BONE HEALTH AND PHYSICAL ACTIVITY IN CHILDREN WITH AUTISM SPECTRUM DISORDER

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By

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PREFACE AND CANDIDATE'S ROLE

Sections of this thesis have been published or submitted for publication as multi-authored papers in refereed journals. This section defines the role of the candidate and co-authors for each publication and related conference presentations.

STUDY 1: BONE HEALTH IN CHILDREN WITH ASD: A SYSTEMATIC REVIEW AND META-ANALYSIS

Publication 1: Rostami Haji Abadi, M., Neumeyer, A., Misra, M., & Kontulainen, S. (2021). Bone health in children and youth with ASD: a systematic review and meta-analysis. *Osteoporosis International. https://doi.org/10.1007/s00198-021-05931-5.*

Mahdi Rostami (MR) conceptualized and designed the study together with supervisor Dr. Saija Kontulainen (SK). MR performed the literature search, data extraction and analyzed the data. MR interpreted the results together with SK and drafted and revised the manuscript based on the feedback from Dr. Ann Neumeyer, Dr. Madhusmita Misra and SK.

The results in this study were presented at local, national and international conferences:

i. *Local Meeting:* Department of Pediatrics University of Saskatchewan Child Health Research Day, Saskatoon, Saskatchewan, Canada; June 18, 2020.
ii. *National:* Canadian Joint and Bone Conference (CJBC). London, Canada, June 12-13, 2020.
iii. *International:* The American Society of Bone and Mineral Research (ASBMR) Annual Meeting. Seattle, US, September 11-15, 2020.

STUDY 2: BONE STRENGTH AND STRUCTURE IN MALE CHILDREN WITH AUTISM SPECTRUM DISORDER

Publication 2: Rostami Haji Abadi. M., Johnston, JD., Vatanparast, Hassanali., & Kontulainen, S. (2021). Muscle power mediates deficits in the tibia bone deficits in male children with autism spectrum disorder. (In preparation).

SK conceived and designed the study. MR analyzed the data, interpreted the findings with SK and drafted as well as revised the manuscript based on the feedback from Dr. J.D. Johnston (JDJ), Dr. Hassanali Vatanparast (HV) and SK.

The results in this study were presented at local, national and international conferences:

i. *Local Meeting:* Department of Pediatrics University of Saskatchewan Child Health Research Day, Saskatoon, Saskatchewan, Canada; April 18, 2019.
ii. *Local Meeting:* Department of Health Sciences of University of Saskatchewan, Life and Health Sciences Research Expo, Saskatoon, Saskatchewan, Canada; May 2, 2019.
iii. *National:* Canadian Society for Exercise Physiology (CSEP), Zooming into future: Exercise Science in the virtual age (online), October 13-16, 2021.
iv. *International:* The XXVII Congress of the International Society of Biomechanics (ISB). Calgary, Canada, July 31 - August 4, 2019.

STUDY 3: MODERATE-TO-VIGOROUS PHYSICAL ACTIVITY IN CHILDREN WITH ASD: A META-ANALYSIS

Publication 3: Rostami Haji Abadi, M., Zheng, Y., Wharton, T., Colleen, D., Vatanparast, Hassanali., Johnston, J., & Kontulainen, S. (2021). Children with autism spectrum disorder spent 30 min less daily time in moderate-to-vigorous physical activity than typically developing peers: a meta-analysis of cross-sectional data. *Rev J Autism Dev Disord (2021). https://doi.org/10.1007/s40489-021-00262-x.*

MR conceptualized and designed the study. MR, Yuwen Zheng (YZ) and Tiffany Wharton (TW) performed the literature search and data extraction. MR analyzed the data and interpreted the results together with SK. MR drafted and revised the manuscript based on the feedback from SK, YZ, TW, Dr. Colleen Dell (CD), HV and JDJ.

The results in this study were presented at national conferences:

i. *National:* Canadian Society for Exercise Physiology (CSEP): For the Health of it, Applying Exercise Science Research to Practice, Kelowna, BC, November 6-9, 2019.

STUDY 4: THERAPY DOG ASSISTED PHYSICAL ACTIVITY INTERVENTION IN CHILDREN WITH AUTISM SPECTRUM DISORDER

Publication 4: Rostami Haji Abadi, M; Hase, B; Dell, C; Johnston, JD; Kontulainen, S. Therapy Dog Assisted Physical Activity Intervention in Children with Autism Spectrum Disorder: A Feasibility and Efficacy Pilot. Anthrozoös (Accepted).

SK conceived the study. BH, CD, JDJ and SK contributed to the study design. BH, CD and SK contributed to data acquisition. MR analyzed the data, interpreted the findings with SK and drafted and revised the manuscript based on the feedback from SK, BH, CD and JDJ.

The results in this study were presented at local, national and conferences:

i. *Local Meeting:* Department of Pediatrics University of Saskatchewan Child Health Research Day, Saskatoon, Saskatchewan, Canada; April 26, 2018.
ii. *Local Meeting:* Department of Pediatrics University of Saskatchewan One Health Leadership Experience, Saskatoon, Saskatchewan, Canada; August 24, 2018.
iii. *National:* Canadian Society for Exercise Physiology (CSEP): Health in Motion, Science in Exercise, Niagara Falls, Ontario, October 31 - November 3, 2018.

ABSTRACT

Objectives. The overall objectives were to synthesize and update the evidence of bone health in children with autism spectrum disorder (ASD), synthesize the evidence of moderate-to-vigorous physical activity (MVPA) in children with ASD vs. typically developing children (TDC), and assess the feasibility and efficacy of an animal-assisted physical activity (PA) intervention in children with ASD.

Methods. I performed two meta-analyses to compare imaged bone properties and MVPA between children with ASD and TDC. I used site-specific MANCOVAs to test bone strength, area and mass differences at distal and shaft sites of radius and tibia between male children with ASD (n=15) and TDC (n=81) and explored mediating effects of PA, selected nutrients, grip strength and long jump distance on bone differences. I assessed the feasibility and efficacy of a pilot animal-assisted PA intervention in children with ASD (n=20).

Results. Compared to TDC, the first meta-analysis indicated 0.7-1.0 SD lower areal bone mineral density, and the qualitative analysis suggested deficits in bone mass, micro-architecture and strength in children with ASD. Our comparison suggested 9-18% lower bone strength, structure, and mass at the distal tibia and the shaft sites of radius and tibia in male children with ASD when compared to TDC. Long jump distance accounted for 40-51% of the variance in bone strength and structure deficits at the tibia. The second meta-analysis indicated that children with ASD spent 30 minutes less in daily MVPA and had 4 times the odds of not meeting the recommended daily MVPA. The animal-assisted PA intervention was feasible, and children with ASD had 13% more minutes of light PA and 22% lower sedentary time in sessions with the therapy dog.

Conclusion. My thesis provided evidence of bone deficits in children with ASD, partly explaining the higher risk of fracture in individuals with ASD. The evidence also suggested that lower PA and muscle performance may contribute to bone deficits in children with ASD. Future PA intervention may benefit from the evidence of feasibility and efficacy of the animal-assisted PA interventions to optimize bone health and development in children with ASD.

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DEDICATION

I would like to dedicate this thesis to my wife, Parvin Pazira. Parvin and I got married when we were master's students at the University of Isfahan, and during my master's and doctoral degrees, Parvin has been incredibly supportive. Without her incredible supports during the past decade, I would not be able to apply and accepted for this PhD position in the first place. I would also dedicate this thesis to my mother, Hurieh Rajabi Moghadam, and my father, Bemanali Rostami Haji Abadi, who always supported me throughout my life. Last but certainly not least, I would like to dedicate my thesis to my son, Arya, who add more happiness and joy to our life.

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LIST OF ABBREVIATIONS

AAI	Animal assisted intervention
aBMD	Areal Bone Mineral Density
aBMD	Areal Bone Mineral Density
ADI-R	Autistic Diagnostic Interview-Revised
ADOS	Autism Diagnostic Observation Schedule
ASD	Autism Spectrum Disorder
BMAD	Bone Mineral Apparent Density
BMC	Bone Mineral Content
BMI	Body Mass Index
BSIc	Bone Strength Index for compression
CCS	Calibrated Severity Scores
CI	Confidence Interval
CoA	Cortical Area
CoC	Cortical Content
CoD	Cortical Density
CPM	Count Per Minutes
CV	Coefficient of Variation
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders-Fourth Edition
DSM-IV-TR®	Diagnostic and Statistical Manual of Mental Disorders-Fourth Edition-Text Revision
DSM-V	Diagnostic and Statistical Manual of Mental Disorders-Fifth Edition
DXA	Dual-energy X-ray Absorptiometry
ES	Effect Size
FN	Femoral neck
HR-pQCT	High Resolution Peripheral Quantitative Computed Tomography
I^2	I-squared
ID	Intellectual Disability
IQ	Intelligence quotient
IQR	Interquartile Range
IV	Inverse Variance

LS	Lumbar Spine
MD	Mean Difference
MRI	Magnetic Resonance Imaging
MuA	Muscle Area
MVPA	Moderate-to-Vigorous Physical Activity
PA	Physical Activity
PAAL	Physical Activity for Active Living
PBM	Peak Bone Mass
PDD-NOS	Pervasive Developmental Disorder—Not Otherwise Specified
PE	Physical Education
PI	Prediction Intervention
pQCT	Peripheral Quantitative Computed Tomography
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
QCT	Quantitative Computed Tomography
SD	Standard Deviation
SE	Standard Error
SMD	Standardized Mean Difference
TB	Total Body
TDC	Typically Developing Children
TH	Total Hip
ToA	Total Area
ToC	Total Content
ToD	Total Density
TrA	Trabecular Area
TrC	Trabecular Content
TrD	Trabecular Density
VPA	Vigorous Physical Activity

LIST OF APPENDICES

1. INTRODUCTION

Autism Spectrum Disorder (ASD) is a developmental disorder with the core symptoms of impaired social, communication, and language skills, along with restricted and repetitive behaviors (1). Children with ASD have concurrent conditions that worsen their overall health and increase healthcare system use (2). For example, individuals with ASD, including children, are at higher risk for the hip, forearm, and spine fractures than those without ASD (3).

The higher fracture risk in individuals with ASD is not fully understood, and it might be linked to poor bone development during childhood. Previous studies reported lower bone mass in children with ASD when compared to typically developing children (TDC) (4–8). Limited evidence also suggests bone structures and strength deficits at the distal radius and tibia in children with ASD (4); however, there are not yet systematic reviews or meta-analyses synthesizing the evidence of bone health in children with ASD.

Although poor bone health in children with ASD is inadequately understood, lower physical activity (PA), muscle strength and power, and poor nutrition are some of the factors that can negatively affect bone development and contribute to observed bone deficits in children with ASD. Children with ASD have lower PA reported in a recent systematic review (9). In addition, children with ASD also have lower muscle strength and power compared to TDC (10–14). Limited vigorous and impact-type activities and muscle force may prevent children with ASD from gaining the loading stimulus required for optimal skeletal development (15–17). However, the evidence linking lower PA activity and muscle strength and power to the bone deficit is lacking in children with ASD. Moreover, interventions aiming to increase PA and muscle strength in children with ASD are scarce.

Although Children with ASD have lower PA and higher sedentary time (9); it is still unknown if children with ASD spent less time in moderate-to-vigorous PA (MVPA) compared to TDC. Previous studies reported inconsistent MVPA differences between children with ASD and TDC (18–26). There are not yet systematic reviews and meta-analyses synthesizing the evidence of MVPA in children with ASD.

Difficulties in social interactions may contribute to the lower PA in children with ASD (27,28). Animal assisted intervention (AAI) offers an attractive option for children with ASD, as the presence of therapy dogs has improved social interaction in children with ASD (29–32). The presence of a therapy dog increased PA in children with obesity (33) and adolescents with

orthopedic limitations (34). In addition, a qualitative study suggested that children with ASD may benefit from integrating a therapy dog into a PA program (35,36). However, no quantitative study has assessed if an AAI with therapy dogs can increase PA in children with ASD.

Together, the overall goals of this thesis were to1) synthesize and update the evidence of bone health in children with ASD; 2) synthesize the evidence of MVPA in children with ASD vs. TDC; 3) assess the feasibility and efficacy of an animal assisted PA intervention in children with ASD.

2. LITERATURE REVIEW

2.2. Bone health measurement in children

2.2.1. The importance of bone health measurement in children

Bone health and development in childhood and adolescence affect the lifetime risk of bone osteoporosis. The size of peak bone strength obtained by childhood and early adulthood is the critical determinant of the lifetime risk for osteoporosis (37). Bone strength is determined by bone mass and size, geometry, and microarchitecture built within childhood and early adulthood (37). Around 90% of peak bone mass (PBM) is accrued by the end of the second decade, and the rest of the PBM is accumulated during the third decade (38). PBM is the primary determinant of bone health and fracture risk in older adults, and a 10% increase in PBM could consequently reduce fracture risk by 50% in healthy adults (39). Therefore, bone gain optimization in the first two decades can assist in preventing osteoporosis later in life. As the awareness of the value of early bone health has improved, there is a concern for young patients to confront threats to the bone deficit (40). This concern has directed to the extended application of bone assessment in pediatrics, particularly those with higher fracture risk (40).

2.2.2. Bone Mass measurement

Bone is a bio-phasic composite material (organic and inorganic), structurally complex and hierarchically designed (41) that its material and structural properties (mass, size, geometry and microarchitecture) determine its stiffness and strength under mechanical loads (42–44). aBMD measured with Dual-Energy X-ray Absorptiometry (DXA) is the most common bone densitometry method. However, the aBMD is a two-dimensional measure that cannot assess the actual volumetric bone density (40). aBMD is considered a surrogate measure of bone strength (40), but aBMD only accounts for 60–70% of the variation in bone strength (43). The results of bone densitometry are used to determine if the bone deficit is present and to predict the risk of future osteoporotic fracture (40); however, the ability of aBMD for predicting osteoporotic fracture is limited (45).

The most common clinical tool for assessing bone mass in children and youth is DXA (38,46), which measures aBMD and BMC. DXA can measure the TB and sites such as the LS, TH and FN (40). Total body and lumbar spine BMC have been considered the preferred methods for measuring bone mass in children (47). DXA is a 2-dimensional tool that undervalues aBMD for smaller bones and overvalues for larger bones (38,46). DXA has an error in measuring

aBMD (4±20%) due to variations in beam absorption properties of other tissues such as muscle, fat, and marrow encircling or inside the bone (48). Therefore, reporting height-adjusted BMC and aBMD Z-scores has been recommended when studying children, particularly those with chronic disease or delayed puberty (47,49).

2.2.3. Bone geometry, structure and strength measurements

The three-dimensional densitometry methods measure volumetric bone mineral density (BMD) independent of bone size. These three-dimensional tools can also evaluate bone structure and geometry and analysis cortical and trabecular bone separately. All these measurements can be done in children with low radiation exposure (50). Therefore, using these tools may provide more information about the bone structure and strength deficits in individuals with high fracture risk.

Quantitative computed tomography (QCT) scanners provide 3-dimensional images that separate cortical and trabecular bone (50). A full-sized QCT scanner can measure both axial and appendicular skeletal sites (50). The new generation of QCT scanners have high resolution (approximately 0.6 mm), short scan time (<30 s), and high precision scanning spine and femur (CV ~1%) (50). In addition, there is no need for positioning support in the new QCT scanner, making the scanner proper for children with disabilities (50). However, the radiation dose is higher than DXA, and it is a high cost (50).

Peripheral Quantitative Computed Tomography (pQCT) can scan the lower and upper extremities and is usually used to scan distal and shaft sides of radius or tibia with a reasonable scan time (50). The total, cortical, and trabecular bone area, content, and density are the primary bone outcomes measured by pQCT from various sites on the radius and tibia in children (51). Both bone area and geometry are essential for estimating bone strength from pQCT images at long bones (51,52). Bone strength (i.e., bone strength in compression, a bone strength index (BSIc), and density-weighted polar section modulus (SSIp)) can be estimated using these data (50). The pQCT bone strength estimated values had been validated at the distal and shaft sites of the radius and tibia (52,53). The bone strength is estimated against compressive loading at the distal sites, determined by multiplying total bone area and squared total bone density (52). At the shaft site, bone resistance against torsional loading is represented by density-weighted polar section modulus (51). Good precision of pQCT outcomes at the distal (CV_{RMS} 4-19%) and shaft sites (CV_{RMS} 4-8%) of radius as well as the distal (CV_{RMS} 2-14%) and shaft (CV_{RMS} 2-6%) sites

of tibia reported in children (51). The most precise outcomes in children were bone density and cortical properties (CV_{RMS} < 5%) (51).

The HR-pQCT has a higher resolution than pQCT, which allows for assessing the microarchitecture of cortical and trabecular bone compartments at distal radius and tibia. The first generation of HR-pQCT has a resolution of 82 µm and the second generation has a higher resolution of 60 µm (54,55). HR-pQCT obtains a nine mm-thick volume of bone in around 3 minutes, requiring the patient to stay still (56). The lengthy scan time needs a stable fixation of the limb as well as a quiet and child-friendly environment (50). HR-pQCT scanners present an adequate resolution for making microstructural finite element models in order to estimate the failure load, a surrogate measure of bone's resistance to fracture, as well as trabecular plate and rod microstructure and cortical porosity (56). HR-pQCT has been validated against bone microarchitecture measurements using micro-CT in adult cadavers (57,58). The first generation of HR-pQCT precision errors were 1-8% for trabecular bone outcomes and 1-11% for cortical bone outcomes at the distal radius and tibia in children (59). The cortical bone outcomes acquired utilizing the advanced cortical evaluation showed lower precision errors compared to cortical outcomes obtained utilizing the standard evaluation (59). The first generation of HR-pQCT voxel size (82 µm) is insufficient to capture smaller bone structures (e.g., cortical pores smaller than 82 µm) in children (60). Although several microarchitectural outcomes such as trabecular number are estimated by the mean diameter of spheres between trabecular ridges, other outcomes such as trabecular thickness and separation depend on underlying bone structure assumptions that were only validated in adults (61,62). The second generation of HR-pQCT has a smaller voxel size (60 µm) which allows direct analysis of trabeculae (63). Due to high resolution and relatively long scan times (3 min), HR-pQCT requires stable limb fixation and a quiet scanning setting to minimize movement artifacts (64).

Magnetic resonance imaging (MRI) is the most recent technique for skeletal assessment in children (40). MRI provides a volumetric measure of bone as well as trabecular and cortical bone microstructures without using ionizing radiation. MRI also gives measures of bone morphometry from which the parameters of bone strength can be estimated (40). MRI scanners scan both the central and appendicular skeleton. In addition, the concurrent scanning of several limbs and scanning multiple anatomical planes without repositioning is possible (40). However, the scanner is noisy, and the scan time is extended, about 20-30 with the positioning, which can

be problematic in children as they should stay still during the scan (50). In addition, the scanner and the room are not child-friendly, and parents should leave the room during the scan, making the use of MRI more challenging in children (50).

2.3. Mechanical loading and bone development and maintenance

Mechanical loads generate stress on load-bearing bones, causing a material strain on bone tissue (65). The mechanostat model illustrates how mechanical loading affects bone structure by altering the mass and architecture to produce a structure that resists mechanical loads from daily activities while minimizing mass for locomotion efficiency (66,67). The mechanostat model explains that bone modeling and remodeling processes are controlled by mechanisms sensing the bone's elastic deformation (68). Bone adaptations to mechanical load result from loads generated by internal body forces due to muscle contractions or external forces such as external reaction forces, including impact loading (69). However, to affect bone, the mechanical loads need to comply with the principles of specificity and overload. Specificity means that only skeletal sites exposed to daily mechanical load alteration will experience adaptation (70). Overload refers to the fact that only mechanical loads exceeding usual loadings conditions can stimulate an adaptive response (70). The substantial evidence indicated that the modeling and remodeling processes occurring on both ends of the strain stimulus spectrum are started by osteocytes (67,71,72). Four main mechanoadaptive pathways begin when osteocytes respond to mechanical stimuli (67). Formation modeling and targeted remodeling happen with strain greater than customary strain stimuli, and resorption modeling and disuse-mediated remodeling occur with strain lower than customary strain stimuli (67). The level of bone modeling is determined not only by genetics but also by the strains that bone is exposed to (73). Expedited bone accrual about the pubertal growth spurt is incredibly crucial and provides a window for weight-bearing and high-impact PA to optimize bone development (74).

2.3.1. Bone Impact measurement in children

Bone strain magnitude is indicated to be linearly proportional to the size of the external mechanical load applied to the bone in animal research (75). Accelerometers are traditionally utilized to estimate energy expenditure or PA intensity; however, recent advancements in accelerometer technology enable them to measure other physical activity outcomes, such as mechanical load on the bone (17). The use of accelerometers to estimate bone impacts has been validated against force plate-derived GRFs in children (76). The accelerometer (ActiGraph

GT3X) PA counts and raw acceleration (resultant vector) values are highly correlated to mean GRF (r=0.90) in children (76). A recent study from our lab showed that 63 daily accelerometer-measured bone impacts (≥3.9g) could result in a 7% increase in tibia bone strength. The assessing bone impact in children with ASD which have bone mass, structure and strength deficits in weight-bearing sites (e.g., tibia) is required to explain if the mechanical loading (e.g., accelerometer measured impacts) that children with ASD collecting are different from TDC and if the bone impacts can explain the deficits in bone (e.g., tibia) in children with ASD (17).

2.3.2. Muscle strength, power and cross-sectional area measurement in children

The skeletal muscles force, which exerts directly to bones, has been recognized as the primary stimulus for bone mechanical signaling (15). Two popular, valid and reliable tests for measuring muscle force and power are GS and standing LJ (77). GS measures by hand dynamometers, which is an isometric test to measure the upper extremity strength. Hand dynamometer measures hand grip in kilogram, and the measured value converts to newtons to represent grip force. The handgrip force is an indicator of upper body muscle strength and is positively associated with bone mass at the TB, LS, TH, and FN, as well as bone structure and strength at distal radius (78-80). The reliability of hand dynamometers, including JAMAR, for measuring grip force has been reported good in children and youth (81,82). High reliability (ICC 0.91) of the GS test was reported in children with ASD (83).

Standing LJ is another reliable test for measuring lower body muscle power in children and youth (77). Standing was strongly correlated with other lower body muscular power tests, including squat jump, countermovement jump and vertical jump (84). High reliability of standing LJ (ICC 0.93) was reported in children with ASD (83).

Muscle cross-sectional area (MuA), which refers to muscle size acquired from bone imaging tools, is considered a good surrogate of muscle force (85,86). A study from our lab reported high precision ($CV\%_{RMS}$ = 2.1-3.7%) for pQCT measured MuA in postmenopausal women (87); however, the precision has not been reported in children. The MuA, measured by pQCT, was correlated (r^2 = 0.79) with DXA measured lean soft tissue mass at the lower leg in children (88).

2.4. Accelerometer-measured physical activity in children

The most common objective measurement of PA in children and adults is accelerometry (89,90). Accelerometers have achieved popularity in children's studies because of their accuracy,

capacity to capture and save vast amounts of data, capturing PA intensity level, administration ease, especially in large studies, and feasibility with young children (91). Accelerometers capture acceleration up to 3 orthogonal planes (92), and the acceleration signals are digitized, and a "count" value per pre-set time interval (epoch) is taken, which matches the magnitude of the acceleration (93). The obtained counts are later interpreted into biological metrics (e.g., energy expenditure) or PA intensity levels (e.g., MVPA) (94). The accelerometer-determined PA intensities have been validated to match energy expenditure (95). ActiGraph is the most extensively used and validated accelerometer for measuring PA in childhood (89,90,96). Accelerometers can be attached to different body parts, including the wrist, thigh, waist and hip (91). However, the hip-worn accelerometers were more accurate when compared with wrist attachment in children (97).

A recent systematic review concluded that accelerometers were reasonably accurate in identifying PA intensity levels in children (97). According to two systematic reviews, accelerometers can accurately measure sedentary behavior in children and youth (97,98). A review of studies reporting accelerometer validation against energy expenditure by calorimetry, direct observation, and metabolic monitoring showed that hip-worn accelerometers had greater than 95% sensitivity and specificity for identifying sedentary behavior (median ≤1.5 METs) in children (97). The sensitivity and specificity for identifying light PA (1.5 to 3.0 METs) were 81 and 71 %, respectively, for hip-worn accelerometers in children (97). The sensitivity and specificity for identifying moderate PA (3.1 to 6.0 METs) were 92 and 88 %, and for vigorous PA (> 6.0 METs) were 93 and 72%, respectively, for hip-worn accelerometers in children (97).

