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ORIGINAL ARTICLE

Joint association of modifiable lifestyle and metabolic health status with incidence of cardiovascular disease and all-cause mortality: a prospective cohort study

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Abstract

Purpose We aimed to identify the joint associations of modifiable lifestyle and metabolic factors with the incidences of cardiovascular disease and all-cause mortality.

Methods We recruited 94,831 participants (men, 79.76%; median age, 51.60 [43.47–58.87]) without a history of cardiovascular disease from the Kailuan study during 2006 and 2007 and followed them until a cardiovascular disease event, or death occurred, or until December 31, 2017. Baseline metabolic health status was assessed using Adult Treatment Panel III criteria, and details of the lifestyles of the participants were recorded using a self-reported questionnaire. We used Cox proportional hazards models to evaluate the joint associations.

Results During a median follow-up of 11.03 years, we recorded 6590 cardiovascular disease events and 9218 all-cause mortality. Participants with the most metabolic risk components and the least healthy lifestyle had higher risk of cardiovascular disease (hazard ratio 2.06 [95% confidence interval (CI) 1.77–2.39]) and mortality (HR 1.53 [95% CI 1.31–1.78]), than participants with fewer metabolic risk components and the healthiest lifestyle. Compared with those in participants with the healthiest lifestyle, the HRs for cardiovascular disease in participants with the least healthy lifestyle were 1.26 (95% CI 1.17–1.37), 1.16 (95% CI 1.03–1.31), and 1.07 (95% CI 0.90–1.27) for those with low, medium, and high metabolic risk, respectively.

Conclusion Healthy lifestyle is associated with a lower risk of cardiovascular disease and there is no significant interaction between metabolic risk and a healthy lifestyle. Therefore, a healthy lifestyle should be promoted, even for people with high metabolic risk.

Keywords Lifestyle · Metabolic health status · Mortality · Cardiovascular disease

Introduction

Cardiovascular disease (CVD) is one of the leading causes of death worldwide and remains a substantial threat to public global health [1]. Clinical therapy has been proven to be beneficial, but it may have adverse effects, and recovery

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of function is often incomplete [2]. Therefore, primary prevention is considered to be the most effective strategy in controlling CVD and its consequences [3]. Some previous studies have shown that both a healthy lifestyle and good metabolic health status reduce the risks of CVD and all-cause mortality [4–8].

In most previous studies, lifestyle and metabolic factors have been considered individually, despite these typically being closely related. Recent studies and meta-analyses have consistently shown that a combination of lifestyle factors is associated with much lower incidences of cardiometabolic abnormalities [9–12]. A few studies have described the relationships of lifestyle factors with the risks of CVD, subtypes of CVD, and all-cause mortality in a population with differing in metabolic risk, but these did not show whether difference in metabolic status might influence the effects of lifestyle [7]. Whereas some studies have reported that lifestyle modification is effective at reducing CVD risk factors and the incidence of CVD, especially stroke, others have not. Therefore, the long-term efficacy of lifestyle interventions for the prevention of CVD requires further assessment [13].

The relationship of lifestyle and metabolic health status with incident CVD has become an important public interest, and its characterization should improve understanding of the modifiable risk factors for CVD. Therefore, in the present study, we aimed to use data from a large-scale population-based prospective cohort study to evaluate the joint associations of lifestyle and metabolic health status with the risk of CVD and all-cause mortality.

Materials and methods

Study design and participants

The Kailuan study is a prospective cohort study that is designed to identify the risk factors for common non-communicable diseases, and especially CVD [14, 15]. The study protocol was approved by the Ethics Committees of both the Kailuan General Hospital and Beijing Tiantan Hospital, and all the participants provided their written informed consent.

The Kailuan study design has been described previously [16]. At baseline, active and retired employees of the Kailuan Group, Tangshan, China, aged ≥ 18 years were invited to participate in the study. A total of 101,510 participants (81,110 men and 20,400 women) aged between 18 and 98 years were enrolled and completed a baseline survey between June 2006 and October 2007. All the participants underwent face-to-face questionnaire assessments, physical examinations, and laboratory assessments in 11 local hospitals. Biennial re-examinations were then performed until the end of the follow-up period, on December 31, 2017.

For the present study, we excluded 3238 participants for whom data for any metabolic parameter were missing at baseline, 3358 participants for whom lifestyle risk factors data were missing, and 83 participants with a history of myocardial infarction (MI) or stroke at baseline. Therefore, a total of 94,831 participants were selected for the present analysis (online Fig. 1 in Supplementary Material).

Metabolic health status

Metabolic health status at baseline was determined on the basis of the physical examinations and laboratory data obtained by trained nurses and physicians. Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured three times with the participants who had been seated for at least 5 min using a mercury sphygmomanometer, and the mean value was used in further analysis [17]. Blood samples were collected after an overnight fast (8–12 h) and the fasting plasma glucose (FPG), total cholesterol (TC), triglycerides (TG), high-density lipoprotein (HDL) cholesterol, and low-density lipoprotein (LDL) cholesterol concentrations were measured using an automatic analyzer (Hitachi 747; Hitachi, Tokyo, Japan) at the local hospital.

