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ORIGINAL ARTICLE

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Allometric considerations when assessing aortic aneurysms in Turner syndrome: Implications for activity recommendations and medical decision-making

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In Turner syndrome, the potential to form thoracic aortic aneurysms requires routine patient monitoring. However, the short stature that typically occurs complicates the assessment of severity and risk because the relationship of body size to aortic dimensions is different in Turner syndrome compared to the general population. Three allometric formula have been proposed to adjust aortic dimensions, all employing body surface area: aortic size index, Turner syndrome-specific Z-scores, and Z-scores based on a general pediatric and young adult population. In order to understand the differences between these formula we evaluated the relationship between age and aortic size index and compared Turner syndrome-specific Z-scores and pediatric/young adult based Z-scores in a group of girls and women with Turner syndrome. Our results suggest that the aortic size index is highly age-dependent for those under 15 years; and that Turner-specific Z-scores are significantly lower than Z-scores referenced to the general population. Higher Z-scores derived from the general reference population could result in stigmatization, inappropriate restriction from sports, and increasing the risk of unneeded medical or operative treatments. We propose that when estimating aortic dissection risk clinicians use Turner syndrome-specific Z-score for those under fifteen years of age.

KEYWORDS
allometry, aortic aneurysm, aortic dissection, aortic size index, aortic Z-scores, risk assessment, Turner syndrome

1 | INTRODUCTION

Catastrophic aortic dissection and rupture has been described in Turner syndrome in girls as young as 4 years of age (Lippe & Kogut, 1972) and in women up to 64 years old (Carlson & Silberbach, 2007). Clinicians therefore must monitor the size of the aorta in order to make decisions about permitting sports participation, initiating medications, and determining the need for operations. Accordingly, aortic measurements throughout the life span have been recommended (Gravholt et al., 2017).

Clinical geneticists, pediatric caregivers, and development biologists continue to grapple with the complex relationship between overall body size and the variable growth of individual organs. Different allometric approaches have been suggested to adjust aortic measurements for body size. For example, Davies et al. (2006) stratified risk in patients with aneurysmal disease using the aortic size index (ASI = aortic diameter (cm)/body surface area (m^2). In adults, the ASI is now routinely employed for medical and operative decision-making. We and others have observed that in adult women with Turner syndrome an ascending ASI >2.5 cm/m^2 is associated with an increased risk of aortic dissection (Carlson, Airhart, Lopez, & Silberbach, 2012; Matura, Ho, Rosing, & Bondy, 2007). However, ASI has never been studied in children. Importantly, ASI calculations in

children may be misleading because of the non-constant variance (heteroscedasticity) associated with rapid somatic growth.

The need for scaling based on body size has led to the practice in pediatric patients of transforming absolute measurements of the aorta into Z-scores employing body surface area (BSA) (Pettersen, Du, Skeens, & Humes, 2008; Sluysmans & Colan, 2005). The Z-score, also known as the standardized score, is the number of standard deviations that an individual's aortic diameter is above or below the mean value of a reference population. In pediatrics, the aortic Z-score is typically calculated by comparison to a healthy general reference population. However, the characteristic short stature, small BSA, and differences in somatic growth trajectories of those with Turner syndrome raise the concern that aortic measurements adjusted for norms based on the general population could lead to exaggerated estimates of aortic dimensions. Employing a non-specific reference population could potentially result in unnecessary restriction of physical activity and/or inappropriate treatment. Accordingly, Quezada et al. (2015) recently reported Turner syndrome-specific aortic Z-score formula by using healthy girls and women with Turner syndrome as the reference population. However, the relationship between Z-scores derived from children with Turner syndrome versus a general population (hereafter referred to as "pediatric/young adult based Z-scores") has not been previously reported.

Therefore, the goals of the present study are: (i) to evaluate the relationship between age and ASI in Turner syndrome and (ii) to compare Turner syndrome-specific Z-scores and pediatric/young adult based Z-scores.

