Hypothetical Lifestyle Strategies in Middle-Aged Women and the Long-Term Risk of Stroke

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Background and Purpose—Long-term effect of lifestyle changes on stroke incidence has not been estimated in randomized trials. We used observational data to estimate the incidence of stroke under hypothetical lifestyle strategies in the NHS (Nurses' Health Study).

Methods—We considered 3 nondietary strategies (smoking cessation, exercising ≥30 min/d, gradual body mass index reduction if overweight/obese) and several dietary strategies (eating ≥3 servings/wk of fish, ≤3 servings/wk of unprocessed red meat, no processed red meat, ≥1 servings/d of nuts, etc). We used the parametric g-formula to estimate the 26-year risk of stroke under these strategies.

Results—In 59 727 women, mean age 52 years at baseline in 1986, the estimated 26-year risks under no lifestyle interventions were 4.7% for total stroke, 2.4% for ischemic stroke, and 0.7% for hemorrhagic stroke. Under the combined nondietary interventions, the estimated 26-year risk of total stroke was 3.5% (95% CI, 2.6%–4.3%) and ischemic stroke was 1.6% (95% CI, 1.1%–2.1%). Smaller reductions in total stroke risk were estimated under isolated dietary strategies of increased intake of fish and nuts and reduced intake of unprocessed red meat. Ischemic stroke risk was lower under reduced intake of unprocessed and processed red meat, and hemorrhagic stroke risk was lower under a strategy of increased fish consumption.

Conclusions—In this population of middle-aged women, sustained, lifestyle modifications were estimated to reduce the 26-year risk of total stroke by 25% and ischemic stroke by 36%. Sustained dietary modifications were estimated to reduce the 26-year risk of total stroke by 23%.   (***Stroke***. 2020;51:1381-1387. DOI: 10.1161/STROKEAHA.119.026761.)

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S troke is the primary cause of preventable disability in the United States.[1,2] While stroke incidence and mortality have decreased,[1] more women than men are experiencing new strokes, as well as dying from stroke.[3] Functional outcomes and quality of life following stroke are also poorer in women.[4] Average age at first stroke in women is 75 years;[3] therefore, midlife lifestyle modifications may be helpful in reducing the burden of stroke in women.

Few randomized trials have examined the effect of lifestyle interventions on stroke.[5–7] The Women's Health Initiative found that, during a mean 8-year follow-up, encouraging postmenopausal women to eat a low-fat diet with higher fruit, vegetable, and grain intake did not reduce stroke risk.[5] In contrast, the PREDIMED study (Prevención con Dieta Mediterránea) concluded that, in a high-risk population, consuming a Mediterranean diet supplemented with nuts or olive oil reduced the 5-year risk of stroke by 31% and 28%, respectively, compared with a low-fat diet.[7] However, it is difficult to investigate the effect of sustained interventions over longer periods in a randomized trial.

Several prospective studies have found an inverse association between healthy lifestyles and stroke risk[8–12] in middle-aged men and women. Dietary observational studies have reported an inverse association between nut,[13] fish,[14] and fruit and vegetable consumption,[15,16] and risk of stroke, as well as a positive association between red meat consumption and stroke risk.[17] Most of these associations are seen with risk of total and ischemic stroke but not hemorrhagic stroke.

It is unlikely that large-scale lifestyle trials will be conducted for stroke prevention; therefore, we sought to estimate the effects of lifestyle on stroke risk using longitudinal observational data from the NHS (Nurses' Health Study). To properly adjust for time-varying confounders that are affected by prior lifestyle risk factors, we used the parametric g-formula.[18]

Methods

Data Availability

Data from the NHS are available by request. Request forms can be found at https://www.nurseshealthstudy.org/researchers.

