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Ideal Cardiovascular Health Metrics and Major Cardiovascular Events in Patients With Prediabetes and Diabetes

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IMPORTANCE Whether optimal cardiovascular health metrics may counteract the risk of cardiovascular events among patients with prediabetes or diabetes is unclear.

OBJECTIVE To investigate the associations of ideal cardiovascular health metrics (ICVHMs) with subsequent development of cardiovascular disease (CVD) among participants with prediabetes or diabetes as compared with participants with normal glucose regulation.

DESIGN, SETTING, AND PARTICIPANTS The China Cardiometabolic Disease and Cancer Cohort Study was a nationwide, population-based, prospective cohort study of 20 communities from various geographic regions in China. The study included 111 765 participants who were free from CVD or cancer at baseline. Data were analyzed between 2011 and 2016.

EXPOSURES Prediabetes and diabetes were defined according to the American Diabetes Association 2010 criteria. Seven ICVHMs were adapted from the American Heart Association recommendations.

MAIN OUTCOMES AND MEASURES The composite of incident fatal or nonfatal CVD, including cardiovascular death, myocardial infarction, stroke, and hospitalized or treated heart failure.

RESULTS Of the 111 765 participants, 24 881 (22.3%) had normal glucose regulation, 61 024 (54.6%) had prediabetes, and 25 860 (23.1%) had diabetes. Mean (SD) age ranged from 52.9 (8.6) years to 59.4 (8.7) years. Compared with participants with normal glucose regulation, among participants with prediabetes, the multivariable-adjusted hazard ratio for CVD was 1.34 (95% CI, 1.16-1.55) for participants who had 1 ICVHM or less and 0.57 (95% CI, 0.43-0.75) for participants who had at least 5 ICVHMs; among participants with diabetes, the hazard ratios for CVD were 2.05 (95% CI, 1.76-2.38) and 0.80 (95% CI, 0.56-1.15) for participants who had 1 ICVHM or less and at least 5 ICVHMs, respectively. Such pattern of association between ICVHMs and CVD was more prominent for participants younger than 55 years (prediabetes and at least 5 ICVHMs: hazard ratio [HR], 0.32; 95% CI, 0.16-0.63; 1 ICVHM or less: HR, 1.58; 95% CI, 1.13-2.21; diabetes and at least 5 ICVHMs: HR, 0.99; 95% CI, 0.44-2.26; 1 ICVHM or less: HR, 2.46; 95% CI, 1.71-3.54; compared with normal glucose regulation) than for participants 65 years or older (prediabetes and at least 5 ICVHMs: HR, 0.80; 95% CI, 0.50-1.26; 1 ICVHM or less: HR, 1.01; 95% CI, 0.79-1.31; diabetes and at least 5 ICVHMs: HR, 0.79; 95% CI, 0.46-1.35; 1 ICVHM or less: HR, 1.73; 95% CI, 1.36-2.22, compared with normal glucose regulation; *P* values for interaction ≤.02). Additionally, the hazard ratio for CVD per additional ICVHM was 0.82 (95% CI, 0.79-0.86) among participants with prediabetes and was 0.85 (95% CI, 0.80-0.89) among participants with diabetes.

CONCLUSIONS AND RELEVANCE Participants with prediabetes or diabetes who had 5 or more ICVHMs exhibited lower or no significant excess CVD risks compared with the participants with normal glucose regulation.

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Invited Commentary
page 883

Supplemental content

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Type 2 diabetes poses a major threat to public health. According to the data from the International Diabetes Federation, 1 in 11 adults aged 20 to 79 years had diabetes globally in 2017 (425 million), and China has become the epicenter of the diabetes epidemic.[1] Cardiovascular complications are the leading cause of disability and mortality among patients with type 2 diabetes.[2-5] Diabetes confers about a 2-fold excess risk of cardiovascular disease (CVD) events independent of conventional risk factors.[6,7] Moreover, among patients with type 2 diabetes, CVD occurs earlier and with greater severity compared with individuals without diabetes.[8] In addition, as a high-risk state for diabetes, prediabetes is also associated with a modest increase in the risk of CVD.[9,10] Given the epidemic proportion of prediabetes worldwide and especially in China and the United States,[1] if a causal relation exists, such modest increase in risk might still translate into substantial burden of CVD events.[9]

In 2010, the American Heart Association (AHA) suggested 7 ideal cardiovascular health metrics (ICVHMs), including healthy lifestyle behaviors and ideal metabolic measures, to promote optimal cardiovascular health in the population.[11] Following the recommendations of the AHA, several population-based studies have supported a beneficial effect of ideal cardiovascular health on CVD events.[12-14] Such evidence has been derived from general populations so far. Individuals with prediabetes or diabetes are at higher risks of developing CVD than those with normal glucose regulation.[6,7,9,10] However, whether patients with prediabetes or diabetes who achieved a greater number of ICVHMs may have lower risk for CVD is unclear.

To this end, in a nationwide prospective population-based study, we investigated the individual and combined associations of ICVHMs with the risk of CVD events among individuals with prediabetes or diabetes compared with the risk of CVD events among individuals with normal glucose regulation.

Key Points

Question Are ideal cardiovascular health metrics (ICVHMs) associated with lower risks of cardiovascular disease among patients with prediabetes or diabetes?

Findings In this cohort study of 111 765 Chinese participants, compared with participants with normal glucose regulation, participants with prediabetes or diabetes who achieved at least 5 ICVHMs had lower or no increased risks of cardiovascular disease events compared with participants with normal glucose regulation.