2 | METHODS

2.1 | Study population

2.1.1 | Patient population and echocardiograms

All data utilized for the current analysis has been reported previously (Quezada et al., 2015). Briefly, 458 subjects with Turner syndrome ages 2–65 had focused echocardiograms performed as part of the Turner syndrome Healthy Heart Project, and all were performed at the annual meetings of the Turner syndrome Society of the United States. The Oregon Health & Science Institutional Review Board approved the protocol and continues to oversee this ongoing longitudinal study. Written consent from adult subjects or legal guardians and assent from children was obtained in all cases. Subjects included in the study were healthy females with Turner syndrome. Bicuspid aortic valve without significant aortic stenosis were included (Doppler-determined aortic valve velocity less than 2 m/sec). Exclusion criteria included greater than trace aortic insufficiency, un-operated, or structural congenital heart disease (other than unobstructed bicuspid aortic valve), and those who had elective surgery because of a dilated aorta, or who had a history of aortic dissection. The focused echo protocol used in this study has been previously described and was performed in accordance with the standard guidelines (Lopez et al., 2010; Quezada et al., 2015).

Aortic size index of the ascending aorta was calculated for all subjects (cm/m^2) using the Haycock body surface area equation (Haycock, Schwartz, & Wisotsky, 1978). For patients <age 30 years, Turner syndrome-specific Z-scores and pediatric/young adult based Z-scores (Colan, 2009; Sluymans & Colan, 2009) were also calculated. The pediatric/young adult aortic Z-scores calculator can be accessed on the web (http://zscore.chboston.org/) as is the calculator for Turner syndrome-specific Z-scores (http://www.parameterz.com/refs/quezada-ajmg-2015). Analyses focused on ascending but not root ASI because we found considerable overlap between healthy subjects and subjects with aortic dissection when aortic root ASI were compared (data not shown). The Turner syndrome-specific and pediatric/young adult based Z-scores for the ascending aorta for each subject are provided in the Supplementary Data.

2.2 | Statistical analysis

Plots demonstrating the relationship between ASI and subject age were subjected to a breakpoint analysis using the Segmented package in R. The breakpoint of 15 years of age was used for all downstream analyses (<15 years and ≥15 years) (Supplementary Figure S1). Mean ascending ASI values for both groups (<15 years and ≥15 years) were compared using a non-parametric Mann–Whitney–Wilcoxon test, where the significance level was <0.05. A chi-squared analysis, with Yate's correction, was performed to assess differences in proportions between < or ≥ 15 years and ASI values > or < 2.5 cm/m^2. Linear regression models were fit for both groups against the outcome variable ascending ASI, where the lines with 95% confidence intervals were plotted and the adjusted R^2 values and significance levels are reported. Plots for quality control of each model are in Supplementary Figures S2 and S3.

For each subject, data points for ascending aorta measurements (cm) versus BSA (m^2) were plotted and lines for Z-scores corresponding to 0 and ±2 standard deviations were overlaid on the plot, where blue solid lines represent Turner syndrome-specific equations and red dashed lines represent the pediatric/young adult population equations (Figure 2). For all subjects <30 years. old: ascending aorta Z-scores using the pediatric/young adult population equations and the Turner syndrome-specific equations were compared by scatter plot and means were compared using the Wilcoxon signed rank test. The difference between (delta) ascending aorta Z-scores were calculated for each subject (pediatric/young adult population Z-scores minus Turner syndrome-specific Z-score), and plotted against BSA (m^2), age (years), AAO dimensions (cm), and BMI (kg/m^2). For all plots, a linear regression model or quadratic regression model was fit to the data to look for an association between delta Z-scores as the outcome variable and either BSA, age, AAO dimension, or BMI as the predictor variable.

3 | RESULTS

3.1 | Aortic size index

The plot of ascending ASI versus age (Figure 1) shows there is a breakpoint at 15 years age where the relationship between ascending

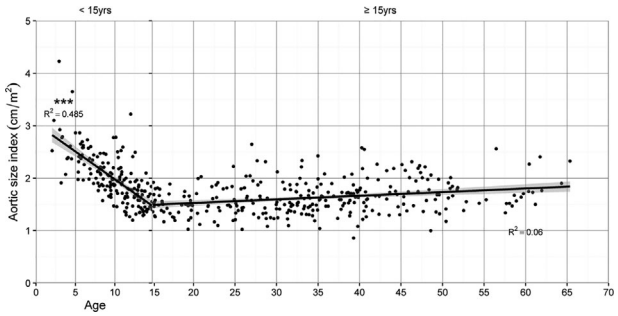

FIGURE 1 Aortic size index (cm/m^2) is independent of age only after 15 years. Regression lines are plotted with shading representing the 95%CI and with adjusted R^2 values of each model (***$p < 0.0001$)

