Early childhood motor skills and later neurodevelopmental, cognitive, and psychiatric outcomes : genetic and phenotypic associations and the potential for digital phenotyping

Early Childhood Motor Skills and Later Neurodevelopmental, Cognitive, and Psychiatric Outcomes: Genetic and Phenotypic Associations and the Potential for Digital Phenotyping

Aislinn Bowler

Birkbeck, University of London

Submitted for the Degree of Doctor of Philosophy in

Psychology, December 2023

Abstract

Evidence suggests that the first years after birth are important for later development. For example, early motor skills are associated with autism, ADHD, schizophrenia, and multiple cognitive outcomes. However, there are several challenges in measuring these early motor skills with longitudinal designs and with the required valid measures. It is also unclear if there are associations with later outcomes for fine motor skills in particular.

The thesis investigated the associations between early motor skills and later outcomes, including neurodevelopmental conditions, psychiatric disorders and traits, and cognition. It aimed to overcome some of the challenges of this field through a range of approaches. Chapter 2 presents a digital phenotyping smartphone app prototype for tracking early motor development. Chapter 3 will present a systematic review and meta-analyses of existing data on motor milestones and motor assessments in infancy and their associations with later diagnoses of neurodevelopmental conditions. Chapter 4 will describe the construction of a fine motor score using data from the longitudinal study, the Twin Early Development Study (TEDS). The chapter will then present a longitudinal multivariate regression analysis between the fine motor composite score and later neurodevelopmental, psychiatric, and cognitive traits from 7-16 years. Finally, Chapter 5 will present polygenic score analyses between the fine motor score and polygenic scores for neurodevelopmental, psychiatric, and cognitive phenotypes.

This thesis introduces research and potential methods to overcome measurement issues in an under-researched area. The thesis presents evidence for associations of delayed gross motor milestones across and between neurodevelopmental conditions. Furthermore, phenotypic and genetic associations between early fine motor skills and later neurodevelopmental, psychiatric, and cognitive traits up to age 16 are described. The research findings have implications for considering early motor skills as part of the pathway to later outcomes and for supporting the investigation of the mechanisms involved in these associations.

Acknowledgements

Firstly, I would like to thank my primary supervisor, Professor Angelica Ronald, for her support and mentorship, and my secondary supervisor, Professor Pasco Fearon, who provided guidance throughout. I would also like to thank all the co-authors of the associated publications, particularly Dr Tomoki Arichi, for his valuable clinical insights and for not giving up on the never-ending search for the systematic review. Lastly, I would like to thank Kumar Jacob and the team at Mindwave Ventures for supporting me during my placement and including me in the team.

This PhD was funded by the Medical Research Council. A significant amount of data came from the Twins Early Development Study (TEDS) and the BASIS-STAARS studies, also funded by the Medical Research Council. I thank the families for their significant contribution to TEDS and BASIS-STAARS.

This PhD wouldn't have been possible without the consistent and ongoing support from my mum and dad, Jane and Keith, who have always been encouraging. I'd also like to thank my mum and dad and my partner's parents, Pete and Paula, for their support with childcare, which has made the PhD doable.

Furthermore, I would like to thank Mamma Swim CIC and its members for the benefits of regular cold-water swimming during my maternity leave, mid-PhD, and once I was back at work.

I would like to extend my biggest thanks to my partner, Joe, who has always supported me and pushed me when I needed it. I would like to dedicate my PhD to our wonderful daughter, Ada, who is an inspiration for my research.

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Supplemental Data

Supplemental Data 1 and 2 can be found online at https://docs.google.com/spreadsheets/d/1wgCZcHq8fuhbJ59iQeTI7T1wZpPRlxc0D84ehbJLTPo/edit?usp=sharing

1 Introduction

This chapter will briefly introduce research on early development, specifically on early brain development and genetic research of early development, both generally and in relation to early motor skills. It will then introduce some examples of findings on infant motor and language milestones. Next, it will provide examples of how motor skills are measured, including standardised measures, motor milestone measurements, and specific motor measures. This chapter will then address relevant research into the association between early motor development and cognition and neurodevelopmental and psychiatric traits and disorders. Relevant findings that distinguish between fine and gross motor skills will then be covered. The primary methodologies used in the thesis will be presented next, which include app prototype design, meta-analysis, constructing a fine motor measure from existing large-scale longitudinal prospective cognitive data, and polygenic scores. Finally, this chapter will summarise the information presented in this introduction and give the aims of this thesis.

1.1 Early development

1.1.1 Early brain development

Grey matter increases sharply in the first year by 149% (Knickmeyer et al., 2008). This period is also marked by substantial brain plasticity (Stiles et al., 2005). Further, there are significant functional changes in the localisation of activation for multiple cognitive processes during this period (M. H. Johnson, 2001). As a result of this, neglect or trauma during this period leads to significant developmental impairments or delays (Nelson et al., 2019; Rutter, 1998), and there are "critical periods" for the achievement of motor and language milestones (Nelson et al., 2019).

1.1.2 Early motor network development

Evidence suggests that motor networks in the brain may involve distinct neurodevelopmental processes in infancy compared to other domains. Infant resting-state functional magnetic resonance imaging studies reveal unique motor trajectories compared to other cognitive networks. Firstly, the motor network has been found to reach functional specialisation prenatally, whereas other areas

continue in long-range functional synchronisation postnatally (M. Cao et al., 2017; Gao et al., 2015). Further, the motor network has a unique "V" shaped (decrease then increase) relationship of connections with other networks over the first two years, whereas language and visual areas increased their connections during this time (Yin et al., 2019). Considering also that motor skills develop considerably over the first two years, this suggests motor skills are heavily reliant on a large number of connections with other cognitive brain regions (Diamond, 2000). This research suggests that the patterning and timing of motor skill acquisition in the first two years are important indicators of neurodevelopmental processes.

1.1.3 Genetics of Early Development

A small proportion of behavioural genetics research focuses on early development (Austerberry et al., 2022). The majority of research that has been conducted is twin research of infant traits. A meta-analysis of 106 infant twin studies reported pooled heritability and environmental estimates for ten categories of infant functioning, disability, and health: sleep functions, attention functions, psychomotor functions, emotional functions, basic cognitive functions, mental functions of language, growth maintenance, basic interpersonal interactions, complex interpersonal interactions, and family relationships. Psychomotor functions (which included phenotypes such as activity level, fine motor skills, and sitting without support) were the most heritable psychologically relevant domain in infancy (pooled h^2, 0.59). In comparison, language skills had the highest shared environment estimate (pooled h^2, 0.59) and a nonsignificant heritability pooled estimate.

1.1.4 Genetics of early motor development

There is relatively little genetic research into early motor skills. While there are genome-wide association studies (GWAS) of later motor phenotypes such as motor coordination (balance, manual dexterity, and ball skills) at 7 years, which did not find any genome-wide significant single nucleotide polymorphisms (Mountford et al., 2021), there are not any currently published GWAS of infant motor development. However, a twin study investigating a trait relating to early motor skills revealed significant heritability of drawing skills at 4 years (h^2= 0.29), which was as high as the heritability for

intelligence (Arden et al., 2014). Consistently, as mentioned in section 1.1.3, psychomotor functions are highly heritable (pooled h^2, 0.59, Austerberry et al., 2022). Further, as discussed in section 1.5.2, there is some emerging evidence for polygenic scores of later traits/conditions to be associated with motor development (Askeland et al., 2022; Hannigan et al., 2021; Serdarevic et al., 2020). These studies support the notion that fine motor skills are highly heritable and indicate the opportunity for investigations into joint genetic underpinnings of fine motor skills and traits seen later in development.

1.2 Infant motor and language milestones

1.2.1 Milestone acquisition

The most important milestones children develop are typically achieved in the first two years after birth. These milestones are most predominantly related to either language or motor skills. Motor milestones include walking, a gross motor skill that is typically achieved at around 1 year (Onis, 2006, but see section 1.2.2) and the pincer grip, a fine motor skill that is typically achieved before the age of 1 (Bedford et al., 2016). Language milestones consist of a pre-linguistic period from birth to, on average, around one year, followed by an infant uttering their first words, an increase in vocabulary, and then language complexity (Conti-Ramsden & Durkin, 2012).

Some evidence suggests motor and language milestones are related. The most prominent example is for walking and expressive language skills. Walking allows for broader access to the world, the ability to hold objects while moving, and more accessible eye contact and communication with caregivers. Consequentially, evidence suggests associations between the age at onset of walking and language and cognitive development (Flensborg-Madsen & Mortensen, 2018; Walle, 2016). However, other studies have found no association between walking and language (Moore et al., 2019). Furthermore, those with high liability for autism, but not those with low liability, had better social communication skills if they were walking compared to not walking, regardless of age (Bradshaw et al., 2018). It is thus unclear if associations exist between age at onset of walking and later language and cognitive outcomes and if the benefits of walking vary by neurodevelopmental profiles.

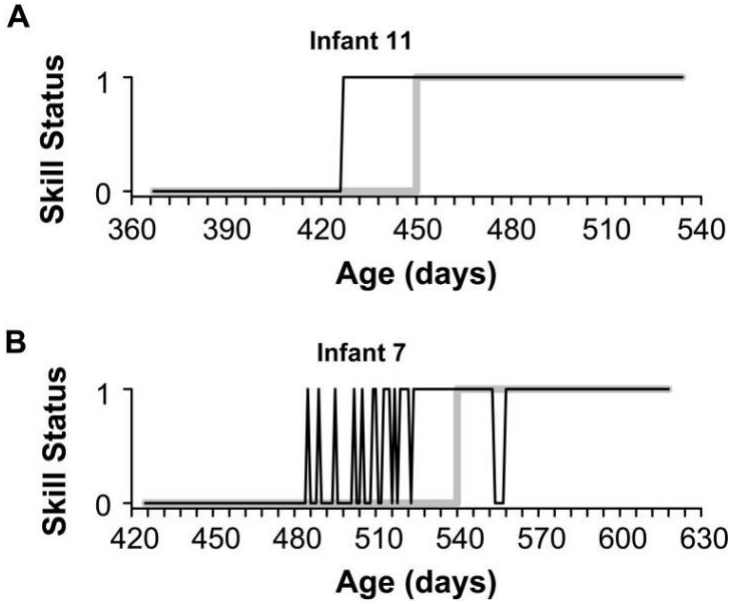
1.2.2 Variability in infant milestone acquisition

Typical development of motor milestones includes significant variability. A large-scale study by the World Health Organisation (WHO) suggests substantial individual differences in the age at which a milestone is achieved. For example, the range of ages of typical walking alone was between 8.2 and 17.6 months (Onis, 2006), suggesting large inter-individual variability.

Variability can also be observed in the skill acquisition process of becoming mature in a motor skill, or the "endpoint", both in the skill acquisition process and what the endpoint looks like (Adolph et al., 2018). There are very important differences seen individually and across infants and cultures due to different cultural norms. Further, within-infant variability is frequently observed across infant milestones, e.g. early crawling but late walking (Adolph, 2015).

In a study aimed at exploring how to measure developmental change optimally, Adolph et al. (2008) conducted a longitudinal study of 32 infants during their first 18 months where variability in transitions between motor milestone data was sampled using home checklist diaries with lists of milestones that could be ticked off each day. Adolph et al. found a substantial reduction in the accuracy of the data when intervals were longer than seven days, with the shortest interval of 1 day being the most accurate. This effect can be seen in Figure 1.1, where the grey lines are what would be concluded from long-interval data collection, and the black lines are what would be concluded from data collected at daily intervals. This finding aligns with the dynamic systems theory, which suggests that motor development is heavily context-dependent, indicating that even when a new skill is acquired, new contexts will lead to variable and unstable skill use (Thelen & Smith, 1994). The dynamic systems theory additionally suggests infants reach the same "endpoints" but through very different dynamic processes (Thelen & Smith, 1994). By measuring at frequent intervals, an assessment of the variability of the skill acquisition can be attained—and allows the further investigation of how this variability is associated with atypical neurodevelopmental or psychiatric traits.

Figure 1.1 Figure from Adolph et al. (2008). Examples of developmental trajectories



*Not*e. Examples of developmental trajectories of standing in two infants.; (a) Abrupt "step-up" trajectory (b) Variable trajectory. Skills Status: 0, not standing; 1: standing. Figure from Figure 2 in Adolph et al. (2008)

1.3 Motor measurement

1.3.1 Standardised assessments

Parent questionnaires include the Ages and Stages Questionnaire (Squires et al., 1997). Health visitors and medical practitioners often use the Ages and Stages Questionnaire in the UK to assess a child's development and to screen for delay.

Clinical assessment of motor skills includes the Denver Developmental Screening Test (Frankenburg et al., 1992) and the Mullen Scales of Early Learning (MSEL, Mullen, 1995), which is used between 0-68 months and includes both gross motor and fine motor subdomains. Further assessments include the Movement Assessment Battery for Children (Henderson et al., 2007) with three subtests: manual dexterity, aiming and catching, and static and dynamic balance.

1.3.2 Motor milestones measurement

Many standardised motor assessments have questions about milestones integrated into the more comprehensive assessment. The Early Motor Questionnaire is a motor questionnaire completed by parents of infants under two and has three subscales: gross motor, fine motor, and perception-

action (Smith & Libertus, 2022). The questions relate to specific stages of milestones such as “take a few (wobbly) steps while holding on to you with one hand” and “walk 4 or 5 steps independently with arms raised”. There are also milestone age norms used, such as Touwen’s norms for fine and gross motor milestones (Touwen, 1976) and the World Health Organisation windows of achievement for gross motor milestones (Onis, 2006). Questionnaires have also been developed for personal use by researchers, such as Sumner et al.’s (2016) questionnaire, based on Brouwer et al.’s (2006) questionnaire.

1.3.3 Specific motor assessments

Motor skills can also be measured for specific skills, such as toe walking (Comings & Comings, 1987), gait (Esposito & Venuti, 2008), posture (Nickel et al., 2013), motor activity (P. Johnson et al., 2014) and reach-to-grasp movement (Sacrey et al., 2018). These methods provide detailed information about an individual’s motor skills in a specific domain. However, it can cause issues when compared to other studies because the methods used are often very different.

1.3.4 General concerns

Some researchers have also recorded whether parents report motor concerns or not (Sacrey et al., 2015) or if there are clinical concerns for their motor development (M. H. Johnson et al., 1992). This method is a very broad way of capturing motor impairments and may thus be more vulnerable to rater bias than systematic assessments. However, often, this is the only motor measure taken in a large longitudinal study.

1.3.5 Limitations in measurement

There are several issues in the measurement of motor skills in infancy. Firstly, a reliance on retrospective recall requires caregivers to remember specific dates and details of behaviour (Bradburn et al., 1987). Secondly, there is potentially some heterogeneity in definitions of milestones in research studies. For example, Corbetta and Bojczyk (2002) define the onset of walking as when “infants took their first unsupported steps.” Walle (2016) defines it as “the infant locomoting bipedally a distance of

10 feet without falling or needing assistance", and Ghassabian (2016) defines the onset as "at least five steps independently in an upright position with no contact with a person or object." This disparity might limit comparability across studies. It is, therefore, vital to develop measures of the age at which infants meet milestones. Thirdly, there is often a small number of assessments to cover early motor skills, which is inconsistent with the rapid rate of acquisition and variability of motor proficiency during this period (Adolph, 2015; Adolph et al., 2008, see section 1.2.2).

There's a lack of large-sample (N> 200) prospective designs using early motor measures in their designs. Further, many studies include early general cognitive and language measures. Some studies include a small amount of gross motor milestone questions, but not many include motor assessments in the early years. It is thus hard to understand the long-term associations between early motor skills and later development. In sum, this section shows that more consistency in research design, larger samples, and more diversity in participant samples are needed to understand the implications of early motor skills.

1.4 Motor development and cognition

This section will provide an overview of the evidence for or against the associations between childhood motor skills and cognitive and education outcomes.

There is consistent evidence for an association between fine motor development and later cognitive outcomes. One study found an association between fine motor tasks at 3 and 4 years and achievement scales (including letter-word identification, passage comprehension, and sound awareness) at 5 years, most strongly with a "design copy" fine motor task (Cameron et al., 2012). Further, a longitudinal study across multiple American cohorts found strong associations between fine motor skills measured through multiple tasks, including block building and drawing at 5 years, with later academic achievement up to age 10 (Grissmer et al., 2010). In later childhood, other studies have found an association between childhood fine motor skills and IQ at 7-13 years in a cross-sectional study (Klupp et al., 2021), and between fine motor skills and short-term memory, fluid intelligence, and visual processing at 4-16 years (van der Fels et al., 2015), and fine motor skills at 6 years and

academic performance between 6-12 years (Katagiri et al., 2021). In addition, a study found both infant gross and fine motor development are associated with childhood cognition and executive function (Wu et al., 2017). However, Piek et al. found that fine motor trajectories between four months and 4 years were not associated with later cognitive outcomes at 6-11 years (2008).

Limited evidence exists for associations between early motor skills and long-term educational outcomes into adolescence. There is some evidence for gross motor milestones, such as walking, to be associated with adult intelligence (Flensborg-Madsen & Mortensen, 2018). However, further investigation is required to understand if these associations extend to educational outcomes.

1.5 Early motor development and later neurodevelopmental conditions and psychiatric disorders

This section will provide an overview of the evidence for phenotypic and genetic associations between early motor development and later neurodevelopmental conditions and psychiatric disorders.

1.5.1 Phenotypic associations between early motor development and later neurodevelopmental conditions and psychiatric disorders

Atypical motor development in the first years of life could be an early marker for the later development of neurodevelopmental or psychiatric disorders. The research centres around fine or gross motor skills and will be summarised below.

1.5.1.1 Gross motor phenotypic associations

There is consistent evidence of a delay in gross motor skills associating with neurodevelopmental or psychiatric conditions. A meta-analysis investigating motor skills in first-degree relatives found evidence for impaired motor skills associating with schizophrenia (Burton et al., 2016). Consistently, infants who go on to gain a diagnosis of schizophrenia have significantly delayed gross motor milestones (Murray, Jones, et al., 2006). Delays in motor skills (as measured with the Denver Developmental Screening Test, (Frankenburg et al., 1992) are also significantly associated

with ADHD (Gurevitz et al., 2014). Further, atypical longitudinal trajectories of infant motor skills are also predictive of autism (Landa et al., 2012; Nishimura et al., 2019).

1.5.1.2 Fine motor phenotypic associations

Associations between fine motor skills have been explored in relation to general psychopathology traits – questionnaire-assessed fine motor skills at age 6 years were associated with psychopathology at 11 years, including peer problems, emotional symptoms, and conduct problems (Katagiri et al., 2021).

Research for neurodevelopmental conditions has also revealed significant associations with fine motor skills. A meta-analysis found evidence of impaired early fine motor skills in individuals with a familial history of schizophrenia (Burton et al., 2016).

Similarly, there is consistent evidence that childhood impairments in fine motor skills may be significantly associated with the neurodevelopmental condition attention deficit hyperactivity disorder (ADHD, Kaiser et al., 2015). However, based on a lack of evidence, a recent systematic review concluded that it remains unclear if early childhood fine motor impairments are seen in those who later develop ADHD (Havmoeller et al., 2019). Therefore, further work is necessary to understand if fine motor skills are an early marker of ADHD.

Associations between early fine motor skills are seen in the first two years after birth. Atypical longitudinal trajectories of early fine motor skills are also associated with autism (B. Choi et al., 2018), in addition to alterations in trajectories that combine early fine motor, gross motor, and language skills (Landa et al., 2012; Nishimura et al., 2019).

Taken together, further work is necessary to understand the associations between impaired early motor skills and areas of psychopathology across the lifespan. Furthermore, some genetic influences are shared across neurodevelopmental and psychiatric conditions (Guilmatre et al., 2009; Ronald, Simonoff, et al., 2008; Rujescu et al., 2009; Stergiakouli et al., 2017). It is, therefore, justified to explore whether there is an association between early fine motor impairments and overall composite scores for all neurodevelopmental and psychiatric conditions and traits.

1.5.2 Genetic associations between early motor development and later neurodevelopmental conditions and psychiatric disorders

A prospective population cohort study has shown that genetic liability for autism is associated with very early neuromotor measures (9–20 weeks, Serdarevic et al., 2020), providing preliminary evidence for a shared genetic risk between early infancy motor development and autism. Further, a study considering overall (fine and gross) motor skills at 3 years did not find consistent associations across PGs p-thresholds for autism at 3 years (and also at 6 months and 18 months, (Askeland et al., 2022). However, Askeland et al. did not find associations for the ADHD or schizophrenia PGS.

1.5.2.1 Gross motor genetic associations

Research into genetic associations between gross motor skills and neurodevelopmental or psychiatric conditions centres around the age at onset of walking. The PGS for autism was associated with later walking, whereas the PGS for ADHD is associated with earlier walking (Hannigan et al., 2021). In support of this finding, superior gross motor skills (measured by the Denver Developmental Screening Test, Dick et al., 1973) at 18 months, and more activity (measured by the Carey Temperament Scale, Carey & McDevitt, 1978), were associated with the PGS ADHD (Riglin et al., 2022). No associations were found for the autism or schizophrenia PGSs. Gross motor skills may thus be an important indicator of later neurodevelopment.

1.5.2.2 Fine motor genetic associations

I am only aware of one study that has investigated associations between neurodevelopmental or psychiatric PGS and early fine motor skills specifically, which found that fine motor skills at 18 months were not associated with the PGS for autism, schizophrenia, or ADHD (Riglin et al., 2022). This study used parent-reported fine motor milestone achievements (Denver Developmental Screening Test, (Dick et al., 1973), which relies on parent recall. Alternatively, these skills can be captured by asking children to complete fine motor tasks as they develop them.

1.6 Distinction between fine and gross motor skills

Fine motor skills are relatively understudied in comparison to gross motor skills. This may be related to the skills being less overt in early development, for example, the development of the pincer grip (fine motor) compared to a child's first steps (gross motor). Furthermore, they are sometimes measured together in a single measure, such as standardised measures of motor skills. This method, therefore, limits the use of the results from published studies, as there is no separation between fine and gross motor domains.

There are important differences between fine and gross motor skills in their association with cognitive outcomes, neurodevelopmental conditions, and psychiatric traits. For example, as described in sections 1.5.2.1 and 1.5.2.2, but briefly here, in PGS analyses, the autism PGS was associated with later walking (Hannigan et al., 2021) but not fine motor skills at 18 months (Riglin et al., 2022). Further, a rare study comparing the differing longitudinal associations of fine or gross motor skills and later cognitive and broad psychosocial traits found differing associations across fine and gross motor skills (Katagiri et al., 2021). Teacher-assessed gross motor skills at 6 years more strongly predicted peer and emotional problems, whereas fine, but not gross, motor skills predicted conduct problems. Fine and gross motor skills associate with later academic achievement across childhood up to 12 years, with fine motor skills having stronger associations. A systematic review comparing evidence for childhood gross and fine motor skills and their associations with different subdomains of cognition found good evidence for associations between fine motor skills and visual processing and other domains, but little or weak evidence for gross motor skills (van der Fels et al., 2015). However, the evidence is mixed as to whether these associations can also be found in infancy and preschool years when significant neurodevelopment occurs.

1.7 Methodologies used in the thesis

This section will summarise the methodologies used in the thesis and include selected relevant literature to give a background to the

1.7.1 App measurement

Collecting data with an app has many advantages; it is possible to create flexible designs and the ability for frequent monitoring. Therefore, it is possible to collect data over long and short periods simultaneously. For long-time measurements, individuals can be asked to use the app for an extended period, with regular reminders to answer the questions on the app. For short time periods of hours or days, a technique called ecological momentary assessment (EMA, see Shiffman et al., 2008) can be used. EMA involves the daily collection of a small amount of data, commonly with just one or two questions at regular intervals. This technique allows for the collection of data that can help understand patterns in behaviour or mood which change daily or weekly. The combination of long-term and short-term methods, called "burst questionnaires" can also be used. This method involves collecting most data at longer intervals, but data for shorter intervals are collected at specific periods of interest, such as when the infant starts walking. This innovative methodology can capture developmental dynamics and set a trend in novel digital tools for data collection.

App-based assessments, with their engagement capabilities, can also improve participation in terms of long-term retention and greater diversity of participants. The home environment impacts motor development (Barnett, 2019; Ronfani et al., 2015). The high take-up of smartphones by parents (84% of over 16s use smartphones in the UK, (*Internet Access – Households and Individuals, Great Britain - Office for National Statistics*, 2023) means that an app-based tool would have the potential of a broad reach in terms of usage.

1.7.2 Meta-analyses

Sample sizes in neurodevelopmental disorder experimental psychology research are often relatively small due to the challenges of recruiting these participants. Further, there is a lack of large-scale longitudinal prospective research that requires significant funding, time, and resources. Therefore, a meta-analysis can be conducted to gain a reliable understanding of behaviour in these groups, combining data across cohorts to understand if there is sufficient evidence for an effect.

Studies often have multiple subgroups for different neurodevelopmental diagnoses or clinical sub-groups). There are often also multiple studies using the same cohort data. To account for these

dependencies of effect sizes to be meta-analyses, 3-level random effects meta-analyses can be used to account for the relatedness of effect sizes within samples (Assink & Wibbelink, 2016).

1.7.3 Constructing a fine motor measure from existing large-scale longitudinal prospective studies

A possible solution to the lack of early fine motor data is to create a motor measure using existing data from early childhood. Cognitive assessments are common in assessments in longitudinal designs and may often have measures indirectly relating to motor skills. To take advantage of this, Chapter 4 covers the creation of a novel fine motor composite score from a validated preschool cognitive assessment in a large longitudinal cohort study.

1.7.4 Polygenic scores

Most neurodevelopmental conditions and psychiatric disorders are influenced by multiple common genetic variants of small effect size (Smoller et al., 2019). PGSs are calculated by summing the genetic risk from common single-nucleotide polymorphisms (SNPs) derived from genome-wide association studies (GWAS), weighted by their effect sizes (S. W. Choi et al., 2018). Polygenic scores sum the effects of additive common genetic variants. Due to this, large participant samples are required to gain enough statistical power for a discovery GWAS from which a PGS is derived. Further, polygenic scores are reliant on how the phenotype is measured (such as clinical diagnosis or questionnaire items).

PGSs are helpful for comparing the genetic association across traits that do not have to be measured in the same sample. Further, the strength of PGSs can be increased using multiple PGSs in a single multivariate model (Krapohl et al., 2018). A meta-analysis of ADHD PGS has found it to be significantly associated with ADHD diagnosis (Ronald et al 2021). However, the small effect sizes suggest that the PGS cannot currently be used clinically for individuals. Nonetheless, as sample sizes increase, PGSs may become clinically relevant in conjunction with other genetically informed (family history), biological, and behavioural assessments (Ronald, 2020).

1.8 Summary

This chapter has highlighted the importance of the first years after birth for later development and how early motor skills may be associated with later outcomes. For example, the association between early motor skills and autism, ADHD, schizophrenia, and multiple cognitive outcomes. It also emphasised the challenges in measuring these skills in sufficient sample sizes, longitudinal designs and with the required valid measures. The specific domain of fine motor skills is also relatively understudied. Furthermore, it has covered potential methods to overcome these challenges and understand the longitudinal associations between motor skills and later outcomes.

1.19 Research questions and the chronology of the thesis

This thesis has multiple overarching research questions, and the order of the chapters follows the order in which the work for the PhD was initiated. Below, I will describe the research questions, how I addressed them, and the order of the completed work.

The first research question was: *How can we design a new smartphone app that collects more reliable and valid infant motor data?* This was the first project of my PhD and will be addressed in Chapter 2, and includes an early prototype of a motor tracking app. I started my placement at Mindwave Ventures at the beginning of my PhD and worked on the app research for 1.5 years.

The second research question was: *What are the associations between early fine and gross motor skills and later neurodevelopmental conditions?* This will be addressed in Chapter 3, in a systematic review and meta-analyses, to understand the evidence that exists in the disparate literature. This work was initiated second and continued for the remainder of the PhD.

The third research question was: *What are the associations between early fine motor skills and later neurodevelopmental, psychiatric and cognitive outcomes across development?* This work included the creation of a fine motor composite score from a wider cognitive measure and a longitudinal phenotypic analysis in a longitudinal prospective cohort sample. This work was initiated after the systematic review and meta-analysis.

Finally, the fourth research question is: *Are there shared genetic pathways underpinning the associations between early fine motor skills and later neurodevelopmental, psychiatric and cognitive outcomes?* This question is addressed in Chapter 5 in single and multiple polygenic score models, which were run after the longitudinal phenotypic analysis, using the same fine motor composite score in the same longitudinal prospective cohort sample and the third research question.

1.20 Aims of the thesis

The thesis will aim to investigate the longitudinal associations between early motor skills and later outcomes, including neurodevelopmental conditions, psychiatric disorders and traits, and cognition. It aims to overcome some of the challenges in understanding a vital part of early development in multiple ways, proposing the use of a digital phenotyping smartphone app (Chapter 2), meta-analysing existing data (Chapter 3), constructing novel fine motor measures from a longitudinal perspective cohort and conducted longitudinal phenotypic analyses (Chapter 4), and conducting polygenetic score analyses (Chapter 5).

2. Designing a Digital Phenotyping Smartphone App to Capture Infant Motor Skills

2.1 Abstract

Current measurement of infant motor milestones in clinical practice and research relies on clinical assessment or parent-rated assessments or questionnaires. Two limitations of these methods are the small number of assessments over the infancy period, which is inconsistent with the rapid rate of acquisition of developmental milestones and the reliance on retrospective parental recall. An app allows more frequent and flexible assessments than traditional methods – capturing 'live' changes in children's motor development and the ability to upload videos and photos. This method could offer a detailed and reliable portrait of developmental milestones and variability within and across infants. To develop this idea during my iCASE industrial placement, I worked with the app development company Mindwave Ventures (an SMC, see https://mindwaveventures.com/) to develop a prototype for an app for parents to use that would capture their child's early motor development. This chapter will present a literature review of why a digital motor measurement app is needed, the design research and user testing I conducted, my final app prototype and wireframing.

2.2 Literature review

2.2.1 Variability in infant milestone acquisition

Variability in Infant Milestone Acquisition was addressed in the Introduction Chapter (Section 1.2.2). But briefly, the typical development of motor milestones includes significant inter-individual variability. A large-scale study by the World Health Organisation (WHO) suggests there are substantial individual differences in the age at which a milestone is achieved (Onis, 2006).

Variability can also be observed in the skill acquisition process of becoming mature in a motor skill, or the "endpoint", both in the process of skill acquisition itself and what the endpoint looks like (Adolph et al., 2018). Further, within-infant variability in milestone attainment is also frequently observed across infant milestones (Adolph, 2015). Dynamic systems theory suggests

infants will reach the same “endpoints” but through very different dynamic processes (Thelen & Smith, 1994). By measuring at frequent intervals, an assessment of the variability of the skill acquisition can be attained—and allows the further investigation of how this variability is associated with atypical neurodevelopmental or psychiatric traits.

2.2.2 Representative participant samples

The home environment is where infants will, in part, develop most of their motor skills. The impact of social deprivation on resources in the home and childcare environments has implications for their motor development. For example, in a prospective cohort study, more physical activity equipment in the home was significantly associated with fine motor skills at nine months and 3.5 years (Barnett, 2019). Further, the home environment mediates the effect of maternal IQ on motor development (Ronfani et al., 2015). Contextual differences in international averages for motor milestones achievement have also been found to reduce to nonsignificance once socioeconomic status (SES) is accounted for (Fink et al., 2019). These effects are notable because low SES groups are less likely to participate in lab-based studies (Bonevski et al., 2014), which has implications for generalisability and equity. Therefore, it is crucial to develop methods that engage individuals from diverse backgrounds to collect representative data on motor skills.

2.2.3 Engagement capabilities of smartphone apps

A prominent strength of smartphone app designs is that they do not require participants to travel to a laboratory for testing. The large majority of people in the UK have smartphones (*Internet Access – Households and Individuals, Great Britain - Office for National Statistics*, 2023) and regularly use apps in their daily lives. Smartphone app designs, therefore, remove some barriers to testing for individuals with limited time or low SES.

Some apps have also been designed with participant engagement in mind, with elements that are not oriented around collecting data but are for increasing the enjoyment and interest in the app, which means participants would be more likely to enter the required information. Missing data is common in smartphone app designs as many require frequent entries over a long time. Participants,

therefore, often miss entries either on purpose, because they forgot, or did not realise they had to input that entry (Heron et al., 2019). Many designs attempt to counteract these issues by adding reminders to add entries. For example, personalisation of the app where users can enter their own images or users being able to export and share progress or data to friends and family. Furthermore, "gamifying" apps extended this by including methods used in the gaming industry, such as winning points and goals that enhance user engagement (Bitrián et al., 2021; Sardi et al., 2017).

2.2.4 Smartphone app-based data collection

Over the last ten years, there has been a large growth in health and research apps in various fields. Below, I will review the significant methods used in these apps.

2.2.4.1 Diary methods

Using a digital diary to track behaviour or mood and emotions enables the efficient storage and tracking of changes over time. The capability of updating the diary as and when a change occurs adds flexibility to data collection designs. Diary methods are used across many health-based smartphone apps. For example, Flo, a period and fertility tracking app where an individual enters fertility and period symptoms into the app to track changes over time (*Flo Period & Ovulation Tracker*, 2023), has been found to improve knowledge of menstruation and pregnancy (Zhaunova et al., 2023), and Google Fit, an app to track health stats and physical activity (*Google Fit*, 2023). Tracking is the most used and sought functionality in health apps, which gives users an "internal sense of control" over specific health issues (Grundy, 2022, p. 124)

2.2.4.2 Ecological momentary assessment

Ecological momentary assessment (EMA) involves the daily collection of a small amount of data, commonly with just one or two questions at regular intervals, and often initiated by a push notification sent to the home/lock screen of the smartphone. This technique allows for the collection of data that can help understand patterns in behaviour or mood that change daily or weekly (Shiffman

et al., 2008). EMA methods promise to enhance our understanding of the dynamic interactions between individuals and their environments (Shiffman et al., 2008). EMA methods in research have been in child and adolescent research for some time to understand time- and environment-relevant changes in psychological functioning, mainly in adolescents (Russell & Gajos, 2020). Research on younger children has investigated parent-child attachment (Bischoff et al., 2023), and infant posture changes (Franchak, 2019). Through questions sent to parents' phones at random times in the day across a week, Franchak (2019) found evidence for age and skill- (e.g. able to sit) related differences in the postures infants were held or placed in between held, supine, reclined, prone, sitting, or upright.

2.2.4.3 Burst designs

These designs provide the opportunity to have flexible timings of assessments. For example, when behaviour is recorded in the app, the app can then send participants a set of questions over a short period of time following this event before resuming the standard timing of assessments (Sliwinski, 2008). The method has been used frequently with adolescent research, for example, research looking at the effects of alcohol and smoking media where the "bursts" were initiated when the young person recorded that they had been exposed to relevant media. Questions about perceptions of drinking and smoking were then sent to the individual's phone. This "burst" methodology can also capture important points in a child's development. For example, the window of time for the transition between non-walking and walking which is associated with increased social and language development (West et al., 2019).

2.2.4.4 Machine learning motion tracking

Apps can allow participants to upload videos of their infants' movements and activity in varying environments, and machine learning motion tracking software is capable of coding infant motor behaviour from videos (van Schaik & Dominici, 2020). Further, the open-source machine learning programme OpenPose (Z. Cao et al., 2019) has been used to code infant neuromotor skills (Chambers et al., 2020) and infant motor strategies (Ossmy & Adolph, 2020). There is potential to

integrate these processes into a smartphone app for parents to upload videos of their child, which could then be coded for motor skills or activity rates.

2.2.5 Validation and evidence-based apps

Health and research-based apps require studies to assess their validity and reliability before they are widely used. These studies often require "gold-standard" comparison tools to compare the app data against. However, suppose no "gold-standard" tool exists, or the app measures the variable differently. In that case, it may be that the app is more ecologically valid due to users entering data when they are in their home environment rather than in a clinical setting. In these cases, correlations between the measures may not be high. Alternatively, apps could be compared against each other if a suitable app can be sought. Reliability must also be assessed by repeating the same measure over a short time, an assessment called test-retest reliability, to assess how well the two scores are associated. A Cronbach alpha (α) can be calculated, with acceptability reliability being an $\alpha > .70$.

2.2.6 Existing motor measurement app - The Kleine Weltentdecker App

During this project's research phase, it became apparent that an early development tracking app had been developed at Zurich University, the Kleine Weltentdecker ("young world explorers") App (Daum et al., 2022). This app collects cognitive, language and motor data through a parental-report app. The app also has engagement functions, including picture uploads and a calendar where parents can view milestones and enter family events.

In the Kleine Weltentdecker app, parents are prompted at intervals between a week and a month to respond if a child can currently complete a specific activity or is saying a specific word and, if so, to enter the day the child completed this or first spoke this word. The internal consistency (reliability) for motor assessments had at least acceptable reliability ($\alpha > .70$) except for fine motor skills between 12 and 18 months ($\alpha = .65$). In comparison, the reliability of the internal consistency questions was mostly low ($\alpha < .70$). The researchers also carried out construct validity analyses, which indicated that the motor and language scales were significantly associated with lab-based motor scales and age. In comparison, the cognitive scales did not show good construct validity. Finally, all scales

were assessed for criterion validity by testing the association with relevant demographic variables, including gestational age, sex, child age, and father and mother education. All scales had good criterion validity. The researchers found that users used the app for, on average, 4.32 months (range: 1-16 months).

These results, therefore, indicate that motor (and language) data can be reliably and validly collected using a smartphone app instead of in-lab measures. In contrast, cognitive measures may be more challenging to collect when not in person. This app, however, does not take advantage of more flexible "burst" data collection designs to gain more accurate motor data by replicating the variability of infant motor skills acquisition. Further, the app includes no functionality to enter milestones directly through a calendar or a video upload capability. Furthermore, the app could add more engagement capabilities to maintain users' engagement for longer than four months.

2.3 Industrial placement

I started my placement in January 2020 and initially worked in the Mindwave Ventures offices for one day a week. During this time, I met with different team members to discuss the processes of developing apps in healthcare and research areas. I gained a good understanding of the multiple steps involved in the design of an app and the patient/user research integrated into this. With support from my industrial supervisor, Kumar Jacob, and the operations and design team, I progressed the designs of a research app. Due to the COVID-19 lockdown, from March 2020, work was shifted to home working, where I learnt how companies could shift their working practices online. During this time, I could participate in more events, such as user testing and meetings for other apps being developed, as well as the all-staff meetings. These experiences gave me valuable insight into the company's multiple innovative projects. I also presented the app at this meeting and received feedback from the staff members. The dates of my placement can be found in Table S2.1 in the Appendix.

2.4. Planning and timeline

The planning and timeline of this project were influenced by the guidance of the project management and design teams at Mindwave Ventures and reviewing relevant literature.

The methodology for this app design was influenced by agile app design, which integrates user feedback into the design. Agile app design requires regular user feedback, which is quickly implemented into the app prototype (K. Wilson et al., 2018). An example of implementing this method for a research app is an app that was designed to test the cognitive skills of individuals with dementia across micro-longitudinal timescales (Fox et al., 2022). The app designers successfully implemented an iterative co-design process for designing the app to ensure the end-users (people with dementia) were able to easily use the app regularly, considering their specific needs. Fox et al. (2022) report the stages of the prototype designs and the feedback received from the user feedback sessions. A similar approach, although on a smaller scale, was implemented in this project.

Through research and/or user interviews or testing, user personas can be developed during the initial stages of app design, which ensures the app design meets the needs of the end-users of the app (Morton et al., 2020). User personas are then used to prioritise functions, ensuring the most important needs or preferences are addressed at the start of the app development process (Bachschmid - Formerly Beutter et al., 2022).