Study Population

The NHS is a longitudinal study that began in 1976 with 121 701 nurses, 30 to 55 years of age, who responded to a mailed questionnaire. The nurses continue to receive follow-up questionnaires every 2 years (we refer to this interval as a period in the study) to update information on potential lifestyle risk factors and to identify newly diagnosed diseases.[19,20] Participants in NHS were first sent an expanded 131-item food frequency questionnaire in 1984[21]; therefore, we used 1986 as our baseline year to allow adjustment for prebaseline confounders. Diet and physical activity were reported every 4 years in the later years. We excluded participants who died or did not return a questionnaire, who were missing risk factor information, who were diagnosed with stroke, myocardial infarction, angina or coronary artery bypass graft procedure, or cancer (other than nonmelanoma skin cancer) before 1986. We also excluded participants who left >70 food frequency questionnaire items blank or who reported implausible total energy intakes (ie, <500 or >3500 kcal/d). We followed eligible participants from 1986 until diagnosis of stroke, death, or June 2012, whichever occurred first. If missing, data on covariates were carried forward for 1 period. If after carrying forward for 1 period, there was still a covariate with missing value, we censored the participant. Participants who did not return 2 consecutive questionnaires were censored at the first instance of not returning a questionnaire.

Outcome Ascertainment

At each questionnaire period, participants were asked whether they had physician-diagnosed stroke since the last period. Participants who reported a stroke were asked for permission to review their medical records. For both nonfatal and fatal strokes, available medical records related to the clinical event such as imaging and autopsy reports were reviewed by physicians who were blind to participants' risk factor status. Strokes were defined according to the National Survey of Stroke criteria[22] and were classified as ischemic or hemorrhagic.[23] Stroke subtyping by physician review was validated using computer tomography, magnetic resonance imaging, or autopsy findings in ≈88% of women with available medical records.[23] In the absence of complete medical records, strokes confirmed by telephone, letter, or death certificate were classified as unknown subtype and only included in the analysis of total stroke. When studying total stroke, we stopped the follow-up after the first diagnosis of any stroke. When studying stroke subtypes, we defined the outcome to be the first event of the selected subtype, so if the first stroke was not of the selected subtype (or was of unknown subtype), we continued the follow-up until the selected subtype occurred (or the participant died or was administratively censored at the end of follow-up). Deaths were identified through reports from relatives or review of the National Death Index.[24]

Lifestyle Risk Factors

Diet was measured using a validated 131-item semiquantitative food frequency questionnaire in 1984, 1986, and every 4 years thereafter.[21] We used these to calculate usual intake of processed and unprocessed red meat, poultry, fruits and vegetables, nuts, whole grains, refined grains, alcohol, and fish intake. Physical activity was measured as hours per week of moderate-to-vigorous activity using a validated questionnaire in 1980, 1982, 1986, 1988, and every 4 years thereafter.[25] Body mass index (BMI) was calculated using self-reported weight and height on each questionnaire.[26,27] We truncated values of dietary intake, physical activity, and BMI at the 99th percentile at each period.

Hypothetical Strategies

In primary analyses, we estimated the risk of total stroke, ischemic stroke, and hemorrhagic stroke between 1986 and 2012, under the following hypothetical strategies of nondietary risk reduction: (1) smoking cessation, (2) moderate-to-vigorous intensity exercise of at least an average of 30 min/d, (3) BMI reduction by 5% at each period if ≥25 kg/m², (4) a joint strategy combining (1) to (3). We also investigated the following dietary strategies: (5) eat ≥3 servings/wk of fish, (6) eat ≥1 serving/d of nuts, (7) eat ≥2 servings/d of whole grains, (8) eat ≥5 servings/d of fruits and vegetables, (9) eat <3 servings/wk of unprocessed red meat, (10) do not eat processed red meat, (11) drink between 5 and 15 g/d of alcohol, and (12) combine dietary strategies (5) to (11). These hypothetical strategies were compared with making no lifestyle changes, also referred to as the natural course (0). All strategies started at baseline in 1986 and were sustained until 2010, the last year of risk factor assessment, the simulated values in this year being used to estimate the risk of stroke between 2010 and 2012.

