Individual and Combined Cardiometabolic Morbidities and the Subsequent Risk of Cardiovascular Events in Chinese Adults: The China Cardiometabolic Disease and Cancer Cohort Study

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Abstract

Background The data regarding the association between main cardiometabolic morbidities such as diabetes, hypertension, and dyslipidemia and the subsequent risk of CVD events in Chinese adults are still limited. Therefore, we investigated the associations between individual and combined cardiometabolic morbidities and incident cardiovascular events in Chinese adults.

Methods

The China Cardiometabolic Disease and Cancer Cohort Study was a prospective, nationwide, and population-based cohort study of 20 Chinese communities from various geographic regions. A comprehensive set of questionnaires, clinical measurements, oral glucose tolerance tests (OGTTs), and laboratory examinations were carried out at baseline (2011-2012) and follow-up visits (2014-2016). 133572 participants aged ≥ 40 years who were free from cardiovascular disease (CVD) at baseline were included in the study.

Results

Compared with participants without diabetes, hypertension and dyslipidemia, participants with only diabetes (hazard ratio [HR], 1.58; 95% confidence interval [CI], 1.32-1.90) or only hypertension (2.04; 1.82-2.28) exhibited significantly higher risk for CVD events, while participants with only dyslipidemia (0.97; 0.84-1.12) exhibited no significantly higher risk for CVD events. When analyzed collectively, participants with diabetes plus hypertension (HR, 2.67; 95%CI, 2.33-3.06), diabetes plus dyslipidemia (1.57; 1.32-1.87), and hypertension plus dyslipidemia (2.12; 1.88-2.39) exhibited significantly higher risk for CVD events. Moreover, participants with the combination of diabetes, hypertension and dyslipidemia exhibited the highest risk for CVD events (HR, 3.06; 95%CI, 2.71-3.46). Multivariable-adjusted HRs (95% CIs) for CVD associated with diabetes based on fasting glucose ≥7.0 mmol/L, OGTT-2h glucose ≥11.1 mmol/L, and hemoglobin A1c ≥6.5% were 1.64 (1.51-1.78), 1.57 (1.45-1.69), and 1.54 (1.42-1.66), respectively; associated with hypertension based on systolic blood pressure ≥140 mmHg and diastolic blood pressure ≥90 mmHg were 1.89 (1.76-2.03) and 1.74 (1.60-1.88), respectively; associated with dyslipidemia based on total cholesterol ≥6.22 mmol/L, low-density lipoprotein cholesterol ≥4.14 mmol/L, high-density lipoprotein cholesterol <1.04 mmol/L, and triglycerides ≥2.26 mmol/L were 1.18 (1.08-1.30), 1.30 (1.17-1.44), 1.00 (0.92-1.09), and 1.10 (1.01-1.20), respectively.

Conclusions

Diabetes, hypertension and dyslipidemia showed additive associations with the risk of CVD events in middle-aged and elderly Chinese adults.

Background

Cardiovascular disease (CVD) is the leading cause of death and disease burden in China [1]. It has been estimated that aging, sedentary lifestyle, and population growth will increase the CVD burden by more than a half over the next 20 years, and the projected unfavorable trends in diabetes, hypertension, and dyslipidemia could largely accelerate the CVD epidemic [2]. China has become the epicenter of diabetes and hypertension. According to data from the China National Survey and the China Hypertension Survey, there were approximately 11.2% and 23.2% of Chinese adults living with diabetes and hypertension, respectively [3–4]. Moreover, diabetes and hypertension will accelerate the increasing prevalence of dyslipidemia, and it has been estimated that these cardiometabolic morbidities will lead to an increase of 9.2 million cases of CVD during 2010 to 2030 in China [2]. A detailed description of the relationships of these cardiometabolic morbidities, individually and collectively, with cardiovascular events could provide valuable public health implications for effective prevention and control of CVD. However, the data regarding the association between main cardiometabolic morbidities such as diabetes, hypertension, and dyslipidemia and the subsequent risk of CVD events in Chinese adults are still limited.

To this end, we investigated the associations between individual and combined cardiometabolic morbidities including diabetes, hypertension, and dyslipidemia and incident cardiovascular events in Chinese adults aged 40 years or older in a nationwide prospective cohort study.

