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

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OBJECTIVE

We aimed to determine the individual and combined associations of lifestyle and metabolic factors with new-onset diabetes and major cardiovascular events among a Chinese population aged ≥40 years.

RESEARCH DESIGN AND METHODS

Baseline lifestyle information, waist circumference, blood pressure, lipid profiles, and glycemic status were obtained in a nationwide, multicenter, prospective study of 170,240 participants. During the up to 5 years of follow-up, we detected 7,847 individuals with new-onset diabetes according to the American Diabetes Association 2010 criteria and 3,520 cardiovascular events, including cardiovascular death, myocardial infarction, stroke, and hospitalized or treated heart failure.

RESULTS

On the basis of 36.13% (population-attributable fraction [PAF]) risk attributed to metabolic risk components collectively, physical inactivity (8.59%), sedentary behavior (6.35%), and unhealthy diet (4.47%) moderately contributed to incident diabetes. Physical inactivity (13.34%), unhealthy diet (8.70%), and current smoking (3.38%) significantly contributed to the risk of major cardiovascular events, on the basis of 37.42% PAF attributed to a cluster of metabolic risk factors. Significant associations of lifestyle health status with diabetes and cardiovascular events were found across all metabolic health categories. Risks of new-onset diabetes and major cardiovascular events increased simultaneously according to the worsening of lifestyle and metabolic health status.

CONCLUSIONS

We showed robust effects of lifestyle status on new-onset diabetes and major cardiovascular events regardless of metabolic status and a graded increment of risk according to the combination of lifestyle and metabolic health, highlighting the importance of lifestyle modification regardless of the present metabolic status.

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Cardiovascular disease remains the leading threat to public health worldwide, to which diabetes confers considerable risk (1). Comprehensive management of lifestyle and metabolic risk factors has become an imperative issue for the prevention of diabetes and cardiovascular disease (2,3). Prior studies have shown that unhealthy lifestyle factors, such as smoking, excess alcohol intake, sedentary behavior, and unhealthy diet, are detrimentally related with an increasing risk of diabetes as well as cardiovascular disease and premature death (4–10). As modifiable conditions, both lifestyle and metabolic health status are rationally outlined as preventive targets (11–14).

While several studies thus far focused on the associations of cardiometabolic abnormalities with lifestyle factors and metabolic factors separately (15–20), few have systematically described the relative relationship of lifestyle factors with the risk of new-onset diabetes and cardiovascular disease across a population at different degrees of metabolic risk (21–23). Beyond that, evidence regarding the joint effect of overall lifestyle and metabolic health status on the cardiometabolic risk is still limited. Actually, it is of substantial interest to conduct risk stratification for diseases with major public health concern by the combining of lifestyle and metabolic health status, which could improve our understanding of the composition of modifiable risk factors, avail the identification of populations with modifiable risks, and further uncover precise targets for interventions.

With a broad spectrum of lifestyle and metabolic factors available in the China Cardiometabolic Disease and Cancer Cohort (4C) Study, a large prospective cohort study, we can draw an artificial distinction between metabolic and lifestyle health status based on the components of metabolic syndrome and traditional lifestyle risk factors and then determine the individual and combined associations of lifestyle and metabolic health status with the risk of new-onset diabetes and major cardiovascular events in a Chinese population aged ≥40 years.

RESEARCH DESIGN AND METHODS

Study Population

The 4C Study is a multicenter, nationwide, population-based prospective cohort study exploring the associations of metabolic factors with specific clinical outcomes, including incident diabetes and cardiovascular events, in Chinese individuals aged ≥40 years. The study protocol and informed consent were approved by the Committee on Human Research at Rui-Jin Hospital affiliated to the Jiao-Tong University School of Medicine, Shanghai, China. All participants signed the written informed consent.

The details of the 4C Study design have been described previously (24–26). The 4C Study included 20 community sites, covering 16 provinces, autonomous regions, or municipalities of mainland China. At baseline, eligible men and women aged ≥40 years at each study site were identified from local resident registration systems. There was no restriction on sex or ethnicity. Trained community health workers visited the homes of eligible individuals and invited them to participate in the study. Generally, 193,846 subjects, with 62.8% urban residents, were enrolled and underwent examination at baseline in 2010–2011. At each site, face-to-face interviews via questionnaires, anthropometric measurements, a standard oral glucose tolerance test (OGTT), and collection of blood samples were completed in 2010–2011. The follow-up investigation was conducted during 2014–2016, and 170,240 individuals remained in the cohort.

