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Original Article

Waist circumference percentile thresholds for identifying adolescents with insulin resistance in clinical practice

Lee JM, Davis MM, Woolford SJ, Gurney JG. Waist circumference percentile thresholds for identifying adolescents with insulin resistance in clinical practice.
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Abstract: We formally evaluated waist circumference (WC) percentile cutoffs for predicting insulin resistance (IR) and whether different cutoffs should be used for adolescents of different race/ethnicities. Analysis was performed for 1575 adolescents aged 12–18 yr from the National Health and Nutrition Examination Survey 1999–2002. Adolescents were classified as having IR if they had a homeostasis model assessment-insulin resistance level, a validated measure of IR, of >4.39, and WC percentile was classified according to previously published universal (all races combined) and race/ethnicity-specific WC percentile cutoffs. Receiver operating characteristic curves for predicting IR were constructed comparing the race/ethnicity-specific vs. universal WC percentile cutoffs, and area under the curve (AUC) was calculated. Comparing universal with race/ethnicity-specific WC percentiles, there were no significant differences in AUC for Black, Mexican-American, or White adolescents. Because race/ethnicity-specific thresholds did not discriminate better than universal WC thresholds, universal WC thresholds may be used effectively to identify adolescents with IR in primary care practices. A WC ≥75th or ≥90th percentile for all race/ethnicities combined would be appropriate to apply in clinical practice for identification of adolescents with IR, a risk factor for development of type 2 diabetes.

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Visceral adiposity is associated with increased risk for a variety of chronic diseases, including hypertension, dyslipidemia, metabolic syndrome, and type 2 diabetes (1). Waist circumference (WC) has been shown to be the best anthropometric indicator of visceral obesity for both adults (2) and children (3) and in adults predicts risk for development of type 2 diabetes beyond traditional cardiometabolic risk factors such as body mass index (BMI), blood pressure, and lipid levels (4).

Based on recommendations from the National Heart Lung and Blood Institute and the American Heart Association, excess WC is defined by a WC >102 cm for adult men and >88 cm for adult women (5). Because WC normally increases from early childhood through adolescence related to the dynamics of childhood growth and development, absolute WC thresholds are not applicable to a pediatric population. One recent consensus panel recommended that a WC percentile cutoff of 90th percentile adjusted for age and sex be used in children (6), but we are unaware of any studies that have validated this WC cutoff using physiologic outcome measures among children.

Insulin resistance (IR) is thought to play a critical role in the pathogenesis of type 2 diabetes among children (7). Recent studies have suggested that WC is an independent predictor of IR, as measured by the

homeostasis model assessment-insulin resistance (HOMA-IR) and gold standard insulin clamp studies (8, 9). Measurement of WC has therefore been advocated for targeting high-risk individuals with IR for diabetes screening and diabetes prevention interventions in both the clinical and the research settings (10). Although one adult study has validated WC cutoffs for predicting IR among adults (11), no such study exists in children.

Because WC may serve as a simple, inexpensive, and convenient tool for identifying children with IR in pediatric clinical practice, we wished to formally evaluate various WC percentile cutoffs for predicting IR in a nationally representative, race/ethnically diverse, population-based sample of adolescents. We also sought to determine whether WC percentile cutoffs should be different for adolescents of different race/ethnicities as some studies have suggested that the relation between visceral fat and IR may be differentially modulated by race/ethnicity (12).

Methods and procedures

Study design

The National Health and Nutrition Examination Survey (NHANES) is a cross-sectional, nationally representative examination study of the US civilian non-institutionalized population that uses a stratified multistage probability sampling design (13) and oversamples non-Hispanic Black and Mexican-American individuals to provide reliable statistical estimates for these subpopulations. Of the 4339 adolescents aged 12–18 yr from NHANES 1999–2002, we analyzed data from the subsample of 1647 adolescents who had insulin and glucose measures after fasting for a minimum of 8 h. We excluded participants who had self-reported diabetes ($n = 4$), were pregnant ($n = 26$), used medications that interfered with glucose metabolism (corticosteroids, androgens, and antihypoglycemic medications; $n = 25$), or had missing WC measurements ($n = 15$). In this sample, unweighted estimates of glucose tolerance status were classified as normal glucose tolerance (glucose < 100; $n = 1389$), impaired fasting glucose (IFG) ($100 \leq$ glucose < 126; $n = 186$), and diabetes (glucose ≥ 126; $n = 2$). We chose to include adolescents with either normal fasting glucose or IFG for this analysis ($n = 1575$) because studies have shown that the HOMA-IR is a valid surrogate measure of IR for non-diabetic children (14).

