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Early motor developmental milestones and schizophrenia: A systematic review and meta-analysis

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ABSTRACT

The neurodevelopmental hypothesis of schizophrenia proposes that impaired brain development is a cause of the illness. Early motor developmental milestones, such as learning to walk, are predictors of later schizophrenia but studies have not been systematically reviewed. The aim of the present systematic review and meta-analysis was to explore the association between early motor developmental milestones and the risk of adult schizophrenia. In addition, we updated a systematic review on motor function and risk of schizophrenia.

The PubMed, PsycINFO and Scopus databases were searched for original research articles published up to July 2015. Motor milestones were measured between ages 0 and 13 years. Random effect meta-analysis calculated effect estimates (Hedges' g) for the association between individual motor milestones and schizophrenia risk. An electronic database and selected articles reference list search identified 5990 articles after removing duplicates. Sixty-nine full text articles were assessed for eligibility of which six were included in the review. Five studies provided sufficient data for meta-analyses.

The following motor milestones were significantly associated with adult schizophrenia risk: walking unsupported ($g = 0.46$; 95% CI 0.27–0.64; $p < 0.001$), standing unsupported ($g = 0.28$; 0.16–0.40; $p < 0.001$) and sitting unsupported ($g = 0.18$; 0.05–0.31; $p = 0.007$). Results for the milestones 'holding head up' and 'grabbing object' were not statistically significant. Delayed walking, sitting and standing unsupported were associated with adult onset schizophrenia. The findings emphasise the importance of timely achievement of these motor milestones in childhood and can contribute to the identification of individuals at risk of psychosis.

1. Introduction

The neurodevelopmental hypothesis of schizophrenia proposes that abnormalities in the developing nervous system betray vulnerability to the illness (Murray and Lewis 1987; Weinberger 1987; Maynard et al. 2001). Evidence from both genetic high risk and population-based cohort studies that observed an association between motor abnormalities or delayed motor development and adult schizophrenia contributed to shaping the theory. In these studies various concepts are used to define the observed phenomenon such as pandysmaturation (Fish 1957), motor coordination (Rosso et al. 2000; Schiffman et al. 2004), fine and gross motor skills (Burton et al. 2016), motor function (Dickson et al. 2012), motor development milestones (Jones et al. 1994; Isohanni et al. 2001; Sorensen et al. 2010), neurological soft and hard signs (Schiffman et al. 2009).

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Few attempts were made to systematically review the evidence in this area and to estimate the effect size for later development of schizophrenia by meta-analysis. The meta-analysis by Dickson et al. (2012) showed a moderate effect size for motor function in youth, but studies on early motor developmental milestones were not included. Recently, in the meta-analysis by Burton et al. (2016), several developmental motor phenomena were explored, namely gross and fine motor development, movements, neurological soft signs, coordination, motor skills and walking. Moderate effect sizes were found for delayed gross and fine motor development, impaired coordination and delayed walking in children with first-degree relatives affected by schizophrenia. More involuntary movements had a small effect size. This review included only one measure for early motor developmental milestone (i.e. walking). Thus, other motor milestones in relation to risk of subsequently developing schizophrenia at individual level were not assessed.

Early motor milestones play a significant role in assessment of child development and delay in these milestones contributes to impaired overall motor function. However, it seems that an important prerequisite of achieving a motor developmental milestone is learning, which is based on a series of attempts (Corbetta and Bojczyk 2002) and recalibration of the sensimotor system (Chen et al. 2007). Since early motor developmental milestones can be seen as a complex interrelation between both motor and cognitive aspects (Diamond 2000; Murray et al. 2006; Piek et al. 2008), it is probably necessary to study them separately from motor function.

Delayed attainment of early motor development milestones, such as walking or standing unsupported and deficits in motor function in future cases of adult schizophrenia have been a key piece of evidence underpinning the neurodevelopment hypothesis of this severe illness, despite the heterogeneity in the method and age of assessment of these motor phenomena in longitudinal studies. To our knowledge, the findings from these studies have not been summarised, and a robust estimate of the association between adult schizophrenia and various early motor developmental milestones has not been provided. The aim of the present study was to systematically review and meta-analyse the scientific evidence regarding early motor developmental milestones and adult schizophrenia risk. In addition, we updated the systematic review of motor function.

2. Methods

2.1. Search strategy

The PubMed, PsycINFO and Scopus databases were searched for original research articles in July 2015. No language restrictions were applied. The following indexing terms (MeSH or Key words) were included: [(infant OR child* OR early) AND (schizophr*OR psychosis OR schizoaff* OR psychotic) AND (impairment OR delay OR skill OR ability OR function OR deficit OR coordination OR performance OR problem OR milestone* OR complication* OR risk* OR functioning OR precursor* OR predictor*) AND (motor OR movement OR neuromuscular OR psychomotor OR neuromotor OR development*)].