We excluded 5,610 participants with missing data for any metabolic component at baseline. After the exclusion of 3,615 participants without data on baseline diabetes status, 39,623 participants with diabetes at baseline based on medical records, OGTT, or hemoglobin A_{1c}, and 17,399 without glucose measures at follow-up, a total of 103,993 participants was selected for metabolic health status and new-onset diabetes analysis. When it came to cardiovascular disease, 11,276 participants with a medical history of cardiovascular disease at baseline and 22,574 without follow-up information on cardiovascular disease were excluded, leaving 130,780 individuals for the analysis of metabolic health status and major cardiovascular events. For the risk according to lifestyle health status and the combined analysis, 81,659 were included in the new-onset diabetes analysis, and 102,382 were included in the major cardiovascular events, after the exclusion of those with missing data on lifestyle risk factors. The mean follow-up period was 3.8 years (Supplementary Fig. 1).

Definitions of Lifestyle Health Status at Baseline

Lifestyle health information at baseline was collected face-to-face by trained staff using a standard questionnaire. Current smokers were defined as participants with at least seven cigarettes per week for at least 6 months. Former smokers were defined as participants who reported not currently smoking cigarettes but had smoked at least seven cigarettes per week for at least 6 months in a lifetime. Alcohol intake was classified into three categories based on the daily alcohol consumption according to sex: <5 g/day, 5–29.9 g/day, and ≥30 g/day for men; and <5 g/day, 5–14.9 g/day, and ≥15 g/day for women. Physical

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activity level was classified into two categories: *1*) ideal physical activity: ≥150 min/week moderate intensity, ≥75 min/week vigorous intensity, or ≥150 min/week moderate and vigorous intensity; and *2*) physical inactivity: 0–149 min/week moderate intensity, 0–74 min/week vigorous intensity, or 0–149 min/week moderate and vigorous intensity. Average sedentary time spent per week was reported and classified into three categories: <20 h/week, 20–29 h/week, and ≥30 h/week. We used a food frequency questionnaire to evaluate dietary habits in the previous year. The healthy diet score included the following four components: fruits and vegetables, ≥4.5 cups/day; fish, 2 or more 3.5-oz servings/week; sweets/sugar-sweetened beverages, ≤450 kcal/week; and soy protein, ≥25 g/day (27).

We calculated the number of lifestyle risk factors according to the presence of five lifestyle risk factors: *1*) current smoking; *2*) excess alcohol intake: ≥30 g/day for men and ≥15 g/day for women; *3*) physical inactivity; *4*) sedentary behavior (sedentary time ≥30 h/week); *5*) unhealthy diet: 0–1 healthy diet score. The lifestyle health status was defined based on the number of lifestyle risk factors and thus classified into three categories: most healthy lifestyle (0–1 risk factor), moderately healthy lifestyle (2 risk factors), and least healthy lifestyle (3–5 risk factors).

Definitions of Metabolic Health Status at Baseline

Metabolic health status at baseline was determined based on the anthropometric measurements and laboratory tests. Body weight, height, waist circumference, and blood pressure measurements were performed by the trained staff. BMI was calculated to evaluate obesity status. Blood samples were collected after an overnight fast. A standard 75-g load OGTT was performed, and postload blood samples were obtained at 2 h. Plasma fasting and postload glucose concentrations were evaluated at local hospitals using the glucose oxidase or hexokinase method. The levels of hemoglobin A_{1c} and lipids were tested at the central laboratory. Hemoglobin A_{1c} was tested using finger capillary whole blood by high-performance liquid chromatography (VARIANT II Systems; Bio-Rad, Hercules, CA). Serum total cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides were tested using an autoanalyser (Abbott Laboratories, Abbott Park, IL) at the central laboratory.

The widely used Adult Treatment Panel-III (ATP-III) criteria were used to determine the metabolic health status according to the presence of the components of metabolic syndrome (28): *1*) central obesity: waist circumference ≥90 cm in men and ≥80 cm in women; *2*) high triglycerides: triglycerides level ≥1.69 mmol/L; *3*) low HDL cholesterol: HDL cholesterol level <1.03 mmol/L in men and <1.29 mmol/L in women; *4*) high blood pressure: blood pressure ≥130/85 mmHg or taking antihypertensive drugs; *5*) high glycemia: fasting plasma glucose level ≥5.6 mmol/L (100 mg/dL) or taking hypoglycemic medications. The metabolic health status was defined based on the number of metabolic risk components and classified into three categories: 0–2 components, 3 components, and 4–5 components.

Outcome Ascertainment

All the above interviews and tests at baseline were repeated during the follow-up investigation.

