Original Contribution

Race/Ethnicity, Cumulative Midlife Loss, and Carotid Atherosclerosis in Middle-Aged Women

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African-American women have elevated rates of cardiovascular disease compared with women of other races or ethnicities, and race/ethnicity-related stressors may play a role. We examined the association between a race/ethnicity-related stressor, midlife loss, and a marker of cardiovascular risk, carotid intima media thickness (IMT), in 1,410 African-American, White, Chinese, and Hispanic women from the Study of Women's Health Across the Nation. Participants were queried about losses annually over 12 years (1996–2013), with IMT assessed in year 12–13 via ultrasound. Linear regression models were used to examine associations between cumulative upsetting losses and IMT, adjusting for covariates. In minimally adjusted models in the full cohort, 3 or more upsetting losses (vs. none) were associated with IMT ($\beta = 0.03$, 95% confidence interval (CI): 0.01, 0.05; $P = 0.0003$). Results were more robust among African-American women ($\beta = 0.042$, 95% CI: 0.01, 0.07; $P < 0.01$) than White ($\beta = 0.014$, 95% CI: –0.01, 0.03; $P = 0.21$), Chinese ($\beta = 0.036$, 95% CI: –0.03, 0.10; $P = 0.25$), or Hispanic ($\beta = 0.036$, 95% CI: –0.07, 0.14; $P = 0.51$) women, although associations among women from racial/ethnic minorities overall were of similar magnitude. Results persisted in fully adjusted models (P for interaction with race/ethnicity = 0.04). Midlife loss may be a pathway through which race/ethnicity influences cardiovascular risk for African-American women and, potentially, Chinese and Hispanic women.

African-American; atherosclerosis; bereavement; psychological stress; social determinants of health; women

Abbreviations: CVD, cardiovascular disease; SWAN, Study of Women's Health Across the Nation; IMT, carotid intima media thickness.

In the United States, African-American women have disproportionately high rates of morbidity and mortality related to cardiovascular disease (CVD) compared with women of other racial/ethnic groups (1–3) that are not completely explained by traditional CVD risk factors (2, 4), socioeconomic status, or access to care (2, 4). Several researchers have posited that the excess CVD risk observed in African-American women, compared with women of other racial/ethnic groups may be due, in part, to race/ethnicity-related stressors (5–9). But to date, studies have primarily been focused on stressors related to segregation (e.g., neighborhood factors) (10, 11), socioeconomic status (e.g., financial strain) (12), and discrimination (11, 13), with limited consideration of other factors. However, research suggests there may be a racial/ethnic disadvantage in the experience of loss (i.e., deaths of close friends and/or family members) (14).

In a recent analysis of large-scale data from the National Longitudinal Study of Youth and the Health and Retirement Survey, researchers found that from childhood through adulthood, African Americans were more likely than Whites to experience the death of a parent or sibling (14). Similarly, from young adulthood through midlife, African Americans were more likely than Whites to experience the death of a spouse or child (14). Researchers also have found racial/ethnic differences in the deaths of friends and confidantes, with African Americans reporting more deaths among friends and confidantes over a 6-year timespan than reported by their White or Hispanic counterparts (15).

The current analysis was designed to examine cumulative loss as a potentially novel contributor to cardiovascular risk in a cohort of middle-aged African-American, White, Chinese, and Hispanic women from the Study of Women's

Health Across the Nation (SWAN). Across studies, experiencing loss, particularly a loss considered upsetting or impactful (16), has been associated with adverse CVD outcomes. However much of this research has focused on widowhood in late life among predominantly White populations (17, 18). Yet, national data indicate that African Americans have the most excess mortality compared with other racial/ethnic groups, with the starkest differences observed in middle age (19).

Consequently, in addition to experiencing more loss across the life course, in midlife, African-American women may be more likely than women of other racial/ethnic backgrounds to experience the loss of similarly aged spouses and other middle-aged family members (e.g., siblings, cousins), as well as friends. Thus, we examined the interrelationships among race/ethnicity, cumulative loss over 12 years, and carotid intima media thickness (IMT), which is a marker of subclinical CVD known to predict later risk of clinical CVD (20–22). We hypothesized that 1) African-American women would report more cumulative losses than women from other racial/ethnic groups, and 2) associations between cumulative losses and IMT would be most apparent among African-American women and less apparent among White, Chinese, and Hispanic women.

METHODS

Participants

SWAN is a community-based, longitudinal study of menopause and aging. Study design and recruitment have been detailed previously (23). Briefly, SWAN has 7 field sites. Each site recruited White women and either African-American (Boston, MA; Chicago, IL; Detroit, MI; Pittsburgh, PA), Hispanic (Newark, NJ), Japanese (Los Angeles, CA), or Chinese (Oakland, CA) women. Initial eligibility criteria included being aged 42–52 years, not pregnant or lactating, having a uterus and ≥ 1 ovary, no exogenous hormone use, and having ≥ 1 menstrual period in the preceding 3 months.

