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Hopelessness, depressive symptoms and carotid atherosclerosis in women: the Study of Women's Health Across the Nation (SWAN) Heart Study

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Abstract

Background and Purpose—Depression and hopelessness are associated with increased cardiovascular disease (CVD) morbidity and mortality; however, few studies have compared these constructs early in the atherogenic process, particularly in women or minorities.

Methods—This cross-sectional study examined associations of hopelessness and depressive symptoms with carotid artery intimal-medial thickening (IMT) in 559 women (62% white, 38% African-American; mean age, 50.2±2.8 years) without evidence of clinical CVD from the Study of Women's Health Across the Nation (SWAN) Heart Study. Hopelessness was measured by 2 questionnaire items; depressive symptoms were measured with the 20-item Center for Epidemiologic Studies Depression (CES-D) Scale. Mean and maximum IMT were assessed via B-mode ultrasonography of the carotid arteries.

Results—Increasing hopelessness was significantly related to higher mean (p=.0139) and maximum IMT (p=.0297) in regression models adjusted for age, race, site, income, and CVD risk factors. A weaker pattern of associations was noted for depressive symptoms and mean (p=.1056) and maximum IMT (p=.0691). Modeled simultaneously in a risk factor-adjusted model, hopelessness was related to greater mean IMT (p=.0217) and maximum IMT (p=.0409) but depressive symptoms were unrelated to either outcome (p>.4). No interactions with race or synergistic effects of depressive symptoms and hopelessness were observed.

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Conclusions—Among middle-aged women, higher levels of hopelessness are associated with greater subclinical atherosclerosis independent of age, race, income, CVD risk factors, and depressive symptoms.

Keywords

atherosclerosis; carotid intimal medial thickness; depression; Women & Minorities; Hopelessness

Depression or depressive symptoms have been associated with increased risk of cardiovascular disease (CVD) morbidity and mortality, though evidence is not unequivocal.[1] Recent investigations have examined depression or depressive symptoms in relation to subclinical CVD, including aortic and coronary calcification, carotid artery intimal-medial thickening, plaque prevalence, pulse wave velocity and endothelial function[2] with mixed results.[3–6] Reasons for these inconsistent findings are unclear.

Increasingly, there is interest in determining whether specific features of depression are more atherogenic than others. Such an approach is consistent with research on Type A behavior that ultimately found hostility to be a particularly "toxic" component of that construct with regard to cardiovascular risk.[7, 8] Hopelessness may be one such toxic aspect of depression. Hopelessness refers to a negative cognitive style and feelings of futility regarding future goals and aspirations and frequently occurs in severe episodes of depression.[9] It commonly is included in depressive symptoms checklists[10], and a subtype of depression with hopelessness as a critical feature is recognized.[11] Nonetheless, hopelessness is not part of the diagnostic criteria for depression in the *Diagnostic and Statistical Manual of Mental Disorders-IV (DSM-IV-TR)*[12] and is not necessary to cause depression; indeed, individuals may experience feelings of hopelessness without meeting criteria for depression.[13] Thus, hopelessness may be distinct from depression – a distinction that may be critical when assessing associated health effects. Hopelessness is strongly associated with CVD outcomes in men, independently of depressive symptoms[14–16]; little is known about its relation with CVD risk in women. Hopelessness has independently predicted clinical cardiovascular outcomes in women with known coronary artery disease (CAD)[17], but its association with subclinical CVD in healthy women has not been studied.

We examined the cross-sectional association of hopelessness and depressive symptoms with carotid artery intimal-medial thickening (IMT) in a community cohort of African-American and white women. Given the inconsistent literature relating depression to subclinical CVD and the emerging evidence showing strong associations between hopelessness and cardiovascular outcomes, we hypothesized that hopelessness and depressive symptoms would individually relate to carotid artery IMT, but when considered simultaneously, hopelessness would be more strongly related to IMT than depressive symptoms. Available data on several important CVD risk factors in SWAN allowed us to examine whether effects of hopelessness and depression on IMT were independent of these CVD risk factors. Secondarily, we examined whether associations differed between African-American and white women.

