Social Isolation, Chronic Inflammation, and Adult Mortality*

September 16, 2011

Yang Yang[a]

Martha McClintock[b]

Michael Kozloski[c]

---

* Submission to the 2012 Annual Meetings of the Population Association of America, Session 403: Biodemographic Influences on Health and Mortality.

[a] Department of Sociology, Lineberger Comprehensive Cancer Center, and Carolina Population Center, University of North Carolina at Chapel Hill.

[b] Institute for Mind and Biology, Department of Comparative Human Development and Psychology, the University of Chicago.

[c] Department of Sociology, Center on Aging at National Opinion Research Center, the University of Chicago.

Corresponding Author:

Yang Yang, Carolina Population Center, 123 W. Franklin St., Chapel Hill, NC 27516; yangy@unc.edu .

Extended abstract

Social relationships have long been believed to be beneficial for optimal social and physical functioning and survival. A large body of literature has shown that social ties and embeddedness in social networks can protect us against illness, enhance coping with stress and illness, and improve illness outcomes, whereas social isolation and alienation can do the opposite. As the evidence for the links between social relations and morbidity and mortality continues to grow, the biophysiological mechanisms underlying these links are just beginning to be elucidated. The role of systemic inflammation in the development of chronic diseases and its impact on longevity has been increasingly recognized. To the extent that inflammation indexes chronic stress, social isolation can lead to a chronic activation of the physiological stress response and increase inflammation and consequently the risk of mortality.

While little, if any, study has directly assessed the potential mediation of the social isolation-mortality link by inflammation, there are studies that have examined the health benefits of social relations and support in regards to inflammation in the context of cardiovascular and malignant diseases that show mixed results. Cancer studies are clinically focused and restricted to small samples of female ovarian and breast cancer patients. Recent studies of population-based samples have further suggested that inflammatory markers such as CRP, albumin, and fibrinogen are predictive of overall mortality as well as mortality due to circulatory diseases and cancer. It remains to be determined whether and how social embeddedness, or the lack thereof, affects disease progression and mortality through its influence on inflammatory responses.

Using a nationally representative population-based mortality follow-up study, we extend previous research to test the hypothesis that social isolation, or the lack of social integration and social ties, leads to all-cause and chronic disease mortality by elevating chronic inflammation. Because prior

research suggests sex differences in the social isolation-inflammation link in both lab animals and human populations and in the effects of social integration on mortality, we further test the hypothesis that the role of inflammation is more pronounced for males in accounting for the relationship between social isolation and mortality. While prior studies focused on individual markers of inflammation, there is a lack of studies using multiple markers which may have different relationships to social isolation and mortality. We address this gap through the inclusion of multiple inflammatory markers to more comprehensively evaluate the specific biological pathways underlying social isolation and mortality.

The data come from the National Health and Nutrition Examination Survey (NHANES) Linked Mortality Study public-use file 1988–2006. The NHANES uses a multistage stratified sampling design and includes a representative sample of the noninstitutionalized US population, with an oversample of older persons and minorities. The study sample consists of 6,729 respondents aged 20+ who attended household interviews and clinical examinations in 1988–1994 and were eligible for mortality follow-up through 2006. We examined two leading causes of death: circulatory diseases and malignant neoplasms. The sample of 3,647 women and 3,082 men in two age groups, middle age (45–64) and old age (65+) for the follow-up period of up to 18 years, recorded 2,775 total deaths. 1,274 of these deaths were from circulatory diseases, and 603 deaths were from cancer. The measure of *social isolation* is derived from the Social Network Index (SNI) that summarizes the number of social ties (ranges 0 – 4) in four domains including marital status, religious attendance, ties with friends and family relatives, and membership in social organizations. We recoded those respondents with a score of 0 to 1 to be socially isolated. We measured *chronic inflammation* with three markers including *CRP*, *fibrinogen*, and *serum albumin*, each dichotomized into high-risk and normal groups based on clinical cutoff points or previous studies, excluding those with CRP values greater than 10 mg/dl that indicated acute infections. We also constructed a summary count index of cumulative inflammation burden that ranges from 0 – 3. We

adjusted for additional demographic and socioeconomic factors (race, education, and income), health behaviors (smoking, drinking, physical activity, and BMI), morbidity, and general health status.

We assessed the mediation role of inflammation in the social isolation and mortality links by conducting three sets of analyses: 1) a Cox proportional hazards regression analysis of the effects of social isolation on causes-specific mortality; 2) an analysis of the associations between social isolation and inflammation measured by individual markers and also by the summary index; and 3) a Cox regression analysis of the effects of social isolation and inflammation on mortality. We estimated all models by sex and age and also compared results both without and with adjustment of additional covariates. All statistical analyses were performed using Stata 10.0 and adjusted for survey design effects using sampling weights.

The results shows strong detrimental effects of social isolation on overall mortality for both sexes, with the hazard ratios (HR) being 1.84 (95% CI, 1.41-2.25) and 1.83 (95% CI, 1.53-2.19) for males and females, respectively, adjusting for age and race. The effects are significant for both age groups, but larger for older adult males. Also for males, social isolation is related to 58% and 94% higher odds of having an elevated CRP and fibrinogen, respectively. The results on the three individual markers are most significant for fibrinogen. In addition, social isolation is significantly related to a higher cumulative inflammation index for males and particularly for older males. Overall, the associations are more pronounced for males than females. Furthermore, social isolation is related to mortality independently from inflammation, but its effect is attenuated by inflammation and there are sex and age variations in this relationship. Inflammation index is highly predictive of mortality in most models including social isolation. And taking inflammation into account reduced the HRs of social isolation for both sexes of all ages in models of overall and circulatory disease mortality and eliminated the effects of social isolation on cancer mortality for males. Adjusting for other covariates also reduced

the effects of social isolation, but the further reductions after the inclusion of inflammation are evident. The degrees of mediation are generally greater for males than females and for the older than middle ages. When social isolation and inflammation are simultaneously considered, the mortality effects of a higher inflammation burden (having 2 or 3 markers at high risks) are usually greater. But for older females, the HRs of inflammation index are not significant whereas the HR of social isolation is large and strongly significant in the model of circulatory disease mortality, suggesting an independent effect of social isolation that begs further explanation. It is also interesting that neither social isolation nor a high inflammation burden is predictive of cancer mortality in females in individual age groups.

In sum, we find evidence that supports the mediation role of chronic inflammation in the social isolation-mortality link. The evidence is particularly strong and consistent for all-cause mortality across sex and age groups. Consistent with our expectation, there are sex and age differences in this relationship. The mortality effects of social isolation are greater for older males and can be attributed in part to their heightened inflammatory responses to social isolation. And a high-risk fibrinogen level may be particularly important in such responses. The findings are similar for circulatory disease-related mortality in older adults and for malignancy-related mortality in middle-aged males. The lack of significance in findings from cause-specific mortality may be due to the smaller numbers of death and, therefore, less statistical power. In the case of cancer mortality, it is also possible that different inflammatory markers, such as those involved in angiogenesis feeding tumor growth (e.g., vascular endothelial growth factor, TNF-α, and NKCC), are more directly related to tumor progression and deaths and need to be considered in future investigations.