The Impact Of Waist Circumference And Diabetes On Incident Of Cardiovascular Death During 9 Years Of Follow Up In General Population

Man Li  
Chinese PLA General Hospital

Shu-xia Wang  
Chinese PLA General Hospital

Yong-kang Su  
Chinese PLA General Hospital

Jin Sun  
Chinese PLA General Hospital

An-hang Zhang  
Chinese PLA General Hospital

Bo-kai Cheng  
Chinese PLA General Hospital

Shuang Cai  
Chinese PLA General Hospital

Ping Zhu (✉ 779664502@qq.com)  
Chinese PLA General Hospital

Research Article

Keywords: Waist circumference, diabetes, obesity, cardiovascular death

Posted Date: November 30th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-1100214/v1

License: This work is licensed under a Creative Commons Attribution 4.0 International License.
Read Full License
Abstract

**Background:** It has been reported that obesity and diabetes are both the risk factors for the development of cardiovascular diseases (CVD). However, recent articles reported that compared with BMI, waist circumference (WC) can better reflect obesity, more closely related to visceral fat tissue which is positively associated with an increased risk of cardiovascular death. Moreover, few studies have both investigated the prognostic value of both WC and diabetes during a long-term follow up. We aimed to investigate whether higher level of WC measurements and diabetes were able to predict cardiovascular mortality in general population.

**Methods:** In this prospective cohort study, a total of 1521 consecutive subjects free of clinical cardiovascular disease were included. The end point was cardiovascular death. The Kaplan-Meier method and Cox regression models were used to evaluate the cumulative risk of outcome at different WC levels with or without diabetes.

**Results:** During a median follow up of 9.2 years, there were 265 patients had the occurrence of cardiovascular death. Kaplan-Meier survival estimates indicated that the patients with higher levels of WC (WC>94cm) coexist with diabetes had significantly increased risk of cardiovascular death (log-rank p<0.05). After adjustment for potential confounders, multiple COX regression models showed that the incidence of cardiovascular death was significantly higher when patients with high WC coexisted with DM (HR 3.78; 95% CI: 3.35–3.98; p<0.001).

**Conclusion:** Patients with high WC and diabetes represent a high-risk population for cardiovascular death. WC and diabetes may provide incremental prognostic value beyond traditional risks factors.

1. **Background**

Recent data from the United States showed that nearly a third of the world's population is now classified as overweight or obese [1]. It is recommended that obesity, which is usually defined as excessive body fat and damage to health, can no longer be assessed only by body mass index (BMI) [2]. In epidemiological studies, BMI is often used to define overweight and obesity. However, BMI has a low sensitivity and there are large individual differences between body fat percentages, partly due to age, gender, and race [3]. Recent studies have indicated that the visceral adipose tissue (VAT) was the major threat to the cardiovascular risk [4]. It has been reported that compared with BMI, Waist circumference (WC) can better reflect body fat distribution, more closely related to VAT[5]. In particular, abdominal obesity is a better predictor of cardiovascular events than obesity measured by BMI alone [6]. Higher cardiometabolic risk is also related to the location of excess fat in visceral adipose tissue and ectopic reservoirs (such as muscle and liver), and when the ratio of fat to lean body mass increases (for example, normal body weight for metabolic obesity) [7].

Moreover, previous studies have demonstrated that compared with BMI-matched non-type 2 diabetic patients, type 2 diabetic patients have a larger waist circumference and more VAT than BMI-matched
individuals without type 2 diabetes mellitus [8]. These patients are all susceptible to cardiovascular abnormalities and cardiovascular diseases; their coexistence should further increase the risk of cardiovascular outcomes [9]. These data indicate that obesity patients with diabetes may be more common than large epidemiological studies have shown and requires more urgent attention. Relying solely on BMI to assess its prevalence may hinder future interventions for obesity prevention and control. Moreover, long-term research on WC and diabetes related to predictive value is still very limited [10]. Therefore, this study ought to investigate the prognostic value of WC on the cardiovascular death during a long-term follow up.

2. Methods

2.1 The study population

From January 2010 to December 2020, a total of 2162 people in Wan Shou Lu Street were included in the study. Among these participants, patients had a history of stroke or cardiovascular disease or cancer were excluded from the study. In the current study, patients were excluded if the patients could not give informed consent, had comorbidities lead to changes abdominal circumference measurement (secondary to chronic ascites, liver disease, cancer, intestinal obstruction, abdominal mass in the abdomen, pre-existing abdominal stoma, incisional hernia). Participants were also excluded if their blood sample or detailed data were not available. Candidates lost follow up were also excluded from the study. Finally, a total of 1521 patients were included in the present study. The flowchart of the study was listed in Figure 1.

