Original Article

Is waist circumference a negative predictor of calcaneal bone mineral density in adult Chinese men with normal weight?

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Background: Our study aimed to evaluate the association between waist circumference (WC) and calcaneal bone mineral density (BMD) in adult Chinese men with normal weight.

Methods: This was a cross-sectional study. A total of 4,663 male participants aged 40 years or older residing in Ningde and Wuyishan, two cities locating in Fujian province of China, were randomly recruited between 2011 and 2012. Each participant should complete a standard questionnaire, undergo anthropometric and calcaneus quantitative ultrasound (QUS) measurements and have blood sample taken. Anthropometric, biochemical and calcaneal QUS parameters of 1,583 male participants with BMI ranging from 18.5 to 22.9 were included in the analysis. WC was divided into quartiles (Q1–Q4: <71, 71–75, 75–78, >78 cm). The relationship between WC (quartiles) and BMD was analyzed by multiple linear regression models.

Results: Mean age of the whole population was 54.6±9.8 years. Anthropometric and biochemical parameters were almost normal. Multiple linear regression analysis showed that BMD was negatively associated with increasing WC quartiles except for Q2 after adjusting for age and BMI, and this relationship remained negative except for Q2 when further adjustment was made for other covariates. Multiple logistic regression model also showed that the risks of osteopenia and osteoporosis increased across WC quartiles.

Conclusions: The present study indicated that WC was a negative predictor of calcaneal BMD in adult Chinese men with normal weight. It suggests that, even for the normal-weight Asian males, monitoring accrual of abdominal adipose is still helpful for the purpose of preventing bone loss.

Keywords: Waist circumference (WC); bone mineral density (BMD); normal-weight; cytokine; adipokine

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Introduction

Osteoporosis is a metabolic skeletal disease characterized by low bone mass and microarchitectural deterioration, which easily leads to increase in bone fragility and susceptibility to fracture (1). Generally, bone mineral density (BMD) is used as a valid parameter to evaluate bone profile, and dual energy X-ray absorptiometry (DXA) is the gold standard for diagnosing osteoporosis and predicting risk of fracture (2). However, compared with DXA, the advantage of calcaneal quantitative ultrasound (QUS) method is cheaper, more portable and less exposed to X-ray. Thus, QUS is considered as a priority in large community-based epidemiological researches.

More recently, the relationship between osteoporosis and obesity, especially for central obesity, has become a new research hotspot. However, the conclusions remain controversial. Fu *et al.* reported that increased central body fat was negatively associated with BMD in Chinese women (3). On the contrary, a study performed in Taiwan came to an opposite conclusion (4). Waist circumference (WC) is regarded as the most reliable surrogate of central obesity (5). Increased WC has been demonstrated to be associated with higher mortality independently of body mass index (BMI) (6). Literature indicates that BMI is a well-described determinant for osteoporosis, and lower BMI is associated with lower BMD (7,8). Moderately increased BMI is thought to protect against osteoporosis (9). Previous researches on the association between abdominal obesity and BMD were completed in overweight or obese population as assessed by BMI (4,10,11), but it remains unclear about the effect of increased WC on BMD in the population with normal BMI (normal weight).

In addition, the lifestyle, diet habit and definition of obesity for Asian population (12) are different from Caucasian population, and more surveys on osteoporosis were performed in women than men. The aim of the present study was to explore the relationship between WC (quartiles) and BMD at the calcaneus in Chinese male adult population with normal-weight (BMI: 18.5–22.9 kg/m^2).

Methods

Study design and population

This was a cross-sectional study. A total of 4,663 male participants aged 40 years or older residing in Ningde and Wuyishan, two cities locating in Fujian province of China, were randomly recruited between 2011 and 2012. Each should complete a questionnaire, undergo anthropometric and calcaneus QUS measurements and have blood sample taken. According to the definition of normal BMI for Asians by International Obesity Taskforce (13), the enrolled male residents with BMI ranging from 18.5 to 22.9 kg/m^2 were included in the analysis. Participants were excluded if they lacked data for necessary items or had been taken the following drugs over the past 2 weeks: thiazide diuretics, glucocorticoids, thiazolidinediones, statin, fibrate, non-steroidal anti-inflammatory drugs, calcium or vitamin D supplement, bisphosphonate, calcitonin, thyroxine, anti-thyroid or any kind of diet pills. Based on this exclusion criteria, 1,583 men were included in the analysis. The study protocol was approved by the ethics committee of Fujian Provincial Hospital and written informed consent was obtained from each participant.

