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Healthy lifestyle, statin, and mortality in people with high CVD risk: A nationwide population-based cohort study

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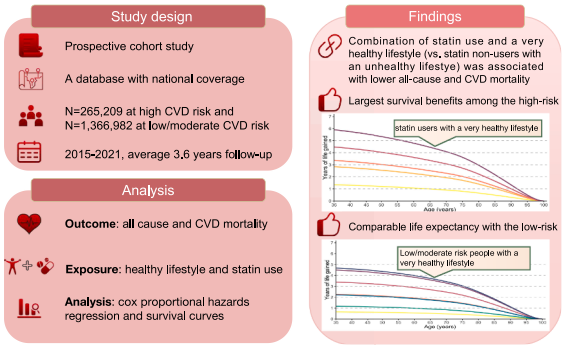
GRAPHICAL ABSTRACT



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ABSTRACT

Objective: To examine the joint association of healthy lifestyles and statin use with all-cause and cardiovascular mortality in high-risk individuals, and evaluate the survival benefits by life expectancy.
Methods: During 2015–2021, participants aged 35–75 years were recruited by the China Health Evaluation And risk Reduction through nationwide Teamwork. Based on number of healthy lifestyles related to smoking, alcohol drinking, physical activity, and diet, we categorized them into: very healthy (3–4), healthy (2), and unhealthy (0–1). Statin use was determined by self-report taking statin in last two weeks.
Results: Among the 265,209 included participants at high risk, 6979 deaths were observed, including 3236 CVD deaths during a median 3.6 years of follow-up. Individuals taking statin and with a very healthy lifestyle had the lowest risk of all-cause (HR: 0.70; 95 %CI: 0.57–0.87) and cardiovascular mortality (0.56; 0.40–0.79), compared with statin non-users with an unhealthy lifestyle. High-risk participants taking statin and with a very healthy lifestyle had the highest years of life gained (5.90 years at 35-year-old [4.14–7.67; $P < 0.001$]) compared with

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statin non-users with an unhealthy lifestyle among high-risk people. And their life expectancy was comparable with those without high risk but with a very healthy lifestyle (4.49 vs. 4.68 years).
Conclusion: The combination of preventive medication and multiple healthy lifestyles was associated with lower risk of all-cause and cardiovascular mortality and largest survival benefits. Integrated strategy to improve long-term health for high-risk people was urgently needed.

1. Introduction

Cardiovascular disease (CVD) is the leading cause of death worldwide [1], with an estimate of 18.6 million cardiovascular death in 2019 [1]. Effective primary prevention strategies for high-risk individuals are essential to reduce the burden of CVD. A lot of evidence indicates both preventive medication [2–5] and healthy lifestyles [6] (e.g., non-smoking, sufficient physical activity, healthy diet, and none or moderate alcohol drinking) are beneficial in reducing CVD risk and extend healthy life expectancy. Statin, the cornerstone of CVD prevention, is recommended by both international and Chinese guidelines for population at high CVD risk [2-5,7]. Clarifying the benefits of the combined effects of statin and healthy lifestyles can help to mitigate the negative impact of the labelling effect, namely that high risk may be perceived as a label that elicits negative self-perceptions.

However, evidence from people at high CVD risk is still lacking. Previous cohort studies have examined the effects of healthy lifestyles and preventive medication (e.g. statin, antihypertensive and antidiabetic medication) on the risk of CVD events or mortality [8–15]. But most of them did not aim to explore combined effects of healthy lifestyles and preventive medication [8-10,12]. Some of them enrolled a generally healthy population [13–15], which may result in underestimation of combined effects, or only focused on patients with hypertension [11]. And some previous studies collected baseline data about healthy lifestyles and medication usage several decades ago [9,13,14], where primary prevention practices differed significantly from the contemporary health care settings. Furthermore, life expectancy is a more quantifiable measure of representing the health status at a population level compared with relative risk of CVD events or mortality, which has been increasingly investigated and incorporated in evidence-based screening and treatment guidelines [16]. But the role of combined healthy lifestyles and statin use in improving life expectancy has not been well-evaluated to date.

Accordingly, using nationwide population-based cohort data from the China Health Evaluation And risk Reduction through nationwide Teamwork (ChinaHEART), we aimed to examine the joint association of healthy lifestyles and statin use with all-cause and cardiovascular mortality in individuals at high CVD risk. In addition, differences in life expectancy were estimated to further evaluate the health benefits of adherence to healthy lifestyles and statin use.

2. Methods

The ChinaHEART is a public health project funded by the Chinese government to screen and manage people at high CVD risk. The details of the project design have been described previously (formerly named China Patient-centered Evaluative Assessment of Cardiac Events Million Persons Project, PEACE MPP) [17]. The project sampled 286 sites (170 rural counties and 116 urban districts) in 31 provinces of mainland China from September 2015 to December 2021. Participants were recruited by local staff via extensive publicity campaigns on television and in newspapers and enrolled if they were aged 35 to 75 years and had lived in the region for at least six months in the previous year. The project was approved by the central ethics committee at Fuwai Hospital (Beijing, China). All enrolled participants provided their informed consent.