Strategies (5), (7), (9), and (10) were designed as approximately isocaloric strategies,[28] in which the increase (or decrease) of the selected food item was replaced with a corresponding decrease (or increase) in another specified food item. Because caloric intake remains constant, these strategies reduce the potential impact for weight gain, which makes them more relevant from a public health and clinical perspective. Specifically, in strategy (5), an increase in fish intake was combined with a decrease in unprocessed red meat intake; in (7), an increase in whole grain intake was combined with a decrease in refined grain intake; in (9), a decrease in intake of unprocessed red meat was combined with an increase in poultry intake; in (10), a decrease in processed red meat intake was combined with an increase in unprocessed red meat intake. All strategies, except quit smoking, specify threshold values.[29] At each period, if the value of the risk factor before intervention was above (or below) the threshold, it was changed to the threshold value. We estimated the average proportion of individuals whose actual values would have need to change under each strategy both cumulatively and at each 2-year period.

Parametric G-Formula

The parametric g-formula is a generalized version of standardization for time-varying exposures and confounders.[30,31] It has previously been described and used to investigate the effect of hypothetical lifestyle strategies on coronary heart disease,[18,28,32] diabetes mellitus,[33] and respiratory disease.[34] A simplified outline of the algorithm is as follows: (1) we fit parametric regression models for 22 selected time-varying covariates at each period k as a function of prior covariate history, fixed baseline covariates (Table I in the Data Supplement), and prebaseline values of the selected lifestyle risk factors; (2) we fit a pooled logistic model to estimate the probability of stroke between periods k and k+1, as a function of covariate history; (3) we used these models to simulate 50 000 individuals under each hypothetical strategy, using observed values at baseline and values of risk factors changed at each interval (if necessary) according to the strategy; (4) we estimated the 26-year risk of stroke in the simulated data. We used a nonparametric sampling with 200 samples to obtain 95% CIs in the main and subgroup analyses and 50 samples in stroke subtype and sensitivity analyses. This approach allows us to have valid variance estimates for the quantities of interest where each participant contributes >1 data point. We compared the estimated risk with that under no intervention. Like all regression-based methods, the parametric g-formula relies on correct model specification. To assess the validity of our parametric assumptions, we confirmed that the estimated means of the outcome and time-varying covariates under no intervention were similar to the observed means (Figure I in the Data Supplement).

In subgroup analyses, we separately studied women who had high stroke risk at baseline as defined by having diabetes mellitus or ≥3 of the following 5 risk factors: smoking, hypertension, high serum cholesterol, overweight/obese, or family history of early coronary heart disease (those who did not satisfy either of these 2 conditions were considered as being at low risk of stroke).[7] In sensitivity analyses, we used alternative order of modeling covariate, we included atrial

fibrillation as a time-varying covariate (it was not measured until 2000), excluded nurses diagnosed with diabetes mellitus before baseline, and estimated the effect of exercising 45 and 60 min/d.

All analyses were conducted using SAS 9.4. The GFORMULA macro is publicly available at http://www.hsph.harvard.edu/causal/software. Informed consent was obtained from all participants in the NHS, and this analysis was approved by the Institutional Review Board at the Harvard T.H. Chan School of Public Health.

Results

There were 59 727 eligible participants in 1986 (Figure). Mean age at baseline was 52.0 years, and mean BMI was 24.5 kg/m²; 95% were white, 21% were smokers, and 54% were postmenopausal (Table 1). During follow-up, 9998 participants died of causes other than stroke, and 10 393 participants were lost to follow-up. We observed 2349 first strokes, of which 1251 were ischemic, 351 were hemorrhagic, and

Figure. Participant selection, Nurses' Health Study. CABG indicates coronary artery bypass graft; and MI, myocardial infarction.

747 were of unknown subtype. The estimated 26-year risk (95% CI) of total stroke under the natural course was 4.7% (4.5%–4.9%). Under a hypothetical joint strategy of smoking cessation, exercise, and weight reduction, the risk of total stroke was 3.5% (2.6%–4.3%), and under a joint dietary strategy with 7 components, it was 3.6% (2.7%–4.5%; Table 2). Smaller risk reductions were estimated under isolated dietary strategies of increased fish and nut intake and reduced unprocessed red meat intake. Isolated strategies of increased whole grains, fruits and vegetables intake, and reduced alcohol intake appeared to have little or no effect.

