J Autism Dev Disord
DOI 10.1007/s10803-017-3358-z

BRIEF REPORT

Brief Report: Physical Activity, Body Mass Index and Arterial Stiffness in Children with Autism Spectrum Disorder: Preliminary Findings

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Abstract We examined the association between physical activity (PA), body mass index (BMI) and novel measures of subclinical cardiovascular disease (CVD) in 15 children with autism spectrum disorder (ASD) (mean age 7 ± 2 years, 2 girls). PA was objectively assessed using accelerometry as time spent in moderate-vigorous physical activity (MVPA). Arterial stiffness was measured via aortic pulse wave velocity (PWV) and taken as a marker of subclinical CVD risk. MVPA was inversely associated with aortic PWV ($r = -0.46$, $p < 0.05$). BMI percentile was positively associated with aortic PWV ($r = 0.61$, $p < 0.05$). Overall findings suggest that reduced PA and higher body mass in children with ASD are associated with increased arterial stiffness which may have a detrimental impact on overall cardiovascular health.

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Keywords Children · Autism spectrum disorder · Blood pressure · Cardiovascular · Physical activity · Accelerometry

Introduction

As the number of children diagnosed with Autism spectrum disorder (ASD) continues to rise, so too will the eventual number of adults with ASD. This is important for many reasons, including findings that the prevalence of metabolic disease, hypertension, and dyslipidemia is higher in adults with ASD compared to adults without ASD (Croen et al. 2015; Fortuna et al. 2016; Tyler et al. 2011) and cardiovascular disease (CVD) is a leading cause of mortality among adults with ASD (Bilder et al. 2013; Mouridsen et al. 2008). Examining arterial health in childhood offers a window into CVD risk in adulthood (Fernhall and Agiovlasitis 2008; Kavey et al. 2003; Williams et al. 2002). The atherosclerotic process begins in childhood as nearly all children have some level of fat deposition in their arteries by age 3 and this process drastically increases after age 8 (Strong et al. 1992).

Increased arterial stiffness is a well-accepted indicator of subclinical CVD risk in children (Urbina et al. 2009). Arterial stiffness reflects the intrinsic elastic nature of arteries to expand and recoil during cardiac contraction and relaxation as a means of accommodating ejected blood volume from the heart (Townsend et al. 2015). Loss of arterial elasticity (e.g. increased stiffness) occurs with aging or in the presence of disease. Increases in arterial stiffness impose increased energetic demand on the heart and transmit pulsatile energy to the systemic circulation, damaging target organs throughout the body (Townsend et al. 2015). As such, increased arterial stiffness is an accepted predictor of future CVD

Published online: 08 November 2017

morbidity and mortality in adults (Townsend et al. 2015; Vlachopoulos et al. 2010).

Two prominent risk factors that contribute to a hastening of the atherosclerotic process and increased arterial stiffness are low levels of physical activity (PA) and overweight/obesity. Low levels of PA and overweight/obesity in children have been associated with increased arterial stiffness (Idris et al. 2015; Sakuragi et al. 2009). Moreover, low PA and overweight/obesity in childhood are strong predictors of elevated blood pressure (BP) and increased arterial stiffness later in life (Cruickshank et al. 2016; Juonala et al. 2005; Palve et al. 2014). Children with ASD engage in less PA then their typically developing peers (Bandini et al. 2013; Memari et al. 2013; Tyler et al. 2014). Thus low levels of PA and high body mass index (BMI) in children with ASD may reduce arterial health (increase arterial stiffness) and increase risk for future CVD. The purpose of this pilot investigation was to examine associations between objectively measured PA, BMI, and novel markers of subclinical CVD in children with ASD. We hypothesize that lower levels of PA and higher BMI will be associated with increased arterial stiffness.

Methods

Participants

Purposive sampling was used to identify possible participants for the study (Creswell 2009) in the form of a critical sampling technique (Cohen et al. 2011). In this technique, a particular group of participants are studied in order to gain knowledge that might have broader implications. Families of children with ASD were contacted via local advocacy listservs. A flyer with study and contact information was included. Parents of children with ASD that were interested in having their child participate in the research study contacted research personnel and were provided additional information via a scripted email and a scripted follow-up phone call. Snowball sampling was also utilized whereby consented/enrolled study participants assisted in recruiting potential future research participants from among their acquaintances.