Meaning Our findings emphasize the importance of promoting the adherence to ICVHMs in the prevention of cardiovascular disease events among patients with prediabetes or diabetes.

Methods

Study Design and Population

The China Cardiometabolic Disease and Cancer Cohort (4C) Study is a multicenter, population-based, prospective cohort study.[15] During 2011 to 2012, 193 846 men and women 40 years or older were recruited from local resident registration systems of 20 communities from various geographic regions in China to represent the general population. During 2014 to 2016, all participants were invited to attend an in-person visit, and 170 240 participants (87.8%) were followed up. At baseline and the follow-up visit, demographic characteristics, lifestyle and dietary factors, and medical history were collected by using standard questionnaires. Anthropometric and blood pressure measurements, oral glucose tolerance tests, and blood samples were obtained following a standard protocol. The analysis included 111 765 participants who had complete baseline information on cardiovascular health metrics and diabetes status and were free from CVD or cancer at baseline. This study was approved by the Medical Ethics Committee of Ruijin Hospital, Shanghai Jiaotong University. All study participants provided written informed consent.

Data Collection

Data collection was performed in local community clinics by trained study personnel according to a standard protocol at baseline and the follow-up visit. A questionnaire comprising information on demographic characteristics, lifestyle factors (including cigarette smoking and alcohol drinking), family history, and medical history was administered by trained interviewers. Current alcohol drinker was defined as a person who drank alcohol regularly in the past 6 months. Education attainment was categorized as less than high school and high school or more. A food frequency questionnaire was used to collect habitual dietary intake by asking the consumption frequency and portion size of typical food items during the previous 12 months. The International Physical Activity Questionnaire was used to assess physical activity.[16] Height and body weight were measured according to a standard protocol, and body mass index (BMI) was calculated as the weight in kilograms divided by height in meters squared.

Three blood pressure measurements were obtained from each participant by using an automated electronic device (OMRON Model HEM-752 FUZZY) in a seated position after at least a 5-minute quiet rest. Participants were required to avoid alcohol, coffee, tea, smoking, and exercise at least 30 minutes before the blood pressure measurement. The 3 readings were averaged for the analysis.

All participants underwent an oral glucose tolerance test after an overnight fast of at least 10 hours, and blood samples were collected at 0 and 2 hours during the test. Fasting and 2-hour plasma glucose concentrations were measured locally using a glucose oxidase or hexokinase method within 2 hours after blood sample collection under a stringent quality control program. Finger capillary whole-blood samples were collected by the Hemoglobin Capillary Collection System (Bio-Rad Laboratories) and were stored at 2°C to 8°C and shipped to the central laboratory in the Shanghai Institute of Endocrine and Metabolic Diseases, which was certificated by the National Glycohemoglobin Standardization Program and the College of American Pathologists Laboratory Accreditation Program. Glycated hemoglobin A_{1c} (HbA_{1c}) was measured within 4 weeks after collection by high-performance liquid chromatography using the VARIANT II Hemoglobin Testing System (Bio-Rad Laboratories). The capillary HbA_{1c} values and the venous values from whole-blood samples collected using ethylene diamine tetraacetic acid dipotassium

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tubes were highly correlated (r = 0.99) in a validation subsample.[17] Total cholesterol was measured at the central laboratory using an autoanalyzer (ARCHITECT ci16200 analyzer; Abbott Laboratories).

Assessment of Prediabetes and Diabetes

Baseline prediabetes and diabetes were defined according to the American Diabetes Association 2010 criteria.[18] Prediabetes was defined as fasting plasma glucose levels between 100.90 mg/dL and 124.32 mg/dL (to convert to millimoles per liter, multiply by 0.0555), 2-hour plasma glucose levels between 140.54 mg/dL and 198.20 mg/dL, or HbA_{1c} concentrations between 5.7% and 6.4% in participants without a prior diagnosis of diabetes (to convert to proportion of total hemoglobin, multiply by 198.20). Diabetes was defined as fasting plasma glucose level of at least 126.13 mg/dL, 2-hour plasma glucose level of at least 200 mg/dL, HbA_{1c} level of at least 6.5%, or by a self-reported previous diagnosis by health care professionals.

Definition of ICVHMs

Seven ICVHMs were adapted from the recommendations of the Goals and Metrics Committee of the Strategic Planning Task Force of the AHA[11]: never smoked or quit smoking more than 12 months prior, BMI less than 23, physical activity at goal (at least 150 minutes/week moderate intensity or 75 minutes/week vigorous intensity or 150 minutes/week moderate plus vigorous intensity), fruit and vegetable intake at least 4.5 cups/d, total cholesterol less than 200 mg/dL (untreated; to convert to millimoles per liter, multiply by 0.0259), blood pressure less than 120/80 mm Hg (untreated), and ideal HbA_{1c} level (<5.7% for prediabetes or <6.5% for diabetes) (eTable 1 in the Supplement). We defined an ideal BMI by a BMI cutoff point of less than 23, which has been proposed as a more reasonable threshold to define a normal BMI for Asian individuals,[19,20] and we have validated that a BMI of at least 23 was associated with greater risks of CVD events and elevated HbA_{1c} than a BMI of at least 24 or at least 25 as compared with their corresponding normal BMI in this study cohort (eTable 2 in the Supplement). We used fruit and vegetable intake to evaluate a healthy diet because data on whole grain and sodium consumption were not collected, and fruits and vegetables are primary dietary components highlighted by the AHA 2020 Strategic Impact Goals and have been associated with lower risks of CVD.[21,22] We replaced fasting plasma glucose with HbA_{1c} as one metric to estimate glucose metabolism in participants with prediabetes or diabetes, in accordance with the stringent HbA_{1c} goals of the current American Diabetes Association clinical practice recommendations.[23]

