TURUN
YLIOPISTO
UNIVERSITY
OF TURKU

CHARACTERISTICS AND RISK MARKERS OF SPECIFIC LEARNING DISORDERS IN FINNISH SPECIALISED HEALTH CARE

A national register-based study

Bianca Arrhenius

TURUN YLIOPISTON JULKAISUJA – ANNALES UNIVERSITATIS TURKUENSIS
SARJA – SER. D OSA – TOM. 1623 | MEDICA – ODONTOLOGICA | TURKU 2022

TURUN
YLIOPISTO
UNIVERSITY
OF TURKU

CHARACTERISTICS AND RISK MARKERS OF SPECIFIC LEARNING DISORDERS IN FINNISH SPECIALISED HEALTH CARE

A national register-based study

Bianca Arrhenius

TURUN YLIOPISTON JULKAISUJA – ANNALES UNIVERSITATIS TURKUENSIS
SARJA – SER. D OSA – TOM. 1623 | MEDICA – ODONTOLOGICA | TURKU 2022

University of Turku

Faculty of Medicine
Department of Child Psychiatry
Doctoral programme in Clinical Research
Research Centre for Child Psychiatry
INVEST Research Flagship

Supervised by

Associate Professor David Gyllenberg
Department of Child Psychiatry,
INVEST Research Flagship,
University of Turku
Department of Adolescent Psychiatry,
Helsinki University Hospital

Director, Professor Andre Sourander
Department of Child Psychiatry,
INVEST Research Flagship,
Turku University Hospital and
University of Turku

Reviewed by

Associate Professor Tuija Aro
Department of Psychology,
University of Jyväskylä

Professor Marja Laasonen
Department of Logopedics,
University of Eastern Finland

Opponent

Professor Leena Haataja
Department of Child Neurology,
Helsinki University Hospital and
University of Helsinki

The originality of this publication has been checked in accordance with the University of Turku quality assurance system using the Turnitin OriginalityCheck service.

ISBN 978-951-29-8822-8 (PRINT)
ISBN 978-951-29-8823-5 (PDF)
ISSN 0355-9483 (Print)
ISSN 2343-3213 (Online)
Painosalama, Turku, Finland 2022

For the love of science

UNIVERSITY OF TURKU
Faculty of Medicine, Department of Child Psychiatry
BIANCA ARRHENIUS: Characteristics and risk markers of specific learning disorders in Finnish specialised health care: A national register-based study
Doctoral Dissertation, 131 pp.
Doctoral Programme in Clinical Research
May 2022

ABSTRACT

Background: Specific learning disorders are common, with prevalence estimates of 3–15% among school children. Despite this, national population-based studies on the risk factors for specific learning disorders are scarce.

Aims: This thesis examined the cumulative incidence and gender distribution of specific learning disorders as well as their associations with maternal social risk markers, prenatal smoking, maternal vitamin D levels during pregnancy, and the child's relative age.

Methods: The sample comprised a source cohort of all children born in Finland 1996–2007 (N = 690,654) and among them, those who were diagnosed with specific learning disorders in specialised services, i.e., reading, arithmetic, or spelling disorder, or a mixture of these (ICD-10 codes F81.x) by the end of 2012 (n = 6,490). The data was retrieved from national registers.

Results: The cumulative incidence was 1.55% for specific learning disorders diagnosed in specialised services by age 15, and the disorders were twice as common among boys. Common comorbidities were developmental disorders of speech, language and coordination (40.4%), and psychiatric disorders (38.4%). December-born children, the youngest in class, were diagnosed 1.77-fold compared to January-born children. Significant associations were found for specific learning disorders and low maternal socioeconomic status, educational level, and single motherhood. Smoking during pregnancy was associated with specific learning disorders when comparing cases to population controls, but the association did not persist when comparing differentially exposed siblings. No association was found between prenatal vitamin D deficiency and specific learning disorders.

Conclusions: The clustering of social risk factors and specific learning disorders needs to be acknowledged in health care and educational service planning. The relative age effect on specific learning disorder diagnoses implies a need to standardise diagnostic procedures, and further research on the benefits of flexible school start timing. Maternal smoking and vitamin D deficiency during pregnancy might not be causal aetiological risk factors for specific learning disorders.

KEYWORDS: specific learning disorder, learning disability, dyslexia, dyscalculia, reading disorder, spelling disorder, math disorder, smoking, vitamin D, relative age, sibling study, epidemiology

TURUN YLIOPISTO
Lääketieteellinen tiedekunta, kliininen laitos
Lastenpsykiatrian oppiaine
BIANCA ARRHENIUS: Erikoissairaanhoidossa todettujen oppimishäiriöiden yleisyys ja riskitekijät: kansallinen rekisteripohjainen tutkimus
Väitöskirja, 131 s.
Turun kliininen tohtoriohjelma
Toukokuu 2022

TIIVISTELMÄ

Tausta: Oppimishäiriöitä esiintyy arviolta 3–15% kouluikäisistä lapsista. Yleisyydestään huolimatta kirjallisuudesta puuttuu väestön kattavia tutkimuksia vallitsevuudesta sekä oppimishäiriöiden varhaisista riskitekijöistä.

Tavoitteet: Tämä väitöskirja tutki erikoissairaanhoidossa diagnosoitujen oppimishäiriöiden kumulatiivista ilmaantuvuutta, sukupuolijakaumaa sekä yhteyksiä sosiaalisten riskitekijöiden, raskaudenaikaisen tupakoinnin, äidin D-vitamiinitasojen sekä lapsen nuoren suhteellisen iän välillä.

Menetelmät: Tutkimusdata koottiin kansallisista rekistereistä. Otos sisälsi kaikki Suomessa vuosina 1996–2007 syntyneet lapset (N = 690,654). Heidän joukostaan poimittiin ne, joilla todettiin oppimishäiriö, eli lukemisen, kirjoittamisen tai matematiikan oppimisvaikeus tai näiden yhdistelmiä (ICD-koodit F81.x) erikoissairaanhoidossa vuoteen 2012 loppuun mennessä (n = 6,490).

Tulokset: Oppimishäiriöiden kumulatiivinen esiintyvyys oli 1.55% 15 ikävuoteen mennessä, ja ne olivat tuplasti yleisempiä pojilla. Päällekkäisyys kielellisten ja motoriikan häiriöiden (40.4%) sekä psykiatristen häiriöiden (38.4%) kanssa oli yleistä. Luokan nuorimmilla eli joulukuussa syntyneillä lapsilla todettiin oppimishäiriöitä 1.77-kertaisesti tammikuussa syntyneisiin verrattuna. Merkitseviä yhteyksiä löytyi oppimishäiriöiden ja äidin matalan koulutustason, sosioekonomisen aseman sekä yksinhuoltajuuden välillä. Yhteys raskaudenaikaisen tupakoinnin ja oppimishäiriöiden välillä havaittiin tapaus-verrokki asetelmassa, mutta yhteys hävisi kun verrattiin eri lailla tupakoinnille altistuneita sisaruksia. Äidin raskaudenaikaisen d-vitamiinitason ja lapsen oppimishäiriön välillä ei löytynyt yhteyttä.

Päätelmät: Oppimishäiriöiden ja sosiaalisten riskitekijöiden kasaantuminen on tärkeä huomioida terveys- ja koulutuspalveluiden suunnittelussa. Nuoren suhteellisen iän vaikutusta diagnostiikkaan voisi mahdollisesti vähentää kehittämällä kansallisia hoitosuosituksia sekä lisäämällä koulunaloituksen ajankohdan joustavuutta. Raskaudenaikainen tupakointi ja d-vitamiinitasot eivät tämän tutkimuksen perusteella näytä olevan syy-yhteydessä oppimishäiriöihin.

AVAINSANAT: oppimishäiriöt, lukemisen häiriö, kirjoittamisen häiriö, matematiikan oppimisvaikeus, tupakointi, d-vitamiini, suhteellinen ikä, ilmaantuvuus, epidemiologia, sisarus-tutkimus

Thesis at a glance

SOURCE COHORT: All 690,654 children born in Finland 1996–2007

6,490 children with specific learning disorders (ICD-10 F81.x) in specialised services

STUDY I
N=6,490
with F81

What is the cumulative incidence of specific learning disorders in specialised services? How are they associated with social risk factors?

The cumulative incidence of specific learning disorders was 1.55% by age 15 in specialised services. Low maternal education, socioeconomic status and single motherhood were associated with offspring specific learning disorders.

STUDY II
N=3,162
with F81

Are children born relatively young more likely to be diagnosed with specific learning disorders compared to their older peers?

December-born children were 1.77 times more likely to be diagnosed with a specific learning disorder than their peers born in January.

STUDY III
N=6,282
with F81

Is smoking during pregnancy associated with specific learning disorders in cases vs controls and cases vs siblings?

Smoking during pregnancy was associated with specific learning disorders in the case-control sample, but the effect was attenuated and no longer statistically significant in the case-sibling subsample.

STUDY IV
N=1,607
with F81

Is maternal serum vitamin D deficiency in early pregnancy associated with specific learning disorders in offspring?

No statistically significant association between maternal serum vitamin D levels in early pregnancy and offspring specific learning disorders.

Table of Contents

Abbreviations

ADHD	Attention-deficit hyperactivity disorder
aOR	Adjusted odds ratio
ASD	Autism spectrum disorder
CI	Confidence interval
CRHC	Care Register for Health Care
DSM	Diagnostic and Statistical Manual for Mental Disorders
DVV	Digital and Population Data Services Agency
FMBR	Finnish Medical Birth Register
FMC	Finnish Maternity Cohort
GWAS	Genome Wide Association Study
HR	Hazard ratio
ICD	International Classification of Diseases
ID	Intellectual disability
IRR	Incidence rate ratio
IQ	Intelligence quotient
IQR	Interquartile range
OR	Odds ratio
PISA	Programme for International Student Assessment
SD	Standard deviation
SES	Socioeconomic status
THL	The Finnish Institute for Health and Welfare (Terveyden ja Hyvinvoinnin Laitos)
WHO	World Health Organization
25(OH)D	25-hydroxyvitamin D

List of Original Publications

This dissertation is based on the following original publications, which are referred to in the text by their Roman numerals:

I Arrhenius B, Gyllenberg D, Chudal R, Sucksdorff M, Sourander O, Virtanen J-P, Torsti J and Sourander A. Social risk factors for speech, scholastic and coordination disorders: a nationwide register-based study. *BMC Public Health*, 2018; 18:739.

II Arrhenius B, Gyllenberg D, Vuori M, Tiiri E, Lempinen L and Sourander A. Relative age and specific learning disorder diagnoses: a Finnish population-based cohort study. *JCPP Advances*, 2021; 1: e12001.

III Arrhenius B, Sariaslan A, Suominen A, Sourander A and Gyllenberg D. Familial confounding affected the associations between maternal smoking during pregnancy and offspring speech and language, scholastic and coordination disorders. *Acta Paediatrica*, 2021; 00: 1–9.

IV Arrhenius B*, Upadhyaya S*, Hinkka-Yli-Salomäki S, Brown A, Cheslack-Postava K, Öhman H and Sourander A. Prenatal vitamin D levels in maternal sera and offspring specific learning disorders. *Nutrients* 2021; 13: 3321.

*Shared first authorship.

1 Introduction

Specific learning disorders are common in the population, with prevalence estimates of 3–15% (Mikkonen et al., 2015; Moll et al., 2014; Zablotsky et al., 2019). Because of their common prevalence, and associated long-term adversities of education, employment and mental health (Eloranta, 2019; Undheim, 2003), they constitute a significant public health burden for society. Specific learning disorders are specific developmental disorders of scholastic skills, i.e., reading, spelling or arithmetic skills (American Psychiatric Association, 2013; World Health Organization, 1992). Children with specific learning disorders have narrow but severe difficulties in these specific domains of cognitive functioning, although their overall intellectual functioning is within the normal range.

The aetiology of specific learning disorders is multifactorial and largely unknown; however, the genetic influence on the risk for learning disorders is considerable, with heritability estimates as high as 40–70% (Willcutt et al., 2010). Further, many pre- and postnatal social, biological, and behavioural factors have been associated with specific learning disorders. These include, for example, maternal smoking during pregnancy, low parental education and socioeconomic status, higher birth order, the amount of cognitive fostering done by parents, and parental psychiatric morbidity (Altarac & Saroha, 2007; Anderko et al., 2010; Sanfilippo et al., 2020).

Nonetheless, considering how common specific learning disorders are, they have not received quite the research attention they deserve. There are only a few large epidemiological population-based studies on the prevalence and its time trends, gender distribution, and risk factors of specific learning disorders. However, a bulk of studies, including large register-based samples, have examined low academic performance or general cognitive function, but these outcomes are not directly comparable to specific learning disorders (D'Onofrio et al., 2010; LeWinn et al., 2020; Specht et al., 2020; Zoëga et al., 2012).

Another understudied topic in the context of specific learning disorders is the relative age effect, which means that the youngest children in an age cohort are more likely to display academic and psychiatric adversities. The relative age effect for attention-deficit hyperactivity disorder (ADHD) is well-established (Holland &

Sayal, 2018), and some studies have indicated the effect might be similar for parent- or school-reported learning disorders (Dhuey & Lipscomb, 2010; Martin et al., 2004).

Some evidence exists that children with learning disorders more frequently come from families with low education and socioeconomic status and have mothers who smoked during pregnancy (Altarac & Saroha, 2007; Anderko et al., 2010). However, the causal effect of smoking during pregnancy is debated, because of possible unmeasured confounding of familial risk factors, including genetic factors (D'Onofrio et al., 2013). Family and sibling studies present a means to partly account for unmeasured confounding, and some within-family studies have indicated that the effects of prenatal smoking exposure on learning outcomes may not be causal (D'Onofrio et al., 2010; Lundberg et al., 2010)

Vitamin D is another biologically interesting prenatal factor regarding later learning problems because it is suspected to influence foetal brain development adversely. Surprisingly, no previous studies have investigated a possible link between maternal vitamin D levels during pregnancy and specific learning disorders in offspring. Studies investigating academic achievement, or cognitive function, have been inconclusive. Some evidence exists of poorer cognitive and language development in toddlers and babies from vitamin D deficient pregnancies (Janbek et al., 2019), whereas the findings for similar outcomes in school-aged children have been mostly null.

Nordic nationwide registers are world-famous for their invaluable offerings as data sources for scientific research. Finnish national registers provided the unique datasets for this thesis, which examined a nationwide sample of all children born between 1996 and 2007 in Finland. The aim was to address unanswered questions in the field of specific learning disorders. These included information on the cumulative incidence and gender distribution of specific learning disorders diagnosed in specialised health care and how the incidence might have changed over time. Further, this thesis examined the relative age effect on specific learning disorders diagnoses, the associations between maternal socioeconomic variables and specific learning disorders, and the possible effects of maternal smoking and vitamin D levels during pregnancy on offspring specific learning disorders. The acquired information has important implications for developing prevention strategies for children and families affected by specific learning disorders, and for health care and educational service planning.

2 Review of the literature

2.1 Specific learning disorders

This chapter will outline how specific learning disorders are defined and diagnosed and how common they are. Further, it will briefly describe what is known about the neurodevelopmental comorbidity and genetics of specific learning disorders.

2.1.1 Terminology and definitions

The two main diagnostic classifications that are used worldwide are the World Health Organization's (WHO's) International Classification of Diseases (ICD) and the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders (DSM), of which the current versions are the ICD-10 and the DSM-5, respectively (American Psychiatric Association, 2013; World Health Organization, 1992). The ICD-10 is commonly used in the Nordic and many European countries, whereas the DSM-5 is used mainly in the United States and Australia.

The ICD-10 defines specific learning disorders as specific developmental disorders of scholastic skills, which comprise disturbances in the normal patterns of scholastic skill acquisition, i.e., reading, writing, spelling, and mathematics that are not explained by a lack of opportunity to learn, a consequence of intellectual disability, acquired brain trauma, or disease (World Health Organization, 1992). In the ICD-10, specific learning disorders include specific reading disorder, spelling disorder, arithmetic disorder, mixed or other specified learning disorders, and unspecified learning disorders (**Table 1**). Reading and spelling difficulties often co-occur, and together they are classified under reading disorder (F81.0) in the ICD-10. The diagnosis of spelling disorder (F81.1) is used only when the spelling difficulties occur without comorbid reading difficulties (World Health Organization, 1992). Developmental dyslexia often refers to difficulties in both reading and spelling (Peterson & Pennington, 2012; Qvarnström, 2013; Sanfilippo et al., 2020), and it is sometimes used as a synonym for reading disorder. The term developmental dyscalculia is a synonym for arithmetic disorders.

The Finnish version of the ICD-10 classification includes the same criteria as the international version (**Table 1**) and further defines that the reading, spelling, or

arithmetic skills in standardised tests should be below two standard deviations (SD) of the age-standardised mean and that the general IQ of the child should not be below 70 (Stakes, 1999).

The content of the diagnostic criteria for specific learning disorders in the DSM classification has many similarities with the ICD-10. At the time of data collection for this thesis, the fourth edition of DSM (DSM-IV) was in use. It included diagnoses for reading disorder, mathematics disorder, written expression disorder, and learning disorder not otherwise specified, and required that the specific impairment of a certain academic skill differs from the child's general IQ (American Psychiatric Association, 1994). This IQ discrepancy criterion has been debated, and it was removed from the current version of the classification, the DSM-V. In comparison to the ICD and the DSM-IV-classifications, the DSM-V further features one overarching category of specific learning disorders, under which the specific difficulty and its severity should be stated. It lacks the unspecified category and it requires both that the diagnosis is made when formal schooling has begun and that the learning difficulty has persisted for six months or longer (American Psychiatric Association, 2013).

Specific learning disorder, scholastic disorder, or simply learning disorder is the medical term used for clinical diagnosis, whereas learning disability is a broader term more commonly used in the educational and legal systems (American Psychiatric Association, 2018). The abbreviation 'LD' is used for both learning disorder and learning disability. This thesis uses the term specific learning disorder because the term LD is sometimes used in a broader sense and the official ICD term "specific developmental disorders of scholastic skills" is cumbersome.

Specific learning disorders have not been studied as abundantly as one would expect based on their common prevalence in the population. Reasons for this have been proposed: varying definitions and terminology (A. E. B. Taylor, 2014), cultural differences (M. Aro, 2011), and possibly funding policies for different neurodevelopmental disorders, in which research on more impairing disorders tend to get more funding (Bishop, 2010). Dyscalculia is particularly understudied considering that it is nearly as common as dyslexia (Räsänen, 2012). There are no previous register-based nationwide studies on diagnosed specific learning disorders. Most of the larger studies on the topic have relied on parent- or teacher reports, or psychological testing in smaller samples.

Table 1. Diagnostic criteria for specfic developmental disorders of scholastic skills in the ICD-10 classification*.

ICD-10 Code and disorder name	Definition
F81 Main category for specific learning disorders	Disorders in which the normal patterns of scholastic skill acquisition are disturbed from the early stages of development. This is not simply a consequence of a lack of opportunity to learn, it is not solely a result of mental retardation, and it is not due to any form of acquired brain trauma or disease.
F81.0 Specific reading disorder	The main feature is a specific and significant impairment in the development of reading skills that is not solely accounted for by mental age, visual acuity problems, or inadequate schooling. Reading comprehension skill, reading word recognition, oral reading skill, and performance of tasks requiring reading may all be affected. Spelling difficulties are frequently associated with specific reading disorder and often remain into adolescence even after some progress in reading has been made.
F81.1 Specific spelling disorder	The main feature is a specific and significant impairment in the development of spelling skills in the absence of specific reading disorder, which is not solely accounted for by low mental age, visual acuity problems, or inadequate schooling. The ability to spell orally and to write out words correctly are both affected.
F81.2 Specific disorder of arithmetical skills	Involves a specific impairment in arithmetical skills that is not solely explicable on the basis of general mental retardation or of inadequate schooling. The deficit concerns mastery of basic computational skills of addition, subtraction, multiplication, and division rather than of the more abstract mathematical skills involved in algebra, trigonometry, geometry, or calculus.
F81.3 Mixed disorder of scholastic skills	A residual category of disorders in which both arithmetical and reading or spelling skills are significantly impaired, used for disorders meeting the criteria for both F81.2 and either F81.0 or F81.1.
F81.8 Other disorders of scholastic skills	For example: expressive writing disorder
F81.9 Unspecified developmental disorder of scholastic skills	Knowledge acquisition disability not otherwise specified.

*Criteria from the International Classification of diseases, 10th edition. Reproduced with permission from the WHO.

2.1.2 Diagnostic procedures

The educational system in Finland uses a stepwise support system for pupils in need of support or interventions in school. Until 2010, the support system was two-tiered: general support and special support (Finnish Ministry of Education and Culture,

2014). Since 2011, it has consisted of three tiers: general support, intensified support, and special support (Finnish National Board of Education, 2014). If children struggle in their learning, teachers usually consult a special needs teacher and/or the school psychologist. Based on the special teacher's and psychologist's assessment, intensified or special support can be offered to the child without a formal diagnosis of a specific learning disorder. This support might be enough for children with milder learning disabilities to proceed in their learning.

If this is not the case, a multidisciplinary expert group can be assembled to assess the child's and family's difficulties more thoroughly. This group might also include the school's social worker, nurse, and medical doctor. The parents can also take the initiative to form such a group. If the learning difficulties are severe and unresponsive to educational interventions, or broader neurodevelopmental disorders are suspected, children are referred from primary care, typically from the school health services, to publicly funded specialist outpatient clinics (Mikkonen et al., 2015).

Apart from the educational support processes, Finnish children are regularly examined in free routine health check-ups in preventive primary care services. The check-ups are performed by a public health nurse once a year, and by a doctor five times before entering school and at ages 7, 11 and 14 (Finnish Ministry of Social Affairs and Health, 2009). Through these processes, children might also be referred to specialist clinics.

In Finland, the diagnosis of specific learning disorders is based on the ICD-10 diagnostic classification and is typically set after a multiprofessional assessment in an outpatient clinic of paediatric neurology, phoniatrics, child psychiatry, or paediatrics. Depending on the child's difficulties, the diagnostic evaluation usually includes assessments by a specialised nurse, medical doctor, and (neuro)psychologist using standardised tests for reading, spelling or arithmetic skills and psychological testing with methods such as the Wechsler Intelligence Scale for Children (Wechsler, D., 2003). Because of the common comorbidities of specific learning disorders, an occupational therapist, speech and language therapist, or physiotherapist might also evaluate the child.

2.1.3 Prevalence

The lifetime prevalence of specific learning disorders varies between 3–15% (American Psychiatric Association, 2018; Moll et al., 2014; Zablotsky et al., 2019), depending on the defined cutoffs and recruitment sources of the outcome. Learning difficulties are continuously distributed among the population, and the cutoff criteria for what is considered a disorder are not consistent in the literature. Commonly, an impairment of 1–2 SDs below the mean grade level functioning in the specific area

of learning is required for diagnosis (Moll et al., 2014; A. E. B. Taylor, 2014). Some studies on school populations have used a performance of under the 20–25th percentile (corresponding to -0.84 to -0.67 SDs) in age-standardised tests as classification criteria (Dirks et al., 2008; Gross-Tsur et al., 1996). In Finnish specialised health care, diagnoses are based on the national ICD-10 diagnostic classification, and the standard impairment required for diagnosis is -2 SDs (Stakes, 1999). Naturally, the prevalence estimates vary considerably depending on whether cutoffs of -1 SD or -2SDs or some other criteria are used for diagnosis. These inconsistencies in the literature make it challenging to compare prevalence rates across studies (Dirks et al., 2008).

In Finland, the prevalence of specific reading disorders among schoolchildren is estimated at 3–10% (Holopainen, 2002; Lyytinen & Erskine, 2006), whereas the prevalence of specific arithmetic disorders is estimated at 5–7% (Niemi & Metsämuuronen, 2010). When diagnoses from specialised services in Finland were examined until 2010, the cumulative incidence by age 14 was 7.7% for a combined group, which included speech and language disorder, coordination disorder, specific learning disorder, and mixed developmental disorder (ICD-10 codes F80–83). However, the prevalence of specific learning disorder was not separately examined (Gyllenberg et al., 2014).

Globally, studies on the prevalence of specific learning disorders have reported varying numbers. A survey-based study from the United States reported a 7–8% prevalence of parent-reported learning disorders with a stable time trend over 2009–2017, even though developmental disorders as a broader entity increased (Zablotsky et al., 2019). A German study on school populations (Moll et al., 2014) found prevalences of 7.0% for reading disorder, 8.8% for spelling disorder and 6.1% for arithmetic disorder, when a -1.5 SD cutoff criterion and DSM-5 criteria were applied. A Chinese study displayed far lower prevalence estimates; only 3% of school-aged children were classified as dyslexic (Liu et al., 2016). Differences in the prevalence of reading disorders across countries are thought to reflect both cross-cultural variation in how the spoken language corresponds to written text in different languages as well as possible cultural stigma (Grigorenko et al., 2019).

