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Racial disparities in stroke incidence in the Women's Health Initiative: Exploring biological, behavioral, psychosocial, and social risk factors

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ABSTRACT

Background: – Disparities in incident stroke risk among women by race and ethnicity persist. Few studies report the distribution and association of stroke risk factors by age group among a diverse sample of women.
Methods: – Data from the Women's Health Initiative (WHI) Observational Study collected between 1993 and 2010 were used to calculate cumulative stroke incidence and incidence rates among non-Hispanic African American (NHAA), non-Hispanic white (NHW), and Hispanic white or African American (HWAA) women by age group in participants aged ≥50 years at baseline (N = 77,247). Hazard ratios (HRs) and 95% CIs for biological, behavioral, psychosocial, and socioeconomic factors overall and by race or ethnicity were estimated using sequential Cox proportional hazard regression models.
Results: – Average follow-up time was 11.52 (SD, 3.48) years. The incident stroke rate was higher among NHAA (306 per 100,000 person-years) compared to NHW (279/100,000py) and HWAA women (147/100,000py) overall and in each age group. The disparity was largest at ages >75 years. The association between stroke risk factors (e.g., smoking, BMI, physical activity) and incident stroke varied across race and ethnicity groups. Higher social support was significantly associated with decreased stroke risk overall (HR:0.84, 95% CI, 0.76, 0.93); the degree of protection varied across race and ethnicity groups. Socioeconomic factors did not contribute additional stroke risk beyond risk conferred by traditional and psychosocial factors.
Conclusions: – The distribution and association of stroke risk factors differed between NHAA and NHW women. There is a clear need for stroke prevention strategies that address factors driving racial disparities in stroke risk.

1. Introduction

Stroke is a leading cause of death and disability in the United States (US) despite significant progress in stroke prevention and treatment, and disparities in stroke risk by sex, race, and ethnicity persist. Lifetime stroke risk is higher among women than men (Persky et al., 2010; Seshadri et al., 2006), and incident stroke occurs approximately twice as often among African Americans than among whites (Kleindorfer et al., 2010). African Americans and Hispanics are more likely to have strokes at younger ages than whites (Benjamin et al., 2019; Sealy-Jefferson et al., 2012). Stroke mortality is almost double in African Americans compared to other race and ethnic groups (Cruz-Flores et al., 2011). Understanding the factors that drive disparities in incident stroke risk are critical for accelerating equitable stroke prevention.

Disparities in incident stroke rates are likely attributable to differences in risk factor prevalence and effect by sex and across racial and ethnic groups (Elkind et al., 2020). For example, atrial fibrillation (AF), elevated fasting blood glucose, and diabetes mellitus confer a higher risk for stroke in women than men (Madsen et al., 2021; Peters et al., 2014; Regensteiner et al., 2015; Volgman et al., 2021). Obesity, an established stroke risk factor, is more prevalent among women than men (Towfighi et al., 2010). Prevalence of many stroke risk factors is higher among African American populations, which is compounded by higher potency of certain risk factors (Carnethon et al., 2017). For example, hypertension is estimated to affect over 50% of African Americans in the US and confers a significantly higher stroke risk among African Americans

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compared to whites (Deere & Ferdinand, 2020; Howard et al., 2013). Several large cohort studies have investigated differences in stroke risk factor prevalence and potency by sex or race/ethnicity, including the Northern Manhattan Stroke Study, the Atherosclerosis Risk in Communities study, and the Greater Cincinnati/Northern Kentucky Stroke Study (Broderick et al., 1998; Sacco et al., 2001; The ARIC Investigators, 1989). Differential associations of risk factors with incident stroke by race or ethnicity within women specifically have been reported by REasons for Geographic and Racial Differences in Stroke (REGARDS) and WHI investigators (Howard et al., 2019; Jiménez et al., 2019).

Traditional risk factors for stroke, such as hypertension and smoking, account for an estimated 53% of disparities in stroke risk between African Americans and whites (Howard, Cushman, et al., 2011), leaving a large proportion of excess stroke risk unexplained. Differential prevalence and associations of psychosocial stressors such as depressive symptoms and social isolation may contribute to stroke risk disparities. The REGARDS study reported depressive symptoms increased stroke risk about 27% among African Americans and whites and called for further research into differential associations of depressive symptoms with stroke risk by race (Ford et al., 2021). A meta-analysis of eight studies found social isolation increased stroke risk by 32% among men and women but did not report differences by other sub-groups (Valtorta et al., 2016). Socioeconomic factors such as education, health insurance, and neighborhood characteristics (e.g., median household income) show an inverse association between stroke risk, where risk is higher within lower socioeconomic levels (Marshall et al., 2015). Analyses of the differential associations of psychosocial stressors and socioeconomic factors on incidence stroke risk could help explain stroke risk disparities.

The purpose of this study is to determine whether there are disparities in incident stroke rates according to race, ethnicity, and age among Women's Health Initiative (WHI) participants and whether there were differences in risk factor prevalence and association. In addition to biological and behavioral factors that are typically considered to explain stroke risk, we examined psychosocial and socioeconomic variables in our analysis to see whether they are associated with stroke risk disparities. We stratified analyses by age since stroke risk increases with advancing age (Tsao et al., 2023). We hypothesize that there will be significant disparities between race and ethnicity groups in stroke rates and differences in risk factor associations across groups. Nuanced understanding of stroke risk disparities and differences in stroke risk factor associations by race or ethnicity among women can inform health initiatives and policy efforts aimed at "reducing health disparities, promoting health equity, and improving health for all people," an overarching goal of Healthy People 2020 (Office of Disease Prevention and Health Promotion - U.S. Department of Health and Human Services, 2020).

2. Materials and methods

2.1. Study sample

WHI is a longitudinal disease prevention study of postmenopausal women ages 50–79 at clinical sites across the US beginning in 1992 (Prentice & Anderson, 2008). The large, multisite study enrolled a total of 161,808 women in either a randomized controlled clinical trial that tested four interventions or an observational cohort (Anderson et al., 1998). Participants were recruited from the general population living near one of 40 trial clinics located across the US. WHI data is well suited for this analysis because it contains adjudicated stroke outcomes, traditional stroke risk factors, psychosocial variables (depressive symptoms, social support), and home addresses that can be used to identify census-level socioeconomic variables. Study investigators took intentional steps to recruit women from racial and ethnic minority groups to build an inclusive study sample (Fouad et al., 2004). WHI designated 10 out of 40 sites as minority recruitment sites based on their history of interactions with, and access to, large population subgroups and engaged in strategic recruiting approaches including conducting community outreach, personal referrals, and developing culturally appropriate recruitment materials (Fouad et al., 2004).