Data collection

Each subject was interviewed by a well-trained interviewer to complete a structured questionnaire. The content of questionnaire referred to personal history of diseases and medication, diet and lifestyle. Participants were asked to provide necessary information about drugs they had taken over the past 2 weeks. The consumption of smoke and alcohol is classified into three levels: current (current consumption over the past 6 months), ever (past consumption for more than 6 months) and never. We regard the first two levels as the positive one.

Anthropometric measurements

A general physical examination was performed for each participant. Height and weight were measured when participants were wearing light clothing and no shoes. Both were measured to the nearest 0.1 kg and 0.1 cm, respectively. BMI was calculated as body weight (kg) divided by height squared (m^2). WC of each participant in a standing position was measured midway between the lateral lower rib margin and the superior anterior iliac crest. Blood pressure was measured by standard method.

Biochemical assay

A 75-g oral glucose tolerance test (OGTT) was administered after an overnight fast, and blood plasma was drawn at 0, 120 min for plasma glucose measurement. All serum lipids were determined in the fasting state. Fasting plasma

glucose (FPG), 2-hour plasma glucose (2hPG), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), triglycerides (TG), total cholesterol (TC) were measured using chemiluminescence methods with an autoanalyzer. Fasting serum insulin concentrations were determined with the Phadebas Insulin Test (Pharmacia, Uppsala, Sweden) by a radioimmunosorbent technique.

Calcaneal QUS assessment

QUS measurements of the calcaneus were assessed using Achilles Express ultrasound (GE Lunar Corp., Madison, WI, USA) in Wuyishan and Sahara (Hologic, Waltham, MA, USA) in Ningde, respectively. Instrument output parameters include BMD (T-score), estimated BMD (eBMD) (g/cm^2), broadband ultrasound attenuation (BUA) (dB/MHz) and speed of sound (SOS) (m/s). T-scores of BMD were calculated using the database of healthy Chinese youngsters in same study area as reference. The ultrasound parameters were measured twice on dominant calcaneus by a well-trained doctor and the mean value was used for analysis. Both QUS instruments were calibrated daily according to the manufacturer's recommendations before measurement.

Diagnostic criteria

Hypertension is defined as systolic blood pressure (SBP) ≥140 mmHg and/or diastolic blood pressure (DBP) ≥90 mmHg. Dyslipidemia was defined as self-reported current treatment with cholesterol-lowering medication or having 1 or more of the following: TC ≥5.17 mmol/L, TG ≥1.69 mmol/L, HDL-C ≤1.03 mmol/L, or LDL-C ≥3.38 mmol/L. Diabetes is diagnosed according to the American Diabetes Association (ADA) criteria (14): FPG ≥7.0 mmol/L or 2hPG ≥11.1 mmol/L. According to the World Health Organization (WHO) definition (15), osteoporosis is defined as a calcaneal BMD of >2.5 standard deviations (SDs) below the average peak BMD of young, healthy Chinese men in same study area (T-score <–2.5), and osteopenia is defined as a calcaneal BMD between 1 and 2.5 SDs below the peak BMD (–2.5< T-score <–1).

Statistical analysis

Variables are expressed as mean ± SD for continuous data or percentage for categorical variables. One-way ANOVA and non-parametric tests were used to compare the statistical difference between continuous variables, and the comparison of proportion was performed by chi-square test. WC was stratified by quartiles (Q1–Q4: <71, 71–75, 75–78, >78 cm). The first quartile was set as reference. Three multiple linear regression models were established to test the association between WC quartiles and calcaneal BMD. Model 1 was adjusted for age and BMI. Model 2 was further adjusted for smoke, drink and physical activity (PA). Lastly, covariates of diabetes mellitus (DM), dyslipidemia, hypertension, product of bean, milk and insulin were added into Model 3 on basis of Model 2 in order to investigate the effects of disease, diet and insulin on BMD. Adjusted for the same confounding factors, another logistic regression model was established to identify the risk of osteopenia and osteoporosis across WC quartiles. SPSS (version 19.0 for windows, SPSS Inc., Chicago, IL, USA) was used for statistical analysis. P<0.05 was considered significant (two-tailed).