Approximately half of the cases with arithmetic disorders have co-occurring reading disorders and vice versa (Korpipää et al., 2020; Landerl & Moll, 2010; Willcutt et al., 2013). Math and reading disorders have been described as two distinct but highly correlated disorders that share many risk factors (Peterson et al., 2017; Willcutt et al., 2013). For example, cognitive skills such as verbal counting and rapid automatised naming seem to correlate with both reading and aritmethic skills and might partly explain their shared variance (T. Koponen et al., 2020).

Specific learning disorders are more frequent among boys than girls, with a typical male to female ratio of 2:1. While community samples have typically

displayed smaller or no differences in gender distribution (Moll et al., 2014; Morsanyi et al., 2018), most large epidemiological studies have reported 1.5–3 times higher prevalences for boys than girls (Altarac & Saroha, 2007; Gyllenberg et al., 2014; Rutter et al., 2004).

2.1.4 Comorbidity with developmental disorders of speech, language, and coordination

Besides being highly comorbid internally, specific learning disorders also frequently co-occur with speech and language disorders (also known as specific language impairment or the more current term developmental language disorder, ICD-10 F80.x). It is estimated that at least half of the children diagnosed with a reading disorder also have speech and language disorders (McArthur et al., 2000; Snowling et al., 2020). However, reading disorder is considered less impeding than developmental language disorder, in which language comprehension is often impaired and comorbid challenges of motor and executive function are more common (Snowling et al., 2019). Further, speech and language disorders are often reliably diagnosed earlier because the delayed development of language comprehension, and often also speech, becomes evident before school start.

Motor coordination disorder (ICD-10: F82) is another common comorbidity; approximately 20% of children with specific learning disorders also suffer from coordination disorders (Margari et al., 2013). This comorbidity pairing is less studied than reading disorder and developmental language disorder, and especially studies on motor disorders and comorbid arithmetic disorders are lacking. A Finnish study that examined early motor development milestones and reading skills among beginning readers found a connection between reading speed and slower motor development, but the finding was restricted to children with a familial risk of dyslexia (Viholainen et al., 2006).

2.1.5 Psychiatric comorbidity

Children and youth with specific learning disorders display psychiatric symptoms and are diagnosed with psychiatric disorders more often than children without learning disorders (T. Aro et al., 2021; Haberstroh & Schulte-Körne, 2019; Willcutt & Pennington, 2000). Furthermore, children suffering from multiple learning disorders, rather than a single disorder, have significantly higher rates of comorbid psychopathology (Willcutt et al., 2013). Neuropsychiatric comorbidities are most common, particularly ADHD, affecting approximately 20–40% of children with specific learning disorders (Boada et al., 2012; Haberstroh & Schulte-Körne, 2019; Morsanyi et al., 2018; Willcutt & Pennington, 2000). The combination of learning

disorders, motor deficits and ADHD is another particularly common triad; this was acknowledged already in the 1990s (Gillberg, 2003).

Assessing the learning abilities of autistic children poses a challenge, as autism spectrum disorders are usually associated with varying degrees of intellectual disability and impaired language development, and further, also comorbid with ADHD. One study estimated the prevalence of specific learning disorders at 10–20% in high-functioning autistic children (Mayes & Calhoun, 2007).

Conduct problems are common among children with specific learning disorders (T. Aro et al., 2021). However, children with learning disorders and conduct problems typically also have ADHD, and there is some evidence that the associations between learning and conduct disorders might be explained by co-occurring ADHD and especially symptoms of inattentiveness (Burke et al., 2002; Carroll et al., 2005). Furthermore, psychoses and schizophrenia are known to be preceded by cognitive impairment and delays in language and motor development (Polanczyk et al., 2010).

Symptoms of depression and anxiety are slightly more common among children and adolescents with learning disorders (Nelson & Harwood, 2011a, 2011b), especially among adolescent girls with reading disorders (Willcutt & Pennington, 2000). However, most studies on internalising symptoms and learning disorders have been cross-sectional and focused on self- or parent-reported symptoms rather than diagnosed psychiatric disorders.

2.1.6 Genetic factors

Specific learning disorders are highly heritable; family and twin studies have consistently demonstrated heritability estimates of 40–80% for reading, spelling and math disorders (Georgitsi et al., 2021; Haworth et al., 2009; Willcutt et al., 2010). Therefore, genetic factors are important to consider when conducting research on specific learning disorders.

Family and twin studies that have investigated the overlapping heritability of specific learning disorders have concluded that there is a common feature for genes affecting learning disorders; they seem to lack specificity for a particular disorder, meaning that the genes that increase the risk for dyslexia also increase the risk for dyscalculia (Haworth et al., 2009). This overlapping of the genes that increase the susceptibility for different subtypes of specific learning disorders is known as the "generalist gene hypothesis", and it was introduced already at the beginning of this century (Plomin & Kovas, 2005).

Research on the molecular genetic basis of reading disorders has been extensive, but despite their common prevalence, arithmetic disorders have received less attention from molecular genetic researchers (Haberstroh & Schulte-Körne, 2019). Genome-wide association studies (GWAS), which means mapping the whole

genome to find genetic variants influencing the outcome of interest and then calculating so-called polygenic risk scores, have explained up to around 20% of the genetic variance of reading abilities (Georgitsi et al., 2021). Genome linkage studies suggest that the aetiology of reading disorders is complex and polygenic (Willcutt et al., 2010). For arithmetic disorders, a GWAS study found ten single nucleotide polymorphisms associated with mathematical disability, and when combined, they explained 3% of the phenotypic variance (Docherty et al., 2010).

Neurodevelopmental disorders in a broader sense also seem to share common genetic risk factors (Cederlöf et al., 2017; Lichtenstein et al., 2010), which explains why they occur together more often than could be expected by chance. Some genetic risk loci found through GWAS studies have been suspected to contain common susceptibility genes for learning disorders as well as ADHD and autism (Georgitsi et al., 2021; Gialluisi et al., 2019). However, the complexity of the comorbid pathways, in which genetic and environmental factors overlap and interact, make aetiological conclusions challenging for a specific disorder, and a major challenge for epidemiological research. The term "multiple deficit model" is sometimes used to describe the continuum and overlap of neurodevelopmental disorders (Pennington, 2006).

2.2 Relative age within the school year

The way that school admissions are organised in most countries means that the youngest children in a grade can be up to a year younger than their older peers. The relative age effect, recognised already in the 1990s (Bell & Daniels, 1990), refers to the fact that younger children in classrooms are at higher risk for various adversities of social and emotional well-being, as well as academic outcomes. Because this thesis examines the association between relative age and specific learning disorders, this chapter will shortly outline what is known about the risks of being relatively young.

2.2.1 Relative age and learning-related outcomes

Previous studies on learning-related themes have reported that younger children in school classes are more likely to receive special education (Dhuey & Lipscomb, 2010; Gledhill et al., 2002; Kivinen, 2018) and perform worse in school (Zoëga et al., 2012). On the other hand, two Dutch studies (Jeronimus et al., 2015; Wienen et al., 2018) did not find any associations between young relative age and poorer academic performance. However, both Dutch studies excluded children in special education.

Only two studies (Dhuey & Lipscomb, 2010; Martin et al., 2004) have looked at relative age and specific learning disorders; they both found a clear association between younger relative age and specific learning disorders. However, the diagnoses relied on parent- or school-reported surveys, possibly limiting their validity, and furthermore, neither of the studies considered comorbidities in their analyses.

Another important term in the literature on relative age is the season of birth. Because of the findings that schizophrenia patients are more commonly born in winter or spring (Davies et al., 2003), season of birth has been explored as a predictor for various other disorders, including learning disorders and more general cognitive outcomes. A large cohort study (Mackay et al., 2016), comprising 801,592 children attending Scottish schools in 2006–2011, found that the proportion of children with learning disabilities in need of special education was higher for children conceived in January–April compared to July–September. The authors hypothesised that this might be linked to lower levels of vitamin D during periods with less sunlight in the first trimester of pregnancy. However, a major limitation in this study was that the relative age effects were not accounted for in any way. Another season of birth study (Grootendorst-van Mil et al., 2017) also found seasonal variation between birth month and the child's IQ, so that spring birth was associated with lower IQ than summer birth, but concluded that maternal IQ and sociodemographic factors might influence the time when mothers conceive and that this could explain the findings. Because of the consistency of relative age findings across countries with varying cutoff timing for school admissions, it is unlikely that the relative age adversities would be caused by seasonality and biological factors, such as seasonally occurring infections.

The literature is unclear regarding young relative age and specific learning disorders. The possible relative age effect for specific learning disorders has important implications for school referral processes and clinical diagnostic practice. Furthermore, the information is needed for policymakers who decide on flexible school start timing principles.

2.2.2 Relative age and psychosocial adversities

Even though relative age effects on specific learning disorder diagnoses are somewhat unclear, relative age discrepancies have been confirmed for ADHD (Caye et al., 2019; Holland & Sayal, 2018), other psychiatric diagnoses (Chen et al., 2021; Goodman, 2003), intellectual disability and depression (Root et al., 2019).

The links between relative age and ADHD are particularly well-established, with consistent approximations of 1.3-fold likelihoods for the youngest in class to receive ADHD diagnoses compared to the oldest in class. These findings may reflect that

younger children in a class are emotionally less mature than their classmates and appear more hyperactive and less concentrated than what could be expected for their school year level. The immature behaviour then leads to more referrals to health care professionals and hence, proportionally more diagnoses.

A recent PISA (Programme for International Student Assessment) report (Givord, 2020), including data from 79 countries, concluded that "the month of birth has a sizeable and significant impact on cognitive and non-cognitive outcomes". The report found that younger children in class suffered from lower self-esteem and had more discouraged attitudes towards learning and school than their older peers.

2.2.3 Long-term effects of young relative age

Most studies have found that relative age differences in academic performance persist at least into adolescence, meaning that the younger children in the academic year perform worse and are more likely to receive special education throughout secondary school (Cobley et al., 2009; Givord, 2020; Lien et al., 2005). Moreover, some studies demonstrate that these academic disadvantages continue even further: relatively young individuals seem to be less likely to attend university (Bedard & Dhuey, 2006), achieve a postsecondary degree, and be employed (Crawford et al., 2013). In a more positive light, the relative age gap does seem to narrow with increasing age (Bedard & Dhuey, 2006), and longer follow-up studies have not found major differences in occupation or total income over the life span (Crawford et al., 2013; Røed Larsen & Solli, 2017).

Regarding ADHD and other psychiatric outcomes, relative age differences also seem to decrease somewhat by adolescence (Lien et al., 2005; Sayal et al., 2017). The cumulative effects of ADHD and young relative age were addressed in a recent paper (Kuntsi et al., 2021), which found persistent (up to the age of 23) adverse effects of both outcomes together and separately on academic achievement and substance abuse. Further, the recent PISA report that tested 15–16-year-olds across the world revealed that the relatively young in a cohort displayed considerable disadvantages in self-confidence and lesser expectations to continue to tertiary education (Givord, 2020). To conclude: relatively young children are more susceptible to several adverse future outcomes (**Figure 1**) and many of the problems also seem quite persistent.

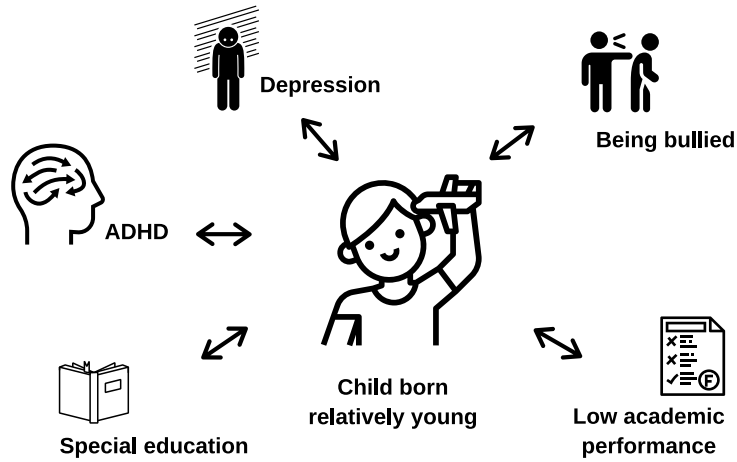

Figure 1. Adversities associated with being born at the end of the academic year. Figure by the author.

2.3 Basic concepts of epidemiology

This thesis includes methods from the field of epidemiology. Therefore, it will now briefly cover the essential definitions and concepts related to epidemiological research.

The Dictionary of Epidemiology (Porta, 2014) defines epidemiology as follows: "Epidemiology is the study of the occurrence and distribution of health-related states, events or processes, including the determinants influencing such processes, and the application of such knowledge to control relevant health problems."

Important ground-breaking epidemiological studies include studies linking smoking to lung cancer in the 1960s, and long-term follow up studies of risk factors for cardiovascular disease. The number of epidemiological studies has increased rapidly in the 20th century because they provide a means to acquire knowledge of associations between exposures and outcomes from large populations at a low cost.

2.3.1 What is causality?

A human being needs to understand the world, and the structuring of cause and effect begins already as an infant – if the infant cries, it leads to being fed. Cause and effect: one thing leads to another, and the same processes are repeated. However, this approach is not enough for scientific purposes because simple associations are not enough to prove *cause*. Throughout history, philosophers have tried to address the questioning of causality. In the 18th century, David Hume established many of the definitions still in use today: for a causal effect to exist, two factors must be

connected in time and space, i.e., if x causes y, it must precede y and be at the same location. Hume also postulated that the events should occur consistently from time to time (Morris, 2021). Later, John Stuart Mill introduced "the System of Logic" in 1856, in which the main conclusion was that if two things occur together in the same fashion every time, they are either cause and effect or linked together in the same causal pathway (Macleod, 2020).

In modern epidemiology, many of these historical principles are still in use. Assessment of causal inference includes (Greenland & Rothman, 1998):

1) if the exposure precedes the outcome
2) the magnitude of the effect size
3) if there exists a sound biological explanation for the association
4) assessment of a possible dose-response effect
5) replicability: have similar findings been observed before?
6) if other factors (confounders) might explain the association.

In 1976, the epidemiologist Kenneth J. Rothman introduced the sufficient cause model (Rothman, 1976), which has served as the conceptual framework for epidemiological research ever since. The model is illustrated by causal pies (**Figure 2**), where the whole pies (numerals I–II) represent sufficient causes for a disease to occur. The pieces in the pie, depicted A–F, are different component causes that together, in various combinations, are enough to cause the disease (the sufficient cause). If a particular component cause is required for a disease to occur, it is called a necessary cause. At least to some extent, disease prevention can be accomplished by blocking one or many individual components of a sufficient cause.

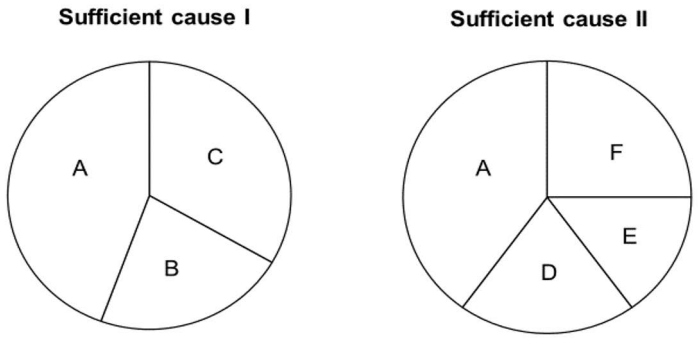

Figure 2. Causal pies. A-F represent component causes, of which A is a necessary cause. Sufficient causes can be composed of various causes (Rothman, 1976, figure by the author).

2.3.2 Confounding

Another important term in epidemiology is confounding. In a simple causal pathway where an exposure causes an outcome (**Figure 3**, panel A), a confounder is a variable that is associated with both the exposure and the outcome. When comparing the frequency of an exposure among cases with a certain outcome disease to the frequency among controls without the disease, the confounder introduces bias to the association. If the confounding variable is measured, it can be accounted for by statistical adjustment. There are, however, scenarios in which a variable is associated with both the exposure and the outcome but still not a true confounder. Mediators and antecedents are examples of this (**Figure 3**, panels B and C**)**. If statistical adjustments are made for mediators, there is a risk of overadjusting the estimate. However, as causal pathways are often complex, variables may act simultaneously as both mediators and confounders.

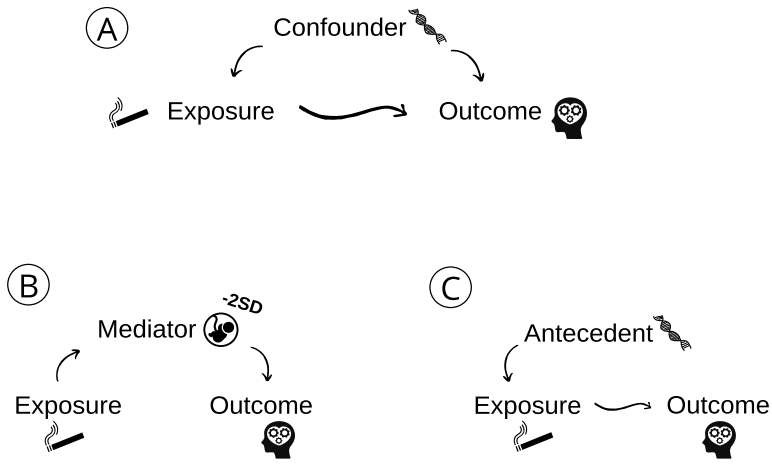

Figure 3. Schematic illustration of a A) confounder, B) mediator and C) antecedent. Figure by the author.

Besides statistical adjustment for confounding variables in a case-control setting, it is also possible to deal with confounding by using other study settings, such as family studies. These settings have gained popularity in the last decade (D'Onofrio et al., 2013) because they provide a design-based means to (partly) circumvent the problem of familial and genetic confounding. As twins, siblings or cousins share some degree of their genetic material (identical twins nearly 100%, full siblings 50%, half-siblings 25%, and cousins 12.5%) and particularly siblings share much of their living environment, familial confounders are partly adjusted for by the study design itself.

Another popular study design that has become more common in epidemiological research is Mendelian randomisation. Mendelian randomisation measures the exposure by using the variation in genes of known function and their effects on an outcome. Like family designs, Mendelian randomisation studies are considered powerful in controlling for confounding (Harrison et al., 2020).

Recently, epidemiologists have called for triangulation of evidence, which refers to the use of several approaches, both statistical and design-based, to achieve the best approximation of a causal effect using observational data (Hammerton & Munafò, 2021). In epidemiology, it is common to study early risk markers, such as prenatal factors, and their associations with some outcomes. This thesis examines two prenatal risk factors, namely smoking and vitamin D during pregnancy.

2.4 Prenatal programming

The first studies that examined foetal conditions and later health outcomes emerged in the 1970s and 80s. The most famous researcher who proposed long-term effects of poor uterine conditions was David Barker, who postulated that "the womb may be more important than the home" and presented epidemiological findings in which poor foetal growth was associated with later cardiovascular disease (Barker, 1990). His findings have since been replicated in various settings, and because of them, we know, for example, that those born small for gestational age are at increased risk for obesity later in life (Meas et al., 2008).

Another groundbreaking study on prenatal effects was the Dutch Famine Study, a natural experiment during the Dutch Hunger Winter in World War II where the population, including pregnant women, was subjected to severe malnutrition. Offspring from the malnourished pregnancies were compared to pregnancies from before or after the Hunger Winter, and they were found to have an increased risk of schizophrenia in follow-up (Susser et al., 1998). However, no similar effects were found for cognitive development or general IQ, and the prenatal environment's effects on cognition and learning are not very well known to this date.

Maternal stress during pregnancy and subsequent epigenetic mechanisms have been implicated as potential prenatal insults contributing to neurodevelopmental disorders in offspring (Kundakovic & Jaric, 2017). Stress hormones cross the placenta, as do many other substances in the maternal bloodstream (Donnelly & Campling, 2014). However, the actual teratogenic effects of most substances are not very well understood. Some drugs and toxins, such as thalidomide, antiepileptics and alcohol, have been studied rigorously, but clear causal effects have not been established for most prenatal factors.

2.5 Environmental factors and learning

Despite the strong genetic component in the aetiology of specific learning disorders, several environmental factors have also been identified as strong predictors. Research to find causal environmental risk factors is important because modifying such risk factors offers the possibility of reducing the risk of specific learning disorders, which is currently not possible for the genetic part of the risk profile.

A child's home and family environment includes a wide array of risk markers for specific learning disorders. Factors that have been associated with specific learning disorders in previous studies include low parental socioeconomic status (SES), low education or household income, single parenthood, adoption, non-supporting parenting styles, immigrant background, and parental stress or psychopathology (Altarac & Saroha, 2007; Lehti et al., 2018; Mascheretti, 2018; Rogers et al., 2020).

Biological and birth-related risk factors that have been associated with specific learning disorders or special education needs in school include birth asphyxia, preterm birth, and low birth weight (Johnson & Breslau, 2000; Mascheretti, 2018; Stanton-Chapman et al., 2001; Tweed et al., 2016). Birth order has been associated with IQ; first-born children tend to have higher IQ than their siblings (Kristensen & Bjerkedal, 2007).

Prenatal exposure to different toxins, drugs and vitamins are less well understood as risk factors for specific learning disorders. Alcohol has a well-established negative impact on learning abilities, with the most severe phenotype of Fetal Alcohol Syndrome as a consequence of heavy drinking (A.M. Koponen et al., 2020). However, moderate drinking has also been associated with milder learning disabilities (Olson et al., 1997) and cognitive impairment in a Mendelian randomisation study (Lewis et al., 2012). Selective serotonin reuptake inhibitors have also been associated with learning disorders (Brown et al., 2016), as well as prenatal cocaine exposure (Morrow et al., 2006), but findings are less replicated. The role of prenatal smoking is not certain, and the same is true for some vitamins, particularly vitamin D, which is known to affect brain development and learning in animals (Pet & Brouwer-Brolsma, 2016). Multiple micronutrient preparations during pregnancy have not shown any beneficial effects on offspring cognition in follow-up (R.M. Taylor et al., 2017).

As the magnitude of genetic influence on specific learning disorders has become evident, the importance of combing genetically informed data with environmental risk factor assessments has increased (Hammerton & Munafò, 2021). Within-family and Mendelian randomisation studies provide examples of such approaches, and both methods additionally provide a means to minimise confounding by unmeasured confounders in observational study settings. This thesis uses a family study approach for one of the research questions, namely smoking during pregnancy.

Next, the thesis will focus more thoroughly on the existing literature on the associations between specific learning disorders and social factors, maternal smoking, and vitamin D levels, which are the focus of this thesis.

2.5.1 Social risk markers

There is no golden standard for defining socioeconomic status (SES), but it is typically based on educational level, occupation, income or a combination of these (Baker, 2014). The links between parental SES and children's general cognitive ability or academic achievement were recognised over fifty years ago (Coleman 1966). In the recent decades, the gaps in academic achievement between children from high and low-income families have grown (Duncan & Murnane, 2011). The same is true for Finland, where the socioeconomic gaps in academic skills have likewise increased. However, the gaps are less pronounced than in most parts of the world (Bernelius & Huilla, 2021).

The mechanisms for the associations between SES and learning-related outcomes have been speculative and are likely both genetic and environmental (Tucker-Drob & Harden, 2012), as SES is often regarded as a proxy for several health-related attributes such as smoking, poor diet, and mental health adversities. A recent extensive study on environmental factors and cognitive ability found that low maternal and paternal education as well as other SES-related variables such as public health insurance, receiving food stamps, and lack of social support were strong predictors for low IQ in offspring (LeWinn et al., 2020). A Finnish study found that pupils in special education were more likely to originate from families with low SES (Mannerkoski et al., 2007).

In the 1990s, Hart et al. discovered a "word gap" of over 30 million words addressed to three-year-old children from low-SES families compared to high-SES families (Hart & Risley, 1995). This landmark study has been criticised (Kuchirko, 2017); however, later studies have confirmed similar word gaps of a more modest magnitude (Gilkerson et al., 2017). Reading aloud and creating stimulating activities for children are other mechanisms that have been proposed to be more common in high-SES households and are likely to contribute to a more fruitful development of academic skills (Christensen et al., 2014). Some studies have demonstrated that children from high-SES families might also be more likely to overcome reading difficulties because parents might seek help more actively (Noble & Mccandliss, 2005). However, from the perspective of behavioural genetics, genetic factors might also contribute to the level of parental cognitive fostering in the home and the socioeconomic variables themselves, and therefore, the proposed mechanisms may not be fully environmental in their origin (**Figure 4**).

