model 1 HRs Adjusted for Age and Race and Model 2 HRs Adjusted for All Covariates.

	Men						Women					
	All Ages		40–64 Years		≥65 Years		All Ages		40–64 Years		≥65 Years	
	Model 1	Model 2	Model 1	Model 2	Model 1	Model 2	Model 1	Model 2	Model 1	Model 2	Model 1	Model 2
All-cause mortality												
Social isolation	1.69***	1.45***	1.47*	1.16	1.88***	1.67***	1.82***	1.46***	1.62*	1.24	1.90***	1.57***
Inflammation index (0)	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
1	1.65***	1.56***	1.74**	1.57*	1.57***	1.50***	1.34**	1.30**	1.59*	1.17	1.25**	1.25*
2 or 3	3.03***	2.60***	5.12***	3.82***	2.41***	2.21***	1.72***	1.48**	2.61***	1.49	1.49***	1.40**
Circulatory disease mortality												
Social isolation	1.66***	1.49**	1.20	1.03	1.97***	1.87***	1.72***	1.47**	1.20	1.12	1.87***	1.63**
Inflammation index (0)	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
1	1.46**	1.35*	1.18	1.08	1.55**	1.46**	1.04	1.01	1.68	1.25	.94	.91
2 or 3	2.50***	2.05***	4.53***	3.04**	2.01***	1.78**	1.50**	1.30	3.65**	2.10	1.25	1.15
Cancer mortality												
Social isolation	1.44	1.21	1.78	1.27	1.19	1.10	1.07	.87	1.09	.75	1.02	.91
Inflammation index (0)	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
1	2.07***	1.99***	1.84	1.48	2.20***	2.14***	1.32	1.25	1.29	.97	1.34	1.46
2 or 3	4.44***	3.94***	5.79***	3.89**	3.99***	3.83***	1.64*	1.36	1.66	1.00	1.63	1.69

Note: HR = hazard ratio.
*$p < .05$, **$p < .01$, and ***$p < .001$ (two-tailed tests).

Table 5. Mediating Role of Inflammation Burden Index in the Association between Social Isolation and Mortality in Men.

	All-Cause Mortality				Circulatory Disease Mortality				Cancer Mortality			
	HR[a] (95% CI)	% Change[b] (95% CI[c])	χ^2 (*df*)	*p*	HR[a] (95% CI)	% Change[b] (95% CI[c])	χ^2 (*df*)	*p*	HR[a] (95% CI)	% Change[b] (95% CI[c])	χ^2 (*df*)	*p*
All ages												
Model 1: age, race-ethnicity	1.84 (1.51 to 2.25)				1.78 (1.34 to 2.37)				1.62 (1.10 to 2.38)			
Model 1 + inflammation vs. Model 1	1.69 (1.40 to 2.05)	−14 (−27 to −3)	89.63 (2)	<.001	1.66 (1.26 to 2.19)	−12 (−35 to −2)	25.85 (2)	<.001	1.44 (.97 to 2.15)	−24 (−121 to −3)	44.04 (2)	<.001
Model 2: Model 1 + controls vs. Model 1	1.53 (1.26 to 1.87)	−30 (−53 to −13)	173.49 (16)	<.001	1.56 (1.16 to 2.10)	−23 (−70 to .2)	106.68 (16)	<.001	1.30 (.87 to 1.95)	−46 (−202 to −12)	42.63 (16)	<.001
Model 2 + inflammation vs. Model 1	1.45 (1.18 to 1.77)	−39 (−63 to −21)	237.66 (18)	<.001	1.49 (1.11 to 2.01)	−31 (−81 to −4)	121.93 (18)	<.001	1.21 (.80 to 1.82)	−60 (−255 to −19)	78.91 (18)	<.001
Model 2 + inflammation vs. Model 2		−13 (−32 to −1)	64.17 (2)	<.001		−10 (−39 to 1)	15.25 (2)	<.001		−27 (−578 to 64)	36.27 (2)	<.001
≥65 years (40−64 years for cancer mortality)												
Model 1: age, race-ethnicity	2.03 (1.60 to 2.58)				2.08 (1.51 to 2.87)				1.91 (1.02 to 3.60)			
Model 1 + inflammation vs. Model 1	1.88 (1.50 to 2.34)	−11 (−24 to −1)	48.09 (2)	<.001	1.97 (1.44 to 2.71)	−7 (−23 to 3)	15.23 (2)	<.001	1.78 (.94 to 3.38)	−11 (−106 to 19)	16.38 (2)	<.001