Methods

Study design and population

The China Cardiometabolic Disease and Cancer Cohort (4C) Study is a population-based, multicenter, prospective cohort study. The study design of the 4C Study has been described in detail previously [5-6]. During 2011 to 2012, 193846 adults aged ≥ 40 years were recruited from 20 different 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 170240 participants (87.8%) were successfully followed up. According to standardized protocols, a comprehensive set of questionnaires, clinical measurements, oral glucose tolerance tests (OGTTs), and laboratory examinations were carried out at baseline and follow-up visits. In this study, 133572 participants who had complete baseline information on diabetes, hypertension, and dyslipidemia, were free from CVD at baseline, and had complete ascertainment of CVD events during follow-up were included in the main analyses of the associations between these morbidities and incident CVD. To analyze the associations between cardiometabolic disorders and CVD events, we further excluded participants without complete information on glucose tolerance status, glycated hemoglobin A1c (HbA1c), blood pressures, and lipid profiles at baseline, and 129072 participants were included in the analyses. This study was approved by the Medical Ethics Committee of Ruijin Hospital, Shanghai Jiao Tong University. All study participants provided written informed consent.

Data collection

According to a standard protocol, data collection was performed in local community clinics by trained study personnel at baseline and the follow-up visit. A questionnaire comprising information on demographic characteristics, lifestyle factors (including alcohol drinking and cigarette smoking) was administered by trained interviewers. Current alcohol drinker was defined as a person who drank alcohol regularly in the past 6 months. Smoking status were categorized as current, former, and never smoking. Education attainment was categorized as less than high school and high school or more. Physical activity was assessed by the International Physical Activity Questionnaire [7]. The metabolic equivalent (MET) was calculated to estimate average weekly energy expenditure. Physical activity was categorized as active (≥600 MET-min per week), insufficiently active (>0 to <600 MET-min per week), and inactive (0 MET-min per week) [8].

Height and body weight were measured according to the standard protocol, and body mass index (BMI) was calculated as the weight in kilograms divided by height in meters squared. After at least a 5-minute quiet rest, every participant needed to measure blood pressure in a seated position for three times, and an automated electronic device (OMRON Model HEM-752 FUZZY) was used to measure blood pressure. Before the blood pressure measurement, alcohol, coffee, tea, smoking, and exercise should be avoided at least 30 minutes. At last, the 3 readings were averaged for the analysis.

After an overnight fast of at least 10 hours, all participants underwent an OGTT, and blood samples were collected at 0 and 2 hours. Fasting and 2-hour plasma glucose concentrations was measured locally within 2 hours after blood sample collection using the glucose oxidase or hexokinase method 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℃ to 8℃ 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. HbA1c was measured by high-performance liquid chromatography using the VARIANT II Hemoglobin Testing System (Bio-Rad Laboratories) within 4 weeks after collection. The capillary HbA1c values and the venous values from whole-blood samples, which collected using ethylene diamine tetraacetic acid dipotassium tubes, were highly correlated (r = 0.99) in a validation subsample [9]. Total cholesterol (TC), low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, and triglycerides (TG) were measured using an autoanalyzer (ARCHITECT ci16200 analyzer; Abbott Laboratories) at the central laboratory.

Diagnosis of Diabetes, hypertension and dyslipidemia

According to the American Diabetes Association 2010 criteria, diabetes was defined as fasting plasma glucose level of 126 mg/dL (7.0 mmol/L) or more, or OGTT-2 h plasma glucose level of 11.1 mmol/L or more, or HbA1c level of 6.5% or more, or by a self-reported previous diagnosis by health care professionals [10]. Dyslipidemia was defined as LDL cholesterol ≥160 mg/dL (4.14 mmol/L), or HDL cholesterol <40 mg/dL (1.04 mmol/L), or triglycerides ≥200 mg/dL (2.26 mmol/L), or total cholesterol

≥240 mg/dL (6.22 mmol/L), or taking lipid-lowering medications [11]. Hypertension was defined as systolic blood pressure (SBP) ≥140 mmHg, or diastolic blood pressure (DBP) ≥90 mmHg, or by a self-reported previous diagnosis by health care professionals [12].

Ascertainment of Cardiovascular Events

The outcome of this study was the composite of incident fatal or nonfatal CVD events, which included myocardial infarction, stroke, cardiovascular death, and hospitalized or treated heart failure. The ascertainment of cardiovascular events has been described in detail previously [6].