When the 1575 adolescents included in the sample were compared with those not included from the entire sample of adolescents, there were no significant statistical differences in gender (52.9 vs. 50.0%, $p = 0.20$) or mean age (14.99 vs. 14.97, $p = 0.80$), although they did have a slightly higher mean BMI z-score (0.49 vs. 0.38, $p = 0.03$).

Anthropometric measures and laboratory procedures

A detailed description of the procedures for measuring WC in subjects in NHANES by trained examiners has been previously published (15). Procedures regarding assessment of fasting status, blood collection, sample processing, and analysis of insulin and glucose have also been described in detail in a previous publication (16).

Data analysis

As is standard, HOMA-IR was calculated by dividing the product of insulin (μU/mL) and glucose (mmol/L) by 22.5. In our previous work using the same insulin and glucose assays, we defined adolescents with a HOMA-IR >4.39 as having IR, which was defined by the upper 2.5 percentile HOMA-IR for normal-weight adolescents with normal fasting glucose (representing 2 SD from the mean) (16). Our selected threshold was felt to be reasonable because it was derived from a standard method for determining abnormal values within a population (16). Although we had evaluated other definitions of IR, we did not select them as they were based on adult studies (11), non-validated measures of IR (17), or a definition of IR based on distribution of HOMA-IR values for the entire adolescent population, which included large numbers of obese children (16).

Age-, sex-, and race/ethnicity-specific WC percentiles (10th, 25th, 50th, 75th, and 90th) were used in this study to be consistent with those generated from a nationally representative sample previously published by Fernandez et al. (18).

For the description of the overall sample, comparisons were made using *t*-tests and chi-squared analysis. Receiver operator characteristic (ROC) curves were constructed using these previously published universal vs. race/ethnicity-specific WC percentile cutoffs to predict IR for each of the three race/ethnicity groups. ROC analysis is a formal method of assessment for considering trade-offs between sensitivity and specificity at various test cutoffs or thresholds. Area under the curve (AUC) can be calculated from an ROC curve, which is a measure of diagnostic accuracy, with 0.5 indicating a test with no test discrimination value and 1.0 indicating a test with perfect discrimination (19). We performed statistical comparisons of AUC using universal (all races combined) vs. race-specific WC percentiles for each race/ethnicity group (White, Black, and Mexican-American) using the roccomp function, which tests the equality of two or more ROC areas. Of the 1575 adolescents in the sample, 114 were classified as 'other' race or 'other Hispanic' (not Mexican-American). One final ROC curve was constructed using universal WC percentiles for predicting IR for

adolescents or all races, including adolescents from the three racial/ethnic groups and adolescents of 'other' race/ethnicity.

Using similar methods as our previous study (16), we also calculated HOMA-IR cutoffs for each race/ethnicity group [>2 SD above the mean for Whites (4.39), Blacks (5.71), and Mexican-Americans (4.69)]. In separate analyses, we constructed ROC curves comparing universal vs. race/ethnicity-specific WC percentiles for predicting IR using the race/ethnicity-specific HOMA-IR cutoffs.

All statistical analyses were performed using STATA 9.0 (Stata Corporation, College Station, TX, USA), which allows application of appropriate sampling weights to adjust for the complex multicluster sample design, including oversampling, subsampling of adolescents with fasting glucose and insulin, and for non-response. Therefore, the fasting subsample is a nationally representative sample. Taylor series linearization was used for variance estimation.