2.2. Inclusion and exclusion criteria

A standardised and reliable assessment of schizophrenia (e.g. registers, clinical diagnoses, interview diagnoses, validated diagnoses by physician, but not self-report) was required. Studies with only childhood onset cases of psychosis (<12 years) were excluded. Included studies assessed early motor developmental milestones between ages 0 and 13 years old. Studies exploring other aspects of motor function rather than milestones were excluded from the meta-analysis. We contacted the authors of articles for additional data so that studies could be included in the meta-analyses if data were not published in a suitable format.

2.3. Study selection

An electronic database and selected articles reference list search identified 5990 articles after removing duplicates (Fig. 1). Abstracts were screened by three reviewers working independently of each other (SF, AF, II), which identified 69 potentially eligible articles. The first author obtained full text and assessed all of these 69 articles, of which 6 studies were included in the systematic review and 5 in the meta-analyses of early motor developmental milestones. In addition, 10 eligible studies on motor function were identified. A list of excluded full-text assessed studies is presented in Supplementary material 2.

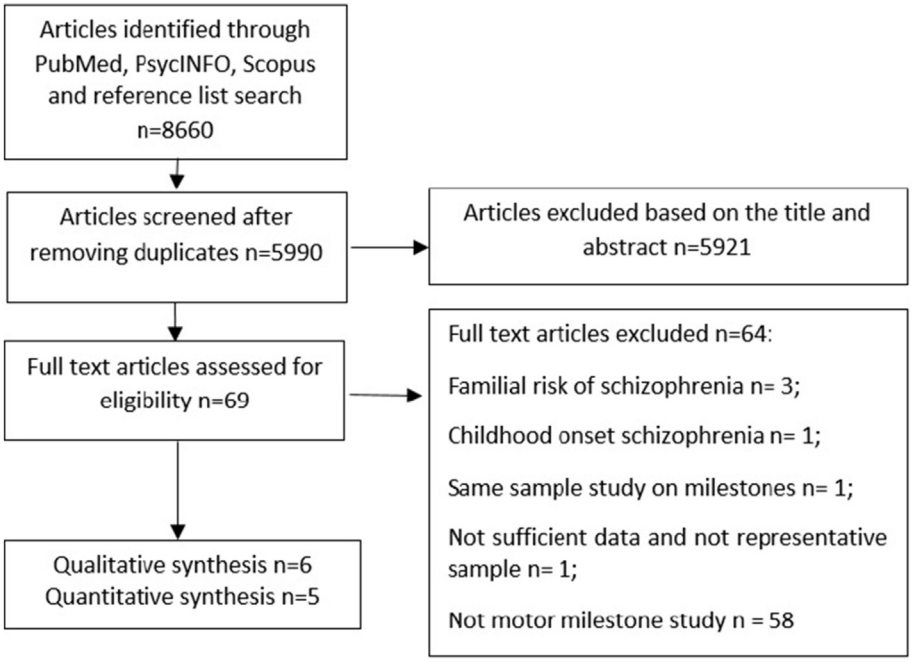

Fig. 1. Selection of the studies for the review of early motor developmental milestones and schizophrenia.

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2.4. Quality assessment analysis of selected studies and statistical analysis

A quality assessment of included studies was performed based on the critically appraised scale (Downs and Black 1998) with small modifications (Supplementary material 1). The scale has been shown to be a reliable instrument according to a recent systematic review (Sanderson et al. 2007). Extracted by the first author, estimates for the meta-analyses were independently checked by a co-author (AF). Only milestones studied at least three times were analysed, and a random effect model that is considered to be a standard for this type of data was applied (Field and Gillett 2010). Hedges' g with 95% confidence intervals (CI) was used to present individual effect sizes for each meta-analysis (Borenstein et al. 2010). This is a variation of Cohen's d, corrected for a small sample size (Hedges. and Olkin, 1985), and the magnitude of the effect can be interpreted as small (0.2), moderate (0.5), large (0.8), and very large (1.3) (Cohen 1992). The magnitude of heterogeneity across studies was assessed by I^2 tests (Higgins et al. 2003) (range: 0% to 100%). Its value of 0% indicates no heterogeneity, 25% low heterogeneity, 50% moderate heterogeneity, and 75% high heterogeneity (Higgins et al. 2003).

Potential publication biases were assessed using funnel plot asymmetry, Egger's test of intercept in a random effect model with p value <0.1, and the trim and fill method (Egger et al. 1997). The analyses were conducted using Stata version 11.

3. Results

3.1. Systematic review and quality assessment of studies on early motor developmental milestones

Six eligible studies from high income countries arising from the 1946 British cohort (Jones et al. 1994), 1959–1961 Copenhagen Perinatal Cohort (Sorensen et al. 2010), 1962 and 1969 Helsinki Birth Cohort (Clarke et al. 2011), 1966 Northern Finland Birth Cohort (NFBC 1966) (Isohanni et al. 2001; Keskinen et al. 2015), and 1972–1973 Dunedin Birth Cohort were identified (Cannon et al. 2002) (Table 1). Measures of early motor developmental milestones included: walking unsupported, standing unsupported, sitting unsupported, holding head up and grabbing object. Some other early motor developmental milestones were identified, such as turning over, touching thumb with index finger, and rolling and crawling. A study by Isohanni et al. (2001) was presented only in a systematic review as Keskinen et al. (2015), used the same data with a longer follow-up. Table 1 summarises the methods and results of the included studies.

