Combined Lifestyle Factors and Cardiovascular Disease Mortality in Chinese Men and Women

The Singapore Chinese Health Study

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Background—Lifestyle factors directly influence cardiovascular disease (CVD) risk, yet little research has examined the association of combined lifestyle factors with CVD mortality, especially in Asian populations.

Methods and Results—We examined the association of 6 combined lifestyle factors (dietary pattern, physical activity, alcohol intake, usual sleep, smoking status, and body mass index) with CVD mortality in 50,466 (44,056 without a history of diabetes mellitus, CVD, or cancer and 6,410 with diabetes mellitus or history of clinical CVD) Chinese men and women in Singapore who were 45 to 74 years of age during enrollment in the Singapore Chinese Health Study in 1993 to 1998 and followed up through 2009. Each lifestyle factor was independently associated with CVD mortality. When combined, there was a strong, monotonic decrease in age- and sex-standardized CVD mortality rates with an increasing number of protective lifestyle factors. Relative to participants with no protective lifestyle factors, the hazard ratios of CVD mortality for 1, 2, 3, 4, and 5 to 6 protective lifestyle factors were 0.60 (95% confidence interval, 0.45–0.84), 0.50 (95% confidence interval, 0.38–0.67), 0.40 (95% confidence interval, 0.30–0.53), 0.32 (95% confidence interval, 0.24–0.43), and 0.24 (95% confidence interval, 0.17–0.34), respectively, among those without a history of diabetes mellitus, CVD, or cancer (P for trend <0.0001). A parallel graded inverse association was observed in participants with a history of CVD or diabetes mellitus at baseline. Results were consistent for coronary heart disease and cerebrovascular disease mortality.

Conclusion—An increasing number of protective lifestyle factors is associated with a marked decreased risk of coronary heart disease, cerebrovascular disease, and overall CVD mortality in Chinese men and women. (Circulation. 2011;124:00-00.)

Key Words: Asian continental ancestry group cardiovascular disease lifestyle mortality risk factors

Cardiovascular disease (CVD) is the leading cause of death worldwide. The increasing rates in developing and recently developed populations mirror historic epidemiological data in high-income nations. The causes of this global epidemic have largely been established to originate in lifestyle factors and their direct impact on established and novel pathways of clinical cardiovascular risk. A rich body of evidence links lifestyle factors such as diet, alcohol intake, physical activity, smoking, and relative weight with CVD. A developing body of literature suggests that sleep patterns are also important.

Clinical Perspective on p

Despite the evidence of individual lifestyle factors being associated with clinical parameters or CVD outcomes, few studies have examined the combined additive associations of multiple lifestyle factors with CVD mortality. Additionally, there has been little ethnic variation in the populations studied. Only 1 study has examined a Chinese population, an ethnic group, along with Asian Indians, that represents the largest swath of the global population. Both south and southeast Asian populations are experiencing an increasing prevalence of CVD and many of its risk factors such as diabetes mellitus as a result of well-documented epidemiological and nutrition transitions.

Therefore, we aimed to examine the combined association of lifestyle factors (dietary pattern, physical activity, alcohol intake, smoking, usual sleep, and relative weight) with risk of CVD mortality and the major subgroups of CVD mortality (coronary heart disease and cerebrovascular disease mortal-
ity) in a population-based cohort study of Chinese men and women in Singapore.

Methods

Study Population
The design of the Singapore Chinese Health Study has previously been described. Briefly, the cohort was drawn from men and women 45 to 74 years of age who belonged to one of the major dialect groups (Hokkien or Cantonese) of Chinese in Singapore. Between April 1993 and December 1998, 63,257 individuals completed an in-person interview that included questions on usual diet, demographics, height and weight, use of tobacco, usual physical activity, menstrual and reproductive history (women only), medical history, and family history of cancer. The institutional review boards at the National University of Singapore and the University of Minnesota approved this study.

Assessment of Lifestyle Risk Factors
At the baseline interview, all lifestyle factors were collected by self-report. Height and weight were used to calculate body mass index (BMI) as weight divided by height squared (kg/m²). Inquiry on smoking habits included smoking status (never, former, or current smoker); former and current (ie, ever) smokers were further asked for age at starting or quitting smoking, number of cigarettes per day, and number of years of smoking. For physical activity, participants were asked the number of hours per week spent on moderate activities such as brisk walking, bowling, bicycling on level ground, and tai chi or chi kung and on strenuous sports such as jogging, bicycling on hills, tennis, squash, swimming laps, or aerobics. The physical activity portion of the questionnaire was modeled after the European Prospective Investigation in Cancer (EPIC) study physical activity questionnaire, which has been shown to be valid and repeatable. Usual sleep duration was assessed by the following question: “On average, during the last year, how many hours in a day did you sleep?” Response categories were ≤5, 6, 7, 8, 9, and ≥10 hours.