2.4.1. Accelerometer-measured PA and bone development in children

Several observational studies used accelerometers to investigate the association of daily PA characteristics with bone strength in children and youth. Daily minutes of MVPA, VPA and impact were positively correlated with estimated bone strength and size (i.e., cortical bone thickness) at the weight-bearing sites in children and adolescences (99). The greater bone strength at the FN, distal, and shaft sites of the tibia was reported in children gathering most daily MVPA than less-active peers (100). Gabel et al. reported that youth who spent more daily time in MVPA (~60 min) had 4%–6% larger total area, 6% greater estimated bone strength (failure load), and ~13% greater cortical porosity at the distal tibia as well as 4% greater trabecular bone volume fraction and 6% greater bone strength at the distal radius when compared

to peers accumulated less daily MVPA (<30 min) (99,101). Kehrig et al. also reported that daily minutes of MVPA and VPA independently predicted the variance in estimated bone strength at the tibia but not at the radius (17). Interestingly, their model showed that daily VPA might have more effect on bone strength compared to daily MVPA (17). The model showed that 10 minutes more daily VPA would result in a 7% increase in bone strength, whereas a 3% increase in bone strength would happen by increasing 10 minutes daily MVPA (17). The results also showed that participants with more daily short VPA bouts (~33 VPA bouts) had 10% stronger distal tibia when compared to those with fewer daily short VPA bouts (~9 VPA bouts) (17). The findings also showed that 63 daily impacts (≥ 3.9g) could result in a 7% increase in tibia bone strength (17). Children with ASD spend less daily time in PA, but the evidence linking accelerometer measured PA, including bone impacts, to bone deficits in children with ASD is lacking.

2.5. Autism spectrum disorder and bone health

2.5.1. Autism spectrum disorder in children

Autism Spectrum Disorder is a developmental disorder with the core symptoms of impaired social, communication, and language skills, along with restricted and repetitive behaviors (1). Individuals with ASD usually have difficulties with social-emotional interactions, nonverbal communication and developing, maintaining, and understanding relationships (102). In recent decades, the prevalence of ASD has increased from 1 in 150 children to 1 in 59 (103). A combined prevalence of 1 in 66 children and youth was reported in Canada in 2015 (104). In the recent edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM)-5, all ASD-related disorders, including autism, Asperger's disorder, childhood disintegrative disorder, or pervasive developmental disorder not otherwise specified, are identified as an ASD (102). Besides communicational and behavioral problems, children with ASD typically have concurrent conditions that worsen their overall health and increase the use of the healthcare system (2). For example, individuals with ASD, including children, are at higher risk for a hip fracture (odds ratio 3-12) than those without ASD (3).

2.5.1. Bone health in children with ASD

Current literature mainly provides evidence of bone mass deficits. The evidence of bone structure and strength deficit and bone development is limited in children with ASD.

2.5.1.1. Bone mass

Several studies have reported lower areal bone mineral density (aBMD) in the total body (TB) (12-18%) (4,5), lumbar spine (LS) (8-19%) (5,6,8,105), total hip (TH) (13-27%) (4,6,7) and femoral neck (FN) (16-22%) (4–7) in children with ASD when compared to TDC or reference data. TB, LS and FN bone mineral content have also been reported as being lower in children with ASD (4,8).

2.5.1.2. Bone structure and strength

Lower bone mass in children with ASD might be related to bone structure deficits, contributing to lower bone strength. Limited evidence suggests bone microstructure and strength deficits at the distal radius and tibia in children with ASD. Hediger et al. reported the initial evidence of bone structure deficit in children with ASD (106). They used radiography to measure the cortical thickness of the second metacarpal of the left hand in 75 male children with ASD (4-8 years old) in comparison to the Fels reference data (107,108). Although there were no differences, the result suggested a trend toward an increasingly negative deviation in cortical thickness from reference medians in children with ASD ($p<0.05$) (106). Neumeyer et al. also reported a 15% lower cortical area at the distal radius and tibia, as well as 20% thinner cortices and 10% thinner trabeculae at the distal radius (4). Children with ASD also had 19 and 13% lower bone strength (stiffness and failure load) at the radius and tibia, respectively, compared to TDC (4).

2.5.1.3. Bone development

Only one study assessed bone mineral accrual in children with ASD. The results indicated no difference in aBMD accrual rate, maintaining the aBMD deficit from baseline to 4-year follow-up in children with ASD (5). However, evidence of bone structure and strength development has not been reported in this population.

2.5.2. Physical activity, muscle strength and power and bone health in children with ASD

Although genetics is the primary determinant of bone mass and strength, lifestyle factors, such as PA, nutrition and medications, also influence bone health and development (109). PA guidelines recommend at least 60 minutes of moderate to vigorous physical activity (MVPA) per day for children (110,111); however, the effects of daily PA on bone health and development have not been well documented in children. A recent systematic review reported a positive association between MVPA and bone outcomes in male children, but the results were mixed in female children. The evidence of how light PA or bone impact affects bone outcomes is limited.

Table 2.1. Related health outcomes of daily MVPA

References & Study design	MVPA measurement	Results
Wachob and Lorenzi, 2015 Observational	- Actigraph (GT3X+) - 7 consecutive days	- A positive relationship between MVPA and sleep efficiency - a negative correlation between MVPA and wake after sleep onset
Garcia et al., 2020 Observational	- Actigraph (GT9X) - 7 days and nights	- Participants with good sleep quality had accumulated more daily MVPA. - Participants who met the sleep recommendations were more likely to meet MVPA (76% vs. 36%) than participants who did not meet sleep duration recommendations. - Participants following both sleep duration and efficiency recommendation had collected more daily MVPA (113.6 min) than those who just met sleep efficiency recommendation (40.2 min) or did not meet either sleep recommendation (67.5 min)
Memari et al., 2017 Observational	- Actigraph (GT3X) - A minimum of 8 h for 7 continuous days	- Cognitive flexibility was associated with MVPA. - The autism social skill profile score was positively correlated with five and ten-minute bouts of MVPA (r = 0.4 to 0.5) - The perseverative error was negatively correlated with MVPA (r = -0.4) as well as five-minute bouts of MVPA (r = -0.4 to -0.3) - Children with lower rates in cognitive function participated less in physical activity
Chu et al., 2020 Observational	- Actigraph (GT1M) - A minimum of 10 h on at least 5 days, including one weekend day	- Percentage of daily MVPA was positively associated with manual strength, agility and coordination
Heffernan et al., 2018 Observational	- ActiGraph (GT9X) - At least 7 consecutive days	- MVPA was inversely correlated with subclinical cardiovascular disease risk (r =- 0.5), determined by aortic arterial stiffness.

Impaired social, communicational, and language skills, as well as restricted and repetitive behaviors, are core symptoms of ASD (1). Beyond these core symptoms, impaired motor skills have also been well documented in children with ASD (112–116). These impairments, combined with personal and physical barriers of PA (23,117,118), may limit participation in PA and meeting activity guidelines important for wellbeing and health (110,119).

Children with autism spectrum disorder (ASD) have lower PA levels and higher sedentary time compared to TDC, as reported by a recent systematic review (9). previous studies reported inconsistent daily moderate to vigorous PA (MVPA) differences between children with ASD and typically developing children (TDC) (18–26). Although few studies reported that children with ASD spent less daily time in MVPA when compared to TDC (13,21), other studies did not report a difference in daily MVPA between children with ASD (19,20,22,25,26). There are not yet systematic reviews or meta-analyses synthesizing the evidence of MVPA in children with ASD.

Evidence of objectively measured MVPA is essential because time spent in MVPA has been associated with several health outcomes in children with ASD (Table 2.1). Daily MVPA has been positively associated with sleep quality (120,121), cognitive function (27), manual coordination (122), as well as strength and agility (122) in children with ASD. In addition, daily MVPA has been negatively associated with subclinical cardiovascular disease risk in children with ASD (123).

Children with ASD have lower muscle strength compared to TDC. Children with ASD had 10-39% lower GS(12–14,124) as well as 22-51% lower muscle strength and endurance at the upper body and abdominal than TDC (10,11). They also had 30% lower muscle power at the lower body, measuring with a standing long jump (LJ) test, compared to children without ASD (12).

The evidence of muscle strength is important in children with ASD as the lower muscle strength might be linked to reported bone mass, structure, and strength deficits, as well as a higher risk of fracture. An association between grip strength (GS) and bone mass at TB, LS, TH, and FN has been reported in children and youth (78,79). GS also has been highly associated with the bone cross-sectional area, cortical area and bone strength at the distal radius in children (80). In addition, muscle power, measuring with a vertical jump test, and tibia shaft muscle cross-

sectional area (MuA) have been positively associated with bone strength at the distal and shaft site of the tibia (125). The MuA also has been positively associated with the cortical area at the radius shaft in children and youth (126). In addition, a higher risk of fracture (odds ratio = 2.1) was reported in children with low GS when participating in exercise (127). However, the evidence associating PA to bone deficits is limited in children with ASD, and the evidence of linking muscle strength and MuA is lacking. Neumeyer et al. (5) reported that several aBMD differences between ASD and TDC did not remain significant after adjusting for PA. In contrast, the difference in estimated bone strength (stiffness and failure load) at the distal radius and tibia between children with ASD and TDC decreased yet remained significant after adjusting for PA (4). Lower PA may contribute to about 25 and 40% of observed bone strength deficits at the distal radius and tibia in children with ASD, respectively (4). However, Soden et al. (105) reported that LS aBMD did not correlate with PA. All these studies used questionnaires to assess PA in children with ASD. The validity of questionnaires to measure daily PA is moderate at best (128). Further, these studies used questionnaires that are not validated to measure weight-bearing PA (129). The evidence of linking objectively measured PA, particularly MVPA, and muscle strength, power and MuA to bone deficits in children with ASD is lacking.

2.5.3. Nutrition and bone health in children with ASD

Nutrition is another lifestyle factor that affects bone health and development in children. As living tissue, bone needs all essential nutrients for growth and maintenance continuously (130). Calcium, phosphorus, vitamin D and protein are key bone nutrients (131). Calcium and phosphorus, as hydroxyapatite crystals deposited along collagen fibrils, are the main bone minerals (130). Adequate calcium intake has an essential role in bone health and development (131). Around 20% weight of bone comprises protein, which is the principal component of bone connective tissue (130). Enough protein intake is crucial for bone matrix synthesis and maintenance (132). A recent meta-analysis indicated that dietary protein intake explained up to 14% of BMC in TDC (133). Low protein intake may adversely influence bone health by impaired calcium absorption. In addition, as a primary hormone in the regulation of calcium and phosphorus metabolism, vitamin D plays a primary role in bone metabolism, health and development (134).

Food selectivity eating and restricted diets (e.g., gluten- or casein-free) are common (135,136) and may result in nutritional deficits in children with ASD (137,138). Several studies

have reported lower vitamin D and calcium intakes in children with ASD compared to TDC (4,6,8,139–142). In addition, children with ASD consumed lower protein (28%), especially lower animal protein 37% than TDC (139,143). However, the evidence linking the nutrients intake in children with ASD to bone deficits is limited. One study reported that the percent of recommended calcium intake was correlated with LS aBMD in children with ASD ($r = 0.5$, $p < 0.05$) (105). A positive association between the calcium, animal protein intake, and aBMD z-score was also reported in children with ASD (143). There is a need to complete the primary evidence linking the nutrients intake to bone deficits in children with ASD.

2.6. Animal-assisted intervention

An animal-assisted intervention (AAI) is ‘‘any intervention that intentionally incorporates animals as part of a therapeutic or ameliorative process or milieu (144)’’. An emerging body of empirical evidence showed the AAI’s effectiveness on children with ASD (30). Although there is no agreement on the AAI theoretical framework, the human-animal interaction (HAI) model is a regularly used framework that explains AAI's theoretical foundations (145). The theory behind working with animals to benefit children with ASD comes from HAI studies, specifically, the research on children's physical and psychological benefits from their reciprocal relationship with animals (29).

2.6.1. Human-Animal Interaction (HAI) model

The HAI model is based on the premise that animals can directly or indirectly increase human social supports (145). The HAI model postulates that human, as a social creature, can develop and engage in social interactions with other animals. Biophilia and social support hypotheses are two explanatory models that have been developed within the HAI model.

The foundation of the biophilia hypothesis is based on human attraction to animals. The biophilia hypothesis recommends that humans are attracted to other living beings mainly due to evolutionary benefits and positive reinforcement (145). Millions of years of human evaluation in nature left its footprint on the human brain and DNA and made humans fascinated and attached to other living creatures (146). Through an experience of attraction, a biophilia mind/body moment happens that is called “hunter’s trance”, which involves an “intensified concentration in which heart, breath, and mind are quieted” (146,147). Human beings' relationship with animals provided protection and increased human survivability and signaled us about the safety or danger of the environment (147). In addition, the interaction with animals provides a calming and

relaxing environment that triggers additional interaction by positive reinforcement (148). The capacity of animals to alleviate anxiety during a stressful situation strengthens the mutual attraction between humans and animals (146). It has been shown that the presence of an animal can act as a social buffer by reducing anxiety and improving positive emotions in children with ASD (149).

The social support hypothesis speculates that engagement with animals facilitates positive social interaction. The social support hypothesis suggests that animals have the ability to diminish isolation by facilitating social interaction with and between people. (145). Animals can also reduce isolation and promote overall health by providing continuous availability, nonjudgmental support and unconditional love (145). Research has inferentially supported this theory by showing that animals' interaction can reduce loneliness, increase social interaction, and improve overall health (150–153). Children with ASD have difficulties in social interactions and animals can support and facilitate social interaction by providing children with ASD with a positive environment without any judgment for social engagement (29).

2.6.2. Animal-assisted physical activity intervention

Difficulties in social interactions in children with ASD may contribute to lower PA (27,28). Animal assisted intervention (AAI) offers an attractive option for children with ASD, as the presence of therapy dogs has improved social interaction in children with ASD (29–32). The presence of a therapy dog increased PA in children with obesity (33) and adolescents with orthopedic limitations (34). In addition, a qualitative study suggested that children with ASD may benefit from integrating a therapy dog into a PA program (35,36). To this date, however, no quantitative study has assessed if an AAI with therapy dogs can increase PA in children with ASD.

2.7. Summary

1. Individuals with ASD, including children, are at higher risk for hip fracture. Although the reasons for the higher risk of fracture in children are not fully understood, it might be linked to poor bone development and related factors (such as low PA) during childhood.
2. Several studies have compared bone mass between children with and without ASD, but no systematic review or meta-analysis synthesizes the evidence of bone health in children with ASD. In addition, the evidence of bone structures and strength is limited in children with ASD. There is a need to synthesize existing evidence comparing bone mass and

extend the primary evidence comparing bone structure and strength between children with ASD and TDC.

3. Children with ASD have lower PA and higher sedentary time; however, previous studies reported inconsistent daily MVPA differences between children with ASD and TDC. There are not yet systematic reviews and meta-analyses are synthesizing the evidence of MVPA in children with ASD.
4. Ethology underpinning bone deficit in children with ASD is poorly understood. Lower physical activity, muscle strength and power, and poor nutrition are some of the factors that can negatively affect bone development and contribute to observed bone deficits in children with ASD. A previous systematic review reported lower PA in children with ASD. Several studies also reported lower GS and lower body muscle power as well as lower intake of vitamin D, calcium and protein in children with ASD. However, the evidence linking these lifestyle factors to the bone deficit in children with ASD is scarce.
5. Difficulties in social interactions in children with ASD may contribute to their lower PA. The presence of therapy dogs has improved social interaction in children with ASD and they may benefit from integrating a therapy dog into a PA program. However, no quantitative study has assessed if an AAI with therapy dogs can increase PA in children with ASD.

2.8. Objectives

The overall objective of this thesis is threefold. First, to synthesize and update the evidence of bone health in children with ASD (chapter 3 and 4). Second, to synthesize the evidence of MVPA in children with ASD vs. TDC (chapter 5). Third, to assess the feasibility and efficacy of animal-assisted PA intervention in children with ASD (chapter 6).

3. STUDY 1: BONE HEALTH IN CHILDREN WITH ASD: A SYSTEMATIC REVIEW AND META-ANALYSIS

SYNOPSIS: Higher risk of fracture reported in individuals with ASD might be linked to poor childhood bone health and development. However, no systematic reviews or meta-analyses have synthesized the evidence of bone differences between children with ASD and TDC. Therefore, this study systematically reviewed studies comparing imaged bone outcomes between children with ASD and TDC or reference data and performed a meta-analysis comparing commonly reported bone outcomes.

3.1. Introduction

A higher risk of fracture reported in individuals with ASD might be linked to poor bone development during childhood. A recent narrative review suggested a lower aBMD in children with ASD (138). However, no systematic reviews or meta-analyses have synthesized the evidence of bone differences between children with ASD and TDC. Therefore, the objective was to systematically review observational studies that compared imaged bone health outcomes between children with ASD and TDC or reference data and perform a meta-analysis to compare commonly reported bone outcomes between children with ASD and TDC.

3.2. Methods

I followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (154) for reporting this systematic review and meta-analysis

3.2.1. Data sources, searches and eligibility criteria

I conducted a systematic literature search of observational studies comparing the imaged bone properties between children with ASD and TDC or reference data. The search was restricted to full articles published until August 31, 2020, using PubMed, Scopus databases, Web of Science Core Collection, EMBASE (Excerpta Medica & EMBASE Classic) and Cochrane Library. Table 3.1 provides the search strategy in detail. Studies that compared imaged bone outcomes between children with ASD and TDC or reference data were included in the qualitative analysis. Those studies that compared bone outcomes between children with ASD and TDC were included in quantitative analysis (meta-analysis).

3.2.2. Data extraction and quality assessment

I extracted study characteristics (design and location), participant characteristics (number, age and sex) and imaged bone outcomes (aBMD, BMC, bone structure, geometry and strength). I also recorded related factors – medication, physical activity and nutrition (when applicable). All extracted data were checked by the second investigator (SK). I assessed the quality of included studies using the modified version of the National Heart, Lung and Blood Institute's Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies (155).

3.2.3. Statistical analysis

I included commonly reported bone outcomes (TB, LS, TH, FN aBMD) between children with ASD and TDC in the quantitative analysis (meta-analysis). I calculated standardized mean difference (SMD) between children with ASD and TDC using the Z-score means (or unadjusted means), standard deviations (SD) and sample sizes of both groups. If the full text did not contain SD, I calculated SD from standard error or confidence interval (CI). I used random-effects models with an inverse variance (IV) method to pool the SMD of included studies in RevMan (Review Manager Version 5.3, The Cochrane Collaboration, 2014). I reported heterogeneity using I-squared (I2). I estimated publication bias visually by funnel plot using Comprehensive Meta-Analysis version 3, and I used Duval and Tweedie's Trim and Fill test to estimate the adjusted (or unbiased) pooled SMD. I report the re-displayed funnel plots after Duval and Tweedie's Trim and Fill adjustment for those measures reported in three or more studies.

3.3. Results

3.3.1. Study selection

A total of seven studies were identified for inclusion in the review, and four were included in the meta-analysis (Figure 3.1). The search of PubMed, Cochrane Library, Web of Science Core Collection, EMBASE (Excerpta Medica & EMBASE Classic) and Scopus provided a total of 690 citations, and 499 citations remained after removing duplicates. Of these, 489 studies were excluded as they did not meet the inclusion criteria after the abstracts were reviewed. One study had participants older than 18 years; however, it was included as the median age of participants was less than 18 years (7). I excluded one study that included both children with ASD and other psychiatric disorders in both case and control groups and did not compare bone outcomes between children with ASD and TDC or reference data (156) (Table 3.2). I excluded another study that compared bone outcomes between children with ASD and those with other psychiatric

disorders (157) (Table 3.2). I also excluded one article reporting previously published bone outcomes that were already included in our analysis (143). I checked the references of 7 studies included in the review, but no additional studies were identified. I included 4 studies comparing DXA-derived aBMD between children with ASD and TDC in the meta-analysis. I included baseline aBMD data reported in Neumeyer et al.'s studies in the meta-analysis (5,6). I did not include DXA-derived BMC or bone microstructure and strength measured using high-resolution peripheral quantitative computed tomography (HR-pQCT) in the meta-analysis since only two studies (4,8) compared BMC (and one of them did not report the mean and SD) and only one study compared HR-pQCT outcomes between ASD and TDC (5). Hence, I included data from four studies (4,5,7,8) that reported TB, LS, TH and FN aBMD in the meta-analysis. Two studies reported TB aBMD with and without the head, and I only included TB less head results in the qualitative review and the meta-analysis as recommended by the International Society for Clinical Densitometry for children and adolescents (47).

3.3.2. Quality assessment

Of the seven included studies, six studies had a fair quality rating, and one study had a poor quality rating (Table 3.3).

3.3.3. Meta-analysis

3.3.3.1. aBMD

The result of the meta-analysis indicated that children with ASD had lower aBMD at the TB (SMD = -0.77; 95% CI, -1.26 to -0.28), LS (-0.69; -1.00 to -0.39), TH (-1.00; -1.82 to -0.17) and FN (-1.07; -1.54 to -0.60) when compared to TDC (Figure 3.2).

3.3.3.2. Heterogeneity of the results

There was no evidence of heterogeneity among studies reporting TB (I^2 = 0 %, p = 0.91), LS (0 %, 0.96) and FN (14 %, 0.33) aBMD. The heterogeneity was moderate among studies reporting TH aBMD (69%, 0.04) showing that the variability in effects was greater than sampling error.