Following the 2010 American Diabetes Association criteria, diabetes was diagnosed during follow-up visits with at least one of the criteria *1*) fasting plasma glucose level of ≥7.0 mmol/L, *2*) OGTT 2-h postload plasma glucose level of ≥11.1 mmol/L, *3*) hemoglobin A_{1c} level of ≥6.5% (≥48 mmol/mol), or *4*) a self-reported diagnosis by clinicians (25).

As mentioned previously (25), information on mortality and its specific cause was collected from local death and disease registries of the National Disease Surveillance Point System and National Health Insurance System. Throughout the study period, the medical records of subjects who visited an emergency department or were hospitalized were collected and adjudicated centrally. Major cardiovascular events were defined as a composite of nonfatal myocardial infarction or stroke, hospitalized or treated heart failure, and cardiovascular death during follow-up.

Statistical Analyses

Baseline characteristics according to metabolic health status are presented as proportions or means ± SD or median (interquartile range). One-way ANOVA was used to compare continuous variables, and χ^2 tests were used to compare categorical variables across metabolic health status.

The cumulative incidence of diabetes was calculated for a mean follow-up of 3.8 years. Relative risk regression was used to detect the individual and combined associations between lifestyle and metabolic health status at baseline and the risk of incident diabetes. Baseline age, sex, urban/rural residence, economic status, BMI, education attainments, family history of diabetes, and hemoglobin A_{1c} were further adjusted. Economic status was assessed by the mean annual income in the year of our baseline survey (2010), which was treated as a dichotomous variable. The mean level of the current sample (¥41,890 per person per year) was used as a cutoff.

The incidence rate of cardiovascular disease (per 1,000 person-years) was calculated, and Cox proportional hazards models were used to evaluate the individual and combined associations, adjusted for baseline age, sex, urban/rural residence, economic status, BMI, education attainments, and family history of diabetes.

We further quantified the effect of the lifestyle risk factors on the prespecified outcomes. By simultaneously fitting all of the lifestyle and metabolic factors into a model other than the covariables as mentioned above, the respective population-attributable fraction (PAF) and 95% CI of each risk factor was calculated for the new-onset diabetes and major cardiovascular events, respectively.

All reported *P* values were two-sided. SAS 9.2 software was used for the statistical analyses.

RESULTS

Baseline Characteristics

Table 1 summarizes the baseline sociodemographic, metabolic, and lifestyle characteristics of subjects in different baseline metabolic health status. Compared with participants with 0–2 metabolic risk components, those at higher risk were older, had a lower level of education, were more likely to be women, and had positive family history of diabetes. As expected, participants with more metabolic risk components tended to have a higher level of BMI, waist circumference, blood pressure, plasma glucose, and adverse lipid profile. The proportion of participants with physical inactivity or

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

		Metabolic health status			
	Overall	0–2 components	3 components	4–5 components	*P* value*
Participants (*n*)	164,630	89,451	39,167	36,012	—
Sociodemographics					
Age at recruitment, years	56.96 ± 9.13	55.74 ± 9.20	57.93 ± 8.90	58.95 ± 8.71	<0.0001
Men	34.44	37.78	33.94	26.70	<0.0001
Education attainment (high school or above)	36.64	38.81	34.92	33.11	<0.0001
Family history of diabetes	13.31	11.66	14.39	16.25	<0.0001
Urban residents	62.39	60.77	62.97	65.77	<0.0001
Metabolic risk factors					
BMI, kg/m^2	24.74 ± 3.63	23.39 ± 3.24	25.81 ± 3.39	26.90 ± 3.34	<0.0001
Waist circumference, cm	84.33 ± 9.89	80.06 ± 8.75	87.93 ± 8.80	91.02 ± 8.30	<0.0001
Systolic blood pressure, mmHg	133.69 ± 20.87	127.75 ± 20.05	138.88 ± 20.03	142.80 ± 18.89	<0.0001
Diastolic blood pressure, mmHg	78.59 ± 11.18	75.66 ± 10.70	81.16 ± 10.84	83.05 ± 10.53	<0.0001
Plasma glucose, mmol/L					
Fasting	5.98 ± 1.66	5.51 ± 1.20	6.24 ± 1.76	6.84 ± 2.06	<0.0001
2-h postload	8.31 ± 3.90	7.16 ± 2.97	8.93 ± 4.08	10.49 ± 4.60	<0.0001
Hemoglobin A_{1c}, %	5.80 (5.50–6.20)	5.70 (5.40–6.00)	5.90 (5.60–6.30)	6.20 (5.80–6.80)	<0.0001
Hemoglobin A_{1c}, mmol/mol	40 (37–44)	39 (36–42)	41 (38–45)	44 (40–51)	<0.0001
Triglycerides, mmol/L	1.32 (0.94–1.92)	1.07 (0.82–1.40)	1.49 (1.09–2.05)	2.21 (1.77–3.00)	<0.0001
LDL cholesterol, mmol/L	2.90 ± 0.88	2.87 ± 0.85	2.99 ± 0.91	2.90 ± 0.91	<0.0001
HDL cholesterol, mmol/L	1.34 ± 0.36	1.46 ± 0.36	1.28 ± 0.33	1.11 ± 0.25	<0.0001
Total cholesterol, mmol/L	4.99 ± 1.13	4.93 ± 1.07	5.05 ± 1.19	5.10 ± 1.19	<0.0001
Lifestyle risk factors					
Smoking status					<0.0001
Never	79.93	42.48	19.13	18.33	
Former	5.08	2.62	1.37	1.10	
Current	14.98	9.28	3.20	2.50	
Alcohol intake					<0.0001
<5 g/day	87.52	47.10	20.62	19.81	
5–29.9 g/day (men); 5–14.9 g/day (women)	4.69	2.66	1.18	0.85	
≥30 g/day (men); ≥15 g/day (women)	7.78	4.51	1.90	1.38	
Physical activity					<0.0001
Ideal physical activity	13.81	7.68	3.21	2.93	
Physical inactivity	86.19	46.54	20.50	19.15	
Sedentary time, h/week					<0.0001
0–19	26.82	14.90	17.79	21.66	
20–29	32.79	6.34	7.73	9.58	
≥30	40.39	5.58	7.27	9.15	
Healthy diet score					<0.0001
3–4	16.02	8.84	3.78	23.11	
2	41.05	21.60	9.87	10.33	
0–1	42.92	23.11	9.58	9.49	

