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Review title

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

Abstract

Objective: This systematic review will assess the association between developmental coordination disorder and low motor competence, and impairments in bone health across the lifespan.

Introduction: Individuals with developmental coordination disorder tend to have a pattern of physical activity associated with bone health impairments. Preliminary studies have found impairments on bone health measures, including fractures, throughout the lifespan with potential public health ramifications. As studies in this area are of small samples across wide age ranges, no comprehensive picture of bone health in this group has been formed, hindering action. A systematic review is needed to determine the potential risk of bone impairment in this population.

Inclusion criteria: Studies that assess the relationship between developmental coordination disorder/low motor competence and bone health, regardless of measures used, will be included in the review. There will be no exclusions based on region, study design, or participant demographic characteristics.

Methods: Published studies and gray literature will be searched, with no limits on publication date or language. Assessment of studies for inclusion, as well as data extraction, will be performed by two reviewers, with data cross checked for accuracy. Studies will be appraised using the appropriate JBI tool for the study design. Data to be extracted include unadjusted results and effect sizes for bone health measures. A narrative synthesis will be performed and if there is a sufficient number of studies, a meta-analysis using the same outcome measures will be performed on odds ratios of abnormal bone phenotype and fracture in this population.

Systematic review registration number: PROSPERO CRD42020167301

Keywords: bone density; bone strength; developmental disabilities; motor control; movement coordination

Abstract word count: 249

Total manuscript word count: 2499

Introduction <level 1 heading>

Developmental coordination disorder (DCD) is a neurodevelopmental disorder involving deficits in the acquisition and performance of coordinated motor skills throughout the lifespan[1]. The condition is estimated to affect 5% of the population worldwide, with diagnosis more common in males[2]. According to the *Diagnostic and Statistical Manual of Mental Disorders*, 5th edition,[1] the diagnostic criteria for DCD specify that acquisition and execution of motor skills are significantly below what is expected given the individual's age and skill learning opportunities (criterion A), which consequently have an ongoing significant impact on age-appropriate daily living activities, leisure, education, or employment (criterion B).[1] As impairments with motor skills can occur due to inactivity and medical conditions, the diagnostic criteria specify that motor deficits must present early in development (criterion C) and be beyond what can be explained by conditions affecting motor skills such as intellectual disability, visual impairment, or neurological conditions affecting movement (eg, cerebral palsy) (criterion D)[1]. Due to low diagnosis rates, research on DCD often includes researcher assessment of a participant's ability to meet diagnostic criteria, with low motor competence (LMC)—a more general term for motor skill difficulty[3]—being used when the full diagnostic criteria have not been assessed[4].

Due to their motor skill deficits, individuals with DCD tend to have low levels of physical activity from a very early age continuing throughout the lifespan[2]. This is particularly applicable for diverse and high-intensity physical activity[2,5,6]. This pattern of physical activity has been linked to impairments in bone health development in other populations[7-9]. Bone health is a dynamic system impacted by a number of factors such as genetics, hormones, and nutrition, alongside physical activity[8]. Some of these conditions occur more commonly in individuals reported to have DCD, either due to a common causative pathway, such as prematurity and low birth weight[10], or due to classification of other intrinsic movement difficulties as DCD[2]. Preliminary studies in this area have found an impairment in bone health in individuals with DCD on a variety of bone health measures across age groups[11-15]. Studies in the pediatric population have found impairments in overall bone health, measured indirectly via skeletal age[14] and directly via bone mineral density[15]. Extended cohort studies in an adolescent population have consistently found decreased bone health measures by peripheral quantitative computed tomography,[11-13] and the only known study in the adult population found decreased bone mineral density in the hip,[16] indicating that this continues through the lifespan. However, current research in this area has contained small samples, broad age ranges, and mixed definitions of DCD and LMC, making it difficult to draw a comprehensive picture.

