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Relationship of normal-weight central obesity with the risk for heart failure and atrial fibrillation: analysis of a nationwide health check-up and claims database

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Aims

There have been scarce data on the relationship of normal-weight central obesity (NWCO) with the subsequent risk for heart failure (HF) and atrial fibrillation (AF). Using a nationwide health check-up and administrative claims database, we sought to clarify whether NWCO would be associated with the incidence of HF and AF.

Methods and results

Medical records of 1 697 903 participants without prior history of cardiovascular disease (CVD) and normal-weight (body mass index of 18.5–23.0 kg/m^2) were extracted from the JMDC Claims Database, which is a health check-up and claims database. We defined NWCO as normal-weight and CO (waist circumference ≥ 90 cm for men or ≥ 80 cm for women). The median age was 44.0 (37.0–52.0) years and 872 578 (51.4%) participants were men. Overall, 154 778 individuals (9.1%) had CO. The mean follow-up period was 3.3 ± 2.6 years. Participants with NWCO were older and more likely to be women than those without. HF and AF occurred in 26 936 (1.6%) and 6554 (0.4%) participants, respectively. People having NWCO were associated with a greater risk for HF [hazard ratio (HR): 1.072, 95% confidence interval (CI) 1.026–1.119] and AF (HR: 1.202, 95% CI: 1.083–1.333) compared with those having normal-weight without CO.

Conclusion

Our analysis of a nationwide health check-up and administrative claims database including ∼1.7 million participants without prevalent CVD history demonstrated the potential impact of NWCO on the risk for HF and AF, suggesting the importance of abdominal obesity in the developing HF and AF even in normal-weight individuals.

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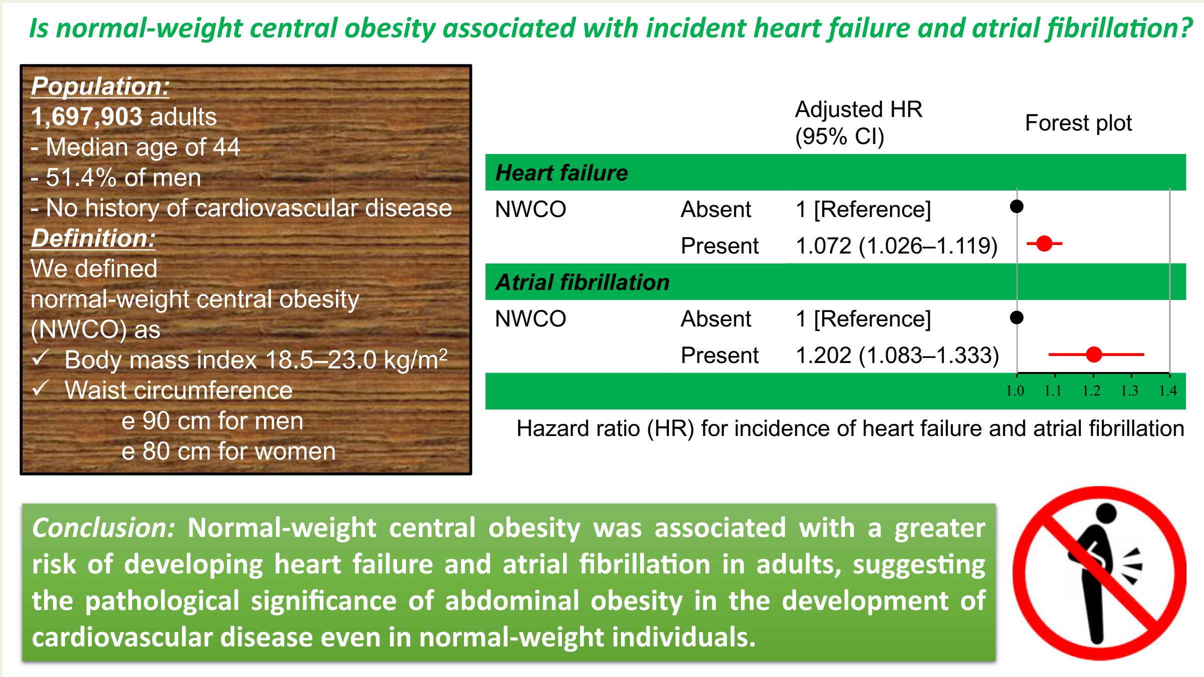
Graphical Abstract



Keywords Normal-weight central obesity • Heart failure • Atrial fibrillation • Preventive cardiology

Introduction

Overweight and obesity, as defined by body mass index (BMI) and waist circumference (WC), are known to be associated with cardiovascular disease (CVD)-related deaths and the development of various metabolic disorders and CVD.[1–7] The Framingham Heart Study found the risk of heart failure (HF) increased with increasing BMI,[8] and the Physicians' Health Study showed that overweight and obesity were associated with higher HF risk.[9]