Values are the proportion, mean ± SD, or median (interquartile range). **P* values were for the ANOVA or χ^2 analyses across the three categories of metabolic health status.

sedentary behavior increased markedly with the deterioration of metabolic health status, whereas the proportion of current smokers and those with moderate drinking behavior and healthy diet habits decreased.

Individual Associations of Lifestyle and Metabolic Health Status With New-Onset Diabetes

Among 103,993 participants without diabetes at baseline, we detected 7,847 individuals with new-onset diabetes after 3.8 years of follow-up (cumulative incidence 7.55%). The multivariable relative risk regression showed a significantly higher risk of new-onset diabetes among subjects with all of the metabolic risk components. As for lifestyle risk factors, excess alcohol intake (relative risk 1.12 [95% CI 1.03–1.22]), physical inactivity (1.14 [1.07–1.22]), sedentary behavior (1.10 [1.04–1.16]), and unhealthy diet (1.26 [1.18–1.35]) were significantly associated with a higher risk of diabetes. The association between smoking and new-onset diabetes was detected in the univariate analysis but disappeared after further adjustment (Fig. 1*A* and *B*).

Individual Associations of Lifestyle and Metabolic Health Status With Major Cardiovascular Events

Among 130,780 participants without a medical history of cardiovascular disease at baseline, 3,520 cardiovascular events were reported during the follow-up period (overall incidence rate: 7.55 per 1,000 person-years), including 513 nonfatal myocardial infarctions, 2,089 nonfatal strokes, 215 hospitalized or treated for heart failure, and 703 cardiovascular deaths. Among all of the metabolic risk factors, central obesity, high triglycerides, high blood pressure, and high