Participants for this study were drawn from the Observational Study cohort (n = 93,676) at baseline (1993–1998) and followed up over the course of the Main Study (1993–2005) and Extension 1 (2005–2010). Data used in this analysis were collected from 1993 to 2010. Study inclusion criteria were non-missing self-reported race and ethnicity, and non-missing outcome data or covariates (Fig. 1). We only include non-Hispanic white (NHW), non-Hispanic African American (NHAA), or Hispanic white or African American (HWAA) women for this analysis (n = 89,260) due to the small sample size for other races and ethnicities. The three race and ethnicity groups were mutually exclusive. The primary outcome for this analysis is incident stroke; therefore, women with a baseline history of stroke or transient ischemic attack (TIA) were excluded. Our final sample includes 77,247 women.

2.2. Variables

Our primary outcome is adjudicated stroke (ischemic, hemorrhagic, or unknown stroke type). Extensive adjudication and subtyping procedures are described elsewhere (Curb et al., 2003). Briefly, a committee of physician adjudicators was established and two physicians reviewed every cardiovascular disease outcome case and came to consensus using

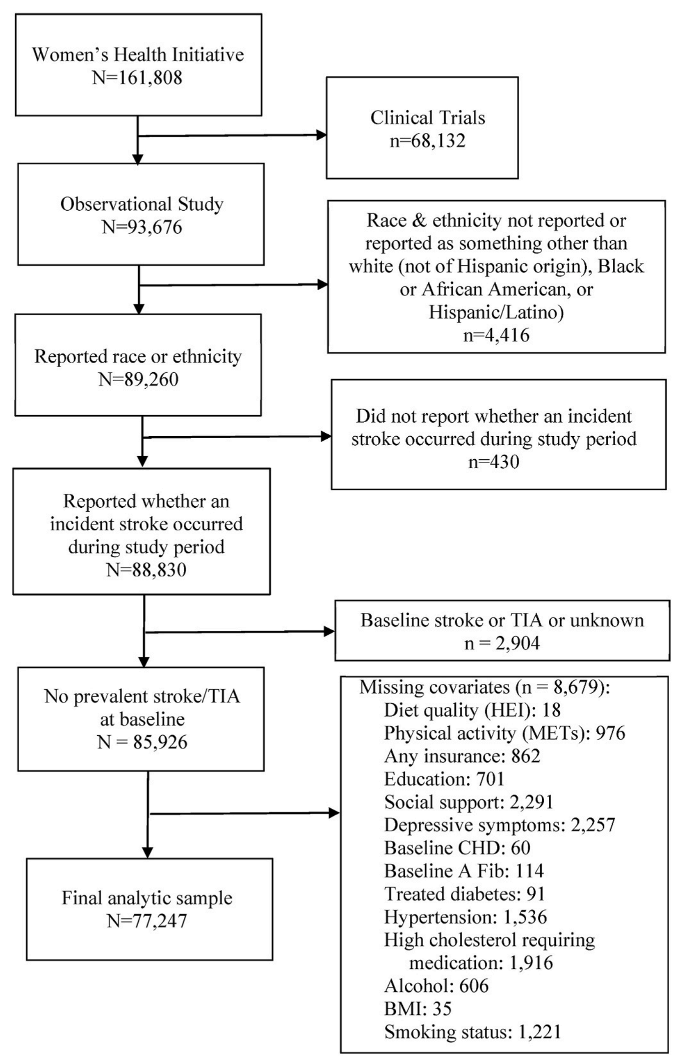

Fig. 1. Participant inclusion diagram and reasons for exclusion among women participating in the Observational Study of the Main Women's Health Initiative (WHI) Trial and Extension I (N = 77,247).

pre-determined outcome definitions; if a consensus could not be reached, the entire 10–20 physician adjudication committee reviewed the case (Curb et al., 2003). The primary exposure variable was self-reported race or ethnicity.

2.2.1. Biological covariates

Study-certified staff conducted physical measurements and blood draws using standardized procedures at WHI clinical centers (Anderson et al., 2003). Demographic information and medical histories were collected through mailed questionnaires. The following measures were considered biological covariates: age; weight and height (used to calculate BMI, kg/m^2); history of high cholesterol that requires medication; hypertension status (never diagnosed, diagnosed but controlled, diagnosed and uncontrolled; hypertension control was defined as clinic-measured blood pressures of systolic blood pressure <140 and diastolic blood pressure <90 mm Hg); history of diabetes (never diagnosed, diagnosed); history of atrial fibrillation (AF) (never, prevalent at baseline, and incident during follow-up); history of coronary heart disease (CHD) at baseline; and incident, physician-reviewed, classified, and adjudicated CHD as defined by WHI during follow-up. Self-reported atrial fibrillation can be used interchangeable with electrocardiogram-detected atrial fibrillation as a predictor of incident stroke (Soliman et al., 2011). Baseline measures were used, except for incident CHD and AF identified during follow up. CHD and AF were WHI outcomes of interest and were assessed throughout the study, unlike other covariates in this analysis.

2.2.2. Behavioral covariates

The following behavioral covariates were self-reported at baseline via standardized questionnaires that were mailed to participants: smoking status (never, former, current); and alcohol consumption (non-drinker, past drinker, <1 drink per week, 1–7 drinks/week, 7 or more drinks per week) (Langer et al., 2003). Diet quality was assessed by the Healthy Eating Index (HEI 2010) based on a self-administered food frequency questionnaire (George et al., 2014). Participants reported frequency of physical activity on a survey (no activity, some activity, 2-<4 episodes per week of moderate activity, 4+ episodes per week of moderate activity). Responses were converted to total expenditure per week as metabolic equivalent of tasks (METs) (Meyer et al., 2009).

2.2.3. Psychosocial covariates

Participants self-reported depressive symptoms at baseline using a short screener that included 6 items from the Center for Epidemiologic Studies of Depression Scale (CES-D) and 2 items from the Diagnostic Interview Schedule (DIS). The eight items were weighted using the Burnam algorithm producing a final range of 0–1 where scores >0.6 indicate significant depressive symptoms (Anderson et al., 2003; Burnam et al., 1988; Wassertheil-Smoller et al., 2004). A composite social isolation variable was constructed using marital status, religious ties, and community/group membership (Cené et al., 2022).

2.2.4. Socioeconomic covariates

Highest level of education and health insurance coverage status were self-reported at baseline. The neighborhood summary z-score was calculated using the following census-derived variables: median household income; median value of housing units; percentage of households receiving interest, dividend, or net rental income; percentage of adults 25 years of age who had completed high school; percentage of adults 25 years of age who had completed college; percentage of employed persons 16 years of age in executive, managerial, or professional specialty occupations (Diez Roux et al., 2001). See Appendix A for neighborhood summary Z-score calculation details.

2.3. Data analysis

Baseline characteristics of the participants, incidence proportion and incident stroke rates were tabulated. We examined the association between race, ethnicity and time to stroke, adjusting for stroke risk factors, psychosocial factors, and socioeconomic factors using sequential Cox proportional hazard regression models to obtain hazard ratios (HRs) and 95% confidence intervals (CIs) for the following models:

Model 0: Adjusted for age.
Model 1: Adjusted for stroke behavioral and biological risk factors including age, hypertension status, smoking, BMI, alcohol intake, HEI, CHD, AF, high cholesterol requiring medication, diabetes, and physical activity.
Model 2: Adjusted for variables in model 1 + psychosocial variables (depressive symptoms, social support).
Model 3: Adjusted for variables in model 2 + socioeconomic variables (education, insurance status).
Model 4: Adjusted for variables in models 3 + Neighborhood Summary Z Score.

