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Associations of chronic individual- and neighborhood-level stressors with incident coronary heart disease: The Multi-Ethnic Study of Atherosclerosis

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Abstract

Background—Several individual-level stressors have been linked to incident coronary heart disease (CHD), but less attention has focused on the influence of neighborhood-level sources of stress. In this study we examined prospective associations of individual- and neighborhood-level stressors with incident CHD.

Methods—Multi-Ethnic Study of Atherosclerosis participants aged 45–84 years at baseline (2000–2002) with complete data were included in the analyses (n=6678 for individual-level and n=6105 for neighborhood-level stressors). CHD was defined as nonfatal myocardial infarction, resuscitated cardiac arrest, or CHD death. Median follow-up was 10.2 years. Multivariable Cox proportional hazards models were fitted to estimate associations of individual- and neighborhood-level stressors (categorized into approximate tertiles) with incident CHD.

Results—Higher reported individual-level stressors were associated with higher incident CHD. Participants in the high individual-level stressor category had 65% higher risk of incident CHD (95% confidence interval (CI): 1.23, 2.22) than those in the low category after adjusting for sociodemographics (P for trend = 0.002). This association weakened but remained significant with

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COMPETING INTERESTS

None declared.

further adjustment for behavioral and biological risk factors. There was a nonlinear relationship between neighborhood-level stressors and incident CHD (P for quadratic term=0.01). Participants in the medium category had 49% higher CHD risk (95% CI: 1.06, 2.10) compared with those in the low category; those in the high category had only 27% higher CHD risk (95% CI: 0.83, 1.95). These associations persisted with adjustment for risk factors and individual-level stressors.

Conclusion—Individual-level and neighborhood-level stressors were independently associated with incident CHD, though the nature of the relationships differed.

Keywords

stress; coronary heart disease; neighborhoods

INTRODUCTION

Several prospective studies have examined relationships of chronic stressors with incident coronary heart disease, but findings are mixed.^{1–11} One explanation for differing results is heterogeneity in CHD definitions. Some studies include angina pectoris in their definition. However, given that angina is diagnosed based on self-report of symptoms, it is possible that individuals who report higher stress may also report more symptoms. For example, two studies found significant associations between perceived stress and incident angina pectoris but no association with incident acute myocardial infarction.^{4, 6}

Another explanation for inconsistent findings is that different types of stressors may differentially impact CHD risk. Studies typically use measures that examine individual-level stressors relating to occupation, close relationships, or life events that do not take into account the chronicity of the exposure.^{1, 2, 8, 10, 11} In addition, features of other environments such as neighborhood environments that may operate as stressors are less commonly assessed. Exposure to certain neighborhood conditions such as poor safety or lack of social cohesion may elicit a physiologic stress response, resulting in higher CHD risk via increased inflammation, hypertension, visceral adiposity, and the development of poor health behaviors to cope with the stressor.^{12, 13} While census-derived indicators of socioeconomic position (SEP) have been examined as proxies for specific features of neighborhood environments that may be stressful,^{14–17} few have investigated the relationship between direct measures of neighborhood stressors and incident CHD.¹⁸

We used the Multi-Ethnic Study of Atherosclerosis (MESA) to investigate associations of individual- and neighborhood-level chronic stressors with incident CHD. We also explored whether these associations varied by race/ethnicity or gender. We built on the existing literature by using a clinically adjudicated measure of CHD events (myocardial infarction, resuscitated cardiac arrest, or CHD death) and by assessing the impact of neighborhood-level sources of stress on CHD risk.

METHODS

Study Population

MESA is an observational cohort study designed to examine the determinants of subclinical cardiovascular disease in adults aged 45–84 years. Participants free of clinical cardiovascular disease at baseline were recruited from six field centers (New York, New York; Baltimore City and County, Maryland; Forsyth County, North Carolina; St. Paul, Minnesota; Chicago, Illinois; and Los Angeles County, California) between 2000 and 2002. Random population samples were selected at each field center using lists of area residents. Additional details are provided elsewhere.¹⁹ Of the selected persons deemed eligible after screening, 59.8% participated in the study. Institutional review board's approval was obtained at each site and all participants gave informed consent. Four additional examinations have been completed since baseline: exam 2 (2002–2004), exam 3 (2004–2005), exam 4 (2005–2007) and exam 5 (2010–2012).