Ascertainment of Cardiovascular Events

The outcome of this study was the composite of incident fatal or nonfatal CVD events including cardiovascular death, myocardial infarction, stroke, and hospitalized or treated heart failure. Myocardial infarction was defined by characteristic changes in levels of troponin T and creatine-kinase-MB isoform, symptoms of myocardial ischemia, changes in electrocardiogram results, or a combination of them. Stroke was defined as a fixed neurologic deficit at least 24 hours because of a presumed vascular cause. Heart failure was identified by hospitalization or an emergency department visit requiring a treatment with infusion therapy for a clinical syndrome presenting with multiple signs and symptoms in consistence with cardiac decompensation or inadequate cardiac pump function. Deaths and clinical outcomes were collected from local vital registries of the National Disease Surveillance Point System and National Health Insurance System. Two members of the outcome adjudication committee independently verified each clinical event and assigned potential causes of death, and discrepancies were adjudicated by discussion involving other members of the committee. All members of the committee were unaware of the baseline risk factors of study participants.

Statistical Analysis

Baseline characteristics of participants with normal glucose regulation, prediabetes, and diabetes were summarized as means with standard deviation for continuous variables and percentages for categorical variables. Person-time for each participant was calculated from the date of enrollment to the date of CVD diagnosis, death, or the end of follow-up, whichever came first. Cox proportional hazards models were used to calculate hazard ratios (HRs) and 95% confidence intervals for CVD events, with multivariable adjustment for age, sex, education attainment, family history of diabetes, and family history of CVD. We first estimated the risk of CVD events according to individual and combined ICVHMs among participants with prediabetes or diabetes compared with participants with normal glucose regulation. In the analysis of the association between each component of the ICVHMs and CVD events, we further adjusted for all other ICVHMs. As a next analysis, we stratified participants into subgroups according to age and sex and examined the association between ICVHMs and CVD risk among participants with prediabetes or diabetes as compared with participants with normal glucose regulation in each age or sex subgroup. Among participants with prediabetes or diabetes, we also analyzed the risk of CVD events according to individual and combined ICVHMs. To test whether the pattern of association varies across stratifications, we estimated multiplicative interactions by including the product term (exposure × stratification variable) in the models. We replicated the main analyses for nonfatal CVD events and CVD mortality in secondary analyses. All reported P values are nominal and 2-sided, and a P value of less than .05 was considered statistically significant. All statistical analyses were performed by using SAS software, version 9.2 (SAS Institute Inc).

Results

Of the 111 765 participants, 24 881 (22.3%) had normal glucose regulation, 61 024 (54.6%) had prediabetes, and 25 860 (23.1%) had diabetes. Mean (SD) age ranged from 52.9 (8.6) years to 59.4 (8.7) years. Baseline characteristics of the study participants according to glucose tolerance status are shown in **Table 1**. Compared with participants with normal glucose regulation, participants with prediabetes or diabetes were older, had higher

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Table 1. Baseline Characteristics of Participants With Normal Glucose Regulation, Prediabetes, and Diabetes (N = 111 765)[a]

Baseline Characteristic	No. (%)		
	Normal Glucose Regulation	Prediabetes	Diabetes
Participants	24 881 (22.3)	61 024 (54.6)	25 860 (23.1)
Age, mean (SD), y	52.9 (8.6)	56.5 (8.7)	59.4 (8.7)
Men	7872 (31.6)	20 018 (32.8)	9945 (38.5)
High school or greater education	9962 (40.0)	22 895 (37.5)	9135 (35.3)
Current alcohol drinker	2487 (10.2)	6501 (10.9)	2767 (10.9)
Family history of diabetes	2530 (10.2)	7400 (12.1)	5346 (20.7)
Family history of CVD	4216 (16.9)	10 495 (17.2)	4189 (16.2)
Smoking status			
Current	4818 (19.4)	11 128 (18.2)	4997 (19.3)
Former, quit ≤12 mo	136 (0.6)	378 (0.6)	228 (0.9)
Never or quit >12 mo	19 927 (80.1)	49 518 (81.2)	20 635 (79.8)
BMI levels			
<23	11 007 (44.2)	20 731 (34.0)	5852 (22.6)
≥23 to <25	6253 (25.1)	14 830 (24.3)	5850 (22.6)
≥25	7621 (30.6)	25 463 (41.7)	14 158 (54.8)
Physical activity at goal	3219 (12.9)	9027 (14.8)	3559 (13.8)
Fruit and vegetable intake, mean (SD), cup/d	4.1 (5.6)	4.6 (4.5)	4.6 (10.2)
Total cholesterol, mean (SD), mg/dL	185.0 (40.6)	192.4 (44.0)	196.6 (46.9)
Systolic blood pressure, mean (SD), mm Hg	128 (20)	132 (20)	138 (21)
Diastolic blood pressure, mean (SD), mm Hg	77 (11)	78 (11)	80 (11)
Glycated hemoglobin A_{1c}, mean (SD), %	5.3 (0.3)	5.8 (0.3)	7.1 (1.5)
ICVHMs, No.			
≤1	494 (2.0)	9004 (14.8)	4865 (18.8)
2	3296 (13.3)	16 710 (27.4)	8036 (31.1)
3	6754 (27.2)	17 937 (29.4)	7450 (28.8)
4	7279 (29.3)	11 641 (19.1)	3893 (15.1)
≥5	7058 (28.4)	5732 (9.4)	1616 (6.3)

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); ICVHMs, ideal cardiovascular health metrics.