A total of 3,929,765 participants were recruited in the project. Those whose serial project ID number ended with 1, 3, 5, or 7 were selected to provide detailed information on multiple cardiovascular disease risk factors (n = 1,891,908). We excluded participants with missing information on lifestyle behaviors or demographic data (n = 141,172). We also excluded participants with a history of CVD or cancer (n = 118,590), and those who were taking other lipid lowering drugs but didn't remember the specific drug name (n = 3973). According to the 2016 Chinese Guidelines for the Management of Dyslipidemia in Adults [7], a risk stratification tool tailored to the Chinese population, the risk of CVD incidence was estimated for each participant on basis of age, smoking status, systolic blood pressure, the presence of diabetes, the presence of hypertension, BMI (body mass index) and total cholesterol (TC) level (Supplementary methods and Fig. S1). Finally, participants with high risk were included in the joint association analyses, while those with low or moderate risk were included for the comparison of life expectancy (Supplementary Fig. S2).

Standardized in-person interviews using electronic questionnaires with real-time logical check function were conducted by trained staff to collect information on demographic and socio-economic characteristics (i.e., age, sex, education, and annual household income), medical history (i.e., self-reported diagnosed hypertension, diabetes, CVD or cancer) and medication use. Statin use was determined by self-report of taking statin in the past two weeks. All measurements of participants were taken using standardized devices and procedures to collect information of weight, height, blood pressure, TC, triglycerides, high-density lipoprotein cholesterol (HDL-C) and glucose. Low-density lipoprotein cholesterol (LDL-C) was calculated (Supplementary methods).

Data on lifestyle behaviors, i.e., smoking, alcohol drinking, physical activity, and diet, were collected through questionnaire interviews. In brief, participants were asked about their smoking status (never, former, or current smokers); ever smokers were additionally inquired about the frequency and type of cigarette smoking and the tobacco consumption per day, and former smokers were asked about the reasons for cessation. Regarding alcohol drinking, the average daily alcohol consumption was estimated based on drinking frequency ('never', 'once or less per month', '2–4 times per month', '2–3 times per week', 'more than 4 times per week') and the amount of alcohol consumption on a typical drinking day for ever drinkers. In terms of physical activity, participants were asked about the frequency and duration of moderate (ball games/walking/gymnastics/folk dancing/Tai-Chi/qigong or other exercise) and vigorous (swimming, running or aerobic exercise as vigorous-intensity activity) aerobic physical activity in a typical week. Dietary information was collected through a qualitative food frequency questionnaire by asking about eating frequency of 12 food groups over the previous year. Five frequency categories were provided for each food group ('daily', '4–6 days per week', '1–3 days per week', '1–3 days per month', 'never or almost never'). A customized electronic data collection system with real-time logical check function was used to ensure the quality and integrity of interview data.

Non-smoking, none or moderate alcohol drinking, sufficient physical activity, and a healthy diet were measured as the top ranked modifiable behavioral risk factors for CVD burden and also widely adopted in the previous studies [1]. The healthy group for smoking was defined as never smokers or former smokers who chose to quit as recommended [18]. The healthy group regarding alcohol drinking was defined as never drinkers, or drinkers with the average daily alcohol consumption no more than 25 g (for male) or 15 g (for female), according to the Chinese dietary guidelines. Sufficient physical activity was defined as at least 150 min of moderate-intensity aerobic activities or 75 min of

vigorous-intensity aerobic activities per week, which was considered healthy for this study [19]. According to the recommendations of Chinese Dietary Guidelines [20], a healthy diet score was calculated by the weekly intake of 6 food groups, including the daily intake of fresh fruit, fresh vegetables, and whole grains, and eating fish and other seafood ≥1 day per week, bean and bean food ≥4 days per week, and red meat < 7 days per week [21,22]. Participants got 1 point for presence of one criterion, otherwise, scored 0. The full mark of the healthy diet score was 6 and the healthy group was defined as those whose score ≥4.

The healthy lifestyle score was created by a composite of the four healthy lifestyles based on previous studies [23–25]. Participants got 1 point for the presence of one healthy lifestyle. Overall healthy lifestyle score was the sum of the individual scores of all four healthy lifestyles, ranging from 0 to 4, with a higher score indicating a healthier lifestyle. Participants were categorized into three groups using the cutoff values of healthy lifestyle score that were most practical and with sufficient statistical power in each category: very healthy (3–4 points), healthy (2 points), and unhealthy (0–1 point) lifestyle.