Supplemental analyses: Models adjusted for i) psychosocial variables and age; ii) socioeconomic factors and age; and iii) Neighborhood Summary Z Score and age.

The primary analysis was total stroke; hazard ratios by ischemic or hemorrhagic subtype were also estimated. Due to the smaller sample size and number of events for Hispanic women, we conducted a set of sensitivity analyses by fitting Models 1–4 with Hispanic women removed. All analyses were done using SAS 9.4 (Cary, NC). Significance level was set at 0.05.

3. Results

3.1. Participant characteristics

Average follow-up time was 11.52 (SD, 3.48) years. Participant characteristics differed between races for many biological and behavioral variables (Table 1). There were more NHW women over 75 years old (7.2%) in the sample than NHAA (5.2%) or HWAA women (3.3%). A higher percentage of NHAA women were current smokers, were obese, and had uncontrolled hypertension and diabetes compared to NHW and HWAA women. Heavy drinking was more prevalent among NHW women. Atrial fibrillation prevalence at baseline was similar among NHW and NHAA women (about 4.5%), and a higher percentage of NHW women developed AF during follow up than NHAA or HWAA women (6.5%, 3.6%, and 3% respectively). HWAA (21.8%) reported more depressive symptoms compared to NHAA (14.2%) and NHW (10.3%); more HWAA women also reported low levels of social support. About 40% of NHW and NHAA women had college degrees compared to 25% of HWAA women. Most women reported having health insurance. Finally, the mean neighborhood summary score was highest for NHW, followed by HWAA, and NHAA.

3.2. Incident strokes

A total of 2462 strokes occurred in this analytic sample; 182 occurred in NHAA, 2242 in white women, and 38 in HWAA women. Of the 2904 women who had a stroke or TIA at baseline or missing information at baseline and were therefore excluded from our analytic sample, 397 were NHAA (13.7%), 2377 were NHW (81.9%) and 130 were HWAA (4.5%). In our analytic sample, the incident stroke rate was highest for NHAA women overall and in each age group (Table 2). Incident stroke rate was 306/100,000 person-years among NHAA women, 279/100,000pys among NHW women, and 147/100,000pys among HWAA women. The disparity was largest among women over 75 years old. Stroke risk and incidence rate was lowest among HWAA women in each age group.

3.3. Incident stroke risk

Adjusting for age only, NHAA women had a higher incident stroke risk compared to NHW women (HR = 1.37, 95% CI, 1.18, 1.59). Compared to NHW women, NHAA women had a similar risk for stroke, whereas HWAA women had a lower risk in models adjusting for stroke risk factors beyond age (Table 3). In the fully adjusted model (Model 4), race and ethnicity were not significantly associated with total stroke risk after adjusting for biological, behavioral, psychosocial, socioeconomic, and neighborhood variables (p = 0.05). NHAA women had similar risk for stroke (HR = 1.04, 95% CI, 0.87, 1.24) compared to NHW women, while HWAA women had a significantly lower risk (HR = 0.65, 95% CI, 0.46, 0.92). Results were similar for models 2 and 3. Hazard ratios for hemorrhagic stroke were not statistically significant and are not presented. Race and ethnicity were not significantly associated with stroke risk when HWAA women were removed from the sample in a sensitivity analysis (Table 3a).

In addition to examining race and ethnicity-related risk of stroke, we also conducted stratified analyses examining the association of stroke risk factors with incident stroke rates among NHW, NHAA and HWAA women separately using Model 4 that was adjusted for biological, behavioral, psychosocial and socioeconomic covariates (Fig. 2, Supplemental Table 1). Advancing age increased stroke risk for both races and Hispanic ethnicity. Advancing age increased NHAA women's stroke risk less than it did among NHW and HWAA women (HR at >75 years = 4.10, 95% CI, 2.51, 6.70 for NHAA, HR = 6.03, 95% CI, 5.26, 6.92 for NHW, and HR = 8.09, 95% CI, 2.51, 26.0 for HWAA women). Smoking was associated with stroke risk in NHW (HR = 1.52, 95% CI, 1.26, 1.82) and NHAA women (HR = 1.48, 95% CI, 0.88, 2.49). BMI was associated with stroke risk for NHAA (BMI = 25–30, HR = 1.60, 95% CI, 1.00, 2.55, BMI >30, HR = 1.09, 95% CI, 0.67, 1.78). BMI was not associated with stroke risk for NHW and HWAA women. Higher levels of physical

Table 1
Participant characteristics by race and ethnicity of women participating in the Observational Study of the Main Women's Health Initiative (WHI) Trial and Extension I (N=77,247).