We used Adult Treatment Panel III (ATP-III) criteria to define the metabolic health status in the present study. This has been widely used to determine metabolic syndrome in adults worldwide. The ATP-III criteria are based on five CVD risk factors [18]: (1) central obesity: waist circumference ≥ 90 cm in men and ≥80 cm in women; (2) high TG: TG concentration ≥ 1.69 mmol/L; (3) low HDL cholesterol: HDL cholesterol concentration < 1.03 mmol/L in men and <1.29 mmol/L in women; (4) high BP: SBP/DBP ≥ 130/85 mmHg, the use of antihypertensive drugs, or a self-reported history of hypertension; and (5) high FPG: FPG concentration ≥ 5.6 mmol/L, the use of hypoglycemic medications, or a self-reported history of diabetes. Metabolic health status was graded from 0 to 5, with lower scores indicating normal metabolism, and was subsequently categorized on the basis of the distribution in this population: low risk (0–2 components), medium risk (3 components), and high risk (4–5 components) (online Table 1 in Supplementary Material).

Lifestyle health status

Lifestyle status information was collected by trained nurses and physicians using a standardized questionnaire interview. Current smoking was defined as smoking at least the previous year. Current alcohol consumption was defined as the average daily strong spirit (alcohol content > 50%) consumption of 100 mL or more than 100 mL for at least the previous year. Physical activity level was categorized as

(1) ideally active: ≥80 min/week moderate and vigorous intensity; (2) moderately active: <80 min/week; and (3) inactive: none. Sedentary behavior was classified into three categories: (1) < 4 h/day; (2) 4–8 h/day; and (3) ≥8 h/day. Given that dietary salt restriction has been shown to play an important role in the prevention of CVD in previous reports [19, 20], salt intake was used as a surrogate for the healthiness of the diet of the participants. Perceived salt intake was assessed by asking the participants to rate their habitual daily salt intake as "low", "medium", or "high". Low salt intake was defined as <6 g/day, medium salt intake as 6–10 g/day, and high salt intake as >10 g/day, as described previously [21, 22]. The healthiness of a diet was categorized as (1) ideal: <6 g/day; (2) intermediate: 6–10 g/day; or (3) poor: ≥10 g/day.

We estimated the lifestyle of the participants in our present study with respect to five risk factors: (1) current smoking; (2) current alcohol consumption; (3) physical inactivity: <80 min/week or none; (4) sedentary behavior: sedentary time ≥ 4 h/day; and (5) unhealthy diet: salt intake ≥6 g/day. Therefore, the lifestyle score ranged from 0 to 5, with higher scores indicating an unhealthy lifestyle, and lifestyle was further categorized as: very healthy (0–1 risk factor), moderately healthy (2 risk factors), and unhealthy (3–5 risk factors) (online Table 2 in Supplementary Material).

Outcome ascertainment

The participants were followed from their baseline examination at 2006 or 2007 up to December 31, 2017 as the end of the follow-up period or to the date of a CVD event or death, whichever came first. CVD events were defined as a composite of nonfatal MI and stroke during the follow-up period [23, 24]. To retrieve potential CVD events, Municipal Social Insurance and Hospital Discharge Register was used. All the medical records of the participants, including from the Emergency department or associated with hospitalization in a local hospital, were collected and adjudicated centrally. Stroke was defined according to the World Health Organization criteria on the basis of clinical symptoms, computed tomography or magnetic resonance images, and other diagnostic reports [25]. MI was defined using cardiac enzymes activities, symptoms, electrocardiographic signs, and necropsy findings [26]. In addition, information regarding mortality was collected from vital statistical offices, with the death certificate being reviewed by the study clinicians [23].

Statistical analyses

The baseline characteristics of the participants are presented as mean ± standard deviation (SD), or median with interquartile range (IQR), or frequencies with percentages. The metabolic status and lifestyle categories of the participants were compared ANOVA or the Kruskal–Wallis tests for continuous variables and the χ^2 test for categorical variables.

The incidence rate of CVD, stroke, MI, and all-cause mortality was reported as per 1000 person-years (PY) with 95% confidence intervals (CIs). Kaplan–Meier curves and the log-rank test were used to evaluate differences in the cumulative incidence of the clinical outcomes, according to baseline metabolic status and lifestyle. Multivariable adjusted hazard ratios (HRs) and 95% CIs for CVD, stroke, MI, and all-cause mortality were calculated using Cox proportional hazards regression analysis after adjustments for covariates. These were age (continuous, years), sex (categorical, male or female), the family average monthly income (categorical, <800 yuan or ≥800 yuan), body mass index (BMI, calculated as continuous), and education (categorical, literacy/primary or middle school, high school or college/university). We first separately explored the relationships of lifestyle and metabolic risk with each clinical outcome. We also tested for an interaction between lifestyle and metabolic risk using the likelihood-ratio test, and analyses were stratified by metabolic risk category. Lastly, we evaluated the joint association by creating a product term reflecting both lifestyle and metabolic health status, with the healthiest lifestyle and lowest metabolic risk group as the reference.

All analyses were conducted using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA). All reported *P* values were based on two-sided test of significance, and $P < 0.05$ was considered statistically significant in the present study.

Results

Baseline characteristics

A total of 94,831 participants (men, 79.76%; median age, 51.60 [43.47–58.87]) were eventually analyzed in our study. Baseline characteristics of the participants with differing baseline metabolic health status are presented in Table 1. Compared with participants with low metabolic risk, the participants in the other two groups were older, were more likely to be women, had a lower self-reported education, had higher BMI, waist circumference, SBP, DBP, and FBG, and had a less satisfactory lipid profile. The proportions of participants with an unhealthy level of salt intake or sedentary behavior increased markedly with the number of metabolic risk components, whereas the proportions of current smokers and those who were physically inactive decreased (Table 1).