Socioeconomic status and diagnosed specific learning disorders have received less attention than general IQ and academic achievement, but some studies have found associations between learning disorders and low socioeconomic status, low parental education, and low parental income (Altarac & Saroha, 2007; Mascheretti et al., 2015; Vermeiren et al., 2018; Zablotsky et al., 2019). One major limitation is that most of these studies have relied on parent-report to determine the outcome, i.e., the child's learning disorder, which might underestimate the actual effects if low-SES families report their children's learning disorders less actively.

Single motherhood has been related to several adverse outcomes for the child, including psychiatric morbidity and even increased mortality (Weitoft et al., 2003). Few studies have examined single motherhood in relation to learning disorders; two studies have indicated an elevated risk for learning disability in offspring of single mothers or from stepfamilies (Altarac & Saroha, 2007; Kabir et al., 2011).

Overall, and somewhat surprisingly, there is a knowledge gap of larger studies on the relationship between parental social risk markers and diagnosed specific learning disorders, as general IQ and academic achievement are not fully comparable to learning disorders. This thesis examines the association between specific learning disorders and maternal SES, education, and marital status.

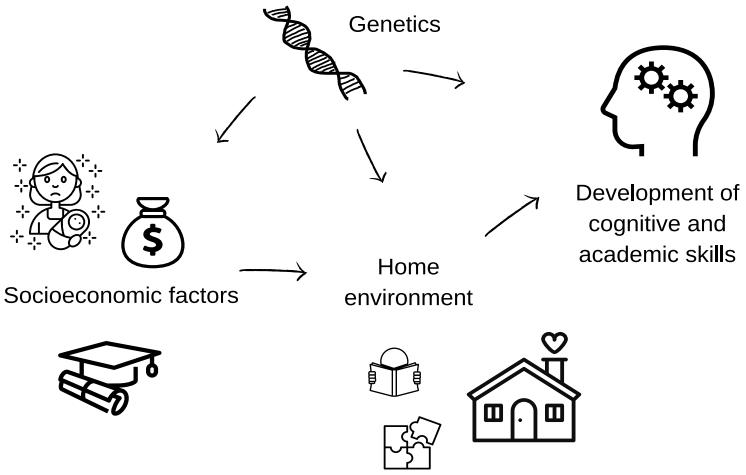

Figure 4. Possible mechanisms and interplay between socioeconomic factors, genetics, and learning. Figure by the author.

2.5.2 Smoking during pregnancy

Smoking during pregnancy is a significant public health problem, as a bulk of epidemiological studies have established likely causal associations with, for example, preterm birth, poor foetal growth, and sudden unexpected infant death

(Anderson et al., 2019; Kuja-Halkola et al., 2014). Despite the widely known adverse effects of prenatal smoking on the offspring, 11% of Finnish women still smoked in the first trimester of pregnancy in 2018, and approximately half of them continued to smoke throughout pregnancy (Kiuru & Gissler, 2018).

The literature concerning smoking during pregnancy and learning outcomes is vast but heterogeneous. Studies have focused predominantly on general cognitive abilities and academic achievement and less on specific learning disorders. Among the studies on learning disorders, findings are mixed. An American study (Anderko et al., 2010) reported odds ratios (ORs) of 1.6 for the association between prenatal smoking and offspring learning disabilities, and odds were even higher if the smoking was combined with postnatal smoking. A British cohort study (Cho et al., 2013), comprising over 14,000 children, likewise found an association between prenatal smoking and poor reading skills, and the results remained significant after adjusting for several confounders. However, other studies have not reported any associations between prenatal smoking and offspring dyslexia (Liu et al., 2016; Mascheretti et al., 2015).

As stated, cognitive or academic performance and their relationship with smoking have been studied abundantly. Three review articles (Clifford et al., 2012; Herrmann et al., 2008; Polańska et al., 2015) that examined one or both variables, concluded that a causal relationship between tobacco exposure during pregnancy and cognitive adversities is plausible. However, there was heterogeneity among the studies included in the reviews: some displayed high odds ratios for cognitive adversities among children exposed to smoking during pregnancy, while others found no effects.

In the recent decade, researchers have aimed to address the problem of familial and genetic confounding related to the smoking variable by conducting family studies. Familial confounding affects maternal smoking during pregnancy particularly, because smoking is closely associated with low SES and related adversities (D'Onofrio et al., 2013). None of the family studies have examined specific learning disorders; however, two Swedish nationwide register studies that examined academic performance (D'Onofrio et al., 2010) and overall intellectual performance (Lundberg et al., 2010) did not find any association between smoking during pregnancy and poorer performance when analysing siblings or cousins who were differentially exposed to smoking. Similar results have been observed in family studies of other psychiatric disorders (Quinn et al., 2017), ADHD (Obel et al., 2016), and intellectual disability (Madley-Dowd et al., 2020).

Other strategies that have been used to circumvent familial confounding are 1) studies that have looked at quitters (Heinonen et al., 2011; MacArthur et al., 2001), i.e., mothers that have quit smoking before pregnancy and their offspring's outcomes, and 2) cross-cohort changes in the association between prenatal smoking

and learning outcomes (Sellers et al., 2020). In the quitter studies, the offspring of quitters still performed worse on cognitive tests compared to controls who never smoked, indicating that other related factors contributed more to the results than the smoking exposure during pregnancy. The cross-cohort study compared learning outcomes of 12,000 children born in 1958 versus 2000–2001 and found a stronger association between prenatal smoking and impaired reading skills in the 2000–2001 cohort than in the 1958 cohort. The association between prenatal smoking and social disadvantage was also stronger. The authors concluded that the time trend changes in the associations between smoking and reading skills indicated the likely effect of familial confounding (Sellers et al., 2020).

To conclude: previous research on smoking during pregnancy and subsequent specific learning disorders in offspring is inconclusive. Furthermore, there are no nationwide register studies on clinically diagnosed specific learning disorders and prenatal smoking. Recent family- and cross-cohort studies on related topics indicate a lack of causality between smoking and several behavioural and cognitive outcomes, but none of these studies have focused on specific learning disorders, which is one of the aims of this thesis.

2.5.3 Maternal vitamin D levels during pregnancy

Vitamin D is acquired from the diet and synthesised in the skin after exposure to sunlight. The liver transforms previtamin D3 to 25-hydroxyvitamin D, 25(OH)D, which is the circulating form of vitamin D that can be measured from blood samples. The definitions and cutoffs for vitamin D deficiency vary; some guidelines regard concentrations under 30 nmol/l as deficiency, while others define concentrations under 50 nmol/l or even 75 nmol/l as deficiency (Pilz et al., 2019). In Finland, vitamin D supplementation with 10 micrograms per day has been recommended since 2005 (Finnish National Nutrition Council, 2005).

Vitamin D serves several important purposes in the human body, of which the effects on bone health and development are the most established. Also, the role in preventing serious infections appears important, as demonstrated in the COVID-19 literature (Ali, 2020; Amrein et al., 2020). Vitamin D deficiency in the expecting mother has been associated with harmful birth-related effects such as gestational diabetes, pre-eclampsia, and offspring low birth weight (Palacios et al., 2019). In the last decade, maternal vitamin D status during pregnancy and its possible adverse effects on brain development have gained research interest. Findings from animal studies have suggested cognitive and behavioural problems in offspring of vitamin D deficient rodents (Pet & Brouwer-Brolsma, 2016).

In humans, a bulk of studies have examined neurodevelopmental outcomes in small children and infants and some have implicated adverse effects of vitamin D

deficiency, when vitamin D was measured from maternal serum during pregnancy or cord blood at birth. Associations have been observed for poorer language development (Hanieh et al., 2014; Tylavsky et al., 2015; Voltas et al., 2020) and general cognitive measures (Melough et al., 2021; Morales et al., 2012; Zhu et al., 2015). In contrast, other studies have not found any associations with neurodevelopmental outcomes in young children (Gould et al., 2017; Wang et al., 2018). Recent systematic reviews have concluded that there might be a small negative effect of vitamin D deficiency on cognitive, motor and language development, particularly in children under five years, but that studies display inconclusive results (Janbek et al., 2019; Pet & Brouwer-Brolsma, 2016; Tous et al., 2020). Further, studies have found possible links between low prenatal vitamin D and offspring autism (Sourander et al., 2021), ADHD (Sucksdorff et al., 2020), and schizophrenia (Eyles et al., 2018).

Vitamin D levels during pregnancy and their relation to subsequent specific learning disorders in offspring have not previously been examined. Six studies have looked at maternal vitamin D levels and learning-related outcomes in school-aged children (**Table 2**). Most of these studies displayed null associations between vitamin D levels and general IQ or scholastic achievement. However, one Australian study (Whitehouse et al., 2012) indicated that vitamin D deficiency in the expecting mother might negatively influence offspring language development, when the language skills were measured at ages five and ten.

A recent Danish study (Specht et al., 2020) measured vitamin D from dried bloodspots drawn at birth and IQ at age 19 and found that general IQ was slightly reduced in the groups with the lowest vitamin D levels compared to the groups with higher concentrations. A Scottish study, which did not measure vitamin D but exposure to sunlight, found that more UVB light during pregnancy seemed to reduce the risk of a learning disability (Hastie et al., 2019). The authors hypothesised that this finding might be related to lower vitamin D levels during periods with less sunlight.

To conclude: the relationship between maternal serum vitamin D and diagnosed specific learning disorders in offspring has not previously been examined. Previous findings on related topics are mixed. This thesis studies the association between maternal vitamin D levels during pregnancy and subsequent specific learning disorders in offspring.

Table 2. Summary of articles about maternal vitamin D and cognitive or academic outcomes in school-aged children.

Article	Author	Sample	Vitamin D sampling	Outcome	Results
Association between Maternal Vitamin D Status in Pregnancy and Neurodevelopmental Outcomes in Childhood: Results from the Avon Longitudinal Study of Parents and Children	Darling, 2017	~4000 children assessed at 7–9 years	Maternal serum at 30 weeks of gestation	1) WISC 2) Neale Analysis of reading ability 3) Strengths and Difficulties questionnaire	No associations for offspring IQ or reading abilities
Association between Maternal Vitamin D Status During Pregnancy and Offspring Cognitive Function During Childhood and Adolescence	Veena, 2017	470 children assessed at 9 and 13 years	Maternal serum at 30 weeks of gestation	1) Kaufman Brief Intelligence Test 2) Other culturally adapted neuropsycho-logical tests	No associations for offspring cognitive ability
Maternal and Cord Blood 25(OH)D Concentrations in Relation to Child Development and Behavior	Keim, 2014	3237 children assessed at 7 years	Maternal serum at ≤26 weeks of gestation and umbilical cord blood	1) Stanford-Binet Intelligence Scale 2) WISC 3) Wide Range Achievement Test 4) Behaviour assessment	No associations for all outcomes except IQ at age 7: (β for 5 nmol/L increment of 25(OH)D = 0.10 (0.00, 0.19).
Vitamin D Measured in Maternal Serum and Offspring Neurodevelopmental Outcomes: A Prospective Study with Long-Term Follow-Up	Ström, 2014	798 children assessed at 15–16 years	Maternal serum at 30 weeks of gestation	Scholastic achievement obtained from national registry	No association for lower scholastic achievement
Maternal Serum Vitamin D Levels During Pregnancy and Offspring Neurocognitive Development	Whitehouse, 2012	~500 children assessed at 5 and 10 years	Maternal serum at 18 weeks of gestation	1) Child Behavior Checklist 2) Peabody Picture Vocabulary Test	Adjusted OR 1.92 (1.00-3.92) for language impairment in the lowest quintile of vitamin D
Maternal Vitamin D Status During Pregnancy and Child Outcomes	Gale, 2007	178 children assessed at 9 years	Maternal serum in 3rd trimester	1) WISC 2) Strengths and Difficulties	No associations for cognitive development

Abbreviations: WISC, Wechsler Intelligence Scale for Children. IQ, intelligence quotient.

2.6 Gaps in the previous literature

Overall, there is a knowledge gap in nationwide population-based studies on specific learning disorders that use established diagnostic criteria (ICD or DSM) for outcome confirmation. To the author's best knowledge, no prior ones exist for any of the aims of this study, i.e., incidence and its time trend, relative age, social risk markers, maternal smoking during pregnancy, or prenatal vitamin D.

More specifically, two studies have looked at young relative age and specific learning disorders, but the diagnoses have been obtained from surveys from parents or schools instead of relying on clinical information. For maternal smoking during pregnancy, findings are mixed in both smaller studies on smoking and specific learning disorders and larger studies on related outcomes such as academic achievement and IQ. Further, some family studies have indicated non-causality for learning-related outcomes. Regarding maternal vitamin D levels during pregnancy, prior studies on cognitive abilities and academic achievement have displayed heterogeneous findings, and none have examined diagnosed specific learning disorders as the outcome.

Information on the incidence and its time trends as well as on possible relative age effects of specific learning disorders diagnosed in specialised health care is elemental for service planning, both in educational and health care settings. Information on risk markers is important for prevention efforts and adds to the literature on aetiological factors of specific learning disorders.

3 Aims

The aim of this thesis was to answer the following research questions:

1) *What is the cumulative incidence of specific learning disorders diagnosed in Finnish specialised services among children born in 1996–2007, followed until the end of 2012, and has the incidence changed over time? (Study I)*

   Based on previous literature, the hypothesis was a stable time trend of diagnosed specific learning disorders.

2) *Are relatively young children more likely to receive a diagnosis of a specific learning disorder than their older peers in the same school grade? (Study II)*

   The hypothesis was to find significantly higher incidences of specific learning disorders among relatively young children born at the end of the year compared to children born at the beginning of the year.

3) *How are maternal social risk markers associated with specific learning disorders? (Study I)*

   The hypothesis was to find associations between low maternal education, low SES, single motherhood, and specific learning disorders in offspring.

4) *Is maternal smoking during pregnancy associated with specific learning disorders in offspring when comparing a) cases and population controls b) cases and their siblings? (Study III)*

   This study expected to find significant associations between prenatal smoking and offspring specific learning disorders in the case-control setting, but the effect to be attenuated in the within-family sibling analyses.

5) *Are maternal serum vitamin D levels during early pregnancy associated with specific learning disorders in offspring? (Study IV)*

   The hypothesis was that vitamin D deficiency in pregnancy would be significantly associated with specific learning disorders in offspring.

4 Materials and Methods

While the original publications of Study I and III included the whole spectrum of developmental speech and language, learning, coordination, and mixed developmental disorders (ICD-10 codes F80–83), the focus of this thesis is on specific learning disorders of scholastic skills (F81). This section is a summary of the methodology used. Specialist readers may be referred to the original publications for more thorough information.

4.1 Study design and subjects

This thesis used cohort (Studies I and II), nested case-control (Studies I, III and IV), and nested case-sibling (Study III) designs, as summarised in **Table 3**. The source cohort was the same in all studies and comprised all 690,654 children born singleton in Finland between 1996 and 2007. The cohort setting was used to examine the cumulative incidence and gender distribution of specific learning disorders as well as the effect of a child's birth month (relative age) on the likelihood of receiving a specific learning disorder diagnosis. The risk marker studies (social risk markers, smoking, and vitamin D) used case-control or case-sibling samples nested in the same cohort.

The cases included all children in the cohort diagnosed with a specific learning disorder (ICD-10: F81.x) by the end of 2012 in Finnish specialised health care. The following exclusion criteria were applied to enhance the validity of the diagnoses:

1) Comorbid intellectual disability (ID, F70–79), because it conflicts with the definition of a specific learning disorder.
2) Comorbid autism spectrum disorders (ASD, F84), for the same reasons, as varying degrees of intellectual disability is often included in the clinical picture of ASD.
3) A diagnosis of a specific learning disorder before the age of 6 was considered unwarranted and such cases were excluded if they were not diagnosed with a speech and language, scholastic, coordination, or mixed developmental disorder (F80–83) again after the age of 6. This criterion was used because the main outcome in two of the original publications (Studies I and III) was

the combined group of F80–83 diagnoses. In Study II, which examined F81 specifically, the following criteria were applied: if a case had received an unwarranted diagnosis of F81 before the age of 6, their F81 diagnosis had to be confirmed again after the age of 6, otherwise, they were excluded.

4) Cases with unknown mother or missing controls (in the case-control settings).

Table 3. Study designs of the original publications included in this thesis.

	Design
Study I	Cohort Nested case-control
Study II	Cohort
Study III	Nested case-control Nested case-sibling
Study IV	Nested case-control

Studies I and III utilised the whole sample of children born 1996–2007 who were diagnosed with developmental disorders of speech and language, scholastic skills, coordination, or combinations of these (mixed developmental disorder) (F80-83), and stratified analyses were conducted for cases with specific learning disorders (F81).

In Studies I and III, the cases were individually matched with four controls and in Study IV with one control. The controls had to be singletons of the same sex and born at most 30 days apart from the case. Additionally, they had to be alive and living in Finland when the matched case was diagnosed, but themselves without a diagnosis of speech and language, specific learning, coordination or mixed developmental disorder, ID, or ASD until the end of follow up in December 2012.

In Study III, cases were additionally matched with their siblings. The siblings included biological full-siblings and maternal half-siblings from singleton births between 1996 and 2007 without speech and language, specific learning, coordination or mixed developmental disorders (F80–83), ID, or ASD. Siblings living in Finland at the time of the respective case's diagnosis were included. The families were categorised into four different exposure groups:

1) cases and siblings both exposed to smoking during pregnancy
2) cases and siblings not exposed to smoking during pregnancy
3) cases but not siblings exposed to smoking during pregnancy and
4) at least one sibling but no case exposed to smoking during pregnancy

In the original publication of Study III, the sibling-matched analyses were conducted with all developmental speech, scholastic, coordination, and mixed developmental disorders (F80–83) as the outcome. Because this thesis focuses on specific learning disorders, stratified sibling analyses for the group with specific learning disorders were performed specifically for this summary.

4.2 National registers

This thesis combined register data from several Finnish nationwide registers with the help of the unique personal identity code of the subjects. A personal identity code is registered for all Finnish residents at birth or upon migration to the country. **Figure 5** summarises the data sources for the variables in this thesis.

The Care Register for Health Care (CRHC) includes all diagnoses from publicly funded specialised services since 1998, and inpatient diagnoses since 1967 (Laugesen et al., 2021). The CRHC has utilised ICD-10 codes since 1996 and used earlier versions of the ICD before that. The sample in this thesis comprised children born 1996–2007, so all diagnoses were coded using the ICD-10. We were able to retrieve F81 diagnoses from all funded specialised services because no diagnosis was set in this sample before 1998, the oldest children having been 2 years old at the time. The population coverage of the diagnoses depends on if the diagnosed condition is typically treated in specialised health care or not; the coverage for diagnoses treated predominantly in specialised care is good, whereas conditions handled mostly by physicians in primary care have lower coverage in the register (Laugesen et al., 2021). The overall validity of the registered diagnoses is considered good, but validation studies have not been performed for all diagnostic classes, including specific learning disorders (Laugesen et al., 2021; Sund, 2012).

The Finnish Maternity Birth Register (FMBR) was established in 1987 and contains extensive data on perinatal variables from all pregnant mothers and newborns in Finland (Gissler & Shelley, 2002). The data includes maternal demographic characteristics, number of previous births, health-related behaviours, medical diagnoses during pregnancy and delivery, and data from the neonatal period. The CRHC and FMBR are maintained by the National Institute for Health and Welfare.

The Digital and Population Data Services Agency (DVV) is a register for basic demographic information of all residents in Finland. It includes name, personal identity code, address information, native language, citizenship, date of birth and death, and the names of family members. The register recently changed its name from the former Finnish Population Register Centre to the current DVV.

Official Statistics Finland is the Finnish public authority responsible for a wide range of different statistics, for example, occupational and socioeconomic variables.

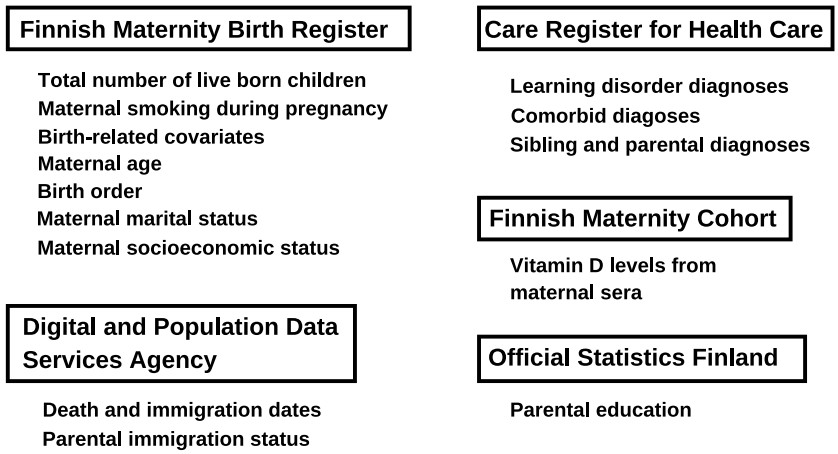

Figure 5. Data sources and registers for different variables included in this thesis. Figure by the author.

4.3 Incidence and time trends

Study I utilised a cohort design to study gender distribution, age of first diagnosis, and temporal changes of specific learning disorder diagnoses in specialised care. This setting included information on gender and month of birth for all singleton births in Finland between 1996–2007. Cumulative incidence was assessed based on the age when a subject received their first diagnosis of a specific learning disorder. The time trend was assessed by dividing the total sample into three subcohorts: those born in 1996–1999, 2000–2003, and 2004–2007. The cumulative incidences were then compared across the cohorts.

4.4 Relative age

To detect differences in the incidence of specific learning disorders by birth month, this thesis utilised data from a subsample of all children born singleton in Finland between 1996–2002 (N = 388,850). To have the same follow-up duration for all participants in the subsample, all subjects who received a diagnosis of specific learning disorder in specialist health care services before the age of 10 were identified, ending the follow-up in 2012.

In Finland, children start school in August of the calendar year they turn seven. Therefore, the oldest children in class are born in January and the youngest in December. Due to various reasons, school start is postponed for approximately 1–2% of all the children in a cohort, and they start school the following year, in the calendar year they turn eight. The proportion of children held back at school start has been decreasing in Finland over the last decade (Official Statistics Finland, 2019).

Because of the well-established effects of young relative age on the likelihood of receiving ADHD diagnoses (Holland & Sayal, 2018) this thesis further examined the role of comorbid disorders on the monthly incidences of specific learning disorder. Specific learning disorder cases were stratified into mutually exclusive groups with ADHD and other developmental disorders of speech and language and coordination. The comorbid ADHD group consisted of specific learning disorder cases diagnosed using ICD-10 codes F90.x and compared to cases without comorbid ADHD diagnoses. Equally, the group with comorbid other developmental disorders comprised cases also diagnosed with speech and language, coordination, or mixed developmental disorders (ICD-codes F80.x and/or F82 and/or F83) and those were compared to cases without other developmental disorders of speech and language or coordination.

4.5 Social risk marker variables

Study I assessed the associations between maternal predictors related to social factors and specific learning disorders in offspring. Because maternal variables have a greater impact on offspring outcomes (Crean & Bonduriansky, 2014) and because of better access to maternal variables via the FMBR, this thesis focused on maternal rather than paternal predictors.

For the main analyses, the education variable was classified as mothers with no college education (completed secondary school but no higher education) and mothers with a college or higher education (a higher vocational or university degree). If a mother completed only comprehensive school, they were reported as missing in the register and therefore assigned to the group with no college education. Marital status was divided into two categories: mothers who were married or in a relationship and those who were single, divorced, or widowed. The SES variable, which was based on the mother's occupation, was also divided into two groups. The first group included white-collar workers and higher professions, while the second group consisted of blue-collar workers and others. The group 'others' included, for example, students, homemakers, and unemployed individuals. Education, marital status, and SES were documented at the time of the offspring's birth. Additionally, a separate variable was created based on how many of the three studied maternal risk factors ('no college education', 'single at the time of birth', and 'other SES than white-collar worker') were present in a pregnancy.

4.6 Measurement of prenatal smoking

Data on smoking during pregnancy was obtained from the FMBR, which acquires the information from all publicly funded maternity clinics or delivery hospitals. This coverage is exceptional, as virtually all pregnant women in Finland (~99.7%) visit

these cost-free maternity clinics (National Institute for Health and Welfare, 2020). The registered smoking information is based on maternal self-report. Since 1991, the register has recorded information in three categories: no smoking during pregnancy, smoking only during the first trimester of pregnancy or smoking throughout the pregnancy (Ekblad et al., 2014). The daily cigarette consumption and possible smoking habits of other family members are not recorded in the register.

4.7 Measurement of prenatal vitamin D

Vitamin D levels, or more precisely 25(OH)D levels, were measured from maternal serum samples collected in the first and early second trimesters of pregnancy. The Finnish Maternity Cohort (FMC) collection includes maternal blood samples from over 950,000 pregnant women, collected since 1983. The prenatal serum specimens are routinely collected in the maternity clinics to screen for congenital infections, anaemia, and aneuploidies. The FMC collection consists of the remaining serum samples that have been stored at -25ºC in a protected biorepository at Biobank Borealis in Oulu, Finland, and are available for scientific research. Informed consent was obtained from the mothers to store the samples in the biobank and use them for research purposes.

