

# Adherence to a Low-Risk, Healthy Lifestyle and Risk of Sudden Cardiac Death Among Women

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**S**UDDEN CARDIAC DEATH (SCD) accounts for more than half of all cardiac deaths, with an incidence of approximately 250 000 to 310 000 cases annually in the United States.<sup>1,2</sup> Although coronary heart disease (CHD) underlies most SCD events, SCD is the first manifestation of CHD for the majority of individuals,<sup>3</sup> particularly among women.<sup>4</sup> Efforts aimed at primary prevention of SCD focus primarily on placement of implantable cardioverter-defibrillators in patients with severe left ventricular dysfunction. However, only 25% to 30% of SCD events occur among this high-risk subgroup and these efforts therefore do not address the majority of SCD events.<sup>3</sup> Prevention strategies applicable to populations at lower risk are needed to reduce SCD.

Modifiable lifestyle factors such as smoking,<sup>5-7</sup> obesity,<sup>4,5,7</sup> and physical inactivity<sup>6,8,9</sup> are independent risk factors for SCD; several dietary factors, including low intake of n-3 fatty acids,<sup>10-12</sup> alcohol abstinence, and heavy alcohol intake, are associated with higher risk of SCD.<sup>13,14</sup> A low-risk lifestyle that includes combinations of not smoking, prudent diet, regular exercise, and

**Context** Sudden cardiac death (SCD) accounts for more than half of all cardiac deaths; the majority of SCD events occur as the first manifestation of heart disease, especially among women. Primary preventive strategies are needed to reduce SCD incidence.

**Objective** To estimate the degree to which adherence to a healthy lifestyle may lower the risk of SCD among women.

**Design, Setting, and Participants** A prospective cohort study of 81 722 US women in the Nurses' Health Study from June 1984 to June 2010. Lifestyle factors were assessed via questionnaires every 2 to 4 years. A low-risk lifestyle was defined as not smoking, body mass index of less than 25, exercise duration of 30 minutes/day or longer, and top 40% of the alternate Mediterranean diet score, which emphasizes high intake of vegetables, fruits, nuts, legumes, whole grains, and fish and moderate intake of alcohol.

**Main Outcome Measure** Sudden cardiac death (defined as death occurring within 1 hour after symptom onset without evidence of circulatory collapse).

**Results** There were 321 cases of SCD during 26 years of follow-up. Women were a mean age of 72 years at the time of the SCD event. All 4 low-risk lifestyle factors were significantly and independently associated with a lower risk of SCD. The absolute risks of SCD were 22 cases/100 000 person-years among women with 0 low-risk factors, 17 cases/100 000 person-years with 1 low-risk factor, 18 cases/100 000 person-years with 2 low-risk factors, 13 cases/100 000 person-years with 3 low-risk factors, and 16 cases/100 000 person-years with 4 low-risk factors. Compared with women with 0 low-risk factors, the multivariable relative risk of SCD was 0.54 (95% confidence interval [CI], 0.34-0.86) for women with 1 low-risk factor, 0.41 (95% CI, 0.25-0.65) for 2 low-risk factors, 0.33 (95% CI, 0.20-0.54) for 3 low-risk factors, and 0.08 (95% CI, 0.03-0.23) for 4 low-risk factors. The proportion of SCD attributable to smoking, inactivity, overweight, and poor diet was 81% (95% CI, 52%-93%). Among women without clinically diagnosed coronary heart disease, the percentage of population attributable risk was 79% (95% CI, 40%-93%).

**Conclusion** Adherence to a low-risk lifestyle is associated with a low risk of SCD.

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maintenance of a healthy weight has been associated with lower risk of CHD,<sup>15</sup> stroke,<sup>16</sup> diabetes,<sup>17</sup> cancer,<sup>18</sup> hypertension,<sup>19</sup> chronic disease,<sup>20</sup> and cardiovascular disease-related and total

mortality<sup>21,22</sup> and may provide an alternative means to prevent SCD. However, no studies have examined the combination of multiple lifestyle factors and risk of SCD. Therefore, we con-

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ducted this study to estimate the burden of SCD that may be attributed to adverse lifestyle factors in the Nurses' Health Study.

## METHODS

### Study Population

The Nurses' Health Study began in 1976 when 121 700 female nurses aged 30 to 55 years provided information on lifestyle and medical history.<sup>23</sup> Data on newly diagnosed disease, lifestyle, and other risk factors are collected repeatedly during ongoing follow-up. Informed consent was obtained from all women or their family members. The institutional review board at Brigham and Women's Hospital approved the research protocol.

Participants first completed an expanded food frequency questionnaire in 1984, which served as the baseline year for this analysis. Women who left 70 or more food items blank on the food frequency questionnaire or reported energy intakes of less than 600 kcal/d or greater than 3500 kcal/d were excluded, which left 81 722 women for this analysis.

### Ascertainment of Lifestyle Factors

We obtained information biennially on smoking status, weight, menopausal status, use of medications, and physician diagnosis of disease. Information on height was collected on the baseline questionnaire and parental history of myocardial infarction (MI) was obtained in 1976 and 1984. Physical activity was assessed every 2 to 4 years using a validated questionnaire.<sup>24</sup> We calculated the hours per week spent engaged in leisure-time activities of moderate (3-6 metabolic equivalent tasks per hour) or vigorous (>6 metabolic equivalent tasks per hour) intensity. Specific activities included brisk walking ( $\geq 3$  mph), jogging, running, bicycling, swimming, tennis, squash, racquetball, rowing, calisthenics, and yoga.

A validated food frequency questionnaire<sup>25</sup> was completed in 1984, 1986, and every 4 years thereafter. For each food item, participants were asked how often a specified portion was con-

sumed during the past year. Nutrient intake was calculated by multiplying the nutrient content of each food item<sup>26</sup> by the frequency of intake and summed across all food items. All nutrients were adjusted for total energy intake by regressing nutrient intake on total energy.<sup>27</sup>

### Definition of Low-Risk Lifestyle

We considered 4 lifestyle factors: smoking, exercise, diet, and weight. We selected these factors based on their associations with SCD and current recommendations for overall cardiovascular disease prevention.<sup>28</sup> For each lifestyle factor, a woman received 1 point if she met the criteria for low risk and 0 points if she did not meet the criteria.

