


# Risk factors in early life for developmental coordination disorder: a scoping review

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## ABBREVIATIONS

BOTMP	Bruininks-Oseretsky Test of Motor Proficiency
DCD	Developmental coordination disorder
ECMO	Extra corporeal membrane oxygenation
MABC	Movement Assessment Battery for Children
MND	Minor neurological dysfunction

**AIM** To perform a scoping literature review of associations between risk factors in early life and developmental coordination disorder (DCD).

**METHOD** PubMed, Embase, CINAHL, PsycINFO, and Web of Science (January 1994–March 2019) were searched to identify studies on early risk factors and motor impairment or DCD. The effect of single and multiple risk factors was assessed. Level of evidence was evaluated following the Centre for Evidence-Based Medicine guidelines. Meta-analysis on the effect of preterm birth was performed.

**RESULTS** Thirty-six studies fulfilled inclusion criteria; 35 had evidence level 3, one had level 4. Highest evidence was available that preterm birth and male sex in term-born children were associated with DCD. The odds ratio of preterm birth was 2.02 (95% confidence interval: 1.43–2.85). Low to moderate evidence was available that parental subfertility, maternal smoking during pregnancy, postnatal corticosteroid treatment in infants born preterm, extra corporeal membrane oxygenation, retinopathy of prematurity, abnormalities on magnetic resonance imaging scans at term age, and accumulating perinatal or neonatal risk factors were associated with motor impairment.

**INTERPRETATION** Limited information on early risk factors of DCD is available. Only preterm birth and male sex were consistently associated with an increased risk of DCD.

Developmental coordination disorder (DCD) is a motor skill disorder that significantly interferes with activities of daily life. By definition DCD is a broad concept.<sup>1,2</sup> It refers to children who lack adequate motor skills required for everyday tasks, such as dressing, eating, tying shoelaces, active play, and writing. These deficits are not explained by the child's age or intelligence, nor by an identifiable neurological disorder.<sup>1</sup>

Surprisingly little is known about the aetiology of DCD, although it is a highly prevalent disorder, estimated to affect 5% to 6% of school-aged children.<sup>2</sup> The only risk factor that is consistently associated with DCD is preterm birth, either defined in terms of low gestational age at birth or low birthweight.<sup>3–5</sup> The higher risk of children born preterm at school age to be diagnosed with DCD was demonstrated in two systematic reviews.<sup>3,4</sup> The first study demonstrated that the risk of being diagnosed with DCD in children born very preterm (<32wks) or with a very low birthweight (<1500g) was 6 to 8 times higher than that in children born at term or with a typical birthweight.<sup>3</sup> The second study indicated that the risk of DCD was 3 to 4 times higher in children born before 37 weeks.<sup>4</sup>

Based on these two reviews and the prevalence of preterm and very preterm birth that vary between 5% and 18%<sup>6</sup> and 7% and 16%,<sup>7</sup> it is estimated that overall in children with DCD, 8% to 10% are born very preterm, and 12% to 44% are born preterm. This implies that although children born very preterm are at risk, the majority of children with DCD are born at term. Except for preterm birth, no other risk factors for DCD have been systematically identified. It is conceivable that DCD has a multifactorial cause consisting of chains of risk factors that are both genetically and environmentally determined.<sup>8</sup> Knowledge on the risk factors for DCD would assist early identification, therewith offering opportunities for intervention in an early phase of the disorder. This is important since school-aged children with DCD tend to withdraw from participation in physical and social activities.<sup>9</sup> Also, children with DCD lose physical fitness over time, and tend to be at risk for the impairments associated with a sedentary lifestyle, including cardiovascular disease and obesity.<sup>10,11</sup>

The aim of this scoping review is to evaluate which sociodemographic, prenatal, perinatal, and neonatal risk factors are associated with DCD.

## METHOD

The scoping review was written in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews (PRISMA-ScR) criteria: Checklist and Explanation guidelines.<sup>12</sup> The scoping review was conducted using the methodological framework developed by Arksey and O'Malley,<sup>13</sup> and further enhanced by the Joanna Briggs Institute.<sup>14</sup> The protocol for this scoping review is provided in Appendix S1 (online supporting information).