METHODS

Participants and Study Design

Participants were women from the Pittsburgh and Chicago sites of the Study of Women's Health Across the Nation (SWAN) who completed an ancillary study of the natural history of subclinical atherosclerosis (SWAN Heart Study). SWAN, a multi-ethnic, community-based, study of the menopausal transition, enrolled 3,302 women in 1996–1997 from seven clinical sites (Chicago, IL; Pittsburgh, PA; Boston, MA; Detroit, MI; Newark, NJ; Oakland, CA; Los Angeles, CA). Women were eligible if they were: aged 42–52 years; had an intact uterus, at

least one ovary, at least one menstrual period and no use of reproductive hormones affecting ovarian or pituitary function in the past 3 months; not currently pregnant or breast-feeding; self-identified as non-Hispanic white or a member of the site-designated minority group: African-American (Chicago, Pittsburgh, Boston, Detroit); Hispanic (Newark); Chinese/Chinese-American (Oakland); and Japanese/Japanese-American (Los Angeles). Complete details of SWAN study design, recruitment, and protocol have been published.[18]

Women enrolled in the SWAN Heart Study from 2001–2003, coincident with their 4th or 5th annual SWAN visit for 93.8% of participants, or with their 6th or 7th visit for the remainder. Participants were eligible for SWAN Heart if they had at least one intact ovary, no history of cardiovascular disease and were not currently using anti-hypertensive or diabetes medications. Of the 608 women enrolled in SWAN Heart, 559 had complete data on menopause status and IMT and provided data for the current analyses; Ns in the analytic models varied based on missing data for the CES-D (n=8) or hopelessness scale (n=46). Comparing those included to those excluded from analyses showed no significant differences between women on predictors, covariates, or outcomes (all p>.3).

The research protocol was approved by each site's Institutional Review Board; all women provided written informed consent.

Measurement of Hopelessness and Depressive Symptoms

Hopelessness was assessed with a 2-item scale[14], administered at the baseline SWAN Heart visit. Items were "The future seems to me to be hopeless, and I can't believe that things are changing for the better" and "I feel it is impossible for me to reach the goals that I would like to strive for." Responses to each item were on a 5-point scale (0-strongly agree; 1-somewhat agree; 2-cannot say; 3-somewhat disagree; 4-strongly disagree), reverse-scored and summed to create a hopelessness score (range, 0–8), with higher values indicating greater hopelessness. Scores on this measure have predicted CVD outcomes in men[14–16] and form an assessment of hopelessness that appears distinct from closely related constructs like depression. In primary analyses, hopelessness scores were modeled continuously; in secondary analyses, a cut-off score (≥5) was used to identify women higher in hopelessness based on conceptualization of responses to the hopelessness items[14–16] and taking into consideration the score distribution.

Depressive symptoms are assessed annually in SWAN by the Center for Epidemiologic Studies Depression Scale (CES-D), which was developed for use in community samples.[10] The 20-item scale measures the frequency of being bothered by depressive symptoms in the previous week on a scale of 0 (rarely) to 3 (most or all of the time). Item responses are summed for a total score (range, 0–60); higher scores indicate more depressive symptomatology. The CES-D score obtained at the SWAN visit coincident with the baseline SWAN Heart visit was used in analyses. CES-D scores were modeled continuously in primary analyses; in secondary analyses, a standard cut-off (≥16) was used to represent clinically significant depressive symptomatology.[19]

Ultrasound Assessments

IMT was assessed through B-mode ultrasonography of the left and right carotid arteries using a Hewlett Packard (Hewlett Packard, Andover, MA) 5500 scanner at the Chicago site and a Toshiba (Toshiba American Medical Systems, Tustin, CA) SSA-270A scanner at the Pittsburgh site. Image quality is comparable between the two systems. Images were obtained from 4 locations each in the left and right carotid arteries: near and far walls of the distal common carotid artery (1 cm proximal to the carotid bulb), and far walls of the carotid bulb (at the point where the near and far walls of the common carotid are no longer parallel, extending to the flow divider), and internal carotid artery (from the flow divider to 1 cm distal

to this point). The lumen-intima interface and the media-adventitia interface were electronically traced across a 1-cm segment to generate a measure of IMT. One measurement was generated for each pixel, resulting in approximately 140 measures for each segment. Average, minimum, and maximum values of these measures were recorded for each location; for analyses, mean of the average readings and mean of the maximum readings were used.

