ORIGINAL RESEARCH

Cumulative Exposure to Ideal Cardiovascular Health and Incident Diabetes in a Chinese Population: The Kailuan Study

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***Background*—**It is unclear whether ideal cardiovascular health (CVH), and particularly cumulative exposure to ideal CVH (cumCVH), is associated with incident diabetes. We aimed to fill this research gap.

***Methods and Results*—**The Kailuan Study is a prospective cohort of 101 510 adults aged 18 to 98 years recruited in 2006–2007 and who were subsequently followed up at 2- (Exam 2), 4- (Exam 3), and 6 (Exam 4)-year intervals after baseline. The main analysis is restricted to those individuals with complete follow-up at all 4 examinations and who had no history of diabetes until Exam 3. Cumulative exposure to ideal CVH (cumCVH) was calculated as the summed CVH score for each examination multiplied by the time between the 2 examinations (score×year). Logistic regression models were used to assess the association between cumCVH and incident diabetes. In fully adjusted models, compared with the lowest quintile of cumCVH, individuals in the highest quintile had ~68% (95% confidence interval [CI] 60-75) lower risk for incident diabetes (compared with 61% [95% CI 52-69] lower risk when using baseline CVH). Every additional year lived with a 1-unit increase in ideal CVH was associated with a 24% (95% CI 21-28) reduction in incident diabetes.

***Conclusions*—**Ideal CVH is associated with a reduced incidence of diabetes, but the association is likely to be underestimated if baseline measures of CVH exposure are used. Measures of cumulative exposure to ideal CVH are more likely to reflect lifetime risk of diabetes and possibly other health outcomes.

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Key Words: cardiovascular disease risk factors • cumulative exposure • diabetes mellitus • epidemiology • health status • ideal cardiovascular health

In January 2010 the American Heart Association (AHA) defined the concept of ideal cardiovascular health (CVH) as the simultaneous presence of 4 ideal health behaviors (nonsmoking, normal body mass index [BMI], being physically active, and having a healthy diet) combined with 3 ideal health factors (normal levels of total cholesterol, blood pressure, and fasting blood glucose).[1] Evidence from prospective studies have suggested that having ideal CVH is associated with a protective effect against the development of subclinical atherosclerosis,[2,3] metabolic syndrome,[4] stroke,[5] cardiovascular disease,[6,7] cancer,[8] and all-cause mortality.[9-11]

An inherent limitation of previous studies, however, has been the reliance on a single time point by which to assess CVH, which may have occurred several decades prior to the

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Accompanying Tables S1 through S5 are available at http://jaha.ahajournals.org/content/5/9/e004132/DC1/embed/inline-supplementary-material-1.pdf

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event and is therefore likely to yield biased estimates of the association. Moreover, there has been no consideration of how these health metrics vary within individuals over time and the subsequent impact that this would have on the cumulative exposure to CVH and future risk of disease. To the best of our knowledge, there have been no data published on the association between ideal CVH—in particular, cumulative exposure to ideal CVH (cumCVH)—and new-onset diabetes, which is an independent predictor of cardiovascular events and all-cause mortality.[12] Hence, the objective of the current study was to explore and quantify the prospective association between cumCVH and incident diabetes in the Chinese population using the Kailuan Study.

Methods

Study Population

The Kailuan Study[7] is a prospective cohort study conducted in the Kailuan community in Tangshan city, China. From June 2006 to October 2007, a total of 101 510 participants (81 110 men and 20 400 women, aged 18–98 years) were recruited (Exam 1) and were followed-up in 3 visits in 2008–2009 (Exam 2), 2010–2011 (Exam 3), and 2012–2013 (Exam 4). The primary analysis is based on a subgroup of 34 323 individuals (25 961 men and 8362 women) for whom complete follow-up data were available and who did not have a diagnosis of diabetes prior to Exam 4 (Figure 1). The study was approved by the Ethics Committees of Kailuan General Hospital following the guidelines outlined by the Helsinki Declaration. All participants agreed to participate in this study and provided written informed consent.

Assessment of Cardiovascular Health Metrics

Information on smoking, physical activity, and salt intake (as a proxy for diet) was collected via questionnaires at baseline and during each of the 3 follow-up visits. Smoking status was based on self-report and classified as "never" (ideal health behavior), "former" (intermediate health behavior), or "current" (poor health behavior). Information on physical activity level (minutes of moderate or vigorous activity per week) was obtained from questionnaires and categorized as follows: ≥80 (ideal); 1 to 79 (intermediate) and; 0 (poor) minutes of moderate or vigorous activity per week.[5] Because information on dietary pattern was not available, the amount of salt used during cooking was used as a surrogate marker, as studies have shown that high intakes of salt are correlated with poor dietary patterns.[13] We collected 24-hour dietary salt intake for this study. A standard spoon was used for participants to recall how much salt they ate in the last 24 hours. Self-reported use of salt was classified as "low" (<6 g/day, representing "ideal"), "medium" (6–10 g/day; "intermediate"), or "high" (>10 g/day; "poor"). In a random sample of 1000 participants, 24-hour natriuresis was measured to determine the correlation with self-reported use of salt. The correlation was high (r=0.78), indicating that self-reported use of salt was associated with actual salt intake in this study.

Height was measured to an accuracy of 0.1 cm using a tape measure, and weight was measured to the nearest 0.1 kg with calibrated platform scales. Body mass index (BMI) was calculated as body weight (kg) divided by the square of height (m^2). Using the AHA definitions,[1] BMI was classified as ideal (<25 kg/m^2), intermediate (25–29.9 kg/m^2), or poor (≥30 kg/m^2).[5,7,11,14] Blood pressure (BP) was measured by a mercury sphygmomanometer. Three readings of systolic and diastolic blood pressure (SBP and DBP) were taken at 5-minute intervals after participants had rested in a chair for at least 5 minutes. Blood pressure was classified as ideal (SBP <120 mm Hg and DBP <80 mm Hg and untreated with BP-lowering medications), intermediate (120 mm Hg ≤ SBP ≤139 mm Hg, 80 mm Hg ≤ DBP ≤89 mm Hg, or treated to SBP/DBP <120/80 mm Hg), or poor (SBP ≥140 mm Hg, DBP ≥90 mm Hg, or treated to SBP/DBP >120/80 mm Hg).

Blood samples were collected from the antecubital vein after overnight fasting. Fasting blood glucose (FBG) was measured using the hexokinase/glucose-6-phosphate-dehydrogenase method.[15] FBG was classified as ideal (<5.6 mmol/L and untreated), intermediate (5.6–6.9 mmol/L or treated to <5.6 mmol/L), or poor (≥7.0 mmol/L or treated to ≥5.6 mmol/L). Total cholesterol (TC) and triglycerides were measured enzymatically. Total cholesterol status was classified as ideal (<200 mg/dL and untreated), intermediate (200–239 mg/dL or treated to <200 mg/dL), or poor (≥240 mg/dL or treated to ≥200 mg/dL), respectively.