In recent years, a phenotype in which BMI does not reach the criteria for overweight or obesity, but only WC is high, is gaining attention and is called normal-weight central obesity (NWCO).[10] The significance of NWCO in the field of primary prevention has been reported. Previous studies showed that the prevalence of metabolic disorders (e.g. hypertension, diabetes) was higher in people with NWCO than in those with normal-weight and normal WC.[11–14] In addition, an analysis of the Third National Health and Nutrition Examination Survey including community-dwelling adults reported that NWCO was associated with a higher all-cause and CVD-related mortality.[15] Furthermore, an analysis of 1346 Finnish men without a CVD history showed that NWCO was associated with an increased risk for coronary artery disease.[4] However, limited studies have reported an association between NWCO and the development of HF and atrial fibrillation (AF).

The HF and AF are still increasing globally. The prevalence of HF is expected to increase by 46% from 2012 to 2030, and the patients suffering from HF would exceed >8 million people in 2030.[16] The people living with AF is estimated to increase from 5.2 million in 2010 to 12.1 million in 2030 in the USA.[17] Hence, preventing HF and AF is an important challenge in the field of primary prevention, but it is not clear whether NWCO is associated with the development of HF and AF. We believe that clarifying this association will stratify the future risk and address the need for preventive measures to reduce the burden of HF and AF, as well as provide the importance of assessing abdominal obesity even in normal-weight individuals. Therefore, we sought to identify the relationship of NWCO with the developing of HF and AF in Japanese adults, using a large-scale health check-up and administrative claims dataset. As secondary outcomes, we also examined the association with the development of myocardial infarction (MI), angina pectoris (AP), and stroke.

Methods

Study design and data source

We performed a retrospective observational analysis using the JMDC Claims Database (JMDC; Tokyo, Japan) between January 2005 and April 2020. The JMDC Claims Database is a health check-up and claims database in Japan.[18,19] The JMDC, which is a health venture company, contracts with more than 60 insurers and includes data for administrative claims records of registered individuals. People enrolled in this dataset are primarily employees of relatively large Japanese companies.

Detailed information on the JMDC Claims Database is described elsewhere.[20] Data on clinical follow-ups obtained by insurance claim records are available in this database as well. Incidence of CVD, including HF, AF, MI, AP, and stroke, was evaluated using the International Classification of Disease, 10th Revision (ICD-10) diagnosis codes recorded in the claim records of each individual.[21] We extracted the data of 2 036 077 normal-weight individuals defined as BMI of 18.5–23.0 kg/m^2 who were enrolled in the JMDC Claims Database between January 2005 and April 2020 and whose health check-up data (including data on WC, physical examination, and laboratory data) were available. Exclusion criteria were as follows: (i) age <20 years ($n = 3005$); (ii) prior history of HF, AF, MI, AP, stroke, renal disease, or dialysis ($n = 71 086$); and (iii) missing data on cigarette smoking ($n = 105 528$) and alcohol consumption ($n = 158 555$). Ultimately, we analyzed 1 697 903 participants in this study (*Figure 1*).

Ethics

We conducted this study according to the ethical guidelines of our institution (approval by the Institutional Review Board of the University of Tokyo: 2018–10862) in accordance with the principles of the Declaration of Helsinki. The requirement for informed consent was waived since all data in this dataset were de-identified. All data were compliant with the International Conference on Harmonization guidelines.[22]

Measurement of waist circumference and body mass index

The WC and BMI measurements were performed by well-trained examiners at health check-ups. The WC was measured to the nearest 0.1 cm by measuring at the umbilical level at the end of expiration in a standing position using a flexible anthropometric tape.[23–25] Height (m) and weight (kg) were each measured in the standing position, and the BMI was calculated as body weight (kg) divided by the height squared (m^2).[23–25]

Definition

We defined CO as WC at an umbilical level ≥ 90 cm in men or ≥ 80 cm in women based on the International Diabetes Federation defined metabolic syndrome for Asians,[26] and NWCO was defined as normal-weight (BMI: 18.5–23.0 kg/m^2)[27] and CO. Hypertension was defined as systolic blood pressure of ≥ 140 mmHg, diastolic blood pressure of ≥ 90 mmHg, or use of blood pressure-lowering medications. Diabetes mellitus was defined as a fasting glucose level of ≥ 126 mg/dL, or use of glucose-lowering medications including insulin. Dyslipidaemia was defined as low-density lipoprotein cholesterol level of ≥ 160 mg/dL,[28] high-density lipoprotein cholesterol level of <40 mg/dL, triglyceride level of ≥ 150 mg/dL, or use of lipid-lowering medications. We obtained information regarding cigarette smoking (current or non-current) and alcohol consumption (every day or not) from self-reported questionnaires at health check-up.