A comprehensive understanding of impaired bone health in this population is necessary, as there is potential for profound ramifications for health. Individuals with DCD have a high fall occurrence,[13,17] which, combined with impaired bone health, substantially increases the risk of osteoporotic fracture. Studies in adolescent DCD populations have found an increased fracture rate compared to population norms[13], which could be reasonably projected to continue into adulthood. Given the high prevlance of DCD in this population, there are public health ramifications if a higher rate of bone health impairment

is found in this group. As such, this review may be useful for creating clinical guidelines for bone density screening. It is likely, however, that the greatest interest will be in association with treatment priorities in pediatric groups, particularly for allied health professionals. Evidence collected by the identification of key gaps in empirical evidence will assist in focusing future research.

The objective of this review is to assess the association between DCD, and more generally LMC, and bone health measures across the lifespan. It aims to do this by determining if the incidence and extent of impaired bone health among DCD and LMC subgroups is greater than seen in the general population. A prelimary search for previous systematic reviews on the topic in PROSPERO, Cochrane Library, and *JBI Database of Systematic Reviews and Implementation Reports* determined that no other systematic reviews on this topic have been performed.

Review question <level 1 heading>

What is the association between developmental coordination disorder/low motor competence and impairment of bone health across the lifespan?

Inclusion criteria <level 1 heading>

Participants <level 2 heading>

All human studies that include a bone health outcome in a DCD/LMC population will be considered, with no restriction based on sample region, age, or sex. Due to the impact of movement limitations on bone health, studies that predominantly include a population with a condition that could be predicted to substantially limit movement, such as cerebral palsy, arthritis, or intellectual disabilities (eg, Rett syndrome), will be excluded from analysis unless movement levels are specified to be within normal ranges. Similarly, studies will be excluded if they predominantly include a population with health conditions that have a documented direct effect on bone. Examples of bone-affecting conditions including genetic conditions (eg, osteogenesis imperfecta), hormonal conditions (eg, premature menopause), and conditions affecting nutrient absorption (eg, celiac disease, inflammatory bowel disease). If the effect of the condition on bone is unclear, the opinions of two bone experts will be sought, with a third bone expert to arbitrate if consensus is not reached. Anti-osteoporotic medication is the only medication whose use is exclusionary.

Exposure <level 2 heading>

The presence of DCD may be identified via a clinical diagnosis or an assessment of the *Diagnostic and Statistical Manual of Mental Disorders*, 5th edition, diagnostic criteria[1]. Using the recommendations of Geuze et al.[18], studies will be assessed to determine if they contain a DCD or LMC population, with those that meet all diagnostic criteria being classified as DCD and those that do not meet criterion C or D as LMC. Studies that do not demonstrate an impairment in age-appropriate motor skills that impacts daily living, as per criterion A and B[1], will be excluded. If it is not clear from the study whether the diagnostic criteria are fulfilled, the study's authors will be contacted. If authors are uncontactable or non-responsive, the classification of the group will be determined in consultation with two known experts in DCD. Where consensus is not reached, a third DCD expert will adjudicate.

Outcome <level 2 heading>

Studies including a measurement known to be an indicator of bone health will be included in the review. This will include direct measurement via dual-energy X-ray absorptiometry, peripheral quantitative computed tomography, quantitative ultrasound, and skeletal or bone age, as well as indirect measurements, such as bone biomarkers and fracture incidence rates.

Types of studies <level 2 heading>

Study designs to be included, based on Guyatt et al.[19] and JBI methodology,[20] are cohort series (prospective and retrospective), case-control studies, cross-sectional studies, case series, and case reports. Experimental study designs, such as randomized controlled trials, will be included for baseline measurements only. Cross-sectional studies will be included regardless of the presence of a comparator population, as measurements may be compared to population norms. Similarly, experimental study designs will be included regardless of whether they include a non-DCD/LMC comparator group. Information about the presence and type of comparator population will be recorded and sensitivity analyses performed, if appropriate.

Methods <level 1 heading>

The protocol will be performed in accordance with JBI methodology for systematic reviews of etiology and risk.[20] This protocol has been registered with the PROSPERO (CRD42020167301).