Stressors

Exposure to chronic stressors resulting from individual circumstances (henceforth referred to as individual-level stressors) was assessed using the Chronic Burden scale, measured at baseline.²⁰ Participants were asked whether or not they had ongoing, financial, job, relationship, or health-related (both self and someone close to the participant) problems lasting over 6 months. In addition, they were asked to indicate how stressful the problems were on a scale ranging from 1 (not very stressful) to 3 (very stressful). A chronic burden score was created by summing the number of domains in which moderate to severe stress was reported. Possible scores ranged from 0 to 5 and were modeled categorically in approximate tertiles as high (2 or more), medium (1), and low (0; referent).

Information on neighborhood characteristics was collected as part of the MESA Neighborhood study, an ancillary study designed to assess neighborhood conditions of potential relevance to cardiovascular disease. Census tracts were used as proxies for neighborhoods. The analytical sample consisted of a median of 2 participants per neighborhood. In addition to MESA participants, a sample of 5,988 individuals (recruited between January and August 2004) residing in the same neighborhoods as MESA participants were asked to rate several aspects of their neighborhood via a telephone survey. Non-participants of MESA were sampled at 3 of the 6 sites in order to reduce the potential for same-source bias and to obtain a more valid measure of the neighborhood characteristics of interest.

Exposure to chronic stressors resulting from neighborhood exposures (henceforth referred to as neighborhood-level stressors) was measured using a combination of scales on neighborhood safety (a composite of three self-reported questions on safety and violence), neighborhood social cohesion (a composite of five self-reported questions on feelings of mutual trust and solidarity with neighbors), and aesthetic quality (a composite of three self-reported questions relating to noise, presence of trash and litter, and overall neighborhood attractiveness). In order to maximize the use of available data, conditional empirical Bayes estimation was used to derive measures of neighborhood stressors by pooling MESA

participant and non-participant data (where available). Models were conditioned on site and adjusted for data source (MESA or non-MESA), age, and gender. The use of the Empirical Bayes estimates reduces the possibility of same source bias and produces more valid neighborhood measures than simple averages even at sites where non-participants were not sampled. This is because responses are pooled across multiple respondents within a tract. In addition, the data are smoothed, meaning they borrow information from other census tracts to improve the estimates of neighborhood characteristics for unreliable tracts (e.g., if there is poor agreement between members of the census tract or there is a small sample size within a tract). Additional details on the development of the scales are provided elsewhere.²¹ The combined scale had values ranging from 3 to 15, with higher scores indicating higher levels of neighborhood stress. In validation testing, the scale demonstrated high internal consistency (Cronbach's alpha = 0.89), and it has been used previously as a measure of neighborhood-level stress.²² Exposure to neighborhood-level stressors was categorized into tertiles as low (scores < 3.78), medium (scores 3.78 – 4.56), and high (scores > 4.56).

Fatal and nonfatal incident CHD

Incident CHD was defined as myocardial infarction, resuscitated cardiac arrest, and CHD death. MESA uses a standard adjudication protocol to classify events.¹⁹ Every 9–12 months, participants (or when necessary their proxies) are contacted to inquire about hospital admissions, cardiovascular diagnoses, and deaths. Possible vascular events are abstracted from hospital records and sent for review and classification by an independent adjudication committee. Outcome follow-up data were available for events occurring on or before and adjudicated through December 31, 2011 (median follow-up 10.2 years).

