UNIVERSITY OF COPENHAGEN
FACULTY OF HEALTH AND MEDICAL SCIENCES

PhD Thesis

Moug Al-Bakri, MD

Childhood cataract – effects on health and life.
A cohort study

This thesis was submitted to the Graduate School of Health and Medical Sciences,
University of Copenhagen: June 15th, 2021

Til min mor og Ayla

Author: **Moug Al-Bakri**, MD
Department of Ophthalmology, Rigshospitalet, Denmark
Department of Clinical Medicine, Faculty of Health and Medical Sciences.
University of Copenhagen, Denmark.

Principal supervisor: Associate Professor **Line Kessel**, MD, PhD, FEBO
Department of Ophthalmology, Rigshospitalet, Denmark.
Department of Clinical Medicine, Faculty of Health and Medical sciences.
University of Copenhagen, Denmark.

Co-supervisors:

Associate Professor **Daniella Bach-Holm**, MD, PhD, FEBO
Department of Ophthalmology, Rigshospitalet, Denmark
Department of Clinical Medicine, Faculty of Health and Medical Sciences. University of Copenhagen, Denmark.

Dorte Ancher Larsen, MD
Department of Ophthalmology, Aarhus University Hospital, Denmark.

Assessment committee:

Chair: Professor **Christina E. Høi-Hansen**, MD, DMSc
Department of Pediatrics and Adolescent Medicine, Rigshospitalet, Denmark and Department of Clinical Medicine, Faculty of Health and Medical Sciences. University of Copenhagen, Denmark.

Opponents:

Professor **Jesper Østergaard Hjortdal** MD, PhD
Department of Ophthalmology, Aarhus University Hospital, Denmark.
Department of Clinical Medicine, Aarhus University, Denmark.

Professor **Marie-José Tassignon**, MD, PhD, FEBO, FEBOS-CR Past Chief and Chair, Department of Ophthalmology Antwerp University
University Hospital Antwerp, Belgium.

This thesis was financially supported by the following foundations:

Øjenfonden
Øjenforening, Værn Om Synet (Fight for Sight Denmark)
Synoptik-Fond
Carl and Nicoline Larsen's Fond

Acknowledgements

Firstly, I wish to express my deepest gratitude to my supervisors, **Line Kessel** and **Daniella Bach-Holm,** for their wise guidance and immense knowledge. Their insightful feedback pushed me to sharpen my thinking and brought my work to a higher level. Their high professionalism, research ethic and thorough work are valuable and inspiring. I would also like to thank my co-supervisor, **Dorte Ancher Larsen**, who made the distance to Aarhus shorter. For this, I am extremely grateful.

Special thanks must go to my collaborators**. Volkert Siersma**, for his valuable statistical assistance and interesting socio-political discussions. **Anne Mette**, for her active participation and for giving this thesis a new interesting twist. Additionally, I owe many thanks to the optometrists **Hanne Nielsen** and **Vibeke Brandt** who opened their doors for me and enthusiastically helped me.

I am deeply grateful to **Mark Alberti** for introducing me to R and Casia OCT. I have the privilege of being surrounded by supportive colleagues at Ø37 that all made my daily life more enjoyable**.** I would particularly like to thank **Hajer** (Haydoori) for her unconditional cheering, **Mohamed** for preserving my pessimistic moments, **Marie** for being diligent in shared tasks**, Jasmine** for being supportive, **Mads** for entertaining and sharing improvement of presentation skills, **Jesper** for his academic discussions, **Kristian** for "proofing" academic thoughts and ideas**, Mette** for believing in my R skills, **Christina** for understanding challenges in a registry study and **Diana** for sharing thoughts.

Additionally, I would like to give a very special acknowledgment to **Afrouz Ahmadzadeh** for being such a unique and true friend - I know that I can always count on her to be there whenever I need it in my private life and career. Afrouz Ahmadzadeh, **Michael Møller** and **Anders Hvid-Hansen**, I appreciate your company – We shared frustrations, happiness and unforgettable Yobi sushi- moments together.

I would thank my friends, **Mina Amiri** and **Kristine Hundrup**, who provided happy distractions to rest my mind outside research. I deeply thank my family for supporting me emotionally throughout this journey and my life in general: my dear mother, **Aumayma Hamdoon,** for her never-ending love. I wish we could experience this millstone together, but severe dementia has unfortunately overtaken this long-awaited joy. However, your lovely spirit will always be my driving force. I would also thank my father, **Adil Al-Bakri**, for taking care of Ayla when I need it, my brother, **Manaf Al-Bakri**, for being extremely supportive to me throughout this entire process and has made countless sacrifices to help me get to this point, my sister, **Mayasa Al-Bakri,** for her motivation and sympathetic ear despite the long geographical distance between us, sister in law, **Zeena Mahdi**, for her invaluable assistance in my private life, and brother in law, **Backer Rassim,** for his encouragement. Finally, I wish to express my heartfelt gratitude to my wonderful daughter, **Ayla**, to give me the daily motivation and meaning in life. I dedicate this milestone to her and to my mother - I love you.

Without such a team behind me, I doubt that I would be in this place today.

Table of contents

Abbreviations

ADHD: Attention-Deficit/Hyperactivity Disorder

AKM: Arbejdsklassifikationsmodulet = Work classification module

ASD: Autism Spectrum Disorders

BEF: Befolkning = Population

BIL: Bag-in-the-Lens

CPR: Det Centrale Personregister = The Danish Civil Registration System

DIAG: Diagnosis/Diagnoses

DPI: Disposable Personal Income

IATS: Infant Aphakia Treatment Study

ICD-10: International Classification of Diseases, 10^{th} revision

IND: Indkomst = Income

IOL: Intraocular lens

NPR: National Patient Registry

OCD: Obsessive Compulsive Disorder

PCO: Posterior capsular opacification

PFV: Persistent fetal vasculature

PSYK: Psykiatrisk = Psychiatric

SDQ: Strengths and Difficulties Questionnaire

UDDA: Uddannelse = Education

VAO: Visual axis opacification

YAG: Yttrium – aluminum -garnet

List of papers

Paper I

Children with congenital and childhood cataract require frequent follow-up visits and examinations in general anaesthesia: considerations for the strain on families

Moug Al-Bakri MD, Birgit Sander M.Sc. PhD, Daniella Bach-Holm MD, PhD, Dorte Ancher Larsen MD, Hanne Jensen MD, D.Med.Sci., Line Kessel MD, PhD.

Status: Accepted and published in 2019, 97 (8): 778-783, DOI: 10.1111

Paper II

Socio-economic status in families affected by childhood cataract

Moug Al-Bakri MD, Daniella Bach-Holm MD, PhD, Dorte Ancher Larsen MD, Volkert Siersma PhD, Line Kessel MD, PhD.

Status: Accepted and published in 2020, DOI: 10.1111, AOS:14768

Paper III

Increased incidence of mental disorders in children with cataract – findings from a population-based study

Moug Al-Bakri MD, Anne Mette Skovgaard MD, DM Sci, Daniella Bach-Holm MD, PhD, Dorte Ancher Larsen MD, Volkert Siersma PhD, Line Kessel MD, PhD.

Status: Manuscript is submitted

Danish summary (Dansk resumé)

Denne afhandling handler om børnekatarakt med særligt fokus på den betydning, sygdommen har for de berørte børn og familier. Vi ønskede derfor I) at evaluere hvor ofte disse børn skal følges og undergå fuld bedøvelse, II) at undersøge familiernes socioøkonomiske forhold samt III) at undersøge børnenes psykiske helbred.

Opfølgning af børn med katarakt kræver et langvarigt og ofte belastende forløb med amblyopi-behandling med klaptræning dagligt hjemme samt mange hospitalsbesøg med henblik på syns - og optisk rehabilitering samt screening for postoperative komplikationer, hvis børnene er opererede. Forældrene er en vigtig og uundværlig del af dette sygdomsforløb.

Paper I: Ved journalgennemgang af 227 børn opgjorde vi antal besøg og operationer/undersøgelser i fuld bedøvelse. Vi fandt, at de opererede børn i gennemsnit har 10 hospitalsbesøg i det første leveår og at 50% af de bilateralt opererede og 25% af de unilateralt opererede børn kommer i fuld bedøvelse 5 gange i de første 7 leveår.

Paper II: Ved brug af nationale registre kunne vi sammenligne den socioøkonomiske status i familier til børn med katarakt med en aldersmatchet baggrundsbefolkning. Vi fandt, at kataraktgruppen i højere grad tilhørte en lavindkomsts population med flere forældre udenfor arbejdsmarkedet, lavere uddannelsesniveau samt en anderledes familiestruktur. Den socioøkonomiske forskel var til stede før kataraktdiagnosen og blev hverken påvirket i positiv eller negativ retning efter diagnosen.

Paper III: Psykisk komorbiditet blandt børn med katarakt og en aldersmatchet baggrundsbefolkning blev undersøgt ved brug af oplysninger fra Landspatientregistret. Vi fandt en fordobling i forekomsten af psykisk komorbiditet og en 4 gange øget risiko for angst i kataraktgruppen, selv når der blev justeret for systemisk komorbiditet, forældrenes mentale helbred, socioøkonomi, barnets fødeland samt andre relevante confoundere. Risikoen for psykiatrisk komorbiditet var især høj i gruppen af børn diagnosticeret med katarakt i de første tre leveår.

Resultaterne i denne afhandling tegner et billede af en udsat population bestående af psykisk skrøbelige børn og forældre med et lavere socioøkonomisk niveau, hvilket samlet set kan påvirke deres compliance og potentielt reducere behandlingsudbyttet. Denne viden motiverer til ændringer i den kliniske tilgang til disse børn og deres familier, hvor mængden, arten og gentagelse af information må justeres i forhold til forældrenes forståelsesniveau, og hvor eksempelvis længere konsultationstid kan hjælpe til at give en bedre forståelse af sygdommen og behandlingen. Tidlig screening af psykisk sygdom kan rette fokus på mulighed for at forebygge psykiatriske følger.

Summary

This thesis focuses on childhood cataract with particular emphasis on the influence of the disease on the affected children and families. We aimed to I) evaluate how often those children are examined and how often they undergo general anesthesia, II) examine the families' socio-economic status and III) examine the children's mental health.

The follow-up of children with cataract is lifelong and can be stressful with several hospital visits aimed at visual and optical rehabilitation and screening for postoperative complications, in addition to amblyopia therapy with daily patching of the better seeing eye at home. The parents are an important and indispensable part of the disease management.

Paper I: Using medical records of 227 children, we were able to determine the number of visits and surgeries/ examinations in general anesthesia. We found that the operated children on average have 10 hospital visits in the first year of life, 50% of the bilaterally operated children and 25% of the unilaterally operated children undergo general anesthesia events 5 times during the first 7 years of life.

Paper II: By using national registries, we were able to compare socio-economic status in families with children affected by cataract with an age-matched background population. We found that the cataract group were more likely to belong to a low-income population with more parents outside the workforce and with a lower educational level and a different family structure. This socio-economic difference was present prior to the cataract diagnosis and did not change neither in a positive nor a negative direction after the diagnosis.

Paper III: Psychiatric comorbidity among children with cataract and an age-matched background population was examined using the National Patient Registry. We found a doubling in the incidence of psychiatric comorbidity and a four-fold increased risk for anxiety even after adjusting for the child's geographical birth origin, systemic comorbidity, parental mental health, socio-economic status and other relevant confounders. The risk for psychiatric comorbidity was higher in the group of children diagnosed with cataract in the first three years of life.

The results in this thesis paint a picture of a vulnerable population consisting of mentally fragile children and parents with lower socioeconomic status which can influence compliance to treatment and reduce the treatment outcome. This knowledge motivates changes to the clinical approach of these patients and their families where the amount, nature and repetition of information must be directed to the parents and child's level of understanding and where longer consultation time may contribute to a better understanding of the disease and the treatment. Early screening for mental disease may assist in avoiding overt psychiatric disease.

Introduction

Childhood cataract is rare but it is the most important cause of treatable childhood blindness worldwide [1]. Cataract refers to a lens opacity [2,3] that impairs visual function and if it is present at birth, it may inhibit early visual development [4] .

The management of children with childhood cataract requires years of close monitoring of visual development and screening for complications if the children are operated, e.g. secondary glaucoma or visual axis opacification. The optical rehabilitation requires constant adjustment as the eye grows and sometimes examinations have to be performed under general anesthesia in order to ensure an optimal examination [5]. Amblyopia therapy is often needed and requires the cooperation of the parents or often day care institutions. Thus, cataract in childhood does not only affect the children but also their immediate family as they are included in follow-up visits at hospitals and are responsible for the amblyopia treatment at home [6].