Outcomes

Clinical follow-up was initiated from the date of the initial health check-up of each participant, and we collected outcome data between January 2005 and April 2020. The primary outcomes included HF (ICD-10 codes: I500, I501, I509, and I110) and AF (ICD-10 codes: I480–I484, and I489). Secondary outcomes included MI (ICD-10 codes: I210–I214, and I219), AP (ICD-10 codes: I200, I201, I208, and I209), and stroke (ICD-10 codes: I630, I631–I636, I638, I639, I600–I611, I613–I616, I619, I629, and G459). We analysed each CVD event separately, which meant, if a participant experienced stroke and then AP 6 months later, we counted both stroke and AP events as separate outcomes. We excluded participants whose disease codes with 'suspect' to ensure validity. Diagnosis of these diseases includes both inpatient and outpatient settings.

Statistical analysis

We performed all statistical analyses using SPSS software (version 25, SPSS Inc., Chicago, IL, USA) and Stata software (version 17, StataCorp LLC, College Station, TX, USA). Categorical and continuous data of the baseline characteristics are presented as percentages (%) and median [interquartile range (IQR)]. The χ^2 test was used to compare the categorical variables between normal-weight participants with and without CO. The unpaired *t*-test was used to compare continuous variables between two groups. We conducted Cox regression analysis to identify the relationship between NWCO and the incidence of each CVD event. Model 1 included NWCO alone (unadjusted model); Model 2 included NWCO, age and sex, and Model 3 included NWCO, age, sex, BMI, hypertension, diabetes mellitus, dyslipidaemia, cigarette smoking, and alcohol consumption. We calculated E values to estimate the potential influence of unmeasured confounders.

To examine the association between the 1-year change in WC and BMI and the development of HF and AF, we included 1 102 233 individuals who also had data on WC and BMI at 1 year after their initial health check-up available. We calculated HRs adjusted for age, sex, BMI, hypertension, diabetes mellitus, dyslipidaemia, cigarette smoking, alcohol consumption, and WC and took into account the interaction term between baseline WC and BMI.

We conducted six sensitivity analyses. First, we defined CO as WC at an umbilical level ≥ 85 cm in men or ≥ 90 cm in women based on diagnostic criteria for metabolic syndrome in Japan,[29,30] and NWCO was defined as normal-weight (BMI: 18.5–23.0 kg/m^2) and CO. Second, we treated WC as a continuous variable and analyzed the relationship of WC with the risk for developing HF or AF. Third, we defined NWCO as BMI 18.5–24.9 kg/m^2 and WC ≥ 90 cm for men or ≥ 80 cm for women.[26] Fourth, we assessed the association of WC as a continuous variable with incident HF and AF using a restricted cubic spline regression model. We used five cut-off points for WC (5, 27.5, 50, 72.5, and 95 percentiles), with the reference point set at 90 cm for an overall population, 90 cm for men, and 80 cm for women. We fitted three cubic spline models using three, four, and five knots, and the model with five knots was selected because it had the lowest Akaike's information criterion. HRs and 95% confidence intervals (CIs) for incident HF and AF were calculated for each WC value. We calculated HRs after adjusting for covariates including age, sex, BMI, hypertension, diabetes mellitus, dyslipidaemia, cigarette smoking, and alcohol consumption. Fifth, we divided our study population by sex or age (≥50 years, <50 years). Sixth, using body fat percentage calculated by the CUN-BAE formula,[31] the association between body fat percentage and the development of HF or AF was examined using cox regression analysis. Following previous studies, we classified the participants into three groups: normal body fatness, overweight, and obesity.[31] Since the CUN-BAE formula is calculated from age, sex, and BMI, multivariate cox regression analysis was performed with hypertension, diabetes mellitus, dyslipidaemia, cigarette smoking, and alcohol consumption.

A probability value of <0.05 was considered statistically significant.

Results

Characteristics of study population

Characteristics of the study participants are shown in *Table 1*. Overall, the median WC was 76.0 (IQR: 72.0–80.0) cm. The median