ASI and age changes, (Supplementary Figure S1). In children with Turner syndrome <15 years, age is strongly negatively correlated with ASI values ($R^2 = 0.485$, $p < 0.0001$). For those ≥15 years with Turner syndrome, the correlation of ASI and age is minimal and is in the opposite direction. ASI values in those <15 years is significantly higher than in those ≥15 years (2.0 ± 0.5 vs. 1.6 ± 0.3, $p < 0.0001$). An ascending ASI >2.5 occurred in 14.0% of those <15 years and 23.2% <10 years. Whereas, in those ≥15 years an ascending ASI >2.5 occurred in 1.4% of subjects ($p < 0.0001$ chi squared, compared to <15 years).

3.2 | Ascending aorta Z-scores

Regression lines using both Turner syndrome-specific and pediatric/young adult based Z-scores corresponding to 0, +2, and −2 standard deviations are plotted for 246 measurements for 171 girls <15 years (Figure 2). Some subjects had multiple measurements performed over the years of the study.

Turner syndrome-specific Z-scores in subjects <15 years are significantly lower than Z-scores calculated according to pediatric/young adult based formula. The mean Z-scores for 246 measurements for subjects <15 years of age are −0.09 ± 0.89 (Turner syndrome-specific) versus 0.54 ± 1.40 (pediatric/young adult based) is significantly different ($p < 0.0001$, Wilcoxon signed rank). A majority, 95.5%, of the Turner syndrome-specific Z-scores were lower than pediatric/young adult based Z-scores (delta range 0–3.5), while only 4.5% had Turner syndrome-specific Z-scores higher than pediatric/young adult based Z-scores (delta range 0 to −0.15). A scatter plot of Turner syndrome-specific Z-scores versus pediatric/young adult based Z-scores shows this trend, where most data points fall below the diagonal line, indicating Turner-specific Z-scores are lower than the pediatric/young adult based Z-scores (Figure 3). However, as BSA increases the difference between the Turner syndrome-specific Z-scores and pediatric/young adult based Z-scores approaches zero (Figure 4a). Similarly, as BMI increases, differences approach zero (Figure 4d), whereas regardless of age pediatric and young adult-based Z-scores are consistently higher than Turner-specific Z-scores (Figure 4b). Importantly, for subjects, <15 years., who have a BSA similar to those who are ≥15 years (mean BSA 1.62 m^2 ± 0.25) there seems to be good agreement between Turner syndrome-specific and pediatric and young adult based Z-scores, although there is a small sample size (Figure 4a and Supplementary Figure S4). A larger AAO absolute diameter correlates with a markedly positive difference between the two Z-scores particularly for values >3 cm (Figure 4c, $R^2 = 0.29$, $p < 0.0001$).