Characteristic	Total N (%)	Non-Hispanic White n (%)	Non-Hispanic African American n (%)	Hispanic White or African American n (%)
Total	77,247	68,664 (88.9)	5,918 (7.7)	2,665 (3.4)
Age group				
50-<65	42,381 (54.9)	36,562 (53.2)	3,926 (66.3)	1,893 (71.0)
65-75	29,526 (38.2)	27,158 (39.6)	1,683 (28.4)	685 (25.7)
>75	5,340 (6.9)	4,944 (7.2)	309 (5.2)	87 (3.3)
Smoking status				
Never	38,675 (50.1)	34,041 (49.6)	2,957 (50.0)	1,677 (62.9)
Former	33,822 (43.8)	30,683 (44.7)	2,330 (39.4)	809 (30.4)
Current	4,750 (6.1)	3,940 (5.7)	631 (10.7)	179 (6.7)
BMI				
<25	32,114 (41.6)	30,080 (43.8)	1,219 (20.6)	815 (30.6)
25 – 30	26,079 (33.8)	23,062 (33.6)	2,023 (34.2)	994 (37.3)
>30	19,054 (24.7)	15,522 (22.6)	2,676 (45.2)	856 (32.1)
Alcohol consumption				
Non-drinker	7,581 (9.8)	6,038 (8.8)	1,072 (18.1)	471 (17.7)
Past drinker	13,995 (18.1)	11,419 (16.6)	1,940 (32.8)	636 (23.9)
<1/week	24,761 (32.1)	22,018 (32.1)	1,828 (30.9)	915 (34.3)
1-7/week	20,705 (26.8)	19,418 (28.3)	793 (13.4)	494 (18.5)
7+/week	10,205 (13.2)	9,771 (14.2)	285 (4.8)	149 (5.6)
Healthy Eating Index score, mean (SD), range (0-100)	68.1 (11.0) (17.8-96.9)	68.6 (10.7) (20.1, 96.6)	64.2 (12.2) (17.8, 94.5)	63.4 (11.4) (22.3, 96.9)
Physical activity (METs)				
0 – 1.5	14,519 (18.8)	12,115 (17.6)	1,708 (28.9)	696 (26.1)
1.5 – 8	19,280 (25.0)	16,838 (24.5)	1,673 (28.3)	769 (28.9)
8 – 19	22,942 (29.7)	20,858 (30.4)	1,434 (24.2)	650 (24.4)
19+	20,506 (26.5)	18,853 (27.5)	1,103 (18.6)	550 (20.6)
High cholesterol requiring medication	10,930 (14.1)	9,541 (13.9)	954 (16.1)	435 (16.3)
Hypertension				
Never	52,509 (68.0)	47,889 (69.7)	2,727 (46.1)	1,893 (71.0)
Current, controlled	6,008 (7.8)	5,252 (7.6)	515 (8.7)	241 (9.0)
Current, uncontrolled	18,730 (24.2)	15,523 (22.6)	2,676 (45.2)	531 (19.9)
Diabetes	2,817 (3.6)	1,969 (2.9)	667 (11.3)	181 (6.8)
Coronary heart disease at baseline	1,654 (2.1)	1,420 (2.1)	200 (3.4)	34 (1.3)
Coronary heart disease developed over follow-up	2,303 (3.0)	2,108 (3.1)	151 (2.6)	44 (1.7)
Atrial fibrillation				
Never	69,151 (89.5)	61,222 (89.2)	5,425 (91.7)	2504 (94.0)
At baseline	3,363 (4.4)	3,006 (4.4)	277 (4.7)	80(3.0)
Developed over follow-up	4,733 (6.1)	4,436 (6.5)	216 (3.6)	81 (3.0)
Depressive symptoms	8,498 (11.0)	7,077 (10.3)	840 (14.2)	581 (21.8)
Social support				
1^{st} tertile	23,866 (30.9)	20,585 (30.0)	2,167 (36.6)	1,114 (41.8)
2^{nd} tertile	26,153 (33.9)	23,319 (34.0)	2,043 (34.5)	791 (29.7)
3^{rd} tertile	27,228 (35.2)	24,760 (36.1)	1,708 (28.9)	760 (28.5)
Education				
Less than high school	3,339 (4.3)	2,090 (3.0)	681 (11.5)	568 (21.3)
High school or vocational training	19,663 (25.5)	17,435 (25.4)	1,460 (24.7)	768 (28.8)
Some college or Associates degree	20,918 (27.1)	18,730 (27.3)	1,518 (25.7)	670 (25.1)
College degree	33,327 (43.1)	30,409 (44.3)	2,259 (38.2)	659 (24.7)
Any health insurance	74,731 (96.7)	66,945 (97.5)	5,491 (92.8)	2,295 (86.1)
Neighborhood summary score, mean (SD)	0.08 (5.32) (-18.16, 14.11)	0.65 (4.99) (-18.12, 14.11)	-5.21 (5.28) (-17.55,13.40)	-4.03 (5.95) (-18.16, 12.84)

Table 2
Number of strokes, women at risk, cumulative incidence, and incidence rates in the entire sample and within three age groups among non-Hispanic white, non-Hispanic African American, and Hispanic white or African American women participating in the Observational Study of the Main Women's Health Initiative (WHI) Trial and Extension I (N=77,247).

	Age group	Stroke Events				Women at risk (n)	Cumulative incidence	Person-years of follow-up	Incidence rate and 95% CI (per 100,000 person-years)
		Total (n)	Hemorrhagic (n)	Ischemic (n)	Unknown type (n)				
Total	50-<65	648	126	476	46	42,381	1.53%	511,938	127 (117,137)
	65-75	1,366	206	1,026	134	29,526	4.63%	326,425	419 (397,441)
	>75	448	59	316	73	5,340	8.39%	52,188	861 (780,938)
	TOTAL	2,462	391	1,818	253	77,247	3.19%	890,551	277 (266,288)
Non-Hispanic White	50-<65	556	110	413	33	36,562	1.52%	452,167	123 (113,134)
	65-75	1,271	198	957	116	27,158	4.68%	303,696	419 (396,442)
	>75	415	56	292	67	4,944	8.39%	48,817	854 (769,932)
	TOTAL	2,242	364	1,662	216	68,664	3.27%	804,679	279 (268,291)
Non-Hispanic African American	50-<65	79	12	57	10	3,926	2.01%	40,702	194 (152,237)
	65-75	75	7	52	16	1,683	4.46%	16,089	466 (362,572)
	>75	28	1	21	6	309	9.06%	2,622	1,062 (675,1,462)
	TOTAL	182	20	130	32	5,918	3.08%	59,413	306 (263,351)
Hispanic White or African American	50-<65	13	4	6	3	1,893	0.69%	19,069	68 (32,106)
	65-75	20	1	17	2	685	2.92%	6,640	316 (170,433)
	>75	5	2	3	0	87	5.75%	748.706	668 (86,1,251)
	TOTAL	38	7	26	5	2,665	1.43%	26,459	147 (99,190)

Table 3
Hazard ratios (HR, 95% CI) for stroke by race and ethnicity among women participating in the Observational Study of the Main Women's Health Initiative (WHI) Trial and Extension I (N=77,247).

	Non-Hispanic White (n=68,664)	Non-Hispanic African American (n=5,918)	Hispanic (n=2,665)	Overall p-value
Strokes	2,242	182	38	
Model 0	1.0	1.37 (1.18,1.59)	0.70 (0.50,0.96)	<0.0001
Model 1	1.0	1.07 (0.91,1.25)	0.67 (0.49,0.93)	0.0351
Model 2	1.0	1.06 (0.91,1.24)	0.66 (0.48,0.91)	0.0285
Model 3	1.0	1.07 (0.91,1.23)	0.65 (0.46,0.91)	0.0279
Model 4	1.0	1.04 (0.87, 1.24)	0.65 (0.46,0.92)	0.0452

Model 0: Adjusted for age.
Model 1: Adjusted for age, smoking status, BMI, alcohol intake, HEI 2010 score, physical activity, high cholesterol requiring pills, hypertension, diabetes, coronary heart disease, and atrial fibrillation.
Model 2: Adjusted for Model 1 covariates + depressive symptoms and social support
Model 3: Adjusted for Model 2 covariates + education and any health insurance
Model 4: Adjusted for Model 3 covariates + neighborhood summary score

Table 3a
Hazard ratios (HR, 95% CI) for stroke by race among women participating in the Observational Study of the Main Women's Health Initiative (WHI) Trial and Extension I, excluding Hispanic women (sensitivity analysis) (n=74,582).

