


ORIGINAL RESEARCH

Healthy Lifestyle for Prevention of Premature Death Among Users and Nonusers of Common Preventive Medications: A Prospective Study in 2 US Cohorts

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BACKGROUND: It remains unknown whether individuals who regularly use preventive medications receive the same benefit from healthy lifestyle as those who do not use medications. We aimed to examine the associations of healthy lifestyle with mortality according to use of major preventive medications, including aspirin, antihypertensives, and lipid-lowering medications.

METHODS AND RESULTS: Among 79 043 women in the Nurses' Health Study (1988–2014) and 39 544 men in the Health Professionals Follow-up Study (1986–2014), we defined a healthy lifestyle score based on body mass index, smoking, physical activity, diet, and alcohol intake. We estimated multivariable hazard ratios (HRs) and population-attributable risks of death from any cause, cardiovascular disease, cancer, and other causes in relation to healthy lifestyle according to medication use. We documented 35 195 deaths. A similar association of healthy lifestyle score with lower all-cause mortality was observed among medication users (HR, 0.82 per unit increment; 95% CI, 0.81–0.82) and nonusers (HR, 0.81; 95% CI, 0.79–0.83) (P interaction=0.54). The fraction of premature deaths that might be prevented by adherence to the 5 healthy lifestyle factors among medication users and nonusers was 38% (95% CI, 32%–42%) and 40% (95% CI, 29%–50%) for all-cause mortality, 37% (95% CI, 27%–46%) and 45% (95% CI, 18%–66%) for cardiovascular disease mortality, and 38% (95% CI, 28%–46%) and 33% (95% CI, 14%–49%) for cancer mortality, respectively.

CONCLUSIONS: Adherence to a healthy lifestyle confers substantial benefit for prevention of premature death among both regular users and nonusers of preventive medications. Adherence to a healthy lifestyle remains important even among individuals regularly using preventive medications.

Key Words: lifestyle ■ mortality ■ nutrition ■ preventive medication ■ primary prevention

Cardiovascular disease (CVD) and cancer are the 2 leading causes of death, accounting for almost a half (CVD, 23%; cancer, 22%) of all deaths in the United States in 2017.¹ Major preventive medications, including aspirin, antihypertensives, and lipid-lowering medications, are among the most commonly used medications in US adults.^{2–5} During 2012 to 2018, ≈47% of adults aged 45 to 75 years reported current use of aspirin for primary prevention of CVD,² 62% of hypertensive patients used antihypertensives,³ and 28% of

those 40 years or older used statins, with the prevalence increasing to 48% among those 75 years or older.⁴ While these medications have an established benefit for reducing CVD incidence in high-risk populations and recurrent events in patients with CVD history,^{6–8} their benefit for primary prevention in an average-risk population remains controversial.^{9–11} Moreover, although some evidence indicates potential of these medications in cancer prevention,¹² the benefit is limited to certain cancer type (ie, aspirin

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CLINICAL PERSPECTIVE

What Is New?

- In this cohort study with a follow-up of 26 years, we found a similar benefit of healthy lifestyle among regular users and nonusers of major preventive medications.

What Are the Clinical Implications?

- The findings indicate that adhering to a healthy lifestyle is always beneficial for health, regardless of the use of preventive medications.

Nonstandard Abbreviations and Acronyms

AHEI	Alternate Healthy Eating Index
BMI	body mass index
CVD	cardiovascular disease
HR	hazard ratio
HPFS	Health Professionals Follow-up Study
NHS	Nurses' Health Study
PAR	population-attributable risk

for colorectal cancer¹³) and remains inconclusive for others.^{14–16}

On the other hand, healthy lifestyle practices, including no smoking, being physically active, eating a healthy diet, limiting alcohol drinking, and maintaining a healthy body weight, have been associated with a substantial reduction in incidence and mortality of CVD¹⁷ and cancer.¹⁸ A recent report revealed that >60% of all-cause premature deaths can be potentially prevented by adherence to healthy lifestyle,¹⁹ indicating an important role of lifestyle modification in the prevention of premature death. Mechanistically, a healthy lifestyle has been shown to act on similar pathways as preventive medications, such as control of blood pressure, reduction of inflammation, and improvement of lipid profiles.^{20–22} However, it remains unknown whether individuals who regularly use preventive medications would still benefit from healthy lifestyle practices as those not using the medications. Addressing this question has great clinical implications as a result of the ever-increasing prevalence of preventive medication use⁵ and related concerns about the “health certificate effect” (medication users may consider being certified healthy and thus have less incentive to make lifestyle modification).²³

Therefore, we prospectively assessed the association of healthy lifestyles with all-cause and cause-specific mortality among users and nonusers of common

preventive medications within 2 large cohorts in the United States, including NHS (Nurses' Health Study) and HPFS (Health Professionals Follow-up Study). We also estimated the population-attributable risk (PAR) associated with healthy lifestyles according to medication use.

METHODS

Because of the sensitive nature of the data collected for this study, requests to access the data set from qualified researchers trained in human subject confidentiality protocols may be sent to Brigham and Women's/Harvard Cohorts at <https://sites.google.com/channing.harvard.edu/cohortdocs/getting-started/collaborations-consortia?authuser=2>.

Study Population

NHS and HPFS are 2 ongoing US cohorts that enrolled 121 700 registered female nurses aged 30 to 55 years in 1976 and 51 529 male health professionals aged 40 to 75 years in 1986, respectively. Similar follow-up procedures have been applied in the 2 cohorts, with over 90% of follow-up.^{24,25} Briefly, follow-up questionnaires were administered at baseline enrollment and every 2 years thereafter to collect updated lifestyle and medical information. Diet was assessed using validated food frequency questionnaires every 4 years.^{26,27} In the current study, we defined baseline as the year of 1988 for NHS and 1986 for HPFS, when we started to assess the use of major preventive medications, including aspirin, antihypertensives, and lipid-lowering medications. Informed consent was obtained from all participants. The study protocol was approved by the institutional review boards of the Brigham and Women's Hospital and Harvard T.H. Chan School of Public Health, and those of participating registries as required.

Among participants who returned baseline questionnaires (NHS, 1988; HPFS, 1986), we excluded participants who had a history of CVD (including myocardial infarction and stroke), cancer (except nonmelanoma skin cancer), or diabetes mellitus; reported implausible energy intakes (<500 or >3500 kcal/d for women; <800 or >4200 kcal/d for men); with a body mass index (BMI) of <18.5 kg/m²; or with missing data on lifestyle exposures or medication use. After these exclusions, 79 043 women and 39 544 men were included in the analysis (Figure S1).

Assessment of Lifestyle Factors

We included 5 lifestyle factors: BMI, cigarette smoking, physical activity, diet, and alcohol intake. Height, body weight, cigarette smoking, and physical activity were self-reported through biennial questionnaires. Cigarette smoking was evaluated based on both pack-years and the current status reported

biennially.²⁸ Physical activity was assessed by the total hours per week of moderate to vigorous intensity activity (including brisk walking) that requires the expenditure of at least 3 metabolic equivalents per hour. Alcohol use and diet were self-reported every 4 years by food frequency questionnaires.^{26,27} Diet quality was assessed with the Alternate Healthy Eating Index (AHEI) 2010 score,²⁹ which was designed to target food choices and macronutrient sources associated with reduced chronic disease risk. Supplemental information of the lifestyle and covariates assessment is provided in Data S1.

For each of the 5 lifestyle factors, we defined a binary criterion, by which the participants received a score of 1 if they met the criterion and 0 otherwise. The healthy lifestyle comprised a BMI ≥ 18.5 and < 27.5 kg/m², never smoking, physical activity for ≥ 30 minutes per day of moderate to vigorous intensity activity, an AHEI score in the upper 40th percentile within each cohort, and light to moderate alcohol intake (> 0 and < 1 drink [14 g alcohol] per day for women and < 2 drinks per day for men). An overall healthy lifestyle score (range, 0–5) was then calculated by summing the 5 scores, with a higher score indicating a healthier lifestyle.

Assessment of Medication Use

We considered aspirin, antihypertensives, and lipid-lowering medications as common preventive medications assessed on the biennial questionnaires. In NHS, we assessed the use of standard-dose (325 mg) aspirin since 1980, baby aspirin (81 mg) since 2000, and antihypertensives and lipid-lowering medications since 1988. Regular aspirin use was defined as use of ≥ 2 tablets of standard aspirin per week. For the years when baby aspirin was separately assessed, the dose of baby aspirin was divided by 4 and combined with standard aspirin. Regular use of antihypertensives and lipid-lowering medications was defined as use ≥ 2 times per week. In HPFS, all medications were assessed since 1986 and the same definitions as in NHS were used to define medication users. Detailed assessment methods are provided in the Data S1.

For each medication, participants were considered as nonusers up until the first time they reported regular use and as users thereafter for the remainder of the follow-up. Duration of regular medication use (in years) was also calculated as a time-varying variable by accumulating the follow-up time during which regular use was reported.

Ascertainment of Deaths

Deaths were identified from state vital statistics records, the National Death Index, next of kin, and the

postal system. Using these methods, we were able to ascertain $> 96\%$ of the deaths in each cohort.^{30,31} The primary cause of death was identified from medical records (65% in NHS and 59% in HPFS), death certificates (26% in NHS and 29% in HPFS), or next-of-kin or other contact person (9% in NHS and 12% in HPFS). For the current analysis, we assessed all-cause and cause-specific deaths caused by CVD (*International Classification of Diseases, Eighth Revision* [ICD-8], codes 390–458), cancer (codes 140–207), and other causes.