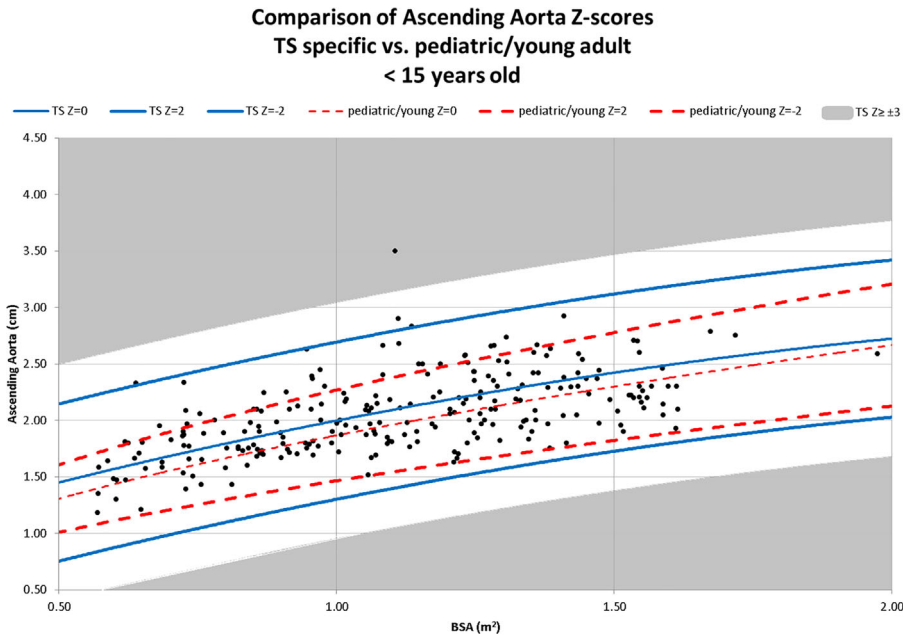

FIGURE 2 Comparison of TS-specific ascending aorta Z-scores to pediatric/young adult based Z-scores, by plotting of AAO dimensions (cm) versus BSA (m^2) for 246 subjects <15years. The lines for Z-scores generated corresponding to 0 and ±2 are overlaid on the plot (blue continuous lines = TS-specific and red dashed lines = pediatric/young adult based based). Gray shading represents TS specific Z-score lines > ±3. (TS, Turner syndrome; AAO, ascending aorta). [Color figure can be viewed at wileyonlinelibrary.com]

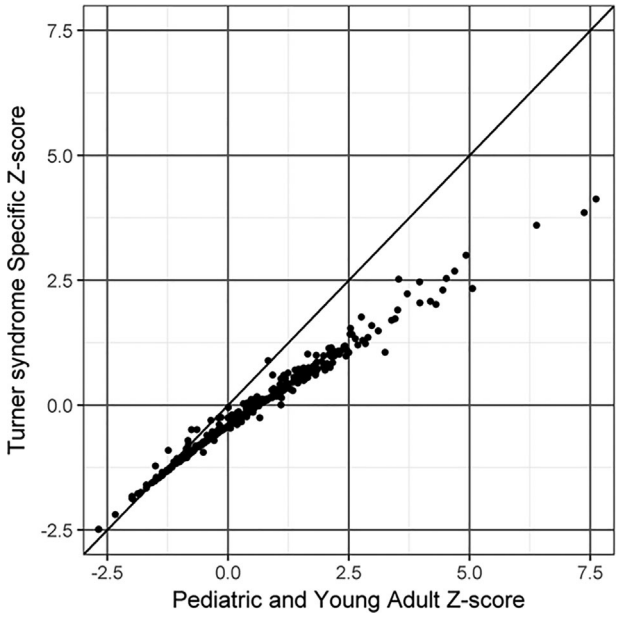

FIGURE 3 Pediatric and young adult based Z-scores plotted against Turner syndrome-specific Z-scores shows that TS specific Z-scores trend lower as the Z-scores becomes higher

4 | DISCUSSION

This study has two principal findings: (i) Ascending ASI in children under 15 years is likely to be a poor predictor of risk because many children have values >2.5 cm/m^2 and (ii) Turner syndrome-specific Z-scores are significantly lower than Z-scores calculated using a pediatric/young adult reference population. Matura et al. (2007) suggested that an ASI >2.5 cm/m^2 is predictive of aortic dissection. Carlson et al. (2012) subsequently confirmed this observation in nine cases of adults with type A aortic dissection where eight of nine had ascending ASI >than 2.5 cm/m^2. In the present study among 246 subjects ≥15 years, none of whom had a history of aortic dissection only 1.4% had an ascending ASI >2.5 cm/m^2. Thus, over the age of 15 years, ascending ASI >2.5 cm/m^2 can alert clinicians to those at risk for aortic dissection without classifying a large percentage of the population as high risk. The average BSA in subjects ≥15 years was 1.62 m^2. Thus, an average size adult woman with Turner whose aorta is >2.5 cm/m^2 is predicted to have absolute ascending aortic diameter of >4 cm. ASI calculation in individuals who are short-statured and obese or those who weigh very little relative to their height should be made with caution. Thus, an absolute value of >4 cm may be better predictor of risk in those with very low or high BMIs. Our results suggest that a child with Turner syndrome under 15 years is 10 times more likely than older healthy individuals to have an ascending ASI >2.5 cm/m^2, increasing the risk of obtaining false positive values. We found that as children approach the age of 15 years their aortic growth slows relative to body size, as indicated by decelerating ascending ASI. On the other hand, as healthy children under the age of 15 years grow, Z-scores remain stable. Therefore, ASI is only useful after 15 years where ASI becomes independent of age. For those older than 15 years of age, employing Z-scores may be reasonable, but there are no studies to date that demonstrate this.