For each of the 4 types of alcoholic beverages (beer, wine, Western hard liquor, and Chinese hard liquor), participants were asked to choose from 8 frequency categories: never or hardly, once a week, 2 to 3 times a week, once a month, 2 to 3 times a month, once a day, and ≥5 times a week. Participants were also asked to choose from 4 defined portion sizes. For beer, the portion sizes were 1 small bottle (375 mL) or less, 2 small bottles, 1 large bottle (750 mL), 2 large bottles, and 3 large bottles or more. For wine, the portion sizes were 1 glass (118 mL) or less, 2 glasses, 3 glasses, and 4 glasses or more. For Chinese or Western hard liquor, the portion sizes were 1 shot (30 mL) or less, 2 shots, 3 shots, and 4 shots or more. One drink was defined as 375 mL beer (13.6 g ethanol), 118 mL wine (11.7 g ethanol), and 30 mL Western or Chinese hard liquor (10.9 g ethanol). We expressed levels of alcohol intake in units of “drinks” per week to facilitate comparison with Western populations.

A semiquantitative food frequency questionnaire specifically developed for this population assessing 165 commonly consumed food items was administered during the baseline interview. The questionnaire has been validated against a series of 24-hour dietary recall interviews and selected biomarkers. A food composition table was also developed in conjunction with the study. Dietary patterns were derived for this study population through the use of principal component analysis including all 165 foods and beverages (besides alcohol) using methods described previously. Briefly, the aim of principal component analysis in nutritional analyses is to account for the maximal variance of dietary intake by combining the many different dietary variables into a smaller number of factors based on the intercorrelations of these variables. A vegetable-, fruit-, and soy-rich pattern characterized by high intake of those respective foods and lower intake of meats, dim sum, Western-style fast food, and sugared soft drinks was included.

Classification of Protective Lifestyle Factors
Lifestyle factors were characterized as protective on the basis of previously published work examining BMI and CVD mortality, as well as sleep and coronary heart disease mortality, in the cohort. For the other lifestyle factors, protective levels were based on the data from the Singapore cohort generally aligning with the literature base on the topic. For alcohol intake, participants who reported no intake or “high or excessive” intake had a greater risk of dying of CVD relative to those reporting “light to moderate” intake of alcohol. The protective definition of dietary intake in the cohort was based on ranking of the vegetable-, fruit-, and soy-rich dietary pattern score. Participants without cancer, CVD, or diabetes mellitus whose dietary pattern was characterized by greater intake of vegetables, fruits and soy (>40th percentile) had a lower risk of CVD mortality relative to participants with a lower score (<40th percentile). This dietary pattern score identified by principal component analysis represents usual intake of the study population as captured by a food frequency questionnaire but does not necessarily reflect the optimal diet in relation to CVD. However, higher ranking on this dietary pattern is consistent with historical evidence on diet and risk of CVD because it represents increasing intake of fruits, vegetables, and soy. Physical activity levels were categorized into ≥2 h/wk of moderate activity or any strenuous activity versus lower levels of activity. Finally, participants were classified as never or ever smokers. All factors were defined the same for persons with a history of clinical diabetes mellitus or CVD at enrollment in the study except the dietary pattern score and BMI. For this subpopulation, only the top 20% of vegetable-, fruit-, and soy-rich dietary pattern was associated with lower risk with CVD mortality, perhaps because those at high risk need to adhere to a dietary pattern that is more prudent than the rest of the population to observe potential benefit. Furthermore, only those who were overweight (<18.5 kg/m²) were at elevated risk of dying of CVD. Each lifestyle factor was coded as 1 (protective) or 0 (referent).

Assessment of Mortality, Diabetes Mellitus, and CVD
Information on date and cause of death was obtained through linkage analysis with the nationwide registry of birth and death in Singapore. Up to 6 different International Classification of Disease, version 9, codes were recorded in the registry. Primary cause of death was used for analysis. Vital status for cohort participants was updated through December 31, 2009. Only 27 persons were lost to follow-up as a result of migration out of Singapore, suggesting that migration of the cohort participants was negligible and that vital statistics follow-up was virtually complete. The end points in the analyses were deaths resulting from CVD (codes 399.4–450.0), coronary heart disease (410.0–414.9, 427.5), and cerebrovascular disease (430.0–438.0).