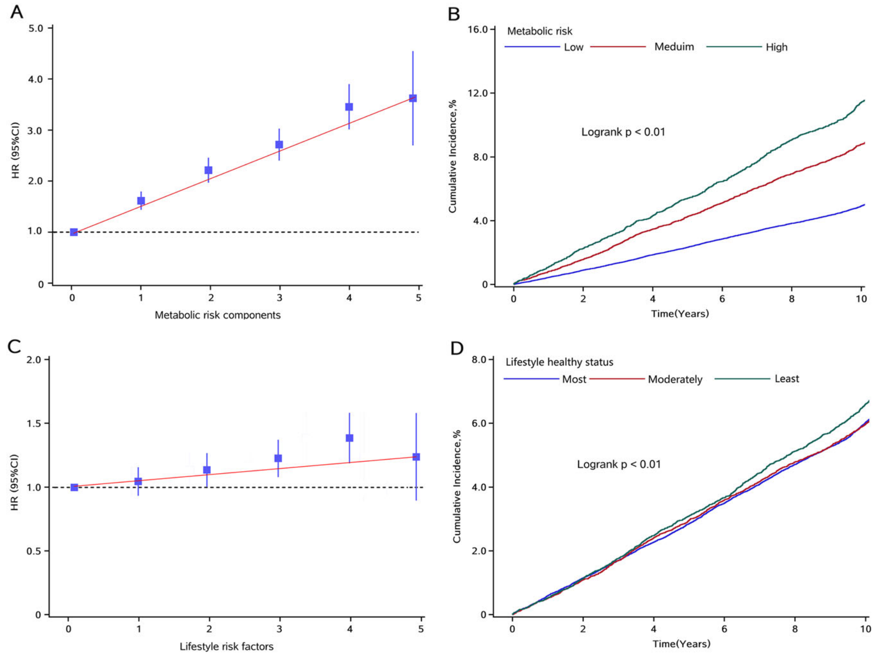

Fig. 1 Effect of metabolic and lifestyle factors on the risk of incident of CVD. **A** Participants were divided into five groups according to their metabolic risk components, and the HRs for each group were compared with those in 0 of the metabolic risk components. **B** The cumulative incidence of CVD in low, medium, and high metabolic risk groups. **C** Participants were divided into five groups according to the number of unhealthy lifestyle factors, and the HRs for each group were compared with those who adopted no unhealthy lifestyle factors. **D** The cumulative incidence of CVD in participants who had a most, moderately and least lifestyle healthy status. CVD cardiovascular disease, MI myocardial infarction, HRs hazard ratios

Individual associations of lifestyle and metabolic health status with clinical outcomes

During a median follow-up period of 11.03 years (IQR: 10.74–11.22 years), there were 6590 CVD events (rate 6.74 per 1000 PY, [95% CI 6.58–6.91]), which included 5233 nonfatal strokes and 1519 nonfatal MIs, 9218 participants died (9.17 per 1000 PY, [95% CI 8.99–9.36]).

The risk of incident CVD increased significantly as the number of metabolic components increased (*P* for trend < 0.001, Fig. 1A). The same pattern was obtained when categories were used instead of the number of metabolic risk components. CVD risk increased monotonically across metabolic health status categories (Fig. 1B). In the multivariable model, the HRs for CVD were 1.47 (95% CI 1.39–1.56) for participants with medium metabolic risk, and 1.85 (95% CI 1.72–2.00) for those with high metabolic risk, compared with those with low metabolic risk (*P* for trend < 0.001, Table 2). With regard to all-cause mortality, the adjusted HR for the participants with medium metabolic risk was 1.34 (95% CI 1.28–1.41), and it was 1.55 (95% CI 1.44–1.66) for those with high metabolic risk, compared with that of those with low metabolic risk. Similar results were obtained for stroke and MI (Table 2 and online Fig. 2 in Supplementary Material).

There was a significant association of CVD risk with the number of unhealthy lifestyle factors (*P* for trend < 0.001, Fig. 1C). The same association was obtained when lifestyle category was used instead of the number of unhealthy lifestyle factors. CVD risk also increased monotonically with the unhealthy lifestyle category (Fig. 1D). In the multivariable model, the HRs for CVD were 1.10 (95% CI 1.03–1.17) for participants with a moderately healthy lifestyle, and 1.23 (95% CI 1.15–2.30) for those with the least healthy lifestyle, compared with those with healthiest lifestyle (*P* for trend < 0.001, Table 3). With regard to all-cause mortality, the adjusted HR for participants with a moderately healthy lifestyle was 1.07 (95% CI 1.02–1.13), and that for those with least healthy lifestyle was 1.08 (95% CI 1.02–1.14), compared with that for participants with the healthiest lifestyle. Similar results were obtained for stroke. However, there was no significant association between lifestyle and MI (Table 3 and online Fig. 3 in Supplementary Material).

