Prospective Associations of Waist-to-Height Ratio With Cardiovascular Events in Postmenopausal Women: Results From the Women's Health Initiative

Kenneth Lo,[1,2,3] Qing Liu,[3] Matthew Allison,[4] Ying-Qing Feng,[1] Katie Chan,[5] Lawrence Phillips,[6] JoAnn Manson,[7] and Simin Liu[1,2,3]

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Clinicians and global health workers need valid, reliable, readily accessible, and cost-effective indicators to screen for individuals at risk for adverse cardiometabolic events in diverse populations, particularly in resource-poor settings. Waist-to-height ratio (WHtR) has recently emerged as one such promising index in assessing cardiovascular disease (CVD) risk. Meta-analyses of receiver operating characteristic curves showed that WHtR had better power than BMI and waist circumference (WC) in classifying CVD risk factors among adults and children (1,2). However, the role of WHtR in relation to the incidence of CVD has not been examined adequately in well-characterized populations of diverse ethnicities, nor has the strength of association been compared with conventional anthropometric indicators in high-quality prospective cohorts.

The national Women's Health Initiative (WHI) includes 161,808 postmenopausal women across 40 clinical centers in the U.S. who were enrolled at baseline from 1994 to 1998; occurrence of CVD events or death were determined during follow-up (3). Incident CVD events were adjudicated by trained physicians following a standardized protocol. The current study excluded participants with self-reported CVD or cancer at baseline and those who developed CVD or were lost to follow-up within 3 years of enrollment. WHtR, BMI, WC, and waist-to-hip ratio (WHR) were measured at baseline. Changes in body weight were examined using data collected at year 3 and baseline. WHtR was categorized as *1*) per 0.1 unit increment and treated as a continuous variable and *2*) "elevated," defined as >0.5 at baseline (1). Overweight and obesity were defined as BMI >25 and >30, respectively, while abdominal obesity was defined as WC >88 cm and/or WHR ≥ 0.85; all cutoff values were based on the World Health Organization guidelines (4). Changes in body weight were categorized into three groups: weight gain ≥ 5 kg, weight loss ≥ 5 kg, and weight change <5 kg.

The independent effect of each anthropometric index on the risk of CVD events was estimated using Cox models and testing the proportional hazard assumption using Schoenfeld residuals (no evidence for violation of assumption). Data analysis was conducted using R 3.6.0. Two models with different sets of covariates were fitted. Model 1 included age at baseline, region in the U.S., race/ethnicity, and WHI subcohort indicators (participating in the observational study or clinical trials). Model 2 additionally adjusted for education, family income, alcohol intake, smoking status, energy expenditure from recreational physical activity, dietary energy, total carbohydrate/sugar/protein intake, dietary glycemic index, use of hormone replacement therapy, history of diabetes/hypertension/high cholesterol requiring medication/hysterectomy at baseline, and family history of diabetes/stroke/heart attack. We additionally performed sensitivity analysis to assess the robustness of findings by excluding participants with incident cancer or diabetes. Last, we assessed potential interactions between WHtR and other anthropometric indexes.

Overall, 109,536 participants were included in the analysis with a median follow-up of 17.9 years. In the fully adjusted model, elevated WHtR (WHtR >0.5) was significantly associated with increased CVD risk (hazard ratio [HR] 1.29 [95% CI 1.22, 1.36]). Moreover, CVD risk increased 15% for every 0.1-unit increment of WHtR (HR 1.15 [1.11, 1.18]). BMI-classified overweight and obesity were significantly associated with CVD events (HR 1.16 [1.09, 1.23] and HR 1.19 [1.11, 1.27], respectively). Other significant associations with CVD events included WC >88 cm (HR 1.23 [1.17, 1.30]),

[1]Department of Cardiology, Guangdong Provincial People's Hospital, Guangdong Academy of Medical Sciences, Guangzhou, China
[2]Department of Endocrinology, Guangdong Provincial People's Hospital, Guangdong Academy of Medical Sciences, Guangzhou, China
[3]Center for Global Cardiometabolic Health and Departments of Epidemiology, Medicine, and Surgery, Brown University, Providence, RI
[4]Department of Family Medicine and Public Health, University of California, San Diego, La Jolla, CA
[5]Departments of Biomedical Sciences and Electronic Engineering, City University of Hong Kong, Hong Kong
[6]Division of Endocrinology, School of Medicine, Emory University, Atlanta, GA
[7]Division of Preventive Medicine, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA

Corresponding author: Kenneth Lo, kenneth_lo@brown.edu, or Simin Liu, simin_liu@brown.edu

