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Social Integration and Reduced Risk of Coronary Heart Disease in Women: The Role of Lifestyle Behaviors

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Abstract

Rationale—Higher social integration is associated with lower cardiovascular mortality; however, whether it is associated with incident coronary heart disease (CHD), especially in women, and if associations differ by case fatality is unclear.

Objectives—This study sought to examine the associations between social integration and risk of incident CHD in a large female prospective cohort.

Methods and Results—76,362 women in the Nurses' Health Study (NHS), free of CHD and stroke at baseline (1992), were followed until 2014. Social integration was assessed by a simplified Berkman-Syme Social Network Index every 4 years. Endpoints included nonfatal myocardial infarction (MI) and fatal CHD. 2,372 incident CHD events occurred throughout follow-up. Adjusting for demographic, health/medical risk factors and depressive symptoms, being socially integrated was significantly associated with lower CHD risk, particularly fatal CHD. The most socially integrated women had a hazard ratio of 0.55 (95% confidence interval, 0.41–0.73) of developing fatal CHD compared to those least socially integrated (p-for-trend < 0.0001). When additionally adjusting for lifestyle behaviors, findings for fatal CHD were maintained but attenuated (p-for-trend = 0.02) whereas the significant associations no longer remained for nonfatal MI. The inverse associations between social integration and nonfatal MI risk were largely

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DISCLOSURES

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explained by health-promoting behaviors, particularly through differences in cigarette smoking; however, the association with fatal CHD risk remained after accounting for these behaviors and thus may involve more direct biological mechanisms.

Conclusions—Social integration is inversely associated with CHD incidence in women, but is largely explained by lifestyle/behavioral pathways.

Subject Terms

Cardiovascular Disease; Epidemiology; Women; Primary Prevention

Keywords

Coronary heart disease risk; marginal structural model; mediation; prospective cohort study; social integration; women and minorities; epidemiology

INTRODUCTION

Coronary heart disease (CHD) is the leading cause of death worldwide.[1] A greater understanding of relevant risk and protective factors and the mechanisms by which they may influence the development of CHD is a priority for prevention efforts. Prior work has suggested that CHD development and manifestations differ by gender;[2] moreover, results from epidemiological studies and evidence on physiological mechanisms suggest risk factors may substantially differ between men and women.[3]

Social interactions play a significant role in human health. Higher levels of social integration are posited to have salutary effects. Social integration refers to structural aspects of social support and is defined according to the characteristics of the network of people surrounding an individual and frequency of his/her interaction with this network; thus, measures of social integration generally assess the number of close contacts, group or church membership, and marital status. With regard to CHD, prior research has shown that social integration may protect against all-cause and CHD-specific mortality.[4–6] Some studies also suggested that social integration is associated with reduced risk of CHD incidence.[4, 5, 7, 8] Importantly, prior work has indicated that the relationship of social integration with physical health is weaker and more complex among women than men.[9–11] Most studies of social integration and CHD incidence have mostly been conducted either in men or within a gender-mixed population without stratification. However, because of sex-specific differences in the underlying biology, a simple assumption that the same association can be extrapolated to women could be problematic.[12, 13] A recent report from the American Heart Association also highlights the need for increased attention to the pathophysiology of heart disease in women, and emphasizes the urgency of closing the research gap in sex disparities by sex-specific examinations.[2] Given that CHD often manifests differently in women and prior findings suggesting associations with social integration and health are less robust in women, examining the relationship specifically in women is important.[14] Studies of CHD progression or mortality that have specifically focused on women suggests that social integration or its components (e.g., being married) may protect women with established CHD from deteriorating or reduce risk of a fatal secondary event. Among the limited extant

studies considering how social relationships may influence the development of CHD among women, few have focused on social integration per se, and findings have generally been inconsistent.[15–20] Measures of social integration varied widely in these studies, ranging from overall or a single aspect of social integration (e.g., marital status) to aspects of social functioning remotely related to social integration (e.g., loneliness).[15–21] As each measure may not capture the same underlying construct, it is unclear whether we should expect findings to be consistent across studies. In addition, social relationships were assessed only at study baseline in most studies, so it was not possible to account for possible changes in the relationships or their configuration over time.[17, 19] Moreover, fatal and nonfatal CHD are usually evaluated as a combined outcome; however, a prior study in men found that lower levels of social integration were primarily related to risk of fatal CHD but not to nonfatal myocardial infarction (MI).[22] Considering if associations of social integration differ with nonfatal MI versus fatal CHD in women may be valuable.

To address these limitations, we used data from a large female prospective cohort to examine the associations between social integration and risk of incident CHD in women. Based on previous literature, we hypothesized that being socially integrated would be associated with lower CHD risk, and the magnitude of effects would be stronger for fatal CHD. As prior research has suggested that both structural and functional aspects of social support might reduce CHD risk through two pathways, health behaviors and stress-related neuroendocrine mechanisms,[23] we further explored whether any observed reduction in risk could be partially explained by lifestyle behaviors.

METHODS

Study population

The Nurses' Health Study (NHS) began in 1976 when 121,701 U.S. female nurses, aged 30–55 years, returned a mailed questionnaire regarding lifestyle and medical history. Participants were followed biennially with a mailed questionnaire to update information on exposures and health outcomes. Detailed descriptions of the NHS have been previously published.[24] The institutional review board at Brigham and Women's Hospital reviewed and approved this study, and participants provided informed consent by returning questionnaires.

