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# Efficacy of neck circumference to identify metabolic syndrome in 3–10 year-old European children: Results from IDEFICS study

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**KEYWORDS**
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**Abstract** *Background and aims:* Several studies demonstrated that larger neck circumference (NC) in children and adolescents may help to identify obesity and cardio-metabolic abnormalities. We aimed to evaluate the correlation between NC and metabolic syndrome (MetS) risk factors and to determine the utility of this anthropometric index to identify MetS in European children.
*Methods and results:* The present cross-sectional analysis includes 15,673 children (3–10 years) participating in the IDEFICS study. A continuous MetS (cMetS) score was calculated summing age and sex standardized *z*-scores of specific MetS risk factors. Receiver Operating Characteristic analysis, stratified by one-year age groups, was used to determine the ability of NC to identify children with unfavorable metabolic profile, corresponding to cMetS score $\geq$ 90th percentile.

The areas under the curve values for NC associated with cMetS score values $\geq$ 90th percentile were significantly greater in girls than in boys ($p < 0.001$), except for $5 < 6$ years group. For boys, optimal NC cut-off values ranged from 26.2 cm for the lowest age group ($3 < 4$ years), up to 30.9 cm for the highest age group ($9 < 10$ years). In girls, corresponding values varied from 24.9 cm to 29.6 cm.
*Conclusion:* The study demonstrated the efficacy of NC in identifying European children with an unfavorable metabolic profile.


*Abbreviations:* MetS, metabolic syndrome; cMetS, continuous metabolic syndrome; BMI, body mass index; WC, waist circumference; NC, neck circumference; IDF, International Diabetes Federation; PQ, parental questionnaire; HDL-C, high-density lipoprotein cholesterol; TRG, triglycerides; HOMA, homeostatic assessment model; SBP, systolic blood pressure; DBP, diastolic blood pressure; ROC, receiver operating characteristic; AUC, area under curve; LR, likelihood ratio.

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## Introduction

The metabolic syndrome (MetS), defined in adults as a cluster of different risk factors [1,2] (central obesity, hyperglycemia, dyslipidemia and elevated blood pressure), is associated with an increased risk of cardiovascular diseases morbidity and mortality [3,4]. The prevalence of MetS in adults has increased worldwide probably in line with the epidemic of overweight and obesity [5].

Given the recent pediatric obesity epidemic [6], it is indeed not surprising that the prevalence of MetS is also rising considerably among children and adolescent [7]. There is robust evidence indicating that pediatric MetS is strongly associated with developing of MetS in adult age [8]. Nonetheless, although MetS has been well defined in the adult population [1,2], there is no current universal definition for MetS in children and adolescents, because there are no clear thresholds above which the cardiometabolic risk factors start to create harms [9,10].

Recently, Ahrens et al. proposed a new definition of MetS in children, according to the different components of the syndrome and based on the cardiovascular risk factor profile obtained from the large European cohort of healthy children aged 2–10 years participating to the IDEFICS (Identification and prevention of Dietary-and lifestyle-induced health Effects in Children and infantS) study [11]. This approach considers a continuous MetS (cMetS) score to represent in children the cluster of the main components used to define MetS in adults.

Obesity has been firmly recognized as a driving factor for the development of MetS [12]. However, recent investigations have highlighted that the contribution of adiposity to the metabolic risk largely depends on body fat distribution [13]. In particular, several studies demonstrated that upper-body adiposity is considered to be more strongly associated with cardiometabolic risk factors, glucose intolerance, hyperinsulinemia, diabetes and hypertriglyceridemia than total adiposity or lower body fat deposition in adults, children and adolescents [14,15].

Thus, although body mass index (BMI) remains a useful measurement of overall adiposity in clinical and epidemiological settings [16], anthropometric indices estimating upper-body fat accumulation were introduced as features of MetS. Among these, waist circumference (WC) measurement is the most widely used for the diagnosis of MetS [1,2]. However, use of WC has a number of limitations. In particular, many studies have proposed different anatomical landmarks for performing the measurement, which influence his absolute value [17,18]. Moreover, WC measurement may also be influenced by the operator expertise and by the fasting or post-prandial status of the subject being measured [19].