The following sections will describe the stages of app design I followed to create an early clickable prototype for an infant motor skills tracking app. The first step was researching existing user interfaces for m-health apps (section 2.5.1). Next, I describe the development of user personas, (section 2.5.2). Different logos were then designed for the app, which are presented in sections 2.5.3. The next stage was the development of an early prototype and user testing of this early prototype and the logos (2.6). The user personas, user testing, and a review of literature were then used to develop the parasitisation of functions. Next, I developed a prototype integrating the feedback from the user testing and the prioritisation of functions (2.8). Finally, the strengths and weaknesses of the app design is discussed in section 2.9.

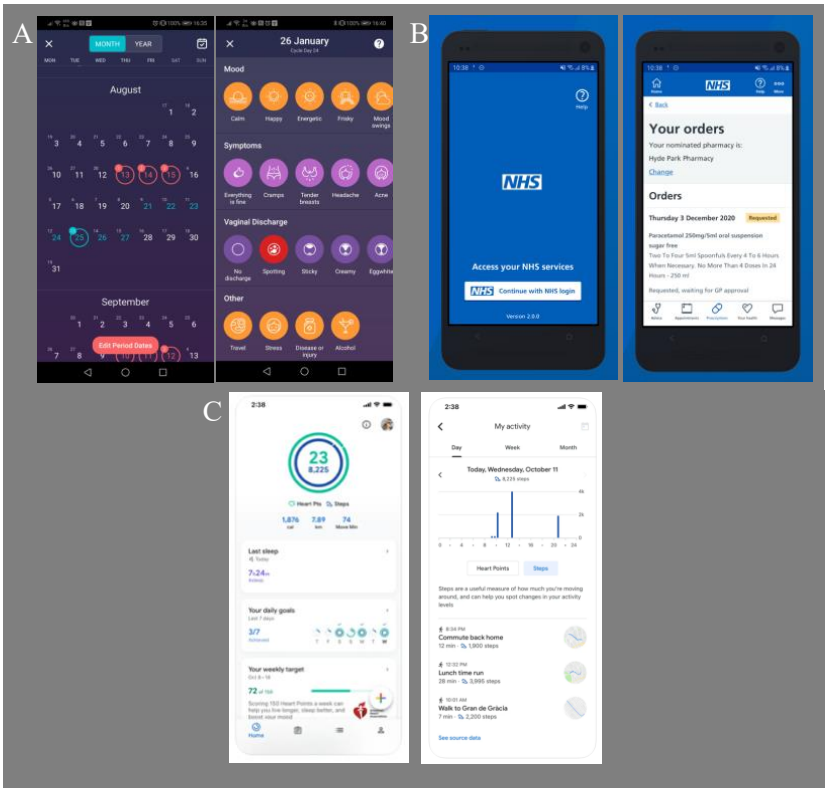
2.5 App design research

At the start of the app development phase, I undertook research on health apps to understand which user interface (UI) and user experience (UX) elements work well and which do not. The research was based on personal experiences or options and, with discussions with other app designers at Mindwave, developing user "personas" to understand the different goals and potential challenges across personas, and researched branding and logo design.

2.5.1 User interface research for health apps

Three health apps were selected as different examples of designs for health apps: The Google Fit health and activity tracking app, the NHS app, and the Flo period and fertility app (Figure 2.1). The positive and negative UX and UI elements in the apps are summarised in Table 2.1. These aspects were considered when designing the app (2.6) and considering the prioritisation of functions (2.7).

Figure 2.1. Examples of User Interfaces in Health Apps



Note. Examples of user interfaces from Health Apps: A, Flo Menstruation and Fertility App; B, NHS App; C, Google Fit App

Table 2.1 Examples of Health Apps

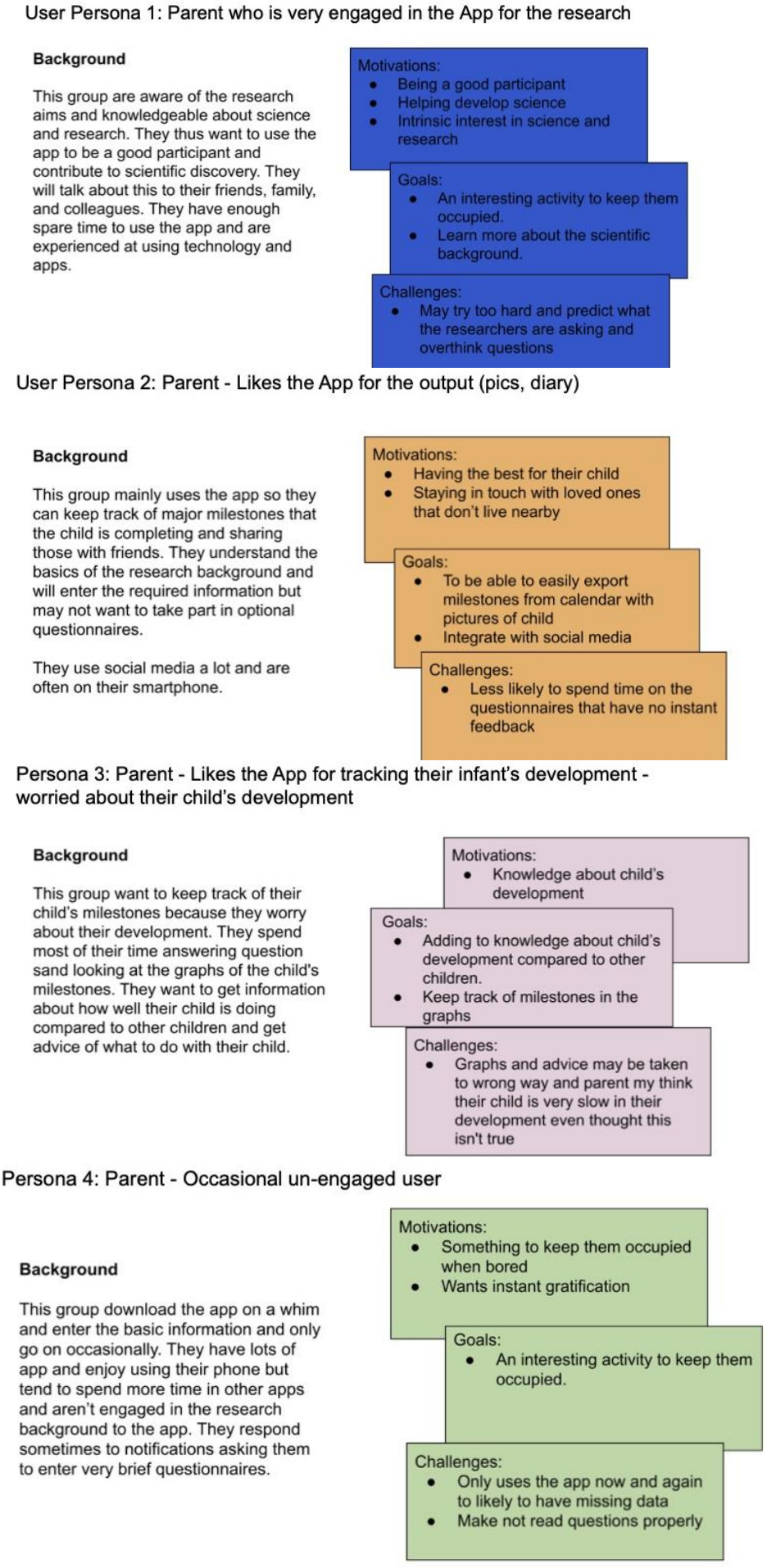
Positive	**Negatives**
Fingerprint login – NHS app	Longer time to load - NHS app
Taken straight to the important information – Flo and Google Fit	Confusing settings and output in the same Menu – Flo
Clear and visually appealing visuals which highlight the most essential information – cycle/mensuration/fertility – Flo	Not able to repeat entries such as physical activity over multiple days which made it time-consuming – Flo
Different "modes" switch the focus of the app - Flo	
Privacy – optional access code - Flo	
Simple graphics to easily add data - Flo	
Integrate other app's data – Flo	
Easy Access to simple reports/graphs – Google fit	

Note. Positive and negative aspects of the user interfaces

2.5.2 User personas

To understand the needs, motivations, and characteristics of the different users of the app, I devised four user personas for potential users. As a result of the purpose of the app and research, the main end-user of the app would be a parent/carer of an infant. Therefore, different variations of interest were devised to understand the challenges of engaging with end-users with different interests. The personas were developed from a literature review of similar apps already developed. Firstly, parent users of the Kleine Weltentdecker ("young world explorers") App (Daum et al., 2022), described in section 2.2.6, engaged well with using the app to track their infant's development, but parents were only engaged for a short time, 4.32 months on average. The design of the research app is for parents to report on their child's early childhood, so four months wouldn't capture sufficient intra-individual model longitudinal change. Research apps are thus potentially not capturing the end-user's attention for long-term engagements. Diary-style health tracking in gives users an "internal sense of control" over specific health issues (Grundy, 2022, p. 124), therefore parents may engage more if this is encouraged in a research app. Furthermore, a study assessing the engagement of the end users of an

Figure 2.2 User personas



app measuring general movements of infants through videos, Baby Moves, indicated that parents were more engaged in using the app when they had health concerns for their child, and less when they had limited spare time (Kwong et al., 2019; Spittle et al., 2016). These are important aspects that were considered when creating the user personas. In Figure 2.2, each user persona is introduced with their background, motivation, goals, and the challenges for engaging with or meeting their goals from the app.

2.5.3 Logo research

After meetings with the design team at Mindwave Ventures, where I introduced the early stages of my app's designs and the app's purpose, the design team and I came up with five logo and name options, which can be found in Figure 2.3. These options were used for later user testing.

Figure 2.3 Logo options for the motor tracking app

Note. Logo and name options developed with the Mindwave Ventures design team and used for user testing

2.6. Early Prototype and user testing

2.6.1 Early app prototype

An early prototype was developed for user testing.

2.6.2 User-testing

In this section, I describe the user testing of the app prototype (Figure 2.4). User testing was conducted in informal sessions, as is common in smartphone app development.

Figure 2.4 Early prototype of a motor tracking app

Note. Example screens from an early prototype that included basic wireframing: buttons are linked to successive screens as they would be in a fully functioning app; A, Home screen; B, Main milestones screen where users select motor modality of the milestone they want to select; C, A selection of potential milestones (gross and fine); D, the user has selected "crawling" and can mark as complete or ask for more information; E, more information about "crawling"; F, the user enters the date of the milestone completing into the calendar

2.6.2.1 Ethical approval

User testing was approved by the Birkbeck Research Ethics Committee (No: 2021001).

2.6.2.2 Methodology

Two methods were used for user testing of the early app prototype. The profiles of the user testing were targeted at the primary users, parents/carers (see section 2.5.2).

Firstly, as a joint public engagement and user-testing exercise, I presented at the "Coffee Morning" event at the Birkbeck BabyLab. The event involved discussing research with parents and carers associated with the centre (N=4), a grandparent (N=1), and other researchers in the field. I gave a brief presentation at the online event and then presented a preview of the app's prototype. I then discussed the app design, the logo/name (Figure 2.3), and the research project with the attendees. I then asked for feedback and answered any questions.

Second, one-on-one informal "friends and family" user testing of the app prototype was conducted with N=8 individuals. All individuals were parents or carers of children. At this stage, the prototype was partly clickable, so parts of the functionality could be previewed. Here, I sent users a link through Adobe XD so they could load the app prototype on their devices and use the clickable links as it would be viewed with a fully functioning app. The users also viewed the different logo and name options. Users were asked the following questions:

1. Do you understand how you would enter milestone information into the app?
2. Do you understand why the app was developed?
3. Which milestone do you think the illustrations (for example. crawling) are related to?
4. Would you use the app if you were a parent/carer of a baby?
5. What logos do you prefer?
6. What app name do you prefer?
7. What do each of the app names make you think of?
8. Do you have any general feedback for the app?

These questions were asked informally and thus I did not receive an answer from each participant, Responses were recorded in digital Post-it notes.

2.6.2.3 Results

The individuals who attended the two user-testing sessions were very similar in their interests with two of the user personas, personas one and two (Figure 2.2). All individuals were very interested in app, either for the research or the potential tracking or output. Although these were selective samples, it supports these personas as potential users of the app. A summary of the feedback from both events is presented in stickers in Figure 2.5. The responses covered a spectrum of positive, neutral, and negative, but the majority (66%) were positive. The feedback related to the different app names can be found in Figure 2.6. “Momentum” was the most popular name.

2.6.2.4 Discussion

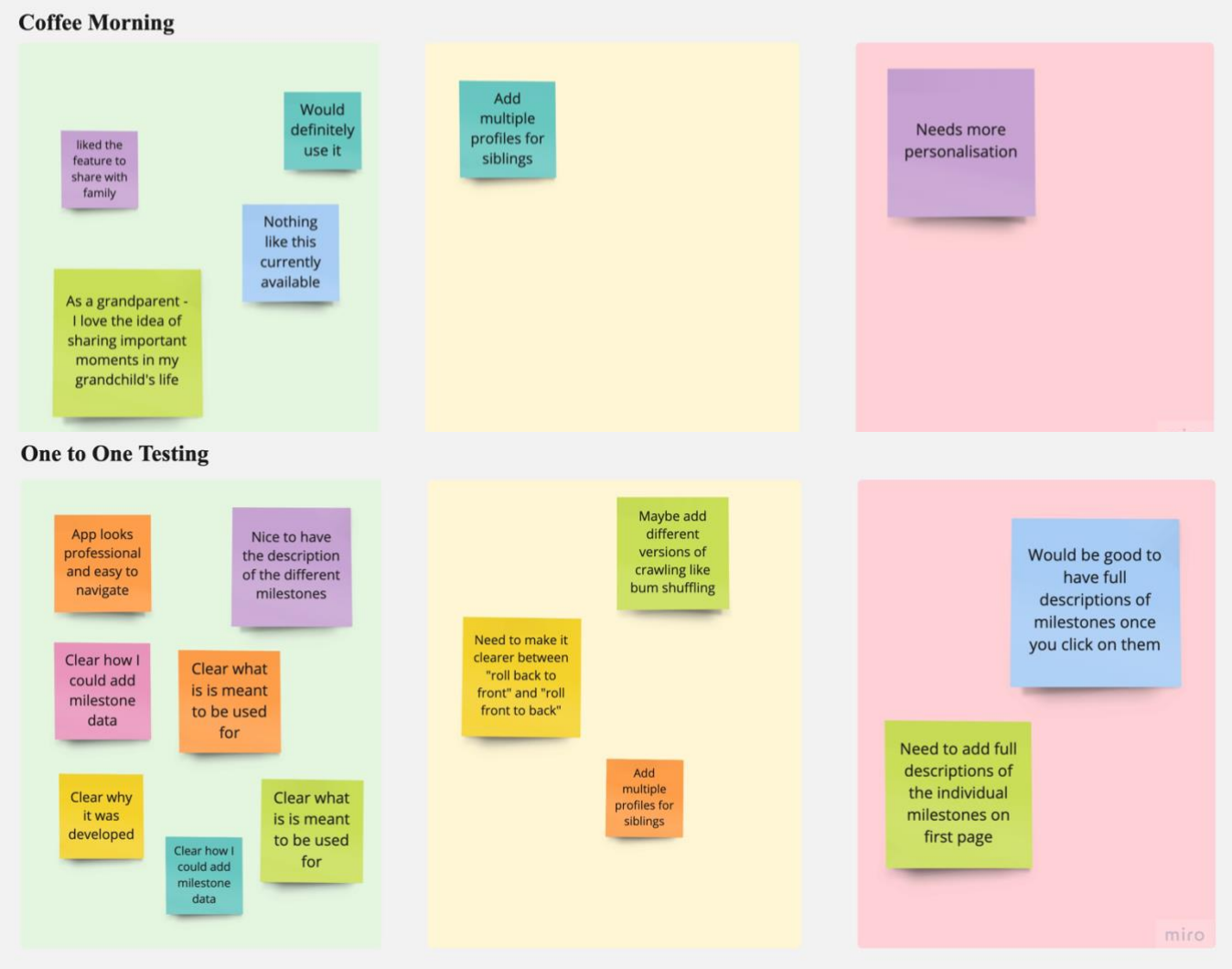
The research and user testing detailed in this section have highlighted important aspects to take forward to the final prototype.

Firstly, the feedback, in general, was positive and revealed that there seemed to be a gap in the available apps specifically orientated to track and share infant motor development. Secondly, the app’s purpose and how users would enter milestone data were clear, demonstrating the success of the app’s design. Third, the user testing suggested that the engagement aspects of the proposed app are a priority for users but not a priority concerning the ease of implementation.

The long-term participation of parents in the app-based study is vital for collecting informative data over the course of child development. Therefore, engagement functions should be prioritised after the most important functions such as consenting to the study, entering milestone data, and researchers being able to export this data.

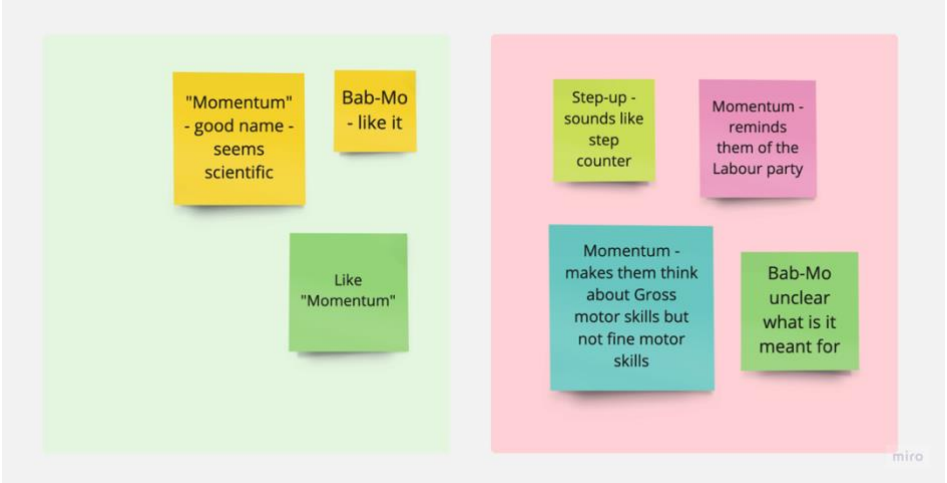
Further important aspects of the feedback from the user testing were that milestone descriptions need to be clearer with descriptions given below illustrations, and that other milestones

Figure 2.5 User testing feedback



Note, feedback from individuals from the “coffee morning” public engagement event and one-to-one user testing. Feedback is ordered by sentiment., green, positive; yellow, neutral; and pink, negative.

Figure 2.6 User testing name feedback



Note, Feedback from individuals from user testing for the different names: “step-up”, “Momentum”, and “Bab-Mo”. Feedback is ordered by sentiment., green, positive; yellow, neutral; and pink, negative.

that infants demonstrate instead of crawling (e.g. bum shuffling) could be introduced into the list of milestones. The user testing additionally highlighted the importance of including the functionality of multiple profiles for siblings.

Lastly, the most popular name was “Momentum”. Although one individual stated it made them only think of gross (rather than fine) motor skills, the feedback was positive. This name will, therefore, be used going forward.

Further work should engage users that are similar to user-personas three and four (Figure 2.2), to test the app with those who are potentially less engaged in the research or app, or with health concerns for their child. Although these sessions provided valuable feedback, it is important to state that this was not a formal study providing data, but the early stages of user feedback conducted as it would be in the early stages of app development.

2.7 Prioritisation of Functions

The prioritisation of functions is a methodology to other app development methods (Bachschmid - Formerly Beutter et al., 2022; Mrklas et al., 2020) and is used to decide which functions would be included in a minimum viable product (MVP) which would include only the most basic functions for the app to meet its purpose (Mrklas et al., 2020). Building on the user personas for parents/carer, functions were listed for the parent/carer as well as the researcher because the needs of the end-user and researcher both need to be considered in app design. Furthermore, grandparents were added as an extension to the parent/carer end user due to the potential for parents/carers to share with extended family. Functions were based on what is needed to collect the data (e.g. “Enter the date their child completed a Milestone”), and what would keep the end-users engaged, thus leading to less missing data and better participant retention (Heron et al., 2019). Section 2.2.3 describes how gamification can be used to increase end-user interest in apps (Bitrián et al., 2021; Sardi et al., 2017). Therefore, functions such as parents being able to “Take and store a picture of their child completing a milestone” And “Look at a graph of their child’s milestones” were added.

Table 2.2 Prioritisation of functions

User	Function	Importance	Ease of Imp	Combined
Parent	Enter basic information about baby/babies	1	1	2
Parent	View data protection details for the app/study	1	1	2
Researcher	Export data for a participant	1	1	2
Researcher	Export data for a study/all data	1	1	2
Researcher	View a database of all users and their completion rates.	1	1	2
Researcher	View the consent status of participants in the database of participants	1	1	2
Parent	Create an account	1	2	3
Parent	Enter the date their child completed a Milestone	1	2	3
Parent	Answer brief questionnaires sent every week	1	2	3
Parent	Consent to take part in a specific study	1	2	3
Researcher	Upload a questionnaire to be sent to users	1	2	3
Researcher	Only see data from those who have consented to send their data	1	2	3
Parent	Contact the research team about the study and the app	2	1	3
Parent	View more information about a milestone	2	1	3
Researcher	Set up participants as part of specific studies for validation	1	2	3
Parent	Change their data preferences relating to the study	2	2	4
Parent	Make a note that the child hasn't been in a normal (i.e. home) environment / is ill	2	2	4
Parent	Consent/agree to use the app but not a specific study and thus receive notifications, etc.	2	2	4
Parent	Change notification frequency	2	2	4
Researcher	Change the frequency of notifications	2	2	4
Researcher	Make changes to the frequency of the questionnaires	2	2	4
Researcher	Change text in the questions	2	2	4
Researcher	Send emails to study participants with invites to download the app	2	2	4
Researcher	Set up daily "burst" notification questions that are initiated by incoming data	2	2	4
Parent	Respond to a notification without having to log in	2	3	5
Parent	Take and store a picture of their child completing a milestone.	2	3	5
Parent	Look at a graph of their child's milestones	2	3	5
Extended family	See an export of a completed milestone from the parent	3	2	5
Parent	Change contact details in the user account	3	2	5
Parent	Personalise the background of the app with a picture	3	2	5
Parent	Create an account for a sibling	3	2	5

Note. Tasks were rated for importance and ease of implementation (highest = 1), and a combined score was calculated as a sum of the two. The functions are put in order from the highest priority to the lowest. Imp, implementation

The prioritisation of functions can be found in Table 2.2. Based on the initial app research (section 2.5), the user personas, user-testing (section 2.6) and literature review, functions were given a score out of three for their ratings of importance to the user (parent/carer, researcher, or grandparent). Next, each element was given a score out of 3 and the ease of implementation. The score was calculated by considering the complexity of the function from discussions with the Mindwave Ventures team. For example, a parent entering basic information about their baby/child is something that all apps require and thus doesn't require significant implementation time. However, responding to a notification without logging in (for example, quickly answering a daily EMA/"burst" question directly from the notification) requires significant implantation time as it would be novel for this app.

Finally, each function was given a final ranking of importance for app development, which was the sum of the two scores. The functions with the lowest scores would be included in the MVP and those with higher scores would be included in future app versions, depending on further user-testing of the MVP as is done in iterative agile design (Mrklas et al., 2020).

2.8 App prototype

The second app prototype was developed in response to user testing. The sections below detail the app's functionality, user interface examples, and the wireframing of the app. Functions were included in the prototype even if they were low on the list of prioritisations. However, when creating a MVP, only the prioritised functions would be included.

2.7.1 Functionality

I designed an app prototype based on app, UI / UX, and user persona research (Figure 2.2), user testing (section 2.6), and the prioritisation of functions. The app prototype was created on Adobe XE (Figures 2.7 and 2.8). The app has several data collection streams listed below:

1. Calendar-based milestone data entry

2. EMA burst questions – the entry of a milestone achievement would trigger these. They involve single-question questionnaires sent to the user's phone daily, asking if they have witnessed the milestone on that day. If not, they will be asked an optional question if they have not been with the child that day.
3. Questionnaire assessment. At the appropriate points in the study or ages of the child, notifications to complete questionnaires will be sent to the user about themselves, their home life, or the child/children.
4. Activity tracking involves the user being instructed to send a video of the child completing a specific activity.

There are also several user experience functionalities which would aid in increasing user engagement:

1. Profile photo upload is where a user can upload a profile photo of their child or children to personalise the app and identify different children if there are multiple profiles.
2. Milestone photo upload is where a user can upload a photo of their child completing the associated milestone and keep it as a memory. This can then be "shared" with friends and family.
3. Milestone reports – This is where milestone activity for each child is summarised in an engaging report that the user can scroll through. For example, the most recent milestone achieved and how many milestones have been reported.

Other elements of the app include elements relating to consent and ethics:

1. Consent page – users consent to participate in the study and for the data relating to milestone and motor information, but not the photographs to be recorded.
2. Study Information page – users can read more about the study.
3. Contact information page – contact information of the study team.

Figure 2.7 Example screens and user interface elements

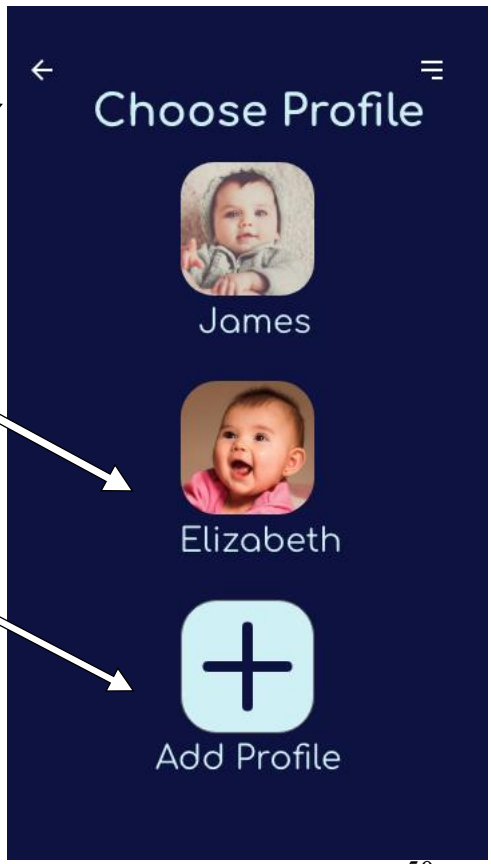
Home page

- This button goes to different parts of the app including settings and setting up/changing child profiles
- Includes logo and main elements of the app:
    - Milestones
    - Calendar
    - Reports
    - Questionnaires
    - Activity (video uploads)
- There is also the Birkbeck Logo which, if pressed, leads to a page about the research study.

Profile Selection Page

This page is where the user (parent) selects a profile they want to enter information in relation to.

- Back button
- Profiles set up by the user with uploaded photos
- Option to add a profile



Milestones Page

This page is separated between two motor types, Gross and Fine. The user can scroll down to all available milestones and select the one they want to enter information about.

- Button to go to the fine motor milestone page
- Picture uploaded by the user
- Circles indicating different milestones: the darkness of the colour indicated a milestone typically achieved later, and if the circle is filled in that means data has been entered for that milestone
- Search button to look up milestones

Calendar Page

The page is where users can view previously added milestone information as well as add new information by selecting the date and then the milestone that has been achieved.

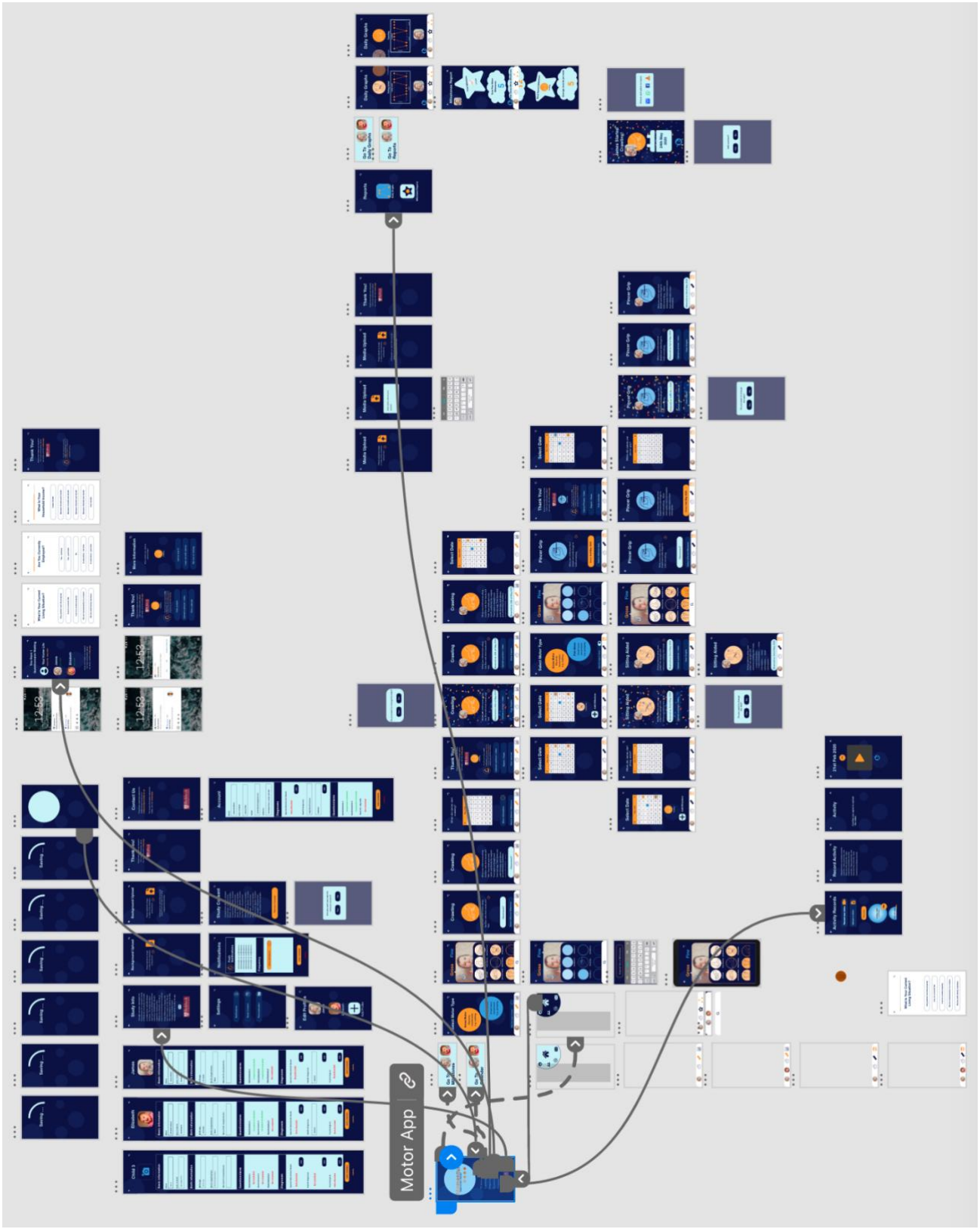
- Orange circles indicate pre-entered gross motor milestones, the blue indicating pre-entered fine motor milestones
- Buttons to other parts of the page:
    - Profile page
    - Home
    - More milestones
    - Home calendar page

2.7.2 Wireframe prototype of the app

Based on the research and user testing previously detailed in Section 2.5.2, I created a wireframe prototype of the app. The wireframe is a schematic version of the final app where all links (e.g., buttons) are set up so the app can be used for user testing. Wireframing includes content hierarchy, space distribution, app user actions, app feasters and transitions between app pages. The app prototype, however, does not collect any of the data, and specific uses would not be possible. Therefore, the prototype presents fictitious motor data so the users can view the app as it would if they had entered data.

An example of the wireframing is given in Figure 2.8, which shows the transitions from the home page. The wireframe prototype includes all main aspects of the app, Milestone calendar, questionnaires, EMA notifications, video uploads, engagement aspects (reports, milestone celebrations), and settings and profiles.

Figure 2.8 Wireframe of motor tracking and assessment app



Note. Wireframe prototype of a motor tracking app showing the links between the buttons on the home screen and the other screens

2.9 Discussion

This chapter comprises a review of psychological and developmental research that has taken advantage of technological innovations in app design and gives examples of the uses of smartphone apps in research studies. The chapter then included the design process and research for a parental smartphone app digital phenotyping tool for motor infant skills and activity. Finally, a prototype of the app and its functionality was introduced.

There has been a large increase in app-based research designs due to the capabilities and widespread use of the technology, including the infant motor measurement app, Kleine Weltentdecker, which was found to be a reliable and valid measure of motor skills in infancy (Daum et al., 2022). However, this app doesn't make use of flexible measurement. The present proposed app design includes "burst" designs, which resemble the inter- and intra-individual variability in infant motor development (Adolph, 2015) and have the potential to capture transition points when milestones are achieved and significant cognitive development occurs (West et al., 2019). The proposed app also has more engagement capabilities to increase interest in the app for a prolonged time compared to the 4.32 months on average for using the Kleine Weltentdecker app. The proposed app, therefore, has the potential to increase the accuracy of its motor measurements and the time spent using the app.

The app has several strengths and weaknesses. A strength is that it has the potential to increase the participation in research to groups who would otherwise not participate and increase sample sizes for an age group (infants) that is demanding to recruit. There are, however, limitations to app-based research. Firstly, although most adults own smartphones, participating in an app-based study requires WIFI or data, battery life, and the knowledge to navigate an app. These factors would limit some individuals' participation in the study. Further, although innovative, the measurement of activity levels with a video upload and machine learning processing method is a new method, and it is unclear if it would accurately measure activity levels in children and if parents were able to capture the quality and meet the requirements of the videos that need to be uploaded.

There are important ethical implications for parents and caregivers using the app to track and share information on their child's development. The users mustn't be given the impression that their child is not developing or missing essential milestones and are "behind" other children. The research

suggests significant inter- and intra-individual variability in infant motor development between skills/milestones (Adolph, 2015). Therefore, individuals mustn't be wrongly given the impression that one "late" milestone would lead to delayed development in general. This concern has been considered by not providing the age of typical achieving for milestones within the app. However, app notifications would be based on typically achieving timelines. Therefore, further work in the pilot study with a fully working app would need to ensure this does not lead to concerns from parents and caregivers.

In conclusion, this chapter includes the literature review, research, design, and prototype of a motor digital phenotyping app that collects data about an infant's motor development and activity levels through parent reports and video uploads. With flexible measurement designs, the app would capture motor skills as they develop. The next steps would be to implement a pilot and validation study to understand the reliability and validity of the tool.

2.9 Appendix

Supplemental Table S2.1 Placement dates

Date	Count	Location
09/01/2020	1	Office
16/01/2020	1	Office
30/01/2020	1	Office
13/02/2020	1	Office
20/02/2020	1	Office
27/02/2020	1	Office
05/03/2020	1	Office
12/03/2020	1	WFH
19/03/2020	1	WFH
26/03/2020	1	WFH
02/04/2020	1	WFH
09/04/2020	1	WFH
16/04/2020	1	WFH
23/04/2020	1	WFH
07/05/2020	1	WFH
14/05/2020	1	WFH
21/05/2020	1	WFH
28/05/2020	1	WFH
04/06/2020	1	WFH
11/06/2020	1	WFH
18/06/2020	1	WFH
25/06/2020	1	WFH
02/07/2020	1	WFH
09/07/2020	1	WFH
16/07/2020	1	WFH
30/07/2020	1	WFH
06/08/2020	1	WFH
13/08/2020	1	WFH
20/08/2020	1	WFH
03/09/2020	1	WFH
10/09/2020	0.5	WFH
17/09/2020	0.5	WFH
24/09/2020	0.5	WFH
01/10/2020	0.5	WFH
08/10/2020	0.5	WFH
15/10/2020	1	WFH
22/10/2020	0.5	WFH
29/10/2020	0.5	WFH
05/11/2020	1	WFH
12/11/2020	1	WFH
19/11/2020	0.5	WFH
26/11/2020	0.5	WFH
03/12/2020	0.5	WFH
10/12/2020	0.5	WFH
17/12/2020	0.5	WFH
24/12/2020	0.5	AL
31/12/2020	0.5	AL
07/01/2021	0.5	WFH
14/01/2021	1	WFH
21/01/2021	0.5	WFH
28/01/2021	0.5	WFH
04/02/2021	0.5	WFH
11/02/2021	1	WFH
18/02/2021	0.5	WFH
25/02/2021	0.5	WFH
04/03/2021	0.5	WFH
11/03/2021	0.5	WFH
18/03/2021	1	WFH
25/03/2021	0.5	WFH
01/04/2021	0.5	WFH
08/04/2021	0.5	WFH
15/04/2021	0.5	WFH
22/04/2021	1	WFH
29/04/2021	0.5	WFH
06/05/2021	0.5	WFH
13/05/2021	0.5	WFH
20/05/2021	0.5	WFH
27/05/2021	0.5	WFH
03/06/2021	1	WFH
10/06/2021	0.5	WFH
17/06/2021	0.5	WFH
24/06/2021	0.5	WFH
01/07/2021	0.5	WFH
08/07/2021	0.5	WFH
15/07/2021	1	WFH
22/07/2021	1	WFH
29/07/2021	0.5	WFH
05/08/2021	0.5	WFH
12/08/2021	0.5	WFH
19/08/2021	0.5	WFH
26/08/2021	0.5	WFH
02/09/2021	0.5	WFH
09/09/2021	0.5	WFH
16/09/2021	0.5	WFH
Total:	62	

Note, Industrial placement dates at Mindwave Ventures. WFH, Working from home; AL, annual leave

3. A Systematic Review and Meta-Analysis of the Associations Between Motor Milestone Timing and Motor Development in Neurodevelopmental Conditions

3.1. Associated Publication

The research for this chapter originated from a manuscript that is soon to be submitted (Bowler, Arichi, Austerberry, Fearon, & Ronald, (Stiles et al., 2005). Tomoki Arichi (TA) and Chloe Austerberry (CA) assisted in the search and quality assessment.

3.2. Introduction

Early motor development allows children to independently explore the environment, increase social interaction, and communicate with caregivers through joint eye contact, gestures and passing objects. Notably, many of the first major fine and gross motor milestones in human childhood, such as walking (gross-motor) and the pincer grip (fine-motor), are typically achieved in the first two years after birth during a period of marked brain plasticity (Stiles et al., 2005). Motor brain regions may also be more vulnerable to early environmental disruption than other regions (Hensch & Bilimoria, 2012), also see section 1.1.2. Motor development, therefore, has the potential to be an important early indicator of later neurodevelopmental conditions (NDC) and could enable the timely initiation of potential early intervention.

Much of the research in atypical infant motor development has focussed individually on motor development in groups with specific NDCs rather than comparing between conditions. However, in light of recent evidence highlighting co-occurrences and overlapping genetic underpinnings between different NDCs (Guilmatre et al., 2009; Ronald, Simonoff, et al., 2008; Rujescu et al., 2009; Stergiakouli et al., 2017), as well as the different needs of individuals with different NDCs, it is crucial to understand if there are significant differences between NDCs in motor development and milestone attainment.

No systematic review has compared motor skills and milestones across several NDCs. Independent systematic reviews have suggested that these conditions may be associated with atypical early motor skills but have focused on different ages and did not find consistent patterns of impairment. Three reviews have been conducted on ADHD. Havmoeller et al. (2019) conducted a review of infant motor development in ADHD and found no agreement between the five extracted studies. However, Kaiser et al.'s (2015) review found evidence of impaired childhood motor skills in ADHD. Further, Athanasiadou et al. (2019) concluded that there was insufficient evidence for atypical early motor signs and that the effects seem non-specific.

One systematic review exists for ASD. West (2019) looked at general motor development between 3 and 42 months, revealing evidence for atypical motor development across domains, which intensified across age.

Two reviews have been conducted on language disorders. A 2001 non-systematic review of motor deficits related to specific language impairment concluded that there is significant evidence for motor deficits in this group (Hill, 2001). Consistently, a meta-analysis of 16 studies comparing children with speech and language impairments against controls found evidence for a large effect of more motor errors in the clinical group and medium effects for more time performing motor tasks and lower motor scores (Rechetnikov & Maitra, 2009). However, no review or meta-analysis has explicitly looked at infant (rather than childhood) motor skills or infant motor milestones in individuals with language or communication disorders. No meta-analysis or systematic review exists for any neurodevelopmental motor or tic disorders.

