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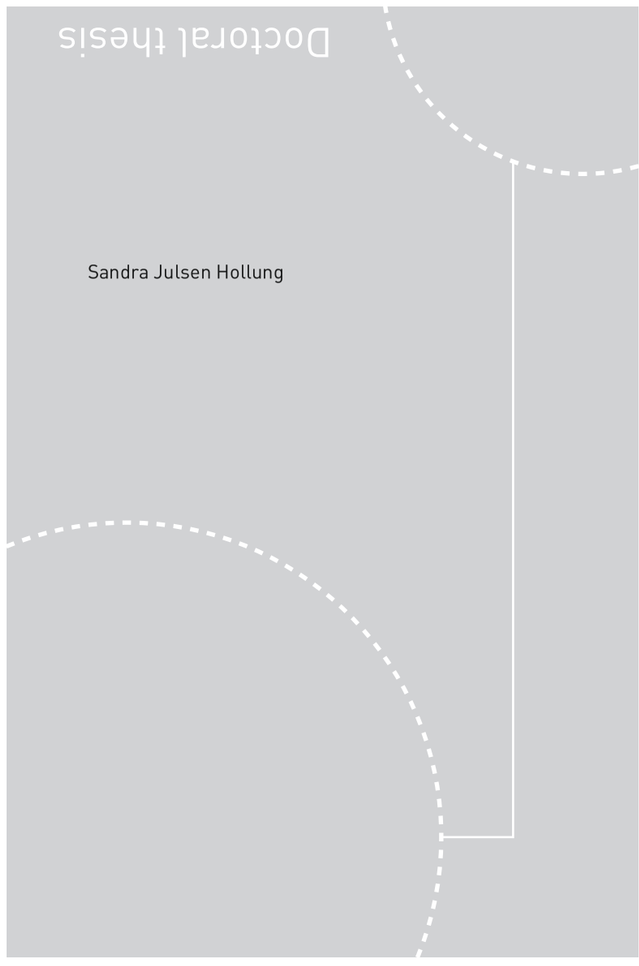
Sandra Julsen Hollung

Surveillance of cerebral palsy in Norway; a national registry-based study

Doctoral thesis



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Trondheim, October 2019

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Overvåking av cerebral parese i Norge; en nasjonal registerbasert studie

Cerebral parese (CP) registre gir unike muligheter til å overvåke, studere og rapportere om CP over tid. Dette inkluderer å studere årsaker, diagnostisering, kliniske manifestasjoner og behandlinger/ tiltak. Denne avhandlingen er en nasjonal registerbasert studie av individer med CP født i årene 1996 til 2010, registrert i Cerebral pareseregisteret i Norge (CPRN) og Norsk pasientregister (NPR). Data fra begge registre ble brukt for å sikre at studiene var populasjonsbasert. Dette ble utført ved å koble CPRN til NPR, og validere alle CP diagnosekoder registrert i NPR, men ikke i CPRN. Artikkel I beskriver resultatene av valideringsstudien, og konsekvensene en komplett og korrekt populasjon kan ha på beregning av prevalensestimater. Den nøyaktige forekomsten av CP for individer født i Norge i denne perioden er 2,4 per 1000 levendefødte.

Artikkel II gir en grundigere beskrivelse av trender i prevalens og alvorlighetsgraden av CP, ved bruk av kliniske data fra CPRN, supplert med data fra NPR. Vi fant en signifikant nedgang i forekomsten av CP fra 2,6 per 1000 levendefødte i 1999 til 1,9 i 2010. Dette var hovedsakelig tilskrevet en nedgang i den mer alvorlige subtypen bilateral spastisk CP (karakterisert av spastisk muskulatur på begge sider av kroppen). Vi fant også en nedgang i andelen personer med CP og alvorlig motorisk funksjonsnedsettelse, epilepsi, utviklingshemming og svært utydelig eller ingen tale. Dette er første gang en reduksjon i forekomsten og alvorlighetsgraden av CP har blitt rapportert i Norge. Nedgangen skyldes mest sannsynlig forbedringer i svangerskaps, fødsels og nyfødt omsorg i Norge de siste tiårene. For å støtte disse funnene, undersøkte vi også statusen for perinatal helse for alle barn født i Norge i løpet av den samme perioden ved hjelp av statistikkbanken til Medisinsk fødselsregister. Vi fant da en nedgang i forekomsten av barn født prematurt, mødre med preeklampsi under graviditet og av flerlinger, som alle er kjente risikofaktorer for CP. I tillegg var det også en nedgang i perinatal dødelighet.

I artikkel III fant vi at personer som fikk diagnosen CP i løpet av studieperioden har en betydelig høyere sykdomsbyrde sammenlignet med jevnaldrende uten CP. Nesten alle personer med CP ble registrert i NPR med en eller flere diagnoser i tillegg til CP (komorbiditeter), fra mild til alvorlig og forbigående eller kronisk. Sammenlignet med risikoen i befolkningen forøvrig, hadde personer med CP en økt risiko for å ha flere medisinske, nevrologiske og psykiske/atferds diagnoser. Som forventet var mange av komorbiditetene forbundet med den samme skaden på den umodne hjernen som forårsaket CP, eller som komplikasjoner til CP. Imidlertid fant vi også at mange komorbiditeter ikke var intuitivt relatert til CP.

Denne studien viser betydningen av kontinuerlig overvåking av CP-populasjonen i Norge. Ved å overvåke variasjoner i prevalens og kliniske manifestasjoner av CP over tid, kan vi gi oppdatert informasjon til helsepersonell og støtte deres arbeid for å forebygge eller minske alvorlighetsgraden av CP.

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TABLE OF CONTENTS

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LIST OF RESEARCH ARTICLES

1. **Completeness and correctness of cerebral palsy diagnoses in two health registers: implications for estimating prevalence**
   Sandra Julsen Hollung, Torstein Vik, Robert Wiik, Inger Johanne Bakken, Guro L. Andersen.
   Dev Med Child Neurol. 2017 59: 402-406. doi:10.1111/dmcn.13341.

2. **Decreasing prevalence and severity of cerebral palsy in Norway among children born 1999 to 2010 concomitant with improvements in perinatal health**
   Sandra Julsen Hollung, Torstein Vik, Stian Lydersen, Inger Johanne Bakken, Guro L. Andersen.
   Eur J Paediatr Neurol. 2018 Vol. 22, Issue 5, 814 – 821. doi:10.1016/j.ejpn.2018.05.001.

3. **Comorbidities in cerebral palsy: a patient registry study**
   Sandra Julsen Hollung, Inger Johanne Bakken, Torstein Vik, Stian Lydersen, Robert Wiik, Kari Modalsli Aaberg, Guro L. Andersen.
   Accepted for publication May 16, 2019. Dev Med Child Neurol. doi:10.1111/dmcn.14307.

ABBREVIATIONS

AFT	Assisted fertilization techniques
CI	Confidence interval
CP	Cerebral palsy
CPRN	Cerebral Palsy Registry of Norway
GMFCS	Gross Motor Function Classification System
ICD-10	International Statistical Classification of Diseases and Related Health Problems, 10th Revision
MACS	Manual Ability Classification System
MBRN	Medical Birth Registry of Norway
NPR	Norwegian Patient Registry
RD	Risk difference
SCPE	Surveillance of Cerebral Palsy in Europe
SSB	Statistics Norway

SUMMARY

Well-established cerebral palsy (CP) registries provide a solid framework to monitor, study and report on CP over time. This includes its causes, diagnosis, clinical manifestations and treatments/interventions. This thesis is a national registry-based study of individuals with CP born 1996 to 2010 and recorded in the Cerebral Palsy Registry of Norway (CPRN) and the Norwegian Patient Registry (NPR). Data from both registries were used to ensure that the studies were population-based. This was performed by linking the CPRN to the NPR, and validating all CP diagnosis codes recorded in the NPR, but not in the CPRN. Article I describes the results of the validation study, and the implications a complete and correct population can have on the calculation of prevalence estimates. The accurate prevalence of CP for individuals born in Norway during this study period is 2.4 per 1000 live births.

Article II continued with a more in-depth investigation of the trends in prevalence and severity of CP, using clinical data from the CPRN and supplemented with data from the NPR. We found a significant decline in the prevalence of CP from 2.6 per 1000 live births in 1999 to 1.9 in 2010. This was mostly attributed to a decrease in the more severe bilateral spastic CP subtype (characterized by muscular stiffness on both sides of the body). We also found a decrease in the proportion of individuals with CP and severe motor impairments, epilepsy, intellectual disability and reduced speech. This is the first time a reduction in the prevalence and severity of CP has been reported in Norway. The decline was most likely due to improvements in antenatal, obstetric and neonatal care that have been introduced nationwide throughout the past few decades. To support these findings, we also explored the status of perinatal health for all children born in Norway during this study period, using summary statistics from the Medical Birth Registry of Norway Statistics Bank. There, we found a decline in the prevalence of children born preterm, mothers with preeclampsia during pregnancy and with multiples, all of which are well-known risk factors for CP. In addition, there was also a decline in perinatal mortality.

Nonetheless, in article III we found that individuals who did receive a diagnosis of CP during this study period have a considerably higher burden of disease when compared with their peers in the general population without CP. Nearly all individuals with CP were recorded in the NPR with one or more disorders in addition to their CP condition (comorbidities), whether mild-to-severe or transient-to-chronic. When compared with the risks in the general population, individuals with CP had an excess risk for multiple medical, neurological and mental/behavioral disorders. As

expected, many of the comorbidities were associated with the injury to the developing brain that caused CP (cocausal) or complications of the main CP condition. However, we also found that many comorbidities were also not intuitively related to CP.

This thesis demonstrates the importance of continual surveillance of the CP population in Norway. By monitoring fluctuations in the prevalence and clinical manifestations of CP over time, we can provide up-to-date information to healthcare professionals and support their work in preventing or minimizing the impact of CP.

1. BACKGROUND AND INTRODUCTION

Cerebral palsy (CP) is the most common cause of permanent motor disabilities in children, and is the result of a non-progressive injury in the developing brain.[1] Although the exact etiology of CP is often impossible to establish, causes are often related to a congenital brain abnormality, infection, trauma or other complications. Several well-known risk factors that occur before, during or after birth in the neonatal period include premature birth, restricted fetal growth and complications during pregnancy and birth.[2-4] Many studies have also suggested that there is causal pathway, or a combined effect of multiple risk factors, that leads to CP.[4-7] Stoknes et al. reported an increased risk of developing CP as the number of risk factors increased in children born in Norway between 1996 and 1998.[8] The study also showed that very few children shared the same combination of risk factors, and thereby could not identify common sequences that lead to CP. In addition, the "panorama" of causes changes over time, as demonstrated by a series of studies performed in western Sweden in individuals with CP born between 1954 and 2010.[9-18]

A brain injury that occurs between 28 days after birth to 2 years is defined as postneonatally acquired CP. It is most often caused by a preventable infection, vascular episode or head injury. This group consists of a very small percentage of the overall population of individuals with CP.[19, 20] Injuries occurring after the age of two years are not considered CP, and are therefore exluded in this thesis.

1.1 CP diagnosis

CP is a clinical diagnosis determined by a pediatrician based on clinical and neurological signs (e.g. motor disturbances and clinical history of known risk factors).[21] The average age at diagnosis is between 1 to 2 years old.[22-24] It can be difficult for a pediatrician to determine if an infant has a motor disturbance that is permanent, resulting in CP, because each child's development of voluntary motor functions is unique and progresses at different rates.[21] As of now, neither blood tests nor image diagnostics are required. However, cerebral magnetic resonance imaging is strongly recommended in order to identify a brain abnormality that can be predictive of CP.[21] In Norway, the Surveillance of Cerebral Palsy in Europe (SCPE) *Decision tree for cerebral palsy* guidelines are used to aid in the diagnostic process.[25]

Once a diagnosis of CP is determined, the pediatrician will record a CP diagnosis code based on the dominating motor disturbance and on which part of the body is affected in the hospital record. In Norway, International Statistical Classification of Diseases and Related Health Problems 10th Revision[26] (ICD-10) CP diagnoses codes are used. To increase the reliability and ease of classifying children with CP according to neurological findings, the SCPE developed the *Classification tree for CP subtypes* and *Classification of CP Subtypes* "to promote a shared understanding of the words and phrases used to describe the clinical, functional and neurological features of CP."[27] ICD-10 CP diagnosis codes can be mapped into SCPE CP subtypes (Table 1).

Table 1: ICD-10 CP diagnosis codes mapped into SCPE CP subtypes, and a description of SCPE CP subtypes based on neurological findings.[26, 27]

ICD-10 CP diagnosis codes	SCPE CP subtype	Description SCPE CP subtype
G80.2 Spastic hemiplegic G80.0 Spastic quadriplegic G80.1 Spastic diplegic	Spastic unilateral bilateral	Increased tone and pathological reflexes. • Increased reflexes • Pyramidal signs
G80.3 Dyskinetic Athetoid Dystonic	Dyskinetic Choreoathetotic Dystonic	Involuntary, uncontrolled, recurring and occasionally stereotyped movements. Primitive reflex patterns predominate. Muscle tone is varying.
G80.4 Ataxic	Ataxic	Loss of orderly muscular coordination, so that movements are performed with abnormal force, rhythm and accuracy.
G80.8 Other/mixed G80.9 Unspecified		Should be classified according to the dominant clinical feature (e.g. spasticity with ataxia and/or dyskinesia).

The age recommended for confirmation of a CP diagnosis is 5 years.[27] All children and youths with CP in Norway have the right to be diagnosed and treated at one of the 21 habilitation centers, located at public hospitals nationwide (ages 0 to 16 years free of charge).[28]

1.2 Clinical characteristics

The clinical characteristics of CP vary considerably, something one would expect from the variation in potential causes. Therefore, it is common practice to classify individuals with CP according motor function. In 1997, the Gross Motor Function Classification System (GMFCS) was developed as a 5-level instrument to describe motor function in regards to sitting, walking and the use of

mobility devices during different situations in daily life.[29] The GMFCS is now widely used, and proven to be a reliable and valid tool to predict gross motor function up to adulthood.[30, 31] Later, in 2006, the Manual Ability Classification System (MACS) was developed as a 5-level instrument to classify fine motor abilities, or how a child uses "use their hands to handle objects in daily activities."[32] MACS is also widely used, and tested to be reliable and valid.[32, 33]

While the diagnosis of CP is based on motor function, there has been an increase in the awareness of comorbidities that are often associated with CP. A comorbidity was defined by Brown and Eunson as any disorder associated with CP, but can also occur as a stand-alone disorder in individuals without CP.[34] This is reflected in the latest definition of CP, where motor impairments are often accompanied by "disturbances of sensation, perception, cognition, communication, and behavior, by epilepsy, and by secondary musculoskeletal problems."[35] In fact, due to the heterogeneous nature of CP, the range and severity of motor function abilities and comorbidities vary greatly. In a literature review by Odding, Roebroeck and Stam, they estimated that 25% to 80% of individuals with CP in Northwest Europe had comorbidities.[36] Novak et al. reported on the most common comorbidities associated with CP in a systematic review based mainly on well-established population-based CP registries in Europe (including Norway), Canada and Australia.[37] They found that on average of 49% of individuals with CP had an intellectual disability (28% severe), 35% had epilepsy, 23% speech impairments, 6% severe eating difficulties (tube-feeding), 4% severe or no hearing and 11% no vision.[37] While the most common aforementioned comorbidities associated with CP are well documented, there has not been, to our knowledge, a comprehensive evaluation of mild-to-severe, transient-to-chronic comorbidities, including those that may not be related to the main CP diagnosis.

1.3 Prevalence of CP

The prevalence of CP is reported to vary between 1.5 and 3.0 per 1000 live births,[38] and to be relatively stable for over fifty years.[39-41] Many researchers and clinicians have taken this stability as evidence that CP is mainly due to events before birth and therefore cannot be prevented.[41, 42] On the other hand, in a 2018 editorial, Sarah McIntyre from the Cerebral Palsy Alliance in Australia questioned if the prevalence of CP has ever been stable? When referring to historical CP-registry data from western Sweden and Western Australia, one can find evidence that the "prevalence of CP has been continually shifting and changing," due to the "many different aetiologies, risk factors and causal pathways that lead to CP that are also constantly changing and vary from region to

region."[43] In other words, the reporting of "stable" prevalence hides the significant changes in the causes leading to CP and the corresponding CP subtypes. One example of such change is the reduced occurrence of choreoathetoid CP, caused by kernicterus, following the introduction of a better treatment and prevention of rhesus immunization.[44] Another example is the increased survival of extremely preterm born children during the past few decades, whereby the survivors have an increased risk for acquiring bilateral CP.[45, 46] Thus, there are good examples that improved antenatal and obstetric care, as well as modern neonatal intensive care may affect the prevalence of CP. This, during a time when worldwide perinatal mortality has been steadily declining.[47] This is supported by several recent studies by the Surveillance of Cerebral Palsy in Europe (SCPE) that have reported a slight decline in the prevalence of CP towards the end of the last century, attributed to improvements in obstetric and neonatal care. Platt et al. showed a decrease in the prevalence of CP among children with a birth weight less than 1500 g born between 1980 and 1996 in 16 countries in Europe.[48] Using the same data source, Andersen et al. found a similar reduction among children born moderately preterm (gestational age 32-36 weeks).[49] More recently, Sellier et al. showed a reduction in the total prevalence of CP in 26 European countries from 1.90 to 1.77 per 1,000 live births for children born between 1980 and 2003, with an almost 2% annual reduction in the prevalence of moderate to severe CP.[50] However, while a main strength of studies performed by the SCPE is the pooling of data based on harmonized standards from several CP registries across Europe, there is a wide variety of data sources used to identify individuals with CP (e.g. hospital, community, social and educational sources) in each respective country/area.[25] This leads to varying degrees of registry completeness that may affect the validity of the prevalence estimates.[51] The overall prevalence in the Sellier et al. study was underestimated when compared with SCPE member registries with documented high levels of completeness.[12-16, 52, 53] Nonetheless, the debate continues regarding whether CP may be prevented or whether it is mainly caused by antenatal factors such as placental lesions or genetic elements that are less likely to be modified by obstetric and neonatal care.[41, 54, 55]

1.3.1 Prevalence of CP in Norway

In Norway, the prevalence of CP has been reported to vary between 1.8 and 3.0, depending on the data source used to identify individuals with CP.[23, 56, 57] Using information from the Norwegian Social Insurance Scheme, Tollånes et al. reported a prevalence of 1.8 per 1000 births for children born between 1967 and 2002.[56] However, not all children with CP receive social benefits and therefore the prevalence of CP using this data source was most likely underestimated. The

prevalence reported by Andersen et al. using preliminary data from the Cerebral Palsy Registry of Norway may also be underestimated at 2.1 per 1000 live births for children born between 1996 and 1998. This, due to the reliance upon summative reports provided by local pediatric habilitation centers. In addition, some CP subtypes may have been more consistently reported to the Cerebral Palsy Registry of Norway, as registration requires an informed consent, increasing the risk for selection bias.[23] Conversely, Surén et al. reported a prevalence of 3.0 per 1000 children born between 1999 and 2010 and residing in Norway. This prevalence was based upon information recorded in the Norwegian Patient Registry which may be overestimated as a result of a CP diagnosis code being recorded in a patient's hospital record by a non-pediatric specialist, or a diagnosis set purely on suspicion.[57]

Even a slight variation in the total number of individuals with CP can lead to inaccurate planning of healthcare resources and have a considerable economic impact on a healthcare system.[58, 59] Therefore, to report accurate prevalence estimates in Norway, a study to verify individual-level data recorded in the aforementioned data sources was necessary.

1.4 Improvements in antenatal, obstetric and neonatal care

Throughout the past few decades, antenatal, obstetric and neonatal care have undergone significant changes in Norway, as well as in other countries. In the 1990s, surfactant therapy for premature babies in respiratory distress was introduced as an effective treatment to reduce the risk of neonatal mortality and morbidity.[60] During this same time, the use of magnesium sulfate for women at risk of a preterm birth was introduced as a neuroprotective treatment for their baby,[61, 62] and is documented to reduce the risk of CP.[63-65] In the early 2000s, there was an increase in the use of fetal monitoring during labor, such as the use of cardiotocography (CTG) or ST waveform analysis (STAN) to assess a baby's well-being, as well as Fetal scalp pH testing to determine if the baby is getting an adequate oxygen supply.[66, 67] However, there is currently neither evidence to support the benefit of widespread use of fetal monitoring during labor, nor an association with a decrease in the prevalence or severity of CP.[68-72] In the mid-2000s, therapeutic hypothermia was recommended as a new neuroprotective treatment for babies born at term with evidence of hypoxic ischemic encephalopathy, a brain injury due to asphyxia.[73-75] National recommendations and guidelines for the use of these new treatments and methods are well established in Norway.[76-79] Has the introduction of these new methods and treatments had an effect on the prevalence and severity of CP in Norway?

1.5 Norwegian national health and medical quality registries

Norway has a long, rich history of population-based health registries. In fact, one of the world's first national medical registries was the National Leprosy Registry of Norway, established in 1856.[80] This registry was noteworthy because it demonstrated the importance of systematically recording detailed health information in order to monitor disease trends. This registry would later lead to the discovery that leprosy was a contagious disease and the eradication of leprosy in Norway.[80] Since that time, the health registry movement in Norway has continued with the establishment of the Norwegian Cause of Death Registry in 1925, the Cancer Registry of Norway in 1951 and the National Registry in 1964. The purpose of the National Registry was to assign a unique personal identification number to each citizen or permanent resident.[81] In the context of health registries, it allows for the identification of individuals for the purpose of health research over the continuum of care. This ID number has become the vital key leading to 18 Norwegian national health registries[82] and 51 national medical quality registries[83] as of 2019.

The national health registries routinely receive a standard set of patient data from many sources, including healthcare service providers (i.e., hospitals and primary care physicians) and service organizations (i.e., laboratories and pharmacies). They are currently regulated by the 2014 Health Register Law, article 8, and are therefore compulsory.[82] National medical quality registries, on the other hand, collect a clearly defined set of clinical data on patients with a specific diagnosis or condition with the aim to monitor and improve healthcare services nationwide. They are often established and maintained locally at a publically financed hospital by specialists who have a deep understanding about their respective patient groups, from setting a diagnosis to developing treatment plans and evaluating outcomes. Although the medical quality registries are not governed by law, the majority require informed consent from a patient before data can be collected.[84] Data are most often collected manually and sent to each medical quality registry by designated health personnel nationwide; however, data submission is not mandatory.

Many studies have shown that combining national health registries and medical quality registries can improve the completeness and correctness of both registries. For example, linking the Norwegian Patient Registry with national medical quality registries has provided a basis for performing validation studies to ensure that a specific patient group is accurately represented.[85-89] However, there continues to be variations in data quality that can be attributed to the diversity of the patient groups (diagnosis and conditions), as well as the different levels of participation from

hospital departments. Nonetheless, Norwegian national health registries and medical quality registries capture a patient's interaction with health services throughout their lifespan, and thereby provide researchers with large population-based data sets to perform comprehensive and statistically powerful observational studies.

In 2012, the Cerebral Palsy Registry of Norway was given the opportunity to be the first national medical quality registry, based on a diagnosis, to link individual-level data with the Norwegian Patient Registry. The initial results showed a large discrepancy in the number of individuals recorded with CP in both registries. Therefore, a study to validate each ICD-10 CP diagnosis code recorded in the NPR and not in the CPRN was initiated. The realization of the importance of a complete and correct population-based data set to accurately monitor and describe the population of CP in Norway formed the basis for this PhD study.

