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ABSTRACT

Background: Childhood overweight and obesity is a global health problem that continues to worsen in many low- and middle-income countries. Low-cost measurements for monitoring overweight and relative metabolic risk, such as neck circumference (NC), should be evaluated in different populations and age groups.
Aim: To test associations of NC and BMI with cardiometabolic parameters in 5-8-year-old Brazilian children.
Methods: This cross-sectional study carried out from 2004–2006 measured height, weight and NC by anthropometry, and estimated fat and fat-free mass by bioelectrical impedance. Cardiometabolic risk factors assessed were systolic and diastolic blood pressure, high- and low-density lipoprotein cholesterol, triglycerides, and homeostatic model assessment of insulin resistance (HOMA). Associations of NC and BMI with cardiometabolic risk factors were tested using multiple regression and precision-recall plot analysis.
Results: Analyses included 371 children (52% female). NC associated positively with BMI, fat mass, and fat-free mass, and with systolic blood pressure and HOMA following adjustment for age in sex-stratified multiple regression models. However, the latter relationships largely disappeared following adjustment for BMI. Area under the curve for NC or BMI in association with systolic blood pressure or HOMA >90th percentile was low in the pooled sample, indicating poor classifier performance.

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Conclusions: NC and BMI demonstrated similar associations with cardiometabolic risk factors, although NC mostly did not correlate with risk factors independently of BMI. In contrast to previous studies, NC was a poor classifier of cardiometabolic risk factors in children. The association of NC with both fat and fat-free mass may aid in explaining its poor performance.

Introduction

The prevalence of overweight and obesity in children and adolescents, as assessed by body mass index (BMI, kg/m^2), has plateaued at high levels in high-income countries, while continuing to increase in many low- and middle-income countries (Abarca-Gómez et al. 2017). Excess weight in young people represents a significant public and global health burden, and is a predictor of adult obesity (Kelishadi and Heidari-Beni 2019). Obesity, in turn, increases susceptibility to chronic non-communicable diseases (NCDs) including cardiovascular disease, diabetes, and cancer (Bull and Willumsen 2019). In Brazil, NCDs were responsible for 72% of deaths in 2007 (Schmidt et al. 2011), and this figure remained virtually unchanged in 2017, at 73%, or 928,000 deaths (Riley et al. 2017).

The *in utero* environment may predispose offspring to later overweight and obesity (Dabelea and Crume 2011). Monitoring and prevention of excess weight in childhood and adolescence is therefore crucial for attempting to interrupt intergenerational obesity trends (Boone-Heinonen et al. 2015). BMI remains useful for monitoring excess weight, however its limitations as a marker of chronic disease risk are increasingly recognized. One major shortcoming is that BMI indexes both fat mass (FM) and fat-free mass (FFM) and, within populations, the ratio of FM to FFM varies considerably at any given BMI (Wells 2000). At the same time, BMI cannot reliably index regional body composition (Neeland and de Lemos 2016), and it is understood that centrally deposited and visceral FM contributes significantly to variability in metabolic risk (Tchernof and Després 2013).

The use of imaging methods (e.g. MRI or dual-energy X-ray absorptiometry) to measure adipose tissue depots is superior (Neeland and de Lemos 2016), but may be limited by time, cost, and access to equipment. Body composition proxies that go beyond BMI, but are simple, scalable, and reliably indicative of relative disease risk, have thus been sought (Wells and Shirley 2016). There is good evidence that measures including waist circumference (WC), waist-to-hip ratio (WHR), and waist-to-height ratio (WHtR) fulfill these criteria in both

adults (Yusuf et al. 2005) and children (Savva et al. 2000), although see
Sardinha et al. (2016) and Li et al. (2020). Neck circumference (NC) has also
received wide interest as a proxy for upper body FM depots, with studies
conducted in children, adolescents, and adults in a range of populations (Nafiu
et al. 2010; Stabe et al. 2013; Katz et al. 2014; Formisano et al. 2016; Castro-
Piñero et al. 2017; Alzeidan et al. 2019; Mastroeni et al. 2019). Across these
studies, NC correlated with other anthropometric parameters (e.g. WC and
BMI), as well as single and clustered cardiometabolic risk factors, and per-
formed well as a tool to identify those with, or at risk of, metabolic syndrome
(Stabe et al. 2013; Formisano et al. 2016; Mastroeni et al. 2019; Alzeidan et al.
2019; Gomez-Arbelaez et al. 2016).

Of several studies conducted in Brazilian children (Silva et al. 2014;
Coutinho et al. 2014; Filgueiras et al. 2019; Mastroeni et al. 2019), none
have examined associations between NC and cardiometabolic risk factors in
children under 10 years of age. To further explore the use of NC as a low-cost
tool for the assessment of cardiometabolic risk, the current study tested
associations of NC with blood pressure, lipid, and glycemic parameters of
5–8-year-old children in Jundiaí city, Brazil.

