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Original Contribution

A Population-based Case-Control Study of Stillbirth: The Relationship of Significant Life Events to the Racial Disparity for African Americans

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Stillbirths (fetal deaths occurring at ≥20 weeks' gestation) are approximately equal in number to infant deaths in the United States and are twice as likely among non-Hispanic black births as among non-Hispanic white births. The causes of racial disparity in stillbirth remain poorly understood. A population-based case-control study conducted by the Stillbirth Collaborative Research Network in 5 US catchment areas from March 2006 to September 2008 identified characteristics associated with racial/ethnic disparity and interpersonal and environmental stressors, including a list of 13 significant life events (SLEs). The adjusted odds ratio for stillbirth among women reporting all 4 SLE factors (financial, emotional, traumatic, and partner-related) was 2.22 (95% confidence interval: 1.43, 3.46). This association was robust after additional control for the correlated variables of family income, marital status, and health insurance type. There was no interaction between race/ethnicity and other variables. Effective ameliorative interventions could have a substantial public health impact, since there is at least a 50% increased risk of stillbirth for the approximately 21% of all women and 32% of non-Hispanic black women who experience 3 or more SLE factors during the year prior to delivery.

African Americans; case-control studies; continental population groups; life change events; psychosocial stress; socioeconomic factors; stillbirth; stress

Abbreviations: PRAMS, Pregnancy Risk Assessment Monitoring System; SCRN, Stillbirth Collaborative Research Network; SLEs, significant life events.

Annually, stillbirths (fetal deaths occurring at ≥20 weeks' gestation) nearly equal the number of US infant deaths (25,972 stillbirths compared with 28,509 infant deaths in 2006) (1). Stillbirth rates have declined very little in recent decades (2) and have been about twice as high for nonwhite births as for white births ever since US vital statistics first began to be published by race/ethnicity in 1922 (3). Racial disparities narrowed somewhat by midcentury but increased again thereafter. In 2006, the highest stillbirth rate of 10.73 per 1,000 births among non-Hispanic black (hereafter black) births equaled the overall US rate 30 years earlier and was more than 2.2 times the lowest rates of 4.89 for Asian/Pacific Island births and 4.81 for non-Hispanic white (hereafter white) births (1, 4).

Causes of the persistent racial disparities remain unclear, although previous stillbirth, a short interpregnancy interval, obesity, late or no prenatal care, low maternal education, and maternal stress occur more frequently among black women than among white women (2). However, a combination of risk factors determinable at the time of pregnancy confirmation explained little of the black-white disparity in the Stillbirth Collaborative Research Network (SCRN) Study (5).

Table 1. Baseline Characteristics of Participants in the SCRN Study, by Stillbirth Case Status, March 2006–September 2008

Characteristic	% of Births		Crude OR	95% CI	*P* Value
	Stillbirths ($n = 614$)[a]	Livebirths ($n = 1,354$)[a]			
Sociodemographic Characteristics					
Maternal age at delivery, years					0.0064
<20	13.4	10.5	1.39	1.04, 1.87	
20–34	69.6	75.6	1.00	Referent	
35–39	12.5	11.8	1.15	0.84, 1.57	
≥40	4.5	2.1	2.35	1.31, 4.22	
Maternal race/ethnicity					<0.0001
Non-Hispanic white	33.4	45.3	1.00	Referent	
Non-Hispanic black	23.1	11.2	2.78	2.12, 3.66	
Hispanic	36.3	35.7	1.38	1.10, 1.73	
Other	7.1	7.7	1.24	0.83, 1.85	
Marital/cohabitation status					<0.0001
Not married or cohabiting	25.4	15.3	2.08	1.62, 2.66	
Cohabiting	25.9	24.0	1.34	1.06, 1.71	
Married	48.7	60.7	1.00	Referent	
Health insurance/method of payment					0.0062
No insurance	5.5	3.5	1.84	1.15, 2.95	
Any public/private assistance	54.4	49.4	1.29	1.05, 1.58	
VA/commercial health insurance/HMO	40.1	47.1	1.00	Referent	
Family income in the past 12 months					0.0969
Only public/private assistance	8.7	6.0	1.55	1.04, 2.30	
Assistance and personal income	37.9	37.5	1.07	0.87, 1.32	
Only personal income	53.4	56.6	1.00	Referent	

Table continues

One possible explanation for black-white disparities in poor pregnancy outcomes is differential exposure to stressful life events (6, 7).

With some exceptions (8, 9), accumulating evidence supports a link between stress and poor pregnancy outcomes, including preterm birth (10–12), stillbirth (13), and low birth weight (14, 15). Stress has also been associated with increased risk of infectious diseases in offspring (16) and congenital malformations (17). While pregnancy-specific stressors seem to be especially predictive of problematic outcomes (18), the association exists regardless of whether the stressor occurred before or during the pregnancy (11, 14). Perhaps living with chronic stress or experiencing a severe stressful life event prior to pregnancy sensitizes women, making them more vulnerable to the effects of pregnancy-related stress. Thus, if exposure to stress is a risk factor for poor pregnancy outcomes and if black women are disproportionately affected by stress—whether through poverty (19, 20), living conditions (20, 21), or racism/discrimination (7, 22)—then exposure to stressful life events may explain some of the black-white disparity in stillbirth.