The quality of selected studies was assessed against 18 criteria (Supplementary material 1). On average, studies fulfilled 15 criteria (range from 13 to 17), reflecting an overall good quality (Table 2). However, only three studies described at least some characteristics of participants and only two some of the characteristics of individuals lost to follow-up. Four out of five studies did not adjust for different lengths of follow-up.

3.2. Meta-analyses of early motor developmental milestones

The following early motor developmental milestones were possible to meta-analyse: walking unsupported (5 studies), standing unsupported (4 studies), sitting unsupported (4 studies), holding head up (3 studies) and grabbing object (3 studies).

3.2.1. Walking unsupported

Meta-analysis, based on 368 schizophrenia cases and 17,514 controls from five population-based longitudinal studies, showed that individuals with schizophrenia had significant delays in achievement of the walking unsupported milestone compared to controls ($g = 0.46$; $p < 0.001$; 95% CI (0.27–0.64) Heterogeneity was moderate ($I^2 = 53.4\%$; $p = 0.072$). (Fig. 2).

3.2.2. Standing unsupported

Meta-analysis, based on 307 schizophrenia cases and 17,351 controls from four population-based longitudinal studies, showed that individuals with schizophrenia had significant delays in achievement of the standing unsupported milestone compared to controls ($g = 0.28$; $p < 0.001$; 95% CI (0.16–0.40). Heterogeneity was not significant ($I^2 = 0\%$; $p = 0.548$) (Fig. 2).

3.2.3. Sitting unsupported

Meta-analysis, based on 386 schizophrenia cases and 19,424 controls from four population-based longitudinal studies, showed that individuals with schizophrenia had significant delays in achievement of the sitting unsupported milestone compared to controls ($g = 0.18$; $p = 0.007$; 95% CI (0.05–0.31). Heterogeneity was not significant ($I^2 = 0\%$; $p = 0.254$) (Fig. 2).

3.2.4. Holding head up

Meta-analysis, based on 352 schizophrenia cases and 13,927 controls from three population-based longitudinal studies, showed that individuals with schizophrenia had no significant delays in achievement of the holding head up milestone compared to controls ($g = 0.10$; $p = 0.09$; 95% CI (−0.08–0.15). Heterogeneity was not significant ($I^2 = 0\%$; $p = 0.495$) (Fig. 2).

3.2.5. Grabbing object

Meta-analysis, based on 351 schizophrenia cases and 13,882 controls from three population-based longitudinal studies, showed that individuals with schizophrenia had no significant delays in achievement of the grabbing object milestone compared to controls ($g = 0.04$; $p = 0.55$; 95% CI (−0.08–0.15). Heterogeneity was not significant ($I^2 = 0\%$; $p = 0.422$) (Fig. 2).

3.3. Publication bias

Funnel plot asymmetry tests were conducted and visual assessment did not show any asymmetry for any of the outcomes. Then Egger's regression method testing for asymmetry was applied. No significant intercepts $\beta 0$ ($p < 0.1$) for any of the milestones were found (not presented in tables). A trim and fill analysis did not identify any missing studies (not presented).

3.4. Systematic review of the motor function and schizophrenia

The search for articles identified 10 studies on motor function in childhood and adult schizophrenia. These studies explored, for example, neuromotor abnormalities (abnormal facial movements, bradykinesia etc.), specific motor skills (alignment, dissociation of movement etc.) or motor coordination and were systematised in Supplementary Table 1.

Poor motor coordination was associated with schizophrenia (Crow et al. 1995; Cannon et al. 1999b; Rosso et al. 2000). Walker et al. (1994) found neuromotor abnormalities in schizophrenia cases, but no differences in motor skills. Cannon et al. (2002) observed that individuals with schizophreniform performed worse than controls on a standard test of motor skills at the age of three, five and nine years. Schiffman et al. (2004) showed no differences in general neuromotor scale or in abnormal hand movements, but in a later follow-up found more coordination deficits in children who developed a schizophrenia spectrum disorder (Schiffman et al. 2009). Two studies using school marks in gymnastics and handcrafts/drawing as a proxy for motor function found that cases performed worse than controls in gymnastics (Cannon et al. 1999a; Helling et al. 2003). In one of the studies, cases had higher marks in drawings (Helling et al. 2003) and in the other one they performed worse in handcrafts (Cannon et al. 1999a).

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Table 1
The summary of the studies on early motor developmental milestones and schizophrenia included in the systematic review and meta-analyses.