Statistical Analysis

Data were analyzed from October 2, 2018, to August 22, 2019. Details about statistical analysis are provided in Data S1. Both medication use and lifestyle factors were analyzed as time-varying variables. To capture long-term exposures and reduce random within-person variation, we calculated cumulative average levels of physical activity, AHEI score, and alcohol intake from our repeated questionnaires. For BMI, to minimize reverse causality resulting from weight loss caused by preexisting diseases, we used the maximum BMI reported throughout the follow-up.³² When data on the lifestyle factors were missing at a given questionnaire cycle, the last nonmissing observation was carried forward. We stopped updating lifestyle information when a participant reported a diagnosis of cancer (except nonmelanoma skin cancer), diabetes mellitus, stroke, coronary heart disease, or angina, because these conditions may lead to lifestyle changes.³³ In analysis of mortality attributable to other causes than CVD and cancer, we also stopped updating lifestyle information when Parkinson disease or chronic obstructive pulmonary disease was reported.

Participants contributed person-time from return of the baseline questionnaire (1988 for NHS and 1986 for HPFS) until the date of death, loss to follow-up, or end of the follow-up period (June 30, 2014, for NHS and January 31, 2014, for HPFS), whichever came first. We used time varying-, age-, period-, and cohort-stratified Cox proportional hazards regression models to estimate the hazard ratios (HRs) and 95% CIs for mortality associated with individual lifestyle factors and healthy lifestyle score. All analyses were performed separately according to medication use. We assessed the interaction between medication use and lifestyle using Wald test for the product term of the 2 variables. In the multivariable analyses, we performed mutual adjustment for the lifestyle factors and also adjusted for several potential confounding factors, including ethnicity; current multivitamin use; family history of diabetes mellitus, cancer, and myocardial infarction; and menopausal status and hormone use (women only).

Table 1. Age-Standardized Characteristics* of Study Participants According to Regular Use of Common Preventive Medications† in NHS and HPFS

	NHS (n=79 043)		HPFS (n=39 544)	
	Medication Users	Medication Nonusers	Medication Users	Medication Nonusers
Person-y, No. (% within cohort)	1 335 136 (72)	529 607 (28)	670 478 (70)	282 956 (30)
Age, y	67.4	59.5	66.2	58.4
White, %	98	97	95	93
Current multivitamin use, %	50	36	50	33
History of hypertension, %	58	18	48	14
History of hyperlipidemia, %	62	40	51	27
Family history of diabetes mellitus, %	29	25	21	18
Family history of myocardial infarction, %	26	20	34	27
Family history of cancer, %	14	14	36	33
Regular use of aspirin, %	79	...	86	...
Regular use of antihypertensives, %	59	...	47	...
Regular use of lipid-lowering medications, %	31	...	29	...
BMI, kg/m ²	28.1	26.4	27.0	26.2
Current smoker, %	12	15	7	8
Pack-y of smoking‡	23.4	24.7	21.4	20.7
Physical activity, min/d	16.9	19.1	29.5	29.7
AHEI score	47.1	46.5	47.7	47.9
Alcohol intake, g/d	5.8	5.6	11.8	9.7
Healthy lifestyle score, %§				
0	5	4	4	3
1	23	19	17	15
2	34	34	30	28
3	25	29	29	30
4	10	13	17	19
5	2	3	5	6
Mean	2.2	2.4	2.5	2.6

HPFS indicates Health Professionals' Follow-up Study; and NHS, Nurses' Health Study.

*Updated information throughout follow-up was used to calculate the means for continuous variables and percentage for categorical variables. All variables are age-standardized except age and person-years.

†The medications included aspirin, antihypertensives, and lipid-lowering medications; regular medication use was defined as use of ≥ 2 tablets per week or ≥ 2 times per week.

‡Among ever-smokers only.

§Healthy lifestyle score (range, 0–5) was defined as the number of the 5 healthy lifestyle factors: healthy body weight (body mass index [BMI], ≥ 18.5 and < 27.5 kg/m²), never smoking, light to moderate alcohol intake (> 0 and < 1 drink [14 g alcohol] per day for women, and > 0 and < 2 drink [28 g alcohol] per day for men), physically active (≥ 30 min/d of moderate to vigorous intensity activity), and high-quality diet (upper 40% of Alternate Healthy Eating Index [AHEI] score).

We calculated the hypothetical PARs³⁴ and 95% CIs³⁵ to estimate the proportion of premature deaths that could have been avoided if all participants in each cohort had adhered to the healthy lifestyle practices, assuming a causal relationship between lifestyle and mortality. To calculate the PARs, we used the multivariable pooled logistic regression models to calculate the relative risk of mortality by comparing participants who met the healthy criteria for all of the 5 lifestyle factors to the remaining participants.³⁶

The analyses were first conducted in each cohort separately. Because no appreciable difference was

detected by cohort (Table S1), we conducted pooled analysis using cohort-stratified Cox proportional hazards regression model. As secondary analyses, we further stratified by tertiles of duration of medication use (1–4, 5–12, and ≥ 13 years among medication users) and by group of medications (aspirin, antihypertensives, and lipid-lowering medications). To assess whether the influence of healthy lifestyle differs by age, we examined the associations separately among participants younger than 70 and those 70 years and older. We also stratified the analysis by the major indications

for use of the medications of interest, including hypertension, hyperlipidemia, myocardial infarction, stroke, angina, and diabetes mellitus.

RESULTS

In the 2 cohorts of 118 587 participants with a median of 26 years (2 818 177 person-years) of follow-up, we documented 35 195 deaths, of which 8259 were caused by CVD, 11 369 by cancer, and 15 567 by other causes. Table 1 shows the characteristics of participants according to medication use. Overall, 72% and 70% of all person-years in NHS and HPFS, respectively, were reported as medication users. Compared with nonusers, medication users were older, more likely to have a history of hypertension and hyperlipidemia, and a lower healthy lifestyle score.

All of the 5 individual lifestyle factors were significantly associated with all-cause mortality, and the associations were similar between medication users and nonusers (all *P* interaction >0.25) (Figure 1). When the 5 factors were analyzed collectively as a healthy lifestyle score, each unit increment in the score was associated with an HR for all-cause mortality of 0.82 (95% CI, 0.81–0.82) among medication users and 0.81 (95

CI, 0.79–0.83) among medication nonusers (*P* interaction=0.54) (Figure 2). Compared with individuals with a healthy lifestyle score of 0, those with a score of 5 had an HR for all-cause mortality of 0.38 (95% CI, 0.35–0.42) and 0.33 (95 CI, 0.27–0.40) among medication users and nonusers, respectively.

For cause-specific mortality, healthy lifestyle score was inversely associated with mortality of CVD, cancer, and other causes in both medication users and nonusers (Figures S2 through S4). The association for CVD mortality appeared to be stronger in medication nonusers (HR, 0.74; 95 CI, 0.69–0.78) than users (HR, 0.81; 95% CI, 0.79–0.82) (*P* interaction=0.01), whereas similar associations were found between the 2 groups for cancer mortality (users: HR, 0.83 [95% CI, 0.81–0.84]; nonusers: HR, 0.84 [95 CI, 0.81–0.87]; *P* interaction=0.49) and other mortality (users: HR, 0.82 [95% CI, 0.81–0.83]; nonusers: HR, 0.82 [95 CI, 0.78–0.85]; *P* interaction=0.94).

We then calculated the PAR of mortality associated with healthy lifestyle practice (Table 2). For all-cause mortality, similar PARs were observed among medication users and nonusers for each of the lifestyle factors. The combined PAR for all of the 5 healthy lifestyle factors was 38% (95% CI, 32%–42%) among medication users and 40% (95% CI, 29%–50%) among nonusers.

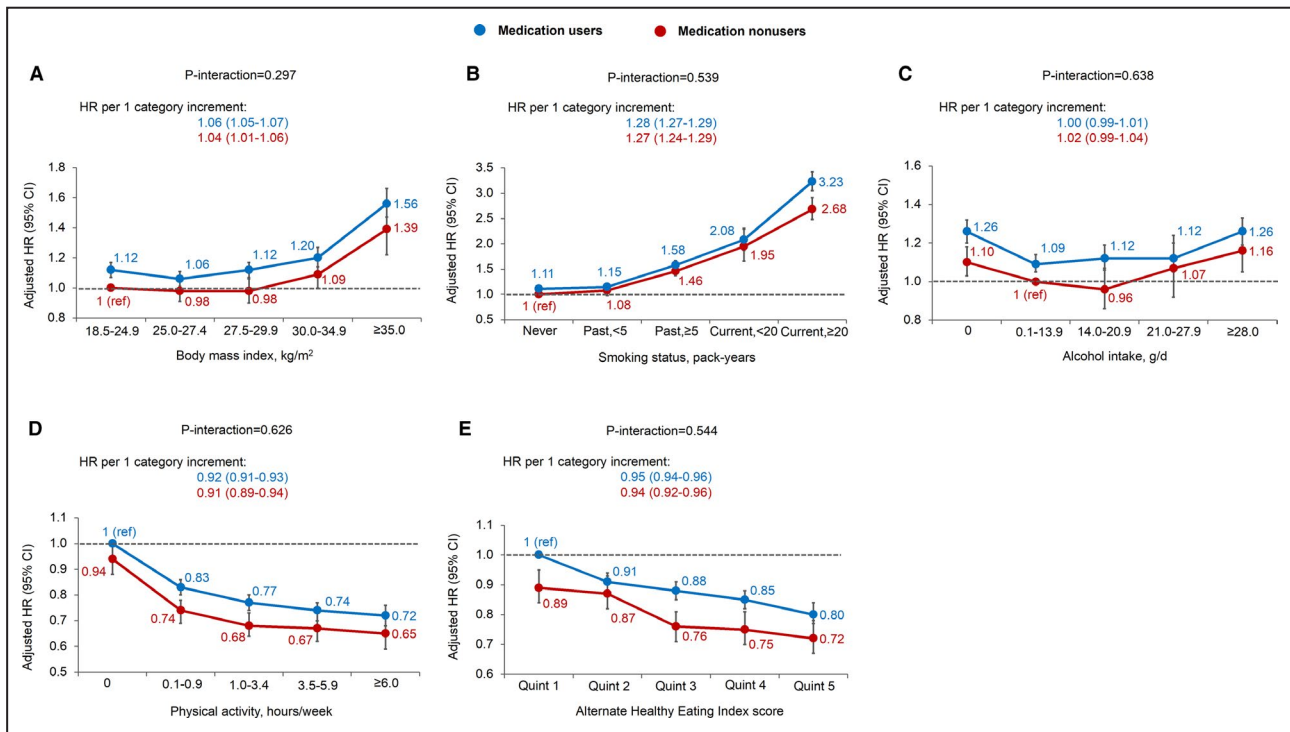


Figure 1. Associations of body mass index (A), smoking (B), alcohol intake (C), physical activity (D), and the Alternate Healthy Eating Index score (E) with all-cause mortality according to regular use of common preventive medications. Common preventive medications included aspirin, antihypertensives, and lipid-lowering medications; regular medication use was defined as use ≥2 tablets per week or ≥2 times per week. Multivariable Cox proportional hazards regression was used to calculate the hazard ratios (HRs) and 95% CIs while adjusting for age, calendar period, ethnicity, current multivitamin use, family history of diabetes mellitus, myocardial infarction, or cancer; menopausal status and hormone use (women only); and the other 4 of the 5 lifestyle factors. Error bars indicate 95% CIs.