Assessment of Potential Covariates

A 10-second 12-lead electrocardiogram was used to measure the resting heart rate (RHR) after the individual had rested in the supine position for 5 minutes. The number of R-R intervals (number of QRS complexes−1) was divided by the time difference between the first and last beat, and the results were converted to beats per minute (bpm).[16] High-density lipoprotein cholesterol (HDL-C) and LDL-C levels were measured using a direct test method[17] (interassay coefficient of variation <10%; Mind Bioengineering Co, Ltd, Shanghai, China). "High-sensitivity" C-reactive protein (hs-CRP) was measured by a high-sensitivity nephelometry assay (Cias Latex CRP-H, Kanto Chemical, Tokyo, Japan). Serum uric acid (UA) concentrations were measured using an oxidase method. All biochemical variables were measured at the central laboratory of Kailuan General Hospital with use of a Hitachi autoanalyzer (Hitachi 747; Hitachi, Tokyo, Japan).

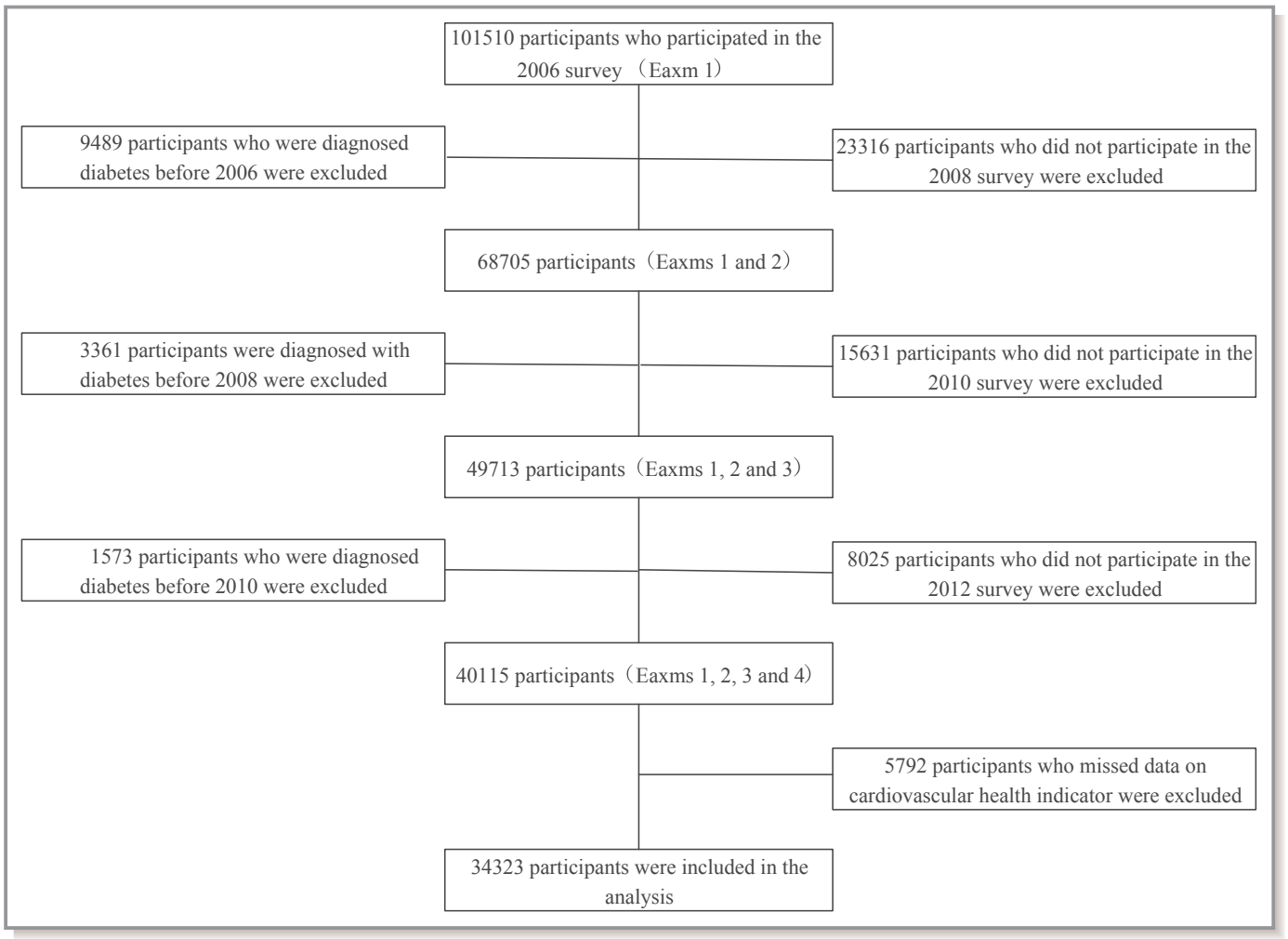

Figure 1. Selection of Kailuan study participants for analysis.

Information on demographic and clinical characteristics (age, sex, alcohol use, personal monthly income, education, and history of diseases) was collected via questionnaire at study baseline. Participants were classified into 3 categories: <40, 40 to 59, and ≥60 years according to baseline age. Previous history of disease, including myocardial infarction, stroke, and cancer, was collected by self-report. The use of antihypertensive, cholesterol-lowering, and glucose-lowering medications within the past 2 weeks before the baseline interview was also self-reported. The average monthly income was categorized as "<¥600," "¥600 to ¥800," or "≥¥800." The educational attainment was categorized as "illiteracy or primary," "middle school," and "high school or above."

Cumulative Exposure to Ideal Cardiovascular Health

To examine the association between cumulative exposure to CVH metrics (except the FBG metric), a dichotomized variable for each component of the health metrics was created: "ideal"=2; "intermediate"=1; and "poor"=0. The total ideal CVH score of each individual was the sum score of the 6 ideal CVH metrics and ranged from 0 to 12. CumCVH was defined as the summed CVH score for each examination multiplied by the time between the two consecutive visits in years: $CVH_1 \times time_{1-2} + CVH_2 \times time_{2-3} + CVH_3 \times time_{3-4}$, where CVH_1, CVH_2, and CVH_3 indicate CVH at examinations 1 (baseline), 2, and 3, and $time_{1-2}$, $time_{2-3}$, $time_{3-4}$, indicate the participant-specific time intervals between consecutive Exams 1 to 3, in years. Participants were categorized into quintiles of cumCVH point score: Quintile 1 <39 points; Quintile 2 39 to 43 points; Quintile 3 44 to 48 points; Quintile 4 49 to 54 points; and Quintile 5 ≥55 points.