Results

Table 1 presents the demographic characteristics of the study population, revealing no significant differences in gender or age across the race/ethnicity groups. A higher percentage of Black and Mexican-American adolescents were overweight or obese and had IR compared with White or adolescents of other race.

Figures 1–3 provide a comparison of ROC curves for predicting IR using universal vs. age- and sex-adjusted WC percentiles for each of the racial/ethnic groups. There were no significant differences in AUC for Black adolescents (0.83 for universal vs. 0.82 for race specific, $p = 0.21$), Mexican-American adolescents (0.84 for universal vs. 0.85 for race specific, $p = 0.26$), or White adolescents (0.90 for universal vs. 0.90 for race specific, $p = 0.64$).

Separate analyses comparing ROC curves using race-specific HOMA-IR cutoffs resulted in essentially the same results as that of the single cutoff of 4.39, showing no significant differences in AUC for Black (0.82 for universal vs. 0.80 for race specific, $p = 0.09$), Mexican-American (0.84 for universal vs. 0.85 for race specific, $p = 0.26$), or White adolescents (0.88 for universal vs. 0.89 for race specific, $p = 0.63$) (data not shown).

Figure 4 provides the ROC curve for predicting IR using age- and sex-adjusted universal WC thresholds among adolescents of all races. Sensitivity was maximized at the lowest WC thresholds, and specificity was maximized at the highest WC thresholds. So that the thresholds may be easily referenced, table 2 presents the age- and sex-specific universal WC thresholds for the 75th and 90th percentiles, which were previously published by Fernandez et al. (18).

Discussion

In our population-based, nationally representative sample of US adolescents, we found that selected race- and ethnicity-specific WC percentiles did not discriminate better than universal WC percentiles for identifying adolescents with IR. Therefore, we suggest the use of universal WC percentiles rather than race- and ethnicity-specific WC percentiles for evaluating WC in adolescents. This practice would simplify the use of IR screening in clinical settings vs. considering separate cutoff points by race/ethnicity.

Table 1. Characteristics of the study population

Characteristics	Black (n = 440) (%)	Mexican-American (n = 592) (%)	White (n = 429) (%)	'Other' race (n = 114) (%)	p-Value
Gender					0.58
Male	52.8	55.2	51.3	47.7	
Female	47.2	44.8	48.7	52.3	
Age (yr)					0.34
12	17.0	15.6	13.8	16.9	
13	18.0	16.7	13.5	18.7	
14	13.4	13.8	14.1	8.7	
15	11.5	10.7	15.9	7.8	
16	14.6	15.1	13.3	17.6	
17	15.1	13.3	17.0	16.8	
18	10.4	14.8	12.4	13.5	
Weight status					0.01
Normal (BMI < 85th %)	59.0	62.6	75.0	72.7	
Overweight (85th % ≤ BMI < 95th %)	18.9	16.2	11.5	12.6	
Obese (BMI ≥ 95th %)	22.1	21.2	13.5	14.7	
% IR[a]	18.9	16.8	9.4	12.0	0.001

BMI, body mass index; HOMA-IR, homeostasis model assessment-insulin resistance; IR, insulin resistance.
n indicates the unweighted number of subjects. Percentages shown are weighted percentages.
[a]IR was defined by a HOMA-IR >4.39 (the upper 2.5 percentile HOMA-IR for normal-weight adolescents with normal fasting glucose and representing 2 SD from the mean) (16).

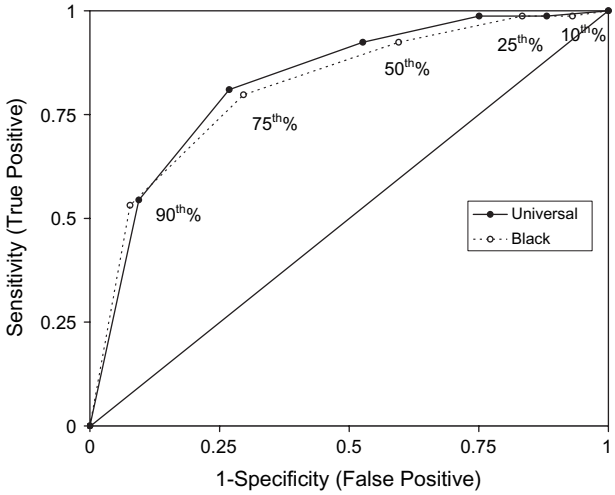

Fig. 1. Comparison of receiver operator characteristic curves for predicting insulin resistance using universal vs. race-specific age- and sex-adjusted waist circumference percentiles among Black adolescents (p = 0.21) (n = 440).