1.6 CP registries

Population-based CP registries have provided a solid framework to monitor, study and report on CP over time. Since the 1950s, they have attributed to increased knowledge in the field of CP from its causes, diagnosis, clinical manifestations to treatments and interventions.[9, 53] In 1998, Christine Cans founded the SCPE to pool data from 14 European Countries with the aim to report on prevalence estimates in different subgroups of individuals with CP with sufficient statistical power.[25] Since that time, the SCPE has been instrumental in the development of tools to harmonize the identification, description and classification of individuals with CP, of which are now commonly used worldwide.[25, 27, 90-92] Twenty years later, the SCPE consists of 23 CP registries in 20 countries, with a central database of over 21,000 individuals with CP and over 30 scientific publications.[51] This includes the Cerebral Palsy Registry of Norway which has been an Associate Member of the SCPE since 2009, and is among the largest contributors of data to the central database. In 2002, the Autism and Developmental Disabilities Monitoring Network was established in the United States,[93] and Australian Cerebral Palsy Register in 2008.[94] According to Goldsmith et al., there are nearly 40 CP registries and surveys across Europe, Australia, Canada and the United States, and the numbers are increasing.[95] Although each CP registry has unique methods to describe CP, data sources used to identify individuals with CP, as well as data collection methods, their many scientific publications provides the opportunity for international comparisons within multiple healthcare settings. The results from several CP registry studies will be discussed throughout this thesis.

2. AIM

The overall aim of the studies included in this thesis was to validate the CP diagnosis codes recorded in the Cerebral Palsy Registry of Norway and the Norwegian Patient Registry to accurately describe trends in the prevalence and severity of CP, as well as the total burden of disease for individuals with CP. The specific research aims for each article was as follows:

Article I: To assess the completeness and correctness of CP diagnosis codes in the Cerebral Palsy Registry of Norway and the Norwegian Patient Registry to obtain an accurate estimate of the prevalence of CP in Norway.

Article II: To examine if the prevalence and severity of CP in Norway have changed over time.

Article III: To examine the total burden of disease for individuals with CP by comparing the occurrence of comorbidities in the CP population with the same disorders in the general population without CP.

3. MATERIALS AND METHODS

This thesis consists of three registry-based observational studies. Data was obtained from the Cerebral Palsy Registry of Norway, Norwegian Patient Registry, Medical Birth Registry of Norway and Statistics Norway. This provided us with a unique opportunity to study CP on a national population level, using already existing data.

3.1 Setting

3.1.1 Cerebral Palsy Registry of Norway

The Cerebral Palsy Registry of Norway (CPRN) is an informed consent-based national medical quality registry approved by the Norwegian Directorate of Health in 2006.[96] It is located at the Vestfold Hospital Trust. The CPRN has recorded detailed clinical data for children and youths with CP from 1996 onwards. This includes CP subtype, motor function, comorbidities (cognitive, language/ communication, eating, visual and/or hearing), congenital anomalies, spasticity and orthopedic treatments and brain imaging results. Data in the CPRN are collected by dedicated specialists (pediatricians, physical therapists, occupational therapists and child psychologists) from each of the 21 habilitation centers in Norway, recorded at three points in time: at diagnosis, and at ages 5 and 15 to 17 years. The main aim of the CPRN is to increase knowledge of the causes and treatments of children and youths with CP through surveillance and systematic analyses, including:

- To describe the prevalence of CP in Norway, including subtypes, severity and comorbidities
- To improve the quality of obstetric and neonatal care
- To ensure equal treatment and follow-up of children and youths with CP in Norway, regardless of where they live in the country

3.1.2 Norwegian Patient Registry

The Norwegian Patient Registry (NPR), under the authority of the Norwegian Directorate of Health, is a compulsory administrative registry that receives data on all patients treated by the national specialist healthcare services.[97] The NPR was established in 1997. However, data was not person-identifiable until 2008. The NPR collects standardized demographic, administrative and clinical patient data (e.g. diagnosis and procedure codes) on inpatient admissions and outpatient clinical consultations from all general and psychiatric hospitals in the country. All children with CP are diagnosed and their treatment performed at pediatric habilitation centers, reporting to the NPR. Data in the NPR can be used according to the purposes outlined in NPR regulations § 1–2.[97]

This includes to contribute to medical and health research that can provide knowledge about the health services, diagnoses, disease causes and prevalence, and quality assurance of disease and quality registries.

3.1.3 Medical Birth Registry of Norway

The Medical Birth Registry of Norway (MBRN) is a national compulsory health registry that has recorded information on all births since 1967 (after 12 weeks of pregnancy and onward).[98] The MBRN is under the jurisdiction of the Norwegian Institute of Public Health. The MBRN receives information on each birth from all maternity units on a standardized birth notification form. This includes information on the mother's health before and during pregnancy and any complications during pregnancy or birth, as well as the child's health at delivery. The main aim of the MBRN is to improve health services for pregnant women and their babies.[98]

3.1.4 Statistics Norway

Statistics Norway (SSB) was established in 1876, and is currently "responsible for collecting, producing and communicating statistics related to the economy, population and society at national, regional and local levels."[99]

3.2 Study design

Article I was a validation study with the aim to link the CPRN and NPR to assess the completeness and correctness of the CP diagnosis codes in each registry, and to use a combined and validated data set to accurately estimate of the prevalence of CP in Norway. Data in the CPRN were collected on the Survey of Children with Cerebral Palsy Form for children born 1996 to 1998,[23] while data for children born 1999 and onward on the CPRN Five Year Consultation Form. The CPRN and NPR were linked using the 11-digit personal identification number unique to each resident. Two veteran pediatricians performed a hospital record review to validate the CP diagnosis codes recorded in the NPR, and not in the CPRN. Live birth data were obtained from the MBRN, and population data from SSB.

Article II was a retrospective cohort study using data obtained from the CPRN to describe trends in the prevalence and clinical characteristics of children with CP. Clinical data were collected on the CPRN Five Year Consultation Form.[100] The NPR provided supplementary data for individuals validated to have CP, but not registered in the CPRN. Summary statistics were obtained from the

on-line MBRN statistics bank to assess perinatal health in the general population.[101] Live birth data were also obtained from the MBRN.

Article III was a retrospective cohort study with the aim to describe the occurrence of comorbidities in individuals with CP compared with the general population without CP. Data were obtained from the NPR for all individuals who attended the national specialist healthcare services between 2008 and 2017. Individuals with CP were identified through the validation study in cooperation with the CPRN. Population data were obtained from SSB. Data from private healthcare providers were excluded because they account for a very small proportion of healthcare services offered in Norway.

Table 2 describes the data sources (registries), data collection methods (e.g. registration forms) and the data access levels (e.g. individual-level or summary statistics) used in each article.

Table 2: Data sources, collection methods and access levels for each article.

	Data sources	Data collection methods	Data access levels
Article I	CPRN	Survey of Children with Cerebral Palsy Form* CPRN Five Year Consultation Form**	Individual-level, identifiable
	NPR	National specialist healthcare services hospital records	Individual-level, identifiable only to NPR and reviewers
	MBRN	MBRN Statistics Bank	Summary statistics
	SSB	SSB Statistics Bank	Summary statistics
Article II	CPRN	CPRN Five Year Consultation Form**	Individual-level, identifiable
	NPR	Validated ICD-10 CP diagnosis codes, not in CPRN	Individual-level, identifiable only to NPR
	MBRN	MBRN Statistics Bank†	Summary statistics
Article III	NPR	National specialist healthcare services hospital records Validated ICD-10 CP diagnosis codes	Individual-level, anonymous
	SSB	SSB Statistics Bank	Summary statistics

* Birth years 1996 to 1998

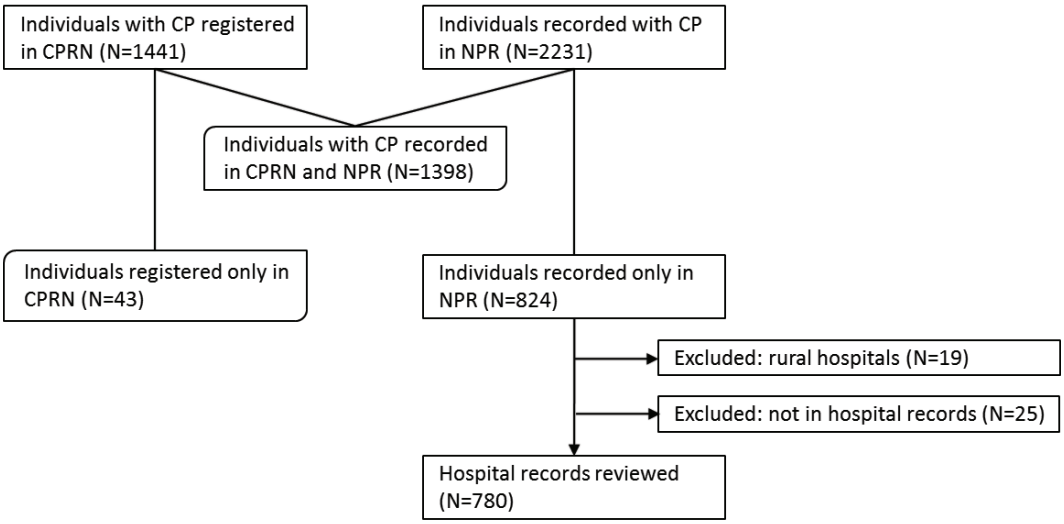
** Birth years 1999 and onwards

† Birth notification form dated December 1, 1998 and onwards

3.3 Study population

Article I included 747 883 Norwegian residents born between 1996 and 2007 and 699 927 live births in Norway during the same years. Of these, 2231 were recorded with a main or secondary ICD-10 CP diagnosis code in the NPR between 2008 and 2012, while 1441 individuals were registered with CP in the CPRN. The diagnosis of CP was considered accurate for the 1398 individuals recorded in both registries, and for the 43 recorded only in the CPRN. Two pediatricians validated the remaining 824 individuals recorded with a CP diagnosis code in the NPR, but not in the CPRN through a hospital record review. However, 19 individuals from rural hospitals were excluded for practical reasons, and 25 were not found in the hospital records. Thus, 780 hospital records were reviewed (Figure 1).

Figure 1: Article I study population flowchart.



After article I was published, a second validation study was completed for 130 individuals born 2007 to 2010 and recorded with an ICD-10 CP diagnosis in the NPR between 2008 and 2014, but not in the CPRN. Each pediatric habilitation center received a list from the NPR with the individuals recorded in their center. A local pediatrician confirmed and reported back to the NPR if the individual(s) had/did not have CP. If the individual had CP, the correct ICD-10 CP diagnosis code was also reported. Of the 130 individuals recorded only in the NPR, 45 (34.6%) were considered to be accurate, while 74 (56.9%) did not have CP and 11 (8.5%) were undeterminable. Therefore, births years included in articles II and III were extended to 2010.

Article II included 707 916 live births in Norway between 1999 and 2010. Of these, 1664 were registered with a validated diagnosis of CP in the CPRN and/or the NPR. More precisely, 1365 children with CP were recorded in both the CPRN and the NPR, 57 only in the CPRN and 242 children only in the NPR. Children born 1996 to 1998 were excluded from this study due to data collection using the CPRN Five Year Consultation Form for individuals born 1999 and onward and the MBRN Birth Notification Form for births recorded December 1, 1998 and onward. Children with postneonatally acquired CP were also excluded (n=70).

Article III included 966 760 Norwegian residents born between 1996 and 2010 and recorded in the NPR between 2008 and 2017. Of these, 2302 individuals with CP were identified from the validation studies previously performed in cooperation with the CPRN.

Table 3 describes the birth years included in each article, as well as the total number of residents, live births and individuals with CP in Norway.

Table 3: Summary of the study populations in articles I-III.

	Birth years	Total no. residents	Total no. live births	Total no. with CP
Article I	1996 - 2007	747 883	699 927	2331 NPR* 1441 CPRN*
Article II	1999 - 2010		707 916	1664
Article III	1996 - 2010	966 760		2302

*non-validated

3.4 Study variables

3.4.1 Cerebral palsy

CP was the primary outcome variable in articles I and II, whereas it was the primary exposure variable in article III.

CP was recorded as present or absent, as determined by a pediatrician for individuals recorded in the CPRN and/or NPR. If CP was confirmed as present, the validated ICD-10 CP diagnosis code and/or SCPE CP subtype was used, respectively.

3.4.2 Clinical characteristics

Article II included seven outcome variables to describe the clinical characteristics of children with CP. Each variable was classified and defined on the CPRN 5 Year Consultation Form as follows (Table 4):

Table 4: Variables included in article II to describe the clinical characteristics of children with CP.

Variable	Classification	Definition
Gross motor function	GMFCS[29]	Level I-II: able to walk with or without assistance Level III: able to walk only with assistance Level IV-V: unable to walk
Epilepsy	Present Not present	≥ 2 unprovoked seizures after neonatal period
Cognition	Normal Intellectually disabled	IQ test ≥ 70 or by clinical evaluation IQ test < 70 or by clinical evaluation
Speech	Viking Speech Scale[102]	Level I-II: normal to imprecise but understandable speech Level III-IV: difficult to understand or no speech
Eating	Independent Needs assistance Partial/full tube feeding	
Vision	Normal Impaired Severely impaired	 blind i.e. <6/60 (<0.1) before correction on best eye
Hearing	Normal Impaired Severely impaired	 loss > 70 dB before correction on best ear

Articles I and II included the variable postneonatally acquired CP (defined as a brain injury occurring between 28 days of life to 2 years old) and if an individual was born abroad. Both were classified as yes or no on the CPRN 5 Year Consultation Form.

3.4.3 Perinatal health indicators

To assess perinatal health in the general population, article II also included variables retrieved in summary form from the MBRN statistics bank (Table 5).[103] The perinatal period is defined as the time between 22 weeks of gestation during a pregnancy until 7 days after birth.[103]

Table 5: Variables included in article II used to describe perinatal health.

Variable	Classification	Definition
Assisted fertilization techniques (AFT)	Yes	Pregnancy may be result of in vitro fertilization, intracytoplasmic sperm injection, artificial insemination or other assisted fertilization methods
Preeclampsia	Present	Occurred before week 34 gestation
Congenital anomalies	Present	
Gestational age	Extremely preterm Very/moderately preterm Term	< week 28 28-36 weeks > 36 weeks Based on an ultrasound before week 20, and if not performed, from last menstrual period
Multiple births	Present	≥ 2 children born to the same mother at the same time
Perinatal mortality	Present	Children either stillborn or died during 1st week after birth, with minimum birth weight of 500 g and week 22 gestation

3.4.4 Disorder categories

Article III included 43 disorder categories as outcome variables. Each disorder category was pre-defined using ICD-10 diagnosis codes before data were extracted from the NPR (Appendix I). Both transient and chronic disorders ranging from mild-to-severe were included. Disorders unlikely to occur in children and youths were excluded. The disorder categories were dichotomized as present or absent for each individual.

Each disorder category was further sorted into three main groups: medical, neurological and mental/behavioral (Appendix I).

Reminder: A comorbidity was defined as any disorder associated with CP, but can also occur as a stand-alone disorder in individuals without CP.[34]
Therefore, when referring to individuals with CP, the term *comorbidity* will be applied.
When referring to the general population (without CP), the term *disorder* will be applied, because a disorder in the general population is not associated with an index condition (not a comorbidity).

Each disorder category was also sorted into three comorbidity categories: cocausal, complications and co-occurring (Appendix II) to describe comorbidities in individuals with CP. Each comorbidity category is defined in Table 6.[104]

Table 6: Comorbidity categories for individuals with CP, as proposed by Brown & Eunson.[34]

Cocausal:	Disorders caused by the same injury to the developing brain which caused CP. (i.e. epilepsy and cognitive impairment)
Complications:	Disorders that are complications of the main CP condition. (i.e. scoliosis and dislocation of hip)
Co-occurring:	Disorders not caused by the injury to the developing brain, nor are complications of the main CP condition.

3.5 Ethics

CPRN

Articles I and II were approved by The Norwegian Data Protection Authority (08/01067-9/EOL) and the Regional Committee for Medical and Health Research Ethics in Central Norway (2011/754). The approvals were based on written informed consent obtained from the parents of each child registered in the CPRN. The consent includes the recording of detailed clinical data for the purpose of surveillance and systematic analyses, and the linkage of the CPRN to the NPR to ascertain the completeness and correctness of the CPRN.

NPR

Articles I and II were conducted under NPR Regulation §2–4, and therefore the validation of the CP diagnosis codes in the NPR did not require patient consent. The NPR performed the linkage of the NPR and CPRN, as well as the validation of CP diagnosis codes recorded only in the NPR in cooperation with the two pediatrician reviewers. The CPRN only had access to anonymous data for

those individuals only recorded in the NPR. Article III was conducted under the NPR Regulations §1-2, and data were delivered pursuant to NPR Regulations §3-5, in an anonymous form. Studies using anonymous data, where information cannot be traced back to an individual, do not require ethical approval.

3.6 Statistical analyses

A combination of statistical programs were used for the data analyses: IBM SPSS Statistics for Windows version 23 for articles I and II and Stata Statistical Software release 15 for articles II and III. Chi-square (χ^2) tests were used to compare the differences in proportions between groups in articles I and II. A p-value < 0.05 was considered statistically significant. In articles I and II, 95% confidence intervals (95% CI) were reported, whereas 99% Wald CIs (99% CI) were reported in article III due to the large number of comparisons.

In article I, to measure data accuracy in the CPRN and the NPR, the completeness and correctness of each registry was investigated. Completeness was defined as the proportion of individuals with a confirmed CP diagnosis code in the registry, according to the combined and validated data set (i.e. equivalent to sensitivity in studies of diagnostic tests). Correctness was defined as the proportion of children with a CP diagnosis code in the registry that were confirmed cases of CP, according to the same data set (i.e. equivalent to positive predictive value in studies of diagnostic tests).[105] The calculation of completeness and correctness are illustrated in Table 7.

Table 7: Calculation of data accuracy in the CPRN and NPR using completeness and correctness in combined and validated data set.∗

	CP present	CP absent	Total	
Registration present	a	b	a + b	Correctness=a/(a+b)‡
Registration absent	c	d	c + d	
Total	a + c	b + d		
	Completeness=a/(a+c)†			

∗ The combined and validated data set includes all individuals registered in the CPRN, and individuals recorded with a confirmed CP diagnosis code only in the NPR.

† Completeness was used to calculate the proportion of individuals with CP that should have been registered, were present in the registry

‡ Correctness was used to assess the proportion of individuals present in the registry that were regarded as confirmed cases of CP.

The number of individuals with CP was calculated as follows:

no. individuals with CP in both CPRN and NPR +
no. individuals only in the CPRN +
no. individuals with confirmed ICD-10 CP diagnosis in NPR hospital record review

The prevalence estimates of CP were calculated as follows:

$$\text{Population–based prevalence} = \frac{\text{No. individuals with CP}}{\text{No. residents}}$$

$$\text{Birth prevalence} = \frac{\text{No. individuals with CP - (No. with postneonatally acquired CP or born abroad)}}{\text{No. live births}}$$

Furthermore, for individuals with CP, Cohen's unweighted kappa was used to evaluate the reliability of the ICD-10 CP diagnosis codes recorded only in the NPR by comparing them to the SCPE CP subtypes determined by the pediatricians during the hospital record review. Kappa values were interpreted as < 0.40 indicating poor, 0.40 - 0.75 intermediate to good, > 0.75 excellent agreement, and a kappa value of 1.0 indicating complete agreement.[106] To assess selection bias in the CPRN, the SCPE CP subtypes determined by the pediatricians during the hospital record review were compared with the proportion of individuals registered in the CPRN.

In article II, logistic regression with birth year as a covariate was used to estimate trends in the prevalence of CP, SCPE CP subtypes and perinatal health indicators per 1000 live births. Fractional polynomials with birth years as a covariate were used to account for nonlinear trends.[107] For prevalence analyses of CP, a worst-case sensitivity analysis was performed to account for the possibility of a child being diagnosed with CP after the age of 7-8 years and not counted in our analyses. This was performed by increasing the total number of children with CP by 10% for birth years 2009 and 2010. This percentage is five times higher than the observed percentage of children with late diagnosed CP born between 1999 and 2000. To compare the differences in proportions between clinical characteristics over time, the χ^2 linear-by-linear association test (for row x columns (r x c) tables with r > 2 and c > 2) and the Cochrane Armitage test for trend (for 2xc tables with c > 2) were used.[108]

In article III, risk differences (RD) were used to compare the occurrence of disorders between individuals with CP and the general population without CP. The occurrence of each population was calculated as follows:

$$\text{CP population} = \frac{\text{No. individuals with CP recorded in NPR with the disorder}}{\text{No. individuals in CP population}}$$

$$\text{General population} = \frac{\text{No. individuals without CP recorded in NPR with the disorder}}{\text{No. individuals in general population}}$$

For individuals with CP, the frequency distribution of ICD-10 CP diagnosis codes per comorbidity category, and the mean number of comorbidities with standard deviation (SD) per ICD-10 CP diagnosis code were also calculated. We also investigated the potential confounding effect of sex by stratification, where males and females were separated into two groups and analyzed separately.

4. SUMMARY OF RESULTS

4.1 Article I: Completeness and correctness of cerebral palsy diagnoses in two health registers: implications for estimating prevalence

4.1.1 Completeness and correctness of the NPR and CPRN

In this study, it was determined that 1905 individuals born between 1996 and 2007 and residing in Norway had CP. The review of the 780 hospital records of individuals recorded only in the NPR revealed that 464 (60%) had a correct ICD-10 CP diagnosis code, 302 (39%) did not have CP and 14 (2%) could not be classified. Therefore, the correctness of the NPR was 86% (302 of the 2231 individuals recorded with a diagnosis of CP in the NPR did not have CP) and the completeness 98% (43 of the 1905 individuals with CP were not recorded in the NPR). The correctness and completeness of the CPRN was 100% (all individuals were considered to have CP) and 76% (464 of the 1905 individuals were not registered in the CPRN), respectively. However, there was a steady increase in completeness of the CPRN up to 91% in 2006 to 2007.

There was acceptable agreement between the 464 ICD-10 CP diagnosis codes recorded only in the NPR and the SCPE CP subtypes classified by the reviewers during the hospital record review (*K*=0.75). Moreover, the distribution of the 464 SCPE CP subtypes classified by the reviewers did not differ from the overall distribution of SCPE CP subtypes registered in the CPRN (p=0.245).

4.1.2 Prevalence of CP

Taking into account the total number of individuals with a validated diagnosis of CP, the population-based prevalence was 2.5 (95% CI: 2.4–2.7) per 1000 residents, and the birth prevalence was 2.4 (95% CI: 2.3–2.6) per 1000 live births (118 were born abroad and 78 had postneonatally acquired CP). Relying solely on information recorded in the NPR, the population-based prevalence would have been 3.0 (95% CI 2.9–3.1) per 1000 residents. The corresponding birth prevalence would have been 2.2 (95% CI 2.1–2.4) per 1000 live births, relying upon summative reports provided by local pediatric habilitation centers to the CPRN (n=1679).

4.2 Article II: Decreasing prevalence and severity of cerebral palsy in Norway among children born 1999 to 2010 concomitant with improvements in perinatal health

4.2.1 Decrease in overall prevalence of CP

In-line with Article I, the average birth prevalence of CP remained 2.4 per 1000 live births (95% CI: 2.2 to 2.5) for children born between 1999 and 2010. However, there was a significant decline in prevalence from 2.6 per 1000 live births in 1999 to 1.9 in 2010. Assuming a linear model, the probability of a child born with CP was reduced by a factor of 0.97 per year ($p < 0.0001$). This corresponded to a 2.8% yearly reduction. The decrease remained nearly constant in the worst-case sensitivity analysis, where the probability of an individual born with CP was reduced by a factor of 0.98 per year, corresponding to a 2.2% yearly reduction ($p = 0.002$).

Update as of 31 December 2018: four children born between 2007 and 2010 were removed from the CPRN (diagnosis revised). Therefore, the number of children with CP born in Norway during the study years was reduced from 1664 to 1660.