Thirty children with ASD participated in this study. Inclusion criteria included a parent report of an ASD diagnosis from a psychologist or by school personnel. Current and Lifetime scores on the Social Communication Questionnaire were conducted to screen for the presence of an ASD diagnosis, with inclusion criteria for the study being a lifetime score of 14 or above (Eaves et al. 2006). Although IQ data were not available for the participants, the Vineland Adaptive Behavior Scales were completed, allowing for further characterization of general adaptive behaviors in our sample to serve as a proxy of level of functioning (Sparrow and Cicchetti 1985). This study was approved by the University Institutional Review Board and all guardians provided written consent.

Study Design

Following consent, parents/guardians provided information on child medical history and medication use via questionnaire. Children underwent anthropometric measures and cardiovascular measures. Children were fit with an accelerometer and parents received detailed instructions on proper device placement and time allotment for the child to wear the device.

Anthropometrics

Height was measured using a stadiometer and weight with an electronic scale (Tanita SC-240). Both measures were made in duplicate and averaged for final analyses. Body mass index (BMI) was calculated as weight (kg)/height $(m)^2$ and expressed according to age- and sex-specific percentiles from the Center for Disease Control (CDC) BMI-for-age growth chart (Kuczmarski et al. 2000). All anthropometric measures were conducted by a single researcher (T.B.) who has 12 years of measurement experience in both children and adults (Barreira et al. 2011, 2012, 2014).

Physical Activity

Parents were asked to assist their child in wearing an ActiGraph Link accelerometer (ActiGraph LLC, Pensacola, FL, USA) at the waist on an elasticized belt, and positioned in line with the right mid-axillary line, for at least 7 consecutive days (plus an initial familiarization day). The belt was to be removed for water-related activities and sleep. Data were collected at a sampling rate of 80 Hz, and subsequently downloaded using ActiLife Software (version 6.13.2, ActiGraph LLC). Raw accelerometer data were integrated into 15 s epochs and with the low-frequency extension filter enabled for the activity counts analysis (Cain et al. 2013) and with the default filter for step counts (Barreira et al. 2013; Tudor-Locke et al. 2015). Non-wear time was determined as any sequence of at least 20 consecutive min of 0 activity counts. Children were only included in this analysis if they had ≥ 4 days of monitoring with at least 10 h per day of waking wear time. The Evenson (Evenson et al. 2008) cut points (activity count ≥ 574 per 15 s) was used to identify moderate-vigorous physical activity (MVPA) and steps/day was used as an index of total PA volume.

Cardiovascular Measures

Brachial BP was measured with children in the seated position using a validated, automated brachial oscillometric cuff (Mobil-O-Graph, I.E.M., Stolberg, Germany) (Weber et al. 2011). Pulse wave analysis was simultaneously performed via the cuff clamping down on diastolic BP for 30 s, enabling acquisition of brachial pressure waveforms. From the brachial pressure waveform, an aortic pressure waveform was derived via the ARCSolver method and used to estimate aortic systolic and diastolic BP along with aortic pulse wave velocity (PWV) as a measure of aortic stiffness (Hametner et al. 2013).

Statistical Analyses

All data are reported as mean ± SD. Normality of distribution was assessed qualitatively using histograms and Q–Q plots as well as quantitatively using the Shapiro–Wilk test and the Kolmogorov–Smirnov test. Correlations of interest were investigated using Spearman correlation coefficients. All analyses were performed using Statistical Package for the Social Sciences (SPSS, version 23, Chicago, IL) with significance set a priori as $p < 0.05$.

Results

Twenty-two of 30 children met inclusion criteria for usable PA measures (minimum of 4 days with ≥ 10 h of daily wear time). Brachial BP was successfully measured in 26 of 30 children. Aortic hemodynamic parameters were further obtained in 19 of 30 children. Reason for missing data was excessive movement artifact causing signal noise, particularly during the sub-diastolic phase of measurement. Overall, 15 children (2 girls) had both PA measures and aortic hemodynamic measures and were thusly included in final analyses.

Descriptive characteristics for included study participants (n = 15) are presented in Table 1. Mean age for the children included was 7 years of age. Four children were taking prescription medications: 3 for attention deficit hyperactivity disorder (methylphenidate, guanfacine, clonidine), 1 for asthma (montelukast sodium) and 1 for obsessive compulsive disorder (fluoxetine). Additionally, 2 children were taking over-the-counter agents for allergies (cetirizine and fluticasone, as needed) and digestive needs related to indigestion and constipation (polyethylene glycol and lansoprazole, as needed).

Three of 15 children met recommendations for ≥ 60-min of MVPA per day, and 1 of 15 met recommendations for ≥ 11,500 steps/day (Adams et al. 2013). According to BMI percentiles, 5 of 15 children were overweight-obese.