Childhood cataract can occur isolated or in combination with somatic comorbidities [2], some of which have an association with mental disorders, e.g. trisomy 21, microcephalia and congenital infections [3,7–12]. Chronic disease and/or visual impairment early in life may potentially result in a higher risk of developing reactive mental disorders like anxiety, eating disorders or mood disorders and interrupt normal social interaction [1,6,13,14].

Main objectives

The main objective of this thesis was to evaluate the load on children and families of children with cataract by conducting three studies specifically by evaluating:

- The amount of time spent on hospital visits and examinations and surgical procedures under general anesthesia.
- The social gradient in families affected by childhood cataract prior to cataract diagnosis compared to an age- and sex-matched groups of children without cataract and to evaluate whether the socio-economic status in cataract families was affected by the diagnosis.
- Exploring the incidence of mental disorders in children with and without cataract, considering potential confounders such as parental socio-economic status, family psychiatric load, and the children's somatic comorbidities associated with increased risk of cataract and mental disorder.

Background

Childhood cataract – definition, aetiology and epidemiology

Congenital cataract refers to a lens opacity present at birth whereas acquired cataract usually presents later in childhood. Cataract in children covers a broad spectrum of severity from visually insignificant to dense blinding cataract. They may be congenital or acquired, inherited or sporadic, unilateral or bilateral, stationary or progressive. Sometimes, congenital cataracts are associated with ocular malformations, e.g. microphthalmia or a persistent hyaloid artery. Childhood cataract can be seen in relation to systemic diseases and syndromes, congenital infections, chromosomal abnormalities or occur secondary to ocular trauma or be iatrogenic due to treatment procedures like corticosteroid use or radiation exposure [3,15–17]. Bilateral cataracts are often caused by genetic changes and they are also more often associated with systemic diseases while unilateral cataracts are typically related to eye malformations [18]. However, in many cases a cause cannot be identified [2].

The incidence of congenital cataract is 1-6 cases per 10,000 live births in developed countries [19–21] and 5-15 cases per 10,000 in developing countries [22]. In Denmark, the 18 years cumulative incidence was estimated to be 10.8 per 10,000 children [23]. Globally, the pooled prevalence is estimated to be 4.24 per 10,000 children [24].

Embryology and function of the lens

The lens is a crystalline transparent biconvex structure that converges the light rays to focus on the retina [2]. Embryologically, the lens is formed from ectodermal surface beginning from the 28th day of gestation and is fully developed during the 3rd gestational month [21,25]. Mutations in genes responsible for the lens structure during the embryological period may disturb the normal developmental of the lens and carries a high risk of visual impairment [26,27]. The hyaloid artery which is a branch of the ophthalmic artery is present in the optic canal and extends from the optic disc to the posterior part of the crystalline lens through the vitreous body in the first months of gestation. It is most prominent around ninth week of gestation and regresses spontaneously during the second trimester in pregnancy [28]. A failure in this involution may result in a persistent fetal vascularization leading to an opacification of the lens [29].

Treatment and follow-up

Early detection and treatment are essential for successful management of the patients with congenital cataract as it optimizes the visual prognosis. A visually disturbing cataract that persists throughout the critical period for visual development will result in permanent deprivational amblyopia [30]. Cataract extraction is the preferred treatment of most visually disturbing cataracts. Every 3 weeks of delay in surgery of bilateral congenital cataract during the first 14 weeks after birth leads to a loss of one line on the visual chart, and surgery after 14 weeks of age results in permanent visual disability because of deprivational amblyopia [30,31]. However, the risk of surgical complications (e.g. secondary glaucoma, visual axis opacification) is higher when children undergo surgery early in life [32–34]. Timing of surgery is thus a balance between visual development and long-term complications that may potentially be blinding [35].

Surgery is performed under general anesthesia and several surgical approaches exist to remove the opaque lens from the visual axis. The child may have the optical power of the natural lens replaced by implantation of an intraocular lens (IOL) or may be left without a lens (aphakia). IOL implantation in children below the age of 6 months can be associated with an increased risk of visual axis opacification [34,36]. The visual outcomes may not significantly differ if IOL implanted or not in bilateral and unilateral cataracts [34,37–40].

Early and late surgical complications

Surgery for cataract in childhood is associated with a risk of early and late postoperative complications including secondary glaucoma, visual axis opacification, amblyopia, IOL subluxation, endophthalmitis and retinal detachment [2,31,41].

Secondary glaucoma is an important and serious postoperative complication after pediatric cataract surgery with an incidence that varies from 5.8 % - 32% after follow-up time ranging from 0 year to 25 years after primary cataract surgery [42–54]. Children with secondary glaucoma have worse visual outcomes [55] and often have to undergo additional treatments [56,57]. Several risk factors (young age at surgery, microcornea, cataract morphology, shorter axial length) are associated to secondary glaucoma development after cataract surgery in pediatric population [35,43,44,58–60]. Identification of the associated risk factors may help to monitor the children and provide treatment in time. The incidence of secondary glaucoma has been suggested to be lower in children with IOL

implantation compared to children who are left aphakic [61–64] whereas others have reported no difference in glaucoma risk in children with or without IOL implantation [33,45,65].

Visual axis opacification (VAO) also called posterior capsular opacification (PCO) is a frequent complication after pediatric cataract surgery [58]. It occurs as a combination of processes including proliferation, migration, and trans-differentiation of residual lens epithelial cells spreading to the visual axis [2]. Visual axis opacification can be removed by YAG laser capsulotomy [66] performed as an out-patient procedure in older and cooperative children. In younger children, general anesthesia and surgical removal is usually required. It has been shown that VAO can be prevented in approximately 90% of children operated for cataract by using IOL designed to place the anterior and posterior capsules between two elliptical plane haptics, Bag-in-the-Lens (BIL) [67], see **Figure 1**.

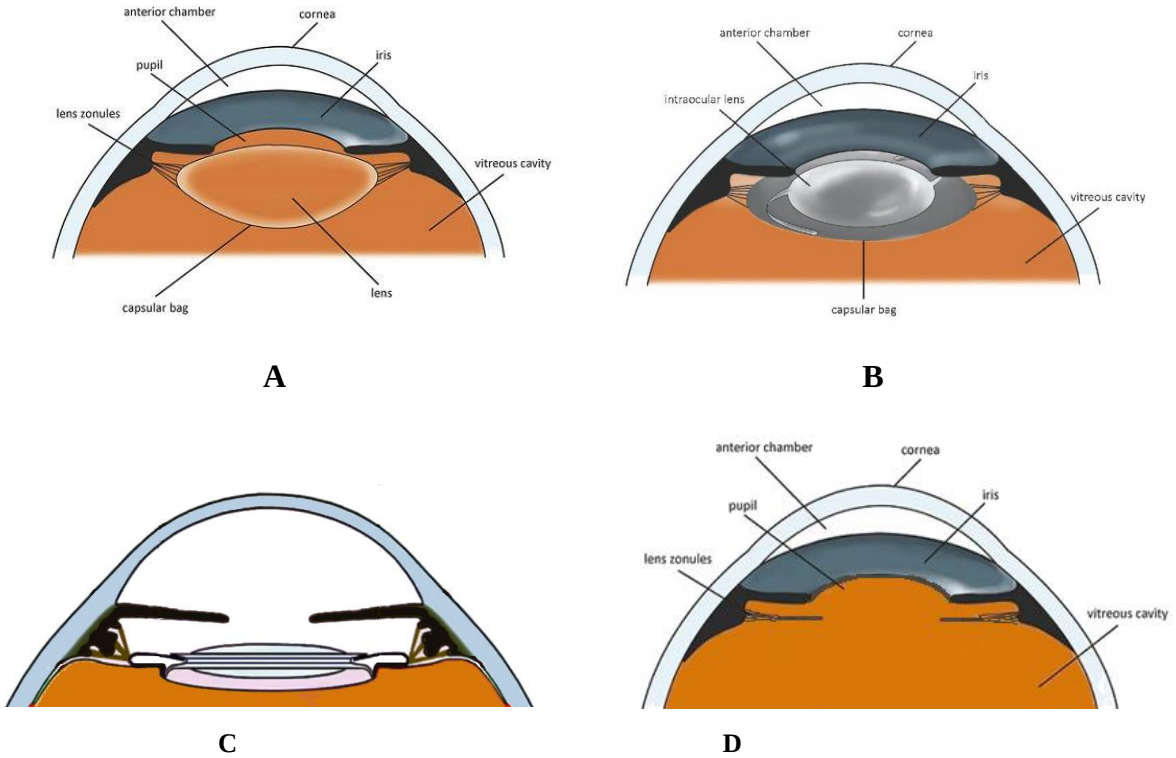


Figure 1: Cross sectional illustrations demonstrating a natural human lens (**A**), lOL implant with radiating two haptic arms insert within the capsule bag (**B**), Bag-in-the-lens implant with two elliptical plane haptics placed in between the anterior and posterior capsules in the perifery (**C**) and aphakia with abcense of lens and implant (**D**). References: Fig. A: https://sen842cova.blogspot.com/2020/04/basic-eye-anatomy.html. Fig .B: https://retinavitreous.com/treatments/dislocated_iol.php. Fig. C: Inspired from a figure presented by Dr. Tassignon at a virtual meeting arranged by Danish Ophthalmological Society in December 2020. Fig. D: Inspired from fig. A and B with own changes.

Amblyopia occurs when an impaired visual stimulation early in life results in suboptimal development of the visual pathways in the brain [2]. In this context, it may happen when retina receives a defocused image due to a cataractous lens resulting in visual stimuli deprivation at the time when the central visual pathways are forming. Early diagnosis and appropriate treatment are therefore essential in preventing poor visual outcomes. Even if the child is operated for cataract, amblyopia treatment may be necessary (most often if the cataractis unilateral). The treatment includes patching of the better seeing eye to improve vision in the poorer seeing eye. The amblyopia treatment is handled by the parents and also often by day care institutions. The compliance with occlusion therapy for amblyopia can be a challenge due to logistical and emotional difficulties [68,69].

Bacterial endophthalmitis is a rare but severe early complication with poor visual prognosis [70]. Different risk factors are associated to development of postoperative endophthalmitis, but prophylactic antibiotic treatment may minimize this risk [71].

IOL can spontaneously subluxate and can require surgical repositioning [2].

Retinal detachment is a serious complication [72] with an incidence of 1.5% 5 years after surgery [73].

Outcomes after surgery for childhood cataracts

Outcomes after surgery for childhood cataract has been reported by several publications [33,37,38,40,45,57,65,74].

So far only one randomized trial has been reported, which is The Infant Aphakia Treatment Study (IATS). 110 children with visually significant unilateral cataract operated at 1-6 months of age were randomized to IOL implantation or aphakia. The exclusion criteria were e.g. corneal diameter < 9mm, intraocular pressure ≥ 25mmHg or retinal disease. The study has 10 years of follow-up. They found no significant difference in glaucoma risk by the age of 5 [45] and 10.5 years [33] or visual acuity grated at 1 year [40] and 10.5 [74] years of age in children with or without IOL implantation but suggested that surgery at younger age increased the risk of glaucoma [45]. They also found a higher risk of visual axis opacification in pseudophakic than aphakic eyes [65].

IoLunder2 was a prospective observational cohort study evaluating 235 uni, - and bilateral operated children at the age of 0-2 years who were followed in 1-5 postoperative years. They found no significant difference in the risk of secondary glaucoma development [37,38] or in visual acuity measured 5 years after surgery [37] in children with or without IOL implantation. In their study, visual axis opacification was more common in IOL group compared to aphakia group [37].

Mataftsi et al. 's study was both based on raw data of infants included in other published studies and on data meta-analysis of results in published studies. 470 children with uni, - and bilateral cataract operated at 3 months (median) of age were included. The study has in median 6 years of follow-up. They found a lower risk of glaucoma in children with primary IOL implantation, but surgery at younger age and additional procedures independently increased the risk of glaucoma [57].