Data collection began in 1996–1997, with follow-ups at approximate 12-month intervals. SWAN protocols were approved by the institutional review boards at each site. All participants provided written informed consent. The current analysis was limited to the 6 SWAN sites (each site except Los Angeles, CA) that participated in a carotid ultrasound protocol during the 12th or 13th visit. Of the 2,806 women enrolled at these 6 sites at SWAN baseline, 2,051 White, African-American, Chinese, and Hispanic women participated in the year 12–13 visit, for an overall retention rate of 76.2% (excluding $n = 114$ deceased participants). Of these, 1,559 completed the IMT assessment. Reasons for not completing the IMT assessment included completion of home/telephone interviews only, scheduling problems, and refusals.

Among women enrolled at the 6 sites for visits 12–13, those who completed the IMT assessment were more likely to be White or Chinese and had a more favorable cardiovascular risk profile with respect to current smoking, systolic blood pressure, body mass index, insulin levels,

and use of antihypertensive and diabetes medication, compared with those who did not complete the IMT assessment. Women who completed the IMT assessment also had lower depressive symptoms than women who did not complete the IMT assessment; however, they only reported slightly fewer overall (mean = 3.59 vs. 4.07) and a similar number of upsetting (mean = 1.88 vs. 1.72) cumulative losses. Of the 1,559 women with IMT data, 149 were missing data on covariates, resulting in a final sample of 1,410 women, 97.7% of whom were postmenopausal.

Measurement of cumulative midlife loss

Annually, from baseline through the 12th follow-up (excluding follow-up 11, which was a truncated visit), women were asked whether: 1) “A close relative (husband/partner, child or parent) died;” or 2) “A close friend or family member other than a husband/partner, child or parent died,” using a life events checklist (24). After each “yes” response, women indicated how upsetting the loss was on a scale of 1–4 (where 1 indicated “not at all upsetting” and 4 indicated “very upsetting and still upsetting”). An initial, overall cumulative loss score was created by summing “yes” responses across visits, for descriptive purposes. Because not all losses are considered upsetting (e.g., those that follow a period of prolonged suffering in, or caregiving for, the decedent can result in relief (25–27)), a cumulative upsetting loss score then was created by summing the number of losses considered “very upsetting” and “very upsetting and still upsetting” across visits, consistent with prior studies (24, 28, 29). Upsetting losses were categorized on the basis of the distribution of the exposure: 0 losses, 1–2 losses, and ≥ 3 losses.

Measurement of common carotid IMT

As in prior studies (30, 31), centrally trained and certified sonographers obtained carotid ultrasound images at each site using a Terason t3000 Ultrasound System (Teratech Corp, Burlington, Massachusetts) equipped with a variable frequency 5–12 MHz linear array transducer. Two digitized images for later reading were obtained of the left and the right distal common carotid artery at end diastole. From each of these 4 images, using semiautomated edge-detection software (32), near- and far-wall common carotid artery IMT measures were obtained by electronically tracing the lumen-intima interface and the media-adventitia interface across a 1-cm segment proximal to the carotid bulb, with 1 measurement per pixel, totaling approximately 140 measures for each segment. The mean of the average across images was used in analyses. Images were read at the University of Pittsburgh Ultrasound Research Laboratory. Reproducibility was good to excellent (intraclass correlation coefficient between sonographers ≥ 0.77 ; between readers > 0.90).

Sociodemographic characteristics

Race/ethnicity and education (high school or less, some college, college or postgraduate) were self-reported at

baseline. Age and marital status (single/never married; currently married/living as married; separated; widowed; divorced) were self-reported at the time of the IMT assessment.

Risk factors. Risk factors were chosen on the basis of their association with loss and/or IMT in prior studies (33–35) and assessed concurrently with the IMT. Smoking status (current, former, or never) and alcohol use were assessed using descriptive categories. Alcohol use was assessed as “none or less than one (drink) per month” to “5 or more (drinks) per day,” and combined on the basis of the distribution of data into 3 groups representing low (less than once a month), moderate (more than once a month but fewer than 2–4 times a week), and high (at least 2–4 times a week) consumption. Body mass index was calculated (weight (kg)/height (m²)) on the basis of measurements.

Systolic blood pressure was calculated as the average of 2 seated measurements. To determine cholesterol and insulin levels, fasting blood samples were frozen and sent to the University of Michigan Pathology Laboratory, which is Clinical Laboratory Improvement Amendments certified and accredited by the College of American Pathologists. Measurements were performed on a Siemens ADVIA 2400 automated chemistry analyzer using Siemens ADVIA chemistry system reagents (Siemens, Munich, Germany). Participants’ serum insulin levels were measured using immunoassay. Lipid fractions were determined from EDTA-treated plasma. Total cholesterol and concentrations were determined by coupled enzymatic methods, with high-density lipoprotein cholesterol isolated using the procedures of Izawa et al. (36). Low-density lipoprotein was measured directly (37). Patients’ use of antihypertensive or insulin-lowering medications was assessed via self-report. Depressive symptoms were assessed with the 20-item Center for Epidemiological Studies Depression scale (38).