Joint effects of lifestyle and metabolic health status with clinical outcomes

The joint associations of lifestyle and metabolic health status with CVD, stroke, MI, and all-cause mortality are shown in Table 4. We found that participants with the

Table 1 Baseline characteristics of the study population according to the baseline metabolic health status

	Overall	Metabolic health status			*P* value
		Low metabolic risk	Medium metabolic risk	High metabolic risk	
Participants (*n*)	94831	69612 (73.41)	17810 (18.78)	7409 (7.81)	
Sociodemographic					
Age, years	51.60 (43.47–58.87)	50.72 (42.40–57.80)	53.83 (47.24–61.05)	54.78 (48.84–61.41)	<0.001
Male, sex	75640 (79.76)	55853 (80.23)	14242 (79.97)	5545 (74.84)	<0.001
Education, high school or above	18984 (20.03)	14775 (21.24)	2961 (16.65)	1248 (16.86)	<0.001
Income, yuan/month, ≥800 yuan	13622 (14.38)	10015 (14.40)	2446 (13.75)	1161 (15.69)	<0.001
Metabolic risk factors					
BMI, kg/m^2	24.86 (22.64–27.24)	24.09 (22.04–26.26)	26.78 (24.79–28.80)	27.70 (25.86–29.76)	<0.001
Waist circumference, cm	87.00 (80.00–93.00)	84.00 (79.00–90.00)	93.00 (88.00–98.00)	95.00 (91.00–100.00)	<0.001
Systolic blood pressure, mmHg	130.00 (119.30–141.30)	121.00 (111.30–140.00)	140.00 (130.00–151.30)	142.00 (130.70–160.00)	<0.001
Diastolic blood pressure, mmHg	80.00 (78.70–90.00)	80.00 (73.30–89.30)	90.00 (80.00–97.30)	90.00 (81.30–100.00)	<0.001
Fasting plasma glucose, mmol/L	5.11 (4.67–5.71)	5.00 (4.59–5.40)	5.61 (4.92–6.34)	6.27 (5.77–7.63)	<0.001
Triglycerides, mmol/L	1.27 (0.90–1.93)	1.11 (0.81–1.50)	1.94 (1.36–2.81)	2.49 (1.95–3.63)	<0.001
LDL cholesterol, mmol/L	2.34 (1.84–2.83)	2.32 (1.84–2.80)	2.40 (1.86–2.90)	2.40 (1.80–2.96)	<0.001
HDL cholesterol, mmol/L	1.51 (1.28–1.77)	1.53 (1.31–1.78)	1.46 (1.23–1.73)	1.35 (1.10–1.64)	<0.001
Total cholesterol, mmol/L	4.93 (4.28–5.60)	4.86 (4.24–5.49)	5.11 (4.40–5.83)	5.22 (4.49–5.98)	<0.001
Lifestyle risk factors					
Current smoking	29428 (31.03)	22007 (31.61)	5305 (29.79)	2116 (28.56)	<0.001
Current alcohol	17034 (17.96)	12320 (17.70)	3402 (19.10)	1312 (17.71)	<0.001
Physical inactivity	79947 (84.30)	59303 (85.19)	14796 (83.08)	5848 (78.93)	<0.001
Sedentary time, h/week, ≥30	10290 (10.85)	7242 (10.40)	2110 (11.85)	938 (12.66)	<0.001
Salt intake, g/day, ≥6	24037 (25.35)	17597 (25.28)	4434 (24.90)	2006 (27.08)	0.001

Values are the number (proportion), mean (SD), or median (interquartile range)

BMI body mass index, *HDL* high-density lipoprotein cholesterol, *LDL* low-density lipoprotein cholesterol, *N* number

fewest metabolic risk components and the healthiest lifestyle had the lowest risk of CVD, whereas those within the most metabolic risk components and the least healthy lifestyle had the highest risk (2.06 [95% CI 1.77–2.39]) of CVD. The same association was present with respect to stroke but not with respect to MI or all-cause mortality.

Metabolic health status was associated with the risk of CVD for participants in each of the lifestyle categories. There were no significant interactions between metabolic risk and lifestyle factors (all $P = 0.15$).

The associations of lifestyle with CVD, stroke, MI, and all-cause mortality were next stratified according to metabolic health status (Fig. 2). Overall, participants with the healthiest lifestyle were associated with a lower risk of CVD in all the metabolic health groups. Compared with those in participants with the healthiest lifestyle, the HRs for CVD in participants with the least healthy lifestyle were 1.26 (95% CI 1.17–1.37) for the category with low metabolic risk, and 1.16 (95% CI 1.03–1.31), 1.07 (95% CI 0.90–1.27) for those with medium and high metabolic risk, respectively. Moreover, even a moderately healthy lifestyle conferred higher risk of CVD in participants with medium metabolic risk (1.24 [95% CI 1.11–1.39]). Similar results were obtained with respect to stroke. There was no significant association between lifestyle and MI among participants with differing metabolic health statuses. For all-cause mortality, there was a significant association between healthy lifestyle and all-cause mortality only in the category with low metabolic risk (online Table 3 in Supplementary Material).

Discussion

In this perspective cohort study, we have identified the joint associations of lifestyle and metabolic risk with the incidence of CVD and all-cause mortality. The findings show that individuals with high metabolic risk and an unfavorable lifestyle have significantly higher risks of incident CVD and all-cause mortality compared with individuals with low metabolic risk and a healthier lifestyle. We found that the association between lifestyle and the risk of CVD was present in individuals with a range of metabolic risk statuses. Finally, the association between metabolic risk and the risk of CVD was not modified by differences in lifestyle.