Assessment of New-Onset Diabetes

In line with the ADA guidelines, participants were diagnosed with diabetes mellitus at Exam 4 (2012–2013) if they were currently treated with insulin or oral hypoglycaemic agents or had a FBG concentration ≥7.0 mmol/L.[18]

Table 1. Characteristics of Studied Participants in 2006 According to Cumulative Exposure of CVH

	Group of Cumulative Exposure of CVH					
	Q1	Q2	Q3	Q4	Q5	*P* Value
Cardiovascular Health scores	5 (5–6)	7 (6–8)	7 (7–8)	8 (8–9)	9 (9–10)	<0.001
No. of participants, n	6864	6865	6864	6866	6864	
Age, y	46.00±9.91	47.34±11.10	47.50±11.46	47.93±12.28	48.35±12.98	<0.001
Men, n (%)	6439 (93.81)	5944 (86.58)	5491 (80.00)	4663 (67.91)	3424 (49.88)	<0.001
Education, n (%)						<0.001
Illiteracy/primary school	468 (6.82)	473 (6.89)	428 (6.24)	422 (6.15)	405 (5.90)	
Middle school	4822 (70.31)	4935 (71.90)	4959 (72.30)	4791 (69.80)	4456 (64.95)	
High school or above	1568 (22.86)	1456 (21.21)	1472 (21.46)	1651 (24.05)	2000 (29.15)	
Income, ¥/month, n (%)						<0.001
<¥600	2582 (37.64)	2036 (29.67)	1896 (27.63)	1805 (26.30)	1540 (22.46)	
¥600 to ¥800	3176 (46.30)	3811 (55.55)	4024 (58.65)	4086 (59.54)	4207 (61.34)	
≥¥800	1102 (16.06)	1014 (14.78)	941 (13.72)	972 (14.16)	1111 (16.20)	
Alcohol drinking, n (%)						<0.001
Never	2305 (33.61)	3486 (50.82)	4149 (60.50)	4725 (68.84)	5248 (76.50)	
Past	250 (3.64)	230 (3.35)	181 (2.64)	150 (2.19)	127 (1.85)	
Current, <1 times/day	2045 (29.81)	1670 (24.34)	1501 (21.89)	1278 (18.62)	1024 (14.93)	
Current, 1+times/day	2259 (32.93)	1474 (21.49)	1027 (14.98)	711 (10.36)	461 (6.72)	
Smoking, n (%)						<0.001
Poor	4293 (62.54)	2763 (40.25)	1884 (27.45)	1076 (15.67)	422 (6.15)	
Intermediate	652 (9.50)	725 (10.56)	690 (10.05)	556 (8.10)	370 (5.39)	
Ideal	1919 (27.96)	3377 (49.19)	4290 (62.50)	5234 (76.23)	6072 (88.46)	
Physical activity, n (%)						<0.001
Poor	1126 (16.40)	752 (10.95)	581 (8.46)	417 (6.07	243 (3.54)	
Intermediate	5140 (74.88)	5394 (78.59)	5471 (79.71)	5431 (79.10)	5158 (75.15)	
Ideal	598 (8.71)	718 (10.46)	812 (11.83)	1018 (14.83)	1463 (21.31)	
Salt intake, n (%)						<0.001
Poor	1485 (21.63)	812 (11.83)	568 (8.28)	416 (6.06)	285 (4.15)	
Intermediate	4970 (72.41)	5551 (80.86)	5704 (83.10)	5801 (84.49)	5603 (81.63)	
Ideal	409 (5.96)	502 (7.31)	592 (8.62)	649 (9.45)	976 (14.22)	
BMI, kg/m^2	27.12±3.41	25.74±3.30	24.84±3.12	24.03±2.87	22.72±2.60	<0.001
Systolic blood pressure, mm Hg	135.38±19.61	130.67±18.99	127.44±18.43	124.04±18.02	117.53±16.47	<0.001
Diastolic blood pressure, mm Hg	87.93±11.67	84.43±10.84	82.44±10.54	80.09±10.05	76.07±9.36	<0.001
Fasting blood glucose concentration, mmol/L	5.13±0.67	5.06±0.66	5.02±0.64	4.98±0.64	4.91±0.60	<0.001
Total cholesterol concentration, mmol/L	5.41±1.22	4.97±1.17	4.77±1.09	4.68±1.04	4.53±0.88	<0.001
Resting heart rate, bpm	74.54±9.86	73.45±9.44	73.01±9.63	72.72±9.63	72.00±9.45	<0.001
Uric acid, μmol/L	314.82±85.49	292.27±80.27	280.16±78.18	270.92±77.70	260.99±74.80	<0.001
High-sensitivity C-reactive protein, mg/L	0.90 (0.40–2.29)	0.75 (0.30–2.08)	0.68 (0.24–1.77)	0.60 (0.22–1.66)	0.45 (0.19–1.30)	<0.001

Education level (elementary school, high school, or college or above), income level (income ≥ ¥800/month, ¥600 to ¥800/month, and <¥600/month), drinking (never, past, current <1 time/day, or current, 1+times/day). BMI indicates body mass index; CVH, ideal cardiovascular health; Q1, quintile 1; Q2, quintile 2; Q3, quintile 3; Q4, quintile 4; Q5, quintile 5.

Table 2. Odds Ratios and 95% Confidence Intervals of Diabetes in Relation to Quintile and Unit Increase in Cumulative Exposure of CVH

	Group of Cumulative Exposure of CVH						
	Q1	Q2	Q3	Q4	Q5	1 Unit Increase	*P* for Trend
Total, n	6864	6865	6864	6866	6864		
Case number, n (%)	423 (6.16)	295 (4.30)	266 (3.88)	167 (2.43)	150 (2.19)		
Model 1*	1.00	0.64 (0.55–0.74)	0.56 (0.48–0.66)	0.33 (0.28–0.40)	0.28 (0.23–0.35)	0.95 (0.95–0.96)	<0.001
Model 2†	1.00	0.63 (0.54–0.74)	0.55 (0.47–0.65)	0.32 (0.27–0.39)	0.28 (0.23–0.34)	0.95 (0.95–0.96)	<0.001
Model 3‡	1.00	0.69 (0.59–0.81)	0.62 (0.52–0.73)	0.35 (0.28–0.43)	0.32 (0.25–0.40)	0.96 (0.95–0.96)	<0.001
Sex							
Women	42 (9.88)	47 (5.10)	63 (4.59)	56 (2.54)	67 (1.95)		
Model 3‡	1.00	0.57 (0.36–0.92)	0.65 (0.41–1.01)	0.39 (0.24–0.62)	0.30 (0.18–0.47)	0.95 (0.94–0.97)	<0.001
Men	381 (5.92)	248 (4.17)	203 (3.70)	111 (2.38)	83 (2.42)		
Model 3‡	1.00	0.71 (0.60–0.84)	0.61 (0.50–0.73)	0.33 (0.26–0.42)	0.35 (0.27–0.46)	0.96 (0.95–0.97)	<0.001
P-interaction		0.311	0.885	0.958	0.218		
Age, y							
<40	65 (3.86)	39 (2.42)	24 (1.44)	13 (0.73)	12 (0.64)		
Model 3‡	1.00	0.75 (0.49–1.14)	0.46 (0.28–0.76)	0.22 (0.12–0.43)	0.23 (0.11–0.47)	0.95 (0.93–0.96)	<0.001
40 to 59	304 (6.51)	210 (4.75)	187 (4.37)	109 (2.72)	97 (2.58)		
Model 3‡	1.00	0.75 (0.62–0.91)	0.69 (0.56–0.84)	0.40 (0.31–0.51)	0.37 (0.28–0.49)	0.96 (0.95–0.97)	<0.001
P-interaction		0.572	0.027	0.017	0.021		
≥60	54 (10.59)	46 (5.51)	55 (6.00)	45 (4.16)	41 (3.33)		
Model 3‡	1.00	0.49 (0.32–0.75)	0.57 (0.37–0.86)	0.33 (0.21–0.53)	0.30 (0.18–0.47)	0.96 (0.94–0.98)	<0.001
P-interaction		0.345	0.209	0.101	0.143		
Sensitivity analysis							
Model 4§	1.00	0.69 (0.59–0.82)	0.63 (0.53–0.74)	0.35 (0.28–0.43)	0.32 (0.26–0.40)	0.96 (0.95–0.97)	<0.001

CVH indicates ideal cardiovascular health; Q1, quintile 1; Q2, quintile 2; Q3, quintile 3; Q4, quintile 4; Q5, quintile 5.
*Adjusted for age (years), sex.
†Adjusted for as Model 1 plus education level (elementary school, high school, or college or above), income level (income ≥ ¥800/month, ¥600 to ¥800/month, and < ¥600/month), and drinking (never, past, current <1 times/day or current 1+times/day).
‡Adjusted for as model 2 plus high-sensitivity C-reactive protein, uric acid, resting heart rate at Exam 1 and medication usage before Exam 4.
§Adjusted for Model 3 and further excluded individuals with cardiovascular disease (myocardial infarction) before Exam 4.