SI conversion factors: To convert cholesterol levels to millimoles per liter, multiply by 0.0259; glycated hemoglobin A_{1c} to proportion of total hemoglobin, multiply by 0.01.

[a] Percentages may not sum to 100% owing to rounding. The number of missing values is 2135 for alcohol drinkers.

proportions of men, had lower level of education attainment, were more likely to have family history of diabetes, and had poorer metabolic profiles and less number of ICVHMs.

During a mean follow-up of 3.8 years (406 065 person-years), we documented 2882 CVD events (2.6%): 526 participants died of cardiovascular cause, 431 had myocardial infarction, 1781 had stroke, and 204 had heart failure; participants may have experienced more than 1 CVD event. Compared with normal glucose regulation, prediabetes (unadjusted HR, 1.23; 95% CI, 1.11-1.37; adjusted HR, 0.98; 95% CI, 0.88-1.09) and diabetes (unadjusted HR, 2.45; 95% CI, 2.20-2.73; adjusted HR, 1.56; 95% CI, 1.40-1.75) were associated with relatively higher risks of CVD events (eTable 3 in the Supplement).

As shown in **Table 2**, compared with participants with normal glucose regulation, participants with prediabetes who had 1 of these ICVHMs exhibited significantly lower risk for CVD: ideal BMI (HR, 0.84; 95% CI, 0.72-0.98), physical activity at goal (HR, 0.78; 95% CI, 0.64-0.95), healthy diet (HR, 0.82; 95% CI, 0.71-0.95), ideal total cholesterol (HR, 0.86; 95% CI, 0.75-0.99), and ideal blood pressure (HR, 0.58; 95% CI, 0.48-0.71). Compared with participants with normal glucose regulation, among participants with prediabetes, the HR for CVD gradually decreased from 1.34 (95% CI, 1.16-1.55) in those who had 1 ICVHM or less to 0.57 (95% CI, 0.43-0.75) in those who had more than 5 ICVHMs. Participants with diabetes who had ideal blood pressure had a marginally lower risk for CVD (HR, 0.91; 95% CI, 0.71-1.18), and the risk for CVD decreased with an increasing number of ICVHMs (≤1 ICVHM: HR, 2.05; 95% CI, 1.76-2.38; ≥5 ICVHMs: HR, 0.80; 95% CI, 0.56-1.15), as compared with participants with normal glucose regulation.

Among participants with prediabetes, the magnitude of the incremental risk for CVD associated with fewer ICVHMs was greatest among participants who were younger than 55 years (≥5 ICVHMs: HR, 0.32; 95% CI, 0.16-0.63; ≤1 ICVHM: HR, 1.58; 95% CI, 1.13-2.21) and was lowest among participants who were 65 years or older (≥5 ICVHMs: HR, 0.80; 95% CI, 0.50-1.26; ≤1 ICVHM: HR, 1.01; 95% CI, 0.79-1.31; *P* for interaction = .02; **Figure 1**A). Similar age-related interactions with the number of ICVHMs were observed among participants with diabetes compared with those with normal glucose regulation (younger than 55 years and ≥5 ICVHMs: HR, 0.99; 95% CI, 0.44-2.26; ≤1 ICVHM: HR, 2.46; 95% CI, 1.71-3.54; 65 years or older and ≥5 ICVHMs: HR, 0.79; 95% CI, 0.46-1.35; ≤1 ICVHM: HR, 1.73; 95% CI, 1.36-2.22; *P* for interaction <.001; Figure 1B). No statistically significant interaction was observed with sex (Figure 1C and D).

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Table 2. Hazard Ratio (95% CI) of CVD Events According to Individual and Combined ICVHMs Among Participants With Prediabetes or Diabetes as Compared With the Overall Participants With Normal Glucose Regulation[a]

Category	Person-Years	No. of Cases	HR (95% CI)[b]
Normal glucose regulation	92 244	453	1 [Reference]
Prediabetes			
Ideal smoking status	178 928	1017	0.89 (0.78-1.02)
Ideal BMI	74 792	383	0.84 (0.72-0.98)
Physical activity at goal	32 903	157	0.78 (0.64-0.95)
Healthy diet	101 941	508	0.82 (0.71-0.95)
Untreated total cholesterol <200 mg/dL	122 210	632	0.86 (0.75-0.99)
Untreated blood pressure <120/80 mm Hg	58 472	156	0.58 (0.48-0.71)
Glycated hemoglobin A_{1c} <5.7%	50 843	311	1.03 (0.89-1.19)
No. of ICVHMs			
≤1	32 967	307	1.34 (1.16-1.55)
2	60 272	436	1.08 (0.95-1.23)
3	64 473	351	0.89 (0.78-1.03)
4	42 146	174	0.75 (0.63-0.89)
≥5	20 906	54	0.57 (0.43-0.75)
Diabetes			
Ideal smoking status	74 324	846	1.33 (1.16-1.52)
Ideal BMI	20 848	235	1.41 (1.19-1.66)
Physical activity at goal	12 868	137	1.31 (1.07-1.61)
Healthy diet	41 844	450	1.31 (1.13-1.52)
Untreated total cholesterol <200 mg/dL	45 014	483	1.33 (1.15-1.53)
Untreated blood pressure <120/80 mm Hg	13 418	71	0.91 (0.71-1.18)
Glycated hemoglobin A_{1c} <6.5%	31 659	337	1.31 (1.13-1.51)
No. of ICVHMs			
≤1	17 554	272	2.05 (1.76-2.38)
2	28 819	366	1.63 (1.42-1.88)
3	26 777	305	1.48 (1.27-1.71)
4	14 000	133	1.29 (1.07-1.57)
≥5	5909	31	0.80 (0.56-1.15)

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); HR, hazard ratio; ICVHMs, ideal cardiovascular health metrics.