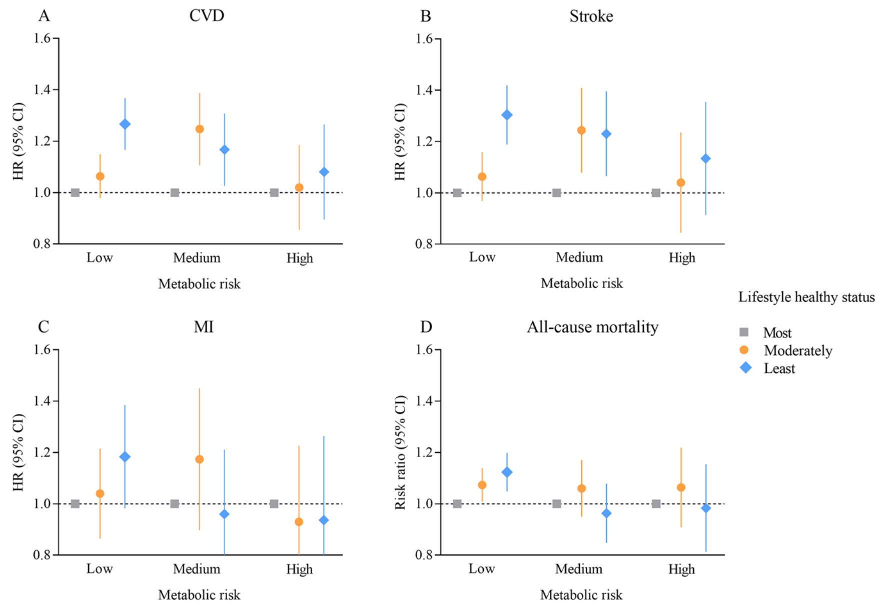

Fig. 2 Combined associations of lifestyle and metabolic health status with CVD, stroke, myocardial infarction, and all-cause mortality. Association of lifestyle health status with CVD (**A**), stroke (**B**), MI (**C**), and all-cause mortality (**D**) across the metabolic health groups. Cox proportional hazards models were used to generate HRs and corresponding 95% CIs, adjusted for age, sex, body mass index, education, and family income at baseline. CVD cardiovascular disease, MI myocardial infarction, HRs hazard ratios

Table 2 Risk of incident cardiovascular disease, stroke, myocardial infarction, and all-cause mortality according to metabolic health categories

	Metabolic health status		
	Low metabolic risk	Medium metabolic risk	High metabolic risk
Cardiovascular disease			
Case, *n* (%)	3925 (5.64)	1749 (9.82)	916 (12.36)
Incidence rate, per 1000 person-years (95% CI)	5.42 (5.25–5.59)	9.75 (9.30–10.21)	12.48 (11.70–13.32)
HR (95% CI)*	Reference	1.47 (1.39–1.56)	1.85 (1.72–2.00)
P value for trend	<0.001		
Stroke			
Case, *n* (%)	3141 (4.51)	1386 (7.78)	706 (9.53)
Incidence rate, per 1000 person-years (95% CI)	4.31 (4.17–4.47)	7.65 (7.26–8.07)	9.51 (8.83–10.23)
HR (95% CI)*	Reference	1.45 (1.36–1.55)	1.77 (1.62–1.93)
P value for trend	<0.001		
Myocardial infarction			
Case, *n* (%)	868 (1.25)	413 (2.32)	238 (3.21)
Incidence rate, per 1000 person-years (95% CI)	1.18 (1.10–1.26)	2.23 (2.03–2.46)	3.12 (2.75–3.54)
HR (95% CI)*	Reference	1.56 (1.38–1.76)	2.13 (1.82–2.48)
P value for trend	<0.001		
All-cause mortality			
Case, *n* (%)	5938 (8.53)	2249 (12.63)	1031 (13.92)
Incidence rate, per 1000 person-years (95% CI)	8.02 (7.81–8.22)	12.03 (11.54–12.54)	13.34 (12.55–14.18)
HR (95% CI)*	Reference	1.34 (1.28–1.41)	1.55 (1.44–1.66)
P value for trend	<0.001		

HR hazard ratio, CIs confidence intervals

*Adjusted for age, sex, body mass index, education, and family income at baseline

Previous studies have shown similar, but not identical, associations between lifestyle factors and cardiometabolic outcomes [8, 9, 13, 27]. A recent meta-analysis showed that a combination of healthy lifestyle factors was associated with substantially lower risks of incident diabetes, mortality, and incident CVD [11]. Furthermore, a previous study

Table 3 Risk of incident cardiovascular disease, stroke, myocardial infarction, and all-cause mortality according to lifestyle health categories

	Lifestyle health status		
	Healthiest lifestyle	Moderately healthy lifestyle	Least healthy lifestyle
Cardiovascular disease			
Case, *n* (%)	3492 (6.76)	1536 (6.76)	1562 (7.65)
Incidence rate, per 1000 person-years (95% CI)	6.57 (6.36–6.79)	6.55 (6.23–6.88)	7.40 (7.04–7.78)
HR (95% CI)*	Reference	1.10 (1.03–1.17)	1.23 (1.15–1.30)
P value for trend	<0.001		
Stroke			
Case, *n* (%)	2758 (5.34)	1207 (5.31)	1268 (6.21)
Incidence rate, per 1000 person-years (95% CI)	5.16 (4.97–5.35)	5.11 (4.83–5.41)	5.97 (5.65–6.31)
HR (95% CI)*	Reference	1.10 (1.03–1.18)	1.27 (1.18–1.36)
P value for trend	<0.001		
Myocardial infarction			
Case, *n* (%)	826 (1.60)	358 (1.58)	335 (1.64)
Incidence rate, per 1000 person-years (95% CI)	1.52 (1.42–1.63)	1.49 (1.35–1.66)	1.55 (1.39–1.72)
HR (95% CI)*	Reference	1.04 (0.92–1.18)	1.08 (0.95–1.23)
P value for trend	0.226		
All-cause mortality			
Case, *n* (%)	5235 (10.13)	2161 (9.51)	1822 (8.92)
Incidence rate, per 1000 person-years (95% CI)	9.59 (9.33–9.85)	8.96 (8.59–9.35)	8.37 (7.99–8.76)
HR (95% CI)*	Reference	1.07 (1.02–1.13)	1.08 (1.02–1.14)
P value for trend	0.003		