2.2 Baseline measurement

The measures of the participants were collected at the time of registration. Anthropometric measurements include weight in kilograms, height in meters, hips circumference and WC. WC was measured on the mid-axillary line between the lowest border of the thoracic cage and the top of the iliac crest to the nearest 0.1 cm. Diabetes mellitus (DM) is defined as the presence of diabetic symptoms and resting plasma glucose concentration ≥200mg/dL, fasting plasma glucose concentration ≥126mg/dL, or 2-hour plasma glucose concentration ≥200mg/dL, or the use of an oral hypoglycemic agent or insulin at the time of admission. BMI is calculated as weight/height $^2$. After resting for 5 minutes, use the right arm in a sitting position and use standard or automated equipment to measure blood pressure, and use the average of the two blood pressure measurements as the final blood pressure. The patient was considered to have hypertension with BP>140/90 mmHg or received antihypertensive medication. Hyperlipidemia is defined as a known but untreated dyslipidemia or current treatment with lipid-lowering drugs. If a current smoker report smoking in the last 30 days, it is defined as smoking.

Baseline data was collected at the time of enrollment. Blood samples were collected in the early morning. On the basis of protocol, the blood was obtained by the EDTA-anticoagulated plastic tubes. All the blood
samples were centrifuged at 1000 g for 10 min and serum samples were stored at ≤80 °C. Enzyme colorimetry was used to assess total cholesterol (TC), triglyceride (TG), high-density lipoprotein cholesterol (HDL-C) levels. A two-point kinetic assay kit (CH 9702, Randox Laboratories Ltd, UK) was used to determine the level of low-density lipoprotein cholesterol (LDL-C). The blood glucose level was measured using commercial reagents following standard procedures.

2.3 Outcome assessment

Patients were followed up until December 2020 or until the occurrence of cardiovascular death. All participants were followed up by analyses of clinical materials and telephone contact quarterly. The endpoint was cardiovascular death. Cardiovascular death was defined as deaths caused by coronary heart disease or stroke, as well as deaths that cannot be classified without evidence of the source. Unless a clear non-cardiac cause is established, all deaths are considered cardiac deaths. Based on the International Classification of Diseases (ICD) codes for confirmation of each cause of death or routine death registration. Excluding the participants who were lost to follow-up, we obtained follow-up of all patients until the primary outcome or date of censoring. The follow-up time was calculated from the date of cardiac death onset to the date of mortality occurrence or the date of the last follow-up. Written informed content was obtained from all study participants, and the study was approved by the ethics committee of Chiness PLA General Hospital.

2.4 Statistical analysis

Patients were firstly divided into three groups according to the levels of WC. Then, the patients were further categorized into six groups as WC with DM and non-DM. Variables with a normal distribution are expressed as the mean ± SD, and in the case of non-normality, the medians are presented. Categorical data are expressed in counts or percentages. Differences in baseline characteristics between the three groups were evaluated by chi-square tests (categorical variables), analysis of variance as appropriate. The Kaplan-Meier method was used to evaluate the cumulative risk of outcome at different WC levels with or without DM, and compared by log-rank tests. Cox multivariate analyses were used to evaluate the association of WC levels and DM with the study endpoints. The results are presented as the hazard ratios (HRs) and 95% confidence intervals (CIs) according to levels of WC. Four multivariate proportional hazards models were fitted. Model 1 contains the following variables: age, sex, BMI, current smokers, hypertension, TC, TG, HDL-C, LDL-C. Variables were input into the model according to their statistical significance in univariate analysis. Model 2 was based on model 1 with the addition of WC. Model 3 contains the Model 1 with the addition of diabetes. Model 4 contains Model 1 with the addition of WC and diabetes. The relationship between the WC levels and the outcome is represented by the COX proportional hazard model with WC as a continuous variable and WC as a categorical variable. Increase of (area under the curve) AUC in ROC (receiver operating characteristic) curve was used to compare the predictive power of the target parameter. In addition, when WC or diabetes was added to the established
model, continuous net weight classification index (NRI) and comprehensive discrimination improvement (IDI) were generated to assess any improvement in prognostic prediction. SPSS 22.0 and R 4.0.0 (R Foundation for Statistical Computing) were used for descriptive data analysis. All statistical tests were 2-tailed, and p values <0.05 were considered statistically significant.

3. Results

3.1 Baseline characteristics

Baseline measurements of WC were available in 1521 patients. We divided the patients into three groups based on the levels of WC. The baseline clinical and laboratory characteristics of the study patients are presented in Table 1. The patients with a higher WC level were older, more likely to be female, more likely to be diabetes. Moreover, they had a higher BMI, hips circumference, fasting blood glucose, 2hPBG level, HbA1c level, uric acid level. Also, they had a higher systolic blood pressure (SBP) and diastolic blood pressure (DBP) level. However, they had a lower HDL-C as well as TC level.
Table 1
Baseline characteristics of the subjects by the waist circumference level

