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Smoking cessation, weight gain, and risk of stroke among postmenopausal women

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ABSTRACT

The relationship between smoking cessation, concurrent weight gain, and stroke events is not yet understood. Thus, we examined the association between smoking cessation and subsequent stroke risk and whether the association was modified by concurrent weight gain.

In 2017, we analyzed data from 109,498 postmenopausal US women enrolled in the Women's Health Initiative from 1993 to 1998. Women with a history of cancer or cardiovascular disease events were excluded. The median length of follow-up time was 14.01 years. Variables of primary focus were smoking cessation, weight change, and clinically confirmed incident cases of hemorrhagic and ischemic stroke. Hazard ratios were estimated for stroke incidences (all, ischemic, and hemorrhagic) associated with smoking cessation using Cox regression. The exposure-outcome relationship of smoking cessation and risk of stroke was evaluated for effect modification by weight change.

Recent quitters between baseline and year 3 had a significantly lower risk for all stroke and ischemic stroke, but not hemorrhagic stroke, when compared to the reference group of continuing smokers. In the multivariable-adjusted model for ischemic stroke, the hazard ratio for recent quitters was 0.66 (95% CI: 0.46, 0.95). In the model for hemorrhagic stroke, the hazard ratio for recent quitters was 0.76 (95% CI: 0.36, 1.61). The association between recent quitting and stroke risk was not significantly modified by weight change.

Smoking cessation was associated with a significant reduction in stroke risk. The benefit of smoking cessation on the risk of stroke was not attenuated by concurrent weight gain.

1. Introduction

Cigarette smoking is an important cause of cardiovascular disease, and smoking cessation substantially reduces the risk (Ambrose and Barua, 2004; Jha et al., 2013; MMWR Morb. Mortal. Wkly Rep., 2008). Specifically, smoking is a modifiable and established risk factor for stroke (Wolf et al., 1988; Kondo et al., 2011; Kawachi et al., 1993; Shinton and Beevers, 1989). However, quitting smoking is associated with weight gain (Filozof et al., 2004). In North America, a mean 3 to 6 kg weight gain occurs within 6 months post-cessation and persists over time (Filozof et al., 2004). As obesity is also a risk factor for cardiovascular disease, weight gain may attenuate the benefits following smoking cessation (Luo et al., 2012; Whitlock et al., 2009).

A previous study has found an association between smoking cessation and a lower risk of cardiovascular events that was not modified by weight gain (Clair et al., 2013). However, this study had limited power and only examined the specific outcome of coronary heart disease (Clair et al., 2013). A later study used data from the Women's Health Initiative (WHI) to assess the association between smoking cessation, weight gain, and subsequent coronary heart disease risk among postmenopausal women with and without diabetes (Luo et al., 2013). The authors found that smoking cessation was associated with a lower risk of coronary heart disease among postmenopausal women with and without diabetes, but concurrent weight gain weakened this

Abbreviations: WHI, Women's Health Initiative; HR, Hazard ratio; CI, Confidence interval

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association, especially for women with diabetes who gained at least 5 kg (Luo et al., 2013). As other studies have only examined the outcome of coronary heart disease, the relationship between smoking cessation, concurrent weight gain, and stroke events is not yet understood. This study aimed to expand the knowledge of the relationship between smoking cessation, weight gain, and cardiovascular disease by examining stroke events.

We hypothesized that smoking cessation is associated with reduced risk of stroke. In our analysis, we also assessed how the association between smoking cessation and stroke was modified by weight change. We hypothesized that the protective association of smoking cessation on the risk of stroke would be attenuated by concurrent weight gain.

2. Methods

2.1. Study population

The WHI recruited 161,808 postmenopausal women aged 50 to 79 years from 1993 to 1998 at 40 sites throughout the United States. Details of the design and implementation of the WHI program have been published elsewhere (Anderson et al., 2003).