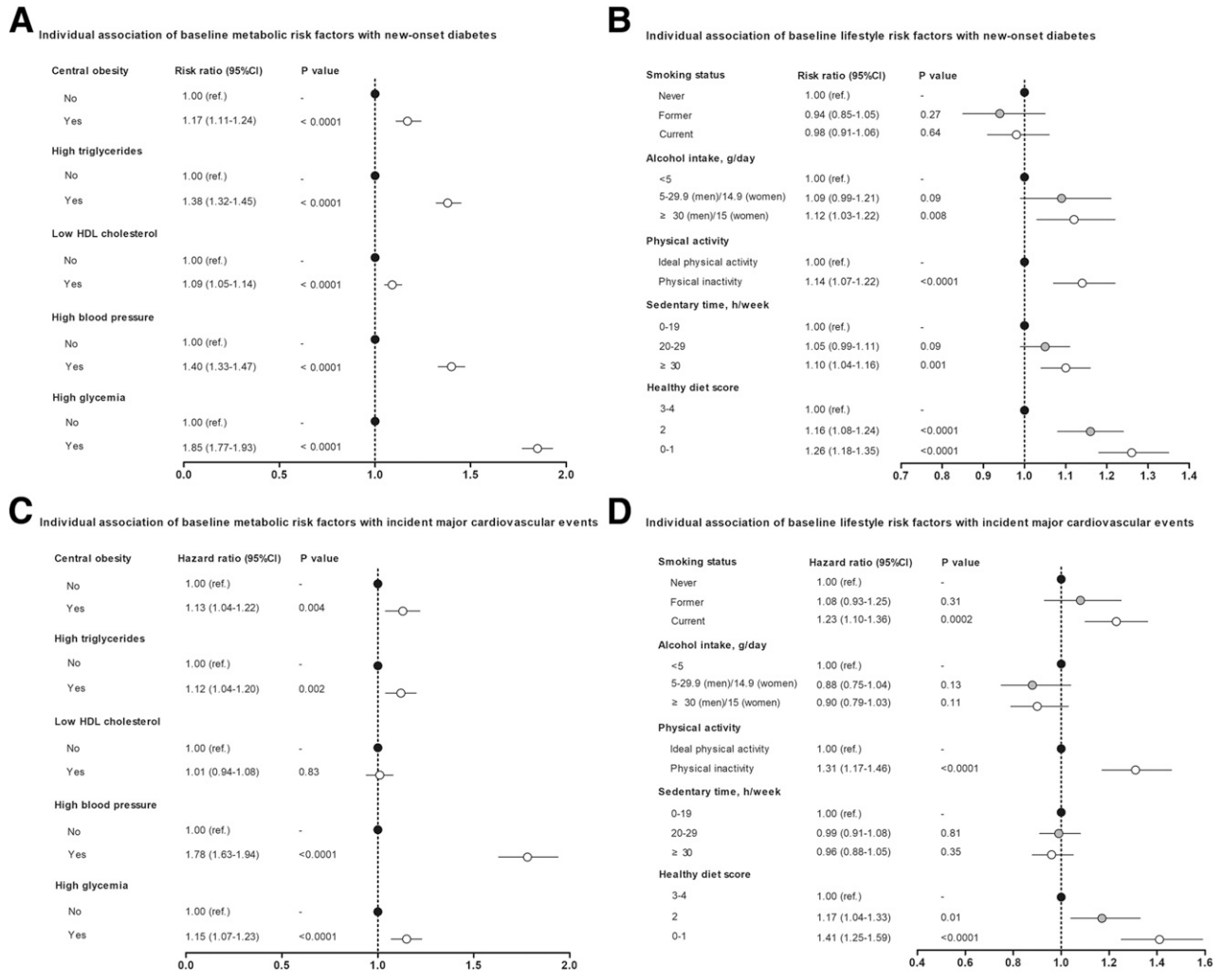

Figure 1—Individual association of metabolic and lifestyle risk factors with new-onset diabetes (*A* and *B*) and major cardiovascular events (*C* and *D*). Relative risk regression analyses were used to generate risk ratios (RRs) and corresponding 95% CIs to detect the risk of new-onset diabetes, adjusted for baseline age, sex, BMI, education attainments, urban/rural residence, economic status, family history of diabetes, and hemoglobin A_{1c}, associated with metabolic (*A*) and lifestyle risk factors (*B*). Cox proportional hazards models were used to generate HRs and corresponding 95% CIs to detect the risk of major cardiovascular events, adjusted for baseline age, sex, BMI, education attainments, urban/rural residence, economic status, and family history of diabetes, associated with metabolic (*C*) and lifestyle risk factors (*D*).

glycemia were independently associated with the incident cardiovascular events. For lifestyle risk factors, current smoking (hazard ratio [HR] 1.23 [95% CI 1.10–1.36]), physical inactivity (1.31 [1.17–1.46]), and unhealthy diet (1.41 [1.25–1.59]) were significantly associated with an increased risk of major cardiovascular events. No statistically significant association was observed for excess alcohol intake and sedentary behavior (Fig. 1*C* and *D*).

Combined Effects of Lifestyle and Metabolic Health Status With New-Onset Diabetes and Major Cardiovascular Events

Associations of lifestyle health status with new-onset diabetes and major cardiovascular events were stratified according to the metabolic health status (Fig. 2*A* and *B*). Overall, participants who had the least healthy lifestyle were associated with a higher risk of diabetes and cardiovascular events across all metabolic health groups. Compared with those with the most healthy lifestyle, the adjusted relative risk (95% CI) of new-onset diabetes for participants with least healthy lifestyle was 1.29 (1.15–1.45) in the category with 0–2 metabolic risk components and was 1.21 (1.06–1.38) and 1.21 (1.07–1.37) for those with 3 and 4–5 metabolic risk components, respectively. Moreover, even a moderately healthy lifestyle conferred an obvious risk of diabetes in those with 0–2 metabolic risk components (1.26 [1.14–1.41]). With regards to cardiovascular events, the adjusted HR for the least healthy lifestyle group was 1.41 (95% CI 1.18–1.69) in the individuals with 0–2 metabolic risk components and was 1.31 (1.05–1.64) and 1.27 (1.02–1.57) for those with 3 and 4–5 metabolic risk components, respectively.

