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Original Article

Joint association of body mass index and central obesity with cardiovascular events and all-cause mortality in prediabetic population: A prospective cohort study

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ABSTRACT

Objective: To assess the joint association of body mass index (BMI) and central obesity with cardiovascular events and all-cause mortality in prediabetic population.
Methods: Altogether 18,703 participants with prediabetes completed follow-up between June 2006 and December 2015 were included in the analyses. Prediabetes was defined as fasting plasma glucose level 5.6–6.9 mmol/L, and without history of diabetes or currently use of hypoglycemic agents. Participants were classified according to the baseline status of BMI as well as the absence/presence of central obesity. We examined these associations in men and women separately.
Results: The mean age was 51.5 ± 11.1 years, and 85.6% (N = 16,002) were male. During a median follow up of 9.0 (interquartile range 8.7–9.2) years, 848 and 88 major CV events occurred in men and women, respectively. Besides, 1111 men and 89 women died. Compared with men of BMI 22–23.9 kg/m^2 and without central obesity, the risk of CV events was increased among men with higher BMI and central obesity (HR 1.32 (95% CI: 1.05–1.67) for BMI 24–27.9 kg/m^2 and 1.31 (1.03–1.66) for BMI $\geq$ 28 kg/m^2, respectively); and the risk of all-cause mortality was the lowest among men of BMI 24–27.9 kg/m^2 but without central obesity (0.75, 0.61–0.92). We found no such association in women.
Conclusion: Among men with prediabetes, both BMI and waist circumference should be included when evaluating the risks of major CV events and mortality. Measurement of adiposity constitutes a simple and cost-effective strategy to identify those at high-risk population in prediabetes.

Introduction

The global trend towards obesity, physical inactivity and energy-dense diets has led to a rapid rise in the number of population with diabetes [1], as well as prediabetes [2]. It was estimated that 415 million people live with diabetes [1] and 840 million people live with prediabetes worldwide [3]. A national cross-sectional survey in China reported that 493.4 million adults had prediabetes in 2010 [4]. About 70% of individuals with prediabetes will eventually develop into diabetes [2]. In addition, individuals with prediabetes are associated with increased risk of cardiovascular complications and premature death [3]. Therefore, it should be

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more cost-effective to identify and manage the high-risk subgroups among prediabetic population.

Several publications have revealed that body mass index (BMI) is inversely associated with mortality (i.e. obesity paradox) in patients with diabetes [5–7], as well as other clinical conditions (e.g. coronary artery disease (CAD) [8], end-stage kidney disease (ESKD) [9]). The possible explanation of this phenomenon is supposed to be the poor correlation between BMI and body fat [8]. To the best of our knowledge, only three cohort studies have investigated the association between obesity and mortality in prediabetic population and the results remain controversial [10–12]. Furthermore, all studies were conducted in western countries, whereas the burden of prediabetes is more severe in Asian countries, such as China [4].

In contrast to BMI, central obesity measured by waist circumference (WC) was considered as a stronger marker of health risk [13]. Observational studies have shown that high WC was related to all-cause mortality among individuals with diabetes [14]. A recent study combined BMI and central obesity to assess the prognosis in patients with CAD, and found that individuals with normal BMI and central obesity were associated with the highest mortality risk [15]. These findings indicated that combining BMI and measures of central obesity might be superior to either index in assessing the adverse outcomes in those individuals. Thus, in order to identify and manage the high-risk individuals among population with prediabetes, we conducted the current study and focused on the combination of BMI with WC, using a large prospective cohort of Chinese population with prediabetes.

Material and methods

Study population

The current study included a large prediabetic subgroup of the Kailuan cohort. The Kailuan study was a prospective cohort study conducted in the community of Kailuan in Tangshan, a large industrial city located in Hebei province of China. The detailed study design and characteristics of the study population have been described previously [16]. Briefly, 101,510 employees aged 18 years and older (including the retired) in Kailuan group participated in a biennially health examination from June 2006 through October 2007 that included face-to-face questionnaires on demographics and other variables, clinical examinations performed by trained medical personnel and laboratory tests, which were conducted in Kailuan General Hospital and its ten affiliated hospitals. These data were recorded and maintained in dedicated health records.

Data of 30,016 individuals with diabetes and prediabetes is available for us. Eligible participants for this study were adults aged 18–85 years and with prediabetes according to ADA 2010 criteria (defined as fasting plasma glucose (FPG) between 100 mg/dL (5.6 mmol/L) and 125 mg/dL (6.9 mmol/L), without self-reported history of diabetes and taking hypoglycemic drugs) [17]. All participants with a history of diabetes (N = 9489), myocardial infarction (MI) and stroke (N = 581), any malignant cancer (N = 59), ESKD (defined as estimated glomerular filtration rate (eGFR) <15 mL/min/1.73m^2) (N = 34), and age > 85 years old (N = 46) at baseline were excluded. We further excluded participants with missing data of BMI and WC (N = 308) and those with BMI < 18.5 kg/m^2 (underweight, N = 214). A total of 19,285 participants (16,511 men, 85.6%) with prediabetes were included in the analysis.

The protocol was approved by the Ethics Committee of both Kailuan General Hospital and Peking University First Hospital in accordance with the Declaration of Helsinki and written informed consent was obtained from each participant.

Data collection

We considered the 2006–2007 survey as the baseline and the first occurrence of the defined main outcomes or December 31, 2015 as the end of the follow up. All individuals completed a questionnaire documenting their socio-demographic status (e.g. age, sex, education and economic status), personal and family health history (e.g. hypertension, diabetes and CVD), and lifestyle habits (smoking status, alcohol consumption, physical activity).

During the in-person visits, anthropometric measurements including height, weight, WC, and blood pressure (BP) were collected according to a standard protocol [16]. Height and WC were averaged to 0.1 cm and weight was averaged to 0.1 kg. BMI was calculated as weight in kilograms divided by height in meters squared. BP was measured using a standardized mercury sphygmomanometer. Systolic BP and diastolic BP were taken at a 5-min interval for two times after participants sitting for at least 5 min. The average of the two readings was used for analysis. If the two measurements differed by >5 mmHg, then the third measurement was conducted and the average of the three readings was used. Fatty liver was diagnosed based on ultrasonographic characteristics, including diffuse hyperechogenicity of the liver relative to the kidneys, ultrasonography beam attenuation, and poor visualization of the intrahepatic vessel borders and diaphragm.