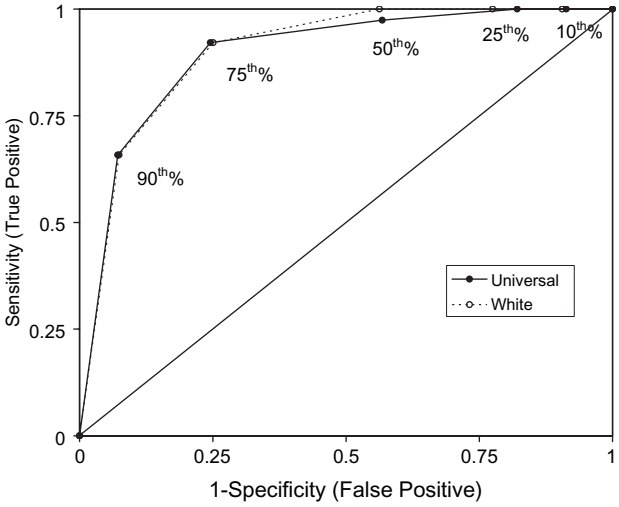

Fig. 3. Comparison of receiver operator characteristic curves for predicting insulin resistance using universal vs. race-specific age- and sex-adjusted waist circumference percentiles among White adolescents (p = 0.64) (n = 429).

Fernandez et al. previously estimated age-, race-, and sex-specific WC percentiles for adolescents and adolescents aged 2 through 18 yr based on NHANES III data (18). However, the various WC percentiles were not related to any physiologic outcomes. Our study is therefore unique in that we compared these WC percentiles with a specific physiologic outcome – IR – related to future risk of type 2 diabetes. Furthermore, we performed formal comparison of universal vs. race- and ethnicity-specific WC percentiles for each of the sample subgroups by plotting ROC curves and calculating AUC. We found no meaningful differences in test performance, even after using race/ethnicity-specific definitions of IR in separate analyses.

In another study, Katzmarzyk used data from the Bogalusa Heart Study to evaluate the performance of WC percentile thresholds for identifying individuals with cardiovascular risk factor clustering (20). They concluded that the optimal WC thresholds for identifying individuals was at the 56th and 50th percentiles for White and Black male subjects and at the 57th and 52nd percentiles for White and Black female subjects, respectively. However, these race-specific WC percentiles were not based on a nationally representative sample, and they did not compare ROC curves for universal vs. race-specific WC percentiles.

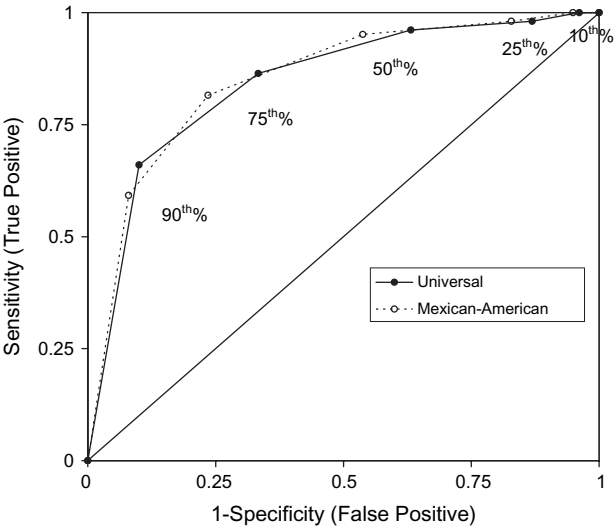

Fig. 2. Comparison of receiver operator characteristic curves for predicting insulin resistance using universal vs. race-specific age- and sex-adjusted waist circumference percentiles among Mexican-American adolescents (p = 0.26) (n = 592).