Statistical Analysis

Continuous variables were presented as means with standard deviations (SDs) and categorical variables were presented as numbers with percentages. Person-time for every participant was calculated from the date of enrollment to the date of CVD diagnosis, death, or the end of follow-up. We first calculated the hazard ratios (HRs) and 95% confidence intervals (CIs) for CVD events using the Cox proportional hazards models in all participants, with multivariable adjustment for age, sex, education attainment (below high school, high school or above), BMI, physical activity (inactive, insufficiently active, active), smoking status (never, former, current), and drinking status (never, former, current). Next, we calculated all these above hazard ratios (HRs) and 95% confidence intervals (CIs) for CVD events among men and women, respectively. We then calculated the multivariable-adjusted HRs and 95% CIs for incident of CVD events for participants with cardiometabolic disorders, which were defined by measures of glucose, blood pressures, and lipids, in comparison with participants without the relative disorders. We also assessed the associations between cardiometabolic disorders and CVD events by sex stratifications. All statistical analyses were performed by using SAS software, version 9.4 (SAS Institute Inc). A two-sided *P* value <0.05 was considered statistically significant.

Results

Baseline key characteristics of 133572 participants (46125 men and 87447 women) are shown in Table 1. Compared with women, men were older, had higher proportions of high school or further education, and were more likely to be current smokers, current drinkers, and be physically inactive. Generally, compared with women, men had poorer cardiometabolic profiles, with higher proportions of diabetes, hypertension, and dyslipidemia, and had higher levels of BMI, fasting glucose, OGTT-2 h glucose, HbA1c, SBP, DBP and LDL cholesterol and a lower level of HDL cholesterol.

Table 1
Baseline characteristics of study participants

Characteristic	Men	Women	*P* value
Age, year	57.4 (9.3)	55.9 (8.8)	< 0.001
High school or further education, n (%)	18376 (39.8)	29488 (33.7)	< 0.001
Smoking status, n (%)			< 0.001
Never	21745 (47.1)	85946 (98.3)	
Former	5855 (12.7)	322 (0.4)	
Current	18525 (40.2)	1179 (1.3)	
Drinking status, n (%)			< 0.001
Never	31301 (67.9)	85652 (98.0)	
Former	2417 (5.2)	358 (0.4)	
Current	12407 (26.9)	1437 (1.6)	
Physical activity, n (%)			< 0.001
Active	28286 (61.3)	55060 (63.0)	
Insufficiently active	15481 (33.6)	28325 (32.4)	
Inactive	2358 (5.1)	4062 (4.7)	
BMI, kg/m^2	24.8 (3.5)	24.5 (3.6)	< 0.001
Diabetes, n (%)	11802 (25.6)	18505 (21.2)	< 0.001
Fasting glucose, mmol/L	6.1 (1.8)	5.9 (1.5)	< 0.001
OGTT 2 h glucose, mmol/L	8.3 (4.1)	8.1 (3.6)	< 0.001
HbA1c, %	6.0 (1.1)	6.0 (1.0)	< 0.001
Hypertension, n (%)	22625 (49.1)	35753 (40.9)	< 0.001
SBP, mmHg	136 (20)	132 (21)	< 0.001
DBP, mmHg	80 (11)	77 (11)	< 0.001
Dyslipidemia, n (%)	21370 (46.3)	34698 (39.7)	< 0.001
TC, mmol/L	4.8 (1.1)	5.1 (1.2)	< 0.001
TG, mmol/L	2.8 (0.8)	2.9 (0.9)	< 0.001

Data are mean (standard deviation) or number (%). P values were calculated by ANOVA for continous variables or by Chi-square for categorical variables.

Characteristic	Men	Women	*P* value
HDL cholesterol, mmol/L	1.3 (0.4)	1.4 (0.4)	< 0.001
LDL cholesterol, mmol/L	1.7 (1.4)	1.6 (1.1)	< 0.001

Data are mean (standard deviation) or number (%). P values were calculated by ANOVA for continous variables or by Chi-square for categorical variables.

During a mean follow-up of 3.60 (SD, 1.03; 480985.90 person-years) years, we documented 3632 CVD events. Compared with participants without diabetes, hypertension and dyslipidemia, participants with only diabetes (HR, 1.58; 95%CI, 1.32–1.90) or only hypertension (2.04; 1.82–2.28) exhibited significantly higher risk for CVD events, while participants with only dyslipidemia exhibited no significantly excess risk (0.97; 0.84–1.12) for CVD events (Table 2). When analyze these morbidities collectively, compared with participants without diabetes, hypertension, and dyslipidemia, participants with diabetes plus hypertension (HR, 2.67; 95%CI, 2.33–3.06), diabetes plus dyslipidemia (1.57; 1.32–1.87), and hypertension plus dyslipidemia (2.12; 1.88–2.39) showed significantly higher risks for CVD events. As expected, participants with the combination of diabetes, hypertension and dyslipidemia exhibited the highest risk for CVD events (HR, 3.06; 95%CI, 2.71–3.46). These association patterns were generally consistent in men and women (Table 3), except that participants with dyslipidemia only (HR, 0.76; 95%CI, 0.59–0.97) exhibited significantly lower risk for CVD events in men.