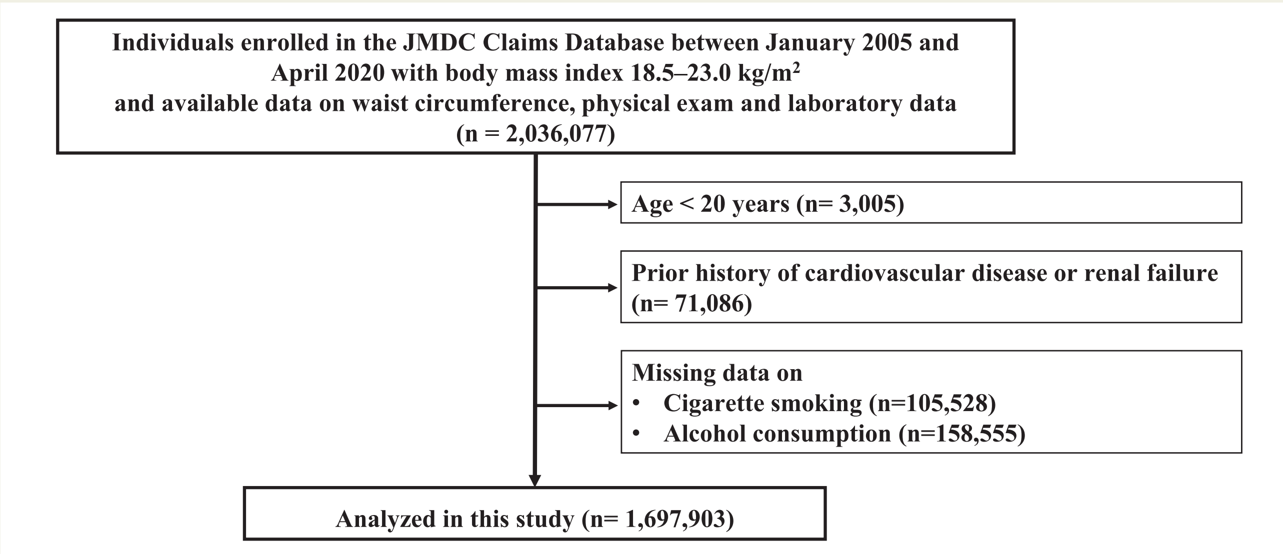


Figure 1 Flowchart. We extracted the data of 2 036 077 normal-weight individuals defined as body mass index of 18.5–23.0 kg/m^2 who were enrolled in the JMDC Claims Database between January 2005 and April 2020 and whose baseline health check-up data (including data on waist circumference) were available. Exclusion criteria were as follows: (i) age < 20 years ($n = 3005$); (ii) prior history of cardiovascular disease or renal failure ($n = 71\,086$); and (iii) missing data on cigarette smoking ($n = 105\,528$), and alcohol consumption ($n = 158\,555$). Ultimately, we analyzed 1 697 903 participants in this study.

Table 1 Clinical characteristics

	Normal-weight central obesity (−) (*n* = 1 543 125)	Normal-weight central obesity (+) (*n* = 154 778)	*P* value
Waist circumference, cm	75.5 (72.0–79.0)	82.5 (81.0–84.6)	<0.001
Age, years	44 (37–52)	50 (42–57)	<0.001
Men, *n* (%)	867 269 (56.2)	5309 (3.4)	<0.001
Body mass index, kg/m^2	20.8 (19.8–21.9)	21.9 (21.1–22.5)	<0.001
Hypertension, *n* (%)	175 170 (11.4)	25 205 (16.3)	<0.001
Systolic blood pressure, mmHg	114 (104–124)	115 (105–126)	<0.001
Diastolic blood pressure, mmHg	70 (63–78)	70 (63–79)	<0.001
Diabetes mellitus, *n* (%)	23 639 (1.5)	2482 (1.6)	0.029
Dyslipidaemia, *n* (%)	279 489 (18.1)	40 914 (26.4)	<0.001
Cigarette smoking, *n* (%)	378 546 (24.5)	17 348 (11.2)	<0.001
Alcohol consumption, *n* (%)	370 919 (24.0)	26 059 (16.8)	<0.001
Laboratory data			
Glucose, mg/dL	90 (85–96)	91 (85–97)	<0.001
Low-density lipoprotein cholesterol, mg/dL	113 (94–134)	122 (102–145)	<0.001
High-density lipoprotein cholesterol, mg/dL	66 (56–78)	69 (59–79)	<0.001
Triglycerides, mg/dL	70 (51–98)	75 (56–104)	<0.001

Data are expressed as median (interquartile range) or number (percentage). We defined normal-weight central obesity as normal body mass index (body mass index: 18.5–23.0 kg/m^2) and waist circumference at umbilical level ≥ 90 cm in men or ≥ 80 cm in women.

age was 44.0 (IQR: 37.0–52.0) years, and 872 578 participants (51.4%) were men. Among the total cohort, 154 778 participants (9.1%) had NWCO. Participants with NWCO were older and were more likely to be women than normal-weight without CO. The prevalence of hypertension, diabetes mellitus, and dyslipidaemia were higher in participants with NWCO than normal-weight without CO.

