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Association of developmental coordination disorder and low motor competence with impaired bone health: a systematic review.

Abstract

Aims
This systematic review explores the association between developmental coordination disorder (DCD) and low motor competence (LMC) with bone health.

Methods and Procedures
Studies were included with assessment of any bone health outcome in a DCD or LMC population. Studies were located by searching published and grey literature. Study bias was assessed using the JBI critical appraisal checklist with publication bias assessed by funnel plot asymmetry. Due to heterogeneity meta-analysis was not possible and narrative synthesis was performed with effect size and direction assessed via harvest plots.

Outcomes and Results
A total of 16 studies were included: 8 paediatric, 7 adolescent and one adult. Deficits were reported for the DCD/LMC group in most bone measures, most frequent in weight-bearing sites such as the tibia. Critical appraisal indicated very low confidence in the results, with issues relating to indirectness due to DCD/LMC identification and imprecision relating to comorbidities.

Conclusions and Implications
Individuals with DCD or LMC appear to be at increased risk of bone health deficits with potential increased risk of fracture. If substantiated, results imply a likely increased risk of osteoporosis in later life, which based on bone impairment location may be due to insufficient loading from physical activity.

Keywords: developmental disabilities, fracture, movement, inactivity, falls, bone.

What this paper adds
This review provides the first synthesis of the evidence of the association between DCD or LMC and low bone health. It indicates that there is evidence of an association between DCD or LMC and poor bone health in paediatrics and adolescence, which may extend to an increase in fracture risk during adolescence. This synthesis provides evidence that these bone health detriments are related to lower levels of physical activity. Importantly, gaps in the literature are identified with guidance for future research to address methodological confidence and imprecision issues.

1. Introduction

Developmental coordination disorder (DCD) is a neurodevelopmental condition typified by difficulty in the acquisition and performance of motor skills such that there is an impact upon everyday functioning (American Psychiatric Association, 2013). DCD is also referred to as low motor competence (LMC) when DCD diagnosis is not possible (Blank et al., 2019). Individuals with DCD have been suggested to be at risk of a variety of health conditions, including impaired bone health (Cantell, Crawford, & Doyle-Baker, 2008; Hands et al., 2015; Tsang, Guo, Fong, Mak, & Pang, 2012). Bone health indicates the vulnerability of the bone to fracture and is indicated by measures including density, architecture, and geometry (Hart et al., 2020; Hart et al., 2017). Bone health impairment may be considered present when bone measurements are more than one standard deviation below age-appropriate reference intervals (World Health Organization, 1994). However, no individual tool is currently able to assess all elements that make up bone health and hence completely assess fracture risk (Hart et al., 2020; Shalof, Dimitri, Shuweihdi, & Offiah, 2021). Bone health follows a lifelong trajectory with growth and development in childhood and adolescence followed by gradual decline in adulthood (World Health Organization, 1994). Therefore, bone health impairment identified at any age can be a predictor for osteoporosis, a term which indicates skeletal frailty and minimal trauma fractures at an earlier age than would otherwise be anticipated (Bishop et al., 2014). As such, impaired bone health in populations with DCD may indicate a group at increased risk of fracture.

Individuals with DCD may be at increased risk of bone health impairment due to risk factors such as low birth weight (Blank, Smits-Engelsman, Polatajko, & Wilson, 2012; Cooper et al., 2006) or medication use for co-occurrent conditions such as attention deficit disorder/attention deficit disorder with hyperactivity (ADD/ADHD)(Feuer, Thai, Demmer, & Vogiatzi, 2016; Landgren, Fernell, Gillberg, Landgren, & Johnson, 2021). Additionally, individuals with DCD

have been reported to have physical activity patterns similar to that associated with impaired bone health in the general population (Faulkner, 2007; Foley, Quinn, & Jones, 2008; Hart et al., 2020), with sustained low levels of physical activity and high rates of sedentary behaviour (Rivilis et al., 2011). Physical activity creates mechanical strain which stimulates bone development in accordance with the type and degree of strain and the life stage in which it occurs (Kontulainen, 2007). The greatest benefits for bone development are observed from high levels of diverse physical activity during childhood and adolescence (Hart et al., 2017). As such, bone health impairments are anticipated in the DCD population with reported low levels of physical activity, particularly seen in childhood (Rivilis et al., 2011).

In the context of bone health impairment, a DCD or LMC population may be at an even greater than expected increased risk of fracture due to a higher rate of falls compared to the general public (Scott-Roberts & Purcell, 2018) and comorbidity with ADD/ADHD (James et al., 2021), which is associated with increased injury risk (Chou, Lin, Sung, & Kao, 2014). Fractures have a substantial impact on quality of life (Fortington & Hart, 2021; Son et al., 2016), with osteoporotic fractures in particular having a high mortality rate (Cauley, 2013). Additionally, fractures have a substantial economic impact, with an estimated direct cost of more than 100 million dollars over a 10-year period for osteoporotic fractures alone in Western Australia (Briggs et al., 2015). Given the estimated population rate of DCD being between five to six percent (Blank et al., 2019), identification of bone health impairment in individuals with DCD is of public health interest.

To ascertain if DCD or LMC population is at increased risk of bone health impairments, it is necessary to determine its prevalence and severity. Hence, this systematic review aims to examine the association between DCD and LMC with bone health measures across the lifespan.

2. Methods

This systematic review was registered within PROSPERO (CRD42020167301). It was performed in accordance with PRISMA guidelines for the reporting of systematic reviews (Page et al., 2021) and the JBI manual for studies of etiology and risk (Moola et al., 2017).

2.1 Eligibility Criteria

2.1.1 Participants.

Assessment of studies for inclusion was performed via two author assessment (JT and PC) of the DCD diagnostic criteria from the diagnostic and statistical manual, version five, (DSM-V)(American Psychiatric Association, 2013). The criteria are:

A: Acquisition and performance of motor skills substantially below that expected given age and experience

B: Motor skill deficit affects age-appropriate activities of daily living, productivity, and leisure

C: Deficit present from early development

D: Another condition does not better explain the motor skill deficit

Studies were included as DCD if they met DSM-V criterion A, with studies not assessing the full criteria classified as LMC. Studies were excluded if participants had a movement limiting or bone affecting condition.

2.1.2 Study design.

Cross sectional studies and longitudinal single or multi-arm studies (including case studies, case series and clinical trials) were included in this review, provided they assessed bone health in human DCD/LMC populations. Only baseline data was extracted from intervention studies as this review did not assess change over time. Review articles and other works such as book

chapters were excluded while conference publications and thesis were included. There were no exclusions based on language or publication date.

2.1.3 Outcome of interest.

Studies assessing bone health via any measure were included. Established measurement outcomes for bone health included dual-energy X-ray absorptiometry (DXA) for bone density measures (bone mineral density and content); peripheral quantitative computed tomography (pQCT) for macroscopic architecture, geometry, and bone density measurements (trabecular and cortical bone area, bone mineral content and density, periosteal and endosteal size, cortical thickness, bone mass, and bone strength indices)(Hart et al., 2020); quantitative ultrasound for overall bone health reflecting density and architecture (Binkley, Berry, & Specker, 2008); and skeletal age assessment for bone maturity. Reliability issues have been reported in paediatric use for tools due to bone size variation (DXA, quantitative ultrasound), movement (pQCT)(Shalof et al., 2021) and ethnicity (skeletal age)(Mansourvar et al., 2013). DXA measurements in adults are used diagnostically as a clinical measurement of bone health using established reference norms (Hart et al., 2020) and a meta-analysis has reported correlation for DXA of 0.57 with pQCT results and quantitative ultrasound (Shalof et al., 2021). Fracture rates were assessed as a secondary indicator of bone health.

2.2 Information Sources

One study author (JT) performed a search (from inception to June 2020, updated in March 2021) of the following databases: PubMed, Cochrane Central Register of Controlled Trials, Informit Health Collection, and ScienceDirect. Grey literature was searched using OpenGrey, Trove, Digital Commons Network, Networked Digital Library of Theses and Dissertations, WorldCat (restricted to theses), DART-Europe E-these portal, EThOs, and Scopus. In addition, conference websites for the American Society for Bone and Mineral Research and International

Conference on Children's Bone Health were searched. International conferences for DCD (National Conference on Developmental Coordination Disorder, International Conference on Developmental Coordination Disorder) did not have comprehensive websites, however, the websites for each year's conference were searched when they were available. Google Scholar, WorldWideScience, and reference lists of key studies (Cantell et al., 2008; Chivers et al., 2019; Hands et al., 2015; Tsang et al., 2012) were searched for additional studies.

2.3 Search Strategy

The search strategy is provided in Table 1 and was amended to individual databases as needed (Appendix A). For database searches, the search strategy was validated by ability to identify key studies (Cantell et al., 2008; Chivers et al., 2019; Hands et al., 2015; Tsang et al., 2012) listed in the database. All records were exported into EndNote (Clarivate Analytics, 2018) where duplicate studies were automatically removed. Study author (JT) uploaded remaining studies to Rayyan (Ouzzani, Hammady, Fedorowicz, & Elmagarmid, 2016) for screening. Studies where a translated English version was not available were translated via online translator ("Google Translate," 2021), with translation crosschecked ("DeepL Translator,").

ENTER TABLE 1 HERE

2.4 Selection Process

Studies were screened for inclusion by title and abstract, and then full text by two pairs of authors (RB and JT or PC and JT) with disagreements resolved via discussion. Study exclusion reasons are listed in Appendix B.

2.5 Data Collection Process

JBI data extraction forms for systematic reviews of etiology and risk (https://tinyurl.com/2pxv2vmu), modified to include motor competence measures and mean and standard deviation (SD) for individual outcomes, were used for data extraction. Data

extraction was performed using an Excel form completed by two authors (JT and PC) working independently and crosschecked by JT for accuracy.

The following general study characteristics and demographic information were extracted to determine if studies were linked and the appropriateness of analysis: publication details; ethical approval details; date, duration and location of data collection; recruitment procedure; motor competence terminology and assessment tool; and data analysis method. Furthermore, the following information was extracted where available for both the LMC/DCD and comparator group: number of participants; age, sex and puberty characteristics; motor competence measures mean and SD; and presence and incidence of comorbidities. Where multiple studies represented a single cohort, all data was extracted and compared to determine the most representative study for sensitivity analysis.

2.5.1 Outcome data items.

All reported measures presented in each study for bone health outcomes were extracted for the LMC/DCD and comparator group, including raw numbers, effect size, mean or median, SD, and 95% confidence interval (CI) and odds ratio (OR) for impairment or fracture rates. Data was extracted for all subgroups and models presented. Data representing the lowest 15th percentile was preferentially used for analysis in accordance with DCD recommendations (Smits-Engelsman, Schoemaker, Delabastita, Hoskens, & Geuze, 2015) as were models that controlled for confounding variables.

2.5.2 Dealing with missing data.

Two studies did not report total group data. One study which reported gendered data only (Chivers et al., 2019), had complete data provided through PC, the corresponding author of the original work. One paper provided correlation data only (Gustafsson et al., 2010), the author of which was contacted and provided unpublished total group data.

2.6 Assessment of Study Quality

Study quality was independently assessed for each study using the JBI critical appraisal checklist for each study design (https://jbi.global/critical-appraisal-tools) by two authors (JT and PC) with disagreement resolved by discussion. The checklist for cross-sectional studies includes items on subject selection, incomplete reporting, and confounders, while the checklist for case series includes items on criteria and completeness of inclusion, and demographic and clinical information reporting. A judgement of overall study quality was performed using a method similar to Hayden et al. (2013) based on number of missing measures and appropriateness to study design. For example, failure to describe inclusion for the sample in detail may not affect study quality if the tool was validated and cut off points known but would reduce the overall quality rating if the tool was not as well established.