Covariates

Information on covariates was obtained at the SWAN Heart baseline visit unless otherwise noted. Age was self-reported and modeled continuously. Women self-identified as either African-American or white (referent). Body mass index (BMI), calculated as weight in kilograms divided by height in meters squared, was modeled continuously. Systolic blood pressure (SBP), the average of two manual measurements after a seated, 5-min rest, was modeled continuously. Four percent of women were missing BMI or SBP data at the SWAN Heart baseline so their most recently available BMI or SBP values from a prior SWAN visit were used. Smoking status was dichotomized as current smokers versus nonsmokers (referent); for 54 women without concurrent smoking data, their most recently available information from a prior SWAN visit was used. Menopausal status is assessed annually in SWAN and defined as premenopausal (bleeding in last 3 months with no cycle irregularity in previous 12 months), early perimenopausal (bleeding in last 3 months with some change in cycle regularity in last 12 months), late perimenopausal (bleeding >3 months ago but within last 12 months), postmenopausal (no bleeding in last 12 months), or undetermined (surgery or hormone use precluded determination of natural menopausal status). Annual household income was modeled categorically (<$20,000, $20,000 to <$35,000, $35,000 to <$50,000, $50,000 to < $75,000, and $75,000 or higher (referent)); the most recently available data from a prior SWAN visit was used for 78 women without concurrent income data. Self-reported highest level of education was categorized as high school degree or less, some college, college degree, or post-college (referent). Consistent with SWAN guidelines, site was a covariate in all analyses.

Analysis

Primary Analyses—We used descriptive statistics to characterize our sample on age, BMI, SBP, menopausal status, education, income, smoking status, hopelessness, depressive symptoms and mean and maximum IMT. We calculated three sets of linear regression models to examine the relation of hopelessness and depressive symptoms with IMT. In the first set of models, covariates included age, race and study site; hopelessness or depressive symptoms were modeled continuously in separate models. These models were repeated, adding covariates representing income, BMI, SBP and smoking to determine if associations were independent of known cardiovascular risk factors. Third, hopelessness and depressive symptoms were modeled *simultaneously* in a risk factor-adjusted model.

Secondary Analyses—The risk factor-adjusted model with hopelessness and depressive symptoms included simultaneously was repeated with both hopelessness by race and CES-D by race interaction terms to determine whether associations differed by race. Separate risk factor-adjusted models tested the hopelessness by CES-D interaction to determine if these constructs had a synergistic effect on IMT, and examined dichotomous hopelessness (<5 versus ≥5) or depression scores (<16 versus ≥16) in relation to IMT.

Covariates were selected based on known associations with CVD. SWAN Heart was designed primarily to assess the impact of menopausal status on subclinical CVD so we examined univariate associations of status with our predictors and IMT; no significant relations were observed so menopausal status was not included as a covariate. However, because hormone therapy potentially positively impacts atherosclerosis, we repeated all models excluding 30 women who reported HRT use at the SWAN Heart baseline; results from these models were

identical to results with the full sample reported below. Income was significantly related to hopelessness, depressive symptoms and IMT in preliminary, univariate analyses ($p<.006$) whereas education was not; therefore, we included income as a marker of socioeconomic status in our risk factor-adjusted models but education is used for descriptive purposes only. Analyses were conducted in PC-SAS (version 9.13, SAS Institute, Cary, NC).

RESULTS

Baseline characteristics are shown in Table 1. At SWAN Heart baseline, women were approximately 50 years old, most had completed at least some college, average SBP was 119 mmHg and mean BMI was 29.1 kg/m^2.

As shown in Table 2, the minimally adjusted ("Model 1") and risk factor-adjusted ("Model 2") linear regression models reveal that increasing hopelessness is associated with higher levels of mean and maximum IMT. Depressive symptoms show similar, but marginally significant, associations with the outcomes.