As the simplified Berkman-Syme Social Network Index (BSSNI)[25] was first incorporated into the 1992 questionnaire, we designated 1992 as the study baseline. To evaluate social integration in relation to incident CHD, 10,800 women with preexisting MI, angina, coronary artery bypass graft, and/or stroke at baseline were excluded. Additionally, 4,611 women who died before 1992 were excluded, as were women who did not answer the 1992 long questionnaire (short questionnaire did not have simplified BSSNI questions; n = 22,247) or had missing data on social integration measures in 1992 (n = 7,530). 151 women born before 1921 were also excluded. A total of 76,362 women with a mean age of 57.9 years (standard deviation [SD], 7.09), free from CHD and stroke at study baseline, were available for analysis.

Social integration

Information on social integration was self-reported from the NHS questionnaires every 4 years from 1992 to 2012 using the simplified BSSNI,[25] including 4 types of social connections in the measure of social integration: (1) marital status (married/having a domestic partnership, separated/divorced, widowed, single), (2) number of close friends (none, 1–2, 3–5, 6–9, 10+ friends), (3) regular attendance at religious services (never or almost never attend, <once/month, 1–3 times/month, once/week, >once/week), and (4) participation in community or volunteer groups or other organizations such as church-connected groups, self-help group, charity, and public service (none, 1–2, 3–5, 6–10, 11–15, 16+ hours/week).

At each time point, we scored each social integration component as shown in Table 1, and summed the bn.category scores to create an overall score (possible range: 0–12).[26] We then categorized the score into 4 groups as close to quartiles as we could according to level of social integration based on the distribution of scores in the sample; these quartile-based groups did not have even numbers because the level of social integration had an ordinal rather than a continuous scale. Women in the lowest group (lowest degree of social integration) comprised the referent. If the social integration information was missing in one of the five questionnaire cycles, and the answers in consecutive cycles before and after the missing value were identical, we carried forward the information reported in the prior questionnaire cycle; otherwise, we censored participants at the cycle when their information on social integration could not be determined.

Covariates

A number of self-reported demographic, health/medical, and lifestyle behavioral factors as well as depressive symptoms collected from the NHS questionnaires were considered as potential confounders or possibly as intermediate variables linking social integration and CHD. Demographic and socioeconomic status (SES) factors included age, education attainment of a participant (RN associate or bachelor/master/doctoral degree) and her husband (some high school or below/high school graduate/college graduate or above), and census-tract median family income (<65,000/≥65,000 per year). Health/medical factors consisted of history of chronic conditions (yes/no: high blood pressure, elevated cholesterol, diabetes), and parental MI history before age 60 years (yes/no). Health-related lifestyle/behavioral factors included cigarette smoking (never/>0–10/>10–20/>20 pack-years), physical activity (<3/3–8.9/9–17.9/18–26.9/≥27 metabolic equivalent tasks (METs) per week), alcohol consumption (0/0.1–4.9/5.0–14.9/≥15.0 grams per day), and alternate healthy eating index (AHEI)-2010 (in quartiles; higher quartile represents better dietary pattern),, a summarized dietary score consistently associated with lower risk of chronic disease in clinical and epidemiologic investigations,[27] and body mass index (BMI, in kg/m^2) (<18.5/18.5–24.9/25.0–29.9/≥30.0). Validation work has demonstrated high accuracy of self-reported lifestyle behaviors (e.g., physical activity, diet, and weight) and chronic diseases.[28–31] Depressive symptoms were assessed using the Mental Health Index-5 (MHI-5) subscale of the Short-Form 36 health status survey.[32] Consistent with prior work in this cohort, we categorized the MHI-5 score into four groups (86–100 [referent)] 76–85, 53–75, and 0–52, with the last category being classified as depressed mood).[33, 34] Information

on age, family income, weight, chronic medical conditions, smoking, and physical activity were updated every 2 years, and alcohol consumption and diet were updated every 4 years since 1990. We carried forward the covariate information in the prior questionnaire cycle if missing during follow-up.

CHD endpoints

The endpoint comprised incident cases of first nonfatal MI and fatal CHD (including fatal MI, CHD death, or sudden cardiac death) that occurred after the return of the 1992 questionnaire but before the end of follow-up on 5/31/2014. If a person had nonfatal MI first, which was then followed by a second event as fatal CHD at a later date, we counted the first occurrence of nonfatal MI and censored the participant afterwards.

All women who reported having a nonfatal MI were asked for permission to access their medical records and cases were confirmed by NHS study physicians blinded to the exposure information from the questionnaire. Nonfatal MI cases were confirmed according to World Health Organization criteria.[35] Women were considered probable cases if an interview or letter confirming hospitalization for the infarction was obtained but the medical records were unavailable.

Fatal CHD was classified by examining hospital records or through an autopsy, or if CHD was the most likely cause and was listed as the cause of death on the death certificate, along with evidence of prior CHD. We designated as probable CHD those cases in which CHD was the underlying cause on the death certificate but for which no medical records concerning the death were available, and included these cases in the analysis. The analyses included confirmed and probable cases. Total CHD included both nonfatal MI and fatal CHD events.