SI conversion factors: To convert cholesterol levels to millimoles per liter, multiply by 0.0259; glycated hemoglobin A_{1c} to proportion of total hemoglobin, multiply by 0.01.

[a] 111 765 participants (24 881 with normal glucose regulation, 61 024 with prediabetes, and 25 860 with diabetes) were included in the analysis.

[b] Adjusted for age, sex, education attainment (less than high school or high school or greater), family history of diabetes (yes or no), and family history of CVD (yes or no). Individual cardiovascular health metrics were mutually adjusted.

Among participants with prediabetes, compared with participants who had 1 ideal metric or none, the HR for CVD was 0.80 (95% CI, 0.69-0.93), 0.66 (95% CI, 0.56-0.77), 0.55 (95% CI, 0.46-0.67), and 0.42 (95% CI, 0.32- 0.57) for participants who had 2, 3, 4, and at least 5 ideal metrics, respectively, and was 0.82 (95% CI, 0.79-0.86) per 1-number increment in ICVHMs. A similar pattern was observed among participants with diabetes; each 1-number increment in ICVHMs was associated with an HR of 0.85 (95% CI, 0.80-0.89) for CVD (**Table 3**). The graded association of more ICVHMs with lower risk for CVD events was consistent across normal glucose regulation, prediabetes, and diabetes strata (eTable 4 in the Supplement).

Consistent results were observed in strata of age, sex, education attainment, family history of diabetes, family history of CVD, and diabetes duration (for participants with diabetes only) (**Figure 2**). We observed an interaction of each 1-number increment in ICVHMs with age on CVD events among participants with prediabetes. The HR for CVD was 0.89 (95% CI, 0.82-0.96) among participants who were 65 years or older and 0.74 (95% CI, 0.67-0.83) among participants who were younger than 55 years (*P* for interaction = .03). There were no other significant interactions. Secondary analyses showed more significant results for nonfatal CVD events but less significant results for CVD mortality (eTables 5 and 6 in the Supplement).

Discussion

In this Chinese nationwide prospective cohort study of 111 765 adults, participants with prediabetes or diabetes who had 5 or more ICVHMs exhibited lower or no significant excess risk of CVD events compared with those with normal glucose regulation. Compared with 1 ICVHM or none, 5 or more ideal metrics were associated with 58% and 61% lower CVD risks among participants with prediabetes and diabetes, respectively. Each additional ICVHM was associated with 18% and 15% lower risks of CVD events among participants with prediabetes and diabetes, respectively.

To the best of our knowledge, this study is the first to comprehensively investigate the association of ICVHMs with CVD events among individuals with diabetes or prediabetes. Randomized clinical trials evaluating cardiovascular effects of multifactorial interventions in individuals with impaired glucose tolerance or type 2 diabetes are sparse and yield mixed

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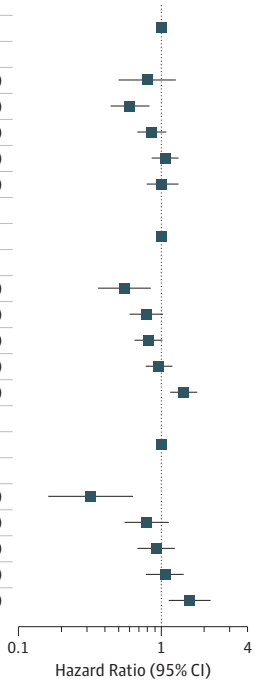
Figure 1. Hazard Ratio (95% CI) of Cardiovascular Disease (CVD) Events in Relation to Number of Ideal Cardiovascular Health Metrics (ICVHMs) Among Participants With Prediabetes or Diabetes Compared With the Overall Participants With Normal Glucose Regulation, According to Age and Sex Categories

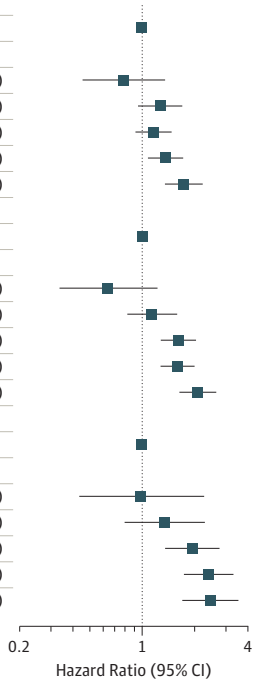
A CVD events among participants with prediabetes