Normal-weight central obesity and incident heart failure and atrial fibrillation

During a mean follow-up of 1189 ± 933 days, 26 936 (1.6%) HF and 6554 (0.4%) AF events were recorded. The event rates for HF were higher in participants with NWCO [62.2 (95% CI = 60.0–64.5) per

		No	No. of events	Incidence	Model 1	Model 2	Model 3
Heart failure							
NWCO	Absent	1543125	23943	48.0 (47.4–48.6)	1 [Reference]	1 [Reference]	1 [Reference]
	Present	154778	2993	62.2 (60.0–64.5)	1.298 (1.249–1.348)	1.133 (1.087–1.181)	1.072 (1.026–1.119)
Atrial fibrillation							
NWCO	Absent	1543125	6038	12.0 (11.7–12.3)	1 [Reference]	1 [Reference]	1 [Reference]
	Present	154778	516	10.6 (9.73–11.6)	0.885 (0.809–0.968)	1.221 (1.104–1.351)	1.202 (1.083–1.333)
Myocardial infarction							
NWCO	Absent	1543125	2295	4.56 (4.38–4.75)	1 [Reference]	1 [Reference]	1 [Reference]
	Present	154778	204	4.19 (3.65–4.80)	0.922 (0.799–1.064)	1.240 (1.057–1.455)	1.067 (0.905–1.258)
Angina pectoris							
NWCO	Absent	1543125	23467	47.1 (46.5–47.8)	1 [Reference]	1 [Reference]	1 [Reference]
	Present	154778	3040	63.3 (61.1–65.6)	1.344 (1.294–1.396)	1.194 (1.146–1.245)	1.105 (1.058–1.154)
Stroke							
NWCO	Absent	1543125	11885	23.7 (23.3–24.2)	1 [Reference]	1 [Reference]	1 [Reference]
	Present	154778	1563	32.3 (30.8–34.0)	1.365 (1.295–1.439)	1.104 (1.042–1.170)	1.059 (0.997–1.125)

Forest plot

Figure 2 The frequency of events, corresponding incidence rates, and hazard ratios of normal-weight central obesity (defined as IDF-Asian) for cardiovascular disease events. The incidence rate was per 10 000 person-years. Cox regression analyses; Model 1 included normal-weight central obesity (unadjusted model); Model 2 included normal-weight central obesity, age, and sex; and Model 3 included normal-weight central obesity, age, sex, body mass index, hypertension, diabetes mellitus, dyslipidaemia, cigarette smoking, and alcohol consumption. IDF-Asian, International Diabetes Federation defined metabolic syndrome for Asians; NWCO, normal-weight central obesity.

	Adjusted HR (95% CI)
Heart failure	
Percent change in waist circumference per 10.0% increase	1.079 (1.032–1.127)
Percent change in body mass index per 10.0% increase	0.968 (0.920–1.017)
Atrial fibrillation	
Percent change in waist circumference per 10.0% increase	1.177 (1.064–1.302)
Percent change in body mass index per 10.0% increase	0.912 (0.810–1.026)

Forest plot

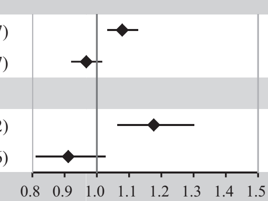


Figure 3 Temporal changes in waist circumference and body mass index for development of heart failure and atrial fibrillation. We included 1 102 233 individuals who also had waist circumference and body mass index data 1 year after the initial health check-up available. We calculated HRs after adjusting for age, sex, body mass index, hypertension, diabetes mellitus, dyslipidaemia, cigarette smoking, alcohol consumption, and waist circumference and took into account the interaction term between baseline waist circumference and body mass index. HR, hazard ratio; CI, confidence interval.

10 000 person-years] than in normal-weight without CO [48.0 (95% CI = 47.4–48.6) per 10 000 person-years] (*Figure 2*). Multivariable Cox regression analyses (Model 3) demonstrated that NWCO was associated with a higher risk for HF (HR: 1.072, 95% CI = 1.026–1.119) and AF (HR 1.202, 95% CI = 1.083–1.333) (*Figure 2*). E-value for the estimates of the relationship between NWCO with incident HF was 1.35 (CI = 1.19). In addition, E-value for the estimates of the relationship between NWCO with incident AF was 1.69 (CI = 1.38).

Normal-weight central obesity and other cardiovascular disease events

During a follow-up period, MI, AP, and stroke occurred in 2499 (0.1%), 26 507 (1.6%), and 13 448 (0.8%), respectively. HRs (95% CI) of NWCO for MI, AP, and stroke were in multivariable Cox regression analyses were 1.067 (0.905–1.258), 1.105 (1.058–1.154), and 1.059 (0.997–1.125), respectively (*Figure 2*).