Management of childhood cataract in Denmark

In Denmark, the treatment of pediatric cataracts (≤6 years of age) is a highly specialized function that since 2010 has been managed by surgical centers at two sites: Rigshospitalet in Copenhagen and Aarhus University Hospital in Aarhus, with three surgeons operating all children. Surgically, the children are operated with a standard cataract procedure. If children are evaluated to not being able to cooperate to a potential later YAG laser capsulotomy, a posterior capsulorhexis with an anterior vitrectomy is performed peroperatively. Traditionally, children below < 6 months of age are left aphakic while children older than 6 months have an intraocular lens (IOL). Postoperatively, the children are followed by a dedicated team of surgeons, pediatric ophthalmologists, optometrists and orthoptics at day 1, week 1, month 1, month 3 and every 3 months to the age of 3 years and every 6 months until 10 years of age. Control intervals are adjusted according to the specific needs of the child, e.g. contact lens use or amblyopia therapy. After 10 years of age, the children are recommended lifelong follow-up in the primary care sector by an ophthalmologist and optometrist.

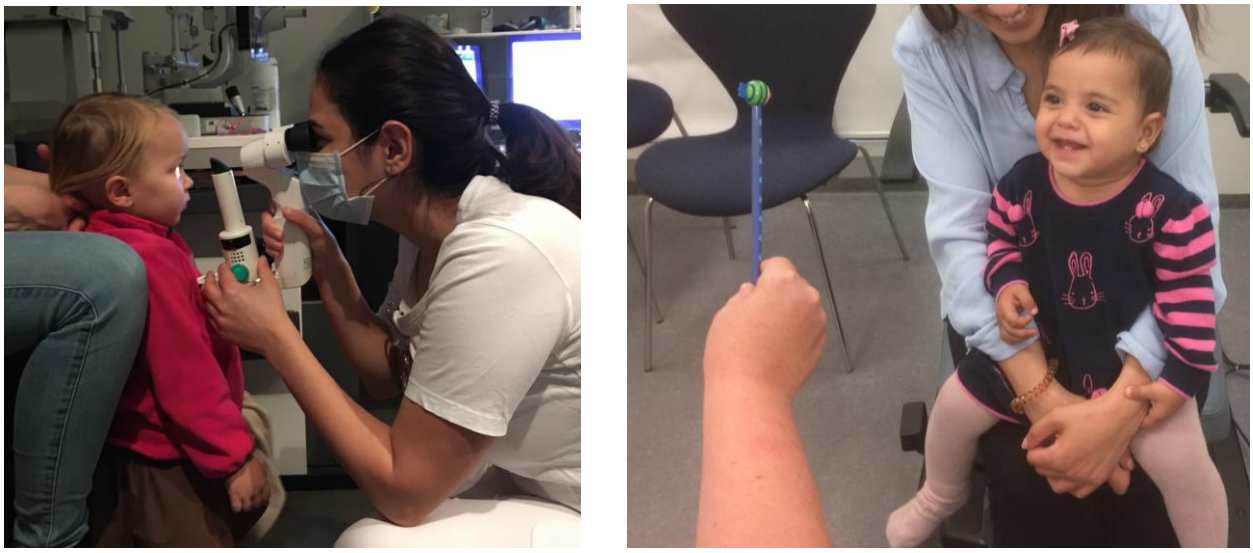


Figure 2: Different techniques are used to examine the children before and after the cataract extraction. Pictures are used with parental permission.

Contact lenses are the preferred optical correction in children with aphakia and unilateral IOLs with high anisometropia but may not always be possible. From the age of 12 to 18 months, children are fitted with bifocal glasses. The government provides financial assistance to the costs of spectacles and/or contact lenses.

A **B**

Figure 3: Applying contact lens (**A**) in an infant. An older child using bifocal glasses (**B**). Pictures are used with parental permission.

Occlusion therapy for amblyopia is prescribed when needed but all infants with unilateral congenital cataract are prescribed full-time occlusion every other day which is later reduced depending on treatment response.

The role of the family in the management of childhood disease

Parents make decisions on management of disease on behalf of their children [75] and their awareness of the child's eye symptoms and knowledge of the disease, including amblyopia, are essential in ensuring compliance with therapy and disease management [76]. Parents with lower socio-economic status including lower educational level typically demonstrate lower health seeking behaviour [76] which may potentially affect the management and treatment outcomes.

The family and in particular the parents play a crucial role in the management and treatment of pediatric cataracts. The journey starts at the time of the diagnosis, sometimes at birth, and continues for years, with numerous visits to the eye department for check-ups and visual training through patching, glasses and/or contact lenses which is demanding for the parents/carers [6,77,78]. The parents are considered to be the child's source of protection, and their positive engagement may contribute to a feeling of security in the child [79] and thus may help to relief the load of the management and treatment course [80].

Effects of chronic disease on childhood development

Early childhood is a critical period for cognitive, linguistic, emotional, social, and behavioural development [81]. Chronic diseases in childhood may disturb the child's development as it can induce restrictions, insecurity, distress, lower self-care and lower social integration [82,83]. Children with one or more chronic diseases are at an increased risk of being vulnerable in several developmental fields like physical wellbeing, social competence, emotional maturity, communication skills, language and cognitive skills when compared to children without a chronic disease [83]. Chronic disease may lead to distress in children which can reduce their adherence to a recommended treatment [84]. Visual impairment can have an impact on the child's participation in daily life. Children with early severe visual impairment or blindness may experience social and cognitive difficulties [85,86] with higher risk of developing anxiety and depression [87–89]. To date, the effect of childhood cataract on the affected child's development is unknown.

Effects of chronic childhood disease on mental health

Children who suffer from chronic somatic illness may have a higher risk of mental health conditions due to the limitations set by a chronic disease course on activities that are important for psychological and social development in childhood and pre-adolescence [90]. Chronic somatic

diseases like diabetes mellitus type I, cerebral palsy, epilepsy and cancer have previously been associated with an increased incidence of mental conditions in children including mood disorders, anxiety, autism spectrum disorders (ASD) or attention deficit/hyperactivity disorders (ADHD) [91–96].

The incidence of mental disorders is estimated to 15-20% of the general pediatric population in developed countries [97,98]. In Denmark, 15% of the general pediatric population is diagnosed with a mental disorder before the age of 18 [99].

Mental disorders can be classified into neurodevelopmental disorders and other disorders including emotional/affective disorders. Neurodevelopmental disorders include intellectual disability, unspecific neurodevelopmental delay disorders, autism spectrum disorders (ASD) and attention deficit/hyperactivity disorders (ADHD) and have a peak incidence in children before 10 years of age [99,100]. They share risk factors like genetic features, pre-and perinatal difficulties, male preponderance and manifestation of neurocognitive deficits [101]. The other disorders (anxiety, schizophrenia, mood disorders, obsessive compulsive disorder (OCD) and eating disorders) show an increased incidence after the age 5 [99,102–105] and can be affected by environmental factors like parental like distress [104] and parental chronic disease [106].

Materials and Methods

Study population

Children diagnosed with any type of cataract before the age of 10 in 2000-2017 were included while children with other types of lens anomalies, including subluxation, posterior lenticonus and persistent prepupillary membranes without lenticular opacities, were excluded.

Paper I: We included all children born from 2000 to the beginning of 2017 and diagnosed with cataract before 10 years of age at the Department of Ophthalmology at Rigshospitalet, Copenhagen. Information about the study population was extracted through medical records. Children who had undergone surgery outside Rigshospitalet, were excluded, see **Figure 4**.

Paper II and III: We included all children born from January 1, 2000 to December 31, 2017 and diagnosed with cataract before 10 years of age at the Department of Ophthalmology at Rigshospitalet, Copenhagen or Aarhus University Hospital, Aarhus. Children with incomplete data were excluded, see **Figure 4**. Each child with cataract was matched with 10 children without cataract (sampled by Statistics Denmark) by age at cataract onset, sex and municipality. The study population was uploaded to a Statistics Denmark server through a secure and encrypted platform allowing us to access information about diagnoses at public hospitals and parental socio-economic status presented through different national registries by Statistics Denmark (see *"Registries"*).

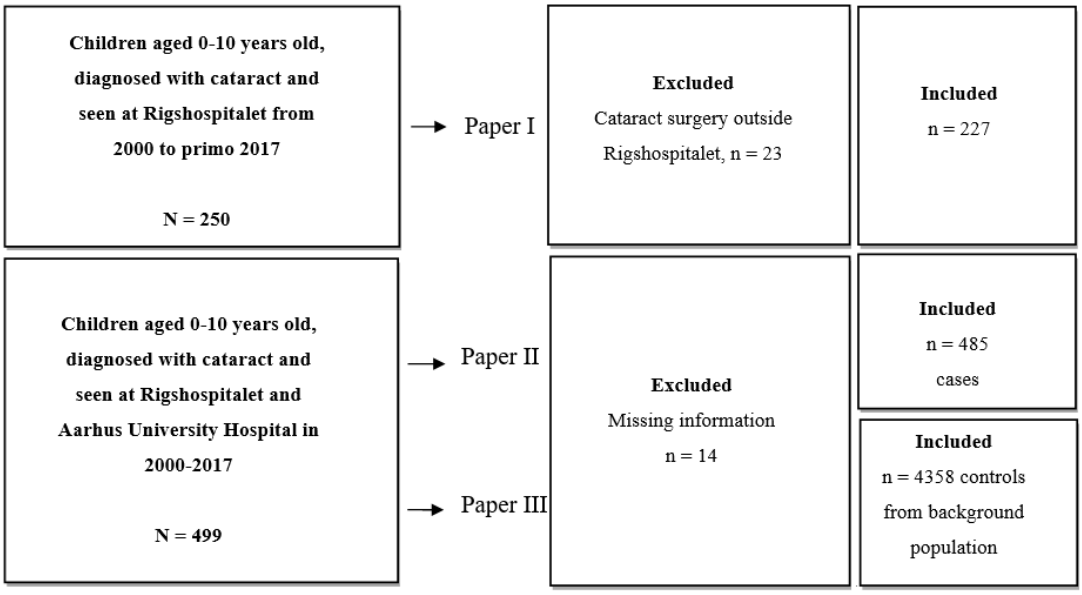


Figure 4: Flow chart showing inclusion and exclusion of the study population in the three papers.

Registries

Paper II and paper III were based on the national Danish registries available from Statistics Denmark.

The *National Patient Registry* (NPR) contains information about diagnostic and procedural ICD-10 codes on all somatic and psychiatric contacts to public hospitals. It was used to extract registered psychiatric and somatic diagnoses in children. In addition, we extracted information on parental mental disorders from NPR.

The *Population Registry* was used to obtain information about sex, civil status and geographical birth origin and parental socio-economic status. Data about parental work status was extracted from *AKM registry (work classification module)*. Parental highest obtained educational level was extracted from *UDDA registry (education registry)*. Information on parental income was attained through the *income registry.* See **Table 1** for overview and details. Entries between registries are linked to individuals by a unique number assigned to all Danish residents, The Danish Civil Registration System (CPR) number, allowing combination of information between registries and between children and their parents.

Name	*Registry*	*Description*	*Full name of registry*
Sex	BEF registry	Gender of the included population extracted from BEF registry (population registry)	BEF = Befolkning
Age at cataract onset	NPR + BEF registry	The date of cataract diagnosis was extracted from NPR (The National Patient Registry) and calculated based on birth date in BEF registry (population registry)	NPR = The National Patient Registry+ BEF = Befolkning
Geographical birth origin	BEF registry	Geographical birth origin is the place where the child was born extracted from BEF registry (population registry)	BEF = Befolkning
Number of siblings	BEF registry	Number of children in a household extracted from BEF registry (population registry)	BEF = Befolkning
Children's mental disorders	PSYK_DIAG_ NPR	Children's mental disorders diagnosed at public hospitals extracted from NPR (The National Patient Registry)	Psyk_diag_NPR= The National Patient Registry with focus on psychiatric diagnoses
Children's systemic diseases	LPR_DIAG	Children's systemic disease diagnosed at public hospitals extracted from NPR (The National Patient Registry)	NPR = The National Patient Registry
Parental civil status	BEF registry	Parental civil status extracted from BEF registry (population registry)	BEF = Befolkning
Parental income	IND registry	Parental income extracted from IND registry (income registry)	IND = Indkomst
Parental work status	AKM registry	Information about parental work status extracted from AKM registry (work classification module)	AKM = Arbejdsklassifikationsmodulet
Parental education	UDDA registry	Information about parental education extracted from UDDA registry (education registry)	UDDA = Uddannelse
Parental mental disorders	PSYK_DIAG_ NPR	Parental mental disorders diagnosed at public hospitals extracted from NPR (The National Patient Registry)	Psyk_diag_NPR= The National Patient Registry with focus on psychiatric diagnoses

Table 1: Description of the used variables and registries.