Diabetes status was assessed by the following question: “Have you been told by a doctor that you have diabetes (high blood sugar)?” If the answer was “yes,” the next question was, “Please also tell me the age at which you were first diagnosed.” A validation study of the self-report of diabetes mellitus cases used 2 different methods and was previously reported. Similarly, CVD was assessed by the following questions: “Have you been told by a doctor that you have had a heart attack or angina (chest pain or exertion that is relieved by medication)?” and “Have you been told by a doctor that you have had a stroke?” If the answer was “yes,” the next question was, “Please tell me the age you were first diagnosed.”

Statistical Analysis
Of the original 63,257 participants, we excluded 1936 with a history of invasive cancer (except nonmelanoma skin cancer) or superficial, papillary bladder cancer at baseline because they did not meet study inclusion criteria and 10,070 participants who were missing measurements of height, weight, or both. We also excluded participants who reported extreme sex-specific energy intake (<600 or >3000 kcal for women; <700 or >3700 kcal for men). The present analyses included 50,466 participants: 44,056 who were “healthy” at enroll-
ment with no reported clinical history of CVD, diabetes mellitus, or cancer and 6410 who reported a history of clinical CVD or diabetes mellitus at enrollment and at high risk. Those with a history of CVD or diabetes mellitus at study enrollment were combined because of their highly similar magnitude of increased risk and rates of CVD mortality.

For each study subject, person-years were counted from the date of baseline interview to the date of death, date of last contact (for the few who migrated out of Singapore), or December 31, 2009, whichever occurred first. Baseline characteristics were calculated for participants across the overall number of protective lifestyle factors. Age- and sex-standardized mortality rates were calculated from the person-year weight of the entire cohort during the follow-up by the following age categories: <50, 50 to 54, 55 to 59, 60 to 64, 65 to 69, and ≥70 years.

Proportional hazards (Cox) regression methods were used to examine the associations between combined lifestyle factors and hazard risk of death owing to CVD among healthy participants (who had no history of CVD, diabetes mellitus, or cancer) and participants with a history of clinical diabetes mellitus or CVD at baseline. All regression analyses were conducted with SAS statistical software version 9.2 (SAS Institute, Cary, NC). We estimated the hazard ratio of death resulting from CVD according to the number of protective lifestyle factors and the corresponding 95% confidence interval. There was no evidence that proportional hazards assumptions were violated, as indicated by the lack of significant interaction between the combined lifestyle factor variable and a function of survival time in the models.

In the analysis considering individual lifestyle factors, the models included all the lifestyle factors simultaneously, as well as age (<50, 50–54, 55–59, 60–64, ≥65 years), sex, year of interview (1993–1995 and 1996–1998), dialect (Hokkien versus Cantonese), level of education (no formal schooling, primary school, secondary school and above), marital status (married, separated/divorced, widowed, never married), and total energy intake (kcal/d). The same adjustments were made in the analysis of the combined protective lifestyle factors. We further adjusted for the age at diagnosis of diabetes mellitus or CVD in participants with a reported history at baseline. The overall number of protective lifestyle factors was the sum of the risk score (0, 1) over all 6 lifestyle factors. Tests for trend were performed by entering the combined lifestyle factor variable into the model as a continuous variable.

Effect modification of the associations was considered by age, sex, educational attainment, and self-reported physician-diagnosed hypertension status at study enrollment. To reduce potential bias caused by nonreported preexisting disease, underlying illness, or severity of disease among those with a reported history of diabetes mellitus or CVD, participants who died within 3 and 5 years were excluded from sensitivity analyses.

Results

During ≈593 118 person-years of follow-up, there were 1971 deaths resulting from CVD in individuals free of diabetes mellitus, CVD, and cancer. Table 1 gives the definition of and association of 6 different independent lifestyle factors with CVD mortality. Each individual factor (dietary pattern, physical activity, alcohol intake, usual sleep, smoking, and relative weight) was associated with CVD mortality, but the prevalence of the protective level of each factor differed.

Table 2 presents participant characteristics at baseline according to the number of protective lifestyle factors in healthy (n=44 056) participants. There was a somewhat statistically normal distribution of protective lifestyle factors in the study population, with the greatest frequency of participants having 2 or 3 protective lifestyle factors and the fewest participants with 0 or 6 protective lifestyle factors. As the number of protective lifestyle factors increased, participants at baseline were younger, more educated, more likely to be currently married, and less hypertensive and had a lower BMI.