Statistical analysis

Person-years of follow-up accrued from the 1992 questionnaire return date until the date of the last returned questionnaire, CHD diagnosis, death, or end of follow-up (5/31/2014), whichever occurred first. To describe the sample and to assess the association of covariates with social integration, we evaluated means and proportions of covariates across the four levels of social integration index score at baseline. Cox proportional hazards models were used to estimate age- and multivariable-adjusted hazard ratios (HRs) and 95% confidence intervals (95% CIs) of incident CHD in women with different levels of social integration. Information on social integration and covariates was updated every 4 years over the course of follow-up. We further tested for possible linear trends across the 4 levels of social integration index score, by using a continuous variable in which participants were assigned the median value of their group. We alternatively examined the risk estimates associated with a continuous measure for a 1 standard deviation (SD) increase in raw social integration index score. The basic model adjusted for age in years. The multivariable-adjusted model 1 (MV1 model) additionally included demographic/SES characteristics: nurses' educational attainment, husband's education, and census-tract median family income. MV2 model additionally included health/medical conditions: individual's history of chronic diseases (high blood pressure, elevated cholesterol, and diabetes) and parental history of MI before

age 60 years. The MV3 model additionally adjusted for depressive symptoms. The fully-adjusted MV4 model included covariates in the MV3 model plus lifestyle/behavioral behaviors: pack-years of cigarette smoking, physical activity, alcohol consumption, cumulative AHEI-2010 score, and BMI. We tested the proportional hazards assumption by including interaction terms between social integration and calendar time or age and using likelihood ratio tests comparing nested models with and without interaction terms. The proportional hazards assumption was met in all analyses.

Time-varying confounding (i.e., when a covariate might both alter the exposure of interest but also result from it) is a potential concern that could lead to biased estimates of the associations under study. For example, in the present study, cigarette smoking in one questionnaire cycle was associated with social integration level assessed at the next questionnaire cycle, which was also associated with cigarette smoking in the following questionnaire cycle. Given the long-running nature of the cohort, we are able to address possible concerns about time-varying confounding that may bias the association in the standard methods by fitting marginal structural models (MSMs)[36] as a sensitivity analysis. We generated stabilized weights for MSMs based on the inverse of the probability of each person's social integration levels, given her prior history of social integration and all other covariates. The MSM findings did not suggest significant time-varying confounding occurring after study enrollment; therefore, we present the MSM results only briefly and present results from Cox models as our primary findings because in the absence of time-varying confounding, the Cox models are more efficient than the MSMs.

In addition to being potential confounders, it seems more plausible that some of the known CHD risk factors may in fact be on the pathway linking social integration to poor cardiovascular health. For example, socially more integrated women are more likely to participate in health-promoting behaviors, including being more physically active, quitting cigarette smoking, or stopped heavy drinking, which then enhance cardiovascular health.[37] We therefore assessed whether health-related lifestyle behaviors (cigarette smoking, physical activity, alcohol consumption, diet, and BMI) singly or jointly explained the relationships between social integration levels and the CHD risk. For the ease of interpretation, we modeled social integration score as a continuous measure for a 1 SD increase rather than categorical variables in the mediation analyses. To do so, we calculated the proportion of mediation and its 95% CI using a publicly available %Mediate macro designed by our group (http://www.hsph.harvard.edu/donna-spiegelman/software/mediate/).[38] This estimates the change in beta-coefficient per SD increase in the overall social integration index score, comparing models without and with potential intermediates when simultaneously adjusting for all other demographic and health/medical covariates as well as depressive symptoms. The mediation proportion represents the proportion of the effect of social integration on CHD incidence occurring through these potential mediators.

Additional secondary analyses were performed. First, we modeled social integration and covariates at baseline to parallel with most prior studies and to examine how much the misclassification would influence the observed association. Second, we analyzed each component of social integration separately to assess the possibility that the overall social

integration index may disguise differential effects of underlying individual components that contribute to the overall social integration measure.

All statistical procedures were performed with the use of SAS version 9.3 (SAS Institute Inc, Cary, NC). All *p*-values were 2-sided ($p < 0.05$).

RESULTS

Descriptive analyses

Age-adjusted baseline characteristics of the study participants by levels of social integration index score are presented in Table 2. Participants with higher level of social integration were generally healthier in terms of better lifestyle behaviors (e.g., higher level of physical activity; lower prevalence of current smokers), fewer chronic conditions (e.g., lower prevalence of high blood pressure and type 2 diabetes), and fewer depressive symptoms. Their husbands also had higher education level. Average time to disease presentation was 10 years (SD=5.5) for nonfatal MI and was shorter for fatal CHD (8.2 years, SD=3.9). In general, there was a gradient in the distributions of these baseline characteristics between those who remained CHD-free throughout the follow-up, those who developed nonfatal MI, and those who developed fatal CHD event during follow-up. For example, CHD-free participants were the youngest (mean of 58 years) whereas fatal CHD group was the oldest (mean of 64 years), with nonfatal MI group in between (mean of 61 years). Compared to participants who develop nonfatal MI over the 22 years of follow-up, those who developed fatal CHD had lower SES, had less healthy lifestyle behaviors, had more medical comorbidity and parental history of MI, were more likely to be depressed, and were less likely to have the highest level of social integration and more likely to have the lowest level of social integration at study baseline. However, in general, differences between women developing fatal versus nonfatal MI were smaller than those between women who did versus did not develop CHD (Online Table I).

Social integration and incident CHD

2,372 incident CHD events (1,964 nonfatal and 408 fatal) occurred during 22-year follow-up. Age-adjusted and multivariable-adjusted hazard ratios of total CHD, nonfatal MI, and fatal CHD by social integration levels are presented in Table 3. When compared with the least socially integrated women (referent), the age-adjusted HR of total CHD in most socially integrated women was 0.73 (95% CI, 0.65–0.82), with statistical evidence of a trend relationship (*p*-for-trend < 0.0001). Additional adjustment for demographic/SES characteristics yielded similar findings. Further adjustment for health/medical risk factors and depressive symptoms did not have substantial impact on the effect estimates. However, when further adjusting for health-related lifestyle behaviors, the association for total CHD incidence was substantially attenuated [most vs. least socially integrated group: HR (95% CI) = 0.92 (0.82–1.03)]. Similarly, one SD increase in total social integration score was significantly associated with 8% lower risk (95% CI, 4%–12%) of CHD in age-adjusted models; the effect estimates did not substantially change when additionally adjusted for demographic/SES risk factors, health/medical conditions, and depressive symptoms.