Table 3.1. Detail of search strategy

Database	Search details
PubMed	((((((("child*"[All Fields] OR "adolescen*"[All Fields]) OR ((((("adolescent"[MeSH Terms] OR "adolescent"[All Fields]) OR "youth"[All Fields]) OR "youths"[All Fields]) OR "youth s"[All Fields])) OR "pediatr*"[All Fields]) OR "boy"[All Fields]) OR "girl*"[All Fields]) AND ((("bone and bones"[MeSH Terms] OR ("bone"[All Fields] AND "bones"[All Fields])) OR "bone and bones"[All Fields]) OR "bone"[All Fields])) AND (((((((("autism spectrum disorder"[MeSH Terms] OR (("autism"[All Fields] AND "spectrum"[All Fields]) AND "disorder"[All Fields])) OR "autism spectrum disorder"[All Fields]) OR (("arthropod struct dev"[Journal] OR "agron sustain dev"[Journal]) OR "asd"[All Fields])) OR (((((("autism s"[All Fields] OR "autisms"[All Fields]) OR "autistic disorder"[MeSH Terms]) OR ("autistic"[All Fields] AND "disorder"[All Fields])) OR "autistic disorder"[All Fields]) OR "autism"[All Fields])) OR (((((("autistic disorder"[MeSH Terms] OR ("autistic"[All Fields] AND "disorder"[All Fields])) OR "autistic disorder"[All Fields]) OR "autistic"[All Fields]) OR "autistics"[All Fields]) OR "autists"[All Fields])) OR ((((("asperger syndrome"[MeSH Terms] OR ("asperger"[All Fields] AND "syndrome"[All Fields])) OR "asperger syndrome"[All Fields]) OR ("asperger s"[All Fields] AND "syndrome"[All Fields])) OR "asperger s syndrome"[All Fields])) OR (((((("child development disorders, pervasive"[MeSH Terms] OR ((("child"[All Fields] AND "development"[All Fields]) AND "disorders"[All Fields]) AND "pervasive"[All Fields])) OR "pervasive child development disorders"[All Fields]) OR (("pervasive"[All Fields] AND "developmental"[All Fields]) AND "disorder"[All Fields])) OR "pervasive developmental disorder"[All Fields]) AND "Not"[All Fields] AND "Otherwise"[All Fields] AND (((((("specified"[All Fields] OR "specifier"[All Fields]) OR "specifiers"[All Fields]) OR "specifies"[All Fields]) OR "specify"[All Fields]) OR "specifying"[All Fields]))) OR "PDD-NOS"[All Fields])
Web of Science	Main search: #3 AND #2 AND #1 Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI, CCR-EXPANDED, IC Timespan=All years #3: (TS= (Autism Spectrum Disorder or ASD or Autism or Autistic or Asperger's Syndrome or Pervasive Developmental Disorder – Not Otherwise Specified or PDD-NOS)) AND DOCUMENT TYPES: (Article) *Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI, CCR-EXPANDED, IC* *Timespan=All years* #2: (TS= (Bone or Bones)) AND DOCUMENT TYPES: (Article) *Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI, CCR-EXPANDED, IC* *Timespan=All years* #1: (TS= (Child* or Adolescen* or Youth or Pediatr* or Boy* or Girl*)) AND DOCUMENT TYPES: (Article) *Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI, CCR-EXPANDED, IC* *Timespan=All years*

EMBASE	#1: (Child* or Adolescen* or Youth or Pediatr* or Boy* or Girl*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word] #2: (Autism Spectrum Disorder or ASD or Autism or Autistic).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word] #3: Asperger syndrome #4: ((Pervasive Developmental Disorder not Otherwise Specified) or PDD NOS).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word] #5: (Bone and Bones).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word] #6: 2 or 3 or 4 #7: 1 and 5 and 6
Scopus	TITLE-ABS-KEY ((child* OR adolescen* OR youth OR pediatr* OR boy* OR girl*) AND (bone) AND (autism AND spectrum AND disorder OR asd OR autism OR autistic))
Cochrane Library	(Child* or Adolescen* or Youth or Pediatr* or Boy* or Girl*) AND (Bone) AND (autism spectrum disorder or ASD or Autism or Autistic or Asperger Syndrome or Pervasive Developmental Disorder Not Otherwise Specified or PDD NOS) Word variations have been searched

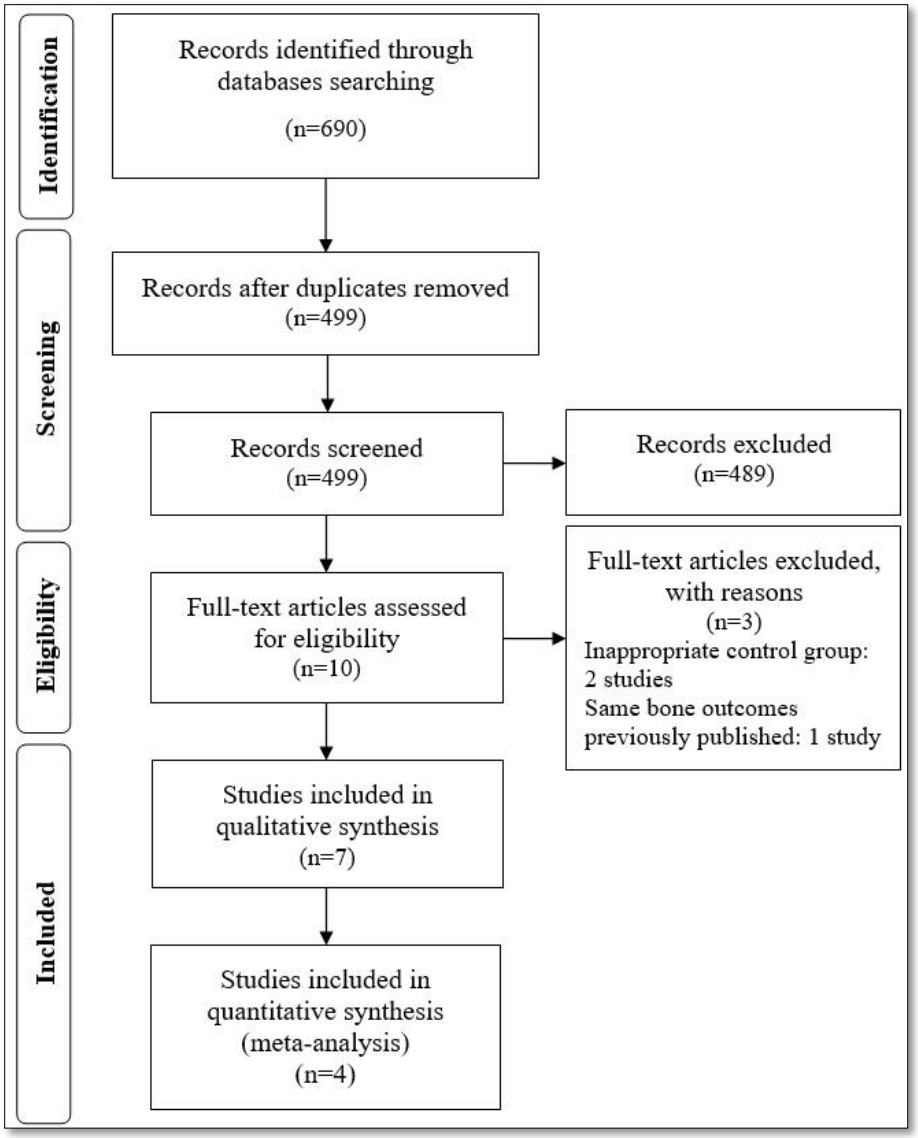

Figure 3.1. Flowchart of studies included in the systematic review and meta-analysis

Table 3.2. Summary of excluded studies measuring imaged bone properties

Reference & Study design	**Sample size (♂/♀) (age range) Age Mean (SD) or (SE)**		**Bone Outcome**		
Calarge, 2017 [**13**]	**ASD[a]**	**Non-ASD[b]**	**DXA**	**ASD[a]**	**Non-ASD[b]**
	30	186	**LS BMC Z-scores, n = 140**		
	(30/0)	(186/0)	Unadjusted mean (SD)	−0.20 (1.03)	0.19 (0.87)
Cross-sectional	(5-18)	(5-18)	LSMeans (SE)	0.01 (0.20)	0.15 (0.08)
	11.6 (2.9)	11.7 (2.8)	**LS aBMD Z-scores, n = 140**		
			Unadjusted mean (SD)	−0.06 (1.01)	0.32 (1.00)
			LSMeans (SE)	0.11 (0.21)	0.31 (0.08)
			TB BMC Z-scores, n = 46		
			Unadjusted mean (SD)	−0.26 (0.66)	0.27 (0.76)
			LSMeans (SE)	0.06 (0.21)	0.18 (0.10)
			TB aBMD Z-scores, n = 46		
			Unadjusted mean values (SD)	−0.12 (0.48)	0.38 (0.83)
			LSMeans (SE)	0.09 (0.24)	0.28 (0.11)
			pQCT (radius 4%)	**ASD[a]**	**Non-ASD[b]**
			Trabecular density, n = 151		
			Unadjusted mean (SD)	302 (47)	327 (55)
			LSMeans (SE)	181.3 (7.4)	205.2 (3.2
			BSIc, n = 151		
			Unadjusted mean (SD)	20.7 (9.1)	23.6 (11.6)
			LSMeans (SE)	18.9 (1.7)	23.9 (0.72)

Roke, 2012 [12]	ASD Case [c]	ASD Control [d]	**DXA**	**ASD Case[c]**		**ASD Control[d]**
				With Hyperprolactinemia Mean (SD)	Without Hyperprolactinemia Mean (SD)	
Cross-sectional	56	47	**LS**			
	(56/0)	(47/0)	aBMD Z-scores	−0.18 (1.0)	0.15 (0.78)	−0.03 (1.17)
	(10-19)	(12-18)	BMAD Z-scores	−0.32 (0.80)	0.12 (0.77)	−0.12 (0.04)

	14.8 (2.2)	15.0 (1.6)	**TB**			
			aBMD Z-scores	0.04 (1.16)	0.08 (0.81)	−0.20 (1.11)

[a] Children with ASD treated with risperidone for at least 6 or 12 months

[b] Children without ASD on risperidone treatment for at least 6 or 12 months and had other psychiatric disorders including, attention deficit hyperactivity disorder, disruptive behavior disorder, depressive disorder, anxiety disorder, or a tic disorder

[c] Case group consisted of male children with ASD (n= 52), or disruptive behavior disorder (n=4) treated with antipsychotic treatment for more than 16 months

[d] Control group consisted of male children with ASD (n=40) or disruptive behavior disorder (n=7) who had never been treated with antipsychotic treatment

aBMD, Areal Bone Mineral Density; ASD, Autism Spectrum Disorder; BMAD, Bone Mineral Apparent Density; BMC, Bone Mineral Content; BSIc, Bone Strength Index; FN, Femoral Neck; LS, lumbar spine; LSMeans, Least Square Mean; TB, Total Body; TH, Total

Table 3.3. Quality Assessment of included studies

	Neumeyer ,2017[1]	Neumeyer, 2017[2]	Barnhill1, 2017	Ekhlaspour, 2016	Neumeyer, 2013	Soden, 2012	Hediger, 2008
1. Was the research question or objective in this paper clearly stated?	Y	Y	Y	Y	Y	Y	Y
2. Was the study population clearly specified and defined?	Y	N	N	Y	N	N	Y
3. Was the participation rate of eligible persons at least 50%?	NR	NR	NR	NR	NR	NR	N
4. Were all the subjects selected or recruited from the same or similar populations (including the same period)? Were inclusion and exclusion criteria for being in the study prespecified and applied uniformly to all participants?	N	N	CD	Y	CD	Y	Y
5. Was a sample size justification, power description, or variance and effect estimates provided?	N	N	N	Y	Y	N	N
6. For independent variable(s) that can vary in amount or level, did the study examine different levels of the independent variable(s) as related to the outcome(s) (e.g., categories of independent variables, or independent variables measured as a continuous variable)? *	N	N	N	N	N	N	Y
7. Were the independent variable (s) clearly defined, valid, reliable, and implemented consistently across all study participants? **	Y	Y	N	Y	Y	Y	Y
8. Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants? ***	Y	Y	Y	Y	Y	Y	Y
9. Were the outcome assessors blinded to the disease status of participants? ***	NR	NR	NR	NR	NR	NA	NA
10. Was loss to follow-up after baseline 20% or less?	N	NA	NA	NA	NA	NA	NA
11. Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between independents variable(s) and outcome(s)? ****	Y	Y	N	N	N	N	N
Quality Rating (Good, Fair, or Poor)	F	F	P	F	F	F	F

Y, yes; N, no; CD, cannot determine; NA, not applicable; NR, not reported; G, good; F, Fair; P, Poor

* Level of disease (mild, moderate, or severe)

** Having ASD vs not having ASD

*** Imaged bone properties

**** If adjusting for age, sex (if applicable), height, body mass index, physical activity, and vitamin D and calcium intake (all of them), the answer was YES otherwise the answer was NO

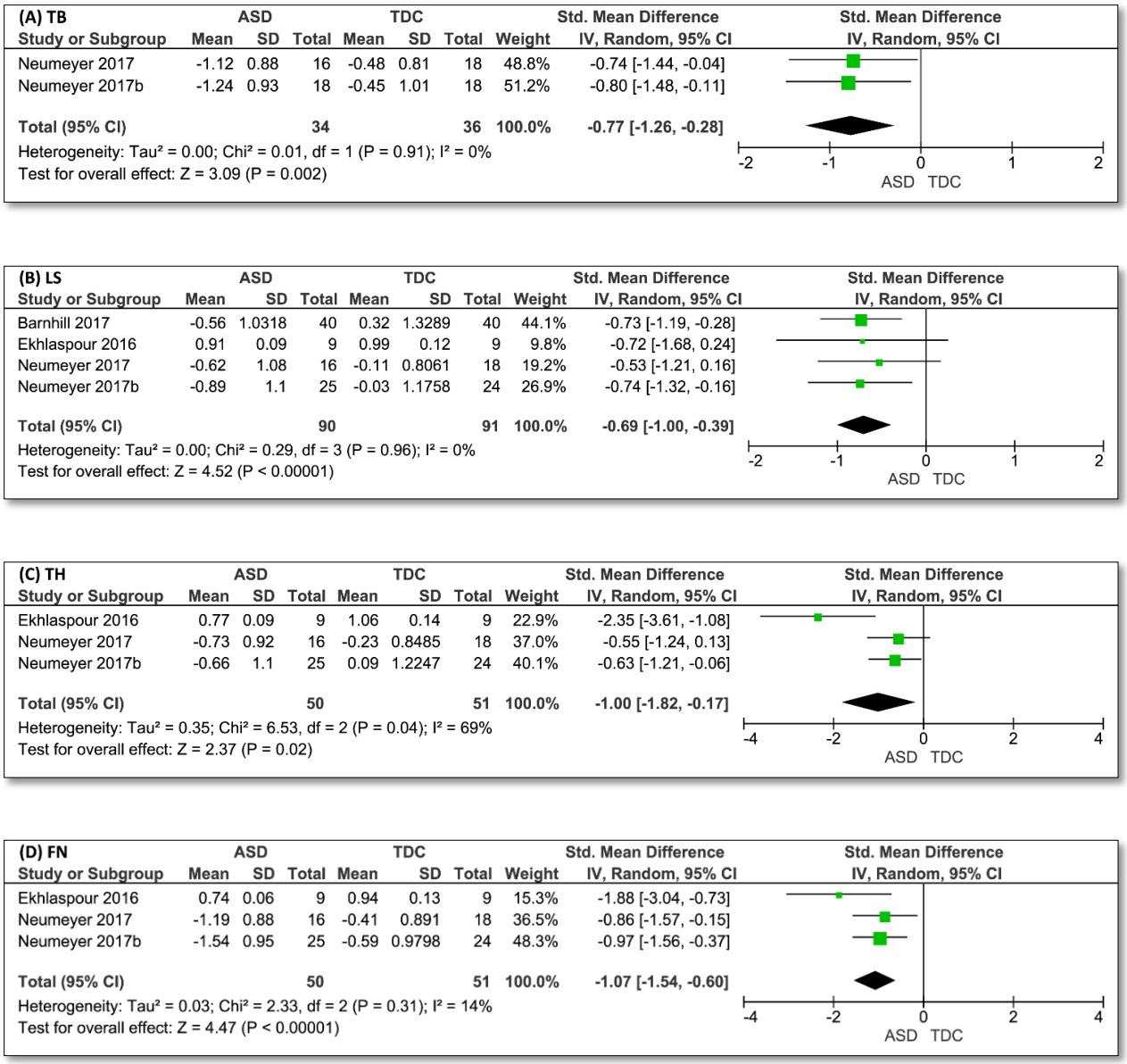

Figure 3.2. Effect of having ASD on aBMD at TB (A), LS (B), TH (C) and FN (D) in children. CI, confidence interval; FN, femoral neck; IV, inverse variance; LS, lumbar spine; TB, total body; TH, total hip.

3.3.3.3. Publication bias

One imputed study was found in re-displayed funnel plots of LS, after Duval and Tweedie's Trim and Fill adjustment, and SMD inconsiderably changed from -0.69 (95% CI, -1.00 to -0.39) to -0.68 (-0.94 to -0.41) (Figure 3.3A). No imputed studies were found in re-displayed funnel plots of TH and FN aBMD, and SMD did not change (Figure 3.3B and C).

3.3.4. Qualitative review

3.3.4.1. aBMD and BMC

Seven observational studies reporting imaged bone outcomes in children with ASD are presented in table 3.4. Our qualitative review supported the results of the meta-analysis that children with ASD had lower aBMD at the TB, LS, TH and FN. Six of the included studies used DXA to measure aBMD at different skeletal sites. Two studies reported 13-18% lower TB aBMD in children with ASD when compared to TDC (4,5). Four studies reported 8-19% lower LS aBMD when compared to TDC (5,6,8) or reference data (105). Similarly, three studies demonstrated 13-27% lower TH aBMD when compared to TDC (4,6,7). Four studies also reported 16-22% lower FN aBMD in children with ASD when compared to TDC (4–7). In addition, two studies reported BMC in children with ASD (4,8). Barnhill et al. (8) reported 13% lower LS BMC in children with ASD than TDC. Neumeyer et al. (4) also reported lower BMC at TB and FN in children with ASD, respectively. Only one study assessed aBMD accrual, and the results indicated no difference in aBMD accrual rate, maintaining the aBMD deficit from baseline to 4-year follow-up in children with ASD (5).

3.3.4.2. Bone structure and estimated strength

Hediger et al. (106) used radiography to measure the cortical thickness of the second metacarpal of the left hand in children with ASD in comparison to the Fels reference data (107,108). There were no differences, but the result suggested a trend toward an increasingly negative deviation in cortical thickness from reference medians in children with ASD ($p<0.05$) (106). One study used HR-pQCT to compare bone microstructure and estimated strength (using finite element analysis) between children with ASD and TDC at the distal radius and tibia. No differences were reported in trabecular, cortical, and total density at the radius and tibia between children with ASD and TDC (4). Cortical thickness, cortical area, and trabecular thickness at the radius were 10-20% lower in children with ASD when compared to TDC. At the distal tibia, the cortical area was 14% lower in children with ASD (4). The estimated bone strength outcomes (stiffness and failure load) were 19 and 13% lower at the distal radius and tibia, respectively, in children with ASD when compared to TDC (4).

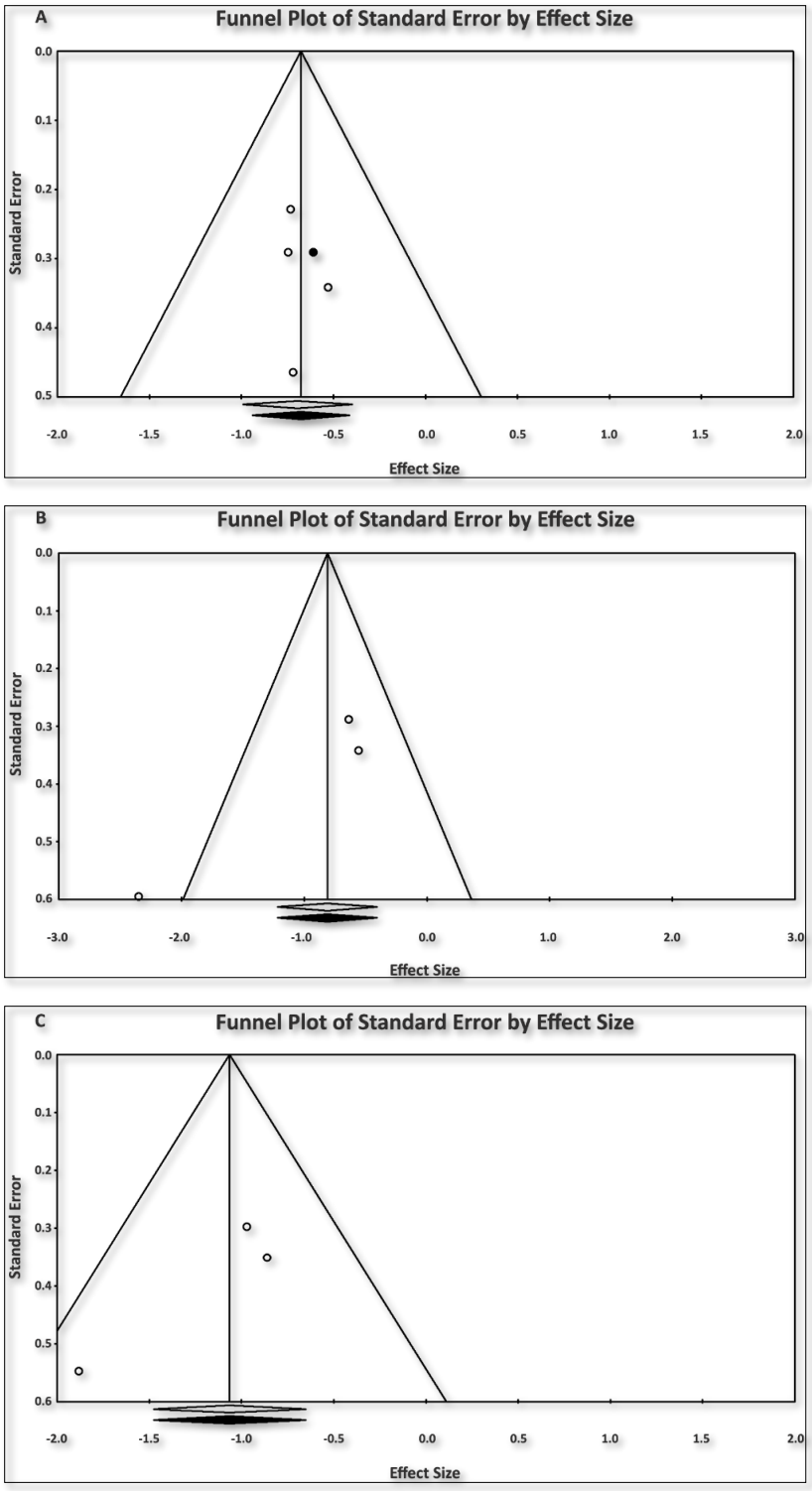

Figure 3.3. Funnel plot of aBMD at LS (A), TH (B) and FN (C). Open circles and diamond are the original ES and pooled ES, respectively; solid circles and diamond are imputed ES and adjusted pooled ES. ES, effect sizes; FN, femoral neck; LS, lumbar spine; TB, total body; TH, total hip.

Table 3.4. Summary of included studies measuring imaged bone properties

Reference & Study design	**Sample size (♂/♀) (age range) Age Mean (SD) or (SE) or (CI 95%) or Median [IQR]**		**Bone Outcomes**		
Neumeyer, 2017 [4]	**ASD**	**TDC**	**DXA**	**ASD (n=16)** Mean (SE)	**TDC (n=17)** Mean (SE)
	16	18	FN aBMD Z-scores	−1.19 (0.22)	−0.41 (0.21)
Cross-sectional	(16/0)	(18/0)	LS aBMD Z-scores	−0.62 (0.27)	−0.11 (0.19)
	(9-18)	(9-18)	TB BMD Z-scores	−1.12 (0.22)	−0.48 (0.19)
	13.6 (0.53)	14.2 (0.56)	TH aBMD Z-scores	−0.73 (0.23)	−0.23 (0.20)
			µFEA (radius)	**ASD (n=11)**	**TDC (n=17)**
			Stiffness	56.7 (5.07)	69.7 (3.28)
			Failure load	3.0 (0.25)	3.7 (0.16)
			µFEA (tibia)	**ASD (n=16)**	**TDC (n=18)**
			Stiffness	183.2 (8.3)	210.0 (10.6)
			Failure load	9.4 (0.41)	10.8 (0.54)
			HR-pQCT (Distal radius)	**ASD (n=11)**	**TDC (n=17)**
			Total area	339.5 (14.9)	351.2 (20.1)
			Log−transformed Total area	5.8 (0.05)	5.8 (0.05)
			Cortical area	19.0 (6.05)	22.3 (2.91)
			Log−transformed Cortical area	1.88 (0.43)	2.8 (0.19)
			Trabecular area	297.2 (15.2)	310.0 (20.5)
			Log−transformed Trabecular area	5.7 (0.05)	5.7 (0.06)
			Percent Cortical area	5.4 (1.78)	7.1 (1.03)
			Cortical thickness	0.24 (0.07)	0.30 (0.04)
			Log−transformed Cortical thickness	−2.5 (0.44)	−1.5 (0.22)
			Cortical porosity	0.049 (0.008)	0.046 (0.004)
			Total density	222.8 (14.4)	239.3 (7.4)

			Cortical density	639.1 (23.8)	680.9 (14.4)
			Trabecular density	175.5 (8.8)	186.2 (5.6)
			Number of trabeculae	2.3 (0.06)	2.2 (0.05)
			Trabecular separation	0.37 (0.01)	0.39 (0.01)
			Trabecular thickness	0.063 (0.002)	0.07 (0.002)
			HR-pQCT (Distal tibia)	**ASD (n = 16)**	**TDC (n=18)**
			Total area	767.0 (34.2)	878.6 (68.3)
			Log−transformed Total area	6.6 (0.05)	6.7 (0.07)
			Cortical area	72.7 (8.87)	84.6 (5.27)
			Log−transformed Cortical area	4.1 (0.13)	4.4 (0.07)
			Trabecular area	680.1 (35.96)	784.0 (69.54)
			Log−transformed Trabecular area	6.5 (0.05)	6.6 (0.08)
			Percent Cortical area	9.8 (1.31)	10.7 (0.95)
			Cortical thickness	0.68 (0.09)	0.76 (0.003)
			Log−transformed Cortical thickness	−0.57 (0.14)	−0.35 (0.09)
			Cortical porosity	0.063 (0.006)	0.060 (0.003)
			Total density	247.9 (11.7)	252.2 (11.2)
			Cortical density	737.7 (18.9)	753.2 (9.9)
			Trabecular density	186.8 (5.0)	189.4 (8.6)
			Number of trabeculae	2.2 (0.07)	2.2 (0.06)
			Trabecular separation	0.39 (0.01)	0.39 (0.01)
			Trabecular thickness	0.071 (0.002)	0.073 (0.003)
Neumeyer, 2017 [5]	**ASD***	**TDC***	**DXA**	**ASD** Mean (SE) or (95% CI)	**TDC** Mean (SE) or (95% CI)
Cross-sectional & Longitudinal	25 (25/0) 10.9 (0.36)	24 (24/0) 11.7 (0.38)	**FN**		
			Accrual aBMD Z-scores		
			Returnees [b]	−1.53 (0.30)	−0.77 (0.32)
			Returnees [f]	−1.41 (0.26)	−0.44 (0.27)
			Returnees [c]	0.12 (−0.19 to 0.43)	0.34 (−0.01 to 0.68)
			Unadjusted aBMD		
			Total Cohort [b]	0.61 (0.02)	0.73 (0.02)
			Returnees [b]	0.60 (0.02)	0.71 (0.03)