Table 3 displays the age- and sex-standardized rates and hazard ratios with 95% confidence intervals for overall CVD, coronary heart disease, and cerebrovascular disease mortality according to number of protective lifestyle factors in the healthy population. A graded monotonic decrease in age- and sex-standardized rate and risk of coronary heart disease, cerebrovascular disease, and overall CVD mortality was observed with an increasing number of protective lifestyle factors. Individuals with 5 to 6 protective lifestyle factors had approximately one fourth the risk of CVD mortality relative to those with no protective lifestyle factors. Of note, in the 289 participants who reported 6 protective lifestyle factors, only 2 deaths were recorded as caused by CVD (none by coronary heart disease). The hazard ratio of CVD mortality for those participants was only 0.06 (95% confidence interval, 0.02–0.25) relative to those with no protective factors. Table 1 in the online-only Data Supplement reports the sex-stratified results for overall CVD mortality and displays a similar monotonic decrease in risk between sexes, although greater absolute rates of CVD mortality occur in men.
The results from the parallel analysis of 6410 participants with a history of clinical CVD or diabetes mellitus at enrollment were analogous across the individual lifestyle factors as presented in Table 4. With an increasing number of protective lifestyle factors, participants were younger, had a younger age of diagnosis of diabetes mellitus or CVD, were more educated, and had higher BMIs (data not presented). Similar to the results of the 44 056 participants without cancer or reported history of major chronic disease at study enrollment, the 6410 participants with a reported history of clinical CVD or diabetes mellitus at enrollment experienced a marked stepwise decrease in rate and risk of dying of CVD with an increasing number of protective lifestyle factors, as shown in the Figure. Comparable results for coronary heart disease and cerebrovascular disease were observed (data not shown).

Table 2. Baseline Participant Characteristics According to the Number of Protective Lifestyle Factors in Healthy Participants (Free of Diabetes Mellitus and History of Cardiovascular Disease)

<table>
<thead>
<tr>
<th>Protective Lifestyle Factors</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>415</td>
<td>3589</td>
<td>11 353</td>
<td>15 998</td>
<td>9764</td>
<td>2648</td>
<td>289</td>
</tr>
<tr>
<td>Age, y</td>
<td>57.8 (7.4)</td>
<td>56.5 (7.6)</td>
<td>55.6 (7.6)</td>
<td>55.1 (7.6)</td>
<td>55.0 (7.9)</td>
<td>55.2 (8.2)</td>
<td>54.2 (8.1)</td>
</tr>
<tr>
<td>Female sex, %</td>
<td>20.7</td>
<td>32.7</td>
<td>50.8</td>
<td>61.6</td>
<td>59.5</td>
<td>52.0</td>
<td>43.3</td>
</tr>
<tr>
<td>Education, %</td>
<td>21.9</td>
<td>21.0</td>
<td>26.7</td>
<td>31.2</td>
<td>41.1</td>
<td>50.5</td>
<td>58.9</td>
</tr>
<tr>
<td>Married, %</td>
<td>76.5</td>
<td>83.2</td>
<td>84.1</td>
<td>85.5</td>
<td>86.5</td>
<td>87.6</td>
<td>88.9</td>
</tr>
<tr>
<td>Hypertension, %</td>
<td>21.4</td>
<td>21.6</td>
<td>21.9</td>
<td>21.1</td>
<td>18.4</td>
<td>15.7</td>
<td>10.0</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>23.1 (4.4)</td>
<td>23.6 (4.1)</td>
<td>23.6 (3.7)</td>
<td>23.2 (3.5)</td>
<td>22.2 (3.0)</td>
<td>21.5 (2.4)</td>
<td>20.5 (1.1)</td>
</tr>
</tbody>
</table>

Percent reporting protective level of lifestyle factor

- BMI: NA 7.4 16.9 29.0 54.3 75.9 100
- Dietary pattern: NA 9.5 30.5 69.8 88.5 95.9 100
- Physical activity: NA 1.9 6.7 16.7 45.7 81.3 100
- Sleep: NA 54.3 77.9 90.3 95.5 98.9 100
- Smoking: NA 23.2 57.2 78.0 87.4 94.1 100
- Alcohol intake: NA 3.7 10.7 16.3 28.6 53.9 100

Data for age and body mass index (BMI) are given as mean (SD).