The following participants were excluded from the entire WHI cohort of 161,808 for this analysis: those missing smoking statuses at baseline or year 3 (23,446 excluded), women with a history of any cancer except for non-melanoma skin cancer at baseline (10,724), participants with previous stroke events or transient ischemic attacks (4346) before year 3, participants with a history of myocardial infarction or congestive heart failure before year 3 (3842), and particpants missing year 3 follow-up (9286). A category of recent smokers (reported smoking at year 3 but were past smokers or never smokers at baseline) was excluded due to insufficient sample size (666). After exclusions, 109,498 women remained for further analysis.

2.2. Measurements

The primary exposure was a change in self-reported smoking status from baseline to year 3. Categories were never smokers (women who never smoked at either time point); former smokers (those who classified themselves as former smokers at both baseline and year 3); continuing smokers (those who continued to smoke at both time points); and recent quitters (who smoked at baseline but quit by year 3). The baseline smoking status of never, past, and current smokers were derived from the 3 survey questions: 1. “During your entire life, have you smoked at least 100 cigarettes?”; 2. “Do you smoke cigarettes now?”; 3. “On the average, how many cigarettes do you (did you) usually smoke each day?” Never smokers were those who responded “no” to question 1. Past smokers were those who answered “yes” to question 1 and “no” to question 2. Current smokers were those who answered “yes” to questions 1 and 2 and responded to question 3. At year 3 participants were asked, “Do you smoke cigarettes now?” For time-dependent analyses, change in smoking status was assessed each year after year 3. For these analyses, a category of “New or resumed smoker” (smoking in the current year but no smoking in the previous year) was included. If smoking status was missing, the status from the previous year was carried forward. Smoking pack-years was a derived variable accounting for years of smoking and number of cigarettes smoked per day on average. The algorithm can be found on the WHI website (Algorithm - Pack Years of Smoking.pdf, n.d.). Categories of smoking pack-years were < 20 pack-years, 20– < 40 pack-years, and ≥40 pack-years.

The primary outcomes were all stroke, ischemic stroke, and hemorrhagic stroke. Stroke was defined using participant medical records based on 7 different diagnostic descriptions: subarachnoid hemorrhage, intraparenchymal hemorrhage, other or unspecified intracranial hemorrhage, occlusion of cerebral arteries with infarction, acute but ill-defined cerebrovascular disease, central nervous system complications during/from the procedure, or missing. The first three categories (subarachnoid hemorrhage, intraparenchymal hemorrhage, and other or unspecified intracranial hemorrhage) comprised hemorrhagic stroke, the fourth category (occlusion of cerebral arteries with infarction) comprised ischemic stroke, and the last 3 categories (acute but ill-defined cerebrovascular disease, central nervous system complications during/from procedure, and missing) comprised undefined stroke. All 7 diagnostic categories were included in all stroke. Ischemic stroke subtypes of cardioembolism, large artery atherosclerosis, and small vessel occlusion (lacune) were diagnosed according to the TOAST classification system. Stroke categories were centrally adjudicated according to standardized procedures (Clair et al., 2013; Luo et al., 2013; WHI, 2012). Follow-up time was measured from year 3 to September 30, 2015, loss to follow-up, date of death, or date of a stroke diagnosis, whichever came first.

Participant weight was measured in kilograms at baseline and year 3. Weight change was calculated from the difference between participant weight in kilograms at year 3 and baseline. Weight change was also categorized into weight loss (< −5 kg), stable weight (≥ −5 kg to < 5 kg), and weight gain (≥5 kg) groups. Weight change was dichotomized into weight gain (≥5 kg) and non-weight gain (< 5 kg) groups to increase sample sizes for additional effect modification analyses. For additional analyses, categories of percent weight change were created: weight loss (< −5%), stable weight (≥ −5% to < 5%), weight gain (≥5%). Body mass index (kg/m^2) and waist to hip ratio (waist circumference (cm)/hip circumference (cm)), were also collected for each participant at baseline.