However, the association was no longer statistically significant after further adjusting for lifestyle-related behaviors (per 1 SD increase: HR: 0.99; 95% CI: 0.95–1.04).

Consideration of CHD outcomes separately by fatal versus nonfatal events showed that social integration was more strongly associated with the risk of fatal events. In the age-adjusted models, women in the highest level of social integration respectively had HR (95% CI) of 0.80 (0.71–0.92) and 0.47 (0.35–0.63) for nonfatal MI and fatal CHD, compared to the referent. Additional adjustment for demographic/SES risk factors, health/medical conditions, and depressive symptoms had modest impact on the effect estimates. However, in models that further adjusted for lifestyle-related behaviors, the highest level of social integration remained significantly associated with fatal CHD [HR (95% CI) = 0.68 (0.51–0.92), *p*-for-trend = 0.02] but not nonfatal MI [HR (95% CI) = 0.97 (0.85–1.10), *p*-for-trend = 0.66]; similarly, every 1 SD increase in social integration score was associated with a significantly lower risk of fatal CHD [HR (95% CI) = 0.87 (0.79–0.96)] but not nonfatal MI [HR (95% CI) = 0.99 (0.95–1.04)]. When applying stabilized weights derived from all covariates, the fully-adjusted model from MSMs conducted to address potential concerns around time-varying confounding similarly suggested that the most socially integrated women had a reduced risk of fatal CHD compared to the referent [HR (95% CI) = 0.67 (0.50–0.90)]. Given these findings, time-varying confounding does not appear to be a significant concern for conventional models in the present study.

Multiple mediation analyses considered potential mechanisms by which social integration may influence CHD risk. These results suggested cigarette smoking may be in an important pathway (Table 4). 48.7% (95% CI, 28.6%–69.1%) of the observed inverse association between social integration and incident CHD was explained by cigarette smoking ($p<0.0001$). When considering associations between types of CHD (case fatality), cigarette smoking appeared to be a stronger mediating factor for nonfatal MI than fatal CHD. Specifically, smoking accounted for 78.1% (95% CI, 10.2%–99.1%) of the association with incident nonfatal MI but only 17.9% (95% CI, 10.9%–28.1%) of the association with fatal CHD. Physical activity was another important risk factor explaining the association between social integration and CHD.

Additional analyses

In secondary analyses in which only baseline information of social integration and covariates were considered, the association patterns were consistent but the effect estimates were attenuated relative to the models that updated measures of social integration and covariates over time (Online Table II).

The results from fully-adjusted multivariable analyses of individual BSSNI components of social integration and incident CHD are presented in Table 5. Attendance at religious meetings or services was most clearly associated with reduced risk of CHD; the association was stronger for fatal CHD. Compared to women who never or almost never attended religious services, frequent attenders (at least once per week) were significantly associated with 18% (95% CI, 7%–28%), 15% (2%–26%), and 29% (3%–49%) reduction in risk of total CHD, nonfatal MI, and fatal CHD, respectively. In addition, being married or having a partnership (compared to unmarried or unpartnered women) was associated with a

significantly lower risk of fatal CHD [HR (95% CI) = 0.78 (0.63–0.97)]. We did not observe significant associations of having more close friends or participating in community/social groups more actively with risk of developing CHD. The results were highly consistent when 4 components of social integration were mutually adjusted for each other (data not shown).

DISCUSSION

We examined prospectively the association between social integration and risk of incident CHD in a large cohort of U.S. women over 22 years of follow-up. Our findings suggest that being more socially integrated is only significantly associated with lower risk of fatal CHD but not nonfatal MI after accounting for known CHD risk factors, particularly lifestyle behaviors. This study provides strong evidence that an important pathway by which social integration may reduce risk of developing nonfatal MI is via enhancing health-promoting behaviors, in particular through avoidance of cigarette smoking, long-identified as a major risk factor for CHD.[39] In contrast, the association of social integration with reduced risk of fatal CHD is less well explained by cigarette smoking and other health-related lifestyle behaviors. It highlights the possibility that social integration may protect against fatal CHD through independent mechanisms beyond traditionally assessed behavioral, psychological, and physiological pathways.

Although the underlying biological mechanisms remained to be elucidated, it has been hypothesized that one of the beneficial effects of being socially integrated on cardiovascular event development is through inflammatory pathways. Recent studies proposed that inflammation may be a key distinctive mechanism, and showed that inflammatory markers (particularly interleukin-6 and C-reactive protein) were more strongly associated with risk for fatal than for nonfatal cardiovascular events.[40–43] In line with these findings, we observed differences in baseline characteristics of demographic and socioeconomic factors, lifestyle behaviors, medical comorbidities, and depressive symptoms between those who developed nonfatal MI and fatal CHD during follow-up. More specifically, although all women were free of clinical manifestation of CHD at baseline, those who developed fatal CHD during follow-up had more factors collectively associated with higher inflammation levels than those who became nonfatal MI (Supplemental Table 1). Social integration may either directly affect inflammation or indirection by buffering toxic effects of psychosocial stress on inflammation as well as reducing cardiovascular reactivity.[44, 45] One possibility is that social integration may impact disease severity which could explain a difference between incident fatal and nonfatal cardiovascular events. In addition, the strength of the beneficial effect of social integration on cardiovascular health may depend on a person's underlying inflammatory level. For example, people with higher initial levels of inflammation may obtain greater benefit from being socially integrated, as inflammation is also associated with higher risk of fatal than nonfatal CHD events.