The results from the parallel analysis of 6410 participants with a history of clinical CVD or diabetes mellitus at enrollment were analogous across the individual lifestyle factors as presented in Table 4. With an increasing number of protective lifestyle factors, participants were younger, had a younger age of diagnosis of diabetes mellitus or CVD, were more educated, and had higher BMIs (data not presented). Similar to the results of the 44 056 participants without cancer or reported history of major chronic disease at study enrollment, the 6410 participants with a reported history of clinical CVD or diabetes mellitus at enrollment experienced a marked stepwise decrease in rate and risk of dying of CVD with an increasing number of protective lifestyle factors, as shown in the Figure. Comparable results for coronary heart disease and cerebrovascular disease were observed (data not shown).

Table 3. Age- and Sex-Adjusted Cardiovascular Disease Mortality Rates and Hazard Ratio and 95% Confidence Interval of Cardiovascular Disease Mortality According to the Number of Protective Lifestyle Factors in Healthy Chinese Men and Women: Singapore Chinese Health Study

<table>
<thead>
<tr>
<th>Protective Lifestyle Factors</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5/6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total CVD mortality (ICD-9 codes 390–459)</td>
<td>415</td>
<td>3589</td>
<td>11 353</td>
<td>15 998</td>
<td>9764</td>
<td>2937</td>
</tr>
<tr>
<td>CVD deaths, n</td>
<td>55</td>
<td>264</td>
<td>616</td>
<td>630</td>
<td>325</td>
<td>81</td>
</tr>
<tr>
<td>Standardized rate*</td>
<td>110</td>
<td>57</td>
<td>41</td>
<td>29</td>
<td>24</td>
<td>20</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>1.00</td>
<td>0.60 (0.45–0.84)</td>
<td>0.50 (0.38–0.67)</td>
<td>0.40 (0.30–0.53)</td>
<td>0.32 (0.24–0.43)</td>
<td>0.24 (0.17–0.34)</td>
</tr>
<tr>
<td>CHD mortality (ICD-9 codes 410.0–414.9, 427.5)</td>
<td>29</td>
<td>152</td>
<td>335</td>
<td>324</td>
<td>158</td>
<td>41</td>
</tr>
<tr>
<td>CHD deaths, n</td>
<td>58</td>
<td>33</td>
<td>22</td>
<td>15</td>
<td>12</td>
<td>10</td>
</tr>
<tr>
<td>Standardized rate*</td>
<td>1.00</td>
<td>0.67 (0.45–0.99)</td>
<td>0.53 (0.36–0.78)</td>
<td>0.40 (0.27–0.59)</td>
<td>0.30 (0.20–0.45)</td>
<td>0.23 (0.14–0.37)</td>
</tr>
<tr>
<td>CERE mortality (ICD-9 430–438)</td>
<td>18</td>
<td>61</td>
<td>193</td>
<td>180</td>
<td>103</td>
<td>28</td>
</tr>
<tr>
<td>CERE deaths, n</td>
<td>36</td>
<td>13</td>
<td>13</td>
<td>8</td>
<td>8</td>
<td>7</td>
</tr>
<tr>
<td>Standardized rate*</td>
<td>1.00</td>
<td>0.41 (0.24–0.69)</td>
<td>0.46 (0.28–0.74)</td>
<td>0.33 (0.20–0.54)</td>
<td>0.30 (0.18–0.50)</td>
<td>0.25 (0.14–0.46)</td>
</tr>
</tbody>
</table>

CVD indicates cardiovascular disease; ICD-9, International Classification of Disease, version 9; HR, hazard ratio; CI, confidence interval; CHD, coronary heart disease; and CERE, cerebrovascular disease. Model was adjusted for age, sex, year of enrollment, dialect, education, marital status, and energy intake.

*Age- and sex-standardized CVD/CHD/CERE mortality rate per 10 000 person-years using person-year time, age, and sex distributions of the Singapore Chinese Health Study.
Table 4. Definition of Lifestyle Factors and the Independent Association With Cardiovascular Disease Mortality (International Classification of Disease, Version 9, Codes 390–459) in Participants With Clinical Cardiovascular Disease or Diabetes Mellitus at Baseline (n=6410)