4.2.2 Decrease in severity of CP

The decrease in the prevalence of CP was most evident in children with bilateral spastic CP, which was reduced from 1.3 per 1000 in 1999 to 0.7 in 2010 ($p < 0.0001$). The probability of a child being diagnosed with bilateral spastic CP was reduced by a factor of 0.95 per year ($p < 0.0001$). Assuming a linear model, this corresponded to a 4.6% yearly decrease. Within the bilateral spastic CP group, the prevalence of diplegia decreased significantly by a factor of 0.96 per year (4.2% yearly) ($p = 0.0009$) assuming a linear model, while quadriplegia had a slight non-linear upside down U-shape trend, with a decrease from birth year 2007 ($p = 0.0002$). Similar to quadriplegia, the prevalence of dyskinetic CP also changed in a non-linear upside down U-shape, with a decrease from birth year 2007 ($p = 0.0013$). Otherwise, the prevalence of unilateral spastic CP remained stable.

Concurrently with the reduction in the prevalence of more severe CP subtypes, the proportion of individuals with CP unable to walk (GMFCS levels IV-V) ($p = 0.013$), with epilepsy ($p < 0.0001$), intellectual disability ($p < 0.0001$) and with incomprehensible or no speech (Viking Speech Scale III-IV) ($p = 0.023$) also decreased. Yet, there were no significant changes over time in the proportion of children with CP who had impaired eating abilities ($p = 0.153$), vision ($p = 0.073$), or hearing ($p = 0.33$).

4.2.3 Improvements in perinatal health in the Norwegian population

During the same time, there were improvements in perinatal health in the entire Norwegian population. This included a decrease in the prevalence of preeclampsia, children born extremely or very/moderately preterm or as a multiple, as well as perinatal mortality. Despite a substantial increase in the prevalence of children born after AFT, the prevalence of multiple births born after AFT decreased. However, the prevalence of congenital anomalies increased during the study period. All of the above statistical analyses had a p-value < 0.0001, with the exception of multiple births with p = 0.017.

4.3 Article III: Comorbidities in cerebral palsy: a patient registry study

4.3.1 Overall disorder occurrence

Of the individuals with a validated diagnosis of CP in Norway born between 1996 and 2010, 95.0% were recorded with a minimum of one comorbidity, and 36.4% had at least one within all three main groups of medical, neurological and mental/behavioral. In comparison, 45.3% of the general population were recorded with the same disorders, while only 2.9% had a disorder within all three main groups.

All medical disorders were more common in individuals with CP compared with their peers. In addition, 60.9% were recorded with at least one neurological disorder and 53.8% with at least one mental/behavioral disorder. In comparison, 7.2% of the general population was recorded with the same neurological disorders and 14.2% mental/behavioral disorders. The most common medical disorders among individuals with CP were musculoskeletal system and connective tissue diseases affecting 49.8%, followed by diseases of the digestive system (39.1%) and congenital malformations (non-nervous system) (33.6%). In the general population, the occurrence of the same disorders was less than 12%. The dominating neurological disorder in individuals with CP was epilepsy, diagnosed in 39.0% compared with 1.2% in the general population. Intellectual disability was the most common mental/behavioral disorder, observed in 28.1% of individuals with CP compared with only 0.7% in the general population.

Individuals with CP had excess risks for the majority of medical, neurological and mental/behavioral disorders compared with the risks in the general population. This was most notable for the same medical disorders mentioned above (RD 16.7% to 40.0%), in addition to malnutrition and eating difficulties (RD 21.7%, 99% CI: 19.5% to 24.0%). The risks of epilepsy (RD:

37.8%, 99% CI: 35.2% to 40.5%) and neurological disorders – other (RD: 26.8%, 99% CI: 24.4% to 29.2%) in individuals with CP were also considerably higher than in the general population, along with the increased risk of intellectual disability (RD: 27.4%, 99% CI: 25.0% to 29.8%).

The excess risks for males and females with CP were similar when compared with the general population without CP.

4.3.2 Comorbidities among individuals with CP

The mean number of comorbidities in individuals with CP ranged from 3.6 (SD: 3.0) among those with spastic hemiplegic CP to 8.1 (SD 4.0) with spastic quadriplegic CP. Among all, 52% had at least one comorbidity within the three cocausal, complications and co-occurring comorbidity categories. Moreover, less than 20% had only one comorbidity solely within the cocausal (5%), complications (7%) or co-occurring (5%) categories. The majority of comorbidities within the medical group were categorized as either complications of the main CP diagnosis or coincidentally co-occurring with CP, while the most common within the neurological and mental/behavioral groups were cocausal, caused by the same injury to the developing brain.

There were no significant differences in risk between males with CP compared with females with CP.

5. DISCUSSION

5.1 Main findings

To accurately estimate prevalence of CP, it is important to combine population-based health registries and validate diagnosis codes on an individual basis. Although the NPR included nearly all individuals with CP born between 1996 and 2007, an additional 14% were recorded with an incorrect diagnosis of CP. In the CPRN, while all individuals were considered to be registered correctly with CP, it only included 76% of the CP population. However, after combining the total number of individuals with a validated diagnosis of CP in the CPRN and/or NPR, we were able to calculate more accurate prevalence estimates. The population-based prevalence was 2.5 per 1000 residents and the birth prevalence was 2.4 per 1000 live births.

There was a notable decline in the prevalence and severity of CP in Norway among children born between 1999 and 2010. The reduction was most pronounced for children with bilateral spastic CP, especially those with diplegia. However, there was also a trend towards a decrease in the prevalence of individuals with quadriplegic and dyskinetic CP from 2007 and onwards. At the same time, there was also a decrease in the proportion of individuals with CP and with severe gross motor impairments, epilepsy, intellectual disability, and with indistinct or no speech. An improvement in perinatal health in the general population also occurred during the study period including a decrease in the prevalence of children born preterm, mother with preeclampsia and multiples, as well as a decline in perinatal mortality.

Regardless, individuals with CP born during the study period had a considerably high burden of comorbidities. The majority (95%) had at least one mild-to-severe, transient-to-chronic comorbidity, and 36% had a minimum of one comorbidity within all three medical, neurological and mental/behavioral groups. The most common comorbidities within the neurological and mental/behavioral groups were most likely cocausal, caused by the same injury to the developing brain that caused CP. In the medical group, complications of the main CP diagnosis and co-occurring comorbidities, not caused by nor complications of CP, were most common. However, regardless of group, comorbidities regarded as co-occurring with CP occurred just as often as cocausal and complications.

5.2 Methodological considerations

In an observational study, random and systematic error can result in the study estimates to be different from the true value.[109] There are two main factors of random error that may influence the precision of a study's estimates: the methods in which the study participants were selected and the variables measured. Systematic error is also referred to as bias. Bias is defined as "any trend in the collection, analysis, interpretation, publication or review of data that can lead to conclusions that are systematically different from the truth."[110] As systematic error is reduced, a study becomes more valid. The concept of validity can be separated into internal and external validity. Internal validity refers to the source population, while external validity refers to the applicability of the results to other populations.[109] There are three main types of systematic error that may affect the internal validity of a study: selection bias, information bias and confounding.[109] Below is a description of each type of error, the study design and statistical methods used to minimize them, as well the applicability of the results to other populations.

5.2.1 Random error

Increasing the number of participants, or sample size, included in a study reduces random error and thereby increases precision of the study estimates. In all three articles, the entire Norwegian population (residents and live births) as well as the total number of individuals with a validated CP diagnosis were included in the sample sizes, thereby increasing the precision of the prevalence estimates and measures of effect.

Confidence intervals (CIs) also indicate the precision of study estimates. While wide CIs signify low precision, narrow CIs signify high precision. The 95% CIs relating to prevalence estimates in articles I and II were narrow, indicating that the estimates were not likely due to random error. In article III, 99% CIs were used due to multiple hypothesis testing (43 disorder categories). If we had used 95% CIs, or a level of 5%, the probability of falsely rejecting at least one true null hypothesis would have been much higher than 5% (familywise error rate (FWER)). Therefore, the FWER was controlled for by decreasing the significance level for each hypothesis test to a level of 1%, or 99% CI. Although 99% CIs are wider than 95% CIs, the influence of random error on the absolute measures of effect (risk differences) in this article were reduced due to a large sample size, as shown in the precision of the CIs.

In article II, while many of the p-values were low (< 0.05) for the trends in proportions of clinical characteristics, caution should be taken in the interpretation as "statistically significant." A p-value is not an absolute threshold, and does not show the magnitude of the effect.[111] For that reason, all actual numbers and corresponding proportions (a summary table) were also reported.

5.2.2 Systematic error

Selection bias

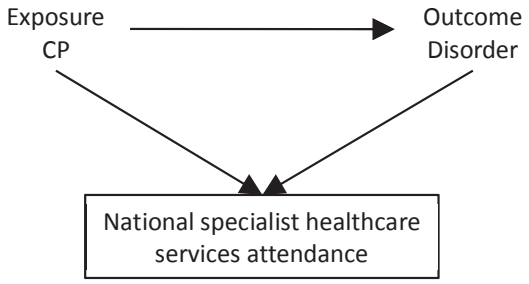
Selection bias can occur as the result of the method in which individuals are selected for inclusion in the study and the likelihood that they remain in the study. If the study population does not represent the intended target population, the study estimates may be distorted and thereby reducing internal validity.

In this thesis, the population-based cohorts are based on mandatory registration in the MBRN (all live births), NPR (all contact with specialist healthcare services) and SSB (all residents). In addition, a pediatrician validated all individuals with a CP diagnosis recorded in both the CPRN and the NPR at a minimum of 5 years old.

In article II, a potential source of selection bias in the population with CP was the possibility that several children would receive a diagnosis of CP after the age of 7-8, and therefore underestimate prevalence in the later years of the study (2009 to 2010). However, the results remained unchanged, as shown in the sensitivity analyses. In fact, four individuals with CP born 2007 to 2010 had their diagnosis removed after the study was completed. Furthermore, the results in article I showed that there was good agreement between the ICD-10 CP diagnosis codes recorded only the NPR compared with the classification assessed by the reviewers, as well as compared with the distribution of SCPE CP subtypes recorded in the CPRN. Therefore, it is unlikely that selection bias had an effect on the main results. In addition, while there were various degrees of missing data for each clinical characteristic variable, the decrease in the proportion of individuals with more severe impairments was most likely not a consequence of selection bias. Individuals with a more severe CP subtype or impairments are actually more likely to be classified and registered in the CPRN than individuals with less severe CP. Moreover, the prevalence of individuals with unilateral CP, who often have less severe impairments than individuals with a more severe CP subtype, remained stable. Therefore, an underreporting of either individuals with less severe or more severe CP subtypes most likely did not influence the results.

A bias in the reported absolute measures of effect (risk differences) in article III may have occurred due to the affect that both the exposure and disease had on the selection of individuals included in the study (Berkson's bias).[109, 112, 113] More specifically, individuals with CP had an increased chance of being recorded in the NPR with multiple disorders because they routinely attended the national specialist healthcare services compared with their peers in the general population without CP (Figure 2).

Figure 2: A directed acyclic graph illustrating Berkson's bias in article III.



Moreover, individuals who had less severe, transient disorders (e.g. respiratory infections) may be underdiagnosed in article III because they are often treated in the primary healthcare services or because one does not seek medical care for them.

On the other hand, expert knowledge should also play a role in the design and analysis of results in an observational study.[114] When conferring with pediatricians specializing in CP, they offer an alternative opinion to Berkson's bias that although individuals with CP regularly attend specialist care, secondary comorbidities (e.g. anxiety or depression) are often not recorded in the patient hospital record. This, due to the already extensive use of coding for the main diagnosis of CP and the treatment of motor impairments and the most common comorbidities.

Information bias

Information bias can occur during the data collection process due to the inaccurate recording of data about the study participants that can distort the true value of the study estimate. For categorical variables, misclassification of an exposure, outcome or confounder can be either differential or non-differential. Differential misclassification occurs when the misclassification of a variable is different among individuals with and without the disease, whereas non-differential misclassification occurs when the misclassification is the same among individuals regardless of

disease status.[115] A non-differential misclassification of a dichotomous variable effects the study estimate towards no association, or a null value. Conversely, a non-differential misclassification of a variable with more than two classifications, or a differential misclassification of a variable can effect a study estimate in either direction.[109, 115]

The misclassification of individuals with CP in articles I – III was substantially minimized due to the individual-level confirmation of each CP diagnosis code by an experienced pediatrician, using international guidelines.

In article II, the classification of clinical characteristics in individuals with CP is a potential source of non-differential information bias. However, clinical information have been consistently classified and recorded on the CPRN 5 Year Consultation Form by experienced pediatricians for over a decade using internationally validated measurement instruments, thereby reducing information bias.

The NPR data used in article III was collected for a purpose other than the aim of the study (secondary data), and thereby introduced an unknown degree of information bias related to the clinical care process. For example, inconsistencies in the coding of diagnoses in a patient's hospital record.[116] Furthermore, the risk differences in article III may be underestimated for disorders that are commonly recorded at a younger age due to missing data in the NPR before 2008. However, these are non-differential misclassifications that may be applied to both individuals in the cohort with and without CP. There was a potential misclassification bias within the main groups (medical, neurological and mental/behavioral) and comorbidity categories (cocausal, complications and co-occurring). Due to the unknown underlying cause of the disorders, a 100% correct classification was not possible. For example, several mental/behavioral disorders can be regarded as either cocausal, complications or co-occurring with CP. Therefore, caution is needed in the interpretation of the exact proportions within these categories. However, this limitation does not affect the main study estimates.

Confounding

A confounder is a variable that distorts the association between exposure and outcome, but are not in the causal pathway. In article III, sex was considered a potential confounder, influencing both CP as the exposure and each disorder category an outcome. A stratification analysis was

performed that showed virtually no difference between the sexes, therefore an effect of sex on the study estimates was unlikely.

5.2.3 External validity

External validity refers to the degree of which the study results can be generalized to other populations and at other times. The results presented in this thesis are representative of all individuals in Norway born over a fifteen-year period from 1996 to 2010. Individuals born before this period may not have had access to the advances in antenatal, obstetric and neonatal care, and those born after may have the advantage of even more advancements in healthcare.

A similar pooled prevalence estimate of 2.1 per 1000 live births was also reported in a systematic review of populations in Australia, Canada, China, Europe, and the United States.[38] In addition, declines in the prevalence of CP in individuals born during similar birth years have been recently reported in several areas of the United States, Denmark and Australia.[117-120] Even though the overall prevalence estimates and downward trends reported in articles I and II are similar to studies in high-income countries, there are limitations associated with differences in socioeconomic status, exposure to environmental factors and access to healthcare. For example, all mothers and children in Norway have access to obstetric and neonatal care, free of charge. However, Forthun et al. recently reported that lower parental education and mothers who did not have a partner during pregnancy increased the risk of CP in Denmark and Norway.[121] Even so, the impact of racial and socioeconomic disparities on the risk of CP play a lesser role in Norway than in other countries such as Australia, Canada, Taiwan, United Kingdom and United States.[117, 122-126]

It is also well documented that the prevalence and severity of CP is higher in low to middle-income countries in Africa, Eastern Europe, South America and South Asia than in high-income countries.[127-132] This is mainly due to the exposure to other types of risk factors (preventable) and lack of access to antenatal, obstetric and neonatal care. For example, in a recent study in Uganda, the main reason for the higher prevalence was attributed to postneonatally acquired CP caused by malaria.[127] Also, the trends in prevalence was opposite, where the prevalence of CP among younger children was higher than in older children due to the high mortality rate of those with a more severe CP subtype and associated impairments.[127]

5.3 Discussion of main findings

This thesis is the first to provide accurate prevalence estimates of CP in Norway, by combining and validating a national health registry and a medical quality registry. Correct and complete data was also crucial in the study of time trends, where, for the first time, we were able to document a significant decline in the prevalence and severity of CP. This, concomitantly with overall improvements in perinatal health in the general Norwegian population. On the other hand, this thesis also documented a substantially higher total burden of disease in the population with CP, regardless of subtype, than their peers in the general population. Surprisingly, this included comorbidities that are not directly associated with the injury to the developing brain, nor complications of the main CP diagnosis.

5.3.1 Completeness and correctness of CP diagnoses

The validation of all CP diagnosis codes in the Norwegian national specialist healthcare system is a milestone. It demonstrates the importance of combining data sources and the validation of individual-level diagnosis codes. It was not surprising that the NPR had nearly 100% completeness, because all individuals with CP in Norway have regular access to care. The 86% correctness was mainly attributed to clinicians, who are not directly responsible for this patient group, who misclassified and recorded an erroneous CP diagnosis in the patient's health record, of which are never removed. The correctness of the CPRN was considered 100%, due to registration by a pediatric specialist. While completeness was lower during the first years (1996 to 1998), it has increased to over 90% in the most recent years (2002 to 2010). This is mainly due to the time it takes to establish a CP register, i.e. data collection procedures to become common practice. In addition, the CPRN and the Cerebral Palsy Follow-Up Program of Norway introduced a common consent form in 2012. This, to improve the procedure of collecting informed consent from parents of children with CP.

No such national validation studies have been performed in Scandinavia. However, the Eastern Denmark CP Register was linked with the Danish National Patient Register in 1987 for individuals born 1979 to 1982. They found a correctness of only 51% in the Danish National Patient Register, while the Eastern Denmark CP register had a completeness of 85%.[133] A study performed in two counties in Sweden linked several data sources including the Swedish Population Register, a local CP register, the CP Follow-Up Program database and the Swedish National Patient Register, to report prevalence estimates and clinical characteristics of individuals with CP born between 1990

and 1997.[134] However, this study did not validate nor report the completeness and correctness of each data source. The ability to link well-established CP registries to several other national health registries is unique to Scandinavia. Although, one main difference is that the CPRN requires informed consent, while this is not the case in Denmark and Sweden.

A similar validation study by the Canadian Cerebral Palsy Registry was published directly after article I in 2017. Data from the Quebec CP Registry was combined with two health administration databases for individuals born between 1999 and 2002.[135] They reported a 66% completeness of the health administration databases, with a 59% correctness. However, the completeness and correctness of the Quebec CP registry was not reported. The authors mention a number of "presumed false-positives" in the health administration databases, but these were not validated, leading to the possibility that some individuals with CP are not recorded in the Quebec CP registry.[135]

Nonetheless, all of the aforementioned validation studies recognized the importance of combining data sources to ensure that accurate prevalence estimates of CP are reported over time.

5.3.2 Decrease in prevalence and severity of CP

This thesis demonstrated a decline in the prevalence and severity of CP in Norway. This finding may be attributed to improvements in antenatal, obstetric and neonatal care. The decrease in prevalence was most evident in children with bilateral spastic CP, specifically diplegia, who are often born preterm. It is well known that children born preterm are more likely to have neurological and developmental disorders.[136] The finding was also supported by an overall decrease in Norwegian children born preterm during the study period, which may be in part due to a reduction in the proportion of mothers with preeclampsia and with multiple births. However, the decrease in children born preterm only accounted for a small reduction in the number of children with CP born during this time. A reduction in children with quadriplegia (a form of bilateral spastic CP) and dyskinetic CP from 2007 and onwards may also have contributed to the decline in prevalence. Children with these CP subtypes are typically born at term with evidence of hypoxic ischemic encephalopathy, and therapeutic hypothermia treatment for this condition were introduced nationally in Norway in the mid-2000s. Congenital anomalies are also known to be more common in children with bilateral spastic CP, with more severe motor and associated impairments than children with CP without anomalies.[137] Therefore, a reduction in the proportion

of congenital anomalies may also explain the decrease in the spastic bilateral CP subtype. However, there was an increase in the proportion of children born with a congenital anomaly in Norway during the study period, although which type of congenital anomalies increased are unknown. Additionally, the stable prevalence of unilateral spastic CP during the study period support our main findings. Children with unilateral spastic CP are mainly born at term with a perinatal stroke, which is a cause that is currently difficult to predict and prevent.[138-140]

As previously discussed in the Background section, three SCPE studies reported a downward trend in the prevalence of CP in Europe in the 1980s to 1990s, albeit based on varying degrees of registry completeness. However, since article II was published, several new studies on the trends in prevalence of CP during the same period as this thesis have been reported by researchers in the United States, Australia, Sweden and Denmark.[18, 117-119] Using five administration databases, researchers in South Carolina reported a decline in the prevalence of CP from 3.6 per 1000 live births in children born 1996 to 2.1 in 2006.[117] Although this study is comparable to the Norwegian population with a similar number of live births per year, there were major weakness that could have an effect on their results. The study inclusion criteria was children recorded with a CP diagnosis code during their first 4 years of life. However, there is international consensus that a CP diagnosis should be confirmed at age 5 years.[27] This, because a CP diagnosis takes time to be confirmed. If given too early, this may lead to either an overestimation (i.e. preterm children with a transient condition) or underestimation (mild unilateral spastic CP not detected until a later age) in prevalence estimates.[27] In addition, the study included children with a progressive neurological disorder, although these children do not meet the definition of CP.[1]

In a 2018 study by the Australian Cerebral Palsy Register Group, a decline in the prevalence of CP in children born between 1995 and 2009 within each Australian state was found, and an overall decline in moderate to severe CP.[119] They based the severity of CP on similar GMFCS and cognition levels used in article II. The decline was attributed to fewer children born preterm and at term. This, despite the fact that there has been an increase in the proportion of children born preterm in Australia between 1991 and 2009.[141, 142] However, when comparing trends in prevalence between the state of Victoria and the Norwegian population, which had a similar number of total live births, the prevalence of CP in the Norwegian population was higher, with a less significant decrease (Table 8).

Table 8: Comparison of prevalence estimates of CP per 1000 live births in Victoria, Australia compared with the population of Norway.

	2001-2003	2004-2006	2007-2009
state of Victoria	2.0	1.7	1.4
Norway	2.5	2.5	2.1

There are two main limitations to this comparison. First, although the Victoria Cerebral Palsy Register is considered to have had population-based ascertainment, there is no mention of validation of CP diagnoses in this registry, and therefore an underestimation of prevalence is possible. In addition, information is lost and variations are underestimated in the Australian prevalence analyses due to the categorization of birth years into 3-birth year intervals. On the other hand, while perinatal mortality declined in Norway during this study period from 7.6 to 5.1 per 1000 live births, it remained stable in Australia at 10 per 1000 live births.[143] Therefore, the higher number of survivors in Norway may be associated with a higher prevalence of CP.