### Search strategy

The search strategy was developed by all authors and performed by two authors (FRTP and JvH) and a librarian. A systematic search was performed to identify relevant studies published from January 1994 until March 2019 using the databases PubMed, Embase, CINAHL, PsycINFO, and Web of Science. We searched from 1994 onwards, as this was the year that an international panel of experts decided to describe children with significant motor coordination problems as having DCD.<sup>15</sup> Before the expert meeting, a wide variation in terminology and diagnostic criteria was used to describe children with these motor coordination problems, which would hamper the external validity of the scoping review.

In the search, we used terms such as 'motor skill disorders', 'developmental coordination', 'coordination disorder', combined with terms for perinatal adversities such as 'prenatal', 'perinatal', or 'pregnancy' (for details of the search string see Appendix S2, online supporting information). The search was conducted in English. The references of the included articles were hand-searched by JvH for further eligible articles.

### Eligibility criteria

In order to be included in the review, studies had to fulfil the following criteria: (1) they had to address children with DCD: children who met the diagnostic criteria for DCD according to the Diagnostic and Statistical Manual of Mental Disorders (DSM), Fourth or Fifth Editions, or children with motor impairment as assessed with a standardized motor test (e.g. Movement Assessment Battery for Children [MABC] score below the 16th centile as a cut-off) or another appropriate, valid, reliable, and standardized motor test (appropriately norm-referenced). Also, articles in which children with probable DCD were identified by means of questionnaires like the DCD Questionnaire were included; (2) the participants' mean age had to be between 5 and 13 years; (3) studies addressed associations between DCD (or motor impairment) and early life factors (i.e. pregnancy-related factors, birth factors, child factors, or sociodemographic determinants). Early life factors were defined as factors occurring in the period ranging from pregnancy until 3 months post-term, since the latter age is characterized by a major neurodevelopmental transition.<sup>16</sup>

### What this paper adds

- Preterm birth is a risk factor for developmental coordination disorder (DCD).
- In term-born children, male sex was consistently associated with DCD.
- Risk factors for DCD are similar to risk factors for cerebral palsy.

We excluded studies that: (1) included fewer than 10 participants; (2) were reviews or case-reports; and (3) specifically addressed the effect of drugs (e.g. caffeine) or nutritional supplements (e.g. vitamin D and vitamin A). The application of the DSM-5 criteria for inclusion also implied that studies that included children with a neurological disorder such as cerebral palsy (CP) were excluded. Studies that addressed the follow-up of specific groups of infants at increased risk of neurodevelopmental disorders (e.g. infants with neonatal hypoxic ischaemic encephalopathy or infants born preterm with a lesion of the brain but no diagnosis of CP) were eligible for our study.

### Data extraction

All articles identified by the search strategy were screened on title and abstract for inclusion or exclusion by JvH and FRTP. Subsequently, these two authors performed de-duplication. For the remaining articles, the full text was assessed and the eligibility criteria were applied. This was independently performed by JvH and FRTP. Disagreements were resolved by consensus with the review team (CvdS, IS, MS, and MHA). When applicable, we followed the patient, intervention (not applicable), comparisons (in our case, which risk factors were analysed in relation to motor impairment), outcomes (what criteria for motor impairment were used), and study design approach in our data extraction. This means that we systematically extracted the following data: size and age of the population of children, risk factors that were or were not significantly associated with DCD, motor outcome measurement and cut-off point, assessment criteria of DCD, and study design. If necessary, authors were contacted for additional information to complete the review.

### Level of evidence

The studies were assigned a level of evidence according to the Centre for Evidence-Based Medicine guidelines.<sup>17,18</sup> Levels of evidence ranged from 1 to 5, with lower numbers indicating higher quality. The level of evidence assessment was performed by two authors (JvH and FRTP) independently, with any disagreements resolved by discussion.