Figure 2*C* shows that metabolic risk factors collectively accounted for 36.13% of the risk to new-onset diabetes in a model containing age, sex, urban/rural residence, economic status, BMI, education attainments, family history of diabetes, hemoglobin A_{1c}, and five individual lifestyle risk factors among our population. Three of the lifestyle risk factors moderately contributed to incident diabetes (PAF: 8.59% for physical inactivity, 6.35% for sedentary behavior,

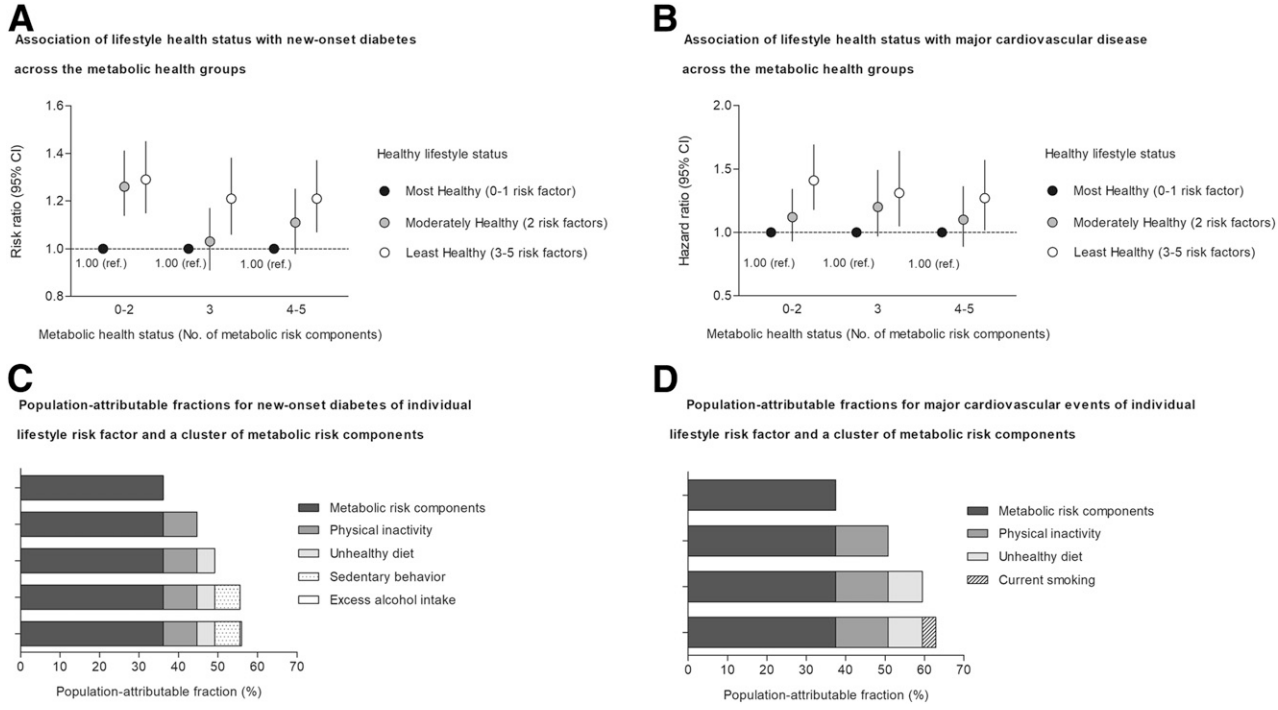

Figure 2—Combined associations of lifestyle and metabolic health status with new-onset diabetes and major cardiovascular events. *A*: Association of lifestyle health status with new-onset diabetes across the metabolic health groups. Relative risk regression analyses were used to generate risk ratios (RR) and corresponding 95% CIs to detect the risk of new-onset diabetes, adjusted for baseline age, sex, BMI, education attainments, urban/rural residence, economic status, family history of diabetes, and hemoglobin A_{1c}. *B*: Association of lifestyle health status with major cardiovascular events across the metabolic health groups. Cox proportional hazards models were used to generate HRs and corresponding 95% CIs, adjusted for baseline age, sex, BMI, education attainments, urban/rural residence, economic status, and family history of diabetes. *C*: PAFs for new-onset diabetes associated with individual lifestyle risk factor and a cluster of metabolic risk components. Model was adjusted for baseline age, sex, BMI, education attainments, urban/rural residence, economic status, family history of diabetes, and hemoglobin A_{1c}. *D*: PAFs for major cardiovascular events associated with individual lifestyle risk factor and a cluster of metabolic risk components. Model was adjusted for baseline age, sex, BMI, education attainments, urban/rural residence, economic status, and family history of diabetes.