Statistical Analyses

Continuous variables were described as mean±standard deviation (SD) and were compared by ANOVA or the Kruskal-Wallis test. Categorical variables were described as percentages and were compared using χ^2 tests. A logistic regression model was used to estimate the risk of diabetes associated with cumCVH metrics (primary analysis) and with CVH at study baseline (secondary analysis). Odds ratios (ORs) and 95% CIs were calculated. We fitted 3 multivariate models. Model 1 adjusted for age and sex. Model 2 additionally adjusted for education level, income level, and alcohol consumption. Model 3 further adjusted for hs-CRP, UA, RHR in 2006, and medication usage before 2012. The interactions of cumCVH with sex and age on risk of diabetes were assessed. Because there were 11 hospitals that conducted the laboratory test assays, we used a random effect for each hospital to account for the potential measurement bias.

We conducted several sensitivity analyses to test the robustness of our findings: first, individuals with a prior history of cardiovascular diseases (CVD) at Exam 4 were excluded; second, because duration of follow-up is likely to have influenced an individual's exposure to cumCVH, a time-weighted cumCVH model was used to assess the association between CVH and incident diabetes. The time-weighted cumCVH was calculated by $(CVH_1 \times time_{1-2} + CVH_2 \times time_{2-3} + CVH_3 \times time_{3-4})/(time_{1-2} + time_{2-3} + time_{3-4})$. Third, to check whether exclusion of missing data (~60%) influenced the main

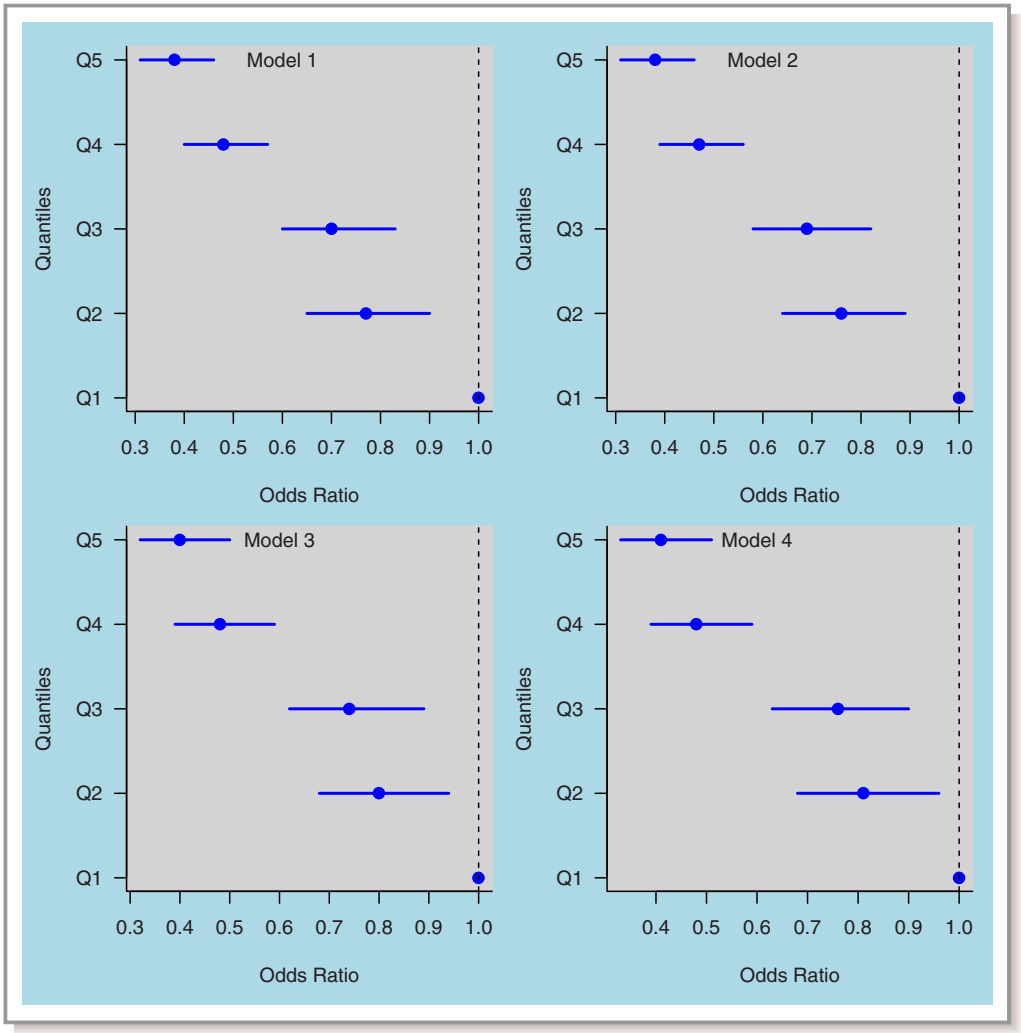

Figure 2. Odds ratios (and 95% confidence intervals) of diabetes in relation to quintile increase in cumulative exposure of ideal cardiovascular health behaviors (smoking, diet, exercise, and BMI). Q1=quintile 1, Q2=quintile 2, Q3=quintile 3, Q4=quintile 4, Q5=quintile 5. Model 1: adjusted for age (years), sex. Model 2: adjusted as for Model 1 plus education level (elementary school, high school, or college or above), income level (income ≥ ¥800/month, ¥600 to ¥800, and income < ¥600/month), and drinking (never, past, current, <1 times/day or current, 1+times/day). Model 3: adjusted as for Model 2 plus high-sensitivity C-reactive protein, uric acid, resting heart rate at Exam 1, and medication usage before Exam 4. Model 4: adjusted as for Model 3 and further excluded individuals with cardiovascular disease (myocardial infarction) before Exam 4. BMI indicates body mass index.

findings, we examined the relationship between CVH at baseline (Exam 1) and incident diabetes (at Exam 2). Finally, the individual influence that each of the 6 CVH metrics had on risk of incident diabetes was examined after excluding each of the 7 metrics from the cumCVH score in turn. All statistical analyses were performed using SAS 9.3 (SAS Institute, Cary, NC). All statistical tests were 2-sided, and the significance level was set at $P<0.05$.