The SCRN Study was a multisite, population-based case-control study (23). Among other objectives, the SCRN Study was designed to identify characteristics associated with the excess stillbirth rate among black women and to measure the association of prenatal exposure to interpersonal and environmental stressors, including a list of significant life events (SLEs) that had been associated in previous research with poor pregnancy outcomes. We report here on the association of SLEs with stillbirth and whether social supports decrease the association of SLEs with stillbirth, and we explore whether different experiences of SLEs may help to explain some of the racial disparity in stillbirth.

MATERIALS AND METHODS

Data source

The overall design and methods of the SCRN Study have been previously reported (23). We selected 59 community and academic hospitals because together they were estimated to include at least 90% of resident deliveries for 5 catchment areas defined a priori by state or county boundaries (3 Texas counties (Bexar, Brazoria, and Galveston counties), 1 Georgia county (DeKalb County), 1 Utah county (Salt Lake County), Rhode Island, and 1 Massachusetts

Table 1. Continued

Characteristic	% of Births		Crude OR	95% CI	*P* Value
	Stillbirths ($n = 614$)[a]	Livebirths ($n = 1,354$)[a]			
Maternal Medical and Physiological Characteristics					
Body mass index[b]					0.0001
<18.5 (underweight)	4.1	3.3	1.66	0.99, 2.75	
18.5–24.9 (normal weight)	38.2	50.2	1.00	Referent	
25.0–29.9 (overweight)	26.0	22.6	1.52	1.18, 1.94	
30.0–34.9 (obese)	15.5	12.4	1.64	1.21, 2.22	
≥35 (morbidly obese)	16.3	11.5	1.86	1.36, 2.54	
Blood type					0.0454
A	30.2	34.5	0.87	0.70, 1.09	
B	13.7	11.4	1.20	0.88, 1.63	
O	51.2	51.1	1.00	Referent	
AB	4.9	3.0	1.63	0.99, 2.69	
Diabetes[c]	5.6	1.6	3.53	2.07, 6.01	<0.0001
Pregnancy-associated Characteristics					
Pregnancy history					<0.0001
Nulliparous; never pregnant or only elective terminations	34.0	29.7	1.58	1.25, 2.00	
Nulliparous with previous spontaneous loss(es)	10.5	5.2	2.80	1.91, 4.12	
Multiparous with no previous losses of <20 weeks' gestation or stillbirths	33.7	46.5	1.00	Referent	
Multiparous with no stillbirth, but previous loss(es) of <20 weeks' gestation	15.1	17.1	1.22	0.91, 1.63	
Multiparous with stillbirth	6.7	1.4	6.41	3.77, 10.91	
Multifetal pregnancy[c]	6.4	1.9	3.62	1.97, 6.65	<0.0001

Abbreviations: CI, confidence interval; HMO, health maintenance organization; OR, odds ratio; SCRN, Stillbirth Collaborative Research Network; VA, Veterans Affairs.

[a] Results shown are weighted for the study design and differential consent based on characteristics recorded in the screened population. The analysis was restricted to women with a maternal interview and chart abstraction, resulting in weighted (unweighted) sample sizes of 614 (614) women with stillbirth and 1,354 (1,816) women with livebirth. The sample sizes varied slightly for some of the characteristics included in the table. Specifically, there were missing values for marital status ($n = 7$), health insurance ($n = 7$), family income ($n = 27$), body mass index ($n = 25$), blood type ($n = 11$), and diabetes ($n = 1$).

[b] Weight (kg)/height $(m)^2$.

[c] For these dichotomous variables, the odds ratios presented are for persons with the characteristic described versus those without it.

county (Bristol County)). We defined study eligibility by maternal residence in the catchment area and delivery at one of these hospitals.

From March 2006 through September 2008, SCRN staff attempted to recruit all eligible women delivering a stillborn infant and a representative sample of eligible women with livebirths, with oversampling of those delivering at <32 weeks' gestation and those of African descent delivering at ≥32 weeks' gestation (23). Stillbirth was defined by Apgar scores of 0 at 1 and 5 minutes and no signs of life by direct observation. Deliveries resulting from termination of a live fetus were excluded. The gestational age criterion of ≥20 weeks was determined by best clinical estimate using an algorithm that included multiple sources (24). Fetal deaths at 18 or 19 weeks without good dating were included to assure that stillbirths occurring at ≥20 weeks but with incorrect dating could be enrolled. Data collection included an in-hospital maternal interview, medical record abstraction for prenatal care and antepartum and delivery hospitalizations, placental pathology examinations (25), and biospecimen collection for all enrolled deliveries. For stillbirths, a standardized postmortem examination was performed, and fetal tissue was collected for future studies (26, 27).

The study was approved by the institutional review boards of the academic centers, the participating hospitals, and the data coordinating center. A limited HIPAA (Health Insurance Portability and Accountability Act) waiver was obtained from all institutional review boards for surveillance, screening, and minimal data collection from potential participants. An advisory board reviewed the progress and safety of the study. All participants in the case-control study gave written informed consent.