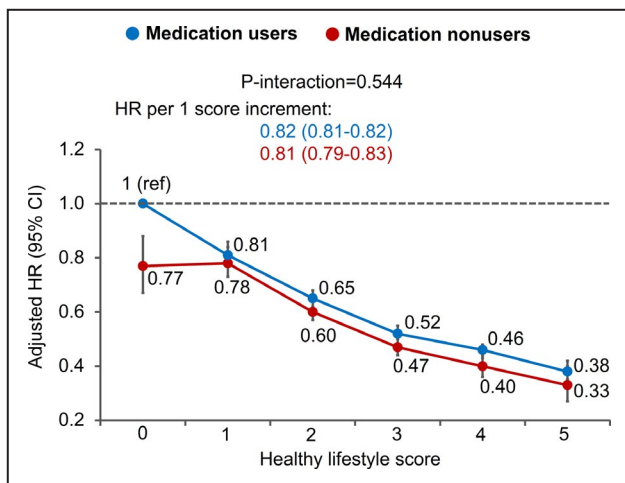


Figure 2. Association of healthy lifestyle score with all-cause mortality according to regular use of common preventive medications. Healthy lifestyle score (range, 0–5) was defined as the number of the 5 healthy lifestyle factors: healthy body weight (body mass index, ≥ 18.5 and < 27.5 kg/m²), never smoking, light to moderate alcohol intake (> 0 and < 1 drink [14 g alcohol] per day for women, > 0 and < 2 drink [28 g alcohol] per day for men), physical active (≥ 30 min/d of moderate to vigorous intensity activity), and high-quality diet (upper 40% of Alternate Healthy Eating Index score). Common preventive medications included aspirin, antihypertensives, and lipid-lowering medications; regular medication use was defined as use ≥ 2 tablets per week or ≥ 2 times per week. Multivariable Cox proportional hazards regression was used to calculate the hazard ratios (HRs) and 95% CIs while adjusting for age, calendar period, ethnicity, current multivitamin use, family history of diabetes mellitus, myocardial infarction, or cancer; and menopausal status and hormone use (women only). Error bars indicate 95% CIs.

For CVD mortality, the PAR was relatively lower among medication users (37%; 95% CI, 27%–46%) than nonusers (45%; 95% CI, 18%–66%). No appreciable difference between the 2 groups was found in the PAR for cancer mortality (users: 38% [95% CI, 28%–46%]; nonusers: 33% [95% CI, 14%–49%]) or for other mortality (users: 33% [95% CI, 25%–41%]; nonusers: 38% [95% CI, 20%–54%]).

We also assessed the PAR among medication users by duration of use and medication groups (Figure 3). A lower PAR was observed among medication users with a duration of ≥ 13 years than those with 1 to 4 and 5 to 12 years for all-cause mortality (31% versus 36% and 43%), CVD mortality (23% versus 43% and 46%), and other mortality (26% versus 40% and 34%). No substantial difference in the PAR was found among users of aspirin, antihypertensives, and lipid-lowering medications, with the estimates ranging from 30% to 38% for all-cause mortality, 24% to 38% for CVD mortality, 36% to 40% for cancer mortality, and 28% to 33% for other mortality. When stratified by age, the PAR was higher among medication users younger than 70 years (51%; 95% CI,

40%–61%) than users 70 years and older (35%; 95% CI, 29%–40%) (Table S2). When stratified by the common indications for use of these medications, we observed similar PARs among medication users who did (36%; 95% CI, 30%–42%) and did not (31%; 95% CI, 18%–43%) have the preexisting conditions (Table S3).

DISCUSSION

In 2 large prospective cohorts, we found that $\approx 40\%$ of total premature deaths in both medication users and nonusers can potentially be prevented by adoption of a healthy lifestyle characterized by never smoking, being physical active, eating a high-quality diet, consuming light to moderate alcohol, and maintaining a BMI ≥ 18.5 and < 27.5 kg/m². Similar estimates according to medication use were found for cancer mortality, whereas the estimate for CVD mortality tended to be higher in medication nonusers (45%) than users (37%). These findings indicate that healthy lifestyle may confer substantial benefit in preventing premature death, regardless of preventive medication use. Adherence to a healthy lifestyle remains important even among individuals regularly using preventive medications.

Common preventive medications, including aspirin, antihypertensives, and lipid-lowering medications, have established benefit mainly in reducing recurrent CVD^{6–8} and certain cancers (eg, aspirin for colorectal cancer¹³). However, a considerable increase in use of these medications for primary prevention of CVD has been documented.^{2,4,37} A recent study showed that a polypill containing anticoagulant aspirin, a cholesterol-lowering statin, and 2 antihypertensives reduced the risk of major cardiovascular events.³⁸ According to the 2017 National Health Interview Survey, 29 million people 40 years and older were taking an aspirin a day despite having no known CVD.³⁷ On the other hand, given the perceived challenges in lifestyle modification,³⁹ individuals who regularly take preventive medication may consider being certified healthy and thus have less incentive to adopt or sustain healthy lifestyle practices (health certificate effect), posing challenges for implementation of primary prevention among presumably high-risk populations.^{23,40} Moreover, there is little evidence regarding whether medication use modifies the health benefit of healthy lifestyle practices. Stamatakis et al⁴⁰ reported that physical activity protected against premature death to a similar extent among medication users and nonusers. Chiuve et al⁴¹ found that a substantial fraction of incident CVD is potentially preventable in both users and nonusers of lipid-lowering and antihypertensive medications. However, because the benefit of these medications is predominantly established

Table 2. Prevalence of Individual and Combined Healthy Lifestyle Factors and Corresponding PAR Estimates for All-Cause and Cause-Specific Mortality According to Regular Use of Common Preventive Medications*

Lifestyle	Medication Users		Medication Nonusers	
	Prevalence, %	PAR (95% CI), % [†]	Prevalence, %	PAR (95% CI), % [†]
All-cause mortality				
Never smoking	44	23 (22–24)	47	24 (21–27)
Physical activity of ≥30 min/d [‡]	24	11 (9–13)	27	10 (5–15)
Diet quality of upper 40% [§]	40	6 (4–7)	38	8 (4–12)
Light to moderate alcohol intake	65	5 (4–6)	63	4 (2–6)
BMI <27.5 kg/m ²	58	3 (2–4)	71	1 (–1 to 3)
All of the 5 healthy lifestyle factors	3	38 (32–42)	4	40 (29–50)
CVD mortality				
Never smoking	44	16 (14–19)	47	24 (17–31)
Physical activity of ≥30 min/d [‡]	24	13 (8–17)	27	5 (–7 to 17)
Diet quality of upper 40% [§]	40	1 (–2 to 4)	38	13 (4–22)
Light to moderate alcohol intake	65	8 (6–9)	63	4 (–2 to 10)
BMI <27.5 kg/m ²	58	7 (5–9)	71	12 (7–17)
All of the 5 healthy lifestyle factors	3	37 (27–46)	4	45 (18–66)
Cancer mortality				
Never smoking	44	29 (27–31)	47	26 (21–30)
Physical activity of ≥30 min/d [‡]	24	5 (1–9)	27	6 (–2 to 13)
Diet quality of upper 40% [§]	40	4 (2–7)	38	5 (–1 to 10)
Light to moderate alcohol intake	65	4 (2–5)	63	0 (–5 to 5)
BMI <27.5 kg/m ²	58	2 (0–4)	71	1 (–2 to 4)
All of the 5 healthy lifestyle factors	3	38 (28–46)	4	33 (14–49)
Other mortality				
Never smoking	44	20 (18–22)	47	19 (14–24)
Physical activity of ≥30 min/d [‡]	24	10 (6–13)	27	14 (7–22)
Diet quality of upper 40% [§]	40	8 (6–10)	38	8 (2–13)
Light to moderate alcohol intake	65	5 (4–7)	63	8 (5–12)
BMI <27.5 kg/m ²	58	1 (0–3)	71	–8 (–14 to –1)
All of the 5 healthy lifestyle factors	3	33 (25–41)	4	38 (20–54)

BMI indicates body mass index; and CVD, cardiovascular disease.

*The medications included aspirin, antihypertensives, and lipid-lowering medications; regular medication use was defined as use ≥2 tablets per week or ≥2 times per week.

[†]Population-attributable risks (PARs) and 95% CIs were calculated while adjusting for age, calendar period, ethnicity, current multivitamin use, family history of diabetes mellitus, myocardial infarction, or cancer; menopausal status and hormone use (women only); and the other 4 of the 5 lifestyle factors (except “all of the 5 healthy lifestyle factors”).

[‡]Physical activity was of moderate to vigorous intensity requiring the expenditure of ≥3 metabolic equivalents per hour.