Methods

This study was approved by the Research Ethics Committee of the School of
Public Health, University of São Paulo. It was conducted as a follow-up to
a cohort study carried out between 1997 and 2000 in the city of Jundiaí,
Southeast Brazil. As described in Rondó et al. (2003), 865 pregnant women
were recruited from health units and public hospitals and followed until the
birth of their babies.

Several years later, 745 of 865 mothers were located, and their children
invited to participate in the current study. Mothers were initially contacted by
phone or visited at home, and a home visit was subsequently carried out for all
potential participants. Study objectives and measurements were explained in
detail, and informed consent was taken from a parent or guardian. Those who
consented on behalf of their children were contacted to schedule a visit to
a health unit for data collection. This phase of the study was conducted from
November 2004 to December 2006, with data collected on children's anthro-
pometry, body composition, blood pressure, and glycemic and lipid profile.

Data were collected following a 10–12 hour fast. Children's weight was
measured in duplicate to the nearest 0.1 kg using a Sohnle 7500 electronic scale
(Murrhardt, Germany). Height was measured in duplicate to the nearest
0.1 cm using a SECA stadiometer (Hamburg, Germany), with children stand-
ing and unshod. NC was measured in duplicate to the nearest 0.1 cm with
a SECA 201 non-stretchable measuring tape (Hamburg, Germany) (Callaway
1988). The child stood erect with their head in the horizontal Frankfurt Plane,

with the tape applied perpendicular to the long axis of the neck, just inferior to the laryngeal prominence. For height, weight, and NC, the average of repeated measurements was taken and used in analyses.

FM and FFM were estimated by bioelectrical impedance (BIA) using a BIA 310 Bioimpedance Analyzer (Biodynamics Corp., Seattle, WA, USA). BIA measures impedance of the body's tissues to a small electric current, with adhesive electrodes placed on the wrist/hand and ankle/foot. Data on height and impedance are used to predict total body water (TBW) (Wells and Fewtrell 2006). Using an assumed hydration constant, TBW is converted to FFM, and FFM can be subtracted from body mass to obtain FM.

Systolic (SBP) and diastolic blood pressure (DBP) were measured with the HDI/PulseWave CR-2000 (Hypertension Diagnostics, Inc., Eagan, MN, USA). Glucose concentration was measured by the glucose hexokinase method using the Bayer Advia 1200 system (Pittsburgh, PA, USA). Insulin was measured by chemiluminescence in an Immulite 2000 analyzer using the Immnlite 2000 insulin kit (DPC, Los Angeles, CA, USA). Glucose and insulin were used to calculate the homeostatic model assessment score (HOMA), which assesses insulin resistance, with the following formula: HOMA = fasting glucose (mmol/l) x fasting insulin (µl U ml)/22.5. Total cholesterol, high-density lipoprotein cholesterol (HDL-c) and triglycerides were assayed by enzymatic methods using the Bayer Advia 1200 system, and serum low-density lipoprotein cholesterol (LDL-c) concentration was calculated with the formula of Friedewald et al. (1972).

Statistical analysis

All statistical procedures were performed using the R language for statistical computing (v. 3.6.1) in R studio (v. 1.1.463). Weight-for-age, height-for-age, and BMI-for-age z-scores were calculated for boys and girls separately using the WHO AnthroPlus R macro (downloaded from who.int/growthref/tools/en/), which is based on growth reference data for children and adolescents aged 5–19 years (de Onis et al. 2007). FFM and FM were normalized for height in a manner akin to BMI, hence FFM index (FFMI) = $FFM/height^2$, and FM index (FMI) = $FM/height^2$.

Variables of interest were assessed for normality, missing observations, and outliers. Due to their skew, descriptive statistics for triglycerides and HOMA were calculated as Median (IQR); all others were Mean (SD). The Wilcoxon rank sum test with continuity correction or the Welch two sample t-test was used to test for sex differences in the case of non-normal or normally distributed data, respectively. Pearson's correlations were calculated for NC with BMI, FFMI, and FMI, stratified by sex.

Two sets of multiple regression models were initially fitted, also stratified by sex. In the first set of models, a cardiometabolic risk factor was entered

independently as the outcome, with NC and age as predictors. In the second set of models, a cardiometabolic risk factor was entered independently as the outcome, with BMI and age as predictors. Triglycerides and HOMA were natural log transformed. In a third set of models, each cardiometabolic risk factor was independently regressed on NC, age, and BMI. Sensitivity analyses to the inclusion of outliers were performed for all models.

Precision-recall (PR) plots using the R package precrec (Saito and Rehmsmeier 2017) were employed to test the ability of NC versus BMI to identify children with SBP or HOMA >90th percentile (see Results: SBP and HOMA were the only cardiometabolic risk factors to associate significantly with NC or BMI). So that children could be pooled for these analyses, sex- and age-specific z-scores were calculated using the LMS method (Cole et al. 1995) (LMS Chartmaker Pro, Medical Research Council, v. 2.54), which accounts for associations of a given variable with age using median (M) and variability (S) parameters, and also addresses any skew in the data, expressed as the power transformation (L) needed for normalization.