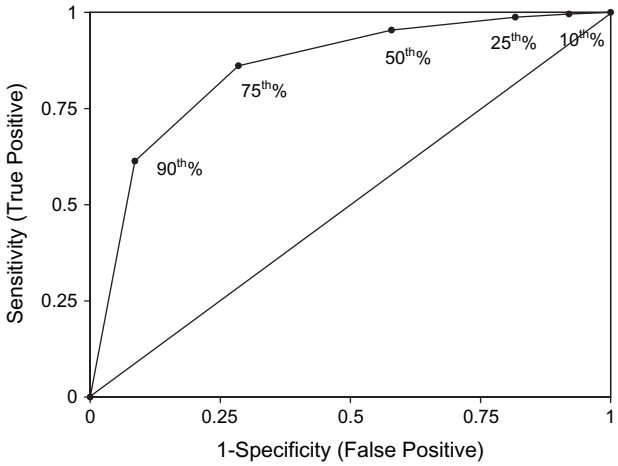

Fig. 4. Receiver operator characteristic curve for predicting insulin resistance using universal age- and sex-adjusted waist circumference percentiles for all races combined, including White, Black, Mexican-American, and adolescents of 'other' race/ethnicity (n = 1575).

Table 2. Age- and sex-specific waist circumference (cm) thresholds designating the 75th and 90th percentiles for adolescents of all races by Fernandez et al. (18)

	Boys		Girls	
Age (yr)	75th %	90th %	75th %	90th %
12	74.3	84.8	73.5	82.7
13	76.8	88.2	75.9	85.8
14	79.4	91.6	78.3	88.8
15	81.9	95	80.7	91.9
16	84.5	98.4	83.1	94.9
17	87	101.8	85.5	98
18	89.6	105.2	87.9	101

Studies have shown that given the same degree of adiposity, Black youths have higher levels of IR compared with their White counterparts (21, 22), which may explain why Black adolescents are thought to be at greater risk for development of type 2 diabetes. Given these findings, one might postulate that there are race-specific differences in the relationship between visceral fat and IR, necessitating the use of race-specific WC percentiles. However, studies have failed to demonstrate that the relationship between visceral fat and IR is differentially modulated by race. Bacha et al. evaluated the association of high levels of visceral adipose tissue as measured by abdominal computerized tomography (CT) scan with insulin sensitivity, measured by hyperinsulinemic–euglycemic clamp, among 50 obese Black and White adolescents (12). When children from both racial groups were divided into groups with low and high visceral fat, Black and White children with high visceral fat demonstrated significant reductions in peripheral insulin sensitivity to an equal degree (~38% decrease for both groups). Gower et al. also evaluated for racial differences in the association between visceral fat, measured by abdominal CT, and insulin sensitivity, measured by the frequently sampled intravenous glucose tolerance test, in a group of 61 Black and White children. They found that there were no significant differences in the association between visceral fat and insulin sensitivity by race (23). The findings from both of these studies using more sophisticated measurement tools for visceral fat and IR lend support to our finding that universal WC percentiles may be applied to the entire population of adolescents, although further validation of these WC percentiles in other populations may be warranted before their inclusion in routine clinical practice.

The International Diabetes Federation (IDF) designated a threshold of 90th % as one of the criteria for the metabolic syndrome among children and adolescents (6). However, when the IDF created a new definition of the metabolic syndrome, they acknowledged that their definition was created based on a number of studies that empirically used the 90th WC percentile as a cutoff and suggested that further studies could help clarify whether this represents an appropriate threshold for defining abnormality.