Significant life events

Maternal interview included the 13-item SLE scale of the Centers for Disease Control and Prevention's Pregnancy Risk Assessment Monitoring System (PRAMS) (28). Participants were asked whether or not each event had occurred during the 12 months prior to their delivery. Cronbach's α for the overall scale was 0.67, with similar values for the individual racial/ethnic groups (α's ranged from 0.64 to 0.67). Prior studies found that the items on the scale could be grouped into 4 factors: financial, emotional, traumatic, and partner-related events (29–31). A confirmatory factor analysis conducted using Mplus (32) verified that the 4-factor structure provided a good fit to the data from the current study (Comparative Fit Index = 0.963, Tucker-Lewis Index = 0.951, and root mean square error of approximation = 0.031); similar fit indices were found when we examined each of the racial/ethnic groups separately. Scoring on the number of SLE factors was categorized as "yes" if any of the items in the factor was present and "no" otherwise, with possible scores ranging from 0 to 4.

Potential confounders

Our goal was to estimate the total effect (33, 34) of SLEs on the risk of stillbirth. We drafted directed acyclic graphs to determine which variables to include as potential confounders (see Web Figure 1, included in the Web Appendix at http://aje.oxfordjournals.org/). We assumed that experience of SLEs may increase the risk of illicit drug use, excessive alcohol drinking, and smoking. Therefore, to measure the total effect of SLEs, we did not include these intermediate variables in the model.

At least some SLEs may be more likely to occur just before or during pregnancy among women with prior poor pregnancy outcomes. For example, partner relationships may be more difficult if the couple is worried about a repeat stillbirth. Thus, it would seem logical to include prior pregnancy history in the model to control for confounding. We also included variables listed in Table 1 that had been associated with stillbirth in the SCRN Study (5) and that hypothetically might affect future exposure to SLEs (34): maternal age, blood type, diabetes, and obesity.

We included a variable indicating multifetal pregnancy, since postconception SLEs may be different for women with multiple conceptions. We controlled for race/ethnicity because both race and ethnicity are likely to affect both previous and current SLE exposure and pregnancy outcomes.

Some sociodemographic variables (income, health insurance status, and marital status at delivery) are closely correlated with specific items in the SLE list. Because we did not know when during the previous 12 months the SLEs had occurred or whether there had been changes in income, insurance, or marital status from conception to delivery, we could not determine the temporality of SLEs vis-à-vis alterations in these variables. For the main analysis, we excluded these correlated variables. We then conducted a type of sensitivity analysis by 1) substituting them for the SLE variable in the final model estimating the total effect of SLEs on stillbirth and 2) including them and the SLEs in a model. We also examined sensitivity models with and without substance use and pregnancy history. We initially included a mediator for social support, using the 6-item PRAMS measure (28). However, we dropped this because more than 90% of women who had stillbirths or livebirths reported positively for all of the social support items. There were no significant associations between the items of social support or the degree of support (number of items) and stillbirth.

Statistical analysis

A total of 953 women with stillbirths and 3,088 women with livebirths were identified as potentially eligible. Of these, 70% of the cases and 63% of the controls consented to participate, yielding 663 stillbirths and 1,932 livebirths (5, 23). Using recorded characteristics of the screened population, we previously determined that there was no difference in those characteristics between the women with stillbirth who enrolled and those who did not consent. For livebirths, we reported slight differences in both race/ethnicity and gestational age between women who enrolled in the study and those who did not (race/ethnicity: whites, 42.2% vs. 41.3%; blacks, 24.8% vs. 21.0%; Hispanics, 27.0% vs. 34.4%; and women of other races/ethnicities, 6.0% vs. 3.3% ($P < 0.001$); gestational age at delivery: 20–23 weeks, 10.0% vs. 7.0%; 24–27 weeks, 7.4% vs. 5.6%; 28–31 weeks, 6.4% vs. 5.0%; 32–36 weeks, 7.3% vs. 7.5%; and ≥37 weeks, 68.9% vs. 74.9% ($P = 0.002$)) (5).

This analysis included all enrolled women who were interviewed and for whom prenatal records were abstracted (614 cases and 1,816 controls). As previously reported, maternal race/ethnicity was similar among excluded and included stillbirths but differed slightly among controls (5).

Using SUDAAN software, version 10.0 (35), and standard survey methods, we computed weight adjustments to account for staggered starts in enrollment across the site hospitals and different sampling probabilities for livebirths by gestational age and race/ethnicity. Then, using generalized exponential models for the propensity to participate, with variables available on all screened women, we added 2 weight adjustments: 1) for women who were eligible but were not approached because their health-care providers did not give assent and 2) for women who were approached but did not consent to participate. We then computed analysis weights as the product of the various weight adjustments (23). The resulting number of weighted controls was smaller than the unweighted number, because of the down-weighting of oversampled groups.