### Statistical analysis

Meta-analysis was performed on the effect of preterm birth on the results of the selected studies using Comprehensive Meta-Analysis version 3.3.070 (Biostat Inc., Englewood, NJ, USA). Since considerable clinical heterogeneity existed between the studies, different study populations and cut-off points applied, and statistical heterogeneity existed ( $Q=71.4$ ,  $df\ 15$ ,  $p<0.001$ ,  $I^2=79.0$ ), separate analyses (random effects) were performed for studies concerning the general population and for studies concerning infants born

preterm. Additionally in the meta-analysis of infants born preterm, three subgroups were distinguished: studies using a cut-off point of the 5th centile on the MABC, studies using a cut-off point of the 15th centile on the MABC, and the study using the Bruininks-Oseretsky Test of Motor Proficiency (BOTMP). The result of Davis et al.<sup>19</sup> and Roberts et al.<sup>20</sup> were entered twice in the meta-analysis: once for the 5th centile and once for the 15th centile. We therefore did not calculate an overall summary statistic for all studies concerning infants born preterm. The meta-analyses resulted in odds ratios (OR) and 95% confidence intervals (CI).

## RESULTS

### Study selection and general characteristics of selected studies

The search identified 7295 publications, of which 2597 were removed after screening for duplicates. The titles and abstracts of the remaining 4698 articles were assessed for relevance. This left 193 papers as potentially eligible. Articles evaluating the same population were considered as one study.<sup>21–24</sup> After full-text reading, 36 studies (in 38 publications, as two studies had been reported in two papers) met our inclusion criteria; these were included in the review (Fig. S1, online supporting information). Populations of included studies were from 11 different countries.

The results of the assessment of the level of evidence are presented in Table S1 (online supporting information). All studies except one were classified as having level 3 evidence; the remaining study had level 4 evidence, as it was a cohort study of poor quality.<sup>25</sup> All publications reported on cohort studies and none used a randomized controlled trial design.

Almost half of the papers (16/36) reported on children born preterm and/or with a low birthweight (Table S1).<sup>19–22,26–38</sup> Preterm birth was either defined as low gestational age ( $n=8$ ), very low birthweight ( $n=1$ ), or low gestation and/or very low birthweight ( $n=7$ ). The criteria for low gestational age differed; most studies evaluated outcome in infants born preterm at or before 32 weeks ( $n=14$ ). Very low birthweight was defined as 1500g or less ( $n=8$ ). A second group of papers studied risk factors of motor impairment in children of the general population ( $n=14$ ). A third group of studies investigated specific groups of infants at risk ( $n=6$ ); they included survivors of extra corporeal membrane oxygenation (ECMO),<sup>39,40</sup> children admitted with hypoxic ischemic encephalopathy,<sup>25,41</sup> children born after diabetic pregnancy,<sup>42</sup> or children born after a difficult birth at term.<sup>43</sup>

Motor impairment was determined using various measurement instruments. The most frequently applied measurements were the MABC<sup>44</sup> and the MABC, Second Edition<sup>45</sup> ( $n=22$ )<sup>21,22,25–30,32–37,39–43,46,47</sup> and the Developmental Coordination Disorder Questionnaire 2007<sup>48</sup> ( $n=8$ ).<sup>49–56</sup> Other tests concerned the ALSPAC Coordination Test, which had been derived from the MABC ( $n=3$ ),<sup>23,24,37,58</sup> the BOTMP<sup>59</sup> ( $n=2$ ),<sup>31,38</sup> and the

Neuromuscular Development Index derived from the McCarron Assessment of Neuromuscular Development<sup>60</sup> ( $n=1$ ).<sup>61</sup> Comprehensive descriptions are provided in Table S1. The cut-off values of the MABC for motor impairment varied. Ten articles used the 15th centile,<sup>28,29,32–35,37,40,41,43</sup> the cut-off value denoting that the child is 'at risk' of movement difficulty; four used the 5th centile,<sup>21,22,27,30,36</sup> indicating significant movement difficulty; eight evaluated the effect of both cut-off values.<sup>19,20,25,26,39,42,46,47</sup> Only in three studies were all DSM DCD diagnosis criteria fulfilled.<sup>23,24,57,58</sup>

For the calculation of the OR for the association between preterm birth and DCD, we excluded one article since data needed were lacking.<sup>55</sup> We included only one paper<sup>57</sup> of the Lingam group<sup>23,24,57</sup> to avoid the risk of overlapping participants; we chose the one that was most in line with the scope of the current review.