			Returnees [f]	0.72 (0.04)	0.88 (0.04)
			Returnees [c]	0.11 (0.07-0.15)	0.17 (0.12-021)
			LS		
			Accrual aBMD Z-scores		
			Returnees [b]	−1.18 (0.34)	−0.33 (0.39)
			Returnees [f]	−1.14 (0.32)	−0.08 (0.36)
			Returnees [c]	0.04 (−0.33 to 0.42)	0.25 (−0.18 to 0.68)
			Unadjusted aBMD		
			Total Cohort [b]	0.59 (0.02)	0.70 (0.03)
			Returnees [b]	0.57 (0.03)	0.64 (0.04)
			Returnees [f]	0.75 (0.05)	0.89 (0.06)
			Returnees [c]	0.18 (0.13-0.23)	0.25 (0.19-0.31)
			TB		
			Unadjusted aBMD		
			2015 Cohort [b]	0.79 (0.03)	0.91 (0.03)
			TH		
			Unadjusted aBMD		
			Total Cohort [b]	0.73 (0.02)	0.84 (0.02)
			Returnees [b]	0.71 (0.03)	0.79 (0.03)
			Returnees [f]	0.81 (0.04)	0.97 (0.05)
			Returnees [c]	0.10 (0.05-0.15)	0.17 (0.12-0.23)
Barnhill, 2017 [6]	**ASD**	**TDC**	**DXA**	**ASD** Mean (95% CI)	**TDC** Mean (95% CI)
Cross-sectional	40 (40/0) (4-8) 6.36 (5.96, 6.76)	40 (40/0) (4-8) 6.55 (6.05, 7.04)	LS aBMD	0.49 (0.47, 0.51)	0.55 (0.52, 0.59)
			LS aBMD Z-scores	−0.56 (−0.88, −0.23)	0.32 (−0.11, 0.74)
			LS BMC	4.06 (3.79, 4.32)	4.68 (4.29, 5.06)
Ekhlaspour, 2016 [8]	**ASD**	**TDC**	**DXA**	**ASD** Mean (SD)**	**TDC** Mean (SD)**
Cross-sectional	9 (8/1) (14-21)	9 (8/1) (14-21)	FN aBMD	0.74 ± 0.06	0.94 ± 0.13
			LS aBMD	0.91 ± 0.09	0.99 ± 0.12
			TH aBMD	0.77 ± 0.09	1.06 ± 0.14

	17.6 [1.87]	16.6 [2.62]			
	** Mean and SD was provided by authors				
Neumeyer, 2013 [7]	**ASD**	**TDC**	**DXA**	**ASD** Mean (SE) or (%)	**TDC** Mean (SE) or (%)
	18	19	**FN**		
Cross-sectional	(18/0)	(19/0)	aBMD	0.60 (0.02)	0.72 (0.02)
	(8–14)	(8–14)	aBMD Z-scores	−1.64 (0.21)	−0.52 (0.24)
	10.6 (0.4)	11.2 (0.3)	aBMD Z-scores>-2	33.3%	0%
			LS		
			aBMD	0.56 (0.03)	0.66 (0.02)
			aBMD Z-scores	−1.13 (0.28)	−0.21 (0.25)
			aBMD Z-scores >-2	27.8%	0%
			TH		
			aBMD	0.70 (0.02)	0.81 (0.02)
			aBMD Z-scores	−0.92 (0.24)	0.14 (0.29)
			aBMD Z-scores>-2	16.7 %	5.3 %
Soden, 2012 [16]	**ASD**	**----**	**DXA**	**ASD** Mean (SD)	**----**
	26		LS aBMD Z-scores	−0.1 (1.51)	
Cross-sectional	(21/5)				
	(10-18)				
	13.4 (2.9)				
Hediger, 2008 [17]	**ASD**	**----**	**Radiography, 2nd metacarpal of the left hand**	**ASD** Mean (SD)	**-----**
	75		Cortical thickness (mm)	2.6 (0.4)	
Cross-Sectional	(75/0)		Medullary width (mm)	3.2 (0.5)	
	(4-8)		Total bone width (mm)	5.9 (0.7)	
	6.6 (1.5)		Cortical area (mm^2)	4.1 (0.7)	

[b] Baseline

[c] Change over time

[f] Follow up

*Total Cohort at baseline

** Mean and SD was provided by authors

aBMD, areal bone mineral density; ASD, autism spectrum disorder; BMC, bone mineral content; FN, femoral neck; LS, lumbar spine; TB, total body; TDC, typically developing children; TH, total hip

3.4. Discussion

This meta-analysis indicated substantially lower aBMD (SMD = -1.1 to -0.7) at the TB, LS, TH and FN in children with ASD. The qualitative review supported the meta-analysis by indicating 8-27% lower aBMD at the TB, LS, TH and FN in children with ASD. Limited evidence also suggested up to 13% lower BMC at the TB, LS and FN as well as 10-20% smaller cortical area and thickness, trabecular thickness and lower bone strength at the distal radius and tibia in children with ASD.

Findings from the meta-analyses indicated up to 1.1 SD lower aBMD in children with ASD. This difference may have clinical importance of contributing to the elevated fracture risk reported in children with ASD (3). This is plausible as deficits in aBMD (0.3-1.0 SD) have been associated with 12-15% greater fracture risk in children with cerebral palsy or muscular dystrophy (158–160). Future studies exploring bone deficits in children with ASD and a history of fracture are warranted.

Planar DXA technique is limited to measures of areal BMD (aBMD, g/cm2), which underestimates aBMD in small children. Reporting height-adjusted aBMD Z-scores has been recommended when studying children with chronic disease or delayed puberty (47,49). I used aBMD Z-scores (without height adjustment) in the meta-analyses for two reasons. First, height did not differ between children with ASD and TDC in the studies included in the meta-analysis. Second, only two of the included studies reported height-adjusted aBMD Z-scores, indicating lower scores at TB (5), LS (7), TH (7) and FN (5,7) in children with ASD compared to TDC.

The qualitative review indicated deficits in BMC, bone size and structure – which all contribute to lower bone strength and possibly to higher fracture risk (158–161). BMC was reported only in 2 of the DXA studies (4,8), preventing the inclusion of BMC in the meta-analysis. Future DXA studies in children with ASD would benefit from reporting BMC as per recommendations and avoiding bias related to body size in aBMD measurements (47). Children with larger bones have (artificially) higher aBMD (16,162). Lower BMC likely contributes to weaker bone structure reported by Neumeyer et al. in children with ASD (4). At the fracture-prone distal radius, children with ASD had 20% thinner cortices and 10% thinner trabeculae resulting in 19% lower bone strength when compared to TDC (4). Future advanced imaging studies are warranted to complement these preliminary findings of bone micro-architecture and strength deficits in children with ASD. However, it is important to note that these differences

appear to exceed reported differences between pediatric fracture cases and controls (161). For example, pediatric fracture cases had 12% thinner cortex and 11% lower bone strength at the distal radius when compared to their peers without distal forearm fracture history (161). Overall, both quantitative and qualitative findings highlight the concern of bone health in children with ASD that needs to be addressed in clinical guidelines and future studies.

Lower physical activity, poor nutrition and medications are some of the factors that can negatively affect bone development and contribute to observed bone deficits in children with ASD. A recent systematic review reported lower physical activity and greater sedentary time in children with ASD when compared to TDC.(9). Lower physical activity in children with ASD may not provide enough loading-stimulus required for optimal muscle and bone development. (16,17). Food selectivity and restricted diets (e.g., gluten- or casein-free) are common (135,136) and may result in nutritional deficits in children with ASD.(137,138). Several studies have reported lower vitamin D and calcium intakes in children with ASD when compared to TDC (4,6,8,139–142). Children with ASD had 37% lower animal protein intake than TDC (139,143). In addition, about 70% of children with ASD take psychoactive medication (163) that negatively affects bone in children with chronic diseases (164–166).

The evidence linking lower physical activity or poor nutrition to bone deficits in children with ASD is limited. Neumeyer et al. (5) reported that many aBMD differences between ASD and TDC did not remain significant after adjusting for physical activity. In contrast, the difference in bone strength (stiffness and failure load) at the distal radius and tibia between children with ASD and TDC decreased yet remained significant after adjusting for physical activity (4). Lower physical activity may contribute to about 25 and 40% of observed bone strength deficits at the distal radius and tibia in children with ASD, respectively (4). Soden et al. (105), however, reported that LS aBMD did not correlate with physical activity. All these studies used questionnaires to assess physical activity in children with ASD. The validity of questionnaires to measure daily physical activity is moderate at best (128). Further, these studies used questionnaires that are not validated to measure weight-bearing physical activity (129). Evidence pertaining to nutrition is also scarce. Two studies reported positive associations between calcium or animal protein intake with aBMD in children with ASD (105,143). Future studies are warranted to carefully explore the lifestyle and other factors contributing to bone deficits in children with ASD.

3.5. Limitations

The findings of this systematic review and meta-analysis should be interpreted with the following considerations. The number of studies providing data for the systematic review and meta-analysis was small and the quality of the included studies was fair at best. The results of the meta-analyses may be susceptible to small study effects. In addition, four of the included studies were from the same research group, which increases the risk of selection bias and limits the generalizability of the review and meta-analysis results. A reliable estimate of heterogeneity needs a reasonably large number of studies; therefore, all reported heterogeneity statistics in our meta-analyses should be interpreted with caution. Because of the few included studies, the power of the tests for assessing publication bias was low, and therefore, our results of publication bias only provide readers with a perspective, not a conclusion of bias.

3.6. Conclusion

The results of this systematic review and meta-analysis indicated lower aBMD at the TB, LS, TH and FN in children with ASD when compared to their typically developing peers (SMD = -1.1 to -0.7). Limited evidence also suggests deficits at TB, LS and FN BMC and bone microstructure and strength at the distal radius and tibia in children with ASD.

4. STUDY 2: BONE ESTIMATED STRENGTH AND STRUCTURE IN MALE CHILDREN WITH AUTISM SPECTRUM DISORDER

SYNOPSIS: The evidence of bone structure and strength is limited in children with ASD. In addition, lower PA, muscle strength and power reported in children with ASD may not provide sufficient stimulus for bone development in individuals with ASD. Lower intake of vitamin D, calcium and protein may also negatively affect bone health in children with ASD. However, the evidence linking these lifestyles factors to the bone deficit in children with ASD is limited. Therefore, this study aimed to compare the bone estimated strength, structure and mass in distal and shaft of radius and tibia between male children with ASD and typically developing peers as well as to explore mediation effects of PA outcomes, nutrients intake and muscle strength and power on bone differences between male children with ASD and typically developing peers.

4.1. Introduction

Our recent meta-analysis indicated that children with ASD had 0.7 to 1 SD lower aBMD and BMC (167). However, the evidence of bone structure and estimated strength is limited in children with ASD. In addition, lower MVPA (30 min/day) (168) and muscle strength and power (10-39%) reported in children with ASD (12,13,124) may not provide enough loading-stimulus required for optimal muscle and bone development (17,99). Several studies have reported lower vitamin D and calcium intakes in children with ASD compared to TDC (4,6,8,139–142). In addition, children with ASD consumed lower protein (28%), especially lower animal protein 37% than TDC (77,81). However, the evidence linking these lifestyles factors to the bone deficit in children with ASD is limited.

Therefore, this study aimed to compare the bone estimated strength, structure, and mass at the distal and shaft of radius and tibia between male children with ASD and TDC. I also aimed to explore mediation effects of PA outcomes, nutrients intake and muscle strength and power on bone differences between male children with ASD and TDC.

4.2. Methods

4.2.1. Ethical approval

This study was approved by the University of Saskatchewan Biomedical Research Ethics Boards: Bio# 17-35.

4.2.2. Participants

Fifteen males with ASD (mean age 10.3, SD 2.7 yrs) were recruited from the community (via Autism Services of Saskatoon) and the Physical Activity for Active Living (PAAL) program run through the University of Saskatchewan PAAL., a PA program for children and youth with physical and/or intellectual impairments, aims to improve skills and social interaction using a variety of physical activity experiences. I recruited 81 TDC males (11.1, 1.9) from a cohort study assessing bone development in TDC in our lab. The parent or legal guardian of each participating child provided written consent. An assent was asked from the participating children.

4.3. Measurements

4.3.1. Anthropometry and somatic biological maturity

Standing and sitting height were measured using a standardized methodology by a wall-mounted Harpenden stadiometer (Holtain Limited Crymych, UK) (169). Weight was measured using a calibrated scale (Toledo Scale Company, Ontario, Canada). The length of the ulna was measured as the distance between the olecranon process and the ulnar styloid process with an anthropometric sliding caliper (Segmometer; Rosscraft Innovations, Canada) (170). The tibia length was measured as the distance between the medial malleolus base and the medial epicondyle's superior margin (170). The height, weight and limb lengths were measured three times, and the median values were used for analysis. I used sex-specific equations to estimate somatic biological maturity by calculating years of age at peak height velocity (171).

4.3.2. Bone and muscle properties

A trained technician obtained and analyzed scans at the distal (4% of the ulna and tibia lengths proximal to the reference line) and shaft (65% of ulna and 66% tibia lengths) sites of the dominant limb using pQCT (XCT 2000, Stratec Medizintechnik GmbH, Pforzheim, Germany) as previously described (51). Briefly, the operator first obtained a scout view over the wrist and ankle joints and placed a reference line above the growth plate using the reference of the bone-cartilage interface (white radiopaque shadow) just below the proximal edge of the medial

epiphysis. Cross-sectional images were scanned at the distal and shaft sites using the following parameters: 0.4 mm pixel size, 2.4 mm slice thickness, and 20 mm/s scanning speed (51). The distal tibia and radius were analyzed with contour model 1 and an outer bone threshold of 200 mg/cm3. The tibia and radius shaft sites were analyzed with separation mode 4 and outer and inner thresholds of 280 and 480 mg/cm3, respectively [10]. The bone strength at the distal sites, BSIc (mg2/mm4) were estimated as the product of total bone area and total bone density squared (52,172). SSIp was used for the bone strength estimation at the shaft sites (52,172). The cross-sectional muscle area (MuA) (mm2) at shaft sites was analyzed from the shaft site scans using contour mode 1 with a threshold of 40 mg/cm3 (173,174). If there were motion artifacts present, the technician retook the scan. If the participant has suffered a fracture at the dominant limb, then the non-dominant limb was measured.

4.3.3. Daily physical activity and dietary intake

The participants' daily PA was measured by asking participants to wear a triaxial accelerometer (model wGT3X-BT, ActiGraph, Pensacola, Fla., USA) above their right hip bone during waking hours for seven consecutive days. They were instructed to remove the accelerometer before participating in activities where the accelerometer might be getting wet. A sampling rate of 30 Hz was chosen for measuring activity (93,175). Activity counts were stored in intervals of 10 seconds. The validated cut-points were used to define light PA (101-2295 count per minutes (CPM)), moderate PA (MPA) (2296-4011 CPM) and VPA (≥4012 CPM) in children (93,175). I defined the bone impacts based on resultant accelerometer peaks ≥ 3.9 g based on the positive relationships between estimated bone strength and the number of accelerometer impact peaks (counts) reported in children (17). The total minutes for each PA outcome was divided by the number of valid days to report average PA and impact outcomes. A day with a minimum of 8 hours' wears time is considered a valid day (176,177). Participants' dietary intakes were assessed using a food frequency questionnaire (Block Questionnaire - 1998 FFQ). I selected the key bone nutrients to report and include in the analysis, including vitamin D, calcium and protein.

4.3.4. Muscle strength and power

Two popular, valid, and reliable tests measuring musculoskeletal fitness are GS and LJ (77). Hand dynamometers measured the GS; the handgrip force is an indicator of upper body muscle strength. Participants squeezed the hand dynamometer (Sammon Preston Inc., Boldingbrook, IL) as hard as they could with elbow flexing 90 degrees and arm away from the body (178). The

lower body muscle power was estimated using the LJ distance. Participants started by standing behind a marked take-off line and jumped as far as possible (83). The LJ distance was measured from the take-off line to the back of the participants' heel closer to the take-off line. These tests were performed three times, and the maximal values were used for further analysis.

4.4. Statistical Analysis

I used MANOVAs to compare background characteristics, PA outcomes, and nutrient intakes (vitamin D, calcium and protein) between male children with ASD and TDC. I reported the prevalence of inadequacy in the intakes of vitamin D and calcium in each group by calculating the percent of participants who did not meet age-specific Estimated Average Requirement (EAR) values (179). I used chi-squared tests to compare the percent participants with vitamin D and calcium inadequacies between the two groups. I used limb-specific ANOVA to compare MuA at shaft sites of radius and tibia between groups. I also used ANOVA to compare the GS and LJ distance between male children with ASD and TDC. I used limb-specific MANCOVAs to compare bone mass, structure and estimated strength between male children with ASD and TDC, adjusting for limb length, which differed between groups. I also used the MuA as covariates in the limb-specific MANCOVAs as it has been reported as a predictor of bone structure and estimated strength in children (126,180). With a significant main effect of group (ASD vs. TDC), I performed a pairwise comparison of bone outcomes with Bonferroni correction. I used the mediation analysis to explore the mediation effects of the PA outcomes (light PA, MVPA, VPA and impacts), nutrient intakes (vitamin D, calcium and protein), grip strength and lower body muscle power on bone mass, structure, and estimated strength difference between male children with ASD and TDC adjusting for limb length and MuA. A series of structural equation modeling was applied to explore how lifestyle factors mediate bone differences between male children with ASD and TDC (Figure 4.1).

Figure 4.1 showed the mediation model in which the independent variable (ASD vs. TDC) is labeled as "X" and the dependent variable (bone outcomes) is labeled as "Y" (181). The pathway "a" explained the effect of groups on the mediator; the pathway "b" describes the association between the mediator and the bone outcome (181). The pathway "C" and "C'" represents the total effect and groups' direct effect on the bone outcome, respectively (181). Mediation (or indirect) effect was calculated using coefficients a*b, and bias-corrected

bootstrapping was used to estimate the 95% CI of the ab coefficient on 5000 samples (181). The mediation effect was calculated by dividing coefficients a*b by pathway "C" (182).

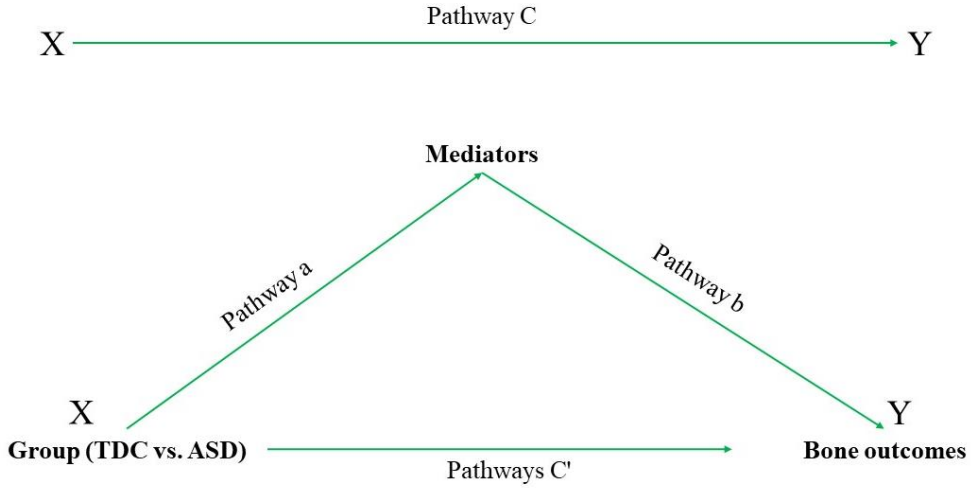

Figure 4.1. Mediation analysis

4.5. Results

Both groups were similar with respect to age, maturity, weight, BMI, daily MVPA and VPA, nutrient intakes (vitamin D, calcium and protein), the prevalence of inadequacy in the intakes of vitamin D and calcium and forearm and lower leg MuA ($P>0.05$) (Table 4.1). Male children with ASD were 7.5 cm smaller in height. The ulna and tibia lengths were also 16.0 and 38.6 mm smaller in male children with ASD. Participants with ASD spent 55% more daily time in light PA, with 57% lower daily bone impact counts compared to TDC. GS and LJ distance also were 27 and 31% lower in male children with ASD, respectively.

Comparisons of bone estimated strength, structure and mass between male children with ASD and TDC after adjusting for limb length and MuA are shown in Table 4.2. Bone estimated strength, structures and mass did not differ between male children with ASD and TDC at distal radius ($P>0.05$). Male children with ASD had 11-18% lower bone estimated strength, total area (ToA) and cortical area (CoA) at the shaft site of radius. Bone estimated strength, ToA, total content (ToC) and trabecular content (TrC) were 11-16% lower in male children with ASD at the distal tibia. ToA and CoA were 9% lower in male children with ASD at the shaft site of the tibia.

The mediation analysis results suggested that PA outcomes, nutrients intake and GS did not account for bone deficits in male children with ASD ($P<0.05$). LJ distance accounted for 40

to 51% of deficits in ToA, ToC and TrC at the distal tibia (Figure 4.2) and CoA at the tibia shaft (Figure 4.3).

4.6. Discussion

This study is one of the first studies to compare the bone estimated strength and structure between male children with ASD and TDC. The results indicated that male children with ASD had 9-18% lower bone estimated strength (radius shaft and distal tibia), ToA (radius and tibia shafts and distal tibia), CoA (radius and tibia shafts) and ToC and TrC (distal tibia). Male children with ASD spent 55% more daily time in light PA and had 57% lower daily bone impact counts when compared to TDC. The GS and LJ distance were also 27-31% lower in male children with ASD, and LJ distance accounted for 40-51% of deficits on ToA, ToC and TrC at the distal tibia as well as CoA at the tibia shaft.

Our findings were first to report bone structure and estimated strength deficit at the shaft sites of the tibia and radius in male children with ASD. These findings add to the Neumeyer et al. (2017) findings of 10–20% lower bone estimated strength and smaller cortical area and thickness, trabecular thickness at the distal radius and tibia in male children with ASD. Our results also indicated that male children with ASD had 11-16% lower total area and content, trabecular content and bone estimated strength at the distal tibia. I did not observe bone estimated strength and structure differences at the distal radius, likely due to low power, as seven distal radius scans were excluded from the analysis due to poor image quality. Future studies are warranted to use a larger sample to have an adequate power to explore bone differences in the radius between children with ASD and TDC.

The lower bone impact counts may not provide sufficient stimulus for bone development in individuals with ASD. Our recent meta-analysis confirmed that children with ASD spend 30 minutes less in MVPA per day (50% daily MVPA recommendation) than TDC (168). The result of the current study showed that our participants with ASD spent comparable time in MVPA per day; however, they had 46 counts lower bone impacts per day than TDC. Although the lower daily bone impacts counts did not account for bone deficits in male children with ASD, a previous study from our lab estimated that adding 60 bone impacts (e.g., jumps) per day could increase tibia bone strength up to 7% in TDC (17). Future randomized control trials are needed to examine if activities with bone impacts could improve bone strength development in children with ASD.