	Non-Hispanic White (n=68,664)	Non-Hispanic African American (n=5,918)	Overall p-value
Strokes	2,242	182	
Model 1	1.0	1.06 (0.91,1.24)	0.4622
Model 2	1.0	1.05 (0.90,1.23)	0.5094
Model 3	1.0	1.07 (0.91,1.26)	0.4141
Model 4	1.0	1.03 (0.86, 1.23)	0.7769

activity were associated with decreased stroke risk overall (HR = 0.86, 95% CI, 0.76, 0.99) and among NHW women (HR = 0.85, 95% CI, 0.74, 0.97). Alcohol consumption and high cholesterol were not associated with stroke risk in this study. Atrial fibrillation increased stroke risk for all three groups. Hypertension, diabetes, and CHD were associated with stroke risk overall, with some variation by race or ethnicity (Fig. 2, Supplemental Table 1).

There were some differences in stroke risk for psychosocial and socioeconomic variables according to race and ethnicity in the fully adjusted model (Model 4). Depressive symptoms were not associated with stroke risk for any group (Fig. 2, Supplemental Table 1). Higher social support was associated with decreased stroke risk overall (HR = 0.84, 95% CI, 0.76, 0.93), and the degree of protection varied across race and ethnic groups. Neighborhood socioeconomic characteristics did not influence stroke risk when biological, behavioral, psychosocial, and socioeconomic covariates were all included in the models.

4. Discussion

This study examined incident stroke risk and risk factors within NHAA, HWAA, and NHW women ages 50 and older who participated in the WHI's Observational Study. Stroke incidence rates were highest among NHAA women, followed by NHW and then HWAA women. After adjusting for biological, behavioral, psychosocial, and socioeconomic covariates, NHAA and NHW women had a similar stroke risk and HWAA women had a lower risk than their peers. Racial disparities in stroke risk between NHAA and NHW, especially in younger age groups, are well documented in the WHI and in other studies (Howard & Howard, 2001; Jiménez et al., 2019; Kissela et al., 2004; Kleindorfer et al., 2010). Stroke incidence rates in this analysis were similar to a recent study of racial variation in stroke risk among women participating in WHI (Jiménez et al., 2019). Small differences in the results may be due to our analytic samples (Observational study only vs. Observational and dietary modification and placebo arms of the WHI Clinical trial), our exclusion of

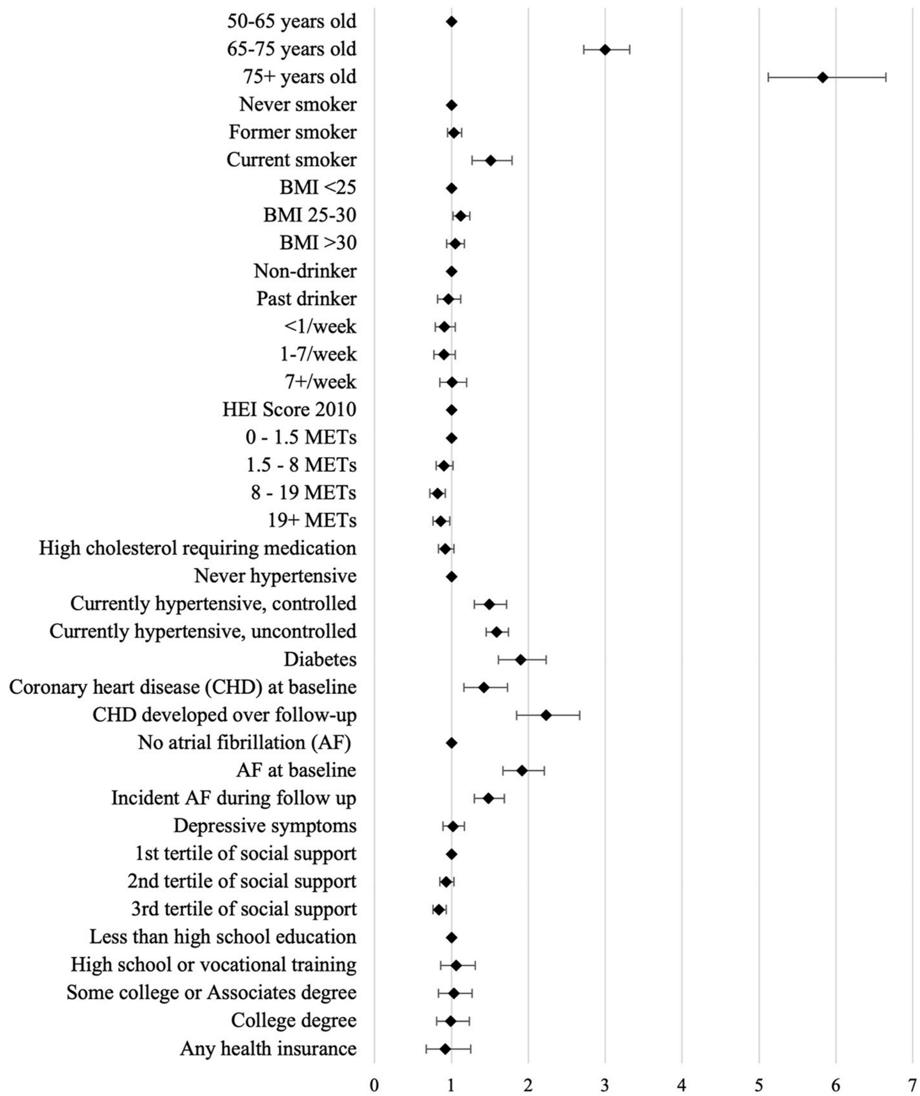

Fig. 2. Forest plot of adjusted hazard ratios and 95% confidence intervals for stroke risk factors among women participating in the Observational Study of the Main Women's Health Initiative (WHI) Trial and Extension I, overall (N=77,247) (a) and by race or ethnicity (b-d).
Hazard ratios, 95% confidence intervals, and p-values were obtained via a Cox proportional hazard regression model that was adjusted for age, smoking status, BMI, alcohol intake, HEI 2010 score, physical activity, high cholesterol requiring pills, hypertension, diabetes, coronary heart disease, atrial fibrillation, depressive symptoms, social support, education, any health insurance, and neighborhood summary score.2a) Forest plot of hazard ratios and 95% confidence intervals for stroke risk factors, overall (N=77,247).

women with a history of TIA at baseline, inclusion of psychosocial covariates, and age groupings (50-<65, 65–75, >75 vs. 50–60, 60-<70, >70) (Jiménez et al., 2019). HWAA women in our sample had a lower risk of stroke than NHW and NHAA women in their age groups; however, these results should be interpreted with caution due to the small number of incident strokes within this subgroup. Two studies of Mexican American men and women found a higher incidence of ischemic stroke compared to non-Hispanic whites (Morgenstern et al., 2013; Sealy-Jefferson et al., 2012). A study of Caribbean Hispanics residing in Northern Manhattan found a significantly greater incident stroke rate among non-Hispanic white women compared to Hispanic women among women under 70 years old (Gardener et al., 2020). Among women 70 years and older, however, incident stroke rate was greater among Hispanic compared to non-Hispanic women. More research investigating disparities in incidence stroke risk and risk factors among Hispanic women is needed.