Although schizophrenia is not typically a childhood-onset condition and is not defined as a neurodevelopmental disorder in the DSM-5 (Insel, 2010; Owen & O'Donovan, 2017), several lines of evidence suggest it has neurodevelopmental origins (Insel, 2010; Owen & O'Donovan, 2017). Further, studies have revealed evidence for early atypical motor development in schizophrenia (Filatova et al., 2017; Murray, Jones, et al., 2006). Schizophrenia will, therefore, be considered an NDC for this review. In contrast, including specific learning disorders is beyond the remit of this review because this condition is explicitly defined in the DSM-5 as not attributable to motor disorders (American Psychiatric Association, 2013). Further, specific intellectual disabilities frequently co-

occur with other included NDC categories in this review, and thus, separating these effects is likely challenging.

Across NDC diagnoses, there is a lack of consensus regarding the role or prevalence of motor impairments. A clear exception is a motor disorder, developmental coordination disorder (DCD), in which motor milestones delays and motor atypicalities such as coordination as part of its diagnostic criteria or features (Gurevitz et al., 2014; Nishimura et al., 2019; Ozonoff et al., 2008). The DSM-5 diagnostic criteria and features for stereotypic motor disorder also refer to "repetitive motor behaviour" that often starts in the first three years. In contrast, the only reference to motor skills for tic disorders is the criteria for "motor tics". Schizophrenia includes "grossly disorganized or abnormal motor behaviour (including catatonia)" as a key DSM-5 feature. For ADHD, excessive motor activity is the only motor-relevant criterion or feature in the DSM-5, and for autism, repetitive motor movements are the only motor-relevant component. However, recent research has revealed evidence of more extensive motor deviations or delays in autism and ADHD, indicating there may be associations of early motor markers with these conditions (Gurevitz et al., 2014; Nishimura et al., 2019; Ozonoff et al., 2008)

This chapter aimed to fill these gaps by systematically assessing the evidence for motor atypicalities and motor milestone delay in NDCs in the same review. It compared infant motor atypicalities and motor milestone delay across NDCs and compared NDC groups against controls without NDCs. It consists of three primary meta-analyses to answer the following questions.

3.2.1 Research Questions

1) Do children with NDCs have delays in the attainment of motor milestones in infancy compared to controls (without any neurodevelopmental condition or psychiatric illness)?
2) At what age do children with NDCs reach motor milestones in infancy? – This was studied by comparing the age of attainment across NDC groups and/or compared to the World Health Organisation's (WHO, (Bowler & Ronald, 2021) average ages of attainment when available.
3) Do children with NDCs differ significantly in standardized assessments of motor skills?

3.3 Method

3.3.1 Study registration and PRISMA guidelines adherence

Before starting the literature search, the protocol for the study was registered with PROSPERO, the International Prospective Register of Systemic Reviews (Bowler & Ronald, 2021). The review was performed in line with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) reporting guideline 2020 statement (Liberati et al., 2009).

3.3.2 Search methods

Database searches were conducted in MEDLINE, EMBASE and PsycINFO using OVID as a provider and Web of Science. The searches were completed individually for each condition group and in two phases between November 2020 and November 2022 (see Table S3.1). The searches that first took place in 2020 and 2021 (on autism, ADHD, schizophrenia, and tic disorders) were repeated in November 2022 to identify more recent publications. The MEDLINE Search for ADHD is presented in Figure 3.1, and all other search terms for each NDC group and database can be found in the online supplemental data (Supplemental Data 1). In addition, reference lists of included studies were searched. There was no restriction on the date published.

Figure 3.1 Search terms for the attention deficit hyperactivity database search

1 *Attention Deficit Disorder with Hyperactivity/	19 standing.mp.
2 (attention deficit adj3 hyperactivity).ab. /freq=2	20 ambulation.mp.
3 ADHD.ab. /freq=2	21 (lift* adj2 head*).mp.
4 Infant/	22 pincer*.mp.
5 Infant Behavior/	23 grip.mp.
6 Child Development/	24 crawl*.mp.
7 (infan* or child*).ab.	25 general movements.mp.
8 Motor Skills/	26 (fine motor or gross motor).mp.
9 Motor Activity/	27 (Motor adj3 skill*).mp.
10 Movement/	28 motor development.mp.
11 Walking/	29 motor milestone*.mp.
12 Head Movements/	30 motor ability.mp.
13 Locomotion/	31 motor coordination.mp.
14 Postural Balance/	32 1 or 2 or 3
15 postural control.mp.	33 4 or 5 or 6 or 7
16 (walk or walking or locomotion or gait).mp.	34 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31
17 pulls.mp	35 32 and 33 and 34
18 (sitting or sit up).mp.	

Note, Search terms for the ADHD search on the MEDLINE database using the OVID provider. For all other search terms, see (Supplemental Data 1).

3.3.3 Search Criteria

Inclusion criteria

1. Have a longitudinal cohort, cross-sectional, or clinical study design.
2. Assessed fine and gross infant motor milestone attainment (typically achieved between 3—24 months), motor skills, neuromotor development, or movement abnormalities.
3. Included infants aged 3–24 months (on average, if across a range).
4. Had an NDC group with a diagnosis of a DSM-V (or similar) “neurodevelopmental disorder” or schizophrenia, apart from an intellectual disability or specific learning disabilities, assessed by a gold-standard clinical tool or by own clinical assessment.
5. Included a control group (or provided an age of milestone attainment for the NDC group).
6. Published in the English language.
7. Published in a peer-reviewed journal.

Exclusion criteria

1. Had a clinical group with a diagnosis of a learning disability.
2. Had a clinical group diagnosed with an additional neurodevelopmental or psychiatric disorder.
3. Review studies or meta-analyses.

Two reviewers (AB, TA) applied eligibility criteria and selected studies for inclusion. AB reviewed all abstracts and screened all records for inclusion, and TA checked these decisions in a random sample of 20% of records. The researchers were blind to each other's decisions. Any disagreements were resolved by the two parties meeting and arriving at a consensus, which was reached for all cases.

3.3.4 Data extraction

Effect sizes and measures of variance for the primary outcome and moderator variables, in addition to supplementary data (for example, country of origin of the study), were extracted from studies where available (See Table S3.3 in the Appendix for a complete list of extracted data). AB extracted the data using the Covidence online tool (*Covidence*, 2021). CA conducted a blind data extraction on a random 20% subset of studies. The percentage of agreement was calculated for the available data extracted for the meta-analysis. When there was insufficient data in a manuscript, contact was made with the authors to gain the data (as noted in Tables 3.2 and 3.3), or data were extracted from figures using WebPlotDigitizer (2023). If data were still missing, it was noted as missing data (primary outcomes) or not reported (NR, supplementary data). If data was ambiguous, agreement was sought between AB and CA. For the NDC group versus control milestone meta-analyses, there was the requirement for at least five effect sizes (across studies) for each milestone to be included; therefore, some data were extracted but not meta-analysed if an insufficient number of effect sizes was found (see section 3.3.6). The systematic review of motor skills included all motor-relevant findings, including those that could not be meta-analysed, for example, posture or clumsiness.

3.3.5 Quality assessment

Individual study quality was assessed using the checklist developed by Downs and Black (1998) which is considered a reliable tool (S. Sanderson et al., 2007). Minor modifications were made in line with Filatova et al. (2017), see Supplemental Data 2 (Supplemental Data 2) for a list of the items. AB conducted a quality assessment, and CA conducted a blind quality assessment on the same random 20% subset of studies from the blind data extraction. Studies with ratings lower than 10 out of 17 will be classified as low quality.

3.3.6 Power for meta-regressions and subgroup analyses

There is no agreement for a minimum number of effect sizes for meta-regressions or subgroup analyses. The Cochrane Handbook recommends ten effect sizes per sub-group (Higgins et al., 2019). A study into the power of subgroup analyses suggested that for an average I^2 of 75% in psychology, at least 42 effect sizes are required to have sufficient statistical power, with a higher number needed if subgroups are unbalanced (Cuijpers et al., 2021). However, these calculations assume studies or cohorts don't have multiple effect sizes. It is unclear how much impact this has on power.

Further, the NDC samples included in the meta-analyses can be challenging to recruit and test. We, therefore, set no minimum total effect sizes for the meta-analysis to have subgroup analyses. However, a minimum of five effect sizes per milestone was set to ensure enough power to compare across milestones in subgroup analyses. Although those subgroups with a small number of effect sizes will have limited power, it is important to include valuable data that is challenging to collect.

3.3.7 Statistical synthesis and analysis

Before conducting the meta-analyses, the extracted means, standard deviations (SD), and other effect sizes were prepared. If convertible data for both groups was reported (for example, median and SE), a mean and SD were calculated. If no measure of variance was reported, the standardized mean differences (d) were calculated using the Practical Meta-Analysis Effect Size Calculator (D. B. Wilson, 2023) or the Estimating the Sample Mean and Standard Deviation Calculator (McGrath et al., 2020) when possible. If means or effect sizes were only given for

subgroups *within* an NDC diagnosis (for example, those with high and low IQ), average effect size and standard deviation were calculated as advised in the Cochrane Handbook (*Chapter 6*, 2023., p. 6).

Three 3-level random-effects meta-analyses were run in the R package metafor (Viechtbauer, 2023) to account for dependency across effect sizes from the same study or cohort. The first level was sampling variance, the second was variance across outcomes within a cohort, and the third was variance across cohorts.

Data synthesis groups were based on data type (milestone or standardized measure) and if there was control milestone data. The first of the three meta-analyses was a meta-analysis of the standardized mean difference of month of milestone attainment between the NDC and control group. Second, a meta-analysis of the mean month of milestone attainment for the NDC group was run. This analysis included papers that only reported the mean from the NDC and not a control group, in addition to the NDC group data of the studies that reported control group means (not including studies that only reported effect sizes). Comparisons of 95% confidence intervals were made between the pooled effect sizes and available World Health Organisation (WHO, (Borenstein et al., 2017). Third, a meta-analysis of the standardized mean difference of standardized motor assessments between the NDC and control group was conducted.

Potential sources of heterogeneity were investigated with meta-regressions and subgroup analyses using the metafor R package. The following meta-regressions or subgroup analyses were conducted:

1. NDC group
2. Milestone (milestone meta-analysis only)
3. Test type (standardized motor meta-analysis only)
4. Study design (retrospective/prospective)
5. Age of measurement (standardized motor meta-analysis only)
6. Motor modality (standardized motor meta-analysis only)

Model comparison statistics (Bayesian information criterion, BIC; and Akaike information criterion, AIC) were used to test if there was an improvement in the model when there were three levels compared to one. Heterogeneity was assessed across levels. High heterogeneity was classified as 75%, medium as 50%, and low as 25% (Borenstein et al., 2017). Differences in heterogeneity (I^2) across levels were assessed using the var.comp R function (Harrer et al., 2019). Effect sizes across NDCs or milestones were compared using the "*anova"* function in Metafor, in which linear combinations of the coefficients in the model are tested using a Wald-type test (Viechtbauer, 2023).

Functions from the Metafor package were used to assess publication bias (Viechtbauer, 2023). Firstly, a funnel plot, which displays each effect estimate by its associated sample size, was created using the "*funnel"* function. Publication bias was evaluated by visually reviewing the funnel plot. Next, Egger's test of the regression intercept of the random effects analysis was used to calculate the amount of asymmetry in the funnel plot using the "*regtest"* function (Egger et al., 1997). The extent of deviation from zero in the model's intercept of the regression line indicated the degree of asymmetry. If there was evidence of asymmetry, a trim and fill analysis was performed with the "*trimfill*" function. This analysis involved trimming off the asymmetric parts of the funnel plot and then estimating the new centre of the funnel plot. Once completed, the trimmed studies were replaced, and the estimated missing studies on the other side of the plot were assessed. The new mean and variance were then calculated and compared against the previous means and variances (Duval & Tweedie, 2000). Finally, cook's distance was used to assess influential cases (Cook, 1977).

3.2.7.1 Sensitivity analyses

Sensitivity analyses were used to see if conclusions still held when studies that did not conduct clinical assessments for diagnosis were excluded or if studies that included sample sizes less than 20 were excluded.

3.4 Results

3.4.1 Preliminary results

3.4.1.1 Included studies

Table 3.1 includes the systematic review results (23 studies), and Table 3.2 (21 studies) and Table 3.3 (10 studies) contain all studies included in the meta-analyses. There were no results for stereotypic movement disorder due to differences in the presentation across DCD and Tics. Although both come under the motor disorders classification in the DSM-5, they were treated as different NDCs due to their distinct motor impairment profiles and their strong distinction in developmental research. Language disorders were included as a single condition due to differences in classification in the included studies, which weren't consistent with the present classifications used in the DSM-5. The PRISMA flow diagrams for all NDC groups can be found in the Appendix (Figures S3.1-6). As is a PRISMA requirement, the studies that appear to meet the inclusion criteria but were excluded are listed in the Appendix (Table S3.2), along with the explanation for exclusion.

Table 3.1 Studies included in the systematic review

Study ID	NDC	Country	Cohort	Des	Age(s) (m)	Sample Size		N Female		Motor Assessment	Outcome detail
						NDC	Control	NDC	Control		
Comings 1987	Tic	USA	NA	R	NA	347	47	NR	NR	**Toe Walking**	No significant group differences in presence of toe walking in childhood
Johnson 1992	Autism	UK	NA	R	6, 12, 18	7—10	3—19	NR	NR	**Clinical Motor Difficulties** One or more clinical motor problems from screening test records coded as: (1) referral to a specialist (2) a note made to re-check a test 3) a note made that the infant appeared unusual in a particular respect.	Comparisons across autistic, mildly learning disabled and control groups: • No significant group differences at 6 months • 12 months not tested • 18 months – Significant differences across all groups(x^2= 5-97, p= **0.051**): autistic, 2/7; control, 0/11; mildly learning disabled, 7/17.
Walker 1994	Schiz or MAD	USA	AOP	R	0—24	23/30	15/21	7/30	14/21	**General Motor Skills** home videos coded by examiners for presence of skills: Mean rating from crawling, grasping, head control, manual manipulation, sitting, walking	No significant group differences (F=1.24(5,70), p= 0.30)
Rosso 2000	Schiz or SAD	USA	NCPP	P	8	47	5415	25	3955	**Gross Neurological** Unusual movements—derived from standardised psychological and neurological examinations	Logistic regression: • No significant group differences (OR 1.8, 95% CI [0.9–3.8])
Isohanni 2001	Schiz	Finland	NFBC	P	12	100	10457	35	5184	**Gross Neurological** Public health nurses and GPs judged deviations in movements in posture, abnormal muscle tone, or other neurological symptoms (yes vs no)	Percent of Schizophrenia group identified as having some form of developmental deviance in at least one domain: • 4.6%. x^2= 10.66(1), ***p*< 0.01**

Study ID	NDC	Country	Cohort	Des	Age(s) (m)	Sample Size		N Female		Motor Assessment	Outcome detail
						NDC	Control	NDC	Control		
Landa 2006	Autism	USA	NA	P	6, 14, 18, 24 (+30,36)	23	53	NR	NR	**Trajectories of motor development** Longitudinal modelling of Mullen Fine and Gross Motor Scores	Fine and gross motor: • No significant group differences at 6 months. • Autistic group poorer motor skills than controls at 14 months through to 24 months Fine motor: • Language group showed poorer motor skills than controls at 6-14 months, 18-24 No significant group differences Gross motor: • No significant difference between groups
	Lang					11					
Esposito 2008	Autism	Italy	ODFLab	R	20	16	16	0	0	**Gait** Walking Observation Scale (Esposito & Venuti, 2004). 11 items in 3 categories: foot movements, arm movements, global movements.	• Significant differences across all groups (autistic, mental retardation, typical development): $F(2,43)= 21.01$, ***p*< 0.001,** $n^2= .22$) • Tukey post hoc comparisons: Autistic group greater severity of disturbance than controls (no *p* value given)
Ozonoff 2008	Autism (Autism: No, Autism: Reg*	USA	NA	R	9—12	26+28	24	1+5	12	**Gross Neurological** Groups split depending on regression in language or social interest or engagement (ADI-R). Movement Abnormalities and Protective Responses: coded from home videos	• No significant differences between groups

Study ID	NDC	Country	Cohort	Des	Age(s) (m)	Sample Size		N Female		Motor Assessment	Outcome detail
						NDC	Control	NDC	Control		
Esposito 2009	Autism	Italy	ODFLab	R	NA	10—12	10—12	NR	NR	**Motor Symmetry** symmetry for sitting or standing position assessed by retrospective home videos where random still images were taken and coded by blind coders	Sitting: • The level of symmetry showed significant differences among the groups (F(2,30)= 4.12**, *p*< 0.05)** • KMeans cluster analysis: All participants in the lower level of symmetry cluster belonged to the autistic group Standing • the level of symmetry showed no significant group differences
Dewrang 2010	Autism	Sweden	NA	R	18	23	13	4	7	**Movement Imitation** **Clumsiness** **Fine Motor** **Gross Motor** Five items on movements and motor skills from the Symptoms of Autism Before Age 2 scale (SAB-2; (Dahlgren & Gillberg, 1989)	Autistic group compared to controls had: • More difficulties imitating movements, F= 30.43, ***p*< .001** • Was more clumsy and ill-coordinated, F= 19.63, ***p*< .001** No significant group differences for: • Would point to objects with the whole of his/her hand, F= 0.21, *p*=ns • His/her movements were agile and graceful: F= 0.01, *p*= ns • Once s/he started to walk s/he did it perfectly at once: F-value: 0.01, *p*= ns
Flanagan 2012	Autism	USA	NA	P	6—36	10	17	0	5	**Head Lag** Archived videos of the pull-to-sit task from the gross motor scale of the Mullen Scales of Early Learning (Mullen, 1995) coded for head lag in all children	More infants later diagnosed with autism exhibited head lag than infants without diagnoses of autism (no risk and social/comm delay, Fisher's exact test, ***p*= .02**)

Study ID	NDC	Country	Cohort	Des	Age(s) (m)	Sample Size		N Female		Motor Assessment	Outcome detail
						NDC	Control	NDC	Control		
Landa 2012	Autism	USA	NA	P	6, 14, 18, 24 (+ 30, 36)	52	121	9	68	**Trajectories of motor development** Latent class growth model membership for subscales of the Mullen Scales of Early Learning (Mullen, 1995) was related to diagnostic outcome at 36 months	Six classes: 1, accelerated; 2, normative; 3, language/motor delay; 4, developmental slowing • Not-autistic group primarily in class 1 and 2 • Autistic group: Spread across classes 2, 3, and 4 • Class 4 almost entirely included autistic individuals • Class 4 contained a higher proportion of autistic children than either class 1, 2, or 3 (***p's* < 0.001**)
Nickel 2013	Autism	USA	NA	P	6, 9, 12, 14	4	18	1	10	**Posture** Infants were videotaped at home during everyday activities and play. All infant postures were coded and classified as to whether they were infant initiated.	Mann-Whitney U tests - 6, 9, and 12 months, but not 14 months, autistic infants posture repertoires were significantly smaller than those of infants in the HR and LR groups combined: • 6m, U= 8, ***p*= .004** • 9m, U= 21, ***p*= .023** • 12m, U= 18.5, ***p*= .014** • 14m, *p*= ns
Jaspers 2013	ADHD	Neth	TRAILS	P	1—15	419	1245	166	702	**Gross Motor** **Fine Motor** Van Wiechen Scheme: GM and FM subscales. If problem present, coded as "yes", "no" if not.	Gross motor skills: • Higher scores associated with ADHD: OR:0.73, 95% CI(0.61,0.88), *p* value not provided Fine motor skills: • No significant association with ADHD– OR: 0.88, 95% CI(0.56,1.38), *p*= ns

Study ID	NDC	Country	Cohort	Des	Age(s) (m)	Sample Size		N Female		Motor Assessment	Outcome detail
						NDC	Control	NDC	Control		
Jeans 2013	Autism	USA	ECLS-B	P	9,24	100 (rounded)	7700 (rounded)	30	3927	**General Motor Skills** Motor Index Score (GM and FM composite) of the Bayley Short Form–Research Edition (BSF-R; (Bayley, 1993)	Significantly lower motor score compared to controls at 24m, but not 9m: • 9m: β= -0.01, SE= 0.30, *p*= .982 • 24m: β= -1.13, SE= 0.15, ***p*< .0001**, OR= 0.32, 95% CI(0.24, 0.44)
Johnson 2014	ADHD	UK	ALSPAC	P	12	16	120	2	38	**Motor Activity** Thirteen motion summaries were created to determine robust indices of general motor activity, summarizing speed, acceleration, variability of speed and acceleration, periodicity, and restlessness.	No significant association between the motion variables measured at age 12 months and diagnosis of ADHD at age 7 years
Sacrey 2015	Autism	Canada	NA	P	6, 9,12, 15, 18, 24 (+36)	62	69	14	28	**Parental Motor Concerns** Interview to collect information about parent concerns during the first 2 years: "Are there any current concerns about motor development?" Yes/no	Percentage of reported concerns for motor skills compared between groups: • Group effect: more concerns in autism group than controls (F^2,1196 40.1, ***p*< 0.001**) • Effect significant at all timepoints between 6-24, *p* < **0.05**
Marin-Mendez 2017	ADHD (Trait measure)	Spain	NA	R	0—36	NR	Total sample 1426	NR	Total sample 719	**Fine and Gross Motor** Parental questionnaire about the presence of problems in FM and GM (and other areas)	Group differences: • Gross motor: *p*= ns • Fine motor: ADHD group more differences than controls, ***p*< 0.05**

Study ID	NDC	Country	Cohort	Des	Age(s) (m)	Sample Size		N Female		Motor Assessment	Outcome detail
						NDC	Control	NDC	Control		
Uljarevic 2017	Autism	Aus	WAABR	R	NR	147	NA	28	NA	**Toe Walking** Parental questionnaire: Early developmental milestones questionnaire - Presence of toe walking	Percentage toe walked: • 51% of children never toe walked • 33.8% child toe walked in the past but no longer does • 15.2% child currently toe-walks
Sacrey 2018	Autism	Canada	GRH	Ret	6, 9, 12, 15, 18, 24 (+36)	10	10	4	3	**Fine Motor** Reach-to-grasp movement was measured using the qualitative Skilled Reaching Rating Scale to determine the presence of any group-related differences in the mechanics of the reach-to-grasp movement.	Autistic group performed worse compared to children in the LR and HR not autistic groups (Benjamini and Hochberg corrections for multiple comparisons; *q*, adjusted alpha for posthoc comparisons): • Reach-to-grasp movement, ***q*< .033**, d= 0.74 • Orient, ***q*< 0.033,** d= 0.47 • Lift, ***q*< 0.017,** (d not reported) • Pronation, ***q*< 0.033**, d= 0.66 No significant group differences: • Advance and grasp, *p*= ns

Study ID	NDC	Country	Cohort	Des	Age(s) (m)	Sample Size		N Female		Motor Assessment	Outcome detail
						NDC	Control	NDC	Control		
Nishimura 2019	Autism	Japan	HBC	P	1, 4, 6, 10, 14, 18, 24	32	1120	NR	NR	**Trajectories of motor development** MSEL (GM, FM, Expressive Lang, Receptive Lang, Visual Reception). Parallel process latent class growth analysis (across all ages) distinguished distinct trajectory groups based on scores of five MSEL domains. Markedly Delayed latent class was associated with early marked delays in motor domains then somewhat later delay in language domains.	Probability of autism diagnosis at 32 months according to latent classes: • High Normal: 0% autistic, 100% Not autistic, N=110 • Normal: 0% autistic, 100% Not autistic, N= 468 • Low Normal: 4.0% autistic, 96.0% Not autistic, N=202 • Delayed: 6.4% autistic, 93.6% Not autistic, N=134 • Markedly Delayed: 32.6% autistic, 67.4% Not autistic, N=38
LeBarton 2019	Autism	USA	NA	P	6	20	51	8	24	**Fine Motor** **Gross Motor** **Visual-Motor Integration** Peabody Developmental Motor Scales - 2 (PDMS-2; (Folio & Fewell, 2000)	Poorer motor skills predicted autism diagnosis at 24-36m in: • Stationary (gross motor, Chi-square= 7.756, ***p*= .021**; $R^{2=}$ .060) • Grasping (fine motor, Chi-square= 6.286, ***p*= .043**; $R^{2=}$ .05) Motor skills did not predict autism diagnosis at 24-36m in: • Visual-Motor Integration (Chi-square= 4.958, *p*= .084)

Study ID	NDC	Country	Cohort	Des	Age(s) (m)	Sample Size		N Female		Motor Assessment	Outcome detail
						NDC	Control	NDC	Control		
Reetzke 2022	ADHD	USA	NA	P	12, 18, 24, (+36)	17	77	6	41	**Motor Activity** Continuous motion-based activity was recorded using tri-axial accelerometers. Two dependent variables of activity level were derived: Mean activity (MA) and mean intensity (MI). Estimates were derived using linear contrasts from linear mixed-effects models with fixed effects for outcome group (ADHD, autism, control), linear, age, and interactions between variables. Pairwise comparisons.	Significantly higher MA and MI compared to the control group from 18m: • 12m MA: *p*= 0.40, d= -0.03, MI: *p*= 0.37, d= -0.04 • 18m - MA: *p*= **0.047**, d= 1.04, MI: *p*= **0.03**, d= 0.91 • 24m - MA: *p*= **0.03**, d= 1,42, MI: ***p*= 0.02**, d= 1.06 Fixed effects for ADHD groups were significant, indicating greater MA and MI than TD group across age (18-36m) Significantly higher MA and MI compared to the TD group from 18m: • 12m MA: *p*= 0.63., d= 0.38, MI: *p*= 0.76., d= 0.38 • 18m: MA: ***p*< 0.001,** d= -0.52, MI: ***p*= 0.001**, d= -0.37 • 24m: MA: ***p*< 0.001**., d= -0.81, MI: ***p*< 0.001**, d= -0.44 Fixed effects for autistic groups were significant, indicating greater MA and MI than TD group across age (18–36m)
	Autism					19		8			

Note: All studies were included in the systematic review and their associated findings. *, two autism subgroups: Autism: No, no language regression, Autism: Reg, language regression; NDC, neurodevelopmental condition; Des, design; Schiz, Schizophrenia; DCD, developmental coordination disorder; ADHD, attention deficit hyperactivity disorder; MAD, major affective disorder; SAD, schizoaffective disorder; USA, united states of America; UK, United Kingdom; Den, Denmark; Aus, Australia; NFBC, NCPP, Philadelphia National Collaborative Perinatal Project; Northern Finland Birth Cohort; WAABR, Western Australian Autism Biological Registry; AOP, Archival-Observational Project; PLD, Perm Longitudinal Database; ODFLab, Observational and Functional Diagnosis Lab; TRAILS, The TRacking Adolescents' Individual Lives Survey; ECLS-B, Early Childhood Longitudinal Study–Birth Cohort; ALSPAC, Avon Longitudinal Study of Parents and Children; GRH, Autism Research Centre at the Glenrose Rehabilitation Hospital; HBC, Hamamatsu Birth Cohort for Mothers and Children; NA, not applicable; NR, not reported; +, sample sizes across subgroups; -, range of sample size across measures or ages; /, N of female out of total sample (not subsample for the measure); FM, fine motor; GM, gross motor; OR, odds ratio.

Table 3.2. Studies included in the milestone meta-analyses

Studies included in neurodevelopmental condition versus control standardised mean difference meta-analysis

Study	NDC Group	Count	Cohort	Des	DG	Sample Size		N Female		Milestones Measured
						NDC	Control	NDC	Control	
Comings (1987)	Tic	USA	NA	R	Cl	347	47	NR	NR	walking unaided
Jones (1994)[d]	Schiz	UK	NSHD	R	Cl	30	4716	10	2259	walking unaided
Ozonoff (2008)	Autism	USA	NA	R	Cl	26+28	24	6	12	walking unaided, sitting unaided, rolling, crawling
Sorensen (2010)	Schiz	Den	CPC	R	Cl	92	4982	44	2444	walking unaided, sitting unaided, standing unaided, holing head up, roll back to front, crawling
Keskinen (2015)	Schiz	Fin	NFBC	R	Cl	152	10131	NR	NR	walking unaided, sitting unaided, standing unaided, hold head up
Sumner (2016)[a]	DCD	UK	NA	R	Cl	28	33	9	9	walking unaided, sitting unaided, crawling
	Autism		NA		PR + T	28		5		
West (2019)	Autism	USA	NA	P	Cl	15	25	4	10	walking unaided
Manicolo (2019)	Autism	Swiz	NA	R	Cl	32	36	5	5	walking unaided, sitting unaided
Farran (2020)	ADHD	UK	NA	R	PR + T	13-16 + 13-19	27-32	9	9	walking unaided, sitting unaided, standing unaided, holing head up
Lee (2021)	DCD	UK	NA	R	PR + T	23-50	17-29	13	16	walking unaided, sitting unaided, standing unaided, hold head up, roll back to front, crawling
	ADHD					34-61 + 2-7		13		
Lavenne-Collot (2021)	Autism	Fr	NA	R	Cl	79	100	30+6	54	walking unaided, sitting unaided, hold head up

Additional studies included in meta-analysis of mean age (no control mean)

Chawarska (2007)	Autism	USA	NA	R	Cl	51	NA	NR	NA	walking unaided
Kim (2008)	Autism	USA	NA	R	Cl	32	NA	6	NA	walking unaided, crawling
Matson (2010)	Autism	USA	NA	R	Cl	331	NA	85	NA	walking unaided, crawling
Lloyd (2013)	Autism	USA	NA	R	Cl	162	NA	22	NA	walking unaided, sitting unaided
Arabameri (2015)[a]	Autism	Teh	NA	R	Cl	88	NA	18	NA	standing unaided, sitting unaided, standing
Bishop (2016)	Autism	USA	NA	R	Cl	903	NA	NR	NA	walking unaided

Uljarevic (2020)	Autism	Aus	WAABR	R	Cl	147	NA	28	NA	walking unaided, sitting unaided, standing unaided, crawling
Ketcheson (2020)	Autism	USA	SPARK	R	Cl	13182	NA	NR	NA	walking unaided, sitting unaided, crawling
Reindal (2020)	Autism	Nor	BUPgen	R	Cl	376	NA	84	NA	walking unaided
Havdahl (2021)[c]	Autism	Nor	MOBA	P	Cl	148+64	NA	22	NA	walking unaided

Note: All studies were included in the meta-analysis of mean age (only the NDC group mean was included for studies with a control group mean); NDC, neurodevelopmental condition; Count, country; Des, design; DG, diagnosis method; a, data extracted from figure; c, means converted from medians and interquartile ranges; d, NDC group, Cohen's d converted from mode and p value; DG, diagnosis; Schiz, Schizophrenia; DCD, developmental coordination disorder; ADHD, attention deficit hyperactivity disorder; USA, united states of America; UK, United Kingdom; Den, Denmark; Fin, Finland; Swiz, Switzerland; Fr, France; Teh, Tehran; Aus, Australia, Nor, Norway; NSHD,; CPC, Copenhagen Perinatal Cohort; NFBC, Northern Finland Birth Cohort; WAABR, Western Australian Autism Biological Registry; MOBA, Norwegian Mother, Father and Child Cohort Study; Cl, clinical; CD confirmed diagnosis; PR, parental report of diagnosis; T, traits; NA, not applicable; NR, not reported; +, sample sizes across subgroups; -, range of sample size across measures.

Table 3.3 Studies included in the standardised assessment of motor scores meta-analyses

Study	NDC Group	Country	Cohort	Design	Sample Size		N Female		Age(s) (m)	Motor Measure	Outcome measure
					NDC	Control	NDC	Control			
Landa (2006)	Lang	USA	NA	P	11	53	NR	NR	6, 14, 24	Mul	FM, GM
	Autism				23		NR				
Ozonoff (2014)[a]	Autism	USA	NA	NR	51	116	8	53	6, 12, 18, 24, (and 36)	Mul	FM
Leonard (2014)	Autism	UK	BASIS	NR	17	24	6	17	7, 14 ,24	Mul, VABS	FM, GM
Libertus (2014)	Autism	USA	NA	NR	22	22	5	13	6	Mul	FM, GM
Estes (2015)	Autism	USA	IBIS	NR	49	98	8	43	6, 12, 24	Mul, VABS	FM, GM
Leonard (2015)	Autism	UK	BASIS	NR	17	48	6	31	7	Mul	GM
St John (2016)	Autism	USA	NA	NR	23/19	50/49	6/5	21/25	12,24	Mul	FM, GM
Pusponegoro (2016)	Autism	Ind	NA	CS	40	40	8	20	12-24	VABS	GM
Choi (2018)	Autism	USA	NA	P	30	69	9	31	6, 9, 12, 24	Mul	FM, GM
Iverson (2019)	Autism	USA	BSRC	P	69	188	20	81	6	Mul	FM, GM

Note: NDC, a, data from communication with authors; neurodevelopmental condition; Lang, language and communication disorders; USA, United States of America; UK, United Kingdom; Aus, Australia; Ind, Indonesia; BASIS, The British Autism Study of Infant Siblings; IBIS, The Infant Brain Imaging Study; BSRC, Baby Siblings Research Consortium; NA, not applicable; NR, not reported; CS, cross-sectional; P, prospective; ASQ, Ages and Stage Questionnaire; Mul, Mullen Scales of Early Learning; VABS, Vineland Adaptive Behavior Scales; FM, fine motor; GM, gross motor.

3.4.1.2 Quality assessment

The range of total scores across all studies was 6-15 out of 17, with a mode and mean of 10.5 (see Supplemental Data 2).

3.4.1.3 Agreement

The agreement for the data extraction was 79%, and the quality assessment was 75% (see Table S3.3 for a list of all data extracted).

3.4.2 Systematic review

The findings from the systematic review can be found in Table 3.1. In the 23 studies in the systematic review (21 of which were new studies not included in the meta-analyses, and 11 originated from the USA), there were 30 relevant findings on infants across 3–24-month-olds, including those with autism, ADHD, schizophrenia, tics, and language disorders. Findings were divided into 16 topics (see Table S3.4 for a table grouped by motor trait type and NDC group).

Studies of infant motor skills in individuals who go on to gain diagnoses of autism (K_{est}=21) tended to reveal the most consistent differences relative to controls, predominately revealing poorer motor skills than controls. However, many of these studies were rated as low-quality or had small samples. The findings included greater motor difficulties in general and gross motor areas. These include head lag measured from a small-scale, rated as low-quality, study (N=27) of videos (Flanagan et al., 2012), greater clumsiness in a small, rated as low-quality, study (N=36) reporting differences in individual questionnaire items (Dewrang & Sandberg, 2010), general motor skills at 24 months measured in a large-scale prospective study (Jeans et al., 2013), and gross motor skills at six months (LeBarton & Landa, 2019). Additionally, impairments were found in autism compared to control groups for posture (at 6, 9, and 12 months, Nickel et al., 2013), and gait (observed at 20 months, (Sacrey et al., 2015). Further, in children who went on to gain autism diagnoses, compared to those who did not, parents reported general motor concerns at two years (Sacrey et al., 2015).

Moreover, in relation to autism, fine motor impairments were additionally revealed for fine motor skills in a small study (N=20) of reach-to-grasp movements (Sacrey et al., 2018) and a larger study (N=71) of motor subscales (Dewrang & Sandberg, 2010). Two studies also found poorer autism compared to control skills in imitating motor skills, movement imitation at 18 months (Dewrang & Sandberg, 2010), and motor symmetry whilst sitting in a small study (N=24) of home videos (Reetzke, 2022). Additionally, greater motor activity was found for the autism group compared to controls at 18 and 24 months (Reetzke, 2022). Lastly, altered developmental trajectories of motor skills were found for autism compared to controls (Landa et al., 2012).

Alternatively, there were multiple findings of no motor impairments in individuals who go on to gain diagnoses of autism. Firstly, although rated as low-quality, one study examined clinical motor

difficulties and did not find evidence of differences across the autistic, control and "mildly learning disabled" groups (M. H. Johnson et al., 1992). Similarly, individual studies reported no autism compared to control differences in pointing at 18 months (fine motor, Dewrang & Sandberg, 2010), precision in the initiation of walking (gross motor, (Ozonoff et al., 2008), gross neurological skills at 9–12 months (Ozonoff et al., 2008), motor activity at 12 months (Reetzke, 2022), motor symmetry for standing (Esposito & Venuti, 2009), or visual motor integration at six months (LeBarton & Landa, 2019).

For ADHD (K_{est}=4), there was mixed evidence for motor differences. For fine motor skills, one large (N=1426) study reported evidence of an association of retrospective parental concerns of a fine motor impairment with ADHD traits (Marin-Mendez et al., 2017), but another large (N= 1664) study found No significant group differences in general fine motor skills measured at 1-15m between ADHD and controls (Jaspers et al., 2013). Further, two studies found evidence for later (18 and 24 months) but not early (12 months) increased activity levels in ADHD cases compared to controls (P. Johnson et al., 2014; Reetzke, 2022). In contrast to the findings for autism, one study reported evidence of superior gross motor skills compared to controls, although this study was rated as low-quality (Jaspers et al., 2013).

For schizophrenia (K_{est}=3), there was no evidence of impairment in motor skills. Specifically, one respective home video study found no evidence of impaired general motor skills compared to controls across 0–24 months (Walker EF et al., 1994). For gross neurological skills, there were no statistically significant differences at eight months (Rosso et al., 2000), and only a small subset (4.6%) of the schizophrenia group (N=100) were identified as having gross neurological deviance at 12 months (Isohanni et al., 2001).

For tic disorders (K_{est}=1), there was only one finding from a study rated as low-quality that found no significant group differences in early toe walking (Comings & Comings, 1987).

For language disorders (K_{est}=1), a small longitudinal modelling study (N=64) found impairments in fine motor skills across 6–14 months compared to controls, but no differences

compared to controls at 18 and 24 months. No gross motor skills impairments were found across 6 to 24 months (Landa & Garrett-Mayer, 2006).

3.4.3 Meta-analyses

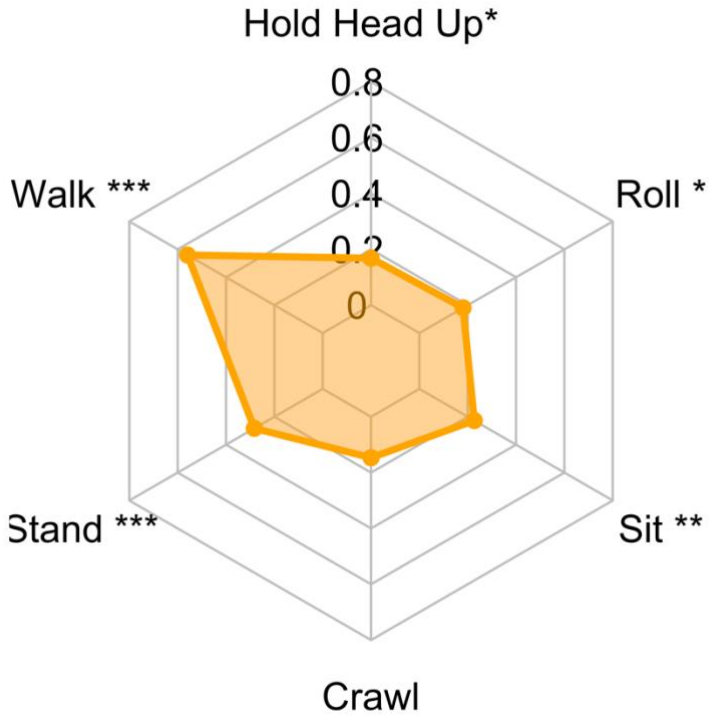
3.4.3.1 NDC group-control meta-analysis of motor milestone attainment

The meta-analysis of milestone attainment between cases and controls (K_{est}= 42) revealed significantly delayed motor milestone attainment for the NDC groups compared to controls (g=0.51, 95% CI[0.28, 0.75], p< 0.001, Figure S3.7) with significant heterogeneity Q(41)= 190.26, p< 0.001. To understand the source of the significant heterogeneity, the heterogeneity across levels was assessed, which suggested the source of heterogeneity was mainly from differences between study cohorts (I^2 Level 2= 25.57%, I^2 Level 3= 62.10%). Model comparison statistics revealed a smaller BIC but a larger AIC for the more parsimonious model (removing level 3, Table S3.5), suggesting that the results were homogenous across levels. The likelihood ratio test comparing the models was not significant (p= 0.06, Table S3.5). Given the correlations between the clustered effect sizes, results were reported from the three-level model. Inspection of the funnel plot (Figure S3.8) and Egger's test of funnel plot asymmetry (z= 0.19, p= 0.853) suggested no evidence of asymmetry or publication bias.