HR hazard ratio, CIs confidence intervals

*Adjusted for age, sex, body mass index, education and family income at baseline

of over 40,000 Chinese participants aged 30–79 years demonstrated that adherence to a healthy lifestyle substantially reduces the risk of diabetes. This study also showed that the attributable risk percentage for diabetes in this population was highest in older and obese participants [28]. In the present study, lifestyle was not significantly associated with the risk of MI, which is not consistent with the results of the INTERHEART Study [29]. Individually, these lifestyle factors were more strongly associated with the risk of stroke than MI, although the power of the study was limited by the few cases of MI. Future studies should focus on identifying in risk factors for each CVD subtype.

Data from the China Cardiometabolic Disease and Cancer Cohort (4C) study have presented robust effects of lifestyle on new-onset diabetes and major cardiovascular events, regardless of metabolic status [7], which is not consistent with our results. The present findings imply that the associations between metabolic factors and the risks of CVD, stroke, and all-cause mortality are not modified by healthy lifestyle. This discrepancy may be the results of differences in the characteristics of the participants or the duration of follow-up. We used a long-term follow-up cohort study to evaluate the possibility that a strategy based on the combination of lifestyle and metabolic health status could be used to help prevent CVD and early death.

The present study had several strengths. The Kailuan study is a large population-based cohort study of Chinese adults. Standardized protocols were used for data collection, including with respect to lifestyle, metabolic health, and potential confounders such as income and education. In addition, long-term follow-up data were available regarding CVD events, which were identified and adjudicated by trained staff. However, several limitations should also be taken into consideration. First, lifestyle factors were self-reported, which render these data susceptible to self-reporting bias. Second, women were underrepresented in the cohort, such that the generalizability of finding is limited. Third, the lifestyle and metabolic health categories were relatively artificial, therefore, considerable caution should be used in interpreting the precise effects of the risk factors. In addition, previous studies considered that moderate alcohol consumption may have protective effects on CVD [30, 31]. However, in our present database, only 30% of

Table 4 Risk of cardiovascular disease, stroke, myocardial infarction, and all-cause mortality in participants according to the combinations of baseline lifestyle and metabolic health status

	Lifestyle health status		
	Healthiest lifestyle	Moderately healthy lifestyle	Least healthy lifestyle
Cardiovascular disease			
Metabolic health status			
Low metabolic risk	Reference	1.05 (0.97–1.14)	1.25 (1.16–1.35)
Medium metabolic risk	1.42 (1.31–1.54)	1.78 (1.60–1.98)	1.72 (1.53–1.92)
High metabolic risk	1.93 (1.75–2.14)	1.92 (1.66–2.22)	2.06 (1.77–2.39)
Stroke			
Metabolic health status			
Low metabolic risk	Reference	1.06 (0.96–1.15)	1.28 (1.17–1.39)
Medium metabolic risk	1.39 (1.27–1.52)	1.74 (1.54–1.96)	1.77 (1.56–2.00)
High metabolic risk	1.83 (1.63–2.05)	1.85 (1.57–2.18)	2.07 (1.75–2.44)
Myocardial infarction			
Metabolic health status			
Low metabolic risk	Reference	1.03 (0.87–1.22)	1.18 (1.00–1.40)
Medium metabolic risk	1.58 (1.34–1.86)	1.83 (1.47–2.27)	1.53 (1.20–1.95)
High metabolic risk	2.37 (1.95–2.89)	2.05 (1.53–2.74)	2.01 (1.46–2.75)
All-cause mortality			
Metabolic health status			
Low metabolic risk	Reference	1.07 (1.01–1.14)	1.13 (1.06–1.21)
Medium metabolic risk	1.39 (1.30–1.48)	1.47 (1.34–1.61)	1.33 (1.20–1.48)
High metabolic risk	1.61 (1.47–1.76)	1.68 (1.48–1.91)	1.53 (1.31–1.78)

The Cox proportional hazards model was used to detect adjusted HRs (95% CIs)

Adjusted for age, sex, body mass index, education, and family income at baseline

the whole population at baseline (2006–2007) had these data. As a result, we could not classify alcohol consumption into a large number of groups. Finally, the population study came from China, and therefore the results may not be generalizable to other ethnicities. Further studies, including in other geographic regions and of participants of other ethnicities, are needed to confirm the generalizability of the present results.

Conclusions

We found that a healthy lifestyle and metabolic health are associated with a lower risk of CVD, whereas an unhealthy lifestyle and the presence of metabolic risk factors are associated with a higher risk of CVD. The association between lifestyle and the risk of CVD is present irrespective of the level of metabolic risk. Our findings highlight the importance of considering both lifestyle factors and metabolic health status in the prevention of CVD and suggest that a healthy lifestyle should be promoted even for people with high metabolic risk.

Data availability

Data are available to researchers on request for purposes of reproducing the results or replicating the procedure by directly contacting the corresponding author.