History of CVD. Reports of CVD, including myocardial infarction, stroke, and heart failure, among others, were assessed annually through visit 12–13 and verified via medical record review.

Change in number of social contacts. Participants were asked annually: “About how many close friends and close relatives do you have, that is, people you feel at ease with and can talk to about what is on your mind?” (39). Because losses over time might reduce an individual’s total number of available confidantes, we created a change score (i.e., the difference between the number of social contacts reported at baseline and those reported at year 12–13) to account for the absolute (i.e., nontime-varying) change in social contacts over follow-up, given the cumulative nature of our exposure.

Analyses

Primary analyses. Racial or ethnic differences in participants’ characteristics were examined using analysis of variance tests for continuous variables and χ^2 tests for categorical variables. Linear regression analyses were conducted to examine associations between cumulative upsetting losses

and IMT among all women. In model 1, we adjusted for site and demographics consistently linked to IMT (i.e., age, race/ethnicity, education). For model 2, we adjusted for risk factors associated with IMT across studies (i.e., body mass index, smoking, and systolic blood pressure). Subsequent models were adjusted for history of any CVD (model 3); other risk factors including alcohol use, and cholesterol and insulin levels (model 4); separate presence or absence of variables for antihypertensive and insulin-lowering medication use (model 5); depressive symptoms (model 6); and change in social contacts (model 7).

Given our primary interest in race/ethnicity-specific associations, we subsequently ran race/ethnicity-stratified models. This allowed us to obtain within-group parameter estimates for cumulative midlife loss and IMT associations, given our a priori hypothesis that associations would be more apparent among African-American women, compared with other racial/ethnic groups. We also tested the race/ethnicity by cumulative upsetting-loss interactions in initial, nonstratified models limited to African-American women and White women, because of the small number of Chinese and Hispanic women.

Because not all women had data on loss every year (66% completed the life-events checklist every study visit), we ran sensitivity analyses restricting our models to women with exposure data from at least 9 visits. Data collection was suspended at the New Jersey site during visits 6–8 and 10–11, due to logistical complications; thus, Hispanic women were excluded from these analyses. Consequently, we ran a second set of sensitivity analyses with the exposure variable expressed as the percentage of time women experienced upsetting losses (ie, number of losses divided by the number of visits attended) to more adequately account for unequal study visits across participants. Additional sensitivity analyses were run to exclude women who reported being widowed at any point over follow-up, given linkages between widowhood and CVD risk. Furthermore, because we controlled for covariates concurrent with the IMT assessment, sensitivity analyses were also conducted to control for time-averaged cardiovascular risk factors (40) with available data from baseline through visit 12–13. Findings from sensitivity analyses were comparable to those from main analyses; thus, to maximize participant data, we used results from primary models.

Secondary analyses. Secondary race/ethnicity-stratified analyses were run excluding women in whom CVD developed before to visit 12–13. We also ran secondary race/ethnicity-stratified analyses examining associations between cumulative overall losses (i.e., irrespective of how upsetting losses were) and IMT. Finally, to determine whether losses were most deleterious for women who were consistently single, we ran exploratory analyses to examine whether within-race/ethnicity associations were modified by marital/partnered status (i.e., consistently single, consistently partnered, neither consistently single nor partnered) over the 12 years. All analyses were conducted using SAS software, version 9.4 (SAS Institute, Inc., Cary, North Carolina). A 2-sided *P*-value threshold of <0.05 was used to determine statistical significance.

Table 1. Participant Characteristics by Race/Ethnicity, Study of Women's Health Across the Nation, 1996–2013^a

Characteristic	African-American (n = 431)			White (n = 725)			Chinese (n = 183)			Hispanic (n = 71)			P Value ^b
	No.	%	Mean (SD)	No.	%	Mean (SD)	No.	%	Mean (SD)	No.	%	Mean (SD)	
Age, years	143	33.2	59.8 (2.8)	405	55.9	60.3 (2.7)	94	51.4	60.7 (2.5)	9	12.7	60.2 (2.9)	0.0005
College education	173	40.1		491	67.7		134	73.2		30	42.3		<0.0001
Currently married/living as married													<0.0001
No. of overall losses			5.4 (3.5)			3.8 (2.6)			3.1 (2.8)			1.7 (1.3)	<0.0001
No. of upsetting losses			2.6 (2.7)			1.8 (1.8)			0.95 (1.6)			0.73 (0.93)	<0.0001
No. of Upsetting Losses													
0	93	21.6		174	24.0		93	50.8		36	50.7		<0.0001
1–2	168	39.0		354	48.8		76	41.5		31	43.7		
≥3	170	39.4		197	27.2		14	7.7		4	5.6		
Prior CVD event ^c	54	12.5		45	6.2		5	2.7		6	8.5		<0.0001
Smoking status													
Current	66	15.3		53	7.3		2	1.1		10	14.1		<0.0001
Former	119	27.6		286	39.5		11	6.0		15	21.1		
Never	246	57.1		386	53.2		170	92.9		46	64.8		
Alcohol use ^d													
< Once per month	266	61.7		261	36.0		145	79.2		46	64.8		<0.0001
> Once per month but < 2–4 times/week	112	26.0		214	29.5		27	14.8		15	21.1		
≥ 2–4 times/week	53	12.3		250	34.5		11	6.0		10	14.1		
BMI ^e			33.1 (7.2)			29.8 (7.1)			24.1 (4.4)			31.3 (6.4)	<0.0001
Obese (BMI ≥ 30)	272	63.1		300	41.4		16	8.7		39	54.9		<0.0001
SBP, mmHg			129.5 (18.3)			119.1 (15.0)			113.3 (13.5)			130.7 (18.0)	<0.0001
Insulin, uIU/mL			15.4 (14.6)			12.5 (16.6)			8.3 (5.5)			18.9 (25.4)	<0.0001
Cholesterol, mg/dL			200.3 (40.0)			207.0 (36.6)			205.6 (38.8)			202.9 (35.8)	0.03
Antihypertension medication use	254	58.9		260	35.9		54	29.5		41	57.8		<0.0001
Insulin-lowering medication use	70	16.2		71	9.8		15	8.2		17	23.9		<0.0001
Depressive symptoms			7.9 (8.5)			7.3 (8.5)			6.5 (6.7)			13.1 (12.0)	<0.0001
Change in no. of social contacts ^f			0.85 (9.2)			−0.29 (5.8)			0.42 (4.6)			1.6 (11.3)	0.02
Carotid IMT, mm			0.84 (0.13)			0.78 (0.11)			0.76 (0.11)			0.80 (0.11)	<0.0001