Baseline alcohol consumption was categorized by groups of non-drinkers, former drinkers, and those consuming < 1 drink per month, < 1 drink per week, 1 to < 7 drinks per week, and 7+ drinks per week. For the ethnicity/race covariate, participants self-reported as American Indian or Alaskan Native, Asian or Pacific Islander, Black or African-American, Hispanic/Latino, White (not Hispanic), or Other. Education level at baseline was categorized as high school or less, some college/technical school, college/some post-college, and Master's degree or higher. Age at enrollment was categorized into < 55 years, ≥75 years, and 5-year intervals in between.

Physical activity was defined as metabolic equivalent task (MET)-hours per week calculated from baseline self-reported recreational physical activity (includes walking, mild, moderate and strenuous physical activity) (Anderson et al., 2003). Categorical variables were used for randomized control trial intervention and control assignments. Dichotomous yes/no response categories were used for baseline self-reported classification of diabetes, hypertension, high cholesterol, and atrial fibrillation. Additional dichotomous yes/no variables were designated for participation in the hormone therapy trial arms, diet modification trial arms, calcium/vitamin D trial arms, and observational study.

2.3. Statistical analysis

In 2017 we performed bivariate analyses for all covariates with change in smoking status and stroke outcomes: ischemic, hemorrhagic, and all stroke. Appropriate chi-square tests or analysis of variance tests were applied.

Hazard ratios (HRs) for risk of stroke by smoking status were estimated with Cox proportional hazards regression in models adjusted for age and additional covariates. Suspected potential confounders and variables associated with both change in smoking status and stroke outcomes were chosen for inclusion in the multivariable-adjusted model. Multivariable-adjusted models included age categories at baseline, categories of weight change, categories of smoking pack-years, diabetes, education, ethnicity/race, alcohol, hypertension, atrial fibrillation, body mass index, waist to hip ratio, and physical activity. Models were assessed using complete data for covariates. We stratified all models by randomized control trial intervention and control assignments. Further, we tested for effect modification of the association

between change in smoking status and risk of stroke by weight change by including in models an interaction term for change in smoking status with weight change. Both dichotomized weight change and trichotomized weight change were tested. Hazard ratios within each category of weight change were estimated from the corresponding interaction model. Interaction models with categories of percent weight change were also assessed. Participants lost to follow-up contributed survival time until the date of censoring. Cause-specific hazard models were applied for outcomes of ischemic and hemorrhagic stroke by censoring all individuals who did not experience the stroke event of interest. These analyses were repeated using the time-dependent change in smoking status. Proportional hazards assumption was assessed with time-dependent coefficients and examination of Schoenfeld residual plots. Analyses were repeated for ischemic stroke subtypes of cardioembolism, large artery atherosclerosis, and small vessel occlusion (lacune) as the outcomes of interest. Analyses were also repeated with categories of percent weight change instead of categories of weight change. Sensitivity analyses for unmeasured confounding were conducted by calculating the E-values for both the hazard ratios and the limit of the confidence interval (CI) closest to the null. The E-value is the minimum strength of association, on the risk ratio scale, that an unmeasured confounder would need to have with both the exposure and outcome, conditional on the measured covariates, to fully explain away a specific exposure-outcome association (VanderWeele and Ding, 2017).

Statistical analyses were performed using SAS version 9.3 (SAS Institute Inc.). The WHI study was approved by institutional review boards at all participating centers. All participants provided written informed consent.

3. Results

Of the 109,498 participants in our sample, 3534 experienced a stroke event; 2656 were classified as ischemic stroke and 533 were classified as hemorrhagic stroke, and 345 as undefined stroke. The median and mean follow-up time was 14.01 years and 12.04 years, respectively. The incidence rates for all stroke, ischemic stroke, and hemorrhagic stroke were 2.68 per 1000 person-years, 2.01 per 1000 person-years, and 0.40 per 1000 person-years, respectively.