In the subgroup of women with a high risk of stroke at baseline, the observed risk of total stroke was 6.6% versus 2.4% in women with low risk of stroke (Tables II and III in the Data Supplement). Among high-risk women, the estimated 26-year risk of total stroke was 4.8% (3.1%–7.0%) under a joint strategy of smoking cessation, exercise, and weight loss and 4.7% (3.2%–6.6%) under a joint strategy of 7 dietary components.

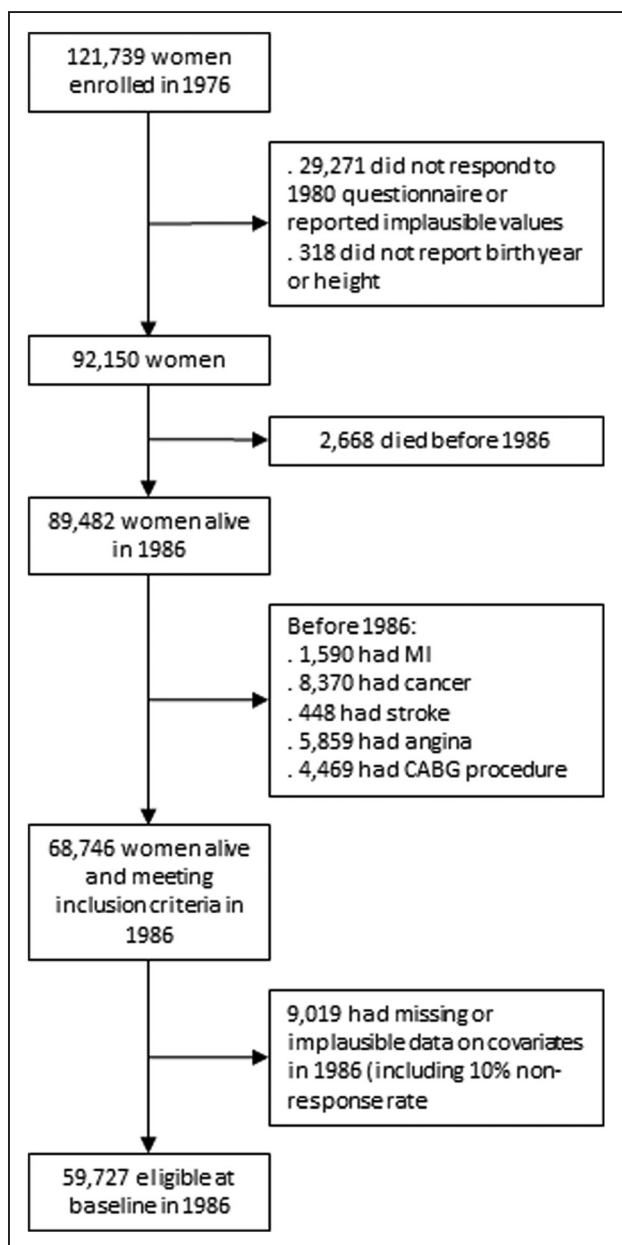The estimated 26-year risk (95% CI) of ischemic stroke under the natural course was 2.5% (2.4%–2.6%). The

Table 1.   Baseline Characteristics of 59 727 Eligible Participants, Nurses' Health Study, 1986

Characteristics	
Age, y	52.0±7.2
White race, %	95
Married, %	92
Family history of early (age ≤60 y) CHD, %	19
History of oral contraceptive use, %	51
Postmenopausal, %	54
Use of postmenopausal hormones, %	23
Current smoker, %	21
BMI	24.5±1.2
Hypertensive, %	23
High risk of stroke,* %	33
Physical activity, min/d†	16.3±24.0
Dietary intakes	
Fish (servings/wk)	2.1±1.7
Nuts (servings/d)	0.3±0.4
Whole grains (servings/d)	1.2±1.1
Fruits and vegetables (servings/d)	5.5±2.8
Unprocessed red meat (servings/d)	0.7±0.4
Processed red meat (servings/d)	0.3±0.3
Alcohol, g/d	6.3±10.1

Values are mean±SD unless otherwise specified. BMI indicates body mass index; and CHD, coronary heart disease.