Results

Baseline participant characteristics stratified by quintile of cumCVH exposure are shown in Table 1. In general, participants in the lowest quintile for cumCVH were younger. In addition, participants in the lowest quintile for cumCVH were predominantly male, were less educated, and had lower monthly incomes than those in higher quintiles. The distribution of CVH indices across quintiles of cumCVH differed by sex most notably for smoking (very few women were current or former smokers) and BMI (more overweight and obese women than men irrespective of quintile) (Table S1).

During a mean±SD follow-up of 6.3±0.50 years there were 1301 (21% women) cases of incident diabetes (Exam 4). Table 2 shows the adjusted odds ratios (ORs) of incident diabetes associated with quintiles of cumCVH exposure. The incidence of new-onset diabetes ranged from 6.16% in the

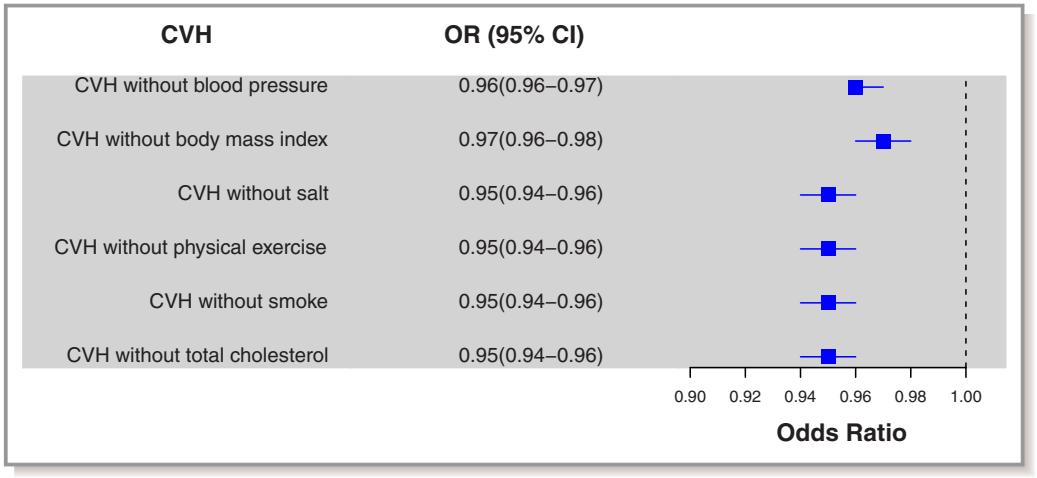

Figure 3. Odds ratios and 95% confidence intervals of diabetes in relation to a 1-unit increase in cumulative exposure of ideal cardiovascular health, following individual exclusion of cardiovascular health metrics. The models adjusted for age, sex, education level, income level, drinking, high-sensitivity C-reactive protein, uric acid, resting heart rate at Exam 1, and medication usage before Exam 4.

lowest quintile of cumCVH to 2.19% in the highest. In the fully adjusted model, compared with participants in the lowest quintile, those in the highest quintile for cumCVH exposure had ~68% lower risk of developing diabetes (OR 0.32; 95%, CI 0.25–0.40). For every unit increase in cumCVH, the risk of diabetes decreased by ~4% (OR 0.96, 95% CI 0.95–0.96). The effect was consistent across sex and age groups (Table 2) and did not materially differ following exclusion of the individual risk factors. Exclusion of individuals with a prior history of CVD did not materially affect the results (Table 2). The ideal health behaviors (smoking, diet, exercise, and BMI) also reduced the odds of diabetes (Figure 2).

The results using the time-weighted cumulative exposure to CVH were highly comparable to the unweighted model (Table S2). In the fully adjusted model every additional year lived with a 1-unit increase in ideal CVH was associated with a 24% (95% CI 21–28) reduction in incident diabetes. Furthermore, when we excluded each of the 6 metrics from the cumCVH score in turn, the association was unaffected following exclusion of individual risk factors (Figure 3).

Table 3 shows the adjusted ORs of incident diabetes associated with quintiles of baseline CVH exposure. In the fully adjusted model, compared with participants in the lowest quintile, those in the highest quintile for CVH exposure were at 61% lower risk of developing diabetes (OR 0.39, 95% CI 0.31–0.48). For every unit increase in CVH, the risk of diabetes decreased by ≈17% (OR 0.83, 95% CI 0.80–0.86). The effect was consistent across sex and age groups (Table 3). Similar results were observed when the analysis was conducted in participants (n=65 185) who attended only the first follow-up examination (Exam 2) (Table S3).

Table S4 shows comparison of demographic and other characteristics of participants and nonparticipants. The individuals included in the present study were significantly younger (47.43±11.62 years) than excluded participants (53.85±12.97 years); had a higher level of education (23.75% vs 18.80%; $P<0.001$); and had lower levels of systolic blood pressure, diastolic blood pressure, fasting blood glucose, total cholesterol, high-sensitivity C-reactive protein concentration, uric acid concentration, and resting heart rate (Table S4).

Discussion

The concept of "ideal cardiovascular health" recognizes that vascular risk factors—such as high blood pressure, diabetes, cigarette smoking, and poor diet—frequently cluster and that an aggregate measure of these risk factors is likely to be a truer reflection of an individual's level of vascular risk than any single risk factor in isolation. Findings from the current study extend previous work[2-4,6,8,9,19] (Table S5) by demonstrating for the first time that ideal CVH is associated with a substantially lower risk of incident diabetes compared with those with poor CVH when measured either at baseline or cumulatively: specifically, every additional year lived with a 1-unit increase in ideal CVH was associated with a 24% reduction in incident diabetes.

The associations were broadly similar in subgroups stratified by sex and age and after adjusting for potential confounders. In addition, participants in the lowest quintile for cumCVH were younger. This might be caused by the fact that younger people have to spend more time working and do not pay attention to their health care. The young have more living pressure because of their low income. Moreover, our results show that the relationship between CVH and incident diabetes (and possibly other vascular outcomes) is likely to be

Table 3. Odds Ratios and 95% Confidence Intervals of Diabetes (Exam 4) in Relation to Quintile Increase of Baseline CVH