Serum samples were collected in the morning after an overnight fast, and serum creatinine (Scr), FPG, lipids profile (including total cholesterol (TC), triglyceride (TG), low-density lipoprotein cholesterol (LDL-C), and high-density lipoprotein cholesterol (HDL-C)) were tested using a Hitachi 7600 auto-analyzer (Hitachi; Tokyo, Japan). Scr were measured by means of Jaffé's kinetic method (Hitachi 7600 analyzer, Tokyo, Japan). eGFR was calculated using the Chronic Kidney Disease Modification of Diet in Renal Disease (CKD-MDRD) equation [18]. FPG was measured using the Hexokinase method (BioSino Bio-Technology & Science Inc., China). Urine protein concentration was assessed by dry chemistry method with the test assay of H12-MA (Changchun Dirui Medical Technology Co., Ltd. Changchun, China) using semi-quantitative dipstick test. All the urine samples were measured using a urine analyzer (N-600, Dirui, Changchun, China) at the central laboratory of the Kailuan hospital.

Study outcomes

Primary outcomes included first occurrence of major cardiovascular (CV) events (defined as first occurrence of non-fatal MI and stroke (including ischemic stroke, intracerebral hemorrhage, and subarachnoid hemorrhage)) and all-cause mortality. Information on the major CV events were collected from biennially personal interviews and confirmed by evaluations of claim data from medical insurance combined with medical records and discharge summaries from Kailuan General Hospital and its ten affiliated hospitals. Given the current insurance coverage rules in the Kailuan population, individuals who seek medical care outside this hospital network may not get their health insurance costs reimbursed. This ensures a high accuracy of capturing the outcomes of interest in this population. Death information was collected from provincial vital statistics office, discharge summaries, and medical records. The above outcomes were collected and recorded every year. All outcomes were validated by the Data Safety Monitoring Board and the Arbitration Committee for Clinical Outcomes.

Other covariates

Hypertension was defined as average systolic BP ≥ 140 mmHg and/or diastolic BP ≥ 90 mmHg, or self-reported history of hypertension, or use of antihypertensive medication. Dyslipidemia was defined by presence of at least one of following: serum TC level ≥200 mg/dL (5.2 mmol/L), TG ≥ 150 mg/dL (1.7 mmol/L), LDL-C ≥130 mg/dL (3.4 mmol/L), HDL-C <40 mg/dL (1.0 mmol/L), or use of lipid-lowering drugs [19]. Hyperuricemia was defined as serum uric acid (UA) concentration greater than 420 μmol/L and 360 μmol/L in male and female, respectively. CKD was defined as eGFR < 60 mL/min/1.73 m^2 and/or urine protein dipstick reading ≥1+. "Inactive" physical activity was defined as "no physical activity" or "occasional (one to two times a week)", and "active" physical activity was defined as "frequent (more than three times a week and each time lasting more than 30 min)". The above covariates were all well-documented risk factors for poor prognosis.

Statistical analysis

The baseline characteristics were described and compared among participants according to combinations of BMI categories (18.5–21.9 kg/m^2, 22.0–23.9 kg/m^2, 24.0–27.9 kg/m^2, and ≥28.0 kg/m^2) [20] and central obesity (defined as WC ≥ 90 cm and ≥80 cm for men and women, respectively) [13]. Continuous variables were described by mean ± standard deviation; if the variable does not satisfy the normal distribution, the median (interquartile range) will be used; categorical variables were presented by number (percentage).

Based on previous reports [15,16], we investigated whether the association between BMI and outcomes varied according to the presence of central obesity. Since a statistically significant interaction was detected regarding the all-cause mortality (wald χ^2 = 10.58; P = 0.001), participants were divided into eight adiposity patterns based on four BMI categories and the presence/absence of central obesity: group A1) BMI 18.5–21.9 kg/m^2 and without central obesity; group A2) BMI 18.5–21.9 kg/m^2 and with central obesity; group B1) BMI 22.0–23.9 kg/m^2 and without central obesity [reference group]; group B2) BMI 22.0–23.9 kg/m^2 and with central obesity; group C1) BMI 24.0–27.9 kg/m^2 and without central obesity; group C2) BMI 24.0–27.9 kg/m^2 and with central obesity; group D1) BMI ≥ 28.0 kg/m^2 and without central obesity; group D2) BMI ≥ 28.0 kg/m^2 and with central obesity. Incidence rate of predefined outcomes were calculated as a whole and among different adiposity patterns. Incidence rates were expressed as per 100,000 person-years.

Cox proportional hazards models and competing risk models were used to assess the risk of mortality and major CV events. *P* value and hazard ratios (HRs) with 95% confidence intervals (CIs) were reported. All analyses were adjusted for age (continuous) (model 1), further adjusted for smoking status (ever or current smoker or not), income (above 800 RMB per capita income vs. below 800 RMB per capita income), education level (high school or above vs. below high school level), physical activity (active or inactive), alcohol consumption (current drinker or not), FPG (continuous), hypertension (yes vs. no), dyslipidemia (yes vs. no), hyperuricemia (yes vs. no), CKD (yes vs. no) (model 2).

The participants with missing values of covariates were also removed from the final analysis (N = 582). Because the majority of participants included in this study were men who have a tendency to store excessive fat in visceral fat deposits, which is a greater risk of developing CVD and can be a very important source of bias. Therefore, we examine these associations in men and women separately.

We also conducted a series of sensitivity analyses. (1) Because over one-third of participants in our study were ever or current smokers, we conducted a sensitivity analysis after excluding these participants. (2) To examine whether the potential association between adiposity patterns and adverse outcomes was due to aging, we repeated the analysis after excluding participants aged 65 years and older. (3) To avoid reverse causation, we excluded participants who suffered from predefined CV events or died during the first 4-year of follow-up. (4) To assess the influence of any changes on the results, we calculated the mean BMI and waist circumference of participants to represent an overall situation during the follow-up period and removed participants who changed their groups from analysis. All P-values were calculated from two-tailed tests of statistical significance. *P* value <0.05 was considered to be of statistical significance. Cumulative hazard plots grouped by exposures suggested no appreciable violations of the proportional hazards assumption. All statistical analyses were performed with SAS System version 9.4 (SAS Institute; Cary, NC).