Table 4.1. Background characteristics of participants with ASD and TDC

Variable	ASD Mean (SD) or n (%)	TDC Mean (SD)	ASD vs. TDC Difference (95% CI)	P-value
	n = 15	**n = 81**		
Chronological age (years)	10.3 (2.7)	11.1 (1.9)	-0.8 (-2.0, 0.3)	0.149
Maturity offset (years)	-2.1 (2.1)	-2.0 (1.5)	-0.2 (-1.1, 0.8)	0.737
Height (cm)	140.8 (15.5)	148.3 (12.7)	-7.5 (-14.8, -0.2)	**0.045**
Ulna length (mm)	221.4 (29.9)	237.4 (23.9)	-16.0 (-29.9, -2.2)	**0.024**
Tibia length (mm)	317.1 (44.1)	355.8 (34.5)	-38.6 (-58.8, -18.5)	**<0.001**
Weight (kg)	37.8 (12.8)	43.4 (14.8)	-5.7 (-13.8, 2.4)	0.167
BMI (kg/m^2)	18.5 (2.8)	19.3 (4.3)	-0.8 (-3.1, 1.4)	0.465
	n = 10	**n = 76**		
Forearm MuA (mm^2)	2146.1 (626.5)	2305.9 (576.0)	-159.8 (-548.9, 229.3)	0.416
	n = 14	**n = 79**		
Lower leg MuA (mm^2)	4341.3 (1277.0)	4351.2 (1095.0)	-9.9 (-656.7,636.9)	0.976
	n = 15	**n = 81**		
GS (N)	14.3 (6.4)	19.7 (6.5)	-5.4 (-9.0, -1.7)	**0.004**
	n = 14	**n = 81**		
LJ (cm)	95.7 (40.0)	139.6 (24.2)	-43.9 (-59.4, -28.4)	**<0.001**
	n = 13	**n = 25**		
Daily Light PA (min)	266.7 (41.6)	171.6 (74.3)	95.1 (49.9, 140.4)	**<0.001**
Daily MVPA (min)	57.9 (30.3)	55.2 (25.6)	2.7 (-16.2, 21.6)	0.416
Daily VPA (min)	19.1 (13.8)	20.9 (12.0)	-1.8 (-10.6, 6.9)	0.864
Daily bone impact (n)	34.8 (33.0)	81.3 (64.7)	-46.4 (-85.4, -7.5)	**0.021**
	n = 12	**n = 48**		
Vitamin D (IU)*	372.9 (238.2)	363.8 (254.8)	9.0 (-153.6, 171.7)	0.912
Vitamin D inadequacy	5 (42%)	29 (60%)		0.241
Calcium (mg)*	1060.1 (465.5)	1118.5 (530.3)	-58.5 (-393.6, 276.6)	0.728
Calcium inadequacy	4 (33%)	20 (48%)		0.598
Protein (g)	79.3 (51.1)	73.2 (38.0)	-6.0 (-20.4, 32.4)	0.650

BMI, Body Mass Index; GS, Grip strength; LJ, Long jump; MuA, Muscle area
* From food and supplement

Table 4.2. Bone outcomes of male children with ASD vs. TDC

Variable	ASD Mean* (SE)	TDC Mean* (SE)	ASD vs. TDC Difference (95% CI)	P-value**
Distal radius	**n = 8**	**n = 76**		
ToA (mm^2)	287.9 (12.5)	270.4 (3.9)	17.5 (-8.7, 43.7)	0.188
ToC (mg/mm)	80.1 (3.5)	77.7 (1.1)	2.4 (-5.1, 9.8)	0.523
ToD (mg/cm^3)	281.2 (10.6)	287.8 (3.4)	-6.6 (-28.9, 15.7)	0.558
TrA (mm^2)	270.1 (15.4)	245.9 (4.8)	24.2 (-8.0, 56.4)	0.139
TrC (mg/mm)	69.2 (4.3)	63.2 (1.4)	6.0 (-3.1, 15.1)	0.190
TrD (mg/cm^3)	255.0 (8.0)	256.5 (2.5)	-1.5 (-18.2, 15.3)	0.860
BSIc (mg^2/mm^4)	22.4 (1.6)	22.5 (0.5)	-0.1 (-3.4, 3.2)	0.942
Radius shaft	**n = 10**	**n = 76**		
ToA (mm^2)	105.4 (7.7)	129.3 (2.4)	-23.9 (-40.1, -7.7)	**0.004**
CoA (mm^2)	68.1 (3.3)	79.9 (1.0)	-11.9 (-18.8, -4.9)	**0.001**
CoC (mg/mm)	62.1 (3.1)	66.8 (1.0)	-4.7 (-11.3, 1.9)	0.159
CoD (mg/cm^3)	860.4 (22.8)	834.4 (7.2)	26.0 (-21.9, 73.8)	0.283
SSIp (mm^3)	171.3 (12.5)	203.0 (3.9)	-31.7 (-57.9, -5.5)	**0.018**
Distal tibia	**n = 14**	**n = 79**		
ToA (mm^2)	686.1 (33.1)	769.0 (12.6)	-82.8 (-155.6, -10.1)	**0.026**
ToC (mg/mm)	195.4 (9.0)	226.0 (3.4)	-30.6 (-50.4, -10.8)	**0.003**
ToD (mg/cm^3)	288.5 (8.5)	295.5 (3.2)	-7.0 (-25.7, 11.6)	0.456
TrA (mm^2)	613.6 (37.5)	688.5 (14.2)	-74.8 (-157.2, 7.5)	0.074
TrC (mg/mm)	149.2 (10.8)	174.9 (4.1)	-25.8 (-49.4, -2.1)	**0.033**
TrD (mg/cm^3)	246.2 (6.3)	252.8 (2.4)	-6.7 (-20.6, 7.2)	0.342
BSIc (mg^2/mm^4)	56.2 (3.5)	67.0 (1.3)	-10.8 (-18.6, -3.0)	**0.007**
Tibia shaft	**n = 14**	**n = 79**		
ToA (mm^2)	460.5 (18.5)	507.7 (7.0)	-47.2 (-87.9, -6.5)	**0.023**
CoA (mm^2)	244.9 (8.7)	268.7 (3.3)	-23.7 (-42.9, -4.6)	**0.016**
CoC (mg/mm)	219.0 (8.3)	235.8 (3.2)	-16.8 (-35.1, 1.5)	0.071
CoD (mg/cm^3)	880.6 (15.2)	874.2 (5.8)	6.4 (-27.0, 39.7)	0.834
SSIp (mm^3)	1361.2 (69.9)	1509.3 (26.6)	-148.0 (-301.6, 5.6)	0.059

*Estimated marginal means adjusted for multiple comparisons

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**Adjusted for ulna length and forearm MuA (for radius) and for tibia length and lower leg MuA (for tibia)

BSIc, Bone Strength Index for compression; CoA, Cortical Area; CoC, Cortical Content; CoD, Cortical density; SSIp, density-weighted polar section modulus; ToA, Total Area; ToC, Total Content; ToD, Total Density; TrA, Trabecular Area; TrC, Trabecular Content; TrD, Trabecular Density

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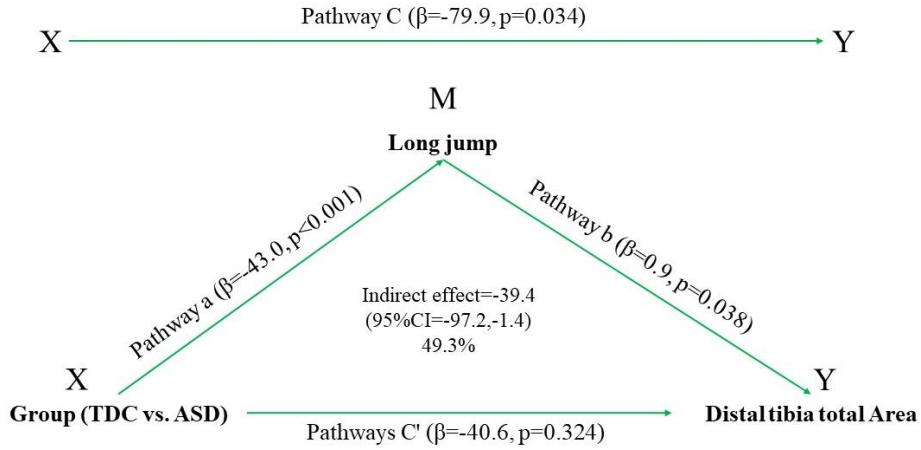
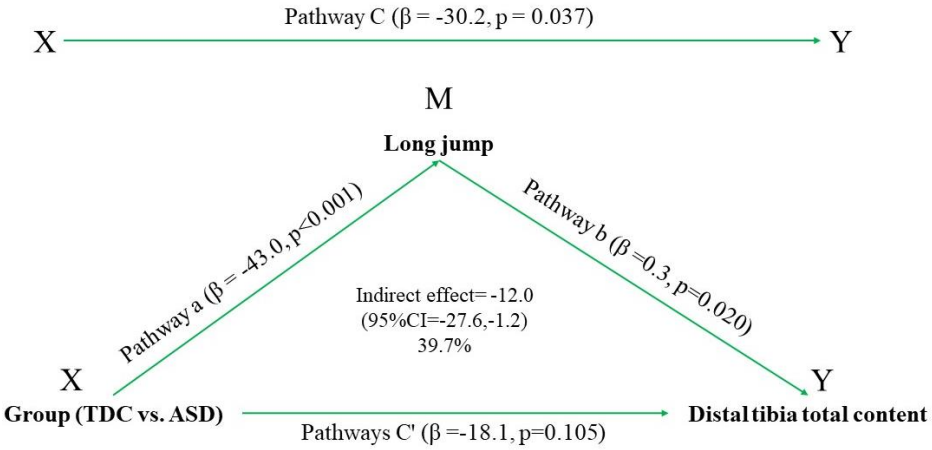
A) Distal tibia total area



B) Distal tibia total content



C) Distal tibia trabecular content

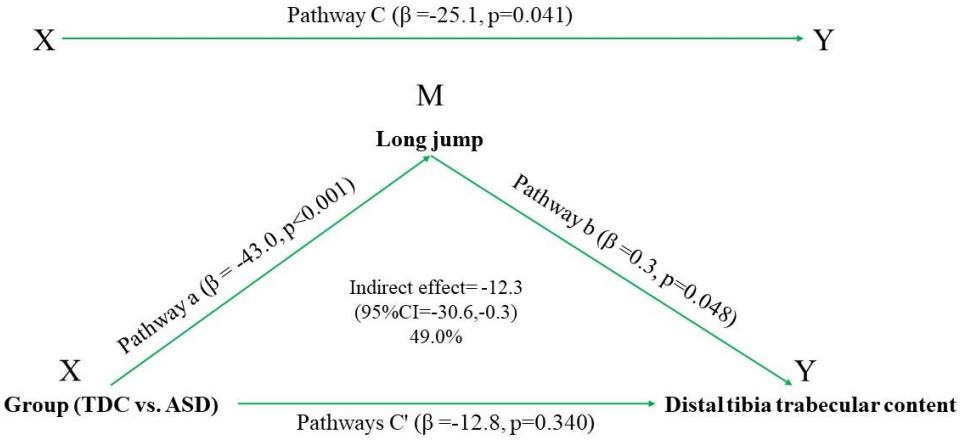


Figure 4.2. Mediation effects of long jump distance on distal Tibia (A) total area (B) total content and (C) trabecular content

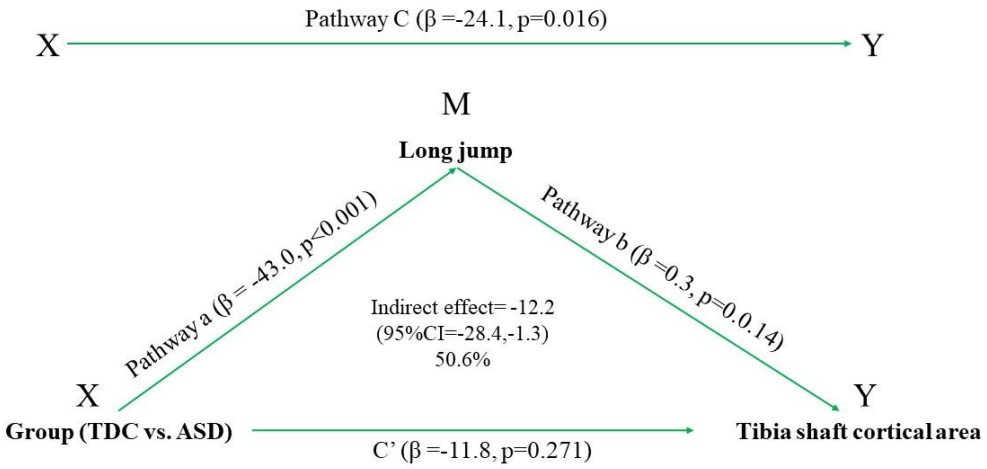


Figure 4.3. Mediation effects of long jump distance on tibia shaft cortical area

In addition to lower bone impacts, lower muscle grip strength and lower body muscle power in male children with ASD also may not provide sufficient stimulus for bone development in individuals with ASD. This study results suggested that even with comparable MuA, male children with ASD have 27-31% lower muscle strength and power than TDC. Lower body muscle power accounted for 40-51% of the bone area and mass deficits tibia. According to the Mechanostat theory, bone development is controlled by its mechanical loading environment (68); and the force generated by skeletal muscles contraction, which exerts directly to bones, has been recognized as the primary stimulus for bone mechanical signaling (15). Future interventions are warranted to increase muscle strength and power to optimize bone development in children with ASD.

Vitamin D and calcium intake did not differ between male children with ASD and TDC; however, vitamin D (42-60%) and calcium (33-48%) inadequacies were high in both groups, which may negatively affect bone development. Previous studies reported lower vitamin D, calcium and protein intake in children with ASD (4,6,8,139–143) as well as a positive association between the calcium and protein intake with aBMD in children with ASD (105,143). The results of this study, however, showed no differences in vitamin D and calcium intakes between groups as well as no mediation effects of vitamin D and calcium on bone mass, structure and estimated strength differences. It is noteworthy to point out that not all participants have nutrients intake data that might affect these results. In addition, 33 to 42% of male children with ASD did not meet EAR for vitamin D and calcium, which is concerning and may negatively

impact bone development. Future studies with larger samples are warranted to explore the effects of vitamin D and calcium inadequacies on bone structure and strength deficits in children with ASD.

The strength of this study was objective PA measures using an accelerometer. Accelerometers provide an accurate, reliable, and practical measure of PA in both children with disabilities, including ASD (183) and TDC (92,184,185), as well as provide the opportunity to estimate the bone impacts (17). Our study has limitations warranted to discuss. First, although most of the participants in both groups had muscle strength and power outcomes, the number of our TDC participants with PA and nutrients intake outcomes was small, affecting the mediation analysis results of PA and nutrients intake. Second, the power of MANCOVA test for distal radius may not be enough due to our small sample size with a usable radius scan. Third, for the aim of this study, I included the key bone health nutrients in the analyses; however, exploring the effects of the dietary pattern (e.g., vegetarian-style, western-like, mixed) on bone health and development is a preferred approach, considering contributions of various aspects of diet (186), for example, positive associations between dietary patterns dominated by the intake of fruits and vegetables and bone have been reported in children (187). Future studies are warranted to investigate differences in dietary patterns in children with ASD and explore the relationship of dietary patterns on bone deficits in this population.

4.7. Conclusion

Male children with ASD had 9-18 % lower estimated bone strength, structure, and mass at the distal tibia and the shaft sites of radius and tibia than TDC. Male children with ASD had 55% higher light PA and 57% lower daily bone impact counts when compared to TDC. GS and LJ distance were 27-31% lower in male children with ASD, and LJ distance accounted for 40-51% of bone mass and structure deficits at the distal and shaft sites of the tibia.

5. STUDY 3: MODERATE-TO-VIGOROUS PHYSICAL ACTIVITY IN CHILDREN WITH ASD: A META-ANALYSIS

SYNOPSIS: It remains unclear if participation in MVPA differs between children with ASD and TDC. Therefore, the primary aim of this meta-analysis was to compare objectively measured daily MVPA between children with ASD and TDC, as well as to examine the odds ratio between having ASD and not meeting the recommendation of MVPA at least 60 min/day. Since school hours are essential for the accumulation of MVPA in children, the secondary aim was to compare in-school MVPA, specifically the percentage of time spent in MVPA during PE and recess, between children with ASD and TDC.

5.1. Introduction

A recent systematic review reported lower PA in children with ASD when compared to TDC (9). However, to the best of our knowledge, no meta-analysis has yet been conducted comparing objectively measured MVPA between children with ASD and TDC. Therefore, the primary aim of this meta-analysis was to compare objectively measured daily MVPA between children with ASD and TDC, as well as to examine the odds ratio (ORs) between having ASD and not meeting the recommendation of MVPA at least 60 min/day (110,119). Since school hours are important for the accumulation of MVPA in children (20,22,188), the secondary aim was to compare in-school MVPA, specifically the percentage of time spent in MVPA during PE and recess, between children with ASD and TDC.

5.2. Methods

I followed the PRISMA guidelines (154,189) for conducting and reporting our meta-analyses.

5.2.1. Search strategy

Three investigators (MR, YZ, TW) independently conducted an electronic search for peer-reviewed publications in three databases (PubMed, SPORTDiscus and Web of Science) to retrieve all papers investigating the difference in objectively measured daily MVPA between children with ASD and TDC. The search was restricted to full articles in English published from January 1, 1990, to May 31, 2020. I employed “Child*”, “Adolescen*”, “Youth”, “Pediatr*”, “Boy”, “Girl”, “Autistic Disorder*”, “Autism Spectrum Disorder*”, “Autism”, “Physical Activit*”, “Moderate to Vigorous Physical Activity” and “MVPA” as key terms in the searches.

I combined the terms using the boolean operators “OR” and “AND”. Table 5.1 provides the search strategy in detail.

5.2.2. Eligibility criteria

I included studies that were published in a peer-reviewed journal, written in English and measured MVPA objectively in participants with ASD (mean age: 6-18 years) (including autism, Asperger syndrome, and pervasive developmental disorder not otherwise specified (PDD-NOS)). I included studies reporting comorbidities (e.g., ADHD). I excluded studies if they did not have a comparison group of TDC. Three investigators, working in groups of two (MR and TW; MR and YZ), selected publications, and disagreements were resolved through a discussion with a fourth investigator (SK) when required.

5.2.3. Data extraction and quality assessment

Three investigators (MR, TW and YZ) extracted the study characteristics (design and location), participant characteristics (number, age and sex), the tool used to diagnose ASD, accelerometer characteristics (type, epoch, wear time, the minimum required wear time, measurement units and cut off points), daily minutes of MVPA, number of participants who met the daily 60 minutes of MVPA, and the percentage of time spent in MVPA during PE and recess. I contacted the authors of six articles to request those PA outcomes of interests that were not reported in their published papers (10,18–21,26). Two authors (19,21) provided the requested data. I estimated means and standard deviation (SD) from figures using GetData Graph Digitizer 2.26 or available data when authors did not respond. Two investigators (MR and YZ) assessed the quality and risk of bias of included studies using the modified version of the Newcastle-Ottawa Quality Assessment Scale (adapted for cross-sectional studies) (190) and the disagreements were resolved through discussion with a third investigator (SK) when required. Studies were scored as good (overall score > 7, selection domain ≥ 3, comparability domain = 2, outcome domain > 2), fair (5 – 7, 2, 1, 2) or poor quality (< 5, 0-1, 0, 0-1) (191). The good, fair and poor quality scores suggested a low, moderate and high risk of bias, respectively (192).

Table 5.1. Detail of search strategy

Database	Search details
PubMed	(((((((("child*"[All Fields] OR "adolescence*"[All Fields]) OR ((((("adolescent"[MeSH Terms] OR "adolescent"[All Fields]) OR "youth"[All Fields]) OR "youths"[All Fields]) OR "youth s"[All Fields])) OR "podiatry*"[All Fields]) OR (("men"[MeSH Terms] OR "men"[All Fields]) OR "boy"[All Fields])) OR (("women"[MeSH Terms] OR "women"[All Fields]) OR "girl"[All Fields])) AND (((((((("autistic disorder"[MeSH Terms] OR ("autistic"[All Fields] AND "disorder"[All Fields])) OR "autistic disorder"[All Fields]) OR "autistic"[All Fields]) OR "autistics"[All Fields]) OR "autists"[All Fields]) AND "disorder*"[All Fields]) OR ((((((("autism s"[All Fields] OR "autisms"[All Fields]) OR "autistic disorder"[MeSH Terms]) OR ("autistic"[All Fields] AND "disorder"[All Fields])) OR "autistic disorder"[All Fields]) OR "autism"[All Fields]) AND (("spectrum"[All Fields] OR "spectrum s"[All Fields]) OR "spectrums"[All Fields]) AND "disorder*"[All Fields])) OR (((((("autism s"[All Fields] OR "autisms"[All Fields]) OR "autistic disorder"[MeSH Terms]) OR ("autistic"[All Fields] AND "disorder"[All Fields])) OR "autistic disorder"[All Fields]) OR "autism"[All Fields]))) AND (((((((("physical examination"[MeSH Terms] OR ("physical"[All Fields] AND "examination"[All Fields])) OR "physical examination"[All Fields]) OR "physical"[All Fields]) OR "physically"[All Fields]) OR "physicals"[All Fields]) AND "activit*"[All Fields]) OR ((((((((("moderate"[All Fields] OR "moderated"[All Fields]) OR "moderately"[All Fields]) OR "moderates"[All Fields]) OR "moderating"[All Fields]) OR "moderation"[All Fields]) OR "moderational"[All Fields]) OR "moderations"[All Fields]) OR "moderator"[All Fields]) OR "moderators"[All Fields]) AND "vigorous"[All Fields] AND ((("exercise"[MeSH Terms] OR "exercise"[All Fields]) OR ("physical"[All Fields] AND "activity"[All Fields])) OR "physical activity"[All Fields]))) OR "MVPA"[All Fields])) AND (1990/1/1:2020/5/31[Date - Publication] AND "English"[Language])
SPORTDiscus	Boolean/Phrase: (child* OR adolescen* OR youth OR pediatr* OR boy OR girl) AND (autistic disorder* OR autism spectrum disorder* OR autism) AND (physical activit* OR moderate to vigorous physical activity OR MVPA) Limiters - Published Date: 19900101-20200531; Language: English Expanders - Apply equivalent subjects; Apply related words
Web of Science	TOPIC: (child* OR adolescen* OR youth OR pediatr* OR boy OR girl) AND TOPIC: (autistic disorder* OR autism spectrum disorder* OR autism) AND TOPIC: (physical activit* OR moderate to vigorous physical activity OR MVPA) AND YEAR PUBLISHED: (1990-2020) AND LANGUAGE: (English) Timespan: All years. Indexes: SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI, CCR-EXPANDED, IC.

5.2.4. Statistical analysis

I estimated mean differences (MD) and standardized mean differences (SMD) of MVPA outcomes (daily minutes and the percentage of time spent in MVPA during PE and recess at school) between children with ASD and TDC. I chose to report MD as a summary statistic due to its easy interpretation (minutes of MVPA) and SMD due to the variety of ways MVPA outcomes were measured across the studies. I performed meta-analyses using random-effects models with the inverse variance method in RevMan (Review Manager Version 5.3, The Cochrane Collaboration, 2014). I reported heterogeneity using a 95% prediction interval (PI) and I-squared (I^2). I performed a sensitivity (subgroup) analysis comparing daily MVPA between children with mean age ≤ 9 vs. > 9 years. I chose the cutoff age based on the reported decline in daily MVPA after 9 years of age in TDC males (-8%) and females (-10%) (193). I used pooled odds ratios (ORs) to estimate the odds of not meeting the recommended daily MVPA in children with ASD vs. TDC. I estimated publication bias visually by funnel plot using Comprehensive Meta-Analysis version 3, and I used Duval and Tweedie's Trim and Fill test to estimate the adjusted (or unbiased) pooled SMD.

5.3. Results

5.3.1. Search results

The search produced a total of 1242 citations, and after removing duplicates, 985 titles remained (Figure 5.1). Of these, 970 studies were excluded as they did not meet the inclusion criteria after the abstract screening, leaving 15 studies eligible for full-text review. I excluded one study as it did not compare children with ASD with TDC (194) and one study as it measured MVPA subjectively reported by parents (195). I also excluded three studies (Pan 2008a; Pan et al. 2011b, 2016) as they reported previously published PA outcomes already included in the meta-analysis (Pan 2008b; Pan et al. 2011a, 2015). Another study was excluded as participants' mean age was less than 6 years old (197). Two studies had participants younger than 6 years; however, they were included as their participants' mean age was higher than 6 years (19,20). I checked the included studies' references for relevant studies, but no additional studies were identified. In total, nine studies met the inclusion criteria for the meta-analyses.

5.3.2. Characteristics of the included studies

Included studies were published between 2005 and 2019 from four countries, including the United States (18–21), Taiwan (Pan 2008b; Pan et al. 2011a, 2015), Sweden (25) and Iran (26).