*High stroke risk was defined as either having diabetes mellitus or ≥3 of the following 5 risk factors: smoking, hypertension, high serum cholesterol, overweight/obese, or family history of early CHD.

†Moderate-to-vigorous physical activity includes brisk walking, jogging, running, bicycling, swimming, participating in calisthenics or aerobic exercises, or playing tennis or racquetball.

Table 2.   Effect of Nondietary and Dietary Lifestyle Strategies on the 26-Year Risk of Total Stroke, Nurses' Health Study* (1986–2012)

No	Strategy	24-y Risk of Stroke, % (95% CI)	Population Risk Ratio (95% CI)	Population Risk Difference, % (95% CI)	Cumulative Percent Intervened on †, %	Average Percentage Intervened on ‡, %
0	Natural course, no intervention	4.7 (4.5 to 4.9)§	Reference	Reference	0	0
1	Smoking cessation	4.4 (4.2 to 4.7)	0.94 (0.92 to 0.96)‖	−0.3 (−0.4 to −0.2)	24	3
2	Exercise at least 30 min/d	3.8 (2.8 to 4.7)	0.80 (0.59 to 1.00)	−0.9 (−1.9 to 0.0)	100	56
3	Lose 5% of BMI if BMI >25 kg/m^2	4.6 (4.4 to 4.9)	0.99 (0.96 to 1.02)	−0.1 (−0.2 to 0.1)	76	58
4	Joint nondietary interventions (No. 1–3)	3.5 (2.6 to 4.3)	0.75 (0.57 to 0.93)	−1.2 (−2.0 to −0.3)	100	81
5	Eat at least 3 servings/wk of fish	4.6 (3.8 to 5.3)	0.98 (0.81 to 1.13)	−0.1 (−0.9 to 0.6)	100	42
6	Eat at least 1 serving/d of nuts	3.9 (3.4 to 4.5)	0.83 (0.72 to 0.96)	−0.8 (−1.3 to −0.2)	100	49
7	Eat at least 2 servings/d of whole grains	5.0 (4.5 to 5.4)	1.07 (0.98 to 1.15)	0.3 (−0.1 to 0.7)	100	33
8	Eat at least 5 servings/d of fruits and vegetables	4.7 (4.3 to 4.9)	0.99 (0.95 to 1.03)	0.0 (−0.2 to 0.2)	87	21
9	Eat ≤3 servings/wk of unprocessed red meat	4.4 (4.1 to 4.7)	0.95 (0.91 to 0.98)	−0.3 (−0.4 to −0.1)	88	20
10	Eat 0 servings/wk of processed red meat	4.5 (4.2 to 4.8)	0.96 (0.90 to 1.02)	−0.2 (−0.5 to 0.1)	97	24
11	Drink 5–15 g/wk of alcohol	4.7 (4.3 to 5.1)	1.00 (0.93 to 1.09)	0.0 (−0.3 to 0.4)	100	35
12	Joint diet-only interventions (No. 5–11)	3.6 (2.7 to 4.5)	0.77 (0.57 to 0.95)	−1.1 (−1.9 to −0.2)	100	54

BMI indicates body mass index.

*Estimated using the parametric g-formula with baseline covariates: age, history of cardiovascular disease at age ≤60 y in first-degree relatives, smoking and oral contraceptive use before 1980, marital status, education, employment, race, BMI at 18 y of age, stress in daily life and work; and time-varying covariates: cigarettes smoked, statin use, postmenopausal hormone use, aspirin use, physical activity, intake of nuts, whole grains, refined grains, fruits and vegetables, fish, unprocessed red meat, processed red meat, poultry, alcohol, calories, BMI, high serum cholesterol, high blood pressure, menopause, cancer, diabetes mellitus, and coronary artery disease.

†Cumulative proportion of individuals who did not follow the strategy.

‡Average proportion of individuals who would have needed to change their lifestyle in any period, had they followed the strategy before that period.

§Observed risk of total stroke of 4.45% based on 2349 events and 1 314 936 person-years.