Authors (year)	Sample, follow-up	Early motor developmental milestone (age 0 to 13 years)	Method of milestone assessment	Age at milestone assessment(s) and at data collection	Covariates	Results
Cannon et al. (2002) 1972–1973 Dunedin Birth Cohort, New Zealand	- 36 schizophreniform individuals - 642 healthy controls - 278 individuals with anxiety/depression - 20 individuals with mania - followed until age of 26	- Sitting up - Walking	- Mothers recall (only if certain) to the nearest month when their child attained milestones	- Retrospectively, nearest month, at age 3 years	- Sex - Social class	Risk of schizophrenia when learned late: - Walking unsupported
Clarke et al. (2011) 1961–1969 Helsinki Birth Cohort, Finland	- 189 individuals with schizophrenia - 189 healthy controls - followed until age of 31–39	- Keeping head up - Grabbing an object - Turning over - Sitting unsupported - Pincer grip - Standing with and without support - Walking with and without support	- Child health cards that were introduced in general use since 1962	- Prospectively during first 12 months	- Obstetric complications - Matched by sex and year of birth	Risks of schizophrenia when learned late: - Sitting without support - Standing with and without support - Walking with and without support - Cumulative effect of developmental delay: with every additional delayed milestone, the odds of developing schizophrenia increased by 20%
Jones et al. (1994) 1946 British Cohort, United Kingdom	- 30 individuals with schizophrenia - 4716 controls - followed until age of 43	- Sitting - Standing - Walking without support	- Recalled by mothers	- Retrospectively, nearest month at age 2 years	- Sex - Social class	Risks of schizophrenia when learned late: - Speech - Gross motor milestones - The greatest difference was for walking
Keskinen et al. (2015) & Isohanni et al. (2001)[a] 1966 Northern Finland Birth Cohort, Finland	- 152 individuals with schizophrenia - 10,131 controls - Followed until age of 46	- Keeping head up - Grabbing object - Turning from back to tummy - Touch thumb with index finger - Standing up - Standing, walking and sitting without support	- Welfare records collected by nurses and doctors interviewing the parents and observing the children during infancy and early childhood during regular visits to the clinics	- Prospectively during first 12 months	- Gender - Perinatal risk - Antenatal maternal depression - Family type - Social class	Risk of schizophrenia when learned late: - Standing and walking without support
Sørensen et al. (2010) 1959–1961 Copenhagen Perinatal Cohort, Denmark	- 92 individuals with schizophrenia - 691 individuals with other psychiatric disorder - 4982 healthy cohort controls - Followed until age of 46–48	- Lifting head on stomach - Head holding when sitting - Grasping after things - Sitting without support - Rolling - Crawling - Crawling longer distance - Standing with/ without support - Walking with/ without support	- Obtained from mothers who were instructed to use a standard diary to recall age at which the child reached developmental milestone	- Prospectively, at age 1 year	- Gender - Parental age - Parental social status - Breadwinner's education - Single mother status - Parity	Risks of schizophrenia when learned late: - Smiling - Lifting head - Sitting without support - Crawling - Walking without support

[a] This study was excluded from the meta-analysis due to an overlap with a study in the same sample.

4. Discussion

4.1. Main findings of meta-analysis of early motor developmental milestones and schizophrenia

Delayed walking, sitting and standing unsupported had a significant small effect size on adult schizophrenia (Cohen 1992). Keeping head up and grabbing object had no significant effect. There is also a link between familial risk of psychosis and delayed walking, as Burton et al. (2016) found an effect size of the same magnitude in their meta-analysis ($g = 0.444$; $p < 0.01$ vs. $g = 0.46$, $p < 0.001$) as in the current meta-analysis regarding individuals' own schizophrenia risk. Interestingly, motor developmental milestones learned later in childhood e.g. walking unsupported were shown to be a significant predictor of adult schizophrenia, while earlier ones e.g. grabbing object were not. On the other hand, only three studies explored the 'holding head up' and 'grabbing object' milestones.

4.2. Quality assessments of the studies included in meta-analysis of early motor developmental milestones and schizophrenia

A quality assessment of the studies has shown that, in general, a majority of the criteria were fulfilled by all of them. Selected studies had a

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Table 2
Quality assessment of studies included in the meta-analysis of motor milestones and schizophrenia.

Study	Clearly described aim	Clearly described main outcomes	Characteristics of participants	Described confounders	Clearly described main findings	Provided estimates of random variability	Described characteristics of lost to follow-up	Reported probability values	Study participants are representative
Cannon et al. (2002)	1	1	1	1	1	1	0	1	1
Clarke et al. (2011)	1	0	0	1	1	1	0	1	1
Jones et al. (1994)	1	1	0	1	1	1	0	1	1
Keskinen et al. (2015)	1	1	1	1	1	1	1	1	1
Sørensen et al. (2010)	1	1	1	1	1	1	1	1	1

Study	Stated data-dredging	Adjusted for different lengths of follow-up	Appropriate statistical tests	Accurate outcome measurement	Accurate exposure measurement[a]	Cases and controls recruited from the same population	Cases and controls recruited over the same period of time	Adjusted for confounding	Losses to follow-up taken into account
Cannon et al. (2002)	1	0	1	1	1	1	1	1	1
Clarke et al. (2011)	0	0	1	1	1	1	1	1	1
Jones et al. (1994)	0	0	1	1	1	1	1	1	1
Keskinen et al. (2015)	0	1	1	1	1	1	1	1	1
Sørensen et al. (2010)	1	0	1	1	1	1	1	1	1