Several authors have used Receiver Operating Characteristic (ROC) curves to assess the diagnostic ability of NC (Nafiu et al. 2010; Katz et al. 2014; Formisano et al. 2016; Mastroeni et al. 2019), however PR plots are more appropriate for imbalanced data sets where there is a large difference in positive vs negative outcomes (Saito and Rehmsmeier 2015). PR plots show precision on the y-axis against recall (sensitivity) on the x-axis. As with ROC analyses, they provide area under the curve (AUC) for model-wide evaluation. However, the PR baseline is determined by the ratio of positive to negative outcomes (y = P/P + N), so that a useless test (random classifier) is not necessarily y = 0.5 (Saito and Rehmsmeier 2015).

Results

All women recruited into the original study were of low socioeconomic status, with healthcare provided by Brazil's National Health Service (Rondó et al. 2003). In the current study, median *per capita* household income was R\$ 264.50 (USD 121.60). Sixty-six percent of the sample had a *per capita* household income below the Brazilian minimum wage, which in 2006 was R\$ 337.50 (USD 144.60).

Figure 1 is a flow diagram illustrating that of the 745 children initially located, 371 were included in the analysis (194 girls and 177 boys, or 52% female). Of the 371, one boy did not have recorded values for SBP and DBP. Additionally, one observation for height z-score and three observations each for weight z-score and BMI z-score were removed from the boys' group after they were flagged as biologically implausible by WHO software. For the same reason, one observation each of height z-score, weight z-score, and BMI z-score was removed from the girls' group. Extremely low SBP/DBP values (i.e. 59/20) were considered biologically implausible and removed for one
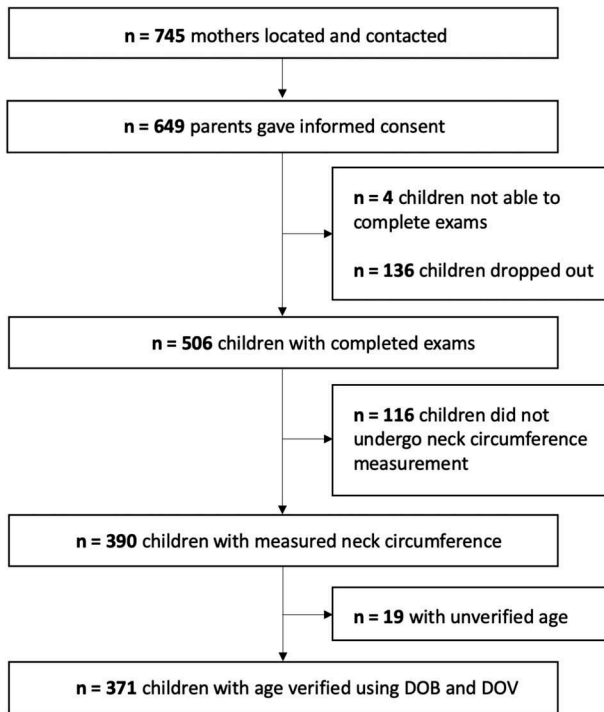
Figure 1. Flowchart illustrating losses and the final sample included in analyses. DOB, date of birth. DOV, date of visit.

5-year-old girl. The following outliers were identified: 2 for HOMA score and 1 for HDL in girls, and 1 for NC, 1 for LDL, and 1 for triglycerides in boys.

The calculation of HOMA scores for 20.5% of the sample (41 boys, 35 girls) was impacted by insulin values being below the measurement instrument's detection threshold. We therefore used two variables for HOMA in analyses: HOMA1 was missing the 20.5% of observations where insulin was below the detection threshold of 2.0 μl U ml, whilst HOMA2 included such observations, calculated with insulin at the threshold value of 2.0 μl U ml.

Descriptive statistics for the sample are given in Table 1. Girls and boys had the same average age, with a range of 5.0–8.6 in girls, and 5.1–8.4 in boys. Mean z-scores for weight, height and BMI in both groups deviated to varying degrees from zero, thus deviating to some extent from the reference population average, although all mean scores were between 0 and 1, and standard deviations close to 1. Average FFMI was larger in boys, while the opposite was observed for FMI. Significant sex differences were also found for measures of NC, SBP, DBP, triglycerides, and HOMA. For these variables, mean or median values were larger for girls, except for NC, which was larger for boys. As shown in Table 2, both boys and girls demonstrated relatively strong

Table 1. Characteristics of the sample.