[§]Diet quality was based on the Alternate Healthy Eating Index score.

^{||}Light to moderate alcohol intake was defined as >0 and <1 drink (14 g alcohol) per day for women, and >0 and <2 drink (28 g alcohol) per day for men.

for CVD and largely unclear for cancer and other diseases, it remains an open question how overall health is influenced by healthy lifestyles among users and nonusers of medications.

The 5 factors examined in the current study are among the most prevalent lifestyle factors that have

been shown to confer a substantial benefit in reducing mortality. Smoking has been the primary cause for nearly 80% of deaths from CVD and chronic obstruction pulmonary disease and at least 30% of cancer deaths.⁴² Heavy alcohol consumption has been significantly associated with increased risk of

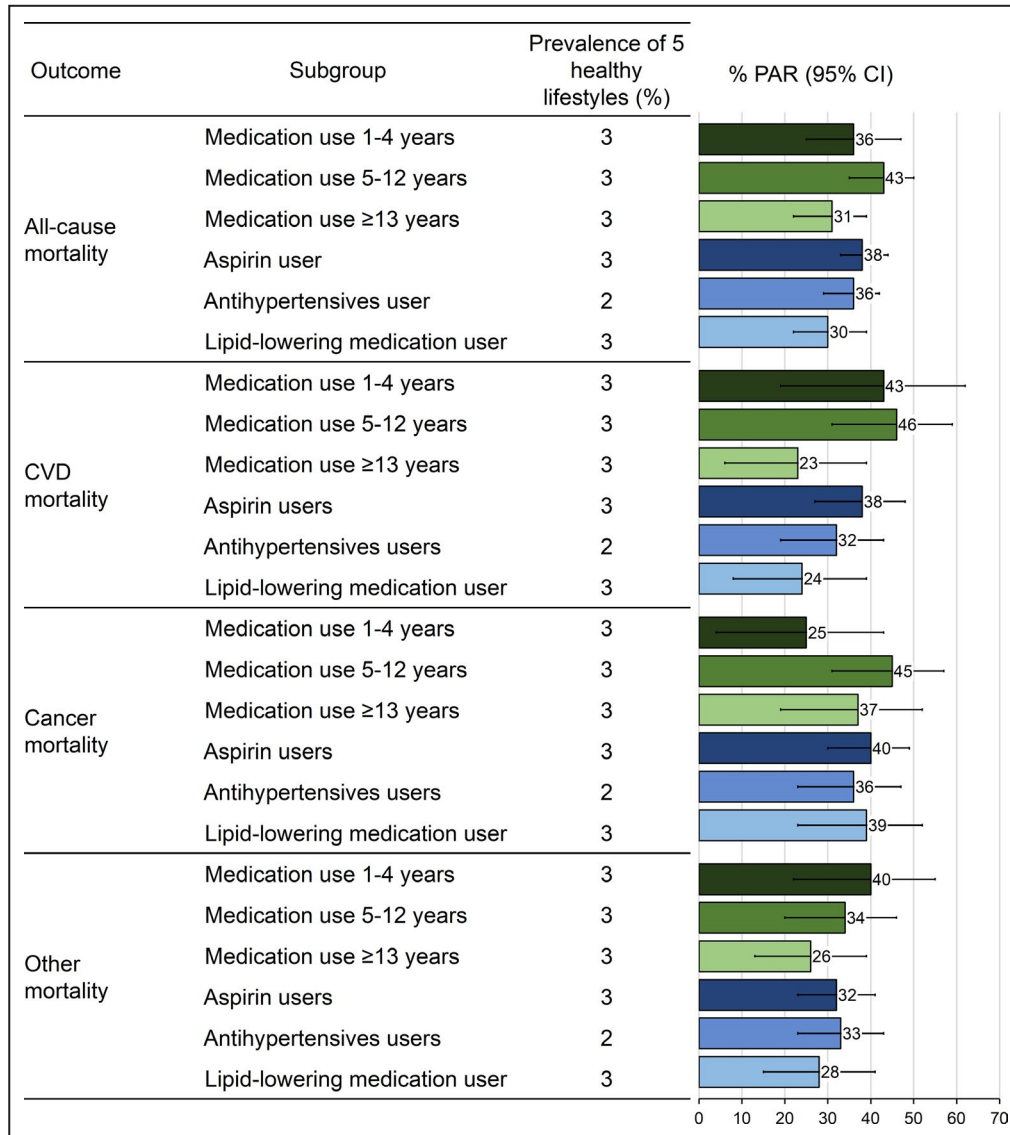


Figure 3. Prevalence and population-attributable risk (PAR) (95% CI) estimates of the 5 healthy lifestyle factors for all-cause and cause-specific mortality among medication users by use duration and medication type. The 5 healthy lifestyles included healthy body weight (body mass index, ≥ 18.5 and < 27.5 kg/m²), never smoking, light to moderate alcohol intake (> 0 and < 1 drink [14 g alcohol] per day for women, > 0 and < 2 drink [28 g alcohol] per day for men), physical active (≥ 30 min/d of moderate to vigorous intensity activity), and high-quality diet (upper 40% of Alternate Healthy Eating Index score). Regular medication use was defined as use ≥ 2 tablets per week or ≥ 2 times per week. PARs and 95% CIs were calculated while adjusting for age, calendar period, ethnicity, current multivitamin use, family history of diabetes mellitus, myocardial infarction, or cancer; and menopausal status and hormone use (women only). Error bars indicate 95% CIs. CVD indicates cardiovascular disease.

all-cause death by 11% and cancer death by 27%.⁴³ Also, risk of all-cause mortality has been increased by 20% to 40% among overweight people and by 2 to 3 times among those with obesity.⁴⁴ In contrast, physical activity and diet quality in accordance with recommendations has a considerable benefit in reducing mortality of all causes, CVD, and cancer.^{45,46} The potential pathways through which healthy lifestyle reduces mortality risk include reduced chronic

inflammation,²⁰ enhanced artery endothelial function,²¹ and improved lipid profiles and insulin sensitivity.^{20,22} Although the benefit of a healthy lifestyle among high-risk or diseased individuals has been reported,⁴⁷⁻⁵⁰ it remains to be determined whether a healthy lifestyle confers a similar benefit among regular users and nonusers of preventive medications. In the current study, we found a similar association between a healthy lifestyle and mortality. Our findings

reinforce the indispensable role of lifestyle modification in preventing premature death, irrespective of medication use.

Our findings have important clinical and public health implications. First, although pharmacological therapy and a healthy lifestyle share certain mechanisms, among individuals regularly using preventive medications, ~40% of premature death cases are still potentially preventable through healthy lifestyle, and this benefit appeared not to vary by preexisting indications of the medication use. Our finding provides supporting evidence for combining lifestyle modification (“lifestyle therapy”⁵¹) and pharmacological therapy to conquer the increasing prevalence of chronic diseases. Second, we observed a different association of healthy lifestyle between medication users and nonusers only with CVD mortality, but not with cancer mortality or other mortality. This finding is in line with the primary benefit of these medications against CVD and suggests that lifestyle factors may reduce mortality attributable to causes other than CVD through mechanisms independent of those by the preventive medications.

Study Strengths and Limitations

Our study has several strengths, including the large sample size, long-term follow-up of up to 28 years, detailed and repeated assessment of medication use, and rigorous adjustment for potential confounding factors. Several limitations should also be noted. First, we applied a less stringent threshold to define healthy lifestyle (eg, the upper limit for BMI was set at 27.5 rather than 25, as commonly used to define normal body weight) to preserve statistical power because even with the current threshold, only 3% to 4% of participants met the healthy criteria for all of the 5 lifestyle factors. Therefore, the PARs for healthy lifestyles may have been underestimated. Second, our medication, lifestyle, and anthropometric (eg, height and weight) data were all based on self-report and thus subject to measurement error. However, the accuracy and stability of these self-reported data have been well documented in our cohorts,^{52–54} as well as other study populations.⁵⁵ Third, our study participants were all health professionals and predominantly white, thereby limiting our ability to stratify the analyses by race and reducing the generalizability of our findings. However, it is unlikely that the biological effect of lifestyle would have a substantial difference between health professionals and the general population. Moreover, given the higher health consciousness and better lifestyle profiles of health professionals, we may have underestimated the benefit of lifestyles on the population scale.

CONCLUSIONS

A healthy lifestyle may confer similar substantial benefit in preventing premature death in regular users and nonusers of preventive medications. Adherence to a healthy lifestyle is still important even among individuals regularly using preventive medications.

ARTICLE INFORMATION

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Disclosures

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Supplementary Materials

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SUPPLEMENTAL MATERIAL

Data S1.

Detailed Methods. Assessment and Statistical Analysis

Assessment of lifestyle and covariates

Height was assessed at baseline. Body weight and cigarette smoking were assessed every 2 years. We also asked participants to recall their body weight at age 18 years in the NHS and 21 years in the HPFS. BMI was calculated as weight in kilograms divided by the square of height in meter (kg/m^2). We assessed physical activity biennially by a validated questionnaire⁵⁶ and calculated the total hours per week for moderate-to-vigorous intensity activity (including brisk walking) that requires the expenditure of at least 3 metabolic equivalents per hour. Diet was assessed every 4 years with a validated food frequency questionnaire^{26, 27} by inquiring the usual frequency of consumption for various foods during the previous year. Nutrient intake was calculated by multiplying the nutrient content of each food by the frequency of intake and then summing across all food items. Nutrient intakes were adjusted for total energy intake using the residual method.⁵⁷ Diet quality was assessed with the Alternate Healthy Eating Index-2010 (AHEI-2010) score,²⁹ which was designed to target food choices and macronutrient sources associated with reduced chronic disease risk. AHEI-2010 score was calculated based on the consumption of vegetables, fruits, whole grains, sugar-sweetened beverages, fruit juice, nuts, legumes, other vegetable proteins, red and processed meat, trans-isomers of fatty acids, n-3 fatty acids, polyunsaturated fatty acids, and sodium.²⁹ The validity of these lifestyle measures have been documented previously in our cohorts.^{26, 27, 52, 53, 56, 58-60}

We also collected detailed information of potential confounders, including age, ethnicity, current multivitamin use, family history of diabetes, cancer and myocardial infarction, and menopausal status and postmenopausal hormone use (women only).