Analysis of maternal 25(OH)D samples were carried out blind to case/control status with the Architect i2000SR automatic analyser using a chemiluminescence microparticle immunoassay. The method has high reproducibility and no major problems with degradation of the frozen serum samples over time (Miettinen et al., 2012).

Maternal 25(OH)D levels were reported in nmol/litre and classified into three clinical categories: deficient (< 30 nmol/L), insufficient (30–49.9 nmol/L) and sufficient levels (> 50 nmol/L). Additionally, the vitamin D levels were examined in quintiles. The cutoff points for the quintiles were based on the distribution of maternal vitamin D levels in the control group. A subsample of children born in 1996–1997 was used for the vitamin D analyses.

4.8 Covariates

The classification and data sources of the covariates are presented in **Table 4.** For more detailed descriptions of the covariates, see the original publications III and IV.

In Study III, potential covariates previously associated with maternal smoking during pregnancy and learning outcomes were assessed. These variables included: maternal age, psychiatric history and education, number of previous births, offspring gestational age, birthweight for gestational age, and Apgar score at 1 minute (**Table 4**).

In Study IV, potential covariates previously associated with vitamin D deficiency and learning outcomes were assessed. These included the following maternal

variables: age, psychiatric history, substance abuse, immigration status, number of previous births, season and gestational week of blood draw. Further, offspring gestational age, birthweight for gestational age, Apgar score and paternal psychiatric history were assessed (**Table 4**).

In Study I, which examined maternal social risk factors, the social variables were adjusted with each other; no additional covariates were used.

Table 4. Summary of covariate categorisation and data sources.

Study	Covariate	Categorisation	Sources
Maternal variables			
III **IV**	Age	< 20, 20–34, 35–39, ≥40 Continuous	FMBR
III, IV	Psychiatric history	Yes, no	CRHC
IV	Immigration	Yes, no	DVV
I	Marital status	Married/in a relationship, single/widowed/divorced	FMBR
I **IV**	Socioeconomic status based on occupation	White collar workers or higher, blue collar workers and others Upper white collar workers, lower white collar workers, blue collar workers, others	FMBR
I,III	Education	College education or higher, no college education	Statistics Finland
III, IV	Number of previous births	0, ≥1	FMBR
III **IV**	Smoking during pregnancy	No smoking, only during first trimester, throughout pregnancy Yes, no	FMBR
IV	Substance abuse	Yes, no	CRHC
Offspring variables			
III, IV	Gestational age	< 37 weeks, ≥ 37 weeks	FMBR
III, IV	Birthweight for gestational age	< -2 SD, -2 SD to +2 SD, > +2 SD	FMBR
III, IV	Apgar score at one minute	0–6, 7–10	FMBR
Other variables			
IV	Paternal psychiatric history	Yes, no	CRHC
IV	Gestational week of blood draw	Continuous	FMC
IV	Season of blood draw	Spring, Summer, Autumn, Winter	FMC

CRHC, Care Register for Health Care. DVV, Digital and Population Data Services Agency. FMBR, Finnish Medical Birth register. FMC, Finnish Maternity Cohort. SD, standard deviation.

4.9 Statistical methods

In the cohort setting of Study I, time-to-event analyses were used to study the cumulative incidence of specific learning disorders. The event was defined as the incidence of the studied diagnosis (F81.x). Cases were censored at the time of the first diagnosis or at the end of follow-up (December 31st, 2012), whichever came first. Cox regression analyses with gender (male/female) and cohort (birth years 1996–1999, 2000–2003, 2004–2007) as the predictors were used to test for gender differences and time trends. The male: female ratios were reported as hazard ratios (HRs) with 95% confidence intervals (CIs).

In Study II, incidences of children diagnosed with specific learning disorders were calculated for each birth month, with the oldest January-born children as baseline. Cumulative incidences were compared for each birth month for the total sample (children born 1996–2002) and by gender. Further, cumulative incidences were compared by using three pooled age groups that each contained four birth months: January to April, May to August, and September to December. The numerator was the number of children with specific learning disorders, and the denominator was the total number of children born during the corresponding period. Incidence rate ratios (IRR) and 95% CIs were then estimated using generalised linear regression with a Poisson error distribution. The denominator of the incidence rate was defined as the average population (all children born) during the specified time interval instead of summed person-years of observation because child mortality in Finland is very low. This approach is commonly used in large epidemiological samples (Centers for Disease Control and Prevention, 2006). The possible effect of comorbid disorders was assessed by calculating the cumulative incidences and corresponding IRRs for children with and without comorbid ADHD and other developmental disorders of speech and language or coordination.

In Studies III and IV, bivariate analyses were used to test the associations between the potential covariates and the predictor variables (smoking and vitamin D during pregnancy) among the population controls, as well as between potential covariates and specific learning disorder diagnoses. Covariates were selected if they were associated ($p < 0.1$) with both the predictor variable among the controls and learning disorder case status in simple bivariate tests (T-, F- or chi-square tests).

In the nested case-control setting of Studies I, III and IV, conditional logistic regression was used to calculate ORs with 95% CIs for the association between the predictor variables (social risk markers, maternal smoking, and vitamin D levels during pregnancy) and specific learning disorders. First, crude ORs were calculated with univariate analyses. Then multivariate analyses were performed by adding the selected covariates to the regression model (Study III and IV) or by entering all the social risk factors simultaneously in the model (Study I).

In the case-sibling comparisons of Study III, cases and their siblings were matched via the mother and the family clusters comprised one or more cases and one or more siblings. Conditional logistic regression with fixed effects was used to calculate crude and adjusted ORs for the within-family associations between prenatal smoking and specific learning disorders. The covariates in the adjusted model included potential confounders that were not shared by siblings, i.e., birth year, gender, birth order, gestational age, and birthweight for gestational age.

The statistical methods used in this thesis are summarised in **Table 5.** Study I & II used R statistical software versions 3.2.4 and 3.5.2, whereas Study III & IV used SAS statistical software, version 9.4. A level of $p < 0.05$ was considered statistically significant in all the main analyses.

Table 5. Summary of the statistical analyses used in substudies I–IV.

Study	Exposure	Outcome	Covariates	Statistical methods
I: Cohort	-	Cumulative incidence of specific learning disorders	-	Time to event analysis
	-	Gender differences in cumulative incidence	-	Cox regression
I: Nested case-control	Maternal social risk factors: SES, education, and marital status	Specific learning disorder diagnosis (F81.x)	The social risk factor variables adjusted with each other in the multivariate model	Conditional logistic regression
II: Cohort	Birth month	Specific learning disorder diagnosis (F81.x)	-	Poisson regression
III: Nested case-control	Smoking during pregnancy	Specific learning disorder diagnosis (F81.x)	Maternal age, education, psychiatric history and parity, offspring gestational age, birthweight for gestational age and Apgar score	Conditional logistic regression
III: Nested case-sibling	Smoking during pregnancy	Specific learning disorder diagnosis (F81.x)	Gender, birth year, parity, gestational age and birthweight for gestational age	Conditional logistic regression (within family effects)
IV: Nested case-control	Vitamin D levels from blood samples in early pregnancy	Specific learning disorder diagnosis (F81.x)	Maternal age, SES, psychiatric history, immigrant status and parity, paternal psychiatric history, offspring gestational age, birthweight for gestational age and Apgar score, gestational week and season of blood draw	Conditional logistic regression

ICD, International Classification of Diseases. SES, socioeconomic status.

4.10 Ethical considerations

Ethical approval of the study protocol was provided by the Ethics Committee of the Hospital District of Southwest Finland and the National Institute for Health and Welfare (Registration number: THL/1803/5.05.00/2013). The study used register-based data that was handled and pseudonymised according to Finnish data protection laws. No cases were contacted, and therefore, informed consent was not required for the register studies. In Study IV, the pregnant mothers provided informed consent to use their serum samples for scientific research.

5 Results

This chapter summarises the most central findings of the studies included in this thesis. Because the focus is on specific learning disorders, some of the results from the original papers have been omitted. Furthermore, some results have been produced explicitly for this summary and have not been published elsewhere.

5.1 Descriptive information

The sample sizes and descriptive characteristics for the subjects in the substudies are presented in **Table 6**. Among all the 690,654 children born in Finland between 1.1.1996–31.12.2007, 7,200 were diagnosed with specific learning disorders in specialised health care by 2012. Of these, 400 (5.6%) children had also received a diagnosis of ASD, 273 (3.8%) of ID, and 37 (0.5%) had received both ASD and ID diagnoses and were therefore excluded. The final sample size was 6,490 children with specific learning disorders.

In Studies I, III, and IV, there were no cases who had received a specific learning disorder diagnosis before the age of 6, but no diagnosis of a speech and language, specific learning, coordination, or mixed developmental disorder (F80–83) in follow up. Therefore, no exclusions were made due to this criterion. In study IV, 265 cases were excluded because their specific learning disorder diagnoses were set before the age of 6 and were not confirmed in follow-up. No cases were excluded due to missing data on the mother or lack of controls.

The median age at the first learning disorder diagnosis ranged between 8.4–10.0, depending on the birth years of the cohorts in each study and differing follow-up durations because of that (**Table 6**). Boys were 2.2–2.3 times more likely than girls to be diagnosed with a specific disorder across the substudies.

Table 6. Descriptive characteristics of the participants in the substudies.

Characteristic	Study I	II	III	IV
Specific learning disorder (F81) cases, N	6,490 Only F81*: 3,868	3,162	6,282	1,607
Birth year range of cases and controls	1996–2007	1996–2002	1996–2007	1996–1997
Age at F81 diagnosis, Median (IQR)	Whole sample: 8.9 (7.4–10.7) Only F81*: 9.3 (7.9–11.2)	8.4 (7.3–9.2)	8.9 (7.4–10.7)	10.0 (8.0–12.0)
Males: females	2.2: 1	2.3: 1	2.2: 1	2.3: 1
Cases: controls	1:4	-	1:4	1:1
Controls, N	14,945**	-	23,171	1,607

All studies used the same source cohort of children diagnosed with specific learning disorders in specialised care (N = 6,490). The number of subjects differed across the substudies because of differences in the included birth years, missing data for certain outcome variables and slightly different exclusion and follow-up criteria in Study II.
*Only F81 refers to the number of cases with only specific learning disorder and no comorbid F80, F82 or F83 diagnoses, this subgroup was used for the case-control analyses in Study I (social risk marker associations).
**Number of controls for the group with only F81.
IQR, interquartile range.

5.1.1 Subgroups of specific learning disorders

In the final sample of 6,490 children diagnosed with specific learning disorders, 1,772 (27.3%) were diagnosed with a reading disorder (F81.0), 518 (7.5%) with a spelling disorder (F81.1), 190 (2.8%) with an arithmetic disorder, 1,997 (30.8%) with a mixed disorder of scholastic skills (diagnostic category for those with both reading and/or spelling and arithmetic disorders), 1,529 (23.6%) with other disorders of scholastic skills (F81.8, for example, expressive written disorder or other specified learning disorders), and 2,046 (28.2%) with an unspecified specific learning disorder (F81.9). The sum of cases with the individual subtypes of specific learning disorders exceeds the number of cases with any specific learning disorder because some cases were diagnosed with multiple disorders, so the groups are not mutually exclusive.

5.1.2 Comorbidity with developmental disorders of speech, language, and coordination

As discussed in the literature review, specific learning disorders frequently co-occur with developmental disorders of speech and language, coordination, and mixed

developmental disorders. This was also the case in this sample, as 2,622 cases (40.4%) of all the 6,490 cases with specific learning disorders displayed some comorbid developmental disorder of speech, language, coordination, or mixed developmental disorders until the end of follow up (**Figure 6**). The most common comorbid disorder was speech and language disorder (often also referred to as specific language impairment or the more current term developmental language disorder), which was diagnosed in 1,280 (19.7%) of the 6,490 cases with specific learning disorders.

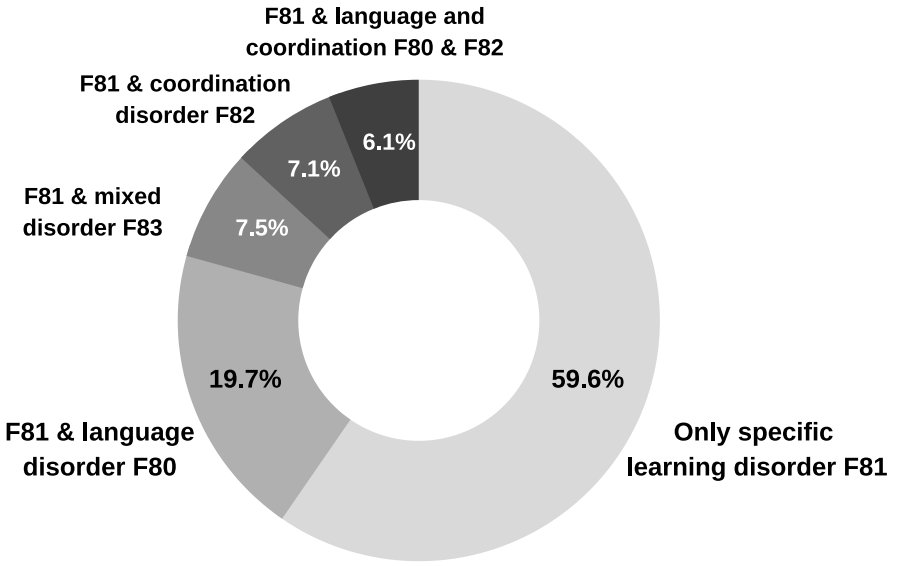

Figure 6. Speech and language disorder was the most common developmental comorbidity among children with specific learning disorders. Note that the group 'only specific learning disorder' is the group free from developmental comorbidities of speech, language and coordination but does not exclude psychiatric comorbidities. Figure by the author.

5.1.3 Psychiatric comorbidities

Out of the 6,490 children with specific learning disorders born between 1996 and 2007, 2,495 children (38.4%) were diagnosed with a psychiatric disorder (ICD F10–99) during follow-up. Among them, 1,466 (22.6%) had ADHD (F90.x) and 788 (12.1%) had conduct disorders (F91–92). The follow-up time was the longest in the birth cohorts 1996–1999, where the children were between 12 and 16 years at the end of follow up in 2012. Many psychiatric disorders typically have their onset in adolescence, which is why this thesis also looked at certain psychiatric comorbid diagnoses only in the oldest cohorts. However, psychotic and bipolar disorders are

typically diagnosed even later, which limits any conclusions regarding them. Of the 3,665 children with specific learning disorders who were born in 1996–1999, 25 (0.7%) had psychotic disorders (F20–29), 15 (0.4%) had bipolar disorders (F30–31), 288 (7.9%) had depressive disorders (F32–39), and 481 (13.1%) had anxiety disorders (F40–42, F93).

When combining the data for developmental and psychiatric comorbidities, 4,078 children (62.8%) of the total sample of 6,490 children with specific learning disorders had some developmental comorbidity of speech and language, coordination, or mixed type (F80, F82 and/or F83), and/or some psychiatric comorbidity (F10–99).

5.1.4 Incidence and time trend

As stated, the oldest cohorts permitted calculations on cumulative incidence with the longest follow-up time. Among children born in 1996–1999, the cumulative incidence of specific learning disorders diagnosed in specialised health care was 1.55% (95% CI 1.50–1.61) by age 15. In the comparison between birth cohorts 1996–1999 versus 2000–2003, the cumulative incidence of specific learning disorders by age 10 was stable over time: it was 0.84% (95% CI 0.80–0.88) for those born in 1996–1999 and 0.87% (95% CI 0.83–0.91) for those born in 2000–2003.

5.1.5 Summary of the descriptive findings

This thesis found that children with specific learning disorders were typically diagnosed in specialised services around the age of 9 and that boys were diagnosed over two times more often than girls. The most common subcategory of specific learning disorders was mixed disorder of scholastic skills (comorbid reading and arithmetic disorders), followed by unspecified specific learning disorder and reading disorder. Arithmetic disorder was rare, occurring in only 2.8% of the children in the referred sample.

Comorbid developmental disorders of speech and language, coordination and mixed developmental disorders were common in the sample. The most common co-occurring developmental disorder was developmental language disorder (F80). Psychiatric comorbidities were also frequent. ADHD was the most common psychiatric comorbidity occurring in approximately 2 out of 10 children with a specific learning disorder. The cumulative incidence of specific learning disorders diagnosed in specialised health care was 1.55% by age 15 and the trend was stable over time.

5.2 Young relative age

In the examination of the association between children's birth month and specific learning disorder diagnoses from specialised health care in the subsample of children born 1996–2002 (N = 388,850), this thesis found significantly higher cumulative incidences for children born at the end of the calendar year, i.e. the youngest in class, compared to those born at the beginning of the year (**Figure 7**).

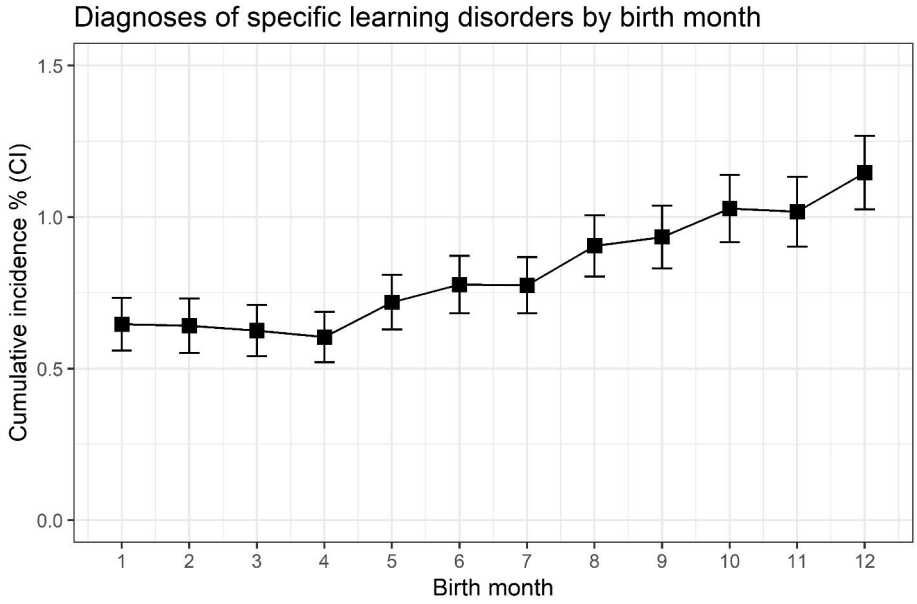

Figure 7. Relatively younger children, born in the higher birth months, received proportionally more diagnoses of specific learning disorders by age 10 in specialised care. The figure includes data for all children born singleton in Finland between 1996 and 2002. Figure from the original publication of Study II. Reproduced with CC BY license.

Of the 3,162 cases with specific learning disorders, 817 (26%) were born in January to April, 1,073 (34%) in May to August, and 1,272 (40%) in September to December. The IRRs for specific learning disorder diagnoses were higher for younger children born at the end of the year; for example, the IRR for children born in December was 1.77 (95% CI 1.50–2.11) compared to children born in January, and the results did not differ between boys and girls. In addition, children born in the summer months also presented higher IRRs for specific learning disorders than children born at the beginning of the year. The peaking trend of the cumulative incidences towards the end of the year (**Figure 7**) was similar regardless of which birth year (1996–2002) was examined.

Comorbid ADHD and comorbid developmental disorders of speech and language or coordination did not affect the findings in the sensitivity analyses. The IRR for children born in December with comorbid ADHD was 1.59 (95% CI 1.13–2.26), and it was 1.84 (95% CI 1.51–2.24) for those without comorbid ADHD (**Table 7**). The IRR for children with comorbid speech and language or coordination disorders was 1.52 (95% CI 1.18–1.98), whereas those with a specific learning disorder only had an IRR of 1.99 (95% CI 1.59–2.52). For more detailed information and IRRs per birth month in pooled and stratified groups, please see the original publication of Study II.

Table 7. Incidence rate ratios of specific learning disorder with and without comorbid ADHD by age 10 per birth month, pooled birth years 1996–2002.

Birth month	Comorbid ADHD		No comorbid ADHD	
	Cases (749)	IRR (95 % CI)	Cases (2,413)	IRR (95 % CI)
January	54	Reference	156	Reference
February	46	0.92 (0.62–1.36)	147	1.02 (0.81–1.27)
March	59	1.05 (0.72–1.52)	153	0.94 (0.75–1.18)
April	55	0.99 (0.68–1.44)	147	0.92 (0.73–1.15)
May	60	1.07 (0.74–1.55)	183	1.13 (0.91–1.40)
June	58	1.05 (0.73–1.53)	199	1.25 (1.02–1.55)*
July	59	1.03 (0.71–1.49)	209	1.26 (1.02–1.55)*
August	66	1.18 (0.82–1.69)	239	1.48 (1.21–1.81)**
September	68	1.23 (0.86–1.77)	242	1.52 (1.24–1.86)***
October	74	1.41 (1.00–2.01)	250	1.65 (1.35–2.02)***
November	71	1.47 (1.03–2.10)*	225	1.61 (1.31–1.98)***
December	79	1.59 (1.13–2.26)*	263	1.84 (1.51–2.24)***

Abbreviations: CI, confidence interval. IRR, incidence rate ratio.
*p < 0.05, **p < 0.001, ***p < 0.0001.
Calculated using generalised linear regression with Poisson error distribution. For total number of children born, see the original publication of Study II, Table 1. Current table adapted from the original publication of Study II.

5.3 Environmental markers

This thesis found significant associations between maternal social risk markers and specific learning disorders. Further, associations were found for prenatal smoking but not for prenatal vitamin D deficiency in the case-control comparisons (**Table 8**).

Table 8. Associations between maternal predictors and offspring specific learning disorders.

Maternal variable	Cases (N, %)	Controls (N, %)	Crude OR (95 % CI)	Adjusted OR (95 % CI)
College education	3,868	14,945		
Yes	1,102 (28.5)	6,194 (41.4)	Reference	Reference
No	2,766 (71.5)	8,751 (58.6)	1.80 (1.67–1.95)	1.61 (1.47–1.77)[a]
Socioeconomic status	3,570	13,806		
White collar/higher	1,918 (53.7)	8,628 (62.5)	Reference	Reference
Blue collar/others	1,652 (46.3)	5,178 (37.5)	1.44 (1.33–1.55)	1.15 (1.06–1.26)[a]
Marital status	3,518	13,679		
Married/in a relationship	3,240 (92.1)	13,108 (95.8)	Reference	Reference
Single/widowed	278 (7.9)	571 (4.2)	1.92 (1.65–2.24)	1.62 (1.37–1.91)[a]
Smoking during pregnancy	6,282	23,171		
No	4,846 (77.1)	19,736 (85.2)	Reference	Reference
Only during first trimester	126 (2.0)	449 (1.9)	1.13 (0.93–1.39)	0.99 (0.81–1.23)[b]
Throughout pregnancy	1,310(20.9)	2,986 (12.9)	1.78 (1.66–1.92)	1.30 (1.20–1.41)[b]
Vitamin D levels	1,607	1,607		
Sufficient (> 50 nmol/L)	377 (23.5)	381 (23.7)	Reference	Reference
Insufficient (30-49 nmol/L)	632 (39.3)	685 (42.6)	0.95 (0.78–1.14)	0.91 (0.75–1.10)[c]
Deficient (< 30 nmol/L)	598 (37.2)	541 (33.7)	1.15 (0.94–1.42)	1.03 (0.83–1.28)[c]

Abbreviations: OR, odds ratio.
Calculations were performed for the group with only specific learning disorders (only F81, no comorbid F80, F82 or F83 diagnoses) for maternal education, SES, and marital status. For smoking and vitamin D, the samples included all subjects with F81, regardless of comorbidities.
[a]Multivariate model: all social variables entered simultaneously in the model (education, SES, marital status).
[b]Adjusted for maternal age, psychiatric history, education, and parity as well as offspring gestational age and weight for gestational age.
[c]Adjusted for maternal age, socioeconomic status, and offspring weight for gestational age.
All p-values significant at < 0.001 in the adjusted analyses, except for smoking only during first trimester p = 0.98 and vitamin D: insufficient p = 0.33, deficient p = 0.78.

5.3.1 Maternal social risk markers

All social risk markers, i.e., maternal education, socioeconomic status, and marital status, were significantly associated with offspring specific learning disorders in both the univariate and the multivariate regression analyses in the case-control setting (**Table 8**). In the multivariate analyses, education and marital status

displayed higher odds ratios than SES. The adjusted odds ratio (aOR) for specific learning disorder were as follows: no maternal college education 1.61 (95% CI 1.47–1.77), single motherhood 1.62 (95% CI 1.37–1.91), and low SES 1.15 (95% CI 1.06–1.26).