About sixty years ago, Vague et al. were the first to consider neck circumference (NC) as an index of upper-body fat accumulation [20]. Recent studies have proposed the use of NC as an effective, easy and practical alternative to WC. NC is unaffected by consumption of meals and breathing, and appears to have very good inter and intra-observer reliability, with no need of multiple measurements for precision and reliability [21]. This measure may thus provide reliable estimates of upper-body fat accumulation [21–23].

Different studies showed a positive association between NC, metabolic and cardiovascular risk factors in adults [24–26] thus introducing the possible use of the NC as a screening measure for identifying metabolic disease risk also in children. Only few studies focused their attention on the association between NC and factors of the MetS in children. There is some evidence that larger neck circumference in children and adolescents may be associated with obesity [27,28] and cardiometabolic abnormalities [29,30]. Kurtoglu et al. were the first to consider NC as a potential indicator for predicting metabolic risk factors in Turkish obese children. They observed that NC $>$ 36 cm for boys and $>$35 cm for girls were cut-off levels for determining children with MetS, defined, this last, according to the criteria of International Diabetes Federation (IDF) [31].

In light of the recent pediatric definition of MetS by Ahrens et al. [11], and the assessment of NC in the European children participating to the IDEFICS study, we aimed: 1) to evaluate the correlation between NC and MetS risk factors; 2) to verify the efficacy of the NC as screening tool of MetS in children; 3) and to calculate pediatric NC cut-off values that can be used in the determination of MetS.

## Methods

### *Study design and participants*

The IDEFICS project is a multilevel epidemiological study, funded within the 6th EU Framework Program, aiming to investigate nutritional and lifestyle factors affecting health status in 2–10 year-old children. The baseline survey was carried out from September 2007 to May 2008 in eight European countries (Italy, Belgium, Cyprus, Estonia, Germany, Hungary, Spain and Sweden) and involved 16,228 children, recruited through schools and kindergartens, who fulfilled the inclusion criteria of the IDEFICS study [32].

The present analysis includes 15,673 children (boys = 7962; girls = 7711; age = 6.0 ± 1.8 years; mean ± standard deviation) with data on NC. Excluded children (boys = 291; girls = 264 age 5.0 ± 1.8; mean ± standard deviation) differed with respect to mean age from the group of children included in the present analysis since they were significantly younger ($p < 0.001$).

The study was conducted according to the standards of the Declaration of Helsinki. All procedures involving human volunteers were approved by the local ethics committees in each of the eight centers engaged in the fieldwork. Parents or legal guardians were asked to sign a written informed consent that offered the opportunity to participate in the whole program or in selected modules of it.

### Physical examination and questionnaires

Children underwent a physical examination within the school premises during which anthropometric indices (weight, height, neck and waist circumference) were measured. A detailed description of the anthropometric measurements in the IDEFICS study, including intra- and inter-observer reliability, has been published [33,34]. The children were weighed in light clothes and without shoes by an electronic balance (Tanita BC 420 SMA, Tanita Europe GmbH, Sindelfingen, Germany) to the nearest 0.1 kg. Height was measured, without shoes, with a calibrated stadiometer (SECA 225 Birmingham, UK) with an approximation of 0.1 cm. BMI was calculated by dividing weight in kilograms by the square of the height in meters. Sex and age-specific *z*-scores were determinate, to normalize BMI measurements, according to the sex- and age-specific *z*-scores by Cole and Lobstein [35].

WC was measured, at the fine of normal expiration, midway between the superior iliac crest and the costal margin, using an inelastic tape (SECA 200), precision 0.1 cm, with the subject in standing position. For each child, normalized (*z*-score) WC values were calculated for statistical analysis [36].

NC was measured at the level of the thyroid cartilage, with inelastic tape (SECA 200) aligned horizontally, with the children standing upright, head held erect, eyes facing forward. The measurement was approximated to the nearest 0.1 cm.

Systolic and diastolic blood pressure were measured with an automatic sphygmomanometer (Welch Allyn 4200B-E2, Welch Allyn Inc. NY, Skaneateles Falls, USA), using a cuff appropriated to the arm circumference of the child, in conformity with the standardized procedures [37]. Children were requested to be seated for at least five minutes before measurement; two records were taken, with two minutes interval in between, plus a further one in case of difference >5% between the two previous readings. Normalized (*z*-score) average systolic and diastolic blood pressure values were calculated for statistical analysis [37].