The number of SLE items and the number of SLE factors were treated as categorical variables in analyses. However,

Table 2. Significant Life Events Experienced by Pregnant Women During the 12 Months Prior to Delivery (Item Summary), by Stillbirth Case Status, SCRN Study, March 2006–September 2008

Characteristic	% of Births		Crude OR	95% CI	*P* Value
	Stillbirths ($n = 614$)[a]	Livebirths ($n = 1,354$)[a]			
No. of SLE items					
0	17.8	25.4	1.00	Referent	<0.0001
1	21.2	24.1	1.26	0.93, 1.71	
2	20.3	20.5	1.42	1.03, 1.94	
3	14.5	11.8	1.75	1.24, 2.48	
4	9.1	8.0	1.63	1.08, 2.45	
≥5	17.2	10.3	2.40	1.70, 3.39	
Test for linear trend					<0.0001
Test for quadratic trend					0.9920
Any SLE item[b]	82.4	74.8	1.58	1.23, 2.03	0.0003
SLE factor[b]					
Financial	38.7	28.2	1.60	1.30, 1.98	<0.0001
Emotional	44.0	39.0	1.23	1.01, 1.50	0.0392
Traumatic	47.2	41.3	1.27	1.04, 1.55	0.0170
Partner-related	46.6	38.7	1.38	1.13, 1.69	0.0014
No. of SLE factors					
0	17.7	25.4	1.00	Referent	0.0001
1	27.4	29.5	1.34	1.00, 1.78	
2	25.9	24.6	1.51	1.12, 2.04	
3	18.7	14.1	1.91	1.38, 2.65	
4	10.2	6.5	2.25	1.49, 3.39	
Test for linear trend					<0.0001
Test for quadratic trend					0.7641

Abbreviations: CI, confidence interval; OR, odds ratio; SCRN, Stillbirth Collaborative Research Network; SLE, significant life event.

[a] Results shown are weighted for the study design and differential consent based on characteristics recorded in the screened population. The weighted sample sizes shown are for women with a maternal interview and chart abstraction. Unweighted sample sizes were 614 and 1,816 for stillbirths and livebirths, respectively. Weighted sample sizes varied slightly for SLE characteristics shown—specifically, from 602 to 608 for stillbirths and from 1,330 to 1,340 for livebirths.

[b] For these dichotomous variables (i.e., any SLE item or an SLE factor), the odds ratios presented are for persons with the characteristic described versus those without it.

tests for linear and quadratic trends in the log odds of stillbirth were also conducted using orthogonal contrasts.

Case and control comparisons

Crude and adjusted odds ratios and 95% confidence intervals were calculated from univariate and multivariable logistic models. All tests were performed at a nominal significance level of $\alpha = 0.05$. All single degree-of-freedom tests were 2-sided. We examined the association between SLEs and stillbirth overall and within race/ethnicity groups. We controlled for potentially confounding variables and tested for interaction between potential confounders and race/ethnicity. We performed further analyses in 2 subgroups to examine risk factors among 1) potentially viable cases and controls (deliveries at ≥24 weeks' gestational age) and 2) deliveries not known to be at high risk of stillbirth (i.e., excluding intrapartum stillbirths and limiting the sample to singleton, nonanomalous deliveries).

RESULTS

Baseline characteristics

Women with livebirths were more likely than women with stillbirths to be 20–39 years of age, white, married, privately insured, of normal weight, and nondiabetic. Conversely, women with stillbirths were more likely to have the AB blood type, to have a multifetal pregnancy, and to be nulliparous or to have experienced a prior spontaneous loss (Table 1). Among all women, race/ethnicity was associated with marital status, family income, and health insurance

Table 3. Significant Life Events Experienced by Pregnant Women During the 12 Months Prior to Delivery (Item Level), by Stillbirth Case Status, SCRN Study, March 2006–September 2008

SLE Item[a]	% of Births		Crude OR	95% CI	*P* Value
	Stillbirths ($n = 614$)[b]	Livebirths ($n = 1,354$)[b]			
Financial					
My husband or partner lost his job	15.2	12.4	1.27	0.96, 1.69	0.0951
I lost my job even though I wanted to go on working	12.4	8.2	1.58	1.13, 2.21	0.0078
I had a lot of bills I couldn't pay	26.9	17.8	1.70	1.34, 2.14	<0.0001
Emotional					
I moved to a new address	39.8	35.7	1.19	0.98, 1.46	0.0844
I was homeless	3.6	2.3	1.59	0.92, 2.75	0.0939
My husband or partner or I went to jail	9.5	5.7	1.76	1.24, 2.50	0.0016
Traumatic					
A close family member was very sick and had to go into the hospital	38.7	34.2	1.22	0.99, 1.49	0.0619
Someone very close to me died	21.6	21.4	1.01	0.79, 1.29	0.9127
Partner-related					
I got separated or divorced from my husband or partner	16.2	11.1	1.55	1.18, 2.05	0.0018
I argued with my husband or partner more than usual	29.0	23.4	1.33	1.07, 1.66	0.0109
My husband or partner said he didn't want me to be pregnant	9.8	5.4	1.93	1.35, 2.76	0.0003
I was in a physical fight	7.6	3.5	2.25	1.50, 3.39	<0.0001
Someone very close to me had a bad problem with drinking or drugs	20.5	16.6	1.30	1.00, 1.68	0.0494

Abbreviations: CI, confidence interval; OR, odds ratio; SCRN, Stillbirth Collaborative Research Network; SLE, significant life event.

[a] Items are dichotomous, and odds ratios are for those with the SLE noted versus those without it.