We ascertained the vital status and causes of death of participants through the National Mortality Surveillance System and Vital Registration of Chinese Center for Disease Control and Prevention, with annual active confirmation from local residential, medical, health insurance and administrative records. All events were coded using International Classification of Diseases (ICD)-10. The outcomes of interest in this study were all-cause and cardiovascular mortality (ICD-10: I00-I99). Mortality data were available up to 31 December 2021. Therefore, we censored the follow-up at this date or the date of death, whichever occurred first.

Participants were categorized into six groups according to different combinations of statin use (users, non-users) and healthy lifestyle (unhealthy, healthy, very healthy). Baseline characteristics were described across these six groups. Categorical variables were summarized as frequencies and percentages, and continuous variables as means ± standard deviations or medians [interquartile range (IQR)].

Cox proportional hazards regression models were employed to examine the associations of statin use and healthy lifestyle with risk of all-cause mortality, participants not taking statin and following unhealthy lifestyle as the reference group. Results were reported as hazard ratio (HR) and corresponding 95 % confidence interval (CI). We adjusted the demographic and socioeconomic characteristics, i.e., age, sex, education, annul household income, BMI, LDL-C, HDL-C, triglyceride, and a history of hypertension and diabetes. The proportional hazard assumption was tested based on Schoenfeld residuals and no violation was found. For outcome of cardiovascular mortality, we performed Fine-Gray analysis with death as competing risk. To examine the interaction between statin use and healthy lifestyles, subgroup analyses stratified by statin use were conducted. The cumulative incidence of all-cause and CVD mortality with Kaplan–Meier curves by statin use and lifestyles was plotted (Supplementary Fig. S3).

Life expectancy was estimated as the area under the survival curve up to 100 years old, conditional on surviving at ages 35 to 100 years old (1-year intervals); survival curves were predicted for each individual and averaged over individuals. Years of life gained were calculated as the difference between the reference group and each of the other five groups. All analyses were adjusted for confounders (i.e., age, sex, education, annual household income, BMI and history of hypertension and diabetes) and performed in Stata version 17.0. To compare the life expectancy of individuals at high CVD risk with that of those at low or moderate CVD risk, we included those at low or moderate CVD risk into the estimation of life expectancy as well.

To examine the robustness of our analysis, two sensitivity analyses was conducted. We re-evaluated the risk of six groups using a weighted healthy lifestyle score. Death as outcome, we fitted Cox regression models and adjusted four health factors, including age, sex, education, household income, BMI, LDL-C, HDL-C, triglyceride, and a history of hypertension and diabetes as covariates. For each factor, the reference group was assigned zero whereas the other group used the point estimates of HR as weighted scores (Supplementary Table S1) [26]. We gave 1 point to excessive drinking for their HR less than 1. The scores were summed up and divided into thirds. Individuals in the highest 33.3 % of scores were placed in Tertile 1 (unhealthy lifestyle) and used as the reference group for comparisons. We also repeated the main analysis using Framingham Risk Score as the risk stratification tool [27].

A two-sided $P < 0.05$ was considered statistically significant. All analyses were conducted with SAS 9.4 (SAS Institute Inc., Cary, North Carolina) and Stata 17.0 (StataCorp).

3. Results

There were 265,209 participants (16.2 %) at high CVD risk and 1,366,982 participants at low or moderate CVD risk. Baseline characteristics of the 265,209 participants with high CVD risk by statin use and healthy lifestyle were shown in Table 1. The average age was 59.1 (8.7), with 48.0 % being female. Among all participants with high CVD risk, 5.7 % (15,076) were taking statin, 24.7 % (65,441) had an unhealthy lifestyle, 47.4 % (125,760) had a healthy lifestyle, and 27.9 % (74,008) had a very healthy lifestyle. And 2.2 % (5942) were taking statin and adhering to a very healthy lifestyle. In addition, a very healthy lifestyle was more prevalent among participants taking statin compared with statin non-users. Compared with participants not taking statin and with an unhealthy lifestyle, those taking statin and having a very healthy lifestyle were more likely to be female, with higher household income and education attainment. But they were more likely to suffer from hypertension and diabetes. The levels of systolic blood pressure, diastolic blood pressure, LDL-C, HDL-C, TC, triglyceride and glucose were similar among the six groups. Baseline characteristics of 1,366,982 participants at low or moderate CVD risk, categorized by healthy lifestyle, were shown in Supplementary Table S2.