Personal and familiar medical history, lifestyles of children and their parents, and socio-demographic indices were assessed by means of a self-administered parental questionnaire (PQ) filled in at home by parents and checked for inconsistencies at the time of the visit.

### Biological samples

Children participating in the IDEFICS baseline survey were asked to provide, on a voluntary basis, a fasting venous blood sample. If consent was not given for venous blood withdrawal, consent for capillary blood was asked the parents and the children. Details of the sample collection and analytical procedures in the IDEFICS survey have already been published [38,39]. Blood glucose, total cholesterol, high-density lipoprotein cholesterol (HDL-C) and triglyceride (TRG) were measured on a single blood drop by an automatic analyser (Colestech, LDX System, Cholestech Corporation, Hayward, CA, USA) [40]. Serum insulin concentrations was measured in a central laboratory through enzyme-linked immunesorbent assay kit. The homeostatic model assessment (HOMA) index was calculated according to formula: HOMA = serum insulin (mU $l^{-1}$) × blood glucose (mmol $l^{-1}$)/22.5] [41]. To normalize measurements for statistical analysis, sex and age-specific *z*-scores of HOMA index, TGR and HDL-C were determined [42,43].

### Metabolic syndrome score

Since there is no universal definition of the metabolic syndrome in children we have used a cMetS score as suggested in a recent publication on the IDEFICS study [11]. The cMetS score was calculated summing age and sex standardized *z*-scores of WC, HOMA index, HDL-C, TRG, systolic blood pressure (SBP) and diastolic blood pressure (DBP) according to following formula by Ahrens et al. [11]: cMetS score = $z_{WC} + (z_{SBP} + z_{DBP})/2 + (z_{TRG} - z_{HDL})/2 + z_{HOMA}$. The components used to calculate cMetS score were the same risk factors used in the adult MetS definition. A higher score was associated with an unfavorable metabolic profile [11]. In our analysis, we considered, as potential unfavorable metabolic profile, cMetS score values ≥ 90th percentile.

### Statistical analysis

All analyses were performed using SPSS Statistics for Windows, version 22.0 (IBM Corp., Armonk, NY, USA). Statistical significance was set at $p < 0.05$. The analyses were performed separately in boys and girls. Data were expressed as mean and 95% Confidence Intervals (CI).

The correlation between NC and MetS risk factors *z*-scores was analyzed using partial correlation coefficients.

In order to evaluate the ability of NC to identify children with unfavorable metabolic profile values ≥ 90th percentile, Receiver Operating Characteristic (ROC) curve [44,45] was performed, separately for one-year age groups (from 3 < 4 group to 9 < 10 group). The area under the ROC curve (AUC), which values range from 0.5 (null test) to 1.0 (perfect test) [46], together with sensitivity, specificity, 95% CI, optimal cut-off and *p*-values was calculated. A sample size = 26 was required to reject the null hypothesis, with a Type 1 error of 0.05 and a Type 2 error of 0.20.

The optimal cut-off values were defined as the point at which the value of "sensitivity + specificity − 1" was maximum (Youden's index) [47]. To verify the efficiency of the cut-off values, we also considered positive (LR+) and negative (LR−) likelihood ratios. LR+ was computed as sensitivity divided 1 − specificity and indicates how much the likelihood of a risk increases when a test is positive, according to Nafiu et al. [28]. On the contrary, LR− was computed as 1 − sensitivity divided specificity and indicates how much the likelihood of a risk decreases when a test is negative [28].

## Results

Table 1 shows the main anthropometric and metabolic characteristics of the study participants according to sex. All variables, except SBP and BMI, were significantly different between boys and girls.

Partial correlation coefficients between NC and MetS risk factors, after adjusting for BMI *z*-score and country of origin, are presented in Table 2. In both boys and girls, NC showed a significant positive correlation with *z*-score of WC, HOMA index and TRG ($p < 0.001$) and a negative association with HDL-C *z*-score ($p < 0.001$ in boys and $p < 0.005$ in girls). Only in girls, NC was positively correlated with SBP *z*-score ($p < 0.005$). No significant correlation was found between NC and DBP *z*-score.