### Sociodemographic factors

#### Sex of the child

In the general population-based studies, male sex was significantly associated with DCD.<sup>23,24,47,50,51,55,56</sup> Yet, in children born preterm, male sex was only associated with DCD in one<sup>19</sup> out of seven studies.<sup>19,21,22,26,29–32</sup>

#### Socioeconomic status

The findings on associations between socioeconomic status, mostly described in terms of parental education and profession (Table S1), and DCD were inconsistent. The studies addressing the general population reported the following: one study described that lower socioeconomic status was associated with impaired motor development,<sup>23,24</sup> one that a higher socioeconomic status increased the risk of motor impairment,<sup>51</sup> whereas the remaining two studies<sup>50,61</sup> did not find an association between parameters of social-economic status and DCD. In children born preterm, only one<sup>33</sup> out of five studies,<sup>26,29,30,33,38</sup> reported that worse socioeconomic status was associated with increased risk of DCD.

Specific socioeconomic factors, such as single or two parent families, ethnicity, number of siblings, and monthly per capita income,<sup>23,24,33,38,57</sup> were generally not associated with motor outcome. The exception to the rule was housing situation: Lingam et al. found that housing status (i.e. tenure at 8wks' gestation) was a significant risk factor for motor performance at 7 to 8 years.<sup>23,24,57</sup>

#### Prenatal factors

**Fertility and maternal age.** In a population-based study, subfertility, defined as conceiving naturally after a waiting period of more than 12 months, was associated with a slightly higher risk of DCD. Yet, subfertility treatment, including in vitro fertilization, was not associated with an increased risk of DCD.<sup>54</sup>

Maternal age was not associated with the child's motor outcome in four population-based studies,<sup>23,24,50,56,60</sup> whereas in a study on children born preterm, younger

maternal age was associated with an increased risk of motor problems at school age.<sup>33</sup>

**Prenatal exposure to smoking, alcohol, and environmental pollutants.** In term-born children, maternal smoking during the first trimester of pregnancy was significantly associated with DCD at 7 years.<sup>51</sup> Maternal smoking in the second or third trimester (determined by a serum cotinin concentration >10ng/ml) was also associated with an increased risk of DCD at 8 to 9 years, but not with an increased risk of DCD at younger ages (5–7y).<sup>49</sup> In two studies, maternal smoking was not associated with DCD at 7 to 8 years<sup>23,24</sup> or 10 years.<sup>61</sup> It should be noted however, that maternal smoking was assessed in less detail in the two studies that showed no association (maternal report of presence of ever smoking during pregnancy)<sup>21,22,59</sup> than in the other two studies.<sup>49,51</sup>

Maternal reports of alcohol exposure and DCD at school age were not significantly associated.<sup>23,24,45,47,51,61</sup> Prenatal recreational drugs exposure<sup>61</sup> and prenatal exposure to environmental pollutants, such as lead, cadmium, mercury, perfluorooctanoic acid, and perfluorooctane sulfate,<sup>52,58</sup> did not increase the risk of DCD at school age.

**Maternal health.** In the general population, maternal anaemia during pregnancy was associated with an increased risk of DCD, but only in females, not in males.<sup>61</sup> In children born preterm, episodes of maternal fever were associated with DCD. Yet, the number of episodes, the maximum temperature, the number of days, and the gestational period in which the episodes had happened were not related to DCD.<sup>31</sup> In children born preterm, maternal illness, gestational diabetes, and renal tract infection during pregnancy were not associated with the child's motor outcome.<sup>21,22,27</sup>

The association between hypertension during pregnancy and the risk of DCD in offspring appeared to be inconsistent. In a population-based cohort, essential hypertension was a significant risk factor for DCD in 10-year-old females, but not in males.<sup>61</sup> No association was found between preeclampsia and DCD.<sup>61</sup> In the three studies evaluating the association between hypertension during pregnancy and the risk of DCD, only one<sup>21,22</sup> found a significant association.<sup>21,22,27,29</sup>

The associations between maternal mental health and DCD were only studied in general populations. Maternal depression and anxiety at 32 weeks of gestation were associated with an increased risk of DCD in the offspring. Yet, maternal depression at 8 weeks after delivery was not associated with DCD of the child.<sup>23,24</sup> In addition, maternal stress during pregnancy was not associated with DCD.<sup>61</sup>