Moderation and subgroup analyses were conducted to investigate the sources of the heterogeneity further. Milestone type moderated the effect of delayed motor milestone attainment for the NDC groups compared to controls (Q(5)= 18.27, p< 0.001). Subgroup analyses revealed delays in holding the head up, sitting, rolling, standing, and walking, but not crawling (see Table 3.4, Table S3.6, Figure 3.2, Figure S3.7). Comparing across milestones, only walking unaided had a significantly larger NDC group/control difference compared to the other milestones (hold head up, p= 0.002; rolling, p= 0.002; sitting unaided, p= 0.006; crawling, p= 0.002; standing unaided, p= 0.035).

NDC group also moderated the effect of delayed motor milestone attainment for the NDC groups compared to controls (Q(4)= 17.26, p< 0.001, Figure 3.3). Tics (K_{est}=1) had significantly later motor milestone attainment than all other NDCs (ADHD, p= 0.01; DCD, p= 0.039; Autism, p= 0.019; Schizophrenia, p= 0.004). The only other significant group difference was for DCD having later

Figure 3.2 Spider plot of multilevel random effects model for standardised mean difference in motor milestone attainment between neurodevelopmental condition groups with milestone type subgroup effects



Note, Meta-analysis of the standardised mean difference in age of attainment of motor milestones between neurodevelopmental condition groups and controls. Hedges' g, ***, p< 0.001, ** p< 0.001, * p< 0.05.

Table 3.4 Neurodevelopmental condition versus control meta-analysis of motor milestone attainment: Milestone type subgroups

Domain	K_{est}	g (95% CI)	*p*	Q (df)	p_Q	I^2 L2	I^2 L3
Hold Head up	5	0.21 (0.05, 0.37)	0.012	5.27 (4)	0.261	0.00	32.69
Rolling	13	0.23 (-0.15, 0.60)	0.240	10.56 (3)	0.014	72.20	0.70
Sitting Unaided	9	0.28 (0.10, 0.47)	0.003	16.25 (8)	0.039	20.31	32.62
Crawling	6	0.19 (0.02, 0.37)	0.030	3.58 (5)	0.611	0.00	12.48
Standing Unaided	5	0.35 (0.11, 0.60)	0.005	9.70 (4)	0.046	68.39	0.00
Walking Unaided	13	0.70 (0.45, 0.95)	<0.001	57.06 (12)	<0.001	0.00	81.77

Note. Higher Hedges g refers to late attainment compared to the control group. k, number of effect sizes; K_{est}, number of effect sizes; Q, Test for Residual Heterogeneity; I^2 L2, % of total variance accounted for by variation within samples/cohorts; I^2 L3, % of total variance accounted for by variation between samples/cohorts; p_Q refers to the significance test of the heterogeneity statistic (Q).

milestone attainment than ADHD (p= 0.003). Subgroup analyses revealed autism was associated with the largest delay in motor milestone attainment based on the magnitude of hedges g (although confidence intervals overlap), followed by DCD, schizophrenia, and ADHD (see Table 3.5; Table S3.7 for model comparisons). There was only one effect size for tics conditions, so this group was excluded from this subgroup analysis.

Sensitivity analyses that excluded studies that did not conduct clinical diagnosis procedures were conducted, which excluded all ADHD studies. Conclusions for the main effect (g= 0.58, *p*< .001) and subgroup analyses did not change (see Table S3.8). Further sensitivity analyses were also conducted that excluded studies with sample sizes under 20 (NDC group or control) (K_{est}= 1: West 2019, age of walking in autism). Conclusions did not change for the NDC group comparison (g= 0.50, *p*< 0.001) or the walking subgroup (g= 0.69, *p*< 0.001, Table S3.9).

Table 3.5 Meta-analysis of neurodevelopmental condition group differences in motor milestone attainment compared to controls

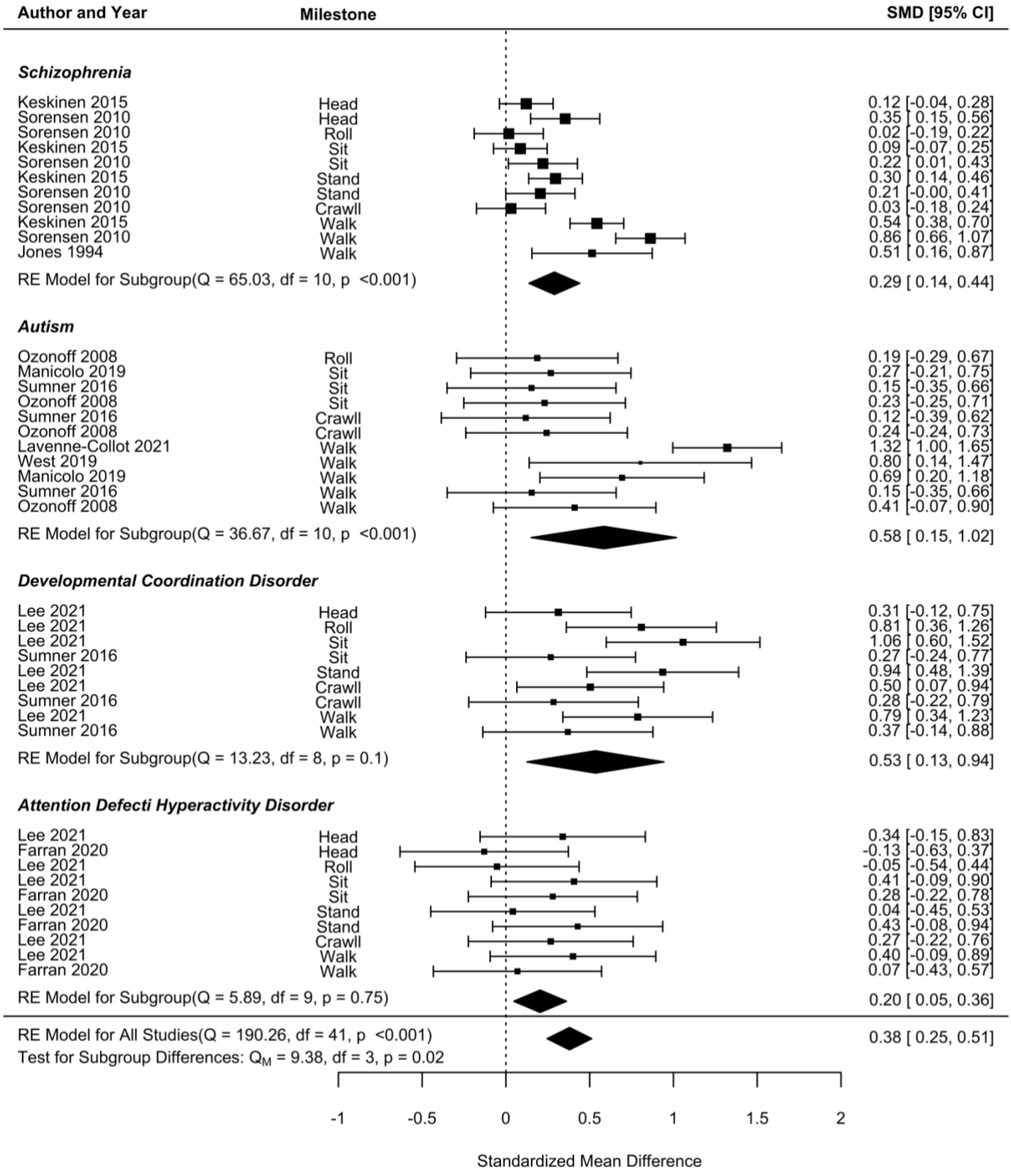
NDC	K_{est}	g (95% CI)	*p*	Q (df)	p_Q	I^2 L2	I^2 L3
ADHD	10	0.20 (0.05, 0.36)	**0.011**	5.89 (9)	0.751	0.00	0.00
DCD	9	0.53 (0.13,0.94)	**0.011**	13.23 (8)	0.104	5.79	52.43
Autism	11	0.58 (0.15,1.02)	**0.008**	36.67 (10)	**<0.001**	0.00	77.84
Schizophrenia	11	0.29 (0.14, 0.44)	**<0.001**	63.38 (10)	**<0.001**	84.91	0.00

Note. Higher Hedges g refers to late attainment compared to the control group. NDC, neurodevelopmental condition; Kest, number of effect sizes; Q, Test for Residual Heterogeneity; I2 L2, % of total variance accounted for by variation within samples/cohorts; I2 L3, % of total variance accounted for by variation between samples/cohorts. pQ refers to the significance test of the heterogeneity statistic (Q).

3.4.3.2 One-mean meta-analysis of the age of motor milestone attainment

The individual one-mean meta-analyses (see section 3.3.7) revealed that, on average, those with NDCs started to lift their head at 1.94 months, roll at 5.06 months, sit at 7.25 months, crawl at 8.88 months, stand at 11.58 months, and walk at 13.98 months (see Table S3.10, and Table S3.11 for

Figure 3.3 Forest plot of multilevel random effects model for standardised mean difference in motor milestone attainment with neurodevelopmental condition group subgroups



Note, Positive effect sizes denote late milestone attainment compared to controls.

model comparisons). Subgroup analyses of differences between NDCs were conducted for all milestones and are detailed in the following sub-sections.

3.4.3.2.1 Walking unaided

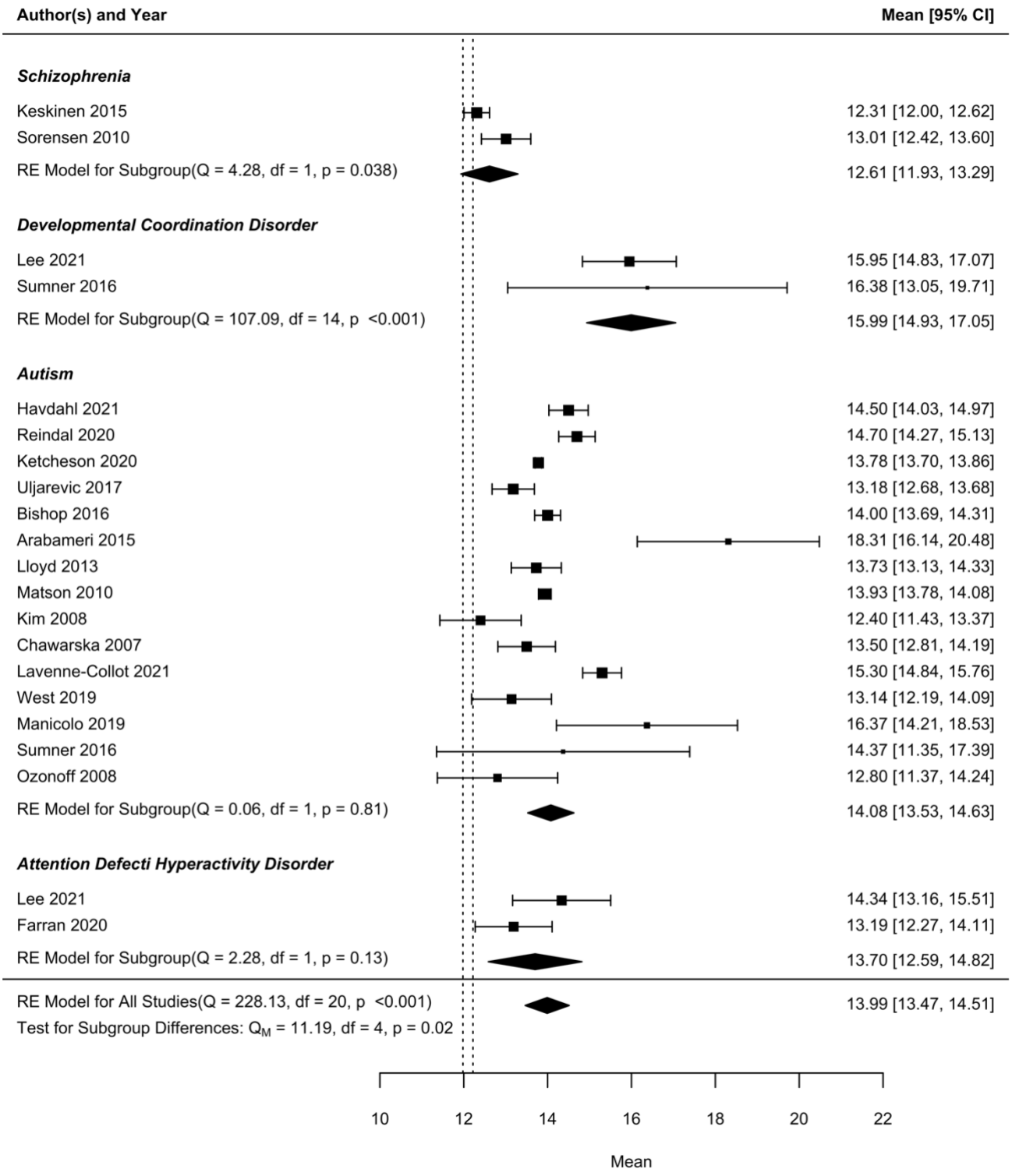
There were 22 effect sizes for walking, so an un-preregistered subgroup analysis of age of walking across NDC groups was conducted. NDC group moderated the pooled age of attainment (Qm= 11.13, *p*= 0.025). DCD (K_{est}=2) was associated with reaching the walking milestone at the latest age (g[pooled age]=15.99, which was later than Schiz *p*= 0.003 and ADHD *p*= 0.013), followed by autism (g[pooled age]== 14.08 which was later than Schiz, *p*= 0.040), ADHD (g=13.70), then schizophrenia (g[pooled age]= 12.61, Table S3.12, Figure 3.4, see Table S3.13 for model comparisons). All the NDC groups except for schizophrenia were above the WHO 95% confidence intervals for the mean attainment age of walking (11.98, 12.22; WHO & Onis, 2007).

The funnel plot (Figure S3.9) revealed no evidence of publication bias, but Egger's test of funnel plot asymmetry suggested there was evidence of asymmetry (z= 2.33, *p*= 0.019). A trim and fill analysis did not suggest any asymmetry, but an inspection of the forest plot and funnel plot indicated that the Arabameri 2015 effect size has a lower standard error than expected for the effect size (mean). Inspection of Cooks' distance (0.30) suggested it was moderately influential. A leave-one-out analysis showed that the average walking age would be slightly reduced to 13.88 (95% CI: 13.46, 14.30, *p*< 0.001) if this effect size was left out.

3.4.3.2.2 Lifting Head

A multi-level random-effects subgroup meta-analysis of the age of sitting (k = 5) revealed that those with NDCs started to lift their head at 1.94 months on average (g=1.94, 95% CI [1.28,2.60]) with significant heterogeneity Q(4) = 148.28, p < .0001. The effect was not moderated by NDC group (Q(2) = 0.95, *p*= 0.62), but was moderated by design (retrospective/prospective, Q(1) = 13.32, *p*< 0.001). Inspection of the Funnel plot (Figure S3.14) and Egger's test of funnel plot asymmetry suggested there was no evidence of asymmetry or publication bias (z = 1.17, *p* = 0.239).

Figure 3.4 Forest plot of multilevel random effects model for mean age of walking with neurodevelopmental condition subgroups



Note. Mean refers to age of walking unaided. Dotted lines represent the WHO 95% confidence intervals for mean age of walking.

3.4.3.2.3 Rolling

A multi-level random-effects subgroup meta-analysis of the age of rolling (k = 4) revealed that those with NDCs started to roll at 5.06 months on average (g=5.06, 95% CI [4.10, 6.01) with significant heterogeneity Q(3) = 59.96, p < .0001. The effect was moderated by NDC group (Q(3) = 59.96, p< 0.001) but not design p = 0.31. Inspection of the funnel plot (Figure S3.13) and Egger's test of funnel plot asymmetry (z = -0.32., p = 0.748) suggested no evidence of asymmetry or outliers.

3.4.3.2.4 Sitting

A multi-level random-effects subgroup meta-analysis of the age of sitting (k = 13) revealed that those with NDCs started to sit at 7.25 months on average (g=7.25, 95% CI [6.61, 7.89]) with significant heterogeneity Q(12) = 139.91, p < .0001. The effect was moderated by NDC group (Q(3) = 14.51, p< 0.01) but not design p = 0.918. Inspection of the Funnel plot (Figure S3.10) and Egger's test of funnel plot asymmetry suggested there was evidence of outliers and thus publication bias (z = 2.59, p < 0.01), which were both from Sumner et al. (2016). Re-running this analysis without these effect sizes gives comparable results: age of sitting was 7.25 months on average (g=6.97, 95% CI [6.63, 7.31]), significant heterogeneity Q(10) = 113.88, p < .0001, which was moderated by disorder group (Q(3) = 8.90, p= 0.031) but not design p = 0.693.

3.4.3.2.5 Crawling

A multi-level random-effects subgroup meta-analysis of the age of crawling (k = 22) revealed that those with NDCs started to walk at 8.89 months on average (g=8.89, 95% CI [8.56, 9.23], p<0.001) with significant heterogeneity Q(9) = 29/67, p < .0001. The effect was not moderated by NDC group (p= 0.14) but not by design p = 1.00. Inspection of the funnel plot (Figure S3.12) and Egger's test of funnel plot asymmetry (z = 0.03, p = 0.977) suggested no evidence of asymmetry or publication bias.

3.4.3.2.6 Standing

A multi-level random-effects subgroup meta-analysis of the age of standing (k = 7) revealed that those with NDCs started to walk at 11.58 months on average (g=11.58, 95% CI [11.73, 12.44, p<0.001) with significant heterogeneity Q(3) = 20.41, p < .0001. The effect was moderated by NDC group (Q(3) = 14.51, *p*< 0.001) but not design *p* = 0.345. Inspection of the funnel plot (Figure S3.11) and Egger's test of funnel plot asymmetry (z = 1.87, *p* = 0.062) suggested no evidence of asymmetry or publication bias.

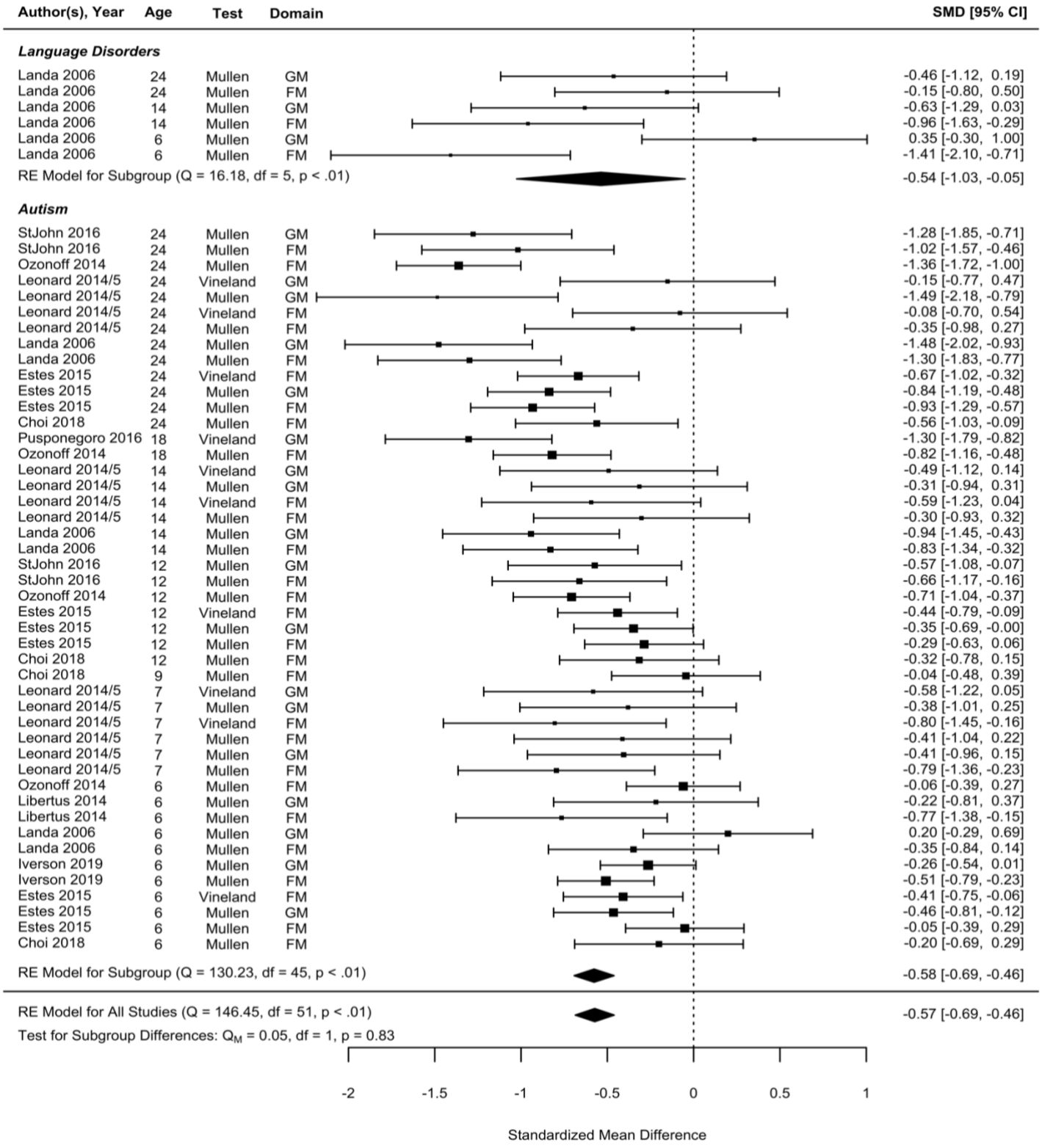
3.4.3.3 Neurodevelopmental condition group versus controls meta-analysis of standardised motor measurement

Effect sizes were only found for autism (K_{est}= 46) and language disorders (K_{est}= 6). A 3-level random-effects meta-analysis (K_{est}= 52) revealed significantly impaired motor skills for these two NDC groups compared to controls (g= -0.57, 95% CI[-0.69, -0.46], *p*< 0.001, Figure 3.5) with significant heterogeneity (Q(51)= 146.45, *p*< 0.001). Within-cohort heterogeneity was medium (I^2 Level 2= 66.12%), and between-cohort heterogeneity was close to zero (I^2 Level 3= 0.00%). Inspection of the funnel plot (Figure S3.15) and Egger's test of funnel plot asymmetry (z= -0.77, *p*= 0.441) suggested no evidence of asymmetry or publication bias.

Model comparison statistics revealed a smaller AIC and BIC for the more parsimonious model (removing level 3, Table S3.14). In addition, the likelihood ratio test comparing the models was not significant (χ2= 0.00, *p*= 1.000), which suggests that the results are homogenous across models. However, as there were correlations between the clustered effect sizes, the results from the three-level model were reported.

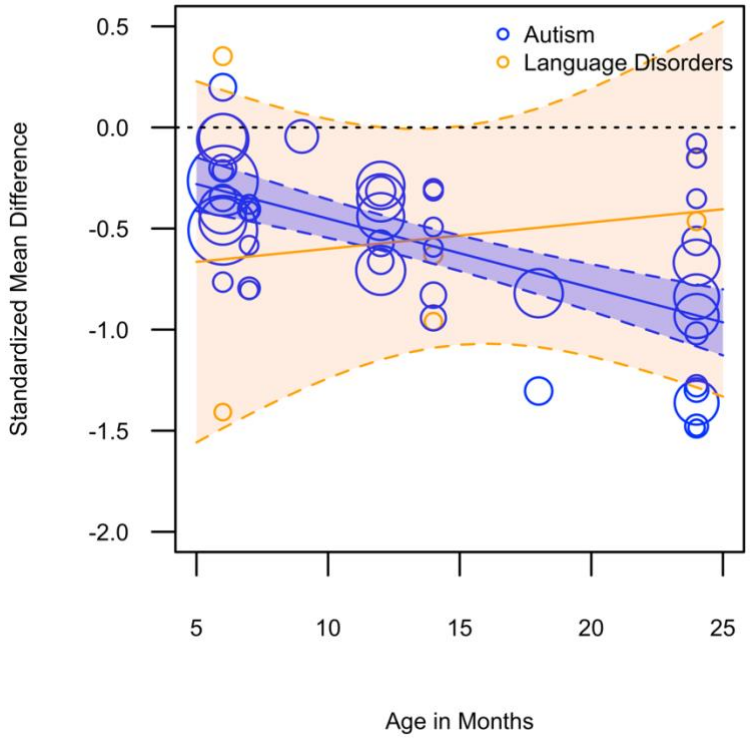
Age of measurement was a significant moderator, with later age of assessment being associated with greater motor impairment (QM(1)= 21.56, *p*< 0.001, g= -0.03, 95% CI[-0.04, -0.02], *p*< 0.001). The age moderator effect was broken down into three age of measurement brackets (6–12, 12–18, and 18–24 months), and the effect size increased as the measurement age increased (Table S3.15; see Table S3.16 for model comparisons). The age moderator effect was explored further in the bubble plot, which shows a greater (negative) standardised mean difference in motor scores (relative

Figure 3.5. Forest plot of multilevel random effects model for standardised motor assessments between neurodevelopmental condition groups with neurodevelopmental condition group subgroups



Note, Negative standardised mean difference indicates lower scores on standardised motor measures for cases compared to controls. Leonard 2014/15 refers to two studies from the same cohort. Vineland, Vineland, Vineland Adaptive Behaviour Scales; Mullen, The Mullen Scales of Early Learning

Figure 3.6 Bubble plot of standardised mean difference in standardised motor assessments across age of measurement



Note, Age in months for measurement of standardised motor measures. Negative standardised mean different indicate lower scores on standardised motor measures for cases compared to controls. Bubbles represent individual effect sizes; sizes of bubbles are proportional to the weight for the effect size in the meta-analysis. Highlighted areas refer to 95% confidence intervals for each group. FM, fine motor; FM, gross motor.

to controls) across measurement age for autism (g= -0.03, 95% CI[-0.05, -0.02], $p< 0.0010$, but not for language conditions (g= -0.01, 95% CI[0.73, -0.06], $p= 0.728$, See Figure 3.6).

NDC group, motor modality, condition group, or test type did not moderate the overall NDC group versus control motor attainment effect ($p= 0.759$, $p=0.972$, $p=0.758$, $p=0.919$, respectively). Subgroup analyses were conducted within the NDC group to investigate the differential motor scores for each condition. For autism ($K_{est}=46$), there was evidence for significantly impaired motor skills compared to controls (g= -0.58, 95% CI[-0.71, -0.46], $p< 0.001$, Table S3.17, see Table S3.18 for model comparisons). There was a similar effect for language conditions but with a greater 95% confidence interval ($K_{est}= 6$, one study; g= -0.54, 95% CI[-1.03, -0.05], $p= 0.031$).

3.5 Discussion

This is the first cross-condition systematic review and meta-analysis of infant motor skills in neurodevelopmental conditions. The review revealed important similarities and differences between NDCs for motor milestones and motor skills, thus contributing new insight into the early signs and clinical presentation of NDCs.

The meta-analysis identified walking as the most delayed motor milestone in infants with NDCs. However, walking age also varied significantly between conditions. Infants with schizophrenia walked the earliest at approximately (13 months on average), and those with DCD walked the latest at (16 months on average). All other included milestones were delayed in infants with NDs compared to controls, apart from rolling, and all other milestones apart from crawling had significant heterogeneity across NDCs.

Tics had the most delayed milestones compared to controls, although this was based on one walking finding from a single sample. DCD had later milestones, on average, than ADHD, and subgroup analyses revealed autism was associated with the highest magnitude delay in motor milestone attainment, followed by DCD, schizophrenia, and ADHD. The significant heterogeneity in the amount of milestone delay for autism and schizophrenia is likely due to having a greater delay in attaining the walking milestone than other motor milestones. In contrast, ADHD and DCD had low heterogeneity in the delay in the attainment across all the motor milestones studied.

The evidence of slight motor delays, typical development, or, in some cases, even enhanced motor skills associated with ADHD suggests that, although there may be similarities in the aetiology of ADHD and autism, motor development diverges in these conditions from an early age. Previous meta-analysis indicated limited or no evidence of early motor delays or impairments in ADHD (Athanasiadou et al., 2020). It is unclear if there are later delays or impairments in motor skills in ADHD, as existing reviews have drawn contrasting conclusions (Havmoeller et al., 2019; Kaiser et al., 2015). This, therefore, warrants further comprehensive investigation.

The present study's results relating to autism suggested delays and impairments across many motor domains and impairments that also increase over age. These findings are consistent with a systematic review of the motor development between 3 and 42 months of individuals who go on to

gain a diagnosis of autism, which revealed evidence for atypical motor development across domains, with effect sizes increasing with age (West, 2019). There is, therefore, strong evidence for early and increasing motor delays and impairments for individuals who later gain a diagnosis of autism.

The study found some evidence of impairments in general motor skills in language disorders, but these impairments were not as large as those found for autism. Further, the systematic review revealed evidence of impaired early- but not late -infancy fine motor skills. This evidence is in keeping with the findings of a non-systematic review of later motor skills, which also suggested some motor impairments in language disorders (Hill, 2001). Similarly, a meta-analysis comparing children with speech and language impairments against controls found evidence of more motor performance errors, slower motor task performance, and lower motor assessment scores in the children with speech and language impairments (Rechetnikov & Maitra, 2009). More research is needed to understand the profile of early motor skills and their development in individuals with language disorders.

The study found evidence for significant and extensive gross motor milestone delay in DCD, which is consistent with the clinical description for DCD in the DSM-V. The search did not find sufficient studies for tics disorders to make any conclusions about this NDC group.

A significant gap in the literature on fine motor skill assessment before 24 months led to no fine motor skill effect sizes in the milestone meta-analyses. However, the systematic review revealed mixed findings for autism and ADHD in fine motor impairments compared to controls, and the meta-analysis of standardised assessments revealed no motor modality moderation of group differences in motor skills. More research is needed to explore this important motor sub-domain earlier in development. Furthermore, more research is needed on tics disorders and DCD as they make up a small proportion of the literature, limiting the ability to compare conditions.

This study has several strengths. We included multiple NDCs and motor assessments in meta-analyses and systematic reviews. We used multilevel models to account for the relatedness of effect sizes and explored multiple sources of heterogeneity.

This study also had several limitations. First, although all the primary meta-analyses had sufficient overall power (K^{est} range: 42–61), the subgroup analyses were unbalanced and had lower relative power (main subgroup analyses, K^{est} range 5–46; un-preregistered walk subgroup analyses 2–

15). Second, there was a bias in the included studies, which mostly originated from Western countries (37 of 39 studies were from North American or European countries), which limits generalisability to non-Western cultures and highlights a need for research across a wider geographical range. Further, many studies used different methods of collecting motor data, often not giving sufficient detail in their manuscripts to compare to other methods. Third, conclusions drawn from the meta-analyses depend on the methodological rigour of the included studies, and it must be noted that seven studies included in the meta-analyses and systematic review were rated as low quality.

Our review and meta-analyses suggest that NDCs involve delayed or impaired infant motor skills and highlight important distinctions across conditions. Walking was the most delayed across most included conditions. Tic disorders, Autism and DCD had the highest magnitude impairment or delays in attainment compared to other conditions. There is also evidence of increases in motor impairments as children with NDCs mature over infancy. Our work also shows that more research is needed for underrepresented conditions, such as tic disorders and DCD, to understand the similarities and differences in motor skills in neurodevelopmental conditions.

3.6 Appendix

Supplemental Table S3.1 Date of individual searches for each NDC group

Search No.	ADHD	Autism	Schizophrenia	Tic Disorders	DCD and Stereotypic Movement Disorder	Language and Communication Disorders
1	November 23, 2020	December 10, 2020	June 22, 2021	July 26, 2021	September 21, 2022	September 26, 2022
2	November 17, 2022	November 18, 2022	November 23, 2022	November 23, 2022	NA	NA

Note. Date of individual searches. The second search was repeated for all publications published since the last search.