Given the strong relationship found between active smoking and SCD in prior studies,<sup>5-7</sup> we defined low risk as not currently smoking. Regular participation in moderate to vigorous intensity exercise also has been associated with lower risk of SCD.<sup>8,9</sup> Based on current exercise recommendations,<sup>29</sup> we defined low risk as engaging in moderate or vigorous intensity activity for 30 minutes per day or longer. Obesity is an independent risk factor for SCD<sup>5</sup>; a 3.3-unit increase in body mass index (BMI; calculated as weight in kilograms divided by height in meters squared) was associated with a 20% higher risk of SCD.<sup>7</sup> We defined optimal weight as having a BMI of less than 25 (the World Health Organization's standard cutoff point for overweight).<sup>30</sup>

For diet, we defined low risk as having an alternate Mediterranean diet score<sup>31</sup> in the top 40% of the cohort distribution. The alternate Mediterranean diet score quantifies adherence to a Mediterranean-style diet, which emphasizes high intake of foods and nutrients that have been associated with lower risk of SCD, including n-3 fatty acids,<sup>10-12</sup> nuts,<sup>32</sup> fish,<sup>33</sup> and moderate alcohol consumption.<sup>13,14</sup> Specifically, the alternate Mediterranean diet score includes 9 components: high intake of vegetables, fruits, nuts, whole grains, legumes, fish; ratio of monounsatu-

rated to saturated fat; moderate intake of alcohol; and low intake of red and processed meat. Women received 1 point for intake above the median and 0 points for intake below the median, except for red and processed meat, in which the score was reversed. Women received 1 point for moderate alcohol intake (0.5-1 drink/day) and 0 for none or higher alcohol intake. Scores for the alternate Mediterranean diet score ranged from 0 to 9 and higher scores represented greater resemblance to the Mediterranean-style diet.

We summed the total number of low-risk factors to create a binary lifestyle score (range, 0-4). Results were similar when we assigned weights to each low-risk factor based on the  $\beta$  coefficients from multivariable regression models with SCD as the outcome. The binary variables do not account for the gradient in risk of SCD with more extreme levels of these lifestyle factors. Thus, we calculated an expanded lifestyle score based on the associations between each lifestyle factor and SCD in the cohort. We assigned scores of 1 (least healthy) to 5 (most healthy) to the categories of the lifestyle factors and summed the points across all 4 factors (score range, 4-20 points). For this analysis, healthiest behavior was defined as never smoking, BMI between 21 and 25, exercise duration of 6 hours/week or longer, and the highest quintile of the alternate Mediterranean diet score.

### End Point Ascertainment and Definitions

We attempted to confirm each cause of death through review of medical records and autopsy reports.<sup>4</sup> If circumstances surrounding the death were not documented adequately, we ascertained additional details through interviews with next of kin. We did not rely on the death certificate to determine the timing of death. Cardiac deaths were considered sudden if the death or cardiac arrest occurred within 1 hour of symptom onset.

To increase the specificity for an arrhythmia-related death, we excluded

women with evidence of circulatory or neurological impairment before death.<sup>34</sup> We included in the analysis unwitnessed deaths that could have occurred within 1 hour of symptom onset and that had autopsy findings consistent with SCD (ie, acute coronary thrombosis or severe coronary artery disease without myocardial necrosis or other pathological findings to explain death;  $n=35$ ). The autopsy rate in this cohort was 7% and was comparable with national autopsy rates (6%).<sup>35</sup>

### Data Analysis

Women contributed person-time from the date of return of the 1984 questionnaire until incident SCD, death, or June 1, 2010, whichever came first. We hypothesized that exercise, BMI, and smoking would have transient effects on SCD risk; these variables were updated at each questionnaire cycle to reflect the most recent information. Although physical activity was assessed repeatedly during follow-up, it was not assessed on the 1984 questionnaire; thus, the mean of activity in 1980 and 1982 represented physical activity at baseline in 1984.

We used the cumulative average of the diet score assessed every 2 to 4 years to represent long-term diet and to reduce measurement error.<sup>27</sup> Because changes in diet after an intermediate end point such as hypercholesterolemia, diabetes, hypertension, transient ischemic attack, or CHD (nonfatal MI, angina, or coronary revascularization) may confound the association between long-term diet and SCD,<sup>36</sup> we stopped updating dietary information when a woman developed an intermediate end point during follow-up. If data were missing at a given time point, the last observation was carried forward for 1 cycle (data that were missing: 13% for alcohol intake, 12% for exercise duration, 8% for BMI, 1% for smoking, 0% for cumulative diet from  $\geq 1$  questionnaire).

To estimate the association between low-risk lifestyle factors and risk of SCD, we used multivariable Cox proportional hazards models to estimate hazard ratios as estimates of the rela-

tive risk (RR) and 95% confidence intervals (CIs), stratifying by age (months), and adjusting for family history of MI before the age of 60 years (yes or no), postmenopausal status (yes or no), current hormone therapy use (yes or no), and history of disease at baseline (hypertension, hypercholesterolemia, diabetes, cancer, CHD, or stroke). Further adjustment for medication use (aspirin, digoxin, blood pressure lowering, cholesterol lowering, and antiarrhythmics) did not appreciably alter the results. All covariates except for family history of MI were updated each questionnaire cycle and included as time-varying covariates in multivariable models. The proportional hazards assumption was not violated.

We conducted a Wald test for linear trend by assigning the median value to each category and modeling this variable as a continuous variable. For smoking, we used an ordinal variable. For BMI and the lifestyle risk scores, we examined potential nonlinear relationships with risk of SCD using restricted cubic spline transformations to model these relationships without prior specification of the risk function.<sup>37</sup> We conducted tests for nonlinearity using the likelihood ratio test and compared the model with the linear term only with the model with both the linear and cubic spline terms.