Outcome variables

Paper I – Number of hospital visits and examinations/surgical procedures performed under general anesthesia were extracted as primary outcome variables. The outcomes were measured and cumulated for the ages of 1, 3, 5 and 7. Examination in combination with a surgical procedure was defined as surgical procedure, otherwise it was counted as examination under general anesthesia. The effect of IOL implantation on the number of hospital visits and general anesthesia events was evaluated as secondary outcome.

Paper II - The socio-economic variables (child's geographical birth origin and number of siblings, parental civil status, parental education, parental workforce and parental income) were extracted one year prior to cataract onset, 1 year and 3 years after, see **Table 2**.

Paper III - The incidence and type of mental disorders were evaluated using ICD-10 diagnostic codes (F00-F99 and R41.8, R62.0, R62.9) given to the child during the first 10 years of life. The codes for unspecific developmental delays (R41.8, R62.0, R62.9) are typically used in young children with attenuated and unspecific symptoms of developmental delays [100]. Mental disorders were grouped into neurodevelopmental disorders and other mental disorders as neurodevelopmental disorders show a different pattern of risk associations compared to the other emotional mental disorders [101]. A child could be diagnosed with different mental disorders but in the analysis of overall incidence of any mental disorder, each child could be counted only once. The cataract population was sub-grouped into an isolated cataract group and a group of cataract children with severe somatic diseases. Some of the somatic diseases were grouped as disease confounders since the disease itself or its treatment was estimated likely to increase both the risk of cataract and mental disorders. In addition, analyses were adjusted for parental socio-economic status (civil status, income and employment status) and parental mental disorders (DF00-99 for one or both parents) since mental disorders are more prevalent with lower socio-economic status [107,108] and as we in paper II observed that children with cataract were more likely to come from socio-economically challenged families [109].

Outcome variable	Definitions, classifications and details
Geographical birth origin	Children not born in Denmark were grouped into Europe, Middle East, Africa and Far East.
Income	Household financial resources based on the disposable personal income (DPI)/adult over a full calendar year. The DPI is the amount of money that a household has available for saving and spending after it taxes have been deducted. For cohabiting parents: Average DPI in the household was used. For separated parents and parents living apart: The highest DPI was used. We analyzed the income by two dichotomizations: ≤ 99.999 DKK/year versus ≥ 100.000 DKK/year and ≤ 499.999 DKK/year versus ≥ 500.000 DKK/year.
Employment status	Family was defined as unemployed if both parents were registered as unemployed for up to six months, received unemployment benefits, had retired early or if they were students. The family was defined as employed if one of the parents was registered with work.
Education	The education was defined as the highest attained education between the parents. Education was grouped into: Primary education (up to 9th grade), high school, vocational (technical) education, short-term higher education programs (e.g. diploma programs), medium-term higher education programs (e.g. professional bachelor programs such as nursing and teaching), bachelor and long-term higher education programs (e.g. bachelor programs at universities, graduate programs and PhD programs). We analyzed the education by two dichotomizations: *Basic education*; where parents had completed the compulsory 9 years of schooling versus education higher than basic education. A*dvanced education;* where parents had completed a university degree education (bachelor and long-term higher education) versus education lower than advanced education.
Number of siblings	Number of persons ≤ 24 years of age without children of their own, living in the household with minimum one adult registered. The child with cataract was subtracted.
Family structure	A household includes all persons living at the same address. Multi-family residential was used to describe when more than one family lived at the same address. The civil status was divided into two groups: single and not single (married, cohabiting couple & multi-family residential).

Table 2: Overview of socio-economic variables included in paper II.

Statistical methods

Statistical analyses were made using the Sigmaplot version 13.0 and SAS version 9.4. in **paper I** and the R software package, V.3.4.1 (The R Foundation for Statistical Computing, http://www.r-project.org) in **paper II** and **paper III**. The significance level was set at < 0.05.
Normally distributed data were reported as mean ± standard deviation (SD). Non-normally distributed data were reported as median ± interquartile range (IQR). Categorical data was analyzed with Pearson´s chi-squared tests. Continuous data was analyzed with t-tests.

Paper I: Number of hospital visits and general anesthesia events are individually summed in relation to the child's age at the time of surgery in the groups: 0 ≤1 year, 1 ≤3 years, 3 ≤ 5 years and 5 ≤7 years. For the data relating to birth year, linear regression model was applied.

Paper II: The socio-economic variables were each evaluated prior to the cataract diagnosis, and one and three years after the diagnosis was made. The difference in prevalence of low socio-economic status in cases and controls at each of the three time points was assessed as an odds ratio (OR) with 95% confidence interval (95% CI) from a conditional logistic regression model. This model was parametrized so that the results at the one- and three-year time points were adjusted for differences already present in the year prior to the cataract diagnosis. Results are reported both unadjusted and adjusted for: age, sex, municipality, season, calendar year and geographical birth origin.

Paper III: The association between childhood cataract and mental disorder was measured as an odds ratio (OR) with 95% confidence interval (95% CI) by a conditional logistic regression model. This was performed both unadjusted and adjusted for the children's age at onset of cataract diagnosis, sex, geographical birth origin, parental socio-economic status, family psychiatric load and the children's somatic comorbidity.

Approvals

The study was approved by the Danish Data Protection Agency (RH-2016-336; I-Suite # 05070), and the Danish Patient Safety Authority (3-3013-1935/1/NAAN). According to the Committee on Health Research Ethics in the Capital Region of Denmark, ethical board review was not required (decision number: 16038234). The study followed the tenets of the Helsinki Declaration.

Results

Paper I

Paper I quantified the strain of childhood cataract for the children and their immediate family by counting the number of hospital visits and surgery and examinations in general anesthesia.

The analyses included 227 children (116 boys and 111 girls) born between 2000 and primo 2017 and followed with childhood cataract at Rigshospitalet.

Hospital visits

Overall, children that underwent cataract surgery were followed more frequently than children with cataract but who had not undergone cataract surgery ($p<0.0001$). The highest number of hospital visits was in particularly seen in children who were operated early in life compared to children diagnosed and operated later. Bilaterally operated children diagnosed before 1 year of age were seen 9 times in median during the first year of life and 27 visits in median when accumulated by the 7th year of life. Corresponding, unilaterally operated children diagnosed within the first year of life were in median seen 11 times by the first year and cumulated 28 times after 7 years. Unoperated children were seen 5 times in median in the first year of life and 16 times when cumulated for all 7 years of life. The number of regular visits tapered over the years for both bilateral and unilateral operated children without significant difference, see **Table 3.**

Cumulated interval / Age at diagnosis	0≤1 year of life	0≤3 years of life	0≤5 years of life	0≤7 years of life
≤1 year				
Bilateral surgery	9 (3-42) [51]	15 (6-52) [42]	20 (0-67) [36]	27 (3-60) [23]
Unilateral surgery	11 (2-36) [44]	14 (2-52) [33]	21 (5-57) [25]	28 (8-57) [19]
No surgery	5 (1-14) [33]	8 (3-20) [20]	14 (9-33) [10]	16 (12-44) [4]
>1 year to ≤3 years				
Bilateral surgery	-	10 (1-18) [14]	17 (11-26) [8]	25 (18-40) [4]
Unilateral surgery	-	9 (2-26) [11]	19 (8-32) [8]	23 (15-44) [6]
No surgery	-	4 (2-12) [13]	9 (5-19) [5]	15 (13-16) [3]
>3 years to ≤5 years				
Bilateral surgery	-	-	14 (6-30) [12]	21 (15-36) [8]
Unilateral surgery	-	-	16 (8-30) [8]	25 (18-33) [8]
No surgery	-	-	5 (2-14) [15]	9 (3-16) [5]
>5 years to ≤7 years				
Bilateral surgery	-	-	-	12 (10-13) [2]
Unilateral surgery	-	-	-	9 (0-19) [6]
No surgery	-	-	-	5 (3-23) [18]

Table 3: The cumulated numbers of hospital visits are given in median (range) and [number of children].

Examinations and surgical procedures in general anesthesia

Children operated bilaterally underwent general anesthesia more often (median = 3) than children operated unilaterally (median = 2) and unoperated children (median = 0) during the first year of life, see **Table 4**.

Cumulated interval / **Age at diagnosis**	**0≤1 year of life**	**0≤3 years of life**	**0≤5 years of life**	**0≤7 years of life**
≤1 year				
Bilateral surgery	3 (1-9) [51]	4 (1-12) [42]	4 (1-12) [36]	5 (1-11) [23]
Unilateral surgery	2 (0-6) [44]	2 (0-6) [33]	0 (0-7) [25]	3 (0-8) [19]
No surgery	0 (0-0) [33]	0 (0-3) [20]	0 (0-3) [10]	2 (0-3) [4]
>1 year to ≤3 years				
Bilateral surgery	-	3 (0-5) [14]	3 (2-5) [8]	3 (3-5) [4]
Unilateral surgery	-	1 (1-5) [11]	2 (2-5) [8]	2 (2-5) [6]
No surgery	-	0 (0-3) [13]	0 (0-1) [5]	0 (0-0) [3]
>3 years to ≤5 years				
Bilateral surgery	-	-	2 (2-4) [12]	2 (2-4) [8]
Unilateral surgery	-	-	2 (2-10) [8]	2 (1-6) [8]
No surgery	-	-	0 (0-0) [15]	0 (0-1) [5]
>5 years to ≤7 years				
Bilateral surgery	-	-	-	3 (2-3) [2]
Unilateral surgery	-	-	-	1 (1-3) [6]
No surgery	-	-	-	0 (0-3) [18]

Table 4: The numbers of cumulated examinations/surgeries in general anesthesia are given in median (range) and [number of children].

Examination was the most frequent reason for repeated general anesthesia followed by cataract and glaucoma surgery, see **Figure 5**.

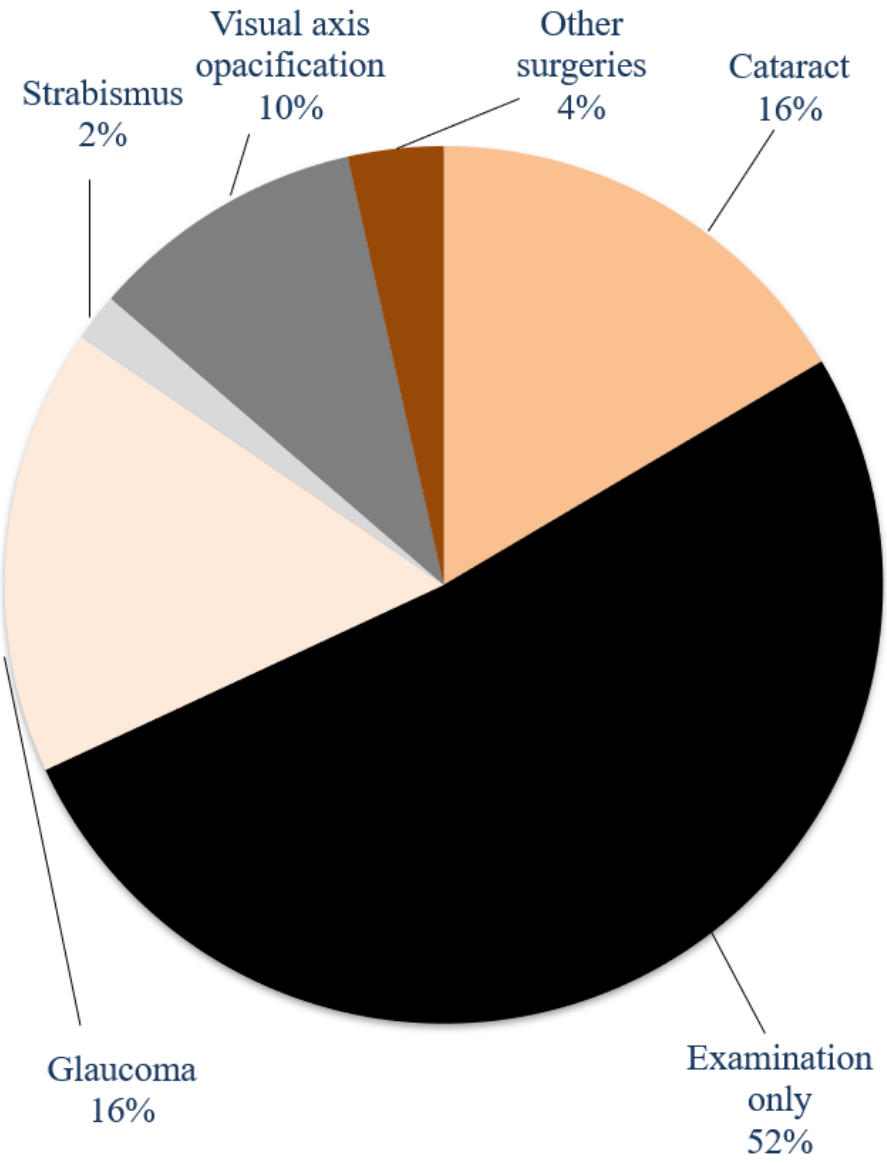


Figure 5: Reasons for general anesthesia in children with childhood cataracts diagnosed ≤1 year of age. Other surgeries included surgical procedures like pupilloplastic operation, removal of anterior synechia, removal of a subluxated IOL, subtenon depot of steroid for uncontrolled uveitis associated to juvenile arthritis, repeat fluorescein angiography and panretinal photocoagulation, retinal detachment, enucleation and traumatic cataracts.