Covariates

Sociodemographic variables including age, sex, race or ethnicity (non-Hispanic White, non-Hispanic Black, Chinese, or Hispanic), education (categorized as less than high school, high school graduate, some college, and college or more completed), and income (modeled in quartiles) were covariates in these analyses. Diabetes was defined as having a fasting glucose ≥ 7.0 mmol/L (126 mg/dl) or being on insulin or oral hypoglycemic medications²³. Seated, resting blood pressure was measured 3 times; systolic blood pressure was modeled continuously based on the average of the final two readings. Plasma total cholesterol was measured by the cholesterol-oxidase method and modeled continuously. Use of blood pressure-lowering and any lipid-lowering medication were each self-reported.²⁴ BMI (kg/m^2) was modeled continuously using measured height (in m) and weight (in kg). Physical activity was categorized as high (≥ 1000 MET-minutes per week of energy expenditure from recreational activity), intermediate (< 1000 MET-minutes per week), or physically inactive based on the 2008 Physical Activity Guidelines for Americans²⁵. Cigarette smoking and alcohol use were dichotomized as current vs. not current. Neighborhood poverty was defined as the percent of the population living below the U.S. Census Bureau-defined poverty threshold.²⁶

Statistical analysis

Baseline participant characteristics were compared across tertiles of individual- and neighborhood-level chronic stressors. The bivariate associations of neighborhood-level and individual-level stressors were also examined.

Age- and sex-adjusted incidence rates of CHD per 10 000 person-years were estimated by tertiles of each chronic stress measure using Poisson regression.²⁷ Cox proportional hazards regression models were used to estimate hazard ratios and 95% confidence intervals (CI) of incident CHD associated with stressors after adjusting for covariates. Marginal Cox proportional hazards regression models were estimated using a robust sandwich estimator to account for any residual correlations for individuals residing in the same census tract.^{28, 29} Marginal models were used instead of multilevel models because they are more robust for the estimation of associations of neighborhood exposures with outcomes (i.e., fixed effects of neighborhood characteristics), as is the goal in this study.^{30, 31} Time in the proportional model was the follow-up time from the date of the baseline exam until the date of the first CHD event (for cases) or to the last contact for outcome information (for non-cases). The proportional hazards assumption was tested by including time-covariate interactions in final models; there was no evidence of violation. The first model adjusted for age, race/ethnicity, gender, education, income, marital status, field center, and neighborhood poverty (as a confounder for the neighborhood stressor measure). The second model further adjusted for total cholesterol, lipid-lowering medication use, systolic blood pressure, blood pressure-lowering medication use, diabetes, body mass index, physical activity, current alcohol use, and current cigarette smoking as potential mediators. A final model was generated for each stress measure that further adjusted for the other stress measure. We also explored whether associations of individual- and neighborhood-level stressors with incident CHD varied by race/ethnicity or gender in sociodemographic-adjusted models.

The primary analyses were based on the 6678 and 6105 participants with complete data on the individual-level and neighborhood-level stressors at baseline, respectively. Multiple imputation (five times) by chained equations was used to impute missing values on other covariates.³² From the sample of 6678 (6105 for the neighborhood-level stress analyses) participants who were included in the primary analyses, 245 (228) were missing data on sociodemographic characteristics, and 49 (42) were missing data on behavioral or biological risk factors. Sensitivity analyses were conducted to assess the robustness of findings using data on participants with complete information (n=6384 for individual-level stressor analyses and n=5835 for neighborhood-level stressor analyses). All analyses were conducted using SAS 9.4 (SAS Institute, Inc., Cary, North Carolina).

RESULTS

Younger participants, women and unmarried participants were more likely to report higher individual level stressors (Table 1). Black participants were more likely than Whites to fall into the highest stressor category; Chinese participants were less likely to report high levels of individual stressors. Individuals in the high stressor category had higher levels of educational attainment; there were no differences in income. All behavioral and biological

risk factors were worse for those in the high stressor category compared with the low category.

Participants who reported high levels of neighborhood-level stressors were more likely to be men, less likely to be married, and more likely to be Black. They also had lower education and income levels. Risk factor levels were less consistently related to categories of neighborhood-level stressors than to individual-level stressors. Figure 1 shows that the distribution of neighborhood-level stressor categories was approximately equal across level of individual-level stressors, suggesting a low correlation between these measures.