The social risk factors were also examined as an additive variable of the sum of risk factors, namely, if a child was exposed to zero, one, two, or three maternal social risk factors. The effect of multiple risk factors on the odds of receiving specific learning disorder diagnoses was additive; the likelihood increased twofold in those with three risk factors compared to zero (**Figure 8**). When the number of risk factors was examined as a continuous variable, the odds of specific learning disorder diagnosis increased by 31% for each additive risk factor (OR=1.31, 95% CI 1.24–1.37). Note that all the analyses for the social risk factors were performed for the group with specific learning disorder only (only F81, N = 3,868).

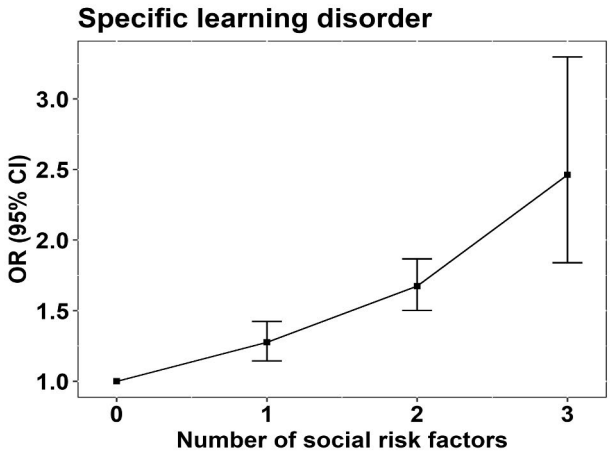

Figure 8. The sum of maternal risk factors (education, SES, and marital status) correlated linearly with the odds of specific learning disorder (the F81 only group). Figure by the author, adapted from original publication of Study I.

5.3.2 Smoking during pregnancy

When cases and population controls were compared, maternal smoking throughout pregnancy increased the likelihood of offspring specific learning disorder (aOR 1.30, 95% CI 1.20–1.41) (**Table 8**). Smoking only during the first trimester did not increase the odds of a specific learning disorder (aOR 0.99, 95% CI 0.81–1.23).

However, as stated previously in the thesis, smoking during pregnancy is related to many socioeconomic and genetic confounders. That is why this thesis also compared smoking during pregnancy in differently exposed siblings, who partly share confounders from the home environment. A flow chart of the sibling sample is

presented in **Figure 9**. The effective sample, i.e., the sample contributing to the regression estimates, consisted of 394 families (11.5% of 3,420 families) with 403 cases (11.5% of the 3,495 cases with siblings) who were differently exposed to maternal smoking than their siblings. The adjusted odds ratio for smoking throughout pregnancy was no longer statistically significant in the sibling comparisons (aOR 1.19, 95% CI 0.95–1.45, **Figure 10**).

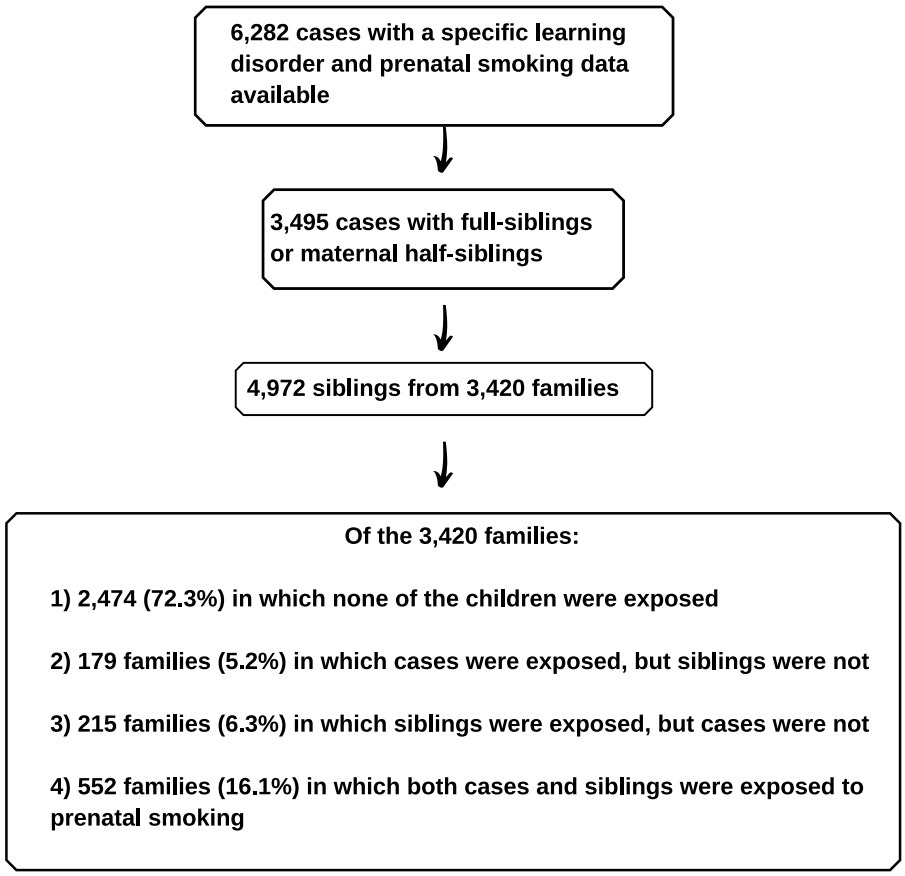

Figure 9. Flow chart of the case-sibling subsample. Figure by the author.

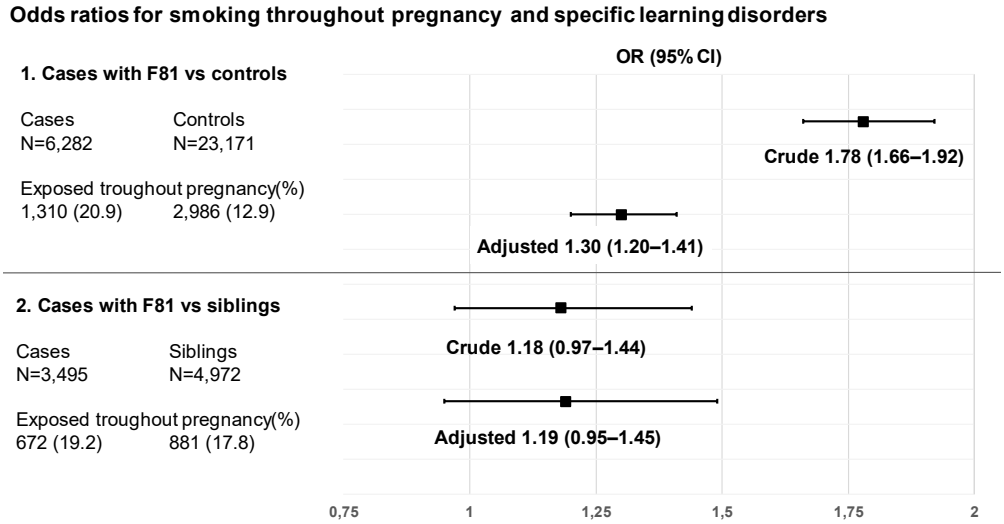

Figure 10. The association between prenatal smoking and specific learning disorders was completely attenuated in the within-family analyses. Case-control analyses were adjusted for maternal age, psychiatric history, education, and parity as well as offspring gestational age and weight for gestational age. Case-sibling analyses were adjusted for birth year, parity, gender, gestational age, and weight for gestational age. Figure by the author.

5.3.3 Vitamin D levels from maternal sera

Among the 115,730 children born in 1996–1997 in Finland, 2,174 were diagnosed with a specific learning disorder by the end of 2012. After excluding cases and controls with ID or ASD, 1,957 cases remained. Among them, 1,607 cases (82.1%) had a maternal serum sample available in the FMC biobank. The mothers of cases had a median vitamin D level of 39.3 nmol/L (SD 18.0; range 10.8–146.8 nmol/L) during early pregnancy, whereas the corresponding level for the mothers of controls was 39.9 nmol/L (SD 17.9; range 10.0–174.0 nmol/L).

There was no association between categorical prenatal vitamin D and specific learning disorders in offspring (aOR for deficient levels compared to sufficient levels: 1.03, 95% CI 0.83–1.28, **Table 8**). Further, no significant associations between continuous log-transformed maternal vitamin D or vitamin D quintiles and specific learning disorders were found in the unadjusted or adjusted analyses.

As demonstrated in **Figure 11**, the frequencies were slightly higher for cases than controls in the lowest quintile of vitamin D; however, the difference was not statistically significant in the crude or adjusted analyses. Comorbid ADHD, specific learning disorder subtype or offspring gender did not affect the findings in the sensitivity analyses (for specifics, see the original publication of Study IV).

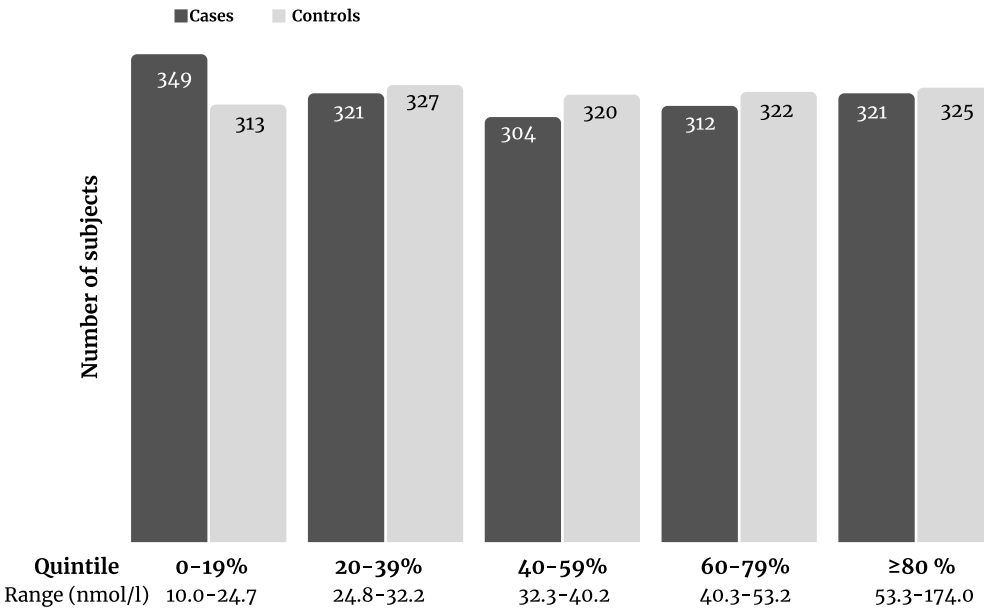

Figure 11. Distribution of maternal 25(OH)D in cases and controls. The number of cases was slightly higher in the lowest quintile, but the difference was not statistically significant in the regression analyses. *Quintiles based on the distribution among controls. Figure by the author, adapted from original publication IV.

5.3.4 Summary of the environmental risk marker findings

Maternal social risk factors, i.e., low education, socioeconomic status, and single motherhood were significantly associated with specific learning disorders in offspring, and the effect was linear with the number of risk factors. Smoking during pregnancy was moderately associated in the case-control setting but not in the sibling setting, suggesting familial confounding in the case-control comparison. Vitamin D levels measured from maternal sera during the first trimester of pregnancy were not associated with specific learning disorders in offspring.

6 Discussion

6.1 Main findings

The main findings of this thesis answered the study questions:

1) *What is the cumulative incidence of specific learning disorders diagnosed in Finnish specialised services among children born in 1996–2007, followed until the end of 2012, and has the incidence changed over time?* The cumulative incidence was 1.55% by age 15 for children born in 1996–1999, who had the longest follow-up time. As hypothesised, the time trend was stable when comparing incidences by age 10 for the 1996–1999 cohorts versus the 2000–2003 cohorts.

2) *Are relatively young children more likely to receive specific learning disorder diagnoses than their older peers in the same school grade?* December-born children were 1.77 times more likely to receive specific learning disorder diagnoses than children born in January. Comorbid ADHD or developmental disorders of speech, language or coordination did not affect the associations between young relative age and specific learning disorders. The main findings were in line with the hypothesis; however, comorbid ADHD did not influence the association as expected.

3) *How are maternal social risk markers associated with specific learning disorders in offspring?* As hypothesised, low maternal education, low SES based on occupation, and single motherhood were associated with specific learning disorders with aORs of 1.15–1.62 across the three variables. The odds increased linearly with the number of social risk factors.

4) *Is maternal smoking during pregnancy associated with specific learning disorders in offspring when comparing a) cases and population controls b) cases and their siblings?* In line with the hypothesis, smoking during pregnancy was significantly associated with specific learning disorders in the case-control setting, but the association was entirely attenuated when comparing differentially exposed maternal full and half-siblings.

5) *Are maternal serum vitamin D levels during pregnancy associated with specific learning disorders in offspring?* Contrary to the hypothesis, no association was found between vitamin D levels during early pregnancy and specific learning disorders.

6.2 Methodological discussion

6.2.1 Study design

The interchangeable use of cohort design, nested case-control, and case-sibling designs in this thesis allowed flexibility to use of the most fitting design to best answer the research question at hand. The cohort design allowed calculations of cumulative incidence, gender ratios, and relative age differences as it compared children who had received specific learning disorder diagnoses in follow up to the whole cohort of unaffected children born in Finland during the inclusion years. This kind of population-based cohort has many strengths. Because the whole population is "enrolled", the results are typically quite generalisable. Furthermore, if registers are used as the data source, there is typically little attrition because the data is collected automatically.

The population-based nested case-control and case-sibling designs display many of the same study strengths as the cohort design, as well as the benefits of the case-control design. When the subjects who develop a disease during follow-up are selected as cases, and non-affected cohort members are randomly selected as controls, it is possible to obtain a large sample cost-effectively. Compare this to a traditional cohort setting, where only few people may develop the outcome of interest if the outcome is rare. The registers also collect the data prospectively, making it easy to establish temporal order, meaning that the exposure comes before the outcome. Further, registers also prevent recall bias. Despite these benefits, the nested case-control and cohort design have the major common limitation of all observational studies: it is impossible to draw definite conclusions on causal inference between exposure and outcome.

The sibling design offers a unique possibility to adjust for confounding variables that siblings share and can therefore decrease the level of residual familial confounding. However, sibling designs have some specific limitations. For example, measurement errors of the exposure are more likely to attenuate the associations in a sibling-paired design, and there is still the issue of confounding from non-shared confounders, i.e. variables that are not shared by the siblings (Frisell et al., 2012). Furthermore, the generalisability of the sibling design can be questioned, as it is only the families where mothers can change their smoking habits across pregnancies that contribute to the estimates. This decreases the sample size and the statistical power

of the analyses. Some studies have expanded their analyses to cousins and half-cousins, making the sample more generalisable to the population (Quinn et al., 2017). The results have remained in line with sibling findings, indicating lack of causality for associations between prenatal smoking and offspring mental health adversities.

6.2.2 Data sources

The diagnoses used for outcome affirmation were derived from the Care Register for Health Care and based on the ICD-10 diagnostic classification, which is a uniform and reliable diagnostic system used by physicians. This data source for the outcome diagnoses can be considered a significant strength, as most previous key studies on learning disorders have relied on survey-based diagnoses reported by parents or schools. If the parents report incorrect diagnoses or the distribution of respondents is uneven, e.g., in socioeconomics, the risk of misclassification is evident.

Finnish national registers are sometimes called national treasures because of their seemingly unlimited possibilities for scientific research. The registers contain a vast number of variables concerning background factors, pre- and perinatal information, and diagnoses that are collected prospectively and blind to any possible outcomes (Laugesen et al., 2021).

In addition to the benefits, the register-based data used in this thesis had some important limitations to consider:

1) The diagnostic data from the Care Register included only specialised health care diagnoses at the time of data collection. Therefore, conclusions are limited to the population of cases diagnosed in specialised services, who typically have more comprehensive challenges and more comorbidities and are therefore possibly more likely to be referred to specialised services. This also means that children with milder learning difficulties, who might receive special education or interventions in primary care or at school, were missed and the results are not directly generalisable to the majority of children without a formal diagnosis of a specific learning disorder. Further, these children may have been misclassified in the control group, which could have attenuated the strength of the associations. Some municipal differences in diagnostic procedures might also have played a role; for example, diagnoses from specialist outpatient clinics that are administratively a part of primary care were not included.
2) A moderate proportion (28%) of the sample of children with specific learning disorders had unspecified learning disorders, which are, by definition, less well defined.

3) There are no validation studies on the specific learning disorder diagnoses from the Care Register for Health Care. However, the overall validity of the diagnoses in the register is considered to be good (Sund, 2012), and validation studies have shown excellent validity for ADHD (Joelsson et al., 2016), Tourette's syndrome (Leivonen et al., 2014), and reactive attachment disorder (Upadhyaya et al., 2020).

4) Even though the national registers contain many variables, they only collect certain information, making it impossible to tailor the variables to be recorded for a specific study. Useful variables in this thesis would have been, for example, information on parental learning disorders, smoking habits of fathers, duration of breastfeeding, BMI for both parents and children, and the birth months of children whose school-start was delayed.

5) As in almost every study, there is the matter of missing data. In terms of register-based data, we cannot know why a specific variable is missing. For the main outcomes, the proportion of missing data was largest for maternal vitamin D levels (17.9%), where a serum sample was available for 1,607 (82.1%) of the 1,957 eligible cases (Study IV). It is possible that the expectant mothers may not have given consent to use their serum sample for scientific research or that the mother entered prenatal health care services at a later stage of pregnancy, when the window for the screening tests was closed. The proportion of missing data ranged from 0–9% for the other main variables.

6.2.3 Measurement of the exposure variables

In Study II, we did not have information on the birth months of children who entered school one year earlier or one year later. However, because the total frequency of children held back was so small (approximately 1% of the cohort yearly), the risk of bias from such misclassification is expected to be small. Another aspect to consider with the relative age finding is its possible effects on the risk marker studies, particularly vitamin D. Even though no statistical adjustment was made for relative age explicitly in the case-control settings, the subjects were matched by age (cases and controls were born 30 days apart at most), and relative age is unlikely to affect other exposure variables than vitamin D. Vitamin D levels are known to vary by season, and covariate testing was therefore done for season of birth, but the results were insignificant.

Smoking during pregnancy is socially unaccepted, which is why smoking is often underreported by pregnant mothers. In some studies, up to 20% of smokers have been misclassified as non-smokers by self-report compared to smoking measured with tobacco biomarkers (Dietz et al., 2011; Ford et al., 1997). However,

in Nordic samples, misclassification has typically been lower, around 5–6% (Lindqvist et al., 2002; Sourander et al., 2019), meaning that similar proportions may have been misclassified in the current study. Other limitations related to the smoking variable include lack of information on the daily number of smoked cigarettes, paternal smoking habits, and potential exposure to second-hand smoke.

In Study IV, the measurement of maternal vitamin D from maternal sera took place only during the first trimester, which means that we cannot know the possible effects of vitamin D deficiency later in the pregnancy. However, a systematic review on vitamin D and neurodevelopmental outcomes concluded that studies were more likely to find significant associations between prenatal vitamin D deficiency and adverse cognitive or developmental outcomes if the serum samples were drawn in the first or second trimester of pregnancy (García-Serna & Morales, 2020). Further, multiple vitamin D measures over the course of pregnancy have been correlated in previous studies (Moon et al., 2015).

The data for this thesis was collected until the end of 2012. Therefore, its generalisability to the present time can be questioned. However, no major changes to the referral processes have been introduced for specific learning disorders during the past decade, and the trend for the cumulative incidence for diagnoses in specialised health care was stable over time.

6.3 Discussion of the findings

6.3.1 Incidence and descriptive findings

The cumulative incidence of specific learning disorders among children born in 1996–1999 was 1.55% by age 15. This percentage represents cases diagnosed in specialised health care only, which explains the low number compared to, for example, school community samples where prevalences have typically been 5–10% (Grigorenko et al., 2019; Moll et al., 2014). As stated previously, most children with learning difficulties are not referred to specialist care in Finland.

This thesis found a stable time trend for specific learning disorders across two cohorts, which aligns with previous studies (Boyle et al., 2011; Zablotsky et al., 2019) that have examined the time trends of parent-reported learning disorders. In contrast, an Italian study (Cainelli & Bisiacchi, 2019) reported an increasing prevalence of specific learning disorders, similar to studies that have looked at other neuropsychiatric disorders such as ADHD (Atladottir et al., 2015).

In this nationwide sample, boys were diagnosed with specific learning disorders more frequently than girls, with a gender ratio of 2.2–2.3:1. This aligns with larger population-based studies (Flannery et al., 2000; Rutter et al., 2004). The reasons for the higher incidences of learning disorders among boys are unknown; however,

males have been found to present with overall greater genetic variability for many cognitive and behavioural traits, resulting in an overrepresentation of boys both among those who perform worst and those who perform best (Machin & Pekkarinen, 2008). Some candidate genes for reading disorders have also been found to have gender-specific effects (Georgitsi et al., 2021). Furthermore, it has been speculated that boys might be referred more often than girls, resulting in higher frequencies of diagnoses (Willcutt et al., 2010).

The low number of diagnosed arithmetic disorders (N = 290, 2.8%) was surprising, considering that reading and math disorders should be equally frequent in the population (Grigorenko et al., 2019). Questions remain on whether math disorders are simply not as well recognised in the Finnish educational and health care system, or if the educational system successfully supports children with numeracy problems without the need for a formal diagnosis.

The proportion of cases with comorbid developmental disorders of speech and language or coordination, as well as psychiatric comorbidities, was high: 40.4% had some developmental comorbidity of speech and language or coordination, and 38.4% had some psychiatric comorbidity. These findings are consistent with previous studies on the comorbidities in referred samples (Gyllenberg et al., 2014; Margari et al., 2013), and it reflects the clinical profiles of children referred to specialist services, who typically display multifaceted challenges.

The median age at first specific learning disorder diagnosis ranged between 8.4 and 10.0 years across studies, reflecting differences in the birth years included in the substudies, and hence, differences in follow-up duration. However, the median age of 9 years is somewhat advanced compared to the age when learning difficulties typically emerge. This might be a problem if the affected children do not receive supportive interventions before being formally diagnosed; however, the three-tiered educational system in Finland does not require a formal diagnosis for the child to receive supportive interventions.

6.3.2 Young relative age

Similar to previous studies on young relative age and learning disorders, academic achievement, and psychiatric diagnoses (Dhuey & Lipscomb, 2010; Holland & Sayal, 2018; Martin et al., 2004; Root et al., 2019), this thesis found a significant relative age effect for the diagnosis of a specific learning disorder by age 10 in specialised health care. The incidence rate ratios in this study were even slightly higher for specific learning disorders than in comparable studies regarding ADHD and depression (IRR 1.77 vs 1.2-1.3) (Holland & Sayal, 2018; Root et al., 2019). The findings are somewhat surprising, considering that the diagnostic procedures for specific learning disorders include age-standardised tests.

The findings suggest referral bias as the primary source of the relative age discrepancy; younger children in class are likely referred to specialised health care more often than older peers. Because they are less mature, both emotionally and academically, it likely causes them to behave and achieve below expectations, resulting in more frequent referrals. This could also mean that the oldest pupils in class, who behave more maturely, might go without their needed learning disorder diagnosis because they do not attract the attention of educational and health care professionals.

6.3.3 Social risk markers

This thesis found strong independent associations between maternal social risk markers and specific learning disorders. The social variables included maternal SES based on occupation, educational level, and marital status. The strongest associations were found for maternal education (aOR 1.61 for no college education) and marital status (aOR 1.62 for single motherhood). Furthermore, the associations were stronger for those with multiple social risk factors. These findings are in line with most previous studies on related outcomes (Bradley & Corwyn, 2002; Friend et al., 2008; Hackman et al., 2010; Mannerkoski et al., 2007; Sirin, 2005). This was, however, the first study to examine the specific associations of social risk marker variables and diagnosed specific learning disorders in a nationwide setting.

The reasons behind the associations are probably both genetic and environmental. To illustrate with an example: parents who themselves suffer from learning disorders are, on average, likely to be less educated (Eloranta, 2019), and because of the strong genetic component (Willcutt et al., 2010) in the aetiology of specific learning disorders, also more likely to have children with learning disorders. Secondly, low SES and education may also be related to less stimulating home environments, which, in turn, do not favour learning (LeWinn et al., 2020). A third possible factor to consider when interpreting the associations is that prenatal environmental risk factors such as substance abuse and SSRIs have been associated with learning disorders (Brown et al., 2016; Lewis et al., 2012; Morrow et al., 2006) and are more common among parents from less advantaged households (Bradley & Corwyn, 2002).

To summarise, the associations between social risk factors and specific learning disorders that this thesis found are likely to reflect the clustering of social, genetic, and environmental risk factors for specific learning disorders in families with low education, low SES, and single mothers. Based on the data, it is impossible to draw conclusions on the causality of the associations. Of note, because the sample is based on diagnoses in specialised care, and referred children typically have more comorbidities, the social risk marker findings might be emphasised in this sample.