Every covariate was significantly associated with smoking status at an alpha level of 0.05 (Table 1) except for high cholesterol, $P = 0.6168$. The average weight change from baseline to year 3 was an increase of 0.36 kg (95% CI: 0.31, 0.43). Never smokers and former smokers gained on average 0.26 kg (95% CI: 0.18, 0.34) and 0.45 kg (95% CI: 0.36, 0.54), respectively. Continuing smokers on average lost weight, −0.13 kg (95% CI: −0.41, 0.15). In contrast, recent quitters had a substantial average weight gain of 3.10 kg (95% CI: 2.61, 3.59). Compared with never smokers, continuing smokers and recent quitters were more likely to be younger, physically inactive, be Black or African American, less educated, have higher alcohol consumption, and less likely to be hypertensive. Recent quitters were more likely to be diabetic and less likely to have high cholesterol than the other groups (Table 1).

3.1. Change in smoking status and risk of stroke

The categories of never smokers, former smokers, and recent quitters all showed significantly protective hazard ratios for all stroke when compared to the reference group of continuing smokers (Table 2). Both never smokers (HR: 0.59; 95% CI: 0.50, 0.70) and former smokers (HR: 0.58; 95% CI: 0.50, 0.68) at enrollment showed directionally lower risk than more recent quitters (HR: 0.67; 95% CI: 0.49, 0.92). The E-values were 2.78, 2.84, and 2.35 for never smokers, former smokers, and recent quitters, respectively. The E-values for the upper limit of the confidence intervals were 2.21, 2.30, and 1.39, respectively. An unmeasured confounder associated with both smoking and stroke by a risk ratio of 2.21, 2.26, and 1.43 for never smokers, former smokers, and recent quitters, respectively, could explain away the upper confidence limit, but weaker confounding could not. These results were similar when modeled with a time-dependent change in smoking status (results not shown). As the smoking dosage information from smoking pack-years is distinct from change in smoking status, we also estimated the association between pack-years and stroke. Greater smoking exposure measured in pack-years 20 to < 40 and ≥40 showed a 20–30% increase in stroke risk compared with pack-years < 20 (Table 2).

Results were similar for ischemic stroke, and all hazard ratios were significant. The hazard ratio for recent quitters vs continuing smokers was 0.66 (95% CI: 0.46, 0.95). The E-values for the hazard ratio and the upper confidence limit were 2.40 and 1.29, respectively. Similarly, increased smoking pack-years versus the reference group significantly increased the risk of ischemic stroke (Table 2).

Further analysis of ischemic stroke subtypes showed no significant associations between change in smoking status with both large artery atherosclerosis and cardioembolic stroke risk in the multivariable-adjusted model, but never and former smokers had significantly lower hazard for small vessel occlusion (lacune) stroke than continuing smokers (Table S1).

Hemorrhagic stroke showed slightly different results. Although the categories of never smoker, former smoker and recent quitter all showed protective hazard ratios when compared to the reference group of continuing smokers, only former smokers had a significantly lower risk (HR: 0.62; 95% CI: 0.41, 0.92). The E-value for the hazard ratio and the upper confidence limit were 2.61 and 1.39, respectively. Smoking 20 to < 40 pack-years versus the reference group had a significantly increased risk of hemorrhagic stroke (Table 2).

3.2. Effect modification

No significant effect modification for stroke risk was found between change in smoking status and weight change after baseline (P interaction = 0.56). The hazard ratios for change in smoking status were similar in each dichotomized weight change strata, < 5 kg and ≥5 kg (Table 3). Similar nonsignificant results were seen for ischemic stroke and hemorrhagic stroke (P interaction = 0.30 and 0.65, respectively, Table 3). Furthermore, no significant effect modification was found with trichotomized weight change, categories of percent weight change, or time-dependent change in smoking status (results not shown).