From a statistical standpoint, using the likelihood ratio test, inclusion of social integration to the model with traditional risk factors and depression significantly improve the model fit for risk of fatal CHD (p=0.02) but not for nonfatal MI (p=0.83), when social integration index score was modeled per standard deviation increase. Using a population attributable risk framework, 21.2% (95% CI, 2.3%–38.6%) of the fatal CHD cases that occurred in the NHS

could have been prevented if all women switched to the highest level of social integration. Such computations require assumptions of causal links which can only be established in randomized trials or other experimental approaches; nevertheless, they are helpful at conveying the benefit of evaluating social integration in the diagnosis/prognosis of CHD in addition to the traditional risk factors of cardiovascular disease. Beyond a statistical argument, however, as noted by many influential scholars, beneficial social connections may be considered a fundamental cause of disease, related to a given disease outcome through multiple pathways that can change over time.[46] For example, in the early 20th century cigarette smoking (a pathway to cardiovascular disease) was more common among higher SES individuals but that pattern has now reversed where cigarette smoking is now more common among individuals of lower SES. However, lower SES continues to be associated with higher risk of many diseases linked to cigarette smoking regardless of this change in patterning. Knowing proximate risk factors and mechanisms may be useful but cannot provide the greatest insight into those upstream factors that strongly pattern disease outcomes in an enduring manner over time. Thus, identifying risk related to an upstream factor that patterns downstream risk and protective factors enables more reliable prediction of who will be at risk, potentially facilitating more effected strategies for prevention and intervention, as well as enabling earlier identification of at-risk individuals or those who may not be immediately detectable according to standard risk factor assessment.

Our findings that smoking substantially explained the relation between social integration and risk of CHD incidence in middle-aged to old healthy women without CHD at baseline are in line with a recent study by Kreibig et al which reported that smoking explained much of the association between social integration and all-cause mortality in predominantly male patients with established CHD.[47] The different magnitudes of lifestyle behaviors mediating the associations between social integration and nonfatal MI versus fatal CHD outcomes highlight different underlying etiology. Having a high level of social integration was significantly associated with decreased risk of fatal CHD even after adjusting for lifestyle behaviors, suggesting that other pathways are also relevant, perhaps through autonomic dysregulation or other neuroendocrine mechanisms.[23] For example, social integration may act as a stress buffer, protecting people from the potentially harmful influence of chronic psychosocial distress and the potentially toxic biological stress response that can occur. These stress responses may include changes in neuroendocrine response patterns and elevating sympathetic activation which can facilitate pathogenic processes involved in CHD.[48]

Of the four aspects of social integration investigated, religious service attendance was independently associated with reduced risk of incident CHD, which was in line with prior research.[17] Religious involvement may be accompanied by direct or indirect encouragement of psychological wellbeing such as better stress management and self-esteem, as well as recommendations against specific harmful health behaviors such as smoking or alcohol consumption.[37, 49] However, associations of religious service attendance and reduced risk of incident CHD were maintained even after adjusting for health behaviors, thus, these are unlikely to fully account for the effects noted here. Our observation that married or partnered women were associated with a significantly lower risk of fatal CHD but not overall CHD incidence was consistent with a prior study.[50] One possible explanation is that married/

partnered women are more likely to have their spouse/partner at home to respond more quickly to such cardiac event than unmarried/unpartnered women who are more likely to live alone and help them seek appropriate treatment more effectively.

The strengths of the current study include its relatively homogeneous study population, large sample size, prospective data collection, lengthy follow-up, and the availability of repeated measures of social integration and a broad range of potential confounders and/or mediating factors. Potential limitations of the study should also be considered. First, it is important to note that the NHS recruited primarily married women in 1976 when the cohort was initiated. Because marital status is a part of the social integration measure, recruiting participants based on marital status may affect the representativeness of the study due to selection of a more socially integrated sample at the outset. However, marriage was the most normative experience among women at the time they enrolled in the study (1976), so cohort selection of predominantly married women is unlikely to be dramatically different from the general population; in addition, changes in marital status (such as divorce and remarriage) were relatively common throughout the follow-up. This results in greater heterogeneity in marital status over time despite some homogeneity at the start of the cohort.[51] Secondly, only frequency but not quality of the social relationships was collected in this study. A growing literature now suggests that the quality of relationships is likely as important as the quantity. If we were able to assess quality of these relationships and characterize levels of positive social integration, we might find even larger effects on CHD risk. Thirdly, behaviors and diseases that occurred prior to 1992, especially those occurring in young adulthood, may influence social integration levels reported in 1992. Because we did not have this information, unmeasured experiences or behaviors occurring before 1992 may still introduce residual confounding, even though the time-varying confounders during the follow-up period were adjusted using the MSMs. Fourthly, although a number of covariates were adjusted for in the study, residual and unmeasured confounding remains possible, as is the case with all observational studies. However, many variables such as self-reported weight, physical activity, dietary intake, and disease outcomes have been shown to be reliably and validly measured through NHS validation studies,[28, 30, 31, 52, 53] so residual confounding due to covariate misclassification should be minimal. Finally, with specific coronary endpoints, we found some evidence that social integration is more strongly associated with fatal CHD than with nonfatal MI. However, if women who are more socially isolated tend to utilize less medical service, those with silent or nonfatal MIs are likely to be missed, and this could lead to an underestimate of an effect of social integration.