Search strategy <level 2 heading>

The search strategy is designed to locate published and unpublished studies. An initial search of PubMed and ScienceDirect was undertaken to identify articles on the topic. Search terms were derived using keywords from titles and abstracts of located articles and index terms to create a search strategy. This will be adapted to each database, and initial limited searches were run to identify any further additional keywords. An example search conducted in PubMed is presented in Appendix I. Reference lists of included studies will be examined to identify additional studies. Authors of major studies will be contacted for unpublished studies. Forward citation searching will be conducted using Scopus. If necessary, after a review of search results and study reference lists, search terms will be updated.

The following databases will be searched from inception until present: PubMed (Ovid), Embase (Ovid), Cochrane Central Register of Controlled Trials (Cochrane Library), Informit Health Collection (Informit Online), and ScienceDirect (Elsevier).

Gray literature will be examined for unpublished data via Google Scholar and WorldWideScience as well as searching the following electronic databases: OpenGrey, Trove, Digital Commons Network, Networked Digital Library of Theses and Dissertations, WorldCat (restricted to theses), DART-Europe E-theses portal, EThOS, and Scopus. In addition, the following conference websites will be searched: American Society for Bone and Mineral Research, International Conference on Children's Bone Health,

National Conference on Developmental Coordination Disorder (UK), and the International Conference on Developmental Coordination Disorder.

There is no limitation based on language or publication date; databases will be searched from inception until present. Studies in languages other than English will be translated as required.

Study selection <level 2 heading>

Following the search, duplicates will be removed using EndNote X9 (Clarivate Analytics, PA, USA) and all remaining articles will be uploaded to Rayyan (Qatar Computing Research Institute, Doha, Qatar)[21] for screening. Two reviewers will independently examine the titles and abstracts for reference to motor competence and bone measurements, which will be sufficient to justify full-text screening. The full texts of the relevant articles will be reviewed independently for fulfilment of inclusion criteria, and non-qualifying studies removed. Disagreements as to the inclusion of articles will be resolved via discussion and then by third author arbitration. Exclusion reasons for full-text articles will be documented and reported in the review. The process of study selection will be detailed in a flow diagram as per Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines.[22]

Assessment of methodological quality <level 2 heading>

Bias will be assessed for each study at the study level using the appropriate JBI critical appraisal checklist for each study design by two independent reviewers, with third author arbitration for disputes.[20] Any identified bias that may reflect the cumulative evidence will be reported in the results. Critical appraisal results will be reported in a table for all studies highlighting the strengths and weakness of each study and how this affects the validity of the study's findings. Given the expected small number of studies in this area, studies will not be excluded from analysis based on study quality; however, the decision to perform meta-analysis will include consideration of level of bias. Meta-analysis will not be conducted if most of the studies show a high level of bias (bias on more than half of measures, bias not justifiable based on study design). Subgroup and sensitivity analyses will be performed to explore the impact of the level of study bias. If there are more than 10 studies included in the meta-analysis, publication and selective reporting bias will be formally tested using funnel plot asymmetry.

Data extraction <level 2 heading>

Data will be extracted by two reviewers following a prescribed data extraction form in Appendix II. This has been modified from the JBI data extraction form for systematic reviews of etiology and risk[20] to include motor competence measures and individual outcomes, as effect measures were considered unlikely to be in all studies. Data will be extracted into MS Excel (Redmond, Washington, USA) and cross-checked. Discrepancies will be discussed and referred to a third party should disagreement remain.

Items extracted will include the diagnostic assessment method, motor impairment measures, measures of bone health, and those required for sensitivity analysis (eg, medication use). Unadjusted results will

be extracted as will effect size, if present. Study authors will be contacted to obtain any missing information.