Results

Descriptive statistics

As shown in *Table 1*, mean age of the whole population was 54.6±9.8 years. Anthropometric and biochemical parameters of participants in the present study were almost normal. The proportion of smokers was nearly 1.6 times as much as that of drinkers. PA was prevalent, and more than 60% of participants had ever taken part in activities.

The baseline characteristics of men across WC quartiles were presented in *Table 2*. Compared with men in the lower quartile, those in the higher quartile were more likely to have significantly higher height, weight, BMI and higher prevalence of PA, DM, dyslipidemia and hypertension, but less likely to smoke. There were no significant differences in eBMD, BUA, SOS, serum insulin, drink, product of bean and milk across quartiles.

Multiple regression analysis

Standardized coefficients of WC for calcaneal BMD by multiple linear regression analysis were shown in *Table 3*. In Model 1, adjustment was made for age and BMI, there was a significant linear relationship between WC quartiles and calcaneal BMD except for quartile 2 (71–75 cm). BMD was negatively associated with WC. Model 2 was further adjusted for smoke, drink and PA on basis of Model 1. Standardized coefficients of Model 2 were attenuated

Table 1 Characteristics of men at baseline

Characteristics	Value (N=1,583)
Age (years)	54.6±9.8
Height (cm)	163.8±6.5
Weight (kg)	56.8±5.5
WC (cm)	75.2±6.2
BMD (T-score)	−0.2±1.4
eBMD (g/cm^2)	0.52±0.13
BUA (dB/MHz)	75.5±17.9
SOS (m/s)	1,548.3±33.9
BMI (kg/m^2)	21.1±1.2
FPG (mmol/L)	5.6±1.3
2hPG (mmol/L)	6.8±3.3
TC (mmol/L)	4.93±0.97
TG (mmol/L)	1.44±1.12
HDL-C (mmol/L)	1.45±0.39
LDL-C (mmol/L)	2.80±0.77
SBP (mmHg)	131.9±18.2
DBP (mmHg)	76.0±10.5
Insulin (μU/mL)	8.1±5.2
Smokers (%)	62.1
Drinkers (%)	39.2
PA (%)	61.3

Data were presented as mean ± SD. SD, standard deviation; WC, waist circumference; BMD, bone mineral density; eBMD, estimated bone mineral density; BUA, broadband ultrasound attenuation; SOS, speed of sound; BMI, body mass index; FPG, fasting plasma glucose; 2hPG, 2-hour plasma glucose; TC, total cholesterol; TG, triglycerides; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure; DBP, diastolic blood pressure; PA, physical activity.

slightly but remained significant. The same situation was also present in the Model 3 after adjusting for DM, dyslipidemia, hypertension, product of bean, milk and insulin. There was no significant difference between BMD and quartile 2 of WC in all three Models.

As shown in *Figure 1*, with Q1 as reference, the fully-adjusted odds ratios (ORs) and 95% confidence intervals (CIs) of osteopenia were 1.188 (0.858, 1.645) for Q2, 1.479 (1.041, 2.100) for Q3, and 1.913 (1.299, 2.816) for Q4, and corresponding results of osteoporosis were 1.493 (0.724, 3.078) for Q2, 2.214 (1.044, 4.695) for Q3, and 2.908 (1.247, 6.779) for Q4. Apparently, a linear trend was observed that higher fully-adjusted OR of osteopenia or osteoporosis was with higher WC quartile. After the same covariates as in the Model 3 of *Table 3* were controlled, the statistical difference was only present in quartile 1, 3, and 4, but not in quartile 2 in both logistic regression models.

Discussion

In the present study, a significant relationship between WC quartiles and calcaneal BMD was present after adjusting for a series of covariates in adult men with normal weight. Our data indicated that, for the normal range of BMI, WC had a significant negative association with calcaneal BMD in adult Chinese men. Correspondingly, the risks of osteopenia and osteoporosis also correlated with WC quartiles positively.