Lopez et al. (2008) determined that Turner syndrome alone is associated with small increases in ascending aorta aortic diameter independently of other factors such as bicuspid aortic valve and aortic stenosis that separately increase aortic size. It is important to note that for an adult sized individual with Turner syndrome, an increase of a Turner syndrome-specific Z-score from 2 to 2.5 represents an increase in the ascending aortic diameter of 1.37 mm, which is approximately the axial resolution of standard echocardiography probes. Thus, a slightly larger aorta is likely to be a benign characteristic of the Turner syndrome phenotype and the higher Z-score estimates for healthy girls with Turner syndrome associated with general population-based reference could result in stigmatization, counterproductive restriction from sports participation and/or inappropriate medical treatment. We found that the difference between Turner syndrome-specific Z-scores and those derived from a general reference population diverged significantly at the largest absolute ascending aorta diameters (Figure 4c). Thus, it appears that the variability of Z-score estimates increases more in general population-based values as vessels reach extremely large diameters, as others have shown (Ronai et al., 2016). It has been reported that among those with adult BSA, there is no difference in Z-scores when the two formula are compared and could be used interchangeably (Prakash, Gen, & Milewicz, 2017) as suggested in (Figure 4a). On the other hand, for subjects at least to the age of 30 years, Turner specific Z-scores are significantly lower when compared to Z-scores based on the pediatric/young adult reference population (Figure 4B and Supplementary Figure S5).

Since ascending aortic ASI is age-dependent for those under 15 years, we believe that Turner syndrome-specific Z-scores may be helpful for decision-making. However, it is important to note that aortic dissection is rare under the age of 15 and no study has demonstrated Z-scores to be predictive of aortic dissection. For clinicians who must make decisions regarding medical/surgical therapies or sports participation, it may be reasonable to extrapolate from the adult experience. Thus, a Turner syndrome-specific Z-score >4 (Z-score calculator http://www.parameterz.com/refs/quezada-ajmg-2015) may serve as an indication of risk for aortic dissection because a Z-score value of four corresponds to an ascending ASI of >2.5 cm/m^2 in an adult with average body size (BSA ~1.6 m^2).

4.1 | Limitations

Aortic dissection under the age of 15 years is rare (Carlson & Silberbach, 2007) and no studies at any age have demonstrated that Z-score measurements are predictive. More follow-up is needed to determine if Turner syndrome-specific Z-scores improve predictive value compared to Z-scores based on a pediatric/young adult reference population. Hopefully, longitudinal data will become available as the Turner syndrome Healthy Heart study, that formed the basis of the present study, proceeds. To advance this research we would urge girls and women with Turner syndrome to join the Turner syndrome research registry (TSRR, http://www.turnersyndrome.org/ts-registry-love). Despite the limitation of available prospective data, the high false positive rate of the ASI for children under the age of 15 years makes Z-score assessment of aortic size in children a valuable tool for clinicians endeavoring to make difficult management decisions. Although, we found that many subjects under the