In summary, our findings suggest that similar to prior work in men, being socially integrated may protect against the development of CHD in women. Our finding of an association between social integration and fatal CHD over and above the contribution of lifestyle behaviors is particularly notable given the association with nonfatal MI was evident but somewhat weaker and more strongly explained by lifestyle behaviors. This may suggest the possibility of distinct mechanisms linking social interactions to cardiovascular risk, particularly with regard to disease severity. Our results have potentially important implications for novel approaches in preventive efforts. Specifically, information on an individual's level of social integration may serve as an informative screening tool for identifying people who may be at higher risk for CHD due to low levels of integration; in

addition, an increased awareness of the role of psychological resources (or lack thereof) in CHD risk will broaden the focus of clinicians or public health practitioners beyond known CHD risk factors, and as a result may add an important new tool for reducing the population burden of CHD. Our findings suggest it will be important for future research to separate nonfatal and fatal CHD events when investigating effects of social relations or interactions. In addition, because our study was conducted in older women (mean age above 57 years at baseline), additional research is needed in younger population, as age-related differences in C-reactive protein level, a biologic risk factor for cardiovascular disease, influenced by social integration have been observed.[41] Furthermore, only structural aspects of social support were examined in this study. Perceived functional support was not collected in our study, and it would be valuable to see how structural support and perceived functional support singly and collectively influence cardiovascular health in future studies and through which specific pathways. One important implication is that psychosocial well-being may substantially influence physical health and disease pathogenesis,[54] so continued efforts to understand effects of being socially integrated and strategies for improving social integration and support are warranted.[55, 56]

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Nonstandard Abbreviations and Acronyms

CHD	coronary heart disease
NHS	Nurses' Health Study
MI	myocardial infarction
BSSNI	Berkman-Syme Social Network Index
AHEI	alternate healthy eating index
BMI	body mass index
MHI-5	5-item Mental Health Index
MSM	marginal structural model
MV	multivariable-adjusted
HR	hazard ratio

95% CI	95% confidence interval
SD	standard deviation
SES	socioeconomic status

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Novelty and Significance

What Is Known?

- Higher social integration is associated with reduced risk of incidence and mortality of coronary heart disease in men.
- Sex-specific differences have been reported for pathophysiological mechanism, clinical manifestation and clinical outcomes of heart disease.
- Whether social integration influences coronary heart disease in women is understudied.

What New Information Does This Article Contribute?

- Higher level of social integration is associated with lower risk of developing coronary heart disease in women.
- The association between social integration and risk of nonfatal events is primarily mediated by avoidance of unhealthy lifestyle behaviors, whereas the link between social integration and fatal CHD may involve different pathways.

Data from prior studies suggest higher levels of social integration is associated with lower risk of developing coronary heart disease in men, but it is unclear whether these associations are similar in women. Research conducted specifically among women is important given sex-specific differences in pathophysiology and clinical outcomes of the disease. In this study, we examined associations between social integration and incident coronary heart disease among women using data from a prospective cohort study. Information on social integration and potential time-varying confounders was obtained repeatedly throughout 22-year follow-up and adjusted for accordingly. We observed higher levels of social integration were significantly associated with lower risk of developing coronary heart disease. However, the association with incident nonfatal myocardial infarction was mainly mediated by lifestyles behaviors, whereas an independent effect of social integration was evident with fatal coronary events after accounting for behavioral mediators. These findings suggest the link between social integration and non-fatal versus fatal coronary heart disease may involve different pathways. Our findings suggest that continued efforts to understand how social integration influences coronary heart disease risk are warranted, and that improving social integration and support may provide novel targets for preventive strategies.

Table 1

Scoring criteria for social integration measure

Item	Score of 3 if:	Score of 2 if:	Score of 1 if:	Score of 0 if:
Marital status	Married, living with a partner	N/A	N/A	Widowed, separated, divorced, or single
Religious service attendance	> once/week	once/week	<once/week	Never
Number of close friends	10+	3–9	1–2	None
Group participation	11+ Hours/week	3–10 Hours/week	1–2 Hours/week	None

N/A: not available

Table 2

Age-adjusted baseline characteristics by level of social integration score in the Nurses' Health Study *

Variables	Social integration index level			
	I (lowest)	II	III	IV (highest)
Social integration range	0–5	6	7–8	9–12
Participants (n)	20,062	12,129	25,490	18,681
Age (years)	57.7±7.1	57.4±7.1	57.7±7.1	58.9±7.0
BMI (kg/m^2)	26.1±5.3	26.0±5.0	26.0±4.9	26.0±4.8
Census-track median family income (in thousands)	65.4±25.7	65.8±25.8	65.1±25.9	63.85±25.1
College graduate or above in husband education (%)	49.6	53.6	55.5	59.1
Master degree or above in nurses' education (%)	10.5	10.5	9.8	9.1
Alcohol (g/d) †	6.1±11.2	5.7±10.1	5.0±8.8	4.2±8.0
Physical activity (METs/week)	17.6±21.4	18.8±22.7	19.5±23.4	21.2±25.3
Alternative health diet index-2010 †	47.7±10.7	48.1±10.4	48.3±10.2	49.0±10.0
Current smoker (%)	21.9	15.9	11.8	7.6
High blood pressure (%)	32.9	32.4	31.9	29.6
Clinician diagnosed type 2 diabetes (%)	4.4	3.9	3.6	3.5
Elevated cholesterol (%)	43.0	43.6	44.1	43.3
Parental history of MI (%)	18.2	18.2	18.8	18.2
Depression (MHI-5 ≤ 52), %	11.9	8.6	6.7	4.2

*All characteristics are obtained from 1992 questionnaire, except if otherwise indicated. Values are mean±SD or percentages and are standardized to the age distribution of the study population.