Sample characteristic	n	Boys (n = 177) Mean (SD) or *Median (IQR)	n	Girls (n = 194) Mean (SD) or *Median (IQR)	p value	95% CI
Age (years)	177	6.7 (0.7)	194	6.7 (0.7)	0.75	−0.13, 0.17
Weight for age z-score	174	0.32 (1.2)	193	0.58 (1.1)	0.03	0.02, 0.50
Height for age z-score	176	0.45 (1.1)	193	0.68 (1.1)	0.05	0.00, 0.46
BMI for age z-score	174	0.05 (1.3)	193	0.27 (1.1)	0.10	−0.04, 0.47
FFMI (kg/m^2)	177	13.6 (1.5)	194	13.3 (1.2)	0.02	−0.59, −0.04
FMI (kg/m^2)	177	2.3 (1.3)	194	2.8 (1.2)	<0.001	0.27, 0.80
Neck circumference (cm)	176	27.8 (1.7)	194	27.3 (1.6)	0.002	−0.86, −0.19
SBP (mmHG)	176	108.4 (11.0)	193	112.2 (12.5)	0.002	1.37, 6.19
DBP (mmHG)	176	56.2 (8.1)	193	59.3 (8.9)	<0.001	1.30, 4.79
HDL-c (mg/dL)	177	56.2 (9.9)	193	54.6 (11.2)	0.16	−3.68, 0.63
LDL-c (mg/dL)	176	86.3 (24.3)	194	89.8 (23.1)	0.17	−1.43, 8.27
TRG (mg/dL)	176	*60.5 (34.3)	194	*67.5 (40.8)	0.009	1.99, 11.9
HOMA1	136	*0.86 (0.5)	157	*1.01 (0.7)	0.02	0.02, 0.21
HOMA2	177	*0.74 (0.5)	192	*0.86 (0.7)	0.03	0.01, 0.17

SD, standard deviation; IQR, interquartile range; CI, confidence interval; BMI, body mass index, FFMI, fat-free mass index; FMI, fat mass index, SBP, systolic blood pressure, DBP, diastolic blood pressure, HDL-c, high-density lipoprotein cholesterol, LDL-c, low-density lipoprotein cholesterol, TRG, triglycerides.

HOMA, homeostatic model assessment of insulin resistance, calculated as fasting glucose (mmol/l) x fasting insulin (µl U ml)/22.5.

HOMA1 missing 20.5% of observations where insulin was below the detection threshold of 2.0 µl U ml; HOMA2 includes such observations, calculated with insulin as 2.0 µl U ml.

p values and 95% confidence intervals are for sex differences, using Wilcoxon rank sum test with continuity correction for TRG, HOMA1, and HOMA2, and Welch two sample t-test for all other variables.

Table 2. Correlation coefficients for neck circumference with BMI and body composition variables.

Neck circumference (cm)		Boys (n = 177)				Girls (n = 194)		
	n	Pearson's r	p	95% CI	n	Pearson's r	p	95% CI
BMI (kg/m^2)	173	0.62	<0.001	0.52, 0.71	193	0.67	<0.001	0.58, 0.74
FFMI (kg/m^2)	177	0.68	<0.001	0.59, 0.75	194	0.63	<0.001	0.53, 0.70
FMI (kg/m^2)	177	0.59	<0.001	0.49, 0.68	194	0.54	<0.001	0.44, 0.64

CI, confidence interval; BMI, body mass index; FFMI, fat-free mass index; FMI, fat mass index

associations between NC and BMI. The same was true for NC with FFMI and FMI, where values for the former were larger than the latter in both sexes.

Given in Tables 3 and 4 are the results of multiple regression models where a given cardiometabolic risk factor was independently regressed on either NC or BMI, with adjustment for age (each table is comprised of the results of 7 separate regression models). Both NC and BMI were associated with SBP and HOMA, but not DBP, HDL-c, LDL-c, or triglycerides. As reflected by adjusted R^2, in boys, NC models explained 6%, 18%, and 20% of the variability in SBP, HOMA1, and HOMA2, respectively. In girls, the corresponding numbers were 3%, 13% and 17%. Adjusted R^2 values demonstrated the same general pattern in the BMI models. Age was not significant in any of the models.

Table 3. Multiple linear regression of individual cardiovascular risk factors on neck circumference, stratified by sex, with adjustment for age.

	Neck circumference (cm)											
	Boys (n = 177)						Girls (n = 194)					
Dependent variable	n	b	se	p	95% CI	Adjusted R2	n	b	se	p	95% CI	Adjusted R2
SBP (mmHg)*	175	1.73	0.5	<0.001	0.76, 2.70	0.06	193	1.51	0.6	0.008	0.40, 2.63	0.03
DBP (mmHg)	175	0.44	0.4	0.24	−0.29, 1.17	−0.00	193	0.62	0.4	0.13	−0.18, 1.43	0.00
HDL-c (mg/dL)	176	−0.49	0.5	0.29	−1.38, 0.41	0.00	193	0.03	0.5	0.96	−0.99, 1.04	−0.01
LDL-c (mg/dL)	175	0.48	1.1	0.67	−1.73, 2.69	−0.01	194	−1.38	1.1	0.19	−3.47, 0.71	−0.00
TRG (mg/dL)	175	0.00	0.0	0.77	−0.03, 0.04	−0.01	194	0.01	0.0	0.53	−0.02, 0.05	−0.01
HOMA1	135	0.11	0.0	<0.001	0.07, 0.15	0.18	157	0.11	0.0	<0.001	0.06, 0.15	0.13
HOMA2	176	0.13	0.0	<0.001	0.09, 0.17	0.20	192	0.14	0.0	<0.001	0.10, 0.19	0.17