The included studies' sample size ranged from 18 (20) to 825 (25). The percentage of females with ASD ranged from 4% (24) to 35% (18) in included studies, and three studies were conducted with only males (Pan et al. 2011a, 2015; Moludi et al. 2019). Six included studies (Pan et al. 2011a, 2015; Bandini et al. 2013; Tyler et al. 2014; Stanish et al. 2017; Moludi et al. 2019) used validated tools for diagnosis of ASD, including the Autism Diagnostic Observation Schedule (ADOS), the Autistic Diagnostic Interview-Revised (IDI-R), Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) or Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR®). Two studies (Pan 2008b; Lobenius-Palmér et al. 2018) used medical records for diagnosis, and one study (20) did not describe the procedure for the determination of ASD. Participants with autism, Asperger's syndrome and PDD-NOS were included in two studies (20,25), whereas three studies (Pan 2008b; Pan et al. 2011a, 2015) included participants with autism, Asperger's syndrome. Participants with autism, Asperger's syndrome and PDD-NOS were included in two studies (20,25), whereas three studies (Pan 2008b; Pan et al. 2011a, 2015) included participants with autism, Asperger's syndrome. Four studies did not report the type of ASD in their participants (18,19,21,26). The type of accelerometer, time-sampling interval (epoch) and cutoff point varied in the included studies (Table 5.2).

5.3.3. Quality of included studies

The studies' quality scores ranged from 5 (20) to 8 (18,21,22,25) out of 9 points (Table 5.3). Included studies had either low (4 studies) and moderate (5 studies) risk of bias.

5.3.4. Risk of bias in included studies

Four included studies had a low risk of bias and five had a moderate risk of bias (Table 5.3). All studies with a low risk of bias also had a low risk of selection, comparability and outcome bias. Three studies with a moderate risk of bias had either moderate comorbidity bias (Moludi et al. 2019; Pan et al. 2011a) or outcome bias (19). Only one study had a high risk of selection bias (20).

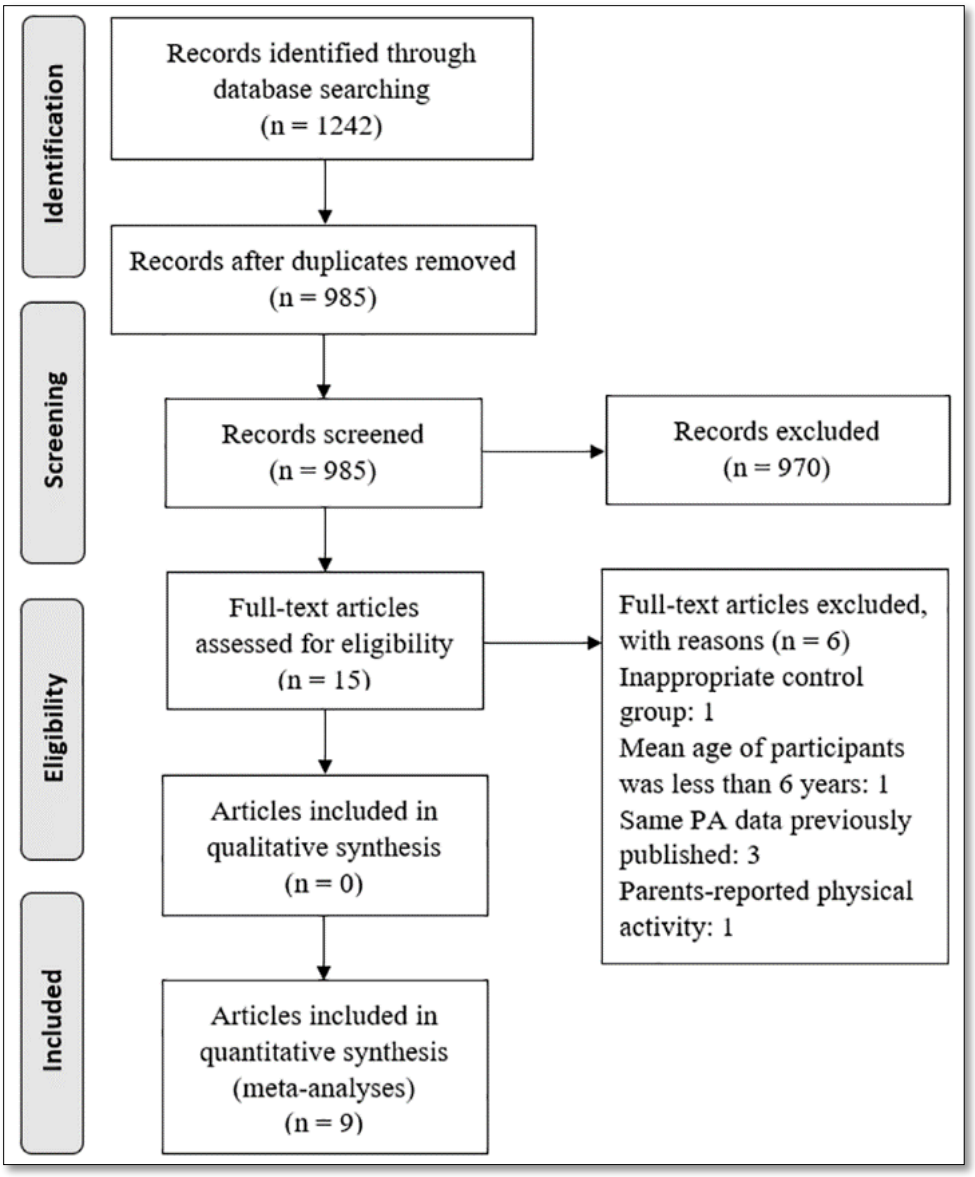


Figure 5.1. The PRISMA flow diagram (Liberati et al. 2009; Moher et al. 2009) of the literature search and article selection.

Table 5.2. General characteristics and daily and in-school MVPA outcomes of the included studies

Author, date, location	**Sample number, sex, age range, mean age (SD)**	- **ASD diagnosis** - **Kind of ASD** - **The severity of ASD** - **IQ (or ID)**	- **Instrument** - **Time-sampling interval (epoch)** - **Cut-point value**	- **Wearing time** - **Minimum required wearing time**	**MVPA (min/day): Mean (SD)** **Recommended daily MVPA: Met: n and/or (%) Did not meet: n** **PE/ Recess: MVPA (Min or %): Mean (SD)**	
					ASD	**TDC**
Moludi et al. 2019 **Iran**	**ASD:** 30 males, 6-13 yrs, 10.3 (2.4) yrs **TDC:** 29 males, 6-13 yrs, 9.83 (2) yrs	- DSM-IV (198) - Kind of ASD was not reported - Children with ID and severe behavior problems were excluded	- ActiGraph GTX3+ - Epoch was not reported - MPA (250-499 counts/minute) Heavy PA (≥ 500 counts/minute) (Kathleen F Janz 1994; in P. S. Freedson et al. 1998)	- 7 consecutive days - Waking hours	MVPA: 200.7 (108.9) [d]	MVPA: 235.9 (113.7) [d]
Lobenius-Palmér et al. 2018 **Sweden**	**ASD:** 25, 19 males & 6 females, 7-20 yrs, 14.0 (3.6) yrs **TDC:** 800, 356 males & 444 females, 8-16 yrs,	- Diagnoses were obtained from medical records - Autism, Asperger syndrome, or PDD-NOS - Severity was not reported - ASD without ID	- Uniaxial Actigraph [c] - 60 s epoch - Age-specific metabolic equivalents (200,201)	- 7 consecutive days - 10 hours per day for 3 days	MVPA: 79 (63) Recommended daily MVPA: Met: 10 (40) Did not Meet: 15[e]	MVPA: 142 (80) Recommended daily MVPA: Met: 665 (83) Did not Meet: 135[e]

	11.8 (3.1) yrs					
Stanish et al. 2017 **USA**	**ASD:** 29, 24 males & 5 females, 13-21 yrs, 15.9 (1.7) yrs **TDC:** 55, 33 males & 22 females, 13-18 yrs, 15.3 (1.5) yrs	- ADI-R (202) - Kind of ASD was not reported - Severity was not reported - 51.4% of adolescents with ASD also had an ID (IQ score of ≤75)	- Actical® - 15 s epoch - MPA (1500–5499 minute-by-minute activity counts) VPA (⩾6500 minute-by-minute activity counts) (203)	- 7 days (5 weekdays and 2 weekend days) - 10 hours per day for 3 weekdays and one weekend day	MVPA: 29.1(26.4) [f] Recommended daily MVPA: Met: 4 [e] (14) Did not Meet: 25 [e]	MVPA: 50 (26.0) [f] Recommended daily MVPA: Met: 16 [e] (29) Did not Meet: 39 [e]
Pan et al. 2015 **Taiwan**	**ASD:** 30 males, 12-17 yrs, 14.5 (1.5) yrs **TDC:** 30 males, 12-17 yrs, 14.7 (1.5) yrs	- DSM-IV-TR® (204) - 25 mild autistic disorder and 10 Asperger syndrome - None of the participants had ID	- Uniaxial ActiGraph - 10 s epoch - Age-specific metabolic equivalents (201)	- Five consecutive school days (8 a.m. to 4 p.m.) - Minimum time was not reported	MVPA: 69.61 (50.3) Recommended daily MVPA: Met: 14 (47 [e]) Did not Meet: 16 [e] **PE** (Min): 14.34 (9.1) (%): 30.26 (19.2) **Recess** (Min): 2.32 (1.9) (%): 21.24 (15.8)	MVPA: 97.07(47.7) Recommended daily MVPA: Met: 22 (73 [e]) Did not Meet: 8 [e] **PE** (Min): 25.27 (8.7) (%): 52.78 (18.3) **Recess** (Min): 3.12 (1.7) (%): 27.38 (13.1)
Tyler et al. 2014 **USA**	**ASD:** 17, 9 males & 6 females, 9-17 yrs, 12.6 (2.3) yrs **TDC:** 12, 6 males & 6 females, 9-	- ADOS (205) - Kind of ASD was not reported - CSS = 8.6 (1.54) - Ratio verbal IQ = 60.1 (25.2) Ratio nonverbal IQ = 65.7 (40.0)	- ActiGraph GTX3+ - Epoch was not reported - MPA (2000-2999 counts/minute)	- 7 days - Minimum time was not reported	MVPA: 165.9 (58.7)	MVPA: 218.3 (65.6)

	14 yrs, 9.0 (1.8) yrs		VPA (>3000 counts/minute) (94)			
Bandini et al. 2013 **USA**	**ASD:** 35, 24 males & 11 females, 3-11 yrs, 6.6 (2.1) yrs **TDC:** 47, 37 males & 10 females, 3-11 yrs, 6.7 (2.4) yrs	- ADI-R (202) - Kind of ASD did was not reported - Severity was not reported - IQ or ID was not reported	- Actical® - 30 s epoch - MPA (1500–5499 minute-by-minute activity counts) - VPA (⩾6500 minute-by-minute activity counts) (203)	- 7 days (5 weekdays and 2 weekend days) - 10 hours per day for 3 weekdays and one weekend day	MVPA: 50.3 (26.0) [f] Recommended daily MVPA: Met: 8 [e] (23) Did not Meet: 27 [e]	MVPA: 56.6 (25.7) [f] Recommended daily MVPA: Met: 20 [e] (43) Did not Meet: 27 [e]
Pan et al. 2011a **Taiwan**	**ASD:** 25 males, grades 7-9, 14.3 (0.89) yrs **TDC:** 75 males, grades 7-9, 14.1 (0.80) yrs	- DSM-IV (198) - 15 mild autistic disorder and 10 Asperger syndrome - IQ or ID did not report	- Uniaxial Actigraph - 10 s epoch - Age-specific metabolic equivalents (200)	Wearing time was not reported.	**PE** (%): 32.96 (18.0)	**PE** (%): 44.63 (15.0)
Pan et al. 2008b **Taiwan**	**ASD:** 24, 23 males & 1 female, 7-12 yrs, 9.2 (1.4)[a] yrs **TDC:** 24, 23 males & 1 female, 7-12 yrs,9.2 (1.4)[a] yrs	- Obtained in the public hospitals by physicians - 9 moderate functioning and 12 mild or high functioning autism - 3 Asperger's syndrome	- Uniaxial ActiGraph - 60 s epoch - Age-specific metabolic equivalents (200) -	- 5 consecutive school days (7:30–7:50 a.m. to, 3:55–4:10 p.m. (whole day) or 11:50 a.m.–12:40 p.m. (half day))	**PE** (%):46.25 (19.3) **Recess** (%): 27.70 (8.8)	**PE** (%): 46.77 (25.4) **Recess** (%): 36.15 (12.0)

		- None of the participants had ID				
Sandt and Frey 2005 **USA**	**ASD** [b]**:** 15, 10 males & 5 females, 5-12 yrs, 9.5 (1.9) yrs **TDC** [b]**:** 13, 8 males & 5 females, 5-12 yrs, 8.9 (2.0) yrs	- No description of ASD diagnosis - 9 Autism, 2 Asperger - Syndrome and 4 PDD-NOS - Severity was not reported - IQ or ID was not reported	- Uniaxial accelerometer (MTI, formerly CSA) - 60 s epoch - Age-specific metabolic equivalents (206)	- 10:00 a.m. – 7:00 p.m for 4 school days and one weekend day	MVPA: 127.5 (72.3) Recommended daily MVPA: Met: 10 (67 [e]) Did not Meet: 5 [e] **PE** (min): 12.8 (6.8) (%): 40.80 (19.9) [g] **Recess** (min): 15.5 (8.8) (%): 57.87 (25.3) [g]	MVPA: 162.1 (45.6) Recommended daily MVPA: Met: 12 (92 [e]) Did not Meet: 1 [e] **PE** (min): 16.7 (4.8) (%): 51.20 (18.4) [g] **Recess** (min): 22.6 (7.8) (%): 69.76 (16.1) [g]

[a] One mean and SD reported for both groups age [b] Number of participants for PE lessons outcomes were 26 children (13 ASD, 13 TDC) and number of participants for recess outcomes were 23 children (12 ASD, 11 TDC) [c] Actigraph activity monitor (model GT1M; Actigraph LLC) were used for ASD, and Actigraph accelerometer (model 7164; ActiGraph LLC, Pensacola, FL) were used for TDC [d] estimated based on available data [e] calculated using available data [f] first author provided data [g] I estimated means and/or SDs from Figureures using GetData Graph Digitizer 2.26

ADI-R, Autistic Diagnostic Interview-Revised; ADOS, Autism Diagnostic Observation Schedule; CCS, Calibrated Severity Scores; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition; DSM-IV-TR®, Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision; ID, Intellectual Disability; IQ, Intelligence quotient; PDD-NOS, Pervasive Developmental Disorder—Not Otherwise Specified

Table 5.3. Quality and risk of bias of included studies

	Questions	Moludi et al. 2019	Palmér et al. 2018	Stanish et al. 2017	Pan et al. 2015	Tyler et al. 2014	Bandini et al. 2013	Pan et al. 2011a	Pan et al. 2008b	Sandt and Frey 2005
Selection (0-5)	Representativeness of the sample (0-1)	*	*	*	*	*	*	*	*	-
	Justification of sample size (0-1)	-	*	-	-	-	-	-	-	-
	Non-respondents rates (0-1)[a]									
	Ascertainment of the exposure (0-2)	**	*	**	**	**	**	**	*	-
	Quality (Risk of Bias)	Good (Low)	Good (Low)	Good (Low)	Good (Low)	Good (Low)	Good (Low)	Good (Low)	Fair (Moderate)	Poor (High)
Comparability (0-2)	Confounding factors are controlled (0-2)	*	**	**	**	**	**	*	**	**
	Quality (Risk of Bias)	Fair (Moderate)	Good (Low)	Good (Low)	Good (Low)	Good (Low)	Good (Low)	Fair (Moderate)	Good (Low)	Good (Low)
Outcome (0-3)	Assessment of the outcome	**	**	**	**	**	**	**	**	**
	Statistical test	*	*	*	*	*	-	*	*	*
	Quality (Risk of Bias)	Good (Low)	Good (Low)	Good (Low)	Good (Low)	Good (Low)	Fair (Moderate)	Good (Low)	Good (Low)	Good (Low)
Quality score (0-9)[a]		7	8	8	8	8	7	7	7	5
Quality (Risk of Bias)		Fair (Moderate)	Good (Low)	Good (Low)	Good (Low)	Good (Low)	Fair (Moderate)	Fair (Moderate)	Fair (Moderate)	Fair (Moderate)
Reported outcome	Daily MVPA	✓	✓	✓	✓	✓	✓	-	-	✓
	%MVPA in PE	-	-	-	✓	-	-	✓	✓	✓
	%MVPA in recess	-	-	-	✓	-	-	-	✓	✓

[a] The possible maximum score was 9 because one of the questions (selection #3) was not applicable to all included studies

* Represent 1 mark

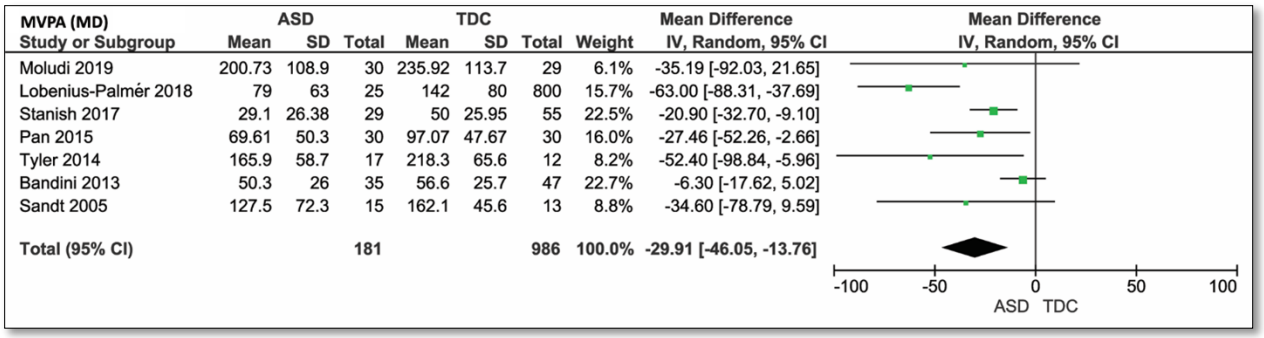


Figure 5.2. Forest plot of MD of daily MVPA in children with ASD and TDC.

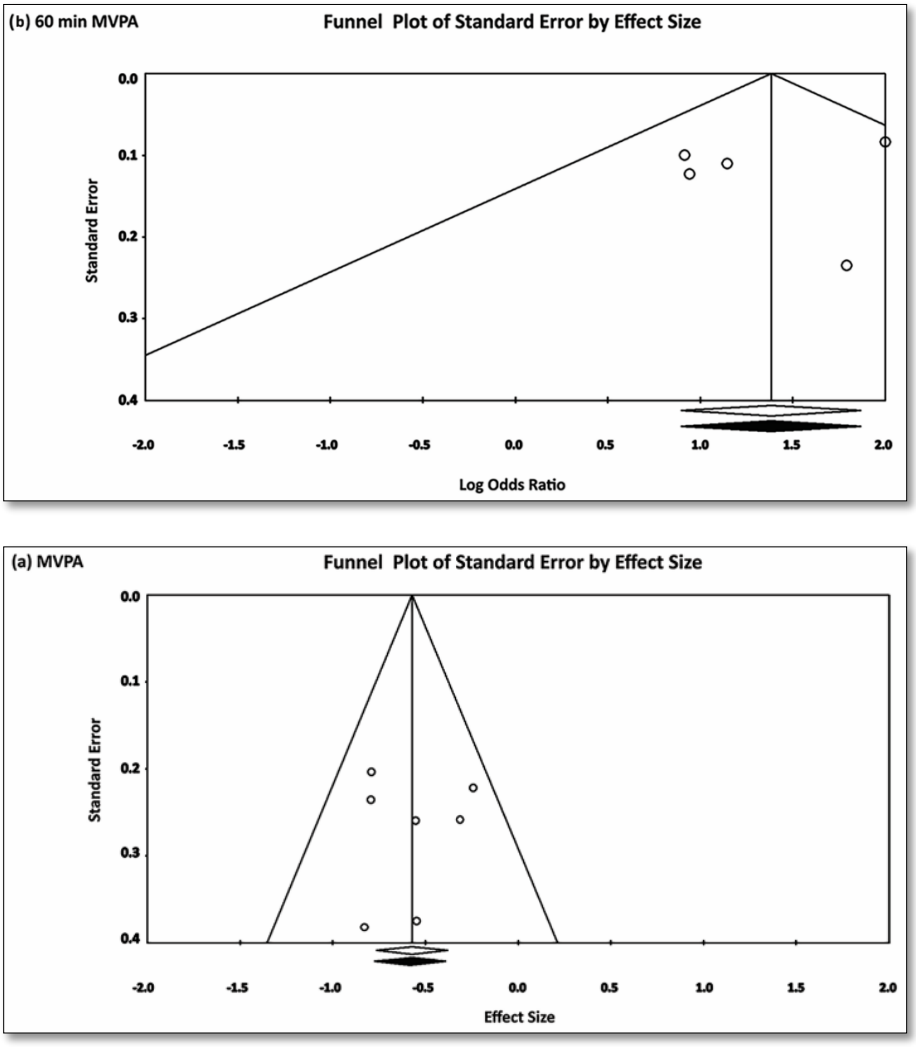


Figure 5.3. Funnel plot of (a) daily MVPA and (b) not meeting the recommended daily MVPA (60 min) in children with ASD and TDC.

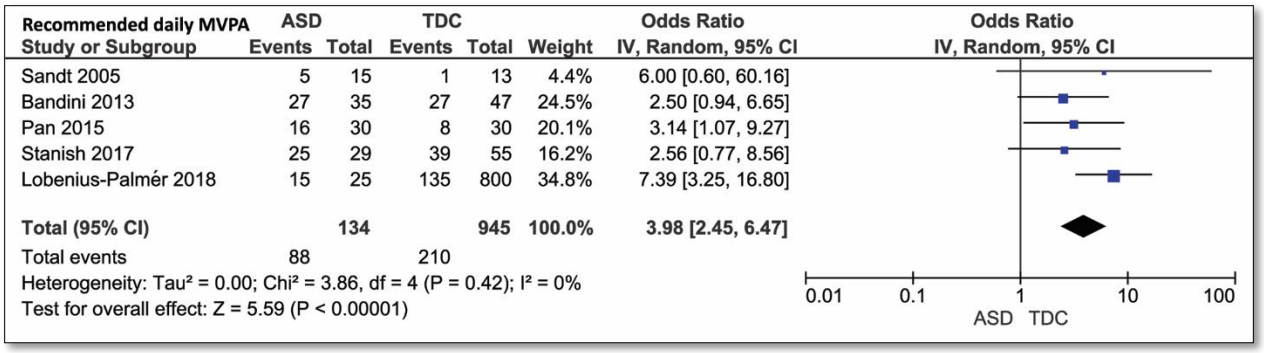


Figure 5.4. Forest plot of not meeting the recommended daily MVPA (60 min) in children with ASD and TDC.

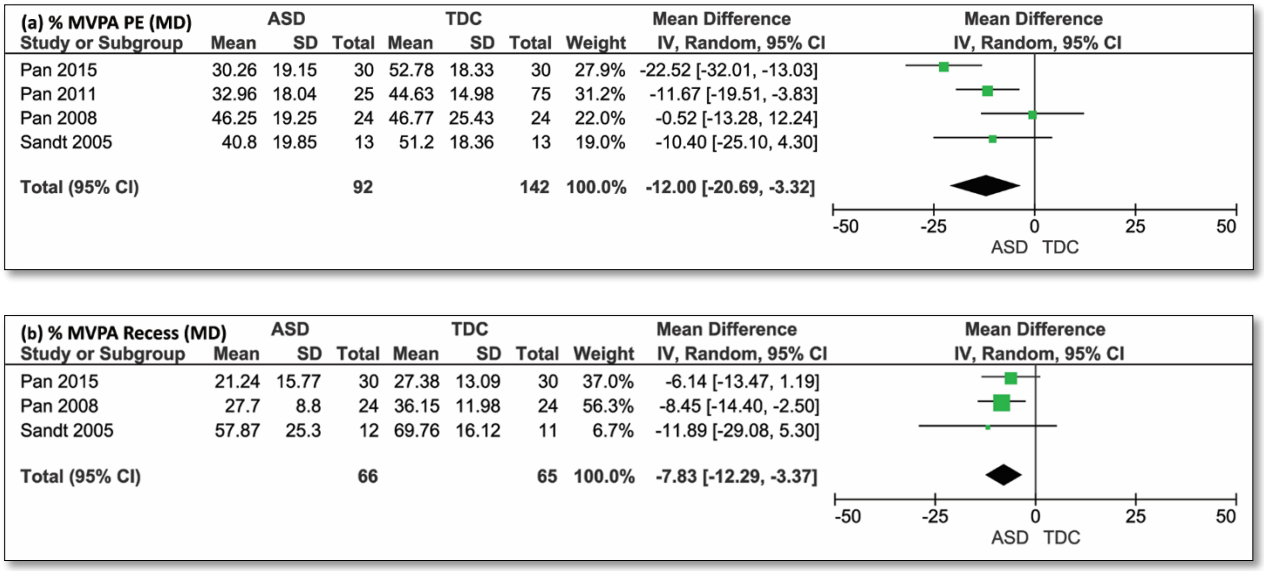


Figure 5.5. Forest plot of MD of %MVPA during (a) PE and (b) recess in children with ASD and TDC.