There were similarities and differences in stroke risk across groups within this study by risk factors. Biological and behavioral risk factors that compose common stroke risk profiles, such as age, smoking and diabetes, were the strongest risk factors in our analyses (Wolf et al., 1991). Age was the strongest risk factor for incident stroke across all groups, supporting similar findings in the literature (Kelly-Hayes, 2010; Virani et al., 2020). Our results indicated that the risk of a stroke in women over 75 years old is almost double the risk for women ages 65–75 years old. Age was the only statistically significant risk factor for HWAA women in our sample, likely due to the small number of incident strokes in that group. Overall stroke risk and prevalence of some stroke risk factors, such as smoking, have been declining since the 1980s, but the decline in risk associated with hypertension has decreased less for African Americans than for whites (Nadruz et al., 2017). Hypertension requiring treatment was the second strongest risk factor for NHAA in our study, whereas the risk posed by hypertension was somewhat lower among NHW women. Our finding that higher BMI was not associated with stroke risk is likely due to the inclusion of hypertension, CHD, and diabetes in the model, which are strongly associated with stroke risk and with obesity. In unpublished results from this dataset, BMI was associated with stroke risk when hypertension and diabetes are removed from the models. Lifestyle interventions targeting hypertension, smoking,

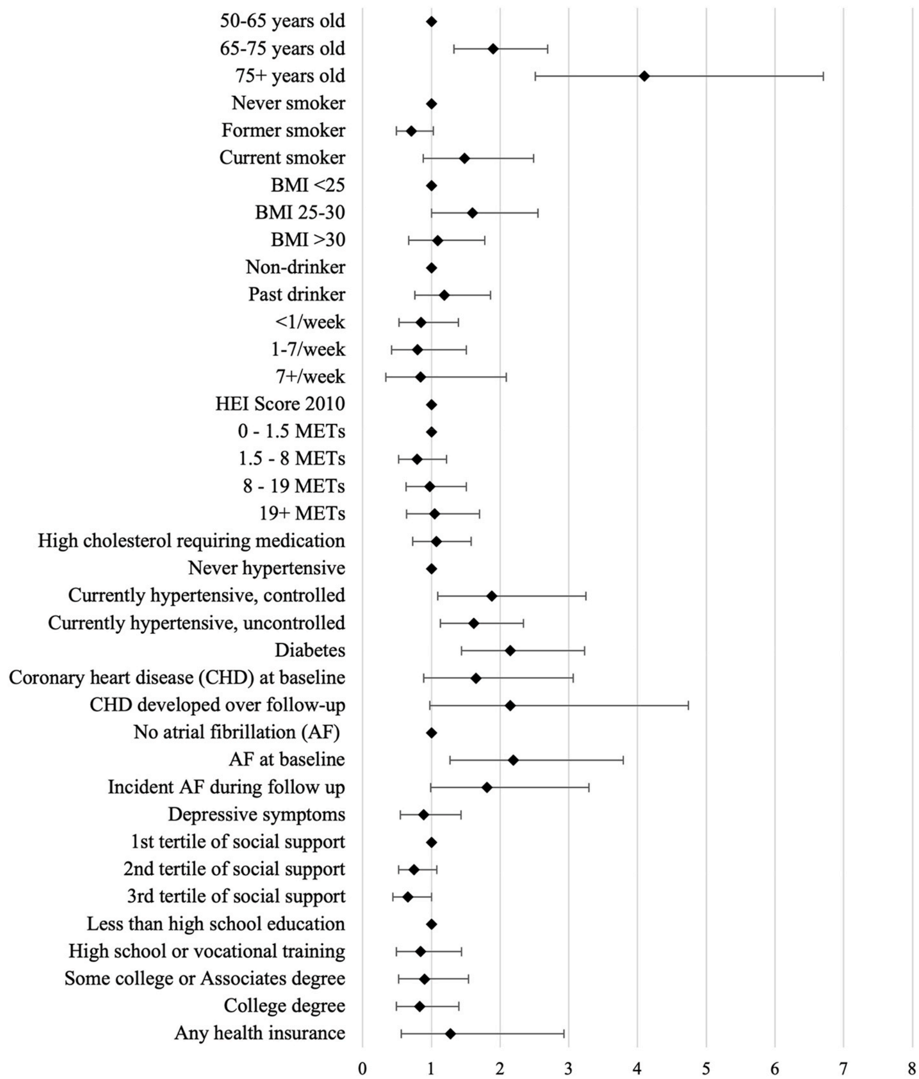

Fig. 2b. Forest plot of hazard ratios and 95% confidence intervals for stroke risk factors among Non-Hispanic African American women (n=5,918) participating in the Observational Study with the Main Women's Health Initiative (WHI) Trial and Extension I.

maintaining a healthy weight, and physical activity may reduce stroke risk overall and may reduce stroke-related disparities (Boehme et al., 2017; Zhang et al., 2011).

In our sample, few factors beyond biological and behavioral risk factors were associated with stroke risk, with the exception of social support. Social support was protective for all groups. One study found that small social networks increased stroke risk but did not find an association between social support and stroke risk, possibly because only a small fraction of that sample reported low levels of social support (Nagayoshi et al., 2014). In addition to potential protective effects against stroke, social support is consistently associated with improved outcomes in the years following a major stroke (Belyea et al., 1993; Kruithof et al., 2013). In contrast to two large meta-analyses, we did not find an association between stroke risk and depressive symptoms (Pan, 2011; Barlinn, 2015). Our sample may not have included enough women with depressive symptoms to detect an association with stroke risk. Education was not statistically associated with stroke risk, though higher levels of education were somewhat protective for NHW women but not for NHAA or HWAA women. About 45.2% of women in our sample were 65 years or older, qualifying them for Medicare, perhaps explaining the lack of association between stroke risk and health insurance status. Finally, neighborhood scores, which were designed to capture socioeconomic conditions beyond the individual level, were not associated with stroke risk. Our analyses indicate that these factors do not contribute additional stroke risk beyond traditional biological and behavioral risk factors. However, social and economic factors shape the opportunities and constraints on individual-level behaviors and related biological factors, and therefore their influence is likely already accounted for when adjusting for behaviors and biological indicators (Glass & McAtee, 2006). Other measures of racialized neighborhood stress such as segregation and perceptions of safety should be examined in future studies. Stroke risk prevention interventions that target policies, systems, and environments to promote equity and healthy behaviors should be studied given their potential broad reach and low-cost relative to clinical and other individual-level interventions (Frieden, 2010).