(continued)

Table 5. (continued)

	All-Cause Mortality				Circulatory Disease Mortality				Cancer Mortality			
	HR[a] (95% CI)	% Change[b] (95% CI[c])	χ^2 (*df*)	*p*	HR[a] (95% CI)	% Change[b] (95% CI[c])	χ^2 (*df*)	*p*	HR[a] (95% CI)	% Change[b] (95% CI[c])	χ^2 (*df*)	*p*
Model 2: Model 1 + controls vs. Model 1	1.78 (1.42 to 2.23)	−19 (−40 to −2)	95.15 (16)	<.001	1.94 (1.40 to 2.69)	−10 (−39 to 13)	62.08 (16)	<.001	1.31 (.69 to 2.48)	−58 (−304 to 27)	39.93 (16)	<.001
Model 2 + inflammation vs. Model 1	1.67 (1.33 to 2.09)	−28 (−54 to −10)	131.66 (18)	<.001	1.87 (1.34 to 2.61)	−15 (−49 to 11)	72.12 (18)	<.001	1.27 (.66 to 2.46)	−63 (−503 to 50)	49.55 (18)	<.001
Model 2 + inflammation vs. Model 2		−11 (−29 to −3)	36.51 (2)	<.001		−6 (−24 to 4)	10.04 (2)	<.001		−11 (−166 to 51)	9.62 (2)	<.001

Note: CI = confidence interval; HR = hazard ratio.

[a]HRs of social isolation reported in Table 2 (Model 1 and Model 2) and Table 4 (Model 1 + inflammation and Model 2 + inflammation).

[b]Percentage change in regression coefficient calculated as $100 \times (\beta_{\text{Model } y} - \beta_{\text{Model } x})/(\beta_{\text{Model } x})$, where β = log(HR) and models being compared (*x* and *y*) are indicated in column 1.

[c]Bias-corrected accelerated bootstrap 95% CI.

ages, social behavioral factors and inflammation burden together accounted for 39 percent, 31 percent, and 60 percent of the associations between social isolation and all-cause, circulatory disease, and cancer mortality, respectively. Comparison of the full model with Model 2 shows that, adjusting for all other covariates, there are further reductions in the HRs of social isolation by inflammation (10 percent to 27 percent for all ages, 6 percent to 11 percent for age-specific groups) that are statistically significant ($p < .001$).

We note that in the cancer mortality model, the 95 percent CIs for HRs and bootstrap intervals for the percentage change estimates are particularly wide, and the corresponding χ^2 statistics are small. Relatedly, the percentage reduction achieved by the inclusion of inflammation is much smaller (11 percent) compared with that achieved by the inclusion of the controls (58 percent) for middle-aged men. This is due largely to the much smaller number of cancer-related deaths in the sample and calls for caution in the interpretation of cancer-related results.

In the final models (Model 2) in Table 4 that include all risk factors for mortality, the adjusted HRs of social isolation remain substantial and significant in models of overall and circulatory disease mortality for both sexes in the older age group. Although the independent effects of inflammation index remain significant for older men, they are no longer significant in the model of circulatory disease mortality for older women. These results suggest a residual effect of social isolation on mortality net of inflammation and all the other factors in late life that begs further explanations.