Abbreviations: BMI, body mass index; CVD, cardiovascular disease; IMT, intima media thickness; SD, standard deviation.

^a Covariate data are from year 12 for 1,364 women and year 13 for 46 women.^b P values refer to analysis of variance tests for differences by race.^c Cardiovascular event (e.g., myocardial infarction, stroke, percutaneous coronary intervention, coronary artery bypass graft, congestive heart failure).^d Initially assessed using descriptive categories ranging from "none or less than one (drink) per month" to "5 or more (drinks) per day" and combined on the basis of the distribution of the data.^e Weight (kg)/height (m²).^f Change from baseline to carotid IMT assessment.

Figure 1. Cumulative upsetting losses and carotid intima media thickness (IMT) in middle-aged women by race/ethnicity in the Study of Women's Health Across the Nation, 1996–2013.

RESULTS

Participant characteristics

Table 1 lists participant characteristics by race/ethnicity. African-American women were slightly younger, reported more cumulative overall and upsetting losses, and had greater IMTs than their White, Chinese, and Hispanic counterparts. African-American and Hispanic women were less educated, less likely to be married or living as married, and had more cardiovascular risk factors than did White and Chinese women. Compared with African-American, White, and Chinese women, Hispanic women reported more depressive symptoms.

Primary analyses

In linear regression models among all women, after adjustment for age, race/ethnicity, education, and site, reporting at least 3 cumulative upsetting losses (vs. none) was associated with greater IMT ($\beta = 0.03$, 95% confidence interval (CI): 0.01, 0.05; $P = 0.0003$), with no association observed between 1 and 2 upsetting losses (vs. none) and IMT ($\beta = 0.005$, 95% CI: -0.01, 0.02; $P = 0.47$). The association between having experienced at least 3 upsetting losses persisted in fully adjusted models ($\beta = 0.023$, 95% CI: 0.01, 0.04; $P = 0.004$). An interaction with race/ethnicity was observed ($P = 0.04$) using least-squared means from adjusted analyses and is depicted in Figure 1. As shown, African-American women with at least 3 cumulative upsetting losses had greater IMT than those who reported none or 1–2 losses only. There were no associations among White women.

In minimally adjusted race/ethnicity-stratified models (Table 2), parameter estimates for at least 3 cumulative upsetting losses (vs. 0) and IMT were largest among African-American women. Parameter estimates for Chinese and Hispanic women were slightly smaller (with wider confidence intervals) than those observed for African-American women, with no associations in White women. Findings were similar in fully adjusted models, with the

largest parameter estimates occurring among Hispanic women.

Secondary analyses

Excluding women with CVD. Models excluding women in whom CVD developed between baseline and the IMT visit are presented in Table 3. Results were consistent with those in primary analyses.

Associations between cumulative overall loss and IMT. Over the 12-year study period, 5.9% of participants ($n = 83$) reported no family or friend losses, 12.5% ($n = 176$) of women reported 1 loss, 17% ($n = 240$) reported 2 losses, 14.9% ($n = 210$) reported 3 losses, and 49.7% ($n = 701$) reported 4 or more losses. Results from race/ethnicity-stratified models examining associations between at least 4 (vs. 0–1) cumulative losses and IMT were consistent with those from primary analyses (Table 4).

Exploratory analyses

In analyses restricted to women reporting marital status at all visits ($n = 669$; this variable had more missing data than did other variables), there were no significant interactions with partnered/unpartnered status in any models (for all, $P > 0.05$).