The AUCs for NC associated with cMetS score values $\geq$ 90th percentile are indicated in Table 3. The AUCs values for each one-year group were significantly greater in girls than in boys ($p < 0.001$), with the exception of children into $5 < 6$ year-old age group. More precisely, based on AUC values, the power of NC to identify children with unfavorable metabolic profile can be defined "highly discriminatory" ($0.9 < AUC < 1.0$) in girls into $6 < 7$, $8 < 9$ and $9 < 10$ year-old age groups and in boys into $8 < 9$ year-old age group. NC showed slightly lower values of AUC ($0.8 < AUC < 0.9$) in all other age groups in both sexes except for children into $3 < 4$ year-old age group for which the power of NC was 0.71 for boys and 0.74 for girls.

Table 4 shows the different cut-off values for NC and their respective sensitivity and specificity values, both in boys and girls. For boys, optimal NC cut-off values, which identify cMetS score values $\geq$ 90th percentile, ranged from 26.2 cm for the lowest age group ($3 < 4$ years), up to 30.9 cm for the highest age group ($9 < 10$ years). In girls, corresponding values varied from 24.9 cm to 29.6 cm. In this table LR+ and LR− are also showed for each cut-off value. LR+ values were higher in boys than in girls with the exception of children into $8 < 9$ and $9 < 10$ year-old age groups.

**Table 2** Partial correlation[a] coefficients between neck circumference and metabolic syndrome risk factors stratified by sex.

| | Boys, $N = 7962$ | Girls, $N = 7711$ |
|---|---|---|
| WC *z*-score | 0.318** | 0.357** |
| SBP *z*-score | 0.030 | 0.050* |
| DBP *z*-score | −0.017 | −0.011 |
| HDL-C *z*-score | −0.060** | −0.056* |
| TRG *z*-score | 0.056** | 0.063** |
| HOMA index *z*-score | 0.068** | 0.111** |

*$p < 0.005$; **$p < 0.001$.
WC, waist circumference; SBP, systolic blood pressure; DBP, diastolic blood pressure; TRG, triglyceride; HDL-C, high-density lipoprotein cholesterol; HOMA, homeostatic model assessment.
[a] Adjusted for BMI *z*-score and country of origin.

## Discussion

In the present study we evaluated whether NC may be considered a potential indicator of MetS in European children participating at the IDEFICS study. In the first part of the analysis we observed a significant correlation between NC and MetS risk factors in both sexes. In particular, NC was correlated positively with *z*-score of WC, HOMA index and TRG and negatively with HDL-C *z*-score. These results are in agreement with Kurtoglu et al. who reported correlations between NC and cardiometabolic factors in children and adolescents between 5 and 18 years according to sex and puberty stage [31]. However, they demonstrated a positive correlation between NC and SBP and of NC and DBP in prepubertal boys and girls, while we only observed a positive correlation with SBP *z*-score in girls, and no significant correlation with DBP *z*-score. Moreover, a study on Greek children and adolescents (9–13 years) demonstrated a positive correlation between NC and HOMA index and a negative correlation one with HDL-C in both sexes [29],which is in line with our findings. In the same study, NC was positively correlated one with DBP and TRG in girls [29].

**Table 1** Characteristics of the sample.

| | Boys, $N = 7962$ | Girls $N = 7711$ | *p*-Value |
|---|---|---|---|
| Age (years) | 6.01 (5.97–6.04) | 6.07 (6.03–6.11) | 0.017 |
| BMI (kg $m^{-2}$) | 16.48 (16.42–16.53) | 16.42 (16.36–16.48) | 0.147 |
| NC (cm) | 26.50 (26.46–26.55) | 25.73 (25.69–25.77) | <0.001 |
| WC (cm) | 54.84 (54.68–55.00) | 54.33 (54.17–54.49) | <0.001 |
| SBP (mmHg) | 100.7 (100.5–100.9) | 100.5 (100.3–100.7) | 0.222 |
| DBP (mmHg) | 62.7 (62.5–62.8) | 63.7 (63.5–63.8) | <0.001 |
| Blood glucose (mmol $l^{-1}$) | 4.74 (4.72–4.75) | 4.62 (4.61–4.63) | <0.001 |
| Insulin (μl U $ml^{-1}$) | 4.1 (4.0–4.2) | 4.7 (4.5–4.8) | <0.001 |
| TC (mmol $l^{-1}$) | 4.05 (4.03–4.07) | 4.16 (4.14–4.18) | <0.001 |
| HDL-C (mmol $l^{-1}$) | 1.36 (1.35–1.37) | 1.32 (1.31–1.33) | <0.001 |
| TRG (mmol $l^{-1}$) | 0.66 (0.65–0.67) | 0.69 (0.69–0.70) | <0.001 |
| HOMA index (unit) | 0.89 (0.87–0.92) | 0.98 (0.95–1.00) | <0.001 |