During a median 3.6 years of follow-up, a total of 6979 deaths were observed, including 3236 CVD deaths. First, we examined the association of statin use and healthy lifestyles with all-cause and CVD mortality, respectively. Compared with participants not taking statin and with an unhealthy lifestyle, those taking statin and having a very healthy lifestyle had the lowest risk of all-cause mortality (HR: 0.70; 95 %CI: 0.57–0.87), and CVD mortality (HR: 0.56; 95 %CI: 0.40–0.79) (Table 2). Furthermore, participants not taking statin but with a very healthy lifestyle had lower risks of all-cause mortality (HR: 0.71; 95 %CI: 0.66–0.77), and CVD mortality (HR: 0.64; 95 %CI: 0.57–0.71); whereas those taking statin but with an unhealthy lifestyle had no significant reduction in risk of all-cause mortality (HR: 0.84; 95 %CI: 0.63–1.12) or CVD mortality (HR: 0.76; 95 %CI: 0.50–1.17). In the analyses stratified by sex, results were generally consistent with findings in the overall population. In the sensitivity analyses, the results were unchanged when using a weighted lifestyle score (Supplementary Table S3) or using Framingham Risk Score as the risk stratification tool (Supplementary Table S4). No significant interaction between statin use and healthy lifestyles was observed (Supplementary Table S5).

Compared with high CVD risk participants who were not taking statin and with an unhealthy lifestyle, all other groups had a longer life expectancy (Fig. 1). Life expectancy increased with the increase in lifestyle score, regardless of statin use and CVD risk. Among high-risk participants, those taking statin and with a very healthy lifestyle had the highest gain of 5.90 (95 %CI: 4.14–7.67; $P < 0.001$) years at the age of 35, compared with statin non-users with an unhealthy lifestyle (Table 3). Statin users with an unhealthy lifestyle had shorter additional life years at the age of 35 (2.84 [0.20–5.48; $P = 0.04$] years of life gained) than those of statin non-users with a very healthy lifestyle (3.48 [3.74–5.22; $P < 0.001$] years of life gained).

We also compared life expectancy between participants with high risk and low or moderate risk. Compared with statin non-users with an unhealthy lifestyle, high-risk participants taking statin and with a very healthy lifestyle could benefit 4.49 (2.92–6.07; $P < 0.001$) additional

Table 1
Baseline characteristics of 265,209 participants at high CVD risk according to healthy lifestyles and statin use.