DISCUSSION

To our knowledge, this is the first investigation of the linkage between exposure to loss and cardiovascular risk in a middle-aged, multiracial/ethnic cohort. We found that experiencing multiple overall and upsetting deaths of friends and/or family members during midlife was more common for African-American women, compared with White, Chinese, and Hispanic women. In addition, African-American women who reported 3 or more upsetting losses over follow-up had greater IMT than did their counterparts who reported no upsetting losses, even after adjusting for a range of cardiovascular risk factors, depressive symptoms, and

Table 2. Linear Regression Models Used to Examine the Association Between Cumulative Upsetting Losses and Carotid Intima Media Thickness by Race/Ethnicity in the Study of Women's Health Across the Nation, 1996–2013

No. of Upsetting Losses and Model	African-American (n = 431)			White (n = 725)			Chinese (n = 183)			Hispanic (n = 71)		
	β^a	95% CI	P Value	β^a	95% CI	P Value	β^a	95% CI	P Value	β^a	95% CI	P Value
Model 1 ^b												
1–2	0.007	–0.02, 0.04	0.64	0.006	–0.01, 0.02	0.54	0.007	–0.03, 0.04	0.68	–0.004	–0.05, 0.04	0.86
≥ 3	0.042	0.01, 0.07	0.01	0.014	–0.01, 0.03	0.21	0.036	–0.03, 0.10	0.25	0.036	–0.07, 0.14	0.51
Model 2 ^c												
1–2	0.004	–0.03, 0.04	0.79	0.002	–0.02, 0.02	0.82	0.010	–0.02, 0.04	0.53	–0.018	–0.07, 0.03	0.46
≥ 3	0.039	0.01, 0.07	0.02	0.003	–0.02, 0.02	0.74	0.044	–0.02, 0.10	0.15	0.031	–0.07, 0.13	0.53
Model 3 ^d												
1–2	0.004	–0.03, 0.04	0.79	0.003	–0.02, 0.02	0.79	0.011	–0.02, 0.04	0.51	–0.019	–0.07, 0.03	0.43
≥ 3	0.039	0.01, 0.07	0.02	0.002	–0.02, 0.02	0.82	0.042	–0.02, 0.10	0.18	0.030	–0.07, 0.13	0.54
Model 4 ^e												
1–2	0.004	–0.03, 0.04	0.80	0.002	–0.02, 0.02	0.80	0.013	–0.02, 0.04	0.42	–0.018	–0.06, 0.03	0.44
≥ 3	0.037	0.01, 0.07	0.02	0.003	–0.02, 0.02	0.77	0.032	–0.03, 0.09	0.29	0.035	–0.06, 0.13	0.49
Model 5 ^f												
1–2	–0.000	–0.03, 0.03	0.98	0.003	–0.02, 0.02	0.78	0.009	–0.02, 0.04	0.57	–0.019	–0.07, 0.03	0.44
≥ 3	0.035	0.01, 0.07	0.03	0.003	–0.02, 0.02	0.77	0.032	–0.03, 0.09	0.29	0.033	–0.07, 0.14	0.53
Model 6 ^g												
1–2	0.000	–0.03, 0.03	0.99	0.002	–0.02, 0.02	0.80	0.011	–0.02, 0.04	0.52	–0.026	–0.07, 0.02	0.30
≥ 3	0.037	0.01, 0.07	0.02	0.003	–0.02, 0.02	0.80	0.036	–0.02, 0.10	0.24	0.047	–0.06, 0.15	0.38
Model 7 ^h												
1–2	–0.000	–0.03, 0.03	0.99	0.003	–0.02, 0.02	0.79	0.009	–0.02, 0.04	0.58	–0.026	–0.07, 0.02	0.29
≥ 3	0.038	0.01, 0.07	0.02	0.003	–0.02, 0.02	0.80	0.021	–0.04, 0.08	0.51	0.046	–0.06, 0.15	0.39

Abbreviation: CI, confidence interval.

^a The referent for all models is 0 upsetting losses.^b Model 1 included adjustments for site, age, and education.^c Model 2 included adjustments for model 1 covariates and smoking status, body mass index, and systolic blood pressure.^d Model 3 included adjustments for model 2 covariates and any cardiovascular event.^e Model 4 included adjustments for model 3 covariates and alcohol use and cholesterol and insulin levels.^f Model 5 included adjustments for model 4 covariates and medication use.^g Model 6 included adjustments for model 5 covariates and depressive symptoms.^h Model 7 included adjustments for model 6 covariates and change in number of social contacts.