2.6.1 Reporting biases.

Publication bias was assessed visually using funnel plot asymmetry (Guyatt, Oxman, Montori, et al., 2011). Informal assessment of publication bias was performed by comparing harvest plots of unpublished results to that of published papers for effect size and direction. The influence of small study bias was addressed by the risk of bias criterion 'study size' based on the number of DCD/LMC participants. Under this criteria studies with fewer than 50 participants were at high risk of small sample bias, 50 to 200 participants moderate risk, and greater than 200 participants low risk (Dechartres, Trinquart, Boutron, & Ravaud, 2013).

2.6.2 Diversity and heterogeneity.

Clinical diversity due to variation in age, gender, and degree of motor competence impairment was addressed by sub-group analyses. Other reasons for clinical diversity, such as comorbidities, were described narratively. For the intended meta-analysis, heterogeneity was assessed visually and via the X^2 and I^2 statistic.

2.7 Data Synthesis

2.7.1 Eligibility for synthesis.

Data synthesis was performed using odd ratios for bone health impairment or fracture where outcomes were available from two different cohorts in the same body region. Reports that appeared to be of the same study were excluded from analysis. Nine studies were excluded in this manner, details of which are in Appendix C. Two sets of papers and conference publications were considered as potentially from the same cohort based on author, population, and ethics details. The first set (adolescent cohort) (Chivers et al., 2019; Hands et al., 2015; Jenkins et al., 2020; Tan et al., 2020) was known to be of the same study cohort without data review as PC and JT were authors. For the other paediatric cohort (Fong et al., 2018; A. W. W. Ma et al., 2018; Yam & Fong, 2017) attempts to contact the author via email were unsuccessful, as corresponding author email account was closed and no other contact information could be located for any of the authors via internet searches. Hence review authors determined based on similarities these were from the same cohort and studies should be linked.

2.7.2 Preparation for synthesis

Odds ratios were calculated preferentially using the number of reported cases in each population when presented (Hands et al., 2015; Hellgren, Gillberg, Gillberg, & Enerskog, 1993; Oettinger; Schlager, Newman, Dunn, Crichton, & Schulzer, 1974). The rates for the control population for Hands et al (2015) paper was determined from the reference paper (Buntain et al., 2004). The fracture rates for Hellgren et al. (1993) paper were calculated by combining the motor deficiency and ADHD group with the motor deficiency only group and comparing with the non-motor deficiency group. Comparison rates for skeletal age deficiency (Oettinger; Schlager et al.) were derived from general population rates as defined by Acheson et al. (1963). Where number of reported cases were not presented, odds ratios were determined by inverting the odds of being at low motor competence with impaired bone (Filteau et al.,

2016) or directly from effect size (Cantell et al., 2008; Fong et al., 2018; Tsang et al., 2012). For all other included studies, odd ratios were calculated using a Z-score (Appendix D), then effect size and odds ratio (Borenstein, Hedges, Higgins, & Rothstein, 2009).

2.7.3 Statistical synthesis.

Maentel-Haenszel fixed effects and inverse variance random effects meta-analysis were performed using Review Manager 5.4 (Cochrane Collaboration, 2020) for fracture data and MetaXL plug in for Excel (Barendregt, Doi, Lee, Norman, & Vos, 2013) for bone health. Due to substantial heterogeneity (I^2 statistic greater than 50% when X^2 is smaller than 0.10)(Higgins & Green, 2008) remaining following removal of factors suspected to increase clinical heterogeneity, meta-analysis results were not appropriate, however are reported in Appendix D. Vote counting was performed instead for evidence and direction of effect. Harvest plots(Ogilvie et al., 2008) were conducted to visualise the impact at both outcome and study level with the height of the bar dependent on degree of difference.

2.7.6.1 Heterogeneity exploration.

Sub-analyses were performed limiting analysis by age group, body region (whole, upper, lower) and DCD/LMC categorisation. Age group categorisation was based on established bone development trajectories, whereby paediatric refers to up to age 12, adolescent as 12 to 25, and adult as over the age of 25 years (Matkovic et al., 1994).

2.7.6.2 Sensitivity analyses.

Sensitivity analyses was performed to assess the effects of linking the paediatric (Fong et al., 2018; A. W. W. Ma et al., 2018; Yam & Fong, 2017) and adolescent cohort (Chivers et al., 2019; Hands et al., 2015; Jenkins et al., 2020; Tan et al., 2020). Harvest plots and tables were structured to visualise the effect of linked cohorts. Further analysis was performed limiting

meta-analysis and harvest plots to the most representative paper from each cohort based on outcomes, publication date, and sample size (Chivers et al., 2019; Fong et al., 2018)

2.8 Assessment of the Certainty of the Evidence

Assessment for overall certainty of the evidence was performed using the Grading of Recommendation, Assessment, Development and Evaluation (GRADE) approach (Huguet et al., 2013) and a summary of findings created using GRADEPRO GDT (McMaster University, On, Canada)(Evidence Prime, 2015). GRADE considers risk of bias, effect estimate imprecision, indirectness of measures, and inconsistency in findings, as well as publication bias, effect size, plausible confounding, and dose response. Decisions were made in accordance with GRADE guidelines (Guyatt, Oxman, Akl, et al., 2011; Guyatt, Oxman, Kunz, Atkins, et al., 2011; Guyatt, Oxman, Kunz, Brozek, et al., 2011; Guyatt, Oxman, Kunz, Woodcock, Brozek, Helfand, Alonso-Coello, Falck-Ytter, et al., 2011; Guyatt, Oxman, Kunz, Woodcock, Brozek, Helfand, Alonso-Coello, Glasziou, et al., 2011; Guyatt, Oxman, Montori, et al., 2011; Guyatt, Oxman, Sultan, et al., 2011; Guyatt, Oxman, Vist, et al., 2011) by author JT and decisions crosschecked by author PC with disagreement resolved by discussion.

2.9 Deviations from Protocol

Provisionally, this review planned to include only studies which met DSM-V criterion B (Tan, Hart, Rantalainen, & Chivers, 2021). As this was not assessed in the majority of studies screened the requirement was removed and sensitivity analysis performed to assess this decision.

3. Results

3.1 Study Selection

The search provided 8388 articles, following screening 16 studies were retained for the systematic review (Cantell et al., 2008; Chivers et al., 2019; Filteau et al., 2016; Fong et al.,

2018; Gustafsson et al., 2008; Hands et al., 2015; Hellgren et al., 1993; Ireland, Sayers, Deere, Emond, & Tobias, 2016; Jenkins et al., 2020; A. W. W. Ma et al., 2018; D. Ma, Morley, & Jones, 2004; Oettinger; Schlager et al., 1974; Tan et al., 2020; Tsang et al., 2012; Yam & Fong, 2017). Figure 1 details exclusion numbers at each stage of screening.

ENTER FIGURE 1 HERE

3.2 Study Characteristics and Study Quality

ENTER TABLE 2 HERE

3.2.1 Bone health impairment.

Studies included in the review showed a broad range in exposure, outcomes, and participant characteristics as detailed in Table 2. Seven studies were of a paediatric population (mean age 5.0 to 8.4 years)(Filteau et al. 2016; Fong et al., 2018; Gustafsson et al., 2008; Oettinger; Schlager et al.; Tsang et al., 2012), five studies from two adolescent cohorts (mean age 14.3 to 17.8 years)(Chivers et al., 2019; Ireland et al., 2016), and one in adulthood (mean age 28.1 years)(Cantell et al., 2008; Schlager et al., 1974). Paediatric studies predominantly used skeletal age as their main bone outcome (Fong et al., 2018; Gustafsson et al., 2008; A. W. W. Ma et al., 2018; Oettinger; Tsang et al., 2012), but bone density via DXA (Fong et al., 2018; Tsang et al., 2012; Yam & Fong, 2017) and overall bone health via ultrasound (Filteau et al., 2016) was also reported. Adolescent studies reported on bone microarchitecture via pQCT (Chivers et al., 2019; Ireland et al., 2016). The tibia was the most frequent site for bone assessments with details of bone area by tool provided in Table 3.

ENTER TABLE 3 HERE

Most studies used appropriate tools for assessment of motor skills, with only the Ages and Stages Questionnaire used by Filteau et al. (2016) having reported validity problems due to low specificity (King-Dowling, Rodriguez, Missiuna, & Cairney, 2016). Only three studies

(Fong et al., 2018; A. W. W. Ma et al., 2018; Tsang et al., 2012), all from the same research group, met all the DSM-V criteria for DCD (Table 4). Six studies reported on comorbidity, specifically ADHD/ADD (Fong et al., 2018; Gustafsson et al., 2008; A. W. W. Ma et al., 2018; Tsang et al., 2012) or stimulant drug use (Fong et al., 2018; Schlager et al., 1974).

ENTER TABLE 4 HERE

Critical appraisal indicated studies were mostly of high quality, however, causality due to confounding was a major concern (Table 5). The use of outcome measures were generally appropriate excepting the use of quantitative ultrasound in a paediatric population (Shalof et al., 2021).The appropriateness of the comparison group was an identified issue for the Jenkins et al. (2020) paper as the comparator population was younger than the LMC group assessed (10.9 years [S.D=0.3] compared to 14.3 [SD =0.2]), which was statistically and clinically significant.

ENTER TABLE 5 HERE

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3.2.2 Fracture rates.

Three LMC studies reported on fracture rates in an adolescent population, with mean age ranging from 12.0 (D. Ma et al., 2004) to 16.5 years (Hellgren et al., 1993). Confounding was assessed in two papers, via assessment of ADD/ADHD (Hellgren et al., 1993) and risk-taking (D. Ma et al., 2004). The absence of controlling for confounding was identified as a detriment in critical appraisal, particularly for the Hands et al. (2015) paper as the comparator population assessed fracture rates over a different time period (Buntain et al., 2004).

3.3 Summary Findings Based on Body Region

3.3.1 Bone health impairment.

3.3.1.1 Whole body.

Skeletal age was reported as being below chronological age for the DCD/LMC group, with a delay being reported in 50-66% of participants (Oettinger, 1975; Schlager et al., 1974). The mean skeletal age delay was reported to be between 0.1 (Gustafsson et al., 2008) and 1.2 years (A. W. W. Ma et al., 2018), with range shown in Figure 2. A skeletal age deficit was also reported in comparator groups with an additional deficit for the DCD group not conclusively shown. Tsang et al. (2012) and Hellgren et al. (2008) reported neutral findings while Fong et al. (2018) reported a deficit of 0.9 years. Whole body DXA studies (Fong et al., 2018; Yam & Fong, 2017) reported significantly lower bone mineral content but only Fong et al. (2018) reported significantly lower bone mineral density (d_{cohen} 3.0, 95% CI 2.5 – 3.5).

ENTER FIGURE 2 HERE

3.3.1.2 Lower body.

DXA studies in the lower body (Table 6) reported a deficit in bone mineral density (Cantell et al., 2008; Fong et al., 2018; Ireland et al., 2016) for the DCD/LMC group. Studies which measured individual bone areas found no deficits in the fibula, while the tibia had significant deficits for the LMC group in a number of outcomes including cortical area (Chivers et al., 2019; Hands et al., 2015; Ireland et al., 2016), cross sectional moment of inertia (Ireland et al., 2016), and stress-strain index (Chivers et al., 2019; Hands et al., 2015). Effect size for statistically significant effects ranged from d_{cohen} 0.1 (Cantell et al., 2008) to 8.9 (Jenkins et al., 2020).

ENTER TABLE 6 HERE

3.3.1.3 Upper body.

Studies in the upper body were limited to one adolescent cohort and a paediatric ultrasound study with significant deficits for the LMC group being reported for the entire upper body, radius, and ulna. Deficits included measures of density (Hands et al., 2015) and stress-strain index (Chivers et al., 2019; Hands et al., 2015; Jenkins et al., 2020). Findings on all measures are reported in Table 7.