‖When compared with a strategy of continuous smoking, that is, smoking 10 cigarettes/d, a strategy of smoking cessation reduced risk of total stroke by 39% (26%–51%).

estimated risk of ischemic stroke was 1.6% (1.1%–2.1%) under a joint strategy of smoking cessation, exercise, and weight loss and 2.0% (1.4%–2.7%) under a joint strategy on 7 dietary components (Table 3). Compared with the risk under the natural course, the estimated risks of ischemic stroke were lower under isolated strategies of smoking cessation, daily exercise, weight reduction, and reducing unprocessed and processed red meat intakes.

The estimated 26-year risk (95% CI) of hemorrhagic stroke under the natural course was 0.7% (0.6%–0.8%), and the estimated risks were similar under most strategies (Table 4), except under an isolated strategy of increased fish intake: 0.5% (0.4%–0.7%).

Sensitivity Analyses

The estimates did not materially change (and their 95% CIs overlapped substantially) when we excluded diabetic women at baseline (1150 or 1.9%), which left 2179 strokes (Tables IV through VI in the Data Supplement), when atrial fibrillation was considered a time-varying confounder, and when we changed the order of covariates in the models (Tables VII and VIII in the Data Supplement). Longer

durations of physical activity strategy did not result in lower risks of stroke (Tables IX through XI in the Data Supplement).

Discussion

We estimated the 26-year risks of total, ischemic, and hemorrhagic stroke under dietary and nondietary lifestyle strategies applied in middle-aged women who were free of cardiovascular disease and cancer at baseline. Compared with the observed risk, lifestyle modifications were estimated to reduce the 26-year risk of total stroke by up to 25% and ischemic stroke by up to 36%. The reductions in risk of total and ischemic stroke were most influenced by smoking cessation, daily exercise, weight loss, increased fish and nut intakes, and decreased unprocessed red meat intake, whereas for hemorrhagic stroke, only increased fish intake alone was associated with a 26% reduced risk. The reduced risk of total stroke was greater in women who had a higher baseline stroke risk. Considering the higher risk of hemorrhagic stroke in women than men, our results highlight lifestyle recommendations may need to take into consideration the differential impacts on stroke subtypes.

Table 3. Effect of Nondietary and Dietary Lifestyle Strategies on the 26-Year Risk of Ischemic Stroke, Nurses' Health Study* (1986–2012)

No.	Strategy	24-y Risk of Stroke, % (95% CI)	Population Risk Ratio (95% CI)	Population Risk Difference, % (95% CI)	Cumulative Percentage Intervened, %	Average Percentage Intervened, %
0	Natural course, no intervention	2.5 (2.4 to 2.6)†	Reference	Reference	0	0
1	Smoking cessation	2.4 (2.2 to 2.5)	0.94 (0.92 to 0.96)	−0.1 (−0.2 to −0.1)	24	3
2	Exercise at least 30 min/d	1.8 (1.2 to 2.4)	0.71 (0.49 to 0.95)	−0.7 (−1.3 to −0.1)	100	56
3	Lose 5% of BMI if BMI >25 kg/m²	2.4 (2.2 to 2.6)	0.96 (0.91 to 0.99)	−0.1 (−0.2 to 0.0)	77	58
4	Joint nondietary interventions (Nos 1–3)	1.6 (1.1 to 2.1)	0.64 (0.42 to 0.86)	−0.9 (−1.5 to −0.4)	100	81
5	Eat at least 3 servings/wk of fish	2.3 (1.9 to 2.9)	0.93 (0.77 to 1.12)	−0.2 (−0.6 to 0.3)	100	42
6	Eat at least 1 serving/d of nuts	2.2 (1.7 to 2.7)	0.87 (0.71 to 1.08)	−0.3 (−0.7 to 0.2)	100	49
7	Eat at least 2 servings/d of whole grains	2.6 (2.3 to 3.0)	1.06 (0.96 to 1.17)	0.2 (−0.1 to 0.4)	100	33
8	Eat at least 5 servings/d of fruits and vegetables	2.5 (2.3 to 2.7)	1.02 (0.97 to 1.08)	0.0 (−0.1 to 0.2)	87	22
9	Eat ≤3 servings/wk of unprocessed red meat	2.3 (2.1 to 2.5)	0.91 (0.86 to 0.98)	−0.2 (−0.3 to −0.1)	88	20
10	Eat 0 servings/wk of processed red meat	2.3 (2.1 to 2.7)	0.93 (0.84 to 1.02)	−0.2 (−0.4 to 0.1)	97	24
11	Drink 5–15 g/wk of alcohol	2.7 (2.4 to 3.1)	1.07 (0.95 to 1.20)	0.2 (−0.1 to 0.5)	100	35
12	Joint diet-only interventions (No. 5–11)	2.0 (1.4 to 2.7)	0.79 (0.57 to 1.06)	−0.5 (−1.0 to 0.2)	100	54