6.3.4 Smoking during pregnancy

The associations between smoking during pregnancy and specific learning disorders were moderate in the case-control setting, with an adjusted odds ratio of 1.30. In the sibling subsample, however, the association was completely attenuated and no longer statistically significant. Both findings are in line with previous studies (Agrawal et al., 2010; Anderko et al., 2010; D'Onofrio et al., 2010; Lundberg et al., 2010; Polańska et al., 2015); however, no prior study had used family design to examine the association between smoking and specific learning disorders.

When combining the results of 1) the odds ratio in the case-control setting, which, because of its modest magnitude, is typical for associations driven by residual confounding, with 2) the null finding in the sibling comparison, the conclusion is that smoking is unlikely to be an aetiological factor for specific learning disorders.

Other studies with slightly different methodologies and outcomes have supported this conclusion. Two studies have examined the outcomes in offspring whose mothers quit smoking before pregnancy. The offspring still performed worse in cognitive tests than subjects whose mothers had never smoked (Heinonen et al., 2011; MacArthur et al., 2001). The authors of one of the studies hypothesised that tobacco might have a long-term hazardous effect on the foetus, even after the mother stops smoking (Heinonen et al., 2011). An alternative explanation could be that smoking does not have a causal effect on cognitive outcomes. That is the most likely explanation, given the findings of this thesis.

A cross-cohort study from the UK (Sellers et al., 2020) compared behavioural and learning outcomes in 12,000 children born in 1958 and 2000–2001. It found that maternal smoking during pregnancy had a stronger association with poorer reading skills and social disadvantages in the 2000–2001 cohort than in the 1958 cohort. The authors concluded that these cross-cohort changes in the associations between smoking and poorer reading skills indicated a likely effect of familial confounding.

This thesis similarly supports the conclusion: it seems that particularly familial confounders have driven previous associations between prenatal smoking and learning outcomes.

6.3.5 Vitamin D during early pregnancy

This thesis did not find an association between prenatal vitamin D deficiency in the expectant mother and offspring specific learning disorders. There are no prior studies on the same outcome, but research on related topics, i.e., general cognitive function or academic achievement in school-aged children, are mostly in line with this finding (Darling et al., 2017; Gale et al., 2008; Strøm et al., 2014; Veena et al., 2017). However, associations have been found for other neuropsychiatric disorders, such as ADHD (Sucksdorff et al., 2020), ASD (Sourander et al., 2021), and schizophrenia

(Eyles et al., 2018). Like maternal smoking, vitamin D status is linked to socioeconomic status and related variables, which might induce residual confounding to the studies and therefore, the causality of those associations remains unclear.

The negative finding between vitamin D and specific learning disorders is straightforward because no speculations regarding the biological mechanisms for a possible relationship are needed. However, one needs to ask: could there be an association that was simply not found? The likely answer to this question is no; the study was well-powered and analyses were performed using several approaches and additional sensitivity analyses.

6.4 Implications for clinical practice and public health

The large number of comorbidities among children with specific learning disorders emphasises the need for interdisciplinary collaboration in the diagnostic procedures and the clinical support of these children. The low number of children with arithmetic disorders in this sample raises the question of whether increased awareness of this disorder is needed among teachers and clinicians.

On a national level, common screening and treatment guidelines could be beneficial, as they might help diminish the referral bias due to relative age and, for example, unify the processes to identify children in need of differential diagnostics in specialised health care. Current care guidelines (Duodecim, 2021) are available in Finland for most common diseases but not for specific learning disorders. The production of such guidelines would require a collaborative effort with representatives from the educational system (school psychologists and social workers in addition to teachers), primary care, including child health clinics and school health care, and specialised health care, particularly child neurology and psychiatry.

Furthermore, the results from Studies I and II have important implications for service planning. More specifically, the mounting genetic and environmental risk factors for adversities of learning and mental health in socially disadvantaged families call for allocating educational and health care resources to areas with proportionally higher numbers of families with lower levels of education and SES.

The relative age findings suggest that educational and health care professionals should always consider a child's relative age when evaluating learning skills. For example, if a child born at the end of the academic year presents with behavioural and learning difficulties in first grade, their skills should not be directly compared to their older peers.

In addition to this, other means exist to try to diminish relative age effects. In Finland, delaying school start is very rare compared to other OECD (The Organisation for Economic Cooperation and Development) countries (Givord, 2020); approximately 1% of children in a cohort are typically held back from starting school with their peer-cohort, and the trend has been declining (Official Statistics Finland, 2019). One possible solution could therefore be to increase the proportion of immature pupils that are held back, with the assumption that the immaturity can decrease over time and the child can become better suited for school start a year later. However, the evidence from countries where parents can easily delay their child's entry into school is not straightforward, and there are socioeconomic differences across countries in terms of which children are held back (Givord, 2020). In most countries, low-SES children are held back more frequently, but for example in the United States, the trend is the opposite (Bassok & Reardon, 2013; Givord, 2020). In Denmark, where holding back is becoming increasingly more common and approximately 10–20% of the children are delayed, findings have been encouraging regarding later mental health outcomes of the children held back (Dee & Sievertsen, 2018). In summary, increased flexibility in school start timing in Finland might be worth considering. Another possible solution could be to start first grade in two cohorts, i.e., with 6-month intervals, to reduce the impact of relative age differences during the first school years, when relative age differences are the largest.

Some teaching-related methods have also been proposed as remedies for relative age differences; for example, grouping pupils in class according to the season of birth in order to increase the teacher's awareness of which pupils are relatively young (Gledhill et al., 2002). In addition, teachers should be able to adjust for age when conducting national standardised tests (Givord, 2020). Other methods which have been shown to benefit relatively young pupils are smaller class sizes and shorter teaching sequences (Givord, 2020).

The null findings of prenatal vitamin D and the sibling analyses of smoking add important knowledge to the understanding of the environmental aetiologic factors of specific learning disorders. However, pregnant mothers should still be encouraged to quit smoking and use vitamin D supplements because of other, well-established risks caused by smoking and vitamin D deficiency during pregnancy.

6.5 Implications for future research

Most importantly, the research field of specific learning disorders would benefit from more uniform criteria for specific learning disorders. Currently, the definitions and cutoff criteria vary across countries and studies, and many studies rely on parent-report, making it difficult to compare findings from different studies.

Worldwide, there is a lack of common comprehensive screening tools for learning difficulties in health care settings. This has been suggested as an important future research target, namely to develop screening tools for 4-to-5-year-old children, which could be used to identify high-risk children before the optimal window for interventions closes (Sanfilippo et al., 2020). Luckily, in Finland, the neurodevelopmental screening instrument LENE (National Institute for Health and Welfare, 2009) is performed by a public health nurse on all 4-year-olds at the annual health check-ups at child health clinics. The LENE tool has been shown to predict academic difficulties in first grade fairly well (Valtonen et al., 2009). However, even though children are screened and challenges are identified, the question remains whether the screen-positive children and their families receive the support and interventions needed, which is an issue that deserves further research. It is also unknown whether LENE can predict specific learning disorders specifically and how the screening tool catches children for whom Finnish or Swedish is not their native language. Another Finnish screening tool developed specifically for early literacy skills is the Lukiva method (Niilo Mäki Institute, 2022), which can also be performed at the child health clinic on 4- or 5-year olds, especially if the child is at risk for reading disorders.

At the school level, no national screening guidelines are currently used to identify children with specific learning disorders (personal e-mail correspondence 28.4.2021 with professor Pirjo Aunio, Faculty of Educational Sciences, University of Helsinki), making it another area of research interest, namely, if learning disorders are feasible as a screening target in schools. There are, however, several different tests available for use by teachers, special teachers, and school psychologists, as summarised by the Lukimat-project (Niilo Mäki Institute, n.d.). However, the implementation of these tests varies across schools and municipalities. Before possibly initiating systematic screening on a national level, studies would also need to be conducted on the pros, cons, and costs of screening and efficient follow-up treatments for the children with a positive screening result.

Even though there is now vast evidence that young relative age increases the likelihood for most neurodevelopmental diagnoses, further studies are needed on the consequences of these diagnostic age discrepancies. Previous findings on the benefits of delaying school start are mixed, and more long-term follow up studies are needed on the educational and mental health outcomes of those relatively young children who were held back compared to those who were not.

The findings of this thesis support previous evidence of non-causal associations between smoking during pregnancy, vitamin D deficiency during pregnancy, and subsequent learning-related outcomes in offspring. The findings for specific learning disorders are novel and therefore require replication. The possible causality of the positive associations with social risk factors requires future research efforts which

triangulate evidence using multiple approaches, including genetically informed methods (Hammerton & Munafò, 2021). A recent study (Leppert et al., 2019) that examined polygenic risk scores in relation to a large number of maternal prenatal risk markers, both behavioural and biological, concluded that genetic confounding is a substantial source of bias and crucial to account for in observational studies of prenatal risk factors and neurodevelopmental outcomes.

7 Conclusions

Specific learning disorders are common in the population and thus have a significant public health impact. They are diagnosed and treated in two settings: the educational and health care systems, which highlights the importance of collaborative efforts and the possible development of national treatment guidelines for specific learning disorders.

This thesis examined specific learning disorders from several important perspectives: their cumulative incidence in public specialised health care and the changes in this incidence over time, the association with social risk factors, and two prenatal exposures in utero, namely tobacco and vitamin D. Further, this thesis studied the impact of young relative age on the likelihood of receiving a diagnosis of a specific learning disorder.

The current findings have societal and clinical implications. For example, the clustering of learning disorders among socially disadvantaged families, and the fact that relatively young children receive proportionally more diagnoses of specific learning disorders than their older peers, need to be accounted for in the planning of educational and health care services.

Smoking and vitamin D deficiency during pregnancy are unlikely to be aetiological factors for specific learning disorders, but a favourable prenatal environment should nevertheless be a priority for maternal and child health clinics and other professionals working in perinatal care.

Future studies need to focus on using standardised definitions for specific learning disorders, triangulating the evidence in observational settings using varying methodology, and long-term outcomes of the pros and cons of delaying school start for immature children.

Acknowledgements

"Don't let the sun go down without saying thank you to someone, and without admitting to yourself that absolutely no one gets this far alone"
– Stephen King

In October 2015, I encountered my supervisor to-be David at the dance floor of a mutual friend's wedding. We started talking about psychiatry and science, and I expressed my interest in research work. A few days later, I was introduced to Andre, and we all started planning the project.

David, thank you for opening the door into the fascinating world of research. Thank you for your knowledge, patience, wisdom, and kindness. A special thanks also for introducing me to the world of programming and R; the former math nerd in me has enjoyed the challenge.

Andre, you immediately welcomed me to join your highly esteemed research team. Your enthusiasm and innovative thinking are truly an inspiration, and I feel privileged to be a part of your team. Besides being the groundbreaking researcher you are, your sense of humour and your disarming presence make you a very approachable person who is fun to work with.

Elina Hermanson, thank you for being part of my follow-up committee, and for encouraging me to do research work long before I started this thesis project. You believed in me and pushed me to follow my dreams.

Next, I want to express my gratitude to the pre-examiners of this thesis, Marja Laasonen and Tuija Aro. Your exceptional knowledge of the research field and your constructive comments helped to improve this thesis substantially. I would also like to thank professor Leena Haataja for agreeing to be the opponent at my public defence.

Thank you to the funding organisations that supported this thesis work: The University of Turku Doctoral Programme in Clinical Research, Finska Läkaresällskapet, Svenska Kulturfonden, and Lastentautien tutkimussäätiö.

Thank you to all my co-authors: Roshan, Minna, Ona, Venla, Juha-Pekka, Jutta, Amir, Auli, Lotta, Miika, Elina, Subina, Sanna, Alan, Keely, and Hanna. Without your comments and ideas, the articles would not have become nearly as presentable.

I want to mention Miika Vuori, Auli Suominen and Amir Sariaslan in particular. Miika, thank you for your supportive and positive attitude and for all the help and ideas for the relative age paper. Auli, thank you for sharing the long process of the smoking paper with me and for always being kind and encouraging. Amir, thank you for your invaluable input to the smoking paper and for teaching me about sibling study methodology in a patient and pedagogical manner.

Thank you to all my fellow PhD students: Subina, Sanju, Miina, Minna, Yuko, Tiia, Ida and others, for peer support, sharing ideas and fun moments together. I want to further express my gratitude to all other researchers and personnel at the Research Center for Child Psychiatry, and Jarna in particular, for help with submissions, press releases and other practicalities.

Mom and Dad, you have always helped me achieve my goals. Thank you for your love and support, and besides being wonderful parents, being even better grandparents. My brother Christian, thank you for your ability to bring in different yet intelligent perspectives and for always being there for me.

Thank you to my amazing friends: Annina, thank you for being open, honest, and witty, and for invaluable peer-support as a mother and a researcher. Sofia, thank you for insightful discussions and for our long-lasting friendship that I highly value. Kugge, thank you for being the wonderful creative person you are, for peer-support and help in writing, and for lending me your super-cosy office. Thank you Marienka, Nina, Micki and all my other dear friends. I am lucky to have you in my life.

My beloved husband Johan, your support has been exceptional throughout this thesis path, and it is difficult to express exactly how thankful I am. You are the funniest, warmest, and well, the best person I know. You are also a talented researcher, and I enjoy discussing scientific topics with you. However, most importantly, thank you for being such a wonderful father to our children. Aina and Frank, I hope that one day you will also find a passion for something like I have found for research. Keep an open and curious mind. I love you to the moon and back.

This thesis journey began at the dance floor and will hopefully end at the dance floor after the dissertation. The circle is now complete.

Helsinki, May 2022
Bianca Arrhenius

References

Agrawal, A., Scherrer, J. F., Grant, J. D., Sartor, C. E., Pergadia, M. L., Duncan, A. E., Madden, P. A. F., Haber, J. R., Jacob, T., Bucholz, K. K., & Xian, H. (2010). The effects of maternal smoking during pregnancy on offspring outcomes. *Preventive Medicine*, *50*(1–2), 13–18. https://doi.org/10.1016/j.ypmed.2009.12.009

Ali, N. (2020). Role of vitamin D in preventing of COVID-19 infection, progression and severity. *Journal of Infection and Public Health*, *13*(10), 1373–1380. https://doi.org/10.1016/j.jiph.2020.06.021

Altarac, M., & Saroha, E. (2007). Lifetime prevalence of learning disability among US children. *Pediatrics*, *119 Suppl 1*, S77-83. https://doi.org/10.1542/peds.2006-2089L

American Psychiatric Association. (1994). *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV)*. American Psychiatric Association Publishing.

American Psychiatric Association. (2013). *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition. (DSM-5)*. American Psychiatric Association Publishing.

American Psychiatric Association. (2018). *What Is Specific Learning Disorder?* https://www.psychiatry.org/patients-families/specific-learning-disorder/what-is-specific-learning-disorder

Amrein, K., Scherkl, M., Hoffmann, M., Neuwersch-Sommeregger, S., Köstenberger, M., Tmava Berisha, A., Martucci, G., Pilz, S., & Malle, O. (2020). Vitamin D deficiency 2.0: An update on the current status worldwide. *European Journal of Clinical Nutrition*, *74*(11), 1498–1513. https://doi.org/10.1038/s41430-020-0558-y

Anderko, L., Braun, J., & Auinger, P. (2010). Contribution of Tobacco Smoke Exposure to Learning Disabilities. *Journal of Obstetric, Gynecologic & Neonatal Nursing*, *39*(1), 111–117. https://doi.org/10.1111/j.1552-6909.2009.01093.x

Anderson, T. M., Ferres, J. M. L., Ren, S. Y., Moon, R. Y., Goldstein, R. D., Ramirez, J.-M., & Mitchell, E. A. (2019). Maternal Smoking Before and During Pregnancy and the Risk of Sudden Unexpected Infant Death. *Pediatrics*, *143*(4). https://doi.org/10.1542/peds.2018-3325

Aro, M. (2011). Oppimisvaikeustutkimuksen haasteita. *Niilo Mäli instituutin NMI-bulletin*, *2*, 4.

Aro, T., Eklund, K., Eloranta, A.-K., Ahonen, T., & Rescorla, L. (2021). Learning Disabilities Elevate Children's Risk for Behavioral-Emotional Problems: Differences Between LD Types, Genders, and Contexts. *Journal of Learning Disabilities*, 00222194211056297. https://doi.org/10.1177/00222194211056297

Atladottir, H. O., Gyllenberg, D., Langridge, A., Sandin, S., Hansen, S. N., Leonard, H., Gissler, M., Reichenberg, A., Schendel, D. E., Bourke, J., Hultman, C. M., Grice, D. E., Buxbaum, J. D., & Parner, E. T. (2015). The increasing prevalence of reported diagnoses of childhood psychiatric disorders: A descriptive multinational comparison. *European Child & Adolescent Psychiatry*, *24*, 173–183. https://doi.org/10.1007/s00787-014-0553-8

Baker, E. H. (2014). Socioeconomic Status, Definition. In *The Wiley Blackwell Encyclopedia of Health, Illness, Behavior, and Society* (pp. 2210–2214). American Cancer Society. https://doi.org/10.1002/9781118410868.wbehibs395

Barker, D. J. (1990). The fetal and infant origins of adult disease. *British Medical Journal*, *301*(6761), 1111–1111. https://doi.org/10.1136/bmj.301.6761.1111

Bassok, D., & Reardon, S. F. (2013). "Academic Redshirting" in Kindergarten: Prevalence, Patterns, and Implications. *Educational Evaluation and Policy Analysis*, *35*(3), 283–297. https://doi.org/10.3102/0162373713482764

Bedard, K., & Dhuey, E. (2006). The Persistence of Early Childhood Maturity: International Evidence of Long-Run Age Effects. *The Quarterly Journal of Economics*, *121*(4), 1437–1472. JSTOR. https://www.jstor.org/stable/25098831

Bell, J. F., & Daniels, S. (1990). Are Summer-Born Children Disadvantaged? The Birthdate Effect in Education. *Oxford Review of Education*, *16*(1), 67–80. JSTOR. http://www.jstor.org/stable/1050142

Bernelius, V., & Huilla, H. (2021). *Koulutuksellinen tasa-arvo, alueellinen ja sosiaalinen eriytyminen ja myönteisen erityiskohtelun mahdollisuudet* [Sarjajulkaisu]. Valtioneuvosto. https://julkaisut.valtioneuvosto.fi/handle/10024/162857

Bishop, D. V. M. (2010). Which Neurodevelopmental Disorders Get Researched and Why? *PLOS ONE*, *5*(11), e15112. https://doi.org/10.1371/journal.pone.0015112

Boada, R., Willcutt, E. G., & Pennington, B. F. (2012). Understanding the Comorbidity Between Dyslexia and Attention-Deficit/Hyperactivity Disorder: *Topics in Language Disorders*, *32*(3), 264–284. https://doi.org/10.1097/TLD.0b013e31826203ac

Boyle, C. A., Boulet, S., Schieve, L. A., Cohen, R. A., Blumberg, S. J., Yeargin-Allsopp, M., Visser, S., & Kogan, M. D. (2011). Trends in the prevalence of developmental disabilities in US children, 1997-2008. *Pediatrics*, *127*, 1034–1042. https://doi.org/10.1542/peds.2010-2989

Bradley, R. H., & Corwyn, and R. F. (2002). Socioeconomic Status and Child Development. *Annual Review of Psychology*, *53*(1), 371–399. https://doi.org/10.1146/annurev.psych.53.100901.135233

Brown, A. S., Gyllenberg, D., Malm, H., McKeague, I. W., Hinkka-Yli-Salomäki, S., Artama, M., Gissler, M., Cheslack-Postava, K., Weissman, M. M., Gingrich, J. A., & Sourander, A. (2016). Association of Selective Serotonin Reuptake Inhibitor Exposure During Pregnancy With Speech, Scholastic, and Motor Disorders in Offspring. *JAMA Psychiatry*, *73*(11), 1163–1170. https://doi.org/10.1001/jamapsychiatry.2016.2594

Burke, J. D., Loeber, R., & Birmaher, B. (2002). Oppositional defiant disorder and conduct disorder: A review of the past 10 years, part II. *J Am Acad Child Adolesc Psychiatry*, *41*, 1275–1293. https://doi.org/10.1097/00004583-200211000-00009

Cainelli, E., & Bisiacchi, P. S. (2019). Diagnosis and Treatment of Developmental Dyslexia and Specific Learning Disabilities: Primum Non Nocere. *Journal of Developmental & Behavioral Pediatrics*, *40*(7), 558–562. https://doi.org/10.1097/DBP.0000000000000702

Carroll, J. M., Maughan, B., Goodman, R., & Meltzer, H. (2005). Literacy difficulties and psychiatric disorders: Evidence for comorbidity. *Journal of Child Psychology and Psychiatry*, *46*(5), 524–532. https://doi.org/10.1111/j.1469-7610.2004.00366.x

Caye, A., Petresco, S., de Barros, A. J. D., Bressan, R. A., Gadelha, A., Gonçalves, H., Manfro, A. G., Matijasevich, A., Menezes, A. M. B., Miguel, E. C., Munhoz, T. N., Pan, P. M., Salum, G. A., Santos, I. S., Kieling, C., & Rohde, L. A. (2019). Relative Age and Attention-Deficit/Hyperactivity Disorder: Data From Three Epidemiological Cohorts and a Meta-analysis. *Journal of the American Academy of Child & Adolescent Psychiatry*. https://doi.org/10.1016/j.jaac.2019.07.939

Cederlöf, M., Maughan, B., Larsson, H., D'Onofrio, B. M., & Plomin, R. (2017). Reading problems and major mental disorders—Co-occurrences and familial overlaps in a Swedish nationwide cohort. *Journal of Psychiatric Research*, *91*, 124–129. https://doi.org/10.1016/j.jpsychires.2017.03.014

Centers for Disease Control and Prevention. (2006). *Principles of Epidemiology in Public Health Practice, Third Edition: An Introduction* (Vol. 2006).

Chen, M.-H., Huang, K.-L., Hsu, J.-W., Tsai, S.-J., Su, T.-P., Chen, T.-J., & Bai, Y.-M. (2021). Effect of Relative Age on Childhood Mental Health: A Cohort of 9,548,393 Children and Adolescents. *Acta Psychiatrica Scandinavica*. https://doi.org/10.1111/acps.13327

Cho, K., Frijters, J. C., Zhang, H., Miller, L. L., & Gruen, J. R. (2013). Prenatal Exposure to Nicotine and Impaired Reading Performance. *The Journal of Pediatrics*, *162*(4), 713-718.e2. https://doi.org/10.1016/j.jpeds.2012.09.041

Christensen, D. L., Schieve, L. A., Devine, O., & Drews-Botsch, C. (2014). Socioeconomic status, child enrichment factors, and cognitive performance among preschool-age children: Results from the Follow-Up of Growth and Development Experiences study. *Res Dev Disabil*, *35*, 1789–1801. https://doi.org/10.1016/j.ridd.2014.02.003

Clifford, A., Lang, L., & Chen, R. (2012). Effects of maternal cigarette smoking during pregnancy on cognitive parameters of children and young adults: A literature review. *Neurotoxicology and Teratology*, *34*(6), 560–570. https://doi.org/10.1016/j.ntt.2012.09.004

Cobley, S., McKenna, J., Baker, J., & Wattie, N. (2009). How pervasive are relative age effects in secondary school education? *Journal of Educational Psychology*, *101*(2), 520–528. https://doi.org/10.1037/a0013845

Coleman, J. S., & et al. (1966). *Equality of Educational Opportunity*. US Department of Health, Education and Welfare. https://eric.ed.gov/?id=ED012275

Crawford, C., Dearden, L., & Greaves, E. (2013). *The impact of age within academic year on adult outcomes*. Institute for Fiscal Studies. https://doi.org/10.1920/wp.ifs.2013.1307

Crean, A. J., & Bonduriansky, R. (2014). What is a paternal effect? *Trends in Ecology & Evolution*, *29*(10), 554–559. https://doi.org/10.1016/j.tree.2014.07.009

Darling, A. L., Rayman, M. P., Steer, C. D., Golding, J., Lanham-New, S. A., & Bath, S. C. (2017). Association between maternal vitamin D status in pregnancy and neurodevelopmental outcomes in childhood: Results from the Avon Longitudinal Study of Parents and Children (ALSPAC). *British Journal of Nutrition*, *117*(12), 1682–1692. https://doi.org/10.1017/S0007114517001398

Davies, G., Welham, J., Chant, D., Torrey, E. F., & McGrath, J. (2003). A Systematic Review and Meta-analysis of Northern Hemisphere Season of Birth Studies in Schizophrenia. *Schizophrenia Bulletin*, *29*(3), 587–593. https://doi.org/10.1093/oxfordjournals.schbul.a007030

Dee, T. S., & Sievertsen, H. H. (2018). The gift of time? School starting age and mental health. *Health Economics*, *27*(5), 781–802. https://doi.org/10.1002/hec.3638

Dhuey, E., & Lipscomb, S. (2010). Disabled or young? Relative age and special education diagnoses in schools. *Economics of Education Review*, *29*(5), 857–872. https://doi.org/10.1016/j.econedurev.2010.03.006

Dietz, P. M., Homa, D., England, L. J., Burley, K., Tong, V. T., Dube, S. R., & Bernert, J. T. (2011). Estimates of nondisclosure of cigarette smoking among pregnant and nonpregnant women of reproductive age in the United States. *American Journal of Epidemiology*, *173*(3), 355–359. https://doi.org/10.1093/aje/kwq381

Dirks, E., Spyer, G., van Lieshout, E. C. D. M., & de Sonneville, L. (2008). Prevalence of Combined Reading and Arithmetic Disabilities. *Journal of Learning Disabilities*, *41*(5), 460–473. https://doi.org/10.1177/0022219408321128

Docherty, S. J., Davis, O. S. P., Kovas, Y., Meaburn, E. L., Dale, P. S., Petrill, S. A., Schalkwyk, L. C., & Plomin, R. (2010). A genome-wide association study identifies multiple loci associated with mathematics ability and disability. *Genes, Brain, and Behavior*, *9*(2), 234–247. https://doi.org/10.1111/j.1601-183X.2009.00553.x

Donnelly, L., & Campling, G. (2014). Functions of the placenta. *Anaesthesia & Intensive Care Medicine*, *15*(3), 136–139. https://doi.org/10.1016/j.mpaic.2014.01.004

D'Onofrio, B. M., Lahey, B. B., Turkheimer, E., & Lichtenstein, P. (2013). Critical Need for Family-Based, Quasi-Experimental Designs in Integrating Genetic and Social Science Research. *American Journal of Public Health*, *103*(S1), S46–S55. https://doi.org/10.2105/AJPH.2013.301252

D'Onofrio Brian M., Singh Amber L., Iliadou Anastasia, Lambe Mats, Hultman Christina M., Neiderhiser Jenae M., Långström Niklas, & Lichtenstein Paul. (2010). A Quasi-Experimental Study of Maternal Smoking During Pregnancy and Offspring Academic Achievement. *Child Development*, *81*(1), 80–100. https://doi.org/10.1111/j.1467-8624.2009.01382.x

Duncan, G. J., & Murnane, R. J. (2011). *Whither Opportunity?: Rising Inequality, Schools, and Children's Life Chances*. Russell Sage Foundation.