### **Perinatal factors**

**Gestational age and birthweight.** In the general population,<sup>23,24,50,51,55,56</sup> gestational age was associated with DCD in several studies: each week of reduction in gestational age resulted in a higher risk.<sup>56</sup> Yet, one study found that preterm birth (<37wks' gestation) was not associated with later motor impairment; however, a birthweight less

than 2000g was associated with poorer motor scores.<sup>61</sup> Imminent preterm birth was associated with an increased risk of motor impairment in females.<sup>61</sup> Being born post-term (≥42wks) did not increase the risk of DCD.<sup>56</sup> The overall OR of preterm birth in the general population was 2.02 (95% CI: 1.43–2.85) (Appendix S3, online supporting information).

The studies of children born preterm demonstrated that children born very preterm (i.e. ≤32wks) had a significantly higher risk of DCD than children born at term.<sup>20–22,26,28,31,33,36,37</sup> When the cut-off value for preterm birth was set at older gestational ages (i.e. at 37wks), the association between preterm birth and DCD disappeared.<sup>34</sup> In the latter study, an increased risk of motor impairment was restricted to the group of children born preterm at or before 32 weeks. Within groups of children born very preterm, the risk of DCD was generally inversely related to gestational age at birth;<sup>19,27,29,32</sup> however, one study did not demonstrate such an association.<sup>38</sup> Ten of the 11 studies on the risk of very preterm birth used the MABC to determine the presence of DCD, whereas the remaining study used the BOTMP.<sup>31</sup> We focussed on the studies using the MABC. The analyses showed that being born before 32 weeks' gestation was associated with the following risks of DCD. DCD defined as a MABC score below the 5th centile resulted in an OR of 5.52 (95% CI: 3.63–8.40) and DCD defined as a MABC score below the 15th centile in an OR of 3.69 (95% CI: 2.51–5.42) (Appendix S4, online supporting information). The study that used the BOTMP<sup>31</sup> reported that very preterm birth was associated with an OR of 17.47 (95% CI: 2.21–138.23).

The effect of intrauterine growth restriction (or being born small-for-gestational age) on risk of DCD was studied both in the general population and in groups of children born preterm. The literature on general populations was inconclusive about the association between intrauterine growth restriction and DCD: two studies did report an association,<sup>51,56</sup> another did not.<sup>61</sup> Two studies addressed this issue in children born very preterm: being small-for-gestational age was not associated with an increased risk of DCD.<sup>26,38</sup>

**Other perinatal risk factors.** The association between antepartum haemorrhage and motor outcome at school age was addressed in four studies: one evaluated children from the general population,<sup>61</sup> three others evaluated children born preterm.<sup>21,27,29</sup> None reported a significant association.

Reports on the associations between DCD and the type of delivery (e.g. caesarean section, elective or not, or vaginal delivery) were inconsistent. In the general population, caesarean section was associated with an increased risk of motor impairment in males only.<sup>61</sup> Three studies<sup>27,29,33</sup> evaluated the association between caesarean section and DCD in children born preterm; none found a significant association.

The use of antenatal corticosteroids to prevent lung disease was evaluated in three preterm groups; it was not associated with impaired motor outcome.<sup>19,26,27</sup> Also single parameters reflecting the infant's condition around birth, including Apgar scores<sup>21,22,29,33</sup> on the time to respond after birth (defined as taking longer than 2mins to breath spontaneously) and fetal distress,<sup>61</sup> were not associated with motor impairment. However, when multiple of these factors, such as abnormal fetal cardiogram, fetal acidosis, and/or low Apgar scores, were present at term birth and had resulted in mild to moderate neonatal encephalopathy, this was associated with an increased risk of motor problems at age 6 years.<sup>43</sup>

### Postnatal factors

*Neonatal morbidity and infant nutrition.* The effect of neonatal morbidity was especially investigated in children born preterm. In these children, no associations were reported between the child's motor development and indicators of neonatal respiratory distress, such as hyaline membrane disease<sup>31</sup> and chronic lung disease (in these papers equivalent to bronchopulmonary dysplasia<sup>19,26,29,31,38</sup> and pneumothorax).<sup>21,22,27,31</sup>