IOL implantation

We did not find any significant differences in the number of examinations and procedures in general anesthesia between children with or without IOL, see **Table 5**.

	0≤1 year of	**0≤3 years of life**	**0≤5 years of life**	**0≤7 years of life**
Bilateral surgery, out-patient visits				
All patients	9 (3-42) [51]	16 (6-52) [42]	20 (0-67) [36]	27 (3-60) [23]
Patients with aphakia	11 (4-42) [38]	16 (6-52) [33]	20 (0-67) [28]	36 (4-60) [17]
Patients with IOL	7 (3-19) [13]	10 (6-29) [9]	16 (1-32) [8]	22 (3-47) [6]
Bilateral surgery, procedures/examinations in general anesthesia				
All patients	3 (1-9) [51]	4 (1-12) [42]	4 (1-12) [36]	5 (1-11) [23]
Patients with aphakia	4 (1-9) [38]	4 (1-12) [33]	5 (1-12) [28]	5 (1-11) [17]
Patients with IOL	3 (1-3) [13]	3 (1-5) [9]	2 (0-5) [8]	2 (0-6) [6]
Unilateral surgery, out-patient visits				
All patients	11 (2-36) [44]	14 (2-52) [33]	21 (5-57) [25]	28 (8-57) [19]
Patients with aphakia	12 (4-36) [18]	17 (8-52) [12]	19 (11-57) [11]	38 (11-57) [8]
Patients with IOL	11 (2-19) [26]	14 (2-27) [21]	23 (5-43) [14]	27 (8-44) [11]
Unilateral surgery, procedures/examinations in general anesthesia				
All patients	2 (0-6) [44]	2 (0-6) [33]	0 (0-7) [25]	3 (0-8) [19]
Patients with aphakia	2 (0-6) [18]	3 (0-6) [12]	3 (0-7) [11]	5 (1-8) [8]
Patients with IOL	2 (0-5) [26]	2 (0-4) [21]	3 (0-6) [14]	3 (0-6) [11]

Table 5: Cumulated number of outpatient visits and examinations/procedures in general anesthesia for children diagnosed before 1 year of age and grouped into operated children with or without IOL. Numbers are given in median (range) and [number of children].

Paper II

In paper II, we evaluated the socio-economic status in families affected by childhood cataract compared to an age-matched background population.

The study included 485 children with cataract (243 boys and 242 girls) and 4358 children without cataract (2177 boys and 2181 girls) matched by sex, municipality and age at the time of cataract diagnosis.

Geographical birth origin of the child

A significantly greater number of children were born outside Denmark compared to the background population (p-value = 0.01). The most frequent birthplace outside Denmark was in the Middle East with 6.8% in the cataract group versus 4.3% in the control group. An increased number of unemployed parents with lower educational level and income was seen among children born in the Middle East, Africa and the Far East compared to the European group ($p<0.05$), see **Table 6**.

Parental income

Low income (≤ 99.999 DKK/year) was more common in parents to children with cataract compared to controls before the cataract diagnosis was made, OR = 1.52, 95% CI (1.05 - 2.20), p-value = 0.03 after adjustment of the child's geographical birth origin. Having a child diagnosed with cataract did not change this difference one and three years after cataract onset, see **Table 7**.

Parental employment status

Parents in the cataract group were more often unemployed before cataract diagnosis onset with OR = 1.81, 95% CI (1.32 - 2.50), p-value < 0.0003 in adjusted analysis. This difference persisted in the years after cataract diagnosis was made, see **Table 7**.

Parental highest attained education

Parents in the cataract group were more likely to have ≤ 9 years of schooling (basic education) as the highest attained education (OR= 1.55, 95% CI (1.16 - 2.08), p-value = 0.003) after adjustment, see **Table 7**.

Number of siblings

Children with cataract had a higher number of siblings (6.2% had ≥ 4 siblings compared to 2.1% in the background population), p-value = 0.0005, see **Table 6**.

Family structure

Children with cataract were more often observed to live in multi-family residencies (13.8%) compared to children without cataract (8%), p-value = 0.001. Parental civil status did not differ between the two groups (p-value = 0.19), see **Table 6**.

Table 6: Baseline characteristics of children with cataract and children without cataract

	Children with childhood cataract (N = 485)	Children without childhood cataract (N = 4358)	Missing	p-value[1]
Age at diagnosis[2], *n (%)*			0	0.98
0 years	229 (47.2)	2077 (47.7)		
1-2 years	66 (13.6)	553 (12.7)		
3-4 years	68 (14.0)	632 (14.5)		
5-7 years	62 (12.8)	562 (12.9)		
> 7 years	60 (12.4)	534 (12.3)		
Age (years), *median (IQR)*	1.22 (0.19 - 5.01)	1.18 (0.19 - 5.03)	0	0.99
Sex, *n (%)*			0	0.99
Boy	243 (50.1)	2177 (50.0)		
Girl	242 (49.9)	2181 (50.0)		
Geographical origin, *n (%)*			0	**0.01**
Denmark	428 (88.2)	4030 (92.5)		
Europe	9 (1.9)	38 (0.9)		
Middle East	33 (6.8)	189 (4.3)		
Africa	5 (1.0)	27 (0.6)		
Far East	10 (2.1)	74 (1.7)		
Number of siblings, *n (%)*			0	**0.0005**
No siblings	56 (11.5)	457 (10.5)		
1-2 siblings	314 (64.7)	3258 (74.8)		
3-4 siblings	85 (17.5)	553 (12.7)		
> 4 siblings	30 (6.2)	90 (2.1)		
Number of siblings, *median (IQR)*	1 (0 - 5)	1 (0 - 4)	0	**0.002**
Parental Civil status, *n (%)*			42	**0.001**
Single	52 (11.0)	519 (12.0)		
Married	222 (47.1)	2182 (50.4)		
Cohabiting couple	132 (28.0)	1282 (29.6)		
Multi-family residential[3]	65 (13.8)	347 (8.0)		
Parental average income [4], *n (%)*			28	**0.02**
< 100.000 DKK	36 (7.6)	187 (4.3)		
100.000 - 200,000 DKK	170 (35.7)	1520 (35.0)		
200.000 - 300,000 DKK	185 (38.9)	1830 (42.2)		
300.000 - 500,000 DKK	77 (16.2)	707 (16.3)		
> 500.000 DKK	8 (1.7)	95 (2.2)		
Income (DKK), *median (IQR)*	211.275 (149.625 - 267.324)	221.345 (168.231 - 277.433)	28	**0.02**
Parental work status, *n (%)*			3	**0.00002**
Outside workforce	58 (12.0)	253 (5.8)		
One parent at work	100 (20.7)	880 (20.2)		
Both parents at work	325 (67.3)	3224 (74.0)		
Highest attained parental education, *n (%)*			41	**0.002**
Primary education (up to 9th grade)	71 (15.1)	390 (9.0)		
High school	18 (3.8)	175 (4.0)		
Vocational education	133 (28.3)	1313 (30.3)		
Short-term higher education	38 (8.1)	364 (8.4)		
Medium-term higher education	94 (20.0)	959 (22.1)		
Bachelor	102 (21.7)	1041 (24.0)		
Long-term higher education	14 (3.0)	90 (2.1)		

[1]P-value: Pearson´s chi-squared test for categorical variables, t-test for continuous variables.

[2]Age at diagnosis: Controls are matched by the age at diagnosis for patients.

Table 7: Selected socio-economic indicators of the families to children with cataract and children without cataract at the time before the diagnosis and adjusted for base-line differences one year and three years after the diagnosis

	Children with childhood cataract (N = 485)				**Children without childhood cataract** (N = 4358)							
	n	**%**	**n**	**%**	**N**	**%**	**n**	**%**	**Crude OR (95% CI)[1]**	**p-value**	**Adjusted OR (95% CI)[2]**	**p-value**
Low Income	≤ 99.999 kr.		≥100.000 kr.		≤ 99.999 kr.		≥ 100.000 kr.					
Pre-diagnosis	36	7.6	440	92.4	187	4.3	4152	95.7	1.60 (1.12 - 2.27)	**0.01**	1.52 (1.05 - 2.20)	**0.03**
1 year after diagnosis	32	6.7	447	93.3	155	3.6	4202	96.4	1.06 (0.71-1.58)	0.79	1.05 (0.69-1.61)	0.80
3 years after diagnosis	21	5.2	380	94.8	92	2.5	3565	97.5	1.18 (0.71-1.96)	0.52	1.15 (0.68-1.92)	0.60
High Income	≤ 499.999 kr.		≥ 500.000 kr.		≤ 499.999 kr.		≥ 500.000 kr.					
Pre-diagnosis	468	98.3	8	1.7	4244	97.8	95	2.2	1.27 (0.61 - 2.65)	0.53	1.22 (0.58 - 2.56)	0.60
1 year after diagnosis	471	98.3	8	1.7	4262	97.8	95	2.2	1.00 (0.44 - 2.24)	0.99	1.00 (0.44 - 2.25)	1.00
3 years after diagnosis	388	96.8	13	3.2	3553	97.2	104	2.8	0.68 (0.30 - 1.56)	0.36	0.67 (0.28 - 1.56)	0.35
Civil status	Single		Cohabiting parents		Single		Cohabiting parents					
Pre-diagnosis	52	11.0	419	89.0	519	12.0	3811	88.0	0.90 (0.67 - 1.20)	0.47	0.82 (0.60 - 1.11)	0.19
1 year after diagnosis	49	11.2	388	88.8	477	11.9	3517	88.1	1.03 (0.81 - 1.30)	0.84	1.03 (0.81 - 1.32)	0.80
3 years after diagnosis	56	15.7	300	84.3	479	14.6	2801	85.4	1.20 (0.89-1.63)	0.24	1.23 (0.89 - 1.69)	0.21
Workforce	Outside		At work		Outside		At work					
Pre-diagnosis	58	12.0	425	88.0	253	5.8	4104	94.2	1.74 (1.34-2.26)	**< 0.0001**	1.81 (1.32 - 2.50)	**0.0003**
1 year after diagnosis	45	10.1	401	89.9	221	5.5	3786	94.5	0.87 (0.68-1.12)	0.29	0.85 (0.62 - 1.16)	0.30
3 years after diagnosis	38	10.4	327	89.6	172	5.2	3122	94.8	0.94 (0.69-1.28)	0.69	0.94 (0.64 - 1.37)	0.74
Highest attained education:	Basic education		Higher		Basic education		Higher					
Pre-diagnosis	71	15.1	399	84.9	390	9.0	3942	91	1.64 (1.27 - 2.13)	**0.0002**	1.55 (1.16 - 2.08)	**0.003**
1 year after diagnosis	65	14.9	370	85.1	335	8.4	3663	91.6	1.06 (0.96 - 1.18)	0.27	1.07 (0.95 - 1.20)	0.27
3 years after diagnosis	47	13.1	311	86.9	250	7.6	3037	92.4	1.00 (0.82 - 1.23)	1.00	1.00 (0.80 - 1.26)	0.99
Highest attained education:	Lower		Advanced education		Lower		Advanced education					
Pre-diagnosis	354	75.3	116	24.7	3201	73.9	1131	26.1	1.05 (0.86 – 1.30)	0.63	1.01 (0.82 – 1.26)	0.87
1 year after diagnosis	330	75.9	105	24.1	2944	73.6	1054	26.4	1.04 (0.98 – 1.11)	0.22	1.05 (0.98 – 1.12)	0.20
3 years after diagnosis	267	74.6	91	25.4	2407	73.2	880	26.8	1.00 (0.89 – 1.12)	0.93	1.00 (0.88 – 1.12)	0.93

[1] The OR at the first and third year after diagnosis refers to unchanged difference in the social-economic status presented at the time before the diagnosis between children with cataract and children without cataract.