We calculated the percentage of population attributable risk and 95% CIs to estimate the proportion of SCD in this cohort that hypothetically would not have occurred if all women were in the low-risk group (assuming a causal relationship).<sup>38</sup> For these analyses, we compared women in the low-risk category (for each factor individually and in combination) with the rest of the women in the population.<sup>39</sup> To calculate the percentage of population attributable risk, we estimated the RR from multivariable pooled logistic regression models to allow for the direct inclusion of age in the model. In this approach, each 2-year interval was treated as an independent follow-up study and observations over all intervals were pooled into a single sample.

When the disease was rare, estimates from pooled logistic regression models approximated estimates from the Cox proportional hazards models.<sup>40</sup> We included women with missing values for lifestyle factors ( $<2\%$  over all questionnaire cycles) in the high-risk category when we calculated the percentage of population attributable risk to provide the most conservative estimate.

We calculated the percentage of population attributable risk within 3 prespecified subgroups. We examined a low-risk lifestyle among women with previous clinically diagnosed CHD and women without CHD. Diagnosis of CHD was reported every 2 years. Once a woman reported a diagnosis, she remained in the CHD group for the remainder of follow-up. Although smoking is a strong risk factor for SCD, more than 80% of women in the United States are not current smokers.<sup>41</sup> Therefore, we assessed the impact of the other lifestyle factors among nonsmokers.

Statistical analyses were conducted using SAS software version 9 (SAS Institute Inc, Cary, North Carolina). All *P* values are 2-sided and a *P* value of less than .05 is considered statistically significant.

## RESULTS

### Association Between Lifestyle Factors and SCD

During 26 years of follow-up (June 1984-June 2010), we documented 321 cases of SCD among women with a mean (SD) age of 72 (8) years. Baseline characteristics of the cohort according to the binary lifestyle score are presented in TABLE 1. Not smoking, exercising, and having a healthy diet each were inversely associated with risk of SCD ( $P<.001$  for linear trend; TABLE 2). The association with BMI appeared J-shaped, with a nadir in SCD risk among women with a BMI of 21.0 to 24.9 ( $P<.001$  for nonlinear trend; Table 2). When these risk factors were collapsed into low-risk binary categories, each lifestyle factor remained significantly associated with lower risk of SCD (even after controlling for the other low-risk factors; TABLE 3).

Overall, the binary lifestyle score was inversely associated with risk of SCD ( $P = .55$  for deviation from linearity;  $P < .001$  for linear trend; FIGURE). The absolute risks of SCD were 22 cases/100 000 person-years among women with 0 low-risk factors, 17 cases/100 000 person-years with 1 low-risk factor, 18 cases/100 000 person-years with 2 low-risk factors, 13 cases/100 000 person-years with 3 low-risk factors, and 16 cases/100 000 person-years with 4 low-risk factors. Compared with women with 0 low-risk factors (3% of the cohort), those with all 4 low-risk lifestyle factors (8% of the cohort) had an RR of 0.08 (95% CI, 0.03-0.23) for SCD (Figure). The expanded lifestyle score was also linearly associated with risk of SCD ( $P = .12$  for deviation from linearity;  $P < .001$  for linear trend). Compared with women with an expanded lifestyle score of 8 or less (6% of the cohort), those with a score of 17 or greater (15% of the cohort) had an RR of 0.13 (95% CI, 0.07-0.23) for SCD.

### Percentage of Population Attributable Risk for SCD

The percentage of population attributable risk for lack of adherence to each low-risk lifestyle factor is shown in Table 3. Although smoking was a strong risk factor for SCD, the estimated percentage of population attributable risk for smoking was only 11% and reflected the low prevalence of current smoking in the cohort (14%). For the other lifestyle factors, the percentage of population attributable risk ranged from 15% for BMI and diet to 26% for exercise. The percentage of population attributable risk associated with lack of adherence to an overall low-risk lifestyle among all women and in prespecified subgroups appears in TABLE 4. In the entire cohort, the percentage of population attributable risk associated with all 4 lifestyle factors was 81% (95% CI, 52%-93%).

Assuming causal relationships, these data suggest that 81% of SCD may have been avoided had all women been in the low-risk group for all 4 lifestyle fac-

**Table 1.** Characteristics of Women in the Nurses' Health Study at Baseline

	Binary Lifestyle Score				
	0 (n = 3391)	1 (n = 20 004)	2 (n = 30 014)	3 (n = 21 262)	4 (n = 7051)
	Mean (SD)				
Age, y	51 (7)	51 (7)	51 (7)	50 (7)	50 (7)
Body mass index <sup>a,b</sup>	29.2 (4.0)	27.2 (5.4)	25.0 (4.7)	23.4 (3.5)	22.1 (1.7)
Alternate Mediterranean diet score <sup>b,c</sup>	2.6 (1.1)	2.9 (1.3)	3.7 (1.7)	4.8 (1.7)	6.0 (1.0)
Moderate to vigorous intensity exercise, h/wk <sup>b</sup>	1.5 (1.0)	1.9 (1.4)	2.7 (2.0)	4.1 (2.1)	5.5 (1.3)
Alcohol intake, median (IQR), g/d	1.8 (0-8.8)	1.8 (0-7.4)	2.0 (0-8.4)	2.8 (0-9.8)	4.7 (0.9-11.0)
	No. (%)				
Current smoking	3391 (100)	8965 (45)	5967 (20)	1685 (8)	0
Family history of MI before 60 y	773 (23)	4099 (20)	5797 (19)	4151 (20)	1280 (18)
Current use of hormone therapy	313 (9)	2243 (11)	3991 (13)	3277 (15)	1209 (17)
Aspirin use $\geq 7$ times/wk	749 (22)	4277 (21)	5923 (20)	3959 (19)	1262 (18)
Physician-diagnosed disease					
Diabetes	178 (5)	917 (5)	988 (3)	513 (2)	112 (2)
High cholesterol	394 (12)	1925 (10)	2642 (9)	1809 (9)	568 (8)
Hypertension	1010 (30)	5602 (28)	6743 (22)	4022 (19)	1005 (14)
Coronary heart disease <sup>d</sup>	140 (4)	902 (5)	1000 (3)	659 (3)	167 (2)
Stroke	16 (0.47)	84 (0.42)	92 (0.31)	60 (0.28)	12 (0.17)
Cancer	46 (1)	306 (2)	411 (1)	307 (1)	93 (1)

Abbreviations: IQR, interquartile range; MI, myocardial infarction.