The risk of motor impairment due to various treatments of lung disease in neonates born preterm was investigated. The use of postnatal corticosteroids was associated with impaired motor outcome in two<sup>19,26</sup> out of three studies.<sup>19,26,33</sup> The number of days of oxygen use was associated with worse motor outcome in one study,<sup>33</sup> but not in four others.<sup>21,22,27,31,38</sup> Inconsistent findings were present for the number of days of mechanical ventilation: two studies<sup>26,38</sup> found a significant association with impaired motor outcome, but three others did not.<sup>27,29,31</sup> The use of surfactant was not associated with impaired motor outcome.<sup>19</sup>

Three studies addressed the association between retinopathy of prematurity and motor outcomes; two found a significant association<sup>26,29</sup> whereas the other did not.<sup>33</sup> Other factors that were evaluated in preterm groups were sepsis,<sup>21,22,26,27,29</sup> positive blood cultures,<sup>33</sup> chorioamnionitis,<sup>21,22,26</sup> necrotising enterocolitis,<sup>26,29,31</sup> neonatal hypoglycaemia,<sup>21,22,27</sup> surgery in the newborn period,<sup>19</sup> patent ductus arteriosus with or without treatment by ligation,<sup>27,31</sup> and neonatal seizures.<sup>54</sup> None of these risk factors were associated with an increased risk of motor impairment.

In groups of children born preterm, composite markers of medical risk, such as 'increased medical risk', defined as any of (cystic) periventricular leukomalacia, intraventricular haemorrhage grade 3 or 4, bronchopulmonary dysplasia, or postnatal corticosteroid treatment,<sup>30</sup> and total hospitalization time<sup>33</sup> were associated with a significantly increased risk of later motor impairment. Yet, the number of the days admitted to the neonatal intensive care unit was not.<sup>31</sup> Multiple births did not elevate the risk of impaired motor outcome; this was true for population norm children<sup>61</sup> and for children born preterm.<sup>26,33</sup>

The two studies that followed a group of term-born children who had been treated with ECMO found that ECMO was associated with an increased risk of impaired motor outcome at 5 and 8 years of age.<sup>39,40</sup>

In the general population, maternal postpartum haemorrhage was associated with an increased risk of motor problems at school age, but only in males.<sup>61</sup> The presence of infantile colic or prolonged crying during early infancy<sup>54</sup> was not associated with the development of motor impairment. Also, parameters of infant nutrition, such as infants born preterm being breastfed during neonatal stay in the hospital,<sup>33</sup> being breastfed for less than 3 months, or being bottle fed,<sup>61</sup> were not associated with DCD.

*Abnormalities on neonatal brain imaging.* Ten studies<sup>19,21,22,26,27,29,31,33,35,38,41</sup> reported on associations between neonatal brain lesions, such as white matter abnormalities, haemorrhages or hydrocephalus, and motor development. One<sup>41</sup> included children born at term after perinatal asphyxia; the others addressed groups of children born preterm. The prospective studies revealed that the presence of intraventricular haemorrhage of various severity was not associated with DCD.

Four studies in groups of children born preterm investigated white matter abnormalities that were defined as white matter abnormalities or periventricular leukomalacia.<sup>19,26,31,35</sup> Periventricular leukomalacia, either diagnosed by ultrasonography<sup>19,31</sup> or by magnetic resonance imaging (MRI) at term equivalent age,<sup>26</sup> was not associated with DCD. However, one study<sup>35</sup> that evaluated white matter abnormalities with MRI at term equivalent age reported that the presence and severity of white matter abnormalities were associated with the severity of motor impairment in children born very preterm without CP.

Other authors found that moderate to severe brain lesions on the neonatal MRI in infants born at term with neonatal encephalopathy were strongly associated with a MABC score at or below the 15th centile at the age of 9 to 10 years.<sup>41</sup>

## DISCUSSION

We reviewed 25 years of research on associations between risk factors in early life and DCD. Thirty-five of the 36 studies available were rated as having level 3 evidence, indicating a moderate level of evidence. The studies revealed that relatively few early life factors were consistently associated with motor impairment in childhood. The highest evidence was available for the association between male sex (investigated in the general population) as well as preterm birth with motor impairment. Lower evidence was available that parental subfertility, maternal smoking during pregnancy, postnatal corticosteroids administered for the treatment of lung disease in infants born preterm, need of ECMO, retinopathy of prematurity, abnormalities on MRI-scans at term, and an accumulation of perinatal or neonatal risk factors were associated with motor impairment.