[b] Results shown are weighted for the study design and differential consent based on characteristics recorded in the screened population. The weighted sample sizes shown are for women with a maternal interview and chart abstraction. Unweighted sample sizes were 614 and 1,816 for stillbirths and livebirths, respectively. Weighted sample sizes varied slightly for SLE items—specifically, from 604 to 608 for stillbirths and from 1,335 to 1,341 for livebirths.

(data not shown). White women were more likely than black or Hispanic women to be married, to have private insurance, and to receive no public assistance.

Frequency of SLEs and association of SLEs with stillbirth

Among the women who delivered a stillborn infant, 82.4% reported at least 1 SLE as compared with 74.8% of women delivering a live infant (Table 2). The most common SLEs were moving to a new address and having a close family member go to the hospital (Table 3). Among the strongest associations with stillbirth were having a lot of bills to pay, going to jail or having a partner who went to jail, having a partner who did not want a pregnancy, and being involved in a physical fight. Compared with no reported events, the odds for stillbirth increased with the number of SLEs experienced (out of a possible 13), from 1.3-fold for 1 event to 2.4-fold for 5 or more events (P for linear trend < 0.0001) (Table 2). All 4 SLE factors were significantly associated with stillbirth. Compared with no factors mentioned, the odds of stillbirth increased with an increasing number of factors, from 1.3-fold for 1 factor to 2.3-fold for 4 factors (P for linear trend < 0.0001).

Results were similar when analyses were restricted to potentially viable fetuses (data not shown). Among deliveries taking place at ≥24 weeks' gestation, the odds of stillbirth increased from 1.2-fold for 1 SLE factor to 2.2-fold for 4 factors (P for linear trend = 0.0001). In the subgroup of singleton, nonanomalous deliveries, excluding intrapartum stillbirths, the odds of stillbirth increased from 1.3 to 2.6 (P for linear trend = 0.0001).

Except for traumatic events, black women were more likely than white and Hispanic women to report SLEs (Table 4). The distribution of SLE factors varied by race/ethnicity; black women experienced fewer traumatic events but

Table 4. Significant Life Events Experienced by Pregnant Women During the 12 Months Prior to Delivery (Factor Summary), by Stillbirth Case Status and Race/Ethnicity, SCRN Study, March 2006–September 2008

Characteristic	Race/Ethnicity																	
	White, Non-Hispanic				Black, Non-Hispanic				Hispanic				Other				All	
	SB, % (n = 205)[a]	LB, % (n = 613)[a]	cOR	95% CI	SB, % (n = 142)[a]	LB, % (n = 152)[a]	cOR	95% CI	SB, % (n = 223)[a]	LB, % (n = 484)[a]	cOR	95% CI	SB, % (n = 44)[a]	LB, % (n = 105)[a]	cOR	95% CI	aOR	95% CI
SLE factor[b]																		
Financial	36.2	24.1	1.79	1.25, 2.57	48.1	39.8	1.40	0.90, 2.19	34.9	28.2	1.36	0.97, 1.92	39.3	35.8	1.16	0.55, 2.47	1.49	1.21, 1.84
Emotional	44.4	37.2	1.35	0.97, 1.88	45.7	50.8	0.82	0.52, 1.27	42.1	37.1	1.23	0.89, 1.71	46.5	40.1	1.30	0.62, 2.72	1.19	0.97, 1.45
Traumatic	48.6	46.1	1.11	0.80, 1.53	44.5	40.2	1.20	0.76, 1.87	47.3	35.5	1.63	1.18, 2.26	49.3	41.2	1.39	0.67, 2.86	1.32	1.08, 1.60
Partner-related	41.1	34.1	1.35	0.96, 1.90	53.8	49.6	1.18	0.76, 1.85	46.5	40.2	1.29	0.93, 1.78	48.9	42.2	1.31	0.64, 2.69	1.29	1.06, 1.58
No. of SLE factors																		
0	18.7	25.4	1.00	Referent	15.5	15.8	1.00	Referent	19.2	28.7	1.00	Referent	11.9	24.2	1.00	Referent	1.00	Referent
1	29.1	31.8	1.24	0.79, 1.96	21.7	30.1	0.73	0.34, 1.57	29.0	27.4	1.58	0.99, 2.53	30.4	24.3	2.53	0.80, 8.00	1.32	0.99, 1.76
2	23.9	25.3	1.28	0.79, 2.08	30.4	22.4	1.39	0.65, 2.94	24.3	24.0	1.51	0.93, 2.44	29.1	25.7	2.30	0.71, 7.43	1.47	1.09, 1.97
3	19.8	11.2	2.40	1.38, 4.16	20.2	21.5	0.95	0.44, 2.08	16.9	14.3	1.77	1.04, 3.01	18.9	19.3	1.99	0.57, 6.89	1.77	1.28, 2.47
4	8.6	6.4	1.82	0.89, 3.74	12.2	10.1	1.23	0.50, 3.02	10.6	5.6	2.84	1.47, 5.50	9.6	6.5	3.01	0.71, 12.8	2.08	1.39, 3.13

Abbreviations: aOR, adjusted odds ratio; CI, confidence interval; cOR, crude OR; LB, livebirths; OR, odds ratio; SB, stillbirths; SCRN, Stillbirth Collaborative Research Network; SLE, significant life event.