Table 2
Multivariable-adjusted HR (95% CI) for cardiovascular events associated with cardiometabolic morbidities

Morbidity	No. of participants	Cases	Person-years	HR (95% CI)*
Without diabetes, hypertension, and dyslipidemia	40902	508	147977	1.00 (Ref.)
Diabetes only	6018	151	21439	1.58 (1.32–1.90)
Hypertension only	23299	851	82444	2.04 (1.82–2.28)
Dyslipidemia only	21646	278	79387	0.97 (0.84–1.12)
Diabetes + hypertension	7285	398	25697	2.67 (2.33–3.06)
Diabetes + dyslipidemia	6628	169	24015	1.57 (1.32–1.87)
Hypertension + dyslipidemia	17418	645	62988	2.12 (1.88–2.39
Diabetes + hypertension + dyslipidemia	10376	632	37039	3.06 (2.71–3.46)
133572 participants were included in the analysis.				
*HRs (95% CIs) indicate risks for incident cardiovascular events for participants with cardiometabolic morbidities, compared with participants without diabetes, hypertension, or dyslipidemia; with adjustment for age, sex, education attainment (below high school, high school or above), body mass index, physical activity (inactive, intermediate active, active), smoking status (never, former, current), and drinking status (never, former, current).				

Table 3
Multivariable-adjusted HR (95% CI) for cardiovascular events associated with cardiometabolic morbidities by sex

Morbidity	No. of participants	Cases	Person-years	HR (95% CI)*
Men (n = 46125)				
Without diabetes, hypertension, and dyslipidemia	11194	195	40199	1.00 (Ref.)
Diabetes only	2154	63	7596	1.50 (1.13-2.00)
Hypertension only	8615	398	30492	2.07 (1.74–2.46)
Dyslipidemia only	7494	91	27800	0.76 (0.59–0.97)
Diabetes + hypertension	2792	181	9688	2.79 (2.26–3.43)
Diabetes + dyslipidemia	2658	93	9709	1.90 (1.48–2.44)
Hypertension + dyslipidemia	7020	288	25451	2.18 (1.81–2.63)
Diabetes + hypertension + dyslipidemia	4198	296	14999	3.26 (2.70–3.94)
Women (n = 87447)				
Without diabetes, hypertension, and dyslipidemia	29708	313	107778	1.00 (Ref.)
Diabetes	3864	88	13843	1.65 (1.30–2.09)
Hypertension	14684	453	51952	2.02 (1.74–2.35)
Dyslipidemia	14152	187	51587	1.14 (0.95–1.36)
Diabetes + hypertension	4493	217	16009	2.59 (2.16–3.11)

133572 participants were included in the analysis.

*HRs (95% CIs) indicate risks for incident cardiovascular events for participants with cardiometabolic morbidities, compared with participants without diabetes, hypertension, or dyslipidemia; with adjustment for age, education attainment (below high school, high school or above), body mass index, physical activity (inactive, intermediate active, active), smoking status (never, former, current), and drinking status (never, former, current).

Morbidity	No. of participants	Cases	Person-years	HR (95% CI)*
Diabetes + dyslipidemia	3970	76	14306	1.31 (1.01–1.68)
Hypertension + dyslipidemia	10398	357	37537	2.10 (1.79–2.46)
Diabetes + hypertension + dyslipidemia	6178	336	22040	2.95 (2.51–3.47)
133572 participants were included in the analysis.				
*HRs (95% CIs) indicate risks for incident cardiovascular events for participants with cardiometabolic morbidities, compared with participants without diabetes, hypertension, or dyslipidemia; with adjustment for age, education attainment (below high school, high school or above), body mass index, physical activity (inactive, intermediate active, active), smoking status (never, former, current), and drinking status (never, former, current).				