On a different note, the Australian Cerebral Palsy Register Group also called attention to variations in the prevalence of CP over time, as reported by the Western Australia Cerebral Palsy Register.[119] This variation can also be seen in articles from western Sweden, where the prevalence of CP has been consistently reported from 1954 to 2010. Figure 3 visualizes the large fluctuations in the prevalence of CP over time in western Sweden.[9-18]

Figure 3: Prevalence of CP per 1000 live births in western Sweden, for birth years 1954 to 2010.[18*]

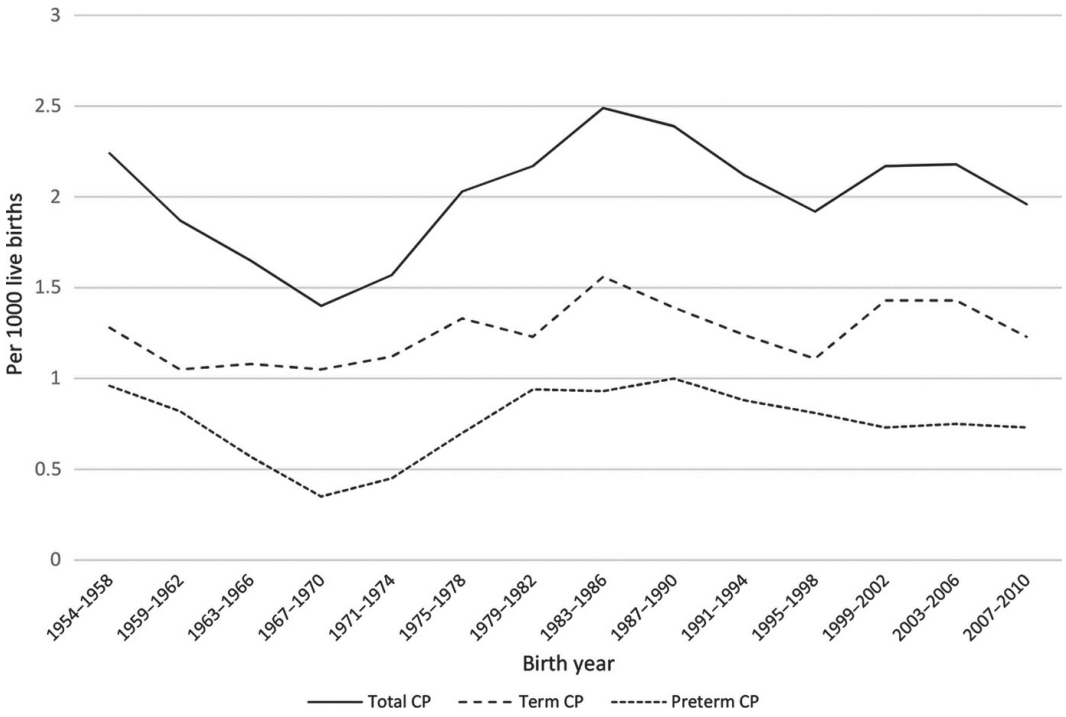


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Table 9 describes possible explanations for each large fluctuation in the prevalence of CP in children born 1970 to 2010 in western Sweden.

Table 9: Possible explanations for the fluctuations in the prevalence of CP in western Sweden for birth years 1970 to 2010.

Birth years	Explanation
1970 to 1986	The increase in prevalence of CP was the result of an increase in the survival of children born preterm.[10, 12]
1987 to 1998	The decline was attributed to a decrease in the prevalence of CP among children born preterm and term. In the latter years, the decrease was mainly in children born very preterm with diplegia. This was explained by improvements in obstetric and neonatal care, along with a reduction in perinatal mortality that resulted in healthier children (without CP).[13-15]
1999 to 2002	The slight increase in prevalence was mainly due to an increase in children with CP born at term. This was supported by an increase in children with dyskinetic CP (mainly born at term with hypoxic ischemic encephalopathy). At the same time, there was a continued decrease in children with CP born preterm, mainly children with bilateral spastic CP, which may be a result of improvements in antenatal, obstetric and neonatal care.[16]
2003 to 2006	Prevalence of CP remained stable during this time. However, there was an increase in children with unilateral CP, as well as children born extremely preterm.[17]
2007 to 2010	A non-significant decrease in prevalence was explained by a slight decrease in children born at term, mainly with dyskinetic CP. This was possibly explained by improvements in obstetric care during delivery.[18]

Similar to the Norwegian and western Swedish populations, the Danish Cerebral Palsy Registry also reported a decline in the prevalence of CP in Denmark, attributed to a decrease in children born at term with bilateral spastic CP, between 1999 and 2007.[118] This was mainly explained by improvements in obstetric care (e.g. a reduction in mothers with preeclampsia) and prenatal care (e.g. fewer children with CP born with hyperbilirubinemia).[118]

In contrast to the decrease in severity of CP in Australia and Scandinavia, the Canadian Cerebral Palsy Registry reported a stable distribution of CP subtypes and clinical characteristics in children born between 1999 and 2010 in Quebec, Canada.[144] This may be partially explained by the unchanged proportion of children born preterm in Canada during the same period, as well as a stable rate in perinatal mortality, even though multiple births were on the rise.[145-147] The Canadian

researchers concluded that a non-ability to reduce the prevalence or severity of CP was due to genetic and antenatal risk factors that cannot be prevented.[144]

Although there was a significant decrease in the prevalence and severity of CP in Norway during the study period, concomitant with improvements in perinatal health, caution should be taken in the interpretation that the trends will either stabilize or continue to decline. It is important to take into account that the results may be a result of ongoing fluctuations.

5.3.3 Comorbidities and CP

This is the first national administration registry study to include a comprehensive evaluation of the occurrence of mild-to-severe and transient-to-chronic comorbidities for individuals with CP. As expected, we found that the higher burden of disease in individuals with CP compared with their peers was mainly explained by the increased risk for comorbidities directly caused by the injury to the developing brain (cocausal) and complications of the main CP condition. However, surprisingly the risks for several co-occurring comorbidities, not intuitively related to CP, were also more common in individuals with CP compared with the risks in the general population. Although, the etiology is unknown for some comorbidities classified as co-occurring. The possibility exists that the injury to the developing brain and/or complications of CP may have directly or indirectly played a role. For example, the increased occurrence of circulatory system diseases might be reasonable because it may be related to reduced physical activity, while the higher prevalence of metabolic and immune disorders are not as evident. Additionally, some of the co-occurring comorbidities may have had a common cause, or are complications that are not apparent in registry-based data.

Many CP-registries and smaller hospital-based studies have reported an increased risk for the most common comorbidities associated with CP, such as epilepsy, intellectual disability, communication and eating difficulties, as well as visual and hearing impairments.[37, 144, 148-151] However, comparisons to our results are impractical due to the various study designs, such as study population inclusion criteria, sample size, classification of comorbidities, and a lack of comparison to a control group.

6. CLINICAL IMPLICATIONS

The aim of this thesis was to provide an accurate, up-to-date status of the CP population in Norway using high quality data from the multiple national health registries. The current decrease in the prevalence and severity of CP demonstrates the clinical significance of improved antenatal, obstetric and neonatal care that has led to reduced neonatal morbidity. On the other hand, individuals with CP have a much higher burden of multiple comorbidities compared with their peers. This provides healthcare professionals, policy-makers and individuals with CP and their families with important information on the evolving causes, clinical manifestations and treatments of CP. This, at a time when early detection of CP has been shown to be essential in the initiation of early interventions that can optimize motor abilities and minimize or prevent comorbidities.[21]

7. FURTHER STUDIES

Further studies are needed to continue to monitor the prevalence and severity of CP in Norway. Additional studies should also be conducted to determine the specific factors behind the current decrease by combining data in the CPRN with other national health and medical quality registries. For example, by linking the CPRN to the Norwegian Neonatal Network database, it would be possible to monitor the effect of therapeutic hypothermia for children born at term who experience hypoxic ischemic encephalopathy 2007 and onwards.[152] Due to the small number of children at risk of hypoxic ischemic encephalopathy, the statistical power of such a study would be greatly increased through international collaboration, combining data with other registries around the world.

Lastly, the studies in this thesis did not include a data set that combined clinical data in the CPRN with the MBRN. Such a combined data set would provide the opportunity to describe trends in CP subgroups, e.g. per gestational age and birth weight. This would allow for better comparisons with studies performed in Scandinavia, Australia, Canada and the United States.

8. CONCLUSION

The overall prevalence of CP for individuals born between 1996 and 2010 in Norway is 2.4 per 1000 births. There was a downward trend in the prevalence of CP to 1.9 per 1000 live births in 2010. This was mainly attributed to a decrease in the prevalence of bilateral spastic CP. There was also a decrease in the proportion of individuals with CP and gross motor function impairments, epilepsy, intellectual disability and speech impairments. This may be explained by improvements in antenatal, obstetric and neonatal care. Nonetheless, individuals with CP continue to have a high burden of a wide range of comorbidities. Thus, early identification of motor impairments and comorbidities, together with the initiation of appropriate interventions, are necessary to prevent or minimize the impact they may have on participation and quality of life.

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APPENDIX I

Disorder categories based on International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10) diagnosis codes

Disorder category	ICD-10 codes included	ICD-10 codes excluded
Medical disorders		
Intestinal infectious diseases	A00-A09	
Malignant neoplasms	Block C	C70-C72 CNS malignant neoplasms
Benign neoplasms	D00-D48	D32-D34 Benign neoplasm of meninges, brain and other parts of central nervous system D42-D43 Neoplasm of uncertain or known behavior of meninges, brain and central nervous system
Blood disorders	D50-D77	
Immune disorders	D80-D89	
Endocrine disorders	E00 E35	
Malnutrition and eating difficulties	E40-E46 R13 R63-R64	
Nutritional deficiencies	E50-E64	
Obesity	E65-E68	
Metabolic disorders	E70-E90	E73 Lactose intolerance E86-E87 Disorders of fluid, electrolyte or acid-base balance E90 Nutritional disorders
Hearing impairment including deafness	H90-H91	
Visual impairment including blindness	H54	
Circulatory system diseases	Block I	I60-I69 Cerebrovascular diseases I80 Phlebitis and thrombophlebitis I83-I99 Edema
Respiratory infections (acute)	J00-J22	
Respiratory diseases	J30-J47 J95-J99	
Digestive system diseases	Block K	
Skin and subcutaneous tissue diseases	Block L	
Musculoskeletal system and connective tissue diseases	Block M	M00-M03 Infectious arthropathies M41 Scoliosis M60 Myositis M65 Synovitis and tenosynovitis M86 Osteomyelitis
Scoliosis	M41	
Urinary tract disorders	N00-N39	
Genital disorders	N40-N99	N41 Inflammatory diseases of prostate
Congenital malformations (excluding nervous system)	Block Q	Q00-Q07 Congenital malformations of nervous system Q90-Q99 Chromosomal abnormalities
Chromosomal abnormalities	Q90-Q99	
Dislocation of hip	S73.0	

Neurological disorders		
CNS infections and inflammatory diseases	A39 A80-A89 B003-B004 B010-B011 B020-B022 B050-B051 G00-G09	
CNS neoplasms (malignant and benign)	C70-C72 D32-D33 D42-D43	
Sleep disorders	F51 G47	
Epilepsy	G40-G41	
Headache disorders	G43-G44 R51	
Cerebrovascular diseases	G45-G46 I60-I69	
Diseases of the nervous system - other	Block G	G00-G09 Inflammatory diseases of the central nervous system G40-G47 Epilepsy, headache, cerebrovascular and sleep disorders G80-G83 Cerebral palsy and other paralytic syndromes
Congenital malformations of the nervous system	Q00-Q07	
Nervous and musculoskeletal system symptoms	R25-R29	
Mental/behavioral disorders		
Depressive episode(s)	F32-F33	
Anxiety disorders	F40-F41	
Obsessive-compulsive disorder	F42	
Eating disorders	F50	
Intellectual disability	F70-F79	
Psychological development disorders	F80-F89	F84 Autism
Autism	F84	
ADHD	F90	
Behavioral and emotional disorders	F91-F98	
Psychiatric disorders - other	Block F	F30-F33 Manic, bipolar and depressive episodes F40-F42 Anxiety and OCD F50-F53 Eating, sleep and puerperal mental disorders F70-F99 Intellectual disability, disorders of psychological development, behavioral, emotional and unspecified

APPENDIX II

Comorbid disorder categories based on International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10) diagnosis codes, and as described by Brown and Eunson[34]

Comorbid disorder category	ICD-10 codes included	ICD-10 codes excluded
Cocausal		
Intellectual disability	F70-F79	
Psychological development disorders	F80-F89	F84 Autism
Autism	F84	
ADHD	F90	
Behavioral and emotional disorders	F91-F98	
Epilepsy	G40-G41	
Hearing impairment including deafness	H90-H91	
Visual impairment including blindness	H54	
Congenital malformations of the nervous system	Q00-Q07	
Chromosomal abnormalities	Q90-Q99	
Nervous and musculoskeletal system symptoms	R25-R29	
Complication		
Blood disorders	D50-D77	
Malnutrition and eating difficulties	E40-E46 R13 R63-R64	
Nutritional deficiencies	E50-E64	
Obesity	E65-E68	
Sleep disorders	F51 G47	
Headache disorders	G43-G44 R51	
Respiratory infections (acute)	J00-J22	
Digestive system diseases	Block K	
Musculoskeletal system and connective tissue diseases	Block M	M00-M03 Infectious arthropathies M41 Scoliosis M60 Myositis M65 Synovitis and tenosynovitis M86 Osteomyelitis
Scoliosis	M41	
Dislocation of hip	S73.0	
Co-occurring		
Intestinal infectious diseases	A00-A09	
CNS infections and inflammatory diseases	A39 A80-A89 B003-B004 B010-B011 B020-B022 B050-B051 G00-G09	

CNS neoplasms (malignant and benign)	C70-C72 D32-D33 D42-D43	
Malignant neoplasms	Block C	C70-C72 CNS malignant neoplasms
Benign neoplasms	D00-D48	D32-D34 Benign neoplasm of meninges, brain and other parts of central nervous system D42-D43 Neoplasm of uncertain or known behavior of meninges, brain and central nervous system
Immune disorders	D80-D89	
Endocrine disorders	E00 E35	
Metabolic disorders	E70-E90	E73 Lactose intolerance E86-E87 Disorders of fluid, electrolyte or acid-base balance E90 Nutritional disorders
Depressive episode(s)	F32-F33	
Anxiety disorders	F40-F41	
Obsessive-compulsive disorder	F42	
Eating disorders	F50	
Psychiatric disorders - other	Block F	F30-F33 Manic, bipolar and depressive episodes F40-F42 Anxiety and OCD F50-F53 Eating, sleep and puerperal mental disorders F70-F99 Intellectual disability, disorders of psychological development, behavioral, emotional and unspecified
Cerebrovascular diseases	G45-G46 I60-I69	
Diseases of the nervous system - other	Block G	G00-G09 Inflammatory diseases of the central nervous system G40-G47 Epilepsy, headache, cerebrovascular and sleep disorders G80-G83 Cerebral palsy and other paralytic syndromes
Circulatory system diseases	Block I	I60-I69 Cerebrovascular diseases I80 Phlebitis and thrombophlebitis I83-I99 Edema
Respiratory diseases	J30-J47 J95-J99	
Skin and subcutaneous tissue diseases	Block L	
Urinary tract disorders	N00-N39	
Genital disorders	N40-N99	N41 Inflammatory diseases of prostate
Congenital malformations (excluding nervous system)	Block Q	Q00-Q07 Congenital malformations of nervous system Q90-Q99 Chromosomal abnormalities

Article I

Completeness and correctness of cerebral palsy diagnoses in two health registers: implications for estimating prevalence

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ABBREVIATIONS

CPRN	Cerebral Palsy Register of Norway
ICD-10	International Statistical Classification of Diseases and Related Health Problems 10th revision
NPR	Norwegian Patient Register
SCPE	Surveillance of Cerebral Palsy in Europe

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AIM To assess completeness and correctness of cerebral palsy (CP) diagnoses in the Cerebral Palsy Register of Norway (CPRN) and the Norwegian Patient Register (NPR), and to estimate CP prevalence.

METHOD Among 747 883 Norwegian residents born from 1996 to 2007, 2231 had a diagnosis of CP in the NPR while 1441 were registered in the CPRN. Children registered in the CPRN were considered to have a valid CP diagnosis. For those with a diagnosis of CP only in the NPR, two paediatricians reviewed the hospital records. The prevalence rate of CP with 95% confidence intervals (CI) was calculated on the basis of the combined data sets.

RESULTS One thousand three hundred and ninety-eight children were registered with a diagnosis of CP in both registers, 43 children were only registered in the CPRN, and 824 only in the NPR. The review of hospital records revealed that 464 (59.5%) had CP. Thus, the NPR was 98% complete, and for 86% the diagnosis was correct. The completeness of the CPRN was 76%, while the diagnosis was considered correct for all children (100%). The resulting prevalence of CP was 2.5 (95% CI 2.4–2.7) per 1000.

INTERPRETATION To gain accurate estimates of prevalence rates of CP, it is essential to combine data sources and to validate register data.

The birth prevalence of cerebral palsy (CP) is considered to be a potential indicator of the quality of perinatal care,[1,2] while population-based prevalence rates provide important information for health care providers and society. In recently published Norwegian studies, the prevalence of CP has varied significantly.[3–5] A study using information from the Norwegian Social Insurance Scheme reported a birth prevalence of 1.8 per 1000 among individuals born from 1967 to 2002.[3] Surén et al. found a population-based prevalence of 3.0 per 1000 Norwegian residents born from 1999 to 2010, using information extracted from the Norwegian Patient Register (NPR).[4] The NPR is a compulsory national administrative health register, established in 1997. The NPR includes person-identifiable data from 2008 onwards. It contains structured data on all patients treated by the national specialist health services, including individual-level demographic, administrative, and clinical data.[6] In a third study, using information collected by the Cerebral Palsy Register of Norway (CPRN), Andersen et al. found the birth prevalence of CP to be 2.1 per 1000 for children born from 1996 to 1998.[5] The CPRN is a consent-based national medical quality register established in 2006. This register contains clinical data on individual children born from 1996 onwards. Dedicated specialists from each of the 21 habilitation centres record data at three points in time: at diagnosis, and at ages 5 and 15 to 17 years. A paediatrician/paediatric neurologist is responsible for determining the CP diagnosis using the 'Decision tree for cerebral palsy' and 'Classification tree of CP subtypes' guidelines developed by the Surveillance of Cerebral Palsy in Europe (SCPE).[7] The age recommended for confirmation of the diagnosis is 5 years old.[7] All children with CP in Norway have the right to be diagnosed and treated at one of the habilitation centres.[8] Finally, the CPRN receives summative, anonymized information on the total number of patients with CP per birth year from each habilitation centre. This information is used to estimate the prevalence of CP in Norway.

Variation in the completeness and correctness of data sources used to identify children with CP is most probably a major cause of variability in prevalence. For instance, using information from the Norwegian Social Insurance Scheme will probably underestimate the prevalence, because not all children with CP receive social benefits.

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Indeed, in a previous study, we found that about 60% of children in the CPRN born from 1996 to 2003 were recorded with CP in the Norwegian Social Insurance Scheme.[9] Furthermore, it is reasonable to assume that the prevalence reported by the CPRN, which relies upon summative reports provided by local paediatric habilitation centres, may be underestimated. Possibly, some CP subtypes could be more consistently reported to the CPRN since registration requires an informed consent, increasing the risk for selection bias.[10] Finally, the prevalence of CP based upon information in the NPR may be overestimated because, in regular hospital care, specialists other than paediatricians/paediatric neurologists might record a CP diagnosis code in the hospital record without being aware of the strict definition of the disorder, or a diagnosis code may be set on suspicion.

A difference in the population-based prevalence of 1 per 1000 (i.e. 2 per 1000 vs 3 per 1000) represents significant differences in absolute numbers of people in need of special care. In Norway, with a population of 5 million, the estimated number varies from 10 000 to 15 000 individuals on the basis of these prevalences. Moreover, imprecise estimates of prevalence may lead to inaccurate conclusions about the assessment of perinatal care, international comparisons, and the study of time trends.

Thus, the aim of this study was to assess the completeness and correctness of the CPRN and the NPR, and to use the combined information to obtain an accurate estimate of the prevalence of CP.

What this paper adds

- Administrative health registers are likely to overestimate the prevalence of cerebral palsy (CP).
- Medical quality consent-based registers are likely to underestimate the prevalence of CP.
- Multiple sources and case review are needed for more accurate prevalence estimates.
- Prevalence of CP in Norway is 2.4 per 1000 live births and 2.5 per 1000 residents born from 1996 to 2007.

METHOD

Study population and design

This register-based study included 747 883 Norwegian residents born from 1996 to 2007 and 699 927 live births in Norway during the same years. In all, 2231 children had a main or secondary G80.0 to G80.9 (G80) diagnosis code from the International Statistical Classification of Diseases and Related Health Problems 10th revision (ICD-10) of 'Cerebral palsy' in the NPR, while 1441 children were recorded with an ICD-10 G80 and SCPE CP subtype[7] in the CPRN. The registers were linked using the 11-digit personal identification number unique to each Norwegian resident. The diagnosis of CP was considered correct for the 1398 children in both registers, and for the 43 children only in the CPRN. This decision was based upon the detailed information recorded in the CPRN. A total of 824 children with a CP diagnosis code in the NPR, but not in the CPRN, were eligible for hospital record review.

Assessment of the correctness of the NPR

To validate the CP diagnosis codes of the 824 children only in the NPR, hospital records were reviewed by two experienced paediatric neurologists according to a predetermined standardized registration form. Nineteen children from rural hospitals were excluded for practical reasons, and 25 children were not found in the hospital records. Thus, 780 (95%) hospital records were reviewed. If the diagnosis of CP was assessed as correct, the reviewer recorded the appropriate ICD-10 G80 code, and the date when a paediatrician had confirmed the diagnosis. If the diagnosis code was assessed as incorrect, the reviewer noted the most likely correct ICD-10 code, whether the child had suffered a postneonatal (≥28d after birth) brain trauma, and, if so, at what age.

Statistical analysis

In line with Hogan and Wagner's description of the validity of health registers,[11] we defined register completeness as the proportion of children with a true CP diagnosis code in the register, according to the combined and validated data set (i.e. equivalent to sensitivity in studies of diagnostic tests). Register correctness was defined as the proportion of children with a CP diagnosis code in the register that were true cases of CP, according to the same data set (i.e. equivalent to positive predictive value in studies of diagnostic tests). The two terms are illustrated in Table I. The use of both completeness and correctness is necessary to provide an accurate measure of data validity in a register.[11]

The reliability of ICD-10 G80 codes only in the NPR was evaluated by comparing them with the classification of subtypes determined by the reviewers using Cohen's unweighted kappa, where a kappa value of 1.0 indicates complete agreement. Kappa values were interpreted as less than 0.40 indicating poor, 0.40 to 0.75 intermediate to good, and greater than 0.75 excellent agreement.[12]

Table I: Calculation of data accuracy in a health register using completeness and correctness

	True health status in combined and validated register data set[a]		
	CP	No CP	Total
Registration present	*a*	*b*	*a*+*b*
Registration absent	*c*	*d*	*c*+*d*
Total	*a*+*c*	*b*+*d*	
	Completeness=*a*/(*a*+*c*)	Correctness=*a*/(*a*+*b*)	

Using the combined and validated data set, completeness was used to calculate the proportion of children with cerebral palsy (CP) that should have been registered were present in the register, and correctness was used to assess the proportion of children present in the register that were regarded as true cases of cerebral palsy.
[a]The combined and validated data set includes all children registered in the CPRN, and children registered with a CP diagnosis code only in the NPR.

To assess selection bias in the CPRN, χ^2 statistics were used to compare the different CP subtypes among children with CP only in the NPR with the proportion of children registered in the CPRN. A *p*-value below 0.050 was considered statistically significant.

The population-based prevalence of CP was calculated by dividing the number of children having a confirmed diagnosis by the number of children residing in Norway.[13] Birth prevalence was calculated by subtracting the number of children either born abroad or with a postneonatal cause from the number of children with a confirmed diagnosis, divided by the number of live births.[14] Ninety-five percent confidence intervals (95% CI) were calculated according to Altman et al.[15]

Statistics Norway[13] provided population data, and the Medical Birth Registry of Norway[14] provided live birth data.

Statistical analyses were performed using VasserStats (www.vassarstats.net; Poughkeepsie, NY).

Ethics

The validation of the CP diagnosis codes in the NPR was conducted under Norwegian Patient Register Regulation §2–4, and did not require patient consent. The NPR linked the two registers, and the CPRN only had access to anonymized, aggregated results. The CPRN is approved by The Norwegian Directorate of Health and The Norwegian Data Protection Authority (08/01067-9/EOL). This study was covered by the CPRN consent form, and did not require specific ethical approval.