ENTER TABLE 7 HERE

3.3.2 Fracture rates.

Out of the three studies reporting fracture rates, two reported increased fracture rates for the LMC population. Odds ratios for fracture occurrence for the whole body was between 3.1 (95% CI 1.2 to 7.9) (Hands et al., 2015) and 8.3 (95% CI 1.0 to 70.5) (Hellgren et al., 1993). The arm was reported to be the most common fracture site (57-90% of fractures respectively). Ma et al.(2004) study, however, was confined in the upper limb and reported no increased risk for LMC individuals with odds ratios between 1.16 (95% CI 0.16 to 4.01) in the upper arm and 1.25 (95% CI 0.56 to 2.81) in the hand.

3.4 Data Syntheses

Study level comparisons using harvest plots found an overall detrimental impact of DCD/LMC upon bone health as indicated in Figure 3. Two paediatric studies reported no effect (Gustafsson et al., 2008; D. Ma et al., 2004). One adolescent study using pQCT (Jenkins et al., 2020) reported bone outcome benefits for the LMC group compared to the healthy comparator group, which was significantly younger, on 87% of measures, prior to statistical adjustment for age, sex and bone length. Similar findings were not reported in studies from the same cohort where a different comparator group was used.

ENTER FIGURE 3 HERE

Harvest plots for individual outcomes (Figure 4) showed variability between individual outcomes by bone area with bone health detriment for the DCD/LMC group being more likely for loading sites than non-loading sites. Findings from pQCT studies on bone architecture found more detriments for the LMC group in areas responsive to bone loading e.g., trabecular density. Where bone detriment was present measurements were between one and two standard deviations lower than the comparator group.

ENTER FIGURE 4 HERE

A sensitivity analysis to examine the effects of including studies from the same cohort, found that limiting the adolescent cohort (Chivers et al., 2019; Hands et al., 2015; Jenkins et al., 2020; Tan et al., 2020) to one representative paper produced more bone detriments overall for the LMC group, via the reduction of beneficial bone health outcomes (Figure 5). Limiting the paediatric cohort to one representative paper reduced the number of bone detriments for the DCD/LMC whole body measurements only. Sensitivity analyses on the effect of including studies that did not fulfill DSM-V criterion B found a reduction in negative outcomes for whole body measurements and no effect for upper and lower body outcomes.

ENTER FIGURE 5 HERE

3.5 Heterogeneity of Studies

Meta-analysis of bone health outcomes found a high level of heterogeneity (I^2=94%). Separate sub-analyses found heterogeneity was higher for studies on adolescents (I^2=97%), than in paediatrics (I^2= 50%). Restricting paediatric analysis to skeletal age did not improve heterogeneity (I^2 between 55 and 71%) nor did sensitivity analysis which removed linked cohorts. Examination of individual outcomes found that negative outcomes were not confined to a particular age group with no difference in overall rate of bone health detriments. Rather,

variation between age group of outcomes was dependent on body part. Paediatric populations had a higher proportion of males (71.7% to 83.5%) than the adolescent population (40.4% to 75.5%). Only adolescent studies reported gender specific data, with gender significantly affecting bone outcomes, with the greatest detriments reported in males.

Sub-analyses based on DCD versus LMC status, found an overall more negative outcome for DCD , with neutral and positive outcomes being confined to LMC studies (Cantell et al., 2008; Chivers et al., 2019; Filteau et al., 2016; Gustafsson et al., 2008; Hands et al., 2015; Hellgren et al., 1993; Ireland et al., 2016; Jenkins et al., 2020; D. Ma et al., 2004; Oettinger; Schlager et al.; Tan et al., 2020). DCD studies, however, were few, confined to a paediatric population, and reported fewer outcomes.

The impact of other factors such as physical activity and comorbidities could not be assessed due to insufficient studies reporting on these outcomes.

3.6 Reporting Biases

Publication bias was not considered to be present as the grey literature did not show a different rate of findings than published literature. Funnel plots did not show evidence of asymmetry for total outcomes, skeletal age, or fractures. Missing results were considered unlikely as studies reported outcomes anticipated for the tool and body area, excepting pQCT studies which reported different outcomes between studies. It was considered possible that fracture rates were underreported given the ease of acquiring this information. As an example, Hands et al. (2015) paper is part of the adolescent cohort, none of whom have reported on fracture rates.

3.7 Certainty of Evidence

Assessment of the body of evidence using the GRADE system produced a very low rating for certainty of evidence, indicating the true effect may be substantially different from that

presented. Summary of findings is presented in Table 8, with rationale for ratings in Appendix D.

ENTER TABLE 8 HERE

4. Discussion

4.1 Interpretation

Outcomes of this systematic review indicate that DCD and LMC are associated with deficits in bone health. These detriments were between one and two standard deviations below the comparator group mean which may indicate low bone health or osteopenia (World Health Organization, 1994). These findings indicate that individuals with DCD and LMC, while not having clinically important bone impairments at the time of study may be at increased risk of osteoporosis in later life. Findings regarding fracture risk were mixed, however, the potential for increased fracture is supported by bone health outcomes. In particular, the finding of decreased skeletal age and bone density which is known to be associated with increased paediatric fracture rate (Jones & Ma, 2005). Additionally bone microarchitecture changes reported (Chivers et al., 2019; Ireland et al., 2016; Tan et al., 2021) suggest increased fracture potential via decreased bone strength measurements, such as fracture load. The absence of clinically significant findings is not unexpected as studies were performed prior to when bone loss would occur and greater deficits could be anticipated in the future.

Although effect size was unable to be determined due to heterogeneity in measurement site, bone impairment locations suggest a loading causality. Studies examining weight-bearing sites, particularly the tibia and the hip, reported more deficits for the DCD/LMC group than non-weight bearing sites such as the fibula (Jenkins et al., 2020) and ulna (Ireland et al., 2016). Measures of bone architecture found more deficits in areas responsive to loading such as cortical area (Chivers et al., 2019; Ireland et al., 2016; Tan et al., 2021) and trabecular density (Chivers et al., 2019). Combined, this indicates bone deficits in a DCD or LMC population

may be due to bone loading variations. Further research is required to establish causation of bone differences in the DCD and LMC group, especially given that most research was in a paediatric population and effects of physical activity in determining optimal bone structure in children and adolescents is not established in the general population (Bland, Heatherington-Rauth, Howe, Going, & Bea, 2020).

Bone deficits found in this review may be compensated in later life (Shalof et al., 2021) as all but one study was performed prior to peak bone mass attainment. Bone detriments, however, were consistent between paediatric and adolescent studies in keeping with longitudinal studies on bone development which showed bone impairments continued into at least late adolescence (Wren et al., 2014). Furthermore, habitual physical activity patterns established in childhood tend to continue into adulthood in individuals with DCD (Missiuna, Moll, King, Stewart, & Macdonald, 2008), which may indicate that bone deficits are unlikely to be regained over the period of adolescence and young adulthood. Therefore, it is anticipated that adults with DCD have bone impairments, with associated clinical implications.

4.2 Limitations of Evidence

The evidence was limited by heterogeneity in bone health measurements and the appropriateness of the tools for the population. Quantitative ultrasound and DXA for paediatric populations tend to produce inconsistent results compared to other modalities due to confounding by bone size (Shalof et al., 2021). pQCT results may be impacted by motion artefact, which has previously been identified as an issue in adolescents with LMC (Rantalainen et al., 2018). Furthermore, methodological review indicated low certainty in the results. The majority of studies did not comment on comorbidities, particularly ADD/ADHD which may have impacted on bone health measures due to increased fracture risk (Chou et al., 2014; Zhang, Shen, & Yan, 2021) and bone affecting medication use (Feuer et al., 2016). As ADD/ADHD was not accounted for in most studies and is estimated to occur in 50% of

individuals with DCD (Kaplan, Dewey, Crawford, & Wilson, 2001) bone impairments found in this review may reflect ADD/ADHD or other conditions rather than DCD or LMC. Furthermore inconsistency in how the DCD/LMC population was identified, although common (Smits-Engelsman et al., 2015), is of particular concern in assessing bone health measures. As such further work is required to differentiate bone impairments in a clinical DCD population rather than a LMC population.

4.3 Limitations of Review Process

Search terms used were extensive to include all studies in this area but may have increased heterogeneity in the sample. The decision to deviate from protocol and include studies that did not assess criterion B of DSM-V may also have increased heterogeneity. Individual perception of motor competence, reflected by criterion B, rather than motor test performance has been reported to be the strongest influencer of physical activity (Utesch et al., 2021.) and so may impact bone health. Sensitivity analysis however did not show an impact of including studies that did not fulfil criterion B.

This review did not include clinical trial registries, outside of the Cochrane Central Register, therefore some unpublished studies may not have been reported.

4.3 Implications and future research

Identified detriments in bone health may have clinical implications, particularly regarding the increased risk of fracture. Due to fractures impact upon quality of life (Hough, Boyd, & Keating, 2010) this should be a particular area for further investigation. Findings suggested impaired bone health was linked to reduced physical activity and so may be responsive to intervention, such as physical activity programs. This provides further support for individuals with DCD to engage in these programs. Although findings of this review indicate a continuance into adulthood, there is an absence of research in this age group. Clinical implications of impaired bone health in later adulthood could be significant and further research

is required in this age group. Longitudinal studies to determine bone change in this population would also be valuable.

Findings of this review were limited by high heterogeneity between studies. This indicates the need for studies to use reliable tools, appropriate comparator populations, and report on comorbidities and DSM-V diagnostic criteria. Clarification is needed in future studies as to whether bone impairments are unique to DCD to shape research and treatment recommendations.

4.4 Conclusion

DCD and LMC show an association with impaired bone health on multiple measures in childhood and adolescence. These detriments are such that they appear to be due to physical activity variations. There is currently insufficient evidence as to the continuation of bone health detriments into adulthood, with a complete absence of information in later adulthood. Further evidence is also required as to whether the presence of bone health impairment has clinical implications.

5. Other information

5.1 Registration and Protocol

This systematic review was prospectively registered within PROSPERO (CRD42020167301).

Protocol for this review is published and can be accessed at doi: 10.11124/JBIES-20-00112

5.2 Availability of Data, Code, and Other Materials

Template data collection forms can be accessed via the protocol. Data extracted and used for analysis will be made available upon request.

References

Acheson, R. M., Fowler, G., Fry, E. I., Janes, M., Koski, K., Urbano, P., & Van Der Werff Ten Bosch, J. J. (1963). Studies in the reliability of assessing skeletal maturity from X-rays: part 1. Greulich Pyle Atlas. *Human Biology, 35*(3), 317-349.

American Psychiatric Association. (2013). *Diagnostic and Statistical Manual of Mental Disorders* [Internet](5th ed.). https://doi.org/10.1176/appi.books.9780890425596.dsm01

Barendregt, J. J., Doi, S. A., Lee, Y. Y., Norman, R. E., & Vos, T. (2013). Meta-analysis of prevalence. *Journal of Epidemiology and Community Health, 67*(11), 974-978. https://doi.org/10.1136/jech-2013-203104

Binkley, T. L., Berry, R., & Specker, B. L. (2008). Methods for measurement of pediatric bone. *Reviews in endocrine and metabolic disorders, 9*(2), 95-106. https://doi.org/10.1007/s11154-008-9073-5

Bishop, N., Arundel, P., Clark, E., Dimitri, P., Farr, J., Jones, G., Makitie, O., Munns, C.F., & Shaw, N. (2014). Fracture prediction and the definition of osteoporosis in children and adolescents: The ISCD 2013 pediatric official positions. *Journal of Clinical Densitometry, 17*(2), 275-280. https://doi.org/10.1016/j.jocd.2014.01.004

Bland, V. L., Heatherington-Rauth, M., Howe, C., Going, S. B., & Bea, J. W. (2020). Association of objectively measured physical activity and bone health in children and adolescents: a systematic review and narrative synthesis. *Osteoporosis International, 31*(10), 1865-1894. https://doi.org/10.1007/s00198-020-05485-y

Blank, R., Barnett, A. L., Cairney, J., Green, D., Kirby, A., Polatajko, H., Rosenblum, S., Sugden, D., Wilson, P., & Vinçon, S. (2019). International clinical practice recommendations on the definition, diagnosis, assessment, intervention, and psychosocial aspects of developmental coordination disorder. *Developmental Medicine and Child Neurology, 61*(3), 242-285. https://doi.org/10.1111/dmcn.14132

Blank, R., Smits-Engelsman, B., Polatajko, H., & Wilson, P. (2012). European Academy for Childhood Disability (EACD): Recommendations on the definition, diagnosis and intervention of developmental coordination disorder (long version). *Developmental Medicine and Child Neurology, 54*(1), 54-93. https://doi.org/10.1111/j.1469-8749.2011.04171.x

Borenstein, M., Hedges, L. V., Higgins, J. P. T., & Rothstein, H. R. (2009). Converting Among Effect Sizes. In M. Borenstein, L. V. Hedges, J. P. T. Higgins, & H. R. Rothstein (Eds.), *Introduction to meta-analysis*.