DISCUSSION

Through a systematic investigation of the associations between social isolation, chronic inflammation, and adult mortality by cause using a nationally representative, population-based sample, we find support for the hypothesis that lack of social embeddedness elevates mortality risk through physiological upregulation of chronic inflammation. Everything else being equal, the inflammatory process at work in socially isolated individuals greatly intensifies the likelihood of their dying. In other words, the survival benefits conveyed by social integration, widely documented in animal and human studies, can be attributed in part to ameliorating subclinical chronic inflammation, which undergirds many of the most prevalent causes of death (Esch and Stefano 2002). The evidence for the mediation role of chronic inflammation in the link between social isolation and mortality is particularly strong in older men for all-cause and circulatory disease mortality and in middle-aged men for cancer mortality. We arrived at these findings through three analyses that contribute to the knowledge about social networks and health in distinct ways.

First, we extended prior studies of social isolation and mortality by generalizing the association to the overall population in the United States. We estimated the effects of social isolation on not only all-cause mortality but also mortality due to two leading causes of death in the United States, circulatory diseases and cancer. We found that social isolation is highly predictive of circulatory disease mortality for both sexes and is also predictive of cancer mortality for men. The association between social isolation and cancer mortality is moderate largely because the small number of malignancy-related deaths yields lower and less reliable estimates of death rates that limited statistical power. Future studies of larger samples with data on cancer are needed to further examine this association in women and various subgroups at risk for health disparities in cancer mortality.

In the second analysis, we found interesting correlations between social isolation and different markers of chronic inflammation that suggest different physiological pathways important to consider in further analysis of the interplay between social and biological factors in disease etiology. Although most prior studies restricted attention to individual inflammatory markers such as Crp, we assessed three different markers of chronic inflammation: elevated Crp and fibrinogen and low serum albumin. This approach led to findings of the relative importance of different biological measures that might not have been possible otherwise. We find that a high fibrinogen level had a particularly strong association with social isolation in both sexes. The commonly used Crp also appears to be significantly related to social isolation, but this relationship is less consistent across sex and age groups. As expected, serum albumin does not seem to be as strongly associated with

social isolation, because it is less specific and is affected by many physiological processes other than inflammation. Combining the three markers of chronic inflammation, which together constitute a single inflammatory factor, solved the problem of biomarker specificity and yielded better model fits. The simultaneous presence of high-risk levels of these individual markers measured by the composite index of inflammation burden shows strong significant correlations with social isolation and may be particularly important in the understanding of the mortality consequences of social isolation, as seen in the third analysis.

The third analysis integrates the two previous analyses and provides direct evidence that chronic inflammation can act as important physiological links between social isolation and mortality. The mediating effects of inflammation are significant for men for not only overall mortality but also disease-specific mortality. Consistent with findings from previous research that indicate lack of empirical support for health behaviors as the main explanatory mechanism (Cacioppo and Hawkley 2003), we found that the independent effects of social isolation on mortality largely remain after adjusting for a wide array of demographic, behavioral, and health factors. It is noteworthy that the single index of cumulative inflammatory burden mediates the social isolation effect on mortality to degrees that are comparable with the entire vector of demographic, behavioral, and health variables in some cases (e.g., circulatory disease mortality in older men). This suggests that inflammation burden should be included as one physiological mechanism contributing to the detrimental effects of social isolation on survival independent of conventional factors in future studies.

We found support for our hypothesis that there are sex differences in the extent to which the inflammatory process mediates the effect of social isolation on mortality, a difference that was manifest more strongly at some ages than others. First, extending previous research on social ties and overall mortality, we found sex differences in the effects of social isolation on cause-specific mortality, with notable age variations. Similar to the finding on overall mortality, the effects of social isolation are larger and more significant for older men on circulatory disease mortality. In contrast, these effects are greater for middle-aged men on cancer mortality. The increased susceptibility to cancer deaths for socially detached men younger than 65 years of age is also unexpected given the much higher rates of cancer incidence and mortality in older ages. Our analyses further suggest that both social behaviors and inflammation were at work to make these middle-aged men particularly vulnerable. If corroborated in additional studies, this finding may have practical import for more effective prevention and control strategies that are targeted at specific demographic groups with a particular disease.