RESULTS

Correctness of the NPR

Review of the 780 hospital records of children only in the NPR revealed that 464 (60%) had a correct CP diagnosis code, whereas 302 (39%) did not have CP and 14 (2%) could not be classified.[16] In 412 (89%) of the 464 children with a correct CP diagnosis, the code had been determined by a paediatrician/paediatric neurologist. Adding the 464 children with a confirmed diagnosis to the number of children in both registers (n=1398) and to the number of children only in the CPRN (n=43) resulted in 1905 children with CP. Of the 2231 children with a diagnosis of CP in the NPR, 302 did not have CP, suggesting a correctness of 86%. Regarding CP subtypes, there was acceptable agreement between the ICD-10 codes only in the NPR, and the subtypes classified by the reviewers (κ=0.75) (Table SI, online supporting information).

For the 302 children with an incorrect CP diagnosis code in the NPR, the most common ICD-10 diagnoses were epilepsy (G40), specific developmental disorder of motor function (F82), unspecified mental retardation (F79), and other disorders of brain (G93) (Table SII, online supporting information). Furthermore, the reviewers noted that 43 (14%) children with incorrect CP diagnosis codes were recorded with a postneonatal cause, acquired at a mean age of 5 years 2 months.

Correctness of the CPRN

The detailed information provided by paediatricians working in habilitation centres indicates that a diagnosis of CP in the CPRN is correct. However, from time to time, the CP subtype may be revised, even in children who are more than 5 years old. Also, in a very few cases, if a diagnosis of CP is later considered to be incorrect, the information for this child is removed from the register. Thus, at any given point in time, the register may contain a few cases of incorrectly diagnosed CP. However, for all practical purposes, the correctness of the CPRN is considered to be 100%. Regarding potential selection bias, Table II shows that the distribution of CP subtypes did not differ between the 464 children assessed by the reviewers to have CP only in the NPR and those recorded in the CPRN.

Completeness of the two registers

Only 43 of the 1905 children with CP were not in the NPR with this diagnosis, indicating a completeness of 98% for the NPR. Among these 43 children, over 60% were born from 1996 to 2001, had unilateral CP, and were registered in the CPRN before 2008, which was the first year NPR held individual-level data. One of the 43 children was deceased before 2008.

In the CPRN, 1441 children were registered with detailed information, suggesting a completeness of 76%. Yet, there was a steady increase in completeness from 61% in 1996 to 1998, to 91% in 2006 to 2007.

Implications for estimating prevalence

A total of 1905 children had a confirmed diagnosis of CP as of 1 January 2013, corresponding to a population-based prevalence of 2.5 (95% CI 2.4–2.7) per 1000 among

Table II: Distribution of cerebral palsy subtypes according to the Surveillance of Cerebral Palsy in Europe (SCPE) and International Statistical Classification of Diseases and Related Health Problems 10th revision (ICD-10) among children registered only in the Norwegian Patient Register (NPR) and validated through hospital record review, compared with children registered in the Cerebral Palsy Register of Norway (CPRN)[16]

			Only in NPR		CPRN	
SCPE[a]		ICD-10	*n*	%	*n*	%
Spastic	Unilateral	G80.2 hemiplegic	172	37.1	574	39.8
	Bilateral	G80.1 diplegic	152	32.8	443	30.7
		G80.0 quadriplegic	82	17.7	217	15.1
Dyskinetic		G80.3 dystonic	24	5.2	95	6.6
		G80.3 athetoid	3	0.6	10	0.7
Ataxic		G80.4 ataxic	22	4.7	66	4.6
Other		G80.8 other	5	1.1	35	2.4
		G80.9 unspecified	4	0.9	1	0.1
Total			464	100.0	1441	100.0

[a]p=0.245 for comparison of the distributions between the SCPE subtypes (i.e. spastic unilateral, spastic bilateral, dyskinetic, ataxic, and other) only in the NPR with the proportions in the CPRN.

Norwegian residents born from 1996 to 2007. Relying upon the information provided only by the NPR, the prevalence rate would have been 3.0 (95% CI 2.9–3.1) per 1000 residents, whereas relying only upon the summative information in the CPRN (*n*=1679), the corresponding prevalence would have been 2.2 (95% CI 2.1–2.4).

Owing to the administrative nature of the NPR, data from this registry could not be used to calculate the birth prevalence of CP. Nor were the summative reports collected by the CPRN useful for this purpose. Using only detailed information on children registered in the CPRN (*n*=118 born abroad; *n*=78 postneonatal cause) and the number of children with a confirmed diagnosis of CP in this study, the corresponding birth prevalence was 2.4 (95% CI 2.3–2.6) per 1000 among the 699 927 live births in Norway from 1996 to 2007.

DISCUSSION

In this study, we found that almost all children with CP were registered with a G80 diagnosis in the NPR, suggesting nearly 100% completeness. Yet, 10% to 15% of the children in this register with this diagnosis code were incorrect. While completeness of the CPRN was under 80% for the entire study period, it reached 90% for children born in the last two years of the birth cohort. In addition, the CPRN was considered 100% correct, and the results did not suggest selection bias of specific CP subtypes. Finally, the results show the importance of combining data sources to obtain more accurate prevalence estimates.

Strengths and limitations

A strength of this study was that it was population-based, covering children with a diagnosis of CP in two national health registers. Moreover, a paediatrician/paediatric neurologist confirmed the CP diagnoses. This allowed us to gain an understanding of the mechanisms behind correctly and incorrectly classified CP diagnoses. Combining information from the two registers made it more likely that all Norwegian children with CP were included, although it cannot be completely excluded that some children with mild CP may not have been recorded in either register. The lower completeness of the CPRN has been explained by work overload among paediatricians.[17] Indeed, 98% of parents invited provided informed consent.[5] It is thus reassuring that the completeness of the CPRN increased significantly during later years, and that the comparison of CP subtypes does not indicate selection bias. Regarding the NPR, our results suggest that some of the older children (i.e. born from 1996 to 2001) with mild CP were not registered with a diagnosis of CP. This was probably because the register did not include person-identifiable data before 2008. It seems likely that the completeness of CP diagnosis codes in the NPR will approach 100% in the future. For the correctness of the diagnosis in the CPRN, there is also a theoretical, albeit small, possibility that the diagnoses in some cases were revised, even when the children were more than 5 years old.

Comparison with other studies

The prevalence rates and the distribution of CP subtypes reported in this study are similar to those reported by other CP registers. Although this is the first Scandinavian study to cover an entire country, similar studies based on CP registers in Denmark and Sweden have been performed for smaller geographical areas. These studies also identified children with CP by using information from national patient registers, followed by medical record review.[18,19] The Cerebral Palsy Registry in eastern Denmark reported a birth prevalence of 2.1 per 1000 for children born from 1995 to 1998.[20] Using multiple sources, a study from southern Sweden reported a population-based prevalence of 2.7 per 1000 residents and a birth prevalence of 2.4 per 1000 live births for children born from 1990 to 1997.[19] Furthermore, both registers reported a similar distribution of CP subtypes as in our study. The National Surveillance of Cerebral Palsy in Portugal reported a birth prevalence of 1.9 per 1000 live births in 2006, 1.4 to 1.7 for birth years 2007 to 2010, and less than 1 for later years, with 84% spasticity (Cadete A, personal communication 2015). In a study in the USA, Maenner et al. estimated the prevalence of CP by comparing two different surveys based on parental reporting to identify children with CP.[21] They reported population-based prevalence rates of 2.6 and 2.9 per 1000 for 2- to 17-year-olds living in the USA from 2011 to 2013. Lastly, compared with Maenner et al., Kirby et al. reported a slightly higher prevalence of CP of 3.3 per 1000 among 8-year-olds in four US areas in 2006.[22] However, they reported that 81% had spastic CP, which is similar to CP subtype rates in Scandinavia and Portugal.

Interpretation of results

The high completeness of the NPR is reasonable, since it is recommended in Norway that children with CP should be seen regularly by specialized health care services. Because specialists other than paediatricians are allowed to record the diagnosis, it is not surprising that some children are incorrectly registered with CP in the NPR. In addition, diagnoses registered in the NPR will not be changed if they are disproved later. Taking these factors into consideration, the proportion of children with an incorrect CP diagnosis code in the NPR seems acceptable.

In the CPRN, the diagnosis can be considered to be correct in close to 100% of the cases, because it is based on strict criteria and is confirmed by a paediatrician/paediatric neurologist when the children are 5 years old. Nonetheless, it is possible that at any point in time there are a few children with an erroneous CP diagnosis in the CPRN. Our experience suggests that this misclassification is unlikely to be present in more than two cases per birth year, and these cases are removed from the CPRN. Thus, for all practical purposes, we consider the diagnosis of CP to be correct in this register. In contrast, the completeness in this register was low for the total birth cohort. We have earlier argued that we consider selection bias of specific

CP subtypes in the register to be less likely. This is supported by the findings in the present study. The improvement in completeness during the later years may have two causes. First, it may take time before data submission to a register is included on a routine basis in the clinic. Second, the process of registration has improved in recent years owing to close cooperation with the Norwegian CP Follow-Up Programme introduced nationally in 2006. This includes a common consent form, allowing the exchange of information. We therefore expect that the completeness of the CPRN will stabilize at or above the high level observed for the later period in the present study.

The differences in completeness and correctness of the two registers affect estimates of prevalence. Multiple sources and critical review of single cases are needed to obtain estimates that are more accurate.

CONCLUSION

In this study, the completeness of children with a CP diagnosis code was excellent and correctness was good in the NPR, whereas in the CPRN completeness was good and correctness excellent.

By combining the information in the two registers and scrutinizing individual cases, we were able to estimate a population-based prevalence of CP of 2.5 per 1000 Norwegian residents born from 1996 to 2007.

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SUPPORTING INFORMATION

The following additional material may be found online:

Table SI: Cross tabulation of the classification of International Statistical Classification of Diseases and Related Health Problems 10th revision (ICD-10) G80 codes of children registered only in the Norwegian Patient Register (NPR) and classified by two paediatric neurologists during a hospital record review.

Table SII: Top 10 International Statistical Classification of Diseases and Related Health Problems 10th revision (ICD-10) diagnosis codes for the 302 children registered only in the Norwegian Patient Register (NPR) and assessed not to have CP by two paediatric neurologists during a hospital record review.

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Table S1: Cross tabulation of the classification of ICD-10 G80 codes of children registered only in the Norwegian Patient Register (NPR) and classified by two pediatric neurologists during a hospital record review [a].

		NPR							
	ICD-10	G80.0	G80.1	G80.2	G80.3	G80.4	G80.8	G80.9	**Reviewer Total**
Reviewer	G80.0	54	9	1	2	0	5	11	**82**
	G80.1	15	119	10	0	0	0	8	**152**
	G80.2	11	13	124	0	0	2	22	**172**
	G80.3	5	2	1	16	1	1	1	**27**
	G80.4	0	0	1	1	16	0	4	**22**
	G80.8	0	0	0	0	0	4	1	**5**
	G80.9	0	0	0	0	0	0	4	**4**
	NPR Total	**85**	**143**	**137**	**19**	**17**	**12**	**51**	**464**

[a] G80.8 (other) and G80.9 (unspecified) ICD-10 codes were excluded from the kappa calculation.

Table S2: Top 10 ICD-10 diagnosis codes for the 302 children registered only in the Norwegian Patient Register (NPR) and assessed not to have CP by two pediatric neurologists during a hospital record review.

ICD-10 code	**ICD-10 text**	**N**
G40	Epilepsy	53
F82	Specific developmental disorder of motor function	42
F79	Unspecified mental retardation	33
G93	Other disorders of brain	33
G81	Hemiplegia	22
G82	Paraplegia and tetraplegia	19
Q99	Other chromosome abnormalities, not elsewhere classified	18
F83	Mixed specific developmental disorders	13
R26	Abnormalities of gait and mobility	12
F84	Pervasive developmental disorders	11
		256

Article II

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Original article

Decreasing prevalence and severity of cerebral palsy in Norway among children born 1999 to 2010 concomitant with improvements in perinatal health

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ABSTRACT

Background: The aim of our study was to explore if the prevalence and clinical characteristics of cerebral palsy (CP), concomitant with perinatal health indicators in the general population, remained unchanged for children born in Norway between 1999 and 2010.
Methods: This national multi-register cohort study included 711 174 children recorded in the Medical Birth Registry of Norway. Among these, 707 916 were born alive, and 1664 had a validated diagnosis of CP recorded in the Cerebral Palsy Registry of Norway and/or the Norwegian Patient Registry. Prevalence per 1000 live births as a function of birth year was analyzed using logistic regression with fractional polynomials to allow for non-linear trends. Chi-square statistics were used to estimate trends in proportions of clinical characteristics.
Results: The prevalence of CP in Norway decreased from 2.62 per 1000 live births in 1999 to 1.89 in 2010. The reduction was most evident among children with bilateral CP, in particular those with diplegia. During the study period, the proportions of children with severe motor impairments, epilepsy, intellectual impairment and reduced speech also decreased. At the same time, perinatal mortality has decreased in Norway, along with the proportion of women with preeclampsia, children born preterm or as a multiple.
Conclusion: We observed a significant decrease in the prevalence and severity of CP subtypes and associated impairments among children with CP in Norway. This coincided with

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improvements in perinatal health indicators in the general population. These improvements are most likely explained by advancements in obstetric and neonatal care.

1. Introduction

Cerebral palsy (CP), the most common cause of permanent motor disabilities in children, is the result of a non-progressive injury in the immature brain that occurs before birth, during delivery or in the neonatal period, and up to two years of age. The injury may be caused by a congenital brain anomaly, infection, trauma, or acute hypoxic-ischemic insults. Known risk factors include preterm birth, restricted fetal growth, and complications during pregnancy and birth.[1–3] Research shows that the panorama of causes has changed over time.[4–7]

CP is categorized into subtypes based on the dominating motor disturbance and on which part of the body is affected. Further classification is regularly based on motor impairment. Associated impairments such as epilepsy, impaired ability to speak/communicate, cognitive impairments, impaired vision and/or hearing, and nutritional problems are common.[8]

The prevalence of CP has been reported to vary between 1.5 and 3 per 1000 in various populations.[9,10] Several studies have reported that the prevalence has been stable for more than fifty years.[4,9–11] This has been taken as evidence that CP is mainly due to events before birth and that improvements in obstetric and neonatal care have not resulted in a measurable prevention of CP.[11,12] However, the stable prevalence may have concealed significant changes in the causes leading to CP and to the various CP subtypes. It is also noteworthy that the prevalence of CP was stable despite a significant reduction in perinatal mortality in the developed world from around 20 per 1000 in the 1970s to less than five per 1000 in the 21st century.[13] In fact, two studies by the Surveillance of Cerebral Palsy in Europe in populations born during the last two decades of the 20th century suggested slight decreases in the prevalence of CP among children born with a very low birth weight[14] or moderately preterm.[15] More recently, Sellier et al. showed a reduction in the prevalence of CP from 1.90 to 1.77 per 1000 live births in populations covered by 20 European registries for children born from 1980 to 2003.[16] A strength of all three studies was the large number of children included, as well as the uniform and validated diagnostic criteria of the CP diagnosis and classifications. These studies attributed the decrease in prevalence of CP to improvements in obstetric and neonatal care of preterm infants towards the end of the 20th and beginning of the 21st century. However, ascertainment of cases was a challenge, and in fact, the reported overall prevalence in the Sellier et al. study was lower than in areas with a documented complete ascertainment of cases.[7,17,18] Despite these findings, the debate continues whether CP may be prevented or whether it is mainly caused by antenatal factors that are less likely to be modified by obstetric and neonatal care.[11,19,20]

We have recently reported high completeness and correctness of CP diagnosis codes in Norway by combining information from two national health registers, resulting in a prevalence of CP of 2.4 per 1000 for children born 1996 to 2007.[17] Since then, new national guidelines have been introduced in Norway aiming to improve obstetric and neonatal care including cardiotocography (CTG), ST waveform analysis of fetal electrocardiogram (STAN), as well as therapeutic hypothermia of term born children with moderate or severe neonatal encephalopathy.[21–23]

On this background, the aim of this study was to examine if the prevalence of CP as well as clinical characteristics have changed in Norway during the first decade of the 21st century. We also wanted to assess potential concomitant changes in other indicators of perinatal health in the general population (e.g. prevalence of preterm birth and perinatal mortality) during the same time period.

2. Method

2.1. Study design

In this register-based cohort study, all children born in Norway during 1999 to 2010 and registered in the Medical Birth Registry of Norway (MBRN) were included. The MBRN has recorded data on all births since 1967, including information on the mother's health during pregnancy, the birth, and the child's health after birth. Registration in the MBRN is compulsory. Data used in this study were collected from the birth notification form dated December 1, 1998.[13] Children with CP were identified through the Cerebral Palsy Registry of Norway (CPRN). The CPRN is a consent-based national medical quality registry that has systematically recorded detailed clinical information on all children with CP born since 1996. In this study, data were collected for children born 1999 and onward on the CPRN Five Year Consultation Form.[24] Children with postneonatally acquired CP were excluded. The completeness of the CPRN for birth years 1999 to 2010 is approximately 90%. This was ascertained by linking the CPRN with the Norwegian Patient Registry (NPR) using the 11-digit personal identification number unique to each resident.[17] The NPR is a compulsory administrative registry that receives standardized data on all patients treated by the national specialist heath care services, with person-identifiable data since 2008.

2.2. Study variables

Cerebral palsy was diagnosed with the International Statistical Classification of Diseases and Related Health Problems 10th revision codes (G80.*) and further classified into a CP subtype of spastic unilateral, spastic bilateral (diplegia and quadriplegia), dyskinetic, ataxic, and mixed/unspecified by a pediatrician.[25] Gross motor function was classified according to the Gross Motor Function Classification System (GMFCS).[26] Epilepsy was defined as present (a minimum of two unprovoked seizures after the neonatal period) or not present. Cognition was defined as either normal (IQ test above 70 or by clinical evaluation) or intellectually disabled (IQ test below 70 or by clinical evaluation). Speech ability was classified using the Viking Speech Scale[27] and eating ability as independent, needs assistance, or partial/full tube feeding. Vision and hearing was described as normal, impaired, or severely impaired (blind i.e. <6/60 (<0.1) before correction on the best eye and loss > 70 dB before correction on the best ear, respectively). For children not registered in the CPRN, the NPR provided aggregated information on CP diagnosis by sex and birth year.

In order to assess changes in perinatal health indicators in the general population during the same time period, we accessed the Norwegian Institute of Public Health's MBRN statistics bank.[13] We collected aggregated data on assisted fertilization techniques (AFT), gestational age (GA), pre-eclampsia, multiple births, congenital anomalies, and perinatal mortality. GA was based on an ultrasound examination before GA week 20, and in the case where this exam was not performed it was calculated from the last menstrual period. Births occurring before GA week 28 were defined as extremely preterm, between weeks 28–36 weeks as very/moderately preterm, and births after 36 weeks as born at term. Pre-eclampsia was included if occurred before week 34. Multiple births were defined as two or more children born to the same mother at the same time. Perinatal mortality was defined as children who were either stillborn or died during the first week after birth, with a minimum birth weight of 500 g and GA week 22.[13]

2.3. Ethics

The CPRN is approved by The Norwegian Data Protection Authority (08/01067-9/EOL). This study was approved by the Regional Committee for Medical and Health Research Ethics in Central Norway (2011/754).

2.4. Statistical analyses

Logistic regression with birth year as covariate was used to estimate time trends in the prevalence of CP and CP subtypes per 1000 live births for children born during 1999 to 2010. Non-linear trends were accounted for using fractional polynomials with birth years as covariate (Figs. 1–3).[28] To account for the possibility of children being diagnosed with CP after the age of 7–8 years and not counted in our analyses, a worst case sensitivity analysis was performed by increasing the total number of children with CP by 10% for birth years 2009 and 2010. This percentage is five times higher than the observed percentage of children with late diagnosed CP born 1999 and 2000. To study trends in proportions of clinical characteristics, we used the linear-by-linear association test (for row × columns (r × c) tables with r > 2 and c > 2) and the Cochran–Armitage test for trend (for 2xc tables with c > 2).[29]

To analyze time trends of perinatal health indicators, aggregated data were retrieved from the MBRN statistics bank for all children born in Norway during our study period. Logistic regression was used to estimate trends in prevalence of each risk factor per 1000 live births.

A p-value below 0.05 was considered statistically significant, and 95% confidence intervals (CI) are reported where relevant. Logistic regression analyses with fractional polynomials were performed using Stata 15, and other analyses using SPSS 23.

2.5. Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the manuscript. SJH and GLA had full access to the data in the study and final responsibility for the decision to submit for publication.

3. Results

In all, 711 174 children were born in Norway during 1999 to 2010. Among these, 707 916 were live births and 1664 were registered with a diagnosis of CP in both the CPRN and NPR (n = 1365), only in the CPRN (n = 57), or only in the NPR (n = 242). Fifty-nine percent of children with CP were males.

3.1. Prevalence of CP

The average prevalence of CP for children born in Norway 1999 to 2010 was 2.35 per 1000 live births (CI: 2.24 to 2.47). The prevalence decreased from 2.62 per 1000 in 1999 to 1.89 in

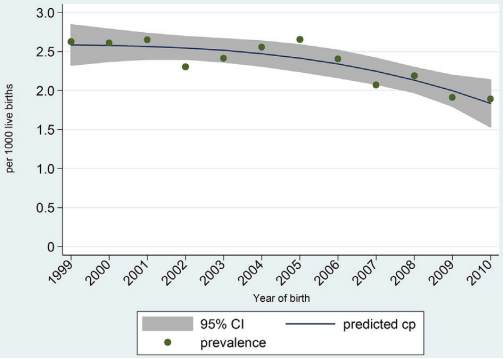

Fig. 1 – Trends in prevalence of cerebral palsy per 1000 live births among children born in Norway from 1999 to 2010. Each point shows the actual prevalence. The solid line represents predicted cerebral palsy (cp) prevalence using logistic regression with fractional polynomials, and the shaded area denotes 95% CI.

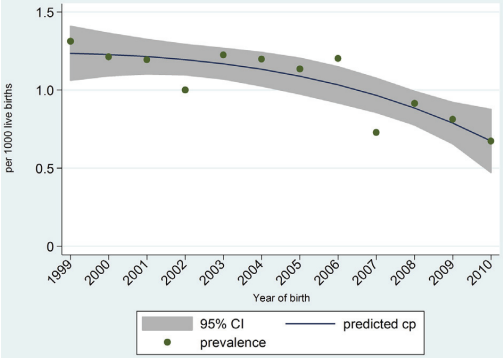

Fig. 2 – Trends in prevalence of spastic bilateral cerebral palsy per 1000 live births among children born in Norway from 1999 to 2010. Each point shows the actual prevalence. The solid line represents predicted cerebral palsy (cp) prevalence using logistic regression with fractional polynomials, and the shaded area denotes 95% CI.

2010. Assuming a linear model, the probability of a child born with CP was reduced by a factor of 0.972 per year, corresponding to a 2.8% yearly reduction ($p = 0.0001$). Fig. 1 illustrates the predicted CP prevalence with CIs during the study period using a non-linear model. In the sensitivity analysis, assuming that 10% of children with CP born during 2009 to 2010 had still not been registered at an age of 7–8 years, the probability of a child born with CP was reduced by a factor 0.978 per year, corresponding to a 2.2% yearly reduction ($p = 0.002$).

The prevalence of unilateral spastic CP remained stable during the study period at around 0.10 per 1000 live births ($p = 0.50$, assuming a linear model) (Figure S1), while bilateral spastic CP decreased significantly from 1.31 per 1000 in 1999 to 0.67 in 2010 ($p < 0.0001$). The probability of a child being diagnosed with bilateral CP was reduced by a factor of 0.954 per year (4.6% yearly), assuming a linear model ($p < 0.0001$). Fig. 2 illustrates the predicted bilateral CP prevalence with CIs during the study period using the non-linear model. Correspondingly, within the bilateral spastic CP group, the prevalence of diplegia decreased significantly by a factor of 0.958 per year (4.2% yearly) ($p = 0.0009$) assuming a linear model, while quadriplegia had a slight non-linear upside down U-shape trend, with a decrease from birth year 2007 ($p = 0.0002$) (Figures S2 and S3). Similar to quadriplegia, dyskinetic CP prevalence also changed in a non-linear upside down U-shape, with a decrease from birth year 2007 ($p = 0.0013$) (Fig. 3). Lastly, ataxic CP remained stable at around 0.009 per 1000 live births ($p = 0.75$, assuming a linear model) (Figure S4). CP subtype data and prevalence estimates are available in Table S1.