Although several epidemiological researches (3,4,10,11) have documented that abdominal fat as measured by different anthropometric parameters is a strong predictor of bone mass, in this area, previous analyses focused more on obese or overweight population. Generally, a higher BMI or weight was thought to protect against bone loss by activating osteoblasts in response to mechanical load and muscle stress (9,16). In contrast, slender figures with low BMI were more likely to suffer osteoporosis and bone loss (17). Therefore, to explore the effect of abdominal fat on bone mass with minimal influence of BMI, a population with normal BMI was defined as the target population in our study. It is the first research to report the negative association between WC and BMD in Asian normal-weight males.

For researches about the effect of abdominal fat on bone, previously, most focused more on the population with whole spectrum of weight or female subjects only. A large cross-sectional survey conducted in Korean population (18), which included obese and overweight participants, demonstrated that WC was negatively correlated with BMD after adjusting for age and weight in both male and female subjects. Even WC was related to BMC independently of fat mass. Study on overweight and obese postmenopausal women in Turkey had conflicting conclusions in different sites, a significant positive association was observed between WC and total hip BMD, whereas WC was negatively associated with BMD in non-weight-bearing site, such as forearm (19). Likewise, the negative associations between abdominal fat and bone mass were also documented in other

Table 2 Baseline characteristics of participants by WC quartiles in men

Characteristics	Q1 (<71 cm)	Q2 (71–75 cm)	Q3 (75–78 cm)	Q4 (>78 cm)	P value
N	473	383	383	344	–
Age (years)	54.8±9.6	53.4±9.4	54.7±10.2	55.7±9.8	<0.05
Height (cm)	161.4±5.8	163.0±6.5	164.6±6.0	166.6±6.2	<0.001
Weight (kg)	52.8±4.2	55.8±4.9	58.4±4.7	60.7±5.0	<0.001
BMI (kg/m^2)	20.3±1.0	21.0±1.1	21.5±1.0	21.8±0.9	<0.001
BMD (T-score)	–0.2±1.4	–0.1±1.5	–0.3±1.4	–0.3±1.5	<0.05
eBMD (g/cm^2)	0.52±0.13	0.55±0.14	0.51±0.13	0.51±0.14	0.300
BUA (dB/MHz)	74.8±18.3	77.6±17.2	75.2±16.7	74.7±19.5	0.693
SOS (m/s)	1,549.6±34.8	1,552.6±32.5	1,545.1±33.0	1,546.0±35.3	0.444
WC (cm)	68.5±3.3	73.4±1.1	77.0±0.8	82.5±6.2	<0.001
Insulin (μU/mL)	7.8±5.6	7.8±7.3	8.4±5.3	8.4±5.9	0.323
Smoker (%)	68.3	62.1	59.5	56.4	<0.01
Drinker (%)	37.0	36.6	42.0	41.9	0.221
PA (%)	56.4	59.3	63.4	67.7	<0.01
Product of bean (%)	77.4	76.8	76.5	78.8	0.889
Milk (%)	50.1	54.8	51.7	52.9	0.572
DM (%)	5.5	8.4	10.4	14.0	<0.001
Dyslipidemia (%)	44.6	53.3	63.2	70.6	<0.001
Hypertension (%)	22.4	31.3	32.4	33.4	<0.01

Data were shown as mean ± SD for continuous variables or percentage for categorical variables. SD, standard deviation; WC, waist circumference; BMI, body mass index; BMD, bone mineral density; eBMD, estimated bone mineral density; BUA, broadband ultrasound attenuation; SOS, speed of sound; PA, physical activity; DM, diabetes mellitus.

studies by alternatives instead of WC (3,10,11,20). However, results were also controversial. In a community-based study on elderly Taiwanese women, WC was correlated positively with lumbar, hip and femoral neck BMD (4). Another research focusing the relations of subcutaneous and visceral fat in healthy females also indicated that WC was positively related with bone (21). Compared with pre-existing researches, the current study was confined to the normal-weight adult Chinese males, which is expected to give some clues for their bone healthcare.