5.3.5. Daily MVPA

Children with ASD spent 30 minutes less daily time in MVPA (MD = -30; 95% CI, -46 to -14, P < 0.001) (Figure 5.2) when compared to TDC (SMD = -0.6; 95% CI, -0.8 to -0.4, P < 0.001) (Appendix A, Figure 3). There was no evidence of heterogeneity (P = 0.47). The 95% PI was -0.8 to -0.3, indicating that the dispersion of effects about pooled SMD was moderate. I^2 was zero, indicating that all of the variances in observed effects were due to sampling error rather than the variance in true effects. There was no evidence of publication bias as no imputed studies were found in re-displayed funnel plots of MVPA, and pooled SMD did not change (Figure 5.3a). The subgroup analysis of age indicated no difference in daily MVPA between studies with

participants' mean age > 9 yrs (-33; -51 to -14, P = 0.001) and studies with participants' mean age ≤ 9 yrs (-24; -54 to 6, P = 0.111) (P = 0.739).

The meta-analysis indicated that children with ASD had 4 times higher odds (OR = 4.0; 95% CI, 2.5 to 6.5, P <0.001) of not meeting the recommended daily MVPA than TDC (Figure 5.4). No evidence of heterogeneity was exhibited (P = 0.425). The 95% PI was 1.8 to 8.8, indicating that the dispersion of effects about pooled SMD was substantial; however, children with ASD were less likely to meet recommended daily MVPA across all samples of included studies. The I^2 was zero. There was no evidence of publication bias and pooled SMD did not change (Figure 5.3b).

5.3.6. MVPA during PE and recess

Children with ASD spent a 12% lower percentage of time in MVPA (MD = -12; 95% CI, -21 to -3) (Figure 5.5a) during PE when compared to TDC (SMD = -0.6; 95% CI, -1.1 to -0.1, P= 0.01) (Appendix A, Figure 2). The heterogeneity was moderate among studies reporting MVPA in PE (P = 0.04). The 95% PI was -2.7 to 1.4, indicating substantial dispersion of effects about pooled SMD. The I^2 was 65%. There was no evidence of publication bias and pooled SMD did not change (Appendix A, Figure 3a).

The meta-analysis indicated that children with ASD spent 8% lower percentage of recess time in MVPA (MD = -8; 95% CI, -12 to -3) (Figure 5.5b) when compared to TDC (SMD = -0.6; 95% CI, -0.9 to -0.2, P= 0.001) (Appendix 1, Figure 2a). There was no evidence of heterogeneity (P = 0.64). The 95% PI was -2.8 to 1.7, indicating substantial dispersion of effects about the pooled SMD. However, I^2 was zero, indicating that variance in observed effects was due to sampling error rather than the variance in true effects. There was no evidence of publication bias and pooled SMD did not change (Appendix A, Figure 3b).

5.4. Discussion

The meta-analyses provided a more precise estimate of lower daily and in school MVPA in children with ASD. Results from the meta-analyses indicated that children with ASD spent an average of 30 minutes less time in MVPA each day and had 4 times the odds of not meeting the MVPA recommendation when compared to TDC. In school, children with ASD spent about 12% and 8% lower percentage of time in MVPA during PE and recess, respectively.

Physical activity, particularly MVPA, is important for growth and development as well as an essential determinant of physical, mental, cognitive, and social health in children (207–209).

Meeting only the MVPA recommendation, as a key component of the 24-hour movement guidelines, has been associated with lower clustering of cardiometabolic risk (210) and related risk factors, including obesity and adiposity (211,212) in children. The difference in daily time spent on MVPA between children with ASD and TDC is about half of the recommended daily MVPA (110,119).

Meta-analysis indicated that children spent 8-12% less time in MVPA during recess and PE. School hours occupy a considerable proportion of children's waking hours, and both children with ASD and TDC accumulate more MVPA during than after school hours (188,213), including a higher percentage of time in MVPA during PE and recess (20,22). These differences may partly explain the lower daily MVPA in children with ASD and highlight school activities' importance in children's PA behavior.

Lower MVPA may be related to social interaction impairment, motor skill difficulties and physical barriers in children with ASD (27,28,118,214,215). Social interaction impairment is one of the core symptoms of ASD (1). Lower MVPA has been associated with social impairment in children with ASD (27,28). Although motor impairment is not a core symptom of ASD, many children with ASD have difficulties in motor skills that may limit PA participation (215). Motor skills impairments may also negatively affect participation in activities necessary for the development of appropriate social and communication skills (214). In addition to these impairments, physical barriers (e.g., lack of a peer partner, parental time, or equipment) may limit PA participation in children with ASD (117). Children with ASD reported more barriers for PA participation than TDC, and the number of barriers correlated negatively with time spent in PA (216). There is a need to create socially friendly environments to reduce barriers and secure opportunities to encourage PA engagement in children with ASD. For example, animal-assisted interventions have improved social interaction in children with ASD (29,30) and integration of therapy dog teams in a physical activity program has been suggested for children with ASD (35).

There are strengths and limitations in the meta-analyses that warrant discussion. First, a strength of this meta-analysis was the inclusion of studies reporting accelerometer monitored PA. Accelerometers provide an accurate, reliable, and practical measure of PA in both children with disabilities, including ASD (183) and TDC (92,184,185). Second, all of the included studies, except one, had high quality scores (7 or 8 out of 9 scores) that indicated the limited risk of bias in the included studies. Third, I used both PI and I^2 for estimating the heterogeneity to provide

more detail about the dispersion of SMD in the included studies (217). Using only the I^2, as common practice for reporting heterogeneity, is deceptive because I^2 is the percentage of the total dispersion due to between studies variance, but it does not provide any information about the total dispersion (217). PI provides information about the total dispersion of the SMD in the included studies (217). Fourth, our age sensitivity analysis suggested that the studies with participants' mean age below or above 9 years in included studies did not affect the daily MVPA meta-analysis consistency. Our meta-analyses also have limitations. First, I chose to include one study (21) that reported adjusted (sex and age) daily MVPA in our meta-analysis as the result did not change after the exclusion of this study. Second, I was not able to examine the association of the sex as none of the included studies reported sex-specific results., however, low level of heterogeneity in daily MVPA meta-analysis, suggesting that the variability within samples of the included studies did not affect the meta-analysis result. Third, a reliable estimate of heterogeneity needs a reasonably large number of studies; therefore, all reported heterogeneity statistics in our meta-analyses should be interpreted with caution. Fourth, because of the low number of included studies, the power for assessing publication bias was low. In addition to these limitations, it is important to consider that most studies reporting daily and in-school MVPA were from the United States and Taiwan, which may limit the generalizability of the results from this meta-analysis to other countries due to heterogeneity in PA across the globe (218).

5.5. Conclusion

Our meta-analyses results indicated that children with ASD spent an average of 30 minutes less daily in MVPA and had 4 times the odds of not meeting the daily recommended MVPA compared to TDC. Children with ASD spent about 12% and 8% lower percentage of time in MVPA during PE and recess, respectively. Tailored interventions to increase daily and in-school MVPA in children with ASD are warranted.

6. STUDY 4: THERAPY DOG ASSISTED PHYSICAL ACTIVITY INTERVENTION IN CHILDREN WITH ASD

SYNOPSIS: Difficulties in social interactions in children with ASD may contribute to lower PA and facilitating social pathways may improve PA participation in children with ASD. Animal assisted intervention may offer an attractive option for children with ASD; however, no quantitative study has assessed if an animal assisted intervention with therapy dogs can increase PA in children with ASD. Therefore, this pilot intervention assesses the feasibility of integrating a therapy dog into exercise sessions and its efficacy to improve PA outcomes in children with ASD.

6.1. Introduction

Inadequate PA may contribute to health concerns reported in children with ASD, such as an elevated rate of obesity and deficits in bone (167,219). Difficulties in social interactions in children with ASD may contribute to lower PA (27,28). The presence of therapy dogs has improved social interaction in children with ASD (29–32). In addition, qualitative studies suggested that children with ASD may benefit from integrating a therapy dog into a PA program (35,36). To this date, however, no quantitative study has assessed if an AAI with therapy dogs can increase PA in children with ASD. This pilot study aimed to assess the feasibility and efficacy of an AAI on PA outcomes during exercise sessions in children with ASD. Based on the existing literature, I hypothesized that the AAI would be feasible, and children with ASD would gain more PA and less sedentary time in AAI PA sessions compared to PA sessions without a therapy dog.

6.2. Method

6.2.1. Ethical approval

This study was approved by the University of Saskatchewan Biomedical Research Ethics Boards: Bio# 17-35.

6.2.2. Study Design

The study design was a randomized crossover AAI where study participants served as their own controls when comparing PA between sessions with and without a therapy dog. Given the pilot nature of this study, a crossover design was chosen as a comparison within participants helps to

reduce confounding factors and eliminate between-subject variability in measured outcomes, and thus, requires a smaller sample size (221). A carryover effect was not expected in this study, and therefore, a washout period of one week was considered adequate. The parent or legal guardian of each participating child provided written consent. An assent was asked from the participating children. The therapy dog handlers provided written consent for the animals to participate.

6.2.3. Participants

Children with ASD were recruited from the community (via Autism Services of Saskatoon) and the PAAL. The inclusion criteria include 6–14 years old children with ASD and no allergy to dogs. 20 children, 17 male and 3 female, were included who met the entry criteria.

6.2.4. Animal assisted intervention

The AAI included one weekly PA session for seven weeks from April to June 2017 at the University of Saskatchewan (Figure 6.1). PA was not measured in the first two sessions to reduce the novelty effect and give the participants the opportunity to become familiar with the two participating therapy dogs and their handlers, the volunteers guiding the PA sessions, wearing the accelerometers, and participating in the physical activities (e.g., circuit exercises). For the following 4 sessions, the participants were randomized into two groups (n=9), and groups were randomized to sessions with or without a therapy dog and handler presence by one of the investigators (SK) using a computer-generated random sequence (Figure 6.1). Participants or their parents/guardians were not informed about the presence or absence of the therapy dog and handler before the PA session. Participants concurrently attended PA sessions in the adjacent gyms, one with and the other without the therapy dog and handler. The last session was held outdoors as requested by the parents/guardians of our participants.

The PA sessions were approximately 60 minutes in duration and were led by two instructors experienced with adapted physical activity programming for children with ASD. Both instructors used the same PA protocol in all sessions. Each session started with a dog-themed warm-up game. These games were 15 minutes on average and included running activities (e.g., participants were instructed to run to a specific spot in the gym and complete additional activities based on the instructor's call). This warm-up was followed by a 30 minute circuit of agility activities incorporating running, walking, walking on all 4s like a dog, and jumping using agility ladders, hurdles, gym mattresses, hoops, and cones. Some of the PA games were competitive.

Sessions ended with a dog-themed cool-down game for approximately 10 minutes and stretching of the major muscle groups in a cycle for 5 minutes.

Each participant was partnered with a student volunteer for the entirety of the PA sessions. All volunteers participated in a mandatory study orientation, and most were from the PAAL program or had previous experience working with children with differing abilities, including children with ASD. The volunteers assisted with the PA activities and encouraged participants to stay on task during the sessions. The therapy dog handlers guided the participant's interactions with the therapy dogs. This ranged from inviting the participants to walk alongside a dog and handler while holding its leash to following a dog through an obstacle course or having the dog follow them in an activity. The therapy dog and handler took part in all the PA session exercises alongside the participants. The participants engaged with the therapy dogs to differing degrees throughout the PA sessions. The handlers were cognizant of 'sharing' the therapy dog the best they could between willing participants, and they engaged in physical activities only alongside the therapy dog. Given the pilot nature of the study, two therapy dogs were chosen to work with.

Both therapy dogs and two handlers were from St. John Ambulance, an international humanitarian organization. Dogs and handlers participating in St. John Ambulance Therapy Dog Program have passed a national suitability test, including dogs passing behavior and personality testing and humans passing a sector check to work with vulnerable persons. The broad aim of a therapy dog program is to provide comfort and support to the individuals in the dogs' visit with in a variety of settings, from university campuses through to senior living centers and hospital emergency departments (222,223). Both participating therapy dogs were a fun-loving and high-energy Boxer breed, which is known to be patient with children (Canadian Kennel Club). One of the dogs' handlers had professional dog training experience from Extreme K-9 in the United States and completed an animal-assisted intervention certificate at Harcum College, also in the United States. The other handler was a registered Social Worker. Combined, the handlers had over 3,000 practice hours in the therapy dog field with various populations, including children with physical and developmental disabilities.

6.2.5. Measurements

To objectively record minutes of PA and sedentary time, each participant was outfitted with an accelerometer (model wGT3X-BT, ActiGraph, Pensacola, Fla., USA) for the entirety of each PA

session. The accelerometer was attached with an adjustable elastic belt and positioned on the participant's right hip (17). Minutes of light PA, MVPA, sedentary time, and estimated bone impacts were recorded in all PA sessions using validated protocols, which have been described in detail previously (17). I defined the bone impacts based on resultant accelerometer peaks $\geq$ 3.9 g based on the positive relationships between bone strength and the number of accelerometer impact peaks (counts) reported in children (17). The Participants' height and weight were measured using our standard protocols (17) and parents/guardians were asked to complete a questionnaire of their child's health (e.g., ASD diagnosis and symptoms).

6.2.6. Statistical analysis

The sample size was based on a previously reported sample (N=12) and effect sizes ($\eta 2>0.8$) in a similar AAI assessing the effect of PA in children with obesity (33). Our recruitment goal was extended to increase our study power and account for possible challenges with the intervention and measurement compliance in our cohort. The participants were randomized into two groups to facilitate a group size of approximately 20 participants (including children, volunteers, instructors, therapy dogs and handlers). I estimated feasibility by assessing attendance in the PA sessions and retention in the 7-week AAI (Figure 6.1). I calculated the %-attendance as the mean of sessions each participant attended over the total sessions after randomization into the crossover PA sessions. I calculated the %-retention rate as the percentage of participants who completed the 7th week intervention divided by the total number of participants who consented to the study.

Before comparing PA outcomes between sessions with and without a therapy dog, I tested and confirmed that PA outcomes did not differ between the sessions between the adjacent gyms (without a therapy dog) (Wilks' Lambda = 0.839, F (5, 12) = 0.461, p=0.798). I also confirmed that the PA outcomes did not differ between the sessions with 1 or 2 therapy dogs (Wilks' Lambda = 0.940, F (5, 10) = 0.127, p=0.983). I imputed the individual PA outcomes from period 1 to 2 for three participants who missed either session with or without a therapy dog in period 2 (Figure 6.1).

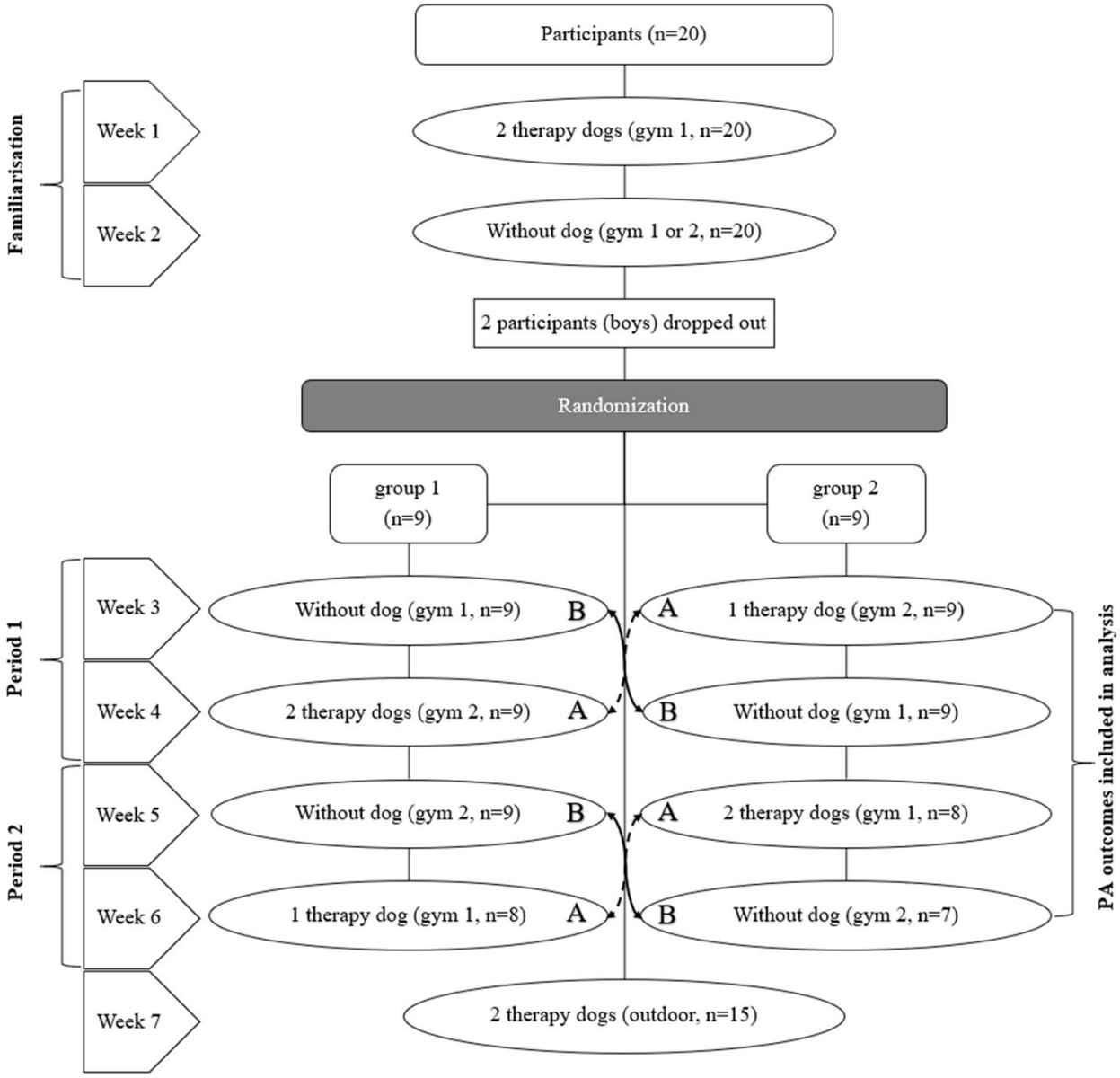


Figure 6.1. Flowchart of dog assisted PA intervention in children with ASD

Table 6.1. Characteristics of participants (N=18*)

Age, years, mean (SD)	10.1 (2.5)
Height, cm, mean (SD)	140.9 (14.7)
Weight, kg, mean (SD)	36.4 (12.0)
Body mass index, kg/m^2, mean (SD)	17.9 (2.7)
Sex, male/female	15/3
ASD (not specified), n (%)	8 (44)
Autism, n (%)	7 (39)
High-Functioning Autism, n (%)	2 (11)
Asperger syndrome	1 (6)**
PDD-NOS, n (%)	1 (6)
Non-verbal	1 (6)
Seizures, n (%)	2 (11)
Speech Impairment, n (%)	8 (44)
Hyperactive Condition, n (%)	2 (11)
Learning Problems, n (%)	7 (39)
Coordination/Balance Problems, n (%)	2 (11)
Inappropriate Behavior, n (%)	3 (17)
Dog at home	6 (33)

*Fifteen participants' parent/guardians provided the participant's comorbidities information

** One participant had both high-functioning autism and Asperger syndrome

Table 6.2. Average PA and mean differences (*Δ*) with the 95% confidence intervals between the sessions without or with therapy dog(s) presence

	Without Dog **Mean* (SE)**	**With Dog(s)** **Mean* (SE)**	**With dog(s) *vs.* without dog** **Δ [95% CI]**	**With dog(s) *vs.* without dog** **% *Δ***	**P-value**
Light PA (min)	26.4 (1.2)	29.9 (1.6)	3.5 [1.2, 5.8]	13	**0.005**
MVPA (min)	21.6 (2.2)	20.7 (2.3)	-0.9 [-2.8, 0.9]	-4	0.303
Bone Impacts (n)	62.8 (8.8)	67.6 (11)	4.8 [-17.7, 8.2]	8	0.451
Sedentary Time (min)	11.0 (1.3)	8.6 (0.9)	-2.4 [-4.3, -0.1]	-22	**0.040**

***** Estimated marginal means adjusted for multiple comparisons *Δ*= mean differences

I compared PA outcomes (minutes spent in light, MVPA, the number of bone impacts, and sedentary time) between 2 sequences (i.e., with or without therapy dog) of PA sessions over 2 periods of crossover sessions (Figure 6.1) using repeated measures MANOVA. With a significant omnibus effect of the sequence (sessions with or without a therapy dog), I performed a pairwise comparison of PA outcomes between the sessions. I used IBM SPSS 25 to perform data analyses and considered $p<0.05$ significant.

6.3. Results

I describe participants' background characteristics and the ASD diagnosis/symptoms in Table 6.1. Attendance in the crossover sessions was 92%. The retention rate was 90% over the 7-week AAI. The PA outcomes, including sedentary time, differed between the sessions with and without a therapy dog (Pillai's Trace = 0.661, $F(4, 14) = 6.820$, $p<0.003$, $\eta p2=0.661$). Participants had 13% greater minutes of light PA (mean difference = 3.5 min; 95% CI 1.2, 5.8 min) and 22% lower sedentary minutes (-2.4; -4.3, -0.1) in sessions with a therapy dog. MVPA and the number of bone impacts did not differ between sessions ($p>0.05$) (Table 6.2).

6.4. Discussion

To my knowledge, this is the first study to assess the feasibility and efficacy of an AAI on PA outcomes and sedentary time in children with ASD. The therapy dog PA intervention was determined to be feasible based on the high attendance and retention rate. It is possible that incorporating an AAI into the PA sessions served as an internal motivator for the participants to adhere to the intervention. This may be explained by the social interaction the therapy dogs can facilitate both internally and within participants, as well as the positive inclination of children with ASD toward animals (29,30). Wohlfarth et al. (2013) suggested that a therapy dog could unconsciously "trigger implicit motives which enhance motivation for activity" in children. In addition, dogs offer non-judgemental companionship, making social engagement and interactions more comfortable for children with ASD (29).

Difficulties in social interactions are a known risk factor for lower PA in children with ASD (27,28,225). The theory behind AAI to benefit children with ASD comes from human-animal interaction studies; specifically, research has identified that a reciprocal relationship with animals can contribute physical and psychological benefits (29). According to two systematic reviews, several studies have reported that the presence of a therapy dog benefits social

interaction in children with ASD (29,30), and social interaction has been associated with the PA intensity in children with ASD (27,28,225).

Children with ASD in our study had 13% more minutes of light PA in the presence of a therapy dog. This may be explained by children's eagerness to walk with the therapy dogs. Wohlfarth et al. (2013) reported in a study of children with obesity that they walked a longer average period of time in the presence of a therapy dog. A similar finding was reported in children and adolescents with orthopedic limitations (34). This is an important finding because increasing light PA may help prevention of obesity in children (226) and reduce high obesity rates in children with ASD (227,228). Emerging evidence is also suggesting cardiometabolic health benefits of light PA in children (229,230).

The presence of therapy dogs in PA sessions decreased sedentary time (22%) in children with ASD. This finding may have clinical relevance as children with ASD have higher sedentary time when compared to their typically developing peers (9). Sedentary time generally has been associated with increased physical and psychological health problems in children (231–234). The bone deficit in children with ASD might be associated with the reported higher sedentary time (235). In addition, the sedentary time has been negatively associated with sleep quality in children with ASD (121).