Figure S3.1 ADHD PRISMA flow diagram

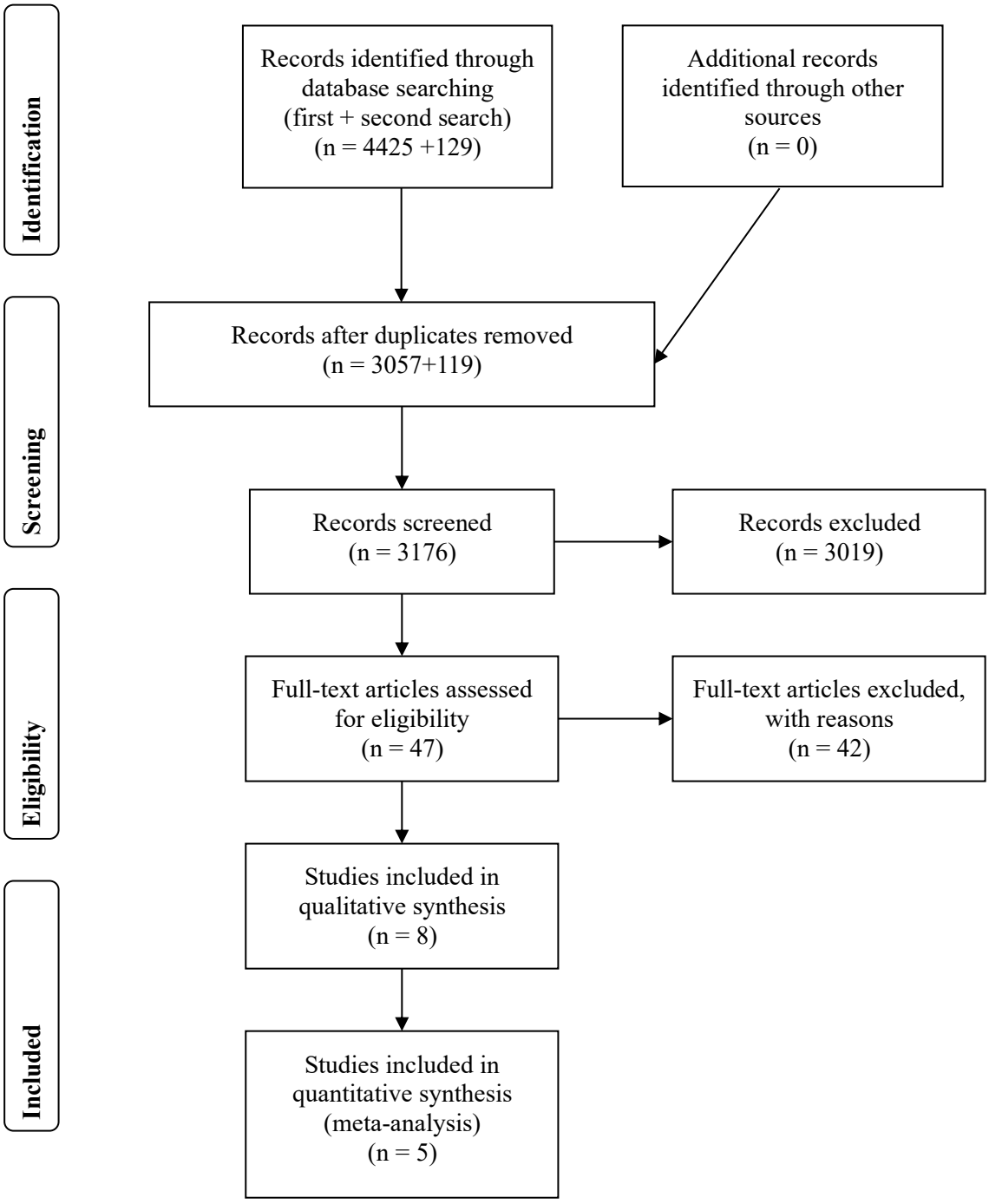


Figure S3.2 Autism PRISMA flow diagram

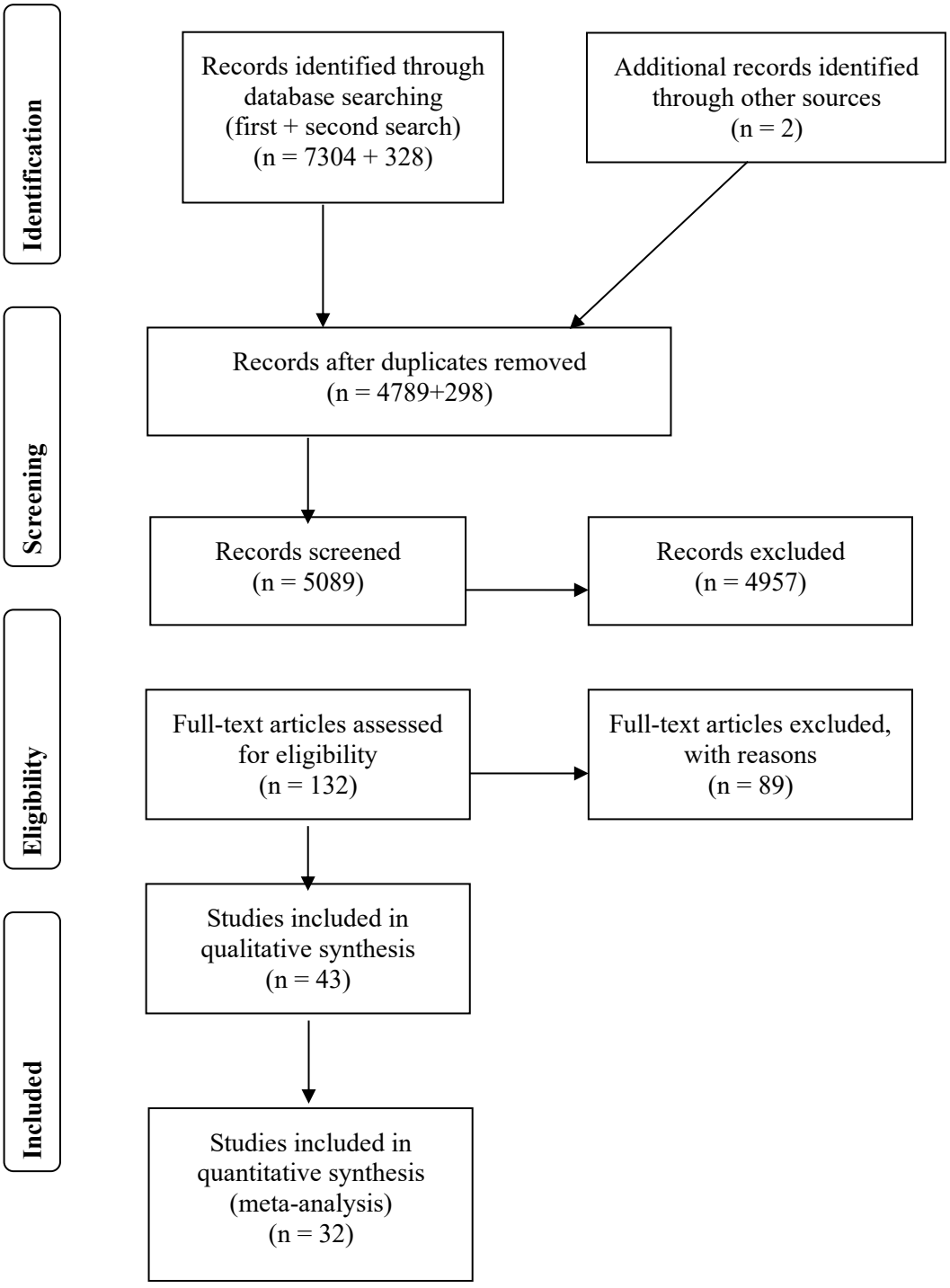


Figure S3.3 Schizophrenia PRISMA flow diagram

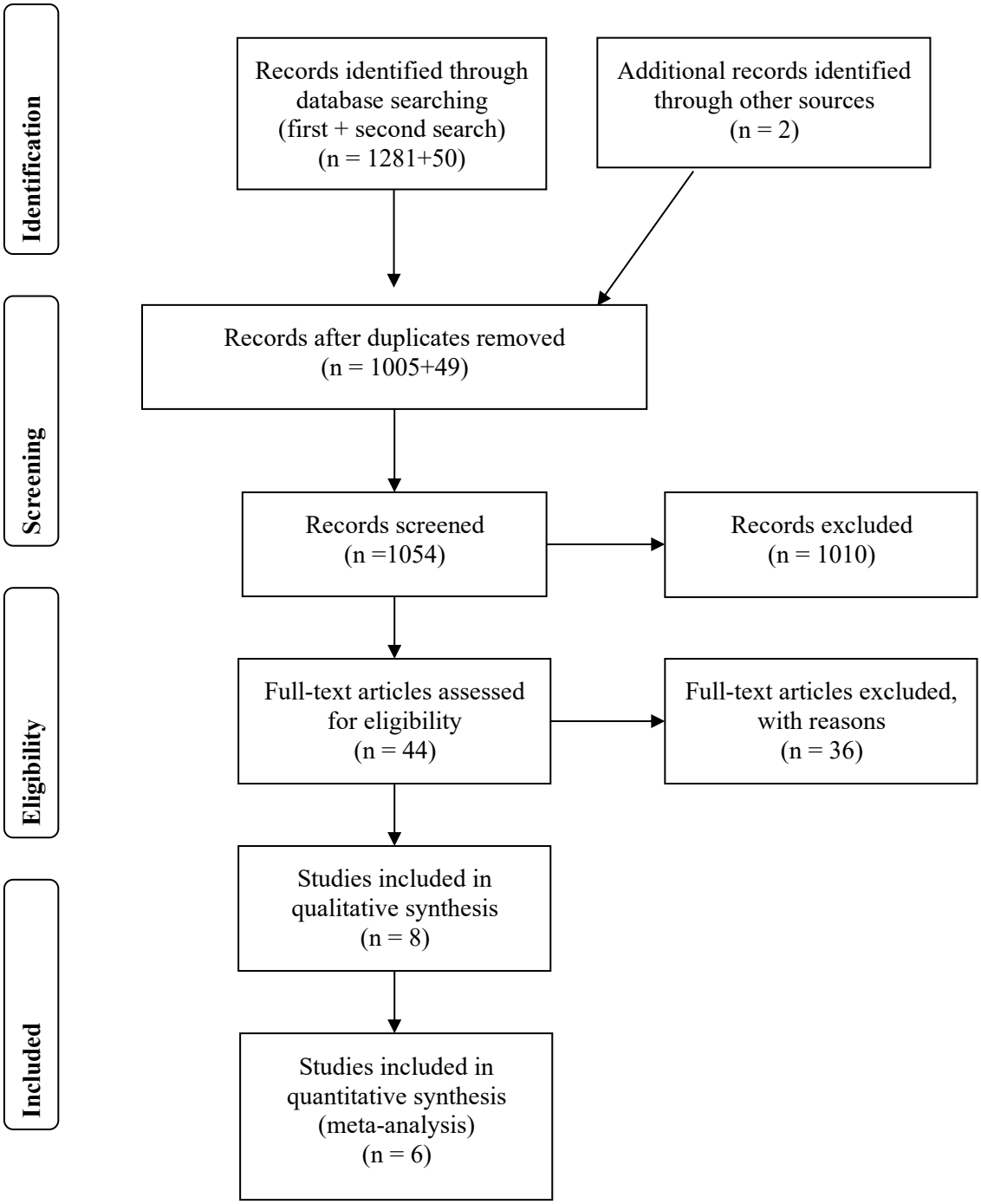


Figure S3.4 Tics PRISMA flow diagram

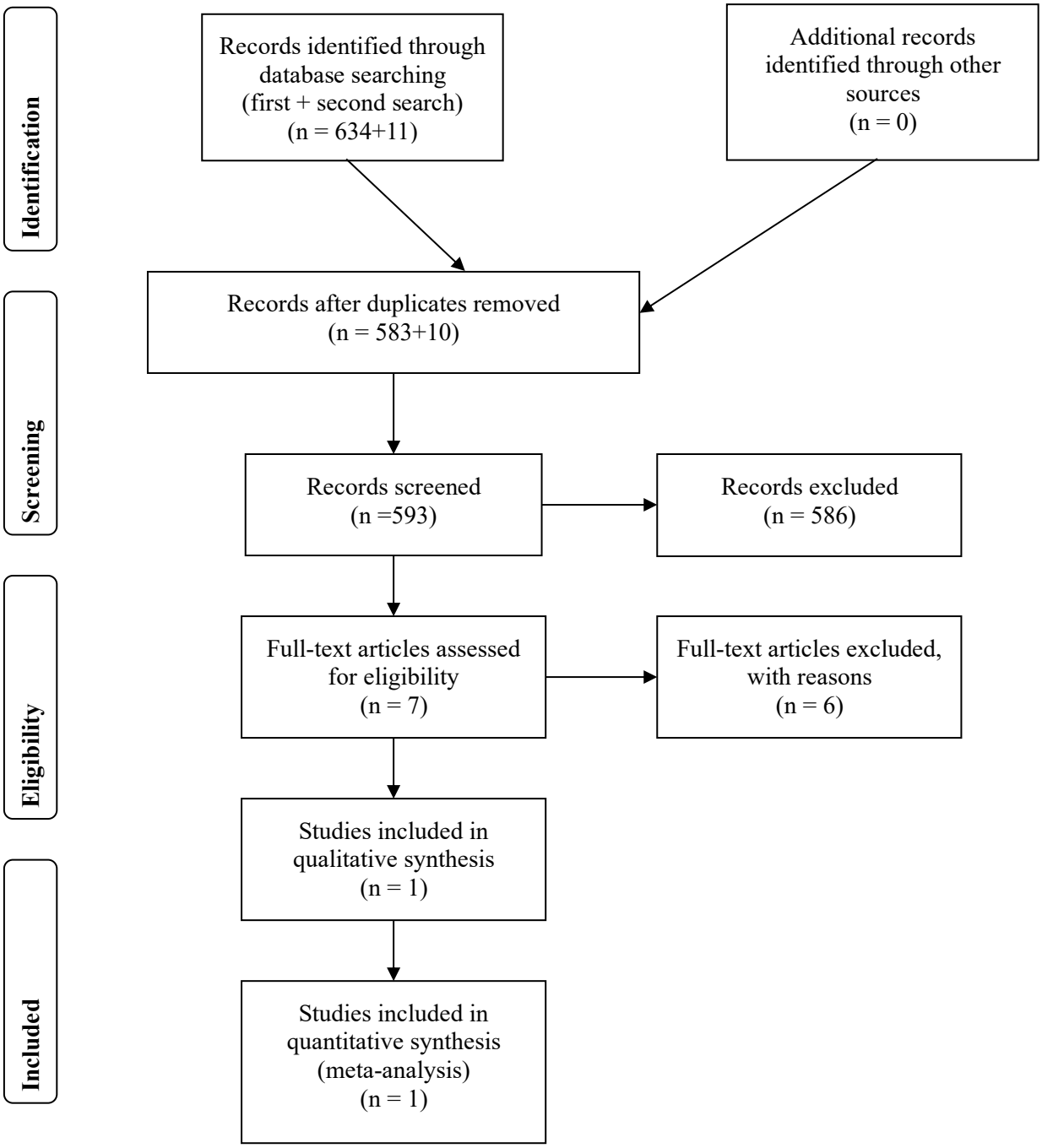


Figure S3.5 DCD and Stereotypic movement disorder PRISMA flow diagram

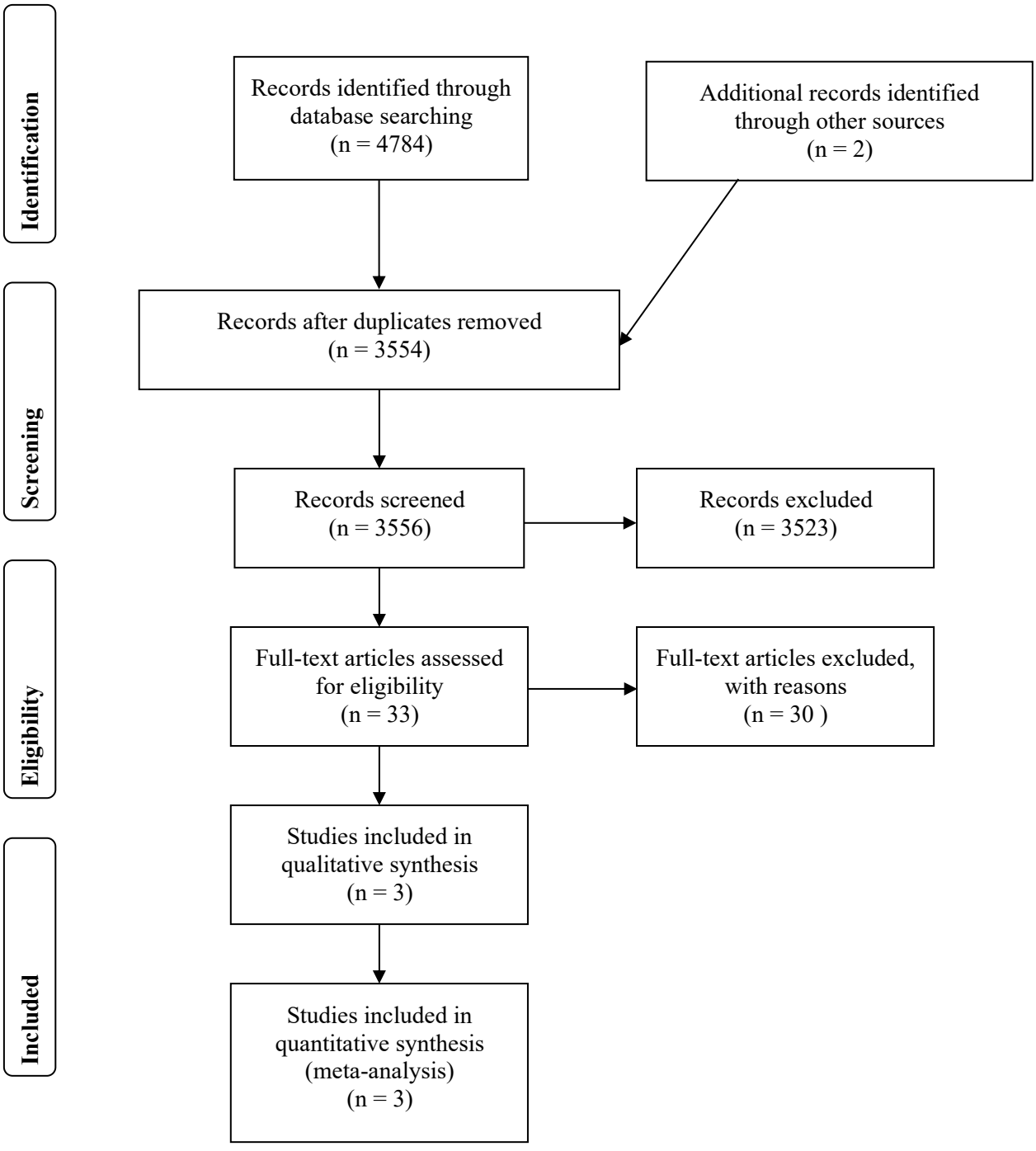
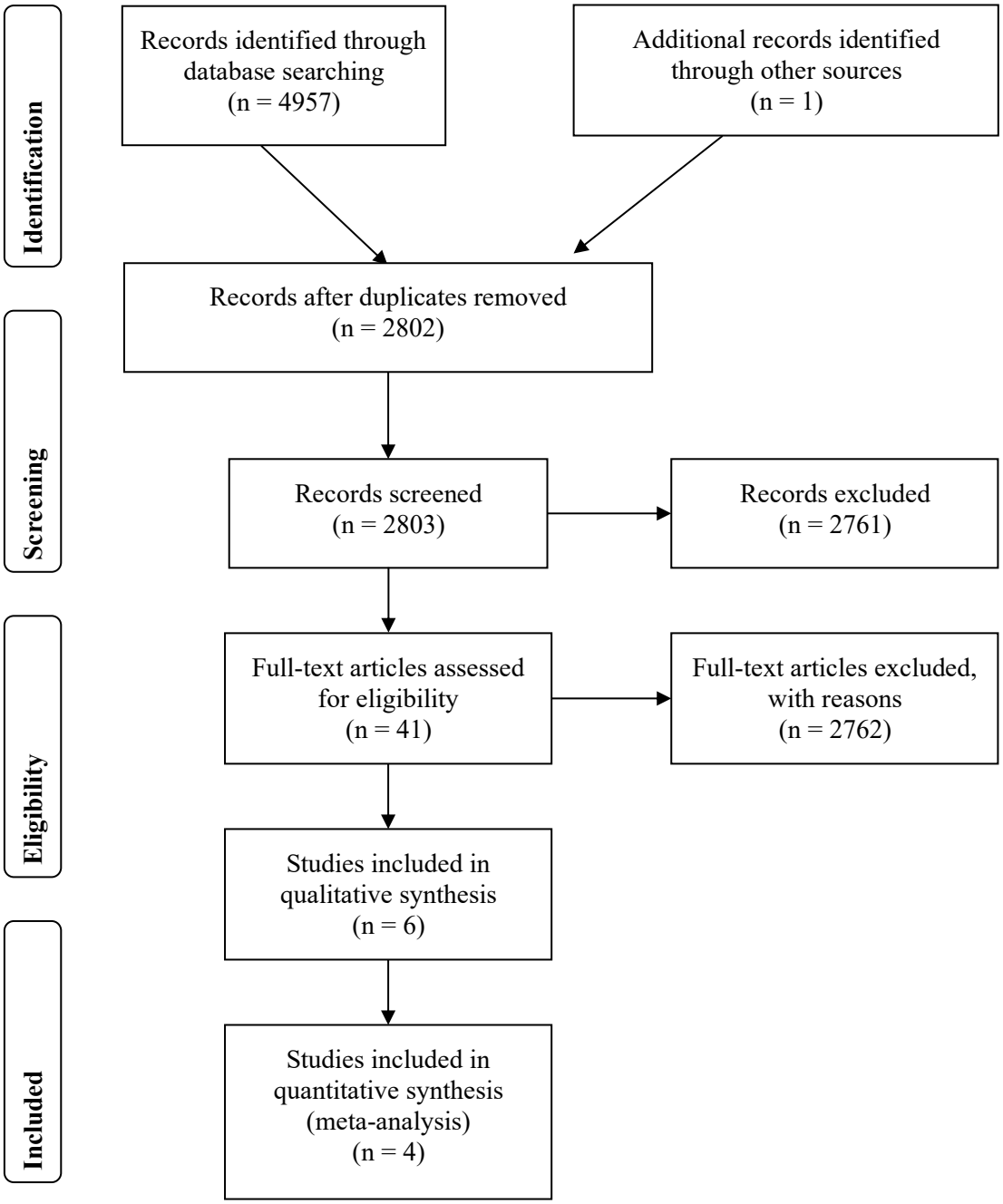


Figure S3.6 Language and communication disorders PRISMA flow diagram



Supplemental Table S3.2 Studies excluded from meta-analyses

Study ID	NDC	ES	Reason
Diepeveen 2018	Language Disorders	Milestones	Effect size unconvertable - % Fail
Fernell 2010	Autism	Milestones	Effect size unconvertable – Median, no SE or SD
Gernsbacher 2008	Autism	Milestones	Effect size unconvertable – Group difference at specific age
Hua 2022	DCD	Milestones	Effect size unconvertable - OR
Isohanni 2001	Schiz	Milestones	Effect size unconvertable - RR
Isohanni 2004	Schiz	Milestones	Effect size unconvertable - Group difference at specific age
Jaaskelainen 2008	Schiz	Milestones	Effect size unconvertable - Group difference at specific age
Karatekin 2003	ADHD	Milestones	Effect size unconvertable - No ES
Lemcke 2016	ADHD	Milestones	Effect size unconvertable – HR
Ming 2007	Autism	Milestones	Effect size unconvertable - % “delayed”
Nickel 2013	Autism	Milestones	Effect size unconvertable - Group difference at specific age
Petruzzelli 2015	Schiz	Milestones	Effect size unconvertable - No ES
Prathanee 2009	Language Disorders	Milestones	Effect size unconvertable - Group difference at specific age
Reynolds 2022	Autism	Milestones	Effect size unconvertable - Group difference at specific age
Clarke 2011	Schiz	Milestones	Effect size unconvertable - OR
Liu 2012	Autism	Milestones	Effect size unconvertable – Z score
Ming 2007	Autism	Milestones	Effect size unconvertable - Group difference at specific age
Gernsbacher 2008	Autism	Milestones	Effect size unconvertable - Group difference at specific age
BegumAli 2020	ADHD	Motor -Other	Wrong study design
Friedman 2005	ADHD	Motor -Other	No group effects
Hadders-Algra 2009	ADHD	Motor -Other	Wrong NDC population;
Wu 2020	ADHD	Motor -Other	Wrong study design
Askeland 2022	ADHD	Motor -Other	No group effects
Achermann 2020	Autism	Motor -Other	No group effects
BegumAli 2020	Autism	Motor -Other	Wrong study design
Bruyneel 2019	Autism	Motor -Other	Wrong NDC population
Heathcock 2015	Autism	Motor -Other	Wrong NDC population
Kozlowski 2012	Autism	Motor -Other	No control group
Serdarevic 2017	Autism	Motor -Other	No infant measure of motor skills
Stevenson 2017	Autism	Motor -Other	Wrong NDC population
Teitelbaum 1998	Autism	Motor -Other	Wrong study design
Lemcke 2013	Autism	Motor -Other	No control group
Oien 2018	Autism	Motor -Other	Wrong NDC population
Ornitz 1977	Autism	Motor -Other	Wrong NDC population
Phagava 2008	Autism	Motor -Other	Infant measure of motor skills too young (<3 months)
Sutera 2007	Autism	Motor -Other	No infant measure of motor skills
Hannigan 2021	Autism	Motor -Other	Wrong study design
MohdNordin 2021	Autism	Motor -Other	No infant measure of motor skills

Note. Studies that were close to meeting inclusion criteria and the reason why they were excluded; OR, odds ratio; RR, risk ratio; ES, effect size; HR, hazard ratio; NDC, neurodevelopmental condition

Supplemental Table S3.3 All Data extracted for meta-analysis

N	Data Extracted
Moderator/Subgroup Analyses	
1	NDC population
2	Year of publication
3	Study design (prospective, retrospective)
4	Age(s) at data collection
Main Analyses	
5	Sample size of NDC participants
6	Sample size of control participants
7	Walking NDC mean (months)
8	Walking NDC SD
9	Walking control M
10	Walking control SD
11	Sitting without support NDC mean (months)
12	Sitting without support NDC SD
13	Sitting without support control M
14	Sitting without support control SD
15	Standing without support NDC mean (months)
16	Standing without support NDC SD
17	Standing without support control M
18	Standing without support control SD
19	Hold head up NDC mean (months)
20	Hold head up NDC SD
21	Hold head up control M
22	Hold head up control SD
23	Roll from back to front NDC mean (months)
24	Roll from back to front NDC SD
25	Roll from back to front control M
26	Roll from back to front control SD
27	Crawl NDC mean (months)
28	Crawl NDC SD
29	Crawl control M
30	Crawl control SD
31	Mullens FM mean NDC
32	Mullens FM mean control
33	Mullens FM SD NDC
34	Mullens FM SD control
35	Mullens GM mean NDC
36	Mullens GM mean control
37	Mullens GM SD NDC
38	Mullens GM SD control
39	Vineland FM mean NDC
40	Vineland FM mean control
41	Vineland FM SD NDC
42	Vineland FM SD control
43	Vineland GM mean NDC
44	Vineland GM mean control
45	Vineland GM SD NDC
46	Vineland GM SD control
Supplemental Data	
47	PubMed ID
48	Author(s)
49	Country of origin of the study
50	Ethnicity of the study population

51	Sex of study population
52	Informant
53	Diagnosis/trait measurement

Note. Data used for data extraction consensus. Data was chosen as the available data included in the meta-analyses from the 20% random selection of studies. M, mean; SD, standard deviation; NDC, neurodevelopmental condition.

Supplemental Table S3.4 Summary of findings from the systematic review of literature which could not have been meta-analysed

Motor Trait	k	NDC	Summary of Findings
Clinical Motor Difficulties	1	Autism	• No significant differences across groups (mildly learning disabled, control, autistic) between 6-18m (M. H. Johnson et al., 1992)
Clumsiness	1	Autism	• Autism group More clumsy and ill-coordinated compared to controls at 18m (Dewrang & Sandberg, 2010)
Fine Motor	5	Autism	• No significant group differences in pointing at 18m (Dewrang & Sandberg, 2010) • Poorer reach to grasp ability compared to controls at 6-24m (Sacrey et al., 2018) • Poorer grasping compared to controls at 6m (LeBarton & Landa, 2019)
		ADHD	• More difficulties reported by parents of infants with ADHD compared to controls 0-36m (Marin-Mendez et al., 2017) • No singificant group differences at 1-15m (Jaspers et al., 2013)
Gait	1	Autism	• Significantly more disturbances in autism group compared to controls at 20m (Esposito & Venuti, 2008)
General Motor Skills	2	Schiz	• No significant group differences at 0-24m (Walker EF et al., 1994)
		Autism	• Lower motor scores in autism group at 12m but not 9m (Jeans et al., 2013)
Gross Motor	2	Autism	• No significant group differences in the perfection of initiation of walking at 18m (Dewrang & Sandberg, 2010) • Poorer gross motor (stationary subscale) skills at 6m predicted autism diagnosis (LeBarton & Landa, 2019)
		ADHD	• Better GM skills in ADHD group compared to controls at 1-15m (Jaspers et al., 2013)
Gross Neurological	3	Autism	• No significant group differences 9-12m (Ozonoff et al., 2008)
		Schiz	• No significant group differences – 8m (Rosso et al., 2000) • 4.6% identified as having some form of developmental deviance in at least one domain at 12m (Isohanni et al., 2001)
Head Lag	1	Autism	• More head lag at 6-36 months in autism group compared to controls (Flanagan et al., 2012)
Motor Activity	3	ADHD	• No significant group differences in motion summaries at 12m (P. Johnson et al., 2014) • More activity in ADHD group at 18, 24, but not 12m (Reetzke, 2022)
		Autism	• More activity in autism group at 18, 24, but not 12m (Reetzke, 2022)
Motor Symmetry	1	Autism	• Less symmetry in sitting but not standing in autism group compared to controls (age not specified, (Esposito & Venuti, 2009)
Movement Imitation	1	Autism	• More difficulties imitating movements in autism group compared to controls at 18m (Dewrang & Sandberg, 2010)

Parental Motor Concerns	1	Autism	• Autistic group's parents had more motor concerns at all measurement time points (6, 9,12, 15, 18, 24m, (Sacrey et al., 2015)
Posture	1	Autism	• 6, 9, and 12m, not at 14 months: autistic group's posture repertoires were significantly smaller than control groups (Nickel et al., 2013)
Toe walking	2	Tics	• No significant group differences in toe walking in the early years (Comings & Comings, 1987)
		Autism	• Autistic group: 51% never toe walked, 33.8% toe walked in the past but no longer do, 15.2% currently toe walk (Uljarevic et al., 2017)
Trajectories of motor development	4	Autism	• FM and GM: Autism group had poorer motor skills than controls at 14 months through to 24 months (Landa & Garrett-Mayer, 2006) • Autism group primarily in more delayed (motor and language) classes compared to controls (Landa et al., 2012) • The probability of a diagnosis of autism in the markedly delayed class (defined by early motor delays and then later language delays) was highest (32.6%) compared with the less/no delayed classes (Nishimura et al., 2019)
		Lang	• FM: Language disorders group poorer motor skills than controls at 6-14 months then catch up, GM: No difference between groups (Landa & Garrett-Mayer, 2006)
Visual-Motor Integration	1	Autism	• Visual-motor integration at 6m did not predict autism diagnosis at 24-36m (LeBarton & Landa, 2019)

Note, Findings across topics for the systematic review in alphabetical order; K, number of separate findings ADHD, attention deficit hyperactivity disorder; Schiz, schizophrenia; Lang, language disorders; ADHD, attention deficit hyperactivity disorder; m, months; FM, fine motor; GM, gross motor.

Supplemental Table S3.5 Model comparison statistics for the neurodevelopmental condition group-control meta-analysis of motor milestone achievement model

	df	AIC	BIC	AICc	logLik	LRT	p	QE
Full	3	36.26	41.41	36.91	-15.13			190.26
Reduced	2	37.77	41.19	38.0 8	-16.88	3.50	0.0613	190.26

Note. Model comparison statistics for analysis of variance (ANOVA) of the full three-level model and the reduced model where the third level is removed. AIC, Akaike information criterion; BIC, Bayesian Information Criterion; AICc, AIC corrected for small samples; logLik, loglikelihood; LRT, loglikelihood ratio test; QE, test for residual heterogeneity.

Supplemental Table S3.6 Model comparison statistics for milestone type subgroup analysis

Domain	Model	df	AIC	BIC	AICc	logLik	LRT	*p*	QE
Hold Head up	Full	3	4.06	2.22	28.06	0.97			
	Reduced	2	2.16	0.93	14.16	0.92	0.97	0.755	5.27
Rolling	Full	3	8.85	6.15	32.85	-1.42			
	Reduced	2	6.84	5.04	18.84	-1.42	0.00	1.000	10.56
Sitting Unaided	Full	3	8.49	8.73	14.49	-1.25			
	Reduced	2	6.75	6.91	9.15	-1.37	0.25	0.614	16.25
Crawling	Full	3	4.07	2.90	28.07	0.96			
	Reduced	2	2.24	1.46	8.24	0.88	0.16	0.686	4.43
Standing	Full	3	8.20	6.36	32.20	-1.10			
Unaided	Reduced	2	6.20	4.97	18.20	-1.10	0.00	1.000	9.70
Walking	Full	3	18.01	19.46	21.01	-6.00			
Unaided	Reduced	2	17.01	17.98	18.34	-6.50	1.00	0.317	57.07

Note. Model comparison statistics for analysis of variance (ANOVA) of the full three-level model and the reduced model where the third level is removed. AIC, Akaike information criterion; BIC, Bayesian Information Criterion; AICc, AIC corrected for small samples; logLik, loglikelihood; LRT, loglikelihood ratio test; QE, test for residual heterogeneity.

Supplemental Table S3.7 Model comparison statistics for neurodevelopmental condition group subgroup analysis

Domain	Model	df	AIC	BIC	AICc	logLik	LRT	p	QE
ADHD	Full	3	3.74	4.33	8.54	1.13			
	Reduced	2	1.73	2.13	3.74	1.13	0.00	1.000	5.89
DCD	Full	3	7.96	8.19	13.96	-0.98			
	Reduced	2	7.77	7.92	10.17	-1.88	1.81	0.179	13.23
Autism	Full	3	10.33	11.24	14.33	-2.17			
	Reduced	2	14.00	14.60	15.71	-5.00	5.67	0.017	36,67
Schizophrenia	Full	3	7.32	8.22	11.32	-0.66			
	Reduced	2	5.32	5.92	7.03	-0.66	0.00	1.000	65.03

Note. Model comparison statistics for analysis of variance (ANOVA) of the full three-level model and the reduced model where the third level is removed. AIC, Akaike information criterion; BIC, Bayesian Information Criterion; AICc, AIC corrected for small samples; logLik, loglikelihood; LRT, loglikelihood ratio test; QE, test for residual heterogeneity.

Supplemental Table S3.8 Sensitivity analysis of neurodevelopmental condition subgroup meta-analysis, excluding studies with non-clinical assessments

NDC Group	K_{est}	g (95% CI)	*p*	Q (df)	p_Q	I^2 L2	I^2 L3
ADHD	0	NA	NA	NA	NA	NA	NA
DCD	3	0.31 (0.01,0.60)	**0.04**	10.09 (2)	0.956	8.56	0
Autism	8	0.70 (0.22,1.19)	**0.001**	28.98 (7)	**0.001**	0.00	77.13

Note. Higher Hedges g refers to late achievement compared to the control group. NDC, neurodevelopmental condition; Results for NDC subgroups which change after excluding studies with non-clinical NDC assessments. K_{est}, number of effect sizes; Q, test for residual heterogeneity; I^2 L2, % of total variance accounted for by variation within samples/cohorts; I^2 L3, % of total variance accounted for by variation between samples/cohorts.

Supplemental Table S3.9 Sensitivity analysis of neurodevelopmental condition subgroup meta-analysis, excluding studies with samples less than 20

NDC Group	K_{est}	g (95% CI)	*p*	Q (df)	p_Q	I^2 L2	I^2 L3
Autism	10	0.55 0.03, 1.06	**0.039**	35.84 (9)	<0.001	0.00	81.98
Domain							
Walking	12	0.69 0.42, 0.96	**<0.001**	56.99 (11)	<0.001	0.00	89.93

Note. Higher Hedges g refers to late achievement compared to the control group. NDC, neurodevelopmental condition; K_{est}, number of effect sizes; Q, test for residual heterogeneity; I^2 L2, % of total variance accounted for by variation within samples/cohorts; I^2 L3, % of total variance accounted for by variation between samples/cohorts.

Supplemental Table S3.10 One-mean meta-analyses of age of motor milestone achievement: Milestone type subgroup analysis

Domain	K_{est}	g (mean age) (95% CI)	WHO Av (95% CI)	Q (df)	Q*p*	I^2 L2	I^2 L3	NDC Q (df)	NDC Q *p*
Hold Head up	5	1.94 (1.28, 2.60)	NA	148.28 (4)	< **.001**	0.00	96.48	0.95 (2)	0.622
Rolling	4	3.67 (2.39, 4.95)	NA	24.66 (4)	< **.001**	87.83	0.00	59.96 (3)	< **0.001**
Sitting Unaided	13	7.25 (6.61, 7.89)	6.0 (5.92,6.08)	139.91 (12)	< **.001**	27.55	70.27	14.51 (3)	**0.002**
Crawling	10	8.89 (8.56, 9.23)	8.5 (8.38, 8.62)	29.67 (9)	< **.001**	60.63	20.41	5.12 (3)	0.138
Standing Unaided	7	11.58 (11.73,12.44)	11.0 (10.87,11.13)	61.65 (6)	< **.001**	94.99	0.00	20.41 (3)	< **0.001**
Walking Unaided	22	13.98 (13.50, 14.47)	12.1 (11.98,12.22)	235.24 (21)	< **.001**	56.50	40.93	14.51 (3)	**0.002**

Note. Higher Hedges g refers to late achievement to the control group. WHO, World Health Organisation; NDC, neurodevelopmental condition; K_{est}, number of effect sizes; Q, test for residual heterogeneity; I^2 L2, % of total variance accounted for by variation within samples/cohorts; I^2 L3, % of total variance accounted for by variation between samples/cohorts.

Supplemental Table S3.11 Model comparison statistics for the one-mean meta-analysis of the age of motor milestone achievement: Milestone type subgroup analysis

Domain	Model	df	AIC	BIC	AICc	logLik	LRT	p	QE
Hold Head up	Full	3	11.90	10.06	35.90	-2.95			
	Reduced	2	12.04	10.82	24.04	-4.02	2.15	0.143	148.28
Rolling	Full	3	14.18	11.47	38.18	-4.08			
	Reduced	2	12.18	10.37	24.28	-4.09	0.00	1.000	59.96
Sitting Unaided	Full	3	49.32	50.77	52.32	-21.66			
	Reduced	2	48.41	49.38	49.74	-22.20	1.09	0.297	139.91
Crawling	Full	3	24.56	25.15	29.36	-9.28			
	Reduced	2	22.60	22.99	24.60	-9.30	0.04	0.845	29.67
Standing Unaided	Full	3	24.91	24.28	36.91	-9.45			
	Reduced	2	22.91	22.49	26.91	-9.45	0.00	1.000	61.65
Walking Unaided	Full	3	76.95	80.08	78.36	-35.47			
	Reduced	2	75.14	77.23	75.81	-35.57	0.20	0.658	235.24

Note. Model comparison statistics for analysis of variance (ANOVA) of the full three-level model and the reduced model where the third level is removed. AIC, Akaike information criterion; BIC, Bayesian Information Criterion; AICc, AIC corrected for small samples; logLik, loglikelihood; LRT, loglikelihood ratio test; QE, test for residual heterogeneity.

Supplemental Table S3.12 One-mean meta-analysis of age of walking: Neurodevelopmental condition group subgroup analysis

NDC	K_{est}	g (mean age) (95% CI)	WHO Av (95% CI)	Q (df)	Q*p*	I^2 L2	I^2 L3
ADHD	2	13.70 (12.59,14.82)	12.1 (11.98,12.22)	2.28 (1)	0.131	28.04	28.04
DCD	2	15.99 (14.93,17.05)	12.1 (11.98,12.22)	0.06 (1)	0.811	0.00	0.00
Autism	15	14.07 (13.53,14.63)	12.1 (11.98,12.22)	107.09 (14)	<.001	48.52	48.52
Schizophrenia	2	12.61 (11.93,13.29)	12.1 (11.98,12.22)	4.28 (1)	0.039	38.33	38.33

Note. Higher Hedges g refers to late achievement compared to the control group. NDC, neurodevelopmental condition; K_{est}, number of effect sizes; Q, test for residual heterogeneity; I^2 L2, % of total variance accounted for by variation within samples/cohorts; I^2 L3, % of total variance accounted for by variation between samples/cohorts.

Supplemental Table S3.13 Model comparison statistics for one-mean meta-analysis of age of walking: Neurodevelopmental condition group subgroup analysis

Domain	Model	df	AIC	BIC	AICc	logLik	LRT	p	QE
ADHD	Full	3	8.42	2.42	32.42	-1.21			
	Reduced	2	6.42	2.42	18.42	-1.21	0.00	1.000	2.28
DCD	Full	3	8.37	2.37	32.37	-1.19			
	Reduced	2	6.37	2.37	18.37	-1.19	0.00	1.000	0.06
Autism	Full	3	53.33	55.25	55.73	-23.66			
	Reduced	2	51.33	52.61	52.42	-23.66	0.00	1.000	107.09
Schizophrenia	Full	3	7.43	1.43	31.43	-0.72			
	Reduced	2	5.43	1.43	17.43	-0.72	0.00	1.000	4.28

Note. Model comparison statistics for analysis of variance (ANOVA) of the full three-level model and the reduced model where the third level is removed. AIC, Akaike information criterion; BIC, Bayesian Information Criterion; AICc, AIC corrected for small samples; logLik, loglikelihood; LRT, loglikelihood ratio test; QE, test for residual heterogeneity.

Supplemental Table S3.14 Model comparison statistics for the neurodevelopmental condition group-control meta-analysis of standardised motor measurement

	df	AIC	BIC	AIC	logLik	LRT	p	QE
Full	3	76.95	80.08	78.36	-35.47			235.24
Reduced	2	**75.14**	**77.23**	75.81	-35.57	0.20	**0.66**	235.24

Note. Model comparison statistics for analysis of variance (ANOVA) of the full three-level model and the reduced model where the third level is removed. AIC, Akaike information criterion; BIC, Bayesian Information Criterion; AICc, AIC corrected for small samples; logLik, loglikelihood; LRT, loglikelihood ratio test; QE, test for residual heterogeneity.

Supplemental Table S3.15 Neurodevelopmental condition group-control meta-analysis of standardised motor measurement: Age of measurement subgroup analysis

Age of Measurement	K_{est}	g (95% CI)	*p*	Q (df)	p_Q	I^2 L2	I^2 L3
6-12 Months	20	-0.34 (-0.47,-0.20)	<**0.001**	35.07 (19)	0.013	42.37	0.00
12-18 Months	17	-0.64 (-0.87,-0.42)	<**0.001**	23.13 (16)	0.110	0.00	53.79
18-24 Months	15	-0.83 (-1.06,-0.59)	<**0.001**	42.83 (14)	<**0.001**	70.24	0.00

Note. Higher Hedges g refers to late achievement compared to the control group. K_{est}, number of effect sizes; Q, test for residual heterogeneity; I^2 L2, % of total variance accounted for by variation within samples/cohorts; I^2 L3, % of total variance accounted for by variation between samples/cohorts.

Supplemental Table S3.16 Model comparison statistics for age of measurement subgroup analysis

Age of Measurement	Model	df	AIC	BIC	AICc	logLik	LRT	p	QE
6-12 Months	Full	3	20.40	23.24	22.00	-7.20			35.07
	Reduced	2	18.40	20.29	19.15	-7.20	0.00	1.000	35.07
12-18 Months	Full	3	6.99	9.31	8.99	-0.49			23.13
	Reduced	2	10.18	11.73	11.10	-3.09	5.19	**0.023**	23.13
18-24 Months	Full	3	25.59	27.50	27.99	-9.79			42.83
	Reduced	2	25.59	24.86	24.68	-9.79	0.00	1.000	42.83

Note. Model comparison statistics for analysis of variance (ANOVA) of the full three-level model and the reduced model where the third level is removed. AIC, Akaike information criterion; BIC, Bayesian Information Criterion; AICc, AIC corrected for small samples; logLik, loglikelihood; LRT, loglikelihood ratio test; QE, test for residual heterogeneity.

Supplemental Table S3.17 Neurodevelopmental condition group-control meta-analysis of standardised motor measurement: Neurodevelopmental condition group subgroup analysis

NDC Group	K_{est}	g (95% CI)	*p*	Q (df)	p_Q	I^2 L2	I^2 L3
Autism	46	-0.58 (-0.71, -0.46)	**<.0001**	130.27 (45)	**<.0001**	62.68	3.83
Language Disorders	6	-0.54 (-1.03, -0.05)	**0.031**	16.18 (5)	**0.006**	69.33	NA

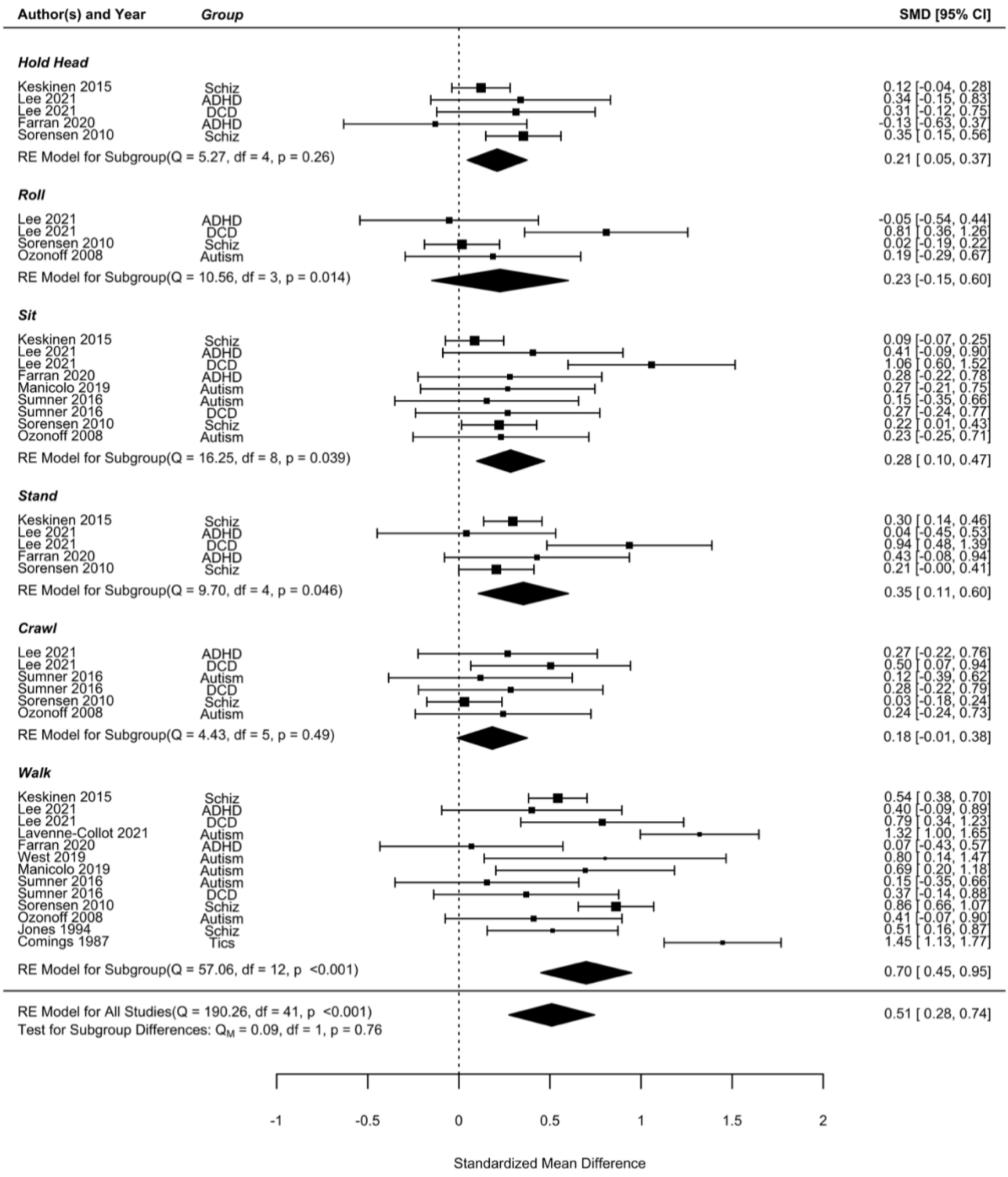
Note. Higher Hedges g refers to late achievement compared to the control group. NDC, neurodevelopmental condition; K_{est}, number of effect sizes; Q, test for residual heterogeneity; I^2 L2, % of total variance accounted for by variation within samples/cohorts; I^2 L3, % of total variance accounted for by variation between samples/cohorts.