Briggs, A. M., Sun, W., Miller, L. J., Geelhoed, E., Huska, A., & Inderjeeth, C. A. (2015). Hospitalisations, admission costs and re-fracture risk related to osteoporosis in Western Australia are substantial: A 10-year review. *Australian and New Zealand Journal of Public Health, 39*(6), 557-562. https://doi.org/10.1111/1753-6405.12381

Buntain, H. M., Greer, R. M., Schluter, P. J., Wong, J. C. H., Batch, J. A., Potter, J. M., . . . Bell, S. C. (2004). Bone mineral density in Australian children, adolescents and adults with cystic fibrosis: a controlled cross sectional study. *Thorax, 59*(2), 149-155. https://doi.org/10.1136/thorax.2003.006726

Cantell, M., Crawford, S. G., & Doyle-Baker, P. K. (2008). Physical fitness and health indices in children, adolescents and adults with high or low motor competence. *Human Movement Science, 27*(2), 344-362. https://doi.org/10.1016/j.humov.2008.02.007

Cauley, J. A. (2013). Public health impact of osteoporosis. *The Journals of Gerontology. Series A, Biological Sciences and Medical Sciences, 68*(10), 1243-1251. https://doi.org/10.1093/gerona/glt093

Chivers, P., Rantalainen, T., McIntyre, F., Hands, B., Weeks, B. K., Beck, B., Nimpuhius, S., Hart, N., & Siafarikas, A. (2019). Suboptimal bone status for adolescents with low motor competence and developmental coordination disorder: it's sex specific. *Research in Developmental Disabilities, 84*. https://doi.org/10.1016/j.ridd.2018.07.010

Chou, I. C., Lin, C. C., Sung, F. C., & Kao, C. H. (2014). Attention-deficit-hyperactivity disorder increases risk of bone fracture: a population-based cohort study. *Developmental Medicine and Child Neurology, 56*(11), 1111-1116. https://doi.org/10.1111/dmcn.12501

Clarivate Analytics. (2018). Endnote (Version X9.3.1) [Reference Management]. Retrieved from endnote.com

Cochrane Collaboration. (2020). Review Manager (Version 5.4).

Cooper, C., Westlake, S., Harvey, N., Javaid, K., Dennison, E., & Hanson, M. (2006). Review: Developmental origins of osteoporotic fracture. *Osteoporosis International, 17*(3), 337-347. https://doi.org/10.1007/s00198-005-2039-5

Dechartres, A., Trinquart, L., Boutron, I., & Ravaud, P. (2013). Influence of trial sample size on treatment effect estimates: meta-epidemiological study. *BMJ (Online), 346*, 23. https://doi.org/10.1136/bmj.f2304

DeepL Translator. Retrieved from https://www.deepl.com/translator

Evidence Prime. (2015). GRADEpro GDT: Guideline Development Tool: McMaster University. Retrieved from gradepro.org

Faulkner, R. A. (2007). Osteoporosis: A pediatric concern. In R. M. Daly & M. A. Petit (Eds.), *Optimizing bone mass and strength: The role of physical activity and nutrition during growth* (Vol. 51). Basel, Switzerland: Karger.

Feuer, A. J., Thai, A., Demmer, R. T., & Vogiatzi, M. (2016). Association of stimulant medication use with bone mass in children and adolescents with attention-deficit/hyperactivity disorder. *JAMA pediatrics, 170*(12), e162804. https://doi.org/10.1001/jamapediatrics.2016.2804

Filteau, S., Rehman, A. M., Yousafzai, A., Chugh, R., Kaur, M., Sachdev, H. P., & Trilok-Kumar, G. (2016). Associations of vitamin D status, bone health and anthropometry, with gross motor development and performance of school-aged Indian children who were born at term with low birth weight. *BMJ Open, 6*(1), e009268. https://doi.org/10.1136/bmjopen-2015-009268

Foley, S., Quinn, S., & Jones, G. (2008). Tracking of bone mass from childhood to adolescence and factors that predict deviation from tracking. *Bone, 44*(5), 752-757. https://doi.org/10.1016/j.bone.2008.11.009

Fong, S. S. M., Vackova, D., Choi, A., Cheng, Y. T. Y., Yam, T. T. T., & Guo, X. (2018). Diversity of activity participation determines bone mineral content in the lower limbs of pre-pubertal children with developmental coordination disorder. *Osteoporosis International, 29*(4), 917-925. https://doi.org/10.1007/s00198-017-4361-0

Fortington, L. V., & Hart, N. H. (2021). Models for understanding and preventing fractures in sport. In G. A. J. Robertson & N. Maffuli (Eds.), *Fractures in sport*: Springer International Publishing.

Google Translate. (2021). Retrieved from https://translate.google.com/

Gustafsson, P., Svedin, C. G., Ericsson, I., Linden, C., Karlsson, M. K., & Thernlund, G. (2010). Reliability and validity of the assessment of neurological soft-signs in children with and without attention-deficit–hyperactivity disorder. *Developmental Medicine and Child Neurology, 52*(4), 364-370. https://doi.org/10.1111/j.1469-8749.2009.03407.x

Gustafsson, P., Thernlund, G., Besjakov, J., Karlsson, M. K., Ericsson, I., & Svedin, C. G. (2008). ADHD symptoms and maturity a study in primary school children. *Acta Paediatrica, 97*(2), 233-238. https://doi.org/10.1111/j.1651-227.2007.00608.x

Guyatt, G., Oxman, A. D., Akl, E. A., Kunz, R., Vist, G., Brozek, J., Norris, S., Falck-Ytter, Y., Glasziou, P., & deBeer, H. (2011). GRADE guidelines: 1. Introduction—GRADE evidence profiles and summary of findings tables. *Journal of Clinical Epidemiology, 64*(4), 383-394. https://doi.org/10.1016/j.jclinepi.2010.04.026

Guyatt, G., Oxman, A. D., Kunz, R., Atkins, D., Brozek, J., Vist, G., Alderson, P., Glasziou, P., Falck-Ytter, Y., & Schünemann, H. J. (2011). GRADE guidelines: 2. Framing the question and deciding on important outcomes. *Journal of Clinical Epidemiology, 64*(4), 395-400. https://doi.org/10.1016/j.jclinepi.2010.09.012

Guyatt, G., Oxman, A. D., Kunz, R., Brozek, J., Alonso-Coello, P., Rind, D., Devereaux, P.J., Montori, V.M., Freyschuss, B., Vist, G., Jaeschke, R., Williams, J.W., Murad, M.H., Sinclair, D., Falck-Ytter, Y., Meerpohl, J., Whittington, C., Thorlund, K., Andrews, J., & Schünemann, H. J. (2011). GRADE guidelines 6. Rating the quality of evidence—imprecision. *Journal of Clinical Epidemiology, 64*(12), 1283-1293. https://doi.org/10.1016/j.jclinepi.2011.01.012

Guyatt, G., Oxman, A. D., Kunz, R., Woodcock, J., Brozek, J., Helfand, M., Helfand, M., Alonso-Coello, P., Falck-Ytter, Y., Jaeschke, R., Vist, G., Akl, E.A., Post, P.N., Norris, S., Meerpohl, J., Shukla, V.K., Nasser, M., & Schünemann, H.J. (2011). GRADE guidelines: 8. Rating the quality of evidence—indirectness. *Journal of Clinical Epidemiology, 64*(12), 1303-1310. https://doi.org/10.1016/j.jclinepi.2011.04.014

Guyatt, G., Oxman, A. D., Kunz, R., Woodcock, J., Brozek, J., Helfand, M., Alonso-Coello, P., Glasziou, P., Jaeschke, R., Akl, E.A., Norris, S., Vist, G., Dahm, P., Shukla, V.K., Higgins, J., Falck-Ytter, Y., & Schünemann, H.J. (2011). GRADE guidelines: 7. Rating the quality of evidence—inconsistency. *Journal of Clinical Epidemiology, 64*(12), 1294-1302. https://doi.org/10.1016/j.jclinepi.2011.03.017

Guyatt, G., Oxman, A. D., Montori, V., Vist, G., Kunz, R., Brozek, J., Alonso-Coello, P., Djulbegovic, B., Atkins, D., Falck-Ytter, Y., Williams, J.W., Meerpohl, J., Norris, S.L., Akl, E.A., & Schünemann, H. J. (2011). GRADE guidelines: 5. Rating the quality of evidence—publication bias. *Journal of Clinical Epidemiology, 64*(12), 1277-1282. https://doi.org/10.1016/j.jclinepi.2011.01.011

Guyatt, G., Oxman, A. D., Sultan, S., Glasziou, P., Akl, E. A., Alonso-Coello, P., Atkins, D., Kunz, R., Brozek, J., Montori, V., Jaeschke, R., Rind, D., Dahm, P., Meerpohl, J., Vist, G., Berliner, E., Norris, S., Falck-Ytter, Y., Murad, M.J., & Schünemann, H.J. (2011). GRADE guidelines: 9. Rating up the quality of evidence. *Journal of Clinical Epidemiology, 64*(12), 1311-1316. https://doi.org/10.1016/j.jclinepi.2011.06.004

Guyatt, G., Oxman, A. D., Vist, G., Kunz, R., Brozek, J., Alonso-Coello, P., Montori, V., Akl, E.A., Djulbegovic, B., Falck-Ytter, Y., Norris, S.L., Williams, J.W., Atkins, D., Meerpohl, J., & Schünemann, H. J. (2011). GRADE guidelines: 4. Rating the quality of evidence—study limitations (risk of bias). *Journal of Clinical Epidemiology, 64*(4), 407-415. https://doi.org/10.1016/j.jclinepi.2010.07.017

Hands, B., Chivers, P., McIntyre, F., Bervenotti, F. C., Blee, T., Beeson, B., Bettenay, F., & Siafarikas, A. (2015). Peripheral quantitative computed tomography (pQCT) reveals low bone mineral density in adolescents with motor difficulties. *Osteoporosis International, 26*(6), 1809-1818. https://doi.org/10.1007/s00198-015-3071-8

Hart, N. H., Newton, R. U., Tan, J., Rantalainen, T., Chivers, P., Siafarikas, A., & Nimphius, S. (2020). Biological basis of bone strength: anatomy, physiology and measurement. *Journal of Musculoskeletal & Neuronal Interactions, 20*(3), 347-371.

Hart, N. H., Nimphius, S., Rantalainen, T., Ireland, A., Siafarikas, A., & Newton, R. U. (2017). Mechanical basis of bone strength: influence of bone material, bone structure and muscle action. *Journal of Musculoskeletal & Neuronal Interactions, 17*(3), 114-139.