	Overall	Statin non-user			Statin user		
		Unhealthy	Healthy	Very healthy	Unhealthy	Healthy	Very healthy
Participants	265,209	63,125 (25.2)	118,942 (47.6)	68,066 (27.2)	2316 (15.4)	6818 (45.2)	5942 (39.4)
Age, years	59.1 (8.7)	56.9 (9.0)	59.2 (8.7)	60.7 (8.2)	57.3 (8.8)	60.7 (8.2)	62.1 (7.5)
Female	127,208 (48.0)	3857 (6.1)	67,844 (57.0)	46,826 (68.8)	194 (8.4)	4141 (60.7)	4346 (73.1)
Education attainment							
Primary school	112,789 (42.5)	25,386 (40.2)	57,355 (48.2)	24,744 (36.4)	689 (29.7)	2898 (42.5)	1717 (28.9)
Middle school	85,421 (32.2)	22,700 (36.0)	35,285 (29.7)	22,630 (33.2)	862 (37.2)	1974 (29.0)	1970 (33.2)
High school	30,673 (11.6)	6851 (10.9)	11,607 (9.8)	10,099 (14.8)	309 (13.3)	807 (11.8)	1000 (16.8)
College	18,922 (7.1)	4272 (6.8)	7374 (6.2)	5790 (8.5)	255 (11.0)	563 (8.3)	668 (11.2)
Unknown	17,404 (6.6)	3916 (6.2)	7321 (6.2)	4803 (7.1)	201 (8.7)	576 (8.4)	587 (9.9)
Household income (Yuan RMB/year)							
<10,000	42,663 (16.1)	10,664 (16.9)	21,319 (17.9)	8692 (12.8)	309 (13.3)	1059 (15.5)	620 (10.4)
10,000–50,000	144,865 (54.6)	35,385 (56.1)	65,332 (54.9)	36,548 (53.7)	1217 (52.5)	3576 (52.4)	2807 (47.2)
>50,000	55,363 (20.9)	12,382 (19.6)	21,996 (18.5)	16,829 (24.7)	608 (26.3)	1574 (23.1)	1974 (33.2)
Unknown	22,318 (8.4)	4694 (7.4)	10,295 (8.7)	5997 (8.8)	182 (7.9)	609 (8.9)	541 (9.1)
Married	241,567 (91.1)	58,525 (92.7)	108,173 (90.9)	61,170 (89.9)	2161 (93.3)	6158 (90.3)	5380 (90.5)
Insured	260,725 (98.3)	62,127 (98.4)	116,953 (98.3)	66,890 (98.3)	2288 (98.8)	6659 (97.7)	5808 (97.7)
Healthy lifestyle behaviours							
Non-smoking	170,051 (64.1)	1678 (2.7)	92,503 (77.8)	64,882 (95.3)	63 (2.7)	5239 (76.8)	5686 (95.7)
None or moderate alcohol drinking	250,992 (94.6)	51,000 (80.8)	117,568 (98.8)	67,924 (99.8)	1856 (80.1)	6719 (98.5)	5925 (99.7)
Sufficient physical activity	91,232 (34.4)	2752 (4.4)	23,007 (19.3)	58,716 (86.3)	148 (6.4)	1424 (20.9)	5185 (87.3)
Healthy diet	28,168 (10.6)	523 (0.8)	4806 (4.0)	20,570 (30.2)	23 (1.0)	254 (3.7)	1992 (33.5)
Body mass index							
Underweight	2370 (0.90)	694 (1.1)	1096 (0.9)	498 (0.7)	8 (0.4)	38 (0.6)	36 (0.6)
Normal weight	76,997 (29.0)	18,471 (29.3)	34,433 (29.0)	20,419 (30.0)	517 (22.3)	1556 (22.8)	1601 (26.9)
Overweight	116,678 (44.0)	27,268 (43.2)	52,295 (44.0)	30,447 (44.7)	1000 (43.2)	2986 (43.8)	2682 (45.1)
Obese	69,164 (26.1)	16,692 (26.4)	31,118 (26.2)	16,702 (24.5)	791 (34.2)	2238 (32.8)	1623 (27.3)
Medical history							
Hypertension	157,742 (59.5)	42,511 (67.3)	66,243 (55.7)	37,356 (54.9)	1845 (79.7)	5280 (77.4)	4507 (75.8)
Diabetes	120,374 (45.4)	13,669 (21.7)	56,720 (47.7)	39,715 (58.3)	956 (41.3)	4702 (69.0)	4612 (77.6)
Metabolic factors							
SBP, mmHg, Median(IQR)	148.5 (133, 164)	150.5 (135, 165)	148.5 (133, 164)	147 (132, 163)	149 (135, 164)	151 (136 165)	147 (133, 163)
DBP, mmHg, Median(IQR)	86 (78, 95)	90 (81.5, 99.5)	85.5 (77.5, 94.5)	83.5 (76.0, 92)	89.0 (81.0, 98.0)	85.5 (77.5, 94)	83.0 (75, 91)
LDL-C, mmol/L, Median(IQR)	2.8 (2.2, 4.0)	2.7 (2.1, 3.4)	2.9 (2.2, 4.2)	3 (2.2, 4.3)	2.5 (1.9, 3.3)	2.6 (1.9, 3.6)	2.5 (1.8, 3.7)
HDL-C, mmol/L, Median(IQR)	1.3 (1.0, 1.6)	1.2 (1.0, 1.5)	1.3 (1.0, 1.6)	1.3 (1.0, 1.6)	1.2 (1.0, 1.5)	1.3 (1.0, 1.6)	1.3 (1.1, 1.6)
TC, mmol/L, Median(IQR)	5.1 (4.3, 6.5)	4.9 (4.3, 5.7)	5.2 (4.4, 7.0)	5.2 (4.4, 7)	4.7 (4.1, 5.7)	4.9 (4.1, 6.2)	4.9 (4, 6.2)
TG, mmol/L, Median(IQR)	1.8 (1.3, 2.7)	1.8 (1.2, 2.7)	1.8 (1.3, 2.8)	1.8 (1.3, 2.7)	2.1 (1.4, 3.2)	2.0 (1.4, 3.1)	1.9 (1.3, 2.9)
Glucose, mmol/L, Median(IQR)	6.7 (5.7, 8.6)	6.2 (5.5, 7.5)	6.8 (5.8, 8.8)	7.2 (5.9, 9)	6.5 (5.6, 8.2)	7.3 (6, 9.1)	7.3 (6.2, 9.0)

Categorical variables were summarized as frequencies and percentages, and continuous variables as means and standard deviations.
SBP, systolic blood pressure; DBP, diastolic blood pressure; LDL-C, low-density lipoprotein cholesterol; HDL-C, high density lipoprotein cholesterol; TC, total cholesterol; TG, triglyceride; IQR, interquartile range. Overall healthy lifestyle score was the sum of the individual scores of all four healthy lifestyles (including non-smoking, none or moderate alcohol drinking, sufficient physical activity, and healthy diet), ranging from 0 to 4 points (1 point for presence of one healthy lifestyle). Participants were categorized into three groups: very healthy (3–4 points), healthy (2 points), and unhealthy (0–1 point) lifestyle.

Table 2
Hazard ratio for all-cause and CVD mortality according to healthy lifestyles and statin use.