<sup>a</sup>Calculated as weight in kilograms divided by height in meters squared.

<sup>b</sup>Indicates age-standardized values.

<sup>c</sup>Range of possible scores was 0 to 9.

<sup>d</sup>Includes nonfatal MI, angina, and coronary revascularization.

tors. Results were similar in sensitivity analyses that included unwitnessed deaths in which the participant was documented to be free of symptoms within the preceding 24 hours and in which circumstances suggested that the death could have been sudden ( $n = 152$ ). Among nonsmokers, the percentage of population attributable risk associated with the remaining 3 lifestyle factors was 78% (95% CI, 46%-92%). Finally, the percentage of population attributable risk associated with lack of adherence to a low-risk lifestyle was similar among women with and without clinically recognized CHD at the time of their most recent questionnaire (Table 4).

### COMMENT

A low-risk lifestyle (not smoking, exercising regularly, having a prudent diet, and maintaining a healthy weight) was linearly and inversely associated with risk of SCD among women. Women at low

risk for all 4 lifestyle factors had a 92% lower risk of SCD compared with women at low risk for none of the 4 lifestyle factors. If these associations are causal, 81% of SCD within this cohort may have been prevented if all women adhered to a low-risk lifestyle. Among women without diagnosed CHD, in whom the majority of SCD events occur, it is possible that 79% of SCD may be attributed to unhealthy lifestyle practices.

Primary prevention of SCD in women is of particular concern. Compared with men, women are 50% less likely to have severe left ventricular dysfunction and 66% less likely to be diagnosed with CHD before SCD and therefore are less likely to meet current guideline recommendations for  $\beta$ -blocker therapy or placement of a prophylactic implantable cardioverter-defibrillator.<sup>42</sup> Prevention efforts that can be applied across broader populations such as healthy lifestyle practices are crucial to prevent SCD, particularly among women.

Substantial evidence supports the benefit of lifestyle modification for the prevention of SCD. Smoking cessation has been associated with reductions in SCD risk,<sup>43</sup> while regular physical activity has been inversely associated with lower risk of SCD in observational studies.<sup>8,9</sup> A Mediterranean-style diet was associated with lower risk

**Table 2.** Risk of Sudden Cardiac Death by Lifestyle Factors

Low-Risk Factor	Person-Years, % <sup>a</sup>	No. of Cases	Incidence Rate per 100 000 Person-Years	Value for Expanded Score	Age-Adjusted RR (95% CI)	P Value for Trend <sup>b</sup>	Multivariable-Adjusted RR (95% CI) <sup>c</sup>	P Value for Trend <sup>b</sup>
Smoking, cigarettes/d								
≥25	3	20	35	1	1 [Reference]	<.001	1 [Reference]	<.001
15-24	6	28	27	2	0.69 (0.39-1.23)		0.73 (0.41-1.30)	
1-14	5	21	21	3	0.43 (0.23-0.81)		0.48 (0.26-0.89)	
Past	42	154	20	4	0.35 (0.22-0.56)		0.40 (0.25-0.65)	
Never	44	98	12	5	0.22 (0.13-0.36)		0.25 (0.15-0.42)	
Exercise, h/wk								
<1.0	46	192	22	1	1 [Reference]	<.001	1 [Reference]	<.001
1.0-1.9	12	36	16	2	0.80 (0.56-1.15)		0.86 (0.60-1.23)	
2.0-3.4	12	34	15	3	0.77 (0.53-1.11)		0.84 (0.58-1.21)	
3.5-5.9	15	35	13	4	0.65 (0.45-0.93)		0.72 (0.50-1.04)	
≥6.0	15	24	9	5	0.39 (0.25-0.59)		0.47 (0.30-0.72)	
BMI <sup>d</sup>								
≥35.0	7	51	37	1	1 [Reference]	.001	1 [Reference]	<.001
30.0-34.9	10	46	25	3	0.61 (0.41-0.91)		0.76 (0.51-1.15)	
25.0-29.9	33	101	17	4	0.40 (0.29-0.57)		0.58 (0.41-0.82)	
21.0-24.9	36	71	11	5	0.27 (0.19-0.38)		0.44 (0.30-0.65)	
<21.0	13	47	20	2	0.48 (0.32-0.72)		0.83 (0.54-1.26)	
Alternate Mediterranean diet score <sup>e</sup>								
<2.5	19	81	22	1	1 [Reference]	<.001	1 [Reference]	<.001
2.5-3.4	20	62	17	2	0.71 (0.51-0.99)		0.78 (0.56-1.09)	
3.5-4.2	20	68	18	3	0.72 (0.52-0.99)		0.80 (0.58-1.11)	
4.3-5.4	20	48	13	4	0.49 (0.34-0.70)		0.58 (0.40-0.83)	
>5.4	21	62	16	5	0.54 (0.39-0.76)		0.60 (0.43-0.84)	

Abbreviations: BMI, body mass index; CI, confidence interval; RR, risk ratio.

<sup>a</sup>Percentages may not sum to 100% within categories due to missing values.

<sup>b</sup>Test for linear trend for smoking, exercise, and alternate Mediterranean diet score and test for nonlinear trend for BMI.

<sup>c</sup>Estimated from Cox proportional hazards models and adjusted for age (months), family history of myocardial infarction (no history, family member <60 years, family member ≥60 years), menopausal status (yes or no), current hormone therapy use (yes or no), and presence of diabetes, hypertension, high cholesterol, cancer, coronary heart disease, or stroke at baseline (all yes or no). Age, menopausal status, and current hormone therapy use were treated as time-varying covariates.