Supplemental Table S3.18 Model diagnostics for neurodevelopmental condition group subgroup analysis

NDC Group	Model	df	AIC	BIC	AICc	logLik	LRT	p	QE
Autism	Full	3	52.16	57.58	52.75	-23.08			130.27
	Reduced	2	50.23	53.84	50.51	-23.11	0.07	0.798	130.27
Language	Full	3	NA	NA	NA	NA			NA
Disorders	Reduced	2	NA	NA	NA	NA	NA	NA	NA

Note. Model comparison statistics for analysis of variance (ANOVA) of the full three-level model and the reduced model where the third level is removed. AIC, Akaike information criterion; BIC, Bayesian Information Criterion; AICc, AIC corrected for small samples; logLik, loglikelihood; LRT, loglikelihood ratio test; QE, test for residual heterogeneity.

Figure S3.7 Forest plot of multilevel random effects model for standardised mean difference in motor milestone achievement between neurodevelopmental condition groups with milestone type subgroups



Note, Positive effect sizes mean late achievement compared to controls. ADHD, attention deficit hyperactivity disorder, DCD, developmental coordination disorder, Schiz, schizophrenia; SMD, standardised mean difference.

Figure S3.8 Funnel plot of standardised mean difference of milestone achievement

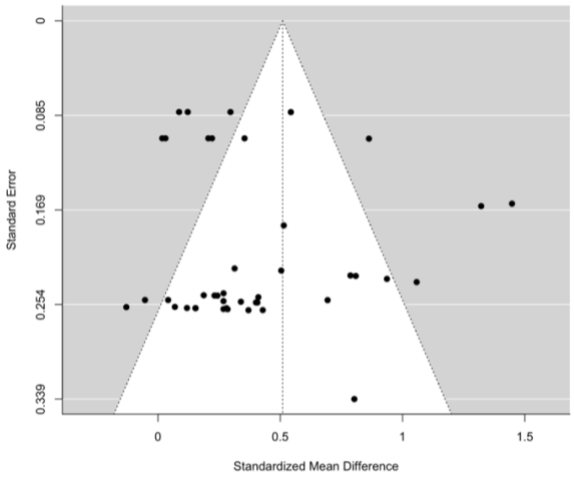


Figure S3.9 Funnel plot of standardised mean difference of age of walking unaided

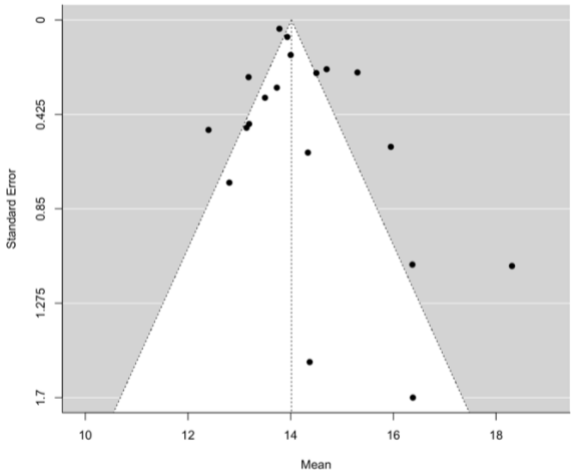


Figure S3.10. Funnel plot of standardised mean difference of age of sitting unaided

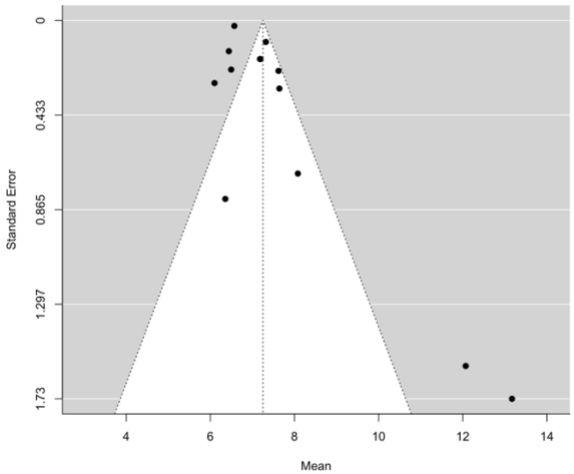


Figure S3.11. Funnel plot of standardised mean difference of age of standing unaided

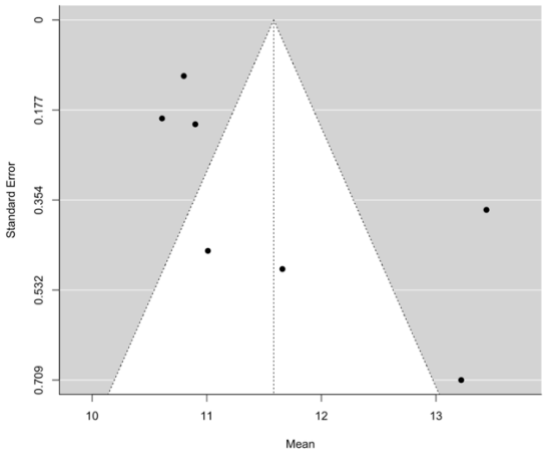


Figure S3.12 Funnel plot of standardised mean difference of age of crawling

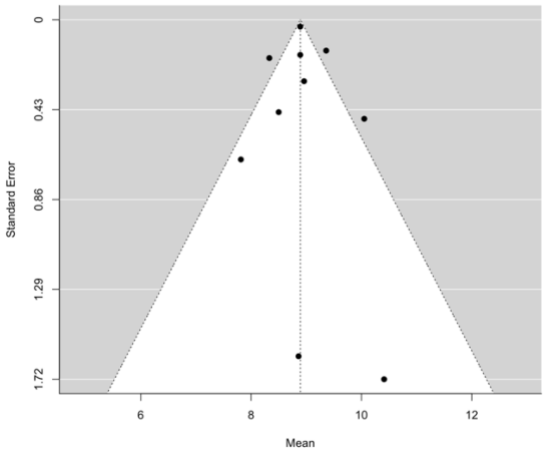


Figure S3.13 Funnel plot of standardised mean difference of age of rolling

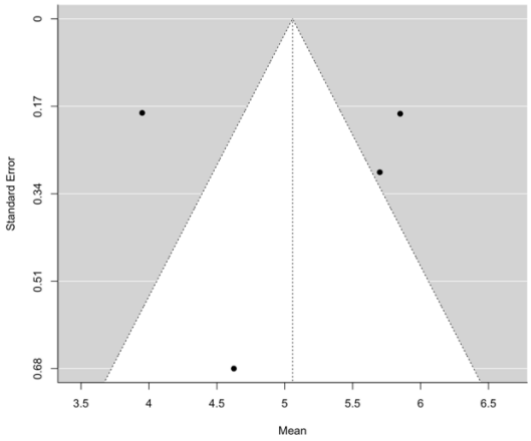


Figure S3.14. Funnel plot of standardised mean difference of age of lifting head

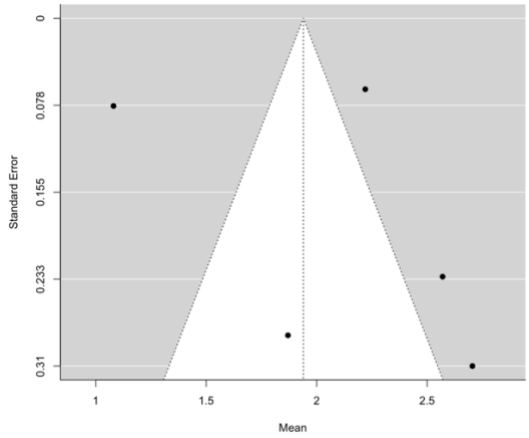
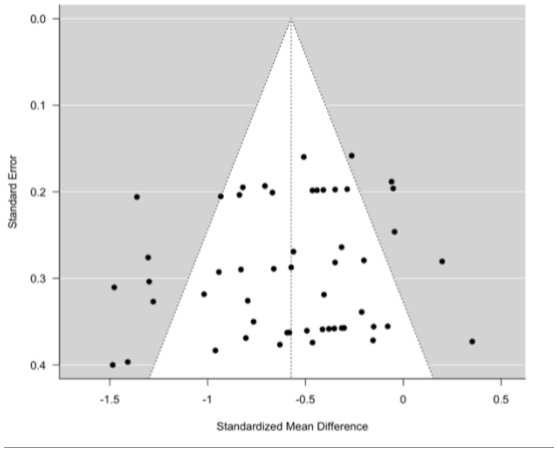


Figure S3.15. Funnel plot of standardised mean difference of standardised motor skills



4. Associations Between Preschool Fine Motor Skills and Later Neurodevelopment, Psychopathology, and Educational Achievement

4.1 Associated publication

The research presented in this chapter and chapter 5 is from a manuscript published in Biological Psychiatry, adapted for the thesis (Bowler, Arichi, Fearon, Meaburn, Begum-Ali, Pascoe, Johnson, Jones & Ronald, 2023).

4.2 Introduction

Proficient motor skills require both the acquisition of physical capabilities such as muscle tone and substantial neurodevelopment, both of which develop steeply over the first years after the birth of a child (Knickmeyer et al., 2008). A large number of lines of evidence suggest that motor skills may sit on the same pathway as multiple neurodevelopmental, psychiatric, and educational outcomes later in development. These were addressed in the Introduction in sections 1.4 and 1.5. Observing fine motor skills early in life could contribute to the ability to pre-empt these later outcomes at a time in development when neuroplasticity is elevated (Morgan et al., 2021).

Atypical motor development in the first years after birth could be an early marker for the later development of neurodevelopmental or psychiatric disorders. However, these associations have not been extensively studied with respect to fine motor skills. However, there is some evidence for an association between fine motor skills and neurodevelopmental and psychiatric outcomes. The meta-analysis in Chapter 3 exemplifies how there is limited research on fine motor skills compared to gross motor skills in early development. However, my meta-analysis in Chapter 3 of standardised assessments in autism and language disorders revealed impaired infant fine motor skills in both conditions (section 3.4.3.3), and my systematic review in Chapter 3 revealed evidence of impaired fine motor skills in autism, ADHD, schizophrenia, and DCD conditions (section 3.4.2). Further, some

genetic influences are shared across neurodevelopmental and psychiatric conditions (Guilmatre et al., 2009; Ronald, Simonoff, et al., 2008; Rujescu et al., 2009; Stergiakouli et al., 2017). It is therefore justified to explore whether there is an association between early fine motor impairments and not only specific neurodevelopmental and psychopathological phenotypes but also an overall composite score spanning these traits.

There is consistent evidence for an association between fine motor development and later cognitive outcomes. Most studies in section 1.4 highlight positive associations between fine motor skills and cognition from early to late childhood. Further investigation is required to understand if early fine motor skills are also associated with educational outcomes.

An investigation has yet to take place into the associations between fine motor skills in early childhood and neurodevelopmental and psychiatric traits at multiple time points across childhood and adolescence. Understanding whether fine motor skills are associated with traits across childhood and adolescence or at specific ages is important. Given that autism, ADHD, and behavioural problems are most commonly diagnosed in early to mid-childhood, the associations with fine motor skills may be stronger earlier in childhood. Depression is diagnosed more commonly in adolescence, and thus, associations with early fine motor skills may be more substantial compared to middle childhood.

In light of the extant literature, our study aimed to assess phenotypic associations between early fine motor skills and later neurodevelopmental, psychiatric, and cognitive traits. A measure of fine motor skills was derived from a combination of questionnaire items and parent-administered tasks on 2-, 3- and 4-year-olds. The derived fine motor measure was then used to investigate phenotypic associations between early fine motor skills and later neurodevelopmental, psychiatric, and cognitive traits from childhood to adolescence. We collated these traits into three ages, mid-childhood (7-8 years), late-childhood (12 years), and adolescence (16 years), and derived psychopathology composite score (across-age) to investigate how associations differ across development.

Our pre-registered hypotheses were:

1. Fine motor skills in early childhood will associate with autistic traits, ADHD, anxiety-depression, depression, behaviour problems, psychopathology composite scores, and psychotic experiences.
2. Fine motor skills in early childhood will more strongly associate with autistic traits, ADHD, and behavioural problems in mid-childhood compared to late-childhood and adolescence.
3. Fine motor skills in early childhood will more strongly associate with anxiety and depression traits in adolescence than in late-childhood and mid-childhood.
4. Higher fine motor skills in early childhood will associate with higher education outcomes (GCSE total score).

4.3 Method

4.3.1 Preregistration

This study's methods and hypotheses were pre-registered on the Open Science Framework (Bowler & Ronald, 2021). Analyses not pre-registered are indicated.

4.3.2 Sample

The participants are from the Twins Early Development Study (TEDS), a longitudinal study of N>10,000 twin pairs from England and Wales (Table 4.2). Children born between 1994 and 1996 were recruited to the sample, which was representative of the UK population in relation to socioeconomic status (SES), ethnicity, and parental occupation (Haworth et al., 2013).

Individuals were excluded based on standard TEDS exclusion criteria based on medical conditions that affect the ability to take part in the study or that are associated with mental impairment. The criteria include: "severe" autism (non-verbal or with severely delayed speech or difficulties completing activities), severe cerebral palsy, chromosomal abnormalities, inherited or genetic conditions having known associations with mental impairment, brain organically affected, (global) developmental delay, deafness, or blindness. Secondly, participants were excluded if there

were extreme adverse conditions that happened before or after birth and may have affected the child's development where twin pairs fell into one or more of the following: very low birth weight (less than 471g for either or both twins), long period of special care after birth (for either or both twins of more than 97 days), long period of hospital admission after birth for either or both twins (of more than 74 days) a very short period of gestation (less than 27 weeks), finally, high weekly consumption of alcohol by mother during pregnancy (14 or more units per week). Also, participants were excluded if they had no first contact data or unknown twin zygosity or gender (Haworth et al., 2013).

Demographic information was collected through questionaries at first contact (1-2 years). The information collected included socioeconomic status (SES), ethnicity, and zygosity. SES was derived from 5 variables related to parent qualifications, employment, and mother's age at birth of first child. The scale was derived by computing the mean of the five standardised SES ratings. For ethnicity, parents were asked, "What is the ethnic origin of your twins?" and given a list of Asian, Black, Mixed Race, White, or Other. The response was then coded as White or Non-White. Finally, zygosity was coded as monozygotic (MZ) or dizygotic (DZ) based on a zygosity algorithm that considered several measures from first contact to later in the study, including DNA markers, questionnaire data, and physical characteristics (for more details on the algorithm see, (*The Zygosity Algorithm*, 2023). The sub-sample with the required fine motor data had a higher percentage of those who identified as white in their ethnicity, a higher mean SES, and a higher proportion of monozygotic individuals (all p's < .001, Table S4.3). However, the effect sizes were modest.

All analyses were limited to unrelated individuals (one twin was randomly selected from each pair) and those who completed preschool fine motor skills assessments at least one age point (at 2, 3, or 4 years, N=9625).

4.3.3 Ethical approval

Ethical approval for TEDS was approved by the Kings College London Ethics Committee (References: PNM/09/10–104 and HR/DP-20/21– 22060). Ethical approval for secondary data analyses was approved by the Birkbeck College Ethics Committee (2021060). Written parental and/or self-consent was obtained from all participants.

4.3.3 Measures

4.3.3.1 Socioeconomic status

Socioeconomic status (SES) was derived from five variables related to parental qualifications, parental employment, and mother's age at birth of first child. This data was taken at first contact when the child was 18 months old. The scale was derived by computing the mean of the five standardised SES ratings. SES has been shown to be stable over the course of the TEDS study; the score at 18 months correlated highly (r= 0.77) with SES at age seven and parental income at age 9 (r=0.55, (Hanscombe et al., 2012).

4.3.3.2 Preschool motor skill assessments

The items were selected from a hybrid assessment consisting of fine motor tasks (delivered by parents) and parent questionnaire items of non-verbal cognition, the Parent Report of Children's Abilities (PARCA), undertaken at ages 2, 3, and 4. This measure has been shown to have good validity for aren't-reported and parent-administered tasks at age two against a gold standard scale of infant development: Mental Development Index (MDI) of the Bayley Scales of Infant Development-I1 ((r= 0.49, p< 0.001; r = 0.41, p< 0.001; respectively; (Bayley, 1993; Saudino et al., 1998).

Specifically, parents were given booklets that included instructions on how to direct their children to complete the tasks, which were either completed directly in the booklet (e.g., drawing) or observed and reported on by the parent (e.g., block-building). The motor-relevant tasks were drawing, block building, folding, and questionnaire items relating to motor activities observed in the home (Tables 4.1a,b). An example of the drawing assessment can be seen in Figure 4.1.

4.3.3.3 Later childhood measures

The later childhood measures (Table 4.1c) were collected at three ages (mid-childhood–age 7/8, late-childhood–age 12, adolescence- age 16). They included multiple raters (parent, self, or teacher). Most traits that were measured across ages used the same questionnaires; however, questionnaires for autistic traits and anxiety/ anxiety-depression varied across age (see Table 4.1c). All

Table 4.1 Phenotypic measure items, age at administration, and rater(s)

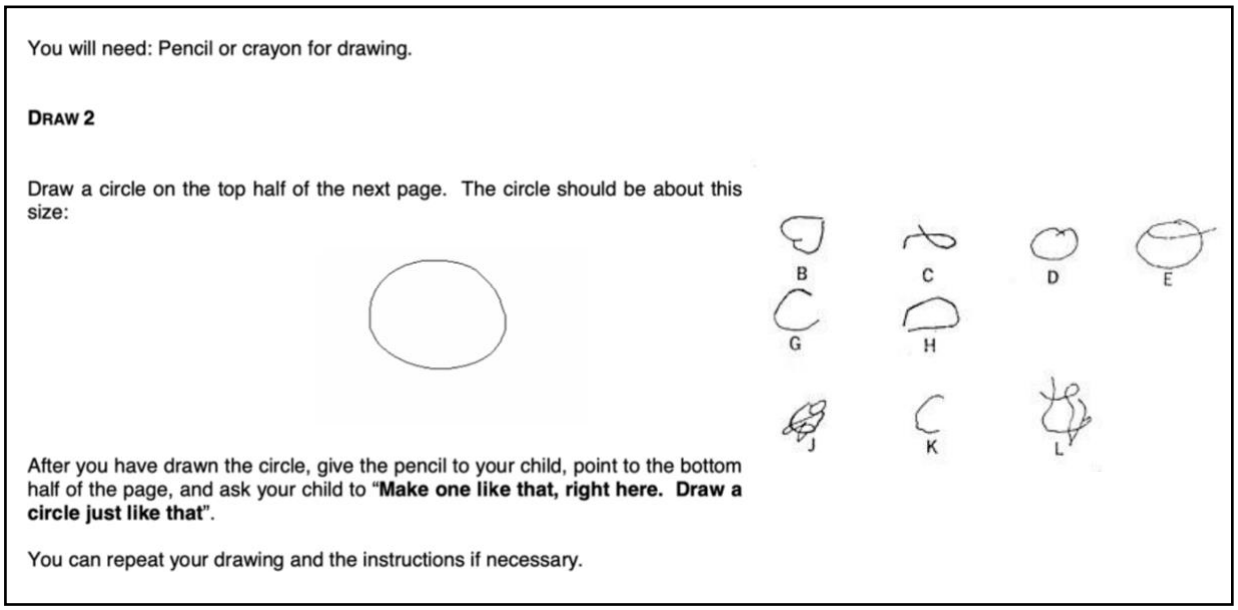
	Measure group	Measure	Age(s)	Rater(s)
a	PARCA Tasks (Total scores)	Design drawing	2,3,4	Parent administered
		Brick building	2	
		Folding task	2	
		Draw-a-man	4	
b	PARCA Parental Questionnaire Items	Can your child stack seven small blocks or toys on top of each other *by him/herself?*	2	parent
		Can your child draw a more or less straight line on paper?	2,3	parent
		Does your child turn, or attempt to turn, pages of a book one at a time?	2	parent
		Does your child build things with bricks (other than a tower), such as a house or a bridge?	3	parent
c	Phenotypic Trait Questionnaires	Strengths and Difficulties Questionnaire Total Problem Behaviours (SDQ(Goodman, 2001)	7,12,16	parent, teacher (7,12), self (16)
		Anxiety and Depression (ANX DEP, (Hogg C et al., 1997)	7	parent, teacher
		Child Autism Spectrum Test (CAST(Williams et al., 2005)	8, 12	parent
		Conners: Parent Rating Scales: ADHD (CPRS, (Conners et al., 1998)	8,12,16	parent
		Moods and Feelings Questionnaire (MFQ, (Messer et al., 1995)	12,16	parent, self (16)
		SPEQ Psychotic experiences (Ronald et al., 2014):		
		Negative Symptoms (Andreasen, 1989) Cognitive Disorganisation (Mason et al., 2005) Grandiosity (Beck et al., 2006) Hallucinations (Bell et al., 2006) Hedonia (Gard et al., 2006) Paranoia (Freeman et al., 2005)	16	parent, self
		Abbreviated Autism Spectrum Quotient (AQ(Baron-Cohen et al., 2006)	16	parent, self
		Anxiety-Related Behaviours Questionnaire (ARBQ(Eley et al., 2003)	16	parent
		Educational Achievement (*Recording Exam Results in TEDS 16 Year Study*, 2022)	16	self
		Psychopathology composite score (See Table S4.2)	7,9,12,16	parent, teacher, self

Note: PARCA, Parent Report of Children's Abilities

phenotypic variables were z-standardised. Sample sizes differed longitudinally due to missing data (mid-childhood, N=4,265; late-childhood, N=3,664; adolescence, N=3,926). For the psychopathology composite score analysis, we used imputation to devise the score for those with at least one phenotypic measure (N=7779).

Cronbach Alpha values were calculated from item-level data for all measures (see Table S4.2). Further information can be found on the TEDS data dictionary website (*TEDS Data Dictionary*, n.d.).

Figure 4.1. Example of a drawing skill assessment from the Parent Report of Children's Abilities Cognitive Assessment in the Twins Early Development Study



Note. Instructions for parents and the coding scheme for the drawing skill assessment from the Parent Report of Children's Abilities Cognitive Assessment in the Twins Early Development Study. More information on the Twins Early Development Study website (*TEDS Data Dictionary*, n.d.)

4.3.3.3.1 Strengths and Difficulties Questionnaire - Total Problem Behaviours (SDQ)

The SDQ was developed by Goodman (2001). The total behavior scale for SDQ comprises 20 items. Items are from four 5-item subscales: conduct problems, anxiety (emotional symptoms), hyperactivity, and peer relationships. The pro-social subscale of the SDQ is not included in the total

behavior score. Items are rated as: “not true”, “somewhat true”/” quite true”, or “certainly true”/” very true”.

4.3.3.3.2 Anxiety and Depression DSM-IV (ANX DEP)

A scale to measure anxiety and depression traits in mid-childhood was used that included items based on the DSM-IV criteria for anxiety disorders and depression (Hogg C et al., 1997). The parent is asked, “*Finally, let’s go back to thinking about how each twin behaves. Below are some different descriptions, and we would like you to tell us if they seem to be Certainly True, Somewhat True or Not True of each twin in turn”*. Examples of items include if the child tends to be: “On edge/tense”, “Afraid in social situations”, or “Anxious”.

4.3.3.3.3 Child Autism Spectrum Test (CAST)

The CAST (formerly the “Childhood Asperger’s Syndrome Test”) assesses autistic traits in children. Raters respond with a “yes” or “no” for each item. The questionnaire was developed by The Autism Research Centre at the University of Cambridge (Williams et al., 2005).

4.3.3.3.4 Conners Parent Rating Scale, Revised (CPRS)

This Conners Parent Rating Scale is an 18-item ADHD symptom scale measuring inattentive and hyperactive-impulsive symptoms (Conners et al., 1998). Raters respond with “not true at all”/ “not at all true”, “just a little true”/“just a little bit true”/“somewhat true”, “pretty much true”/“mainly true”, “very much true”/“definitely true”.

4.3.3.3.5 Moods and Feelings Questionnaire - Short Version (MFQ)

The MFQ is a screening tool for depression in children and young people (Messer et al., 1995). The questionnaire includes descriptive phrases about how the subject has been feeling or acting in the past two weeks. Respondents are asked whether descriptions in the questionnaire are “not true”, “somewhat true” / “quite true” or “certainly true” / “very true”.

4.3.3.3.6 Subscales of the Specific Psychotic Experiences Questionnaire (SPEQ)

SPEQ measures specific psychotic experiences in adolescents and young people (Ronald et al., 2014). It includes five self-report subscales (paranoia, hallucinations, cognitive disorganisation, grandiosity, and hedonia) and one parent-rated subscale (parent-rated negative symptoms). More information for each subscale can be found in the appendix.

4.3.3.3.7 Abbreviated Autism Spectrum Quotient (AQ)

The AQ quantifies autistic traits in adolescents and adults(Baron-Cohen et al., 2006). Respondents respond with “definitely agree”, “slightly agree”, “slightly disagree”, or “definitely disagree” to statements.

4.3.3.3.8 Anxiety-Related Behaviours Questionnaire (ARBQ)

The ARBQ is a parent-reported, 19-item questionnaire on anxiety-related behaviours in children (Eley et al., 2003). Items are rated on a 3-point scale: “not true”, “quite true”, or “very true”.

4.3.3.3.9 Educational achievement

Educational Achievement (EA) was measured in qualifications at school at age 16, including GCSEs, vocational qualifications (BTEC, OCRN, Key Skills), and any AS levels completed early. GCSEs were given grade values ranging from 4 (grade G) to 11 (grade A*) and workload values of 0.5 or 1. A score was generated by multiplying the grade score by the workload value and then summing across qualifications. The score thus ranged from 0 upwards (a score of 0 indicates no GCSE results). The subject categories included maths, English, science, technology, humanities, languages, and vocational subjects. More information on coding can be found on the TEDS website (*Recording Exam Results in TEDS 16 Year Study*, 2022).

4.3.4 Statistical Analysis

4.3.4.1 Fine motor composite score

Fine motor data from all ages (2, 3, and 4 years) were used to derive a fine motor composite score using a PCA method. The following preliminary steps were taken to prepare the data for the PCA. Firstly, a PCA-based imputation method was used on the data using the imputePCA function from the missMDA R package (Husson & Josse, 2020). This method considers the similarities between the observations and the relationship between variables. The function imputes missing values using an iterative PCA algorithm to ensure the imputed values do not affect PCA results (Josse & Husson, 2016). To do this, the function estim_ncpPCA is used to estimate the number of dimensions. The default approach of generalised cross-validation revealed the requirement of 1 dimension.

Secondly, missing data was assessed for whether it was missing completely at random (MCAR) using the mcar_test function from the naniar R package (Tierney et al., 2021). The data was not MCAR. As it is difficult to ascertain whether the data was *missing at random* or *missing not at random*, it was assumed to be missing at random (Bhaskaran & Smeeth, 2014). Next, a Bartlett Test of Sphericity conducted with all variables was significant ($p<.05$), indicating that no items needed to be removed. A Kaiser-Meyer-Olkin test, which tests how suitable the data are to a PCA, revealed two items, both at two years, with values lower than 0.5 (0.47, 0.51; "*Can your child stack three small blocks or toys on top of each other by him/herself"* and "*Can your child mark on a piece of paper using the tip of a crayon, pencil, or chalk?*"). After exploring these items, which were both questionnaire items, there was an apparent ceiling effect. Removing these items increased the Cronbach Alpha value by 0.002 and 0.003, respectively, and the overall KMO test increased from 0.61 to 0.79. We, therefore, removed these items. A PCA with one principal component was derived using the *principal* function from the *psych* R package (Revelle, 2023). The final score was regressed on sex and gestational age and z-standardised. There were no significant differences between monozygotic and dizygotic twins' fine motor scores ($t(6389.7)= -1.52$, $p= 0.128$).

4.3.4.2 *Psychopathology composite score*

A psychopathology composite score for three raters (self, parent, teacher) was generated by including all psychiatric and neurodevelopmental traits between 7-16 years as in Allegrini et al.'s p factor score (Allegrini et al., 2020, see Table S4.1). Missing data was assessed for whether it was missing completely at random (MCAR) using the *mcar_test* function from the *naniar* R package (Tierney et al., 2021). The data was not MCAR, so it was assumed to be missing at random. All individuals with at least one non-missing phenotypic variable were included. To create a complete dataset necessary for a PCA analysis, we used a PCA-based imputation method on the data using the imputePCA function from the *missMDA* R package (Husson & Josse, 2020).

4.3.4.3 Longitudinal Phenotypic Analysis

A multivariate regression analysis of fine motor skills predicting multiple phenotypic traits was performed for each age of assessment (mid-childhood, late-childhood, and adolescence, cross-age psychopathology composite score) using the Lavaan R package (Rosseel et al., 2023). All regressions included measures from all available raters (self, parent, teacher). Each p-value was false discovery rate (FDR) corrected for the multiple comparisons within each model (mid-childhood, N=5; late-childhood, N=8; adolescence, N=15; and psychopathology composite (N=3). All analyses controlled for gestational age, age of assessment, and sex, apart from the psychopathology composite score analysis, which did not control for age due to multiple assessments.

4.3.4.4 Sensitivity analyses

Three sensitivity analyses were run to determine if the results remained once individual changes were made to the analyses.

Firstly, we re-ran the main analyses with an additional exclusion with those that the World Health Organization classifies as very preterm (gestational age of < 32 weeks) as opposed to the standard TEDS exclusion of extremely premature (gestational age of < 27 weeks). N= 920 were excluded, leaving N=8806. The demographics table for the sub-sample can be found in Table S4.4.

Secondly, in a non-pre-registered analysis, all main models were repeated using a fine motor composite score, which did not include any questionnaire items. Five parental questionnaire items were removed, leaving six parent-administered items (see Tables 4.1b and c). Otherwise, the same methodologies of deriving the composite score with a PCA, as detailed in section 4.3.4.1, and the same regression models in 4.2.4.3 were used.

Finally, all phenotypic models were repeated, controlling for socioeconomic status (SES, see section 4.3.3.1) in addition to the existing covariates (see section 4.3.4.3). Otherwise, the same method, as detailed in section 4.3.4.3, was used.

4.3.4.5 Supplementary analysis - Comparison of sample demographics between those selected and not selected

Demographic information was collected through questionaries at first contact (1-2 years). The information included SES (described in section 4.3.3.1), ethnicity, and zygosity. For ethnicity, parents were asked, “What is the ethnic origin of your twins?” and given a list of Asian, Black, Mixed Race, White, or Other. The response was then coded as White or Non-White. Finally, zygosity was coded as monozygotic (MZ) or dizygotic (DZ) based on a zygosity algorithm that considered several measures from first contact to later in the study, including DNA markers, questionnaire data, and physical characteristics (*The Zygosity Algorithm*, 2023).

4.4 Results

The demographics of the study sample are presented in Table 4.2. Figure 4.2 and Table 4.3 show the full longitudinal phenotypic multivariate analysis results. All *p* values are FDR corrected. The mid-childhood model revealed significant associations between higher fine motor scores and lower scores for all phenotypic traits, for example, autistic traits (CAST parent-rated, ß= -0.10, 95% 95% CI: -0.12, -0.07, $p<0.001$), and ADHD traits (CPRS parent-rated, ß= -0.15, 95% CI: -0.17, -0.12, $p<0.001$).

The late-childhood model revealed significant associations between higher fine motor scores and lower scores for all phenotypic traits, for example, autistic traits (CAST parent-rated, ß= -0.10, 95% CI: -0.13, -0.06, p<0.001), ADHD (CPRS parent-rated, ß= -0.13, 95% CI: -0.17, -0.10, p<0.001), and depression traits (MFQ parent-rated, ß= -0.08, 95% CI: -0.12, -0.05, p<0.001; and self-rated, ß= -0.09, 95% CI: -0.19, -0.05, p<0.001).

The adolescence regression model revealed significant associations between higher fine motor scores and scores for multiple phenotypic traits, including lower autistic traits (AQ, parent-rated, ß= -0.12, 95% CI: -0.15, -0.08, p<0.001), ADHD (CPRS parent-rated, ß= -0.11, 95% CI: -0.14, -0.08, p<0.001), depression traits (MFQ parent-rated, ß= -0.07, 95% CI: -0.10, -0.04, p<0.001), and higher educational achievement (ß= 0.25, 95% CI: 0.22, 0.28, p<0.001). However, no associations were found for autism traits (AQ, self-rated, p= 0.114), depression traits (MFQ, self-rated, p= 0.998), and multiple self-rated psychotic experiences scales (SPEQ): paranoia (PARA, p= 0.136); hedonia, (HED, p= 0.979); hallucinations, (HAL, p= 0.748); and grandiosity (GRAND, p= 0.425).

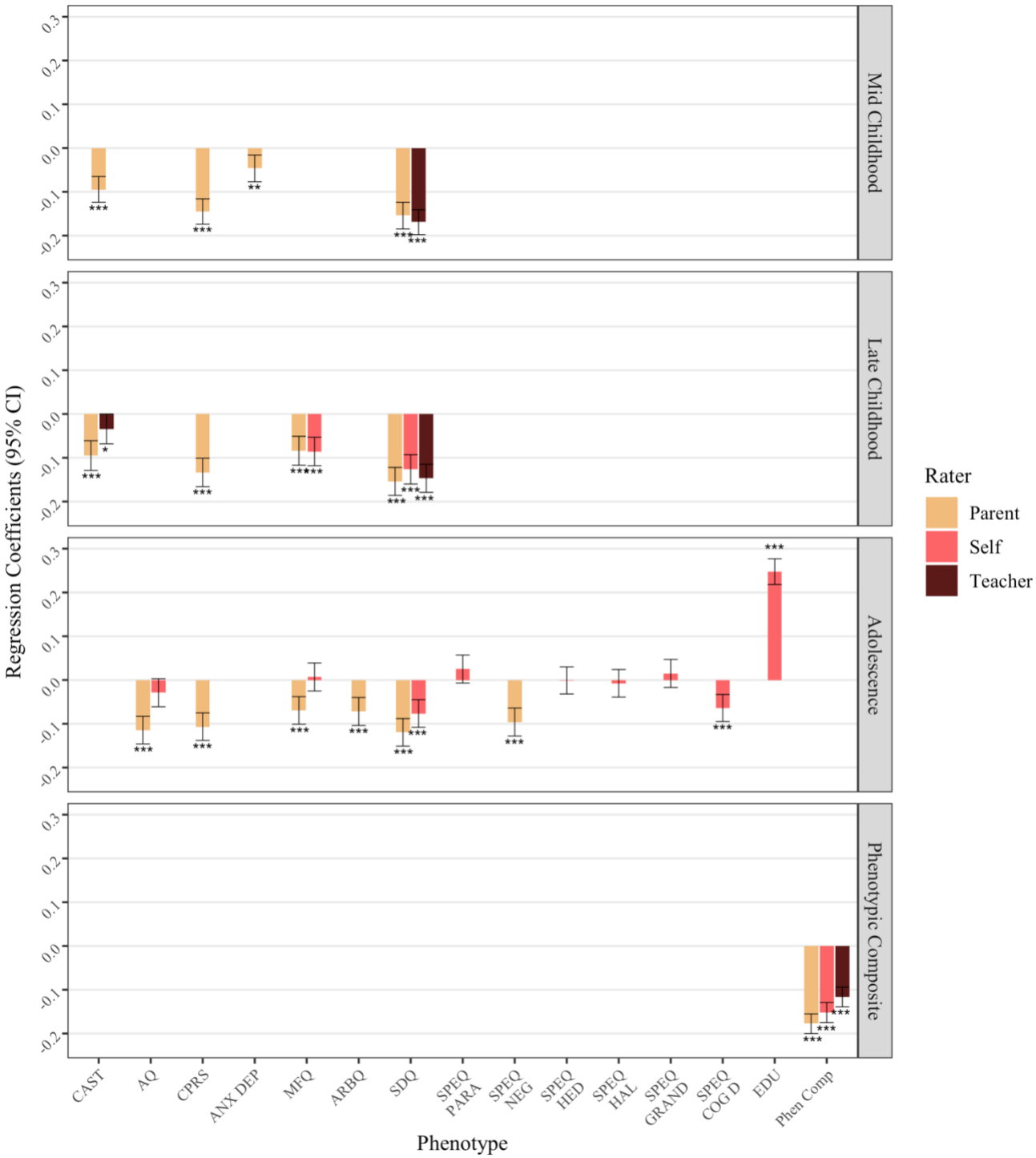
The psychopathology composite score regression model revealed significant associations between higher fine motor skills and lower parent-rated (ß= -0.18, 95% CI: 0.20, 0.16, p<0.001), self-rated (ß= -0.15, 95% CI: -0.18, -0,13, p<0.001), and teacher-rated (ß= -0.12, 95% CI: -0.14, -0.09, p<0.001) psychopathology composite scores.