4. Discussion

Our findings corroborate that smoking cessation is associated with a decreased risk of overall stroke. These findings align with previous research from the Framingham Study, Nurse's Health Study, and others (Wolf et al., 1988; Kawachi et al., 1993; Rost et al., 2001; Folsom et al., 2000). The Framingham Study found that the hazard ratio (HR) for stroke was 1.42 ($P < 0.05$) for male smokers and 1.61 ($P < 0.05$) for female smokers versus nonsmokers, after adjusting for confounders. Two years after cessation of cigarette smoking, stroke risk decreased significantly, and was at the level of nonsmokers by five years (Wolf et al., 1988). Furthermore, the Nurse's Health Study found a stroke risk ratio of 2.58 (95% CI: 2.08–3.19) for smokers compared to nonsmokers and 1.34 (95% CI: 1.04–1.73) for former smokers (Kawachi et al., 1993). Stroke risk declined with time post-cessation (Lightwood and Glantz, 1997; O'Donnell et al., 2010; Shah and Cole, 2010; Song and Cho, 2008).

The pathophysiological effects of cigarette smoking that lead to stroke are not yet fully understood (Ambrose and Barua, 2004; Khaw, 1996). However, a dose-response relationship is present between the number of cigarettes smoked and increased stroke risk (Shinton and Beevers, 1989). Smoking results in many pathologies associated with a higher risk of stroke (Ambrose and Barua, 2004; Jha et al., 2013; Iida

Table 1
Baseline characteristics of participants by change in smoking status[a], Women's Health Initiative, 1993–1998.

	Never smoker 57,676 (52.67%)	Former smoker 45,105 (41.19%)	Continuing smoker 4844 (4.42%)	Recent quitter 1873 (1.71%)
Smoking pack-years (mean, 95% CI)	0	18.13 (17.94, 18.32)	31.02 (30.39, 31.66)	22.31 (21.30, 23.32)
Weight[b] difference: year 3 – baseline (kg, mean, 95% CI)	0.26 (0.18, 0.34)	0.45 (0.36, 0.54)	−0.13 (−0.41, 0.15)	3.10 (2.61, 3.59)
Age at enrollment (yr, mean, 95% CI)	63.25 (63.19, 63.31)	62.83 (62.77, 62.90)	60.89 (60.70, 61.07)	60.87 (60.57, 61.16)
Body mass index baseline[c] (kg/m^2, mean, 95% CI)	27.65 (27.60, 27.70)	27.83 (27.78, 27.89)	26.65 (26.50, 26.81)	27.34 (27.08, 27.60)
Waist to hip ratio (mean, 95% CI)	0.80 (0.803, 0.804)	0.81 (0.810, 0.811)	0.82 (0.818, 0.822)	0.82 (0.817, 0.824)
Physical activity (MET hours/wk, mean, 95% CI)	12.40 (12.29, 12.51)	13.88 (13.75, 14.02)	9.17 (8.82, 9.52)	10.44 (9.88, 11.00)
Ethnicity/race, # (%)				
American Indian or Alaskan Native	203 (0.35%)	158 (0.35%)	30 (0.62%)	6 (0.32%)
Asian or Pacific Islander	2277 (3.96%)	744 (1.65%)	95 (1.97%)	30 (1.60%)
Black or African-American	4376 (7.61%)	3212 (7.13%)	635 (13.14%)	233 (12.46%)
Hispanic/Latino	2473 (4.30%)	1095 (2.43%)	165 (3.41%)	91 (4.87%)
White (not Hispanic)	47,556 (82.66%)	39,372 (87.46%)	3847 (79.60%)	1487 (79.52%)
Other	644 (1.12%)	437 (0.97%)	61 (1.26%)	23 (1.23%)
Education, # (%)				
High school or less	12,938 (22.59%)	8345 (18.63%)	1230 (25.55%)	414 (22.21%)
Some college/technical school	20,436 (35.68%)	17,018 (38.00%)	2085 (43.31%)	789 (42.33%)
College/some post-college	13,187 (23.03%)	11,011 (24.58%)	913 (18.97%)	380 (20.39%)
Master's degree or higher	10,707 (18.70%)	8416 (18.79%)	586 (12.17%)	281 (15.08%)
Alcohol, # (%)				
< 1 drink/week	39,560 (68.98%)	23,083 (51.35%)	2704 (56.04%)	1001 (53.62%)
1 to < 7 drinks/week	13,448 (23.45%)	14,128 (31.43%)	1214 (25.16%)	513 (27.48%)
7 + drinks/week	4344 (7.57%)	7744 (17.23%)	907 (18.80%)	353 (18.91%)
Diabetes[b], yes # (%)	2734 (4.74%)	2004 (4.45%)	177 (3.66%)	96 (5.13%)
Hypertension[c], yes # (%)	18,009 (31.40%)	13,801 (30.79%)	1279 (26.56%)	503 (26.98%)
High cholesterol[d], yes # (%)	6901 (12.45%)	5470 (12.58%)	576 (12.49%)	210 (11.57%)
Atrial fibrillation[e] yes # (%)	2051 (3.60%)	1569 (3.52%)	135 (2.83%)	50 (2.70%)