Temporal changes in waist circumference and body mass index for development of heart failure and atrial fibrillation

After adjustment for age, sex, BMI, hypertension, diabetes mellitus, dyslipidaemia, cigarette smoking, alcohol consumption, and WC, the HRs of 1-year change in WC (per 10%) for HF or AF were 1.079 (1.032–1.127) and 1.177 (1.064–1.302), respectively. In contrast, the HRs of 1-year change in BMI (per 10%) for HF or AF were 0.968 (0.920–1.017) and 0.912 (0.810–1.026), respectively (*Figure 3*).

Sensitivity analyses

First, even when we defined NWCO as ≥ 85 cm for men or ≥ 90 cm for women, our main results did not change (see Supplementary material online, *Figure S1*). Second, we analyzed WC as a continuous

	Model 1	Model 2	Model 3	Forest plot
Heart failure				
Waist circumference per 5 cm	1.240 (1.227–1.254)	1.087 (1.075–1.100)	1.074 (1.058–1.089)	
Atrial fibrillation				
Waist circumference per 5 cm	1.400 (1.376–1.426)	1.127 (1.100–1.154)	1.169 (1.134–1.205)	

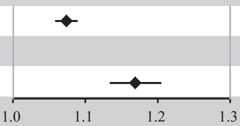


Figure 4 Waist circumference and the risk of heart failure and atrial fibrillation. Cox regression analyses; Model 1 included waist circumference per 5 cm (unadjusted model); Model 2 included the hazard ratios of waist circumference per 5 cm adjusted for age and sex; and Model 3 included the hazard ratios of WC per 5 cm adjusted for age, sex, body mass index, hypertension, diabetes mellitus, dyslipidaemia, cigarette smoking, and alcohol consumption.

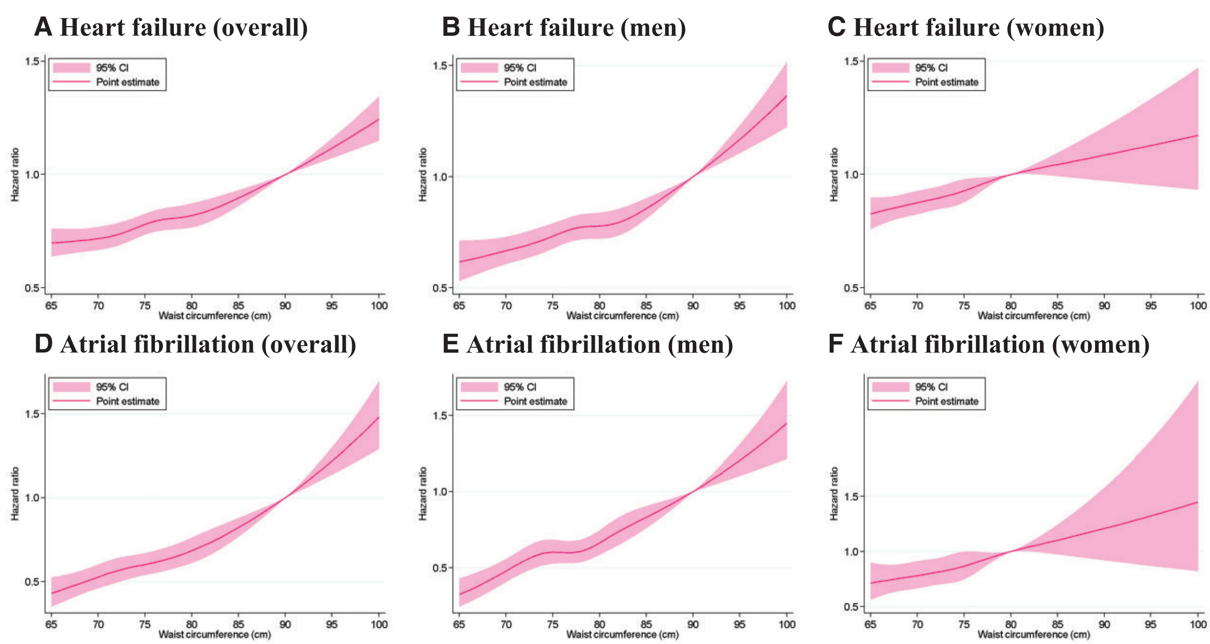


Figure 5 Restricted cubic spline. The relationship between waist circumference and the incidence of heart failure (overall) (*A*), heart failure (men) (*B*), heart failure (women) (*C*), atrial fibrillation (overall) (*D*), atrial fibrillation (men) (*E*), and atrial fibrillation (women) (*F*) was modelled using multivariable-adjusted spline regression models. We fitted three cubic spline models using three, four, and five knots, and the model with five knots was selected because it had the lowest Akaike's information criterion. Hazard ratios and 95% confidence intervals for incident heart failure and atrial fibrillation were calculated for each waist circumference value. We calculated hazard ratios after adjusting for covariates including age, sex, body mass index, hypertension, diabetes mellitus, dyslipidaemia, cigarette smoking, and alcohol consumption. CI, confidence interval.