[a] Results shown are weighted for the study design and differential consent based on characteristics recorded in the screened population. The weighted sample sizes shown are for women with a maternal interview and chart abstraction. Unweighted sample sizes were 614 and 1,816 for stillbirths and livebirths, respectively. Weighted sample sizes varied slightly for the SLE characteristics shown—specifically, from 604 to 608 for stillbirths and from 1,331 to 1,339 for livebirths.

[b] For these dichotomous variables (i.e., an SLE factor), the odds ratios presented are for persons with the characteristic described versus those without it.

Table 5. Results From Multivariable Analysis of the Association Between Significant Life Events and Stillbirth Case Status, SCRN Study, March 2006–September 2008[a]

Characteristic	SLE—Excluding Marital Status, Health Insurance, and Income			Marital Status, Health Insurance, and Income—Excluding SLE			SLE + Marital Status, Health Insurance, and Income		
	aOR	95% CI	*P* Value	aOR	95% CI	*P* Value	aOR	95% CI	*P* Value
Sociodemographic Characteristics									
Maternal age at delivery, years			0.0386			0.0487			0.0366
<20	1.12	0.80, 1.58		1.02	0.70, 1.46		1.01	0.70, 1.46	
20–34	1.00	Referent		1.00	Referent		1.00	Referent	
35–39	1.28	0.91, 1.79		1.25	0.89, 1.76		1.28	0.90, 1.81	
≥40	2.28	1.22, 4.25		2.24	1.22, 4.09		2.35	1.26, 4.36	
Maternal race/ethnicity			<0.0001			0.0001			0.0003
Non-Hispanic white	1.00	Referent		1.00	Referent		1.00	Referent	
Non-Hispanic black	2.62	1.80, 3.80		2.39	1.62, 3.51		2.33	1.57, 3.46	
Hispanic	1.32	1.00, 1.74		1.17	0.87, 1.57		1.20	0.90, 1.62	
Other	1.12	0.74, 1.71		1.09	0.72, 1.66		1.07	0.70, 1.64	
Marital/cohabitation status						0.0023			0.0092
Not married or cohabiting				1.76	1.28, 2.42		1.66	1.20, 2.31	
Cohabiting				1.29	0.97, 1.71		1.24	0.93, 1.65	
Married				1.00	Referent		1.00	Referent	
Health insurance/method of payment						0.0462			0.0667
No insurance				1.93	1.15, 3.25		1.86	1.09, 3.15	
Any public/private assistance				1.12	0.83, 1.51		1.08	0.80, 1.46	
VA/commercial health insurance/HMO				1.00	Referent		1.00	Referent	
Family income in the past 12 months						0.3559			0.2201
Only public/private assistance				0.96	0.60, 1.52		0.95	0.59, 1.53	
Assistance and personal income				0.83	0.63, 1.08		0.79	0.60, 1.04	
Only personal income				1.00	Referent		1.00	Referent	
Maternal Medical/Physiological Characteristics									
Body mass index[b]			0.0030			0.0007			0.0008
<18.5 (underweight)	1.45	0.83, 2.51		1.61	0.94, 2.75		1.47	0.85, 2.56	
18.5–24.9 (normal weight)	1.00	Referent		1.00	Referent		1.00	Referent	
25.0–29.9 (overweight)	1.42	1.10, 1.84		1.46	1.13, 1.90		1.44	1.11, 1.88	
30.0–34.0 (obese)	1.67	1.20, 2.32		1.80	1.29, 2.50		1.79	1.28, 2.50	
≥35 (morbidly obese)	1.66	1.19, 2.31		1.68	1.21, 2.34		1.75	1.25, 2.45	
Blood type			0.0476			0.0511			0.0326
A	0.89	0.70, 1.13		0.94	0.74, 1.19		0.90	0.71, 1.15	
B	1.13	0.82, 1.57		1.18	0.86, 1.64		1.19	0.85, 1.65	
O	1.00	Referent		1.00	Referent		1.00	Referent	
AB	1.82	1.08, 3.06		1.89	1.13, 3.16		1.90	1.13, 3.20	
Diabetes[c]	2.58	1.43, 4.67	0.0017	2.45	1.39, 4.32	0.0020	2.47	1.38, 4.42	0.0024

Table continues

the greatest number of SLEs (Web Table 1). Experiencing incarceration (partner or self) and undergoing either separation or divorce were reported more than twice as frequently by black and Hispanic women as by white women. Black women also reported being in a physical fight more frequently than did white or Hispanic women. Inability to pay bills was associated with increased stillbirth risk for both whites and blacks. Among whites, the partner's not wanting the pregnancy increased stillbirth risk almost 3-fold. Among Hispanics, the uniquely significant stillbirth risks were: husband or partner went to jail, hospitalization of someone close, and being in a physical fight.