and 4.47% for unhealthy diet, respectively); whereas excess alcohol intake contributed modestly. As shown in Fig. 2*D*, 37.42% of the PAF for major cardiovascular events was attributed to a cluster of metabolic risk factors in a model containing age, sex, urban/rural residence, economic status, BMI, education attainments, family history of diabetes, and five individual lifestyle risk factors among our population. Physical inactivity, unhealthy diet, and current smoking

Table 2—Risk of new-onset diabetes and major cardiovascular disease in participants according to the combinations of baseline lifestyle and metabolic health status

	Lifestyle health status					
	Most healthy lifestyle (0–1 factor)		Moderately healthy lifestyle (2 factors)		Least healthy lifestyle (3–5 factors)	
New-onset diabetes*	RR (95% CI)	*P* value	RR (95% CI)	*P* value	RR (95% CI)	*P* value
Metabolic health status						
Metabolic risk components						
0–2	1.00 [Reference]	—	1.27 (1.14–1.41)	<0.0001	1.30 (1.16–1.45)	<0.0001
3	1.54 (1.33–1.77)	<0.0001	1.59 (1.42–1.79)	<0.0001	1.90 (1.68–2.14)	<0.0001
4–5	2.06 (1.79–2.36)	<0.0001	2.27 (2.03–2.54)	<0.0001	2.1 (2.14–2.72)	<0.0001
Major cardiovascular disease†	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Metabolic health status						
Metabolic risk components						
0–2	1.00 [Reference]	—	1.12 (0.94–1.35)	0.21	1.40 (1.17–1.68)	0.0002
3	1.27 (0.99–1.62)	0.058	1.51 (1.25–1.84)	<0.0001	1.69 (1.39–2.06)	<0.0001
4–5	1.46 (1.15–1.86)	0.002	1.60 (1.32–1.94)	<0.0001	1.86 (1.52–2.26)	<0.0001

RR, risk ratio. *Adjusted for age, sex, BMI, education attainment, urban/rural residence, economic status, presence or absence of a family history of diabetes, and hemoglobin A_{1c} at baseline. Relative risk regression was used to detect adjusted RRs (95% CIs) among 81,659 participants with information on all of the 10 modifiable risk factors. †Adjusted for age, sex, BMI, education attainment, urban/rural residence, economic status, and presence or absence of a family history of diabetes at baseline. The Cox proportional hazards model was used to detect adjusted HRs (95% CIs) among 102,382 participants with information on all of the 10 modifiable risk factors.

significantly contributed to the risk of major cardiovascular events (PAF: 13.34% for physical inactivity, 8.70% for unhealthy diet, and 3.38% for current smoking respectively).

We conducted risk stratification of diabetes and cardiovascular events based on the combination of lifestyle and metabolic health status. Relative to the group with the most healthy status for both lifestyle and metabolic conditions, the risk of new-onset diabetes and major cardiovascular events increased simultaneously according to the worsening of lifestyle and metabolic health status (Table 2).

CONCLUSIONS

The current study described the individual association of the lifestyle and metabolic risk factors with the incident of new-onset diabetes and major cardiovascular events based on a nationwide, prospective cohort study conducted in China. Crucially, we presented the two-dimensional grid by the combination of lifestyle and metabolic health status and thereby calibrated the risk stratification to determine the risk of diabetes and cardiovascular events.

Recently, the new American Diabetes Association and European Society of Endocrinology guidelines recommended regular screening for all five components of metabolic risk and identifying individuals at high metabolic risk, for whom lifestyle management would be the first priority in the prevention of subsequent diabetes and cardiovascular disease (29). The recommendation placed a prime emphasis on the evaluation of metabolic status and subsequent lifestyle modification. However, studies are limited about the effects of lifestyle patterns and specific lifestyle factors on diabetes and cardiovascular disease in a population classified into hierarchical degrees of metabolic health status. Our study, for the first time, comprehensively detected the contribution of lifestyle health status as determinants of diabetes and cardiovascular events with the metabolic health status in a large-scale prospective cohort in China. Overall, we demonstrated that the least healthy lifestyle status was independently associated with an increased risk of diabetes and cardiovascular events, regardless of the temporal metabolic status. The diabetes and cardiovascular risk in lifestyle-unhealthy individuals was significantly higher than in their lifestyle-healthy counterparts across all metabolic health categories, independently of socioeconomic status, family history, and BMI level.