	Group of Baseline CVH						
	Q1	Q2	Q3	Q4	Q5	1 Unit Increase	*P* for Trend
Total, n	4877	5078	7177	7634	9557		
Case number, n (%)	298 (6.11)	244 (4.81)	321 (4.47)	226 (2.96)	212 (2.22)		
Model 1*	1.00	0.75 (0.63–0.90)	0.68 (0.58–0.81)	0.45 (0.37–0.54)	0.35 (0.29–0.42)	0.81 (0.78–0.83)	<0.001
Model 2†	1.00	0.74 (0.62–0.88)	0.66 (0.56–0.78)	0.42 (0.35–0.51)	0.33 (0.27–0.40)	0.80 (0.77–0.83)	<0.001
Model 3‡	1.00	0.78 (0.65–0.94)	0.73 (0.61–0.87)	0.50 (0.41–0.60)	0.39 (0.31–0.48)	0.83 (0.80–0.86)	<0.001
Sex							
Women	18 (7.29)	42 (7.07)	70 (5.43)	63 (3.28)	82 (1.90)		
Model 3‡	1.00	1.00 (0.54–1.86)	0.91 (0.51–1.64)	0.63 (0.35–1.15)	0.44 (0.24–0.81)	0.81 (0.73–0.89)	<0.001
Men	280 (6.05)	202 (4.50)	251 (4.26)	163 (2.85)	130 (2.48)		
Model 3‡	1.00	0.75 (0.62–0.91)	0.71 (0.59–0.85)	0.48 (0.39–0.60)	0.41 (0.32–0.52)	0.84 (0.80–0.87)	<0.001
P-interaction		0.376	0.547	0.614	0.757		
Age, y							
<40	42 (4.13)	33 (3.04)	29 (1.87)	21 (1.13)	28 (0.90)		
Model 3‡	1.00	0.82 (0.51–1.33)	0.54 (0.33–0.90)	0.35 (0.20–0.61)	0.32 (0.18–0.56)	0.82 (0.74–0.91)	<0.001
40 to 59	215 (6.43)	173 (5.23)	222 (4.91)	161 (3.48)	136 (2.55)		
Model 3‡	1.00	0.79 (0.64–0.98)	0.78 (0.63–0.96)	0.55 (0.44–0.70)	0.40 (0.31–0.52)	0.84 (0.80–0.88)	<0.001
P-interaction		0.875	0.053	0.021	0.035		
≥60	41 (7.95)	38 (5.53)	70 (6.35)	44 (3.85)	48 (4.26)		
Model 3‡	1.00	0.74 (0.46–1.20)	0.80 (0.51–1.23)	0.50 (0.31–0.82)	0.56 (0.34–0.92)	0.87 (0.79–0.95)	<0.001
P-interaction		0.976	0.110	0.112	0.008		

CVH indicates ideal cardiovascular health; Q1, quintile 1; Q2, quintile 2; Q3, quintile 3; Q4, quintile 4; Q5, quintile 5.

*Adjusted for age (years), sex.

†Adjusted for as Model 1 plus education level (elementary school, high school, or college or above), income level (income ≥ ¥800/month, ¥600 to ¥800/month, and income < ¥600/month), and drinking (never, past, current <1 time/day, or current 1+times/day).

‡Adjusted for as Model 2 plus high-sensitivity C-reactive protein, uric acid, resting heart rate at Exam 1, and medication usage before Exam 4.

underestimated when a single measure of exposure at study baseline is used as opposed to a cumulative measure. These findings thus provide the first evidence that mid- to long-term exposure to CVH is not only strongly associated with future risk of diabetes but that it is likely to be a more accurate indicator of the true magnitude of risk as compared with a single measure of CVH done several years before the onset of diabetes.

Over the last 2 decades the prevalence of diabetes in China has more than quadrupled from 2.5% in 1994 to an estimated 11.6% in 2010, paralleling the rapid increase in the prevalence of overweight and obesity in the population that has occurred.[20] By 2030 it is estimated that the prevalence of diabetes in China will increase further to 42.3 million people living with diabetes.[21] Although much of the estimated increase in diabetes prevalence is due to China's aging population,[22,23] our findings suggest that widespread adoption of public health interventions that target the prevention or prompt reversal of adverse health behaviors such as smoking, high salt intake, and physical inactivity may have a beneficial impact on reducing the incidence of diabetes across the life course. This proposition is supported by intervention and observational studies that have shown that diabetes is amenable to lifestyle interventions.[24-29] For example, in the Finnish Diabetes Prevention Study, Tuomilehto et al reported a lower incidence of diabetes among middle-aged men who adopted a healthier lifestyle that included weight loss, improved dietary habits, and increased physical activity relative to men who did not alter their behavior.[25] Smoking cessation has also been associated with a reduced risk of incident diabetes,[27] whereas cumulative exposure to obesity (ie, duration and degree of overweight) is positively associated with diabetes risk.[30-32] In our study cumulative exposure to healthy behaviors (not smoking, diet, exercise, and weight loss) is also associated with a reduced diabetes incidence.

The current study is unique in that the measure of cumulative CVH exposure included 5 (smoking, BMI, physical

activity, blood pressure, and total cholesterol) out of the 7 indices that define the AHA's ideal CVH index (with salt use as a proxy of diet). Furthermore, each of these individual risk factors appeared to confer similar risks of diabetes, as the association between cumCVH exposure and incident diabetes was attenuated to a comparable extent following their individual removal from the model (Figure 3). These findings imply that preventative efforts to reduce diabetes incidence that encompass strategies that promote a more holistic approach to optimal vascular health (eg, smoking cessation, weight loss, increased physical activity, low-fat diets) may yield greater benefits than would be expected by targeting individual health behaviors alone.

The biological mechanisms underpinning the association between low ideal CVH and incident diabetes remain speculative but are likely to be driven by increased insulin resistance and inflammation. Obesity, cigarette smoking, physical inactivity, and poor diet have each been reported to increase insulin resistance,[33-36] which in turn is associated with increased plasma concentrations of free fatty acids,[37] elevated plasma concentrations of proinflammatory cytokines,[38,39] and increased oxidative stress.[40,41]

Strengths and Limitations

Our study has several strengths: it is the first prospective study to address the association between cumulative exposure to CVH and incident diabetes in a well-characterized population. Other strengths of our study include its large sample size and information on a broad spectrum of biological and behavioral covariates. However, as with all observational studies, there are some inherent limitations. First, we had no information on dietary habits and therefore used self-reported salt intake as a surrogate indicator of dietary behavior. Previous studies have documented the correlation between the "healthfulness" of different dietary patterns with salt intake and showed that the least optimal diets were those containing the most salt. In the current study the correlation between self-reported salt intake and 24-hour natriuresis among 1000 randomly selected participants was high (r=0.78), indicating good agreement between self-reported salt intake and salt excretion. Second, as all participants were recruited from Tangshan city (an industrial city located in northern China), the cohort is not nationally representative, and thus the findings pertaining to the prevalence of CVH are not generalizable to other parts of China. In contrast, the primary outcome was the estimate of the relative risk of diabetes associated with cumCVH exposure that should be generalizable to the Chinese population (which is supported by the robustness of the findings across age and sex groups).Third, the diagnosis of diabetes was based on a single measure of FBG at Exam 4 without using the oral glucose tolerance test (OGTT), which is due to lack of availability of oral glucose tolerance test data for such a large cohort. Finally, a substantial portion of the participants were dropped from subsequent exams, which might underestimate the benefits of CVH on diabetes. When we compared the characteristics of the final participants and the excluded participants, the results showed that the excluded participants potentially have a higher risk of diabetes compared with the included participants.

In summary, the current findings demonstrate the importance of reducing chronic exposure to adverse health behaviors and risk factors in order to minimize the future risk of diabetes. The study also highlights the need to take into consideration cumulative exposure when estimating risk rather than relying on a single measure of exposure that can often precede the outcome by several decades. In China, public health campaigns that promote, encourage, and support individuals to maintain or adopt a healthier lifestyle early in life or during midlife could have significant beneficial effects in stemming the growing prevalence of diabetes.

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Disclosures

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SUPPLEMENTAL MATERIAL

Table S1.The percentages of each of the seven cardiovascular health indices according to cumulative exposure of CVH.