	Hazard Ratio (95 %Confidence Interval)					
	Statin non-user			Statin user		
	Unhealthy	Healthy	Very healthy	Unhealthy	Healthy	Very healthy
Person years	221,096.5	408,334.2	233,794.3	6884.5	19,839.5	17,512.9
All-cause mortality						
Deaths,	2047	3249	1400	49	140	94
Overall [a]	Reference	0.93 (0.87–0.99)	0.71 (0.66–0.77)	0.84 (0.63–1.12)	0.84 (0.70–1.00)	0.70 (0.57–0.87)
Male [b]	Reference	0.93 (0.87–1.00)	0.73 (0.66–0.80)	0.83 (0.62–1.12)	0.93 (0.73–1.18)	0.91 (0.67–1.23)
Female [b]	Reference	0.79 (0.65–0.96)	0.61 (0.50–0.75)	0.89 (0.33–2.42)	0.65 (0.48–0.88)	0.50 (0.36–0.71)
CVD mortality						
Deaths,	1010	1506	600	22	62	36
Overall [a]	Reference	0.87 (0.80–0.95)	0.64 (0.57–0.71)	0.76 (0.50–1.17)	0.75 (0.58–0.97)	0.56 (0.40–0.79)
Male [b]	Reference	0.88 (0.80–0.97)	0.64 (0.55–0.74)	0.76 (0.49–1.18)	0.79 (0.54–1.14)	0.68 (0.41–1.14)
Female [b]	Reference	0.94 (0.69–1.27)	0.69 (0.50–0.94)	1.05 (0.25–4.40)	0.76 (0.49–1.20)	0.53 (0.31–0.89)

Participants not using statin medication and following an unhealthy lifestyle as the reference. CVD: cardiovascular disease. Overall healthy lifestyle score was the sum of the individual scores of all four healthy lifestyles (including non-smoking, none or moderate alcohol drinking, sufficient physical activity, and healthy diet), ranging from 0 to 4 points (1 point for presence of one healthy lifestyle). Participants were categorized into three groups: very healthy (3–4 points), healthy (2 points), and unhealthy (0–1 point) lifestyle.

[a] Adjusted for age (continuous), sex (male, female), education attainment (primary school, middle school, high school, college), annul household income (<10,000, 10,000–50,000, >50,000), body mass index (underweight, normal weight, overweight, obese), low-density lipoprotein cholesterol, high density lipoprotein cholesterol, triglyceride, presence of hypertension and diabetes.

[b] Adjusted for age (continuous), education attainment (primary school, middle school, high school, college), annul household income (<10,000, 10,000–50,000, >50,000), body mass index (underweight, normal weight, overweight, obese), low-density lipoprotein cholesterol, high density lipoprotein cholesterol, triglyceride, presence of hypertension and diabetes.

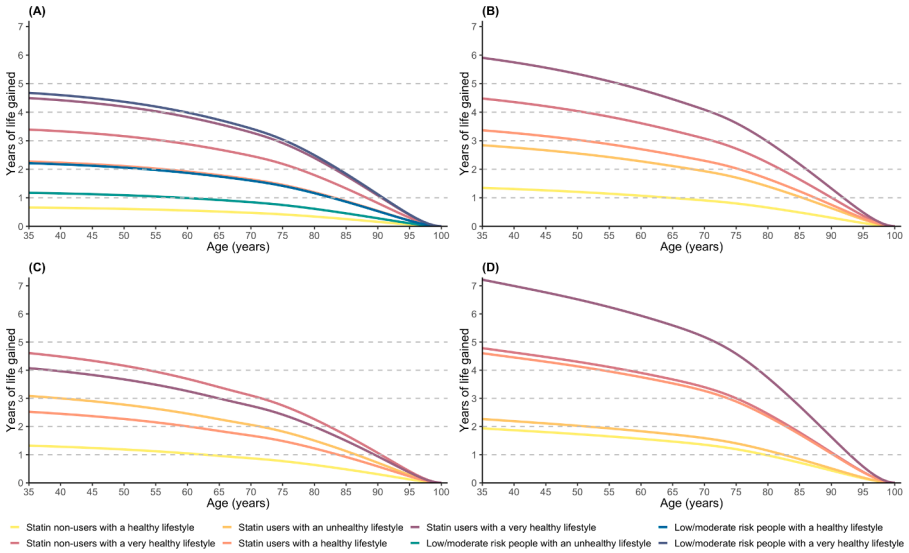

Fig. 1. Years of life gained associated with statin use and lifestyles.
Participants not using statin medication and following an unhealthy lifestyle as the reference. Model adjusted for age, sex, education, annual household income, body mass index and a history of hypertension and diabetes when appropriate. (A) Years of life gained in people with and without high cardiovascular disease (CVD) risk. (B) Years of life gained in people with high CVD risk. (C) Years of life gained in male participants with high CVD risk. (D) Years of life gained in female participants with high CVD risk. Overall healthy lifestyle score was the sum of the individual scores of all four healthy lifestyles (including non-smoking, none or moderate alcohol drinking, sufficient physical activity, and healthy diet), ranging from 0 to 4 points (1 point for presence of one healthy lifestyle). Participants were categorized into three groups: very healthy (3–4 points), healthy (2 points), and unhealthy (0–1 point) lifestyle.