<table>
<thead>
<tr>
<th>Factor</th>
<th>Percent With Protective</th>
<th>Protective: HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dietary pattern</td>
<td>20.0</td>
<td>0.84 (0.71–0.98)</td>
</tr>
<tr>
<td>Physical activity</td>
<td>29.8</td>
<td>0.82 (0.72–0.94)</td>
</tr>
<tr>
<td>Sleep</td>
<td>77.9</td>
<td>0.82 (0.72–0.94)</td>
</tr>
<tr>
<td>BMI</td>
<td>95.5</td>
<td>0.75 (0.58–0.96)</td>
</tr>
<tr>
<td>Alcohol intake</td>
<td>11.4</td>
<td>0.76 (0.62–0.93)</td>
</tr>
<tr>
<td>Smoking</td>
<td>64.3</td>
<td>0.73 (0.64–0.84)</td>
</tr>
</tbody>
</table>

BMI indicates body mass index; HR, hazard ratio; and CI, confidence interval. Model includes all factors simultaneously and is adjusted for age, age at diagnoses of diabetes mellitus or cardiovascular disease, sex, dialect, year enrolled, education, marital status, and energy intake.

There was no evidence that the nature of the strong inverse association varied by age, sex, educational attainment, or hypertensive status at baseline in the 44,056 participants in the main analysis or in those with diabetes mellitus or a history of CVD at baseline. Indeed, the pattern of relative risk was similar across the multiple stratified analyses, but the absolute rates were greater in participants who were older, male, hypertensive, and less educated (data not presented by age, hypertensive status, and education level). The exclusion of deaths within 3 or 5 years of enrollment did not materially change the nature of the results for those who were healthy or had a history of diabetes mellitus or CVD.

Discussion

Chinese men and women free of major chronic disease with protective lifestyle factors represented by a dietary pattern plentiful in vegetables, fruit, and soy; higher relative levels of physical activity; light to moderate alcohol consumption; average usual sleep of 6 to 8 h/d; no history of smoking; and healthy relative weight were at a significantly reduced risk of dying of CVD relative to their peers who did not adhere to these protective lifestyle factors. In combination, a marked decrease in rate and risk of dying of CVD was observed with each additional protective lifestyle factor. The nature of the association did not differ materially among population subgroups or length of follow-up. Very similar results were observed in participants with a history of diabetes mellitus and CVD at study enrollment, enhancing the generalizability to both primary and secondary prevention.

Few studies have addressed the combination of different lifestyle factors with death resulting from CVD despite the large body of evidence linking them with CVD. Knoops et al11 examined the combination of a Mediterranean diet index, moderate alcohol consumption, physical activity, and nonsmoking in 2339 European men and women 70 to 90 years of age and observed a decreasing risk of death caused by coronary heart disease and overall CVD with each increasing protective factor. In the EPIC-Norfolk study, >20,000 men and women 45 to 79 years of age who were free of CVD and cancer had 4 combined healthy lifestyle factors defined as plasma vitamin C as a marker of a fruit/vegetable-rich diet, noncurrent smoker, light to moderate alcohol consumption; average usual sleep of 6 to 8 h/d; no history of smoking; and healthy relative weight were at a significantly reduced risk of dying of CVD relative to their peers who did not adhere to these protective lifestyle factors. In combination, a marked decrease in rate and risk of dying of CVD was observed with each additional protective lifestyle factor. The nature of the association did not differ materially among population subgroups or length of follow-up. Very similar results were observed in participants with a history of diabetes mellitus and CVD at study enrollment, enhancing the generalizability to both primary and secondary prevention.

Participants experienced a significant increase in risk of CVD mortality with each poor lifestyle factor. Comparable results were observed in 2057 participants with CVD or cancer at study baseline, similar to our study.

Figure. Hazard ratios (HRs) and 95% confidence intervals (CIs) of cardiovascular disease (CVD) mortality (International Classification of Disease, version 9, codes 390–459) according to number of protective lifestyle factors in individuals with a history of clinical CVD or diabetes mellitus at enrollment (n=6410; CVD deaths, 1184; P for trend <0.0001). Respective n (CVD deaths) for 0/1, 2, 3, 4, and 5 to 6 low-risk lifestyle factors: 358 (104), 1602 (370), 2505 (460), 1451 (203), and 394 (47). Age- and sex-standardized CVD mortality rates across categories: 311, 214, 149, 113, and 94.
In the Nurses’ Health Study (NHS), 77,782 women 34 to 59 years of age who were free of CVD and cancer, had a lower healthy eating index score, were less physically active, ever smoked, drank heavily or abstained, and carried excess weight (BMI \(\geq 25.0 \text{ kg/m}^2\)) were at a marked increased risk of dying of CVD during follow-up relative to women who adhered to healthy levels of these lifestyle factors. Similar results were seen in 4886 men and women in the United Kingdom who were \(\geq 18\) years of age and had low fruit/vegetable intake, had low physical activity levels, currently smoked, or excessively consumed alcohol. In 38,110 men 20 to 84 years of age who were free of CVD and cancer, a combination of a high level of cardiorespiratory fitness, moderate or higher levels of physical activity, light to moderate alcohol intake, normal relative weight, and not currently smoking was associated with a decreasing risk of CVD death.