Values are means (95% confidence interval), and *p* values are by one-way ANOVA.
NC, neck circumference; WC, waist circumference; BMI, body mass index; DBP, diastolic blood pressure; SBP, systolic blood pressure; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; TRG, triglyceride; HOMA, homeostatic model assessment.

**Table 3** Area under the curve values for neck circumference associated with an unfavorable metabolic profile (cMetS score ≥ 90th percentile) stratified by sex.

| Age groups (one-year) | Boys ($N$ = 323) | | | Girls ($N$ = 316) | | |
|---|---|---|---|---|---|---|
| | $N$ | AUC (95% CI) | $p$-Value | $N$ | AUC (95% CI) | $p$-Value |
| 3 < 4 | 40 | 0.713 (0.622–0.804) | <0.001 | 44 | 0.741 (0.662–0.820) | <0.001 |
| 4 < 5 | 49 | 0.805 (0.740–0.871) | <0.001 | 43 | 0.823 (0.764–0.883) | <0.001 |
| 5 < 6 | 39 | 0.874 (0.820–0.928) | <0.001 | 32 | 0.839 (0.772–0.906) | <0.001 |
| 6 < 7 | 48 | 0.895 (0.856–0.934) | <0.001 | 38 | 0.921 (0.884–0.958) | <0.001 |
| 7 < 8 | 81 | 0.885 (0.848–0.922) | <0.001 | 83 | 0.897 (0.862–0.933) | <0.001 |
| 8 < 9 | 59 | 0.907 (0.872–0.942) | <0.001 | 70 | 0.924 (0.898–0.950) | <0.001 |
| 9 < 10 | 7 | 0.881 (0.772–0.991) | =0.001 | 6 | 0.984 (0.955–1.000) | <0.001 |

Data are AUC (95% confidence interval). The AUC value was calculated for one-year age groups by Receiver Operating Characteristic (ROC) curve analysis. AUC, Area Under Curve.

The precise mechanisms involved in the correlation between NC and cardiometabolic risk factors are not still understood, but the lipolytic activity of upper-body fat may be one mechanism to explain this association [48]. Elevated systemic free fatty acids are directly associated with insulin resistance, low HDL-C, high TGR production, oxidative stress, endothelial dysfunction and development of hypertension [48,49]. Studies about regional lipolysis have demonstrated that upper-body fat is responsible for a much larger proportion in systemic free fatty acid release than visceral fat, particularly in obese individuals [50]. Since upper-body subcutaneous fat can be effortlessly evaluated by NC measurement [23], studies suggested that this measure may be considered a useful screening tool of metabolic risk also in children [29,31].

In the second part of the analysis, we evaluated the efficacy of NC as potential indicator of cMetS score ≥ 90th percentile in European children by using ROC analysis. We used cMetS score as a proxy of the MetS in our population. Several studies have supported the use of cMetS in pediatric epidemiological research [11,51] as it is statistically more powerful and less error prone compared to the categorical approach. Furthermore, the continuous score has a better correspondent to the fact that MetS refers to a complex concept where the factors are continuous variables and interact in a comprehensive ways [11]. A higher score indicates a less favorable metabolic profile [11]. We considered cMetS score values ≥ 90th percentile as potential unfavorable metabolic profile, because several studies that attempted to estimate the prevalence of MetS in children and adolescents have used this percentile as a cut-off values for various components, such as WC, TRG, HOMA index, blood pressure [52–54].