| Variables                  | Total (n=1521) | Waist circumference level |          |          |          |          |          |
|----------------------------|----------------|---------------------------|----------|----------|----------|----------|----------|
|                            |                | 82cm (n=438) | 82-94cm (n=752) | 94cm (n=331) |          |          |          |
| Age, years                 | 70.96±7.18     | 69.98±7.23 | 70.86±6.90 | 72.49±7.48 | 0.000    |          |          |
| Male, n%                   | 900 (59.4)     | 336 (76.71) | 430 (57.18) | 134 (40.48) | 0.000    |          |          |
| T2DM, n (%)                | 449 (29.52)    | 106 (24.20) | 215 (28.59) | 128 (38.67) | 0.000    |          |          |
| Hypertension, n (%)        | 785 (51.61)    | 174 (39.73) | 410 (54.52) | 201 (60.73) | 0.411    |          |          |
| Current smokers, n (%)     | 253 (16.63)    | 84 (19.18)  | 113 (15.03) | 56 (16.92)  | 0.531    |          |          |
| BMI (kg/m2)                | 24.88±3.46     | 21.98±2.84 | 25.01±2.31 | 28.39±2.98 | 0.000    |          |          |
| Hips circumference (cm)    | 97.97±8.36     | 90.88±7.40 | 98.54±5.24 | 106.06±7.35 | 0.000    |          |          |
| Fasting blood glucose (mmol/L) | 5.68±0.99  | 5.46±0.77  | 5.67±1.02  | 5.97±1.12  | 0.000    |          |          |
| 2hPBG (mmol/L)             | 8.08±3.29      | 7.19±2.73  | 8.19±3.32  | 9.00±3.61  | 0.000    |          |          |
| HbA1c                      | 5.86±1.045     | 5.70±0.62  | 5.87±1.17  | 6.04±1.17  | 0.000    |          |          |
| SBP (mmHg)                 | 137.42±19.13   | 132.77±17.30 | 138.43±17.89 | 141.36±19.51 | 0.000    |          |          |
| DBP (mmHg)                 | 76.97±9.96     | 73.84±8.74 | 77.79±9.28 | 79.23±9.21 | 0.000    |          |          |
| TC (mmol/L)                | 5.29±0.99      | 5.37±0.97  | 5.29±1.01  | 5.16±0.95  | 0.016    |          |          |
| HDL-C (mmol/L)             | 1.44±0.39      | 1.62±0.42  | 1.40±0.34  | 1.30±0.39  | 0.000    |          |          |
| LDL-C (mmol/L)             | 3.26±0.85      | 3.24±0.84  | 3.30±0.92  | 3.17±0.85  | 0.055    |          |          |
| TG (mmol/L)                | 1.63±0.82      | 1.42±0.76  | 1.65±0.82  | 1.85±0.82  | 0.341    |          |          |
| Creatinine (umol/L)        | 74.46±22.22    | 70.64±24.98 | 74.42±19.77 | 79.62±22.64 | 0.271    |          |          |
| Uric acid (umol/L)         | 309.06±89.27   | 282.59±74.79 | 307.99±91.22 | 346.61±89.54 | 0.000    |          |          |

3.2 Association between WC and diabetes and prognosis of cardiovascular death

During the median follow up of 9.2 years, 265 participants had the occurrence of cardiovascular death. The death rate of the higher WC group was significantly higher than the lower group (23.3% VS 16.0% VS
Kaplan–Meier curves were used to show the cumulative event curves for cardiovascular death stratified according to WC levels (Figure 2a) and diabetes (Figure 2b): patients with higher level of WC or patients with diabetes were more likely to have a higher cardiovascular death rate (log-rank test, p<0.05, respectively). Table 2 shows the univariate and multivariate Cox regression analysis of cardiovascular death predictors. After adjusting for potential confounding factors, patients with higher WC level group (WC>94 cm) (adjusted HR =3.02; 95% CI: 1.88 to 3.83; p=0.001) (Figure 3a) or diabetes (adjusted HR =1.59; 95% CI: 1.46 to 1.77; p=0.001) (Figure 3b) had a significantly higher risk of cardiovascular death. Age, BMI, hypertension, hips circumference, fasting blood glucose, 2hPBG, HbA1c, SBP, DBP, current smoking, Hypertension, DM, TC, TG, HDL-C, LDL-C, Creatinine, Uric acid were included in the confounding factors.

In subgroups, the patients were further categorized into six groups as high WC with DM and non-DM, moderate WC with DM and non-DM, and low WC with DM and non-DM. The incidence of cardiovascular death was significantly higher when patients with high WC coexisted with DM (low WC: 25.9% vs 11.8%; moderate WC: 26.9 % vs 14.9%; high WC: 27.6% vs 18.7%, p<0.05, respectively). Patients with higher level of WC (WC>94 cm) with diabetes have the highest cardiovascular death rate (27.6%) (log-rank test, p<0.05). Besides, as shown in Figure 2c, the Kaplan–Meier analysis curves presented the highest risk of in patients with high WC with DM compared with other subgroups (log rank test, p<0.001). Multivariate Cox regression analysis showed that patients with higher level of WC were more likely to have a higher cardiovascular death rate (adjusted HR =3.78; 95% CI: 3.35 to 3.98; p=0.001) (Figure 3c).