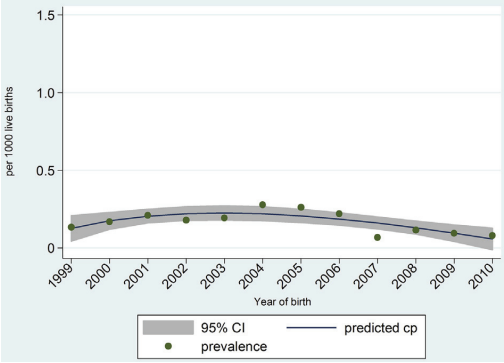

Fig. 3 – Trends in prevalence of dyskinetic cerebral palsy per 1000 live births among children born in Norway from 1999 to 2010. Each point shows the actual prevalence. The solid line represents predicted cerebral palsy (cp) prevalence using logistic regression with fractional polynomials, and the shaded area denotes 95% CI.

3.2. *Clinical characteristics of CP*

Table 1 shows that the proportion of children with CP able to walk without assistance (GMFCS level I-II) steadily increased while the proportion of children with CP able to walk only with assistance (GMFCS level III) or unable to walk (GMFCS levels IV-V) decreased over the study period ($p = 0.013$). Table 1 also shows that among children with CP there has been a decrease in the proportion recorded with epilepsy ($p < 0.0001$), intellectual disability ($p < 0.0001$), and with difficult to understand or no speech (Viking Speech Scale III-IV) ($p = 0.023$). However, there were no changes over time in the proportion of children with CP who had impaired eating abilities ($p = 0.153$), vision ($p = 0.073$), and/or hearing ($p = 0.33$) (Table 1).

3.3. *Changes in perinatal health indicators in the general population*

Perinatal mortality in Norway decreased from 7.6 per 1000 in 1999 to 5.1 in 2010 ($p < 0.0001$). The prevalence of extremely preterm born children decreased from 5.0 per 1000 births in 1999 to 3.6 in 2010 ($p < 0.0001$). Children born very/moderately preterm also decreased from 59.1 per 1000 births in 1999 to 54.9 in 2010 ($p < 0.0001$). The prevalence of multiple births decreased from 18.1 per 1000 births in 1999 to 16.7 in 2010 ($p = 0.017$). Despite a significant increase in the prevalence of children born after AFT from 18.4 per 1000 births in 1999 to 33.7 in 2010 ($p < 0.0001$), the prevalence of multiple births born after AFT decreased from 8.3 per 1000 in 1999 to 6.6 in 2010 ($p < 0.0001$). The prevalence of congenital anomalies increased from 39.8 per 1000 births in 1999 to 46.8 in 2010 ($p < 0.0001$), while the prevalence of preeclampsia decreased from 43.7 per 1000 births in 1999 to 33.5 in 2010 ($p < 0.0001$).

4. Discussion

4.1. *Main findings*

We found a marked decline in the overall prevalence of CP in Norway among children born 1999 to 2010. This reduction was

Table 1 – Summary of clinical characteristics among children with cerebral palsy born in Norway from 1999 to 2010.

	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
GMFCS												
I-II	65 (67.0)	64 (61.5)	67 (70.5)	77 (70.0)	72 (62.1)	76 (63.3)	84 (66.7)	83 (61.5)	89 (81.7)	92 (73.6)	77 (72.0)	79 (73.8)
III	6 (6.2)	8 (7.7)	9 (9.5)	3 (2.7)	12 (10.3)	11 (9.2)	9 (7.1)	10 (7.4)	4 (3.7)	9 (7.2)	4 (3.7)	11 (10.3)
IV-V	26 (26.8)	32 (30.8)	19 (20.0)	30 (27.3)	32 (27.6)	33 (27.5)	33 (26.2)	42 (31.1)	16 (14.7)	24 (19.2)	26 (24.3)	17 (15.9)
Epilepsy												
Present	39 (39.8)	42 (42.0)	27 (28.4)	38 (37.3)	39 (40.2)	27 (25.2)	34 (30.4)	38 (31.7)	27 (28.1)	27 (23.9)	22 (22.7)	23 (23.7)
Not present	59 (60.2)	58 (58.0)	68 (71.6)	64 (62.7)	58 (59.8)	80 (74.8)	78 (69.6)	82 (68.3)	69 (71.9)	86 (76.1)	75 (77.3)	74 (76.3)
Cognition												
Normal	57 (68.7)	56 (67.5)	51 (70.8)	55 (63.2)	49 (61.3)	58 (67.4)	71 (74.7)	72 (74.2)	60 (84.5)	68 (77.3)	51 (70.8)	62 (91.2)
Intellectually disabled	26 (31.3)	27 (32.5)	21 (29.2)	32 (36.8)	31 (38.8)	28 (32.6)	24 (25.3)	25 (25.8)	11 (15.5)	20 (22.7)	21 (29.2)	6 (8.8)
Viking Speech Scale												
I	48 (51.1)	52 (50.5)	47 (49.0)	48 (47.1)	36 (36.0)	52 (49.1)	65 (58.6)	66 (54.5)	49 (53.3)	63 (55.8)	52 (54.7)	57 (64.8)
II	17 (18.1)	16 (15.5)	20 (20.8)	17 (16.7)	23 (23.0)	22 (20.8)	15 (13.5)	11 (9.1)	23 (25.0)	16 (14.2)	16 (16.8)	11 (12.5)
III	17 (18.1)	15 (14.6)	14 (14.6)	21 (20.6)	15 (15.0)	11 (10.4)	13 (11.7)	20 (16.5)	12 (13.0)	13 (11.5)	11 (11.6)	12 (13.6)
IV	12 (12.8)	20 (19.4)	15 (15.6)	16 (15.7)	26 (26.0)	21 (19.8)	18 (16.2)	24 (19.8)	8 (8.7)	21 (18.6)	16 (16.8)	8 (9.1)
Eating abilities												
Independent	74 (77.9)	78 (75.0)	73 (76.8)	74 (74.0)	64 (70.3)	80 (76.2)	84 (77.1)	86 (71.1)	81 (84.4)	89 (78.1)	75 (75.8)	88 (90.7)
Needs assistance	15 (15.8)	14 (13.5)	11 (11.6)	9 (9.0)	17 (18.7)	14 (13.3)	7 (6.4)	13 (10.7)	8 (8.3)	10 (8.8)	14 (14.1)	4 (4.1)
Partial/full tube feeding	6 (6.3)	12 (11.5)	11 (11.6)	17 (17.0)	10 (11.0)	11 (10.5)	18 (16.5)	22 (18.2)	7 (7.3)	15 (13.2)	10 (10.1)	5 (5.2)
Vision												
Normal	63 (64.9)	65 (65.0)	51 (53.1)	52 (57.1)	62 (64.6)	66 (62.3)	71 (65.1)	69 (61.6)	60 (65.9)	70 (65.4)	61 (64.9)	70 (77.8)
Impaired	33 (34.0)	28 (28.0)	40 (41.7)	34 (37.4)	29 (30.2)	36 (34.0)	37 (33.9)	35 (31.3)	27 (29.7)	34 (31.8)	28 (29.8)	17 (18.9)
Severely impaired	1 (1.0)	7 (7.0)	5 (5.2)	5 (5.5)	5 (5.2)	4 (3.8)	1 (0.9)	8 (7.1)	4 (4.4)	3 (2.8)	5 (5.3)	3 (3.3)
Hearing												
Normal	84 (91.3)	88 (90.7)	80 (87.9)	85 (92.4)	84 (93.3)	93 (93.0)	98 (95.1)	104 (93.7)	88 (97.8)	102 (95.3)	91 (93.8)	90 (96.8)
Impaired	4 (4.3)	5 (5.2)	10 (1.0)	5 (5.4)	4 (4.4)	2 (1.9)	2 (1.9)	5 (4.5)	1 (1.1)	2 (1.9)	3 (3.1)	3 (3.2)
Severely impaired	4 (4.3)	4 (4.1)	1 (1.1)	2 (2.2)	2 (2.2)	5 (2.9)	3 (2.9)	2 (1.8)	1 (1.1)	3 (2.8)	3 (3.1)	0 (0.0)
Total number of children with CP	156	155	151	129	138	147	152	142	122	134	120	118

GMFCS = Gross Motor Function Classification System.
CP = cerebral palsy.

most evident for children with bilateral spastic CP, in particular those with diplegia. There was also a trend towards a decrease in the prevalence of children with quadriplegic and dyskinetic CP from 2007 and onwards. The prevalence of unilateral CP remained stable. We also found a decrease in the proportion of children with CP and more severe gross motor impairments, epilepsy, intellectual disability, and with limited speech. During the study period, there were significant improvements in perinatal health indicators in the general Norwegian population including a decrease in perinatal mortality, as well as in the prevalence of preterm born children, preeclampsia, and multiple births.

4.2. *Strengths and limitations*

To our knowledge, this is the first study to combine information on children with CP, as well as perinatal health information on the general population, from three nationwide population-based health registers to explore trends in prevalence rates and clinical characteristics. The CP diagnosis codes in the CPRN and NPR have been validated to ensure completeness and correctness of the CP population in Norway, confirmed at a minimum age of 5 years.[17] This included a comparison of the CP diagnosis codes recorded only in the NPR with the proportion recorded in the CPRN, which did not indicate selection bias. An additional potential selection bias may have occurred if a large proportion of children are diagnosed with CP after 7–8 years of age, thereby leading to an erroneously low prevalence in children born 2009 and 2010. However, after performing a worst case sensitivity analysis by increasing the total number of children with CP by 10% for these birth years, the results remained nearly unchanged. Conversely, there is also the possibility that a child currently registered in the CPRN may have been misdiagnosed with CP, and will be removed from the registry at a later age. Misdiagnoses, in particular progressive disorders, are more likely to be discovered with increasing age and would be expected to be more common in the later part of the study period. This would lead to an erroneously high prevalence in the later years. Thus, we consider it most unlikely that our main findings have been affected by selection bias.

The proportions of missing data for clinical characteristics recorded only in the CPRN varied during the study period, and some caution should be taken when interpreting the trends in clinical characteristics. On the other hand, children with a more severe CP subtype and associated impairments are more likely to be assessed and registered earlier and more thoroughly than children with less severe CP and associated impairments. We therefore consider it unlikely that underreporting of severe cases explains the decrease in the proportion of children with more severe impairments. Moreover, it may be considered reassuring that there was no change in the prevalence of unilateral CP, normally having less severe impairments than children with bilateral or dyskinetic CP.

4.3. *Comparison of other studies*

Similar to our study, a reduction in the prevalence of CP for neonatal survivors was found for children born in Victoria, Australia between 1993 and 2006, including a reduction in bilateral CP and the severity of motor and associated impairments.[30] The authors concluded that this might have been attributed to improvements in perinatal care, as well as neuroprotective strategies for HIE. In 2016, Durkin et al. reported a decline in the population prevalence of 8 year old children with CP living within four areas in the US from 3.5 per 1000 in 2006 to 2.9 in 2010.[31] Although they were not able to directly associate this decline with an improvement of obstetric and neonatal care, it is the first report of decline in the prevalence of CP from the US. Additionally, three consecutive studies performed in a smaller population in Western Sweden reported a nonsignificant decrease in the prevalence of CP in liveborn children from 1999 to 2002 (2.18 per 1000), 2003 to 2006 (2.18 per 1000), and 2007 to 2010 (1.96 per 1000).[5–7] The decrease in the latter study was a result of a reduction in all CP subtypes, including children born with HIE at or near term.[7] This was attributed to the introduction of therapeutic hypothermia in 2007 and/or improvements in obstetric care in Sweden. Lastly, a study performed in Okinawa, Japan also reported a decrease in the prevalence of CP in liveborn children from 1988 to 2007.[32] The decrease was accredited to a reduction of preterm born children or with a low birth weight between 1998 and 2007. The study also reported a decline in neonatal mortality, indicating improved access to perinatal interventions.

4.4. *Interpretation*

The decrease in the prevalence of CP and improved clinical picture, along with a decrease in perinatal mortality and in the proportion of preterm born children may be explained by general improvements in obstetric and neonatal care during the last 20 years in Norway. This interpretation is supported by the decrease in perinatal morbidity during the same time period. The decrease in diplegia is consistent with the decrease in the prevalence among children born preterm, which may be in part ascribed to the decrease in the occurrence of preeclampsia, or in the reduction of multiple births, mainly a result of improved AFT. However, the overall estimated reduction in children born preterm can only account for approximately nine of the ~32 fewer children with CP born 2009 and 2010 as compared to those born 1999 to 2000. We therefore consider that other improvements in obstetric and neonatal care have had a major impact on the reduction in the prevalence of CP. This interpretation is supported by the decrease in quadriplegia and dyskinetic CP, considered to be the result of HIE injuries at birth, during the latter part of the study. Although we are unable to assess which treatments may be responsible for the improved outcome, it is noteworthy that therapeutic hypothermia was introduced in Norway in 2007, which is the year when a decrease in the more severe CP subtypes become most evident. Congenital anomalies are common among children with CP, and we have recently shown that these children have more severe motor and associated impairments compared with children with other or unknown causes.[33] A reduction in the proportion of children with congenital anomalies could therefore also explain the reduction in CP. On the other hand, data acquired from the MBRN suggested a slight increase in the number of children with congenital anomalies in the general population,

indirectly lending support to our interpretation that the decrease is due to overall improved care. During the study period, the proportions of women with high maternal age,[34] and of overweight women[35] have increased, while the prevalence of smoking at the beginning of pregnancy[36] and multiple births have decreased in Norway. Although a recent study from Australia suggested a reduced risk for CP in mothers who smoked cigarettes at the beginning of pregnancy,[37] high maternal age, overweight and multiple births are all factors associated with increased risk for CP.[38–40] We therefore consider it unlikely that changes in such background factors explain our findings.

The lack of change in the prevalence of unilateral CP, which is considered to be caused by perinatal stroke mainly in term born infants, may still be consistent with the interpretation of the main findings. Although some cases of unilateral CP are caused by intracerebral bleeding in the preterm born, by twin–twin transfusion or by perinatal HIE injuries, the majority of identified causes (congenital heart disease, low protein C, low levels of antithrombin III, vascular anomalies, neonatal lupus and thrombocytopenia, neonatal leukemia and sepsis, or meningitis) are not expected to be prevented or predicted through current regular ante-, peri-, or neonatal treatment.[41,42]

5. Conclusion

We found that the prevalence of CP declined for children born in Norway from 2.62 per 1000 in 1999 to 1.89 in 2010. Our results also show that there was a substantial improvement in the severity of clinical characteristics over time as prevalence for bilateral CP decreased, along with a decrease in the proportion of children with severe motor impairments, epilepsy, intellectual disability, and difficult to understand or no speech. At the same time, there have been fewer pregnancies with preeclampsia, children born preterm or as a multiple, as well as fewer perinatal deaths of children born in Norway. This may be explained by improvements in obstetric and neonatal care in Norway during the first decade of the 21st century.

Contributors

SJH, TV, IJB and GLA designed the study. SJH performed the data collection. SJH and SL performed the data analyses. SJH drafted the manuscript. All authors interpreted the data, and contributed to revisions and final approval of the manuscript.

Declaration of interests

The authors have no conflicts of interest to disclose.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.ejpn.2018.05.001.

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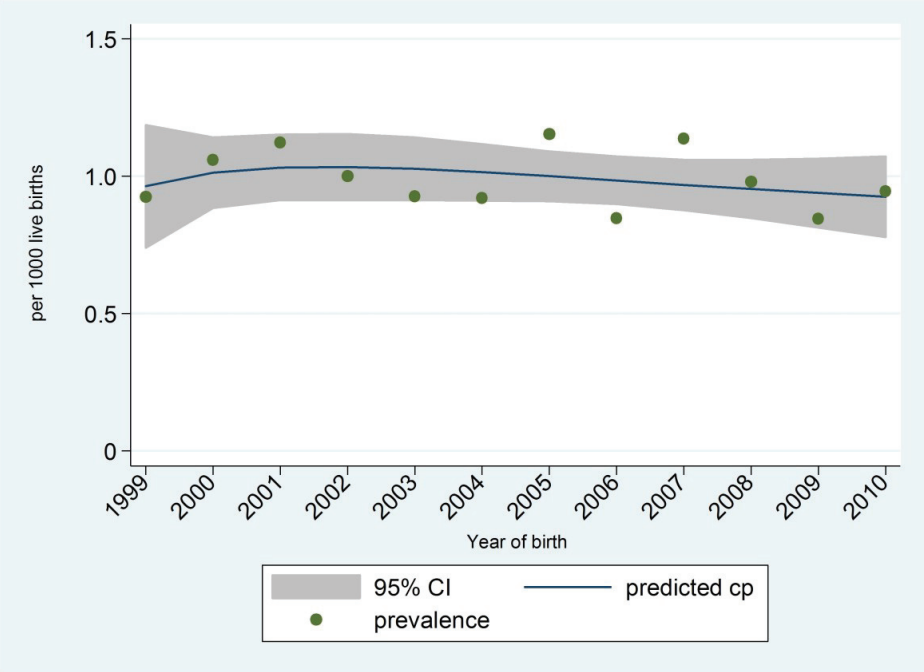
Supplementary Materials

Supplement to: Decreasing prevalence and severity of cerebral palsy in Norway among children born 1999-2010 concomitant with improvements in perinatal health.

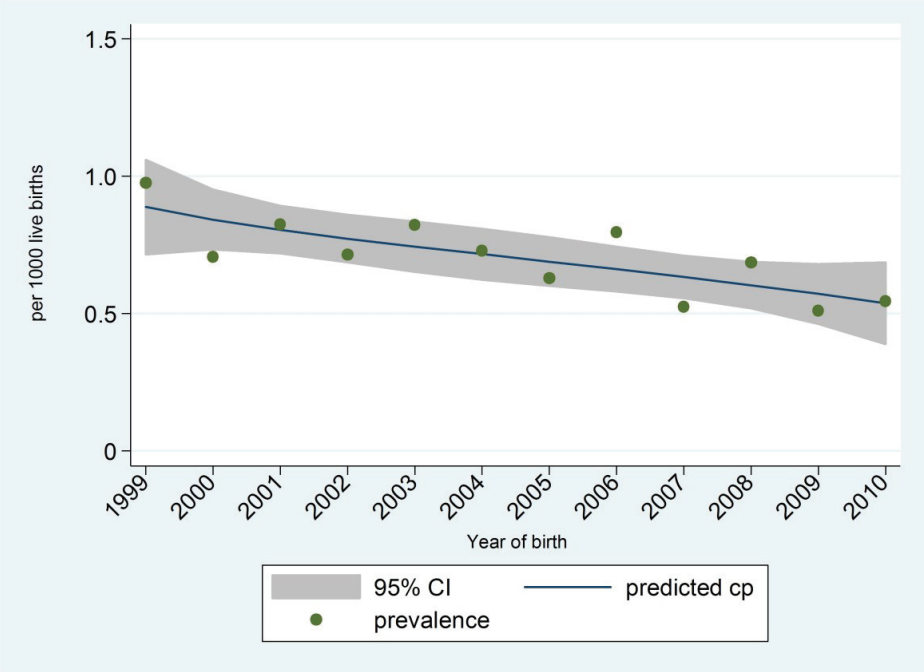
Table of Contents:

Figure S1: Trends in prevalence of unilateral spastic cerebral palsy per 1000 live births among children born in Norway from 1999 to 2010



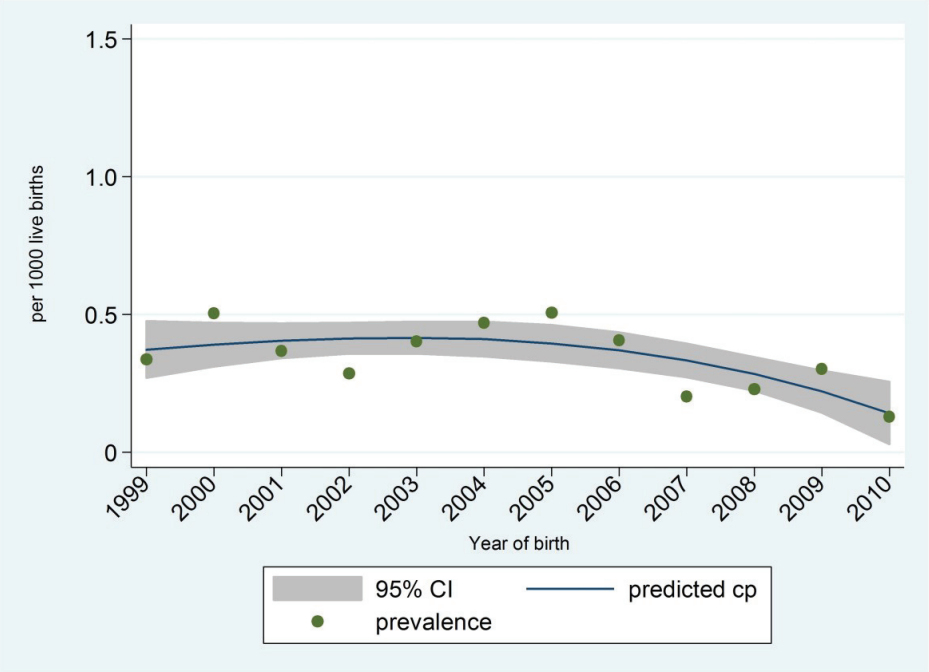
Each point shows the actual prevalence. The solid line represents predicted cerebral palsy (cp) prevalence using logistic regression with fractional polynomials, and the shaded area denotes 95% CI.

Figure S2: Trends in prevalence of bilateral spastic diplegia cerebral palsy per 1000 live births among children born in Norway from 1999 to 2010



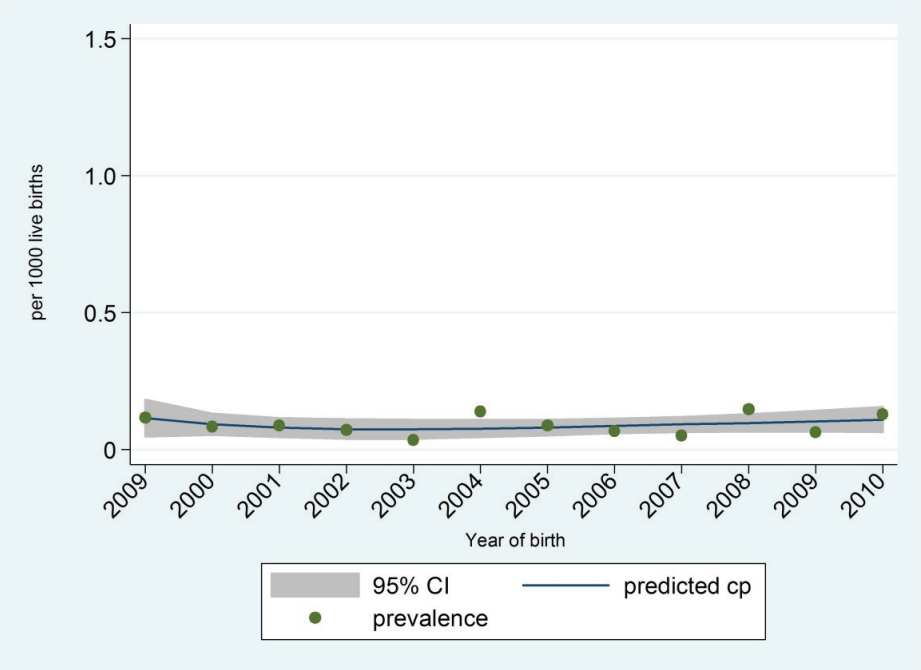
Each point shows the actual prevalence. The solid line represents predicted cerebral palsy (cp) prevalence using logistic regression with fractional polynomials, and the shaded area denotes 95% CI.