BMI indicates body mass index.

*Estimated using the parametric g-formula with baseline covariates: age, history of cardiovascular disease at age ≤60 y in first-degree relatives, smoking and oral contraceptive use before 1980, marital status, education, employment, race, BMI at 18 y of age, stress in daily life and work; and time-varying covariates: cigarettes smoked, statin use, postmenopausal hormone use, aspirin use, physical activity, intake of nuts, whole grains, refined grains, fruits and vegetables, fish, unprocessed red meat, processed red meat, poultry, alcohol, calories, BMI, high serum cholesterol, high blood pressure, menopause, cancer, diabetes mellitus, and coronary artery disease.

†Observed risk of ischemic stroke of 2.4% based on 1251 events and 1 325 206 person-years.

No randomized trials have attempted to implement lifestyle modifications over a 26-year period; therefore, our estimates cannot be compared with those of trials. The PREDIMED trial reported a 28% reduction in 5-year stroke risk in those assigned to a Mediterranean diet supplemented with 30 g/d of nuts and a 31% reduction in those assigned to a Mediterranean diet supplemented with 1 L/wk of olive oil, compared with those assigned to a low-fat diet.[7] While the trial specified dietary interventions similar to our strategies, the main intervention was increased olive oil and unsalted nut intake. In our analysis, we similarly found that eating ≥30 g/d of nuts was associated with a 21% lower stroke risk over a 26-year period, when we excluded individuals with diabetes mellitus at baseline.

Previous observational studies found that reduced risk of ischemic, but not hemorrhagic, stroke was associated with higher physical activity levels and lower BMI[35–37] and lower red meat intake[17,38,39] and higher fish intake.[14] A meta-analysis of omega-3 fatty acids (polyunsaturated fatty acids) from seafood found that increased intake of polyunsaturated fatty acids was associated with reduced risk of total, ischemic, and hemorrhagic stroke in women.[40] Other studies found that a healthy index score defined using 5 lifestyle factors (no smoking, moderate alcohol consumption, consuming a healthy diet, being physically active, and having a lower BMI) was associated with a 65% to 80% lower risk of total and ischemic stroke but not with hemorrhagic stroke risk.[8,10,11]

Compared with these studies, our estimates have a more natural interpretation because we explicitly modeled the effect of lifestyle modifications with a well-specified starting point (which requires adjustment for prebaseline dietary and nondietary risk factors) and evaluated the absolute risk that would have been observed if all participants had followed those strategies for a fixed time period. For better interpretability, we also specified strategies based on food items and servings instead of dietary indices or combined scores and used isocaloric strategies to specify food substitutions.[33] On the other hand, our analyses do not overcome the usual difficulties in interpreting estimates under interventions that can be achieved through multiple mechanisms, such as weight loss, each with a potentially different effect on stroke risk.[41] Also, our relative effect estimates may not be transportable to other populations (eg, the US population) as participants in this study were mostly white and educated and healthier than the general population.[33,42] For example, we estimated a 5% reduction in total stroke risk under a smoking cessation strategy because only 21% of women in our study smoked at baseline.