Hayden, J. A., van der Windt, D. A., Cartwright, J. L., Côté, P., & Bombardier, C. (2013). Assessing bias in studies of prognostic factors. *Annals of Internal Medicine, 158*(4), 280. https://doi.org/10.7326/0003-4819-158-4-201302190-00009

Hellgren, L., Gillberg, C., Gillberg, I. C., & Enerskog, I. (1993). Children with deficits in attention, motor control and perception (DAMP) almost grown up: general health at 16 years. *Developmental Medicine and Child Neurology, 35*(10), 881-892. https://doi.org/10.1111/j.1469-8749.1993.tb11565.x

Higgins, J. P. T., & Green, S. (2008). *Cochrane handbook for systematic reviews of interventions*. Chichester, England; Hoboken, NJ;: Wiley-Blackwell.

Hough, J. P., Boyd, R. N., & Keating, J. L. (2010). Systematic review of interventions for low bone mineral density in children with cerebral palsy. *Pediatrics, 125*(3), e670-e678. https://doi.org/10.1542/peds.2009-029

Huguet, A., Hayden, J. A., Stinson, J., McGrath, P. J., Chambers, C. T., Tougas, M. E., & Wozney, L. (2013). Judging the quality of evidence in reviews of prognostic factor research: adapting the GRADE framework. *Systematic reviews, 2*(1), 71-71. https://doi.org/10.1186/2046-4053-2-71

Ireland, A., Sayers, A., Deere, K. C., Emond, A., & Tobias, J. H. (2016). Motor competence in early childhood is positively associated with bone strength in late adolescence. *Journal of Bone and Mineral Research, 31*(5), 1089-1098. https://doi.org/10.1002/jbmr.2775

James, M. E., King-Dowling, S., Graham, J. D., Missiuna, C., Timmons, B. W., & Cairney, J. (2021). Effects of comorbid developmental coordination disorder and symptoms of attention deficit hyperactivity disorder on physical activity in children aged 4–5 years. *Child Psychiatry and Human Development*. https://doi.org/10.1007/s10578-021-01155-0

Jenkins, M., Hart, N. H., Nimphius, S., Chivers, P., Rantalainen, T., Rothacker, K. M., Beck, B.R., Weeks, B.K., McIntyre, F., Hands, B., Beeson, B.P., & Siafarikas, A. (2020). Characterisation of peripheral bone mineral density in youth at risk of secondary osteoporosis - A preliminary insight. *Journal of Musculoskeletal Neuronal Interactions, 20*(1), 27-52.

Jones, G., & Ma, D. (2005). Skeletal age deviation assessed by the Tanner–Whitehouse 2 method is associated with bone mass and fracture risk in children. *Bone, 36*(2), 352-357. https://doi.org/10.1016/j.bone.2004.11.001

Kaplan, B. J., Dewey, D. M., Crawford, S. G., & Wilson, B. N. (2001). The term comorbidity is of questionable value in reference to developmental disorders: data and theory. *Journal of Learning Disabilities, 34*(6), 555-565. https://doi.org/10.1177/002221940103400608

King-Dowling, S., Rodriguez, M. C., Missiuna, C., & Cairney, J. (2016). Validity of the Ages and Stages Questionnaire to detect risk of Developmental Coordination Disorder in preschoolers. *Child: Care, Health and Development, 42*(2), 188-194. https://doi.org/10.1111/cch.12314

Kontulainen, S., Hughes J., MacDonald H, Johnston J. . (2007). The Biomechanical Basis of Bone Strength Development during Growth (Medicine and Sports Science Vol. 51). In R. P. M. Daly (Ed.), *Optimizing bone mass and strength: the role of physical activity and nutrition during growth* (pp. 13-32). Basel (Switzerland): Karger.

Landgren, V., Fernell, E., Gillberg, C., Landgren, M., & Johnson, M. (2021). Attention-deficit/hyperactivity disorder with developmental coordination disorder: 24-year follow-up of a population-based sample. *BMC Psychiatry, 21*(1), 161. https://doi.org/10.1186/s12888-021-03154-w

Ma, A. W. W., Fong, S. S. M., Guo, X., Liu, K. P. Y., Fong, D. Y. T., Bae, Y. H., Yuen, L., Cheng, Y.T.Y., & Tsang, W. W. N. (2018). Adapted Taekwondo Training for Prepubertal Children with Developmental Coordination Disorder: a Randomized, Controlled Trial. *Scientific Reports, 8*(1), 10330. https://doi.org/10.1038/s41598-018-28738-7

Ma, D., Morley, R., & Jones, G. (2004). Risk-taking, coordination and upper limb fractures in children: A population based case-control study. *Osteoporosis International, 15*(8), 633-638. doi:https://doi.org/10.1007/s00198-003-1579-9

Mansourvar, M., Ismail, M. A., Raj, R. G., Kareem, S. A., Aik, S., Gunalan, R., & Antony, C. D. (2013). The applicability of Greulich and Pyle atlas to assess skeletal age for four ethnic groups. *Journal of Forensic and Legal Medicine, 22*, 26-29. https://doi.org/10.1016/j.jflm.2013.11.011

Matkovic, V., Jelic, T., Wardlaw, G. M., Ilich, J. Z., Goel, P. K., Wright, J. K., Andon, M.B., Smith, K.T., & Heaney, R. P. (1994). Timing of peak bone mass in Caucasian females and its implication for the prevention of osteoporosis. Inference from a cross-sectional model. *Journal of Clinical Investigation, 93*(2), 799-808. https://doi.org/10.1172/JCI117034

Missiuna, C., Moll, S., King, G., Stewart, D., & Macdonald, K. (2008). Life experiences of young adults who have coordination difficulties. *Canadian Journal of Occupational Therapy. Revue Canadienne D'Ergothérapie, 75*(3), 157-166. https://doi.org/10.1177/000841740807500307

Moola, S., Munn, Z., Tufanaru, C., Aromataris, E., Sears, K., Sfetcu, R., Currie, M., Lisy, K., Qureshi, R., Mattis, P., & Mu, P. (2017). Chapter 7: Systematic reviews of etiology and risk. In E. Aromataris & Z. Munn (Eds.), *Joanna Briggs Institute Reviewer's Manual*. Retrieved from https://reviewersmanual.joannabriggs.org/

Oettinger, L. (1975). Letter: Bone age and minimal brain dysfunction. *Journal of Pediatrics, 87*(2), 328.

Ogilvie, D., Fayter, D., Petticrew, M., Sowden, A., Thomas, S., Whitehead, M., & Worthy, G. (2008). The harvest plot: A method for synthesising evidence about the differential effects of interventions. *BMC Medical Research Methodology, 8*(1), 8. https://doi.org/10.1186/1471-2288-8-8

Ouzzani, M., Hammady, H., Fedorowicz, Z., & Elmagarmid, A. (2016). Rayyan-a web and mobile app for systematic reviews. *Systematic reviews, 5*(1), 210. https://doi.org/10.1186/s13643-016-0384-4

Page, M. J., McKenzie, J. E., Bossuyt, P. M., Boutron, I., Hoffmann, T. C., Mulrow, C. D., . . . Moher, D. (2021). The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. *Journal of Clinical Epidemiology, 134*, 178-189. https://doi.org/10.1016/j.jclinepi.2021.03.001

Rantalainen, T., Chivers, P., Beck, B. R., Robertson, S., Hart, N. H., Nimphius, S., Weeks, B.K., McIntyre, F., Hands, B., & Siafarikas, A. (2018). Please don't move—evaluating motion artifact from peripheral quantitative computed tomography scans using textural features. *Journal of Clinical Densitometry, 21*(2), 260-268. https://doi.org/10.1016/j.jocd.2017.07.002

Rivilis, I., Hay, J., Cairney, J., Klentrou, P., Liu, J., & Faught, B. E. (2011). Physical activity and fitness in children with developmental coordination disorder: a systematic review. *Research in Developmental Disabilities, 32*(3), 894-910. https://doi.org/10.1016/j.ridd.2011.01.017

Schlager, G., Newman, D. E., Dunn, H. G., Crichton, J. U., & Schulzer, M. (1974). Bone age in children with minimal brain dysfunction. *Developmental Medicine and Child Neurology, 21*(1), 41-51.

Scott-Roberts, S., & Purcell, C. (2018). Understanding the functional mobility of adults with developmental coordination disorder (DCD) through the international classification of functioning (ICF). *Current Developmental Disorders Reports, 5*(1), 26-33. https://doi.org/10.1007/s40474-018-0128-3

Shalof, H., Dimitri, P., Shuweihdi, F., & Offiah, A. C. (2021). Which skeletal imaging modality is best for assessing bone health in children and young adults compared to DXA? A systematic

review and meta-analysis. *Bone (New York, N.Y.)*, 116013. https://doi.org/10.1016/j.bone.2021.116013

Smits-Engelsman, B., Schoemaker, M., Delabastita, T., Hoskens, J., & Geuze, R. (2015). Diagnostic criteria for DCD: Past and future. *Human Movement Science, 42*, 293-306. https://doi.org/10.1016/j.humov.2015.03.010

Son, M. A. C., Vries, J., Roukema, J. A., Gosens, T., Verhofstad, M., & Oudsten, B. (2016). The course of health status and (health-related) quality of life following fracture of the lower extremity: a 6-month follow-up study. *Quality of Life Research, 25*(5), 1285-1294. https://doi.org/10.1007/s11136-015-1167-4

Tan, J., Hart, N. H., Rantalainen, T., & Chivers, P. (2021). Association between developmental coordination disorder or low motor competence, and risk of impaired bone health across the lifespan: protocol for a systematic review and meta-analysis. *JBI Evidence Synthesis, 19*(5), 1202-1210. https://doi.org/10.11124/jbies-20-00112

Tan, J., Siafarikas, A., Rantalainen, T., Hart, N. H., McIntyre, F., Hands, B., & Chivers, P. (2020). Impact of a multimodal exercise program on tibial bone health in adolescents with Development Coordination Disorder: an examination of feasibility and potential efficacy. *Journal of Musculoskeletal & Neuronal Interactions, 20*(4), 445.

Tsang, W. W. N., Guo, X., Fong, S. S. M., Mak, K. K., & Pang, M. Y. C. (2012). Activity participation intensity is associated with skeletal development in pre-pubertal children with developmental coordination disorder. *Research in Developmental Disabilities, 33*(6), 1898-1904. https://doi.org/10.1016/j.ridd.2012.05.015

Utesch, T., Eggelbusch, M., Dreiskaemper, D., Estevan, I., Tietjens, M., & Bardid, F. (2021). The mediating role of perceived motor competence in the relationship between actual motor competence and physical activity in children. *Journal of Sport and Exercise Psychology, 43*(S1), S21-S22. https://doi.org/10.1080/02640414.2015.1122202

World Health Organization. (1994). *Assessment of fracture risk and its application for screening for postmenopausal osteoporosis*. Retrieved from Geneva: http://apps.who.int/iris/bitstream/handle/10665/39142/WHO_TRS_843_eng.pdf?sequence=1&isAllowed=y

Wren, T. A. L., Kalkwarf, H. J., Zemel, B. S., Lappe, J. M., Oberfield, S., Shepherd, J. A., Winer, K.K., & Gilsanz, V. (2014). Longitudinal tracking of dual-energy x-ray absorptiometry bone measures over 6 years in children and adolescents: persistence of low bone mass to maturity. *The Journal of pediatrics, 164*(6), 1280-1285.e1282. https://doi.org/10.1016/j.jpeds.2013.12.040