With hopelessness and CES-D modeled simultaneously in a risk factor-adjusted model, hopelessness was significantly associated with higher mean and maximum IMT, whereas depressive symptoms were unrelated to IMT. As shown in Table 3, each 1-point higher hopelessness score related to 0.0061-mm greater mean IMT and 0.0074-mm greater maximum IMT. Age, race, site, BMI and SBP were significant covariates, whereas income and smoking status were nonsignificant.

In secondary analyses to determine whether associations of hopelessness or depressive symptoms with IMT differed by race, all interactions were nonsignificant (mean IMT: hopelessness by race $p=.844$, CES-D by race $p=.161$; maximum IMT: hopelessness by race $p=.260$, CES-D by race $p=.124$). Separate risk factor-adjusted models showed no interaction between hopelessness and depressive symptoms for mean ($p>.81$) or maximum IMT ($p>.96$). Four percent of women had a high hopelessness score (≥ 5) and 20% of women had a high CES-D score (≥ 16). In separate risk factor-adjusted models, women with high hopelessness scores had greater mean (estimate=0.066, $p=.0008$) and maximum (estimate=0.068, $p=.012$) IMT than more hopeful women, whereas depressed and non-depressed women did not differ on mean ($p>0.4$) or maximum IMT ($p>.5$).

DISCUSSION

This study examined the associations of depressive symptoms and hopelessness with carotid atherosclerosis in a cohort of healthy African-American and white women. As hypothesized, higher levels of hopelessness were associated with more IMT whereas depressive symptoms were not, independent of important CVD risk factors, when these constructs were considered simultaneously. Findings are consistent with previous studies reporting that hopelessness relates to CVD in men,[14–16] and clinical outcomes in women with documented CAD.[17] To our knowledge, this is the first study to report the association of hopelessness with subclinical CVD among healthy women.

Clinical significance of our findings is highlighted by considering the magnitude of difference in IMT observed with increasing hopelessness; each 1-point higher hopelessness score related to a .0061-mm higher mean IMT and a .0074-mm higher maximum IMT (Table 3). Thus, a 2-SD difference in hopelessness score would relate to a .0195-mm difference in mean IMT and a .0237-mm difference in maximum IMT. Moreover, women with high hopelessness scores had more than .06-mm greater levels of both mean and maximum IMT than women with lower hopelessness scores. These differences are potentially clinically significant. Average annual change in common carotid artery IMT over 10 years among black and white women in the

Atherosclerosis Risk in Communities study was .008 to .009 mm[20]; other studies report that IMT increases by .01–.03 mm per year.[21] Such small, incremental differences in IMT are associated with increasing cardiovascular risk[21] as well as incident CVD and stroke.[22]

Mechanisms linking hopelessness with subclinical atherosclerosis need to be elucidated. Age, BMI and resting SBP were significant covariates, yet none diminished the relation of hopelessness with IMT. Similarly, the relation of hopelessness with IMT was independent of smoking and income (nonsignificant in the multivariable models), and race (significantly related to mean IMT; marginally related to maximum IMT). Effects of hopelessness have been robust, independent of behavioral, biologic and demographic characteristics[14–17], indicating other mechanisms should be considered. Animal studies show exposure to learned helplessness and uncontrollable stressors – analogs to hopelessness in humans – triggers autonomic, inflammatory and neuroendocrine alterations[23, 24] that can potentiate atherogenesis. Alterations in serotonergic function centrally and peripherally may contribute to mood alterations, including depression and hopelessness, and exacerbate CVD risk.[25] Significant positive associations of whole blood serotonin (WBS) with hopelessness have been reported in a cohort of older women and men[26] but WBS is unrelated to IMT in that cohort.[27] Hopelessness likely operates through multiple pathways to influence atherosclerotic risk; future work should focus on several potential mediating mechanisms.

This study raises the question of how hopelessness and depressive symptoms are related. DSM-IV-TR diagnostic criteria for depression do not include hopelessness[12], but consistent evidence for a hopelessness subtype of depression exists[11] and hopelessness commonly is included in depressive symptom checklists, such as the CES-D. Moreover, severe depression often is accompanied by feelings of hopelessness. In our study, the correlation between the 2-item measure of hopelessness and the 20-item CES-D is small but statistically significant ($r=0.27$, $p<.0001$); the association of the single CES-D item, "I felt hopeful about the future," with the hopelessness scale also is small ($r=-0.31$, $p<.0001$). The correlation of the hopelessness scale with the CES-D is strikingly similar to its association with other depressive symptom checklists.[28] It is clear this measure captures feelings of futility or loss of hope that do not map directly onto other depressive symptoms. Moreover, our pattern of findings suggests hopelessness confers unique risk of CVD.