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Author contributions Y.Z. and H.L. wrote the manuscript. Y.Z., A.W., S.C., X.T., and H.L. collected the data. S.C. and X.T. researched data and contributed to discussion. S.W. and D.M. reviewed and edited the manuscript. A.W. contributed to the discussion and reviewed/edited the manuscript. All authors read and approved the final manuscript.

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Compliance with ethical standards

Conflict of interest The authors declare no competing interests.

Ethical approval The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was performed according to the guidelines of the Helsinki Declaration and was approved by the Ethics Committee of Kailuan General Hospital (approval number: 2006-05) and Beijing Tiantan Hospital (approval number: 2010-014-01). Written consents were obtained from all participants or their legal representatives.

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References

1. GBD 2017 Causes of Death Collaborators. Global, regional, and national age-sex-specific mortality for 282 causes of death in 195 countries and territories, 1980–2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet **392**(10159), 1736–1788 (2018)
2. S.C. Cramer, W.J. Koroshetz, S.P. Finklestein, The case for modality-specific outcome measures in clinical trials of stroke recovery-promoting agents. Stroke **38**(4), 1393–1395 (2007)
3. L.B. Goldstein, R. Adams, M.J. Alberts, L.J. Appel, L.M. Brass, C.D. Bushnell, A. Culebras, T.J. DeGraba, P.B. Gorelick, J.R. Guyton, R.G. Hart, G. Howard, M. Kelly-Hayes, J.V. Nixon, R.L. Sacco, Primary prevention of ischemic stroke: a guideline from the American Heart Association/American Stroke Association Stroke Council: cosponsored by the Atherosclerotic Peripheral Vascular Disease Interdisciplinary Working Group; Cardiovascular Nursing Council; Clinical Cardiology Council; Nutrition, Physical Activity, and Metabolism Council; and the Quality of Care and Outcomes Research Interdisciplinary Working Group. Circulation **113**(24), e873–e923 (2006)
4. C.P. Wen, J.P. Wai, M.K. Tsai, Y.C. Yang, T.Y. Cheng, M.C. Lee, H.T. Chan, C.K. Tsao, S.P. Tsai, X. Wu, Minimum amount of physical activity for reduced mortality and extended life expectancy: a prospective cohort study. Lancet **378**(9798), 1244–1253 (2011)
5. S.E. Chiuve, K.M. Rexrode, D. Spiegelman, G. Logroscino, J.E. Manson, E.B. Rimm, Primary prevention of stroke by healthy lifestyle. Circulation **118**(9), 947–954 (2008)
6. T.T. van Sloten, M. Tafflet, M.C. Périer, A. Dugravot, R.E.D. Climie, A. Singh-Manoux, J.P. Empana, Association of change in cardiovascular risk factors with incident cardiovascular events. JAMA **320**(17), 1793–1804 (2018)
7. M. Li, Y. Xu, Q. Wan, F. Shen, M. Xu, Individual and combined associations of modifiable lifestyle and metabolic health status with new-onset diabetes and major cardiovascular events: the China Cardiometabolic Disease and Cancer Cohort (4C) Study. Diabetes Care **43**(8), 1929–1936 (2020)
8. A.S. Gami, B.J. Witt, D.E. Howard, P.J. Erwin, L.A. Gami, V.K. Somers, V.M. Montori, Metabolic syndrome and risk of incident cardiovascular events and death: a systematic review and meta-analysis of longitudinal studies. J. Am. Coll. Cardiol. **49**(4), 403–414 (2007)
9. F.B. Hu, J.E. Manson, M.J. Stampfer, G. Colditz, S. Liu, C.G. Solomon, W.C. Willett, Diet, lifestyle, and the risk of type 2 diabetes mellitus in women. N. Engl. J. Med. **345**(11), 790–797 (2001)
10. D. Mozaffarian, A. Kamineni, M. Carnethon, L. Djoussé, K.J. Mukamal, D. Siscovick, Lifestyle risk factors and new-onset diabetes mellitus in older adults: the cardiovascular health study. Arch. Intern. Med. **169**(8), 798–807 (2009)
11. Y. Zhang, X.F. Pan, J. Chen, L. Xia, A. Cao, Y. Zhang, J. Wang, H. Li, K. Yang, K. Guo, M. He, A. Pan, Combined lifestyle factors and risk of incident type 2 diabetes and prognosis among individuals with type 2 diabetes: a systematic review and meta-analysis of prospective cohort studies. Diabetologia **63**(1), 21–33 (2020)
12. X.F. Pan, Y. Li, O.H. Franco, J.M. Yuan, A. Pan, W.P. Koh, Impact of combined lifestyle factors on all-cause and cause-specific mortality and life expectancy in Chinese: the Singapore Chinese Health Study. J. Gerontol. Ser. A, Biol. Sci. Med. Sci **75**(11), 2193-2199 (2019)
13. E.S. Horton, Effects of lifestyle changes to reduce risks of diabetes and associated cardiovascular risks: results from large scale efficacy trials. Obesity **17**(Suppl 3), S43–S48 (2009)
14. S. Wu, Z. Huang, X. Yang, Y. Zhou, A. Wang, L. Chen, H. Zhao, C. Ruan, Y. Wu, A. Xin, K. Li, C. Jin, J. Cai, Prevalence of ideal cardiovascular health and its relationship with the 4-year cardiovascular events in a northern Chinese industrial city. Circ. Cardiovasc. Qual. Outcomes **5**(4), 487–493 (2012)
15. A. Wang, Y. Sun, X. Liu, Z. Su, J. Li., Y. Luo, S. Chen, J. Wang, X. Li, Z. Zhao, H. Zhu, S. Wu, X. Guo, Changes in proteinuria and the risk of myocardial infarction in people with diabetes or pre-diabetes: a prospective cohort study. Cardiovasc Diabetol **16**(1), 104 (2017)
16. C. Wang, Y. Yuan, M. Zheng, A. Pan, M. Wang, M. Zhao, Y. Li, S. Yao, S. Chen, S. Wu, H. Xue, Association of Age of onset of hypertension with cardiovascular diseases and mortality. J. Am. Coll. Cardiol. **75**(23), 2921–2930 (2020)
17. S. Wu, Y. Song, S. Chen, M. Zheng, Y. Ma, L. Cui, J.B. Jonas, Blood pressure classification of 2017 associated with cardiovascular disease and mortality in young Chinese adults. Hypertension **76**(1), 251–258 (2020)
18. C.E. Tan, S. Ma, D. Wai, S.K. Chew, E.S. Tai, Can we apply the National Cholesterol Education Program Adult Treatment Panel definition of the metabolic syndrome to Asians? Diabetes Care **27**(5), 1182–1186 (2004)
19. X.Y. Li, X.L. Cai, P.D. Bian, L.R. Hu, High salt intake and stroke: meta-analysis of the epidemiologic evidence. CNS Neurosci. Ther. **18**(8), 691–701 (2012)
20. D. Mozaffarian, S. Fahimi, G.M. Singh, R. Micha, S. Khatibzadeh, R.E. Engell, S. Lim, G. Danaei, M. Ezzati, J. Powles, Global sodium consumption and death from cardiovascular causes. N. Engl. J. Med. **371**(7), 624–634 (2014)
21. S.M. El Dayem, A.A. Battah, M. El Bohy Ael, A. El Shehaby, El, E.A. Ghaffar, Relationship of plasma level of chemerin and vaspin to early atherosclerotic changes and cardiac autonomic neuropathy in adolescent type 1 diabetic patients. J. Pediatr. Endocrinol. Metab. **28**(3–4), 265–273 (2015)
22. Y. Li, Z. Huang, C. Jin, A. Xing, Y. Liu, C. Huangfu, A.H. Lichtenstein, K.L. Tucker, S. Wu, X. Gao, Longitudinal change of perceived salt intake and stroke risk in a Chinese population. Stroke **49**(6), 1332–1339 (2018)
23. S. Wu, S. An, W. Li, A.H. Lichtenstein, J. Gao, P.M. Kris-Etherton, Y. Wu, C. Jin, S. Huang, F.B. Hu, X. Gao, Association of trajectory of cardiovascular health score and incident cardiovascular disease. JAMA Netw. Open **2**(5), e194758 (2019)
24. A. Wang, X. Liu, Z. Su, S. Chen, N. Zhang, Y. Wang, Y. Wang, S. Wu, Two-year changes in proteinuria and risk for myocardial infarction in patients with hypertension: a prospective cohort study. J. Hypertens. **35**(11), 2295–2302 (2017)
25. World Health Organization. Recommendations on stroke prevention, diagnosis, and therapy. Report of the WHO Task Force on Stroke and other Cerebrovascular Disorders. Stroke **20**(10), 1407–1431 (1989)
26. H. Tunstall-Pedoe, K. Kuulasmaa, P. Amouyel, D. Arveiler, A.M. Rajakangas, A. Pajak, Myocardial infarction and coronary deaths in the World Health Organization MONICA Project. Registration procedures, event rates, and case-fatality rates in 38 populations from 21 countries in four continents. Circulation **90**(1), 583–612 (1994)
27. A. Towfighi, E.M. Cheng, V.A. Hill, F. Barry, M. Lee, N.P. Valle, B. Mittman, M. Ayala-Rivera, L. Moreno, A. Espinosa, H. Dombish, D. Wang, D. Ochoa, A. Chu, M. Atkins, B.G. Vickrey, Results of a pilot trial of a lifestyle intervention for stroke survivors: healthy eating and lifestyle after stroke. J. Stroke Cerebrovasc. Dis. **29**(12), 105323 (2020)