†Information on alcohol consumption and alternative health diet index were obtained from 1990 questionnaire

Abbreviations: BMI, body mass index; METs, metabolic equivalent tasks; MI, myocardial infarction; MHI-5, 5-item Mental Health Index

Table 3

Age- and multivariable-adjusted hazard ratios for coronary heart disease and subcategories according to level of social integration index score updated over time, Nurses' Health Study, 1992–2014 (n=76,362)*

	Social integration index level				*p*-for-trend
	I (lowest)	IV	III	IV (highest)	
Total CHD					
Number of cases	782	344	728	518	
Age-adjusted Hazard Ratio (95% CI)	1.00 (referent)	0.87 (0.76–0.98)	0.84 (0.76–0.93)	0.73 (0.65–0.82)	<0.0001
Multivariable-Adjusted Hazard Ratio (95% CI) Model 1 (MV1) †	1.00 (referent)	0.87 (0.76–0.98)	0.84 (0.75–0.92)	0.73 (0.65–0.81)	<0.0001
Multivariable-Adjusted Hazard Ratio (95% CI) Model 2 (MV2) ‡	1.00 (referent)	0.88 (0.78–1.00)	0.86 (0.77–0.95)	0.76 (0.68–0.85)	<0.0001
Multivariable-Adjusted Hazard Ratio (95% CI) Model 3 (MV3) §	1.00 (referent)	0.89 (0.79–1.01)	0.88 (0.79–0.97)	0.79 (0.70–0.88)	<0.0001
Multivariable-Adjusted Hazard Ratio (95% CI) Model 4 (MV4) ‖	1.00 (referent)	0.95 (0.84–1.08)	0.97 (0.87–1.08)	0.92 (0.82–1.03)	0.17
Nonfatal MI					
Number of cases	622	285	604	453	
Age-adjusted Hazard Ratio (95% CI)	1.00 (referent)	0.90 (0.80–1.08)	0.87 (0.78–0.97)	0.80 (0.71–0.90)	0.0002
Multivariable-Adjusted Hazard Ratio (95% CI) Model 1 (MV1) †	1.00 (referent)	0.90 (0.80–1.08)	0.87 (0.77–0.97)	0.79 (0.70–0.90)	0.0002
Multivariable-Adjusted Hazard Ratio (95% CI) Model 2 (MV2) ‡	1.00 (referent)	0.91 (0.82–1.10)	0.88 (0.79–0.99)	0.83 (0.73–0.93)	0.002
Multivariable-Adjusted Hazard Ratio (95% CI) Model 3 (MV3) §	1.00 (referent)	0.92 (0.87–1.17)	0.90 (0.80–1.01)	0.84 (0.74–0.96)	0.007
Multivariable-Adjusted Hazard Ratio (95% CI) Model 4 (MV4) ‖	1.00 (referent)	0.97 (0.84–1.12)	0.98 (0.88–1.10)	0.97 (0.85–1.10)	0.66
Fatal CHD					
Number of cases	160	59	124	65	
Age-adjusted Hazard Ratio (95% CI)	1.00 (referent)	0.73 (0.54–0.99)	0.72 (0.57–0.91)	0.47 (0.35–0.63)	<0.0001
Multivariable-Adjusted Hazard Ratio (95% CI) Model 1 (MV1) †	1.00 (referent)	0.73 (0.54–0.99)	0.72 (0.57–0.91)	0.47 (0.35–0.62)	<0.0001
Multivariable-Adjusted Hazard Ratio (95% CI) Model 2 (MV2) ‡	1.00 (referent)	0.76 (0.56–1.03)	0.76 (0.60–0.96)	0.51 (0.38–0.68)	<0.0001
Multivariable-Adjusted Hazard Ratio (95% CI) Model 3 (MV3) §	1.00 (referent)	0.79 (0.58–1.07)	0.79 (0.62–1.00)	0.55 (0.41–0.73)	<0.0001
Multivariable-Adjusted Hazard Ratio (95% CI) Model 4 (MV4) ‖	1.00 (referent)	0.88 (0.65–1.19) 9	0.93 (0.73–1.19) 9	0.68 (0.51–0.92)	0.02

*Social integration and all covariates were time-updated except as noted

† MV1 adjusted for age (continuous), husband's highest education reported in 1992 (some high school or below, high school graduate, or college graduate and above), nurse's academic degree reported in 1992 (RN associate or bachelor, master, or doctoral degree), and census-tract median family income (<65,000, ≥65,000 per year).

‡ MV2 adjusted for variables in MV1 plus history of hypertension (yes, no), diabetes (yes, no), high cholesterol (yes, no), and parental history of myocardial infarction < 60 years old (yes, no)

§ MV3 adjusted for variables in MV2 plus depressive symptoms (5-item Mental Health Index score of 86–100, 76–85, 53–75, 0–52)

// MV4 adjusted for variables in MV3 plus pack-years of cigarette smoking (never, >0–10, >10–20, >20), alcohol drinking (0, 0.1–4.9, 5.0–14.9, or ≥15.0 grams per day), physical activity (<3, 3–8.9, 9–17.9, 18–26.9, or ≥27 METs/wk), alternative health diet index-2010 dietary score (in quartiles), and body mass index (<18.5, 18.5–24.9, 25.0–29.9, or ≥30)

Abbreviations: CHD, coronary heart disease; MI, myocardial infarction

Table 4

The mediation proportion for the effect of social integration index score (per standard deviation increase) on CHD risk explained by health-related lifestyle behaviors, Nurses' Health Study, 1992–2014 (n=76,362)*