Table 3. Linear Regression Models Used to Examine the Association Between Cumulative Upsetting Losses and Carotid Intima Media Thickness by Race/Ethnicity, Excluding Participants Who Had Any Cardiovascular Events ($n = 110$), in the Study of Women's Health Across the Nation, 1993–2013

No. of Upsetting Losses and Model	African-American ($n = 377$)			White ($n = 680$)			Chinese ($n = 178$)			Hispanic ($n = 65$)		
	β^a	95% CI	P Value	β^a	95% CI	P Value	β^a	95% CI	P Value	β^a	95% CI	P Value
Model 1 ^b												
1–2	0.020	–0.01, 0.05	0.25	0.002	–0.02, 0.02	0.81	0.014	–0.02, 0.05	0.40	0.006	–0.05, 0.06	0.82
≥ 3	0.053	0.02, 0.09	0.002	0.008	–0.01, 0.03	0.46	0.029	–0.03, 0.09	0.37	0.045	–0.06, 0.15	0.42
Model 2 ^c												
1–2	0.015	–0.02, 0.05	0.37	–0.001	–0.02, 0.02	0.89	0.017	–0.01, 0.05	0.29	–0.013	–0.06, 0.04	0.63
≥ 3	0.048	0.01, 0.08	0.006	0.004	–0.02, 0.02	0.94	0.039	–0.02, 0.10	0.22	0.035	–0.07, 0.14	0.49
Model 3 ^d												
1–2	0.015	–0.02, 0.05	0.37	–0.002	–0.02, 0.02	0.87	0.020	–0.01, 0.05	0.21	–0.007	–0.06, 0.04	0.79
≥ 3	0.046	0.01, 0.08	0.008	–0.001	–0.02, 0.02	0.96	0.031	–0.03, 0.09	0.32	0.037	–0.06, 0.14	0.47
Model 4 ^e												
1–2	0.009	–0.02, 0.04	0.59	–0.001	–0.02, 0.02	0.88	0.016	–0.02, 0.05	0.31	–0.009	–0.06, 0.04	0.74
≥ 3	0.043	0.01, 0.08	0.01	–0.000	–0.02, 0.02	0.98	0.033	–0.03, 0.09	0.28	0.034	–0.07, 0.14	0.52
Model 5 ^f												
1–2	0.009	–0.02, 0.04	0.58	–0.001	–0.02, 0.02	0.90	0.017	–0.01, 0.05	0.29	–0.016	–0.07, 0.03	0.52
≥ 3	0.044	0.01, 0.08	0.01	0.000	–0.02, 0.02	0.99	0.035	–0.03, –.10	0.26	0.052	–0.05, 0.16	0.34
Model 6 ^g												
1–2	0.009	–0.02, 0.04	0.58	–0.001	–0.02, 0.02	0.90	0.015	–0.02, 0.05	0.34	–0.016	–0.07, 0.03	0.53
≥ 3	0.044	0.01, 0.08	0.01	0.000	–0.02, 0.02	0.99	0.022	–0.04, 0.08	0.48	0.052	–0.05, 0.16	0.34

Abbreviation: CI, confidence interval.

^a The referent for all models is 0 upsetting losses.^b Model 1 included adjustments for site, age, and education.^c Model 2 included adjustments for model 1 covariates and smoking status, body mass index, and systolic blood pressure.^d Model 3 included adjustments for model 2 covariates and alcohol use and cholesterol and insulin levels.^e Model 4 included adjustments for model 3 covariates and medication use.^f Model 5 included adjustments for model 4 covariates and depressive symptoms.^g Model 6 included adjustments for model 5 covariates and change in number of social contacts.

Table 4. Linear Regression Models Used to Examine the Association Between Cumulative Any Losses and Carotid Intima Media Thickness by Race/Ethnicity in the Study of Women's Health Across the Nation, 1996–2013

No. of Losses and Model	African-American (n = 431)			White (n = 725)			Chinese (n = 183)			Hispanic (n = 71)		
	β^a	95% CI	P Value	β^a	95% CI	P Value	β^a	95% CI	P Value	β^a	95% CI	P Value
Model 1 ^b												
2–3	0.022	–0.02, 0.07	0.31	–0.002	–0.02, 0.02	0.85	0.017	–0.02, 0.06	0.42	0.036	–0.01, 0.09	0.16
≥ 4	0.044	0.01, 0.08	0.0244	0.011	–0.01, 0.03	0.31	0.009	–0.03, 0.05	0.68	0.003	–0.10, 0.10	0.95
Model 2 ^c												
2–3	0.019	–0.02, 0.06	0.39	–0.003	–0.02, 0.02	0.78	0.011	–0.03, 0.05	0.58	0.018	–0.03, 0.07	0.45
≥ 4	0.040	0.01, 0.08	0.0383	0.004	–0.02, 0.02	0.72	0.005	–0.04, 0.05	0.83	–0.015	–0.11, 0.08	0.76
Model 3 ^d												
2–3	0.019	–0.02, 0.06	0.39	–0.002	–0.02, 0.02	0.83	0.010	–0.03, 0.05	0.61	0.019	–0.03, 0.07	0.46
≥ 4	0.040	0.01, 0.08	0.0369	0.003	–0.02, 0.02	0.74	0.003	–0.04, 0.04	0.90	–0.015	–0.11, 0.08	0.76
Model 4 ^e												
2–3	0.018	–0.02, 0.06	0.40	–0.003	–0.02, 0.02	0.77	0.015	–0.02, 0.05	0.45	0.033	–0.02, 0.08	0.19
≥ 4	0.039	0.01, 0.08	0.0449	0.003	–0.02, 0.02	0.80	0.004	–0.04, 0.04	0.85	0.005	–0.09, 0.10	0.91
Model 5 ^f												
2–3	0.019	–0.02, 0.06	0.39	–0.003	–0.02, 0.02	0.79	0.015	–0.02, 0.05	0.45	0.033	–0.02, 0.08	0.20
≥ 4	0.038	0.01, 0.08	0.04	0.003	–0.02, 0.02	0.76	0.003	–0.04, 0.04	0.90	0.003	–0.09, 0.10	0.95
Model 6 ^g												
2–3	0.019	–0.02, 0.06	0.39	–0.003	–0.02, 0.02	0.79	0.016	–0.02, 0.05	0.43	0.034	–0.02, 0.08	0.18
≥ 4	0.039	0.01, 0.08	0.04	0.003	–0.02, 0.02	0.77	0.005	–0.04, 0.05	0.81	0.008	–0.09, 0.10	0.87
Model 7 ^h												
2–3	0.018	–0.03, 0.06	0.42	–0.003	–0.02, 0.02	0.78	0.016	–0.02, 0.05	0.41	0.034	–0.02, 0.08	0.18
≥ 4	0.039	0.01, 0.08	0.04	0.003	–0.02, 0.02	0.77	0.000	–0.04, 0.04	0.99	0.008	–0.09, 0.10	0.87