Assessment of medication use

We considered all medications of these 3 groups on the US market during the study period. Specifically, aspirin included standard-dose and baby aspirin; antihypertensives included thiazide diuretic, furosemide-like diuretics, beta blockers, calcium channel blockers, angiotensin converting enzyme (ACE) inhibitor, potassium, angiotensin receptor blockers (ARB), and other antihypertensives; lipid-lowering medications included lovastatin, simvastatin, rosuvastatin, pravastatin, atorvastatin, fluvastatin, and other lipid-lowering medications.

Statistical analysis

We calculated cumulative average levels of physical activity, AHEI score, and alcohol intake from our repeated questionnaires. For example, in the NHS, physical activity data collected on the 1988 questionnaire was used to assess risk of death that occurred between 1988 and 1990, the average of the 1988 and 1990 physical activity measurements was used for mortality between 1990 and 1992, the average of the 1988, 1990 and 1992 measurements was used for mortality between 1992 and 1994, and so on. For BMI, to minimize reverse causality resulting from weight loss caused by preexisting diseases, we used the maximum BMI reported throughout the follow-up.³² For example, in the NHS we used the maximum value of BMI reported for age 18 years and between the cohort enrollment in 1976 and 1988 to associate mortality between 1988 and 1990, and the maximum BMI for age 18 and from 1976 to 1990 for mortality between 1990 and 1992, and so on.

The analyses were conducted using SAS version 9.4 (SAS Institute, Cary, NC). All statistical tests were two sided and $P < 0.05$ was considered statistically significant.

Figure S1. Flowchart of participants' selection in the Nurses' Health Study and Health Professionals Follow-up Study.

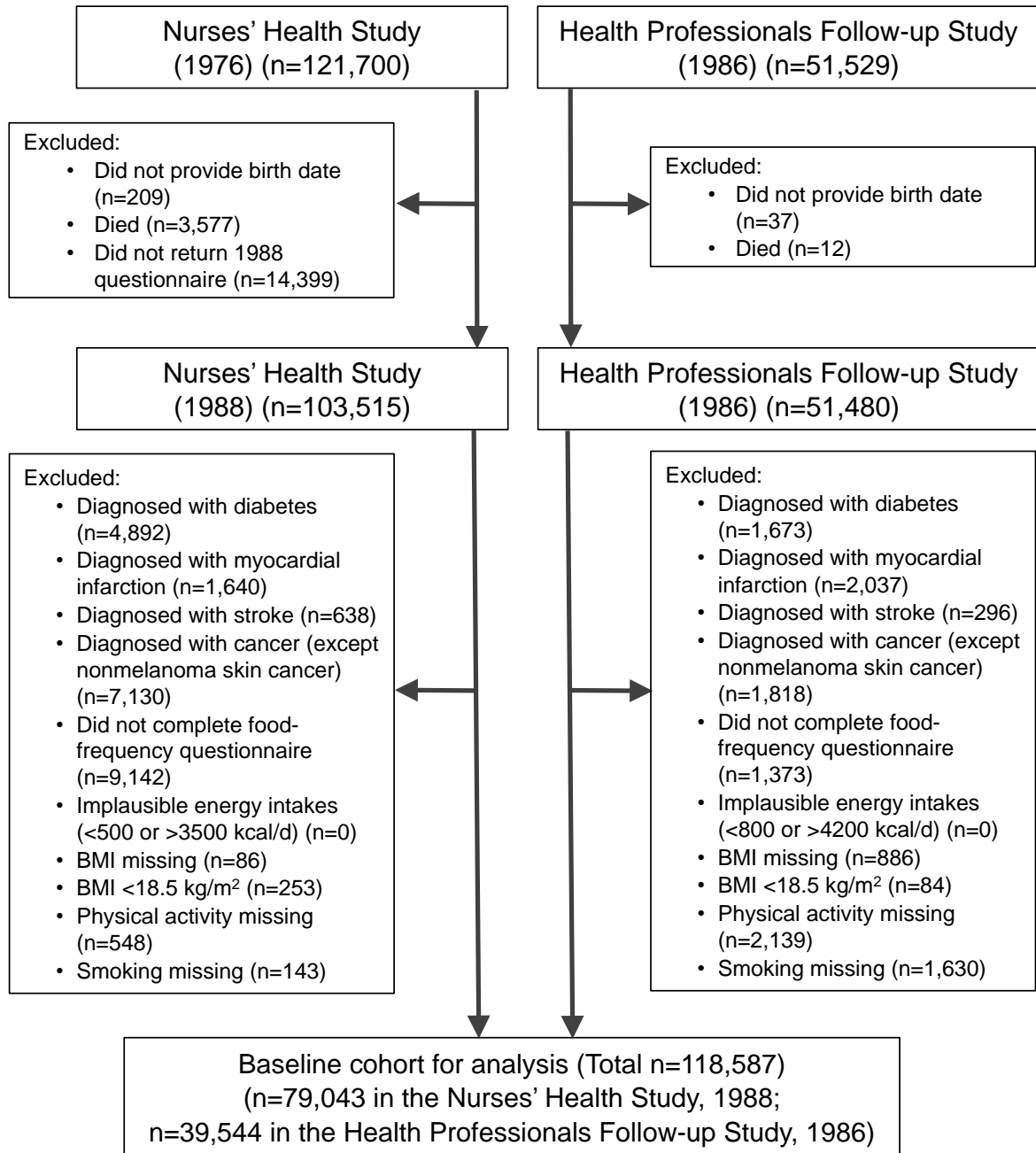
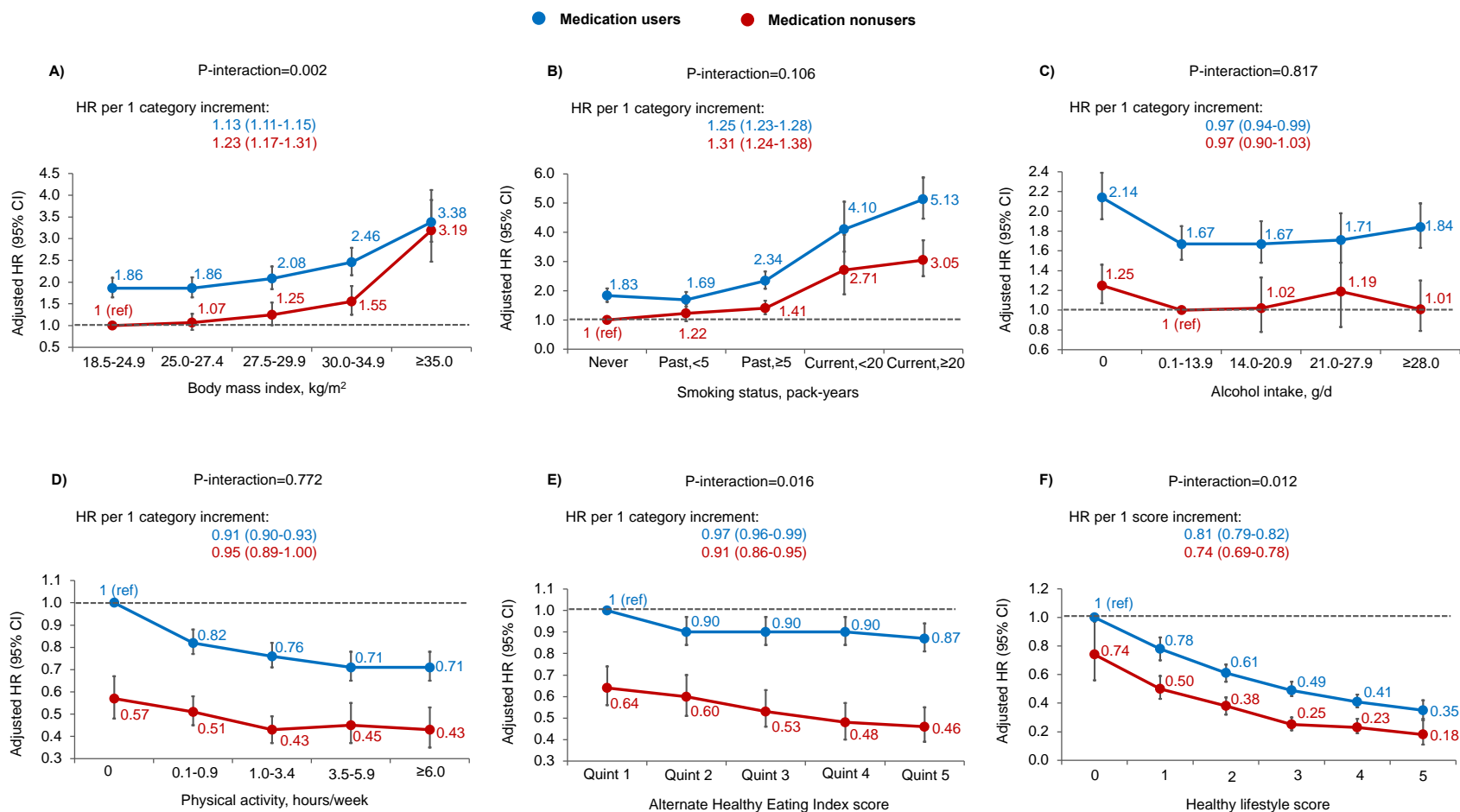