**Table 2**

Univariate and multivariate Cox regression analysis of cardiovascular death predictors
| Variables                  | Univariable analysis                          | Multivariable analysis                          |
|---------------------------|-----------------------------------------------|-------------------------------------------------|
|                           | Crude HR | 95%CI | P Value | Crude HR | 95%CI | P Value |
| Age, years                | 1.18     | 1.16 to 1.20 | 0.00 | 1.16     | 1.13 to 1.18 | 0.00 |
| Male, n (%)               | 1.02     | 0.96 to 1.03 | 0.12 |           |       |         |
| BMI (kg/m2)               | 0.97     | 0.96 to 0.98 | 0.00 | 0.95     | 0.90 to 1.01 | 0.09 |
| Hips circumference(cm)    | 0.99     | 0.97 to 1.00 | 0.07 |           |       |         |
| Fasting blood glucose (mmol/L) | 1.08     | 1.03 to 1.14 | 0.00 | 1.09     | 0.92 to 1.30 | 0.34 |
| 2hPBG(mmol/L)             | 1.03     | 0.99 to 1.06 | 0.14 |           |       |         |
| HbA1c                     | 1.11     | 1.04 to 1.19 | 0.00 | 1.04     | 0.92 to 1.19 | 0.53 |
| SBP (mmHg)                | 1.01     | 1.002 to 1.012 | 0.01 | 1.00     | 0.99 to 1.01 | 0.25 |
| DBP (mmHg)                | 0.99     | 0.98 to 0.99 | 0.03 | 0.99     | 0.97 to 1.00 | 0.11 |
| T2DM, n (%)               | 1.56     | 1.45 to 1.69 | 0.00 | 1.59     | 1.46 to 1.77 | 0.00 |
| Hypertension, n (%)       | 1.07     | 0.89 to 1.26 | 0.00 | 1.08     | 0.85 to 1.22 | 0.06 |
| Current smokers, n (%)    | 1.02     | 0.89 to 1.07 | 0.18 |           |       |         |
| TC (mmol/L)               | 0.75     | 0.68 to 0.85 | 0.00 | 1.28     | 0.64 to 2.57 | 0.49 |
| HDL-C(mmol/L)             | 0.97     | 0.74 to 1.28 | 0.84 |           |       |         |
| LDL-C(mmol/L)             | 0.78     | 0.69 to 0.88 | 0.00 | 0.75     | 0.36 to 1.55 | 0.44 |
| TG (mmol/L)               | 0.71     | 0.61 to 0.83 | 0.00 | 0.58     | 0.42 to 0.80 | 0.00 |
| Creatinine (umol/L)       | 1.01     | 1.008 to 1.013 | 0.00 | 1.01     | 1.01 to 1.02 | 0.00 |
| Uric acid (umol/L)        | 1.003    | 1.002 to 1.004 | 0.00 | 1.002    | 1.001 to 1.004 | 0.00 |
| Group                     |          |       |         |          |       |         |
| WC≤82cm                   | 1        |       |         | 1        |       |         |
| WC:82-94cm                | 1.06     | 0.53 to 1.32 | 0.05 | 1.68     | 1.18 to 2.41 | 0.01 |
| WC≥94cm                   | 1.59     | 0.97 to 2.57 | 0.07 | 3.02     | 1.88 to 3.83 | 0.00 |
3.3 Construction of the prediction models and the model performance.

We adjusted four prediction models to evaluate the prognostic value. Model 1 was adjusted by the clinical confounders (age, sex, BMI, hips circumference, fasting blood glucose, 2hPBG, HbA1c, SBP, DBP, Current smokers, hypertension, TC, HDL-C, LDL-C, TG, creatinine, uric acid). Model 2 included model 1 with the addition of WC, Model 3 included model 1 with the addition of WC, Model 4 included model 1 with the addition of WC+DM.

Finally, to evaluate the effect of WC and diabetes on the accuracy of cardiovascular death risk assessment, discriminatory abilities were compared between models with WC and diabetes. As shown in Table 3, adding WC and diabetes can significantly increase the static value of C from 0.693 (95%CI: 0.656-0.730) to 0.847 (95%CI: 0.724-0.891). Compared with the clinical model, there is a significant difference (p <0.01). In addition, adding WC category to Model 1 can significantly improve NRI = 0.195 (95% CI: 0.135-0.203, p <0.05); IDI = 0.009 (95% CI: 0.003-0.014, p <0.001) (Table 3).

| Model                  | Estimate (95%CI) | P value   |
|------------------------|------------------|-----------|
| C static               |                  |           |
| Model1                 | 0.693 (95%CI: 0.656-0.730) | -         |
| Model2: Model1+WC      | 0.812 (95%CI: 0.782-0.842) | 0.031     |
| Model3: Model1+DM      | 0.785 (95%CI: 0.769-0.812) | 0.025     |
| Model4: Model1+WC+DM   | 0.847 (95%CI: 0.724-0.891) | 0.001     |
| NRI                    |                  |           |
| Model1                 | REF              | -         |
| Model2: Model1+WC      | 0.178 (95% CI: 0.094-0.262) | 0.042     |
| Model3: Model1+DM      | 0.182 (95% CI: 0.135-0.203) | 0.031     |
| Model4: Model1+WC+DM   | 0.195 (95% CI: 0.135-0.203) | 0.012     |
| IDI                    |                  |           |
| Model1                 | REF              | -         |
| Model2: Model1+WC      | 0.012 (95% CI: 0.007-0.015) | 0.229     |
| Model3: Model1+DM      | 0.014 (95% CI: 0.013-0.020) | 0.174     |
| Model4: Model1+WC+DM   | 0.009 (95% CI: 0.006-0.014) | 0.030     |

4. Discussion
4.1 Principal findings

In this perspective, observational study on a large Chinese cohort with long-term follow-up, we examined the prognostic association of DM with outcomes in patients with different degree of WC. Our results suggested that higher WC and diabetes were both significant and independent predictors of cardiovascular death (Figure 4a). In addition, our results suggested that patients with higher levels of WC coexist with diabetes had the worst outcome, the association is still significant after adjustment of other clinical confounders (Figure 4b). In summary, our results suggested that the addition of WC and diabetes to established cardiovascular risk factors may further improve risk stratification in general population. Our results provided updated information about the long-term prognostic role of WC and diabetes in general population.