*Each row is a regression model with an individual cardiovascular risk factor entered as the dependent outcome, and neck circumference and age entered as predictors.
b, coefficient; se, standard error; CI, confidence interval; SBP, systolic blood pressure; DBP, diastolic blood pressure; HDL-c, high-density lipoprotein cholesterol; LDL-c, low-density lipoprotein cholesterol; TRG, triglycerides; HOMA1, and HOMA2 variables natural log transformed.
HOMA, homeostatic model assessment of insulin resistance, calculated as fasting glucose (mmol/l) x fasting insulin (μl U ml)/22.5.
HOMA1 missing 20.5% of observations where insulin was below the detection threshold of 2.0 μl U ml; HOMA2 includes such observations, calculated with insulin as 2.0 μl U ml.

Table 4. Multiple linear regression of individual cardiovascular risk factors on BMI, stratified by sex, with adjustment for age.

	BMI (kg/m²)											
	Boys (n = 177)						Girls (n = 194)					
Dependent variable	n	b	se	p	95% CI	Adjusted R2	n	b	se	p	95% CI	Adjusted R2
SBP (mmHg)*	173	1.20	0.4	0.001	0.47, 1.93	0.05	193	1.22	0.4	0.003	0.42, 2.02	0.04
DBP (mmHg)	173	0.50	0.3	0.09	−0.09, 1.09	0.01	193	0.35	0.3	0.24	−0.24, 0.93	−0.00
HDL-c (mg/dL)	174	0.19	0.4	0.61	−0.53, 0.90	−0.00	193	−0.50	0.4	0.17	−1.23, 0.22	0.00
LDL-c (mg/dL)	173	1.20	0.9	0.17	−0.54, 2.94	0.00	194	−0.18	0.8	0.81	−1.69, 1.33	−0.01
TRG (mg/dL)	173	−0.00	0.0	0.95	−0.03, 0.03	−0.01	194	0.02	0.0	0.08	−0.00, 0.05	0.01
HOMA1	133	0.07	0.0	<0.001	0.04, 0.10	0.12	156	0.09	0.0	<0.001	0.06, 0.12	0.17
HOMA2	174	0.09	0.0	<0.001	0.06, 0.12	0.15	191	0.11	0.0	<0.001	0.07, 0.14	0.18

*Each row is a regression model with an individual cardiovascular risk factor entered as the dependent outcome, and BMI and age entered as predictors.
BMI, body mass index; b, coefficient; se, standard error; CI, confidence interval; SBP, systolic blood pressure; DBP, diastolic blood pressure; HDL-c, high-density lipoprotein cholesterol; LDL-c, low-density lipoprotein cholesterol; TRG, triglycerides; HOMA1, and HOMA2 natural log transformed.
HOMA, homeostatic model assessment of insulin resistance, calculated as fasting glucose (mmol/l) x fasting insulin (µl U ml)/22.5.
HOMA1 missing 20.5% of observations where insulin was below the detection threshold of 2.0 µl U ml; HOMA2 includes such observations, calculated with insulin as 2.0 µl U ml.

Table 5 shows an additional series of models where a given cardiometabolic risk factor was independently regressed on NC, with adjustment for both age and BMI. With BMI included, NC was no longer a significant predictor of SBP or HOMA1 in boys or girls. NC remained significant in the HOMA2 model for girls, however the beta coefficient decreased by half.

The foregoing results are from analyses performed with outliers excluded. Sensitivity analysis results are provided in Supplementary Tables 1–4. Overall, the inclusion of outliers did not appreciably alter results, however R^2 values were attenuated somewhat in multiple regression models, particularly where HOMA1 or HOMA2 was the dependent variable. Supplementary Table 4 shows that the inclusion of outliers rendered NC significant in the boys' HOMA2 model, controlling for BMI and age. However, R^2 was little changed, and the lower bound of the 95% CI for NC was consistent with a non-significant effect on HOMA2.

Figure 2 **(panel a)** shows PR plots constructed using data pooled for boys and girls, which tested the ability of NC or BMI to classify children with SBP or HOMA2 > 90th percentile. The dotted grey line denotes a random classifier, with its location depending on the ratio of positive to negative outcomes. The area above and below the dotted line indicates good versus poor performance. A perfect classifier is reflected by a straight line from the top left corner (0.0, 1.0) to the top right corner (1.0, 1.0), and a second straight line from the top right corner to the dotted line (1.0, P/(P + N) (Saito and Rehmsmeier 2015). When two curves are plotted, the curve closer to the top right corner is relatively better performing. AUC values are given for the performance of NC and BMI. The closer the AUC value is to 1.0, the better the performance of the test.