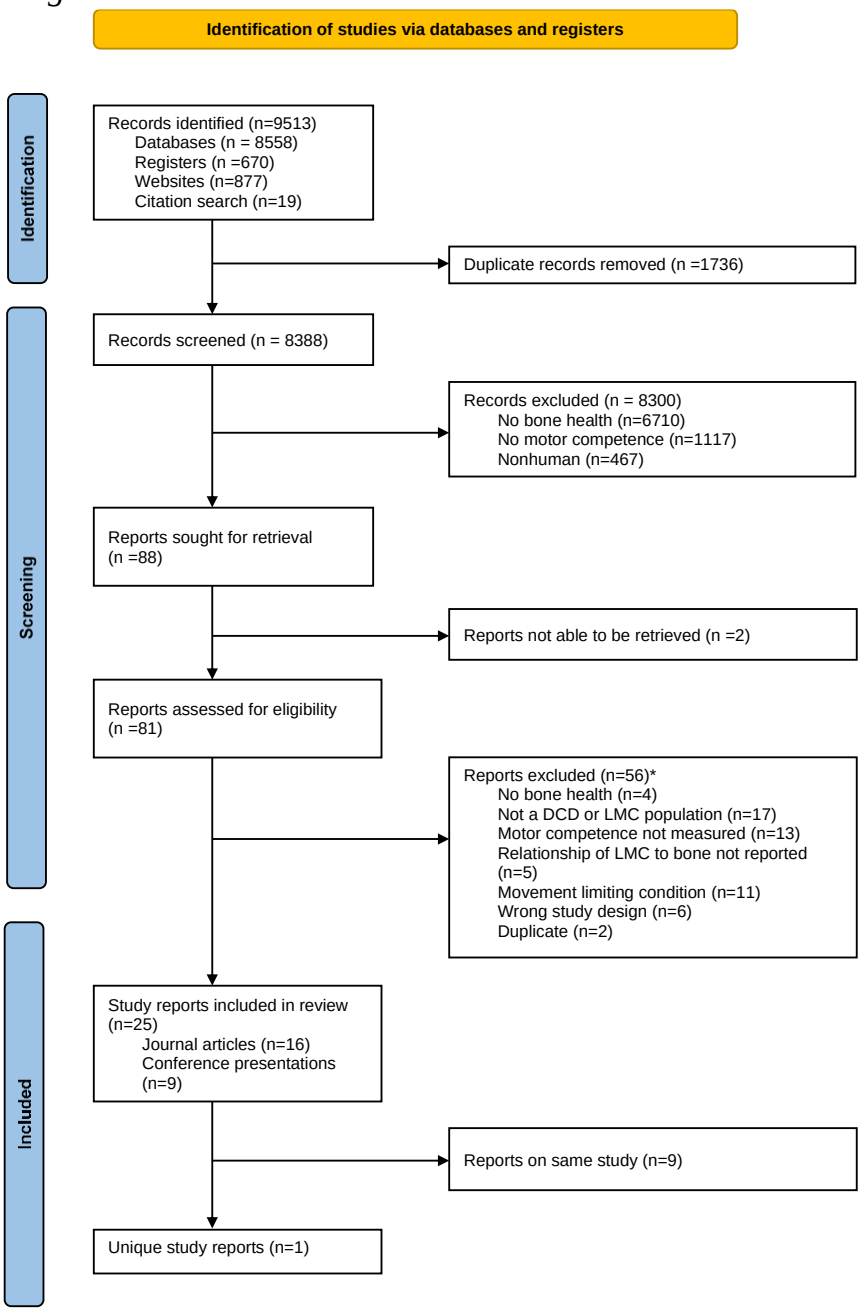
Yam, T. T. T., & Fong, S. M. (2017). *A comparison of bone mineral density and body composition between children with developmental coordination disorder and typical development: Dual-energy X-ray absorptiometry*, Presentation at the World Confederation for Physical Therapy, Cape Town, South Africa.

Zhang, S. W., Shen, D., & Yan, Y. T. (2021). ADHD, stimulant medication use, and the risk of fracture: a systematic review and meta-analysis. *Arch Osteoporos, 16*(1), 81. https://doi.org/10.1007/s11657-021-00960-3

Figures

Figure 1

Flow of Studies Through the Review



*Adapted from PRISMA 2020 (Page et al., 2021). *some studies are in multiple categories*

Figure 2

Delay in Skeletal Age by Study

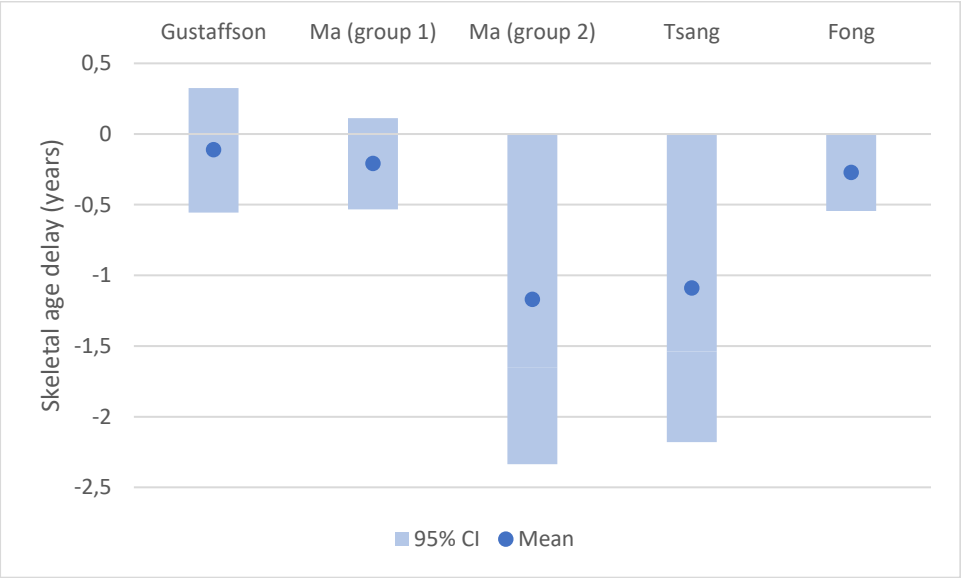
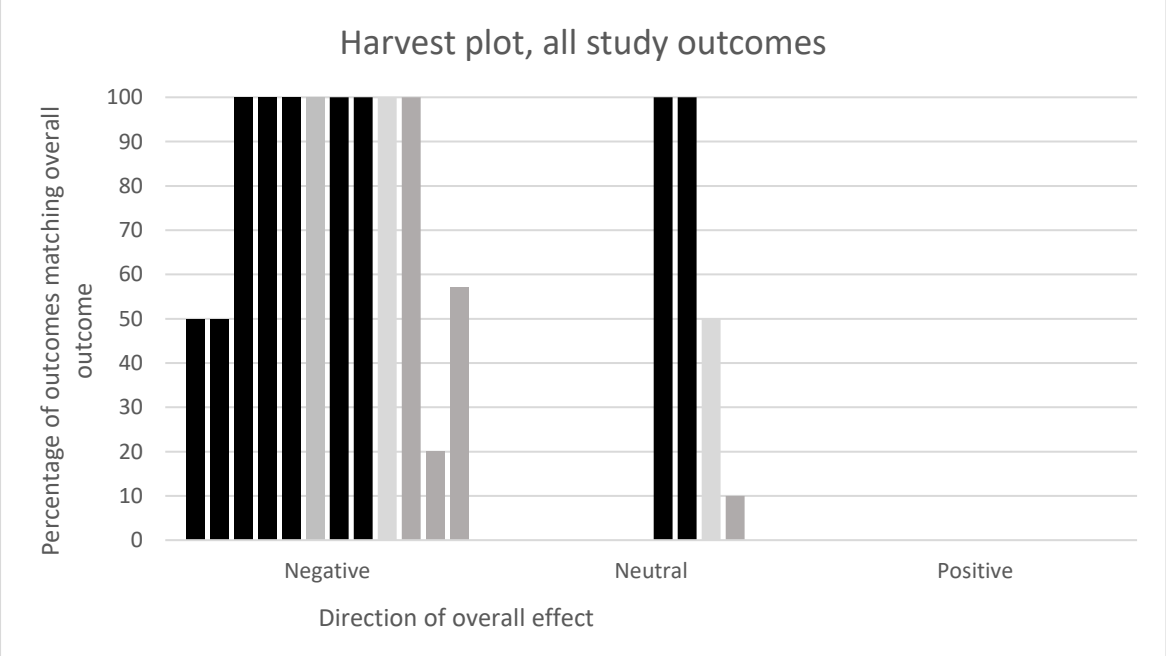


Figure 3

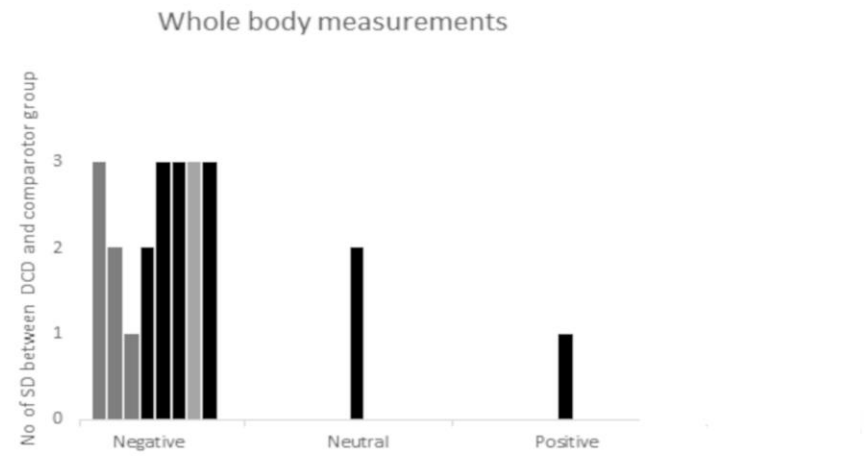
Harvest Plot for Overall Outcomes by Study

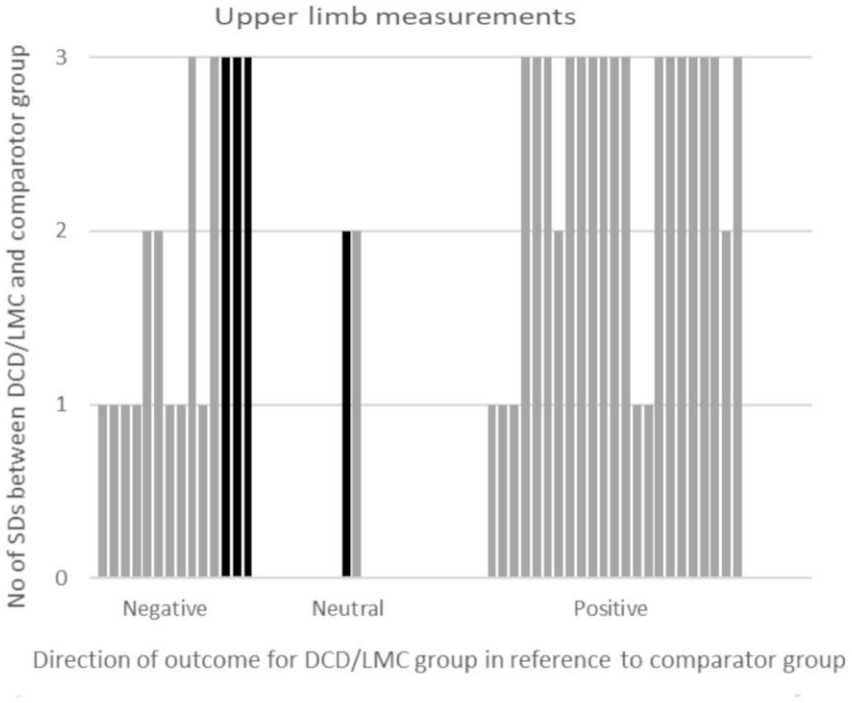


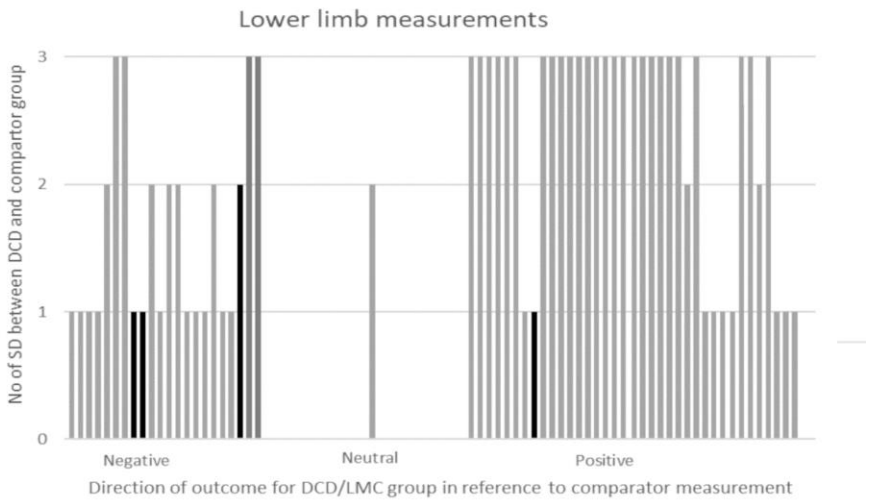
Paediatric cohort light grey, adolescent studies dark grey, unique studies black.
Negative label indicates an overall bone deficit for DCD/LMC group. Neutral indicates balance of outcomes is inconclusive. Positive indicates an overall bone deficit for comparator group.