4.2 Limitations of BMI

Adipose tissue is now considered to be a key organ for the fates of excessive dietary lipids, which may determine whether it will maintain body homeostasis (metabolic healthy obesity) or whether it will produce inflammation/insulin resistance, which can have harmful cardiovascular consequences. Obesity, especially visceral obesity, can also cause various structural adaptations/changes in the structure/function of CV. Adipose tissue can now be regarded as an endocrine organ that coordinates important interactions with vital organs and tissues (such as the brain, liver, skeletal muscle, heart, and blood vessels themselves).

The most commonly used anthropometric tool for assessing relative weight and classifying obesity is BMI, which is expressed as the ratio of total body weight to the square of height (kg/m$^2$). Individuals with a BMI <18.5 kg/m$^2$ are considered underweight, while individuals with a BMI between 18.5 and 24.9 kg/m$^2$ are classified as normal or acceptable weight. Individuals with a BMI between 25 and 29.9 kg/m$^2$ are classified as overweight, while those with a BMI of $\geq$ 30 kg/m$^2$ are obese. BMI itself is associated with clinical outcomes and mortality in a U or J type [11]. This inverse relationship has triggered controversy in the literature, called the "obesity paradox" [12]. Compared with non-obese patients, patients with elevated BMI with chronic diseases have a higher survival rate and fewer cardiovascular (CV) events [13]. Moreover, previous research reported that patients with an increased BMI were found to show lower mortality [14]. In addition, BMI cannot distinguish between weight gain due to high levels of lean body mass and fat body mass. Generally, excess body fat (BF) is more often associated with metabolic abnormalities than high levels of lean body mass. Another explanation for this paradox is the lack of control over the main individual differences in the regional BF distribution. Therefore, more and more scholars believe that the BMI has its limitations to fully capture cardiometabolic risk. It is partially related to the fact that BMI in isolation is an insufficient biomarker of abdominal adiposity [5]. By using the BMI, one must rely on the assumption that adipose tissue is distributed evenly over the body, which does not take into account the heterogeneity of regional body fat deposition [15].
The level of obesity must be considered in the risk stratification. In a recent meta-analysis of 2.88 million people, all levels of obesity combined were associated with increased mortality, with a hazard ratio of 1.18 (95% CI, 1.12-1.25). However, when analyzing separately, grade 1 obesity (table 1) is associated with a higher risk of death with a hazard ratio of 0.97 (95% CI, 0.90–1.04), compared with normal body weight. In contrast, serious obesity (grades 2 and 3) and risk of death (hazard ratio 1.34 – 95% CI, 1.21 – 1.47) [16]. The prognostic value of BMI needs to pay attention to the length of follow-up time. There was a J-type association between BMI and sudden cardiac death, and the lowest risk was observed within the normal weight range. However, in studies with a longer follow-up period, the increased risk of low BMI was attenuated [17]. In other words, the obesity phenotype may change over time to reflect the increase in abdominal obesity. For example, Ian Janssen and colleagues studied the changes in waist circumference for a given BMI over a 30-year period in a Canadian sample35. It is worth noting that for a given BMI, Canadians had a larger waist circumference in 2007 than in 1981. Specifically, the researchers observed that between 1981, men with a BMI of 25 kg/m2 increased their waist circumference by 1.1 cm, and women with a BMI of 4.9 cm and 2007. Similarly, Sandra Albrecht and colleagues studied 36 long-term changes in waist circumference in the United States (1988-2007), the United Kingdom (1992-2008), China (1993-2011), and Mexico (1999-2012), and reported significant statistics Academic significance in all countries and in most subgroups, waist circumference values have increased relative to BMI. The result of one study involving more than 58 000 elderly persons, during a 5-year-follow-up, showed that increased mortality risks for elderly people with an increased WC—even across BMI categories— and for those who were classified as ‘underweight’ using BMI. Part of the reason why BMI cannot fully capture cardiometabolic risks is that BMI alone is an insufficient biomarker for the whole body. More importantly, the central abdominal fat mass does not explain the extreme changes in intra-abdominal (visceral) fat mass. Fat distribution between individuals [18]. Compared with BMI, waist circumference has a higher predictive value for cardiovascular death [19].