AUC values were similar for BMI in SBP and HOMA plots, while NC performed better for HOMA than SBP. AUC values were generally low, however, and no curve appreciably approached the top right corner of the plot. Supplementary Figure 1 provides a PR plot with the sexes pooled where the HOMA1 variable was used in place of HOMA2; results were comparable for the two HOMA variables. Sensitivity analysis to the exclusion of outliers was not performed for PR plots.

The second panel in Figure 2 **(panel b)** provides boxplots demonstrating considerable overlap in NC and BMI distributions for children above or below the 90th percentile for SBP and HOMA2. This may aid in explaining the poor classifier performance of NC and BMI for these outcomes.

Discussion

In the current study, NC was associated with BMI, FMI, and FFMI in 5–8-year-old Brazilian children. In multiple regression models stratified by sex, adjusting

Table 5. Multiple linear regression of individual cardiovascular risk factors on neck circumference, stratified by sex, with adjustment for age and BMI.

	Neck circumference (cm)												
	Boys (n = 177)						Girls (n = 194)						
Dependent variable	n	b	se	p	95% CI	Adjusted R2	n	b	se	p	95% CI	Adjusted R2
SBP (mmHg)*	172	0.12	0.7	0.86	−1.23, 1.47	0.05	193	0.66	0.8	0.40	−0.88, 2.19	0.04
DBP (mmHg)	172	−0.22	0.6	0.69	−1.31, 0.87	0.00	193	0.55	0.6	0.33	−0.56, 1.67	−0.00
HDL-c (mg/dL)	173	−0.65	0.7	0.34	−1.98, 0.69	−0.00	193	0.99	0.7	0.16	−0.41, 2.40	0.01
LDL-c (mg/dL)	172	−0.07	1.6	0.97	−3.31, 3.16	−0.00	194	−2.30	1.5	0.12	−5.19, 0.59	−0.00
TRG (mg/dL)	172	0.00	0.0	0.96	−0.05, 0.05	−0.02	194	−0.02	0.0	0.43	−0.07, 0.03	0.00
HOMA1	132	0.04	0.0	0.19	−0.02, 0.09	0.24	156	0.04	0.0	0.21	−0.02, 0.10	0.17
HOMA2	173	0.05	0.0	0.06	−0.00, 0.11	0.16	191	0.08	0.0	0.01	0.02, 0.14	0.20

*Each row is a regression model with an individual cardiovascular risk factor entered as the dependent outcome, and neck circumference, BMI, and age entered as predictors. Parameters reported in the table are for the neck circumference predictor.
b, coefficient; se, standard error; CI, confidence interval; SBP, systolic blood pressure; DBP, diastolic blood pressure; HDL-c, high-density lipoprotein cholesterol; LDL-c, low-density lipoprotein cholesterol; TRG, triglycerides; TRG, HOMA1, and HOMA2 variables natural log transformed.
HOMA is homeostatic model assessment of insulin resistance, calculated as fasting glucose (mmol/l) x fasting insulin (μl U ml/I)/22.5.
HOMA1 missing 20.5% of observations where insulin was below the detection threshold of 2.0 μl U ml; HOMA2 includes such observations, calculated with insulin as 2.0 μl U ml.
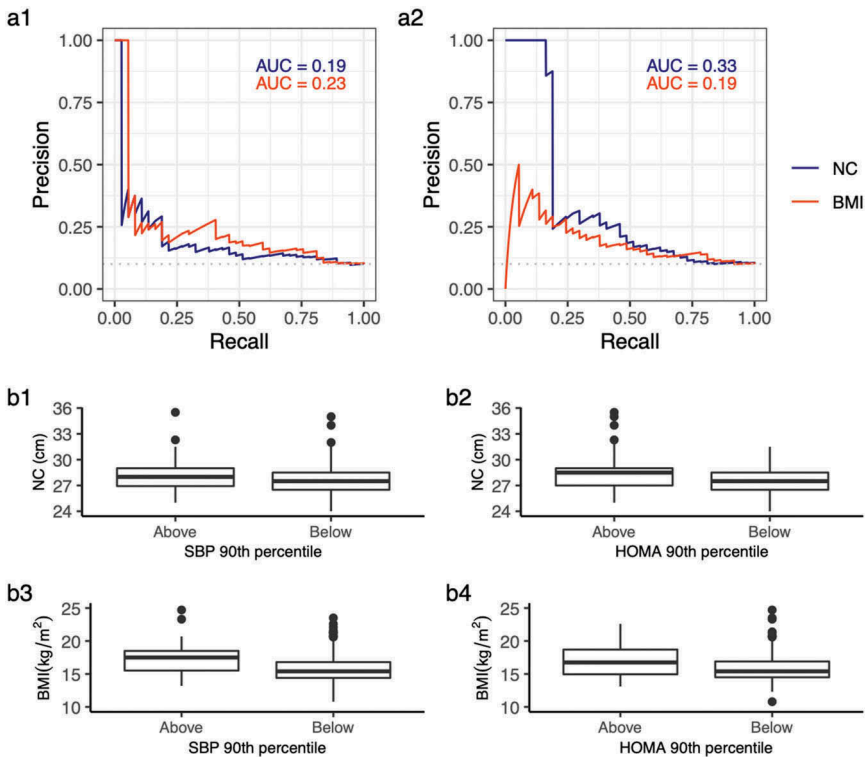
Figure 2. NC and BMI as classifiers of children with SBP or HOMA >90th percentile. Precision-recall plots (panel a) for the performance of NC and BMI in identifying SBP (a1) or HOMA (a2) >90th percentile, with data for both sexes pooled. Well performing curves are those approaching the upper right corner of the plot with higher AUC values. Boxplots (panel b) demonstrate considerable overlap in NC (b1, b2) and BMI (b3, b4) distributions for children above or below the 90th percentile for SBP and HOMA. AUC, area under the curve. NC, neck circumference. BMI, body mass index. SBP, systolic blood pressure. HOMA is HOMA2, including observations calculated with insulin at the instrument detection threshold value of 2.0 μl U ml.