As shown in Table 4, multivariable-adjusted HRs (95% CIs) for CVD events associated with diabetes based on fasting glucose ≥ 7.0 mmol/L, OGTT-2 h glucose ≥ 11.1 mmol/L, and HbA1c ≥ 6.5% were 1.64 (1.51–1.78), 1.57 (1.45–1.69), and 1.54 (1.42–1.66), respectively. The HRs (95% CIs) for CVD events associated with hypertension based on SBP ≥ 140 mmHg and DBP ≥ 90 mmHg were 1.89 (1.76–2.03) and 1.74 (1.60–1.88), respectively. And the corresponding HRs (95% CIs) associated with dyslipidemia based on TC ≥ 6.22 mmol/L, LDL cholesterol ≥ 4.14 mmol/L, HDL cholesterol < 1.04 mmol/L, and TG ≥ 2.26 mmol/L were 1.18 (1.08–1.30), 1.30 (1.17–1.44), 1.00 (0.92–1.09), and 1.10 (1.01–1.20), respectively. These results were quite consistent by sex (Table 5), except that participants with TG ≥ 2.26 mmol/L exhibited no significant association with CVD events in men (HR, 0.99; 95%CI, 0.86–1.14).

Table 4
Multivariable-adjusted HR (95% CI) for cardiovascular events associated with cardiometabolic disorders

Disorder	No. of participants	Cases	Person-years	HR (95% CI)*
Diabetes-related				
Fasting glucose ≥ 7.0 mmol/L	15358	754	54400	1.64 (1.51–1.78)
OGTT-2 h glucose ≥ 11.1 mmol/L	19697	950	70455	1.57 (1.45–1.69)
HbA1c ≥ 6.5%	19151	904	68446	1.54 (1.42–1.66)
Hypertension-related				
SBP ≥ 140 mmHg	43572	2023	154711	1.89 (1.76–2.03)
DBP ≥ 90 mmHg	19852	826	71156	1.74 (1.60–1.88)
Dyslipidemia-related				
TC ≥ 6.22 mmol/L	16276	542	58296	1.18 (1.08–1.30)
LDL cholesterol ≥ 4.14 mmol/L	10334	392	37251	1.30 (1.17–1.44)
HDL cholesterol < 1.04 mmol/L	24194	710	89655	1.00 (0.92–1.09)
TG ≥ 2.26 mmol/L	22133	651	79696	1.10 (1.01–1.20)
129072 participants with complete cardiometabolic disorders were included in the analysis.				
*HRs (95% CIs) indicate risks for incident cardiovascular events for participants with cardiometabolic disorders, compared with participants without the relative disorders; with adjustment for age, sex, education attainment (below high school, high school or above), body mass index, physical activity (inactive, intermediate active, active), smoking status (never, former, current), and drinking status (never, former, current).				

Table 5
Multivariable-adjusted HR (95% CI) for cardiovascular events associated with cardiometabolic disorders by sex

Disorder	No. of participants	Cases	Person-years	HR (95% CI)*
Men (n = 44264)				
Diabetes-related				
Fasting glucose ≥ 7.0 mmol/L	6584	382	23375	1.76 (1.57–1.98)
OGTT-2 h glucose ≥ 11.1 mmol/L	7862	440	28048	1.58 (1.41–1.77)
HbA1c ≥ 6.5%	7158	422	25485	1.71 (1.52–1.92)
Hypertension-related				
SBP ≥ 140 mmHg	16692	912	59163	1.90 (1.71–2.11)
DBP ≥ 90 mmHg	9078	428	32671	1.77 (1.58–1.98)
Dyslipidemia-related				
TC ≥ 6.22 mmol/L	4118	166	14698	1.23 (1.05–1.44)
LDL cholesterol ≥ 4.14 mmol/L	2730	134	9773	1.41 (1.18–1.69)
HDL cholesterol < 1.04 mmol/L	11771	424	43822	1.04 (0.93–1.17)
TG ≥ 2.26 mmol/L	8651	250	31333	0.99 (0.86–1.14)
Women (n = 84808)				
Diabetes-related				
Fasting glucose ≥ 7.0 mmol/L	8774	372	31025	1.53 (1.36–1.71)
OGTT-2 h glucose ≥ 11.1 mmol/L	11835	510	42407	1.56 (1.40–1.72)
HbA1c ≥ 6.5%	11993	482	42961	1.41 (1.27–1.56)
Hypertension-related				
SBP ≥ 140 mmHg	26880	1111	95547	1.88 (1.71–2.07)

129072 participants with complete cardiometabolic disorders were included in the analysis.

*HRs (95% CIs) indicate risks for incident cardiovascular events for participants with cardiometabolic disorders, compared with participants without the relative disorders; with adjustment for age, education attainment (below high school, high school or above), body mass index, physical activity (inactive, intermediate active, active), smoking status (never, former, current), drinking status (never, former, current).