4.3 Visceral adipose tissue and the underlying mechanisms

Visceral adipose tissue has been proved to be independently associated with elevated CVD (cardiovascular disease) risk [20]. Data from several past epidemiological studies 30 years of experience shows that VAT is an independent sign of morbidity and mortality [21]. In some populations, WC has been found to be more predictive of overall mortality, coronary heart disease (CHD), and CVD mortality than BMI. However, prospective data on the impact of abdominal obesity on CVD incidence is still scarce. Many experimental studies support the potential connection between VAT and biological pathways that are important in the pathogenesis of multiple disease outcomes. Adipokines are biologically active molecules secreted by adipose tissue and are key components of these pathways, including inflammatory cytokines, angiogenic factors, lipid metabolites, and extracellular matrix components [22]. The secretion of adipokines among specific fat depots appears to be different [23], and compared with subcutaneous adipose tissue (SAT), VAT exhibits more pro-inflammatory and pro-angiogenic gene expression. In addition, compared with SAT, small arteries in VAT are more likely to exhibit endothelial dysfunction [24], indicating that VAT has a potentially toxic effect on the vasculature. Visceral adipocytes
differ from subcutaneous adipocytes in that they release secreted proteins that are known or potential risk factors for CHD. In at least one study, visceral fat expressed and released more plasminogen activator inhibitor-1, a fibrinolysis inhibitor, than subcutaneous fat [25]. Angiotensinogen is a potential blood pressure regulator and is also highly expressed in visceral adipose tissue.

There are currently multiple methods to assess body fat distribution. The most accurate method is costly and time-consuming. It is not suitable for large-scale population research. Since routine access to CT, magnetic resonance imaging (MRI) may too expensive to be feasible for many clinicians, and the use of these methods to image visceral and ectopic fat has historically been reserved for research purposes. Perhaps the most widely used and these measurements are taken for waist circumference. Ashwell and colleagues were the first to show that there is a correlation between visceral fat mass and waist-to-hip ratio. However, compared with waist-to-hip ratio, waist circumference has a stronger correlation with visceral fat mass [26].

4.4 Obesities, Type 2 Diabetes Mellitus, and Cardiovascular Outcomes

Obesity is an important driving factor for the development of type 2 diabetes. Compared with BMI-matched non-type 2 diabetic patients, type 2 diabetic patients have a larger waist circumference and more VAT [8]. A patient with VAT or severe obesity and type 2 diabetes is susceptible to cardiovascular abnormalities and cardiovascular disease; their simultaneous presence should further increase the risk of cardiovascular outcomes [27]. The underlying mechanisms maybe ectopic and visceral obesity are related to insulin resistance, this may partially mediate the link between obesity, type 2 diabetes and cardiovascular risk. Metabolic syndrome and insulin resistance have been recognized as risk factors for cardiovascular morbidity and mortality [28]. Studies have also shown that the presence of metabolic syndrome increases the risk of heart failure. The result of a cross-sectional study has shown that obesity and type 2 diabetes have an additive effect on left ventricular remodeling in normotensive patients[29]. A recent study of patients with type-2 diabetes mellitus showed that compared with those in the first quartile of WC, male patients in the fourth quartile of WC (WC≥126) had a HR of 1.24 (95% CI 1.05–1.46) for major adverse cardiovascular events (MACEs); female patients in the fourth quartile of WC (WC≥122 cm) had an HR of 1.22 (95% CI 0.96–1.56) for MACEs [30]. Our results suggested that patients with higher levels of WC coexist with diabetes had the worst outcome, the association is still significant after adjustment of other clinical confounders. Our results provided updated information about the long-term prognostic role of WC and diabetes in general population.

Limitations of our study

The limitation of our study is the relatively small cohort patients; therefore, a larger sample of research is needed. Another limitation would be the lack of "gold standard" methods for abdominal obesity, such as
computed tomography (CT) or MRI, may be another limitation of current research. However, the effectiveness of WC has previously been confirmed in cross-sectional studies and prospective studies.

**Conclusion**

In conclusion, our study demonstrated that an increased WC (WC≥94cm) was associated with an increased cardiovascular death in general population. Patients with higher levels of WC coexist with diabetes had the worst outcome. WC and diabetes may provide incremental prognostic value beyond traditional risks factors.

**Abbreviations**
| Abbreviation | Description                        |
|--------------|------------------------------------|
| AUC          | area under the curve               |
| BF           | body fat                           |
| BMI          | body mass index                    |
| BP           | blood pressure                     |
| CI           | confidence intervals               |
| CT           | computed tomography                |
| CV           | cardiovascular                      |
| CVD          | cardiovascular disease             |
| CHD          | coronary heart disease             |
| DBP          | diastolic blood pressure           |
| T2DM         | type 2 diabetes mellitus           |
| HDL-C        | high-density lipoprotein cholesterol |
| HR           | hazard ratio                       |
| ICD          | international classification of diseases |
| IDI          | integrated discrimination improvement |
| LDL-C        | low-density lipoprotein cholesterol |
| MACEs        | major adverse cardiovascular events |
| MRI          | magnetic resonance imaging         |
| NRI          | net reclassification index          |
| ROC          | receiver operating characteristic  |
| SAT          | subcutaneous adipose tissue        |
| SBP          | systolic blood pressure            |
| SD           | standard deviation                 |
| TC           | total cholesterol                  |
| TG           | triglyceride                       |
| VAT          | visceral adipose tissue            |
| WC           | waist circumference                |

**Declarations**
Ethics approval and consent to participate

This study was approved by the Ethics Board of the Chinese PLA General Hospital.