Figure S3: Trends in prevalence of bilateral spastic quadriplegia cerebral palsy per 1000 live births among children born in Norway from 1999 to 2010



Each point shows the actual prevalence. The solid line represents predicted cerebral palsy (cp) prevalence using logistic regression with fractional polynomials, and the shaded area denotes 95% CI.

Figure S4: Trends in prevalence of ataxic cerebral palsy per 1000 live births among children born in Norway from 1999 to 2010



Each point shows the actual prevalence. The solid line represents predicted cerebral palsy (cp) prevalence using logistic regression with fractional polynomials, and the shaded area denotes 95% CI.

Table S1: Summary of cerebral palsy subtypes and prevalence estimates per 1000 live births among children born in Norway from 1999 to 2010

Cerebral palsy subtype:	1999 n (PE)	2000 n (PE)	2001 n (PE)	2002 n (PE)	2003 n (PE)	2004 n (PE)	2005 n (PE)	2006 n (PE)	2007 n (PE)	2008 n (PE)	2009 n (PE)	2010 n (PE)
Spastic unilateral	55 (0·93)	63 (1·06)	64 (1·12)	56 (1·00)	53 (0·93)	53 (0·92)	66 (1·15)	50 (0·85)	67 (1·14)	60 (0·98)	53 (0·84)	59 (0·95)
Spastic bilateral	78 (1·31)	72 (1·21)	68 (1·19)	56 (1·00)	70 (1·22)	69 (1·20)	65 (1·14)	71 (1·20)	43 (0·73)	56 (0·92)	51 (0·81)	42 (0·67)
Diplegia	58 (0·97)	42 (0·71)	47 (0·83)	40 (0·71)	47 (0·82)	42 (0·73)	36 (0·63)	47 (0·79)	31 (0·53)	42 (0·69)	32 (0·51)	34 (0·54)
Quadriplegia	20 (0·34)	30 (0·50)	21 (0·37)	16 (0·29)	23 (0·40)	27 (0·47)	29 (0·51)	24 (0·41)	12 (0·20)	14 (0·23)	19 (0·30)	8 (0·13)
Dyskinetic	8 (0·13)	10 (0·17)	12 (0·21)	10 (0·18)	11 (0·19)	16 (0·28)	15 (0·26)	13 (0·22)	4 (0·07)	7 (0·11)	6 (0·10)	5 (0·08)
Ataxic	7 (0·12)	5 (0·08)	5 (0·09)	4 (0·07)	2 (0·03)	8 (0·14)	5 (0·09)	4 (0·07)	3 (0·05)	9 (0·15)	4 (0·06)	8 (0·13)
Mixed/unclassified	8 (0·13)	5 (0·08)	2 (0·04)	3 (0·05)	2 (0·03)	1 (0·02)	1 (0·02)	4 (0·07)	5 (0·08)	2 (0·03)	6 (0·10)	4 (0·06)
Total CP	156 (2·62)	155 (2·61)	151 (2·65)	129 (2·30)	138 (2·41)	147 (2·56)	152 (2·66)	142 (2·41)	122 (2·07)	134 (2·19)	120 (1·91)	118 (1·89)
Total live births	59 444	59 399	56 932	55 988	57 148	57 525	57 245	58 997	58 955	61 180	62 756	62 347

PE = prevalence estimate
CP=cerebral palsy

Article III

DEVELOPMENTAL MEDICINE & CHILD NEUROLOGY ORIGINAL ARTICLE

Comorbidities in cerebral palsy: a patient registry study

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ABBREVIATION
NPR Norwegian Patient Registry

AIM To describe the total burden of disease in individuals with cerebral palsy (CP) in Norway.
METHOD A comprehensive set of disorder categories were extracted from the Norwegian Patient Registry using International Statistical Classification of Diseases, 10th Revision diagnosis codes for individuals born between 1996 and 2010 who received specialist healthcare between 2008 and 2017 (0–21y). Individuals with CP were identified through a validation study in cooperation with the Cerebral Palsy Registry of Norway. Risk differences (proportions of individuals recorded with each disorder) were used to compare individuals with CP with the general population without CP.
RESULTS The study included 966 760 individuals. Among these, 2302 (0.24%) had CP (1330 males, 972 females). Of the individuals with CP, 95.0% were recorded with one or more comorbidity, and the risks of medical, neurological, and mental/behavioural disorders were higher compared with the risks in the general population. The most common neurological and mental/behavioural disorders were cocausal, i.e. attributed to the same injury to the developing brain that caused CP, while medical disorders were most often complications of CP or coincidentally co-occurring with CP.
INTERPRETATION Individuals with CP have a considerably higher burden of medical, neurological, and mental/behavioural disorders compared with the general population, including disorders that are not directly caused by, or complications to, the brain injury.

Cerebral palsy (CP) is a group of permanent disorders of motor impairment resulting from a non-progressive injury in the developing brain.[1] The prevalence of CP has been reported to vary between 1.5 and 3.0 per 1000 live births.[2,3] However, in the past decades there has been a decline in the prevalence and severity of the disorder.[4–7] According to the latest definition of CP, motor impairments are often accompanied by 'disturbances of sensation, perception, cognition, communication, and behavior, by epilepsy, and by secondary musculoskeletal problems'.[8] This definition has led not only to an increase in the awareness of the occurrence of comorbidities in individuals with CP, but also of the need for interdisciplinary management of these comorbidities as they change over the lifespan.[9–12]

Brown et al. defined a comorbidity as any disorder associated with CP, but which can also occur as a stand-alone disorder in individuals without CP.[9] Furthermore, while some disorders may be caused by the same injury to the developing brain which caused CP (i.e. epilepsy and intellectual impairment), other disorders may be regarded as complications of the main CP condition (i.e. scoliosis and hip dislocation). Thus, Brown et al. categorized types of comorbidities in individuals with CP as comorbid (hereafter referred to as co-occurring), cocausal, and complications (Table I).[9] While disorders defined as cocausal and complications of CP are more likely to occur in individuals with CP, one might expect that coincidentally co-occurring disorders, i.e. those not caused by or complications of CP, would not be more common in this population than in the general population.

Furthermore, it is important to recognize that one comorbidity may influence another.[10] For example, oral motor impairments are often associated with eating difficulties, poor nutrition, and impaired growth. Moreover, a characteristic feature of oral motor impairment is disturbed coordination of swallowing and breathing and/or gastro-esophageal reflux, which may lead to aspiration of food into the trachea and lower respiratory tract, followed by choking and respiratory tract infections. Thus, comorbidities may adversely affect the quality of life and health of an individual with CP more than the motor impairment itself.

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The aim of this study was to describe the total burden of disease in individuals with CP in Norway, by comparing the occurrence of comorbidities in the population with CP with the same disorders in the general population. We also describe the overall distribution of cocausal, complications, and co-occurring comorbidities that are likely to be associated with CP.

What this paper adds

- Nearly all individuals with cerebral palsy (CP) had one or more comorbidity.
- Fifty-two per cent had at least one comorbidity attributed to the same cause as CP, complications of CP, and coincidentally co-occurring with CP.
- Risks of medical, neurological, and mental/behavioural disorders were considerably higher than in the general population.

METHOD

Study design and population

The data used in this study were obtained from the Norwegian Patient Registry (NPR). The NPR is a compulsory registry that records demographic, administrative, and clinical health data on all patients treated by the national specialist healthcare services, with person-identifiable data from 2008. This includes inpatient admissions and outpatient clinics at public general and psychiatric hospitals. The NPR provided data recorded between 2008 and 2017 for children and adolescents born between 1996 and 2010 (0–21y). The data included diagnosis codes grouped into disorder categories according to the International Statistical Classification of Diseases, 10th Revision (ICD-10; Table SI, online supporting information) and information on birth year and sex. In addition, ICD-10 CP diagnosis codes (G80.*) were added for individuals with CP previously identified through a validation study in cooperation with the Cerebral Palsy Registry of Norway.[3] All individuals with CP in Norway are diagnosed by a paediatrician in the specialized healthcare services, and are routinely seen by a multidisciplinary team. We included both transient and chronic disorders, ranging from mild to severe, excluding disorders unlikely to occur in children and adolescents (Table SI). Data from private hospitals were excluded because they account for a very small proportion of services. However, it is possible that some disorders may not have been recorded in the NPR. The total number of individuals born during the same time and residing in Norway as of 31st December 2017 by birth year and sex was obtained from Statistics Norway (https://www.ssb.no).

We further sorted each disorder category into three main groups: medical, neurological, and mental/behavioural to compare the occurrence of comorbidities in individuals with CP with the same disorders in the general population (Table SI). To assess the relative burden of comorbidities for individuals with CP, comorbidity categories were grouped into cocausal, complications, or co-occurring, as described by Brown et al.[9] (Table SII, online supporting information).

Table I: Comorbidity categories for individuals with cerebral palsy (CP), as proposed by Brown et al.[9]

Cocausal	Disorders caused by the same injury to the developing brain that caused CP (i.e. epilepsy and cognitive impairment)
Complications	Disorders that are complications of the main CP condition (i.e. scoliosis and hip dislocation)
Co-occurring	Disorders not caused by the injury to the developing brain, nor are complications of the main CP condition

Statistical analyses

In this study, risk was defined as the occurrence of a disorder, i.e. the number of individuals who were recorded with the disorder in the NPR, divided by the total number of individuals in the respective population. Risk differences with 99% Wald confidence intervals (CIs) were computed between individuals with CP and the general population without CP. We used 99% CIs because of the large number of comparisons. We also calculated the frequency distribution of ICD-10 CP diagnosis codes per comorbidity category and the mean number of comorbidities with standard deviation (SD) per CP diagnosis code. Stata 15.1 software (StataCorp LP, College Station, TX, USA) was used for the analyses.

Ethics approval

This study was conducted under the NPR Regulations 1 and 2. Data were delivered pursuant to NPR Regulations 3 to 5, in an anonymous form. Studies using anonymous data, where information cannot be traced back to an individual, do not require ethical approval.

RESULTS

In total, 966 760 Norwegian residents born between 1996 and 2010 were included. Among these, 691 003 were recorded in the NPR and 2302 (0.24%) had a validated diagnosis of CP. The distribution of ICD-10 CP diagnosis codes is shown in Table II. The proportion of males was slightly higher in the population with CP (n=1330, 57.8%) than in the general population (n=496 064, 51.4%).

Overall disorder occurrence

Of the individuals with CP, 95.0% had at least one recorded comorbidity, and 36.4% had at least one disorder within the three main groups of medical, neurological, and mental/behavioural disorders. In comparison, 45.3% of the general population were recorded with the same disorders, while only 2.9% had a disorder within the three main groups.

All medical disorders were more common in individuals with CP compared with their peers (Table III). The most common disorders among individuals with CP were musculoskeletal system and connective tissue diseases, affecting 49.8%, followed by diseases of the digestive system (39.1%), congenital malformations (non-nervous system; 33.6%), and respiratory diseases and infections (29.7% and 27.2% respectively). In the general population, the

Table II: Occurrence of comorbidity categories in individuals with cerebral palsy (CP) born between 1996 and 2010 by ICD-10 CP diagnosis code

Comorbidity category			Cocausal		Complications		Co-occurring	
ICD-10 code	ICD-10 text	*n* (%)	*n*	%	*n*	%	*n*	%
G80.0	Spastic quadriplegic	376 (16.3)	335	89.1	356	94.7	331	88.0
G80.1	Spastic diplegic	664 (28.8)	448	67.5	522	78.6	506	76.2
G80.2	Spastic hemiplegic	803 (35.0)	458	57.0	523	65.1	547	68.1
G80.3	Dyskinetic	129 (5.6)	110	85.3	111	86.0	110	85.3
G80.4	Ataxic	93 (4.0)	79	84.9	70	75.3	72	77.4
G80.8	Other (mixed)	29 (1.3)	25	86.2	23	79.3	24	82.8
G80.9	Unspecified (NOS)	208 (9.0)	157	75.5	162	77.9	163	78.4
	Total	2302 (100.0)	1612	70.0	1767	76.8	1753	76.2

Data recorded in the Norwegian Patient Registry between 2008 and 2017. ICD-10, International Statistical Classification of Diseases, 10th Revision; NOS, not otherwise specified.

occurrence of the same disorders varied between 7.6% (respiratory infections) and 13% (respiratory diseases; Table III). Moreover, individuals with CP had an excess risk of almost all medical disorders compared with the risk in the general population. This was most notable for the disorders mentioned above (risk difference 16.7–40.0%), in addition to malnutrition and eating difficulties (risk difference 21.7%, 99% CI 19.5–24.0%) and scoliosis (risk difference 14.3%, 99% CI 12.4–16.3%; Fig. 1).

Among individuals with CP, 60.9% had at least one recorded additional neurological disorder, while this was the case for 7.2% of their peers. The dominating neurological disorder in individuals with CP was epilepsy, diagnosed in 39.0% compared with 1.2% in the general population (Table III). The risks of epilepsy and 'neurological disorders – other' in individuals with CP were considerably higher than in the general population (Fig. 1). In addition, nervous and musculoskeletal system symptoms and congenital malformations of the nervous system occurred more often among individuals with CP (Table III), and the risk of sleep, cerebrovascular, and headache disorders were increased compared with the general population (Fig. 1).

Individuals with CP were also recorded more frequently with mental/behavioural disorders (53.8%) compared with the general population (14.2%). The risk of intellectual disability was considerably higher for individuals with CP (risk difference 27.4%, 99% CI 25.0–29.8%), observed in 28.1% compared with only 0.7% in the general population (Fig. 1 and Table III). Individuals with CP had an excess risk of psychological developmental disorders 16.8% (99% CI 14.7–18.9%) compared with their peers. Although the occurrence of all other mental/behavioural disorders was less than 10% in individuals with CP, the risk was higher than in the general population (Table III and Fig. 1).

Sex differences

Analyses showed that the excess risk of comorbidities was similar for males and females with CP compared with the general population. There was also no significant difference in risk for males versus females with CP (Table SIII, online supporting information).

Comorbidities among individuals with CP

Fifty-two per cent of individuals with CP had at least one disorder within the three comorbidity categories of cocausal, complications, and co-occurring (Fig. 2). Figure 2 also illustrates that less than 20% had only one comorbidity within either the cocausal (5%), complications (7%), or co-occurring (5%) categories. Table III shows that within the medical disorders group, most comorbidities were categorized as either complications or co-occurring, while less than 13% were categorized as cocausal. Similarly, four of the five disorders with the highest excess risk were complications of CP (musculoskeletal system and connective tissue diseases, digestive system diseases, malnutrition and eating difficulties, and respiratory infections). Within the group of neurological disorders, cocausal comorbidities such as epilepsy, nervous and musculoskeletal system symptoms, and congenital malformations of the nervous system were most common. Although, it may be noted that more than 25% had a 'neurological disorders – other' comorbidity, categorized as co-occurring. Within the group of mental/behavioural disorders, the majority of the most common comorbidities were categorized as cocausal (Table III).

Comorbidities according to ICD-10 CP subtype

As many as 98.4% of individuals with spastic quadriplegic CP had at least one comorbidity, and the proportion of disorders within the three comorbidity categories was higher in spastic quadriplegic CP than in any other subtype (Table II). Individuals with this subtype also had the highest mean number of comorbidities (mean 8.1 [SD 4.0]). However, individuals with other subtypes also had a high number of comorbidities ranging from a mean number of 3.6 (SD 3.0) among individuals with spastic hemiplegic CP to 6.5 (SD 3.5) for those with dyskinetic CP.

DISCUSSION

Main findings

In this national registry study, using validated CP diagnosis codes, we found that individuals with CP have a considerably higher burden of medical, neurological, and mental/behavioral disorders than the general population. The

Table III: Occurrence of comorbidities in individuals with cerebral palsy (CP) born between 1996 and 2010 versus the same disorders in the general population (GP)

		CP (*n*=2302)		GP (*n*=964 458)	
Disorder category	Comorbidity category[a]	*n*	%	*n*	%
Medical disorders		1994	86.6	461 010	47.8
Musculoskeletal system and connective tissue diseases (excl. scoliosis)	Complications	1147	49.8	95 124	9.9
Digestive system diseases	Complications	900	39.1	115 008	11.9
Congenital malformations (excl. nervous system)	Co-occurring	774	33.6	81 207	8.4
Respiratory diseases	Co-occurring	683	29.7	125 541	13.0
Respiratory infections	Complications	626	27.2	73 329	7.6
Malnutrition and eating difficulties	Complications	529	23.0	11 968	1.2
Skin and subcutaneous tissue diseases	Co-occurring	358	15.6	77 848	8.1
Scoliosis	Complications	346	15.0	6589	0.7
Intestinal infectious diseases	Co-occurring	250	10.9	25 552	2.6
Hearing impairment/deafness	Cocausal	214	9.3	18 353	1.9
Urinary tract disorders	Co-occurring	201	8.7	26 559	2.8
Endocrine disorders	Co-occurring	173	7.5	19 820	2.1
Genital disorders	Co-occurring	159	6.9	41 277	4.3
Blood disorders	Complications	131	5.7	10 954	1.1
Visual impairment/blindness	Cocausal	90	3.9	792	0.1
Circulatory system diseases	Co-occurring	89	3.9	12 515	1.3
Benign neoplasms	Co-occurring	80	3.5	25 278	2.6
Obesity	Complications	75	3.3	9856	1.0
Chromosomal abnormalities	Cocausal	69	3.0	3580	0.4
Metabolic disorders	Co-occurring	36	1.6	4039	0.4
Nutritional deficiencies	Complications	35	1.5	3031	0.3
Immune disorders	Co-occurring	29	1.3	1192	0.1
Dislocation of hip	Complications	21	0.9	177	0.0
Malign neoplasms	Co-occurring	19	0.8	2212	0.2
Neurological disorders		1403	60.9	69 710	7.2
Epilepsy	Cocausal	898	39.0	11 347	1.2
Neurological disorders - other	Co-occurring	666	28.9	20 567	2.1
Nervous and musculoskeletal system symptoms	Cocausal	423	18.4	16 843	1.7
Congenital malformations of nervous system	Cocausal	239	10.4	1962	0.2
Sleep disorders	Complications	192	8.3	8663	0.9
Headache disorders	Complications	132	5.7	23 891	2.5
Cerebrovascular diseases	Co-occurring	109	4.7	822	0.1
CNS infections and inflammatory diseases	Co-occurring	52	2.3	2520	0.3
CNS neoplasms	Co-occurring	17	0.7	914	0.1
Mental/behavioral disorders		1239	53.8	136 691	14.2
Intellectual disability	Cocausal	647	28.1	6997	0.7
Psychological developmental disorders (excl. autism)	Cocausal	449	19.5	26 200	2.7
Behavioral and emotional disorders	Cocausal	226	9.8	47 663	4.9
ADHD	Cocausal	193	8.4	37 516	3.9
Psychiatric disorders - other	Co-occurring	110	4.8	33 047	3.4
Autism	Cocausal	99	4.3	11 816	1.2
Anxiety disorders	Co-occurring	70	3.0	19 422	2.0
Depressive episode	Co-occurring	50	2.2	19 486	2.0
Eating disorders	Co-occurring	26	1.1	5096	0.5
Obsessive-compulsive disorder	Co-occurring	21	0.9	3826	0.4

Data recorded in the Norwegian Patient Registry between 2008 and 2017. [a]Comorbidity category refers only to individuals with CP. CNS, central nervous system; ADHD, attention-deficit/hyperactivity disorder.

majority (95%) of individuals with CP had at least one additional disorder, but somewhat surprisingly, nearly half (45%) of the general population were also recorded in the specialist healthcare services with the same mild-to-severe and transient-to-chronic disorders. However, while 36% of individuals with CP had at least one disorder within all the three categories of medical, neurological, and mental/behavioural disorders, this was only 3% for the general population.

For individuals with CP, the most common comorbidities within the neurological and mental/behavioural disorder categories were cocausal, i.e. caused by the same injury to the developing brain that caused CP. In the medical category, complications of the main CP diagnosis and comorbidities coincidentally co-occurring with CP were most common. Nonetheless, the proportion of individuals with comorbidities regarded as co-occurring with CP occurred just as often as cocausal and complications. Nearly all individuals with spastic quadriplegic CP had at least one comorbidity and, on average, more than eight. However, even individuals with spastic hemiplegic CP had an average of more than three comorbidities.

Strengths and limitations

A strength of this study is that it provides a comprehensive evaluation of mild-to-severe and transient-to-chronic

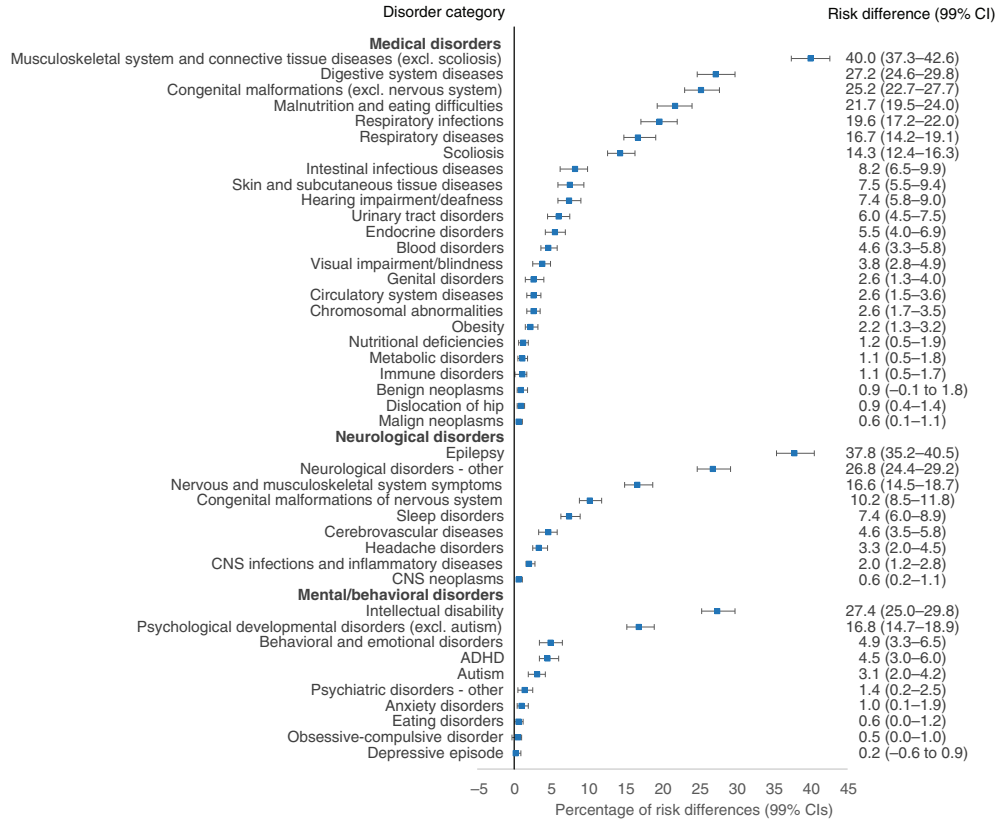

Figure 1: Risk differences with 99% confidence intervals (CIs) comparing the occurrence of disorders between individuals with cerebral palsy and the general population born from 1996 to 2010. CNS, central nervous system; ADHD, attention-deficit/hyperactivity disorder. [Colour figure can be viewed at wileyonlinelibrary.com]

comorbidities in individuals with CP, including a comparison of the distribution of the same disorders in the general population. In addition, we attempted to classify comorbidities associated with CP as cocausal, complications, or co-occurring, to gain a better understanding of how the brain injury may influence the overall burden of disease.