Male sex was a risk factor for DCD in the general population but not in children born preterm. It is well known that the male sex is a risk factor for neurodevelopmental disorders, including CP,<sup>62</sup> autism spectrum disorder,<sup>63</sup> and attention-deficit/hyperactivity disorder.<sup>64</sup> The finding that male sex is associated with DCD in the general population corresponds to this male vulnerability. Yet, this sex effect was absent in children born preterm, in line with the report of Powls et al.<sup>65</sup> This difference in male disadvantage for DCD in infants born preterm and at term corresponds to that for CP: in term-born infants, male sex is a risk factor for CP, but not in infants born preterm.<sup>66,67</sup> This may imply that the biological risk of motor disorders associated with preterm birth outweighs that of male sex.

Consistent with other reviews, very preterm birth (i.e. gestational age  $\leq 32$ wks or expressed by a very low birthweight) was a significant risk factor for DCD. The results of our meta-analysis confirmed this risk with ORs varying between 3.69 and 10.10. We omitted the study by Holsti et al.<sup>31</sup> from the meta-analysis, as it was the only study using the BOTMP to determine DCD. Holsti et al. reported an OR that exceeded those of the other studies; it also had the widest CIs. Multiple factors may explain the discrepant finding of Holsti et al., apart from the use of another measurement instrument to determine DCD. First, their study population included infants born extremely preterm (birthweight <800g) who were born in the 1980s. All other studies included children born in the 1990s. It is conceivable that the substantial advances in quality of neonatal intensive care occurring over time were associated with improved outcome of the children. Second, Holsti et al. suggested that the relatively aggressive resuscitation policy of extremely low birthweight infants at that time in their region could also have contributed to the infants' high risk of DCD.

In the general population, the meta-analysis indicated that preterm birth (<37wks gestation) was associated with a doubling of the risk of DCD – in line with the findings reported by others.<sup>3,56</sup> Moreover, the results of our review also indicated that in general each week of reduction in gestational age at birth is associated with a minor increase of the risk of DCD.

Apart from male sex and preterm birth, low to moderate evidence was present for three other risk factors. First, parental subfertility was associated with DCD, but subfertility treatment was not. This corresponds to reports that subfertility is associated with an increased risk of minor neurological dysfunction (MND) at school age, but the *in vitro* procedures used for subfertility treatment are not.<sup>68,69</sup> Second, maternal smoking during pregnancy is most likely associated with impaired motor outcome at school age. The two studies<sup>49,51</sup> that used the most precise indicators of maternal smoking reported this association, whereas the association was not found in the studies that used less accurate measures of maternal smoking.<sup>23,24,61</sup> Third, the results of our review suggest that postnatal corticosteroids for the treatment of lung disease in infants born preterm

may be associated with DCD. This implies that postnatal corticosteroid administration is not only associated with an increased risk of CP,<sup>70</sup> but also of DCD. These results correspond to those of Zwicker et al. who reported that postnatal steroid exposure, male sex, and low birthweight in children aged 4 years 6 months with a very low birthweight were associated with DCD.<sup>71</sup> Other risk factors that are most likely associated with DCD can be regarded as parameters reflecting an accumulation of prenatal, perinatal, and neonatal adversities. Examples are general indicators of medical risk,<sup>30</sup> total hospitalization time,<sup>33</sup> term birth resulting in mild to moderate encephalopathy,<sup>43</sup> need of ECMO,<sup>39,40</sup> and retinopathy of prematurity.<sup>26,29</sup> Also brain lesions documented by neuroimaging belong to this category. The limited data available suggest that MRI at term age is especially helpful in documenting the lesions that are associated with DCD.<sup>35,41</sup> This corresponds to the evidence that MRI at term equivalent age is a powerful tool in predicting CP.<sup>72</sup> The notion that DCD seems to be particularly associated with parameters that reflect an accumulation of prenatal, perinatal, and neonatal adversities also corresponds to the aetiology of CP.<sup>73</sup>