Table 1 Descriptive characteristics ($n = 15$)

Variable, units	Mean ± SD
Age, years	7 ± 2
SCQ-L	23.06 ± 5.89
SCQ-C	15.93 ± 3.63
Vineland	
Communication	82.3 ± 12.2
Daily living skills	81.2 ± 15.6
Socialization	77.7 ± 11.7
Adaptive behavior composite	77.7 ± 10.4
BMI, percentile	67.8 ± 25.6
Brachial SBP (mmHg)	107 ± 8
Brachial DBP (mmHg)	67 ± 6
Heart Rate (bpm)	95 ± 16
Aortic SBP (mmHg)	98 ± 9
Aortic DBP (mmHg)	69 ± 6
Aortic pulse wave velocity (m/s)	4.5 ± 0.3
MVPA (min/day)	44.7 ± 17.8
Mean steps/day	7752 ± 1763

SCQ-L social communication questionnaire-lifetime, *SCQ-C* social communication questionnaire-current, *Vineland* Vineland Adaptive Behavior Scales standard scores with M = 100, SD = 15

The Vineland Adaptive Behavior Scales were completed for 13 of the 15 participants

BMI body mass index, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *MVPA* moderate-vigorous physical activity

A correlation matrix is displayed in Table 2. MVPA was inversely associated with aortic PWV ($p < 0.05$). Steps/day were inversely associated with aortic ($p < 0.05$) but not brachial ($p > 0.05$) systolic BP. Steps/day was also inversely associated with aortic PWV ($p < 0.05$). Moreover, BMI percentile was positively associated with aortic PWV ($p < 0.05$), aortic systolic BP ($p < 0.05$) and brachial systolic BP ($p < 0.05$). Physical activity and aortic hemodynamic parameters were not associated with SCQ-L, SCQ-C or Vineland adaptive behavior metrics ($p > 0.05$ for all, data not shown).

Discussion

Blood pressure (BP) remains a standard clinical measure with respect to assessing risk for CVD. BP is conventionally measured in the arm (i.e. brachial artery) but this may not accurately reflect hemodynamic stress placed on major blood vessels throughout the body such as the aorta or target organs throughout the body such as the heart (Roman et al. 2007). Recent methodological advances now allow for the non-invasive assessment of aortic BP (i.e. blood pressure just outside the heart) and aortic stiffness, both of which hold greater prognostic capability as measures of

Table 2 Correlation coefficients for measures among children with ASD ($n = 15$)

Variable	MVPA	Steps/day	$BMI_{percentile}$	$SBP_{brachial}$	SBP_{aortic}	PWV
Steps/day	0.782					
$BMI_{percentile}$	−0.304	−0.440*				
$SBP_{brachial}$	−0.265	−0.201	0.604*			
SBP_{aortic}	−0.492*	−0.489*	0.505*	0.667*		
PWV	−0.462*	−0.586*	0.611*	0.670*	0.907*	
Age	−0.144	0.267	−0.178	0.014	0.102	0.01

MVPA moderate-vigorous physical activity, *BMI* body mass index, *SBP* systolic blood pressure, *PWV* pulse wave velocity

*$p < 0.05$

subclinical CVD than conventional BP in adults and children alike (Townsend et al. 2015; Urbina et al. 2009). The novel finding of this preliminary investigation was that both lower PA (assessed as total volume of activity with steps/day and intensity of activity with MVPA) and higher BMI were each associated with increased aortic BP and aortic stiffness in children with ASD. Measures of PA and subclinical CVD risk did not correlate with the severity of ASD symptoms or adaptive behavior level. Overall findings suggest that reduced PA and higher BMI may have a detrimental impact on cardiovascular health in children with ASD.

Lower PA in children is associated with obesity and higher blood pressure (Leary et al. 2008) and increases risk for CVD in adulthood (Baker et al. 2007; Ried-Larsen et al. 2015). This may be important as the prevalence of obesity is higher in children with ASD possibly contributing to a higher prevalence of hypertension in young adults with ASD (Croen et al. 2015; Fortuna et al. 2016; Tyler et al. 2011). Our results are consistent with the literature and support that in general, children with ASD did not meet current PA recommendations (Bandini et al. 2013; Memari et al. 2013; Tyler et al. 2014). A strength of our current study was objectively measuring PA via accelerometry, which has only been done in limited fashion in this population. According to normative data from over 1300 typically developing children without ASD, based on age and sex, children with ASD herein were in the 5th percentile for steps/day (Barreira et al. 2015). Children with ASD are also at a particularly high risk for obesity (Broder-Fingert et al. 2014; Curtin et al. 2010; Zuckerman et al. 2014) and approximately 1/3 of participants in the present study were overweight/obese.