It is important to note that children with ASD accumulated an average of 20 minutes of MVPA and 60 bone impacts in each PA session, regardless of the presence of a therapy dog. These results were encouraging, as the PA sessions had been designed to include running and jumping activities, with a goal to engage children with ASD in both intensive aerobic and impact-type of PA. Engaging at least 60 minutes of daily MVPA and activities loading bone is recommended for all children due to related health benefits (99,208). Children with ASD are less likely to meet the MVPA guidelines and spend about 30min less in MVPA per day when compared to typically developing children (168). Physical activities providing loading stimulus for the skeleton are important because children with ASD have deficits in bone mass and strength (167). Recorded MVPA and bone impacts during the pilot sessions were promising when compared to the estimations of related benefits in bone strength (Kehrig et al., 2019). It has been estimated that adding 20 min of MVPA or 60 bone impacts (e.g., jumps) per day could increase tibia bone strength up to 7% in typically developing children (17).

Our study had key strengths that warrant discussion. The crossover design facilitated PA comparison between sessions with and without a therapy dog within the same group of participants. Comparison within participants can reduce confounding factors, eliminate between-subject variability in measured outcomes, and require a smaller sample size (221). Second, the distribution of sex (15 male, 3 female) was a representative sample as males are four times more likely to be diagnosed with ASD (102). Third, accelerometers with a validated methodology were used to objectively quantify PA outcomes and sedentary time (93,175). This is a unique contribution to both the ASD and AAI literature. Fourth, the same volunteers were matched with each participant throughout the PA sessions to keep the level of encouragement and assistance consistent.

There are also some key limitations in our study. The first limitation pertains to a possible selection bias in our sample, as the majority of participants were recruited from an adapted PA program. Thus, the study findings may only be generalized to children with ASD who have participated in adapted PA and did not have an allergy to dogs (as per our exclusion criteria). Second, I only assessed the AAI's feasibility in the PA sessions by calculating attendance and retention rate but did not assess other feasibility aspects (e.g., acceptability) (236). Third, I did not assess any interactions between the participants and therapy dogs or handlers. Since the therapy dog and handler formed a unit, I cannot separate the effect of the therapy dog from the effect of the handler on PA. Future studies may have handlers engaged in all PA sessions and randomize only the therapy dog presence to tease out the role of the therapy dog on children's PA in AAI.

The findings of this pilot study, coupled with its strengths and limitations, can help guide the design of future, more robust AAI PA intervention for children with ASD (30–32). For example, investigators may consider including a broader assessment of activity behaviors, including sleep quality. Future studies could also benefit from systematically monitoring children’s interaction with the therapy dogs in relation to their physical activity measurements.

6.5. Conclusion

In summary, the AAI PA intervention in children with ASD was feasible. Children with ASD had 13% greater minutes of light PA and 22% lower sedentary minutes in the therapy dog sessions. MVPA and the number of bone impacts did not differ between sessions with and without a therapy dog ($p>0.05$).

7. DISCUSSION AND CONCLUSION

7.1. Overview of Findings

The overall aim of this thesis was to synthesize and update the evidence of bone health in children with ASD, synthesize the evidence of MVPA in children with ASD vs. TDC as well as to assess the feasibility and efficacy of animal assisted PA intervention in children with ASD.

7.1.1. Objective 1: Synthesizing and updating the evidence of bone health in children with ASD

The meta-analysis results (study 1) showed that children with ASD have 0.7 to 1 SD lower aBMD at TB, LS, TH and femoral neck when compared to typically developing children. This difference may have the clinical importance of contributing to the elevated fracture risk reported in children with ASD. The qualitative review (study 1) also highlighted deficits in BMC, bone size and structure, which contribute to lower bone strength and possibly to higher fracture risk (158–161). Lower BMC likely contributes to weaker bone structure reported in children with ASD (4). At the fracture-prone distal radius, children with ASD had 20% thinner cortices and 10% thinner trabeculae resulting in 19% lower bone strength when compared to TDC (4). However, it is important to note that these differences appear to exceed reported differences between pediatric fracture cases and controls (161). For example, pediatric fracture cases had 12% thinner cortex and 11% lower bone strength at the distal radius when compared to their peers without distal forearm fracture history (161). The review revealed a need for future advanced imaging studies to complement the preliminary findings of bone micro-architecture and strength deficits in children with ASD.

The primary results of the second study showed that male children with ASD had 11-18% lower bone strength, total area and cortical area at radius shaft, as well as bone estimated strength, total area and content and trabecular content at the distal tibia and total and cortical area at tibia shaft when compared to TDC. These results extended the results of the previous study reporting 10-20% lower bone estimated strength and smaller cortical area and thickness and trabecular thickness at the distal radius and tibia in male children with ASD. The study also indicated that the lower muscle strength and power might not provide sufficient stimulus for bone development in individuals with ASD. The GS and lower body muscle power were 27-31% lower in male children with ASD and lower body muscle power accounted for 40-51% of

deficits in total area and total and trabecular content at the distal tibia as well as cortical area at the tibia shaft.

7.1.2. Objective 2: Synthesizing the evidence of MVPA in children with ASD vs. TDC

The primary result of meta-analysis (study 3) indicated that children with ASD spent an average of 30 minutes less time in MVPA each day and had 4 times the odds of not meeting the MVPA recommendation when compared to TDC. The difference in daily time spent on MVPA between children with ASD and TDC is about half of the recommended daily MVPA, and it is concerning and clinically important as lower MVPA may adversely affect development and overall health in children with ASD. For example, this difference may be associated with higher overweight and obesity rates reported in children with ASD (219,237–239). In addition, lower daily MVPA may be related to bone deficits in children with ASD (167), as daily minutes of MVPA have been positively associated with bone health in childhood and adolescence (17,240). Lower MVPA during school hours might explain lower daily MVPA in children with ASD as school hours occupy a considerable proportion of children's waking hours, and both children with ASD and TDC accumulate more MVPA during than after school hours (188,213), including a higher percentage of time in MVPA during PE and recess (20,22). The meta-analysis results indicated that children spent 8-12% less time in MVPA during recess and PE. The results emphasize that interventions to increase daily and in-school MVPA in children with ASD are warranted.

7.1.3. Objective 3: Assessing the feasibility and efficacy of animal-assisted PA intervention in children with ASD

The results showed the AAI PA intervention in children with ASD was feasible and it can help guide the design of future AAI PA intervention for children with ASD. Children with ASD had 13% greater minutes of light PA in the therapy dog sessions. This is an important finding because increasing light PA may reduce high obesity rates in children with ASD (227,228). The study results also indicated that the presence of therapy dogs in PA sessions decreased sedentary time (22%) in children with ASD. This finding may have clinical relevance as children with ASD have higher sedentary time when compared to their typically developing peers (9). Sedentary time generally has been associated with increased physical and psychological health problems in children (231–234). In addition, the sedentary time has been negatively associated with sleep quality in children with ASD (121). It is also important to note that children with ASD accumulated an average of 20 minutes of MVPA and 60 bone impacts in each PA session (~60

min), regardless of the presence of a therapy dog. These results were encouraging as children with ASD are less likely to meet the MVPA guidelines, based on the meta-analysis results, and they also accumulated 46 less bone impact per day when compared to TDC, based on the second study results.

7.2. Strengths

First, PA was measured objectively using the accelerometer recordings in studies 2 and 4. I also focused on studies reporting accelerometer measured MVPA in the meta-analysis (study 3). Accelerometers provide an accurate, reliable, and practical measure of PA in both children with disabilities, including ASD (178) and TDC (92,179,180) as well as provides the opportunity to estimate the bone impacts (17).

In the third study, the included studies in the meta-analysis (study 3), except one, had high-quality scores (7 or 8 out of 9 scores) that indicated the limited risk of bias in the included studies. I used both prediction interval and I^2 for estimating the heterogeneity to provide more detail about the dispersion of SMD in the included studies (217). Using only the I^2, as common practice for reporting heterogeneity, is deceptive because I^2 is the percentage of the total dispersion due to between studies variance; However, it does not provide any information about the total dispersion (217). The prediction interval provides information about the total dispersion of the SMD in the included studies (217).

In the fourth study, the crossover design facilitated PA comparison between sessions with and without a therapy dog by reducing the confounding factors, eliminating the between-subject variability in measured outcomes, and requiring a smaller sample size (221). The distribution of sex (15 male, 3 female) was a representative sample as males are four times more likely to be diagnosed with ASD (102). The same volunteers were matched with each participant throughout the PA sessions to keep the level of encouragement and assistance consistent.

7.3. Limitations

The findings of the first study should be interpreted with the following considerations. The number of studies providing data for the systematic review and meta-analysis was small and the quality of the included studies was fair at best; therefore, all reported heterogeneity and publication bias statistics in our meta-analyses should be interpreted with caution. The results of the meta-analyses may be susceptible to small study effects. In addition, four of the included

studies were from the same research group, which increases the risk of selection bias and limits the generalizability of the review and meta-analysis results.

In the second study, although most of the participants in both groups had muscle strength and power outcomes, the number of our TDC participants with PA and nutrients intake outcomes was small, affecting the mediation analysis results of PA and nutrients intake. Second, the power of MANCOVA test for radius may not be enough due to our small sample size with a usable radius scan. Third, I included the key bone health nutrients in the analyses; however, exploring the effects of whole dietary patterns on bone health and development is a preferred approach.

In the third study, I was not able to examine the association of the sex as none of the included studies reported sex-specific results; however, low level of heterogeneity in daily MVPA meta-analysis, suggesting that the variability within samples of the included studies did not affect the meta-analysis result. Because of the low number of included studies, all reported heterogeneity and publication bias statistics in our meta-analyses should be interpreted with caution.

There are also some limitations in our fourth study. The first limitation pertains to a possible selection bias in our sample, as most participants were recruited from the PAAL, an adapted PA program. Thus, the study findings may only be generalized to children with ASD who have participated in adapted PA and did not have an allergy to dogs (as per our exclusion criteria). In addition, the AAI's feasibility in the PA sessions was only assessed by calculating attendance and retention rate but not other feasibility aspects (e.g., acceptability) (236). For example, future studies may investigate the satisfaction rate of both parents (e.g., with survey) and participants (e.g., with smile detecting method).

7.4. Advance in scientific knowledge

This thesis advances our knowledge about the bone deficit in children with ASD by synthesizing the current evidence of bone mass in children (study 1) and updating the evidence of bone strength and structure in children with ASD (study 2). This evidence may partly explain the higher risk of fracture in children with ASD. For the first time, the results from our study also indicated lower bone impacts activities and muscle strength and power in children with ASD (study 2), which may partly explain the bone strength and structure deficit in weight-bearing skeletal sites (i.e., tibia).

Although previous studies compared MVPA between children with ASD and TDC, the results were contradictory. The Meta-analysis from my thesis (study 3) showed that children with ASD spent 30 minutes less daily in MVPA, which is half of the daily recommendation for children. This evidence is clinically crucial as daily MVPA has been linked to physical and psychological health in children with ASD. The results of in school MVPA also advance our understanding of engaging children with ASD during school hours. Results reveal that children with ASD spent less time in MVPA during recess and PE and it may partly explain lower daily MVPA.

The results of AAI PA (study 4) were also promising as therapy dog PA intervention was feasible and increased light PA and decreased sedentary time in children with ASD. The therapy dog presence may facilitate PA engagement by improving social interaction, which has been liked to lower MVPA in children with ASD. Since the therapy dog and handler formed a unit, I cannot separate the effect of the therapy dog from the effect of the handler on PA. Future studies may have handlers engaged in all PA sessions and randomize only the therapy dog presence to tease out the role of the therapy dog on children's PA in AAI.

7.5. Conclusion

Overall, my thesis provides evidence of bone deficits, particularly the bone structure and strength deficits in children with ASD, partly explaining the higher risk of fracture in individuals with ASD. In addition, the evidence also suggested that lower PA, particularly MVPA, and muscle performance may contribute to bone deficits in children with ASD. Future PA intervention may benefit from the evidence of feasibility and efficacy of the animal-assisted PA interventions to optimize bone health and development in children with ASD.

7.6. Future Directions

Areas of future study include (but are not limited to):

1. As I mentioned in study 1, the difference in the bone mass, structure, and strength between children with ASD and TDC may be contributing to the elevated fracture risk reported in children with ASD. Future studies exploring bone deficits in children with ASD and a history of fracture are warranted.
2. As I discussed in study 2, children with ASD had 46 counts lower bone impacts per day than TDC. It has been estimated that adding 60 bone impacts (e.g., jumps) per day could increase tibia bone strength up to 7% in typically developing children. The fourth study

showed that children with ASD accumulated 60 impacts in one hour of PA session. Future randomized control trials are needed to examine if activities with bone impacts could improve bone strength development in children with ASD.

3. As I discussed in study 2, muscle strength and power were lower in male children with ASD, and muscle power partially accounted for the tibia bone deficits in male children with ASD. Therefore, future interventions are warranted to increase muscle strength and power to optimize bone health and development in children with ASD.
4. As discussed in study 2, not all of the participants in this study (especially in the control group) have nutrition data, which may affect the findings. In addition, I included the key bone nutrients in the analyses; however, exploring the effects of whole dietary patterns on bone health and development is a preferred approach. Hence, future studies with larger samples are warranted to explore the effects of dietary patterns on bone deficits in children with ASD.
5. As I mentioned in study 3, most studies reporting daily and in-school MVPA were from the United States and Taiwan, which may limit the generalizability of the meta-analysis results to other countries due to heterogeneity in PA across the globe (218). Future studies are warranted to compare PA between children with ASD and TDC in other contourites as well.
6. As I mentioned in study 3, children with ASD may benefit from accumulating MVPA and bone impacts during PA compared to the estimations of related benefits in bone strength (17). Future randomized control AAI is needed to examine the efficacy of impact-type of PA to optimize bone strength development in children with ASD.

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APPENDIX A. SUPPLEMENTARY FIGURES

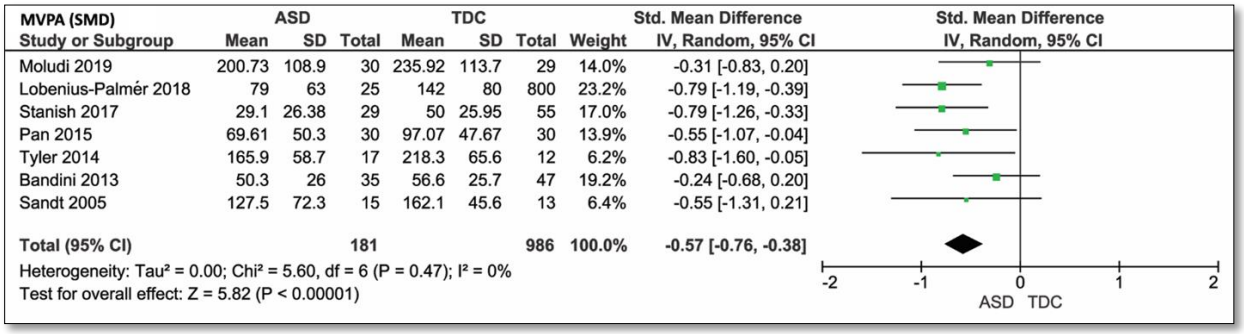
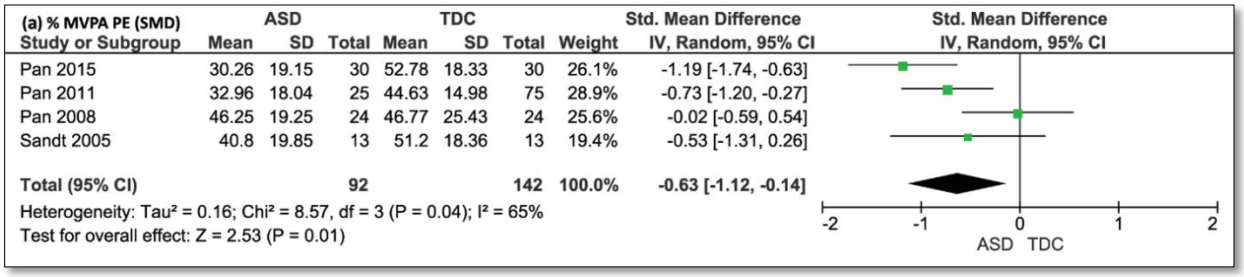


Figure 1. Forest plot of SMD of daily MVPA in children with ASD and TDC



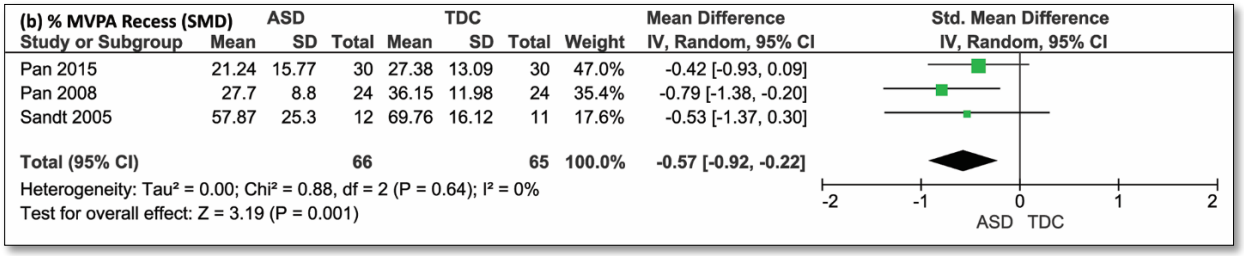


Figure 2. Forest plot of SMD of %MVPA during (a) PE and (b) recess in children with ASD and TDC

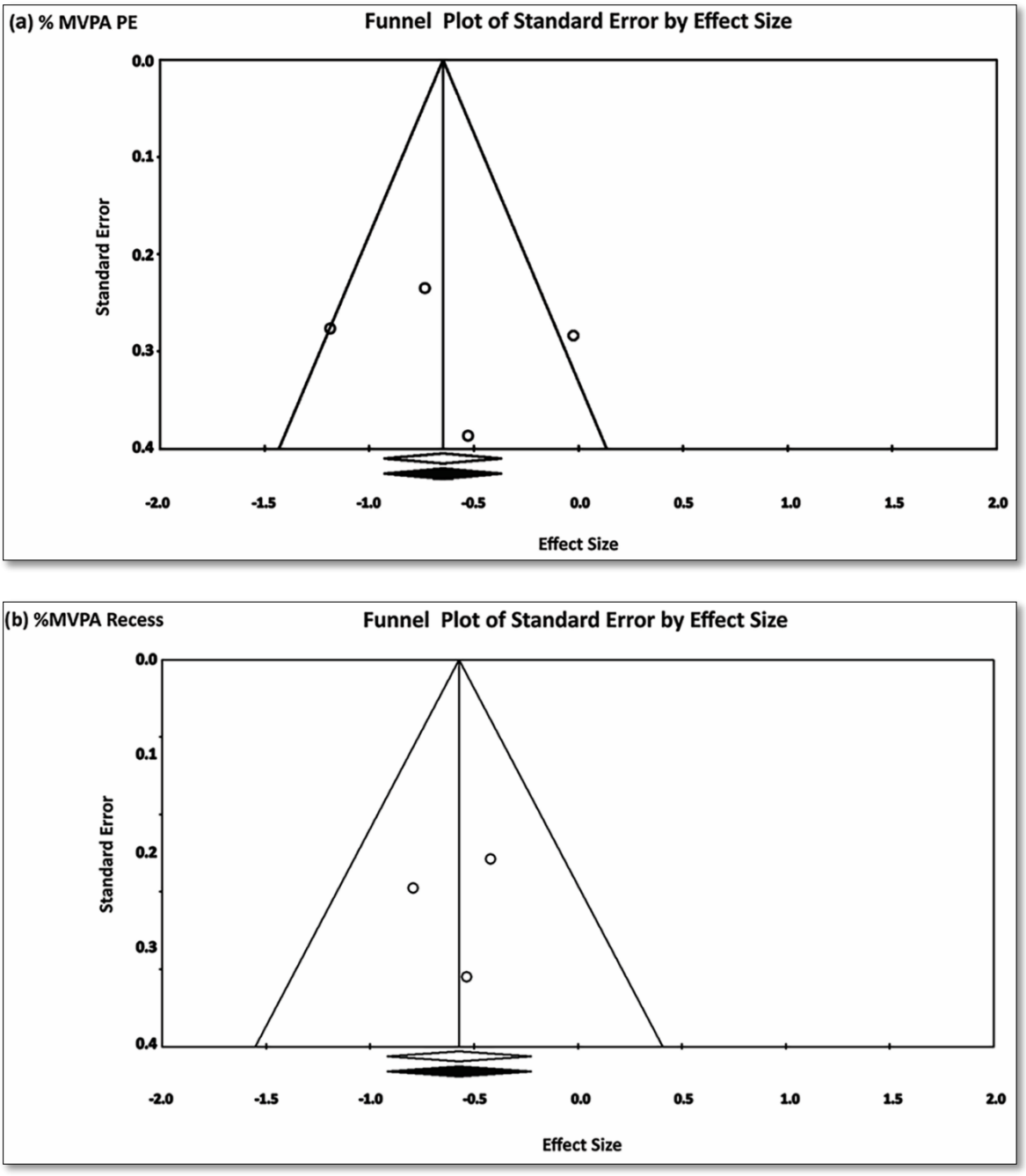


Figure 3. Funnel plot of %MVPA during (a) PE and (b) recess in children with ASD and TDC

APPENDIX B. COPYRIGHT AGREEMENTS

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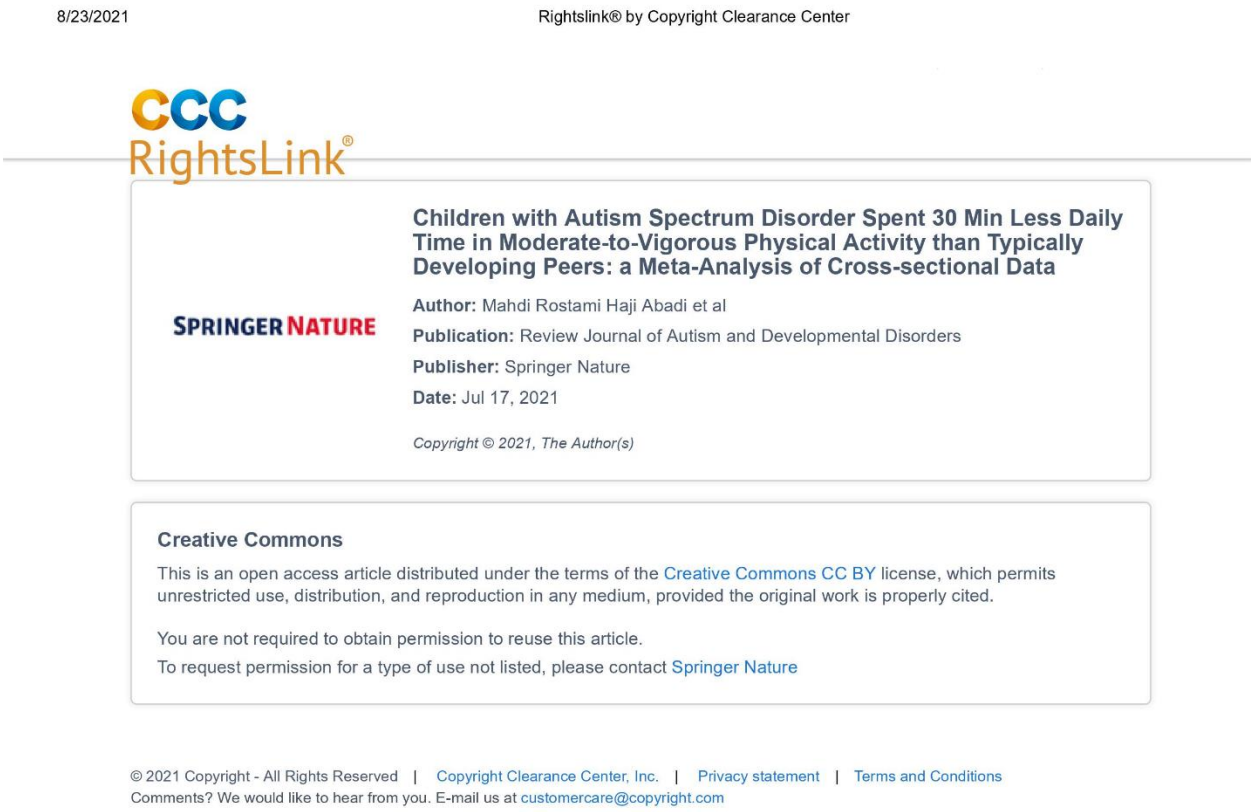

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