Duodecim. (2021). *Current Care Guidelines*. https://www.kaypahoito.fi/en/

Ekblad, M., Gissler, M., Korkeila, J., & Lehtonen, L. (2014). Trends and risk groups for smoking during pregnancy in Finland and other Nordic countries. *European Journal of Public Health*, *24*(4), 544–551. https://doi.org/10.1093/eurpub/ckt128

Eloranta, A.-K. (2019). *A follow-up study of childhood learning disabilities: Pathways to adult-age education, employment and psychosocial wellbeing* [Dissertation]. University of Jyväskylä.

Eyles, D. W., Trzaskowski, M., Vinkhuyzen, A. A. E., Mattheisen, M., Meier, S., Gooch, H., Anggono, V., Cui, X., Tan, M. C., Burne, T. H. J., Jang, S. E., Kvaskoff, D., Hougaard, D. M., Cohen, A., Mors, O., Sah, P., Wray, N. R., Mortensen, P. B., & McGrath, J. J. (2018). The association between neonatal vitamin D status and risk of schizophrenia. *Scientific Reports*, *8*(1), 17692. https://doi.org/10.1038/s41598-018-35418-z

Finnish Ministry of Education and Culture. (2014). *Oppimisen ja hyvinvoinnin tuki. Selvitys kolmiportaisen tuen toimeenpanosta* (p. 120).

Finnish Ministry of Social Affairs and Health. (2009). *Maternity and child welfare clinics, school and student health care and preventive oral care, grounds and application directives for decree (380/2009)*.

Finnish National Board of Education. (2014). *National Core Curriculum for Basic Education 2014*. https://www.oph.fi/sites/default/files/documents/perusopetuksen_opetussuunnitelman_perusteet_2014.pdf

Finnish National Nutrition Council. (2005). *Suomalaiset ravitsemussuositukset: Ravinto ja liikunta tasapainoon.* Edita. Publication on nutritional recommendations by the Finnish government, in Finnish.

Flannery, K., Liederman, J., Daly, L., & Schultz, J. (2000). Male prevalence for reading disability is found in a large sample of Black and White children free from ascertainment bias. *Journal of the International Neuropsychological Society*, *6*, 433–442.

Ford, R. P., Tappin, D. M., Schluter, P. J., & Wild, C. J. (1997). Smoking during pregnancy: How reliable are maternal self reports in New Zealand? *Journal of Epidemiology & Community Health*, *51*(3), 246–251. https://doi.org/10.1136/jech.51.3.246

Friend, A., DeFries, J. C., & Olson, R. K. (2008). Parental Education Moderates Genetic Influences on Reading Disability. *Psychological Science*, *19*(11), 1124–1130. https://doi.org/10.1111/j.1467-9280.2008.02213.x

Frisell, T., Öberg, S., Kuja-Halkola, R., & Sjölander, A. (2012). Sibling Comparison Designs: Bias From Non-Shared Confounders and Measurement Error. *Epidemiology*, *23*(5), 713–720. https://doi.org/10.1097/EDE.0b013e31825fa230

Gale, C. R., Robinson, S. M., Harvey, N. C., Javaid, M. K., Jiang, B., Martyn, C. N., Godfrey, K. M., & Cooper, C. (2008). Maternal vitamin D status during pregnancy and child outcomes. *European Journal of Clinical Nutrition*, *62*(1), 68–77. https://doi.org/10.1038/sj.ejcn.1602680

García-Serna, A. M., & Morales, E. (2020). Neurodevelopmental effects of prenatal vitamin D in humans: Systematic review and meta-analysis. *Molecular Psychiatry*, *25*(10), 2468–2481. https://doi.org/10.1038/s41380-019-0357-9

Georgitsi, M., Dermitzakis, I., Soumelidou, E., & Bonti, E. (2021). The Polygenic Nature and Complex Genetic Architecture of Specific Learning Disorder. *Brain Sciences*, *11*(5), 631. https://doi.org/10.3390/brainsci11050631

Gialluisi, A., Andlauer, T. F. M., Mirza-Schreiber, N., Moll, K., Becker, J., Hoffmann, P., Ludwig, K. U., Czamara, D., St Pourcain, B., Brandler, W., Honbolygó, F., Tóth, D., Csépe, V., Huguet, G.,

Morris, A. P., Hulslander, J., Willcutt, E. G., DeFries, J. C., Olson, R. K., … Schulte-Körne, G. (2019). Genome-wide association scan identifies new variants associated with a cognitive predictor of dyslexia. *Translational Psychiatry*, *9*(1), 77. https://doi.org/10.1038/s41398-019-0402-0

Gilkerson, J., Richards, J. A., Warren, S. F., Montgomery, J. K., Greenwood, C. R., Kimbrough, O. D., Hansen, J. H. L., & Paul, T. D. (2017). Mapping the Early Language Environment Using All-Day Recordings and Automated Analysis. *American Journal of Speech-Language Pathology*, *26*(2), 248–265. https://doi.org/10.1044/2016_AJSLP-15-0169

Gillberg, C. (2003). Deficits in attention, motor control, and perception: A brief review. *Arch Dis Child*, *88*, 904–910.

Gissler, M., & Shelley, J. (2002). Quality of data on subsequent events in a routine Medical Birth Register. *Medical Informatics and the Internet in Medicine*, *27*, 33–38. https://doi.org/10.1080/14639230110119234

Givord, P. (2020). *How a student's month of birth is linked to performance at school: New evidence from PISA*. OECD. https://www.oecd-ilibrary.org/education/how-student-s-month-of-birth-is-linked-to-performance-at-school_822ea6ce-en

Gledhill, J., Ford, T., & Goodman, R. (2002). Does Season of Birth Matter?: The Relationship between Age within the School Year (Season of Birth) and Educational Difficulties among a Representative General Population Sample of Children and Adolescents (Aged 5–15) in Great Britain. *Research in Education*, *68*(1), 41–47. https://doi.org/10.7227/RIE.68.4

Goodman, R. (2003). Child psychiatric disorder and relative age within school year: Cross sectional survey of large population sample. *BMJ*, *327*(7413), 472–0. https://doi.org/10.1136/bmj.327.7413.472

Gould, J. F., Anderson, A. J., Yelland, L. N., Smithers, L. G., Skeaff, C. M., Zhou, S. J., Gibson, R. A., & Makrides, M. (2017). Association of cord blood vitamin D with early childhood growth and neurodevelopment. *Journal of Paediatrics and Child Health*, *53*(1), 75–83. https://doi.org/10.1111/jpc.13308

Greenland, S., & Rothman, K. (1998). *Modern Epidemiology, 2nd Edition*. https://www.rti.org/publication/modern-epidemiology-2nd-edition

Grigorenko, E. L., Compton, D. L., Fuchs, L. S., Wagner, R. K., Willcutt, E. G., & Fletcher, J. M. (2019). Understanding, educating, and supporting children with specific learning disabilities: 50 years of science and practice. *American Psychologist*, *75*(1), 37. https://doi.org/10.1037/amp0000452

Grootendorst-van Mil, N. H., Steegers-Theunissen, R. P. M., Hofman, A., Jaddoe, V. W. V., Verhulst, F. C., & Tiemeier, H. (2017). Brighter children? The association between seasonality of birth and child IQ in a population-based birth cohort. *BMJ Open*, *7*(2), e012406. https://doi.org/10.1136/bmjopen-2016-012406

Gross-Tsur, V., Manor, O., & Shalev, R. S. (1996). Developmental dyscalculia: Prevalence and demographic features. *Developmental Medicine and Child Neurology*, *38*(1), 25–33. https://doi.org/10.1111/j.1469-8749.1996.tb15029.x

Gyllenberg, D., Gissler, M., Malm, H., Artama, M., Hinkka-Yli-Salomaki, S., Brown, A. S., & Sourander, A. (2014). Specialized service use for psychiatric and neurodevelopmental disorders by age 14 in Finland. *Psychiatr Serv*, *65*, 367–373. https://doi.org/10.1176/appi.ps.201200544

Haberstroh, S., & Schulte-Körne, G. (2019). The Diagnosis and Treatment of Dyscalculia. *Deutsches Ärzteblatt International*, *116*(7), 107–114. https://doi.org/10.3238/arztebl.2019.0107

Hackman, D. A., Farah, M. J., & Meaney, M. J. (2010). Socioeconomic status and the brain: Mechanistic insights from human and animal research. *Nature Reviews Neuroscience*, *11*(9), 651–659. https://doi.org/10.1038/nrn2897

Hammerton, G., & Munafò, M. R. (2021). Causal inference with observational data: The need for triangulation of evidence. *Psychological Medicine*, *51*(4), 563–578. https://doi.org/10.1017/S0033291720005127

Hanieh, S., Ha, T. T., Simpson, J. A., Thuy, T. T., Khuong, N. C., Thoang, D. D., Tran, T. D., Tuan, T., Fisher, J., & Biggs, B.-A. (2014). Maternal Vitamin D Status and Infant Outcomes in Rural Vietnam: A Prospective Cohort Study. *PLoS ONE*, *9*(6), e99005. https://doi.org/10.1371/journal.pone.0099005

Harrison, S., Howe, L., & Davies, A. R. (2020). Making sense of Mendelian randomisation and its use in health research. *Public Health Wales NHS Trust & Bristol University*, 23.

Hart, B., & Risley, T. R. (1995). *Meaningful differences in the everyday experience of young American children*. P.H. Brookes.

Hastie, C. E., Mackay, D. F., Clemens, T. L., Cherrie, M. P. C., King, A., Dibben, C., & Pell, J. P. (2019). Antenatal exposure to solar radiation and learning disabilities: Population cohort study of 422,512 children. *Scientific Reports*, *9*(1), 9356. https://doi.org/10.1038/s41598-019-45562-9

Haworth, C. M. A., Kovas, Y., Harlaar, N., Hayiou-Thomas, M. E., Petrill, S. A., Dale, P. S., & Plomin, R. (2009). Generalist genes and learning disabilities: A multivariate genetic analysis of low performance in reading, mathematics, language and general cognitive ability in a sample of 8000 12-year-old twins. *Journal of Child Psychology and Psychiatry*, *50*(10), 1318–1325. https://doi.org/10.1111/j.1469-7610.2009.02114.x

Heinonen, K., Räikkönen, K., Pesonen, A.-K., Andersson, S., Kajantie, E., Eriksson, J. G., Wolke, D., & Lano, A. (2011). Longitudinal study of smoking cessation before pregnancy and children's cognitive abilities at 56months of age. *Early Human Development*, *87*(5), 353–359. https://doi.org/10.1016/j.earlhumdev.2011.02.002

Herrmann, M., King, K., & Weitzman, M. (2008). Prenatal tobacco smoke and postnatal secondhand smoke exposure and child neurodevelopment. *Current Opinion in Pediatrics*, *20*(2), 184–190.

Holland, J., & Sayal, K. (2018). Relative age and ADHD symptoms, diagnosis and medication: A systematic review. *European Child & Adolescent Psychiatry*. https://doi.org/10.1007/s00787-018-1229-6

Holopainen, L. (2002). *Development in reading and reading related skills: A follow-up study from pre-school to the fourth grade* [Dissertation]. University of Jyväskylä.

Janbek, J., Specht, I. O., & Heitmann, B. L. (2019). Associations between vitamin D status in pregnancy and offspring neurodevelopment: A systematic literature review. *Nutrition Reviews*, *77*(5), 330–349. https://doi.org/10.1093/nutrit/nuy071

Jeronimus, B. F., Stavrakakis, N., Veenstra, R., & Oldehinkel, A. J. (2015). Relative Age Effects in Dutch Adolescents: Concurrent and Prospective Analyses. *PLoS ONE*, *10*(6). https://doi.org/10.1371/journal.pone.0128856

Joelsson, P., Chudal, R., Gyllenberg, D., Kesti, A.-K., Hinkka-Yli-Salomäki, S., Virtanen, J.-P., Huttunen, J., Ristkari, T., Parkkola, K., Gissler, M., & Sourander, A. (2016). Demographic Characteristics and Psychiatric Comorbidity of Children and Adolescents Diagnosed with ADHD in Specialized Healthcare. *Child Psychiatry & Human Development*, *47*(4), 574–582. https://doi.org/10.1007/s10578-015-0591-6

Johnson, E. O., & Breslau, N. (2000). Increased risk of learning disabilities in low birth weight boys at age 11 years. *Biological Psychiatry*, *47*(6), 490–500. https://doi.org/10.1016/S0006-3223(99)00223-1

Kabir, Z., Connolly, G. N., & Alpert, H. R. (2011). Secondhand Smoke Exposure and Neurobehavioral Disorders Among Children in the United States. *Pediatrics*, *128*(2), 263–270. https://doi.org/10.1542/peds.2011-0023

Kiuru, S., & Gissler, M. (2018). *Perinataalitilasto—Synnyttäjät, synnytykset ja vastasyntyneet 2018*. Terveyden ja Hyvinvoinnin laitos (THL).

Kivinen, A. (2018). *The Effect of Relative School Starting Age on Having an Individualized Curriculum in Finland* [VATT Institute for Economic Research]. https://www.ssrn.com/abstract=3120222

Koponen, A. M., Nissinen, N.-M., Gissler, M., Autti-Rämö, I., Sarkola, T., & Kahila, H. (2020). Prenatal substance exposure, adverse childhood experiences and diagnosed mental and behavioral

disorders – A longitudinal register-based matched cohort study in Finland. *SSM - Population Health*, *11*, 100625. https://doi.org/10.1016/j.ssmph.2020.100625

Koponen, T., Eklund, K., Heikkilä, R., Salminen, J., Fuchs, L., Fuchs, D., & Aro, M. (2020). Cognitive Correlates of the Covariance in Reading and Arithmetic Fluency: Importance of Serial Retrieval Fluency. *Child Development*, *91*(4), 1063–1080. https://doi.org/10.1111/cdev.13287

Korpipää, H., Moll, K., Aunola, K., Tolvanen, A., Koponen, T., Aro, M., & Lerkkanen, M.-K. (2020). Early cognitive profiles predicting reading and arithmetic skills in grades 1 and 7. *Contemporary Educational Psychology*, *60*, 101830. https://doi.org/10.1016/j.cedpsych.2019.101830

Kristensen, P., & Bjerkedal, T. (2007). Explaining the Relation Between Birth Order and Intelligence. *Science*, *316*(5832), 1717–1717. https://doi.org/10.1126/science.1141493

Kuchirko, Y. (2017). On differences and deficits: A critique of the theoretical and methodological underpinnings of the word gap. *Journal of Early Childhood Literacy*, *19*(4), 533–562. https://doi.org/10.1177/1468798417747029

Kuja-Halkola, R., D'Onofrio, B. M., Larsson, H., & Lichtenstein, P. (2014). Maternal Smoking During Pregnancy and Adverse Outcomes in Offspring: Genetic and Environmental Sources of Covariance. *Behavior Genetics*, *44*(5), 456–467. https://doi.org/10.1007/s10519-014-9668-4

Kundakovic, M., & Jaric, I. (2017). The Epigenetic Link between Prenatal Adverse Environments and Neurodevelopmental Disorders. *Genes*, *8*(3), 104. https://doi.org/10.3390/genes8030104

Kuntsi, J., Larsson, H., Deng, Q., Lichtenstein, P., & Chang, Z. (2021). The Combined Effects of Young Relative Age and Attention-Deficit/Hyperactivity Disorder on Negative Long-Term Outcomes. *Journal of the American Academy of Child & Adolescent Psychiatry*. https://doi.org/10.1016/j.jaac.2021.07.002

Landerl, K., & Moll, K. (2010). Comorbidity of learning disorders: Prevalence and familial transmission. *Journal of Child Psychology and Psychiatry*, *51*(3), 287–294. https://doi.org/10.1111/j.1469-7610.2009.02164.x

Laugesen, K., Ludvigsson, J. F., Schmidt, M., Gissler, M., Valdimarsdottir, U. A., Lunde, A., & Sørensen, H. T. (2021). Nordic Health Registry-Based Research: A Review of Health Care Systems and Key Registries. *Clinical Epidemiology*, *13*, 533–554. https://doi.org/10.2147/CLEP.S314959

Lehti, V., Gyllenberg, D., Suominen, A., & Sourander, A. (2018). Finnish-born children of immigrants are more likely to be diagnosed with developmental disorders related to speech and language, academic skills and coordination. *Acta Paediatrica*, *107*(8), 1409–1417. https://doi.org/10.1111/apa.14308

Leivonen, S., Voutilainen, A., Hinkka-Yli-Salomaki, S., Timonen-Soivio, L., Chudal, R., Gissler, M., Huttunen, J., & Sourander, A. (2014). A nationwide register study of the characteristics, incidence and validity of diagnosed Tourette syndrome and other tic disorders. *Acta Paediatrica*, *103*, 984–990. https://doi.org/10.1111/apa.12708

Leppert, B., Havdahl, A., Riglin, L., Jones, H. J., Zheng, J., Davey Smith, G., Tilling, K., Thapar, A., Reichborn-Kjennerud, T., & Stergiakouli, E. (2019). Association of Maternal Neurodevelopmental Risk Alleles With Early-Life Exposures. *JAMA Psychiatry*, *76*(8), 834. https://doi.org/10.1001/jamapsychiatry.2019.0774

LeWinn, K. Z., Bush, N. R., Batra, A., Tylavsky, F., & Rehkopf, D. (2020). Identification of Modifiable Social and Behavioral Factors Associated With Childhood Cognitive Performance. *JAMA Pediatrics*, *174*(11), 1063–1072. https://doi.org/10.1001/jamapediatrics.2020.2904

Lewis, S. J., Zuccolo, L., Smith, G. D., Macleod, J., Rodriguez, S., Draper, E. S., Barrow, M., Alati, R., Sayal, K., Ring, S., Golding, J., & Gray, R. (2012). Fetal Alcohol Exposure and IQ at Age 8: Evidence from a Population-Based Birth-Cohort Study. *PLOS ONE*, *7*(11), e49407. https://doi.org/10.1371/journal.pone.0049407

Lichtenstein, P., Carlström, E., Råstam, M., Gillberg, C., & Anckarsäter, H. (2010). The Genetics of Autism Spectrum Disorders and Related Neuropsychiatric Disorders in Childhood. *American Journal of Psychiatry*, *167*(11), 1357–1363. https://doi.org/10.1176/appi.ajp.2010.10020223

Lien, L., Tambs, K., Oppedal, B., Heyerdahl, S., & Bjertness, E. (2005). Is relatively young age within a school year a risk factor for mental health problems and poor school performance? A population-based cross-sectional study of adolescents in Oslo, Norway. *BMC Public Health*, *5*(1), 102. https://doi.org/10.1186/1471-2458-5-102

Lindqvist, R., Lendahls, L., Tollbom, O., Aberg, H., & Håkansson, A. (2002). Smoking during pregnancy: Comparison of self-reports and cotinine levels in 496 women. *Acta Obstetricia Et Gynecologica Scandinavica*, *81*(3), 240–244. https://doi.org/10.1034/j.1600-0412.2002.810309.x

Liu, L., Wang, J., Shao, S., Luo, X., Kong, R., Zhang, X., & Song, R. (2016). Descriptive epidemiology of prenatal and perinatal risk factors in a Chinese population with reading disorder. *Scientific Reports*, *6*(1), 36697. https://doi.org/10.1038/srep36697

Lundberg, F., Cnattingius, S., D'Onofrio, B., Altman, D., Lambe, M., Hultman, C., & Iliadou, A. (2010). Maternal smoking during pregnancy and intellectual performance in young adult Swedish male offspring. *Paediatric and Perinatal Epidemiology*, *24*(1), 79–87. https://doi.org/10.1111/j.1365-3016.2009.01073.x

Lyytinen, H., & Erskine, J. (2006). Early Identification and Prevention of Reading Problems. *Encyclopedia on Early Childhood Development*, 7.

MacArthur, C., George Knox, E., & Lancashire, R. J. (2001). Effects at age nine of maternal smoking in pregnancy: Experimental and observational findings. *British Journal of Obstetrics and Gynaecology*, *108*(1), 67–73. https://doi.org/10.1016/S0306-5456(00)00006-1

Machin, S., & Pekkarinen, T. (2008). Global Sex Differences in Test Score Variability. *Science*, *322*(5906), 1331–1332. https://doi.org/10.1126/science.1162573

Mackay, D. F., Smith, G. C. S., Cooper, S.-A., Wood, R., King, A., Clark, D. N., & Pell, J. P. (2016). Month of Conception and Learning Disabilities: A Record-Linkage Study of 801,592 Children. *American Journal of Epidemiology*, *184*(7), 485–493. https://doi.org/10.1093/aje/kww096

Macleod, C. (2020). John Stuart Mill. In *The Stanford Encyclopedia of Philosophy*. Metaphysics Research Lab, Stanford University.

Madley-Dowd, P., Kalkbrenner, A. E., Heuvelman, H., Heron, J., Zammit, S., Rai, D., & Schendel, D. (2020). Maternal smoking during pregnancy and offspring intellectual disability: Sibling analysis in an intergenerational Danish cohort. *Psychological Medicine*, 1–10. https://doi.org/10.1017/S0033291720003621

Mannerkoski, M. K., Aberg, L. E., Autti, T. H., Hoikkala, M., Sarna, S., & Heiskala, H. J. (2007). Newborns at risk for special education placement: A population-based study. *European Journal of Paediatric Neurology*, *11*, 223–231. https://doi.org/10.1016/j.ejpn.2007.01.005

Margari, L., Buttiglione, M., Craig, F., Cristella, A., de Giambattista, C., Matera, E., Operto, F., & Simone, M. (2013). Neuropsychopathological comorbidities in learning disorders. *BMC Neurology*, *13*(1), 198. https://doi.org/10.1186/1471-2377-13-198

Martin, R. P., Foels, P., Clanton, G., & Moon, K. (2004). Season of Birth Is Related to Child Retention Rates, Achievement, and Rate of Diagnosis of Specific LD. *Journal of Learning Disabilities*, *37*(4), 307–317. https://doi.org/10.1177/00222194040370040301

Mascheretti, S. (2018). Beyond genes: A systematic review of environmental risk factors in specific reading disorder. *Research in Developmental Disabilities*, 6.