Results

Baseline characteristics of study population

The detailed procedure of participant recruiting was shown in Fig. 1. Overall 18,703 prediabetic participants were included in the analyses. The mean age was 51.5 ± 11.1 years, and 85.6% (N = 16,002) were male. The baseline characteristics of men and women stratified by adiposity patterns were shown in Table 1. Within the same BMI levels, participants with central obesity were older. In addition, the levels of SBP, and percentage of dyslipidemia, hypertension, fatty liver were higher in participants with central obesity than those without in both men and women (Table 1).

Incidence rate of major CV events and all-cause mortality

During a median follow-up of 9.0 (interquartile range 8.7–9.2) years, a total of 848 (5.3%) and 88 (3.3%) major CV events occurred in men and women, respectively. Besides, 1111 men (6.9%) and 89 (3.3%) women died. Overall, the incidence rates of major CV events were 618.5 and 374.8 per 100,000 person-years in men and women, respectively. And the incidence rates of all-cause mortality were 792.1 and 373.2 per 100,000 person-years in men and women, respectively. The lowest incidence rates of all-cause mortality were among both men and women of BMI 24.0–27.9 kg/m^2 without central obesity. In addition, for the same BMI level, participants with central obesity had higher incidence rates of major CV events and all-cause mortality than those without (Table 2).

Effects of different adiposity patterns on adverse outcomes

The results of multivariate Cox proportional hazard regression analysis were shown in Table 2. After adjusting for age, men with high BMI and central obesity were associated with higher risk of major CV events (1.41 (95% CI 1.11–1.77) for BMI 24.0–27.9 kg/m^2 and 1.51 (95% CI 1.19–1.91) for BMI ≥ 28.0 kg/m^2, respectively), whereas those with high BMI but without central obesity were not significantly associated with increased risk of major CV events. In addition, compared to participants with normal BMI and without central obesity, those with a BMI 24.0–27.9 kg/m^2 but without central obesity were associated with the lowest risk of all-cause mortality (HR 0.75 (95% CI 0.61–0.92)). The above findings did not substantially change after further adjusted for multivariate factors (model 2). However, we did not found such associations in women.

Sensitivity analysis

The results of the analyses that assessed residual confounders and reverse causation in men were depicted in Fig. 2. For the all-cause mortality, after excluding those with ever and current smokers (n = 7132; Fig. 2. A), or aged 65 years and older (n = 2012; Fig. 2B), or died during the first 4 years of follow-up (n = 288; Fig. 2C), or those changed their groups (n = 5624; Fig. 2D), the association between adiposity patterns and all-cause mortality did not differ substantially from those of the primary analysis. For the CV

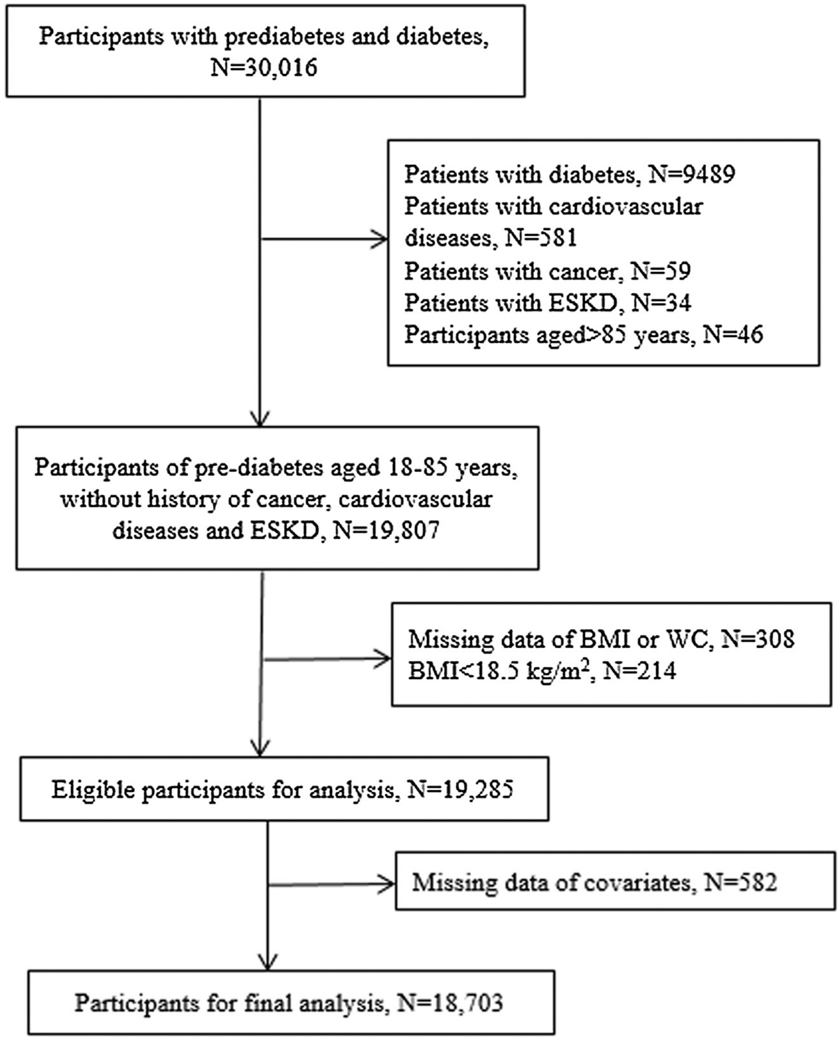

Fig. 1. Flow chart of the study population.

events, we observed largely consistent results in the sensitivity analysis. However, the association was disappeared after excluding participants who smoked (Fig. 2E).

Discussion

This is the first prospective community-based cohort study demonstrating the association of BMI and central obesity on mortality and CV events among a large Asian population with prediabetes. We found that men with a higher BMI (overweight but not obese) and without central obesity had the lowest risk of all-cause mortality, while those with higher BMI and central obesity experienced increased risk of CV events, independent of age, education, income, smoking, drinking, physical activity, FPG, hypertension, dyslipidemia, hyperuricemia and CKD. Previous studies indicated that failure to control for smoking, aging and reverse causation were classic confounding of the mortality outcome of obesity [21]. Nevertheless, we eliminated these conditions by sensitivity analysis. In nonsmokers, we did not observe the higher risk of CV events in men with high BMI, thus no smoking is beneficial for CV events. One possible reason why we did not found such association in women is the relatively small sample size. Our finding enriches the knowledge on the relationship between different adiposity patterns and adverse outcomes in populations with prediabetes, which might be helpful for easier identifying high-risk populations that could be targeted for prevention strategies accordingly.