Stroke risk emerges from a complex system of biological, behavioral, social and economic factors. Results from this study can inform simulation models that can synthesize information from many studies to provide a fuller picture of complex phenomena, such as stroke disparities, than any one study can examine (Diez Roux, 2011). For example, our stratified stroke risk factor findings could be included in an agent-based model, microsimulation model, or system dynamics model that aims to create a laboratory for understanding stroke disparities within a population and testing potential interventions. Moreover, simulation models can inform decisions and policies because they can be

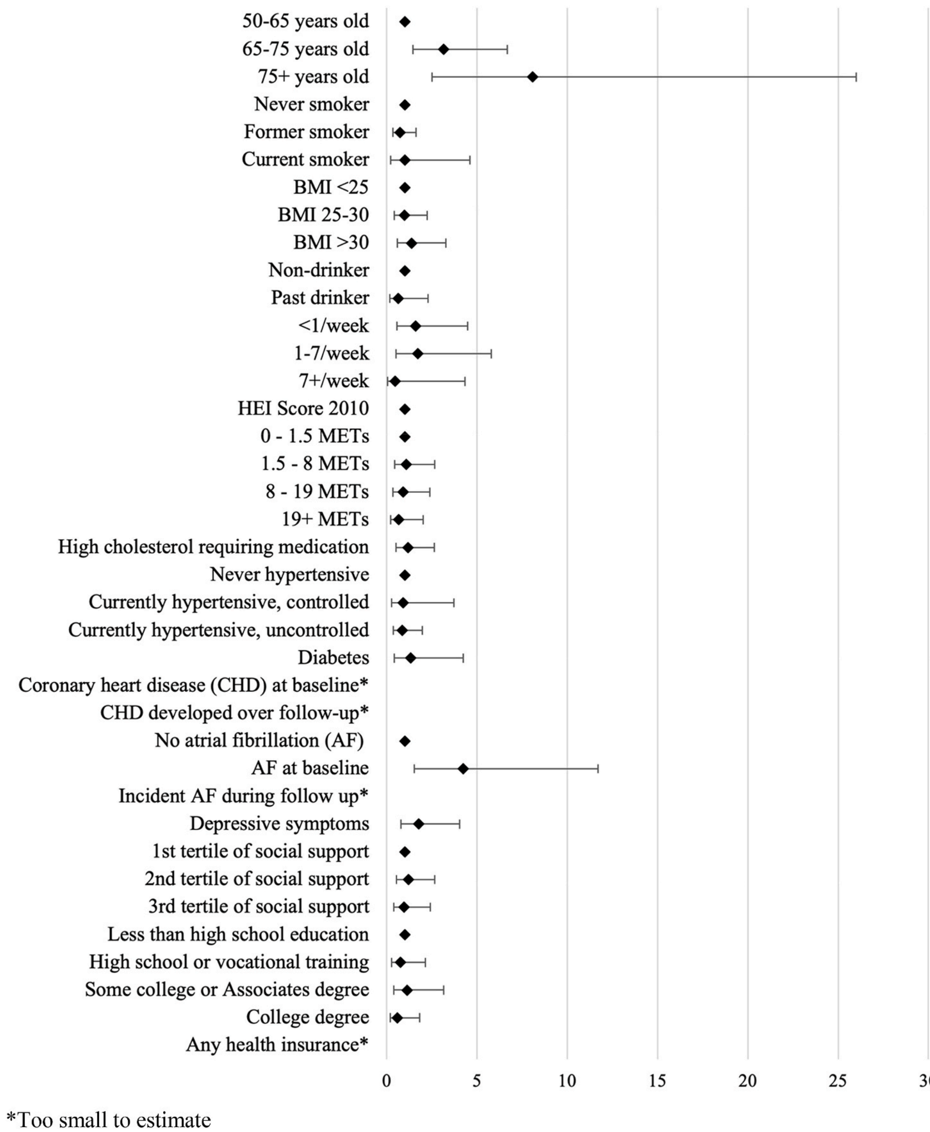

Fig. 2c. Forest plot of hazard ratios and 95% confidence intervals for stroke risk factors among Hispanic white or African American women (n=2,665) participating in the Observational Study with the Main Women's Health Initiative (WHI) Trial and Extension I.

programmed to analyze complex "what if" scenarios that are relevant for decision-makers (Freebairn et al., 2018; Maglio et al., 2014; Minyard et al., 2014; Powell et al., 2017). Health disparities emerge from complex social systems where opportunities and constraints on health differ between socially defined groups and are the type of public health challenge that are well suited for investigation with systems science methods.

This study had limitations. Our analysis examined additional associations of psychosocial and socioeconomic factors with stroke risk above and beyond the association with biological and behavioral factors by building up a series of models, adding new variables with each step. Other analytic approaches such as structural equation modeling, mediation analysis, and hierarchical linear modeling could provide more insight into the direct and indirect relationships between biological, behavioral, psychosocial, and socioeconomic factors and stroke risk. We did not consider genetic contributions to stroke risk in this study, which includes risks associated with rare and common polymorphisms and gene-environment interactions (Boehme et al., 2017). We did not consider female-specific risk factors, such as hormone concentrations and pregnancy history; examining sex-specific factors is an area of on-going research (Poorthuis et al., 2017). The study sample may not have captured the full extent of disparities in incident stroke risk since those with the highest risk for stroke may have had a stroke event before they became eligible to enroll in the WHI at age 50. This is particularly relevant for studying racial disparities in stroke risk since African American women have a higher risk of stroke at younger ages than white women (Howard, Kleindorfer, et al., 2011; Stansbury et al., 2005). Race and ethnicity were considered mutually exclusive categories, limiting us from considering intersecting identities of race and ethnicity. Another limitation is the potential for cohort effects since data was collected between 1993 and 2010 from women who were fifty and older at the time. As stated previously, results for Hispanic women should be interpreted with caution due to the small sample size and number of events. Very large sample sizes are needed to conduct stratified analyses and test for interactions between factors, especially for relatively rare outcomes such as strokes and stroke sub-types. Still, WHI is an excellent dataset for investigating strokes and other health outcomes that often occur later in life due to the long follow-up time, high study retention rate, outcome adjudication process, and the breadth of variables collected through validated assessments (Curb et al., 2003; Prentice & Anderson, 2008).