Mascheretti, S., Marino, C., Simone, D., Quadrelli, E., Riva, V., Cellino, M. R., Maziade, M., Brombin, C., & Battaglia, M. (2015). Putative Risk Factors in Developmental Dyslexia: A Case-Control Study of Italian Children. *Journal of Learning Disabilities*, *48*(2), 120–129. https://doi.org/10.1177/0022219413492853

Mayes, S. D., & Calhoun, S. L. (2007). Learning, attention, writing, and processing speed in typical children and children with ADHD, autism, anxiety, depression, and oppositional-defiant disorder. *Child Neuropsychology : A Journal on Normal and Abnormal Development in Childhood and Adolescence*, *13*, 469–493.

McArthur, G. M., Hogben, J. H., Edwards, V. T., Heath, S. M., & Mengler, E. D. (2000). On the "Specifics" of Specific Reading Disability and Specific Language Impairment. *Journal of Child Psychology and Psychiatry*, *41*(7), 869–874. https://doi.org/10.1111/1469-7610.00674

Meas, T., Deghmoun, S., Armoogum, P., Alberti, C., & Levy-Marchal, C. (2008). Consequences of being born small for gestational age on body composition: An 8-year follow-up study. *The Journal of Clinical Endocrinology and Metabolism*, *93*(10), 3804–3809. https://doi.org/10.1210/jc.2008-0488

Melough, M. M., Murphy, L. E., Graff, J. C., Derefinko, K. J., LeWinn, K. Z., Bush, N. R., Enquobahrie, D. A., Loftus, C. T., Kocak, M., Sathyanarayana, S., & Tylavsky, F. A. (2021). Maternal Plasma 25-Hydroxyvitamin D during Gestation Is Positively Associated with Neurocognitive Development in Offspring at Age 4-6 Years. *The Journal of Nutrition*, *151*(1), 132–139. https://doi.org/10.1093/jn/nxaa309

Miettinen, M. E., Reinert, L., Kinnunen, L., Harjutsalo, V., Koskela, P., Surcel, H.-M., Lamberg-Allardt, C., & Tuomilehto, J. (2012). Serum 25-hydroxyvitamin D level during early pregnancy and type 1 diabetes risk in the offspring. *Diabetologia*, *55*(5), 1291–1294. https://doi.org/10.1007/s00125-012-2458-8

Mikkonen, K., Nikander, K., & Voutilainen, A. (2015). Koulun ja terveydenhuollon keinot oppimisvaikeuksien tunnistamisessa ja hoidossa. *Lääkärilehti*. https://www.laakarilehti.fi/tieteessa/katsausartikkeli/koulun-ja-terveydenhuollon-keinot-oppimisvaikeuksien-tunnistamisessa-ja-hoidossa/?public=a9daa60d467ff899df151967de85de82

Moll, K., Kunze, S., Neuhoff, N., Bruder, J., & Schulte-Körne, G. (2014). Specific Learning Disorder: Prevalence and Gender Differences. *PLOS ONE*, *9*(7), e103537. https://doi.org/10.1371/journal.pone.0103537

Moon, R. J., Crozier, S. R., Dennison, E. M., Davies, J. H., Robinson, S. M., Inskip, H. M., Godfrey, K. M., Cooper, C., & Harvey, N. C. (2015). Tracking of 25-hydroxyvitamin D status during pregnancy: The importance of vitamin D supplementation. *The American Journal of Clinical Nutrition*, *102*(5), 1081–1087. https://doi.org/10.3945/ajcn.115.115295

Morales, E., Guxens, M., Llop, S., Rodriguez-Bernal, C. L., Tardon, A., Riano, I., Ibarluzea, J., Lertxundi, N., Espada, M., Rodriguez, A., & Sunyer, J. (2012). Circulating 25-Hydroxyvitamin D3 in Pregnancy and Infant Neuropsychological Development. *Pediatrics*, *130*(4), e913–e920. https://doi.org/10.1542/peds.2011-3289

Morris, W. E. (2021). David Hume. In *The Stanford Encyclopedia of Philosophy*. Metaphysics Research Lab, Stanford University. <https://plato.stanford.edu/archives/spr2021/entries/hume/>

Morrow, C. E., Culbertson, J. L., Accornero, V. H., Xue, L., Anthony, J. C., & Bandstra, E. S. (2006). Learning disabilities and intellectual functioning in school-aged children with prenatal cocaine exposure. *Developmental Neuropsychology*, *30*(3), 905–931. https://doi.org/10.1207/s15326942dn3003_8

Morsanyi, K., Bers, B. M. C. W. van, McCormack, T., & McGourty, J. (2018). The prevalence of specific learning disorder in mathematics and comorbidity with other developmental disorders in primary school-age children. *British Journal of Psychology*, *109*(4), 917–940. https://doi.org/10.1111/bjop.12322

National Institute for Health and Welfare. (2009). *Leikki-ikäisen neurologinen kehitys (Lene)—Lastenneuvolakäsikirja—THL*. https://thl.fi/fi/web/lastenneuvolakasikirja/terveystarkastusten-menetelmat/neurologis-kognitiivinen-kehitys/lene

National Institute for Health and Welfare. (2020). *Maternity health care in Finland*. https://thl.fi/fi/web/lapset-nuoret-ja-perheet/peruspalvelut/aitiys_ja_lastenneuvola/aitiysneuvola

Nelson, J. M., & Harwood, H. (2011a). Learning disabilities and anxiety: A meta-analysis. *Journal of Learning Disabilities*, *44*, 3–17. https://doi.org/10.1177/0022219409359939

Nelson, J. M., & Harwood, H. R. (2011b). A meta-analysis of parent and teacher reports of depression among students with learning disabilities: Evidence for the importance of multi-informant assessment. *Psychology in the Schools*, *48*(4), 371–384. https://doi.org/10.1002/pits.20560

Niemi, E., & Metsämuuronen, J. (2010). *Miten matematiikan taidot kehittyvät? Matematiikan oppimistulokset peruskoulun viidennen vuosiluokan jälkeen vuonna 2008*. Finnish National Agency for Education.

Niilo Mäki Institute. (2022). *Lukiva*. https://materiaalit.nmi.fi/lukiva/

Noble, K. G., & Mccandliss, B. D. (2005). Reading Development and Impairment: Behavioral, Social, and Neurobiological Factors. *Journal of Developmental & Behavioral Pediatrics*, *26*(5), 370–378.

Obel, C., Zhu, J. L., Olsen, J., Breining, S., Li, J., Grønborg, T. K., Gissler, M., & Rutter, M. (2016). The risk of attention deficit hyperactivity disorder in children exposed to maternal smoking during pregnancy—A re-examination using a sibling design. *Journal of Child Psychology and Psychiatry*, *57*(4), 532–537. https://doi.org/10.1111/jcpp.12478

Official Statistics Finland. (2019). *Pre-primary and comprehensive school education* [E-publication]. http://www.stat.fi/til/pop/2019/pop_2019_2019-11-14_tie_001_en.html

Olson, H. C., Streissguth, A. P., Sampson, P. D., Barr, H. M., Bookstein, F. L., & Thiede, K. (1997). Association of Prenatal Alcohol Exposure With Behavioral and Learning Problems in Early Adolescence. *Journal of the American Academy of Child & Adolescent Psychiatry*, *36*, 1187–1194. http://dx.doi.org/10.1097/00004583-199709000-00010

Palacios, C., Kostiuk, L. K., & Peña-Rosas, J. P. (2019). Vitamin D supplementation for women during pregnancy. *Cochrane Database of Systematic Reviews*, *7*. https://doi.org/10.1002/14651858.CD008873.pub4

Pennington, B. F. (2006). From single to multiple deficit models of developmental disorders. *Cognition*, *101*(2), 385–413. https://doi.org/10.1016/j.cognition.2006.04.008

Pet, M. A., & Brouwer-Brolsma, E. M. (2016). The Impact of Maternal Vitamin D Status on Offspring Brain Development and Function: A Systematic Review1. *Advances in Nutrition*, *7*(4), 665–678. https://doi.org/10.3945/an.115.010330

Peterson, R. L., Boada, R., McGrath, L. M., Willcutt, E. G., Olson, R. K., & Pennington, B. F. (2017). Cognitive Prediction of Reading, Math, and Attention: Shared and Unique Influences. *Journal of Learning Disabilities*, *50*(4), 408–421. https://doi.org/10.1177/0022219415618500

Peterson, R. L., & Pennington, B. F. (2012). Developmental dyslexia. *The Lancet*, *379*(9830), 1997–2007. https://doi.org/10.1016/S0140-6736(12)60198-6

Pilz, S., Zittermann, A., Trummer, C., Theiler-Schwetz, V., Lerchbaum, E., Keppel, M. H., Grübler, M. R., März, W., & Pandis, M. (2019). Vitamin D testing and treatment: A narrative review of current evidence. *Endocrine Connections*, *8*(2), R27–R43. https://doi.org/10.1530/EC-18-0432

Plomin, R., & Kovas, Y. (2005). Generalist genes and learning disabilities. *Psychol Bull*, *131*, 592–617. https://doi.org/10.1037/0033-2909.131.4.592

Polanczyk, G., Moffitt, T. E., Arseneault, L., Cannon, M., Ambler, A., Keefe, R. S., Houts, R., Odgers, C. L., & Caspi, A. (2010). Etiological and clinical features of childhood psychotic symptoms: Results from a birth cohort. *Archives of General Psychiatry*, *67*, 328–338. https://doi.org/10.1001/archgenpsychiatry.2010.14

Polańska, K., Jurewicz, J., & Hanke, W. (2015). Smoking and alcohol drinking during pregnancy as the risk factors for poor child neurodevelopment – A review of epidemiological studies. *International Journal of Occupational Medicine and Environmental Health*, *28*(3), 419–443. https://doi.org/10.13075/ijomeh.1896.00424

Porta, M. (2014). *A Dictionary of Epidemiology*. Oxford University Press. https://www.oxfordreference.com/view/10.1093/acref/9780195314496.001.0001/acref-9780195314496

Quinn, P. D., Rickert, M. E., Weibull, C. E., Johansson, A. L. V., Lichtenstein, P., Almqvist, C., Larsson, H., Iliadou, A. N., & D'Onofrio, B. M. (2017). Association Between Maternal Smoking During Pregnancy and Severe Mental Illness in Offspring. *JAMA Psychiatry*, *74*(6), 589. https://doi.org/10.1001/jamapsychiatry.2017.0456

Qvarnström, M. (2013). Lukivaikeus. *Duodecim*, *129(2)*, 176–181. https://www.duodecimlehti.fi/lehti/2013/2/duo10741?keyword=lukivaikeus

Räsänen, P. (2012). Laskemiskyvyn häiriö eli dyskalkulia. *Duodecim*, *128*, 1168–1177.

Røed Larsen, E., & Solli, I. F. (2017). Born to run behind? Persisting birth month effects on earnings. *Labour Economics*, *46*, 200–210. https://doi.org/10.1016/j.labeco.2016.10.005

Rogers, A., Obst, S., Teague, S. J., Rossen, L., Spry, E. A., Macdonald, J. A., Sunderland, M., Olsson, C. A., Youssef, G., & Hutchinson, D. (2020). Association Between Maternal Perinatal Depression and Anxiety and Child and Adolescent Development: A Meta-analysis. *JAMA Pediatrics*, *174*(11), 1082–1092. https://doi.org/10.1001/jamapediatrics.2020.2910

Root, A., Brown, J. P., Forbes, H. J., Bhaskaran, K., Hayes, J., Smeeth, L., & Douglas, I. J. (2019). Association of Relative Age in the School Year With Diagnosis of Intellectual Disability, Attention-Deficit/Hyperactivity Disorder, and Depression. *JAMA Pediatrics*, *173*(11), 1068–1075. https://doi.org/10.1001/jamapediatrics.2019.3194

Rothman, K. J. (1976). Causes. *American Journal of Epidemiology*, *104*(6), 587–592. https://doi.org/10.1093/oxfordjournals.aje.a112335

Rutter, M., Caspi, A., Fergusson, D., Horwood, L. J., Goodman, R., Maughan, B., Moffitt, T. E., Meltzer, H., & Carroll, J. (2004). Sex differences in developmental reading disability: New findings from 4 epidemiological studies. *JAMA*, *291*(16), 2007–2012. https://doi.org/10.1001/jama.291.16.2007

Sanfilippo, J., Ness, M., Petscher, Y., Rappaport, L., Zuckerman, B., & Gaab, N. (2020). Reintroducing Dyslexia: Early Identification and Implications for Pediatric Practice. *Pediatrics*, *146*(1). https://doi.org/10.1542/peds.2019-3046

Sayal, K., Chudal, R., Hinkka-Yli-Salomäki, S., Joelsson, P., & Sourander, A. (2017). Relative age within the school year and diagnosis of attention-deficit hyperactivity disorder: A nationwide population-based study. *The Lancet Psychiatry*, *4*(11), 868–875. https://doi.org/10.1016/S2215-0366(17)30394-2

Sellers, R., Warne, N., Rice, F., Langley, K., Maughan, B., Pickles, A., Thapar, A., & Collishaw, S. (2020). Using a cross-cohort comparison design to test the role of maternal smoking in pregnancy in child mental health and learning: Evidence from two UK cohorts born four decades apart. *International Journal of Epidemiology*, *49*(2), 390–399. https://doi.org/10.1093/ije/dyaa001

Sirin, S. R. (2005). Socioeconomic Status and Academic Achievement: A Meta-Analytic Review of Research. *Review of Educational Research*, *75*(3), 417–453. https://doi.org/10.3102/00346543075003417

Snowling, M. J., Hayiou-Thomas, M. E., Nash, H. M., & Hulme, C. (2020). Dyslexia and Developmental Language Disorder: Comorbid disorders with distinct effects on reading comprehension. *Journal of Child Psychology and Psychiatry*, *61*(6), 672–680. https://doi.org/10.1111/jcpp.13140

Snowling, M. J., Nash, H. M., Gooch, D. C., Hayiou-Thomas, M. E., Hulme, C., & Wellcome Language and Reading Project Team. (2019). Developmental Outcomes for Children at High Risk of Dyslexia and Children With Developmental Language Disorder. *Child Development*, *90*(5), e548–e564. https://doi.org/10.1111/cdev.13216

Sourander, A., Sucksdorff, M., Chudal, R., Surcel, H.-M., Hinkka-Yli-Salomäki, S., Gyllenberg, D., Cheslack-Postava, K., & Brown, A. S. (2019). Prenatal Cotinine Levels and ADHD Among Offspring. *Pediatrics*, *143*(3), e20183144. https://doi.org/10.1542/peds.2018-3144

Sourander, A., Upadhyaya, S., Surcel, H.-M., Hinkka-Yli-Salomäki, S., Cheslack-Postava, K., Silwal, S., Sucksdorff, M., McKeague, I. W., & Brown, A. S. (2021). Maternal vitamin D levels during pregnancy and offspring autism spectrum disorder. *Biological Psychiatry*, *0*(0). https://doi.org/10.1016/j.biopsych.2021.07.012

Specht, I. O., Janbek, J., Thorsteinsdottir, F., Frederiksen, P., & Heitmann, B. L. (2020). Neonatal vitamin D levels and cognitive ability in young adulthood. *European Journal of Nutrition*, *59*(5), 1919–1928. https://doi.org/10.1007/s00394-019-02042-0

Stakes. (1999). *Tautiluokitus ICD-10*. https://koodistopalvelu.kanta.fi/codeserver/pages/classification-view-page.xhtml?classificationKey=23&versionKey=58

Stanton-Chapman, T. L., Chapman, D. A., & Scott, K. G. (2001). Identification of Early Risk Factors for Learning Disabilities. *Journal of Early Intervention*, *24*(3), 193–206. https://doi.org/10.1177/105381510102400305O1

Strøm, M., Halldorsson, T. I., Hansen, S., Granström, C., Maslova, E., Petersen, S. B., Cohen, A. S., & Olsen, S. F. (2014). Vitamin D Measured in Maternal Serum and Offspring Neurodevelopmental Outcomes: A Prospective Study with Long-Term Follow-Up. *Annals of Nutrition and Metabolism*, *64*(3–4), 254–261. https://doi.org/10.1159/000365030

Sucksdorff, M., Brown, A. S., Chudal, R., Surcel, H.-M., Hinkka-Yli-Salomäki, S., Cheslack-Postava, K., Gyllenberg, D., & Sourander, A. (2020). Maternal Vitamin D Levels and the Risk of Offspring Attention-Deficit/Hyperactivity Disorder. *Journal of the American Academy of Child & Adolescent Psychiatry*, *60*(1), 142-151.e2. https://doi.org/10.1016/j.jaac.2019.11.021

Sund, R. (2012). Quality of the Finnish Hospital Discharge Register: A systematic review. *Scandinavian Journal of Public Health*, *40*, 505–515. https://doi.org/10.1177/1403494812456637

Susser, E., Hoek, H. W., & Brown, A. (1998). Neurodevelopmental Disorders after Prenatal Famine: The Story of the Dutch Famine Study. *American Journal of Epidemiology*, *147*(3), 213–216. https://doi.org/10.1093/oxfordjournals.aje.a009439

Taylor, A. E. B. (2014). *Diagnostic Assessment of Learning Disabilities in Childhood*. Springer New York. https://doi.org/10.1007/978-1-4939-0335-1

Taylor, R. M., Fealy, S. M., Bisquera, A., Smith, R., Collins, C. E., Evans, T.-J., & Hure, A. J. (2017). Effects of Nutritional Interventions during Pregnancy on Infant and Child Cognitive Outcomes: A Systematic Review and Meta-Analysis. *Nutrients*, *9*(11), E1265. https://doi.org/10.3390/nu9111265

Tous, M., Villalobos, M., Iglesias, L., Fernández-Barrés, S., & Arija, V. (2020). Vitamin D status during pregnancy and offspring outcomes: A systematic review and meta-analysis of observational studies. *European Journal of Clinical Nutrition*, *74*(1), 36–53. https://doi.org/10.1038/s41430-018-0373-x

Tucker-Drob, E. M., & Harden, K. P. (2012). Early childhood cognitive development and parental cognitive stimulation: Evidence for reciprocal gene–environment transactions. *Developmental Science*, *15*(2), 250–259. https://doi.org/10.1111/j.1467-7687.2011.01121.x

Tweed, E. J., Mackay, D. F., Nelson, S. M., Cooper, S.-A., & Pell, J. P. (2016). Five-minute Apgar score and educational outcomes: Retrospective cohort study of 751 369 children. *Archives of Disease in Childhood - Fetal and Neonatal Edition*, *101*(2), F121–F126. https://doi.org/10.1136/archdischild-2015-308483

Tylavsky, F. A., Kocak, M., Murphy, L. E., Graff, J. C., Palmer, F. B., Völgyi, E., Diaz-Thomas, A. M., & Ferry, R. J. (2015). Gestational Vitamin 25(OH)D Status as a Risk Factor for Receptive Language Development: A 24-Month, Longitudinal, Observational Study. *Nutrients*, *7*(12), 9918–9930. https://doi.org/10.3390/nu7125499

Undheim, A. M. (2003). Dyslexia and psychosocial factors. A follow-up study of young Norwegian adults with a history of dyslexia in childhood. *Nordic Journal of Psychiatry*, *57*(3), 221–226. https://doi.org/10.1080/08039480310001391

Upadhyaya, S., Chudal, R., Luntamo, T., Hinkka-Yli-Salomäki, S., Sucksdorff, M., Lehtonen, L., & Sourander, A. (2020). Perinatal risk factors and reactive attachment disorder: A nationwide population-based study. *Acta Paediatrica*, *109*(8), 1603–1611. https://doi.org/10.1111/apa.15156

Valtonen, R., Ahonen, T., Tolvanen, A., & Lyytinen, P. (2009). How does early developmental assessment predict academic and attentional–behavioural skills at group and individual levels? *Developmental Medicine & Child Neurology*, *51*(10), 792–799. https://doi.org/10.1111/j.1469-8749.2009.03290.x

Veena S. R., Krishnaveni G. V., Srinivasan K., Thajna K. P., Hegde B. G., Gale C. R., & Fall C. H. (2017). Association between maternal vitamin D status during pregnancy and offspring cognitive function during childhood and adolescence. *Asia Pacific Journal of Clinical Nutrition*, *26*(3), 438–449. https://doi.org/10.6133/apjcn.032016.07

Vermeiren, A. P., Willeboordse, M., Oosterhoff, M., Bartelink, N., Muris, P., & Bosma, H. (2018). Socioeconomic multi-domain health inequalities in Dutch primary school children. *European Journal of Public Health*, *28*(4), 610–616. https://doi.org/10.1093/eurpub/cky055

Viholainen, H., Ahonen, T., Lyytinen, P., Cantell, M., LicSSc, A. T., & Lyytinen, H. (2006). Early motor development and later language and reading skills in children at risk of familial dyslexia. *Developmental Medicine & Child Neurology*, *48*(5), 367–373. https://doi.org/10.1017/S001216220600079X

Voltas, N., Canals, J., Hernández-Martínez, C., Serrat, N., Basora, J., & Arija, V. (2020). Effect of Vitamin D Status during Pregnancy on Infant Neurodevelopment: The ECLIPSES Study. *Nutrients*, *12*(10). https://doi.org/10.3390/nu12103196

Wang, H., Yu, X. D., Huang, L. S., Chen, Q., Ouyang, F. X., Wang, X., & Zhang, J. (2018). Fetal vitamin D concentration and growth, adiposity and neurodevelopment during infancy. *European Journal of Clinical Nutrition*, *72*(10), 1396–1403. https://doi.org/10.1038/s41430-017-0075-9

Wechsler, D. (2003). *WISC-IV - Wechsler Intelligence Scale For Children—IV*. NCS Pearson, Ltd.

Weitoft, G. R., Hjern, A., Haglund, B., & Rosen, M. (2003). Mortality, severe morbidity, and injury in children living with single parents in Sweden: A population-based study. *Lancet*, *361*, 289–295. https://doi.org/10.1016/S0140-6736(03)12324-0

Whitehouse, A. J. O., Holt, B. J., Serralha, M., Holt, P. G., Kusel, M. M. H., & Hart, P. H. (2012). Maternal Serum Vitamin D Levels During Pregnancy and Offspring Neurocognitive Development. *Pediatrics*, *129*(3), 485–493. https://doi.org/10.1542/peds.2011-2644

Wienen, A. W., Batstra, L., Thoutenhoofd, E., de Jonge, P., & Bos, E. H. (2018). Teachers' perceptions of behavioral problems in Dutch primary education pupils: The role of relative age. *PLOS ONE*, *13*(10), e0204718. https://doi.org/10.1371/journal.pone.0204718

Willcutt, E. G., & Pennington, B. F. (2000). Psychiatric Comorbidity in Children and Adolescents with Reading Disability. *Journal of Child Psychology and Psychiatry*, *41*(8), 1039–1048. https://doi.org/10.1111/1469-7610.00691

Willcutt, E. G., Pennington, B. F., Duncan, L., Smith, S. D., Keenan, J. M., Wadsworth, S., DeFries, J. C., & Olson, R. K. (2010). Understanding the complex etiologies of developmental disorders: Behavioral and molecular genetic approaches. *Journal of Developmental and Behavioral Pediatrics : JDBP*, *31*(7), 533–544. https://doi.org/10.1097/DBP.0b013e3181ef42a1

Willcutt, E. G., Petrill, S. A., Wu, S., Boada, R., DeFries, J. C., Olson, R. K., & Pennington, B. F. (2013). Comorbidity Between Reading Disability and Math Disability: Concurrent Psychopathology, Functional Impairment, and Neuropsychological Functioning. *Journal of Learning Disabilities*, *46*(6), 500–516. https://doi.org/10.1177/0022219413477476

World Health Organization. (1992). *International classification of diseases, 10th Revision*.

Zablotsky, B., Black, L. I., Maenner, M. J., Schieve, L. A., Danielson, M. L., Bitsko, R. H., Blumberg, S. J., Kogan, M. D., & Boyle, C. A. (2019). Prevalence and Trends of Developmental Disabilities among Children in the United States: 2009-2017. *Pediatrics*, *144*(4). https://doi.org/10.1542/peds.2019-0811

Zhu, P., Tong, S.-L., Hao, J.-H., Tao, R.-X., Huang, K., Hu, W.-B., Zhou, Q.-F., Jiang, X.-M., & Tao, F.-B. (2015). Cord Blood Vitamin D and Neurocognitive Development Are Nonlinearly Related in Toddlers. *The Journal of Nutrition*, *145*(6), 1232–1238. https://doi.org/10.3945/jn.114.208801

Zoëga, H., Valdimarsdóttir, U. A., & Hernández-Díaz, S. (2012). Age, Academic Performance, and Stimulant Prescribing for ADHD: A Nationwide Cohort Study. *Pediatrics*, *130*(6), 1012–1018. https://doi.org/10.1542/peds.2012-0689

TURUN
YLIOPISTO
UNIVERSITY
OF TURKU

Painosalama, Turku, Finland 2022

ISBN 978-951-29-8822-8 (PRINT)
ISBN 978-951-29-8823-5 (PDF)
ISSN 0355-9483 (Print)
ISSN 2343-3213 (Online)