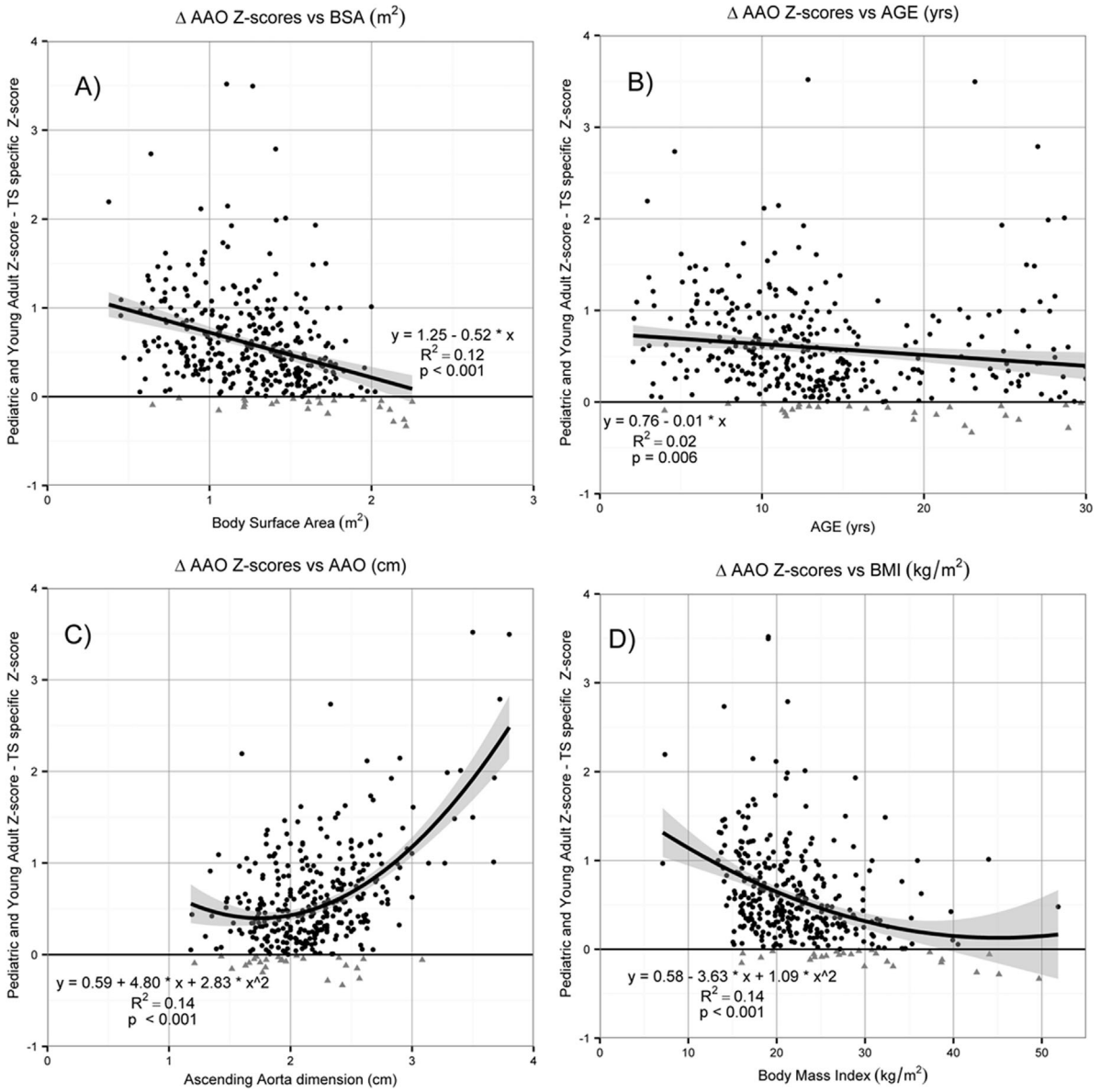

FIGURE 4 Plots of the difference between pediatric and young adult based Z-scores and Turner syndrome-specific Z-scores versus BSA, age, AAO dimensions, and BMI. The linear or quadratic regression lines were plotted with shading representing the 95%CI, along with equations and R^2. Gray triangles are cases where the difference between TS-specific Z scores is higher than pediatric and young adult based Z-scores. (AAO, ascending aorta; BSA, body surface area; BMI, body mass index; TS, Turner syndrome; CI, confidence interval)

age of 15 years and very few >15 years had ASI >2.5 cm/m^2 it is possible that longitudinal study may demonstrate a predictive value of the ASI in the young despite its low sensitivity.

In summary, ascending ASI in those under 15 years of age is significantly larger than those ≥15 years, increasing the likelihood for overestimation of the risk for aortic dissection. Therefore, for those <15 years, Z-score estimates of aortic size adjusted for body size are preferable. Furthermore, Turner syndrome-specific Z-score estimates in those who have BSAs <1.62 m^2 are lower than Z-scores based on the general pediatric/young adult reference population. We encourage the use of Turner syndrome-specific Z-scores because diagnosis of aortic enlargement using general population-based Z-score formulas may result in increased stigmatization, inappropriate restriction from sports, exclusion from other heart healthy activities, and increasing the risk of unneeded medical or operative treatments.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

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