Disorder	No. of participants	Cases	Person-years	HR (95% CI)*
DBP ≥ 90 mmHg	10774	398	38485	1.71 (1.53–1.91)
Dyslipidemia-related				
TC ≥ 6.22 mmol/L	12158	376	43598	1.16 (1.04–1.30)
LDL cholesterol ≥ 4.14 mmol/L	7604	258	27477	1.25 (1.09–1.42)
HDL cholesterol < 1.04 mmol/L	12423	286	45833	0.95 (0.84–1.08)
TG ≥ 2.26 mmol/L	13482	401	48364	1.19 (1.06–1.32)
129072 participants with complete cardiometabolic disorders were included in the analysis.				
*HRs (95% CIs) indicate risks for incident cardiovascular events for participants with cardiometabolic disorders, compared with participants without the relative disorders; with adjustment for age, education attainment (below high school, high school or above), body mass index, physical activity (inactive, intermediate active, active), smoking status (never, former, current), drinking status (never, former, current).				

Discussion

In this Chinese nationwide prospective cohort study of 133572 middle-aged and elderly adults, we provided comprehensive data on relationships of individual and combined cardiometabolic morbidities including diabetes, hypertension, and dyslipidemia with the subsequent risk of CVD events. In this study, compared with participants without diabetes, hypertension, and dyslipidemia, participants with diabetes or hypertension only exhibited significantly higher risk of CVD events, while participants with dyslipidemia only showed no excess risk of CVD. When analyzed collectively, these morbidities showed an additively increased risk of CVD events, with the combination of diabetes, hypertension, and dyslipidemia conferred the highest risk for CVD events. Our findings were independent from controversial risk factors, and were generally consistent by sex.

Cardiovascular complications are the leading cause of disability and mortality in patients with type 2 diabetes [13–14], and diabetes increases the risk of CVD events for more than 2-fold independent of conventional risk factors [15–16]. Recently, findings from the Da Qing IGT and Diabetes Study revealed that during 23 years of follow-up, CVD was the predominant cause of deaths among Chinese adults with newly diagnosed diabetes, responsible for 47.5% of deaths in men and 49.7% in women [17]. As for hypertension, a prospective observational global study of 1 million people from 61 populations with an average follow up of 12 years provided robust data that clinic SBP or DBP was independently, directly, positively and continuously associated with the risk of cardiovascular mortality, stroke, and coronary heart disease events [18]. The Asia Pacific cohort study (APCSC) including 13 Chinese populations also confirmed that elevated blood pressures significantly increased the risk for ischemic heart disease and stroke events [19]. And interestingly, these above associations were stronger in Asian populations than in New Zealand and Australia populations: in Australian and New Zealand populations, with every

10 mmHg increase in SBP, the risks of stroke and fatal myocardial infarction increased 24% and 21%, respectively; while the corresponding risks were 53% and 31% in Asian populations [19]. Our findings were in line with previous studies by supporting the strong and independent impacts of diabetes and hypertension on incident CVD events, and extended previous findings by highlighting the comprehensive management of diabetes and hypertension could be more effective for the prevention and control of CVD events.

In the primary prevention of CVD, treatment measures and intervention goals for blood lipids should be determined according to the degree of CVD risk, and it is necessary to take personalized comprehensive treatment decisions to minimize the overall risk of CVD patients [20]. Emerging evidence suggested that TC and LDL-C are positively correlated with the CVD risk, and lowering LDL-C level has been regarded as the primary intervention target of lipid regulation therapy [21]. The Fenofibrate Intervention and Event Lowering in Diabetes study [22] and Helsinki Heart Study [23] showed that a reduction in TG was associated with a lower risk of atherosclerotic CVD. Because no research intervention has targeted only HDL, it is difficult to determine whether increasing HDL levels alone is clinically beneficial from clinical trials [24–25]. However, the Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial documented that increasing HDL and lowering TG significantly reduced the rate of coronary events in individuals with ASCVD and low HDL-C [25–26]. In this study, compared with adults without diabetes, hypertension, and dyslipidemia, adults with only dyslipidemia exhibited no significant excess risk for CVD events. However, participants with TC ≥ 6.22 mmol/L, LDL-C ≥ 4.14 mmol/L or TG ≥ 2.26 mmol/L did confer higher CVD risks than those with normal blood lipids. Meanwhile, we found dyslipidemia in combination with diabetes or hypertension exhibited significantly higher risks for CVD events. Our observations might be explained, at least partly, by the potential reason that adults with dyslipidemia were more prone to be accompanied with obesity, diabetes and hypertension, and the complex interplay between dyslipidemia and multiple risk factors largely determined the overall risk of CVD events [27].