Table 5. Continued

Characteristic	SLE—Excluding Marital Status, Health Insurance, and Income			Marital Status, Health Insurance, and Income—Excluding SLE			SLE + Marital Status, Health Insurance, and Income		
	aOR	95% CI	*P* Value	aOR	95% CI	*P* Value	aOR	95% CI	*P* Value
Pregnancy-associated Characteristics									
Pregnancy history			<0.0001			<0.0001			<0.0001
Nulliparous, never pregnant or only elective terminations	1.87	1.44, 2.42		1.80	1.38, 2.34		1.81	1.38, 2.36	
Nulliparous with previous spontaneous loss(es)	2.78	1.88, 4.12		2.93	1.96, 4.38		2.80	1.87, 4.20	
Multiparous with no previous losses of <20 weeks' gestation or stillbirths	1.00	Referent		1.00	Referent		1.00	Referent	
Multiparous with no stillbirth, but previous loss(es) of <20 weeks' gestation	1.15	0.84, 1.56		1.16	0.85, 1.59		1.16	0.85, 1.59	
Multiparous with stillbirth	5.77	3.23, 10.33		6.09	3.38, 10.99		6.06	3.35, 10.97	
Multifetal pregnancy[c]	4.39	2.50, 7.71	<0.0001	4.38	2.49, 7.71	<0.0001	4.44	2.51, 7.87	<0.0001
Significant Life Events									
No. of SLE factors			0.0024						0.0253
0	1.00	Referent					1.00	Referent	
1	1.30	0.96, 1.76					1.31	0.96, 1.77	
2	1.35	0.99, 1.85					1.34	0.98, 1.85	
3	1.72	1.22, 2.42					1.66	1.17, 2.35	
4	2.22	1.43, 3.46					1.91	1.20, 3.04	
Test for linear trend			0.0001						0.0027
Test for quadratic trend			0.7284						0.9039

Abbreviations: aOR, adjusted odds ratio; CI, confidence interval; HMO, health maintenance organization; SCRN, Stillbirth Collaborative Research Network; SLE, significant life event; VA, Veterans Affairs.

[a] Results shown are weighted for the study design and differential consent based on characteristics recorded in the screened population. The analysis was restricted to women with a maternal interview and chart abstraction, resulting in weighted (unweighted) sample sizes of 614 (614) women with stillbirth and 1,354 (1,816) women with livebirth. The sample size was further reduced due to inclusion of variables in the model that had missing values for some women with a maternal interview and chart abstraction. The weighted (unweighted) sample sizes for women with stillbirth and women with livebirth included in the model were: 593 (593) and 1,322 (1,779) for model 1; 588 (588) and 1,323 (1,777) for model 2; and 582 (583) and 1,311 (1,764) for model 3. In addition to the variables shown in the table, clinical site (catchment area) was included in the multivariable models.

[b] Weight (kg)/height $(m)^2$.

[c] For these dichotomous variables, the odds ratios presented are for persons with the characteristic described versus those without it.

The proportion of women with multiple SLE factors was also higher among black women. With the exception of emotional factors, SLE factors were significantly associated with stillbirth when results were adjusted for race/ethnicity, and the association with stillbirth increased with an increasing number of factors when results were adjusted for race/ethnicity (Table 4).

Multivariate analysis

The adjusted odds ratios for number of SLE factors increased from 1.3-fold for 1 SLE factor to 2.2-fold for 4 factors (*P* for linear trend = 0.0001) (Table 5). There was no interaction between the number of SLE factors and race/ethnicity, or with race/ethnicity and other variables in the model (data not shown). Marital status and health insurance, but not family income, were significantly associated with stillbirth in the substitution model (Table 5). When these and SLE factors were included, only marital status remained significant. The reduction in adjusted odds ratios for SLE factors was less than 10% (a commonly used threshold for determining confounding) for 1–3 factors but was 14% for 4 factors (adjusted odds ratio = 1.91, 95% confidence interval: 1.20, 3.04). Sensitivity analyses for pregnancy history and substance use also did not affect the main results (Web Appendix).

DISCUSSION

Almost 1 in 5 women with stillbirths and 1 in 10 women with livebirths in this study had recently experienced 5 or more SLEs; 3 in 4 livebirths and 4 in 5 stillbirths had been preceded by at least 1 SLE. As the number of SLEs increased and as the number of types of SLEs increased, the odds of stillbirth increased. Differences in kinds of SLEs by race/ethnicity did not appear to have an impact on the association of the number of SLEs or the number of SLE factors

with stillbirth. Rather, the association of stress with stillbirth, as estimated by number of SLE factors, was independently associated with stillbirth, even after controlling for other sociodemographic risk factors such as marital status and income.

Both financial and relational difficulties undoubtedly underlie higher rates of SLEs. However, SLEs appear to be intermediate in the social-determinants pathway for stillbirth. Through identifying women who are experiencing immediate impacts of upstream effects and attempting to provide them with additional support, health-care providers might help mitigate some of the damage from negative social determinants. If this were to be successful, some of the racial disparity in stillbirth could be reduced, because proportionately more black women are in the high-risk stream.

More than one-third of the participants reported that a close family member had been hospitalized in the previous 12 months, and a similar proportion reported that they had moved to a new address. These high frequencies are consistent with available data. About 12% of US adults were hospitalized in 2005 (36), and a young mother is likely to have at least 3 close adult family members. Residential mobility during pregnancy has been reported by 12%–32% of Western women (37–41). The somewhat higher reported mobility among SCRN participants might reflect the impact of the concurrent Great Recession.