Consent for publication

Written informed consent for publication was obtained from each author and each patient.

Availability of data and material

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests

Funding

This work was supported by The National Key Research and Development Program of China (2020YFC2008900) and National Defense Science and Technology Innovation Special Zone Project (19-163-15-ZD-009-001-10) and the Key Projects of Logistics Scientific Research Project of Chinese PLA (19BJZ30)

Authors' contributions

Ping Zhu made substantial contributions to the conception or design of the work. Man Li and Shu-xia Wang contributed equally to the work, they contributed to the data collection, data interpretation, and critical review and drafting of the manuscript. Yong-kang Su, Jin Sun, An-hang Zhang, Bo-kai Cheng, Shuang Cai contributed to the data collection. All of the authors read and approved the final manuscript.

Acknowledgements

Not applicable

References

1. Chooi YC, Ding C, Magkos F: The epidemiology of obesity. Metabolism 2019, 92.
2. Piché M-E, Tchernof A, Després J-P: Obesity Phenotypes, Diabetes, and Cardiovascular Diseases. *Circ Res* 2020, 126(11):1477-1500.

3. Kim R, Kawachi I, Coull BA, Subramanian SV: Contribution of socioeconomic factors to the variation in body-mass index in 58 low-income and middle-income countries: an econometric analysis of multilevel data. *Lancet Glob Health* 2018, 6(7):e777-e786.

4. Neeland IJ, Ross R, Després J-P, Matsuzawa Y, Yamashita S, Shai I, Seidell J, Magni P, Santos RD, Arsenault Bet *et al*: Visceral and ectopic fat, atherosclerosis, and cardiometabolic disease: a position statement. *Lancet Diabetes Endocrinol* 2019, 7(9):715-725.

5. Ross R, Neeland IJ, Yamashita S, Shai I, Seidell J, Magni P, Santos RD, Arsenault B, Cuevas A, Hu FB *et al*: Waist circumference as a vital sign in clinical practice: a Consensus Statement from the IAS and ICCR Working Group on Visceral Obesity. *Nat Rev Endocrinol* 2020, 16(3):177-189.

6. Fox CS, Massaro JM, Hoffmann U, Pou KM, Maurovich-Horvat P, Liu C-Y, Vasan RS, Murabito JM, Meigs JB, Cupples LA *et al*: Abdominal visceral and subcutaneous adipose tissue compartments: association with metabolic risk factors in the Framingham Heart Study. *Circulation* 2007, 116(1):39-48.

7. Kaess BM, Pedley A, Massaro JM, Murabito J, Hoffmann U, Fox CS: The ratio of visceral to subcutaneous fat, a metric of body fat distribution, is a unique correlate of cardiometabolic risk. *Diabetologia* 2012, 55(10):2622-2630.

8. Balkau B, Deanfield JE, Després J-P, Bassand J-P, Fox KAA, Smith SC, Barter P, Tan C-E, Van Gaal L, Wittchen H-U *et al*: International Day for the Evaluation of Abdominal Obesity (IDEA): a study of waist circumference, cardiovascular disease, and diabetes mellitus in 168,000 primary care patients in 63 countries. *Circulation* 2007, 116(17):1942-1951.

9. Gallagher D, Kelley DE, Yim J-E, Spence N, Albu J, Boxt L, Pi-Sunyer FX, Heshka S: Adipose tissue distribution is different in type 2 diabetes. *Am J Clin Nutr* 2009, 89(3):807-814.

10. Karlsson T, Rask-Andersen M, Pan G, Höglund J, Wadelius C, Ek WE, Johansson Å: Contribution of genetics to visceral adiposity and its relation to cardiovascular and metabolic disease. *Nature medicine* 2019, 25(9):1390-1395.

11. van der Meer TGLA, Verhoeven P, Beentjes JWJ, Vliegenthart R: Disrupting gatekeeping practices: Journalists' source selection in times of crisis. *Journalism (Lond)* 2017, 18(9):1107-1124.

12. Elagizi A, Kachur S, Lavie CJ, Carbone S, Pandey A, Ortega FB, Milani RV: An Overview and Update on Obesity and the Obesity Paradox in Cardiovascular Diseases. *Prog Cardiovasc Dis* 2018, 61(2):142-150.

13. Bastien M, Poirier P, Lemieux I, Després J-P: Overview of epidemiology and contribution of obesity to cardiovascular disease. *Prog Cardiovasc Dis* 2014, 56(4):369-381.

14. Morse SA, Gulati R, Reisin E: The obesity paradox and cardiovascular disease. *Curr Hypertens Rep* 2010, 12(2):120-126.

15. Després JP, Lemieux I, Prud'homme D: Treatment of obesity: need to focus on high risk abdominally obese patients. *BMJ* 2001, 322(7288):716-720.
16. Flegal KM, Kit BK, Orpana H, Graubard BI: Association of all-cause mortality with overweight and obesity using standard body mass index categories: a systematic review and meta-analysis. *JAMA* 2013, 309(1):71-82.