Strengths And Limitations

To the best of our knowledge, this is the first study to comprehensively investigate the associations between individual and combined cardiometabolic morbidities and incident CVD events in Chinese adults. Our findings emphasized the importance of a comprehensive management of cardiometabolic morbidities to promote the efficiency of prevention and control of CVD events. The strengths of this study included the prospective study design, the large nationwide sample size, and the comprehensive cardiometabolic measurements. However, this study also has several limitations. First, the follow-up duration was relatively short, which might limit the statistical power for CVD events. Second, although we have carefully adjusted for a series of confounders in the analyses, the residual and unmeasured confounders and possible reverse causation could not be fully ruled out and the bias is likely to be present. Third, our analyses were restricted to middle-aged and elderly Chinese adults, therefore the generalization of our findings to other ethnic groups should be cautious.

Conclusions

This prospective nationwide population-based study of Chinese adults provided quantitative data that main cardiometabolic morbidities including diabetes, hypertension, and dyslipidemia, individually and collectively, associated with increased risks of CVD events. Our findings underlined the importance of taking into account of diabetes, hypertension, and dyslipidemia together in the primary prevention and control of CVD to reduce the disease burden.

Abbreviations

OGTTs: Oral glucose tolerance tests; CVD: Cardiovascular disease; HR: Hazard ratio; CI: Confidence interval; HbA1c: Glycated hemoglobin A1c; MET: Metabolic equivalent; BMI: Body mass index; TC: Total cholesterol; LDL: Low-density lipoprotein; HDL: High-density lipoprotein; TG: Triglycerides; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; SDs: Standard deviations; APCSC: Asia Pacific cohort study.

Declarations

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Authors' contributions

Drs Jiao Wang, Yanyan Zhao, and Guijun Qin conceived and designed the study. Dr Jiao Wang analyzed data. All authors collected data, were involving in writing and revising the manuscript, and had final approval of the submitted and published versions. Dr Guijun Qin is the guarantors of this work and had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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Availability of data and materials

Data and study materials are available.

Ethics approval and consent to participate

The research protocol was approved by the Medical Ethics Committee of Ruijin Hospital, Shanghai Jiao Tong University. All study participants provided written informed consent.

Consent for publication

All authors give the consent to publish the present article.

Competing interests

All authors declare no competing interests.

References

1. Institute for Health Metrics and Evaluation (IHME). GBD compare data visualization [EB/OL]. [2018-11-27]. http://vizhub healthdataorg/gbd-compare.
2. Andrew Moran, Dongfeng Gu, Dong Zhao, et al. Future cardiovascular disease in china: markov model and risk factor scenario projections from the coronary heart disease policy model-china. Circ Cardiovasc Qual Outcomes. 2010;3(3):243-52.
3. Yongze Li, Di Teng, Xiaoguang Shi, et al. Prevalence of diabetes recorded in mainland China using 2018 diagnostic criteria from the American Diabetes Association: national cross sectional study. BMJ. 2020; 369:m997.
4. Zengwu Wang, Zuo Chen, Linfeng Zhang, et al; China Hypertension Survey Investigators. Status of Hypertension in China: Results From the China Hypertension Survey, 2012-2015. Circulation. 2018; 137(22):2344-56.
5. Jieli Lu, Jiang He, Mian Li, et al; 4C Study Group. Predictive Value of Fasting Glucose, Postload Glucose, and Hemoglobin A 1c on Risk of Diabetes and Complications in Chinese Adults. Diabetes Care. 2019; 42(8):1539-48.
6. Tiange Wang, Jieli Lu, Qing Su, et al; 4C Study Group. Ideal Cardiovascular Health Metrics and Major Cardiovascular Events in Patients With Prediabetes and Diabetes. JAMA Cardiol. 2019; 4(9):874-83.
7. Craig CL, Marshall AL, Sjöström M, et al. International physical activity questionnaire: 12-country reliability and validity. Med Sci Sports Exerc. 2003; 35(8):1381-95.
8. B E Ainsworth, W L Haskell, A S Leon, et al. Compendium of physical activities: classification of energy costs of human physical activities. Med Sci Sports Exerc. 1993; 25(1):71-80.
9. Yu Xu, Limin Wang, Jiang He, et al; 2010 China Noncommunicable Disease Surveillance Group. Prevalence and control of diabetes in Chinese adults. JAMA. 2013; 310(9):948-59.