Mediation proportion (%)	HR (95% CI)	HR (95% CI) adjusted for each potential mediator	Percent mediated (95% CI)
Total CHD			
Cigarette smoking	0.91 (0.87–0.95)	0.95 (0.92–0.99)	48.7 (28.6–69.1)
Physical activity	0.91 (0.87–0.95)	0.93 (0.89–0.97)	22.1 (13.4–34.2)
Alcohol drinking	0.91 (0.87–0.95)	0.91 (0.87–0.94)	Not mediated
Diet	0.91 (0.87–0.95)	0.92 (0.88–0.95)	7.8 (4.4–13.4)
BMI	0.91 (0.87–0.95)	0.91 (0.88–0.95)	1.8 (0.6–5.1)
Nonfatal MI			
Cigarette smoking	0.94 (0.90–0.98)	0.99 (0.94–1.03)	78.1 (10.2–99.1)
Physical activity	0.94 (0.90–0.98)	0.96 (0.92–1.00)	27.3 (11.0–53.2)
Alcohol drinking	0.94 (0.90–0.98)	0.94 (0.90–0.98)	Not mediated
Diet	0.94 (0.90–0.98)	0.95 (0.91–0.99)	10.9 (4.4–24.5)
BMI	0.94 (0.90–0.98)	0.94 (0.90–0.98)	Not mediated
Fatal CHD			
Cigarette smoking	0.77 (0.70–0.84)	0.80 (0.73–0.88)	17.9 (10.9–28.1)
Physical activity	0.77 (0.70–0.84)	0.80 (0.73–0.88)	17.2 (11.2–25.5)
Alcohol drinking	0.77 (0.70–0.84)	0.77 (0.70–0.85)	2.1 (0.8–5.4)
Diet	0.77 (0.70–0.84)	0.78 (0.71–0.85)	4.6 (2.3–8.8)
BMI	0.77 (0.70–0.84)	0.78 (0.71–0.85)	5.6 (3.3–9.3)

*The base model adjusted for age (continuous), husband's highest education reported in 1992 (some high school or below, high school graduate, or college graduate and above), nurse's academic degree reported in 1992 (RN associate or bachelor, master, or doctoral degree), and census-tract median family income (<65,000, ≥65,000 per year), history of hypertension (yes, no), diabetes (yes, no), high cholesterol (yes, no), parental history of myocardial infarction < 60 years old (yes, no), and depressive symptoms (5-item Mental Health Index score of 86–100, 76–85, 53–75, 0–52). Each individual mediation test compared models with and without additional potential mediating variables listed on the left column. One standard deviation of social integration score equaled to 2.26 points.

Abbreviations: CHD, coronary heart disease; MI, myocardial infarction; BMI, body mass index; HR, hazard ratio; CI, confidence interval

Table 5

Individual component of social integration index on CHD incidence, Nurses' Health Study, 1992–2014*

Social integration components	Total CHD			Nonfatal MI			Fatal CHD		
	# cases	HR	(95% CI) †	# cases	HR	(95% CI) †	# cases	HR	(95% CI) †
Religious attendance									
almost never	608	1.00	(referent)	487	1.00	(referent)	121	1.00	(referent)
1–3/month-<once/month	388	0.97	(0.85–1.10)	320	0.98	(0.84–1.13)	68	0.94	(0.68–1.24)
once/wk	955	0.97	(0.87–1.07)	802	1.00	(0.89–1.12)	153	0.84	(0.66–1.07)
>once/wk	398	0.82	(0.72–0.93)	336	0.85	(0.74–0.98)	62	0.71	(0.51–0.97)
Community group participation per week									
0 hr	858	1.00	(referent)	682	1.00	(referent)	176	1.00	(referent)
1–2 hrs	625	0.95	(0.86–1.05)	528	0.99	(0.88–1.11)	97	0.81	(0.62–1.04)
3–10 hrs	718	1.00	(0.90–1.11)	609	1.04	(0.93–1.16)	109	0.84	(0.66–1.08)
11+ hrs	121	1.10	(0.90–1.34)	101	1.13	(0.91–1.39)	20	1.02	(0.64–1.63)
Number of close friends									
0	52	1.00	(referent)	41	1.00	(referent)	11	1.00	(referent)
1–2	370	0.94	(0.70–1.25)	303	0.95	(0.68–1.31)	67	0.91	(0.48–1.73)
3–9	1493	1.02	(0.77–1.35)	1237	1.03	(0.75–1.41)	2656	1.01	(0.55–1.85)
10+	410	1.02	(0.76–1.37)	342	1.04	(0.75–1.44)	68	0.96	(0.50–1.84)
Marital status									
Unmarried or unpartnered	765	1.00	(referent)	606	1.00	(referent)	159	1.00	(referent)
Married or partnered	1597	0.94	(0.85–1.03)	1353	0.98	(0.88–1.08)	244	0.78	(0.63–0.97)

*Social integration and all covariates were time-updated except as noted

†Model adjusted for age (continuous), husband's highest education reported in 1992 (some high school or below, high school graduate, or college graduate and above), nurse's academic degree reported in 1992 (RN associate or bachelor, master or doctoral degree), and census-tract median family income (<65,000, ≥65,000 per year), history of hypertension (yes, no), diabetes (yes, no), high cholesterol (yes, no), parental history of myocardial infarction < 60 years old (yes, no), depressive symptoms (5-item Mental Health Index score of 86–100, 76–85, 53–75, 0–52), pack-years of cigarette smoking (never, >0–10, >10–20, >20), alcohol drinking (0, 0.1–4.9, 5.0–14.9, or ≥15.0 grams per day), physical activity (<3, 3–8.9, 9–17.9, 18–26.9, or ≥ METs/wk), alternative health diet index-2010 dietary score (in quartiles), and body mass index (<18.5, 18.5–24.9, 25.0–29.9, or ≥30)

Abbreviations: CHD, coronary heart disease; MI, myocardial infarction; HR, hazard ratio; CI, confidence interval