Table 3
Years of life gained at age 35 and 60 years according to healthy lifestyles and statin use in high-risk participants.

	Overall	*P* value	Female	*P* value	Male	*P* value
Years of life gained (95 %CI), 35 years						
Statin non-users with an unhealthy lifestyle	Reference		Reference		Reference	
Statin non-users with a healthy lifestyle	1.34 (0.74–1.96)	<0.001	1.93 (0.06–3.81)	0.04	1.32 (0.61–2.03)	<0.001
Statin non-users with a very healthy lifestyle	3.48 (3.74–5.22)	<0.001	4.78 (2.84–6.73)	<0.001	4.61 (3.65–5.57)	<0.001
Statin users with an unhealthy lifestyle	2.84 (0.20–5.48)	0.04	2.27 (−6.71–11.24)	0.62	3.09 (0.13–6.04)	0.04
Statin users with a healthy lifestyle	3.37 (1.75–4.98)	<0.001	4.60 (1.92–7.28)	<0.001	2.52 (0.11–4.94)	0.04
Statin users with a very healthy lifestyle	5.90 (4.14–7.67)	<0.001	7.22 (4.53–9.91)	<0.001	4.01 (1.13–7.02)	0.01
Years of life gained (95 %CI), 60 years						
Statin non-users with an unhealthy lifestyle	Reference		Reference		Reference	
Statin non-users with a healthy lifestyle	1.01 (0.59–1.56)	<0.001	1.57 (0.06–3.06)	0.04	1.04 (0.49–1.60)	<0.001
Statin non-users with a very healthy lifestyle	3.61 (3.02–4.21)	<0.001	3.91 (2.35–5.46)	<0.001	3.69 (2.92–4.46)	<0.001
Statin users with an unhealthy lifestyle	2.27 (0.14–4.41)	0.04	1.83 (−5.48–9.15)	0.62	2.46 (0.08–4.84)	0.04
Statin users with a healthy lifestyle	2.70 (1.40–4.01)	<0.001	3.76 (1.58–5.93)	<0.001	2.01 (0.07–3.94)	0.04
Statin users with a very healthy lifestyle	4.79 (3.34–6.23)	<0.001	5.94 (3.75–8.12)	<0.001	3.25 (0.87–5.65)	0.01

Participants not using statin medication and following an unhealthy lifestyle as the reference. CI: confidence interval. Model adjusted for age, sex, education, annual household income, body mass index and history of hypertension and diabetes when appropriate.

life years at the age of 35, which was comparable with those without high CVD risk who adhered to a healthy lifestyle (4.68 [4.19–5.16; $P < 0.001$] years of life gained), and longer than those without high CVD risk but with a lower level of healthy lifestyle (unhealthy and healthy lifestyle) (1.17–2.21 years of life gained). The pattern of results was similar at the age of 65 years (Table 3).

4. Discussion

In this study, we found that the combination of statin use and healthy lifestyles was significantly associated with a 30 % and 44 % lower risk of all-cause and cardiovascular mortality in participants with high CVD risk compared with participants not taking statin and with an unhealthy lifestyle. The greatest health benefit of the combination of statin use and healthy lifestyles has also been observed regarding to life expectancy. In addition, high-risk participants taking statin and adhering to a very healthy lifestyle had a life expectancy comparable to that of those without high CVD risk who adhered to a very healthy lifestyle, and a higher life expectancy than those without high CVD risk but not adhering to healthy lifestyles.

Previous studies have investigated the combined effects of preventive medication and multiple healthy lifestyles on health outcomes, but these studies did not target to candidates for primary prevention of CVD [11,13-15] or were limited by outdated lifestyle data [9,13,14]. Our study extends the existing research in several ways and has some potential clinical implications. First, using data from large-scale cohort of the ChinaHEART, we found the greatest protective effect of the combination of statin use and adherence to healthy lifestyles on all-cause and CVD mortality among people with high CVD risk. In addition, for participants with an unhealthy lifestyle, there was no significant reduction in mortality risk even if they were taking statin. Therefore, our findings support the combination of statin use and adhering to multiple healthy lifestyles could maximize the health benefits. However, adherence to healthy lifestyle behaviors in Chinese population has been suboptimal and the rate of statin use remains very low among those with high CVD risk [28], which highlights great opportunities to increase management

of high-risk persons. In the primary care settings, the assessment of CVD risk should be promoted, and primary health care physicians should strongly recommend the combination of statin use and healthy lifestyles to maximize the health benefits for population with high CVD risk. For those at high CVD risk, applying technology tools is a potential strategy to improve adherence by monitoring and confirming health behaviors and medication in real-time [29]. From a public health perspective, improving accessibility and affordability of health care is also essential to control the risk of CVD, for financial barriers may negatively affect health insurance coverage and patient adherence [30].