We found that men of high BMI and without central obesity were not associated with excess CV risk, despite high BMI combined central obesity revealed significantly increased risk of CV events (but not in those never smoked). Previous studies had explored the association of obesity profile and outcomes, among general population, as well as diabetic population. For example, a study found no association between BMI and CV events but waist-hip ratio in a representative Iranian population with T2D [22], another study reported a linear association between BMI and CVD events in a Korean general population [23]. However, WC could identify patients who are at increased risk for obesity-related cardio-metabolic disease beyond the measurement of BMI [24]. In our results, individuals with central obesity have significantly higher prevalence of hypertension, dyslipidemia, hyperuricemia than those without, which might partly account for the excess CV risk in these populations. Obesity, especially visceral obesity is a major risk factor for CV events [25]. Previous studies have also revealed that central obesity is frequently clustered with multiple CV risk factors [26]. An interventional study had observed decreased cardio-metabolic risks after the control of WC by lifestyle interventions [27]. Central obesity measured by WC was considered to be an indicator of visceral fat accumulation, which was implicated in the pathogenesis of hypertension, production of pro-

Table 1
Baseline characteristics of men and women stratified and adiposity patterns.

Characteristics	Total	BMI 18.5–21.9 kg/m^2		BMI 22.0–23.9 kg/m^2		BMI 24.0–28.0 kg/m^2		BMI ≥ 28.0 kg/m^2	
		Central obesity		Central obesity		Central obesity		Central obesity	
		No	Yes	No	Yes	No	Yes	No	Yes
Men	16,002	1891	165	2540	472	3885	3455	595	2999
Age, year	51.8 ± 11.2	52.0 ± 12.5	58.4 ± 12.1	51.0 ± 11.1	57.2 ± 10.1	49.7 ± 10.6	54.4 ± 10.4	47.9 ± 11.0	51.5 ± 11.3
High school or above, N(%)	2770 (17.3)	354 (18.7)	12 (7.3)	435 (17.1)	51 (10.8)	687 (17.7)	560 (16.2)	87 (14.6)	584 (19.5)
¥800 per capital or above, N(%)	2176 (13.6)	231 (12.2)	9 (5.5)	319 (12.6)	42 (8.9)	532 (13.7)	485 (14.0)	53 (8.9)	505 (16.4)
BMI, kg/m^2	25.7 ± 3.3	20.7 ± 0.9	20.8 ± 0.9	23.1 ± 0.6	23.2 ± 0.6	25.6 ± 1.1	26.3 ± 1.1	29.8 ± 2.2	30.2 ± 2.1
WC, cm	88.4 ± 9.3	77.3 ± 5.7	95.8 ± 6.3	81.2 ± 4.8	94.0 ± 4.7	84.0 ± 4.1	94.9 ± 4.9	84.8 ± 4.3	99.0 ± 6.5
SBP, mmHg	135 ± 21	128 ± 20	130 ± 20	131 ± 20	136 ± 21	133 ± 20	137 ± 21	136 ± 20	140 ± 21
DBP, mmHg	86 ± 12	81 ± 10	82 ± 11	84 ± 12	85 ± 11	86 ± 11	87 ± 11	88 ± 11	90 ± 12
FPG, mmol/L	5.9 (5.7, 6.2)	5.9 (5.7, 6.2)	5.9 (5.8, 6.2)	6.0 (5.8, 6.3)	6.0 (5.8, 6.3)	6.0 (5.8, 6.3)	6.0 (5.8, 6.3)	6.0 (5.8, 6.4)	6.0 (5.8, 6.3)
Ever or current smoker, N(%)	7132 (44.6)	952 (50.3)	49 (29.7)	1231 (48.5)	145 (30.7)	1797 (46.3)	1461 (42.3)	193 (32.4)	1304 (43.5)
Current drinker, N(%)	7883 (49.3)	920 (48.7)	48 (29.1)	1334 (52.5)	163 (34.5)	1975 (50.8)	1649 (47.7)	241 (40.5)	1553 (51.8)
Physical activity, N(%)	2563 (16.0)	304 (16.1)	17 (10.3)	402 (15.8)	69 (14.6)	582 (15.0)	592 (17.1)	67 (11.3)	530 (17.7)
Dyslipidemia, N(%)	10435 (65.2)	991 (52.4)	98 (59.4)	1444 (56.9)	303 (64.2)	2441 (62.3)	2470 (71.5)	396 (66.6)	2292 (76.4)
Hypertension, N(%)	8821 (51.4)	647 (34.2)	168 (41.2)	1117 (44.0)	238 (50.4)	1915 (49.3)	1926 (55.8)	357 (60.0)	1953 (65.1)
CKD, N(%)	2082 (13.0)	184 (9.7)	18 (10.9)	309 (12.2)	50 (10.6)	502 (12.9)	468 (13.6)	117 (19.7)	434 (14.5)
Fatty liver, N(%)	6127 (38.5)	153 (8.2)	21 (12.7)	446 (17.7)	109 (23.1)	1269 (32.9)	1622 (47.1)	337 (56.9)	2170 (72.6)
Hyperuricemia, N(%)	1524 (7.8)	66 (3.5)	7 (4.2)	108 (4.3)	25 (5.3)	206 (5.3)	348 (10.1)	40 (6.7)	448 (14.9)
Women	2701	303	124	250	262	218	895	27	622
Age, year	51.2 ± 10.6	44.3 ± 11.7	51.1 ± 10.5	44.2 ± 10.1	51.2 ± 10.1	46.1 ± 9.6	53.2 ± 9.2	46.3 ± 13.4	52.3 ± 9.8
High school or above, N(%)	718 (26.6)	129 (42.6)	15 (12.1)	105 (42.0)	54 (20.6)	76 (34.9)	199 (22.2)	7 (25.9)	133 (21.4)
¥800 per capital or above, N(%)	405 (15.0)	61 (20.1)	9 (7.3)	51 (20.4)	36 (13.7)	34 (15.6)	130 (14.5)	2 (7.4)	82 (13.2)
BMI, kg/m^2	25.7 ± 3.8	20.5 ± 1.0	21.0 ± 0.8	23.0 ± 0.6	23.1 ± 0.6	25.2 ± 0.9	26.0 ± 1.1	31.1 ± 3.6	31.0 ± 2.8
WC, cm	85.1 ± 10.6	71.2 ± 4.6	87.1 ± 7.7	73.7 ± 4.1	86.1 ± 6.3	75.7 ± 3.4	88.2 ± 7.1	74.2 ± 5.9	94.7 ± 8.7
SBP, mmHg	129 ± 22	117 ± 18	126 ± 19	119 ± 19	126 ± 19	122 ± 20	131 ± 20	126 ± 19	138 ± 23
DBP, mmHg	82 ± 11	76 ± 9	81 ± 10	78 ± 10	80 ± 10	79 ± 11	83 ± 10	81 ± 11	87 ± 12
FPG, mmol/L	5.9 (5.7, 6.2)	5.9 (5.7, 6.1)	5.9 (5.7, 6.1)	5.9 (5.7, 6.1)	5.9 (5.8, 6.2)	5.8 (5.7, 6.2)	6.0 (5.7, 6.3)	6.1 (5.8, 6.5)	6.0 (5.8, 6.3)
Ever or current smoker, N(%)	40 (1.5)	6 (2.0)	2 (1.6)	3 (1.2)	2 (0.8)	2 (0.9)	12 (1.3)	1 (3.7)	12 (1.9)
Current drinker, N(%)	152 (5.6)	27 (8.9)	3 (2.4)	21 (8.4)	11 (4.2)	15 (6.9)	45 (5.0)	2 (7.4)	28 (4.5)
Physical activity, N(%)	384 (14.2)	30 (9.9)	14 (11.3)	28 (11.2)	37 (14.1)	32 (14.7)	140 (15.6)	2 (7.4)	101 (16.2)
Dyslipidemia, N(%)	1682 (66.3)	125 (41.3)	73 (58.9)	131 (52.4)	171 (65.3)	124 (56.9)	613 (68.5)	13 (48.2)	432 (69.5)
Hypertension, N(%)	1064 (39.4)	45 (14.9)	43 (34.7)	54 (21.6)	87 (33.2)	56 (25.7)	410 (45.8)	12 (44.4)	357 (57.4)
CKD, N(%)	410 (15.2)	28 (9.2)	16 (12.9)	31 (12.4)	43 (16.4)	40 (18.4)	146 (16.3)	6 (22.2)	100 (16.1)
Fatty liver, N(%)	1073 (39.8)	14 (4.7)	14 (11.3)	20 (8.1)	78 (30.0)	51 (23.4)	430 (48.1)	10 (37.0)	456 (73.3)
Hyperuricemia, N(%)	1248 (7.8)	10 (3.3)	5 (4.0)	8 (3.2)	17 (6.5)	11 (5.1)	71 (7.9)	2 (7.4)	86 (13.8)