Another strength of this study is the reduction of selection bias by the use of data from a large, national, population-based registry. Moreover, the NPR has a service to evaluate the quality of diagnosis codes recorded in the NPR versus each of the Norwegian national quality medical registries,[13] where numerous studies have shown high completeness of data in the NPR. This includes a validation study of all CP diagnosis codes recorded in the NPR for individuals during our study period, in cooperation with the Cerebral Palsy Registry of Norway.[3] The completeness (sensitivity) of CP diagnosis codes in the NPR was reported to be 98%, and there was good agreement between the distribution of ICD-10 CP subtypes recorded in the NPR and the Cerebral Palsy Registry of Norway.[3] On the other hand, most of the remaining diagnosis codes have not been through a validation process, and, therefore, data quality may vary. Additionally, because the NPR became person-identifiable from 2008, data from before this time are missing. Although this information bias is a non-differential misclassification that applies to the entire population, it may result in an underestimation of risk of those disorders that are often recorded only at an early age.

Using diagnosis codes recorded in a national administration registry is not unproblematic. Data in this study solely describe those disorders recorded by the specialist healthcare services. Therefore, less severe disorders, such as respiratory infections, are underdiagnosed because they are often treated in the primary healthcare services, or because medical care is not sought for them. Moreover, there may be a disproportionately higher recording of milder

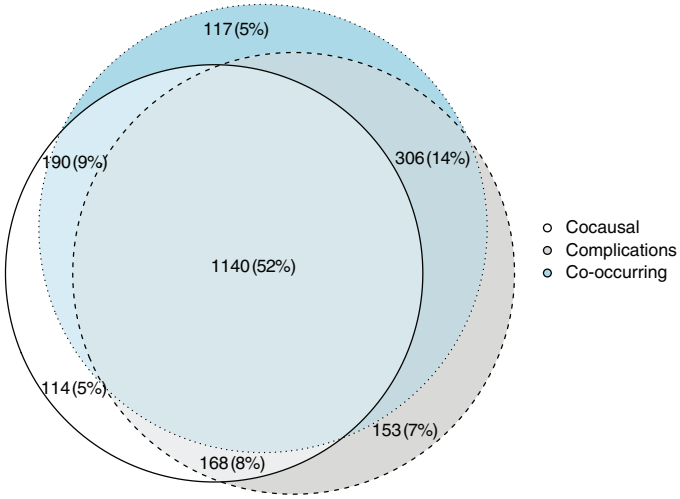

Figure 2: Area-proportional Venn diagram of the proportion of individuals with cerebral palsy per comorbidity category.

conditions for individuals with CP, who are already being followed by the specialist healthcare services, than for the general population. In fact, because individuals with CP are continually followed-up by specialists, the chances of being diagnosed with a comorbidity and recorded in the NPR is increased (Berkson's bias).[14]

Also, because clinical information is not reported to the NPR, a 100% correct classification of disorders within the medical, neurological, and mental/behavioural disorder categories, as well as within the comorbidity categories (cocausal, complications, and co-occurring) in individuals with CP is not likely to be possible. This limitation is particularly evident regarding the categorization of mental/behavioural disorders, which can be regarded as either cocausal, a complication, or co-occurring with CP. For example, disorders such as anxiety and eating disorders, classified as co-occurring, may be more likely to develop in individuals with a vulnerability due to an early brain insult or the experience of being different from peers, and, therefore, may also be categorized as cocausal or complications. Thus, caution is needed in the interpretation of the exact proportions of each comorbidity category. However, this limitation does not affect the main results showing the high overall burden of disease in individuals with CP. It is also noteworthy that some co-occurring disorders (i.e. genital and immune disorders) that are not intuitively considered cocausal or complications were more commonly diagnosed in the population with CP than in the general population.

Comparison with other studies

Several studies have reported on the most common comorbidities associated with CP. In 2009, a smaller study was performed describing five comorbidities (cortical blindness, severe hearing impairment, non-verbal communication, gavage feeding, and seizures) in children born between 1999 and 2002 and recorded in the Quebec Cerebral Palsy Registry.[15] Although we are not able to compare distributions of comorbidities between that study and ours because of the explicit severity of their chosen comorbidities, and a lack of comparison with a control group, both studies found that children with more severe CP subtypes had a higher proportion and number of comorbidities.

Meehan et al. reported on paediatric hospital admissions between 2008 and 2012 for children born between 1993 and 2008 and registered in the Victorian Cerebral Palsy Register.[16] They used ICD-10 diagnosis codes to explore admission rates and found that 66% of children with CP had one or more hospital admission. This proportion is lower than in our study most likely because we included all hospitals in the country, as well as both inpatient admissions and outpatient consultations. Meehan et al. found respiratory disease was the most common medical disorder and musculoskeletal system diseases the most common surgical disorder; both are also among the most common medical disorders in our study. Lastly, Novak et al. performed a systematic review of the rates of 13 comorbidities in individuals with CP.[11] Although a comparison in proportions between this review and our study is difficult because of differences in the categorization of comorbidities, the proportion of individuals with epilepsy and hip dislocation were similar. However, Novak et al. reported a higher proportion of intellectual disability (49%) compared with 28% in our study, as well as 23% with a sleep disorder, compared with 8% in our study. Although the

findings of the aforementioned studies are consistent with our results of an increased risk of the same disorders, along with a higher occurrence for those with a more severe CP subtype, these studies lack a comprehensive evaluation of disorders, as well as a comparison to the general population.

Interpretation

The higher burden of disease in individuals with CP compared with their peers in the general population is mainly explained by the excess risk of disorders categorized as cocausal with CP as well as complications of CP. However, even disorders classified as coincidentally co-occurring with CP were significantly more common in individuals with CP than in the general population. Nevertheless, we speculate that for some comorbidities classified as co-occurring, the exact aetiology is unknown, and it is possible that the injury to the developing brain and/or complications of CP may directly or indirectly play a role. For some of these disorders (e.g. circulatory system diseases), the higher occurrence might be reasonable since they may be related to reduced physical activity, while a higher prevalence of metabolic and immune disorders is not as evident. In addition, some of the co-occurring comorbidities may have a common cause, or may be complications that are not apparent in registry-based data. Conversely, several of the comorbidities are not intuitively related to CP. Therefore, before reasonable speculations on mechanisms can be explained, more research should be undertaken and results confirmed in other populations.

CONCLUSION

Individuals with CP have a considerably higher burden of medical, neurological, and mental/behavioural disorders compared with the general population. As expected, comorbidities considered to be cocausal with CP or complications of CP were common. However, surprisingly, this was also the case for comorbidities regarded as coincidentally co-occurring with CP, i.e. that are not directly caused by or complications of CP. In addition, the majority of individuals with CP, regardless of subtype, had a high number of comorbidities. Thus, identification of comorbidities and appropriate interventions are necessary to minimize or prevent the impact they may have on participation and quality of life.

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SUPPORTING INFORMATION

The following additional material may be found online:

Table SI: Disorder categories based on ICD-10 diagnosis codes.

Table SII: Comorbidity categories based on ICD-10 diagnosis codes, and as described by Brown et al.[9]

Table SIII: Occurrence of comorbidities in individuals with cerebral palsy born 1996 to 2010 versus the same disorders in the general population born during the same years, per sex.

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Table S1: Disorder categories based on International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10) diagnosis codes.

Disorder category	ICD-10 codes included	ICD-10 codes excluded
Medical disorders		
Intestinal infectious diseases	A00-A09	
Malignant neoplasms	Block C	C70-C72 CNS malignant neoplasms
Benign neoplasms	D00-D48	D32-D34 Benign neoplasm of meninges, brain and other parts of central nervous system D42-D43 Neoplasm of uncertain or known behavior of meninges, brain and central nervous system
Blood disorders	D50-D77	
Immune disorders	D80-D89	
Endocrine disorders	E00 E35	
Malnutrition and eating difficulties	E40-E46 R13 R63-R64	
Nutritional deficiencies	E50-E64	
Obesity	E65-E68	
Metabolic disorders	E70-E90	E73 Lactose intolerance E86-E87 Disorders of fluid, electrolyte or acid-base balance E90 Nutritional disorders
Hearing impairment including deafness	H90-H91	
Visual impairment including blindness	H54	
Circulatory system diseases	Block I	I60-I69 Cerebrovascular diseases I80 Phlebitis and thrombophlebitis I83-I99 Edema
Respiratory infections (acute)	J00-J22	
Respiratory diseases	J30-J47 J95-J99	
Digestive system diseases	Block K	
Skin and subcutaneous tissue diseases	Block L	
Musculoskeletal system and connective tissue diseases	Block M	M00-M03 Infectious arthropathies M41 Scoliosis M60 Myositis M65 Synovitis and tenosynovitis M86 Osteomyelitis
Scoliosis	M41	
Urinary tract disorders	N00-N39	
Genital disorders	N40-N99	N41 Inflammatory diseases of prostate
Congenital malformations (excluding nervous system)	Block Q	Q00-Q07 Congenital malformations of nervous system Q90-Q99 Chromosomal abnormalities
Chromosomal abnormalities	Q90-Q99	
Dislocation of hip	S73.0	

Disorder category	ICD-10 codes included	ICD-10 codes excluded
Neurological disorders		
CNS infections and inflammatory diseases	A39 A80-A89 B003-B004 B010-B011 B020-B022 B050-B051 G00-G09	
CNS neoplasms (malignant and benign)	C70-C72 D32-D33 D42-D43	
Sleep disorders	F51 G47	
Epilepsy	G40-G41	
Headache disorders	G43-G44 R51	
Cerebrovascular diseases	G45-G46 I60-I69	
Diseases of the nervous system - other	Block G	G00-G09 Inflammatory diseases of the central nervous system G40-G47 Epilepsy, headache, cerebrovascular and sleep disorders G80-G83 Cerebral palsy and other paralytic syndromes
Congenital malformations of the nervous system	Q00-Q07	
Nervous and musculoskeletal system symptoms	R25-R29	
Mental/behavioral disorders		
Depressive episode(s)	F32-F33	
Anxiety disorders	F40-F41	
Obsessive-compulsive disorder	F42	
Eating disorders	F50	
Intellectual disability	F70-F79	
Psychological development disorders	F80-F89	F84 Autism
Autism	F84	
ADHD	F90	
Behavioral and emotional disorders	F91-F98	
Psychiatric disorders - other	Block F	F30-F33 Manic, bipolar and depressive episodes F40-F42 Anxiety and OCD F50-F53 Eating, sleep and puerperal mental disorders F70-F99 Intellectual disability, disorders of psychological development, behavioral, emotional and unspecified

Table SII: Comorbidity categories based on International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10) diagnosis codes, and as described by Brown and Eunson.[1]

Comorbidity category	ICD-10 codes included	ICD-10 codes excluded
Cocausal: Disorders caused by the same injury to the immature brain which caused CP.		
Intellectual disability	F70-F79	
Psychological development disorders	F80-F89	F84 Autism
Autism	F84	
ADHD	F90	
Behavioral and emotional disorders	F91-F98	
Epilepsy	G40-G41	
Hearing impairment including deafness	H90-H91	
Visual impairment including blindness	H54	
Congenital malformations of the nervous system	Q00-Q07	
Chromosomal abnormalities	Q90-Q99	
Nervous and musculoskeletal system symptoms	R25-R29	
Complications: Disorders that are complications of the main CP condition.		
Blood disorders	D50-D77	
Malnutrition and eating difficulties	E40-E46 R13 R63-R64	
Nutritional deficiencies	E50-E64	
Obesity	E65-E68	
Sleep disorders	F51 G47	
Headache disorders	G43-G44 R51	
Respiratory infections (acute)	J00-J22	
Digestive system diseases	Block K	
Musculoskeletal system and connective tissue diseases	Block M	M00-M03 Infectious arthropathies M41 Scoliosis M60 Myositis M65 Synovitis and tenosynovitis M86 Osteomyelitis
Scoliosis	M41	
Dislocation of hip	S73.0	
Co-occurring: Disorders not caused by the injury to the immature brain, nor are complications of the main CP condition.		
Intestinal infectious diseases	A00-A09	
CNS infections and inflammatory diseases	A39 A80-A89 B003-B004 B010-B011 B020-B022 B050-B051 G00-G09	

[1] Brown JK, Eunson P, Bax M. Heterogeneity in Cerebral Palsy: Variations in Neurology, Comorbidity and Associated Conditions. In: Bax M, Gillberg C, editors. *Comorbidities in Developmental Disorders*. London: Mac Keith Press; 2010. p. 20-39.

Comorbidity category	ICD-10 codes included	ICD-10 codes excluded
Co-occurring (continued)		
CNS neoplasms (malignant and benign)	C70-C72 D32-D33 D42-D43	
Malignant neoplasms	Block C	C70-C72 CNS malignant neoplasms
Benign neoplasms	D00-D48	D32-D34 Benign neoplasm of meninges, brain and other parts of central nervous system D42-D43 Neoplasm of uncertain or known behavior of meninges, brain and central nervous system
Immune disorders	D80-D89	
Endocrine disorders	E00 E35	
Metabolic disorders	E70-E90	E73 Lactose intolerance E86-E87 Disorders of fluid, electrolyte or acid-base balance E90 Nutritional disorders
Depressive episode(s)	F32-F33	
Anxiety disorders	F40-F41	
Obsessive-compulsive disorder	F42	
Eating disorders	F50	
Psychiatric disorders - other	Block F	F30-F33 Manic, bipolar and depressive episodes F40-F42 Anxiety and OCD F50-F53 Eating, sleep and puerperal mental disorders F70-F99 Intellectual disability, disorders of psychological development, behavioral, emotional and unspecified
Cerebrovascular diseases	G45-G46 I60-I69	
Diseases of the nervous system - other	Block G	G00-G09 Inflammatory diseases of the central nervous system G40-G47 Epilepsy, headache, cerebrovascular and sleep disorders G80-G83 Cerebral palsy and other paralytic syndromes
Circulatory system diseases	Block I	I60-I69 Cerebrovascular diseases I80 Phlebitis and thrombophlebitis I83-I99 Edema
Respiratory diseases	J30-J47 J95-J99	
Skin and subcutaneous tissue diseases	Block L	
Urinary tract disorders	N00-N39	
Genital disorders	N40-N99	N41 Inflammatory diseases of prostate
Congenital malformations (excluding nervous system)	Block Q	Q00-Q07 Congenital malformations of nervous system Q90-Q99 Chromosomal abnormalities

Table SIII: Occurrence of comorbidities in individuals with cerebral palsy (CP) born 1996 to 2010 versus the same disorders in the general population (GP) born during the same years, per sex.

	CP				CP		GP							
	male (n=1330)		female (n=972)		male versus female		male (n=496 064)		female (n=468 394)		CP versus GP male		CP versus GP female	
Disorder category	n	%	n	%	RD	99% CI	n	%	n	%	RD	99% CI	RD	99% CI
Medical disorders	1162	87.4	832	85.6	0.02	-0.01 - 0.04	242307	48.8	218703	46.7	0.39	0.36 - 0.41	0.39	0.36 - 0.42
Musculoskeletal system and connective tissue diseases (excl. scoliosis)	677	50.9	470	48.4	0.03	-0.01 - 0.06	45232	9.1	49892	10.7	0.42	0.38 - 0.45	0.38	0.34 - 0.42
Digestive system diseases	529	39.8	371	38.2	0.02	-0.02 - 0.05	59573	12.0	55435	11.8	0.28	0.24 - 0.31	0.26	0.22 - 0.30
Congenital malformations (excl. nervous system)	463	34.8	311	32.0	0.03	-0.01 - 0.06	45824	9.2	35383	7.6	0.26	0.22 - 0.29	0.24	0.21 - 0.28
Respiratory diseases	406	30.5	277	28.5	0.02	-0.03 - 0.07	69289	14.0	56252	12.0	0.17	0.13 - 0.20	0.17	0.13 - 0.20
Respiratory infections	372	28.0	254	26.1	0.02	-0.01 - 0.05	40534	8.2	32795	7.0	0.20	0.17 - 0.23	0.19	0.16 - 0.23
Malnutrition and eating difficulties	313	23.5	216	22.2	0.01	-0.03 - 0.06	6334	1.3	5634	1.2	0.22	0.19 - 0.25	0.21	0.18 - 0.25
Skin and subcutaneous tissue diseases	214	16.1	144	14.8	0.01	-0.03 - 0.05	40913	8.2	36935	7.9	0.08	0.05 - 0.10	0.07	0.04 - 0.10
Scoliosis	194	14.6	152	15.6	-0.01	-0.05 - 0.03	2476	0.5	4113	0.9	0.14	0.12 - 0.17	0.15	0.12 - 0.18
Intestinal infectious diseases	150	11.3	100	10.3	0.01	-0.02 - 0.04	13597	2.7	11955	2.6	0.09	0.06 - 0.11	0.08	0.05 - 0.10
Hearing impairment/deafness	134	10.1	80	8.2	0.02	-0.01 - 0.05	9805	2.0	8548	1.8	0.08	0.06 - 0.10	0.06	0.04 - 0.09
Genital disorders	105	7.9	54	5.6	0.02	-0.00 - 0.05	30324	6.1	10953	2.3	0.02	-0.00 - 0.04	0.03	0.01 - 0.05
Urinary tract disorders	95	7.1	106	10.9	-0.04	-0.07 - -0.01	10391	2.1	16168	3.5	0.05	0.03 - 0.07	0.08	0.05 - 0.10
Endocrine disorders	79	5.9	94	9.7	-0.04	-0.07 - -0.01	8460	1.7	11360	2.4	0.04	0.03 - 0.06	0.07	0.05 - 0.10
Blood disorders	81	6.1	50	5.1	0.01	-0.02 - 0.03	5468	1.1	5486	1.2	0.05	0.03 - 0.07	0.04	0.02 - 0.06
Visual impairment/blindness	56	4.2	34	3.5	0.01	-0.01 - 0.03	408	0.1	384	0.1	0.03	0.02 - 0.05	0.03	0.02 - 0.05
Circulatory system diseases	53	4.0	36	3.7	0.00	-0.02 - 0.02	6369	1.3	6146	1.3	0.03	0.01 - 0.04	0.02	0.01 - 0.04
Chromosomal abnormalities	46	3.5	23	2.4	0.01	-0.01 - 0.03	1976	0.4	1604	0.3	0.03	0.02 - 0.04	0.02	0.01 - 0.03
Obesity	44	3.3	31	3.2	0.00	-0.02 - 0.02	4808	1.0	5048	1.1	0.02	0.01 - 0.04	0.02	0.01 - 0.04
Benign neoplasms	38	2.9	42	4.3	-0.02	-0.04 - 0.01	11417	2.3	13861	3.0	0.01	-0.01 - 0.02	0.01	-0.00 - 0.03
Metabolic disorders	21	1.6	15	1.5	0.00	-0.01 - 0.01	2002	0.4	2037	0.4	0.01	0.00 - 0.02	0.01	0.00 - 0.02
Nutritional deficiencies	19	1.4	16	1.6	-0.00	-0.02 - 0.01	1454	0.3	1577	0.3	0.01	0.00 - 0.02	0.01	0.00 - 0.02
Immune disorders	15	1.1	14	1.4	-0.00	-0.02 - 0.01	666	0.1	526	0.1	0.01	0.00 - 0.02	0.01	0.00 - 0.02
Dislocation of hip	15	1.1	6	0.6	0.01	-0.01 - 0.02	109	0.0	68	0.0	0.01	0.00 - 0.02	0.01	-0.00 - 0.01
Malignant neoplasms	10	0.8	9	0.9	-0.00	-0.01 - 0.01	1238	0.2	974	0.2	0.01	-0.00 - 0.01	0.01	-0.00 - 0.02
Neurological disorders	813	61.1	590	60.7	0.00	-0.05 - 0.06	35876	7.2	33834	7.2	0.54	0.51 - 0.57	0.54	0.49 - 0.58
Epilepsy	527	39.6	371	38.2	0.02	-0.04 - 0.07	6170	1.2	5177	1.1	0.38	0.35 - 0.42	0.37	0.33 - 0.41
Neurological disorders - other	400	30.1	266	27.4	0.03	-0.02 - 0.08	11019	2.2	9548	2.0	0.28	0.25 - 0.31	0.25	0.22 - 0.29
Nervous and musculoskeletal system symptoms	243	18.3	180	18.5	-0.03	-0.05 - 0.04	9003	1.8	7840	1.7	0.17	0.14 - 0.19	0.17	0.14 - 0.20

Congenital malformations of nervous system	142	10.7	97	10.0	0.01	-0.03 - 0.04	1029	0.2	933	0.2	0.11	0.08 - 0.13	0.10	0.07 - 0.12
Sleep disorders	115	8.6	77	7.9	0.01	-0.02 - 0.04	4840	1.0	3823	0.8	0.08	0.06 - 0.10	0.07	0.05 - 0.10
Headache disorders	70	5.3	62	6.4	-0.01	-0.04 - 0.01	10370	2.1	13521	2.9	0.03	0.02 - 0.05	0.04	0.02 - 0.06
Cerebrovascular diseases	57	4.3	52	5.3	-0.01	-0.03 - 0.01	474	0.1	348	0.1	0.04	0.03 - 0.06	0.05	0.03 - 0.07
CNS infections and inflammatory diseases	28	2.1	24	2.5	-0.00	-0.02 - 0.01	1392	0.3	1128	0.2	0.02	0.01 - 0.03	0.02	0.01 - 0.04
CNS neoplasms	8	0.6	9	0.9	-0.00	-0.01 - 0.01	492	0.1	422	0.1	0.01	-0.00 - 0.01	0.01	0.00 - 0.02
Mental/behavioral disorders	726	54.6	513	52.8	0.02	-0.04 - 0.07	75911	15.3	60780	13.0	0.39	0.36 - 0.43	0.40	0.36 - 0.44
Intellectual disability	402	30.2	245	25.2	0.05	0.00 - 0.10	4216	0.8	2781	0.6	0.29	0.26 - 0.33	0.27	0.21 - 0.28
Psychological developmental disorders (excl. autism)	269	20.2	180	18.5	0.02	-0.03 - 0.06	17410	3.5	8790	1.9	0.17	0.14 - 0.20	0.17	0.13 - 0.20
Behavioral and emotional disorders	136	10.2	90	9.3	0.01	-0.02 - 0.04	29847	6.0	17816	3.8	0.04	0.02 - 0.06	0.06	0.03 - 0.08
ADHD	132	9.9	61	6.3	0.04	0.01 - 0.07	26198	5.3	11318	2.4	0.05	0.03 - 0.07	0.04	0.02 - 0.06
Autism	75	5.6	24	2.5	0.03	0.01 - 0.05	9029	1.8	2787	0.6	0.04	0.02 - 0.06	0.02	0.01 - 0.03
Psychiatric disorders - other	55	4.1	55	5.7	-0.02	-0.04 - 0.01	14271	2.9	18776	4.0	0.01	-0.00 - 0.03	0.02	-0.00 - 0.04
Anxiety disorders	24	1.8	46	4.7	-0.03	-0.05 - -0.01	6758	1.4	12664	2.7	0.00	-0.01 - 0.01	0.02	0.00 - 0.04
Depressive episode	17	1.3	33	3.4	-0.02	-0.04 - -0.00	5833	1.2	13653	2.9	0.00	-0.01 - 0.01	0.01	-0.01 - 0.02
Obsessive-compulsive disorder	11	0.8	10	1.0	-0.00	-0.01 - 0.01	1811	0.4	2015	0.4	0.01	-0.00 - 0.01	0.01	-0.00 - 0.01
Eating disorders	8	0.6	18	1.9	-0.01	-0.03 - -0.00	714	0.1	4382	0.9	0.01	-0.00 - 0.01	0.01	-0.00 - 0.02

Data recorded in the NPR between 2008 and 2017

CNS=central nervous system

RD=risk difference