[2] Adjusted for age at diagnosis, sex, birth origin, diagnosis year, diagnosis season and number of siblings; categorized as indicated in Table 1

Paper III

Paper III evaluated the incidence of mental disorders among children with cataract compared to an age-matched background population (the same population as in paper II).

Children with cataract and severe somatic diseases have an increased incidence of neurodevelopmental disorders (15.4%) and other mental disorders (9.0%) compared to children with isolated cataract (neurodevelopmental disorders: 5.8% and other mental disorders: 2.3%), see **Table 8**.

	Isolated cataract	**Cataract and severe somatic diseases**	**p-value** [a]
	N= 407	N=78	
Sex *Girls/Boys (%)*	197/210 (48.4/51.6)	45/33 (57.7/42.3)	0.168
Age at cataract diagnosis (year) *Median (IQR)*	1.4 (0.19 - 5.1)	0.6 (0.14 - 4.4)	0.344
Age at surgery (year) *Median (IQR)*	2.1 (0.3 - 4.9)	0.6 (0.2 - 4.0)	0.243
Operated/non-operated, n (%)	232/175 (57.0/43.0)	50/28 (64.1/35.9)	0.299
Any mental disorders [b]**, n (%)**	34 (8.4)	17 (21.8)	0.0008*
Neurodevelopmental disorder, n (%)	28 (5.8)	12 (15.4)	0.023*
Other mental disorders, n (%)	11 (2.3)	7 (9.0)	0.018*

[a] P-value: Pearson´s chi-squared test for categorical variables, t-test for continuous variables.

[b] Each child could be diagnosed with different mental disorders. The number of children with neurodevelopmental and other mental disorders does therefore not sum up to the number of children with any mental disorders.

Table 8: Background characteristics of children with cataract (N=485).

The incidence of mental disorders was doubled in children with cataract (10.5 %, n = 51/485) compared to the matched background population (5.2%, 225/4358), OR = 1.83, 95% CI (1.28 – 2.63), p-value = 0.0009 after adjustment for geographical birth origin, somatic disease confounders, parental socio-economic status and parental mental disorders. The incidence of mental disorders was highest in children diagnosed with cataract in the first 3 years of life (10.7%, n = 35/327), see **Table 9**.

	Children with cataract	Children without cataract	Unadjusted		Adjusted	
	N = 485	N = 4358	OR (95%CI)	p-value	OR (95%CI)	p-value
	n/N (%)					
Any mental disorders	51/485 (10.5)	225/4358 (5.2)	2.16 (1.57 - 2.78)	< 0.00001*	1.83 (1.28 - 2.63)	0.0009*
0-3 years [a]	35/327 (10.7)	118/2912 (4.1)	2.84 (1.91 - 4.22)	< 0.00001*	2.36 (1.53 - 3.64)	0.0001*
4-10 years [a]	16/158 (10.1)	107/1446 (7.4)	1.41 (0.81 - 2.45)	0.224	1.24 (0.66 - 2.30)	0.504
Neurodevelopmental disorders	40/485 (8.2)	148/4358 (3.4)	2.56 (1.78 - 3.67)	< 0.00001*	2.05 (1.35 - 3.11)	0.0007*
0-3 years [a]	28/327 (8.6)	77/2912 (2.6)	3.45 (2.20 - 5.40)	< 0.00001*	2.64 (1.59 - 4.4)	0.0002*
4-10 years [a]	12/158 (7.6)	71/1446 (4.9)	1.59 (0.84 – 3.00)	0.152	1.37 (0.68 – 2.76)	0.376
Other mental disorders	18/485 (3.7)	95/4358 (2.2)	1.73 (1.04 - 2.89)	0.036*	1.69 (1.0 - 2.87)	0.052
0-3 years [a]	12/327 (3.7)	50/2912 (1.7)	2.18 (1.15 - 4.14)	0.017*	2.22 (1.18 - 4.18)	0.014*
4-10 years [a]	6/158 (3.8)	45/1446 (3.1)	1.23 (0.52 – 2.98)	0.642	1.12 (0.40 – 2.85)	0.814

[a] Age at cataract onset

Table 9: Incidence of mental disorders in the study population.

The risk of neurodevelopmental disorders was doubled in children with cataract (OR = 2.05, 95% CI (1.35 – 3.11), p-value = 0.0007) after adjustment for selected confounders. The most frequent neurodevelopmental disorder was unspecific developmental delay (4.5%, n = 22/485). The incidence of unspecific developmental delay disorders was increased in the children with cataract compared to the controls, OR = 2.66, 95% CI (1.45 - 4.90), p-value = 0.0017, see **Table 10**.

The risk of anxiety disorders was quadrupled in children with cataract (2.1%, n = 10/485 versus 0.5%, n=23/4358) compared to the control group, OR = 4.10, 95% CI (1.90 - 8.84), p-value = 0.0003, see **Table 10**.

	Children with cataract	Children without cataract	Unadjusted		Adjusted	
	N = 485	N = 4358	OR (95%CI)	p-value	OR (95%CI)	p-value
	n/N (%)					
Neurodevelopmental disorders	40/485 (8.2)	148/4358 (3.4)	2.56 (1.78 - 3.67)	< 0.00001*	2.05 (1.35 - 3.11)	0.0007*
Autism spectrum disorders	11/485 (2.3)	55/4358 (1.3)	1.82 (0.94 - 3.49)	0.074	1.62 (0.78 - 3.39)	0.192
ADHD	6/485 (1.2)	43/4358 (1.0)	1.26 (0.53 - 2.97)	0.602	1.31 (0.50 - 3.46)	0.581
Unspecific developmental delay	22/485 (4.5)	54/4358 (1.2)	3.79 (2.29 - 6.28)	< 0.00001*	2.66 (1.45 - 4.90)	0.0017*
Other mental disorders [a]	18/485 (3.7)	95/4358 (2.2)	1.73 (1.04 - 2.89)	0.036*	1.69 (1.0 - 2.87)	0.052
Anxiety disorders	10/485 (2.1)	23/4358 (0.5)	3.97 (1.88 - 8.39)	0.0003*	4.10 (1.90 - 8.84)	0.0003*

Notably, a child could be diagnosed with two or more different mental disorders but counts once in the total number.

[a] Increased risk of eating disorders was found, but the number of children were too few to allow for publication according to rules of Statistics Denmark.

Table 10: The incidence of the most often diagnosed mental disorders in children with cataract compared to corresponding diagnoses in children without cataract.

Discussion

The present thesis explores the effects of childhood cataract on health and life of the children and their parents. Using hospital records, we quantified hospital visits and procedures in general anesthesia and found that the operated children were more often seen in the first year of life compared to not operated children. Bilaterally operated children were more frequently exposed for general anesthesia with approximately one event per year in the first seven years of life compared to unilaterally operated children and children without surgery. Based on national population registries, we found that children with cataract more often belong to socio-economically disadvantaged families with lower educational level, income and parents more often outside workforce and a different family structure than the background population. Finally, we found that risk of neurodevelopmental delay and anxiety disorders was increased in children with cataract.

Follow-up

Children with cataract are followed lifelong to detect and monitor postoperative complications [6]. The burden of hospital visits and procedures in the first 10 years of life was quantified in **paper I** where we found that operated children had particularly frequent outpatient follow-up with approximately 10 hospital visits in the first year of life and an average of nearly 30 hospital visits for the first 7 years of life. 50% of the bilaterally operated children and 25% of the unilaterally operated children had undergone general anesthesia at least 5 times by the 7th year of life. General anesthesia in infants may not be entirely risk free [110] as it may affect intelligence and growth [110–114] as it can impair the cognition and induce structural brain changes [111]. Hence, it is necessary to balance the advantages of thorough examinations in general anesthesia with the disadvantages and burden of repeated anesthesia. The need for examinations in full anaesthesia is highest in children below 3 years of age since they are more difficult to examine when awake, and they are at a higher risk of developing postoperative complications that may adversely affect visual outcome if not detected and treated timely. In contrast to the findings from The Infant Aphakia Treatment Study [115], we did not find that children with IOLs had more intraocular surgeries than children who were left aphakic. In our institution, children below the age of 6 months were typically left aphakic while children older than 6 months usually received IOL. Postoperative complications are more often observed in children operated early in life. Furthermore, complicated eyes are usually left aphakic why the difference between our and their finding may be explained by age differences in

the IOL group and aphakia group rather than the effect of IOL itself on the number of general anesthesia events.

To the authors best knowledge, this study is the first to quantify the number of hospital visits and general anaesthesia events in children with cataract, but findings may be different in centres with a different follow-up regime. The mean follow-up frequency found in paper I is close to the recommended standard follow-up regime in our institution.

Socio-economic status

The intensive management with frequent hospital visits and general anaesthesia events may not only affect the child but also the family as they participate in the many follow-up visits and also play a central role in amblyopia treatment [6] which is typically associated with a high degree of distress and logistical problems for children and parents [68,116,117]. Lower parental socio-economic status is associated to health issues in children [118].

Thus, in **paper II** we evaluated the socio-economic status of families affected by childhood cataract prior to and after cataract was diagnosed compared to children without cataract matched by sex, municipality and age at the time of cataract diagnosis. We found that families of children with cataract had lower income, lower parental educational level, were more likely to be outside the workforce and to live in multi-family residencies with a higher number of children per family. In addition, more children with cataract were born outside Denmark.

Interestingly, we observed that the socio-economic differences between families affected by childhood cataract and the background population were present already prior to the cataract was diagnosed and persisted after the diagnosis, indicating that the strain on families by the frequent hospital visits described in paper I did not aggravate the socio-economic disadvantage. However, the families could potentially have reached the lowest income prior to the cataract diagnosis ("floor effect") with regards to income which makes it difficult to measure the effect of cataract on their income. Some of the parents had possibly suffered from the same condition as well, and visually impaired individuals are more likely to face socio-economic deprivation [119]. This is not without consequences as socio-economically disadvantaged individuals often face a higher risk of disease and health care access inequalities [118,120,121]. Denmark has free access to health care for all socio-economic groups in the community which in addition provides financial assistance to spectacles

and/or contact lenses for children with cataract. We observed a socio-economic challenged population with fewer parents of children with cataract who had completed schooling beyond basic education. Lower socio-economic status including lower education levels may be important barriers to affect the care-seeking behavior among parents to children with pediatric cataract [122]. It may therefore not be without consequences as lower educational background may result in a poor understanding of the risks associated with childhood cataract and may impact how parents recognize symptoms of cataract or its complications, and how they cope and fulfill with the treatment and follow-ups [123]. Socio-economic status of parents to cataract affected children has not previously been managed as a primary outcome measure. Previously, the socio-economic status has either been evaluated for adults who suffered from cataract in childhood [124] or a minor part of the parental socio-economic status was included in baseline characteristics of the population rather than assessed as a main outcome [125].

Mental disorders

Previous suggestions of a higher risk of mental disorders in persons suffering from chronic and demanding course of a disease [91–96] made it interesting and relevant to evaluate whether the chronicity and burden of childhood cataract also have an impact on the child's mental health, especially as research results in this field are limited. Thus, in **paper III**, we explored all pediatric mental disorders in children diagnosed with cataract before the age of 10 and compared that to age and sex-matched controls by using a nationwide database, taking into account the potential influences of a range of confounders like geographical birth origin of the child, somatic disease confounders, parental socio-economic status and parental mental disorders. We demonstrated a more than fourfold increased risk of anxiety disorders and a more than twofold increased risk of developmental delay in children with cataract.

Neurodevelopmental disorders were more prevalent among children with severe somatic disease and in those diagnosed with cataract ≤3 years of age compared to those who were diagnosed later in childhood. Unspecific developmental delay was the most frequent diagnosis. In addition to that, we found a higher risk of mental disorders in the group of children who had cataract in combination with systemic comorbidities suggesting that the load of somatic disease is likely to influence the risk of mental disorders [126]. Though we corrected for disease confounders, the incidence of developmental delay disorders remained higher in the cataract group.