Source	Hazard Ratio (95% CI)
Age ≥65 y	
Normal glucose regulation	1.00 [Reference]
Prediabetes ideal metrics	
≥5	0.80 (0.50-1.26)
4	0.60 (0.44-0.82)
3	0.85 (0.68-1.08)
2	1.06 (0.86-1.31)
≤1	1.01 (0.79-1.31)
Age ≥55 y to <65 y	
Normal glucose regulation	1.00 [Reference]
Prediabetes ideal metrics	
≥5	0.55 (0.36-0.84)
4	0.78 (0.60-1.02)
3	0.81 (0.65-1.01)
2	0.96 (0.78-1.19)
≤1	1.43 (1.16-1.78)
Age <55 y	
Normal glucose regulation	1.00 [Reference]
Prediabetes ideal metrics	
≥5	0.32 (0.16-0.63)
4	0.78 (0.55-1.12)
3	0.92 (0.68-1.24)
2	1.06 (0.78-1.43)
≤1	1.58 (1.13-2.21)



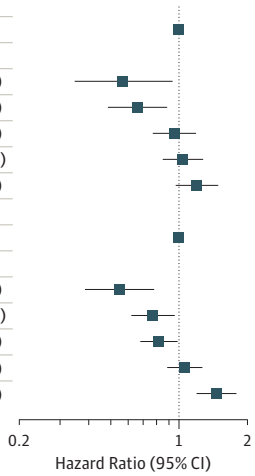
B CVD events among participants with diabetes

Source	Hazard Ratio (95% CI)
Age ≥65 y	
Normal glucose regulation	1.00 [Reference]
Diabetes ideal metrics	
≥5	0.79 (0.46-1.35)
4	1.27 (0.95-1.69)
3	1.16 (0.92-1.47)
2	1.36 (1.09-1.71)
≤1	1.73 (1.36-2.22)
Age ≥55 y to <65 y	
Normal glucose regulation	1.00 [Reference]
Diabetes ideal metrics	
≥5	0.64 (0.34-1.22)
4	1.14 (0.83-1.58)
3	1.62 (1.29-2.03)
2	1.60 (1.28-1.99)
≤1	2.08 (1.64-2.64)
Age <55 y	
Normal glucose regulation	1.00 [Reference]
Diabetes ideal metrics	
≥5	0.99 (0.44-2.26)
4	1.36 (0.80-2.29)
3	1.94 (1.36-2.77)
2	2.40 (1.74-3.32)
≤1	2.46 (1.71-3.54)



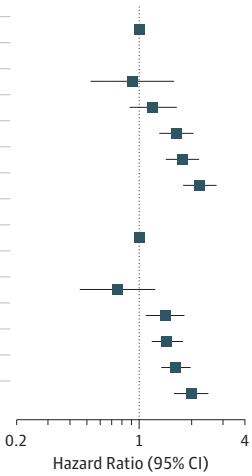
C CVD events among participants with prediabetes

Source	Hazard Ratio (95% CI)
Men	
Normal glucose regulation	1.00 [Reference]
Prediabetes ideal metrics	
≥5	0.57 (0.39-0.94)
4	0.66 (0.49-0.89)
3	0.96 (0.77-1.19)
2	1.04 (0.85 -1.28)
≤1	1.20 (0.97-1.49)
Women	
Normal glucose regulation	1.00 [Reference]
Prediabetes ideal metrics	
≥5	0.55 (0.39-0.78)
4	0.77 (0.62-0.96)
3	0.82 (0.68-0.99)
2	1.06 (0.89-1.27)
≤1	1.46 (1.20-1.79)



D CVD events among participants with diabetes

Source	Hazard Ratio (95% CI)
Men	
Normal glucose regulation	1.00 [Reference]
Diabetes ideal metrics	
≥5	0.91 (0.53-1.58)
4	1.20 (0.88-1.64)
3	1.63 (1.30-2.04)
2	1.77 (1.42-2.19)
≤1	2.21 (1.78-2.75)
Women	
Normal glucose regulation	1.00 [Reference]
Diabetes ideal metrics	
≥5	0.75 (0.46-1.23)
4	1.41 (1.09-1.81)
3	1.44 (1.18-1.77)
2	1.62 (1.34-1.96)
≤1	1.98 (1.58-2.48)



A total of 111 765 participants (24 881 with normal glucose regulation, 61 024 with prediabetes, and 25 860 with diabetes) were included in the analysis. Hazard ratios (95% CI) were adjusted for age, sex, education attainment (less than high school or high school or greater), family history of diabetes (yes or no), and family history of CVD (yes or no). Interaction between the combination of glucose tolerance status with number of ICVHMs and age on CVD: *P* for interaction = .02 (A); *P* for interaction <.001 (B). Interaction between the combination of glucose tolerance status with number of ICVHMs and sex on CVD: *P* for interaction = .59 (C); *P* for interaction = .35 (D).

results.[24-28] In the Steno-2 Study[27] of 160 patients with type 2 diabetes and microalbuminuria, implementations of behavior modification and pharmacologic therapy significantly reduced CVD risk by more than 50% after a follow-up of 7.8 years. In contrast, results from the Look AHEAD (Action for Health in Diabetes)[26] of 5145 overweight or obese individuals

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Table 3. Hazard Ratio (95% CI) of CVD Events According to Individual and Combined ICVHMs Among Participants With Prediabetes or Diabetes[a]