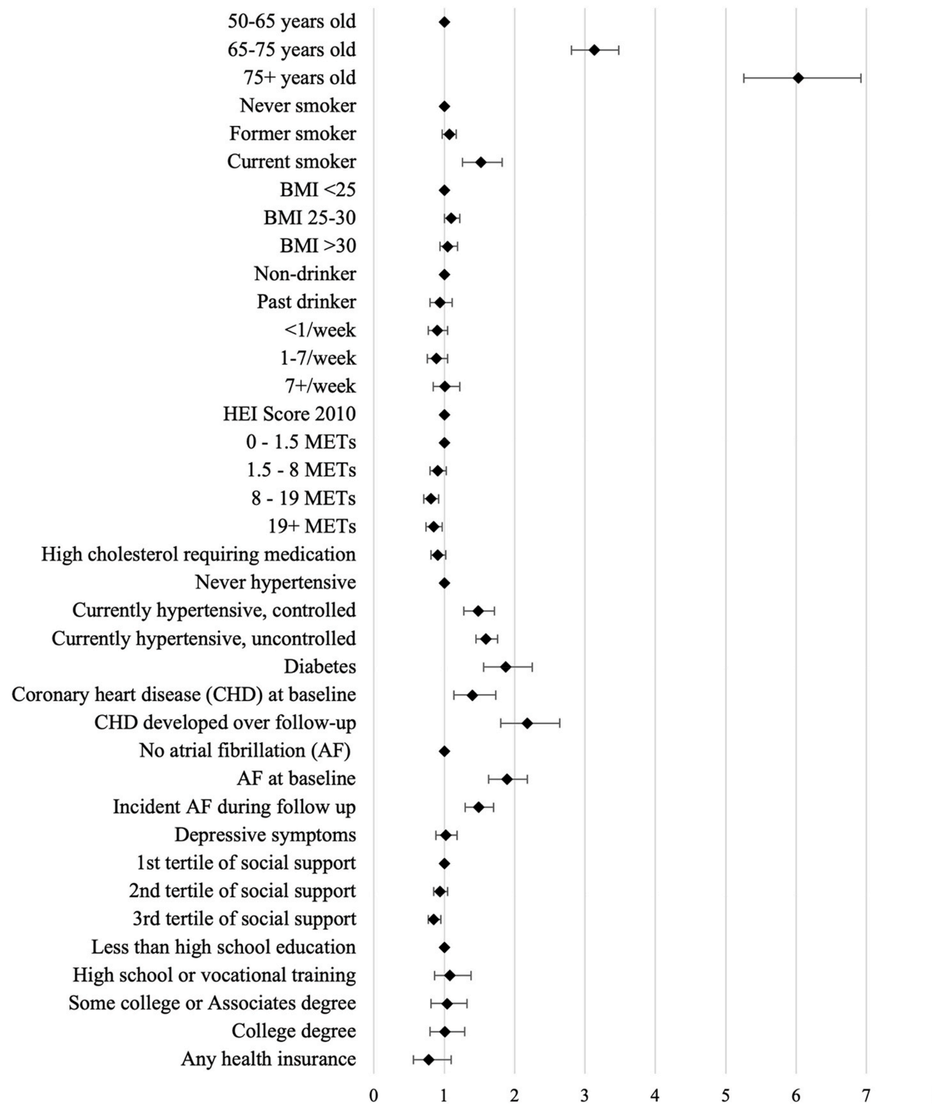

Fig. 2d. Forest plot of hazard ratios and 95% confidence intervals for stroke risk factors among non-Hispanic white women (n=68,664) participating in the Observational Study with the Main Women's Health Initiative (WHI) Trial and Extension I.

Compared to other multi-center collaborative studies at the time, WHI contains a large subgroup of women from underrepresented minority groups (Bao et al., 2016; Fouad et al., 2004).

4.1. Implications

Our study contributes to a body of literature highlighting the need for stroke prevention strategies that are specifically tailored for African American women to address the variety of factors contributing to elevated stroke risk at younger ages. Carnethon and colleagues suggest engaging a broad set of stakeholders across multiple disciplines to identify and implement strategies that are likely to promote equity in cardiovascular health for African Americans (Carnethon et al., 2017). One approach to promoting cardiovascular health that appears to be effective among African Americans are community health worker interventions focused on preventing and controlling hypertension (Brownstein et al., 2007; Nasser & Ferdinand, 2018). Studies from around the country show promising results and suggest that the approach may be cost-effective and scalable (Allen et al., 2014). An important feature of such interventions is the provision of social support, which was protective against stroke risk in our study (Gale et al., 2018).

Despite a sample size of over 77,000 women, certain subgroup analyses were challenging due to small sample sizes within groups and due to the relative infrequency of strokes. Elkind and colleagues offer approaches to studying racial and ethnic disparities in stroke, including an important call to use measures such as disability-adjusted life years or healthy life expectancy to study disparities in quality of life associated with neurological events and disorders (Elkind et al., 2020). Datasets that oversample minority populations are valuable opportunities to investigate a variety of factors that might be driving health disparities. Another important opportunity for studying drivers and consequences of health disparities is harmonizing data and measures across datasets when possible to create a larger, diverse sample (Brown et al., 2019; Komro et al., 2016). As technology such as electronic medical records and secure systems for data sharing progress, harmonized longitudinal datasets hold great promise for studies investigating the mechanisms driving health disparities in the US as well as tools for evaluating policies and interventions aiming to reduce disparities.

5. Conclusion

The distribution and association of stroke risk factors differed between NHAA and NHW women aged ≥50 years who enrolled in the WHI Observational Study. Psychosocial and socioeconomic factors did not account for disparities in incident stroke risk beyond that explained by traditional biological and behavioral factors. Social systems shape the policies and environments that promote or constrain opportunities for healthy behaviors and related biological outcomes. Those systems, policies, and environments are important targets for interventions aiming to reduce stroke disparities in the US.

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Ethical statement

The authors have no conflicts of interest to disclose.

CRediT authorship contribution statement

Larissa Calancie: Conceptualization, Visualization, Writing – original draft, Writing – review & editing. **Xiaoyan Iris Leng:** Formal analysis, Writing – review & editing. **Eric A. Whitsel:** Writing – review & editing. **Crystal Cené:** Writing – review & editing. **Kristen Hassmiller Lich:** Supervision, Writing – review & editing. **Gaurav Dave:** Writing – review & editing. **Giselle Corbie:** Supervision, Writing – review & editing.

Data availability

The authors do not have permission to share data.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ssmph.2023.101570.

Appendix A. Neighborhood summary z-score calculation for women participating in the Observational Study with the Main Women's Health Initiative (WHI) Trial and Extension I

We selected a single geocoding vendor from four candidates on the basis of its accuracy geocoding WHI Observational Study (OS) participant addresses following a standardized protocol (Whitsel et al., 2004, 2006). The vendor assigned year 2000 U.S. Census Federal Information Processing Standards (FIPS) codes to the addresses (US Census of Population and Housing, 2000). We linked year 2000 U.S. Census tract-level socioeconomic data to each address using the FIPS codes. We estimated a summary measure of each participant's neighborhood socioeconomic environment using six variables representing several dimensions of wealth and income (Diez Roux et al., 2001):

- (1) Natural log (median household income)
- (2) Natural log (median value of housing units)
- (3) Percentage of households receiving interest, dividend, or net rental income
- (4) Percentage of adults ≥25 years of age who had completed high school
- (5) Percentage of adults ≥25 years of age who had completed college
- (6) Percentage of employed persons ≥16 years of age in executive, managerial, or professional specialty occupations

We converted each of the six variables into z scores by subtracting the population-specific mean from individual participant values and then dividing them by the population-specific standard deviation. The six resulting z scores indicated the deviation of a given value from the corresponding, population-specific mean and summed to zero. For example, a z score of +1.0 for log (median household income) indicated that the value was one standard deviation above the population-specific mean. We then constructed a neighborhood summary z score by summing the z scores of variables one through six. Increasing summary z scores imply increasing neighborhood socioeconomic advantage.

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