Note: Continuous variables were described by mean ± standard deviation or median (interquartile range); categorical variables were presented by number (percentage). Abbreviation: BMI = body mass index; WC = waist circumference; SBP = systolic blood pressure; DBP = diastolic blood pressure; FPG = fasting plasma glucose; CKD = chronic kidney disease.

inflammatory cytokines, as well as insulin resistance [13]. Our results revealed that the prevalence of fatty liver was obviously higher in the participants with central obesity than those without. Except for WC, fatty liver was also a marker for visceral fat, as well as a strong predictor for CV events [28]. The possible mechanisms linking fatty liver and CV risk might be the increased oxidative stress, accelerated atherosclerosis, and over-expression of multiple proatherogenic mediators [28]. Based on our findings, the combination of BMI and WC should be more valuable in target the high-risk subgroup in prediabetes. Maintaining a proper level of WC should be advocated at the national policy level.

However, unlike CV events, men with a higher BMI (but without central obesity) had the lowest risk of all-cause mortality. The possible reasons for different patterns of the association between BMI and mortality and CV events may be that overweight people who once experienced a CV event were at a low risk of mortality due to their attention and more aggressive medical treatment [23]. The existence and mechanism of obesity paradox among prediabetes population remains to be elucidated. Several studies have explored the association between BMI and mortality in patients with diabetes, and these results are not consistent [5–7,16,29–32]. Five studies demonstrated that being overweight or obese were associated with a better survival rate, i.e. obesity paradox [5–7,16,30]. In contrast, two studies revealed that individuals of high BMI were associated with increased risk of mortality, with U-shaped or J-shaped relationship [31,32]. One study showed no association between BMI and mortality [29]. The differences in population, follow-up period, study design, as well as inconsistent definitions might partially explain the above inconsistent results. In addition, BMI has been demonstrated to have a suboptimal correlation with body fat content and distribution, and the latter was more closely related to poor prognosis [26].

To the best of our knowledge, only three cohort studies investigated the association between adiposity and mortality in population with prediabetes [10–12]. All studies involved cardiorespiratory fitness (CRF), a measure quantified as duration of a maximal treadmill exercise test. Two studies demonstrated that low CRF, rather than BMI, was a significant predictor for all-cause mortality [10,12]. Another study found that overweight individuals were related to lower risk of mortality, but the negative association was modified by CRF [11]. Our study combined BMI and WC (a simple marker and easy to achieve), firstly to explore their association with adverse outcomes in prediabetic population. We found that men who are overweight but without central obesity have the lowest risk of mortality. Although obesity is a risk factor for adverse events, diminished abdominal fat content might attenuate obesity-related health risk [33]. Individuals with high BMI but without metabolic disorders (i.e. metabolically healthy but obese phenotype) have been reported in a considerable proportion of the obese population, who demonstrated the lower amounts of abdominal fat, higher insulin sensitivity, better CRF, as well as relatively benign prognosis [34]. Therefore, it was speculated that individuals of slight high BMI but without central obesity might represent those metabolically health but obese phenotype, who have more muscle

Table 2
Incidence rates and hazard ratios (95% CI) for major CV events and all-cause mortality stratified by adiposity patterns.