Category	Person-Years	No. of Cases	HR (95% CI)[b]
Prediabetes			
Smoking status			
Nonideal	41 835	305	1 [Reference]
Ideal	178 928	1017	0.81 (0.69-0.95)
BMI			
Nonideal	145 971	939	1 [Reference]
Ideal	74 792	383	0.84 (0.74-0.95)
Physical activity			
Nonideal	187 860	1165	1 [Reference]
Ideal	32 903	157	0.81 (0.69-0.96)
Healthy diet			
Nonideal	118 821	814	1 [Reference]
Ideal	101 941	508	0.83 (0.74-0.93)
Total cholesterol			
Nonideal	98 553	690	1 [Reference]
Ideal	122 210	632	0.83 (0.75-0.93)
Blood pressure			
Nonideal	162 291	1166	1 [Reference]
Ideal	58 472	156	0.58 (0.49-0.69)
Glycated hemoglobin A_{1c}			
Nonideal	169 920	1011	1 [Reference]
Ideal	50 843	311	1.12 (0.98-1.27)
ICVHMs, No.			
≤1	32 967	307	1 [Reference]
2	60 272	436	0.80 (0.69-0.93)
3	64 473	351	0.66 (0.56-0.77)
4	42 146	174	0.55 (0.46-0.67)
≥5	20 906	54	0.42 (0.32-0.57)
Each 1-number increment in ICVHMs	NA	NA	0.82 (0.79-0.86)
Diabetes			
Smoking status			
Nonideal	18 734	261	1 [Reference]
Ideal	74 324	846	0.81 (0.69-0.96)
BMI			
Nonideal	72 210	872	1 [Reference]
Ideal	20 848	235	0.99 (0.85-1.14)
Physical activity			
Nonideal	80 190	970	1 [Reference]
Ideal	12 868	137	0.91 (0.76-1.08)
Healthy diet			
Nonideal	51 214	657	1 [Reference]
Ideal	41 844	450	0.89 (0.78-0.99)
Total cholesterol			
Nonideal	48 044	624	1 [Reference]
Ideal	45 014	483	0.83 (0.74-0.94)
Blood pressure			
Nonideal	79 641	1036	1 [Reference]
Ideal	13 417	71	0.54 (0.42-0.69)
Glycated hemoglobin A_{1c}			
Nonideal	61 400	770	1 [Reference]
Ideal	31 658	337	0.85 (0.74-0.96)
No. of ICVHMs			
≤1	17 554	272	1 [Reference]
2	28 819	366	0.81 (0.69-0.95)
3	26 777	305	0.74 (0.63-0.87)
4	14 000	133	0.64 (0.52-0.79)
≥5	5909	31	0.39 (0.27-0.56)
Each 1-number increment in ICVHMs	NA	NA	0.85 (0.80-0.89)

Abbreviations: BMI, body mass index; HR, hazard ratio; ICVHMs, ideal cardiovascular health metrics; NA, not applicable.

[a] 61 024 participants with prediabetes and 25 860 with diabetes were included in the analysis.

[b] Adjusted for age, sex, education attainment (less than high school, high school or greater), family history of diabetes (yes or no), family history of CVD (yes or no), and diabetes duration (for participants with diabetes only). Individual cardiovascular health metrics were mutually adjusted.

with type 2 diabetes showed that intensive lifestyle intervention focused on weight loss did not reduce CVD events over a median of 9.6 years of follow-up. Prospective observational studies with regard to cardiovascular effects among patients with diabetes are limited and have mainly assessed lifestyle behaviors.[29-31] In this study, taking advantage of the AHA ICVHMs, we analyzed a comprehensive cardiovascular risk factor profile to ascertain its association with CVD risk. Importantly, we found that patients with prediabetes or diabetes who had 5 or more ICVHMs appeared to have no significant excess or even lower risk of CVD events compared with the overall population with normal glucose regulation. In view of the rising epidemic of prediabetes and diabetes globally and in China, our findings emphasize the importance of an early intervention targeting both lifestyle behaviors and metabolic profiles among individuals with prediabetes and diabetes for the prevention of CVD.

Interestingly, we detected that among younger individuals, patients with prediabetes who had 5 or more ICVHMs showed lower CVD risk than individuals with normal glucose regulation, while such an association was not seen among older individuals. We speculate that the high prevalence of comorbidities and medications for chronic diseases among the elderly population may compromise the benefit of the ICVHMs.[14] However, our results did indicate that even among the elderly individuals with prediabetes or diabetes, each additional ICVHM was associated with substantially lower risk of CVD (11% to 13%), highlighting the benefit of achieving and maintaining an ideal cardiovascular health across the life course.[32]

With regard to each component of cardiovascular health metrics, an ideal blood pressure was predominantly associated with lower CVD risks among individuals with prediabetes or diabetes. Surprisingly, an ideal HbA_{1c} level was not independently associated with the CVD risk among individuals with prediabetes. In 2018, the Whitehall II Study[10] of 5427 participants aged 50 to 79 years reported that the risk of CVD associated with prediabetes defined by HbA_{1c} was absolutely