While we expected to find a higher risk of neurodevelopmental disorders in children affected by cataract, we were surprised to find a fourfold risk of anxiety disorders. This could potentially be a consequence of the chronicity of the disease with repeated examinations under anesthesia, hospital appointments and restraining, e.g. with amblyopia patching [6] or/and an effect of visual impairment itself impeding normal social interaction and response to visual stimuli, e.g. facial expressions [1,13,14]. Anxiety is well described features in young blind and visually impaired [87–89]. We assessed children up to the age of 10 years but the risk of anxiety peaks in teenage years [99] which means that our incidence evaluations are likely underestimated seen in a longer perspective.

The knowledge on the incidence of mental disorders in childhood cataract is to date limited to two questionnaire based studies that reported a higher risk of conduct problems, learning problems, psychosomatic, impulsiveness/hyperactivity, anxiety problems [127] and a lower psychosocial health level [128]. The higher incidence of anxiety symptoms agreed with our findings, but learning problems were not evaluated in paper III. However, challenges in learning environment have previously been described in pediatric cataract population who rated their subjective visual function related to academic achievements including reading as poor [129]. One of the questionnaire studies has reported a higher incidence of ADHD, but this association was not observed in our study. Our evaluation was based on mental disorders diagnosed by physicians in a hospital setting which is likely to only represent the tip of the iceberg since milder disorders like ADHD and ASD may be treated exclusively by physicians in private practice. A British study of 41 children who had previously been diagnosed with congenital cataract explored the health-related quality of life by questionnaire studies about social and emotional functioning and found a lower psychosocial health level among cataract affected children compared to children with other systemic diseases [128] which is in agreement with our results.

Our results highlight the psychological burden on children who live with chronic disease. The psychological load may in some cases influence treatment outcome, e.g. in adults with Type 1 Diabetes Mellitus [130–132]. Adult patients suffering from anxiety have a higher risk of being noncompliant with their medical treatment recommendations [133]. Compliance is essential for visual outcome in amblyopia treatment which is often included in the management of childhood

cataract [2]. Treatment of amblyopia can be associated with a high level of challenges and stress [68,116,117] resulting in a reduced compliance, in particularly among persons with mental disorders [134]. Hence, mental disorders in children can result in a lower adherence to patching and consequently affect visual outcome. Patching in mental challenged children can potentially worsen their mental health.

Strengths and limitations

Paper I is a retrospective descriptive study without a control group. However, it consists of a large number of medical records including ophthalmological, optometrist and orthoptic evaluation during the years. In addition, children without eye problems are not expected to be seen at eye departments therefore the number of visits to eye department is believed to be close to zero for the general pediatric population. The count of visits did not include appointments at other departments than the Department of Ophthalmology at Rigshospitalet.

The major strength of **paper II** and **III** is their nationwide character with no attrition bias. To minimize the interaction of potential confounders, we adjusted for relevant variables such as geographical birth origin of the child in both paper II and III, disease confounders, parental socio-economic status and parental mental disorders were also included in paper III. However, in paper II, a longer follow-up would have been welcome, but it was not possible because 25% of cataract cases were diagnosed so recently that they were evaluated as missing data at a five-year follow-up time point. In paper III, there may be risk of selection bias since children seen and treated by child psychiatrists working in private practice are not always reported into NPR resulting in an underestimated true incidence of mental disorders. Referral bias must be considered when extracting data about mental disorders in controls versus cases because the case group is expected to be more at hospital and therefore has better odds to be diagnosed earlier. On the other hand, it could also be underrepresented due to the parents' exhaustion that potentially makes them reluctant to have further follow-up and tendency to interpret the child's behavior into eye disease context.

Conclusion

In this thesis, we studied aspects of childhood cataract which have not previously been described well in the literature. Overall, we showed that childhood cataract is a demanding chronic condition with many years of follow-up visits with consequences to the child's mental health status. We also found that families of children with cataract have a higher risk of being socio-economically vulnerable with lower educational level. Our findings underscore the potential psychological burden on children living with chronic disease or handicap and a need to inform and prepare the families about the course early at the disease onset and to support them continuously with e.g. longer consultation time in order to optimize the management and treatment. The use of psychiatric screening may reduce the potential risk of emotional burden on the child and may help with compliance. Mental health assessment and treatment should be an integral component of comprehensive care of chronically ill children

Future perspectives

An increased awareness of the challenges associated with childhood cataract may improve the quality of life in these children and support their vulnerable families by incorporating additional approaches and strategies in the ophthalmic clinical environment. The changes to patient management include longer consultation time and psychiatric screening instruments like Strengths and Difficulties Questionnaire (SDQ) [135]. In addition, treatment and management may be organized individually considering the child's overall health and the parental background. Furthermore, it could be interesting to examine the school performance of our cohort in order to provide support in this area if needed.

References

1. Foster, A., Gilbert, C. & Rahi, J. Epidemiology of cataract in childhood: a global perspective. *J. Cataract Refract. Surg.* **23 Suppl 1**, 601–604 (1997).
2. Lambert, S. R. Childhood cataracts. in *Taylor and Hoyt's Pediatric Ophthalmology and Strabismus* 346–361 (Elsevier Inc., 2017).
3. Robert W. Hered. Pediatric Opthalmology and Strabismus, section 6. in *American Academy of Ophthalmology* 200–206 (2018).
4. Putzar, L., Hötting, K., Rösler, F. & Röder, B. The development of visual feature binding processes after visual deprivation in early infancy. *Vision Res.* **47**, 2616–2626 (2007).
5. Lim, M. E., Buckley, E. G. & Prakalapakorn, S. G. Update on congenital cataract surgery management. *Curr. Opin. Ophthalmol.* **28**, 87–92 (2017).
6. Yorston, D. Surgery for congenital cataract. *Community eye Heal.* **17**, 23–25 (2004).
7. Harbord, M. G., Baraitser, M. & Wilson, J. Microcephaly, mental retardation, cataracts, and hypogonadism in sibs: Martsolf's syndrome. *J. Med. Genet.* **26**, 397–400 (1989).
8. Chess, S., Fernandez, P. & Korn, S. Behavioral consequences of congenital rubella. *J. Pediatr.* **93**, 699–703 (1978).
9. Chauhan, N., Sen, M. S., Jhanda, S. & Grover, S. Psychiatric manifestations of congenital rubella syndrome: A case report and review of literature. *Journal of pediatric neurosciences* vol. 11 137–139 (2016).
10. Gentile, I. *et al.* Prevalence of Congenital Cytomegalovirus Infection Assessed Through Viral Genome Detection in Dried Blood Spots in Children with Autism Spectrum Disorders. *In Vivo* **31**, 467–473 (2017).
11. Shaw, D., Bar, S. & Champion, J. D. The impact of developmental behavioral pediatrics in a population of children with Down syndrome. *J. Pediatr. Nurs.* **57**, 38–42 (2020).
12. da Cunha, R. P. & Moreira, J. B. Ocular findings in Down's syndrome. *Am. J. Ophthalmol.* **122**, 236–244 (1996).
13. DeCarlo, D. K., Swanson, M., McGwin, G., Visscher, K. & Owsley, C. ADHD and Vision Problems in the National Survey of Children's Health. *Optom. Vis. Sci. Off. Publ. Am. Acad. Optom.* **93**, 459–465 (2016).
14. Wrzesińska, M., Kapias, J., Nowakowska-Domagała, K. & Kocur, J. Visual impairment and traits of autism in children. *Psychiatr. Pol.* **51**, 349–358 (2017).
15. Liu, Y.-C., Wilkins, M., Kim, T., Malyugin, B. & Mehta, J. S. Cataracts. *Lancet (London,*

England) **390**, 600–612 (2017).

16. Gillespie, R. L. *et al.* Personalized diagnosis and management of congenital cataract by next-generation sequencing. *Ophthalmology* **121**, 2122–2124 (2014).
17. Haargaard, B., Wohlfahrt, J., Fledelius, H. C., Rosenberg, T. & Melbye, M. A nationwide Danish study of 1027 cases of congenital/infantile cataracts. *Ophthalmology* **111**, 2292–2298 (2004).
18. Chia, W.-L. A. & Martin, F. Childhood cataracts. *Clin. Experiment. Ophthalmol.* **29**, 75–80 (2001).
19. Rahi, J. S. & Dezateux, C. National cross sectional study of detection of congenital and infantile cataract in the United Kingdom: role of childhood screening and surveillance. The British Congenital Cataract Interest Group. *BMJ* **318**, 362–365 (1999).
20. Wirth, M. G., Russell-Eggitt, I. M., Craig, J. E., Elder, J. E. & Mackey, D. A. Aetiology of congenital and paediatric cataract in an Australian population. *Br. J. Ophthalmol.* **86**, 782–786 (2002).
21. Lambert, S. R. & Drack, A. V. Infantile cataracts. *Surv Ophthalmol* **40**, 427–458 (1996).
22. Rahi, J. S., Sripathi, S., Gilbert, C. E. & Foster, A. Childhood blindness in India: causes in 1318 blind school students in nine states. *Eye (Lond).* **9 (Pt 5)**, 545–50 (1995).
23. Haargaard, B., Wohlfahrt, J., Fledelius, H. C., Rosenberg, T. & Melbye, M. Incidence and cumulative risk of childhood cataract in a cohort of 2.6 million Danish children. *Invest. Ophthalmol. Vis. Sci.* **45**, 1316–1320 (2004).
24. Wu, X., Long, E., Lin, H. & Liu, Y. Prevalence and epidemiological characteristics of congenital cataract: a systematic review and meta-analysis. *Sci. Rep.* **6**, 28564 (2016).
25. Jamieson, J. R. B. G. and R. V. Clinical embryology and development of the eye. in *Taylor and Hoyt's Pediatric Ophthalmology and Strabismus* 17–24 (Elsevier Inc., 2017).
26. Weisschuh, N., Aisenbrey, S., Wissinger, B. & Riess, A. Identification of a novel CRYBB2 missense mutation causing congenital autosomal dominant cataract. *Mol. Vis.* **18**, 174–180 (2012).
27. Li, J., Xia, C.-H., Wang, E., Yao, K. & Gong, X. Screening, genetics, risk factors, and treatment of neonatal cataracts. *Birth defects Res.* **109**, 734–743 (2017).
28. Birnholz, J. C. & Farrell, E. E. Fetal hyaloid artery: timing of regression with US. *Radiology* **166**, 781–783 (1988).
29. Chen, C., Xiao, H. & Ding, X. Persistent Fetal Vasculature. *Asia-Pacific J. Ophthalmol. (Philadelphia, Pa.)* **8**, 86–95 (2019).

30. Birch, E. E., Cheng, C., Stager, D. R., Weakley, D. R. & Stager, D. R. The critical period for surgical treatment of dense congenital bilateral cataracts. *J. Am. Assoc. Pediatr. Ophthalmol. Strabismus* **13**, 67–71 (2009).
31. Lagrèze, W. A. Treatment of congenital and early childhood cataract. *Ophthalmologe* (2021) doi:10.1007/s00347-021-01370-z.
32. Vishwanath, M., Cheong-Leen, R., Taylor, D., Russell-Eggitt, I. & Rahi, J. Is early surgery for congenital cataract a risk factor for glaucoma? *Br. J. Ophthalmol.* **88**, 905–910 (2004).
33. Freedman, S. F. *et al.* Glaucoma-Related Adverse Events at 10 Years in the Infant Aphakia Treatment Study: A Secondary Analysis of a Randomized Clinical Trial. *JAMA Ophthalmol.* **139**, 165–173 (2021).
34. Bothun, E. D. *et al.* Outcomes of Bilateral Cataracts Removed in Infants 1 to 7 Months of Age Using the Toddler Aphakia and Pseudophakia Treatment Study Registry. *Ophthalmology* **127**, 501–510 (2020).
35. Haargaard, B. *et al.* Risk of glaucoma after pediatric cataract surgery. *Invest. Ophthalmol. Vis. Sci.* **49**, 1791–6 (2008).
36. Lambert, S. R. *et al.* Intraocular Lens Implantation during Early Childhood: A Report by the American Academy of Ophthalmology. *Ophthalmology* **126**, 1454–1461 (2019).
37. Solebo, A. L., Cumberland, P. & Rahi, J. S. 5-year outcomes after primary intraocular lens implantation in children aged 2 years or younger with congenital or infantile cataract: findings from the IoLunder2 prospective inception cohort study. *Lancet. Child Adolesc. Heal.* **2**, 863–871 (2018).
38. Solebo, A. L., Rahi, J. S. & British Congenital Cataract Interest Group. Glaucoma following cataract surgery in the first 2 years of life: frequency, risk factors and outcomes from IoLunder2. *Br. J. Ophthalmol.* bjophthalmol-2019-314804 (2019) doi:10.1136/bjophthalmol-2019-314804.
39. Bothun, E. D. *et al.* Outcomes of Unilateral Cataracts in Infants and Toddlers 7 to 24 Months of Age: Toddler Aphakia and Pseudophakia Study (TAPS). *Ophthalmology* **126**, 1189–1195 (2019).
40. Lambert, S. R. *et al.* A randomized clinical trial comparing contact lens with intraocular lens correction of monocular aphakia during infancy: grating acuity and adverse events at age 1 year. *Arch. Ophthalmol. (Chicago, Ill. 1960)* **128**, 810–818 (2010).
41. Haargaard, B. *et al.* Risk of retinal detachment after pediatric cataract surgery. *Invest.*

Ophthalmol. Vis. Sci. **55**, 2947–2951 (2014).