	Total	BMI 18.5–21.9 kg/m^2		BMI 22.0–23.9 kg/m^2		BMI 24.0–28.0 kg/m^2		BMI $\geq$ 28.0 kg/m^2	
		Central obesity		Central obesity		Central obesity		Central obesity	
		No	Yes	No	Yes	No	Yes	No	Yes
Men									
No. of CV events	848	67	7	105	37	186	231	24	191
Per 100,000 person-years	618.5	411.8	504.7	480.4	925.2	553.5	789.2	466.2	747.0
Model 1	–	0.78 (0.58,1.07)	0.68 (0.31, 1.48)	Reference	1.43 (0.98, 2.10)	1.26 (0.99, 1.60)	**1.41 (1.11, 1.77)**	1.14 (0.73, 1.77)	**1.51 (1.19, 1.91)**
Model 2	–	0.85 (0.62,1.15)	0.75 (0.35, 1.63)	Reference	1.45 (1.00, 2.12)	1.21 (0.95, 1.54)	**1.32 (1.05, 1.67)**	1.01 (0.64, 1.58)	**1.31 (1.03, 1.66)**
No. of death	1111	149	27	179	50	182	283	29	212
Per 100,000 person-years	792.1	902.8	1919.5	805.5	1215.7	530.4	938.0	554.3	806.0
Model 1	–	0.94 (0.76,1.17)	1.24 (0.83, 1.87)	Reference	0.94 (0.69, 1.28)	**0.75 (0.61, 0.92)**	0.90 (0.75, 1.09)	0.89 (0.60, 1.32)	0.94 (0.77, 1.14)
Model 2	–	0.97 (0.78,1.21)	1.31 (0.87, 1.97)	Reference	0.97 (0.71, 1.33)	**0.75 (0.61, 0.92)**	0.91 (0.75, 1.10)	0.84 (0.57, 1.25)	0.89 (0.73, 1.10)
Women									
No. of CV events	88	4	4	3	3	5	35	0	34
Per 100,000 person-years	374.8	151.6	367.6	138.2	129.4	261.7	450.5	0	635.5
Model 1	–	0.94 (0.21, 4.34)	1.57 (0.34, 7.38)		0.55 (0.10, 2.91)	1.68 (0.40, 7.04)	1.78 (0.51, 6.16)	–	2.61 (0.76, 9.02)
Model 2	–	1.00 (0.22, 4.61)	1.55 (0.33, 7.30)	Reference	0.53 (0.10, 2.80)	1.63 (0.39, 6.90)	1.57 (0.45, 5.53)	–	2.14 (0.59, 7.71)
No. of death	89	11	3	7	7	1	31	0	29
Per 100,000 person-years	373.2	415.3	272.0	319.4	301.3	52.0	390.6	0	528.8
Model 1	–	1.12 (0.43, 2.88)	0.45 (0.12, 1.75)	reference	0.50 (0.17, 1.43)	0.14 (0.02, 1.17)	0.61 (0.27, 1.40)	–	0.87 (0.38, 2.01)
Model 2	–	0.99 (0.38,2.60)	0.40 (0.10, 1.56)	reference	0.50 (0.17, 1.45)	0.14 (0.02, 1.15)	0.60 (0.26, 1.38)	–	0.79 (0.34, 1.86)

Note: Model 1 was adjusted for age; model 2 was further adjusted for smoke status, alcohol consumption, income, education, physical exercise, hypertension, dyslipidemia, CKD, FPG, hyperuricemia. The meaning of bold values is $P < 0.05$.
Abbreviation: BMI = body mass index; CV = cardiovascular; CI = confidence interval.