for age, NC was significantly associated with SBP and HOMA, but not DBP, HDL-c, LDL-c, or triglycerides. BMI showed similar associations with these variables after adjustment for age. The percentage of variability in SBP explained by NC versus BMI models was likewise similar: 6% and 5%, respectively, for boys, and 3% and 4%, respectively, for girls.

NC and BMI were better predictors of HOMA than SBP. In the model where the HOMA2 variable was regressed on NC and age, 20% of the outcome was explained in boys, and 17% in girls. In contrast, variation in BMI and age explained a greater portion of variation in HOMA2 in girls than

boys: 18% versus 15% (although adjusted R^2 was reduced in girls' HOMA-BMI models following sensitivity analyses, see Supplementary Table 3).

With the exception of the girls' model where HOMA2 was the dependent variable, however, the relationship of NC with SBP and HOMA disappeared after controlling for BMI (see Table 5). Overall, this suggests that measures of NC and BMI contain similar information, and thus may fail to explain additional variability in the outcome when set as joint, rather than single, predictors. These results are consistent with studies where NC was able to classify individuals with elevated BMI (Hatipoglu et al. 2010; Nafiu et al. 2010; Katz et al. 2014; Taheri et al. 2016), although predicting BMI from NC may be of limited value if the goal is to move beyond BMI to more useful markers of metabolic risk.

That NC did not associate with SBP or HOMA independently of BMI (except where HOMA2 was used in the girls' group) also suggested it was unlikely to perform better than BMI at identifying individuals with elevated SBP or HOMA measures.

Indeed, the similar performance of NC and BMI was evident from the results of PR plot analyses in the pooled sample. AUC values suggested that, in fact, neither NC nor BMI performed particularly well as tools for identifying elevated SBP or HOMA, defined as >90th percentile following previous authors (Kuciene et al. 2015; Formisano et al. 2016). We used PR plots rather than ROC plots (Saito and Rehmsmeier 2015) because there were ultimately few children identified as having SBP or HOMA >90th percentile, thus the sample was imbalanced, with many fewer positive than negative values (i.e. children with SBP or HOMA ≤90th percentile).

The interest in body girth measures has arisen because, despite the utility of BMI for assessing excess weight in large studies, it suffers from several limitations (Wells 2000; Tchernof and Després 2013; Neeland and de Lemos 2016), including that it cannot provide information on metabolic risk associated with fat distribution. Measures indexing fat distribution such as WC, WHR, and WHtR, in comparison to BMI, were found to associate more strongly with myocardial infarction in adults (Yusuf et al. 2005), and better predict cardiovascular disease risk factors in children (Savva et al. 2000). More recently, however, an analysis pooling data from five studies reported similar associations of BMI, WC, and WHtR with clustered cardiometabolic risk outcomes in children and adolescents (Sardinha et al. 2016).

As a relatively simple anthropometric measurement, NC, like WC, was proposed as an easy-to-employ proxy for metabolically harmful FM deposited in the upper body (Tchernof and Després 2013). Studies have shown that NC and WC associate with one another (Hatipoglu et al. 2010; Nafiu et al. 2010; Katz et al. 2014; Hassan et al. 2015; Taheri et al. 2016; Castro-Piñero et al. 2017), and that their degree of association with outcomes such as overweight/obesity, HOMA, and SBP is similar (Hatipoglu et al. 2010;

Androutsos et al. 2012). At the same time, some have argued that NC is preferable to WC, as the former does not demonstrate pre- versus post-prandial variation, depend on the consistency of measurements taken at the end of an expired breath, or necessitate the removal of clothing (Hatipoglu et al. 2010; Nafiu et al. 2010; Taheri et al. 2016). Of note, recent analyses by Sardinha et al. (2016) and Li et al. (2020) call into question the precision and effectiveness of BMI and waist indices for identifying metabolically at-risk individuals, however these authors did not examine NC.