Results from our second analysis also support the proposed sex differences in the associations of social networks with physiological stress response from studies of animals (Hermes et al. 2006; Taylor et al. 2000) and small samples of humans (Seeman et al. 2002). Our study contributes new empirical evidence for such sex differences in a large nationally representative sample of adults in the extent of innate immune function impairment. Our data show that social isolation is correlated with more adverse inflammatory responses (such as elevated fibrinogen and cumulative inflammation burden) in men (particularly older men) than women that persist after the adjustment of potential confounding factors. These findings are consistent with the biobehavioral hypothesis about sex differences in physiology and vital capacity that give rise to sex-specific stress reactivity patterns, which evolved as adaptations to different social and biological roles (Austad 2006; Taylor et al. 2000). That is, the physiological response typical of women has likely evolved as an adaptation to their maternal and caregiving roles (tend-and-befriend pattern) and acts to downregulate innate immune responses such as inflammation.

The third analysis further shows that inflammation plays different roles in accounting for the mortality effects of social isolation in men and women of different ages. Although health behavioral factors are more important pathways by which social isolation increases mortality risk for middle-aged men, cumulative inflammation burden is a more prominent factor that explains the higher mortality risks for socially isolated older men. And when all confounding factors are controlled, inflammation remains to play a significant part in

mediating the effects of social isolation on mortality for older men. In all, the results suggest that the mortality effects of social isolation are larger for older men and can be attributed in part to their heightened inflammatory responses.

For women in this sample, social isolation is less strongly predictive of mortality regardless of adjustment for other covariates. This indicates that female mortality seems to be affected by social isolation through other social, psychological, behavioral, and biological processes beyond those included in the study. We raise several possibilities in the discussion below of the limitations of this study that should be addressed by future investigations.

First, the measures of social relationship available in the NHANES data are restricted to social networks that represent quantitative and structural aspects of social relations. As we mentioned before, qualitative and functional dimensions of social affiliation may be important to consider as psychosocial mechanisms mediating the link between social isolation and mortality and sex differences therein. The largest gender differences in social affiliative behaviors have been found to be in seeking and using social support (Luckow, Reifman, and McIntosh 1998), with women being more likely to be engaged in their social networks and to benefit from social support (Taylor et al. 2000). In addition, there are gender differences in social norms and expectations for social support to the extent that women can be less vulnerable to social loss and isolation that are perceived as normal and expected (Berkman et al. 1993). The larger female advantages in actual and expected social support, together with the greater stress-buffering effects of social support, may thus contribute to a better survival prospect. Therefore, it is possible that sex differences in the links between social relations and mortality are smaller if additional gender-specific measures of social relations are assessed. There is evidence, however, that the number of social network ties measured by the SNI is more significantly related to disease and mortality than perceived social support (Stringhini et al. 2012). Future studies using data on both social support and biological measures are needed to determine the roles of the quality of social relationships and inflammation as psychosocial and physiological mechanisms and to test for the possibility of sex differences.

Second, the biomarkers of inflammation in the NHANES data are limited and are restricted to those closely related to circulatory diseases. It is possible that additional proinflammatory cytokines, such as those involved in angiogenesis feeding tumor growth, are more directly related to tumor progression and cancer related deaths. Preliminary evidence has been found in small clinical studies on the associations between social ties and support and some of these markers, including vascular endothelial growth factor as a cytokine fueling angiogenesis (Lutgendorf et al. 2002), tumor necrosis factor−α as a reactive oxygen cytokine (Marucha et al. 2005), and natural killer cell cytotoxicity (Lutgendorf et al. 2005), as well as IL-6 (Lutgendorf et al. 2000).