<sup>d</sup>Calculated as weight in kilograms divided by height in meters squared.

<sup>e</sup>Components were high intake of vegetables, fruits, nuts, whole grains, legumes, and fish; high ratio of monounsaturated to saturated fat; low intake of red and processed meats; and moderate alcohol intake.

**Table 3.** Risk of Sudden Cardiac Death by Low-Risk Factor Status

Lifestyle Factor	Definition of Low Risk	Person-Years at Low Risk, %	Incidence Rate per 100 000 Person-Years in Low-Risk Women	RR (95% CI) <sup>a</sup>		Model 2, PAR (95% CI), % <sup>c,d</sup>
				Model 1 <sup>b</sup>	Model 2 <sup>c</sup>	
Smoking	Not currently smoking	86	16	0.50 (0.38-0.65)	0.50 (0.37-0.66)	11 (6-15)
Exercise	≥30 min/d	30	11	0.62 (0.46-0.82)	0.67 (0.50-0.90)	26 (7-43)
Diet	Top 2 quintiles on alternate Mediterranean diet score <sup>e</sup>	41	14	0.69 (0.55-0.87)	0.75 (0.59-0.95)	15 (2-28)
BMI <sup>f</sup>	<25	49	13	0.80 (0.63-1.01)	0.78 (0.61-0.99)	15 (2-28)

Abbreviations: BMI, body mass index; CI, confidence interval; PAR, population attributable risk; RR, relative risk.

<sup>a</sup>Calculated using Cox proportional hazards models. The reference group for each lifestyle factor is all other women in the population.

<sup>b</sup>Adjusted for age (months), family history of myocardial infarction (no history, family member <60 years, family member ≥60 years), menopausal status (yes or no), current hormone therapy use (yes or no), and presence of diabetes, hypertension, high cholesterol, cancer, coronary heart disease, or stroke at baseline (all yes or no). Age, menopausal status, and current hormone therapy use were treated as time-varying covariates.

<sup>c</sup>Adjusted for variables in model 1 plus all 4 low-risk lifestyle factors simultaneously.

<sup>d</sup>Calculated using pooled logistic regression models.

<sup>e</sup>Components were high intake of vegetables, fruits, nuts, whole grains, legumes, and fish; high ratio of monounsaturated to saturated fat; low intake of red and processed meats; and moderate alcohol intake.

<sup>f</sup>Calculated as weight in kilograms divided by height in meters squared.

of cardiovascular disease in clinical trials and observational studies.<sup>44,45</sup> The association between the Mediterranean diet and cardiovascular disease appears stronger for fatal compared with nonfatal events,<sup>31</sup> which may be driven partially through protection against ventricular arrhythmias and SCD. Furthermore, several key components of a Mediterranean-style diet, including consumption of nuts, fish, and omega-3 fatty acids and moderate intake of alcohol, have been associated with lower risk of SCD.<sup>10-14,32,33</sup> Consistent with prior evidence, we found a strong inverse association between the alternate Mediterranean diet score and risk of SCD.

The J-shaped association between BMI and risk of SCD parallels the association with all-cause mortality.<sup>46</sup> The elevated risk among women with BMIs of less than 21.0 is likely biased by reverse causation from preexisting disease, residual confounding by smoking, and effect modification by age.<sup>47,48</sup> Body mass index in midlife, which is largely unaffected by underlying disease, may more accurately quantify the effect of adiposity on SCD.<sup>49</sup>

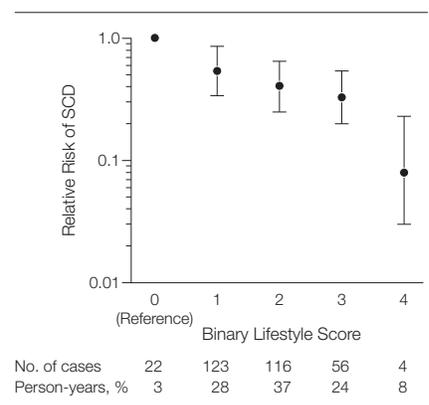
More than 80% of the women in the United States are not current smokers<sup>41</sup>; however, the prevalence of other healthful habits is low.<sup>41</sup> Among women aged 45 to 74 years in the United States, fewer than 40% maintain a BMI of less than 25, 25% drink light to moderate amounts of alcohol,

and 22% exercise regularly at a light to moderate intensity.<sup>41</sup> Nationally representative data are not available for the alternate Mediterranean diet score but data from the National Health and Nutrition Examination Surveys suggest that poor dietary habits are highly prevalent.<sup>28</sup> Our data suggest that a substantial portion of SCD risk among nonsmokers was associated with poor diet, lack of exercise, and unhealthy weight. Improvement in these lifestyle factors, while ultimately a personal choice, may be facilitated through changes in environmental settings and social norms, in part through public health policies that promote more healthful lifestyle choices.<sup>50</sup>

There are several limitations to our measure of the population attributable risk that warrant consideration. First, the population attributable risk assumes a causal relationship between the low-risk lifestyle factors and risk of SCD. Our study was not randomized and this is a large assumption. However, a long-term trial assessing the effects of multiple lifestyle factors on risk of SCD, particularly for primary prevention, has inherent challenges (eg, the necessity of a large sample size, long duration of follow-up, and participant adherence to assigned dietary and exercise prescriptions).<sup>51</sup> In lieu of such data, carefully performed observational studies provide a reasonable approach for evaluating the association of multiple lifestyle factors on SCD risk.