Considering our findings, NC turns out to be an excellent tool to identify cMetS score ≥ 90th percentile in European children. NC showed a high discriminatory power in almost all age groups in both sexes. Another novelty of this analysis was determining the cut-off values of NC for the identification of children with unfavorable metabolic profile. Our study established that, for boys, optimal NC cut-off values ranged from 26.2 cm for the lowest age group (3 < 4 years), up to 30.9 cm for the highest age group (9 < 10 years). In girls, corresponding values varied from 24.9 cm to 29.6 cm. These values, as already reported by Kurtoglu et al. [31], were higher in boys than in girls. It is well established that body fat distribution and its metabolic complications are different in boys and girls [16], but even though it is conceivable that sex hormones are connected with this difference, a precise cause has not been determined [55].

A strength of the present study is the large sample size and the use of precisely standardized phenotypic measurements within the eight European countries participating in the survey. In fact, all measurements were conducted according to detailed standard operation procedures. In particular, subsamples of study participants

**Table 4** Optimal cut-off values, Sensitivity, Specificity, LR+ and LR− of neck circumference to develop unfavorable metabolic profile (cMetS score ≥ 90th) stratified by sex.

| Age groups (one-year) | Boys, $N$ = 323 | | | | | Girls, $N$ = 316 | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Cut-off (cm) | Sensitivity (%) | Specificity (%) | LR+ | LR− | Cut-off (cm) | Sensitivity (%) | Specificity (%) | LR+ | LR− |
| 3 < 4 | **26.25** | 47.5 | 89.5 | 4.52 | 0.59 | **24.95** | 63.6 | 78.6 | 2.97 | 0.46 |
| 4 < 5 | **26.60** | 58.5 | 86.4 | 4.98 | 0.48 | **25.15** | 81.4 | 74.4 | 3.18 | 0.25 |
| 5 < 6 | **27.10** | 82.0 | 78.6 | 4.04 | 0.22 | **26.15** | 75.0 | 81.0 | 3.95 | 0.31 |
| 6 < 7 | **27.60** | 83.2 | 79.9 | 4.18 | 0.21 | **26.45** | 94.7 | 73.8 | 3.61 | 0.07 |
| 7 < 8 | **28.30** | 79.6 | 80.3 | 4.05 | 0.25 | **27.10** | 88.6 | 76.3 | 3.75 | 0.15 |
| 8 < 9 | **28.65** | 88.1 | 78.0 | 4.03 | 0.15 | **27.80** | 93.6 | 79.0 | 4.46 | 0.08 |
| 9 < 10 | **30.90** | 71.4 | 88.1 | 6.00 | 0.32 | **29.65** | 1.00 | 95.0 | 21.28 | 0.00 |

The optimal cut-off values calculated for one-year age groups by Youden index are displayed in bold. Sensitivity and specificity for each cut-off value of neck circumference are calculated by Receiver Operating Characteristic (ROC) curve analysis. LR+, likelihood ratios positive; LR−, likelihood ratios negative.

were examined repeatedly to calculate the inter- and intra-observer reliability of anthropometric measurements [34].

The present analysis has also certain limitations. The first one, common to most studies exploring metabolic syndrome in childhood, is the lack of clinically relevant, prospective outcomes in relation to the definition of the metabolic syndrome or its single components, forcing to use statistical definition instead, with plausible percentile values used to define cutoffs [11]. The findings are based on a cross-sectional study, which by its nature excluded the identification of causality. Moreover, the values of the parameters included in the cMetS score and the cut-off values of NC are population-specific. Therefore, the application of the present cut-off values should be made with caution in different populations.

Despite these limitations, this was the first study demonstrating the efficacy of NC in identifying European children with cMetS score values $\geq$ 90th percentile. The presented IDEFICS cut-off values of NC from our analysis, which correctly identified the majority of children with an adverse metabolic profile, could be used as a reference for boys and girls who are aged 3–10 years. Additional studies are warranted to evaluate the usefulness of NC as an index of adiposity in older children and adolescents.

In conclusion, as a simple anthropometric technique the assessment of NC may be used in clinical practice and in epidemiologic studies as an effective proxy for the identification of MetS during childhood.

## Conflict of interest statement

The authors declare that no conflict of interest existed.

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