Table 4.2 Sample demographics

	Preschool Measures/Overall (N=9625)			Mid-Childhood (N=7404)	Late-Childhood (N=6365)	Adolescence (N=6503)	Phenotypic Composite (N=7779)
	Age 2 (N=3945)	Age 3 (N =5811)	Age 4 (N=7798)				
Sex							
Male	4742 (49.3%)			3753 (51.2%)	3303 (51.9%)	3380 (52.5%)	3809 (49.0%)
Female	4883 (50.7%)			3576 (48.8%)	3062 (48.1%)	3061 (47.5%)	3970 (51.0%0
Self					11.32 (0.71)	16.35 (0.68)	
GCSEs						16.35 (0.68)	
Parent	2.07 (0.14)	3.03 (0.14)	4.04 (0.13)	"Age 7" – 7.06 (0.25) "Age 8" – 7.90 (0.53)	11.31 (0.69)	16.30 (0.29)	
Teacher				7.20 (0.28)	11.56 (0.66)		
MZ	3295 (34.2%)			2593 (35.4%)	2287 (35.9%)	2323 (35.7%)	2743 (35.3%)
DZ	6330 (65.8%)			4736 (64.6%)	4078 (64.1%)	4180 (64.3%)	5036 (64.7%)

Note: PGS, Polygenic score; SD, standard deviation; MZ, monozygotic; DZ, dizygotic

Figure 4.2 Model results for the longitudinal phenotypic multivariate regression models regressing outcomes on early fine motor skills



Note: Covariates: gestational age, age of measurement, sex; Mid-Childhood, 7-8 years; Late-childhood, 12 years; Adolescence, 16 years; Psychopathology Composite, composite score of all neurodevelopmental and psychiatric traits across childhood and adolescence; β, standardised coefficient; CI, confidence intervals; FDR p's: *p <0.05, ** p <0.01, *** p <0.001; SDQ, Strengths and Difficulties Questionnaire – Total behavioral problems; CAST, Child Autism Spectrum Test; CPRS, Conners: Parent Rating Scale; ANX DEP, anxiety and depression traits; MFQ, Moods and Feelings Questionnaire; AQ, Abbreviated Autism Spectrum Quotient; ARBQ, Anxiety-Related Behaviours Questionnaire; SPEQ, Specific Psychotic Experiences Questionnaire; PARA, Paranoia; NEG, Negative Symptoms; HED, hedonia; HAL, Hallucinations; GRAND, Grandiosity; CogD, Cognitive Disorganization; EDU, educational achievement

Table 4.3 Model results for the longitudinal phenotypic multivariate regression models regressing outcomes on early fine motor skills

	Age when dependent variable measured			
Dependent variable	Mid Childhood	Late Childhood	Adolescence	Phenotypic Composite
CAST Parent	-0.095***(-0.124, -0.065)			
CPRS Parent	-0.145***(-0.174, -0.116)			
ANX DEP Parent	-0.046**(-0.077, -0.016)			
SDQ Parent	-0.154***(-0.185, -0.124)			
SDQ Teacher	-0.169***(-0.198, -0.141)			
CAST Parent		-0.095***(-0.129, -0.061)		
CAST Teacher		-0.034*(-0.068, 0.000)		
CPRS Parent		-0.134***(-0.166, -0.101)		
MFQ Parent		-0.084***(-0.117, -0.051)		
MFQ Self		-0.086***(-0.118, -0.053)		
SDQ Parent		-0.154***(-0.186, -0.122)		
SDQ Self		-0.126***(-0.160, -0.093)		
SDQ Teacher		-0.147***(-0.179, -0.115)		
AQ Parent			-0.115***(-0.146, -0.083)	
AQ Self			-0.029 (-0.061, 0.003)	
CPRS Parent			-0.107***(-0.138, -0.075)	
MFQ Parent			-0.069***(-0.101, -0.038)	
MFQ Self			0.007 (-0.025, 0.039)	
ARBQ Parent			-0.072***(-0.104, -0.040)	
SDQ Parent			-0.119***(-0.151, -0.088)	
SDQ Self			-0.077***(-0.108, -0.045)	
SPEQ PARA Self			0.025 (-0.007, 0.057)	
SPEQ NEG Parent			-0.096***(-0.128, -0.064)	
SPEQ HED Self			-0.001 (-0.032, 0.030)	
SPEQ HAL Self			-0.008 (-0.039, 0.024)	
SPEQ GRAND Self			0.015 (-0.017, 0.047)	
SPEQ CogD Self			-0.064***(-0.095, -0.033)	
EDU Self			0.248***(0.218, 0.277)	
Phen comp Parent				-0.177***(-0.200, -0.155)
Phen comp Self				-0.152***(-0.175, -0.129)
Phen comp Teacher				-0.116***(-0.139, -0.094)

Note: Covariates: gestational age, age of measurement, sex; Mid-Childhood, 7-8 years; Late-childhood, 12 years; Adolescence, 16 years; Phen comp, Psychopathology composite score, composite score calculated from all available neurodevelopmental and psychiatric traits across childhood and adolescence; β, standardised coefficient; 95% confidence intervals in brackets; FDR p's:*p <0.05,** p <0.01,*** p <0.001; SDQ, Strengths and Difficulties Questionnaire – Total behavioural problems; CAST, Child Autism Spectrum Test; CPRS, Conners: Parent Rating Scale; ANX DEP, anxiety and depression traits; MFQ, Moods and Feelings Questionnaire; AQ, Abbreviated Autism Spectrum Quotient; ARBQ, Anxiety-Related Behaviours Questionnaire; SPEQ, Specific Psychotic Experiences Questionnaire; PARA, Paranoia; NEG, Negative Symptoms; HED, Hedonia; HAL, Hallucinations; GRAND, Grandiosity; CogD, Cognitive Disorganization; EDU, educational achievement

4.3.1 Sensitivity analyses

4.3.1.1 Prematurity sensitivity analyses

When repeating the analyses on the sub-sample of only the children born after 32 weeks (see section 4.3.4.4), all main findings remained except for two previously significant associations, which did not reach significance (CAST, autistic traits, teacher-rated, late-childhood; AQ, autistic traits, self-rated, adolescence; Table S4.5).

4.4.1.2 Fine motor score composition sensitivity analyses

All phenotypic findings remained when questionnaire items were excluded from the fine motor score composition (see section 4.3.4.4), except for one previously significant association, which did not reach significance (CAST autistic traits, teacher-rated, late-childhood; Table S4.6).

4.4.1.3 Socioeconomic score sensitivity analyses

All phenotypic findings remained when controlling for SES in the models (see section 4.3.4.4), except for two previously significant associations which did not reach significance (anxiety-depression traits, mid-childhood, parent-rated; CAST, autism traits, teacher-rated, late-childhood; Table S4.7).

4.5 Discussion

This study investigated phenotypic and genetic associations between preschool fine motor skills and later neurodevelopment, psychopathology, and educational achievement. Lower fine motor skills were associated with increased traits for autism, ADHD, anxiety and/or depression, behavioural problems, negative symptoms, cognitive disorganisation, psychopathology composite scores, and better educational outcomes. These results support emerging evidence of an association between early fine motor skills and later neurodevelopmental and psychiatric traits and educational outcomes (Lim et al., 2021; West, 2019).

The associations between fine motor skills and educational performance accounted for the highest effect sizes in our study. Our results concur with previously reported associations between fine motor skills and cognitive performance (Cameron et al., 2012; Flensborg-Madsen & Mortensen, 2018; Katagiri et al., 2021; Klupp et al., 2021; Murray, Veijola, et al., 2006, 2006; Oudgenoeg-Paz et al., 2012; van der Fels et al., 2015; Wu et al., 2017). These findings, however, differ from Piek et al.'s (2008) findings of no short-term associations between fine motor skills and cognitive skills. In contrast, the current study considered long-term educational outcomes (GCSEs). Achieving specific GCSE grades is typically vital for post-16 education or employment. Our finding indicates that, although effect sizes were small, early fine motor skills may be important early indicators of life outcomes in adolescence.

The association between ADHD and lower fine motor skills supported pre-registered hypotheses. This finding contrasts with some studies in the systematic review (Chapter 3). Firstly, a large prospective study of early infancy found no fine motor skill differences, measured with a standardised assessment at 1-15 months (Van Wiechen Scheme, Jacobusse et al., 2006), compared to controls without ADHD (Jaspers et al., 2013). However, a large retrospective study reported more parental infant fine motor concerns than controls for children with higher ADHD traits compared to those in the population-based cohort without ADHD traits (Marin-Mendez et al., 2017). Further, work is needed to investigate fine motor skills in ADHD prospectively.

We found associations between lower fine motor skills and autism traits across multiple ages, supporting previous evidence in infancy (B. Choi et al., 2018; Landa et al., 2012; LeBarton & Landa, 2019; Nishimura et al., 2019; Sacrey et al., 2018). However, this study extends the existing literature by finding associations between fine motor skills and autism traits in adolescence and childhood, suggesting fine motor skills may be an important inter-related aspect of autism traits across development.

Contrary to our stated hypotheses, confidence intervals indicated there were no measurement age differences in associations between fine motor skills and ADHD, anxiety, and/or depression traits. In support of our hypotheses, some of the behavioural problems and autistic traits associations with fine motor skills in mid- and/or late-childhood were stronger in magnitude than in adolescence,

according to the confidence intervals, suggesting the associations for these traits with fine motor skills may diminish over time.

Confidence intervals indicated a larger magnitude association with fine motor skills for parental-, compared to self-rated, autistic and depression traits in adolescence. Further, the association between fine motor skills and the parent-rated psychopathology composite score was higher in magnitude than the association with the teacher-rated psychopathology composite score. These findings align with rater differences in capturing psychopathology (Francis et al., 2023; Merwood et al., 2013; Ronald, Happé, et al., 2008; Stumm et al., 2023).

Non-preregistered sensitivity phenotypic analyses, with SES as a covariate, revealed the majority of the phenotypic associations remained the same in relation to significance. Most of the findings also remained the same in relation to significance once infants born at less than 32 weeks were excluded. The results are, therefore, robust and do not disappear when controlling for these factors.

The study had several strengths. Firstly, a large prospective design in a representative community sample that included multiple raters was employed. Further, a novel preschool fine motor skills score was derived. The study had some limitations. First, we are assuming our results from twins are generalisable to singletons. However, the generalisability is supported by evidence showing that twins are similar to singletons in cognitive ability, externalising behaviours, and motor milestones (Brouwer et al., 2006; Christensen et al., 2006; Robbers et al., 2010). In addition, while the phenotypic longitudinal data could have been analysed using growth models, this would not have tested our hypotheses to test phenotypic associations at separate stages in childhood and adolescence. It is also important to note that many of the traits were not measured by the same questionnaire longitudinally. Lastly, information about gross motor skills was not collected in the TEDS study, so we could not make comparisons across fine and gross motor skills.

Skills such as drawing and block building in the first years after birth are associated with neurodevelopmental, psychiatric, and educational traits between three to twelve years later. Further work is necessary to understand the mechanisms for these associations, such as genetic propensities

for these traits leading to impaired fine motor skills. Our results suggest fine motor skills may have a role in pathways leading to major life outcomes.

4.6 Appendix

4.6.1 Supplemental methods

4.6.1.1 Subscales of the Specific Psychotic Experiences Questionnaire (SPEQ)

The five self-report subscales of the SPEQ (Ronald et al., 2014) are detailed below. Internal consistency for each subscale, as rated by Cronbach's Alpha, can be found in Table S4.2.

The paranoia subscale included 15 items adapted from the Paranoia Checklist (Freeman et al., 2005). The Questionnaire included questions about the past month, and respondents rated each question using a 6-point scale: "Not at all" (0), "Rarely" (1), "Once a month" (2), "Once a week" (3), "Several times a week" (4), "Daily" (5).

The hallucinations subscale included nine items from the Cardiff Anomalous Perceptions Scale (Bell et al., 2006). The Questionnaire included questions about the past month, and respondents rated each question using a 6-point scale: "Not at all" (0), "Rarely" (1), "Once a month" (2), "Once a week" (3), "Several times a week" (4), "Daily" (5).

The cognitive disorganisation subscale included 11 items from the short version of the Oxford-Liverpool Inventory of Feelings and Experiences (O-LIFE,(Mason et al., 2005). The Questionnaire included questions about the past month, and participants responded with either "Yes" or "No".

The grandiosity subscale included eight items. Three items were obtained from the "Myself" sub-scale of the Cognition Checklist for Mania-Revised (CCL-M-R, Beck et al., 2006), and two items from the Peters et al. Delusions Inventory (PDI, Peters et al., 2004), and three items were developed based on clinical case studies (Ronald et al., 2014). The subscale included questions about the past month, and respondents rated each question using a 4-point scale: "Not at all" (0), "Somewhat" (1), "A great deal" (2), and "Completely" (3).

The hedonia subscale included ten items obtained from the anticipatory pleasure subscale of the Temporal Experience of Pleasure Scale (TEPS, Gard et al., 2006). The Questionnaire included questions about the past month, and respondents rated each question using a six-point scale: "Very false for me" (0), "Moderately false for me" (1), "Slightly false for me" (2), "Slightly true for me" (3), "Moderately true for me" (4), and "Very true for me" (5). The total score is reversed to create a score of hedonia.

The Negative Symptoms subscale includes ten items from the Scale for the Assessment of Negative Symptoms (SANS, (Andreasen, 1989). The Questionnaire included questions about the previous six months, and respondents rated each question using a four-point scale: 'Not at all true" (0), "Somewhat true" (1), "Mainly true" (2), and "Definitely true" (3). The reporting period was six months prior to the date the questions were answered.

Supplemental Table S4.1 Psychopathology composite score items, rater(s), and age of administration

Rater	**Questionnaire**	**Age(s)**
Parent	Strengths and Difficulties Questionnaire (SDQ)	7, 9, 12, 16
	Psychopathy Screening Device (PSD)	7
	Antisocial Process Screening Device (APSD)	9
	DSM-IV criteria items (AUT)	7
	Child Spectrum Test (CAST)	9, 12
	Reactive and Proactive Aggression (RPA)	9
	Moods and Feelings Questionnaire (MFQ)	12, 16
	Antisocial Process Screening Device (APSD)	12
	Conners: Parent Rating Scales: ADHD (CBCL)	12, 16
	Abbreviated Spectrum Quotient (AQ)	16
	Inventory of Callous-Unemotional Traits (ICUT)	16
	Anxiety-Related Behaviours Questionnaire (ARBQ)	16
Teacher	SDQ	7, 9, 12
	PSD	7
	APSD	9
	AUT	7
	CAST	9, 12
	RPA	9
	APSD	12
Self	SDQ	9, 12, 16
	CAST	9
	MFQ	12, 16
	AQ	16
	ICUT	16
	ARBQ	16

Supplemental Table S4.2 Cronbach alpha levels for the late childhood measures between raters and age of measurement

	Mid Childhood	Late Childhood	Adolescence	M
SDQ Parent	0.77	0.74	0.76	0.76
SDQ Teacher	0.83	0.76		0.79
SDQ Self		0.79	0.65	0.72
CAST Parent	0.71	0.72		0.71
CAST Teacher		0.77		0.77
CONN Parent	0.91	0.91	0.90	0.91
ANX DEP Parent	0.75			0.75
MFQ Parent		0.83	0.87	0.85
MFQ Self		0.85	0.89	0.87
AQ Self		0.77		0.77
AQ Parent		0.85		0.85
ARBQ Parent			0.83	0.83
SPEQ PARA Self			0.93	0.93
SPEQ NEG Parent			0.86	0.86
SPEQ HED Self			0.77	0.77
SPEQ HAL Self			0.88	0.88
SPEQ GRAND Self			0.86	0.86
SPEQ CogD Self			0.77	0.77

Note: Cronbach Alpha for each trait measure across rater and age of measurement; Mid-Childhood, 7-8 years; Late-childhood, 12 years; Adolescence, 16 years; M, mean; SDQ, Strengths and Difficulties Questionnaire – Total behavioral problems; CAST, Child Autism Spectrum Test; CPRS, Conners: Parent Rating Scale; ANX DEP, anxiety and depression traits; MFQ, Moods and Feelings Questionnaire; AQ, Abbreviated Autism Spectrum Quotient; ARBQ, Anxiety-Related Behaviours Questionnaire; SPEQ, Specific Psychotic Experiences Questionnaire; PARA, Paranoia; NEG, Negative Symptoms; HED, hedonia; HAL, Hallucinations; GRAND, Grandiosity; CogD, Cognitive Disorganization

Supplemental Table S4.3 Comparison of sample demographics for sub-sample with the required data and the wider TEDS sample

	Remaining Sample (N = 4318)	Included Sample (N = 9625)	*p*
Ethnicity (White)	3599 (83.35%)	8936 (92.84%)	$p < .001$
Missing	245 (5.67%)	29 (0.30%)	
SES score[A]	-0.20	0.07	$p < .001$
Missing	1377 (31.89%)	723 (7.51%)	
Zygosity (MZ)	1218 (28.21%)	3295(34.23%)	$p < .001$
Missing	390 (9.03%)	0 (0%)	

Note: p-values are reported from a t-test for continuous variables and X^2 tests for categorical variables. Remaining Sample, those that did not have any preschool fine motor measures; Included sample, those that had relevant data and thus were included in the study; A, standardised (z-scored) composite scale; SES, socioeconomic status; MZ, monozygotic.

Supplemental Table S4.4 Study demographics for the sensitivity analysis which excludes those born at very preterm (<32 weeks).

	Overall (N=8806)
Sex	
Male	4333 (49.2%)
Female	4473 (50.8%)
Zygosity	
MZ	2957 (33.6%)
DZ	5849 (66.4%)

Note: MZ, monozygotic; DZ, dizygotic

Supplemental Table S4.5 Model results for the sensitivity analysis of longitudinal phenotypic multivariate regression models regressing outcomes on early fine motor skills, excluding those born very preterm (<32 weeks)

	Age when dependent variable was measured			
Dependent variable	Mid Childhood	Late Childhood	Adolescence	P factor
CAST Parent	-0.083***(-0.115, -0.051)			
CPRS Parent	-0.131***(-0.162, -0.100)			
ANX DEP Parent	-0.036*(-0.068, -0.003)			
SDQ Parent	-0.130***(-0.163, -0.097)			
SDQ Teacher	-0.157***(-0.187, -0.126)			
CAST Parent		-0.067***(-0.104, -0.030)		
CAST Teacher		*-0.031 (-0.068, 0.005)*		
CPRS Parent		-0.100***(-0.135, -0.066)		
MFQ Parent		-0.067***(-0.103, -0.031)		
MFQ Self		-0.063***(-0.098, -0.029)		
SDQ Parent		-0.121***(-0.155, -0.086)		
SDQ Self		-0.095***(-0.130, -0.059)		
SDQ Teacher		-0.126***(-0.161, -0.092)		
AQ Parent			-0.108***(-0.143, -0.074)	
AQ Self			*-0.038*(-0.072, -0.004)*	
CPRS Parent			-0.083***(-0.116, -0.049)	
MFQ Parent			-0.050**(-0.083, -0.017)	
MFQ Self			0.002 (-0.032, 0.036)	
ARBQ Parent			-0.052**(-0.086, -0.018)	
SDQ Parent			-0.084***(-0.118, -0.051)	
SDQ Self			-0.063***(-0.096, -0.029)	
SPEQ PARA Self			0.024 (-0.01, 0.058)	
SPEQ NEG Parent			-0.073***(-0.107, -0.039)	
SPEQ HED Self			-0.004 (-0.037, 0.029)	
SPEQ HAL Self			-0.004 (-0.038, 0.030)	
SPEQ GRAND Self			0.006 (-0.028, 0.040)	
SPEQ CogD Self			-0.059***(-0.092, -0.026)	
EDU Self			0.202***(0.170, 0.235)	
Phen comp Parent				-0.140***(-0.165, -0.115)
Phen comp Self				-0.154***(-0.178, -0.129)
Phen comp Teacher				-0.101***(-0.126, -0.076)

Note: Covariates: gestational age, age of measurement, and sex; Mid-Childhood, 7-8 years; Late-childhood, 12 years; Adolescence, 16 years; Phen comp, Psychopathology composite score, composite score calculated from all available neurodevelopmental and psychiatric traits across childhood and adolescence; β, standardised coefficient; 95% confidence intervals in brackets; FDR p's: *p <0.05, ** p <0.01, *** p <0.001; SDQ, Strengths and Difficulties Questionnaire – Total behavioural problems; CAST, Child Autism Spectrum Test; CPRS, Conners: Parent Rating Scale; ANX DEP, anxiety and depression traits; MFQ, Moods and Feelings Questionnaire; AQ, Abbreviated Autism Spectrum Quotient; ARBQ, Anxiety-Related Behaviours Questionnaire; SPEQ, Specific Psychotic Experiences Questionnaire; PARA, Paranoia; NEG, Negative Symptoms; HED, Hedonia; HAL, Hallucinations; GRAND, Grandiosity; CogD, Cognitive Disorganization; EDU, educational achievement

Supplemental Table S4.6 Sensitivity analysis - Model results for the longitudinal phenotypic multivariate regression models regressing outcomes on early fine motor skills using fine motor score excluding questionnaire items from the fine motor composite score

	Age when dependent variable measured			
Dependent variable	Mid Childhood	Late Childhood	Adolescence	Phenotypic Composite
CAST Parent	-0.083*** (-0.113, -0.052)			
CPRS Parent	-0.139*** (-0.167, -0.11)			
ANX DEP Parent	-0.043** (-0.074, -0.012)			
SDQ Parent	-0.148*** (-0.178, -0.118)			
SDQ Teacher	-0.171*** (-0.2, -0.143)			
CAST Parent		-0.082*** (-0.116, -0.048)		
CAST Teacher		*-0.032 (-0.066, 0.002)*		
CPRS Parent		-0.111*** (-0.143, -0.079)		
MFQ Parent		-0.072*** (-0.105, -0.039)		
MFQ Self		-0.083*** (-0.116, -0.051)		
SDQ Parent		-0.136*** (-0.168, -0.104)		
SDQ Self		-0.120*** (-0.153, -0.087)		
SDQ Teacher		-0.141*** (-0.173, -0.109)		
AQ Parent			-0.110*** (-0.142, -0.078)	
AQ Self			-0.029 (-0.061, 0.003)	
CPRS Parent			-0.105*** (-0.136, -0.073)	
MFQ Parent			-0.071*** (-0.103, -0.04)	
MFQ Self			0.000 (-0.032, 0.032)	
ARBQ Parent			-0.073*** (-0.105, -0.042)	
SDQ Parent			-0.111*** (-0.142, -0.08)	
SDQ Self			-0.072*** (-0.103, -0.041)	
SPEQ PARA Self			0.026 (-0.005, 0.058)	
SPEQ NEG Parent			-0.094*** (-0.125, -0.062)	
SPEQ HED Self			-0.002 (-0.033, 0.03)	
SPEQ HAL Self			-0.007 (-0.039, 0.025)	
SPEQ GRAND Self			0.016 (-0.016, 0.047)	
SPEQ CogD Self			-0.059*** (-0.09, -0.028)	
EDU Self			0.236*** (0.206, 0.266)	
Phen comp Parent				-0.16*** (-0.182, -0.138)
Phen comp Self				-0.145*** (-0.168, -0.123)
Phen comp Teacher				-0.117*** (-0.14, -0.095)

Note: Covariates: gestational age, age of measurement, sex; Mid-Childhood, 7-8 years; Late-childhood, 12 years; Adolescence, 16 years; Phen comp, Psychopathology composite score, composite score calculated from all available neurodevelopmental and psychiatric traits across childhood and adolescence; β, standardised coefficient; 95% confidence intervals in brackets; FDR p's:*p <0.05,** p <0.01,*** p <0.001; SDQ, Strengths and Difficulties Questionnaire – Total behavioral problems; CAST, Child Autism Spectrum Test; CPRS, Conners: Parent Rating Scale; ANX DEP, anxiety and depression traits; MFQ, Moods and Feelings Questionnaire; AQ, Abbreviated Autism Spectrum Quotient; ARBQ, Anxiety-Related Behaviours Questionnaire; SPEQ, Specific Psychotic Experiences Questionnaire; PARA, Paranoia; NEG, Negative Symptoms; HED, Hedonia; HAL, Hallucinations; GRAND, Grandiosity; CogD, Cognitive Disorganization; EDU, educational achievement

Supplemental Table S4.7 Sensitivity analysis - Model results for the longitudinal phenotypic multivariate regression models regressing outcomes on early fine motor skills including socioeconomic status as a covariate.

	Age when dependent variable measured			
Dependent variable	Mid Childhood	Late Childhood	Adolescence	Phenotypic Composite Score
CAST Parent	-0.075***(-0.106, -0.044)			
CPRS Parent	-0.131***(-0.161, -0.102)			
ANX DEP Parent	*-0.028 (-0.059, 0.003)*			
SDQ Parent	-0.131***(-0.162, -0.099)			
SDQ Teacher	-0.156***(-0.186, -0.127)			
CAST Parent		-0.060**(-0.095, -0.024)		
CAST Teacher		*-0.031 (-0.066, 0.004)*		
CPRS Parent		-0.103***(-0.137, -0.07)		
MFQ Parent		-0.065***(-0.099, -0.03)		
MFQ Self		-0.064***(-0.098, -0.031)		
SDQ Parent		-0.125***(-0.158, -0.092)		
SDQ Self		-0.091***(-0.125, -0.056)		
SDQ Teacher		-0.129***(-0.162, -0.096)		
AQ Parent			-0.096***(-0.129, -0.063)	
AQ Self			-0.030 (-0.063, 0.002)	
CPRS Parent			-0.076***(-0.108, -0.044)	
MFQ Parent			-0.048**(-0.08, -0.016)	
MFQ Self			0.008 (-0.025, 0.04)	
ARBQ Parent			-0.051**(-0.084, -0.018)	
SDQ Parent			-0.085***(-0.117, -0.052)	
SDQ Self			-0.054**(-0.086, -0.021)	
SPEQ PARA Self			0.023 (-0.009, 0.056)	
SPEQ NEG Parent			-0.067***(-0.099, -0.034)	
SPEQ HED Self			-0.005 (-0.037, 0.027)	
SPEQ HAL Self			0.004 (-0.028, 0.037)	
SPEQ GRAND Self			0.012 (-0.021, 0.044)	
SPEQ CogD Self			-0.048**(-0.079, -0.016)	
EDU Self			0.198***(0.166, 0.229)	
Phen comp Parent				-0.140***(-0.163, -0.117)
Phen comp Self				-0.133***(-0.157, -0.11)
Phen comp Teacher				-0.107***(-0.13, -0.084)

Note: Covariates: gestational age, age of measurement, sex; Mid-Childhood, 7-8 years; Late-childhood, 12 years; Adolescence, 16 years; Psychopathology composite score, across childhood and adolescence; β, standardised coefficient; 95% confidence intervals in brackets; FDR p's:*p <0.05,** p <0.01,*** p <0.001; SDQ, Strengths and Difficulties Questionnaire – Total behavioural problems; CAST, Child Autism Spectrum Test; CPRS, Conners: Parent Rating Scale; ANX DEP, anxiety and depression traits; MFQ, Moods and Feelings Questionnaire; AQ, Abbreviated Autism Spectrum Quotient; ARBQ, Anxiety-Related Behaviours Questionnaire; SPEQ, Specific Psychotic Experiences Questionnaire; PARA, Paranoia; NEG, Negative Symptoms; HED, Hedonia; HAL, Hallucinations; GRAND, Grandiosity; CogD, Cognitive Disorganization; EDU, educational achievement

5. Genetic Associations Between Preschool Fine Motor Skills and Later Neurodevelopment, Psychopathology, And Educational Achievement

5.1 Associated Publication

See section 4.1 for details on the associated publication for this chapter.

5.2 Introduction

Early childhood motor skills are heritable (Austerberry et al., 2022), see section 1.1.4), and there are emergent associations with neurodevelopmental PGSs (Askeland et al., 2022; Hannigan et al., 2021; Serdarevic et al., 2020, see section 1.5). In Chapter 4, associations between fine motor skills in preschool and later cognitive, neurodevelopmental, and psychiatric traits were reported. It was hypothesised that there may also be genetic associations between fine motor skills and cognitive, neurodevelopmental, and psychiatric traits.

As discussed in sections 1.1.3 and 1.1.4, studies indicate that infant and preschool motor skills, such as drawing and psychomotor skills, are heritable (Arden et al., 2014; Austerberry et al., 2022). These studies indicate the opportunity for investigations into joint genetic underpinnings of fine motor skills and traits seen later in development.

Polygenic scores (PGS) are a recent methodology that enables the exploration of genetic associations. PGSs are calculated by summing the genetic risk from common single-nucleotide polymorphisms (SNPs) derived from genome-wide association studies (GWAS), weighted by their effect size. A prospective population cohort study has shown that the autism PGS is associated with early neuromotor measures (9–20 weeks, Serdarevic et al., 2020), providing preliminary evidence for shared genetic influences between early infancy motor development and autism. In the gross motor domain, age of first unsupported walking was associated with PGSs for neurodevelopmental

disorders: Specifically, a PGS for ADHD associated with earlier walking, and a PGS for autism with later walking (Hannigan et al., 2021); the PGS for autism (but not ADHD or schizophrenia) also associated with overall (fine and gross) motor skills at age 3 years, but not 6 or 18 months (Askeland et al., 2022).

I am only aware of one study investigating neurodevelopmental or psychiatric disorder PGSs and early fine motor skills specifically, which found that fine motor skills at 18 months were not associated with the PGS for autism, schizophrenia, or ADHD (Riglin et al., 2022). This study used parent-reported fine motor milestone achievements, which rely on parent recall. Alternatively, these skills can be captured by asking children to complete fine motor tasks as they develop them.

In light of the extant literature, the present chapter aimed to assess genetic associations between early fine motor skills and later neurodevelopmental, psychiatric, and cognitive traits. In single- and multi-polygenic score analyses, associations between PGSs and fine motor skills were tested. PGSs were selected based firstly on traits, where available, that were comparable to those in the phenotypic analysis in Chapter 4 (e.g. autism PGS to compare to autism traits). Further, PGS were selected based on evidence, as alluded to above, that suggests there may be associations with the infant motor domain, namely, autism, ADHD, schizophrenia, and educational outcomes, and those whose associations are as yet unclear: obsessive-compulsive disorder (OCD), major depressive disorder (MDD), and anxiety.

In the polygenic score analysis, the pre-registered predictions were:

1. Higher fine motor skills will be associated with lower autism, ADHD, schizophrenia, and psychopathology composite score PGSs and higher years in education PGS. Associations with OCD, anxiety, and MDD PGSs will be smaller.

2 Variance explained in fine motor skills in the multiple PGS model will be greater than in any single polygenic score analysis.

5.3 Method

5.3.1 Preregistration

This study's methods and hypotheses were pre-registered on the Open Science Framework (Bowler & Ronald, 2021). Analyses not pre-registered are indicated.

5.3.2 Sample

The full sample information for the TEDS study can be found in section 4.3.2. The sample for this chapter will be a subset of the main sample that had PGS data (N=4514, Table 5.1).

A non-pre-registered replication analysis (N=202) was completed on an independent sample – The British Autism Study of Infant Siblings and the Studying Autism and ADHD in the Early Years (BASIS-STAARS, Begum-Ali et al., In Press). The sample was derived of infants with an older sibling or parent with ADHD and/or autism in addition to infants with no sibling parent with ADHD or ASD and two participants with half-siblings with autism (Table S5.1). Participants were recruited in the UK between 2013 and 2019 via a volunteer database, community flyers, internet advertisements, or clinical networks. Further information can be found in the Appendix section 5.6.1.

Table 5.1 Sample demographics

	PGS Data (N=4514)
Male	2178 (48.2%)
Female	2336 (51.8%)
MZ	1164 (25.8%)
DZ	3350 (74.2%)

Note: PGS, Polygenic score; MZ, monozygotic; DZ, dizygotic

5.3.3 Ethical approval

Ethical approval information for TEDS and secondary data analysis can be found in section 4.3.3. Ethical approval for BASIS-STAARS was obtained from the National Research Ethics Service

and Research Ethics Committee of the Department of Psychological Sciences, Birkbeck, University of London. Written parental and/or self-consent was obtained from all participants.

5.3.4 Measures

5.3.4.1 TEDS Measures

5.3.4.1.1 Fine motor composite score

The same fine motor composite score in Chapter 4 will be used in these analyses. Full details can be found in sections 4.3.3.2 and 4.3.4.1.

5.2.4.1.2 Genotyping and polygenic score calculation

Data were available for N=1411 individuals (one individual per twin pair) genotyped on the Affymetrix GeneChip 6.0 based on buccal cell DNA samples and N=3103 individuals genotyped on HumanOmniExpressExome-8v1.2 arrays using DNA that was extracted from saliva samples. Genotypes from the two platforms were separately imputed and then harmonised. Standard quality control procedures were followed, see (S1 Methods, Supplementary Methods, Selzam et al., (2018). Samples were removed based on no-European ancestry, heterozygosity anomalies, a genotype call rate< 0.98, and genetic relatedness other than dizygotic twin status. SNPs were excluded with a minor allele frequency < 0.5%.

Polygenic scores were created for N=4514 for ADHD (Demontis et al., 2019), autism (Grove et al., 2019), schizophrenia (Pardiñas et al., 2018), OCD (International Obsessive Compulsive Disorder Foundation Genetics Collaborative (IOCDF-GC) and OCD Collaborative Genetics Association Studies (OCGAS), 2018), MDD (Howard et al., 2019), anxiety (Purves et al., 2020), and years in education (Lee et al., 2018).

Polygenic score calculation was conducted using LDpred software, which has been shown to increase prediction accuracy compared to standard p-thresholding (pT+clump), which can remove informative markers (Vilhjálmsson et al., 2015). LDpred re-weights SNPS effect sizes based on a prior on the effect size and the associated linkage disequilibrium (using a radius of a two-megabase window) in the sample (TEDS). The prior used was 1, which assumes all markers contribute to the

development of a trait. SNPS with less-than-perfect imputation scores (info < 1) were removed. Next, trait-associated alleles were summed, weighted by the posterior effect size, and totalled across the genome, giving the final PGS. For further details, see Selzam et al. (2019). As is standard practice (Jansen et al., 2020), PGSs at p-thresholds of (0.01, 0.3, 1) were created. All PGSs were regressed on ten principal components of genetic ancestry, genotyping chip, sex, and gestational age, and then z-standardised (see page 2 for information on the use of pre-collected data).

5.3.4.2 Measures in an independent sample

5.3.4.2.1 Fine motor assessments

Fine motor skills were measured at 24 and 36 months with a standardised assessment, the Mullen Scales of Early Learning (Mullen, 1995). The published fine motor t-score was used. The Mullen scales at ages 24 and 36 months were administered by the same research team with the same protocol. The score was z-standardised and regressed on age of measurement.

5.3.4.2.2 Genotyping and polygenic score calculation

Genome-wide genotype data were obtained from saliva and buccal cheek-swab DNA. The linkage disequilibrium estimation for clumping ($r^2 < 0.1$; 250-kilobase distance from index variant) was based on the 1000 Genomes Project reference panel. The sample was limited to those with European genetic ancestry as identified by principal component analysis anchored to the 1000 Genomes Phase 3 dataset of 2504 individuals.

PGSs for N=202 were calculated using a pT+clump approach with the software PRSice-2, which has shown to be less accurate in prediction than methods that model linkage disequilibrium (Pain et al., 2021). Polygenic scores were created for the following phenotypes: ADHD (Demontis et al., 2019), anxiety (Purves et al., 2020), and years in education (Lee et al., 2018). PGSs were calculated at the p-thresholds of 0.01, 0.5, and 1. All PGSs were regressed on ten principal components of genetic ancestry, tissue, and sex, and then z-standardized. The full gestational age data was unavailable at the time of writing, so the variable could not be included as a covariate. For further details on the genotyping and polygenic scoring methods in this sample, see (Gui et al., 2021).

5.3.5 Statistical analysis

5.3.5.1 Single polygenic score models: Permutation-based correction for multiple testing

Individual regression analyses were run for each PGS. Typical methods for correcting for multiple testing assume non-independence of tests, which is not the case for PGS analyses that include multiple p-thresholds (PT) of the same PGSs. The pre-registered regression with an exclusively FDR correction would thus over-correct by assuming non-independence. The pre-registered results can be found in the Appendix (Table S5.2).

The un-preregistered permutation-based method was used to generate an empirical p-value for the best-performing p-threshold for each PGS (S. W. Choi & O'Reilly, 2019). To do this, simple regressions were conducted for all PGSs and all three PTs (0.01, 0.3, 1). Following this, 10,000 permutations were created for the phenotype, the fine motor score. The best-performing p-threshold was selected for each PGS. The regression Beta was then calculated from the simple regression analysis between the PGS at the selected p-threshold and all 10,000 permutations of the phenotype. Finally, a p-value is generated from the ratio of Beta's larger than the initial Beta (from the simple regression analyses) and the N of permutations (10,000).

5.3.5.2 Multiple polygenic score model: Regularised regression

The multiple regression model used each PGS at the p-thresholds (pTs) selected in the permutation-based analysis. All variables were forced into the model. An elastic net regularised regression method was used to account for multicollinearity and improve prediction (Pain et al., 2021). The model was run using the *glmnet* R package (Friedman et al., 2022). Elastic net regression constitutes a linear combination of two regularisation methods: L2 regularisation (ridge regression, which shrinks parameters) and L1 regularisation (LASSO regression, which excludes parameters, (Zou & Hastie, 2005). The model allows for the joint prediction from multiple predictors but uses penalties to reduce multicollinearity and overfitting and consistently improves prediction compared to single-PGS models (Pain et al., 2021; Zou & Hastie, 2005). Elastic net regularised regression employs two hyper-parameters, alpha and lambda. The alpha parameter corresponds to the extent of L1 or L2

regression with $\boldsymbol{\alpha}$ = 0 corresponding to a ridge and $\boldsymbol{\alpha}$ = 1 corresponding to lasso regression, and values in between having a balance between the two. Lamda is a shrinkage parameter. When λ=0, there is no shrinkage. As λ increases, the coefficients are shrunk more strongly. Final model coefficients are equivalent to a conventional multiple linear regression output in that they allow the ranking of predictors by the magnitude of their contribution to predicting the outcome. The coefficients have, however, been regularised (i.e., shrunk), so their fit is reduced, and they also account for the multicollinearity.

One polygenic score threshold (0.01, 0.3, 1) per PGS was selected in the analyses based on those selected in the single polygenic score permutation analysis described above. The data was split into training (80%) and hold-out sets (20%). The training set was used for model training and variable selection, and the hold-out testing set was used for calculating the regression coefficients and R squared. Ten-fold repeated cross-validation was conducted 100 times with random dataset partitions to reduce bias in the model (J.-H. Kim, 2009). After tuning in the testing set, the final hyperparameters selected for the model were alpha = 0.600 and lambda = 0.025.

5.3.5.3 Polygenic score replication Analysis in an independent sample

A non-preregistered replication analysis was completed in the independent sample BASIS-STAARS. The cohort consisted of three phases of recruitment, with the first two phases consisting of autism recruitment and the last phase consisting of autism, ADHD, and co-occurring autism and ADHD recruitment. As before, PGS were analysed at three similar p thresholds (0.01, 0.5, 1). The PGS was found to be significantly associated with fine motor skills in the multi-PGS model in the original sample (TEDS) and was tested in the replication sample. Two regression models were performed, one for each age measurement, 24 and 36 months. A permutation-based correction was used, as previously.

5.2.5.4 Sensitivity analyses

Two out of three sensitivity analyses were run as they were in Chapter 4 (section 4.3.4.4): the prematurity items sensitivity analysis and the sensitivity analysis using a fine motor composite score, which did not include any questionnaire items. The analyses were conducted as described and with the sub-samples described previously.

5.4 Results

5.4.1 Polygenic score results

Results revealed significant associations between higher scores on years in education PGS and higher fine motor scores (EA, PT= 1, ß= 0.07, 95% CI: 0.04, 0.10, empirical $p < 0.001$, R^2= 0.005), a significant association between lower scores for ADHD PGS with a higher fine motor score (PT= 0.01, ß= -0.04, 95% CI: -0.07, -0.01, empirical $p = 0.011$., R^2= 0.002), and higher scores for anxiety PGS with a higher fine motor score (PT= 0.3, ß= 0.03, 95% CI: 0.00, 0.06, empirical p= 0.040, R^2= 0.001, see Figure 5.1, Table 5.2). The pre-registered analysis results with FDR correction can be found in the appendix; conclusions are similar (Table S5.2).

In line with the regression results, higher quantiles on the years in education and anxiety PGS were associated with higher fine motor scores (Figure 5.2a and c, respectively), and higher quantiles in ADHD PGS were associated with lower fine motor scores (Figure 5.2b).

The multi-PGS regularised regression model retained three PGS variables (Figure 5.3, Table 5.3). There was a positive association for years in education PGS (EA, ß= 0.07), a negative association for ADHD PGS (ß= -0.03), and a positive association for anxiety PGS (ß= 0.01) with fine motor skills. The model R^2 was 0.0048, which was 1.75% higher than the best-performing single-score model (years of education, R^2= 0.0047).