Second, to estimate the population attributable risk, we dichotomized each lifestyle factor, although the relationships between lifestyle factors and SCD risk are more complex. When we used the expanded risk score, which accounts for the associations across the distribution of the lifestyle factor, the results were similar to the binary life-

**Figure.** Sudden Cardiac Death (SCD) by the Binary Lifestyle Score



The total number of person-years was 1.86 million. Low risk was defined as not currently smoking, exercising for 30 minutes per day or longer at a moderate to vigorous intensity, diet in the top 40% of the alternate Mediterranean diet score distribution, and body mass index (calculated as weight in kilograms divided by height in meters squared) of less than 25. The relative risks are estimated from Cox proportional hazards models adjusted for age (months), family history of myocardial infarction (no history, family member <60 years, family member ≥60 years), menopausal status (yes or no), current hormone therapy use (yes or no), and presence of diabetes, hypertension, high cholesterol, cancer, coronary heart disease, or stroke at baseline (all yes or no). Age, menopausal status, and current hormone therapy use were treated as time-varying covariates. Error bars indicate 95% confidence intervals.

**Table 4.** Risk of Sudden Cardiac Death by Low-Risk Lifestyle<sup>a</sup>

Population	Person-Time in Population, %	Person-Years at Low Risk, %	Total Cases	No. of Cases at Low Risk	Incidence Rate per 100 000 Person-Years in Low-Risk Women	RR (95% CI) <sup>b,c</sup>	PAR (95% CI), % <sup>b,d</sup>
All women	100	8	321	4	3	0.18 (0.07-0.49)	81 (52-93)
Not current smokers	86	9	252	4	3	0.21 (0.08-0.56)	78 (46-92)
Clinically diagnosed CHD							
No	91	8	213	3	2	0.19 (0.06-0.60)	79 (40-93)
Yes	9	5	108	1	11	0.17 (0.02-1.23)	80 (40-97)

Abbreviations: CHD, coronary heart disease; CI, confidence interval; PAR, population attributable risk; RR, relative risk.

<sup>a</sup> Defined as not currently smoking (former smokers), alternate Mediterranean diet score in top 40% of distribution, duration of exercise at moderate to vigorous intensity for 30 minutes/day or longer, and body mass index (calculated as weight in kilograms divided by height in meters squared) of less than 25. In never smokers, low-risk lifestyle defined as alternate Mediterranean diet score in top 40% of distribution, duration of exercise at moderate to vigorous intensity for 30 minutes per day or longer, and body mass index of less than 25.

<sup>b</sup> Adjusted for age (months), family history of myocardial infarction (no history, family member <60 years, family member ≥60 years), menopausal status (yes or no), current hormone therapy use (yes or no), and presence of diabetes, hypertension, high cholesterol, cancer, coronary heart disease, or stroke at baseline (all yes or no). Age, menopausal status, and current hormone therapy use were treated as time-varying covariates.

<sup>c</sup> Calculated using Cox proportional hazards models. The reference group is all other women in the population.

<sup>d</sup> Calculated using pooled logistic regression models.

style score. Furthermore, due to its distributive property, the population attributable risk from a multilevel exposure equals the population attributable risk calculated from collapsing the categories into a binary variable.<sup>39</sup> The simplicity of binary cut points for the lifestyle factors mirrors the dichotomous cut points used to define low risk for clinical risk factors (ie, total cholesterol <200 mg/dL or systolic/diastolic blood pressure <120/80 mm Hg) and may help provide discrete guidance for patients in the clinical setting. The set of binary low-risk factors that we used for the prevention of SCD is also similar to an a priori low-risk lifestyle related to lower risk of CHD,<sup>15</sup> stroke,<sup>16</sup> cardiovascular disease mortality,<sup>21</sup> diabetes,<sup>17</sup> and cancer.<sup>18</sup> A single message for the prevention of cardiovascular disease and other chronic diseases provides a simple strategy to minimize overall morbidity and premature death.

The population attributable risk is valid only when the RRs and prevalence estimates used to calculate the population attributable risk are unbiased. The high degree of homogeneity in this cohort minimizes confounding by socioeconomic status and potentially other factors associated with a healthy lifestyle.<sup>15</sup> We used multivariable models to adjust for additional confounders; however, the potential for residual confounding remains. Although measurement error in self-reported variables is unavoidable, information bias is minimal among participants in the Nurses' Health Study who provide valid information on questionnaires.<sup>24,25</sup> Moreover, such error is likely to be nondifferential with respect to SCD, and likely underestimates the true effect.

The population attributable risk is population-specific; thus, the population attributable risk estimated among mainly white female health professionals may not be generalizable to men or women of other ethnicities. The prevalence of low-risk factors in the Nurses' Health Study is similar to the prevalence among US white women but

higher than the prevalence among black and Hispanic women.<sup>41</sup> Additionally, incidence of SCD is greater and survival after cardiac arrest is lower among US blacks.<sup>52</sup> Therefore, the impact of a low-risk lifestyle may be greater in more racially diverse populations.

We focused on the influence of modifiable lifestyle habits on SCD. It should be acknowledged that favorable levels of clinical risk factors such as blood pressure and diabetes are also associated with lower SCD risk.<sup>4</sup> The association between lifestyle factors and SCD is at least partially mediated through these clinical risk factors; however, these later medical conditions are also influenced by factors other than lifestyle. Therefore, we did not include these clinical risk factors in our population attributable risk estimate.

Our study has several important strengths. The repeated assessments of lifestyle factors allow us to update lifestyle habits throughout follow-up. The large number of rigorously confirmed SCD events, which is a difficult phenotype to classify in population studies, is a unique strength. Although we likely missed cases of SCD within this cohort, the high specificity of our defined cases provides a less biased risk estimate.<sup>53</sup> Finally, we provide 95% CIs surrounding the percentage of population attributable risk, which are essential for describing estimation uncertainty but are not always presented.<sup>54</sup>

## CONCLUSION

The primary prevention of SCD remains a major public health challenge because most SCD occurs among individuals not identified as high risk. In this cohort of female nurses, adherence to an overall healthy lifestyle was associated with a lower risk of SCD and may be an effective strategy for the prevention of SCD. Because SCD accounts for more than 50% of CHD mortality, widespread adoption of a healthy lifestyle in the population may make a substantial impact on reaching the American Heart Association's 2020 Impact Goal of further lowering cardiovascular disease mortality.<sup>28</sup>

**Author Contributions:** Dr Chiuev had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

**Study concept and design:** Chiuev, Manson, Albert.  
**Acquisition of data:** Fung, Rexrode, Spiegelman, Manson, Albert.