A total of 279 events occurred over the follow-up period (Table 2). Age- and sex-adjusted incidence rates were higher among participants in the high individual-level stressor category (65.2 per 10,000 person-years) compared with participants in the low individual-level stressor category (36.7 per 10,000 person-years). After adjusting for sociodemographic characteristics, participants in the high individual-level stressor category had 65% (95% Confidence Interval (CI): 1.23, 2.22) higher risk of incident CHD compared with participants in the low category. The association attenuated with adjustment for behavioral and biological risk factors (Hazard Ratio (HR): 1.51; 95% CI: 1.12, 2.04) but remained significant. Findings were unchanged with further adjustment for neighborhood-level stressors.

For neighborhood-level stressors, age- and sex-adjusted incidence rates of CHD were highest for participants in the medium category (45.5 per 10,000 person-years). Participants in the high category were 1.27 times (95% CI: 0.83, 1.95) more likely to develop CHD compared with those in the low category, while those in the medium category were 1.49 times (95% CI: 1.06, 2.10) more likely to develop CHD. These associations persisted following adjustment for risk factors and individual-level stressors. To evaluate a potential nonlinear relationship between neighborhood-level stressors and incident CHD, we estimated the hazard ratio for incident CHD adjusting for neighborhood-level stressors modeled continuously with a quadratic term. Consistent with our finding that the medium category were most likely to develop CHD, both the coefficient for the linear term ($\beta = 1.82$; $P = 0.006$) and the quadratic term ($\beta = -0.19$; $P = 0.01$) were significant in fully adjusted models.

Associations of individual- and neighborhood-level stressors with incident CHD did not vary significantly by race/ethnicity (P for interaction = 0.4) or gender (P for interaction = 0.62). In addition, all findings were similar when analyses were restricted to those with complete data on all covariates (not shown).

DISCUSSION

We observed that higher exposure to individual-level chronic stressors was associated with greater incident CHD independent of sociodemographic characteristics. By contrast, there was a non-graded association between neighborhood-level stressors and incident CHD where participants in the high and medium stressor tertiles had higher incident CHD than

those in the low tertile. These associations were independent of all covariates, including exposure to individual-level stressors.

Our findings are consistent with several previous studies showing higher exposure to individual-level stressors is associated with higher incident CHD. Several studies have shown higher job strain is associated with higher CHD risk.^{9, 11, 33} Negative aspects of close relationships and general work- and home-related stressors have also been significantly associated with incident CHD. There are also studies that have shown no associations with incident CHD, including studies of major life events and more general stressors.^{1, 3-6} Differences in the way stress was measured may account for some of these mixed findings. One advantage of our measure of individual-level stressors over the majority of those used in other studies is that participants were asked not only whether they had been exposed to the particular stressor, but also whether it was chronic (lasting more than 6 months) and how stressful each chronic problem was to them. Thus, this measure was likely better able to capture the chronicity and the appraisal of each stressor, both factors that influence the impact of a stressor on health.³⁴ It has been argued that previously reported associations may have been biased because of the inclusion of angina pectoris, a condition that is more dependent on self-reported symptoms, in the definition of CHD.⁴⁻⁶ However, we excluded angina pectoris from our definition of CHD and still found significant associations, suggesting this type of bias was not likely an issue in our study.

In contrast to the graded relationship we found for individual-level stressors and incident CHD, we found a nonlinear relationship between neighborhood-level stressors and CHD risk. As with our finding that the distribution of neighborhood-level stressor categories were not related to individual-level stressor categories, this different pattern of association suggests this measure may be capturing a different type of stressor than what is being assessed in the individual-level chronic burden scale. While multiple studies have examined associations of neighborhood-level socioeconomic position with incident CHD,¹⁴⁻¹⁷ only one to our knowledge has examined relationships between direct measures of neighborhood-level stressors with incident CHD.¹⁸ In contrast with our findings, a study of neighborhood violent crime and incident CHD in Stockholm County, Sweden found a graded association such that men and women living in areas with higher crime rates were more likely to develop CHD than those living in low crime areas. Reasons for these different findings include the geographic location of participants (the U.S. versus Sweden) and the use of a self-reported versus objective measure of the neighborhood social environment. Further work is needed to better understand how different levels and types of neighborhood-level stressors influence CHD risk. An important issue is whether the associations we observed with neighborhood stressors are confounded by other aspects of the neighborhood physical environment not captured by neighborhood poverty. The apparent non-linear effect also needs to be confirmed in other analyses, and if verified, further explored.