variable, and found that HRs (95% CI) of WC per 5 cm for HF or AF were 1.074 (1.058–1.089) and 1.169 (1.134–1.205), respectively (*Figure 4*). Third, even we defined NWCO as BMI 18.5–24.9 kg/m^2 and WC $\geq$ 90 cm for men or $\geq$ 80 cm for women, our main results were unchanged (see Supplementary material online, *Figure S2*). Fourth, *Figure 5* presents the dose–response association of WC with the risk of HF and AF events. The relationship between WC and the incidence of HF and AF was modelled using multivariable-adjusted spline regression models. The risk of HF and AF increased linearly with WC. This linear association was present in both men and women. Fifth, NWCO was associated with a higher risk for developing HF and AF irrespective of sex and age (*Figure 6*). Sixth, higher body fat percentage calculated by the CUN-BAE formula increased the risk of developing HF and AF (see Supplementary material online, *Figure S3*).

Discussion

The present analysis of a large-scale health check-up and administrative claims database included approximately 1.7 million normal-weight people with no history of CVD, and we found that NWCO was associated with a higher risk for HF and AF. In addition, temporal changes in WC were associated with a higher risk of HF and AF in adults with normal weight. We confirmed the robustness of our results by conducting various sensitivity analyses.

We used the optimal definition of normal-weight and CO for Asians and examined the association between NWCO and the development of various CVD, including HF and AF. We examined the relationship of NWCO with incident CVD by adjusting for existing CVD risk factors to minimize the influence of confounders. To date, there have been few studies on CO in

		HR	95% CI	Forest plot
Heart failure				
Sex	Men	1.321	1.147–1.521	
	Women	1.092	1.040–1.146	
Age	≥ 50 years	1.080	1.021–1.142	
	< 50 years	1.130	1.053–1.212	
Atrial fibrillation				
Sex	Men	1.503	1.190–1.898	
	Women	1.203	1.062–1.363	
Age	≥ 50 years	1.297	1.144–1.470	
	< 50 years	1.121	0.925–1.358	

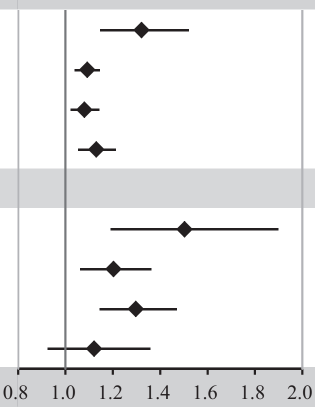


Figure 6 Subgroup analyses. Adjusted for age, body mass index, hypertension, diabetes mellitus, dyslipidaemia, cigarette smoking, and alcohol consumption in the subgroup analyses stratified by sex. Adjusted with age, sex, body mass index, hypertension, diabetes mellitus, dyslipidaemia, cigarette smoking, and alcohol consumption in the subgroup analyses stratified by age. HR, hazard ratio, CI, confidence interval.

normal-weight adults. To the best of our knowledge, this is the first report of an association between NWCO and the development of various types of CVD, including HF and AF, using a large-scale real-world dataset.

In a previous study, NWCO was reported to be associated with an increased risk of developing coronary artery disease.[4] In agreement with the previous study,[4] we also found that NWCO was associated with a greater risk of developing AP. Although the relationship of NWCO with incident MI did not reach statistical significance, it may be due to a small event number.

The result of the present study is generally concordant with preceding studies including our previous study,[4,15,32,33] but this study is distinguishable from other studies in that we found the robust association between NWCO and a greater risk for developing HF and AF in adults using a large-scale epidemiological dataset. Furthermore, we also found that 1-year increase in WC was associated with a higher risk of developing HF and AF even in normal-weight individuals, suggesting the potential prognostic importance of WC. Several possible mechanisms could be suggested to explain the results of the present study. First, abdominal obesity causes activation of neurohumoral factors such as the renin–angiotensin–aldosterone system and activation of the sympathetic nervous system,[34,35] which may contribute to the development of HF and AF. Second, various studies have reported that excess of visceral fat deposition was associated with cardiac and metabolic abnormalities, independently of the amount of total or subcutaneous fat accumulation.[36–38] Obesity including CO also causes structural changes, such as an increase in the left atrial size and volume, which contributes to the development of HF and AF.[39–41] Third, CVD risk factors (hypertension, diabetes, dyslipidaemia, and so on) are directly associated with the development of CVD, and this association has been reported in the NWCO.[11–14] Fourth, although BMI is an indicator of overweight/obesity, it cannot distinguish between fat and skeletal muscle mass. Therefore, the presence of NWCO despite a normal BMI reflects a high body fat percentage, and increased body fat percentage may predispose to cardiac dysfunction. These potential mechanisms would explain the results of this study. Further studies are needed to clarify the association between NWCO and the risk of incident HF, AF, and other CVD events.