**Analysis and interpretation of data:** Chiuev, Rexrode, Spiegelman, Manson, Stampfer, Albert.

**Drafting of the manuscript:** Chiuev.

**Critical revision of the manuscript for important intellectual content:** Fung, Rexrode, Spiegelman, Manson, Stampfer, Albert.

**Statistical analysis:** Chiuev, Spiegelman.

**Obtained funding:** Chiuev, Rexrode, Spiegelman, Albert.

**Administrative, technical, or material support:** Rexrode, Spiegelman, Manson, Stampfer.

**Study supervision:** Manson, Albert.

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## REFERENCES

1. Chugh SS, Reinier K, Teodorescu C, et al. Epidemiology of sudden cardiac death: clinical and research implications. *Prog Cardiovasc Dis*. 2008; 51(3):213-228.
2. Roger VL, Go AS, Lloyd-Jones DM, et al; American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics—2011 update: a report from the American Heart Association. *Circulation*. 2011;123(4):e18-e209.
3. Stecker EC, Vickers C, Waltz J, et al. Population-based analysis of sudden cardiac death with and without left ventricular systolic dysfunction: two-year findings from the Oregon Sudden Unexpected Death Study. *J Am Coll Cardiol*. 2006;47(6):1161-1166.
4. Albert CM, Chae CU, Grodstein F, et al. Prospective study of sudden cardiac death among women in the United States. *Circulation*. 2003;107(16):2096-2101.
5. Kannel WB, Doyle JT, McNamara PM, Quickenton P, Gordon T. Precursors of sudden coronary death: factors related to the incidence of sudden death. *Circulation*. 1975;51(4):606-613.
6. Wannamethee G, Shaper AG, Macfarlane PW, Walker M. Risk factors for sudden cardiac death in middle-aged British men. *Circulation*. 1995;91(6):1749-1756.
7. Jouven X, Desnos M, Guerot C, Ducimetière P. Predicting sudden death in the population: the Paris Prospective Study I. *Circulation*. 1999;99(15):1978-1983.
8. Lemaitre RN, Siscovick DS, Raghunathan TE, Weinmann S, Arbogast P, Lin DY. Leisure-time physical activity and the risk of primary cardiac arrest. *Arch Intern Med*. 1999;159(7):686-690.
9. Whang W, Manson JE, Hu FB, et al. Physical exertion, exercise, and sudden cardiac death in women. *JAMA*. 2006;295(12):1399-1403.