In addition, if population studies are to more precisely document the physiological effects of social isolation, they must include direct measures of the general adaptation syndrome (Selye 1956), which exacerbate diseases and conditions sharing inflammation as a common component (Esch and Stefano 2002). The biobehavioral model of sex differences further suggests that health and survival advantages for women may be conferred through the neurobiological mechanisms such as decreased HPA and sympathoadrenal activities and stress related neurohormones such as cortisol and norepinephrine under the influence of oxytocin and estrogen (Taylor et al. 2000). Future studies that include these additional biological measures are needed to explicate the neuroendocrine processes that further mediate the effects of social isolation on mortality in sex-specific contexts.

The use of prospective mortality follow-up data enhances our ability to make inferences about the effects of social isolation and inflammation on subsequent risk for mortality. The possibility of a reciprocal relationship between social isolation and inflammation, however, cannot be ruled out. For instance, animal and laboratory studies suggest that chronic inflammation is characterized by increased circulating cytokines, which affect the brain via the vagus nerve and increase illness behaviors such as withdrawal from social interactions and depression (Maier and Watkins 1998). Because the data on social isolation and inflammation in our study are from one cross-sectional survey, it is impossible to determine their

interrelationship with one another. In this sense, the evidence for the mediating role of inflammation in the social isolation and mortality link should be considered preliminary. Future investigations using longitudinal data will be particularly helpful to ascertain the physiological effects of social isolation and their joint effects on mortality through analysis of how both baseline measures and changes of social ties lead to changes in inflammation over time and, in turn, risk for death.

APPENDIX

Content and Coding of Variables in the SNI (Adapted from Ford et al. 2006)

1. Marital status:
   1 = now married, living together with someone as married
   0 = widowed, divorced, separated, or has never been married

2. Frequency of contacts: "In a typical week, how many times do you talk on the telephone with family, friends, or neighbors?" (range 0–7) and "How often do you get together with friends or relatives (per year); I mean things like going out together or visiting in each other's homes?" (range 0–73)
   1 = had ≥156 such contacts per year
   0 = had <156 such contacts per year

3. Religious attendance: "How often do you attend church or religious services (per year)?" (range 0–1,825)
   1 = four or more
   0 = less than four

4. Social organization membership: "Do you belong to any clubs or organizations such as church groups, unions, fraternal or athletic groups, or school groups?"
   1 = yes
   0 = no

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NOTES

1. Crp is an early surveillance molecule produced by the liver in response to pathogens and damaged cells, which stimulates the production of pr-inflammatory cytokines such as IL-6 (Du Clos 2000). Fibrinogen binds leukocytes regulating inflammation independently of its blood-clotting function (Davalos and Akassoglou 2012). Serum albumin is downregulated during inflammation, which conserves amino acids for positive acute-phase proinflammatory molecules.
2. For example, low serum albumin levels indicate not only catabolism associated with inflammation but also liver disease impairing its synthesis, nephrotic syndrome increasing its excretion, and malnutrition impairing protein intake.
3. Young adult respondents in NHANES III aged 20 to 39 years were included in the preliminary analysis of individual biomarkers but were excluded in the final analyses because one of the three inflammatory markers, fibrinogen, is available only for respondents aged 40 years and older. Comparison of these two sets of analyses shows no difference in the results regarding the other two biomarkers.
4. Crp level is divided into three categories that indicate increasing degrees of inflammation: normal (<1 mg/dL), low chronic (1–3 mg/dL), and high chronic (>3 mg/dL, the clinically significant high-risk group). We used the refined three-group categorization in the analysis of Crp alone and the dichotomized measure elsewhere (normal to low risk vs. high risk). We also did additional robustness analyses using age-specific and sex-specific high-risk cut points for individual markers that are statistically defined (as top quartiles for Crp and fibrinogen and bottom quartile for albumin within each subsample) and found that results are robust to the choice of cut points.

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