Given the small number of research projects in this area, care will be taken to avoid multiple reports from the same study cohort being included. To assist in this, data will be extracted on the authors, institution, dates of data collection, and ethical approval details. If it is considered likely that reports are from the same study, the study author will be contacted. Multiple reports by the same study group will be linked for inclusion in the study. Data extraction will otherwise be performed as per the Cochrane Handbook for Systematic Reviews of Interventions[23] and JBI methodology.[20]

Data synthesis <level 2 heading>

A narrative synthesis will be performed as per JBI methodology for etiology and risk,[20] and reported in accordance with PRISMA reporting guidelines. This will include a description of the clinical and methodological characteristics of the studies, including evidence of bias and the plausible impact of any other outcomes reported (e.g. physical activity levels). Patterns across studies will be explained, including any heterogeneity between studies, particularly between DCD and LMC populations and for age-based differences. Quantitative data, including point and interval estimates, with effect sizes presented as counts for dichotomous data and mean differences for continuous data, will be included in the narrative summary and graphs used for study comparison.

If two or more studies are identified of having low bias with the same outcome measure, a meta-analysis will be performed. Odds ratios of abnormal bone phenotype and fracture will be pooled for meta-analyses. If odds ratios are not presented in the text, they will be calculated where possible. Incidence of abnormal bone phenotype will be calculated when absent using the methodology described in Bekkering et al[24] . Abnormal bone phenotype will be considered present when results are more than one standard deviation below reference scores for the relevant tool and population, in keeping with World Health Organization recommendations[25]. Heterogeneity will be assessed visually and using the I^2 statistic. Both the Mantel-Haenszel fixed effects method and the DerSimonian and Laird random effects method will be used for meta-analyses, with the random effects model being reported if there are sufficient events and funnel plot shows no asymmetry[23]. If events are considered rare, the Maentel-Haneszel model will be used[23]. If considerable heterogeneity is present, only a narrative synthesis will be presented.

Subgroup analyses will be done via stratification on a DCD versus a LMC population, and by age group. For age analyses, studies will be classified based on the primary age group present, as defined by the mean and 95% confidence interval, based on established trajectories of bone health parameters[26,27] into a pediatric (primary age group up to age 12 years), adolescent (12 to 25 years) and adult (older than 25 years). If possible, adults will be further classified as being between 25 to 40 years of age and older than 40 years. Sensitivity analyses will be performed as required, for example, to examine the effects of excluding studies based on sample size or to compare between fixed and random effects models .

If there are insufficient studies for meta-analysis, vote counting will be used to determine evidence of an effect and its direction. Statistical significance and size of effect will not be considered. The impact will be visualized using harvest plots, with studies weighted using the inverse-variance method.

Assessing certainty in the findings <level 2 heading>

Quality of evidence will be assessed using a modified Grading of Recommendation, Assessment, Development and Evaluation (GRADE) approach for prognostic studies as defined by Huguet et al.[28] and a Summary of findings created using GRADEpro GDT (McMaster University, ON, Canada). The Summary of Findings will include the absolute risk for DCD/LMC populations, relative risk estimate, and a ranking of the quality of the evidence. Assessment of bias and quality will be done by two assessors working independently who will meet to discuss the results for final appraisal. If agreement cannot be reached, a decision will be referred to an independent third party. A narrative summary will be provided of the overall methodological quality of the included studies.

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Conflicts of interest

The authors declare no conflict of interest.

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348 **Appendix I: Search strategy**