17. Aune D, Schlesinger S, Norat T, Riboli E: Body mass index, abdominal fatness, and the risk of sudden cardiac death: a systematic review and dose-response meta-analysis of prospective studies. *Eur J Epidemiol* 2018, 33(8):711-722.

18. Neeland IJ, Poirier P, Després JP: Cardiovascular and Metabolic Heterogeneity of Obesity: Clinical Challenges and Implications for Management. *Circulation* 2018, 137(13):1391-1406.

19. Bigaard J, Frederiksen K, Tjønneland A, Thomsen BL, Overvad K, Heitmann BL, Sørensen TI: Waist circumference and body composition in relation to all-cause mortality in middle-aged men and women. *Int J Obes (Lond)* 2005, 29(7):778-784.

20. Kouli GM, Panagiotakos DB, Kyrou I, Georgousopoulou EN, Chrysohoou C, Tsigos C, Tousoulis D, Pitsavos C: Visceral adiposity index and 10-year cardiovascular disease incidence: The ATTICA study. *Nutr Metab Cardiovasc Dis* 2017, 27(10):881-889.

21. Hiuge-Shimizu A, Kishida K, Funahashi T, Ishizaka Y, Oka R, Okada M, Suzuki S, Takaya N, Nakagawa T, Fukui T *et al.*: Absolute value of visceral fat area measured on computed tomography scans and obesity-related cardiovascular risk factors in large-scale Japanese general population (the VACATION-J study). *Ann Med* 2012, 44(1):82-92.

22. Ouchi N, Parker JL, Lugus JJ, Walsh K: Adipokines in inflammation and metabolic disease. *Nat Rev Immunol* 2011, 11(2):85-97.

23. Hocking SL, Wu LE, Guilhaus M, Chisholm DJ, James DE: Intrinsic depot-specific differences in the secretome of adipose tissue, preadipocytes, and adipose tissue-derived microvascular endothelial cells. *Diabetes* 2010, 59(12):3008-3016.

24. Farb MG, Ganley-Leal L, Mott M, Liang Y, Ercan B, Widlansky ME, Bigornia SJ, Fiscale AJ, Apovian CM, Carmine Bet *et al.*: Arteriolar function in visceral adipose tissue is impaired in human obesity. *Arterioscler Thromb Vasc Biol* 2012, 32(2):467-473.

25. Bruno MEC, Mukherjee S, Stromberg AJ, Saito H, Starr ME: Visceral fat-specific regulation of plasminogen activator inhibitor-1 in aged septic mice. *J Cell Physiol* 2021.

26. Snijder MB, van Dam RM, Visser M, Seidell JC: What aspects of body fat are particularly hazardous and how do we measure them? *Int J Epidemiol* 2006, 35(1):83-92.

27. Schramm TK, Gislason GH, Køber L, Rasmussen S, Rasmussen JN, Abildstrøm SZ, Hansen ML, Folke F, Buch P, Madsen Met *et al.*: Diabetes patients requiring glucose-lowering therapy and nondiabetics with a prior myocardial infarction carry the same cardiovascular risk: a population study of 3.3 million people. *Circulation* 2008, 117(15):1945-1954.

28. Lakka H-M, Laaksonen DE, Lakka TA, Niskanen LK, Kumpusalo E, Tuomilehto J, Salonen JT: The metabolic syndrome and total and cardiovascular disease mortality in middle-aged men. *JAMA* 2002, 288(21):2709-2716.
29. De Jong KA, Czeczor JK, Sithara S, McEwen K, Lopaschuk GD, Appelbe A, Cukier K, Kotowicz M, McGee SL: Obesity and type 2 diabetes have additive effects on left ventricular remodelling in normotensive patients-a cross sectional study. *Cardiovasc Diabetol* 2017, 16(1):21.

30. Xing Z, Peng Z, Wang X, Zhu Z, Pei J, Hu X, Chai X: Waist circumference is associated with major adverse cardiovascular events in male but not female patients with type-2 diabetes mellitus. *Cardiovasc Diabetol* 2020, 19(1):39.

**Figures**

![Flowchart of the study](image)

**Figure 1**

The flowchart of the study
Figure 2

Kaplan–Meier curves in different subgroups. a: Kaplan–Meier survival rate of the participants according to the different WC levels. b: Kaplan–Meier survival rate of the participants with or without DM. c: Kaplan–Meier survival rate of the participants with DM and non-DM according to different degree of WC.
Figure 3

Cox-adjusted event-free survival curves for freedom of cardiovascular death in the different subgroups after adjustment for potential clinical confounders. a: Cox-adjusted event-free survival curves of the participants according to the different WC levels. b: Cox-adjusted event-free survival curves of the participants with or without DM. c: Cox-adjusted event-free survival curves of the participants with DM and non-DM according to different degree of WC.
Figure 4

a: Associations of clinical confounders and the prevalence of cardiovascular death. b: Associations of different degrees of WC and DM and the prevalence of cardiovascular death in different subgroups