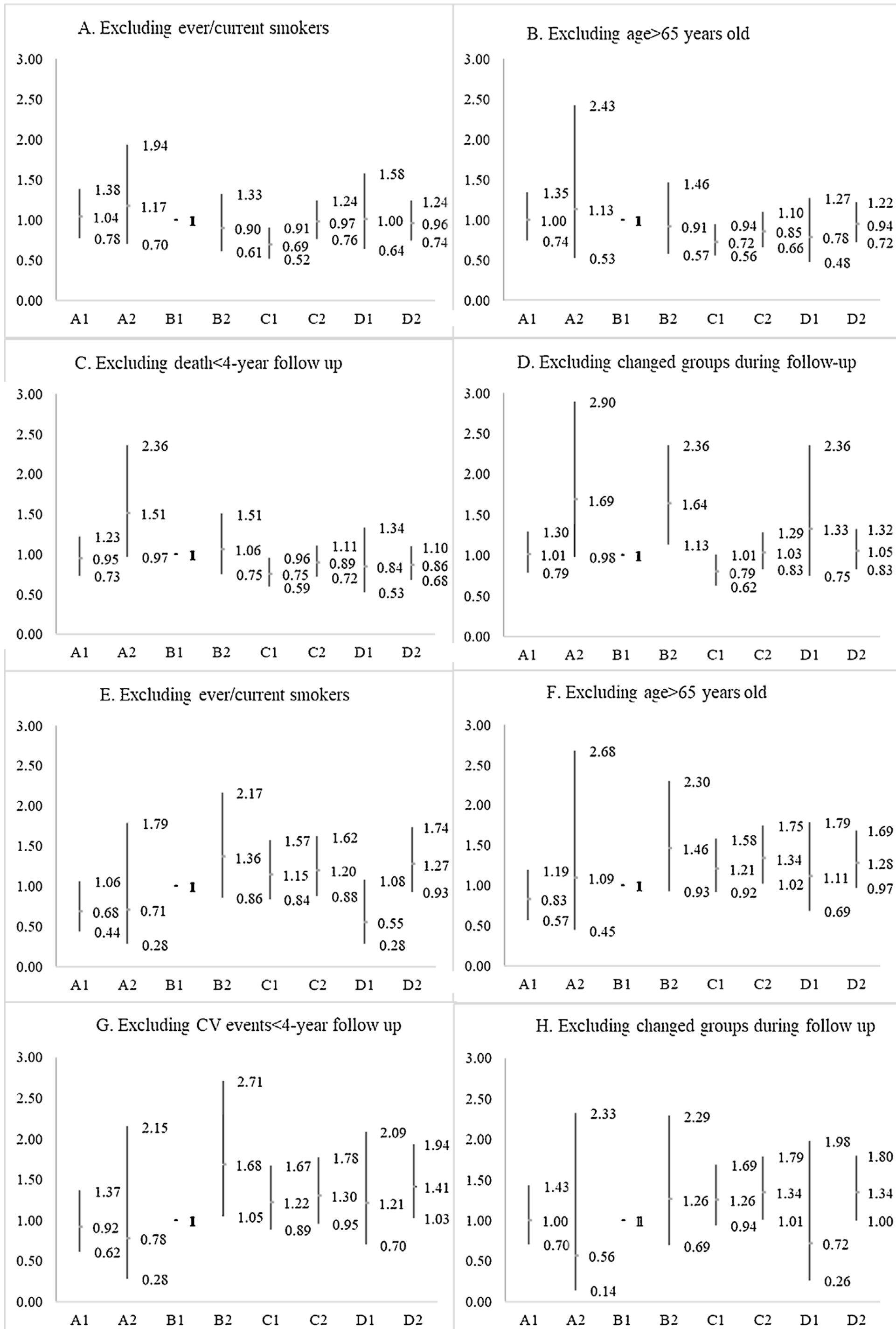

Fig. 2. Hazard Ratios for all-cause mortality (A–D) and major CV events (E–H) among participants with pre-diabetes, according to adiposity patterns.
Note: A–D demonstrate all-cause mortality according to different categories of adiposity patterns. A for the total study population (1288 deaths), B for those who had never smoked (748 deaths), C for those aged <65 years (684 deaths), and D excluded deaths during the first 4 years of follow up (958 deaths). E–H demonstrate major CV events according to different categories of adiposity patterns. E for the total study population (1006 CV events), F for those who had never smoked (568 CV events), G for those aged <65 years (727 CV events), and H excluded CV events during the first 4 years of follow up (584 CV events). All estimates have been adjusted for age, sex, smoke status, alcohol consumption, income, education, physical exercise, hypertension, dyslipidemia, CKD, FPG, hyperuricemia. The bars represent 95% confidence intervals. Group A1: BMI 18.5–21.9 kg/m^2 and without central obesity; goup A2: BMI 18.5–21.9 kg/m^2 and with central obesity; group B1: BMI 22.0–23.9 kg/m^2 and without central obesity [reference group]; group B2: BMI 22.0–23.9 kg/m^2 and with central obesity; group C1: BMI 24.0–27.9 kg/m^2 and without central obesity; group C2: BMI 24.0–27.9 kg/m^2 and with central obesity; group D1: BMI ≥ 28.0 kg/m^2 and without central obesity; group D2: BMI ≥ 28.0 kg/m^2 and with central obesity.

mass rather than abdominal fat mass, and thus lower mortality risk. Our findings improved the understanding of the different adiposity patterns with adverse outcomes. Metabolically healthy and slightly high BMI might be suitable in population with prediabetes.

Our study has some strengths and limitations. Strengths include the large sample size, long-term follow-up period. In addition, we combined BMI with WC to assess outcomes for the first time among individuals with prediabetes. However, there are certain limitations that should be mentioned. First, our study was based on a population with a majority of men and that may limit generalizability of the study findings to women. Second, despite adjusted for age, we did not know whether the two markers have special value for different age groups. Third, some unmeasured causal factors unevenly distributed between BMI/WC groups such as diet, nutrition and family history of CVD may have influenced results despite we have adjusted for multiple confounders. Finally, we did not have the measure of oral glucose tolerance test, which could result in the inclusion of individuals with diabetes. A national survey in China reported the prevalence of prediabetes measured by FBG was 27.2%, and the prevalence of diabetes identified by IGT was only 3.5% [4]. Thus, the proportion of individuals who were misclassified as prediabetes was low, and unlikely to influence our results.

In conclusion, among men with prediabetes, BMI and WC should both be included for the risk-stratification, and central obesity is an important marker for long-term adverse outcomes. This information might better guide public policymaker to develop strategies towards individuals of different adiposity patterns among huge prediabetic population.

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Author contributions

LL and BG contributed equally to this work. LL and BG designed the study, interpreted the results, and drafted the manuscript. LL, JW and CY analyzed the data. WY, SC, QL, HZ and GW were involved in data collection and data cleaning. SW, MC, RB, MZ and LZ made critical revision of the manuscript for important intellectual content. MZ, LZ and MC obtained funding. All authors have read and approved the final manuscript. LZ is the study guarantors.

Ethical statement

The protocol was approved by the Ethics Committee of both Kailuan General Hospital and Peking University First Hospital in accordance with the Declaration of Helsinki and written informed consent was obtained from each participant.

Declaration of interest

None.