Abbreviation: CI, confidence interval.

^a The referent for all models is 0–1 losses.^b Model 1 included adjustments for site, age, education^c Model 2 included adjustments for model 1 covariates and smoking status, body mass index, and systolic blood pressure.^d Model 3 included adjustments for model 2 covariates and any cardiovascular event.^e Model 4 included adjustments for model 3 covariates and alcohol use and cholesterol and insulin levels.^f Model 5 included adjustments for model 4 covariates and medication use.^g Model 6 included adjustments for model 5 covariates and depressive symptoms.^h Model 7 included adjustments for model 6 covariates and change in number of social contacts.

change in social contacts. Moreover, although prior research has indicated that upsetting losses are the most impactful for psychological and physiological outcomes (16, 24, 25, 41), in secondary analyses, we also observed fairly strong associations between reporting 4 or more overall (i.e., not necessarily upsetting) losses and IMT among African-American women, but not women from other racial/ethnic backgrounds.

It is noteworthy that although there were no associations among White women, the magnitude of the association between 3 or more upsetting losses and IMT among Chinese and Hispanic women was only slightly smaller than that observed among African-American women. But due to the small number of Chinese and Hispanic women reporting 3 or more upsetting losses ($n = 14$ and $n = 4$, respectively), it is difficult to draw firm conclusions about these results. Because we had fewer years of available data for Hispanic women, the number of cumulative losses captured for this group was likely an underestimate; still, our sample size of Hispanic women is of concern. Our fully adjusted models among Hispanic women, in particular, should be interpreted with considerable caution, given the large number of covariates and the likelihood of overfitting. Nonetheless, findings suggest that upsetting midlife losses could potentially have an impact on cardiovascular risk for Chinese and Hispanic women, as well as African-American women.

Our findings are consistent with the extant literature on loss in late life and cardiovascular risk in elderly populations (17, 42, 43) but extend this literature in important ways. The literature on loss in elderly populations primarily focuses on spousal loss, that is, widowhood. Yet, given the wide range of losses experienced across the life course and existing racial/ethnic disparities in those losses (44), this analysis defined loss more broadly than widowhood. Observed findings support the merits of this approach, because although some women were widowed over follow-up, findings were similar with and without those participants, indicating that our loss and cardiovascular risk associations were not limited to the effects of spousal loss alone. Furthermore, our focus on mid rather than late life allowed for an examination of the influence of loss on cardiovascular risk earlier in the lifespan in a cohort including African-American women, a subgroup in the United States with a relatively high rate of exposure to loss.

Our findings suggest that African-American women may be especially vulnerable to the impact of midlife loss on cardiovascular risk relative to White women, and potentially women from other racial/ethnic groups, for reasons that are currently unknown. Consistent with national trends (45), African-American women in SWAN were the least likely to be married/partnered among all participants; thus, given the possibility that close friends and/or family members play a larger role in the lives of women who are single, we examined whether midlife loss would be more deleterious for consistently single (vs. partnered) women in race/ethnicity-stratified exploratory analyses. Associations were not more pronounced among single compared to partnered African-American women (or women from other racial/ethnic groups), indicating that factors other than married/partner status may underlie our observed relationships.

Evidence from prior studies suggests that social ties may have a greater impact on cardiovascular risk among African Americans, especially African-American women, compared with men and women from other racial/ethnic groups (46, 47). For example, in 1 study of middle-aged African-American men and women and White men and women, researchers found that the frequency of social contacts (i.e., talking or visiting with friends and relatives) was more strongly associated with reductions in blood pressure dipping for the (predominantly female) African Americans in their cohort relative to Whites (47). In another cohort of middle-aged African-American men and women and White men and women, researchers found that the beneficial effects of social cohesion (e.g., neighborhood level social connectedness) on inflammation were only observed among the African-American women in the cohort and not among African-American men, White women, or White men (46). Some scholars have posited that African-American women may be more embedded in their social networks than are those of other race or gender groups, due to gender-role norms (e.g., communalism, caretaking) in the context of social disadvantage (48–50), which could explain some of the stronger associations among this group. Although, to our knowledge, studies in this area have not focused on loss per se, it is conceivable that, similar to the presence of social ties, the loss of social ties also may have more influence on cardiovascular risk among African-American women. Additional research in this area is warranted.