Additionally, for the first time, we evaluated life expectancy to quantify the benefits of the combination of statin use and healthy lifestyles in high-risk people, and compared their life expectancy with people without high CVD risk. We found that life expectancy of those taking statin and with a very healthy lifestyle was the longest among high-risk participants, with 5.90 years longer life expectancy than statin non-users with an unhealthy lifestyle. Furthermore, life expectancy increased with higher lifestyle scores, irrespective of statin use and CVD risk, with up to 3.39 years for statin non-users, 2.25 years for statin users and 3.50 years for low or moderate participants. This was consistent with findings from other cohort studies that have shown a very healthy lifestyle to be associated with a 17.9-year increase in life expectancy at age 20 for the population from Canadian Community Health Surveys [31], and 6.3 years (for male) and 7.6 years (for female) at age 45 for population with cardiometabolic multimorbidity from UK biobank [32], and 8.8 years (for male) and 8.1 years (for female) at age 30 from China Kadoorie Biobank [23], and 18.5 years (for male) and 15.7 years (for female) at age 40 from EPIC-Heidelberg cohort in Germany [33]. The estimates of years of life gained in our study were lower than those of the studies mentioned above. This inconsistency might be due to differences in the composition and definition of healthy lifestyles and study population. In addition, our results indicated that life expectancy of those taking statin and with a very healthy lifestyle was comparable with that of those without high CVD risk and with the same level of healthy lifestyles. The high-risk approach is one of the primary prevention strategies for CVD, but one of its limitations is the “labelling effect”, whereby the psychological impact of the assessment can lead to high risk being perceived as a label that evokes stress, anxiety, impaired confidence or negative self-perception, quite apart from the state of physical health itself [34]. Our findings could help high risk population relieve their psychological stress and enhance their health confidence to control CVD risk. In clinical practice, people at high CVD risk should be encouraged to adopt a positive attitude towards their suboptimal health status and follow medical advices including preventive medication and healthy lifestyles, to achieve better health status as those with low or moderate risk.

This study has some potential limitations. First, recall bias was inevitable in self-reported assessments of lifestyle factors and medication use, even using the standardized questionnaire interview and drug packaging (boxes) check. Second, we considered four lifestyle factors to construct lifestyle score, which may not be representative of all aspects of lifestyle. Moreover, it may be controversial to attribute equal weight to different risk factors. Thus, we constructed a weighted healthy lifestyle score in the sensitivity analysis and the results were not materially changed. Third, participants were asked about statin use within last two weeks, but the change of adherence to medication treatment over time may lead to potential bias. Fourth, due to the observational study design, residual and unmeasured confounding may exist. Future prospective cohort studies with repeated measurement of lifestyles and long-term medication adherence are needed to examine the joint association of healthy lifestyles and preventive medication on health outcomes. Fifth, life expectancy might be overestimated due to no consideration of risk factors that increase with age, other diseases and their outcomes. However, this study did not aim to describe life expectancy in the Chinese population, but to compare life expectancy and years of life gained across different groups, thus reflecting the importance of following a healthy lifestyle and taking statin in population with high CVD risk.

The combination of preventive medication use and adhering to multiple healthy lifestyles was significantly associated with a lower risk of all-cause and CVD mortality, as well as had remarkable benefits in life expectancy. These findings highlight the importance of the combination of preventive medication use and adherence to healthy lifestyles to reduce mortality risk and increase life expectancy for people with high CVD risk.

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Ethics approval

The study protocol for the ChinaHEART was approved by the central ethics committee at Fuwai Hospital (Beijing, China). All participants provided written informed consent.

Data availability statement

The data are not publicly available. China Health Evaluation And risk Reduction through nationwide Teamwork only provides conditional data access for qualified researchers with legitimate requests; a formal application and research proposal is required. Please contact cvd-project@nccd.org.cn to seek approval for data access.

Dissemination to participants and related patient and public communities

Results of this study will be disseminated to the general public via science articles, and social media channels where available.

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CRediT authorship contribution statement

Wenyao Peng: Formal analysis, Writing – original draft. **Xueke Bai:** Formal analysis, Writing – original draft. **Yang Yang:** Writing – review & editing. **Jianlan Cui:** Writing – review & editing. **Wei Xu:** Writing – review & editing. **Lijuan Song:** Writing – review & editing, Writing – review & editing. **Hao Yang:** Writing – review & editing. **Wenyan He:** Writing – review & editing. **Yan Zhang:** Writing – review & editing. **Xingyi Zhang:** Writing – review & editing. **Xi Li:** Writing – review & editing, Funding acquisition, Software, Supervision. **Jiapeng Lu:** Conceptualization, Funding acquisition, Methodology, Supervision, Writing – review & editing, Formal analysis, Writing – original draft.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ajpc.2024.100635.

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