Figure 5.1 Associations between polygenic scores and fine motor skills with permutation correction

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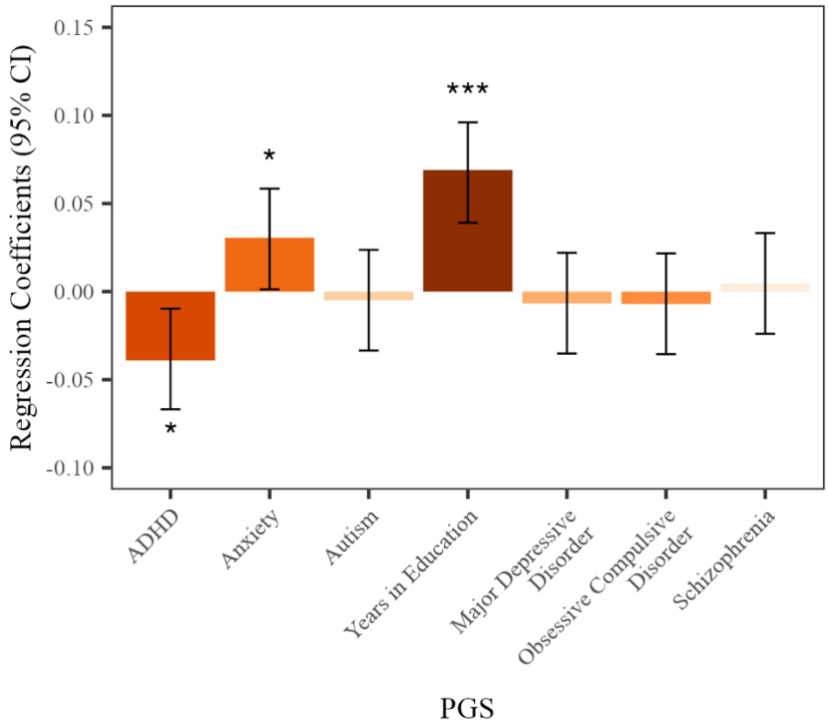


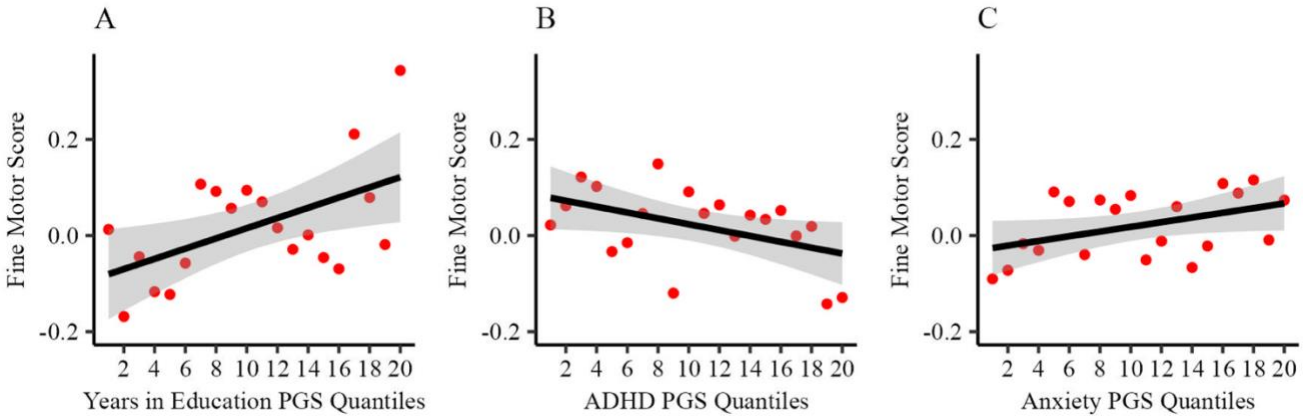
Note: Covariates: Chip, ten genetic ancestry principal components, gestational age, and sex; β, standardised coefficient; CI, confidence intervals; Empirical p's: $^{*}p$ <0.05, $^{***}p$ <0.001; PGS, Polygenic score; ADHD, attention deficit hyperactivity disorder

Table 5.2 Associations between polygenic scores and fine motor skills with permutation correction

PGS	***p*T <**	**β**	**CI5**	**CI95**	**Empirical p**	**R^2**
ADHD	0.01	-0.039	-0.067	-0.010	0.011*	0.002
Autism	1	0.008	-0.020	0.037	0.575	0.000
Anxiety	0.3	0.031	0.001	0.058	0.040*	0.001
MDD	0.01	-0.007	-0.035	0.022	0.594	0.000
OCD	0.01	-0.007	-0.035	0.022	0.663	0.000
SCZ	0.01	0.005	-0.024	0.033	0.787	0.000
EA	1	0.069	0.039	0.096	<0.001***	0.005

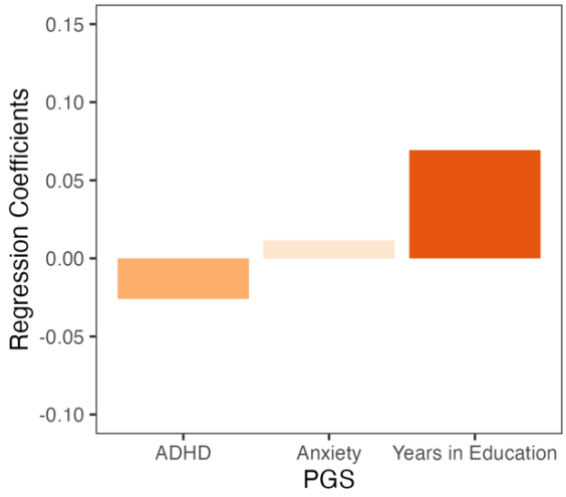
Note: Covariates: Chip, ten genetic ancestry principal components, gestational age, and sex; Empirical *p's*:* p <0.05, *** *p* <0.001; PGS, Polygenic score; pT, significance threshold for inclusion of variants in the polygenic score; β, standardised coefficient; CI, confidence intervals; ADHD, attention deficit hyperactivity disorder; MDD, major depression disorder; OCD, obsessive compulsive disorder; SCZ, schizophrenia; EA, years in education

Figure 5.2 Quantile plots for mean fine motor score with polygenic scores A) Years in education, B) ADHD, C) Anxiety



Note: Covariates: Chip, ten genetic ancestry principal components, gestational age, and sex; Mean fine motor scores are plotted for each of the 20 quantiles of the PGS; PGS, Polygenic score; ADHD, attention deficit hyperactivity disorder

Figure 5.3 Multi-polygenic score model showing associations between polygenic scores and fine motor skills score



Note: *Covariates: Chip, ten genetic ancestry principal components,* gestational age, and sex; Regression coefficient calculated from a hold-out set of 20% of the data; PGS, Polygenic score; ADHD, attention deficit hyperactivity disorder

Table 5.3 Multi-polygenic score model showing associations between polygenic scores and fine motor skills score

PGS	β	
	Train	**Test**
ADHD	-0.016	-0.026
Anxiety	0.029	0.011
EA	0.049	0.069

Note: β, standardised coefficient; results for train and test sets for each predictor retained the model; An unbiased estimate of variance explained from the hold-out set of 20% of the data was R2 = 0.005. PGS, Polygenic score; ADHD, Attention Deficit Hyperactivity Disorder; EA, years in education

Tests for replication of the significant PGS findings from TEDS in an independent sample, BASIS-STAARS, revealed a significant association between lower ADHD PGS and higher fine motor scores at 36- months (PT= 0.01, ß= -0.15, 95% CI: -0.29, -0.01, empirical *p*= 0.043., R^2= 0.023, Table 5.4), consistent with the TEDS results. No significant association was found at 24 months. The EA PGS (empirical *p's*= 0.421, 0.129) and Anxiety PGS (empirical *p's*= 0.285, 0.240) associations did not replicate at either age in BASIS-STAARS.

Table 5.4 Replication analysis: Associations between polygenic scores and fine motor skills with permutation correction

PGS	***Age (M)***	***p*T <**	**β**	**CI5**	**CI95**	**Empirical p**	**R^2**
ADHD	24	1	0.020	-0.117	0.157	0.779	0.000
	36	0.01	-0.152	-0.287	-0.011	0.043*	0.023
Anxiety	24	0.01	-0.079	-0.215	0.058	0.285	0.006
	36	0.5	0.092	-0.05	0.231	0.240	0.008
EA	24	0.5	-0.059	-0.195	0.079	0.421	0.003
	36	0.01	0.114	-0.027	0.257	0.129	0.013

Note: Covariates: Tissue, ten genetic ancestry principal components, age of measurement and sex; Empirical p's: * p <0.05; PGS, Polygenic score; β, standardised coefficient; CI, confidence intervals; pT, significance threshold for inclusion of variants in the polygenic score; ADHD, attention deficit hyperactivity disorder; EA, years in education

5.4.3 Sensitivity analyses

5.4.3.1 Fine motor score composition sensitivity analyses

All main findings remained in the single PGS analysis (Table S5.3). Results revealed significant associations between higher scores on years in education PGS and higher fine motor scores (EA, PT= 1, ß= 0.06, 95% CI: 0.03, 0.08, empirical $p < 0.001$, R^2= 0.003), a significant association between lower scores for ADHD PGS with a higher fine motor score (PT= 0.01, ß= -0.04, 95% CI: -0.06, -0.01, empirical $p = 0.0191$., R^2= 0.001), and higher scores for anxiety PGS with a higher fine motor score (PT= 0.3, ß= 0.04, 95% CI: 0.01, 0.07, empirical p= 0.011, R^2= 0.001).

5.4.3.1 Prematurity sensitivity analyses

All main findings remained in the single PGS analysis (Table S5.4). Results revealed significant associations between higher scores on years in education PGS and higher fine motor scores (EA, PT= 1, ß= 0.06, 95% CI: 0.03, 0.09, empirical $p < 0.001$, R^2= 0.001), a significant association between lower scores for ADHD PGS with a higher fine motor score (PT= 0.01, ß= -0.04, 95% CI: -0.07, -0.01, empirical $p = 0.007$., R^2= 0.001), and higher scores for anxiety PGS with a higher fine motor score (PT=1, ß= 0.03, 95% CI: 0.02, 0.06, empirical p= 0.038, R^2= 0.001).

5.5 Discussion

In the previous chapter (Chapter 4), I reported phenotypic associations between fine motor skills in the first years and later neurodevelopment, psychopathology, and educational achievement across development. Using polygenic scores in a subset of the previous sample, this chapter included an investigation of the genetic associations between the same preschool fine motor skill score and PGS for similar neurodevelopmental, psychopathology, and educational achievement outcomes. The polygenic score analyses revealed fine motor skills were associated with a lower genetic propensity for ADHD and a higher propensity for anxiety and educational attainment.

The associations between fine motor skills and the years in education PGS accounted for the highest effect sizes in this chapter. Our results concur with previously reported phenotypic associations between fine motor skills and cognitive performance (Cameron et al., 2012; Flensborg-Madsen & Mortensen, 2018; Katagiri et al., 2021; Klupp et al., 2021; Murray, Veijola, et al., 2006, 2006; Oudgenoeg-Paz et al., 2012; van der Fels et al., 2015; Wu et al., 2017), and extend these findings with evidence for genetic associations between the two domains. The PGS associations between fine motor skills and educational attainment were, however, not replicated, and effect sizes are modest. Further work is needed to test if these findings replicate in other samples.

The association between the genetic propensity for ADHD and lower fine motor skills supported pre-registered hypotheses and was reinforced by an un-preregistered replication result in an independent sample. This association is also consistent with the phenotypic associations in Chapter 4. The finding contrasts with findings of genetic associations of ADHD PGS with superior gross motor skills (earlier walking, Hannigan et al., 2021), which suggests that there may be a distinction in the directions of associations of the association between the ADHD PGS and fine versus gross motor domains. The finding is also in contrast to a finding of no genetic association between the ADHD PGS and fine motor skill milestone achievement (Riglin et al., 2022). These differences in results may be related to age of measurement (here 2-4 years; Riglin et al., 2022 - 18 months; also note that there was no replication of the ADHD PGS association at 24 months) or measurement employed (Riglin et al., 2022 used retrospective milestone achievements measures). Further work investigating ADHD PGS associations with fine motor skills across infant and preschool years is needed.

The association between a higher genetic propensity for anxiety and superior fine motor skills was not predicted. The phenotypic associations with anxiety or anxiety and depression traits in Chapter 4 were, however, negative. Considering the lack of replication in the independent sample and the inconsistency in the direction of associations with the phenotypic results, our findings of associations with anxiety require further exploration.

The lack of genetic association for the autism PGS with fine motor skills is inconsistent with the phenotypic associations with autistic traits found across development in Chapter 4. Phenotypic associations between lower fine motor skills and autistic traits across multiple ages were found. The

lack of an association between the autism PGS and fine motor skills is, however, consistent with previous findings of no genetic associations of the autism PGS with fine motor skills (Riglin et al., 2022). Furthermore, autism and autistic traits are not the same phenotypes, though they are genetically related (Robinson et al., 2016). Further investigation once larger GWAS with statistical power is achieved in future would be of interest.

The study had several strengths. This is the first study to investigate the genetic associations of directly assessed early fine motor skills with childhood outcomes. Further, I part-replicated the genetic results in a sample that used an alternative fine motor measure, suggesting the ADHD PGS association with lower fine motor skill is not specific to the sample, twins, or the measure employed. Lastly, the results remained when excluding participants based on prematurity and excluding questionnaire-assessed fine motor items from the composite score. To improve prediction, a novel PGS analysis method was used to control for multiple comparisons and multiclonality.

The study had some limitations. Firstly, it is recognised that, although comparable to other PGS studies, the effect sizes were low, which limits clinical significance for individuals. Associations with PGS are partly dependent on the reliability of the PGS. At present, there is no standard statistical approach for adjusting for variations in the reliability of PGS (see section 6.3.2). Secondly, the study assumes our results from twins are generalisable to singletons. This is supported by evidence showing that twins are similar to singletons in cognitive ability, externalising behaviours, and motor milestones (Brouwer et al., 2006; Christensen et al., 2006; Robbers et al., 2010). Finally, the replication PGS analysis used a more basic PGS calculation methodology, which may have limited the prediction accuracy (Pain et al., 2021).

Skills such as drawing and block building in the first years after birth are genetically associated with ADHD and years in education. Further work is necessary to understand if this is due, in part, to shared common genetic pathways or early developmental alternations. Our results suggest fine motor skills may have a role in pathways leading to major life outcomes.

5.6 Appendix

5.6.1 Polygenic score replication analysis in an independent sample

5.6.1.1 Participant screening and assessment

A telephone screening form was used to assess ASD and ADHD presence in family members before enrolment. The parent/caregiver also completed a "Medical and Psychiatric History Interview," and medical updates were obtained at each visit. Diagnostic letters were requested from parents, and the parents completed the Development and Well-Being Assessment ASD and ADHD sections, which were reviewed by the senior clinician (Goodman et al., 2000). Finally, the parents completed the Conners Questionnaire (Conners, 2008, for ADHD) and Social Communication Questionnaire (Rutter et al., 2003, for autism) on family members with a diagnosis and, when possible, on other family members.

Families reporting suspected ADHD were assessed using shortened versions of the Conners Questionnaire (Conners, 2008). Siblings under 6 years were assessed using the Conners Early Childhood form, while those 6 years or older were assessed using the Conners 3. To be included, individuals needed to score positively on the impairment scale and exhibit at least 6 ADHD traits on either the hyperactivity/impulsivity or inattention scale. For parents, the Conners Adults ADHD Rating Scale was used, with a positive score on the impairment scale and at least 5 ADHD traits on either the hyperactivity/impulsivity or inattention scale as thresholds for inclusion. Families received reimbursements for travel and subsistence expenses, and infants were given a certificate and t-shirt at each visit.

Supplemental Table S5.1 Replication analysis sample demographics

	Family Liability Group					
	No Family Liability (N=39)	Autism (N=138)	ADHD (N=13)	Autism and ADHD (N=10)	Half Sibling Autism (N=2)	Total (N=202)
Sex						
Male	21 (53.8%)	69 (50.0%)	8 (61.5%)	8 (80.0%)	2 (100%)	108 (53.5%)
Female	18 (46.2%)	69 (50.0%)	5 (38.5%)	2 (20.0%)	0 (0%)	94 (46.5%)
Age in Months - 2 years						
Mean (SD)	25.2 (1.37)	25.8 (1.86)	24.7 (0.70)	25.1 (1.31)	26.3 (0.12)	25.6 (1.73)
Missing	5 (12.8%)	3 (2.2%)	2 (15.4%)	1 (10.0%)	0 (0%)	11 (5.4%)
Age in Months - 3 years						
Mean (SD)	38.9 (2.30)	38.6 (2.05)	38.8 (3.65)	37.2 (1.31)	41.6 (2.19)	38.6 (2.20)
Missing	7 (17.9%)	4 (2.9%)	3 (23.1%)	2 (20.0%)	0 (0%)	16 (7.9%)

Note: ADHD, attention deficit hyperactivity disorder; SD, standard deviation

Supplemental Table S5.2 Single polygenic score regression analysis with false discovery rate correction

	***pT* < 0.01**				***pT* < 0.3**				***pT* < 1**			
PGS	**β (CI)**	***p***	**FDR *p***	**R^2**	**β (CI)**	***p***	**FDR *p***	**R^2**	**β (CI)**	***p***	**FDR *p***	**R^2**
ADHD	-0.039 (-0.067, -0.01)	0.009**	0.054	0.002	-0.035 (-0.062, -0.005)	0.020*	0.086	0.001	-0.033 (-0.061, -0.004)	0.025*	0.088	0.001
Autism	-0.005 (-0.033, 0.024)	0.738	0.946	0.000	0.008 (-0.021, 0.036)	0.599	0.946	0.000	0.008 (-0.02, 0.037)	0.580	0.946	0.000
Anxiety	0.031 (0.002, 0.059)	0.035*	0.096	0.001	0.031 (0.001, 0.058)	0.040*	0.096	0.001	0.030 (0.001, 0.058)	0.041*	0.096	0.001
MDD	-0.007 (-0.035, 0.022)	0.653	0.946	0.000	0.002 (-0.027, 0.03)	0.905	0.946	0.000	0.001 (-0.028, 0.030)	0.946	0.946	0.000
OCD	-0.007 (-0.035, 0.022)	0.636	0.946	0.000	-0.004 (-0.033, 0.025)	0.785	0.946	0.000	-0.004 (-0.032, 0.025)	0.789	0.946	0.000
SCZ	0.005 (-0.024, 0.033)	0.750	0.946	0.000	-0.003 (-0.032, 0.026)	0.834	0.946	0.000	0.002 (-0.027, 0.030)	0.895	0.946	0.000
EA	0.038 (0.009, 0.066)	0.010*	0.054	0.001	0.053 (0.024, 0.081)	<0.001***	0.004**	0.003	0.069 (0.039, 0.096)	<0.001***	<0.001***	0.005

Note: Covariates: Chip, ten genetic ancestry principal components, gestational age, and sex; FDR p's; Empirical p's: *p <0.05, ** p <0.01, *** p <0.001; PGS, Polygenic score; pT, significance threshold for inclusion of variants in the polygenic score; β, standardised coefficient; CI, confidence intervals; FDR, false discovery rate; ADHD, attention deficit hyperactivity disorder; MDD, major depression disorder, OCD; obsessive compulsive disorder SCZ, schizophrenia; EA, years in education

Supplemental Table S5.3 Sensitivity Analysis - Associations between polygenic scores and fine motor skills with permutation correction – Excluding questionnaire items in fine motor composite score.

PGS	*p*T <	β	CI5	CI95	Empirical p	R^2
ADHD	0.01	-0.035	-0.063	-0.006	0.019*	0.001
Autism	0.01	-0.005	-0.034	0.024	0.719	0.000
Anxiety	0.3	0.038	0.008	0.066	0.011*	0.001
MDD	0.01	0.005	-0.024	0.033	0.757	0.000
OCD	0.01	-0.010	-0.039	0.019	0.491	0.000
SCZ	0.01	0.010	-0.019	0.039	0.499	0.000
EA	1	0.056	0.027	0.084	<0.001***	0.003

Note: Covariates: Covariates: Chip, ten genetic ancestry principal components, gestational age, and sex; Empirical p's: * p <0.05, *** p <0.001; PGS, Polygenic score; pT, significance threshold for inclusion of variants in the polygenic score; β, standardised coefficient; CI, confidence intervals; ADHD, attention deficit hyperactivity disorder; MDD, major depression disorder; OCD, obsessive compulsive disorder; SCZ, schizophrenia; EA, years in education

Supplemental Table S5.4 Sensitivity Analysis - Associations between polygenic scores and fine motor skills with permutation correction, excluding those born very preterm (<32 weeks)

PGS	*p*T <	β	CI5	CI95	Empirical p	R^2
ADHD	0.01	-0.042	-0.071	-0.012	0.007**	0.001
Autism	1	0.010	-0.020	0.040	0.536	0.000
Anxiety	1	0.033	0.002	0.062	0.038*	0.001
MDD	0.01	-0.006	-0.035	0.024	0.710	0.000
OCD	0.3	-0.008	-0.038	0.022	0.616	0.000
SCZ	1	0.008	-0.022	0.038	0.592	0.000
EA	1	0.063	0.032	0.091	<0.001***	0.001

Note: Covariates: Chip, ten genetic ancestry principal components, gestational age, and sex; pT, significance threshold for inclusion of variants in the polygenic score; β, standardised coefficient; CI, confidence intervals; empirical p's: * *p* <0.05; *** *p* <0.001; PGS, Polygenic score; FDR, false discovery rate; ADHD, attention deficit hyperactivity disorder; MDD, major depression disorder; OCD, obsessive compulsive disorder; SCZ schizophrenia; EA, years in education

6. Discussion

6.1 Aims and findings for each chapter

This thesis included the first cross-neurodevelopmental condition (NDC) meta-analysis and systematic review of infant motor skills, a prototype of a digital phenotyping motor measurement app, the first study to investigate phenotypic associations with fine motor skills at multiple time points from childhood to adolescence, and the first study to investigate genetic associations using a fine motor measure that captures the skills as they happen rather than respective accounts. The evidence presented in chapters 3, 4 and 5 all demonstrated associations between motor skills in the first years after birth and later outcomes. These associations stretch across childhood and adolescence, suggesting early preschool motor skills are important predictors of later outcomes. Further large-scale longitudinal work is needed to assess the replicability of these effects.

Below, I will address key themes across chapters, including issues relating to the measurement of early motor skills, the lack of research on motor skills in some NDC groups, and the potential to improve this research area by using smartphone apps. I will then discuss the links between NDC and early motor skills, implications for cognition and educational outcomes, mechanisms and pathways between motor skills and later outcomes, and what implications the findings have for intervention or prediction.

6.1.1 Chapter 1: Introduction

This introduction chapter aimed to briefly introduce research in early development, including early brain development and genetic research of early development, introduce examples of findings on infant motor and language milestones, and provide examples of how motor skills are measured. It then aimed to address relevant research into the association between early motor development and cognition and neurodevelopmental and psychiatric traits and disorders. Relevant findings that distinguish between fine and gross motor skills were also discussed. The main methodologies used in the thesis were then presented next, which include app prototype design, meta-analysis, constructing a fine motor measure, and polygenic scores.

6.1.2 Chapter 2: Development of an app prototype for digital phenotyping of motor skills

Chapter 2 included a discussion of relevant literature on why a digital phenotyping motor measurement app is needed. Following this, I outlined the design research and user testing I conducted for a digital phenotyping motor measurement app, an app prototype and the wireframing of the app prototype. The user research I conducted revealed a gap in the market for such an app, and potential users were positive about its usability. The app would capture motor development with flexible measurement designs.

6.1.2 Chapter 3: Systematic review of motor skills in neurodevelopmental disorders

Chapter 3 included meta-analyses and a systematic review. The meta-analyses aimed, firstly, to investigate whether children with NDCs have delays in the age of attainment of motor milestones in infancy compared to controls. Secondly, the chapter aimed to investigate what age children with NDCs reach motor milestones in infancy. Lastly, the chapter aimed to investigate whether children with NDCs differ significantly in standardised assessments of motor skills. The systematic review also summarised all infant motor data that couldn't be meta-analysed. The review and meta-analyses reported evidence for delayed or impaired infant motor skills in NDCs but highlighted important distinctions across conditions. Walking was the most delayed across the included conditions. Tic disorders, Autism and developmental coordination disorder (DCD) had the highest magnitude impairment or delays in attainment compared to other conditions. There was also evidence of increases in motor impairments over infancy for autism and language disorders.

6.1.3 Chapter 4: Phenotypic associations between fine motor skills and later neurodevelopmental, psychiatric, and cognitive traits

Chapter 4 aimed to assess phenotypic associations between early fine motor skills and later neurodevelopmental, psychiatric, and cognitive traits. Fine motor skills were measured from tasks at 2, 3 and 4 years. The derived fine motor measure was then used to investigate phenotypic associations between early fine motor skills and later neurodevelopmental, psychiatric, and cognitive traits from childhood to adolescence. Longitudinal multivariate regression models revealed lower fine motor

skills were associated with increased autism traits, ADHD traits, anxiety and/or depression traits, behavioural problems, negative symptoms, cognitive disorganisation, psychopathology composite scores, and better educational outcomes.

6.1.4 Chapter 5: Genetic associations between fine motor skills and later neurodevelopmental, psychiatric and cognitive traits

Chapter 5 aimed to assess genetic associations between early fine motor skills and later neurodevelopmental, psychiatric, and cognitive traits using polygenic scores (PGS). Associations between PGSs and fine motor skills were tested in single- and multi-polygenic score analyses. The PGSs included autism, ADHD, schizophrenia, educational outcomes, obsessive-compulsive disorder (OCD), major depressive disorder (MDD), and anxiety. The polygenic score analyses revealed fine motor skills were associated with a lower genetic propensity for ADHD and a higher propensity for anxiety and educational attainment. Furthermore, the PGS analyses were repeated in an independent sample. The negative association between ADHD and fine motor skills was replicated at 36 months but not at 24 months. The educational attainment and anxiety associations were not replicated.

6.2 Themes Across Chapters

6.2.1 Issues with the measurement and studies of early motor skills

The meta-analysis of motor milestones in Chapter 3 revealed a need for more research on fine motor skills. It was not possible to extract enough effect sizes to add any fine motor skills milestones to the milestone meta-analysis. We found a large number (N=13 neurodevelopmental control group/control analysis; N=22, age of walking analysis) of walking milestone effect sizes but minimal or no fine motor effect sizes, such as the pincer grip. Consistently, In Chapter 4, as there was a lack of fine motor data in large datasets, it was necessary to devise a novel measure of fine motor skills from a general cognitive assessment to conduct a longitudinal study of the associations between fine motor skills and later outcomes in a population cohort. As highlighted in Chapters 4 and 5, early fine motor skills have phenotypic and genetic associations with later childhood and adolescent outcomes. More

data is required to understand these processes further. Early developmental, longitudinal, and NDC studies should include standalone fine motor measures in their designs to support research in the area.

6.2.2 Lack of research on motor skills in some neurodevelopmental condition groups and the potential to improve this by using smartphone apps

The meta-analysis and systematic review in Chapter 3 found limited studies investigating early motor development in some NDC groups, such as tics and language disorders, and a large number for autism. Due to the overlap in aetiology across NDCs (Guilmatre et al., 2009; Ronald, Simonoff, et al., 2008; Rujescu et al., 2009; Stergiakouli et al., 2017), it is essential to understand if motor delays and impairments can be seen across all groups of conditions or if there are substantial differences.

If validated, the digital phenotyping app proposed in Chapter 2 would enable more data to be collected on motor skills at a population level. Individuals could be followed up with neurodevelopmental questionnaires, potentially capturing individuals with early traits or diagnoses, including in the lesser investigated groups. The app could, therefore, provide prospective data on early motor skills and NDCs. As shown in section 2.2.2, but briefly here, the home environment and socioeconomic status (SES) impacts motor development (Fink et al., 2019). Apps also allow individuals to participate in research that wouldn't otherwise be due to issues related to their socioeconomic status or due to their specific personal or physical requirements, which make laboratory studies unsuitable (Bonevski et al., 2014). Therefore, digital phenotyping wouldn't just provide larger datasets which include under-represented NDC groups; it also had the potential to collect more representative data.

6.2.3 Deprivation and motor development

The home environment is where infants develop most of their motor skills. The impact of social deprivation on the home environment has implications for their motor development. For example, in a prospective cohort study, more physical activity equipment in the home was significantly associated with fine motor skills at 9 months and 3.5 years (Barnett, 2019). Further, the

home environment mediates the effect of maternal IQ on motor development (Ronfani et al., 2015). Contextual differences in international averages for motor milestones achievement have also been found to reduce to insignificance once SES is accounted for (Fink et al., 2019). These effects are significant because low SES groups are less likely to participate in lab-based studies (Bonevski et al., 2014), which has implications for the validity of lab-based studies. Chapter 2 introduced a smartphone app to counteract these issues in data collection.

Further, controlling for SES did not, however, substantially change the longitudinal phenotypic findings from Chapter 4. Fine motor skills may, thus, still be important for later outcomes when considering SES. We could not control for SES in the genetic models in Chapter 5 due to collider bias (see section 6.3.1).

6.2.4 Neurodevelopmental conditions and early motor skills

This thesis presented research across and between NDCs. Themes across NDCs will be presented below.

6.2.4.1 Across neurodevelopmental conditions, what patterns do we see?

Walking was the most delayed milestone for all NDCs across the tested gross motor milestones. However, there was heterogeneity across NDCs in this effect. Walking was achieved across all NDCs at 13.98 months (95% CI: 13.50, 14.47), which is later than the WHO mean age of 12.1 months (95% CI: 11.89, 12.23, (Onis, 2006). The gross motor milestones holding the head up, rolling, sitting unaided, and standing unaided were also delayed compared to individuals without NDCs. Focusing on these gross motor milestones in clinical observations and intervention may be beneficial.

Contrastingly, crawling wasn't significantly delayed compared to controls. It is important to note that infants often use alternative pre-walking strategies, such as bum shuffling, which impact the age at onset of walking (Bottos et al., 1989; Størvold et al., 2013). It is unclear if and how this could

impact the lack of a delay in the neurodevelopment condition group. Therefore, further work is needed to capture these alternative strategies in research designs.

Furthermore, an important finding from one of the meta-analyses in Chapter 3 was that motor impairment measures using standardised measures increased with age. This finding is limited because it is based only on autism and language disorder conditions. However, the age of measurement effect was seen for both conditions and suggests there may be cascading effects of motor impairment, which increased the impairment across age. Further investigation is required to understand if this finding can be replicated and if it is seen in other NDCs.

6.2.4.2 Different motor presentations across attention deficit hyperactivity disorder and autism

As the systematic review and meta-analysis in Chapter 3 showed, compared to other NDCs, there is considerable research on early motor skills in autism. There was evidence of impaired motor skills compared to controls without autism in those who go on to develop autism. Supporting previous evidence (West, 2019), there was evidence of delayed infant motor milestones (Chapter 3), delayed infant gross and fine motor skills, which increase over 3-24 months (Chapter 3), and phenotypic associations with autism traits across childhood and adolescence (Chapter 4). However, the findings were mixed because there was no evidence of genetic associations between the autism PGS and fine motor skills (Chapter 5).

For ADHD, a condition that has overlapping genetic aetiology to autism (Ronald, Simonoff, et al., 2008; Stergiakouli et al., 2017) and often cooccurs with autism (Lai et al., 2014), the picture is mixed. Similar to autism, there was evidence of associations between ADHD traits and impaired fine motor skills. However, there were lower magnitude delays in the acquisition of gross motor milestones, and there were genetic associations with impaired fine motor skills. Motor skills, therefore, may be important early traits that distinguish between condition groups.

6.2.4.3 Schizophrenia

There is emerging evidence of associations between individuals with schizophrenia having childhood motor delays and impairments (Burton et al., 2016; Filatova et al., 2017; Isohanni et al., 2001; Murray, Veijola, et al., 2006). Consistently, the meta-analysis in Chapter 3 revealed delays in infant gross motor milestones. However, the schizophrenia effect size of the NDC-control difference was small in magnitude compared to the other NDC groups, and there was significant heterogeneity in the NDC-control difference across milestones. The longitudinal phenotypic analysis in Chapter 4 found differential associations between preschool fine motor skills across subscales of the Specific Psychotic Experiences Questionnaire (SPEQ) in adolescence. Significant associations were found for cognitive disorganisation and negative symptoms, but no other subscales were significant (Paranoia, Hedonia, Hallucinations, and Grandiosity). However, the clinically diagnosed condition, schizophrenia, represents only the extreme end of the distribution of these psychotic experience traits (Os et al., 2009), and the associations between the SPEQ and the PGS for Schizophrenia are inconclusive (Pain et al., 2018; Sieradzka et al., 2014). Therefore, these traits may not be related to the condition itself. Lastly, there was no genetic association with schizophrenia in the PGS analyses with preschool fine motor skills. Therefore, the evidence presented supports small gross motor milestone delays in schizophrenia but suggests there may not be genetic associations.

6.2.5 Implications for cognitive and educational outcomes

In Chapter 4, the association between superior fine motor skills and better educational attainment at 16 years of age was the strongest magnitude of phenotypic associations with early fine motor skills. Further, in Chapter 5, the association between superior fine motor skills and higher genetic liability for better educational attainment was the strongest magnitude of genetic association with early fine motor skills. This adds to consistent evidence of fine motor skills having important associations with cognition (see section 1.4) but extends this research further by looking at long-term outcomes (age 16) and genetic associations. Investigation is needed to investigate the benefits of improving fine motor skills in early years education and at home to improve later outcomes.

6.2.6 Mechanisms and pathways between motor skills and later outcomes

The pathways between early motor skills and later outcomes are highly likely to be complex. Denisova and Zhao (2017) found that individuals with a high family liability of autism had very early context-inflexible sensorimotor signatures at 1-2 months, which were more inflexible if they also had delayed developmental trajectories in toddlerhood (Mullen, 1995). Individuals with a low family liability of autism had flexible sensorimotor signatures, potentially allowing them to optimally process visual and auditory information and learn from their environment. A possible mechanism, therefore, could be that a higher genetic liability to an NDC leads to atypical early sensorimotor alterations, which then impact neurodevelopmental outcomes and developmental trajectories, including motor skills. Further, early motor skills are vital for developing mature executive functioning (Koziol & Lutz, 2013), which would impact educational attainment. However, a suitable (home and educational) environment is vital for cognitive development, and without this, genetic propensities have far less of an impact (Turkheimer et al., 2003). Therefore, genetic liabilities may impact early motor sensorimotor impairments, which then impact early motor skills, later cognition, and neurodevelopmental development through developmental cascades.

Impairments and delays in motor skills such as walking may, in addition, or instead, impact the acquisition of social experience, leading to further developmental disruption. For example, evidence suggests associations between the age at onset of walking and language and cognitive development (Flensborg-Madsen & Mortensen, 2018; Walle, 2016). Further, Bradshaw et al. (2018) found evidence that infants at high, not low, familial likelihood of autism had significantly better language skills when they had walking experience than pre-walkers. It is likely that the mechanisms are multidirectional and require further investigation.

6.2.7 What implications are there for intervention or prediction?

The majority of PGSs predict a very low percentage of a phenotype, and whether they can be viewed as “predictive” can be questioned. However, PGSs are becoming more powerful as a result of increasing genome-wide association study (GWAS) sample sizes and improvements in phenotypic measures; multiple psychiatric and neurodevelopmental PGS have the potential to “predict” 10% of

individual differences of the same phenotype (Plomin, 2022). A strongly "predictive" PGS could be helpful, especially considering those at high and low quantiles of the spectrum where prediction is stronger (Plomin & von Stumm, 2022). Educational attainment had the strongest genetic association with fine motor skills, and the associated GWA studies have the largest sample sizes (Lee et al., 2018). Therefore, the educational attainment of PGS may be usual for predicting future fine motor impairments in preschool children.

To consider explanation rather than prediction, Mendelian randomisation models can test for causal effects using genetic data (E. Sanderson et al., 2022). Mendelian randomisation uses the same randomisation method that clinical trials use when they randomise participants into treatment or placebo groups. Once a GWAS of an early motor phenotype has been conducted, it would be beneficial to investigate the causal effects of a motor phenotype on cognitive and neurodevelopmental outcomes. Further, bidirectional associations with neurodevelopmental outcomes could be explored to understand if early manifestations of an NDC, such as autism, have a causal effect on later walking. This focus on causation and explanation would aid the complex understanding of the mechanisms of the associations found in this thesis with early motor skills and for the aetiology of neurodevelopmental disorders.

6.3 Limitations

6.3.1 Socioeconomic status and collider bias

Although SES sensitivity analyses were conducted in the phenotypic analyses in Chapter 4 and revealed similar results, it was not possible to control for SES in the genetic models since SES could act as a collider in the model, leading to biased estimates of the association (Pingault et al., 2022). SES is heritable and associated with many PGSs, most strongly the educational attainment PGS (Krapohl & Plomin, 2016). Similarly, the heritability of IQ is modified by SES (Turkheimer et al., 2003). SES is additionally associated with motor skills (Morley et al., 2015). Therefore, SES has associations with the independent PGS variables and the outcome variable (motor skills).

Consequently, adjusting for SES unblocks a path between the genetic and unmeasured variables, leading to collider bias (Pingault et al., 2022; Robinson et al., 2016). Pingault et al. (2022) suggested an effective method to account for this effect, including the PGS of the outcome. This method is not currently possible because there are no GWAS of motor skills. However, this would be an informative area of research when it becomes available.

6.3.2 Limitations of polygenic score analyses

As indicated in section 5.5, it is not currently possible to control for the limitations of PGS in regression models. These limitations include differences in the statistical power as a result of the sample size of the GWAS that the PGS was calculated from (Plomin, 2022) or measurement error in the measurement of the phenotype for the GWAS (Pingault et al., 2022). Further, biases include assortative mating and genetic nurture (familial genetic) effects. There could also be gene-environment interactions in which the PGS–phenotype associations are the result of gene-environment interactions (e.g., active, evocative), but also passive interactions where a child's genetics are correlated with their environments as a result of parental genetics (Kong et al., 2018). One method that accounts for familial genetic effects is to conduct trio designs using parental and child genetics and construct PGS for non-transmitted genes to understand the non-genetic associations between parental risk factors and child outcomes (Pingault et al., 2022). Further, Mendelian randomisation methods can be used to understand causality (Hwang et al., 2021, see section 6.2.7).

6.4 Future Directions

6.4.1 Digital phenotyping validation

Developing the app presented in Chapter 2 during my PhD was not feasible due to time and cost constraints and practicalities. However, if the app were to be developed, further formal one-to-one user testing would be conducted with all of the groups listed in the user profiles. From this, further versions of the prototype would be developed. Next, a validation study would establish the app's reliability and validity as a measure of infant motor skills. The app's test-retest reliability would be

measured by sending all participants the same weekly app-based questionnaires twice within a short timeframe (e.g., two days apart). The test-retest reliability could be compared to the reliability the Kleine Weltentdecker app (α >.70, Daum et al., 2022). Secondly, the app's construct validity would be assessed by comparing the existing parent report questionnaire (Ages and Stages Questionnaire, Squires et al., 1997) and lab-based motor measures (Mullen Scales of Early Learning, Mullen, 1995) with the app-based measurements. Finally, the criterion validity would be assessed testing the association between the motor measures and gestational age, child age, and father and mother education. I would expect a positive association between motor skills and gestational age and child's age. Finally, I would look at the extent of missing data and how long individuals use the app (average number of months).

6.5 Conclusion

This thesis has reported research findings related to individual differences in motor skills in the first years after birth. Motor skills may be important signs of later neurodevelopmental, cognitive, and psychiatric outcomes through adolescence. However, more longitudinal prospective work is needed to understand the mechanisms. An app prototype for digital phenotyping is presented as a potential method to increase the amount of generalisable longitudinal prospective datasets. Further work is also needed to address issues in prediction and causation and overcome issues in polygenic score prediction with methods such as Mendelian randomisation and trio design analyses. This work has implications for clinicians and education to consider fine and gross motor skills as important early markers of later development.

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