[a] Associations were tested for significance with analysis of variance for continuous variables and chi-square tests for categorical variables. All associations were significant, $P < 0.05$, except for high cholesterol.
[b] Diabetes defined as did a doctor ever say that you had sugar diabetes or high blood sugar.
[c] Hypertension defined as did a doctor ever say that you had hypertension or high blood pressure.
[d] High cholesterol defined as has a doctor told you that you have high cholesterol requiring pills.
[e] Atrial fibrillation defined as a condition that a doctor said you had: Atrial fibrillation (a type of irregular heart beat).

et al., 1998; Peters et al., 2013). Specifically, smoking impairs vasodilator function by decreasing the availability of nitrous oxide, a primary dilator (Ambrose and Barua, 2004; Iida et al., 1998). Smoking also causes immediate cerebral vasoconstriction, increased mean arterial pressure, and increased blood glucose that causes further cerebral vasodilation impairment (Iida et al., 1998). Smoking has also been associated with increased blood viscosity and dyslipidemia (Ambrose and Barua, 2004; Mainali et al., 2015). The complex relationship between cigarettes and stroke risk is likely a combination of factors (Peters et al., 2013). Correspondingly, smoking cessation leads to increased cardiovascular health for all ages (Bakhru and Erlinger, 2005; Taylor et al., 2002). A study of two separate populations found that at 5 years post-smoking cessation, inflammatory markers returned to baseline, indicating a mechanism by which some of the cardiovascular effects of smoking may be reversible (Bakhru and Erlinger, 2005).

We found that weight change was significantly associated with change in smoking status. Animal studies have indicated that nicotine in cigarettes reduces weight by decreasing appetite (Chen et al., 2005; Mangubat et al., 2012). Additionally, we found recent quitters gained significantly more weight than any other smoking category. It has been previously reported that smoking cessation leads to weight gain back to pre-smoking levels with an average weight gain of 2–4 kg (Albanes et al., 1987; Williamson et al., 1991). Women gain an average of 1–2 kg more weight post-cessation than men (Williamson et al., 1991), and are

Table 2
Hazard ratios for stroke associated with change in smoking status, pack years, and weight change[a], Women's Health Initiative, 1993–2015.