There are several behavioral and biological pathways that may link exposure to individual- and neighborhood-level stressors to incident CHD. Individuals may adopt certain behaviors as a result of chronic exposure to psychosocial stressors that are related to CHD risk, including cigarette smoking, high fat and carbohydrate food consumption, physical inactivity, and heavy alcohol use.^{35, 36} In addition, chronic stress may result in physiologic

dysregulation of the sympathetic nervous system and the HPA axis, which in turn may increase CVD risk via inflammation, endothelial dysfunction, and atherosclerosis.^{34, 37–39} In our study, the relationship between individual-level stressors and incident CHD weakened with adjustment for several behavioral and biological risk factors, supporting the role of these factors as mediators of the relationship between stress and CHD. However, associations of neighborhood-level stressors with incident CHD remained largely unchanged after adjusting for these risk factors.

This study has important strengths. A key strength is the use of a well-defined and clinically adjudicated measure of CHD. Another is that we evaluated the impact of both individual- and neighborhood-level stressors on incident CHD. One notable limitation of this study is that we were not able to account for other factors that may impact the extent to which a stressor is actually perceived as stressful. The relationship between stress and health is influenced not only by the presence of a stressor, but also the appraisal of the stressor and the resources available to cope with it.³⁴ Our measure of individual-level stressors was likely better able to capture appraisal of each stressor by asking how stressful each chronic problem was, but our measure of neighborhood-level stressors did not. In addition, while we did account for individual- and neighborhood-level socioeconomic indicators that may influence resources available to cope with stressors, there are likely other factors that we did not measure that could influence coping ability.

In summary, we found evidence of a graded association of individual-level stressors with incident CHD, and a nonlinear relationship of neighborhood-level stressors with incident CHD, each independent of sociodemographic characteristics. A better understanding of the differential contributions of individual- and neighborhood-level sources of stress may help guide efforts to develop targeted interventions to promote stress management and lower CVD risk.

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What is already known on this subject

Several studies have examined associations of individual-level sources of stress with coronary heart disease risk, but findings are mixed. Few studies have investigated the contributions of neighborhood-level sources of stress to incident coronary heart disease.

What this study adds

This study uses a well-defined, adjudicated measure of incident coronary heart disease to show that both individual- and neighborhood-level sources of stress are associated with coronary heart disease risk independent of sociodemographic characteristics.

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Figure 1.
Distribution of neighborhood-level stressor categories by individual-level stressor categories