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Table 1—Associations between anthropometric indexes and CVD events among participants in the WHI study (1994–2017)

	Primary analysis, HR (95% CI)[a]		Sensitivity analysis, HR (95% CI)[b]	
	Model 1 (N = 109,536)[c]	Model 2 (N = 82,370)[c]	Model 1 (N = 79,641)[c]	Model 2 (N = 59,835)[c]
WHtR				
>0.5	1.61 (1.54, 1.68)	1.29 (1.22, 1.36)	1.50 (1.42, 1.58)	1.29 (1.21, 1.38)
Per 0.1-increment	1.31 (1.29, 1.34)	1.15 (1.11, 1.18)	1.28 (1.24, 1.32)	1.17 (1.12, 1.21)
BMI				
Normal	Ref	Ref	Ref	Ref
Underweight	1.07 (0.83, 1.38)	1.10 (0.82, 1.48)	0.95 (0.70, 1.28)	1.03 (0.73, 1.45)
Overweight	1.27 (1.21, 1.33)	1.16 (1.09, 1.23)	1.24 (1.17, 1.32)	1.19 (1.11, 1.27)
Obese	1.58 (1.50, 1.67)	1.19 (1.11, 1.27)	1.47 (1.38, 1.57)	1.22 (1.12, 1.32)
Interaction with WHtR[d] (P value)		0.15		0.16
WC >88 cm	1.57 (1.50, 1.63)	1.23 (1.17, 1.30)	1.46 (1.39, 1.54)	1.23 (1.16, 1.31)
Interaction with WHtR[d] (P value)		0.02		0.02
WHR ≥0.85	1.61 (1.54, 1.67)	1.25 (1.19, 1.32)	1.50 (1.42, 1.58)	1.25 (1.17, 1.34)
Interaction with WHtR[d] (P value)		<0.01		<0.01
Weight change in kg[e]				
<5 kg	Ref	Ref	Ref	Ref
Loss ≥5 kg	1.28 (1.20, 1.37)	1.19 (1.10, 1.29)	1.30 (1.19, 1.41)	1.23 (1.11, 1.36)
Gain ≥5 kg	1.16 (1.09, 1.25)	1.03 (0.95, 1.12)	1.17 (1.07, 1.27)	1.05 (0.95, 1.16)
Interaction with WHtR[d] (P value)		0.84		0.52

[a]Adjusted for baseline diabetes status; excluded CVD and cancer cases at baseline. [b]Excluded diabetes and cancer cases at baseline and follow-up. [c]Covariates in model 1: age at baseline, region in the U.S., race/ethnicity, and subcohort indicators (participating in observational study or clinical trials). Model 2: covariates in model 1 plus alcohol intake, smoking status, energy expenditure from recreational physical activity, dietary energy, total carbohydrates/sugar/protein, dietary glycemic index, hysterectomy history, use of hormone replacement therapy, personal history of diabetes, personal history of hypertension, personal history of high cholesterol requiring medication, family history of diabetes, family history of stroke or heart attack, education, and family income. [d]P value for interaction with WHtR. [e]Due to missing anthropometric data at year 3 follow-up, 95,696 participants were included in model 1 and 72,451 participants were included in model 2; for sensitivity analysis, 69,240 participants were included in model 1 and 52,381 participants were included in model 2.

WHR ≥0.85 (HR 1.25 [1.19, 1.32]), and weight loss ≥5 kg (HR 1.19 [1.10, 1.29]). We also identified significant interactions of WHtR with WC or WHR. In the sensitivity analysis excluding women who developed diabetes or cancer during follow-up, the magnitude of associations did not change materially (Table 1).

In these postmenopausal women followed for an average of 18 years, WHtR >0.5, WC >88 cm, WHR ≥0.85, BMI >25, and weight loss ≥5 kg were each directly associated with greater risk of CVD, independent of other known CVD risk factors. Weight loss ≥5 kg in the first 3 years may indicate underlying subclinical disorders such as malnutrition/depletion of energy or protein reserves that may increase CVD risk (5). We also observed significant interactions of WHtR with WHR or WC but not with BMI in predicting CVD risk. BMI may be less predictive than WHtR because it is a less specific measure of abdominal adiposity (6). While WC, WHR, and WHtR capture specific changes in abdominal fat, WC is less sensitive to CVD risk, particularly in women with the same abdominal fat but different heights (2). WHtR appeared to overcome the limitations of conventionally used anthropometric indexes and could be readily integrated into both clinical and community settings for screening individuals with elevated CVD risk. To further evaluate the clinical utilities of WHtR, prospective studies of men and children are warranted.

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