28. J. Lv, C. Yu, Y. Guo, Z. Bian, L. Yang, Y. Chen, X. Hu, W. Hou, J. Chen, Z. Chen, L. Qi, L. Li, Adherence to a healthy lifestyle and the risk of type 2 diabetes in Chinese adults. Int. J. Epidemiol. **46** (5), 1410–1420 (2017)
29. K.K. Teo, L. Liu, C.K. Chow, X. Wang, S. Islam, L. Jiang, J.E. Sanderson, S. Rangarajan, S. Yusuf, Potentially modifiable risk factors associated with myocardial infarction in China: the INTERHEART China study. Heart **95**(22), 1857–1864 (2009)
30. R.J. Song, X.T. Nguyen, R. Quaden, Y.L. Ho, A.C. Justice, D.R. Gagnon, K. Cho, C.J. O'Donnell, J. Concato, J.M. Gaziano, L. Djoussé, Alcohol consumption and risk of coronary artery disease (from the Million Veteran Program). Am. J. Cardiol. **121**(10), 1162–1168 (2018)
31. X.Y. Zhang, L. Shu, C.J. Si, X.L. Yu, D. Liao, W. Gao, L. Zhang, P.F. Zheng, Dietary patterns, alcohol consumption and risk of coronary heart disease in adults: a meta-analysis. Nutrients **7**(8), 6582–6605 (2015)