	Group of cumulative exposure of CVH											
	Women						Men					
CVH metrics	Q1	Q2	Q3	Q4	Q5	*P* value	Q1	Q2	Q3	Q4	Q5	*P* value
Smoking, %						<0.001						<0.001
Ideal	92.24	97.39	97.31	98.73	99.65		23.71	41.72	53.80	65.60	77.22	
Intermediate	2.59	0.87	1.31	0.68	0.23		9.95	12.06	12.24	11.60	10.57	
Poor	5.18	1.74	1.38	0.59	0.12		66.33	46.21	33.96	22.80	12.21	
Body mass index, %						<0.001						<0.001
Ideal	8.00	21.61	41.95	63.23	85.90		26.00	43.19	55.22	66.55	82.80	
Intermediate	52.00	56.35	49.09	33.86	13.14		56.00	50.02	41.27	31.83	16.68	
Poor	40.00	22.04	8.96	2.91	0.96		18.00	6.80	3.51	1.63	0.53	
Physical activity, %						<0.001						<0.001
Ideal	10.12	9.88	9.18	10.26	15.84		8.62	10.55	12.49	16.98	26.81	
Intermediate	80.47	82.63	83.90	84.34	81.57		74.51	77.96	78.66	76.62	68.69	
Poor	9.41	7.49	6.92	5.40	2.59		16.87	11.49	8.85	6.39	4.50	
Salt intake, %						<0.001						<0.001
ideal	5.65	5.65	5.61	7.35	12.85		5.98	7.57	9.38	10.44	15.60	
Intermediate	77.65	82.74	84.49	86.65	83.63		72.06	80.57	82.75	83.47	79.61	
Poor	16.71	11.62	9.91	5.99	3.52		21.96	11.86	7.87	6.09	4.79	
Total cholesterol, %						<0.001						<0.001
Ideal	21.41	39.20	52.80	64.32	77.94		39.52	59.76	69.82	76.54	84.11	

Intermediate	41.18	38.44	34.74	27.87	18.84		38.52	30.74	25.31	19.86	14.57	
Poor	37.41	22.37	12.45	7.81	3.23		21.96	9.51	4.86	3.60	1.31	
Blood pressure, %						<0.001						<0.001
Ideal	5.65	11.83	21.49	33.09	55.32		10.86	17.66	20.83	25.43	35.08	
Intermediate	46.82	54.94	59.14	57.10	40.76		54.65	57.50	58.77	60.15	57.97	
Poor	47.53	33.22	19.37	9.80	3.92		34.49	24.83	20.40	14.41	6.95	
Fasting blood glucose, %						<0.001						<0.001
Ideal	80.47	82.84	86.02	87.38	89.45		75.37	78.62	79.84	81.15	84.61	
Intermediate	19.53	17.16	13.98	12.62	10.55		24.64	21.38	20.16	18.85	15.39	
Poor	--	--	--	--	--		--	--	--	--	--	

Abbreviation: CVH, ideal cardiovascular health;Q1=quintile1, Q2=quintile2, Q3=quintile3, Q4=quintile4, Q5=quintile5.

Table S2. Odds ratios and 95% confidence intervals of diabetes according to the time weighted cumulative exposure of CVH.

	Group of cumulative exposure of CVH						
	Q1	Q2	Q3	Q4	Q5	One score increase	P for trend
Total, n	6864	6865	6865	6865	6864		
Case number, n (%)	426(6.21)	311(4.53)	255(3.71)	186(2.71)	123(1.79)		
Model 1 *	1.00	0.68(0.59-0.80)	0.55(0.47-0.65)	0.39(0.32-0.47)	0.26(0.22-0.33)	0.73(0.70-0.76)	<0.001
Model 2 †	1.00	0.67(0.58-0.78)	0.54(0.46-0.63)	0.38(0.31-0.45)	0.26(0.21-0.32)	0.72(0.69-0.76)	<0.001
Model 3 ‡	1.00	0.72(0.62-0.85)	0.60(0.51-0.71)	0.42(0.35-0.52)	0.29(0.23-0.37)	0.76(0.72-0.79)	<0.001
Sex							
Women,	39(7.75)	54(5.91)	63(4.95)	58(2.88)	61(1.67)		
Model 3 ‡	1.00	0.94(0.59-1.50)	0.92(0.58-1.45)	0.58(0.36-0.93)	0.37(0.22-0.62)	0.75(0.67-0.84)	<0.001
Men	387(6.08)	257(4.32)	192(3.43)	128(2.64)	62(1.94)		
Model 3 ‡	1.00	0.70(0.59-0.83)	0.56(0.46-0.68)	0.41(0.33-0.51)	0.31(0.23-0.41)	0.76(0.72-0.80)	<0.001
P-interaction		0.321	0.105	0.413	0.933		
Age ,years							
<40ys	63(4.13)	39(2.67)	21(1.38)	15(0.91)	15(0.61)		
Model 3 ‡	1.00	0.74(0.49-1.13)	0.39(0.23-0.66)	0.26(0.14-0.48)	0.18(0.09-0.35)	0.70(0.62-0.80)	<0.001
40-59ys	304(6.55)	216(4.88)	181(4.15)	126(3.03)	80(2.25)		
Model 3 ‡	1.00	0.75(0.62-0.91)	0.65(0.53-0.80)	0.47(0.37-0.60)	0.32(0.24-0.43)	0.78(0.74-0.83)	<0.001
P-interaction		0.648	0.023	0.017	0.015		
≥60ys	59(8.44)	56(5.73)	53(5.42)	45(4.25)	28(3.24)		
Model 3 ‡	1.00	0.67(0.45-1.01)	0.66(0.44-1.00)	0.46(0.29-0.72)	0.42(0.25-0.70)	0.76(0.68-0.86)	<0.001
P-interaction		0.988	0.046	0.048	0.006		

Abbreviation: CVH, ideal cardiovascular health;time weighted cumulative exposure of CVH: $(CVH_1 \times time_{1\text{-}2} + CVH_2 \times time_{2\text{-}3} + CVH_3 \times time_{3\text{-}4})/(time_{1\text{-}2} + time_{2\text{-}3} + time_{3\text{-}4})$. Q1=quintile1, Q2=quintile2, Q3=quintile3, Q4=quintile4, Q5=quintile5.

* Adjusted for age (years), sex.

†Adjusted for as model 1 plus education level (elementary school, high school or college or above), income level (income≥800 ¥/month, ¥600-800, and income<600 ¥/month) and drinking (never, past, current, <1times/d or current, 1+times/d).

‡ Adjusted for as model 2 plus High sensitive C-reactive protein, uric acid, resting heart rate at exam1, and medication usage before exam4.

Table S3.Odds ratios and 95% confidence intervals of diabetes (exam2) in relation to quintile increase of baseline exposure of CVH (exam1).