As previously reported, WC is frequently employed as a surrogate for abdominal adiposity and it contains abdominal subcutaneous and visceral fat depots (21,22). Increased WC means that abdominal fat including subcutaneous and visceral fat increases proportionally. Increment of abdominal adipose not only stimulates osteoblast differentiation by adding a mechanical load to bone, but also releases adipocyte-derived and pro-inflammatory cytokines to regulate bone metabolism. Several potential mechanisms probably account for our findings. Firstly, obesity and osteoporosis have been proven to share the same pathogenesis of chronic inflammation (23). As a marker of systemic inflammation, C-reactive protein (CRP) is elevated in abdominal obesity (24) and positively correlates with WC (25). Likewise, adipose tissue also produces other pro-inflammatory cytokines (26), such as tumor necrosis factor-α (TNF-α) and interlukin-6 (IL-6). These upregulated cytokines promote osteoporosis by stimulating osteoclast activity and bone resorption through the regulation of RANKL/RANK/OPG pathway (23,27). In addition, adipocyte and osteoblast arise from the same multipotential mesenchymal stem cell (28). The stem cell

Table 3 Standardized coefficients of WC quartiles for calcaneal BMD by multiple regression analysis in Chinese men

Model	Q1 (<71 cm)	Q2 (71–75 cm)	Q3 (75–78 cm)	Q4 (>78 cm)	P value for trend
Model 1					<0.001
β	–	–0.025	–0.131	–0.140	
P value	–	0.412	<0.001	<0.001	
Model 2	–				<0.001
β	–	–0.021	–0.123	–0.129	
P value	–	0.483	<0.001	<0.001	
Model 3	–				<0.001
β	–	–0.021	–0.119	–0.124	
P value	–	0.494	<0.001	<0.001	

Values of β are standardized regression coefficients. Standardized coefficients for calcaneal BMD by WC with the 1st quartile as reference. Model 1 was adjusted for: age and BMI; Model 2 was further adjusted for smoke, drink and PA on basis of Model 1; Model 3 was further adjusted for DM, dyslipidemia, hypertension, product of bean, milk and insulin on basis of Model 2. BMD, bone mineral density; WC, waist circumference; BMI, body mass index; PA, physical activity; DM, diabetes mellitus.

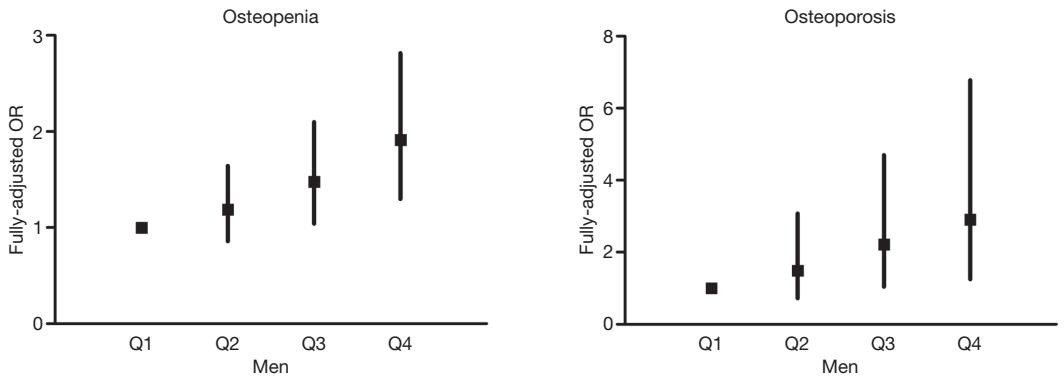

Figure 1 Fully-adjusted odds ratios and 95% confidence intervals (CIs) of osteopenia and osteoporosis by quartiles of WC in Chinese men. Q1 was set as reference. The ORs and 95% CIs were estimated by multiple logistic regression model adjusted for age, BMI, smoke, drink, PA, DM, dyslipidemia, hypertension, product of bean, milk and insulin. Significant difference (P<0.05) was found in Q1, Q3 and Q4, but not in Q2. WC, waist circumference; OR, odds ratio; BMI, body mass index; PA, physical activity; DM, diabetes mellitus.