African-Americans have significantly greater mean IMT than whites in our cohort; however, no significant interactions with hopelessness or depressive symptoms were observed. Other reports from SWAN Heart have observed racial differences. CES-D scores were significantly related to aortic calcification amongst African-American participants only in a multivariable model[29], but hopelessness was not included in those analyses. Aortic calcification and IMT represent structural changes to the vasculature and are considered early markers of the atherosclerotic disease process in women[30]; however, these two indices are only modestly correlated in SWAN ($r=.2$, $p<.001$) and may represent differing underlying processes.[31, 32]

Our study has several strengths. The SWAN Heart Study focuses on community-dwelling women, thus enhancing generalizability of findings. We used state-of-the-art assessments of IMT in a well-characterized cohort of women. Finally, we controlled for important CVD risk factors to demonstrate the independent associations of hopelessness and depressive symptoms with IMT.

Limitations include the cross-sectional nature of the data. It remains to be seen whether hopelessness influences atherosclerotic progression in women. Also, SWAN women are relatively healthy and the majority came from middle or upper-middle income households; it is unknown if similar associations would be observed in women with more adverse

cardiovascular profiles or who experience greater socioeconomic disadvantage, for example, or who differ in other ways from our cohort.

In conclusion, this study demonstrates that hopelessness is a strong and significant correlate of subclinical atherosclerosis in African-American and white women, independent of depressive symptoms and known CVD risk factors. Further research is needed to understand mechanisms that may mediate this association and to determine whether hopelessness predicts accelerated progression of atherosclerosis in women.

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Table 1

Baseline participant characteristics: SWAN Heart Study (N=559).

	mean (SD)	%
Age [years]	50.2 (2.8)	
Education		
≤ High school		15.4
Some college		30.2
College degree		21.8
Post-college		32.6
Annual Income		
< $20,000		6.7
$20,000 to < $35,000		7.4
$35,000 to < $50,000		14.6
$50,000 to < $75,000		25.4
≥ $75,000		46.0
Race		
White		62.4
African-American		37.6
Menopausal status		
Premenopausal		10.4
Early perimenopausal		45.8
Late perimenopausal		9.8
Postmenopausal		28.6
Undetermined		5.4
BMI [kg/m^2]	29.1 (6.3)	
SBP [mmHg]	119.3 (16.7)	
Smokers		16.6
CES-D	7.22 (7.9)	
Hopelessness	1.54 (1.6)	
IMT		
Mean [mm]	0.668 (0.10)	
Maximum [mm]	0.870 (0.13)	

Table 2

Individual Associations of Hopelessness and Depressive Symptoms With Mean and Maximum Carotid Artery Intimal-Medial Thickening: SWAN Heart Study.