Strengths of the SCRN Study include data from prespecified and diverse populations, including relatively large numbers of black and Hispanic women. Participants were enrolled and interviewed before hospital discharge at a time proximal to the events. Matching each case to 1 or more ongoing pregnancies at the same gestational age would have been ideal for collection of SLE data matched on time period. However, this design was not feasible for SCRN, as it would have required identification and longitudinal follow-up of ongoing pregnant women sampled as controls, and could have produced other biases. For example, for practical reasons, it is likely that pregnant women would have been recruited from prenatal care clinics and therefore would not have been representative of all ongoing pregnancies at earlier gestational ages. In a preliminary subanalysis, we estimated the effect of SLEs on stillbirths and livebirths occurring at ≥36 weeks' gestation, for which the recall period for SLEs would have been virtually identical for cases and controls. In this subset of women, the increased risk of stillbirth with the number of SLE factors persisted.

There were no measurable differences in sociodemographic characteristics between women identified through active surveillance for stillbirth and those who enrolled (5, 23). We used a validated measure of maternal stress that relies on recall of concrete events, thereby minimizing recall errors. Prenatal records, abstracted for most enrolled women, provided data on maternal obesity, complications, and other medical measures not reliably obtained by maternal interview (5). Using variables from both maternal interview and medical record abstraction, we controlled for many potential confounders.

Limitations of the SCRN Study include retrospective collection of some information, including SLEs. However, in a prospective study carried out in Denmark (13), information collected at 30 weeks' gestation on psychological stress yielded estimates similar to our findings for women who delivered at ≥24 weeks' gestation. We attempted to account for differential consent (30% and 37%, respectively, of screened women with stillbirths and livebirths did not participate in the study) through weight adjustment, as summarized above. Further, differences between included and excluded pregnancies due to missing interviews or prenatal records were slight and probably did not affect observed associations.

Numerous epidemiologic studies support the concept that maternal stress is associated with preterm birth (10–12, 42–44), and there is considerable overlap in the pathophysiology of preterm birth and stillbirth (45, 46). For example, in SCRN, 43% of stillbirths occurring at <24 weeks were intrapartum deaths (47). Spontaneous preterm labor after 24 weeks would likely lead to a cesarean delivery and preterm livebirth rather than stillbirth. The oversampled preterm livebirths were down-weighted in our analysis so that the resulting weighted sample would be representative of all livebirths in the catchment area covered by the study network. Because of the appropriate down-weighting of preterm births, they had little effect on our overall results.

Biologically plausible potential mechanisms for how stress may lead to preterm birth and/or stillbirth include early or excessive activation of neuroendocrine pathways. These pathways, considered to be a major contributor to some cases of spontaneous preterm birth (48), are stimulated by release of corticotropin-releasing hormone and other stress-related hormones. In addition, stress hormones activate inflammatory and vasoactive mediators, which are implicated in different pathways for preterm labor (49). In general, pregnancy is marked by indices of increased innate immune mechanisms, including inflammation. Inflammatory markers and increased activity of monocytes and macrophages have been noted in normal pregnant women. Notably, in women with spontaneous preterm birth associated with maternal stress, levels of proinflammatory markers are further increased. Activation of the hypothalamic-pituitary-adrenal axis may in this circumstance actually increase the inflammatory responsiveness of a primed maternal immune system. While this was not specifically addressed in the current analysis, we speculate that similar mechanisms may be involved in the pathophysiology of stillbirth associated with higher maternal stress indices.

We considered including several potential psychosocial measures but rejected most of them because they could be affected by delivery trauma (e.g., depression, resilience, pregnancy anxiety, and state anxiety). We hypothesized that SLEs would be less subject to selective recall because they are concrete events. However, this 1 measure cannot provide a comprehensive assessment of psychosocial risk for stillbirth. For example, the SLE measure does not include the woman's assessment of how stressful each event was to her or the time at which the event occurred. The timing in gestation of the stressful event might influence the risk of preterm birth (42, 43). Thus, our findings may be an underestimate of experienced stresses. Finally, while this was a large, population-based case-control study and, to our knowledge, the first to report results for maternal stress by race/ethnicity, it had limited power to assess factors that have weak associations with stillbirth.

Without screening for SLEs, prenatal care providers may not be aware of their patients' burdens or possible need for professional support. Further research is needed to assess the value of psychosocial intervention to reduce the risk of adverse pregnancy outcomes, including risks of preterm birth and stillbirth, among women with multiple SLEs. While a recent Cochrane review of randomized trials of professional social support during prenatal care for women identified as high-risk for poor pregnancy outcomes concluded that such intervention provided no improvement in rates of low birth weight, preterm birth, or stillbirth (50), a randomized trial carried out among African-American women in the District of Columbia with at least 1 of 4 risk factors (smoking, environmental tobacco smoke exposure, depression, and intimate partner violence) (51, 52) was not included in that review. Provision of support for these women reduced rates of psychosocial risk factors (51) and very preterm birth (52). The potential public health impact of effective interventions could be substantial, since there is at least 50% increased risk of stillbirth among the approximately 21% of all women and 32% of black women who experience at least 1 event in 3 SLE factors or at least 1 event in all 4 SLE factors during the year prior to their delivery.

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Dr. Carol J. R. Hogue had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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