349 PubMed (National Library of Medicine). Search conducted on 23 June 2020.

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Search	Query	Records retrieved
#1	"Bone and Bones"[mh:exp] OR "bone density"[MeSH Terms] OR "fractures, bone"[MeSH Terms] OR ("osteoporosis, postmenopausal"[MeSH Terms] OR "osteoporosis"[MeSH Terms]) OR "age determination by skeleton"[MeSH Terms] OR "tomography, x-ray computed"[MeSH Terms] OR "Bone health"[tw] OR "osteoporosis"[tw] OR ("bone"[tw] AND "density"[tw]) OR ("bone"[tw] AND "mineral"[tw] AND "content"[tw]) OR ("fractures"[tw] AND "bone"[tw]) OR ("bone"[tw] AND "fracture"[tw]) OR "age determination by skeleton"[MeSH Terms] OR ("age"[tw] AND "skeleton"[tw]) OR "age determination by skeleton"[tw] OR "bone mineral density"[tw] OR (Skeletal[tw] AND "growth"[tw] AND "development"[tw])	1,192,153
#2	"motor skills disorders"[MeSH Terms:exp] OR "apraxias"[MeSH Terms] OR "movement disorders"[MeSH Terms:exp] OR "developmental disabilities"[MeSH Terms:exp] OR "learning disabilities"[MeSH Terms:exp] OR "psychomotor disorders"[MeSH Terms] OR "motor skills"[MeSH Terms:exp] OR "motor activity/physiopathology"[Mesh Terms] OR ("motor"[tw] AND "skills"[tw] AND "disorders"[tw]) OR ("developmental"[tw] AND "coordination"[tw] AND "disorder"[tw]) OR "motor competence"[tw] OR Clumsiness[tw] OR "apraxias"[tw] OR "dyspraxia"[tw] OR (Motor[tw] AND difficulties[tw]) OR ("learning"[tw]) AND difficulties[tw]) OR "physical awkwardness"[tw] OR "ataxia"[MeSH Terms] OR "ataxia"[tw] OR ("coordination"[tw] AND "disorder"[tw]) OR ("coordination"[tw] AND "impairment"[tw]) OR "specific developmental disorder of motor function"[tw] OR (motorically[tw] AND awkward[tw]) OR "minimal cerebral dysfunction"[tw] OR ("minimal"[tw] AND "brain"[tw] AND "dysfunction"[tw]) OR ("motor"[tw] AND "control"[tw])	229,982
#3	#1 AND #2	5900
Limited to humans		5661

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353 **Appendix II: Data extraction table**

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Study details	**Variable**
Reviewer	
Study ID/record number	
Date	
Study title	
Authors	
Year	
Journal	
Institution name	
Aim of the study	
Methods	
Motor competence terminology	
Setting (eg, clinical, general population, rural, urban)	
Location	
Study design	
Date of data collection	
Duration of data collection	
Ethical approval	
Method of data analysis	
Participants	
Recruitment procedure used	
Tool used to measure DSM-5 criterion A (impairment of motor skills)	
Tool used to measure DSM-5 criterion B (impact on daily living)	
Tool used to assess DSM-5 criterion C (onset in early development)	
Tool used to assess DSM-5 criterion D (not better explained by comorbidities)	
Total number of participants	
Age characteristics	
Sex characteristics	
Pubertal stage (if applicable)	
Motor skill measure (mean, standard deviation, 95% confidence interval)	
Mean score on daily living measure (mean, standard deviation, 95% confidence interval)	
Comorbidities	

Comparison group	
Presence	
Criteria	
Age characteristics	
Sex characteristics	
Pubertal stage (if applicable)	
Outcomes	
Tool used for measurement of bone health	
Body area assessed	
Primary outcome measures	
Secondary outcome measures	
Unit of measurement	
Other factors measured (include tool used and units of measurement)	
Results	
Risk ratio/relative risk/odds ratio of impaired bone health *P* value and 95% confidence interval	
Individual outcome measures • Estimate of effect with confidence interval • Standard error of effect • *P* value	
Other outcome measure (eg, physical activity levels, body mass index, muscle density, muscle size, cardiorespiratory fitness measures) • Estimate of effect with confidence interval • Standard error of effect • Pvalue	
Effect measures (risk ratio, relative risk ratio, odds ratio)	
Results of any subgroup analysis	
Bias	
Presence of incomplete outcome data	
Selective outcome reporting	
Any other bias concerns, such as funding	
Miscellaneous	
Key conclusion of study authors	
Miscellaneous comments from the study authors	
Any other information necessary for analysis of the quality of the study	
Any other comments	

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