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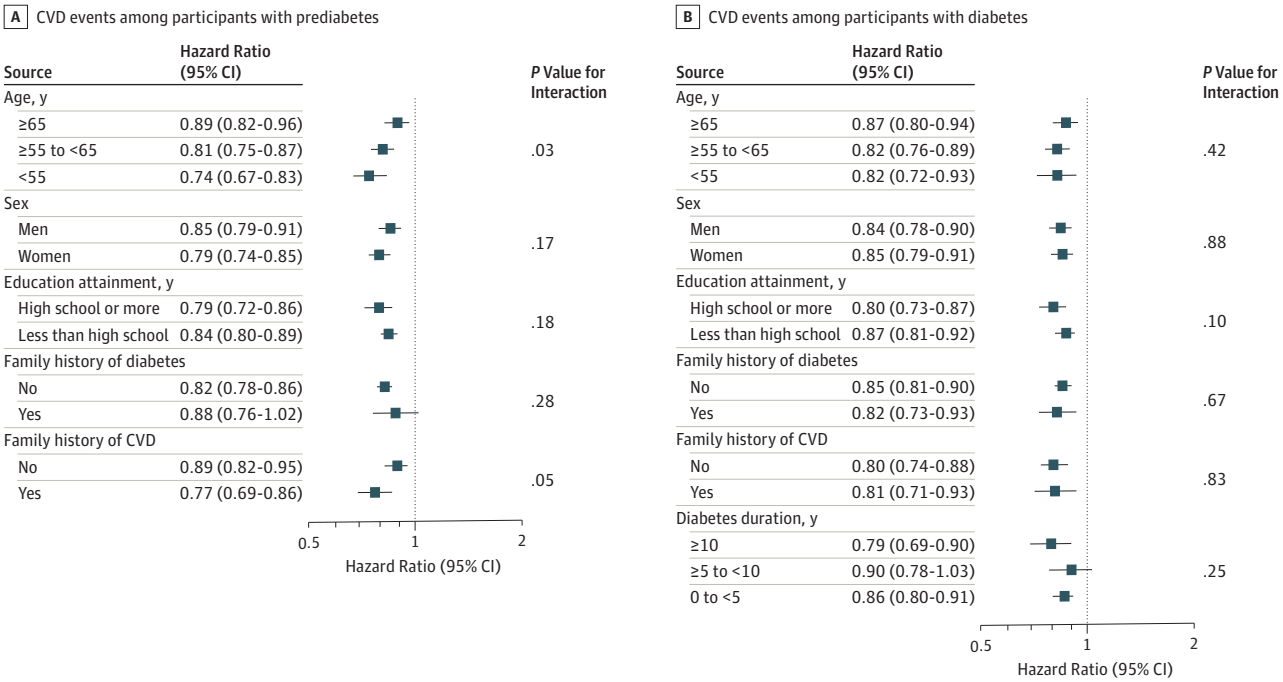
Figure 2. Hazard Ratio (95% CI) of Cardiovascular Disease (CVD) Events per 1-Number Increment in Ideal Cardiovascular Health Metrics (ICVHMs) According to Stratification Categories Among Participants With Prediabetes or Diabetes



A total of 61 024 participants with prediabetes and 25 860 with diabetes were included in the analysis. Hazard ratios (95% CI) were adjusted for age, sex, education attainment (less than high school or high school or greater), family history of diabetes (yes or no), family history of CVD (yes or no), and diabetes duration (for participants with diabetes only).

eliminated after adjustment for cardiovascular risk factors such as smoking, cholesterol levels, and systolic blood pressure, suggesting that the excess risk of CVD among individuals with prediabetes may be mainly explained by the clustering of other cardiovascular risk factors associated with hyperglycemia. Together with existing evidence, our findings suggest that the primary prevention of CVD in individuals with prediabetes or diabetes should focus on a combination of cardiovascular risk factors.

Strengths and Limitations

The strengths of this study included the large nationwide sample size, the prospective study design, the well-validated definitions of the CVD outcomes, and the comprehensive analyses including individuals with normal glucose regulation, prediabetes, or diabetes. Our study also has notable limitations. First, the relatively short follow-up duration might limit the statistical power for CVD events. Second, the cardiovascular health metrics were evaluated only at baseline, so changes in the metrics over time could not be accounted for in this study. Participants who were excluded owing to missing data on cardiovascular health metrics included a slightly higher proportion of men, so a selection bias may exist. The results, then, should be interpreted cautiously. Third, we evaluated an ideal diet mainly on the basis of fruit and vegetable intake, and the absence of comprehensive dietary data may underestimate the actual association of a healthy diet with CVD events. Fourth, we could not fully rule out all the residual and unmeasured confounders, such as genetic predisposition, medications, and psychological status and possible reverse causation.

Conclusions

In this Chinese nationwide prospective population-based study, patients with prediabetes or diabetes who achieved a greater number of ICVHMs exhibited lower or no significant excess risks of CVD events compared with individuals with normal glucose regulation. In addition, among patients with prediabetes or diabetes, each additional ICVHM was associated with at least 15% lower risk of CVD. Our findings emphasize the importance of promoting the adherence to ICVHMs in the prevention of CVD events among patients with prediabetes or diabetes.

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Invited Commentary

Improving Global Cardiovascular Health
Lessons From Healthy Lifestyles in China

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Cardiovascular diseases are the leading cause of death and disability in the world. In 2016, ischemic heart disease and stroke accounted for a combined 15.2 million deaths. The United Nations member states, acting through the World Health Assembly, have pledged to reduce cardiovascular mortality by 25% by 2025. Reports from China, the most populous country in the world, about the growing prevalence of cardiovascular disease (CVD) are worthy of attention.[1] The number of deaths from ischemic heart disease have more than doubled in the last 2 decades and stroke, the leading cause of death in China, accounts for almost one-third of the total worldwide mortality from stroke. The marked urbanization in China with its associated changes in lifestyle have resulted in a proliferation of cardiovascular risk factors resulting in CVD, among which diabetes is a major component.

Related article page 874

The association of rapid urbanization in China with cardiovascular risk factors and lifestyles provides a message for other countries with rapidly developing economies.[2] Physical activity has declined 31% in adult men and 42% in adult women between 1991 and 2011. In 2012, only 19% of Chinese adults

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