The present study has several strengths. This study is the largest study examining the impact of NWCO on wide-range CVD outcomes. This large sample size enabled a multitude of sensitivity analyses which strengthened our primary findings. Further, the JMDC Claims Database has a high retention rate because of electronic linkage to administrative insurance records. On the other hand, we acknowledge several limitations to this study. In this study, we performed multivariable Cox regression analyses and further conducted a variety of sensitivity analyses to confirm the robustness of our results. However, given that the clinical backgrounds differed markedly between the groups, we could not eliminate the possibility of unmeasured confounders and residual bias. Furthermore, E values were relatively low in the present study, and therefore, our results should be interpreted cautiously. In addition, the Japanese Ministry of Health, Labour, and Welfare requests health care professionals involved in the Japanese health check-up system to follow the recommended protocol for WC measurements. However, in actual settings on a nationwide scale, adherence to the protocol may be limited. The JMDC Claims Database targets working-age individuals who are in employment. The target population of this study is primarily young and middle-aged working people, and therefore, we acknowledge the possibility of a 'healthy worker' bias in the present study. In addition, it has been reported that Asians are more likely to have visceral fat for a given BMI when compared with Europeans.[42,43] Therefore, studies on NWCO have been widely conducted in Asia.[11–13] Further investigation is needed to determine whether the results of this study can be generalized to other populations of races or ethnicity. Since the JMDC Claims Database is an administrative insurance database in Japan, we must consider the limitations of using administrative data for CVD diagnosis (in particular, overestimation of CVD events). For example, some physicians may register certain disease names only for reimbursement. If brain natriuretic peptide level is measured in a patient with possible HF, most physicians in Japan register 'suspected HF'. Therefore, we excluded participants whose disease code with 'suspect' to ensure validity. In addition, the validity of diagnostic codes in Japanese administrative data is generally high, and specificity has been reported to exceed 90%.[44] Furthermore, the incidence of CVD in the JMDC Claims Database used in our study is comparable to that in other epidemiological data in Japan.[45–47] Hence, the possible overestimation of CVD incidence does not seem to influence the present results to a significant degree. However, uncertainty remains regarding the accuracy of the diagnosis of HF, AF, MI, AP, and stroke, which is a weakness of this study. In the present study, when NWCO was defined as BMI 18.5–23.0 kg/m^2 and WC $\geq$ 90 cm for men or $\geq$ 80 cm for women, 96.6% of NWCO participants were female and only 3.4% of them were male (*Table 1*). On the other hand, when NWCO was defined as BMI 18.5–23.0 kg/m^2 and WC $\geq$ 85 cm for men or $\geq$ 90 cm for women, 95.1% of NWCO participants were male and only 4.9% of them were female (see Supplementary material online, *Table S1*). Thus, depending on the definition of CO, the male/female ratio of NWCO significantly varies. Hence, further studies are needed to validate the cut-off values of WC for the development of CVD by gender.

In conclusion, our analysis of a nationwide health check-up and administrative claims database demonstrated that NWCO was associated with a greater risk of developing HF and AF compared with normal-weight without CO. Although our results should be interpreted carefully because the participants in this study were mainly Japanese employed workers, the present study suggests that abdominal obesity should not be underestimated even in normal-weight individuals. Further studies using other independent datasets are needed to validate our results and to identify the optimal management strategy for people having NWCO.

Lead author biography

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Author contributions

H.K., K.K., H.I., A.O., and I.K. contributed to conception and design; K.U., H.I., A.O., S.M., Y.S., K.F., N.M., T.J., and H.Y. contributed to analysis of data; K.U., H.K., K.K., H.I., A.O., N.T., H.M., J.A., T.Y., and I.K. contributed to interpretation of data; K.U., H.K., A.O., N.T., H.M., K.N., and H.Y. contributed to the drafting of the manuscript; H.Y. and I.K. contributed to the final approval of the manuscript. All authors read the manuscript and approved the final version. All authors had access to all the data in the study. All authors verified the data and had final responsibility for the decision to submit for publication.

Data availability

The JMDC Claims Database used in this study is available for anyone who purchases it from the JMDC inc (https://www.jmdc.co.jp/en/index), which is a medical venture company in Japan.

Supplementary material

Supplementary material is available at *European Heart Journal Open* online.

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