	All stroke			Ischemic stroke			Hemorrhagic stroke		
Exposure	Stroke cases	Adjusted model[a]		Stroke cases	Adjusted model[a]		Stroke cases	Adjusted model[a]	
		HR	95% CI		HR	95% CI		HR	95% CI
Change in smoking status	3449			2598			519		
Continuing smoker	216	1.00	Referent	158	1.00	Referent	34	1.00	Referent
Never smoker	1832	0.59	0.50, 0.70	1383	0.62	0.51, 0.76	278	0.67	0.43, 1.04
Former smoker	1345	0.58	0.50, 0.68	1017	0.60	0.50, 0.73	197	0.62	0.41, 0.92
Recent quitter	56	0.67	0.49, 0.92	40	0.66	0.46, 0.95	10	0.76	0.36, 1.61
Smoking pack-years	3449			2598			519		
< 20	2725	1.00	Referent	2054	1.00	Referent	403	1.00	Referent
20– < 40	415	1.20	1.05, 1.35	303	1.17	1.01, 1.35	73	1.50	1.10, 2.03
≥40	309	1.27	1.11, 1.46	241	1.34	1.14, 1.57	43	1.40	0.96, 2.03

HR, hazard ratio; CI, confidence interval.
[a] Adjusted for age categories at baseline, weight change (< −5 kg, ≥ −5 kg to < 5 kg, ≥5 kg), categories of smoking pack-years, diabetes, education, ethnicity/race, alcohol, hypertension, high cholesterol, atrial fibrillation, body mass index, waist to hip ratio, and physical activity.

Table 3
hazard ratios for stroke associated with change in smoking status by weight change[a], Women's Health Initiative, 1993–2015.

Exposure	Weight change (kg)						Interaction
	< 5 kg			≥ 5 kg			
	Stroke cases	Adjusted model		Stroke cases	Adjusted model		
		HR	95% CI		HR	95% CI	P
			All stroke				
Change in smoking status	3092			357			0.56
Continuing smoker	190	1.00	Referent	26	1.00	Referent	
Never smoker	1657	0.587	0.49, 0.70	175	0.601	0.38, 0.94	
Former smoker	1202	0.581	0.49, 0.69	143	0.563	0.36, 0.88	
Recent quitter	43	0.757	0.53, 1.07	13	0.479	0.24, 0.96	
			Ischemic stroke				
Change in smoking status	2338			260			0.30
Continuing smoker	140	1.00	Referent	18	1.00	Referent	
Never smoker	1255	0.622	0.50, 0.77	128	0.636	0.37, 1.08	
Former smoker	910	0.604	0.50, 0.73	107	0.599	0.35, 1.02	
Recent quitter	33	0.801	0.54, 1.20	7	0.342	0.13, 0.88	
			Hemorrhagic stroke				
Change in smoking status	454			65			0.65
Continuing smoker	28	1.00	Referent	6	1.00	Referent	
Never smoker	250	0.698	0.44, 1.11	28	0.508	0.19, 1.37	
Former smoker	171	0.632	0.41, 0.97	26	0.539	0.20, 1.43	
Recent quitter	5	0.560	0.19, 1.60	5	0.950	0.27, 3.29	

HR, hazard ratio; CI, confidence interval.
[a] Adjusted for age categories at baseline, weight change (< 5 kg, ≥ 5 kg), categories of smoking pack-years, diabetes, education, ethnicity/race, alcohol, hypertension, high cholesterol, atrial fibrillation, body mass index, waist to hip ratio, and physical activity.

more likely to gain a substantial amount of weight (> 13 kg) 4 to 6 years after smoking cessation (Williamson et al., 1991; Lean, 2007; Shinton et al., 1991). This gender difference has been contradicted by other studies showing either greater increases of weight in men or no differences (Locatelli et al., 2014; Doherty et al., 1996; Chinn et al., 2005; Robertson et al., 2014; Tian et al., 2015).

Our hypothesis that weight gain would attenuate the protective association of smoking cessation on stroke risk was not supported in our results. This outcome is similar to the findings of Rigotti et al., and dissimilar from another study using data from the WHI that found weight gain attenuated the protective association of being a former smoker or recent quitter on the risk of cardiovascular disease particularly in women with diabetes (Clair et al., 2013; Luo et al., 2013). However, that study did not formally test for interaction. Effect modification may not have been found in our study because the weight change over the three-year assessment interval may be temporary and not reflective of long-term weight change. We did not consider weight changes after year 3, which may have caused some misclassification. However, this misclassification is likely to be non-differential which would likely bias our results toward the null. In addition, change in smoking status and weight change were assessed during the same 3-year timeframe which makes causal inferences on the relationship between these two factors impossible.