10. American Diabetes Association. Diagnosis and classification of diabetes mellitus. Diabetes Care. 2010; 33 Suppl 1 (suppl 1): S62-9.
11. Expert Panel on Detection E, and Treatment of High Blood Cholesterol in Adults. Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, And Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III). JAMA. 2001; 285(19):2486-97.
12. ACCORD Study Group; William C Cushman, Gregory W Evans, Robert P Byington, et al. Effects of intensive blood-pressure control in type 2 diabetes mellitus. N Engl J Med. 2010; 362(17):1575-85.
13. American Diabetes Association. 9: Cardiovascular disease and risk management. Diabetes Care. 2017; 40(suppl 1): S75-87.
14. Sho-Ichi Yamagishi, Nobutaka Nakamura, Takanori Matsui. Glycation and cardiovascular disease in diabetes. A perspective on the concept of metabolic memory. J Diabetes. 2017; 9(2):141-8.
15. Sreenivasa Rao Kondapally Seshasai, Stephen Kaptoge, Alexander Thompson, et al; Emerging Risk Factors Collaboration. Diabetes mellitus, fasting glucose, and risk of cause-specific death. N Engl J Med. 2011; 364(9): 829-41.
16. Emerging Risk Factors Collaboration; N Sarwar, P Gao, S R Kondapally Seshasai, et al. Diabetes mellitus, fasting blood glucose concentration, and risk of vascular disease: a collaborative meta-analysis of 102 prospective studies. Lancet. 2010; 375(9733):2215-22.
17. Yali An, Ping Zhang, Jinping Wang, et al. Cardiovascular and All-Cause Mortality Over a 23-Year Period Among Chinese With Newly Diagnosed Diabetes in the Da Qing IGT and Diabetes Study. Diabetes Care. 2015; 38(7):1365-71.
18. Sarah Lewington, Robert Clarke, Nawab Qizilbash, Richard Peto, Rory Collins, Prospective Studies Collaboration. Prospective Studies Collaboration Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. Lancet. 2002; 360(9349):1903-13.
19. Donald M Lloyd-Jones, Martin G Larson, Eric P Leip, et al; Framingham Heart Study. Lifetime risk for developing congestive heart failure: the Framingham Heart Study. Circulation. 2002; 106(24):3068-72.
20. François Mach, Colin Baigent, Catapano AL, et al; ESC Scientific Document Group. 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. Eur Heart J. 2020; 41(1):111-88.
21. Paul S Jellinger YH, Paul D Rosenblit, Zachary T Bloomgarden, et al. AMERICAN ASSOCIATION OF CLINICAL ENDOCRINOLOGISTS AND AMERICAN COLLEGE OF ENDOCRINOLOGY GUIDELINES FOR MANAGEMENT OF DYSLIPIDEMIA AND PREVENTION OF CARDIOVASCULAR DISEASE. Endocr Pract. 2017; 23(4):479-97.
22. A Keech, R J Simes, P Barter, et al; FIELD study investigators. Effects of long-term fenofibrate therapy on cardiovascular events in 9795 people with type 2 diabetes mellitus (the FIELD study): randomised controlled trial. Lancet. 2005; 366(9500):1849-61.

23. Leena Tenkanen MM, Petri T Kovanen, Hanna Virkkunen, Vesa Manninen. Gemfibrozil in the treatment of dyslipidemia: an 18-year mortality follow-up of the Helsinki Heart Study. Arch Intern Med. 2006; 166(7):743-8.
24. A M Gotto Jr. Prognostic and therapeutic significance of low levels of high-density lipoprotein cholesterol: current perspectives. Arch Intern Med. 1999; 159(10):1038-40.
25. H B Rubins, S J Robins, D Collins, et al. Gemfibrozil for the secondary prevention of coronary heart disease in men with low levels of high-density lipoprotein cholesterol. Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial Study Group. N Engl J Med. 1999; 341(6):410-8.
26. S J Robins, D Collins, J T Wittes, et al; VA-HIT Study Group. Veterans Affairs High-Density Lipoprotein Intervention Trial. Relation of gemfibrozil treatment and lipid levels with major coronary events: VA-HIT: a randomized controlled trial. JAMA. 2001; 285(12):1585-91.
27. Xueli Yang, Jianxin Li, Dongsheng Hu, et al. Predicting the 10-Year Risks of Atherosclerotic Cardiovascular Disease in Chinese Population: The China-PAR Project (Prediction for ASCVD Risk in China). Circulation. 2016; 134(19):1430-40.