Of the relatively few studies which have measured NC and cardiometabolic outcomes in children, several have documented the positive associations we observed for NC with BMI, SBP, and HOMA. However, others have also identified positive relationships between NC, DBP and triglycerides, and a negative relationship between NC and HDL cholesterol (Formisano et al. 2016; Castro-Piñero et al. 2017; Kurtoglu et al. 2012; Androutsos et al. 2012). Differences in methodology, sample size, and population characteristics are likely to contribute to variation in results. The lack of consistency in variables used for model adjustment may also complicate comparisons of results across studies. In testing NC-risk factor relationships, authors have variously controlled for fat intake and physical activity (Androutsos et al. 2012), BMI and country of origin (Formisano et al. 2016), or sex and pubertal stage (Kurtoglu et al. 2012; Castro-Piñero et al. 2017).

In contrast to our findings, significant associations of NC with SBP, HDL-c, triglycerides, and HOMA remained for both boys and girls when Formisano et al. (2016) adjusted models for BMI. These authors (Formisano et al. 2016) and others (Gomez-Arbelaez et al. 2016; Castro-Piñero et al. 2017; Mastroeni et al. 2019) have also found evidence that NC performs well in identifying individuals with elevated metabolic syndrome scores or cardiometabolic risk scores. We opted not to explore associations with a calculated risk score, owing to the observed correlation (pre-BMI adjustment) of NC with just SBP and HOMA in our sample, and its poor performance as a classifier of elevated measures.

The poor classifier performance may result from the fact that NC and BMI distributions were overlapping for children above and below the 90th percentile for SBP and HOMA (see Figure 2, panel b). In other words, children with high NC and BMI were not necessarily those with elevated SBP and HOMA. One possible explanation is that BMI inevitably indexes both FM and FFM. This is also the case for NC, which cannot distinguish FM from FFM in the underlying tissue. Table 2 shows that NC is associated with FMI in both boys and girls, but the correlation coefficients are in fact larger for NC with FFMI in both sexes. Children with greater NC may have greater FM, but they may also have greater FFM, the latter which includes organs and skeletal muscle mass, a metabolically protective tissue (Bayol et al. 2014). The fact that metabolic risk may ultimately depend on the ratio of FM to FFM,

and not the absolute size of either compartment, highlights one of the central limitations of simple girth measurements for metabolic risk assessment.

One limitation of the current study is its small sample size relative to similar investigations in the literature. The sample of children originally located was reduced substantially due to dropouts, but also because NC measurements were added to the protocol once the study was already underway. The data were collected cross-sectionally, which precludes any potential identification of causal links between predictors and outcomes. Additionally, the data were collected from 2004–2006, and thus may not accurately reflect the associations one may find in conducting a similar study in 5–8-year-old children in Jundiaí, Brazil today. With regard to the collection of FM and FFM data using BIA, the fact that the BIA measurements were not specifically calibrated to the current population must also be recognized as a limitation. Finally, we were only able to assess single cardiometabolic risk factors, while a combined score may better index metabolic risk (Castro-Piñero et al. 2017), and we were unable to include in our analysis further anthropometric measurements such as WC and WHtR for comparison with NC and BMI. At the same time, certain potentially confounding variables that have been included in prior studies were not available for the current sample, including physical activity, nutrient intake, and pubertal stage.

On the other hand, it has been noted that data on NC, metabolic parameters, and associations therein are likely to differ between populations (Formisano et al. 2016; Castro-Piñero et al. 2017), and it is therefore important to collect and report such data for different populations of children. Here, we have reported results from a low-income population in Southeast Brazil, which do indeed demonstrate differences to results reported in children from other countries. Prior studies in Brazil have examined NC as a potential proxy for obesity or metabolic risk (Coutinho et al. 2014; Silva et al. 2014; Filgueiras et al. 2019; Mastroeni et al. 2019), however none to our knowledge have examined associations between NC and cardiometabolic risk parameters in children under 10 years of age.

In conclusion, associations of NC or BMI with single cardiometabolic risk factors after adjustment for age were similar. However, associations observed for NC with SBP and HOMA disappeared following adjustment for BMI in the majority of multiple regression models. This suggests that, while NC could potentially serve as a simple, scalable marker of risk in lieu of BMI, it may not perform better or add additional information to that achieved with BMI. The fact that here both NC and BMI performed rather poorly at identifying children with SBP or HOMA >90th percentile should serve as a reminder that simple anthropometric measurements cannot distinguish fat from fat-free tissues, which may diminish their ability as classifiers. Our results, however, stand in contrast to previous studies where NC performed well as a classifier of metabolic

risk in children, adolescents, and adults (Formisano et al. 2016; Gomez-Arbelaez et al. 2016; Alzeidan et al. 2019; Mastroeni et al. 2019).

Disclosure statement

No potential conflict of interest was reported by the author.

Funding

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