Our results showed a slightly larger magnitude of the association for lifestyle health status in incident cardiovascular disease than in diabetes. It was in line with a recent study using data from the Whitehall II study showing that the metabolically unhealthy status increased the risk of diabetes but not cardiovascular disease among obese individuals (30). As was found in the current study, individuals with severe metabolic abnormality but adhering to the most healthy lifestyle had a comparable risk increment of major cardiovascular events, compared with those with only 0–2 metabolic risk components but adopting a least healthy lifestyle (HR 1.46 vs. 1.40). Moreover, the trend of diabetes risk grew steeper across lifestyle categories in the group with fewer metabolic risk factors. Hence, our study highlights the importance of lifestyle modification regardless of the established metabolic status of individuals during regular screening.

As for individual lifestyle factors, physical activity patterns and diet habits seemed to be distinctly important for the risk of new-onset diabetes as well as the risk of major cardiovascular events, which is in line with most previous studies, whichever diet score was applied (19,20). Current smoking was found to confer risk for cardiovascular events but not incident diabetes independently. Moderate alcohol consumption has been recommended to alleviate the cardiometabolic abnormality as a result of its beneficial effects on insulin sensitivity and inflammatory state. However, evidence also emerged that the association of moderate alcohol consumption and clinical outcome was complex and incongruous (6,7). Whether moderate alcohol intake is a protective factor remains disputable. In our study, no significant protective effect was found, while excess alcohol intake did pose a markedly increased risk to new-onset diabetes.

Previous studies have reported similar but not identical associations of lifestyle factors and cardiometabolic outcomes (4–10,14–16,19,20). The inconsistencies between studies might be due to varying economic levels and socioeconomic status of the study population and the related different proportion of the specific lifestyle risk factor. The Cardiovascular Health Study showed that physical inactivity, unhealthy diet, and smoking were all associated with an increased risk of diabetes, but alcohol use was related to a lower risk among the U.S. population aged ≥65 years (15). The recently published Prospective Urban Rural Epidemiology (PURE) study, conducted in those aged 35–70 years in 21 countries, reported that a 6.1% (PAF) of cardiovascular disease can be attributed to unhealthy diet and 6.1% (PAF) to smoking, whereas physical inactivity contributed modestly to the risk (1.5% PAF) (21). Data from the China Kadoorie Biobank (CKB) study have presented the contribution of healthy diet, physical activity, and moderate alcohol intake on the prevention of diabetes and cardiovascular disease as well as the greater effect of smoking on cardiovascular disease than diabetes, which is consistent with our results (19,20). We extended the previous knowledge by including the evaluation of metabolic health status simultaneously and found a graded increment in the risk of diabetes and cardiovascular events according to the deterioration of combined lifestyle and metabolic health status, and thereby proposed a risk evaluation strategy based on the combination to stratify diabetes and cardiovascular risk.

Strengths of the study include a large sample size, a comprehensive evaluation of metabolic and lifestyle factors, and its nationwide, multicenter, population-based prospective design. Importantly, we were able to evaluate the diabetes risk precisely by all three glycemic indexes (fasting and OGTT-2 h postload plasma glucose, and hemoglobin A_{1c}) for the diagnosis of diabetes.

The study also has several limitations. First, the follow-up duration was relatively short, which limited the number of cardiovascular events and influenced the study's statistical power for the analysis of stroke and coronary heart disease separately. Hence, a composite of major cardiovascular events was used as an outcome, and 3,520 cardiovascular events were observed. Second, lifestyle and metabolic factors were measured once at baseline and might not reflect the trajectory. Third, given the coexistence and intricate interaction between lifestyle and metabolic risk factors, distinguishing between lifestyle and metabolic health

status is artificial, indicating that considerable caution should be taken in quantifying the precise effect of risk factors. Finally, the 4C Study was not designed to reflect a nationally representative sample, which might lead to a selection bias and an overestimated prevalence of metabolic abnormality, so that generalizability of the study findings is limited. Nevertheless, our study represents a population-based cohort from 20 communities covering 16 provinces, autonomous regions, or municipalities of mainland China, and our results could be considered reliable because of the large-sized nationwide study population.

Conclusion

Our study showed a robust effect of lifestyle risk factors on the risk of new-onset diabetes and major cardiovascular events regardless of metabolic status and presented a graded increment of risk according to the combination of lifestyle and metabolic health. Our findings highlight the importance of both lifestyle and metabolic health status in the prevention of diabetes and cardiovascular disease and suggest the compelling need of lifestyle modification regardless of the present metabolic status.

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