Note: 0 = no or unable to determine and 1 = yes.
[a] This criterion is based on Sanderson et al. (2007).

cohort data and in three of the studies, data on early motor developmental milestones were collected prospectively. However, descriptive characteristics of participants and the lost to follow-up are missing for some of studies. It may indicate heterogeneity of the studied populations. On the other hand, it may reflect quality of reporting rather than quality of the studies. In addition, the results of all studies were controlled for confounding by sex, age or sociodemographic factors and two of them by such clinical factors as obstetric complications, perinatal risk and antenatal maternal depression. A majority of studies report both population and sample size, showing that the proportion was unlikely to affect the main findings. Two studies had to rely on retrospective assessment of milestones and three studies on mothers' assessment, which are also limitations.

In the included studies, the schizophrenia diagnosis was established by a physician or identified through registers. While both of the methods are eligible, register studies have more reliability (Miettunen 2011). In addition, studies used slightly different diagnostic systems (DSM or ICD) and/or criteria for schizophrenia. For example, in Clarke et al. (2011) schizophrenia was defined broadly, while Keskinen et al. (2015) reported results for schizophrenia and other psychoses separately. Previously, observational studies on precursors of schizophrenia were criticised for lack of specificity (Jones and Tarrant 1999). Thus, we were not able to distinguish specific early motor developmental milestones for schizophrenia versus all other psychoses in the meta-analyses. However, Keskinen et al. (2015) found that estimates for milestones were similar among schizophrenia and other psychosis groups. In both groups, standing up, standing, and walking without support were significantly delayed.

4.3. Early motor developmental milestones in relation to motor function

Previously, two related meta-analyses have been published. Burton et al. (2016) observed delays in gross and fine motor development ($g = 0.644$; $p < 0.001$), coordination deficits ($g = 0.625$; $p < 0.001$) and more involuntary movements ($g = 0.291$; $p < 0.02$) in the childhood of individuals with first-degree relatives affected by schizophrenia. Dickson et al. (2012) found that deficits in motor function at age of 16 years or younger had a moderate effect on individual schizophrenia ($d = 0.56$; $p < 0.001$). In the systematic review part, we identified the same four studies on motor function as in Dickson et al. (2012) in addition to six other studies on motor function and schizophrenia. Motor function phenomena explored in all these ten studies varied significantly. It seems methodologically challenging to meta-analyse these findings and to be also able to address heterogeneity. Thus, further attempts are needed to explore different motor function phenomena and adult schizophrenia in meta-analysis.

4.4. 4.3. Early motor developmental milestones and other aspects of neurodevelopment

Early motor development milestones are associated with many aspects of neurodevelopment. Dickson et al. (2012) found that individual

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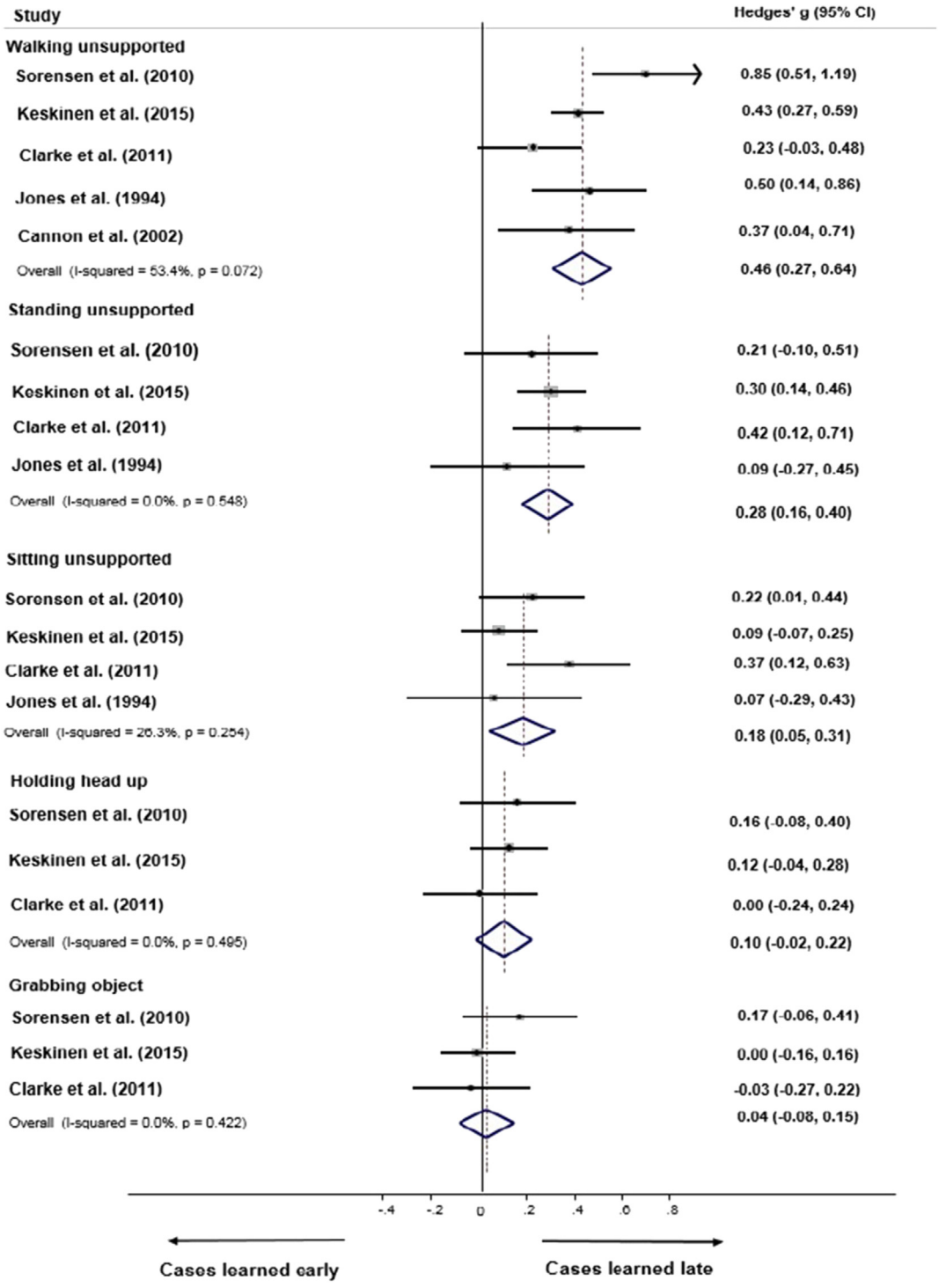