10. Siscovick DS, Raghunathan TE, King J, et al. Dietary intake and cell membrane levels of long-chain n-3 polyunsaturated fatty acids and the risk of primary cardiac arrest. *JAMA*. 1995;274(17):1363-1367.
11. Marchioli R, Barzi F, Bomba E, et al; GISSI-Prevenzione Investigators. Early protection against sudden death by n-3 polyunsaturated fatty acids after myocardial infarction: time-course analysis of the results of the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico (GISSI)-Prevenzione. *Circulation*. 2002;105(16):1897-1903.
12. Albert CM, Campos H, Stampfer MJ, et al. Blood levels of long-chain n-3 fatty acids and the risk of sudden death. *N Engl J Med*. 2002;346(15):1113-1118.
13. Siscovick DS, Weiss NS, Fox N. Moderate alcohol consumption and primary cardiac arrest. *Am J Epidemiol*. 1986;123(3):499-503.
14. Albert CM, Manson JE, Cook NR, Ajani UA, Gaziano JM, Hennekens CH. Moderate alcohol consumption and the risk of sudden cardiac death among US male physicians. *Circulation*. 1999;100(9):944-950.
15. Stampfer MJ, Hu FB, Manson JE, Rimm EB, Willett WC. Primary prevention of coronary heart disease in women through diet and lifestyle. *N Engl J Med*. 2000;343(1):16-22.
16. Chiuve SE, Rexrode KM, Spiegelman D, Logroscino G, Manson JE, Rimm EB. Primary prevention of stroke by healthy lifestyle. *Circulation*. 2008;118(9):947-954.
17. Hu FB, Manson JE, Stampfer MJ, et al. Diet, lifestyle, and the risk of type 2 diabetes mellitus in women. *N Engl J Med*. 2001;345(11):790-797.
18. Platz EA, Willett WC, Colditz GA, Rimm EB, Spiegelman D, Giovannucci E. Proportion of colon cancer risk that might be preventable in a cohort of middle-aged US men. *Cancer Causes Control*. 2000;11(7):579-588.
19. Forman JP, Stampfer MJ, Curhan GC. Diet and lifestyle risk factors associated with incident hypertension in women. *JAMA*. 2009;302(4):401-411.
20. Ford ES, Bergmann MM, Kröger J, Schienkiewitz A, Weikert C, Boeing H. Healthy living is the best revenge: findings from the European Prospective Investigation Into Cancer and Nutrition-Potsdam study. *Arch Intern Med*. 2009;169(15):1355-1362.
21. van Dam RM, Li T, Spiegelman D, Franco OH, Hu FB. Combined impact of lifestyle factors on mortality: prospective cohort study in US women. *BMJ*. 2008;337:a1440.
22. Knuops KT, de Groot LC, Kromhout D, et al. Mediterranean diet, lifestyle factors, and 10-year mortality in elderly European men and women: the HALE project. *JAMA*. 2004;292(12):1433-1439.
23. Colditz GA, Stampfer MJ, Willett WC, Rosner B, Speizer FE, Hennekens CH. A prospective study of parental history of myocardial infarction and coronary heart disease in women. *Am J Epidemiol*. 1986;123(1):48-58.
24. Wolf AM, Hunter DJ, Colditz GA, et al. Reproducibility and validity of a self-administered physical activity questionnaire. *Int J Epidemiol*. 1994;23(5):991-999.
25. Willett WC, Sampson L, Stampfer MJ, et al. Reproducibility and validity of a semiquantitative food frequency questionnaire. *Am J Epidemiol*. 1985;122(1):51-65.
26. US Department of Agriculture. *Composition of Foods—Raw, Processed, and Prepared: Agricultural Handbook No. 8*. Washington, DC: US Govt Printing Offices; 1963.
27. Hu FB, Stampfer MJ, Rimm EB, et al. Dietary fat and coronary heart disease: a comparison of approaches for adjusting for total energy intake and modeling repeated dietary measurements. *Am J Epidemiol*. 1999;149(6):531-540.
28. Lloyd-Jones DM, Hong Y, Labarthe D, et al; American Heart Association Strategic Planning Task Force and Statistics Committee. Defining and setting national goals for cardiovascular health promotion and disease reduction: the American Heart Association's strategic impact goal through 2020 and beyond. *Circulation*. 2010;121(4):586-613.
29. US Department of Health and Human Services. 2008 physical activity guidelines for Americans. <http://www.health.gov/PAGuidelines>. Accessed January 31, 2011.
30. WHO Expert Committee. Physical status: the use and interpretation of anthropometry. *World Health Organ Tech Rep Ser*. 1995;854:1-452.
31. Fung TT, Rexrode KM, Mantzoros CS, Manson JE, Willett WC, Hu FB. Mediterranean diet and incidence of and mortality from coronary heart disease and stroke in women. *Circulation*. 2009;119(8):1093-1100.
32. Albert CM, Gaziano JM, Willett WC, Manson JE. Nut consumption and decreased risk of sudden cardiac death in the Physicians' Health Study. *Arch Intern Med*. 2002;162(12):1382-1387.
33. Albert CM, Hennekens CH, O'Donnell CJ, et al. Fish consumption and risk of sudden cardiac death. *JAMA*. 1998;279(1):23-28.
34. Hinkle LE Jr, Thaler HT. Clinical classification of cardiac deaths. *Circulation*. 1982;65(3):457-464.
35. Shojania KG, Burton EC, McDonald KM, Goldman L. Changes in rates of autopsy-detected diagnostic errors over time: a systematic review. *JAMA*. 2003;289(21):2849-2856.
36. Shekelle RB, Stamler J, Paul O, Shryock AM, Liu S, Lepper M. Dietary lipids and serum cholesterol level: change in diet confounds the cross-sectional association. *Am J Epidemiol*. 1982;115(4):506-514.
37. Durrleman S, Simon R. Flexible regression models with cubic splines. *Stat Med*. 1989;8(5):551-561.
38. Spiegelman D, Hertzmark E, Wand HC. Point and interval estimates of partial population attributable risks in cohort studies: examples and software. *Cancer Causes Control*. 2007;18(5):571-579.
39. Wacholder S, Benichou J, Heineman EF, Hartge P, Hoover RN. Attributable risk: advantages of a broad definition of exposure. *Am J Epidemiol*. 1994;140(4):303-309.
40. D'Agostino RB, Lee ML, Belanger AJ, Cupples LA, Anderson K, Kannel WB. Relation of pooled logistic regression to time dependent Cox regression analysis: the Framingham Heart Study. *Stat Med*. 1990;9(12):1501-1515.
41. Schoenborn CA, Adams PF. Health behaviors of adults: United States, 2005-2007. *Vital Health Stat 10*. 2010;(245):1-132.
42. Chugh SS, Uy-Evanado A, Teodorescu C, et al. Women have a lower prevalence of structural heart disease as a precursor to sudden cardiac arrest: The Ore-SUDS (Oregon Sudden Unexpected Death Study). *J Am Coll Cardiol*. 2009;54(22):2006-2011.
43. Peters RW, Brooks MM, Todd L, Liebson PR, Wilhelmsen L; Cardiac Arrhythmia Suppression Trial (CAST) Investigators. Smoking cessation and arrhythmic death: the CAST experience. *J Am Coll Cardiol*. 1995;26(5):1287-1292.
44. de Lorgeril M, Salen P, Martin J-L, Monjaud I, Delaye J, Mamelle N. Mediterranean diet, traditional risk factors, and the rate of cardiovascular complications after myocardial infarction: final report of the Lyon Diet Heart Study. *Circulation*. 1999;99(6):779-785.
45. Sofi F, Abbate R, Gensini GF, Casini A. Accruing evidence on benefits of adherence to the Mediterranean diet on health: an updated systematic review and meta-analysis. *Am J Clin Nutr*. 2010;92(5):1189-1196.
46. Berrington de Gonzalez A, Hartge P, Cerhan JR, et al. Body-mass index and mortality among 1.46 million white adults. *N Engl J Med*. 2010;363(23):2211-2219.
47. Ajani UA, Lotufo PA, Gaziano JM, et al. Body mass index and mortality among US male physicians. *Ann Epidemiol*. 2004;14(10):731-739.
48. Baik I, Ascherio A, Rimm EB, et al. Adiposity and mortality in men. *Am J Epidemiol*. 2000;152(3):264-271.
49. Adams KF, Schatzkin A, Harris TB, et al. Overweight, obesity, and mortality in a large prospective cohort of persons 50 to 71 years old. *N Engl J Med*. 2006;355(8):763-778.
50. Roger VL. Lifestyle and cardiovascular health: individual and societal choices. *JAMA*. 2009;302(4):437-439.
51. Willett WC. The WHI joins MRFIT: a revealing look beneath the covers. *Am J Clin Nutr*. 2010;91(4):829-830.
52. Zheng ZJ, Croft JB, Giles WH, Mensah GA. Sudden cardiac death in the United States, 1989 to 1998. *Circulation*. 2001;104(18):2158-2163.
53. Copeland KT, Checkoway H, McMichael AJ, Holbrook RH. Bias due to misclassification in the estimation of relative risk. *Am J Epidemiol*. 1977;105(5):488-495.
54. Hildebrandt M, Bender R, Gehrman U, Blettner M. Calculating confidence intervals for impact numbers. *BMC Med Res Methodol*. 2006;6:32.