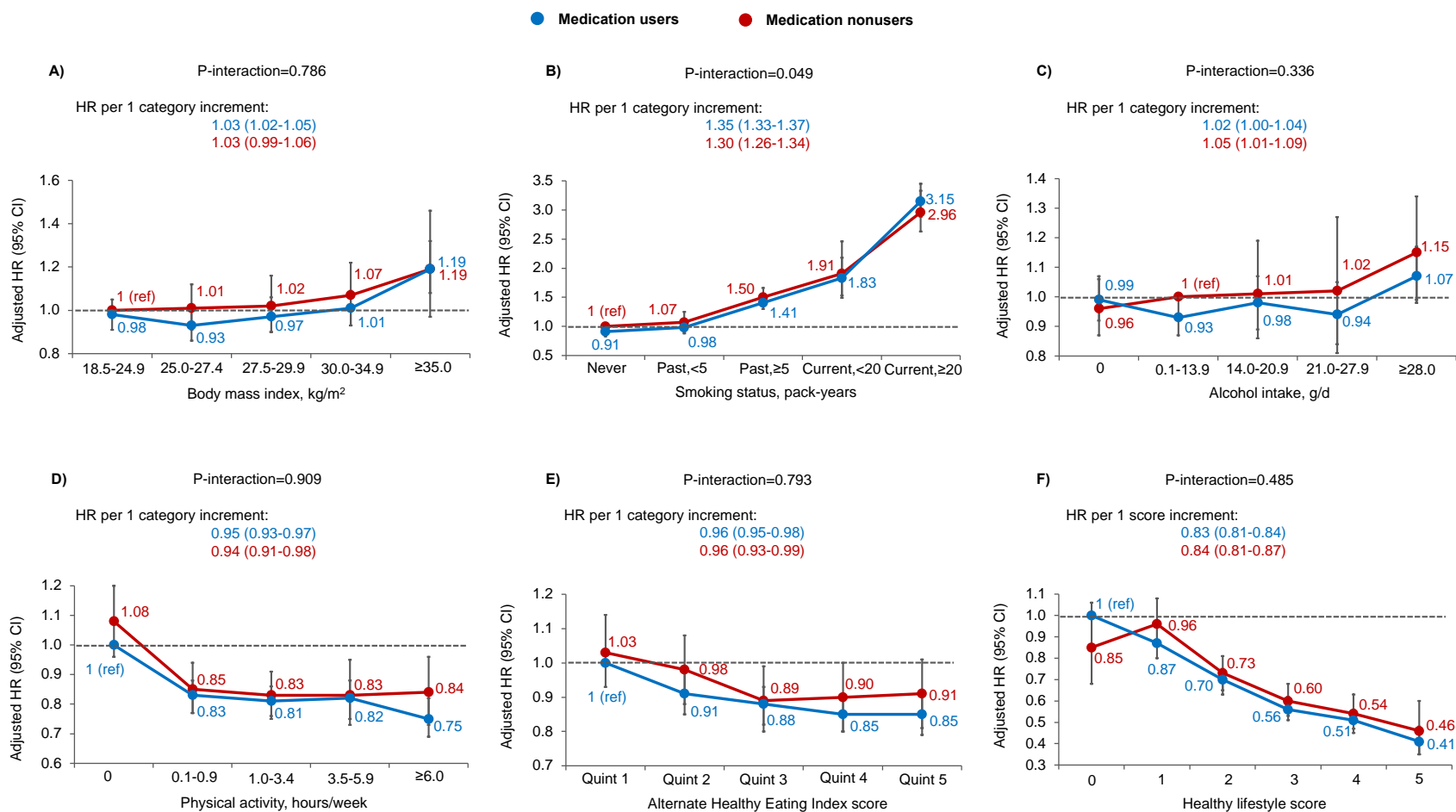
Figure S2. Associations of body mass index (panel A), smoking (panel B), alcohol intake (panel C), physical activity (panel D), the Alternate Healthy Eating Index score (panel E), and healthy lifestyle score (panel F) with cardiovascular disease (CVD) mortality according to regular use of common preventive medications.



Healthy lifestyle score (range, 0-5) was defined as the number of the 5 healthy lifestyle factors: healthy body weight (body mass index, ≥18.5 and <27.5 kg/m²), never smoking, light-to-moderate alcohol intake (>0 and <1 drink [14g alcohol]/d for women, >0 and <2 drink [28g alcohol]/d for men), physical active (≥30 min/d of moderate-to-vigorous intensity activity), and high quality diet (upper 40% of Alternate Healthy Eating Index

score). Common preventive medications included aspirin, antihypertensives, and lipid-lowering medications; regular medication use was defined as use ≥ 2 tablets/week or ≥ 2 times/week. Multivariable Cox proportional hazards regression was used to calculate the hazard ratios (HRs) and 95% confidence intervals (CIs) while adjusting for age, calendar period, ethnicity, current multivitamin use, family history of diabetes, myocardial infarction, or cancer, menopausal status and hormone use (women only), and the other 4 of the 5 lifestyle factors (except healthy lifestyle score). Error bars indicate 95% CIs.

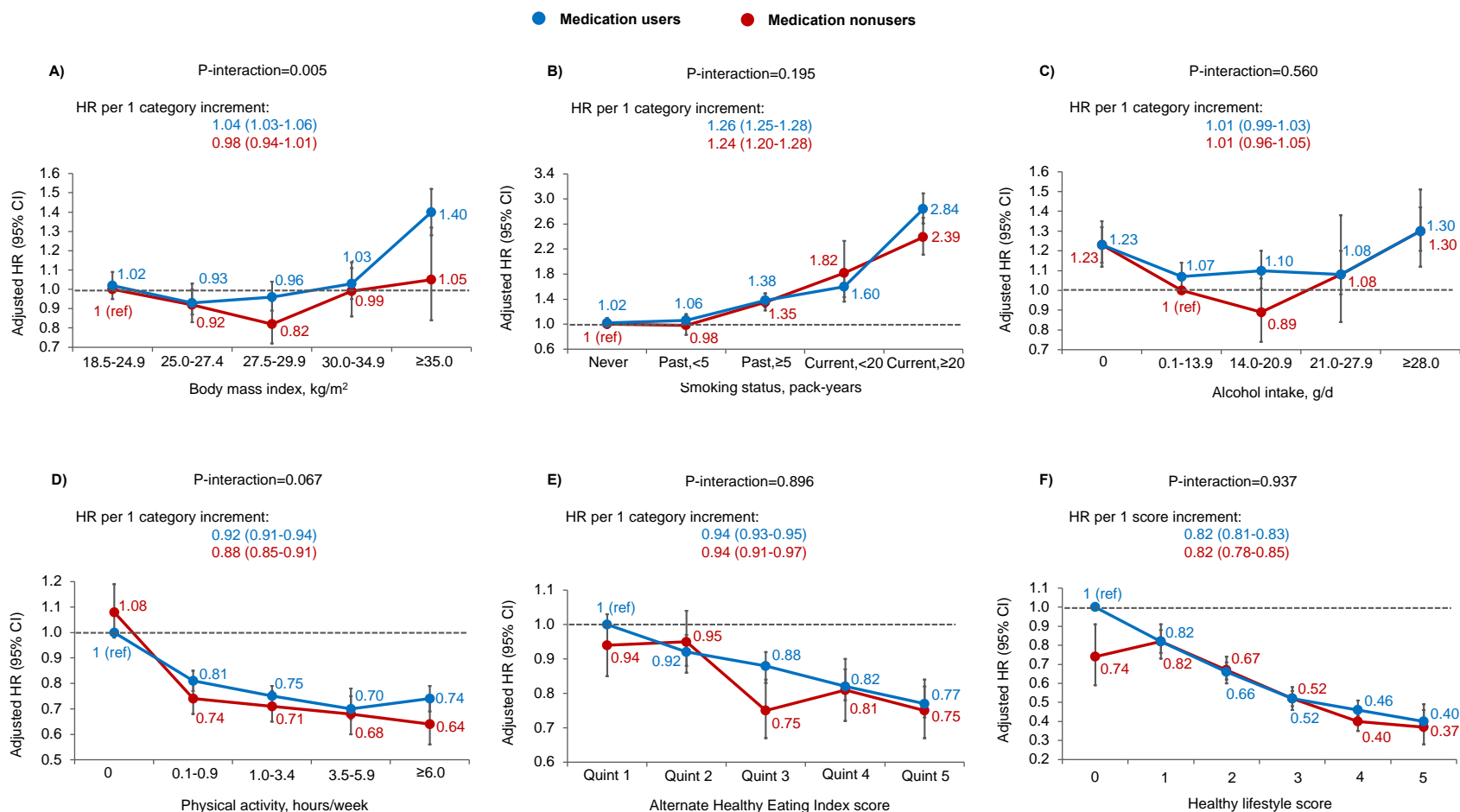
Figure S3. Associations of body mass index (panel A), smoking (panel B), alcohol intake (panel C), physical activity (panel D), the Alternate Healthy Eating Index score (panel E), and healthy lifestyle score (panel F) with cancer mortality according to regular use of common preventive medications.



Healthy lifestyle score (range, 0-5) was defined as the number of the 5 healthy lifestyle factors: healthy body weight (body mass index, ≥18.5 and <27.5 kg/m²), never smoking, light-to-moderate alcohol intake (>0 and <1 drink [14g alcohol]/d for women, >0 and <2 drink [28g alcohol]/d for men), physical active (≥30 min/d of moderate-to-vigorous intensity activity), and high quality diet (upper 40% of Alternate Healthy Eating Index)

score). Common preventive medications included aspirin, antihypertensives, and lipid-lowering medications; regular medication use was defined as use ≥ 2 tablets/week or ≥ 2 times/week. Multivariable Cox proportional hazards regression was used to calculate the hazard ratios (HRs) and 95% confidence intervals (CIs) while adjusting for age, calendar period, ethnicity, current multivitamin use, family history of diabetes, myocardial infarction, or cancer, menopausal status and hormone use (women only), and the other 4 of the 5 lifestyle factors (except healthy lifestyle score). Error bars indicate 95% CIs.