Table 1

Selected baseline participant characteristics

	Individual-level stressors (n=6678)			Neighborhood-level stressors (n=6105)		
	High (n=1576)	Medium (n=1813)	Low (n=3289)	High (n=2003)	Medium (n=2087)	Low (n=2015)
Age, years, mean (SE)	59.3 (0.2)	62.4 (0.2)	63.3 (0.2)	61.3 (0.2)	62.6 (0.2)	61.9 (0.2)
Men, %	35.9	44.3	54.4	44.6	47.3	50.5
Married, %	53.6	59.8	64.8	52.0	60.9	70.9
Race/ethnicity, %						
Non-Hispanic White	41.4	43.8	34.4	23.0	37.6	58.0
Chinese	6.3	8.2	16.8	8.6	18.2	7.3
Non-Hispanic Black	32.0	25.8	26.1	33.2	23.5	26.2
Hispanic	20.3	22.2	22.7	35.2	20.7	8.5
Education, %						
< High school diploma	15.0	15.9	20.9	27.0	17.2	5.9
High school diploma	16.7	18.0	18.9	20.4	17.2	17.0
Some college	31.7	29.7	26.3	27.7	26.5	31.2
College degree or more	36.6	36.4	33.9	24.9	39.1	45.9
Income, %						
<\$16,000	20.6	17.3	19.4	25.1	19.1	8.4
\$16,000 – \$34,999	26.1	24.4	26.4	33.4	25.0	18.3
\$35,000 – \$74,999	34.4	34.2	31.3	30.3	32.1	38.7
\$75,000	18.9	24.1	22.9	11.2	23.8	34.6
Neighborhood poverty, %	-	-	-	25.7	14.2	6.6
Current smoking, %	16.8	13.1	11.3	16.4	10.9	10.6
Current alcohol use, %	56.3	59.2	53.2	52.1	56.3	61.4
Physical activity, %						
High	42.6	45.5	46.7	42.4	47.3	48.7
Intermediate	32.3	32.0	31.2	31.0	30.0	33.3
None	25.1	22.5	22.1	26.6	22.7	18.0
Diabetes, %	15.4	12.2	11.5	14.1	11.6	10.0
Systolic blood pressure, mm Hg, mean (SE)	126.0 (0.6)	126.1 (0.5)	127.0 (0.4)	126.1(0.5)	125.5 (0.5)	126.6 (0.5)

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	Individual-level stressors (n=6678)			Neighborhood-level stressors (n=6105)		
	High (n=1576)	Medium (n=1813)	Low (n=3289)	High (n=2003)	Medium (n=2087)	Low (n=2015)
Blood pressure-lowering medication use, %	39.2	37.1	36.2	38.2	35.6	36.3
Total cholesterol, mmol/L, mean (SE)	5.0 (0.02)	5.1 (0.02)	5.0 (0.02)	5.0 (0.02)	5.0 (0.02)	5.0 (0.02)
Lipid-lowering medication use, %	15.7	15.5	16.7	14.5	16.9	17.4
Body mass index, kg/m ² , mean (SE)	29.5 (0.2)	28.4 (0.1)	27.7 (0.09)	28.9 (0.1)	27.8 (0.1)	28.3 (0.1)

* SE = standard error

Table 2

Age- and sex-adjusted rates and multivariable adjusted hazard ratios (95% confidence intervals) for associations of chronic individual- and neighborhood-level stressors with incident coronary heart disease

	No. of Events	Rate per 10,000person-years	HR	95% CI	HR	95% CI	HR	95% CI	
			Model 1*			Model 2†			Model 3‡
Chronic individual stressors									
High	75	65.2	1.65	(1.23–2.22)	1.51	(1.12–2.04)	1.51	(1.12–2.03)	
Medium	73	41.3	1.10	(0.88–1.38)	1.08	(0.81–1.45)	1.09	(0.82–1.46)	
Low	131	36.7	1.00	(ref)	1.00	(ref)	1.00	(ref)	
<i>P</i> for trend			0.002			0.01		0.01	
Neighborhood stressors									
High	74	40.4	1.27	(0.83–1.95)	1.21	(0.80–1.84)	1.21	(0.79–1.84)	
Medium	95	45.5	1.49	(1.06–2.10)	1.47	(1.05–2.05)	1.50	(1.07–2.10)	
Low	74	36.5	1.00	(ref)	1.00	(ref)	1.00	(ref)	
<i>P</i> for trend			0.30			0.42		0.43	

* Adjusted for age, race/ethnicity, gender, education, income, marital status, field center, and neighborhood poverty (for the neighborhood stressors only)

† Adjusted for Model 1, total cholesterol, lipid-lowering medication use, systolic blood pressure, blood pressure-lowering medication use, diabetes, body mass index, physical activity, current alcohol use, and current cigarette smoking

‡ Adjusted for Model 2 and neighborhood stressors (for in the individual stressors model) or individual stressors (for the neighborhood stressors model)