Unmeasured confounding must also be considered. E-values were moderately high and thus a strong unmeasured confounder would be necessary to explain away the associations. The study population was post-menopausal; changes in levels of estrogen may have altered both weight gain and stroke risk. In a recent animal study, Stubbins et al. found that estrogen provided protection against weight gain in female mice; this protection was lost following ovariectomy, and regained upon exogenous hormone replacement (Stubbins et al., 2012). Furthermore, the high baseline body mass index of our study base could cause predisposition to stroke, which may have attenuated our findings (Strazzullo et al., 2010). Differential loss to follow-up is a concern as women who were healthier and at lower risk of stroke were more likely to remain in the study and through the extensions.

An important consideration in any examination of stroke is the distinction between ischemic and hemorrhagic strokes. Distinguishing the etiology of hemorrhagic stroke from ischemic stroke has often been difficult due to the relative rarity of hemorrhagic stroke. In our study, smoking cessation was associated with a reduced risk of all stroke and ischemic stroke but was not associated with hemorrhagic stroke, likely due to the few cases, 11, among recent quitters. Many other studies have shown a relationship between smoking status and risk of hemorrhagic stroke, such as the INTERSTROKE study, which found current smokers to have an odds ratio of 1.45 (95% CI: 1.07–1.96) of hemorrhagic stroke compared to never or former smokers. However, the increased risk from smoking was stronger for ischemic than hemorrhagic stroke (O'Donnell et al., 2010).

We acknowledge that smoking is a dynamic behavior with multiple quit attempts and high relapse rates after cessation. As such, our categorization of change in smoking status may not capture the trajectories of smoking behavior and is a limitation. To address this issue, we assessed the stability of our categorization by comparing if participants ever reported smoking in the any of the follow-up surveys after year 3 with our change in smoking status groups. We found that 18.8% of recent quitters reported smoking in a later follow up survey, i.e. "relapsed." Similarly, 14.3% of the continuing smokers never reported smoking in the follow-up surveys. Presumedly these individuals quit smoking (Table 1). Furthermore, we performed time-dependent analyses but found similar results. A reason may be that this misclassification was largely nondifferential. We found similar percentages of stroke among recent quitters who "relapsed" (2.96%) compared to recent quitters who never reported smoking in follow-up (3.06%). Similarly, the percentage of stroke among continuing smokers who never reported smoking in follow-up (4.52%) was nearly identical to continuing smokers who continued smoking (4.50%). Only with ischemic stroke and among continuing smokers who quit smoking (2.55%) versus those who continued smoking (3.44%) was there a noticeable variation. Though this is likely due to the small number of cases (only 22) for continuing smokers who quit. These results are surprising as we expect that risk of stroke would vary among those with different

smoking behavior trajectories. Ultimately this may be a limitation of the questionnaire in capturing a behavior as complex as smoking.

The strengths of our study include a prospective cohort study design, a large sample size, and the breadth of adjudicated health metrics allowing for the distinction between types of stroke. Furthermore, the separate evaluation of hemorrhagic and ischemic stroke cases should help distinguish the different etiologies of ischemic and hemorrhagic stroke. Our focus on postmenopausal women is important for future prevention efforts in this population. However, the restriction of our study population to postmenopausal women limits our generalizability.

5. Conclusions

Despite modest weight gains concurrent with smoking cessation, these weight gains did not diminish the reduction in overall risk of stroke associated with smoking cessation in post-menopausal women. The public health message to quit smoking should not be tempered due to concerns over post-cessation weight gain, and benefits of smoking cessation should be promoted unequivocally.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ypmed.2018.10.018.

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