Figure 4

Harvest Plots of Individual Measurement Outcomes by Body Region


Whole body measurements
No of SD between DCD and comparotor group
3
2
1
0
Negative
Neutral
Positive
Direction of outcome for DCD/LMC group in reference to comparator group

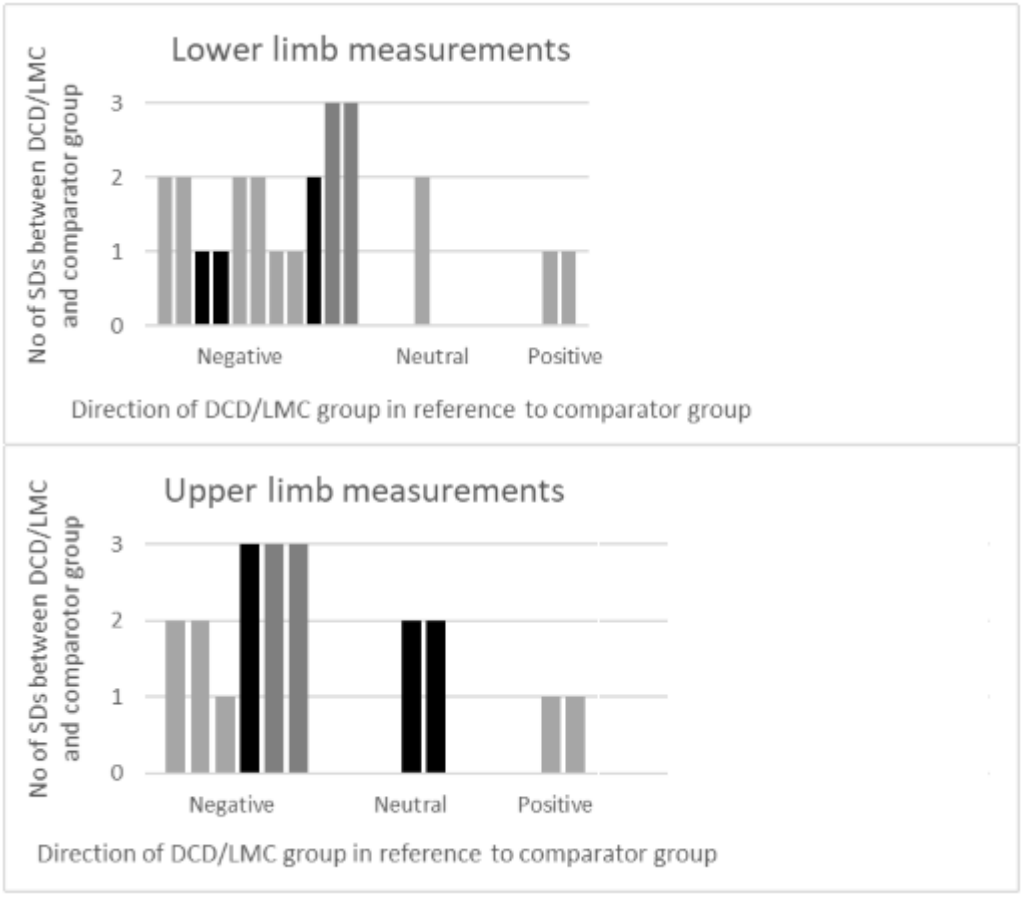

Upper limb measurements
No of SDs between DCD/LMC and comparotor group
3
2
1
0
Negative
Neutral
Positive
Direction of outcome for DCD/LMC group in reference to comparator group


Lower limb measurements
No of SD between DCD and compartor group
3
2
1
0
Negative
Neutral
Positive
Direction of outcome for DCD/LMC group in reference to comparator measurement

Linked cohort studies are grey, unique studies are black. Negative label indicates bone measures are lower for DCD/LMC group than comparator. Neutral indicates no or extremely small difference. Positive indicates bone measures ae higher for DCD/LMC group than comparator. Except in neutral category, height represents degree of difference 1≤ 1 SD, 2 = 1 to 2 SD, 3 ≥2 SD.

Figure 5

Sensitivity Analysis of Lower and Upper Limb Outcomes for Adolescent Cohort



Adolescent cohort study is grey, other studies are black bars. Negative label indicates bone measures are lower for DCD/LMC group than comparator. Neutral indicates no or extremely small difference. Positive indicates bone measures ae higher for DCD/LMC group than comparator. Except in neutral category, height represents degree of difference 1≤ 1 SD, 2 = 1 to 2 SD, 3 ≥2 SD.

Tables

Table 1

Systematic Review Search Strategy

Number	Combiners	Terms
1	Problem of Interest	Bone health OR bone density OR fractures OR osteoporosis OR skeletal age OR pQCT OR bone mineral content
2	Participants	Developmental coordination disorder OR motor competence OR clumsiness OR apraxia OR dyspraxia OR motor difficulty OR physical awkwardness OR coordination impairment OR specific developmental disorder of motor function OR motorically awkward OR minimal cerebral dysfunction OR minimal brain dysfunction OR deficits in attention, motor control and perception
3		#1 AND #2
	Limitations	Human, study design as per inclusion criteria

Table 2

List of Included Studies

Authors (date)	Title	Study design	Study population	Motor assessment	Bone assessment	Notes

			N	Mean age/age range (years)			
Paediatric studies							
Schlager et al. (1974)	Bone age in children with minimal brain dysfunction	Case series	54	8.5	Minimal brain dysfunction diagnosis (Clements criteria)	Skeletal age (Greulich and Pyle)	
A. W. W. Ma et al. (2018)	Adapted taekwondo training for prepubertal children with developmental coordination disorder: a randomized, controlled trial	RCT	145	7.4/7.5	Bruininiks-Osteretsky Test of Motor Proficiency, or MABC[a]; DCD questionnaire	Ultrasonic bone age	Paediatric cohort
Gustafsson et al. (2008)	ADHD symptoms and maturity a study in primary school children	Cross-sectional	208	8.4 (Md)	Motor Skill Development as a Basis of Learning	Skeletal age (Greulich and Pyle)	
Oettinger (1975)	Letter: Bone age and minimal brain dysfunction	Case series	105		Minimal brain dysfunction diagnosis	Skeletal age (Greulich and Pyle)	Letter to the editor

Tsang et al. (2012)	Activity participation intensity is associated with skeletal development in pre-pubertal children with developmental coordination disorder	Cross-sectional	33	7.8	DCD diagnosis; MABC-2[a]	Ultrasonic bone age; DXA	
Fong et al. (2018)	Diversity of activity participation determines bone mineral content in the lower limbs of pre-pubertal children with developmental coordination disorder	Cross-sectional	52	7.5	Bruininiks-Osteretsky Test of Motor Proficiency or MABC	Ultrasonic bone age ; DXA	Paediatric cohort
Yam and Fong (2017)	A comparison of bone mineral density and body composition between children with developmental coordination disorder and typical development: Dual-energy X-ray absorptiometry	Cross-sectional	77	8.1	Physiotherapy assessment	DXA	Conference presentation. Paediatric cohort
Filteau et al. (2016)	Associations of vitamin D status, bone health and anthropometry, with gross motor development and performance of school-aged Indian	Cross-sectional	560	5.0	Ages and Stages Questionnaire	Quantiative ultrasound	

	children who were born at term with low birth weight						
Adolescent studies							
Jenkins et al. (2020)	Characterisation of peripheral bone mineral density in youth at risk of secondary osteoporosis – A preliminary insight	Cross-sectional	51	14.3	MAND	pQCT	Adolescent cohort
Hands et al. (2015)	Peripheral quantitative computed tomography (pQCT) reveals low bone mineral density in adolescents with motor difficulties	Cross-sectional	33	14.3	MAND[b]	pQCT; Fracture rate	Adolescent cohort
Chivers et al. (2019)	Suboptimal bone status for adolescents with low motor competence and developmental coordination disorder—It's sex specific	Cross-sectional	39	14.4	MAND[b]	pQCT	Adolescent cohort

Tan et al. (2020)	Impact of a multimodal exercise program on tibial bone health in adolescents with Development Coordination Disorder: an examination of feasibility and potential efficacy.	Case series	28	14.1	MAND[b]	pQCT	Adolescent cohort
Ireland et al. (2016)	Motor competence in early childhood is positively associated with bone strength in late adolescence	Cross-sectional	443	17.8	Gross motor score at 18 months old	PQCT; DXA	
Hellgren et al. (1993)	Children with deficits in attention, motor control and perception (DAMP) almost grown up: general health at 16 years	Cross-sectional	59	16.5	Neurological and neuropsychological examinations	Fracture rate	
D. Ma et al. (2004)	Risk-taking, coordination and upper limb fractures in children: a population based case-control study	Case-Control	642	12.0-13.5	MABC[a]	Fracture rate	

Adult studies					
Cantell et al. (2008)	Physical fitness and health indices in children, adolescents, and adults with high or low motor competence	Cross-sectional	66	28.1	MABC[a](experimental);DXA DCD questionnaire

A: Movement Assessment Battery for Children; b McCarron Assessment of Neuromuscular Development

Table 3

Body Areas Scanned by Tool

	DXA	pQCT	QUS[a]	Total (including skeletal age)
Total body	**3**	**0**	**0**	**8**
Spine	1	0	0	1
Lower body	**3**	**4**	**1**	**8**
Hip	2	0	0	2
Tibia	0	4	1	4
Fibula	0	1	0	1
Upper body	**1**	**3**	**1**	**5**
Radius	0	3	1	4
Ulna	0	1	0	1

A: quantitative ultrasound

Table 4

DCD Diagnostic Criteria Assessment

	Criterion A	Criterion B	Criterion C	Criterion D	Classification
Paediatric					
Schlager et al. (1974)	Yes	No	No	Yes	LMC
Oettinger (1975)	Yes	Not reported	Not reported	Not reported	LMC
Gustafsson et al. (2008)	Yes	No	No	No	LMC
Tsang et al. (2012)	Yes	Yes	Yes	Yes	DCD
Filteau et al. (2016)	Yes	Partial[a]	No	No	LMC
Yam and Fong (2017)	Yes	No	No	No	LMC
Fong et al. (2018)	Yes	Yes	Yes	Yes	DCD
A. W. W. Ma et al. (2018)	Yes	Yes	Yes	Yes	DCD
Adolescent					
Hellgren et al. (1993)	Yes	No	Yes	Yes	LMC
D. Ma et al. (2004)	Yes	No	No	No	LMC
Hands et al. (2015)	Yes	Not exclusion	No	Yes	LMC