Figure S4. Associations of body mass index (panel A), smoking (panel B), alcohol intake (panel C), physical activity (panel D), the Alternate Healthy Eating Index score (panel E), and healthy lifestyle score (panel F) with mortality due to other causes than cardiovascular diseases (CVD) and cancer according to regular use of common preventive medications.



Healthy lifestyle score (range, 0-5) was defined as the number of the 5 healthy lifestyle factors: healthy body weight (body mass index, ≥18.5 and <27.5 kg/m²), never smoking, light-to-moderate alcohol intake (>0 and <1 drink [14g alcohol]/d for women, >0 and <2 drink [28g alcohol]/d for men), physical active (≥30 min/d of moderate-to-vigorous intensity activity), and high quality diet (upper 40% of Alternate Healthy Eating Index)

score). Common preventive medications included aspirin, antihypertensives, and lipid-lowering medications; regular medication use was defined as use ≥ 2 tablets/week or ≥ 2 times/week. Multivariable Cox proportional hazards regression was used to calculate the hazard ratios (HRs) and 95% confidence intervals (CIs) while adjusting for age, calendar period, ethnicity, current multivitamin use, family history of diabetes, myocardial infarction, or cancer, menopausal status and hormone use (women only), and the other 4 of the 5 lifestyle factors (except healthy lifestyle score). Error bars indicate 95% CIs.

Table S1. Associations of individual lifestyle factors and healthy lifestyle score with all-cause mortality according to regular use of common preventive medications* in women (NHS) and men (HPFS).

Lifestyle factors	HR (95% CI) [†]			
	Women (NHS)		Men (HPFS)	
	Medication users	Medication nonusers	Medication users	Medication nonusers
BMI, kg/m ²				
18.5-24.9	1.11 (1.04-1.17)	1.00 (reference)	1.14 (1.05-1.23)	1.00 (reference)
25.0-27.4	1.04 (0.98-1.11)	0.99 (0.90-1.08)	1.10 (1.02-1.19)	0.98 (0.89-1.09)
27.5-29.5	1.07 (1.00-1.14)	1.00 (0.89-1.12)	1.21 (1.12-1.31)	0.98 (0.87-1.12)
30.0-34.9	1.15 (1.08-1.22)	1.07 (0.96-1.19)	1.35 (1.23-1.47)	1.16 (1.00-1.34)
≥35.0	1.52 (1.42-1.63)	1.41 (1.22-1.64)	1.70 (1.51-1.92)	1.34 (1.03-1.75)
P-interaction	0.657		0.183	
Smoking, pack-years				
Never	1.10 (1.03-1.18)	1.00 (reference)	1.14 (1.05-1.23)	1.00 (reference)
Past smoker, <5	1.12 (1.03-1.22)	1.10 (0.95-1.27)	1.17 (1.07-1.29)	1.04 (0.91-1.20)
Past smoker, ≥5	1.70 (1.58-1.81)	1.65 (1.51-1.80)	1.44 (1.33-1.56)	1.27 (1.15-1.40)
Current smoker, <20	2.12 (1.85-2.43)	2.13 (1.75-2.59)	2.01 (1.70-2.36)	1.64 (1.23-2.17)
Current smoker, ≥20	3.35 (3.11-3.60)	2.85 (2.58-3.14)	3.00 (2.72-3.30)	2.37 (2.05-2.73)
P-interaction	0.628		0.750	
Alcohol intake, g/d				
0	1.21 (1.14-1.29)	1.08 (1.00-1.17)	1.36 (1.26-1.47)	1.13 (1.01-1.25)
0.1-13.9	1.05 (1.00-1.11)	1.00 (reference)	1.15 (1.08-1.23)	1.00 (reference)
14-20.9	1.11 (1.03-1.20)	0.90 (0.77-1.04)	1.15 (1.06-1.25)	1.04 (0.89-1.21)
21-27.9	1.12 (1.02-1.23)	1.03 (0.82-1.28)	1.15 (1.04-1.26)	1.12 (0.91-1.37)
≥28	1.30 (1.20-1.41)	1.29 (1.11-1.49)	1.30 (1.20-1.40)	1.14 (1.00-1.30)
P-interaction	0.505		0.483	
Physical activity, h/wk [‡]				
0	1.00 (reference)	0.95 (0.87-1.04)	1.00 (reference)	0.93 (0.83-1.04)
0.1-0.9	0.79 (0.76-0.83)	0.73 (0.68-0.79)	0.92 (0.86-0.97)	0.74 (0.66-0.81)
1.0-3.4	0.74 (0.70-0.77)	0.66 (0.61-0.71)	0.82 (0.78-0.87)	0.72 (0.65-0.79)
3.5-5.9	0.71 (0.66-0.75)	0.66 (0.59-0.74)	0.79 (0.73-0.84)	0.70 (0.62-0.79)
≥6	0.71 (0.66-0.76)	0.66 (0.57-0.75)	0.75 (0.70-0.80)	0.66 (0.58-0.74)
P-interaction	0.750		0.981	
Diet quality [§]				
Quint 1	1.00 (reference)	0.93 (0.86-1.00)	1.00 (reference)	0.84 (0.76-0.93)
Quint 2	0.91 (0.87-0.95)	0.89 (0.82-0.96)	0.90 (0.85-0.95)	0.84 (0.76-0.93)
Quint 3	0.87 (0.83-0.91)	0.74 (0.67-0.81)	0.89 (0.84-0.94)	0.78 (0.71-0.87)
Quint 4	0.84 (0.80-0.88)	0.78 (0.71-0.85)	0.86 (0.81-0.91)	0.72 (0.65-0.80)
Quint 5	0.77 (0.73-0.81)	0.72 (0.66-0.79)	0.85 (0.80-0.90)	0.73 (0.65-0.81)
P-interaction	0.649		0.638	
Healthy lifestyle score				
0	1.00 (reference)	0.83 (0.70-0.97)	1.00 (reference)	0.66 (0.52-0.84)
1	0.80 (0.75-0.85)	0.79 (0.72-0.86)	0.83 (0.76-0.91)	0.77 (0.68-0.87)
2	0.64 (0.60-0.68)	0.62 (0.57-0.67)	0.68 (0.62-0.74)	0.59 (0.53-0.66)
3	0.50 (0.47-0.53)	0.46 (0.41-0.50)	0.56 (0.51-0.61)	0.50 (0.45-0.56)
4	0.42 (0.39-0.45)	0.37 (0.33-0.43)	0.50 (0.46-0.55)	0.43 (0.37-0.49)
5	0.35 (0.30-0.40)	0.31 (0.23-0.42)	0.42 (0.37-0.47)	0.35 (0.28-0.44)

P-interaction	0.471		0.808	
% PAR of healthy lifestyle score of 5	44 (36-51)	47 (29-61)	30 (23-37)	36 (21-49)

HR, hazard ratio; CI, confidence interval; BMI, body mass index; PAR, population-attributable risk.

* Common preventive medications included aspirin, antihypertensives, and lipid-lowering medications; regular medication use was defined as use ≥ 2 tablets/week or ≥ 2 times/week.

† HRs and 95% CIs were calculated adjusting for age, calendar period, ethnicity, current multivitamin use, family history of diabetes, myocardial infarction, or cancer, menopausal status and hormone use (women only), and the other 4 of the 5 lifestyle factors (except healthy lifestyle score).

‡ Physical activity was of moderate-to-vigorous intensity requiring the expenditure of ≥ 3 metabolic equivalents per hour.

§ Diet quality was based on Alternate Healthy Eating Index (AHEI) score.

Table S2. Associations of individual lifestyle factors and healthy lifestyle score with all-cause mortality according to regular use of common preventive medications* in participants aged <70 and ≥70 years.