The only other study to examine combined lifestyle factors with CVD mortality in an Asian population was the Shanghai Women’s Study, which included 71,243 women 40 to 70 years of age who did not smoke or drink alcohol. Women who had a BMI between 18.5 and 25 kg/m\(^2\), had a low waist-to-hip ratio, were physically active, reported a high level of fruit and vegetable intake, and had a spouse who did not report smoking experienced a significant decrease in risk of dying of CVD.

In summary, our study and the other noted research suggest that a plant-based dietary pattern, greater levels of physical activity, avoidance of smoking, maintenance of a healthy weight range, and light to moderate alcohol consumption all contribute independently to the prevention of death resulting from CVD. Our study also raises the point that sleep patterns are another important lifestyle factor to consider for CVD risk. Sleep deprivation results in adverse physiological changes central to CVD risk, whereas longer sleep duration may be a marker of underlying CVD, mental health status, or poor thyroid function, all of which affect CVD risk.

The results from our study examining participants with a history of CVD or diabetes mellitus and thus at significantly increased risk for CVD mortality reaffirm prior or ongoing randomized trials focused on lifestyle factors in similar high-risk populations and provide the important message that delaying or preventing death caused by CVD is possible with an increasing number of protective lifestyle factors in individuals with a history of diabetes mellitus or CVD. The results observed in our study are without information on clinical treatment. However, a previous study found that an unhealthy lifestyle increases the risk of CVD independently of pharmacological treatment. Another aspect to consider in the interpretation of these results is that lifestyle at enrollment may be a marker of severity of disease. However, the consistency with healthy participants in the cohort, other aforementioned studies, and no material difference in the results relative to follow-up time suggest that disease severity or some other bias is not the driving factor in the association. With the increasing global prevalence of type 2 diabetes mellitus and the increase in rates of CVD in developing and recent developed populations, the results of a protective lifestyle, concomitant with usual medical treatment in this high-risk population, suggest a potential for significant benefit.

An important facet to consider in studies examining lifestyle factors in relation to CVD mortality is that the statistical distribution of combined protective lifestyle factors is a somewhat normal bell shape across populations. For example, in this study, participants with 0 or 5 to 6 combined protective lifestyle factors were the least common, whereas participants with 2 or 3 combined protective lifestyle factors were most numerous and contributed the majority of deaths resulting from CVD. This distribution of combined lifestyle factors is consistent with the distribution of clinical data (eg, lipids, blood pressure) from previous studies. Thus, efforts to increase the prevalence of protective lifestyle factors will likely have a significant influence on lowering the rates of CVD incidence and mortality. Indeed, evidence from surveillance, initiatives, and policy efforts suggests significant potential benefit related to increasing population levels of healthy lifestyle factors in relation to lessening CVD.

There are a number of strengths to consider in the interpretation of this study. The large prospective design with a non-Western population uniquely contributes to the literature. Furthermore, there are few long-term prospective data on lifestyle factors in individuals with a history of diabetes mellitus or CVD and risk of CVD mortality. Other strengths include the high participant response rate, detailed collection of data through face-to-face interviews, thorough adjustment for confounders, very low level of participants lost to follow-up, and nearly complete mortality assessment with objectively obtained records on time and cause of death.

Limitations also need to be considered. The self-report of lifestyle data may result in some misclassification and residual confounding while underestimating the associations assuming nondifferential misclassification. Despite the face validity for the results of all the different lifestyle factors, objective measures other than self-report would be ideal. Furthermore, the lifestyle factors were dichotomized, which may lead to underestimation of risk because there are graded associations among some of the lifestyle factors. However, our results are consistent with the previous published studies on the topic in strength and gradient. Repeated assessments of the lifestyle factors would have allowed us to examine change in lifestyle in relation to CVD mortality and would have complemented our data. We also relied on self-report of physician-diagnosed diabetes mellitus and CVD for categorization of individuals, which results in some misclassification.