Fig. 2. Forest plots with effect size and heterogeneity of the five motor outcomes: walking unsupported, standing unsupported, sitting unsupported, holding head up and grabbing object.

who developed schizophrenia had significant deficits in IQ ($d = 0.51$; $p < 0.001$), and meta-analysis by Khandaker et al. (2011) showed significant decrements in premorbid IQ ($d = -0.43$, $p < 0.001$). Jones et al. (1994) observed more speech problems in cases than controls, and Cannon et al. (2002) poorer receptive language skills.

Moreover, an association between early motor developmental milestones, school achievements, and schizophrenia was observed. In NFBC 1966, Isohanni et al. (2004) found that among children who developed schizophrenia in adulthood, those who learned to stand late, were also more likely to perform poorly at school in subjects involving motor domain at age 16 years compared to earlier learners. Later, Taanila et al. (2005) observed lower scores in teacher ratings at 16 years and a worse education level at 31 years in those who reached standing or walking unsupported later than faster learners. Castle and Murray (1991) described a "neurodevelopmental subtype" of schizophrenia that was more common among men. Its features were early onset and poor pre-morbid social functioning. This is interesting, since achievement of each early motor developmental milestone changes an infant's social interaction and is an important step in social development (Campos et al. 2000; Clearfield 2011). Indeed, earlier walkers have showed more interactions with their mother compared to later walkers (Biringen et al. 1995). One might also presume that motor milestones

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such as delayed walking, standing and sitting unsupported may relate to cognitive development more than keeping head up and grabbing objects, and also, in the end, may relate to social development later in childhood.

4.5. 4.4. Strengths and limitations

The search was conducted in several databases: PubMed, PsycINFO and Scopus. The abstract check and data extraction were performed by three persons independently. Narrow inclusion criteria for the meta-analysis were used. For instance, childhood schizophrenia cases were excluded due to inconsistent diagnosis in this period (McKenna et al. 1994), and motor milestones had to be assessed before the age of 13 to avoid reverse causation. However, some early motor developmental milestones (e.g. turning from back to tummy, crawling) were rarely explored and could not be meta-analysed. A test exploring asymmetry showed no publication biases, but due to low number of studies (<10), this test lacked power in our meta-analyses (Deeks et al. 2008). In summary, a lack of studies exploring some of the motor developmental milestones indicates a need to continue exploration of these phenomena. Overall, included studies had a good quality, but they had some limitations.

5. Conclusions

The results of this meta-analysis showed that schizophrenia has a small significant association with delayed walking, sitting, and standing unsupported. The findings support neurodevelopment theories of schizophrenia and the importance of monitoring the achievement of these early motor developmental milestones in childhood. It can contribute to earlier identification of individuals at risk of psychosis, but the predictive value of delayed motor developmental milestones on a population level is relatively small.

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.schres.2017.01.029.

Conflict of interest

None.

Contributors

NH and SF performed the databases search. AF and II helped with abstract check. SF collected and analysed the data and constructed the draft manuscript. HKH, NH, AF, II, TH, GMK, PBJ, KM and JM assisted with writing and editing of manuscript. All authors contributed to and have approved the final manuscript.

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References

Biringen, Z., Emde, R.N., Campos, J.J., Appelbaum, M.I., 1995. Affective reorganization in the infant, the mother, and the dyad: the role of upright locomotion and its timing. Child Dev. 66 (2), 499–514.