	Mean Intimal-Medial Thickening						Maximum Intimal-Medial Thickening					
	Model 1			Model 2			Model 1			Model 2		
	Estimate	SE	p-value	Estimate	SE	p-value	Estimate	SE	p-value	Estimate	SE	p-value
Hopelessness	0.0056	0.0026	.0312	0.0062	0.0025	.0139	0.0070	0.0035	.0468	0.0076	0.0035	.0297
Age	0.0058	0.0014	<.0001	0.0040	0.0014	.0031	0.0084	0.0019	<.0001	0.0062	0.0019	.0010
Race												
African-Amer.	0.0376	0.0083	<.0001	0.0184	0.0087	.0344	0.0428	0.0114	.0002	0.0191	0.0120	.1105
White	referent			referent						referent		
Annual Income	---	---	---				---	---	---			
< $20K				0.0010	0.0171	.9550				−0.0032	0.0236	.8924
$20K to <$35K				0.0199	0.0157	.2054				0.0140	0.0217	.5196
$35K to <$50K				0.0214	0.0115	.0641				0.0362	0.0159	.0235
$50K to <$75K				−0.0049	0.0095	.6072				−0.0084	0.0131	.5233
$75K or more				referent						referent		
BMI	---	---	---	0.0032	0.0007	<.0001	---	---	---	0.0043	0.0009	<.0001
SBP	---	---	---	0.0009	0.0003	.0010	---	---	---	0.0011	0.0004	.0049
Smoking												
Current	---	---	---	−0.0142	0.0107	.1874	---	---	---	−0.0070	0.0148	.6375
Nonsmoker				referent						referent		
CES-D	0.0008	0.0005	.1007	0.0008	0.0005	.1056	0.0013	0.0007	.0593	0.0012	0.0007	.0691
Age	0.0057	0.0014	<.0001	0.0041	0.0013	.0023	0.0083	0.0019	<.0001	0.0062	0.0018	.0008
Race												
African-Amer.	0.0400	0.0081	<.0001	0.0199	0.0084	.0181	0.0460	0.0111	<.0001	0.0209	0.0117	.0744
White	referent			referent			referent			referent		
Annual Income	---	---	---				---	---	---			.9374
< $20K				0.0047	0.0165	.7738				0.0018	0.0229	.6158
$20K to <$35K				0.0145	0.0152	.3405				0.0106	0.0211	.0427
$35K to <$50K				0.0197	0.0113	.0823				0.0320	0.0158	.8784
$50K to <$75K				−0.0007	0.0093	.9365				−0.0020	0.0129	
$75K or more				referent						referent		

	Mean Intimal-Medial Thickening						Maximum Intimal-Medial Thickening					
	Model 1			Model 2			Model 1			Model 2		
	Estimate	SE	p-value	Estimate	SE	p-value	Estimate	SE	p-value	Estimate	SE	p-value
BMI	---	---	---	0.0031	0.0006	<.0001	---	---	---	0.0041	0.0009	<.0001
SBP	---	---	---	0.0010	0.0003	.0003	---	---	---	0.0011	0.0004	.0020
Smoking												
Current	---	---	---	−0.0118	0.0103	.2530	---	---	---	−0.0070	0.0143	.6262
Nonsmoker				referent						referent		

Note. N=513 (Model 1) or 510 (Model 2) in hopelessness models; N=551 (Model 1) or 548 (Model 2) in CES-D models. All models included a covariate representing study site. For hopelessness models, mean IMT, R^2 = 0.22, and maximum IMT R^2 = 0.17. For CES-D models, mean IMT, R^2 = 0.22, and maximum IMT R^2 = 0.16.

Table 3

Hopelessness and Depressive Symptoms Modeled Simultaneously in Relation to Mean and Maximum Carotid Artery Intimal-Medial Thickening: SWAN Heart Study.

	Mean Intimal-Medial Thickening			Maximum Intimal-Medial Thickening		
	Estimate	**SE**	**p-value**	**Estimate**	**SE**	**p-value**
Hopelessness	0.0061	0.0026	.0217	0.0074	0.0036	.0409
CES-D	0.0004	0.0005	.4495	0.0006	0.0007	.4097
Age	0.0038	0.0014	.0059	0.0059	0.0019	.0019
Race						
African-Amer.	0.0190	0.0088	.0310	0.0198	0.0121	.1011
White	referent			referent		
Annual Income						
< $20K	−0.0018	0.0175	.9186	−0.0125	0.0241	.6038
$20K to <$35K	0.0173	0.0159	.2766	0.0100	0.0219	.6470
$35K to <$50K	0.0197	0.0116	.0906	0.0334	0.0160	.0370
$50K to <$75K	−0.0047	0.0096	.6241	−0.0079	0.0132	.5523
$75K or more	referent			referent		
BMI	0.0031	0.0007	<.0001	0.0042	0.0009	<.0001
SBP	0.0009	0.0003	.0008	0.0011	0.0004	.0037
Smoking						
Current	−0.0161	0.0109	.1398	−0.0110	0.0150	.4629
Nonsmoker	referent			referent		

Note. N=502. Both models included a covariate representing study site. For mean IMT, $R^2 = 0.22$, and maximum IMT $R^2 = 0.17$.