Ireland et al. (2016)	Yes	No	Yes	No	LMC
Tan et al. (2020)	Yes	Not exclusion	No	Yes	LMC
Jenkins et al. (2020)	Yes	Not exclusion	No	Yes	LMC
Adult					
Cantell et al. (2008)	Yes	Yes	No	Partial[b]	LMC

A: Via Ages and Stages Questionnaire. B: Intelligence testing only

Table 5

Methodological Quality of All Studies

	Overall bias	Study size bias	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8
DXA										
Cantell et al. (2008)	Low	High	X		X	X			X	X
Yam and Fong (2017)[c]	High	Moderate			U	U			X	X
pQCT										
Ireland et al. (2016)[e]	Low	Low	X	X	X	X	X	X	X	X
Jenkins et al. (2020)	Low	Moderate		X	X	X	X		X	X
Tan et al. (2020)[a]	Low	High	X	X	X	X	U	X	X	
Chivers et al. (2019)	Low	High	X	X	X	X	X		X	X
Skeletal age										
A. W. W. Ma et al. (2018)	Low	Moderate	X	X	X	X	X	X	X	X
Fong et al. (2018)	Low	Moderate	X	X	X	X	X		X	X
Tsang et al. (2012)[e]	Low	High	X	X	X	X	X	X	X	X
Gustafsson et al. (2008)	Low	High	X	X	X				X	X
Schlager et al. (1974)[a]	Medium	Moderate	X	X	X	X	U	X		
Oettinger (1975)[a,d]	High	Moderate		U					U	U
Qualitative ultrasound										
Filteau et al. (2016)	High	Low			X	X	X	X	X	
Fracture rates										
D. Ma et al. (2004)[b]	Low	Moderate	X	X	X	X	U	U	X	U
Hellgren et al. (1993)	Low	High	X	X	X	X			X	X
Hands et al. (2015)[e]	Low	High	X	X	X	X	X	X	X	X

X= Present. U=Unclear. Cross-sectional questionnaire used unless specified a (Case series questionnaire) or b (case control questionnaire). ; D=letter to the editor; E=Also DXA; F=Also pQCT

Crossectional. Q1: Criteria for inclusion clearly defined. Q2: Subjects and setting described in detail. Q3; Exposure measurement valid and reliable. Q4: Condition measurement used objective, standard criteria. Q5; Confounding factors identified. Q6; Strategies to deal with confounding factors stated. Q7; Outcome measurement valid and reliable. Q8; Appropriate statistical analysis.

Case series. Q1: Clear criteria for inclusion. Q2: Condition measurement standard reliable and valid., Q3: Consecutive, complete inclusion of participants Q4: Clear reporting of the demographics.. Q5: Clear reporting of clinical information. Q6: Outcomes clearly reported. Q7: Clear reporting of presenting site(s) demographic information. Q9: Appropriate statistical analysis.

Case control. Q1: Groups comparable other than presence of condition. Q2: Cases and controls identified using same criteria and matched appropriately. Q3: Exposure measured in standard, valid and reliable way. Q4: Exposure measured consistently for cases and controls. Q5: Confounding factors identified. Q6:Strategies to deal with confounding factors stated Q7: Outcomes assessment standard, valid and reliable. Q7: Appropriate statistical analysis.

Table 6

Low Limb Effect Sizes

			Confidence interval		
	Bone outcome	d_{Cohen}	Lower	Upper	P value
Fong et al. (2018)					
	Bone mineral content	4.8	4.0	5.5	.001
	Bone mineral density	6.0	5.1	6.9	<.001
Tibia					
Hands et al. (2015)					
	Trabecular density[b]	-0.3[a]	-0.8	0.2	.226
	Cortical density[b]	-0.2[a]	-0.6	0.3	.455
	SSI[b]	0.7[a]	0.2	1.2	<.001
Filteau et al. (2016)					
		-0.1			
Ireland et al. (2016)					
	50% cortical area[b,c]	0.4	0.3	0.6	<.001
	50% cortical bone mineral content[b,c]	0.4	0.3	0.6	<.001
	50% cortical bone mineral density[b,c]	0.04	-0.1	0.2	.216
	50% periosteal circumference [b,c]	0.3	0.2	0.5	<.001
	50% cortical thickness[b,c]	0.4	0.3	0.5	<.001
	50% endocortical circumference [b,c]	0.0	-0.1	0.1	.089
	50% cross-sectional moment of inertia[b,c]	-6.5	-6.8	-6.2	.003
Chivers et al. (2019)					
	Functional muscle-bone unit[b,c]	0.7	0.3	1.0	.214[d]
	Total area[b,c]	0.4	-0.04	0.8	.440[d]
	Stress-strain index[b,c]	0.5	0.02	0.9	.030[d]
	Robustness index[b,c]	0.4	0.001	0.9	.078[d]
	Cortical density[b]	-0.1	-0.5	0.2	.155
	Cortical area[b]	0.3	-0.1	0.6	.001
	Endocortical volumetric density [b,c]	-0.4	-0.9	-0.01	.063
	Midcortical volumetric density [b,c]	-0.3	-0.7	0.2	.353
	Pericortical volumetric density [b,c]	0.1	-0.3	0.5	.458
Jenkins et al. (2020)					
	4% cortical density	7.4	6.7	8.0	>.05
	4% cortical area	-6.4	-7.0	-5.8	>.05
	4% stress strain index	-6.5	-7.1	-5.9	>.05
	4% total area	-12.1	-13.1	-11.0	>.05
	4% compressive bone strength	-0.4	-0.7	-0.1	>.05
	4% pericortical radius	-12.6	-13.7	-11.5	>.05
	4% trabecular density	6.7	6.0	7.3	>.05
	66% cortical density	-4.6	-5.1	-4.1	>.05
	66% cortical area	-8.9	-9.7	-8.1	.011
	66% stress strain index	-9.7	-10.6	-8.9	>.05
	66% total area	-11.8	-12.8	-10.8	>.05
	66% compressive bone strength	-6.7	-7.3	-6.1	>.05

	66% midcortical ring density	-0.6	-0.9	-0.3	>.05
	66% endocortical ring density	-11.7	-12.7	-10.7	>.05
	66% pericortical ring density	-12.6	-13.6	-11.5	>.05
Tan et al. (2020)					
	4% trabecular density[b]	0.1[a]	-0.4	0.6	
	66% cortical area[b]	0.8[a]	0.3	1.4	
	66% cortical density[b]	0.03[a]	-0.5	0.6	
	Stress-strain index[b]	0.7[a]	0.1	1.2	
Hip					
Cantell et al. (2008)					
	Hip t-scores	0.1[a]			.03
Ireland et al. (2016)					
	Cross-sectional moment of inertia[c]	0.3	0.2	0.4	<.001
	Bone mineral density[c]	0.2	0.1	0.3	
Fibula					
Jenkins et al. (2020)					
	4% cortical density	-3.9	-4.4	-3.5	>.05
	4% cortical area	-7.2	-7.9	-6.6	>.05
	4% stress strain index	-7.7	-8.4	-7.0	>.05
	4% total area	-9.2	-9.9	-8.4	>.05
	4% compressive bone strength	-6.3	-6.9	-5.7	>.05
	4% pericortical radius	-9.0	-9.8	-8.3	>.05
	4% trabecular density	1.6	1.3	1.9	>.05
	66% cortical density	-5.8	-6.3	-5.2	>.05
	66% cortical area	-8.1	-8.9	-7.4	>.05
	66% stress strain index	-7.5	-8.1	-6.8	>.05
	66% total area	-9.1	-9.8	-8.3	>.05
	66% compressive bone strength	-8.1	-8.9	-7.4	>.05
	66% pericortical radius	-10.0	-10.9	-9.2	>.05
	66% midcortical radius	-7.2	-7.9	-6.6	>.05

A: Values presented in text, otherwise calculated. b= No comparator group , results compared to population norms. C=Male data only. D=Total group (for gendered data).

Table 7

Upper Limb Effect Sizes

			Confidence interval		
	Bone outcome	d_{Cohen}	Lower	Upper	P value
Fong et al. (2018)					
	Bone mineral content	0.4	0.1	0.8	.150
	Bone mineral density	3.0	2.5	3.5	.012
Radius					
Hands et al. (2015)					
	4% trabecular density[b]	0.3[a]	-0.2	0.8	.106
	4% total density[b]	0.9[a]	0.4	1.4	<.001
	66% cortical density[b]	0.7[a]	0.2	1.2	.038
	66% stress strain index[b]	1.0[a]	0.5	1.5	<.001
Filteau et al. (2016)					
	Quantitative ultrasound Z score	-0.1			
Chivers et al. (2019)					
	Functional muscle bone unit[c]	0.6	0.2	1.1	.300
	Total area[c]	0.7	0.2	1.1	.053
	Stress strain index[c]	0.7	0.2	- 1.1	.040
	Robustness index[c]	0.6	0.2	1.0	.092
	Cortical density	-0.4	-0.7	-0.1	.071

	Cortical area	0.2	-0.1	0.6	.243
	Endocortical volumetric density	-0.3	-0.6	0.1	.342
	Midcortical volumetric density	-0.5	-0.8	-0.1	.010
	Pericortical volumetric density	0.1	-0.2	0.5	.726
Jenkins et al. (2020)					
	4% cortical density	0.3	-0.02	0.6	.854
	4% cortical area	-5.9	-6.5	-5.3	1.000
	4% stress strain index	-8.1	-8.8	-7.3	1.000
	4% total area	-12.8	-13.9	-11.7	1.000
	4% compressive bone strength	-3.0	-3.4	-2.6	.251
	4% pericortical radius	-13.4	-14.5	-12.3	1.000
	4% trabecular density	9.2	8.4	10.0	.512
	66% cortical density	-9.3	-10.1	-8.5	1.000
	66% cortical area	-6.7	-7.4	-6.1	.043
	66% stress strain index	-4.8	-5.3	-4.3	<.001
	66% total area	-5.2	-5.7	-4.7	.010
	66% midcortical ring density	-2.9	-3.3	-2.5	.315
	66% endocortical radius	-2.5	-2.9	-2.1	.134
	66% pericortical radius	-5.5	-6.0	-4.9	.007
Ulna					
Jenkins et al. (2020)					
	4% cortical density	1.3	0.9	1.6	.754
	4% cortical area	-11.9	-12.9	-10.9	1.00
	4% stress strain index	-10.2	-11.0	-9.3	1.00
	4% total area	-12.7	-13.8	-11.7	1.00
	4% compressive bone strength	-4.8	-5.3	-4.4	1.00
	4% pericortical radius	-12.1	-13.1	-11.1	1.00
	4% trabecular density	4.1	3.6	4.5	1.00
	66% cortical density	-8.3	-9.0	-7.5	1.00
	66% cortical area	-6.3	-6.9	-5.7	.046
	66% stress strain index	-4.9	-5.4	-4.4	<.0001
	66% total area	-4.9	-5.4	-4.4	.032
	66% compressive bone strength	-8.2	-8.9	-7.5	.842
	66% midcortical ring density	-0.2	-0.5	0.1	.086
	66% endocortical radius	-2.0	-2.4	-1.7	.156
	66% pericortical radius	-5.6	-6.1	-5.1	.021

A: Values presented in text, otherwise calculated. B= No comparator group , results compared to population norms. C=Male data only.

Table 8

GRADE Summary of Findings

Risk of bias	Inconsistency	Indirectness	Imprecision	Other Considerations	Overall certainty of evidence
Bone health					
Serious	Serious	Serious	Not serious	None	Very low
Fracture rate					
Serious	Serious	Serious	Serious	Publication bias suspected Strong association	Very low

Ratings explanation in appendix E.

Appendices