As for any observational study, the validity of our estimates relies on the assumptions of no residual confounding and no model misspecification.[18,43] While we cannot rule out residual confounding, we included many important fixed and time-varying confounders and adjusted for the latter using the parametric g-formula. Approximately correct model specification cannot be guaranteed, but it seems plausible as our

Table 4.   Effect of Nondietary and Dietary Lifestyle Strategies on the 26-Year Risk of Hemorrhagic Stroke, Nurses' Health Study* (1986–2012)

No.	Strategy	24-y Risk of Stroke, % (95% CI)	Population Risk Ratio (95% CI)	Population Risk Difference, % (95% CI)	Cumulative Percentage Intervened, %	Average Percentage Intervened, %
0	Natural course, no intervention	0.7 (0.6 to 0.8)†	Reference	Reference	0	0
1	Smoking cessation	0.6 (0.6 to 0.8)	0.96 (0.90 to 1.01)	0.0 (−0.1 to 0.0)	24	3
2	Exercise at least 30 min/d	0.9 (0.6 to 1.4)	1.35 (0.77 to 2.17)	0.2 (−0.2 to 0.8)	100	56
3	Lose 5% of BMI if BMI >25 kg/m²	0.7 (0.6 to 0.8)	1.06 (1.00 to 1.13)	0.0 (0.0 to 0.1)	77	58
4	Joint nondietary interventions (No. 1–3)	0.9 (0.6 to 1.5)	1.37 (0.81 to 2.10)	0.3 (−0.1 to 0.8)	100	81
5	Eat at least 3 servings/wk of fish	0.5 (0.4 to 0.7)	0.74 (0.51 to 0.99)	−0.2 (−0.4 to 0.0)	100	42
6	Eat at least 1 serving/d of nuts	0.7 (0.5 to 1.0)	0.98 (0.78 to 1.38)	0.0 (−0.2 to 0.3)	100	49
7	Eat at least 2 servings/d of whole grains	0.7 (0.6 to 0.9)	1.07 (0.82 to 1.30)	0.1 (−0.1 to 0.2)	100	33
8	Eat at least 5 servings/d of fruits and vegetables	0.6 (0.6 to 0.7)	0.93 (0.86 to 1.04)	−0.1 (−0.1 to 0.0)	87	22
9	Eat ≤3 servings/wk of unprocessed red meat	0.7 (0.6 to 0.8)	1.08 (0.97 to 1.16)	0.1 (0.0 to 0.1)	87	20
10	Eat 0 servings/wk of processed red meat	0.7 (0.6 to 0.9)	1.02 (0.86 to 1.25)	0.0 (−0.1 to 0.2)	97	24
11	Drink 5–15 g/wk of alcohol	0.7 (0.5 to 0.9)	1.01 (0.85 to 1.21)	0.0 (−0.1 to 0.2)	100	35
12	Joint diet-only interventions (No. 5–11)	0.5 (0.3 to 1.0)	0.77 (0.44 to 1.51)	−0.2 (−0.4 to 0.4)	100	54

BMI indicates body mass index.

*Estimated using the parametric g-formula with baseline covariates: age, history of cardiovascular disease at age ≤60 y in first-degree relatives, smoking and oral contraceptive use before 1980, marital status, education, employment, race, BMI at 18 y of age, stress in daily life and work; and time-varying covariates: cigarettes smoked, statin use, postmenopausal hormone use, aspirin use, physical activity, intake of nuts, whole grains, refined grains, fruits and vegetables, fish, unprocessed red meat, processed red meat, poultry, alcohol, calories, BMI, high serum cholesterol, high blood pressure, menopause, cancer, diabetes mellitus, and coronary artery disease.

†Observed risk of hemorrhagic stroke of 0.7% based on 351 events and 1 332 456 person-years.

models resulted in estimated means for outcome and time-varying covariates similar to those in the observed data. Because none of our participants followed the combined nondietary and dietary strategies over the entire follow-up (Tables 3 and 4), the estimated risks under these strategies should be interpreted more cautiously as they partly rely on model extrapolation. Finally, the data used here only allowed us to examine the potential impact of the selected lifestyle strategies among middle-aged women. Similar analyses of cohorts of younger or older individuals would inform potential effect modification by age.

In summary, our results support the importance of healthy lifestyles in reducing stroke risk in middle-aged women, even when adopted in midlife or later. Smoking cessation, 30 min/d of physical activity, gradual weight loss, and eating more fish and nuts and less processed and unprocessed red meat appear to substantially reduce stroke risk in middle-aged women.

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