could differentiate into adipocyte or osteoblast equally. This balance is maintained by a series of common factors, such as PPARγ, Wnt, TGF-β, leptin, and estrogen (29). The imbalance between osteogenesis and adipogenesis is controlled by PPARγ (30), which predicts that increasing abdominal adipose may increase adipocyte differentiation and fat accumulation but decrease osteoblast differentiation and bone formation (osteoblastogenesis) (23). Thirdly, abdominal adipose tissue is also an organ to release the adipocyte-derived cytokines, especially for leptin and adiponectin. Leptin, which stimulates inflammatory and platelet response (31), has detrimental effect on bone in a mouse model (32). Adiponectin, another adipokine, inhibits osteoclastogenesis, reduces bone resorption, and increases bone mass (33). In contrast with leptin, adiponectin suppresses inflammatory responses by inhibiting TNF-α-induced NF-κB activation (34). Generally, it reduces in obese population. For the relation with abdominal adipose, Zhuo *et al.* reported that adiponectin was inversely correlated with WC in Chinese population (35), and another study also found that it was inversely associated with visceral fat (36). Fourthly, the effect of testosterone on bone metabolism should not be ignored. With age increasing, serum testosterone concentration declines in men (37),

which is significantly associated with bone loss (38). Moreover, the reduced total and free testosterones were related with higher WC (39). It may suggest that WC should be an anthropometric measurement to predict endogenous testosterone levels preferably.

Only 27% and 38% of total body weight in white men and women is attributable to fat mass, respectively (40). Since abdominal fat is a part of total fat mass, that means the proportion of abdominal fat among body weight is small. Although increased body weight protects against bone loss, weight-associated gravitational forces due to increased fat mass may be insufficient to explain the impact of fat mass on bone. It is notable that positive relationship between body weight and bone mass is conditioned by body composition parameters (lean mass and fat mass). Lean mass quite matters in this relation instead of fat mass. For example, increase in lean mass is associated with higher bone mineral content at femoral neck in men, and significance disappears after adjusting for lean mass, indicating the principal role of lean mass in the maintenance of bone mass (41). In addition, correlation between lean mass and BMD is higher than that between fat mass and BMD in adult men (42). Note that, our focus is normal-weight Asian males, the positive effect of weight on BMD must be much less than overweight or obese population and is further statistically removed by regression model (Model 1 showed that result remained significant independently of age and BMI). Its beneficial effect on bone metabolism may be counteracted by the comprehensively detrimental effects of increased pro-inflammatory cytokines and leptin, reduced adipokines and declining age-dependent testosterone. However, we didn't measure these cytokines or hormones in the current study. From this viewpoint, the raised cytokine-hormone hypothesis perhaps explains the results partially and remains to be verified by further investigations.

The strength of the present study is that the amount of sample was large. In this population-based research, a total of 1,583 male participants were included in the final analysis. Application of calcaneal QUS ensured that data about bone status could be obtained in the large community-based epidemiological survey. Additionally, we used WC as the predictor of abdominal fat to explore the association with BMD rather than others, because it was easy to be measured precisely and conveniently. More importantly, except for the generally accepted confounders, the other confounding factors including chronic diseases, diet and fasting insulin, which may disturb the valid relation of WC with BMD, were also controlled.

Our study had some limitations as well. Firstly, the research was performed in the adult Chinese male population with normal BMI. The result can't be extrapolated to women or other ethnicities. Secondly, the cross-sectional study design limited our ability to prove causality. Thirdly, DXA as the gold standard for measuring BMD was not used in the present study, which may lower the precision of BMD measurement to some extent. The reason why we used QUS is because this is a community-based epidemiological survey and QUS is more convenient and suitable for us to do research than DXA. Fourthly, we didn't determine the concentrations of CRP, pro-inflammatory cytokines, leptin, adiponectin and testosterone, further studies should be done to complete the measurements.

In conclusion, WC is a negative predictor of calcaneal BMD in the adult Chinese men with normal weight. Correspondingly, the risks of osteopenia and osteoporosis also increased across WC. It is the first time to investigate the relationship between WC and BMD in normal-weight Asian males. It is implicated that, even for the normal-weight adult men, caution of increased WC is still meaningful for the prevention of osteoporosis.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The study protocol was approved by the ethics committee of Fujian Provincial Hospital (No. 2011011) and written informed consent was obtained from each participant.

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