Of particular concern, both lower PA and higher BMI were each associated with higher aortic BP and aortic stiffness in children with ASD. According to recently published normative data collected in over 1400 typically developing children without ASD, based on age and sex, children with ASD herein were in the 95th percentile for aortic BP and aortic stiffness (Elmenhorst et al. 2015). Taken together and our findings support our hypothesis that lower PA and higher body mass were associated with increased aortic hemodynamic burden and subclinical CVD risk in children with ASD.

In children without ASD, literature is emerging noting favorable associations between increased PA (volume and intensity) and reduced arterial stiffness (Sakuragi et al. 2009). Similarly, normal weight children tend to have lower arterial stiffness compared to overweight/obese children (Hudson et al. 2015). Low levels of PA and overweight/obese status is known to have an unfavorable effect on metabolic regulation (dyslipidemia, insulin resistance and poor glucose homeostasis) and promotes systemic low-grade inflammation. Metabolic dysregulation and inflammation have been suggested to cause premature vascular aging, ultimately having negative effects on arterial elastic properties and preferentially increasing aortic BP (Totaro et al. 2015).

The gold standard measure of aortic stiffness is carotid-femoral PWV using applanation tonometry (Townsend et al. 2015). We chose an oscillometric method as we surmised greater participant comfort with this cuff-based approach; the gold standard tonometric approach necessitates ECG (electrode placement on the chest/shoulders and lower rib cage/upper abdomen) and carotid (neck) femoral (groin) palpation. Oscillometric approaches do not require ECG use or surface palpation of various pulse sites. A cuff is wrapped around the upper arm and sensors detect the underlying brachial pulse to re-create a blood pressure waveform. From this waveform, aortic blood pressure and stiffness can be derived. Unfortunately, this method proved to be sensitive to movement and we were unable to obtain high quality brachial pressure waveforms in approximately 35% of participants precluding calculation of aortic BP and aortic stiffness in all children. Moreover, some children were uneasy with the measurement as it reminded them of a visit to a physician, a stress-provoking scenario to some children. We suggest use of low-cost home brachial BP monitors along with storyboards as a way to habituate children to the process of BP measurement prior to research data acquisition. Storyboards can include pictures of the blood pressure machines along with pictures of the research lab environment. Parents can prepare their

child for the sensation of the cuff "squeezing" the arm by explaining that the cuff will give an "arm hug" that will not be long in duration. Parents can utilize home BP monitors to familiarize their child to the method, demonstrate the measurement, and have the child perform measures on the parent and then on themselves. Additional studies using tonometric and other oscillometric approaches are needed to reveal the most efficacious manner to monitor aortic hemodynamic properties in children with ASD.

Limitations to this study should be noted. The final sample size for this study was small and this is a notable limitation. Medications used to treat health conditions associated with ASD may have impacted blood pressure and arterial stiffness (Kelly et al. 2014; Steinmann et al. 2015). This study was not powered to fully explore the impact of medications on the aortic hemodynamic profile in children with ASD. We used the Evenson (Evenson et al. 2008) cut point for MVPA and other cut points could provide different results, however it has been demonstrated that the Evenson cut point is the most accurate for this age group (Trost et al. 2011).

In conclusion, lower levels of PA and higher BMI were each associated with increased aortic BP and increased aortic stiffness, indices of subclinical CVD risk. Children with ASD that do not engage in appropriate levels of habitual PA and maintain a healthy body habitus have less than ideal cardiovascular health. Studies will be needed to explore if promoting increased PA and weight management in children with ASD has favorable effects on cardiovascular health, potentially mitigating future risk for CVD.

Acknowledgments Support for this study provided by the Jim and Julie Boeheim Foundation and the John P. Hussman Foundation.

Author Contributions All authors were involved with study conceptualization, study design, study analyses, data interpretation and manuscript preparation. KSH oversaw all cardiovascular data acquisition and interpreted all cardiovascular results. TVB oversaw measurement of height, weight, and physical activity. TVB also analyzed all physical activity data and interpreted all results. NR oversaw all behavioral assessments and interpretations. LC, BAM and CEA assisted with participant recruitment. MLN assisted with study visit organization and data collection.

Compliance with Ethical Standards

Conflict of interest The authors declare that they have no competing interests.

Ethical Approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed Consent Informed consent was obtained from all individual participants (guardians) included in the study.

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