Our findings suggest that the majority of risk factors associated with DCD are similar to those associated with CP. Nevertheless, the associations between the early risk factors and DCD were less consistent than those reported for early risk factors and CP. It is conceivable that the difference in the strength of the associations can be attributed to the type of diagnosis: CP is a neurological diagnosis with its origin in a structural lesion or malformation of the brain, whereas DCD is a neurodevelopmental disorder according to the DSM-5. Children with DCD, by definition, do not have a specific neurological diagnosis with known aetiology but they do often have MND.<sup>74</sup> Signs of MND can be determined with a standardized and age-specific assessment.<sup>74</sup> Basically, two forms of MND can be distinguished: simple and complex MND.<sup>75</sup> At school age, it is based on the number of domains of dysfunction; children with complex MND show dysfunction in more neurological domains than children with simple MND. DCD is clearly associated with complex MND, but not all children with DCD have complex MND – they may also present with simple MND or occasionally with a typical neurological condition.<sup>76</sup> As complex MND is – like CP – strongly associated with early risk factors, but simple MND is not,<sup>74</sup> this may explain why early risk factors are less strongly associated with DCD than with CP.

### Strengths and limitations

One strength of this study is that we were able to review 25 years of research. A second strength of this scoping review is that it did not only focus on infants born preterm, but also included children from the general population. Additionally, to provide insight in the associations between early risk factors and the occurrence of DCD, we chose to include studies that described children without CP but with lesions of the brain, such as hypoxic ischemic

encephalopathy, white matter abnormalities, hydrocephalus, and perinatal asphyxia. We are aware that there is some controversy including these studies; however other papers addressing the association between high risk, brain lesions, and DCD support this strategy.<sup>77,78</sup> Yet, the study has a limitation: we were only able to find studies with level 3 evidence at best. This implies that no firm conclusions can be drawn.

### Concluding remarks

The vast majority of studies reviewed had level 3 evidence, implying that the review does not allow for firm conclusions. The highest evidence available suggested that male sex and preterm birth were associated with DCD. There was limited evidence for the association between DCD and parental subfertility, maternal smoking, postnatal corticosteroids in infants born preterm, and the accumulation of perinatal or neonatal risk factors. This suggests that the risk factors for DCD resemble those associated with CP.

The European Standards of Care for Newborn Health<sup>79</sup> recommend that infants born very preterm receive neurodevelopmental follow-up to and including school age. Since the ORs indicate substantial risk and the prevalence rates for DCD are high (up to more than 40%) and tend to increase in children born very preterm,<sup>34</sup> we suggest that follow-up procedures pay specific attention to DCD. This may be easily implemented by using questionnaires like the DCD Questionnaire (for children 5–15y) or Little DCD Questionnaire (for children 3–4y),<sup>80</sup> or the DCD Daily Questionnaire that assesses activities in daily living and also considers the acquisition and quality of motor performance.<sup>81</sup>

Our review indicates that the knowledge on risk factors of DCD is limited, especially in the large group of children born at term. We suggest that the scientific community – before embarking on more risk factor studies – first engages in a Delphi study in order to achieve consensus

about the risk factors to be studied, including their definitions. To increase the level of evidence, large and well-documented birth cohort studies are needed. Knowledge on early risk factors facilitates the early detection of children at risk of DCD. In a similar way, knowledge on the as yet unclear significance of early signs, such as a delay in developmental milestones, may pave the way for early detection. As we currently lack this information, future studies need to address this, in particular as DSM-5's criterion C states that the onset of symptoms of DCD must occur in the early developmental period. Finally, we suggest that future studies not only address early risk factors and early signs, but also protective factors for DCD.

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### DATA AVAILABILITY STATEMENT

The data that supports the findings of this study are available in the supplementary material of this article.

### SUPPORTING INFORMATION

The following additional material may be found online:

**Appendix S1:** Scoping review protocol according to Joanna Briggs Institute instructions.

**Appendix S2:** Search strings.

**Appendix S3:** Forest plot of the risk of preterm birth for DCD in the general population.

**Appendix S4:** Forest plot of the risk of birth before 32 weeks of gestation for DCD in studies of infants born preterm.

**Figure S1:** Study selection flow chart.

**Table S1:** Risk factors for DCD: findings in the included studies

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