Borenstein, M., Hedges, L.V., Higgins, J.P., Rothstein, H.R., 2010. A basic introduction to fixed-effect and random-effects models for meta-analysis. Res. Synth. Methods 1 (2), 97–111.

Burton, B.K., Hjorthoj, C., Jepsen, J.R., Thorup, A., Nordentoft, M., Plessen, K.J., 2016. Research review: do motor deficits during development represent an endophenotype for schizophrenia? A meta-analysis. J. Child Psychol. Psychiatry 57 (4), 446–456.

Campos, J.J., Anderson, D.I., Barbu-Roth, M.A., Hubbard, E.M., Hertenstein, M.J., Witherington, D., 2000. Travel broadens the mind. Infancy 1 (2), 149–219.

Cannon, M., Jones, P., Huttunen, M.O., Tanskanen, A., Murray, R.M., 1999a. Motor coordination deficits as predictors of schizophrenia among Finnish school children. Hum. Psychopharmacol. Clin. Exp. 14 (7), 491–497.

Cannon, T.D., Rosso, I.M., Bearden, C.E., Sanchez, L.E., Hadley, T., 1999b. A prospective cohort study of neurodevelopmental processes in the genesis and epigenesis of schizophrenia. Dev. Psychopathol. 11 (3), 467–485.

Cannon, M., Caspi, A., Moffitt, T.E., Harrington, H., Taylor, A., Murray, R.M., Poulton, R., 2002. Evidence for early-childhood, pan-developmental impairment specific to schizophreniform disorder: results from a longitudinal birth cohort. Arch. Gen. Psychiatry 59 (5), 449–456.

Castle, D.J., Murray, R.M., 1991. The neurodevelopmental basis of sex differences in schizophrenia. Psychol. Med. 21 (3), 565–575.

Chen, L.C., Metcalfe, J.S., Jeka, J.J., Clark, J.E., 2007. Two steps forward and one back: learning to walk affects infants' sitting posture. Infant Behav. Dev. 30 (1), 16–25.

Clarke, M.C., Tanskanen, A., Huttunen, M., Leon, D.A., Murray, R.M., Jones, P.B., Cannon, M., 2011. Increased risk of schizophrenia from additive interaction between infant motor developmental delay and obstetric complications: evidence from a population-based longitudinal study. Am. J. Psychiatry 168 (12), 1295–1302.

Clearfield, M.W., 2011. Learning to walk changes infants' social interactions. Infant Behav. Dev. 34 (1), 15–25.

Cohen, J., 1992. A power primer. Psychol. Bull. 112 (1), 155–159.

Corbetta, D., Bojczyk, K.E., 2002. Infants return to two-handed reaching when they are learning to walk. J. Mot. Behav. 34 (1), 83–95.

Crow, T.J., Done, D.J., Sacker, A., 1995. Childhood precursors of psychosis as clues to its evolutionary origins. Eur. Arch. Psychiatry Clin. Neurosci. 245 (2), 61–69.

Deeks, J.J., Higgins, J., Altman, D.G., 2008. Analysing Data and Undertaking Meta-analyses. Cochrane Handbook for Systematic Reviews of Interventions: Cohrane Book Series pp. 243–396.

Diamond, A., 2000. Close interrelation of motor development and cognitive development and of the cerebellum and prefrontal cortex. Child Dev. 71 (1), 44–56.

Dickson, H., Laurens, K.R., Cullen, A.E., Hodgins, S., 2012. Meta-analyses of cognitive and motor function in youth aged 16 years and younger who subsequently develop schizophrenia. Psychol. Med. 42 (4), 743–755.

Downs, S.H., Black, N., 1998. The feasibility of creating a checklist for the assessment of the methodological quality both of randomised and non-randomised studies of health care interventions. J. Epidemiol. Community Health 52 (6), 377–384.

Egger, M., Davey Smith, G., Schneider, M., Minder, C., 1997. Bias in meta-analysis detected by a simple, graphical test. BMJ 315 (7109), 629–634.

Field, A.P., Gillett, R., 2010. How to do a meta-analysis. Br. J. Math. Stat. Psychol. 63 (Pt 3), 665–694.

Fish, B., 1957. The detection of schizophrenia in infancy; a preliminary report. J. Nerv. Ment. Dis. 125 (1), 1–24.

Hedges, L., Olkin, I., 1985. The Power of Statistical Tests in Meta-analysis.

Helling, I., Ohman, A., Hultman, C.M., 2003. School achievements and schizophrenia: a case-control study. Acta Psychiatr. Scand. 108 (5), 381–386.

Higgins, J.P., Thompson, S.G., Deeks, J.J., Altman, D.G., 2003. Measuring inconsistency in meta-analyses. BMJ 327 (7414), 557–560.

Isohanni, M., Jones, P.B., Moilanen, K., Rantakallio, P., Veijola, J., Oja, H., Koiranen, M., Jokelainen, J., Croudace, T., Jarvelin, M., 2001. Early developmental milestones in adult schizophrenia and other psychoses. A 31-year follow-up of the Northern Finland 1966 Birth Cohort. Schizophr. Res. 52 (1–2), 1–19.