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References

[1] Chatterjee S, Khunti K, Davies MJ. Type 2 diabetes. Lancet 2017;389:2239–51.
[2] Tabak AG, Herder C, Rathmann W, Brunner EJ, Kivimaki M. Prediabetes: a high-risk state for diabetes development. Lancet 2012;379:2279–90.
[3] Perreault L, Faerch K. Approaching pre-diabetes. J Diabetes Complicat 2014;28:226–33.
[4] Xu Y, Wang L, He J, Bi Y, Li M, Wang T, et al. Prevalence and control of diabetes in Chinese adults. JAMA 2013;310:948–59.
[5] Kokkinos P, Myers J, Faselis C, Doumas M, Kheirbek R, Nylen E. BMI-mortality paradox and fitness in African American and Caucasian men with type 2 diabetes. Diabetes Care 2012;35:1021–7.
[6] Carnethon MR, De Chavez PJ, Biggs ML, Lewis CE, Pankow JS, Bertoni AG, et al. Association of weight status with mortality in adults with incident diabetes. JAMA 2012;308:581–90.
[7] Logue J, Walker JJ, Leese G, Lindsay R, McKnight J, Morris A, et al. Association between BMI measured within a year after diagnosis of type 2 diabetes and mortality. Diabetes Care 2013;36:887–93.
[8] Romero-Corral A, Montori VM, Somers VK, Korinek J, Thomas RJ, Allison TG, et al. Association of bodyweight with total mortality and with cardiovascular events in coronary artery disease: a systematic review of cohort studies. Lancet 2006;368:666–78.
[9] Lu JL, Kalantar-Zadeh K, Ma JZ, Quarles LD, Kovesdy CP. Association of body mass index with outcomes in patients with CKD. J Am Soc Nephrol 2014;25:2088–96.
[10] Lyerly GW, Sui X, Lavie CJ, Church TS, Hand GA, Blair SN. The association between cardiorespiratory fitness and risk of all-cause mortality among women with impaired fasting glucose or undiagnosed diabetes mellitus. Mayo Clin Proc 2009;84:780–6.
[11] McAuley PA, Artero EG, Sui X, Lavie CJ, Almeida MJ, Blair SN. Fitness, fatness, and survival in adults with prediabetes. Diabetes Care 2014;37:529–36.
[12] Nylen ES, Ni D, Myers J, Chang M, Plunkett MT, Kokkinos P. Cardiorespiratory fitness impact on all-cause mortality in prediabetic veterans. J Endocrinol Metab 2015;5:215–9.
[13] Eckel RH, Grundy SM, Zimmet PZ. The metabolic syndrome. Lancet 2005;365:1415–28.
[14] Katzmarzyk PT, Hu G, Cefalu WT, Mire E, Bouchard C. The importance of waist circumference and BMI for mortality risk in diabetic adults. Diabetes Care 2013;36:3128–30.
[15] Coutinho T, Goel K, Correa de Sa D, Carter RE, Hodge DO, Kragelund C, et al. Combining body mass index with measures of central obesity in the assessment of mortality in subjects with coronary disease: role of "normal weight central obesity". J Am Coll Cardiol 2013;61:553–60.
[16] Liu H, Wu S, Li Y, Sun L, Huang Z, Lin L, et al. Body mass index and mortality in patients with type 2 diabetes mellitus: a prospective cohort study of 11,449 participants. J Diabetes Complicat 2017;31:328–33.
[17] American Diabetes A. Standards of medical care in diabetes—2010. Diabetes Care 2010;33 Suppl 1:S11–61.
[18] Ma YC, Zuo L, Chen JH, Luo Q, Yu XQ, Li Y, et al. Modified glomerular filtration rate estimating equation for Chinese patients with chronic kidney disease. J Am Soc Nephrol 2006;17:2937–44.
[19] Joint Committee for Guideline Revision. 2016 Chinese guidelines for the management of dyslipidemia in adults. J Geriatr Cardiol 2018;15:1–29.
[20] Zhou BF, Cooperative Meta-Analysis Group of the Working Group on Obesity in C. Predictive values of body mass index and waist circumference for risk factors of certain related diseases in Chinese adults—study on optimal cut-off points of body mass index and waist circumference in Chinese adults. Biomed Environ Sci 2002;15:83–96.
[21] Preston SH, Stokes A. Obesity paradox: conditioning on disease enhances biases in estimating the mortality risks of obesity. Epidemiology 2014;25:454–61.
[22] Afsharian S, Akbarpour S, Abdi H, Sheikholeslami F, Moeini AS, Khalili D, et al. Risk factors for cardiovascular disease and mortality events in adults with type 2 diabetes—a 10-year follow-up: Tehran Lipid and Glucose Study. Diabetes Metab Res Rev 2016;32:596–606.
[23] Kong KA, Park J, Hong SH, Hong YS, Sung YA, Lee H. Associations between body mass index and mortality or cardiovascular events in a general Korean population. PLoS One 2017;12:e0185024.
[24] Klein S, Allison DB, Heymsfield SB, Kelley DE, Leibel RL, Nonas C, et al. Waist circumference and cardiometabolic risk: a consensus statement from Shaping America's Health: association for Weight Management and Obesity Prevention; NAASO, The Obesity Society; the American Society for Nutrition; and the American Diabetes Association. Am J Clin Nutr 2007;85:1197–202.
[25] DeFronzo RA, Abdul-Ghani M. Assessment and treatment of cardiovascular risk in prediabetes: impaired glucose tolerance and impaired fasting glucose. Am J Cardiol 2011;108:3B–24B.
[26] Oliveros E, Somers VK, Sochor O, Goel K, Lopez-Jimenez F. The concept of normal weight obesity. Prog Cardiovasc Dis 2014;56:426–33.
[27] Nakao YM, Miyamoto Y, Ueshima K, Nakao K, Nakai M, Nishimura K, et al. Effectiveness of nationwide screening and lifestyle intervention for abdominal obesity and cardiometabolic risks in Japan: the metabolic syndrome and comprehensive lifestyle intervention study on nationwide database in Japan (MetS ACTION-J study). PLoS One 2018;13:e0190862.
[28] Lonardo A, Sookoian S, Pirola CJ, Targher G. Non-alcoholic fatty liver disease and risk of cardiovascular disease. Metabolism 2016;65:1136–50.

[29] McEwen LN, Karter AJ, Waitzfelder BE, Crosson JC, Marrero DG, Mangione CM, et al. Predictors of mortality over 8 years in type 2 diabetic patients: translating research into action for diabetes (TRIAD). Diabetes Care 2012;35:1301–9.
[30] Thomas G, Khunti K, Curcin V, Molokhia M, Millett C, Majeed A, et al. Obesity paradox in people newly diagnosed with type 2 diabetes with and without prior cardiovascular disease. Diabetes Obes Metab 2014;16:317–25.
[31] Tobias DK, Pan A, Jackson CL, O'Reilly EJ, Ding EL, Willett WC, et al. Body-mass index and mortality among adults with incident type 2 diabetes. N Engl J Med 2014;370:233–44.
[32] Khalangot M, Tronko M, Kravchenko V, Kulchinska J, Hu G. Body mass index and the risk of total and cardiovascular mortality among patients with type 2 diabetes: a large prospective study in Ukraine. Heart 2009;95:454–60.
[33] Wedell-Neergaard AS, Eriksen L, Gronbaek M, Pedersen BK, Krogh-Madsen R, Tolstrup J. Low fitness is associated with abdominal adiposity and low-grade inflammation independent of BMI. PLoS One 2018;13:e0190645.
[34] Ortega FB, Lee DC, Katzmarzyk PT, Ruiz JR, Sui X, Church TS, et al. The intriguing metabolically healthy but obese phenotype: cardiovascular prognosis and role of fitness. Eur Heart J 2013;34:389–97.