Lifestyle factors	HR (95% CI) [†]			
	<70 years old		≥70 years old	
	Medication users	Medication nonusers	Medication users	Medication nonusers
BMI, kg/m ²				
18.5-24.9	1.10 (1.01-1.19)	1.00 (reference)	1.14 (1.07-1.21)	1.00 (reference)
25.0-27.4	1.01 (0.92-1.10)	0.91 (0.82-1.01)	1.09 (1.02-1.16)	1.02 (0.93-1.11)
27.5-29.5	1.07 (0.98-1.18)	0.96 (0.85-1.09)	1.14 (1.07-1.22)	0.99 (0.89-1.11)
30.0-34.9	1.14 (1.04-1.24)	1.04 (0.92-1.19)	1.24 (1.16-1.32)	1.11 (0.98-1.24)
≥35.0	1.50 (1.35-1.66)	1.43 (1.20-1.71)	1.59 (1.48-1.71)	1.28 (1.06-1.55)
P-interaction	0.537		0.262	
Smoking, pack-years				
Never	1.04 (0.95-1.14)	1.00 (reference)	1.12 (1.05-1.19)	1.00 (reference)
Past smoker, <5	1.17 (1.04-1.32)	1.11 (0.95-1.30)	1.14 (1.05-1.23)	1.07 (0.94-1.21)
Past smoker, ≥5	1.63 (1.49-1.77)	1.49 (1.34-1.65)	1.56 (1.46-1.67)	1.45 (1.33-1.58)
Current smoker, <20	2.47 (2.08-2.94)	2.09 (1.67-2.62)	1.90 (1.66-2.16)	1.84 (1.46-2.32)
Current smoker, ≥20	3.51 (3.20-3.86)	2.97 (2.65-3.32)	3.08 (2.86-3.31)	2.31 (2.05-2.60)
P-interaction	0.055		0.135	
Alcohol intake, g/d				
0	1.36 (1.25-1.47)	1.18 (1.07-1.30)	1.22 (1.15-1.29)	1.04 (0.95-1.13)
0.1-13.9	1.09 (1.02-1.17)	1.00 (reference)	1.08 (1.02-1.14)	1.00 (reference)
14-20.9	1.12 (1.00-1.26)	1.09 (0.93-1.28)	1.11 (1.04-1.18)	0.86 (0.74-1.00)
21-27.9	1.11 (0.97-1.28)	1.00 (0.79-1.26)	1.11 (1.02-1.20)	1.11 (0.91-1.35)
≥28	1.32 (1.19-1.46)	1.25 (1.08-1.45)	1.23 (1.15-1.32)	1.07 (0.94-1.22)
P-interaction	0.496		0.989	
Physical activity, h/wk [‡]				
0	1.00 (reference)	0.83 (0.74-0.92)	1.00 (reference)	0.97 (0.88-1.06)
0.1-0.9	0.73 (0.67-0.78)	0.64 (0.58-0.70)	0.86 (0.83-0.90)	0.77 (0.71-0.83)
1.0-3.4	0.65 (0.60-0.70)	0.63 (0.57-0.69)	0.80 (0.77-0.84)	0.69 (0.64-0.74)
3.5-5.9	0.63 (0.57-0.70)	0.59 (0.51-0.67)	0.77 (0.73-0.81)	0.70 (0.63-0.78)
≥6	0.59 (0.53-0.66)	0.61 (0.53-0.70)	0.75 (0.71-0.79)	0.64 (0.57-0.71)
P-interaction	0.011		0.141	
Diet quality [§]				
Quint 1	1.00 (reference)	0.92 (0.83-1.01)	1.00 (reference)	0.85 (0.78-0.93)
Quint 2	0.88 (0.82-0.95)	0.87 (0.78-0.96)	0.91 (0.87-0.95)	0.87 (0.79-0.94)
Quint 3	0.88 (0.81-0.95)	0.75 (0.67-0.83)	0.88 (0.84-0.92)	0.76 (0.70-0.83)
Quint 4	0.80 (0.74-0.87)	0.74 (0.66-0.83)	0.86 (0.82-0.89)	0.76 (0.70-0.83)
Quint 5	0.83 (0.76-0.91)	0.73 (0.65-0.82)	0.80 (0.76-0.83)	0.72 (0.66-0.79)
P-interaction	0.399		0.713	
Healthy lifestyle score				
0	1.00 (reference)	0.87 (0.71-1.06)	1.00 (reference)	0.64 (0.53-0.78)
1	0.84 (0.75-0.93)	0.76 (0.67-0.86)	0.81 (0.76-0.86)	0.77 (0.70-0.84)
2	0.61 (0.55-0.68)	0.58 (0.52-0.65)	0.67 (0.63-0.70)	0.60 (0.56-0.65)
3	0.46 (0.41-0.51)	0.42 (0.37-0.48)	0.54 (0.51-0.57)	0.50 (0.46-0.54)
4	0.40 (0.35-0.45)	0.35 (0.30-0.42)	0.47 (0.44-0.50)	0.42 (0.37-0.47)
5	0.28 (0.22-0.36)	0.32 (0.24-0.43)	0.41 (0.37-0.45)	0.33 (0.26-0.42)

P-interaction	0.566		0.523	
% PAR of healthy lifestyle score of 5	51 (40-61)	37 (18-53)	35 (29-40)	41 (26-54)

HR, hazard ratio; CI, confidence interval; BMI, body mass index; PAR, population-attributable risk.

* Common preventive medications included aspirin, antihypertensives, and lipid-lowering medications; regular medication use was defined as use ≥ 2 tablets/week or ≥ 2 times/week.

† HRs and 95% CIs were calculated adjusting for age, calendar period, ethnicity, current multivitamin use, family history of diabetes, myocardial infarction, or cancer, menopausal status and hormone use (women only), and the other 4 of the 5 lifestyle factors (except healthy lifestyle score).

‡ Physical activity was of moderate-to-vigorous intensity requiring the expenditure of ≥ 3 metabolic equivalents per hour.

§ Diet quality was based on Alternate Healthy Eating Index (AHEI) score.

Table S3. Associations of individual lifestyle factors and healthy lifestyle score with all-cause mortality according to regular use of common preventive medications* in participants having and not having major medication indications†

Lifestyle factors	HR (95% CI)‡			
	Having indications		Not having indications	
	Medication users	Medication nonusers	Medication users	Medication nonusers
BMI, kg/m ²				
18.5-24.9	1.12 (1.04-1.19)	1.00 (reference)	1.06 (0.98-1.15)	1.00 (reference)
25.0-27.4	1.06 (0.99-1.13)	0.98 (0.89-1.09)	0.99 (0.91-1.08)	0.95 (0.87-1.04)
27.5-29.5	1.12 (1.04-1.20)	0.98 (0.87-1.10)	1.04 (0.93-1.15)	0.96 (0.85-1.09)
30.0-34.9	1.20 (1.12-1.29)	1.10 (0.97-1.23)	1.12 (1.00-1.26)	1.05 (0.92-1.20)
≥35.0	1.57 (1.46-1.70)	1.54 (1.31-1.80)	1.33 (1.10-1.59)	1.13 (0.90-1.41)
P-interaction	0.977		0.605	
Smoking, pack-years				
Never	1.08 (1.01-1.16)	1.00 (reference)	1.08 (0.99-1.18)	1.00 (reference)
Past smoker, <5	1.12 (1.04-1.22)	1.03 (0.90-1.19)	1.09 (0.95-1.25)	1.13 (0.98-1.31)
Past smoker, ≥5	1.54 (1.43-1.65)	1.38 (1.26-1.51)	1.57 (1.44-1.72)	1.58 (1.44-1.73)
Current smoker, <20	1.98 (1.75-2.23)	2.28 (1.83-2.84)	2.40 (1.85-3.12)	1.73 (1.36-2.20)
Current smoker, ≥20	3.12 (2.90-3.36)	2.67 (2.38-3.00)	3.28 (2.94-3.67)	2.73 (2.43-3.05)
P-interaction	0.732		0.269	
Alcohol intake, g/d				
0	1.27 (1.20-1.35)	1.18 (1.08-1.29)	1.28 (1.17-1.41)	1.03 (0.93-1.13)
0.1-13.9	1.12 (1.05-1.18)	1.00 (reference)	1.01 (0.94-1.08)	1.00 (reference)
14-20.9	1.16 (1.08-1.24)	0.93 (0.79-1.09)	0.99 (0.87-1.11)	0.99 (0.86-1.15)
21-27.9	1.15 (1.06-1.24)	1.11 (0.89-1.37)	1.03 (0.87-1.21)	1.02 (0.83-1.26)
≥28	1.29 (1.20-1.38)	1.26 (1.09-1.45)	1.13 (1.00-1.29)	1.09 (0.95-1.25)
P-interaction	0.987		0.091	
Physical activity, h/wk [§]				
0	1.00 (reference)	0.97 (0.88-1.06)	1.00 (reference)	0.93 (0.81-1.05)
0.1-0.9	0.84 (0.81-0.87)	0.75 (0.70-0.81)	0.80 (0.71-0.89)	0.71 (0.63-0.79)
1.0-3.4	0.78 (0.75-0.81)	0.68 (0.63-0.74)	0.69 (0.61-0.77)	0.67 (0.60-0.75)
3.5-5.9	0.75 (0.71-0.78)	0.73 (0.65-0.82)	0.67 (0.59-0.77)	0.61 (0.53-0.71)
≥6	0.74 (0.70-0.78)	0.64 (0.56-0.73)	0.61 (0.53-0.70)	0.63 (0.55-0.73)
P-interaction	0.389		0.296	
Diet quality				
Quint 1	1.00 (reference)	0.92 (0.85-1.00)	1.00 (reference)	0.93 (0.83-1.03)
Quint 2	0.90 (0.86-0.93)	0.87 (0.79-0.94)	0.97 (0.88-1.08)	0.94 (0.84-1.05)
Quint 3	0.88 (0.84-0.91)	0.75 (0.69-0.83)	0.90 (0.80-1.00)	0.81 (0.72-0.91)
Quint 4	0.85 (0.82-0.88)	0.75 (0.68-0.82)	0.83 (0.74-0.93)	0.82 (0.73-0.92)
Quint 5	0.80 (0.77-0.83)	0.73 (0.66-0.80)	0.83 (0.74-0.93)	0.77 (0.68-0.87)
P-interaction	0.392		0.922	
Healthy lifestyle score				
0	1.00 (reference)	0.78 (0.66-0.93)	1.00 (reference)	0.74 (0.57-0.95)
1	0.81 (0.77-0.86)	0.79 (0.72-0.86)	0.83 (0.70-0.98)	0.77 (0.64-0.91)
2	0.66 (0.63-0.69)	0.61 (0.56-0.66)	0.60 (0.51-0.71)	0.59 (0.50-0.70)
3	0.53 (0.50-0.56)	0.47 (0.43-0.52)	0.46 (0.39-0.55)	0.47 (0.39-0.56)
4	0.46 (0.43-0.49)	0.40 (0.35-0.45)	0.42 (0.35-0.51)	0.39 (0.32-0.47)
5	0.38 (0.35-0.42)	0.33 (0.25-0.44)	0.37 (0.29-0.47)	0.32 (0.24-0.43)

P-interaction	0.452		0.467	
% PAR of healthy lifestyle score of 5	36 (30-42)	39 (21-55)	31 (18-43)	40 (25-53)

HR, hazard ratio; CI, confidence interval; BMI, body mass index; PAR, population-attributable risk.

* Common preventive medications included aspirin, antihypertensives, and lipid-lowering medications; regular medication use was defined as use ≥ 2 tablets/week or ≥ 2 times/week.

† The medication indications included diabetes, hypertension, hyperlipidemia, myocardia infraction, stroke, and angina.

‡ HRs and 95% CIs were calculated adjusting for age, calendar period, ethnicity, current multivitamin use, family history of diabetes, myocardial infarction, or cancer, menopausal status and hormone use (women only), and the other 4 of the 5 lifestyle factors (except healthy lifestyle score).

§ Physical activity was of moderate-to-vigorous intensity requiring the expenditure of ≥ 3 metabolic equivalents per hour.

|| Diet quality was based on Alternate Healthy Eating Index (AHEI) score.