Isohanni, M., Murray, G.K., Jokelainen, J., Croudace, T., Jones, P.B., 2004. The persistence of developmental markers in childhood and adolescence and risk for schizophrenic psychoses in adult life. A 34-year follow-up of the Northern Finland 1966 birth cohort. Schizophr. Res. 71 (2–3), 213–225.

Jones, P.B., Tarrant, C.J., 1999. Specificity of developmental precursors to schizophrenia and affective disorders. Schizophr. Res. 39 (2), 121–125 (discussion 161).

Jones, P., Rodgers, B., Murray, R., Marmot, M., 1994. Child development risk factors for adult schizophrenia in the British 1946 birth cohort. Lancet 344 (8934), 1398–1402.

Keskinen, E., Marttila, A., Marttila, R., Jones, P.B., Murray, G.K., Moilanen, K., Koivumaa-Honkanen, H., Maki, P., Isohanni, M., Jaaskelainen, E., Miettunen, J., 2015. Interaction between parental psychosis and early motor development and the risk of schizophrenia in a general population birth cohort. Eur. Psychiatry 30 (6), 719–727.

Khandaker, G.M., Barnett, J.H., White, I.R., Jones, P.B., 2011. A quantitative meta-analysis of population-based studies of premorbid intelligence and schizophrenia. Schizophr. Res. 132 (2–3), 220–227.

Maynard, T.M., Sikich, L., Lieberman, J.A., LaMantia, A.S., 2001. Neural development, cell-cell signaling, and the "two-hit": hypothesis of schizophrenia. Schizophr. Bull. 27 (3), 457–476.

McKenna, K., Gordon, C.T., Lenane, M., Kaysen, D., Fahey, K., Rapoport, J.L., 1994. Looking for childhood-onset schizophrenia: the first 71 cases screened. J. Am. Acad. Child Adolesc. Psychiatry 33 (5), 636–644.

Miettunen, J., 2011. Use of register data for psychiatric epidemiology in the Nordic countries. In: Tsuang, M., Tohen, M., Jones, P.B. (Eds.), Textbook in Psychiatric Epidemiology. John Wiley & Sons, Ltd, pp. 117–131.

Murray, R.M., Lewis, S.W., 1987. Is schizophrenia a neurodevelopmental disorder? BMJ 295 (6600), 681–682.

Murray, G.K., Veijola, J., Moilanen, K., Miettunen, J., Glahn, D.C., Cannon, T.D., Jones, P.B., Isohanni, M., 2006. Infant motor development is associated with adult cognitive categorisation in a longitudinal birth cohort study. J. Child Psychol. Psychiatry 47 (1), 25–29.

Piek, J.P., Dawson, L., Smith, L.M., Gasson, N., 2008. The role of early fine and gross motor development on later motor and cognitive ability. Hum. Mov. Sci. 27 (5), 668–681.

Rosso, I.M., Bearden, C.E., Hollister, J.M., Gasperoni, T.L., Sanchez, L.E., Hadley, T., Cannon, T.D., 2000. Childhood neuromotor dysfunction in schizophrenia patients and their unaffected siblings: a prospective cohort study. Schizophr. Bull. 26 (2), 367–378.

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Sanderson, S., Tatt, I.D., Higgins, J.P., 2007. Tools for assessing quality and susceptibility to bias in observational studies in epidemiology: a systematic review and annotated bibliography. Int. J. Epidemiol. 36 (3), 666–676.

Schiffman, J., Walker, E., Ekstrom, M., Schulsinger, F., Sorensen, H., Mednick, S., 2004. Childhood videotaped social and neuromotor precursors of schizophrenia: a prospective investigation. Am. J. Psychiatry 161 (11), 2021–2027.

Schiffman, J., Sorensen, H.J., Maeda, J., Mortensen, E.L., Victoroff, J., Hayashi, K., Michelsen, N.M., Ekstrom, M., Mednick, S., 2009. Childhood motor coordination and adult schizophrenia spectrum disorders. Am. J. Psychiatry 166 (9), 1041–1047.

Sorensen, H.J., Mortensen, E.L., Schiffman, J., Reinisch, J.M., Maeda, J., Mednick, S.A., 2010. Early developmental milestones and risk of schizophrenia: a 45-year follow-up of the Copenhagen Perinatal Cohort. Schizophr. Res. 118 (1–3), 41–47.

Taanila, A., Murray, G.K., Jokelainen, J., Isohanni, M., Rantakallio, P., 2005. Infant developmental milestones: a 31-year follow-up. Dev. Med. Child Neurol. 47 (9), 581–586.

Walker, E.F., Savoie, T., Davis, D., 1994. Neuromotor precursors of schizophrenia. Schizophr. Bull. 20 (3), 441–451.

Weinberger, D.R., 1987. Implications of normal brain development for the pathogenesis of schizophrenia. Arch. Gen. Psychiatry 44 (7), 660–669.

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