	Group of baseline exposure of CVH						
	Q1	Q2	Q3	Q4	Q5	One score increase	P for trend
Total, n	10422	10218	13701	14016	16817		
Case number, n (%)	794(7.61)	623(6.10)	677(4.94)	583(4.16)	437(2.60)		
Model 1 *	1.00	0.77(0.69-0.86)	0.61(0.55-0.68)	0.52(0.46-0.58)	0.35(0.31-0.39)	0.82(0.80-0.83)	<0.001
Model 2 †	1.00	0.75(0.67-0.83)	0.58(0.52-0.64)	0.48(0.43-0.54)	0.32(0.28-0.36)	0.80(0.78-0.82)	<0.001
Model 3 ‡	1.00	0.79(0.70-0.88)	0.62(0.55-0.69)	0.53(0.47-0.60)	0.36(0.32-0.41)	0.82(0.80-0.84)	<0.001
Sex							
Women,	49(9.42)	99(8.82)	94(4.13)	124(3.75)	119(1.68)		
Model 3 ‡	1.00	1.11(0.75-1.64)	0.53(0.36-0.79)	0.61(0.42-0.89)	0.37(0.25-0.54)	0.79(0.74-0.84)	<0.001
Men	745(7.52)	524(5.76)	583(5.10)	459(4.29)	318(3.27)		
Model 3 ‡	1.00	0.75(0.67-0.85)	0.64(0.56-0.72)	0.52(0.46-0.60)	0.40(0.34-0.46)	0.84(0.81-0.86)	<0.001
P-interaction		0.143	0.131	0.746	0.035		
Age ,years							
<40ys	65(4.01)	46(2.73)	67(2.98)	43(1.59)	40(0.84)		
Model 3 ‡	1.00	0.73(0.49-1.08)	0.87(0.60-1.25)	0.49(0.32-0.75)	0.35(0.22-0.55)	0.84(0.77-0.90)	<0.001
40-59ys	593(8.11)	417(6.26)	416(4.79)	363(4.31)	272(2.94)		
Model 3 ‡	1.00	0.77(0.67-0.88)	0.57(0.50-0.66)	0.52(0.45-0.60)	0.38(0.32-0.45)	0.82(0.80-0.85)	<0.001
P-interaction		0.552	0.167	0.188	0.024		
≥60ys	136(9.07)	160(8.55)	194(6.99)	177(6.16)	125(4.46)		
Model 3 ‡	1.00	0.94(0.74-1.22)	0.75(0.59-0.96)	0.67(0.52-0.86)	0.47(0.36-0.62)	0.86(0.82-0.90)	<0.001
P-interaction		0.148	0.947	0. 018	0.002		

Abbreviation: CVH, ideal cardiovascular health; Q1=quintile1, Q2=quintile2, Q3=quintile3, Q4=quintile4, Q5=quintile5.

* Adjusted for age (years), sex.

†Adjusted for as model 1 plus education level (elementary school, high school or college or above), income level (income≥800 ¥/month, ¥600-800, and income<600 ¥/month) and drinking (never, past, current, <1times/d or current, 1+times/d).

‡ Adjusted for as model 2 plus High sensitive C-reactive protein, uric acid, resting heart rate, and medication usageat exam1.

TableS4. Comparison of Demographic and Other Characteristics of Participants and Non-Participants

	Participants	**Non-Participants**	***P-Value***
n	34323	52764	
Age (Years)	47.43 ± 11. 62	53.85 ± 12.97	<0.001
Male Sex, n (%)	25961 (75.64)	43174(81.82)	<0.001
High School Educational Level or above, n (%)	8147 (23.75)	9289 (18.80)	<0.001
Income ≥¥800/month, n (%)	5140 (14.98)	6896(13.97)	<0.001
Current Smoker, n (%)	10438(30.41)	15647 (31.28)	<0.001
Current Alcohol Drinker, n (%)	5932 (17.29)	9108 (18.19)	<0.001
Physical Activity ≥80 min, n (%)	4609 (13.43)	8092 (16.44)	<0.001
High Salt Intake, n (%)	3566 (10.39)	5352 (10.86)	0.058
Body Mass Index (kg/m^2)	24.89 ±3.42	24.81 ± 3.47	<0.001
Systolic Blood Pressure (mmHg)	127.02 ± 19.30	131.66 ± 21.40	<0.001
Diastolic Blood Pressure (mmHg)	82.20 ± 11.26	83.54 ± 11.89	<0.001
Fasting Blood Glucose Concentration (mmol/l)	5.02 ± 0.65	5.06 ± 0.69	<0.001
Total Cholesterol Concentration (mmol/l)	4.87 ± 1.13	4.93 ± 1.11	<0.001
High-Sensitive C-Reactive Protein Concentration (mg/L)	0.68 (0.25-1.80)	0.85 (0.30-2.30)	<0.001
Uric Acid Concentration (μmol/L)	283.83 ± 81.52	294.79 ± 84.41	<0.001
Resting Heart Rate (Beats / Minute)	73.15 ± 9.64	73.47 ± 10.14	0.048

Table S5. Previous analyses of the relationship between ideal cardiovascular health metrics and risk of outcomes.

Study (Author, Year)	Journal, publication date	Name of Cohort(s)	Location	Baseline Year	Participants	Outcomes	Follow Up (Years)
Shah AM[1], 1987	Circulation, 2015	ARIC study	United States	1987-1989	15,792 individuals	cardiovascular structure and function	25
Sping B[2],1985	Circulation 2014;130:10-17	CARDIA Study	United States	1985-1986	5115 adults	Coronary artery calcification and carotid intima-media thickness	20
Xanthakis V[3],1995	Circulation 2014;130:1676-1683	Framingham Offspring Study	United States	1995-1998	2680 participants	CVD biomarker levels and subclinical disease	0
Pahkala K[4],1990	Circulation 2013;127:2088-2096	STRIP study	Finland	1990-1992	1062 infants	Vascular intima-media thickness and elasticity	20
Aatola H[5],1980	Journal of the American Heart Association2014;3	Cardiovascular Risk in Young Finns Study	Finland	1986	1143 white adults	pulse wave velocity	21
Tomi T. Laitinen[6], 1980	Circulation 2012;125:1971-1978	Cardiovascular Risk in Young Finns Study	Finland	1986	856 subjects	cardiometabolic outcomes hypertension, metabolic syndrome, carotid artery intima-media thickness	21
Qian Zhang[7],2006	Stroke2013;44:2451-2456	Kailuan study	China	2006	101510 subjects	stroke	4
Chuanhui Dong[8],1993	Circulation 2012;125:2975-2984	Northern Manhattan Study	United States	1993	2981 subjects	Myocardial Infarction, Stroke, and Vascular Death	11

Shouling Wu[9],2006	Circ Cardiovasc Qual Outcomes2012;5:487-493	Kailuan study	China	2006	101510 subjects	Cardiovascular Events	4
Laura J. Rasmussen Torvik[10],1987	Circulation 2013;127:1270-1275	ARIC study	United States	1987-1989	13,253 subjects	cancer	17-19
Earl S. Ford[11],1999	Circulation 2012;125:987-995	National Health and Nutrition Examination Survey	United States	1999-2002	7622 adults	Mortality From All Causes and Diseases of the Circulatory System	5.8
Enrique G. Artero[12],1987	Mayo Clinic proceedings. Mayo Clinic. 2012;87:944-952	Aerobics Center Longitudinal Study	United States	1987-1999	11993 subjects	deaths from all causes, cardiovascular disease (CVD), and cancer	11.6

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