The selection of an optimal threshold value depends on a number of factors, including the prevalence of IR, the costs of various approaches to managing adolescents with IR, and possible negative consequences of falsely identifying adolescents with IR. Using the 90th % WC threshold would ensure a high level of specificity (91.4%) but at the expense of a lower sensitivity (61.3%). As an example, WC could be utilized in the primary care setting as a simple non-invasive screening tool for determining which adolescents likely have IR and should therefore undergo diagnostic testing for carbohydrate abnormalities (prediabetes or type 2 diabetes). In this case, the 75th % WC threshold may represent a more reasonable cutoff, as this would improve sensitivity (86.1%), allowing detection of a greater number of adolescents with carbohydrate abnormalities. The higher number of false-positive results (specificity 71.5%) associated with this threshold may be acceptable, given that diagnostic testing for prediabetes or type 2 diabetes is not extremely invasive (requiring a simple venipuncture).

The American Diabetes Association (ADA) uses BMI percentiles for designating which children should be screened, recommending that children with a BMI $\geq$85th percentile for age and sex with any two additional risk factors, including family history, race or ethnicity, or signs of IR, should be screened for diabetes (24). Because of the high burden of childhood obesity, the Centers for Disease Control (CDC) estimates that approximately 2.5 million children in the USA potentially qualify for diabetes screening based on the ADA screening guidelines (25), highlighting the need for efficient and cost-effective strategies for screening. Given that some studies in adults suggest that WC is superior to BMI for explaining obesity-related health risks (26), future studies are needed to determine whether WC percentiles vs. BMI percentiles are better and possibly more cost-effective for identifying adolescents with IR. Furthermore, studies are also needed to evaluate the validity of the proposed WC cutoffs for identifying children with abnormal cardiovascular risk factors, such as systolic blood pressure, triglycerides, and high-density lipoprotein cholesterol.

We used WC percentile cutoffs that were generated based on a cohort of children from NHANES III (1988–1994) (18) and applied them to the 1999–2002 NHANES sample. We feel that this was most appropriate based on the fact that rates of obesity and mean WC for children in the USA have increased significantly between these two survey periods (15). Creation of a new set of WC percentiles for the 1999–2002 NHANES cohort that is heavier and of wider girth would simply 'normalize' higher WC levels.

Furthermore, although fasting insulin levels may also be used to screen for IR, that measure is not generally

available in a routine primary care visit but rather would require a return visit to a laboratory in a fasting state.

There are some limitations to our study. Because of the lack of fasting glucose and insulin levels among younger children, we were unable to evaluate WC percentile thresholds for adolescents 11 yr and younger. We also were unable to assess the impact of puberty on HOMA-IR levels because of lack of pubertal data in NHANES. In addition, given that the data are cross-sectional, we were unable to link childhood WC thresholds to adult disease outcomes.

We recognize possible concerns regarding the definition of a HOMA-IR cutoff of >4.39 for defining IR, but our sensitivity analyses using race-specific cutoffs for IR yielded similar results. HOMA-IR is considered a validated measure of IR, with some studies showing correlations of 0.7–0.9 (14, 27). However, other studies have shown more modest correlations with clamp or frequently sampled intravenous glucose tolerance test (FSIVGTT) measures (28–30). Although HOMA-IR may not be as sensitive a method for determining IR compared with the gold standard methods of the hyperinsulinemic–euglycemic clamp or the minimal model frequently sampled intravenous glucose tolerance test, it is unlikely that more definitive measurements using these invasive and expensive gold standard methods will be conducted in as large and diverse a population.

Studies have shown a high correlation between BMI and WC, raising the question of whether WC offers incremental utility above that of BMI. Although studies are certainly needed to answer this question, the establishment of abnormal WC percentiles is first needed so that comparison to standardized BMI percentiles can be conducted. If future studies confirm the utility of WC in the clinical setting, further validation of this measure in clinical practice may be warranted as WC measurements may be subject to greater error compared with BMI, particularly among young children.

Conclusions

In summary, race/ethnicity-specific WC percentile thresholds did not discriminate better than universal WC percentile thresholds, suggesting that universal WC thresholds may be used effectively to identify adolescents with IR in primary care practices. Application of universal WC thresholds may simplify implementation and adoption of WC as a screening measure for diabetes risk among adolescents in primary care and specialty care practices.

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