In short, an increasing number of protective lifestyle factors in healthy Chinese men and women is associated with marked decreasing rates and risk of dying of CVD. A similar association occurred in high-risk participants with a history of diabetes mellitus or CVD at study enrollment. Overall, our study highlights in a large cohort study of Chinese adults that multiple modifiable lifestyle factors are of paramount importance in improving population-wide cardiovascular risk reduction in both primary and secondary prevention.
Acknowledgments
We thank Siew-Hong Low of the National University of Singapore for supervising the field work of the Singapore Chinese Health Study and Kazuko Arakawa and Renwei Wang for the development and maintenance of the cohort study database. Finally, we acknowledge the founding, longstanding principal investigator of the Singapore Chinese Health Study, Mimi C. Yu.

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Disclosures
None.

References
Clinical Perspective

Lifestyle factors directly affect established and novel pathways of cardiovascular risk. Despite this evidence, few studies have examined the combined association of multiple lifestyle factors with cardiovascular disease (CVD) mortality. Furthermore, there has been little ethnic variation in the populations studied or examination of this topic in patients with a history of diabetes mellitus and/or CVD. Therefore, this study examined the combined association of lifestyle factors with CVD mortality and its major subgroups in healthy Chinese men and women and a high-risk subcohort with a history of diabetes mellitus and CVD during study enrollment in the Singapore Chinese Health Study (1993–98) and followed up through 2009. In 50,466 healthy and high-risk Chinese men and women, protective lifestyle factors were represented by a dietary plentiful in vegetables, fruit, and soy; higher relative levels of physical activity; light to moderate alcohol consumption; average usual sleep of 6 to 8 h/d; no history of smoking; and normal weight (ie, not underweight or overweight). In combination, a marked decrease in rate and risk of dying as a result of CVD was observed with each additional protective lifestyle factor in healthy and high-risk participants. Overall, data from this large cohort of Chinese adults highlight that multiple modifiable lifestyle factors are of paramount importance in improving population-wide cardiovascular risk reduction in both primary and secondary prevention. Efforts to increase the prevalence of protective lifestyle factors in healthy and high-risk populations should significantly influence CVD mortality.
Combined Lifestyle Factors and Cardiovascular Disease Mortality in Chinese Men and Women: The Singapore Chinese Health Study
Andrew O. Odegaard, Woon-Puay Koh, Myron D. Gross, Jian-Min Yuan and Mark A. Pereira

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Table S1: Sex Stratified Results for Total Cardiovascular Disease Mortality (ICD-9 390-459): Age Adjusted Rates and Hazard Ratios According to Number of Protective Lifestyle Factors in Healthy Chinese Women and Men: SCHS

<table>
<thead>
<tr>
<th>Number of Protective Lifestyle Factors</th>
<th>Women</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5/6</td>
</tr>
<tr>
<td>N CVD Deaths / N</td>
<td>11 / 86</td>
<td>67 / 1,174</td>
<td>218 / 5,764</td>
<td>277 / 9,860</td>
<td>151 / 5,807</td>
<td>30 / 1,502</td>
</tr>
<tr>
<td>*Standardized rate</td>
<td>22</td>
<td>15</td>
<td>14</td>
<td>13</td>
<td>11</td>
<td>7</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>1.00</td>
<td>0.51 (0.27-0.96)</td>
<td>0.39 (0.21-0.72)</td>
<td>0.31 (0.17-0.56)</td>
<td>0.28 (0.15-0.52)</td>
<td>0.20 (0.10-0.41)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Men</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5/6</td>
</tr>
<tr>
<td>N CVD Deaths / N</td>
<td>44 / 329</td>
<td>197 / 2,415</td>
<td>398 / 5,589</td>
<td>353 / 6,138</td>
<td>174 / 3,957</td>
<td>51 / 1,435</td>
</tr>
<tr>
<td>*Standardized rate</td>
<td>88</td>
<td>43</td>
<td>26</td>
<td>16</td>
<td>13</td>
<td>13</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>1.00</td>
<td>0.67 (0.45-0.99)</td>
<td>0.53 (0.36-0.78)</td>
<td>0.40 (0.27-0.59)</td>
<td>0.30 (0.20-0.45)</td>
<td>0.23 (0.14-0.37)</td>
</tr>
</tbody>
</table>

SCHS = Singapore Chinese Health Study

*Standardized rate = Age standardized CVD mortality rate per 10,000 person years using person year time, and age distributions of SCHS by sex

HR (95% CI) = Hazard Ratio; 95% confidence interval: Model adjusted for age, year of enrollment, dialect, education, marital status, and energy intake

P Trend <0.0001