It is also possible that the deaths of close friends and/or family members represent a collective threat for African-American women (44). Although we did not inquire about the racial/ethnic background of the friends and/or family members who died, given prior data documenting substantial racial/ethnic homogeneity in family and friend circles (51–53), it is likely that most of the women experienced the deaths of same-race/ethnicity friends and family members. Compared with individuals from other racial/ethnic backgrounds, African Americans are more likely to endorse a sense of linked fate (54, 55), that is, believing that what happens to other members of their racial/ethnic group has direct consequences for them as individuals (56). In this respect, for African-American women, the deaths of close friends and family members who are also African-American might increase their sense of personal vulnerability to death, as a result of their shared group membership (44). Consequently, in addition to the overall stress of cumulative loss, African-American women who have a greater sense of linked fate might experience additional stress due to the potential threat to self and/or community that these losses signify. Research is needed to examine the interrelationships among loss, collective threat after loss, and cardiovascular risk in vulnerable populations.

There are several physiological pathways through which cumulative midlife loss might affect carotid atherosclerosis among African-American women. Studies have documented associations between exposure to loss and dysregulated hypothalamic-pituitary-adrenal axis functioning (57–59) and immune function (41, 60–62). Fewer studies have examined autonomic pathways; yet there is evidence that loss may also be associated with greater autonomic dysregulation

(60, 63). All these factors could result in greater carotid atherosclerosis and increased CVD risk. To date, however, much of the research in this area has been conducted in predominantly White populations (41, 56, 58, 59, 63). Additional research on physiological mechanisms linking various forms of loss to CVD risk among racial/ethnic minority groups, and African-American women in particular, is needed.

This study has limitations. First, our cohort was limited to women. Because women live longer than men, particularly among African Americans (64), it is possible that both the exposure to and impact of loss on CVD risk are greatest among this group. Nonetheless, studies are needed to determine whether similar associations are observed in men, given evidence that certain losses (e.g., widowhood) affect middle-aged men more strongly than women (65). In addition, we had relatively few Chinese and Hispanic women in our analysis. Thus, we cannot definitively conclude whether the impact of midlife loss on cardiovascular risk is stronger among African-American women compared with women from these other racial/ethnic minority groups or is comparable among racial/ethnic minority women overall. But because Chinese and Hispanic populations in the United States live longer than African Americans (and Whites) (64), it is probable that exposure to midlife loss is substantially lower among Chinese and Hispanic women, relative to their African-American counterparts. Consequently, the overall population-level burden of loss on CVD risk is also likely to be lowest among these groups. However, additional research with larger multiracial/ethnic cohorts of women is needed. Furthermore, although we inquired about the occurrence of loss, information about the nature of the loss (i.e., expected vs. unexpected, due to natural vs. unnatural causes) is unknown. Authors of at least 1 prior study of women found no difference in the impact of unnatural versus natural deaths among friends or family member on indices of health (61), but this is an area of research that requires more exploration. We are also unable to determine exactly who died. Although research suggests that African Americans and other racial/ethnic minority groups have family-like relationships with individuals outside of their biological families (e.g., “fictive kin”) (66, 67), it is possible that the deaths of biological family members either inside (e.g., partner, child) or outside (e.g., parent, sibling, other close relative) of the home are more impactful than the deaths of close friends. Finally, we only assessed IMT at 1 timepoint; consequently, we do not know whether midlife loss contributes to increases in IMT over time.

Despite these limitations, our study has several strengths. The SWAN cohort is well characterized and is 1 of the largest studies of midlife women in the United States. Because of the nature of the design, we were able to assess loss prospectively for over a decade throughout midlife, a time when racial/ethnic disparities in loss are likely to be most pronounced. This allowed us to examine the impact of a highly salient psychosocial exposure in a relatively understudied population of women. Our outcome, IMT, was assessed using well-validated techniques, and we adjusted for a comprehensive range of physical, behavioral, and psychosocial confounders.

In sum, our findings suggest that cumulative loss may be an important race/ethnicity-related stressor to consider in future research. Because the average age of CVD onset in women overall (including African-American women) is older than 65 years (3, 68, 69), our use of a surrogate marker of CVD was appropriate, given the age of women in the SWAN cohort at the time of the IMT assessment. However, prospective, longitudinal studies are needed to determine whether exposure to loss is associated with incident clinical CVD events. Additional studies identifying the physiological and psychological pathways through which cumulative loss affects CVD risk and incident CVD might also prove useful. Finally, research focused on designing and evaluating interventions after loss for African-American women and other vulnerable groups may be warranted.

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