42. Rabiah, P. K. Frequency and predictors of glaucoma after pediatric cataract surgery. *Am. J. Ophthalmol.* **137**, 30–37 (2004).
43. Asrani, S. *et al.* Does primary intraocular lens implantation prevent 'aphakic' glaucoma in children? *J. AAPOS Off. Publ. Am. Assoc. Pediatr. Ophthalmol. Strabismus* **4**, 33–39 (2000).
44. Abdelmassih, Y., Beaujeux, P., Dureau, P., Edelson, C. & Caputo, G. Incidence and Risk Factors of Glaucoma Following Pediatric Cataract Surgery With Primary Implantation. *Am. J. Ophthalmol.* **224**, 1–6 (2020).
45. Freedman, S. F. *et al.* Glaucoma-Related Adverse Events in the First 5 Years After Unilateral Cataract Removal in the Infant Aphakia Treatment Study. *JAMA Ophthalmol.* **133**, 907–914 (2015).
46. Nyström, A., Haargaard, B., Rosensvärd, A., Tornqvist, K. & Magnusson, G. The Swedish National Pediatric Cataract Register (PECARE): incidence and onset of postoperative glaucoma. *Acta Ophthalmol.* **98**, 654–661 (2020).
47. Simon, J. W., Mehta, N., Simmons, S. T., Catalano, R. A. & Lininger, L. L. Glaucoma after pediatric lensectomy/vitrectomy. *Ophthalmology* **98**, 670–674 (1991).
48. Robb, R. M. & Petersen, R. A. Outcome of treatment for bilateral congenital cataracts. *Ophthalmic Surg.* **23**, 650–656 (1992).
49. Stech, M. *et al.* Risk of aphakic glaucoma after pars plana-lensectomy with and without removal of the peripheral lens capsule. *Eye (Lond).* **33**, 1472–1477 (2019).
50. Mills, M. D. & Robb, R. M. Glaucoma following childhood cataract surgery. *J. Pediatr. Ophthalmol. Strabismus* **31**, 355–60; discussion 361 (1994).
51. Magnusson, G., Abrahamsson, M. & Sjöstrand, J. Glaucoma following congenital cataract surgery: an 18-year longitudinal follow-up. *Acta Ophthalmol. Scand.* **78**, 65–70 (2000).
52. Keech, R. V, Tongue, A. C. & Scott, W. E. Complications after surgery for congenital and infantile cataracts. *Am. J. Ophthalmol.* **108**, 136–141 (1989).
53. Johnson, C. P. & Keech, R. V. Prevalence of glaucoma after surgery for PHPV and infantile cataracts. *J. Pediatr. Ophthalmol. Strabismus* **33**, 14–17 (1996).
54. Egbert, J. E. *et al.* A prospective study of ocular hypertension and glaucoma after pediatric cataract surgery. *Ophthalmology* **102**, 1098–1101 (1995).
55. Vera, L. *et al.* Visual outcomes and complications of cataract surgery with primary implantation in infants. *J. Fr. Ophtalmol.* **40**, 386–393 (2017).

56. Eibenberger, K., Kiss, B., Schmidt-Erfurth, U. & Stifter, E. Clinical characteristics and treatment of secondary glaucoma, glaucoma suspects and ocular hypertension after congenital cataract surgery. *Eur. J. Ophthalmol.* 1120672121991356 (2021) doi:10.1177/1120672121991356.
57. Mataftsi, A. *et al.* Postoperative glaucoma following infantile cataract surgery: an individual patient data meta-analysis. *JAMA Ophthalmol.* **132**, 1059–1067 (2014).
58. Murphy, M. *et al.* Secondary glaucoma and visual axis opacification in aphakic and pseudophakic patients following congenital cataract surgery: A 28-year longitudinal case series. *Eur. J. Ophthalmol.* 112067211986287 (2019) doi:10.1177/1120672119862878.
59. Parks, M. M., Johnson, D. A. & Reed, G. W. Long-term visual results and complications in children with aphakia. A function of cataract type. *Ophthalmology* **100**, 821–826 (1993).
60. Solebo, A. L. & Rahi, J. S. Glaucoma following cataract surgery in the first 2 years of life: frequency, risk factors and outcomes from IoLunder2. *Br. J. Ophthalmol.* **104**, 967–973 (2020).
61. Sahin, A. *et al.* Secondary glaucoma after pediatric cataract surgery. *Int. J. Ophthalmol.* **6**, 216–220 (2013).
62. Zhang, S. *et al.* The role of primary intraocular lens implantation in the risk of secondary glaucoma following congenital cataract surgery: A systematic review and meta-analysis. *PLoS One* **14**, e0214684 (2019).
63. Swamy, B. N. *et al.* Secondary glaucoma after paediatric cataract surgery. *Br. J. Ophthalmol.* **91**, 1627–1630 (2007).
64. Lawrence, M. G. *et al.* Glaucoma following cataract surgery in children: surgically modifiable risk factors. *Trans. Am. Ophthalmol. Soc.* **103**, 46–55 (2005).
65. Plager, D. A., Lynn, M. J., Buckley, E. G., Wilson, M. E. & Lambert, S. R. Complications, adverse events, and additional intraocular surgery 1 year after cataract surgery in the infant Aphakia Treatment Study. *Ophthalmology* **118**, 2330–2334 (2011).
66. Sharma, N., Pushker, N., Dada, T., Vajpayee, R. B. & Dada, V. K. Complications of pediatric cataract surgery and intraocular lens implantation. *J. Cataract Refract. Surg.* **25**, 1585–1588 (1999).
67. Tassignon, M.-J. Bag-in-the-Lens Cataract Surgery. *https://www.aao.org/clinical-video/bag-in-lens-cataract-surgery*.
68. Dixon-Woods, M., Awan, M. & Gottlob, I. Why is compliance with occlusion therapy for

amblyopia so hard? A qualitative study. *Arch. Dis. Child.* **91**, 491–494 (2006).

69. Drews-Botsch, C., Celano, M., Cotsonis, G., DuBois, L. & Lambert, S. R. Parenting Stress and Adherence to Occlusion Therapy in the Infant Aphakia Treatment Study: A Secondary Analysis of a Randomized Clinical Trial. *Transl. Vis. Sci. Technol.* **8**, 3 (2019).
70. Gower, E. W. *et al.* Characteristics of Endophthalmitis after Cataract Surgery in the United States Medicare Population. *Ophthalmology* **122**, 1625–1632 (2015).
71. Prophylaxis of postoperative endophthalmitis following cataract surgery: results of the ESCRS multicenter study and identification of risk factors. *J. Cataract Refract. Surg.* **33**, 978–988 (2007).
72. Yorston, D., Yang, Y. F. & Sullivan, P. M. Retinal detachment following surgery for congenital cataract: presentation and outcomes. *Eye (Lond).* **19**, 317–321 (2005).
73. Chrousos, G. A., Parks, M. M. & O'Neill, J. F. Incidence of chronic glaucoma, retinal detachment and secondary membrane surgery in pediatric aphakic patients. *Ophthalmology* **91**, 1238–1241 (1984).
74. Lambert, S. R. *et al.* Long-term Effect of Intraocular Lens vs Contact Lens Correction on Visual Acuity After Cataract Surgery During Infancy: A Randomized Clinical Trial. *JAMA Ophthalmol.* **138**, 365–372 (2020).
75. Glascoe, F. P. Parents' evaluation of developmental status: how well do parents' concerns identify children with behavioral and emotional problems? *Clin. Pediatr. (Phila).* **42**, 133–138 (2003).
76. Senthilkumar, D., Balasubramaniam, S. M., Kumaran, S. E. & Ramani, K. K. Parents' awareness and perception of children's eye diseases in Chennai, India. *Optom. Vis. Sci. Off. Publ. Am. Acad. Optom.* **90**, 1462–1466 (2013).
77. Gyllén, J., Magnusson, G. & Forsberg, A. Parents' Reported Experiences When Having a Child with Cataract-Important Aspects of Self-Management Obtained from the Paediatric Cataract Register (PECARE). *Int. J. Environ. Res. Public Health* **17**, (2020).
78. Gyllén, J., Magnusson, G. & Forsberg, A. The Core of Parents' Main Concerns When Having a Child With Cataract and Its Clinical Implications. *J. Pediatr. Nurs.* **44**, e45–e51 (2019).
79. Noreña Peña, A. L. & Cibanal Juan, L. The experience of hospitalized children regarding their interactions with nursing professionals. *Rev. Lat. Am. Enfermagem* **19**, 1429–1436 (2011).
80. Melo, E. M. de O. P. de, Ferreira, P. L., Lima, R. A. G. de & Mello, D. F. de. The

involvement of parents in the healthcare provided to hospitalzed children. *Rev. Lat. Am. Enfermagem* **22**, 432–439 (2014).

81. Keating DP, H. C. *Developmental Health and the Wealth of Nations. New York, NY: The Guilford Press* (1999).
82. Detmar, S. B. *et al.* The development and validation of a handicap questionnaire for children with a chronic illness. *Clin. Rehabil.* **19**, 73–80 (2005).
83. Bell, M. F., Bayliss, D. M., Glauert, R., Harrison, A. & Ohan, J. L. Chronic Illness and Developmental Vulnerability at School Entry. *Pediatrics* **137**, (2016).
84. Geist, R., Grdisa, V. & Otley, A. Psychosocial issues in the child with chronic conditions. *Best Pract. Res. Clin. Gastroenterol.* **17**, 141–152 (2003).
85. Keil, S., Fielder, A. & Sargent, J. Management of children and young people with vision impairment: diagnosis, developmental challenges and outcomes. *Arch. Dis. Child.* **102**, 566–571 (2017).
86. Sonksen, P. M. & Dale, N. Visual impairment in infancy: impact on neurodevelopmental and neurobiological processes. *Dev. Med. Child Neurol.* **44**, 782–791 (2002).
87. Lopes, N. *et al.* Humanistic and Economic Burden of Blindness Associated with Retinal Disorders in a Brazilian Sample: A Cross-Sectional Study. *Adv. Ther.* (2021) doi:10.1007/s12325-021-01672-3.
88. Augestad, L. B. Mental Health among Children and Young Adults with Visual Impairments: A Systematic Review. *J. Vis. Impair. Blind.* **111**, 411–425 (2017).
89. Ishtiaq, R., Chaudhary, M. H., Rana, M. A. & Jamil, A. R. Psychosocial implications of blindness and low vision in students of a school for children with blindness. *Pakistan J. Med. Sci.* **32**, 431–434 (2016).
90. Adams, J. S., Chien, A. T. & Wisk, L. E. Mental Illness Among Youth With Chronic Physical Conditions. *Pediatrics* **144**, (2019).
91. Dybdal, D. *et al.* Increasing risk of psychiatric morbidity after childhood onset type 1 diabetes: a population-based cohort study. *Diabetologia* **61**, 831–838 (2018).
92. Craig, F., Savino, R. & Trabacca, A. A systematic review of comorbidity between cerebral palsy, autism spectrum disorders and Attention Deficit Hyperactivity Disorder. *Eur. J. Paediatr. Neurol. EJPN Off. J. Eur. Paediatr. Neurol. Soc.* **23**, 31–42 (2019).
93. Butler, A. *et al.* Mental disorder in children with physical conditions: a pilot study. *BMJ Open* **8**, e019011 (2018).
94. Bertelsen, E. N., Larsen, J. T., Petersen, L., Christensen, J. & Dalsgaard, S. Childhood

Epilepsy, Febrile Seizures, and Subsequent Risk of ADHD. *Pediatrics* **138**, (2016).

95. LaGrant, B., Marquis, B. O., Berg, A. T. & Grinspan, Z. M. Depression and anxiety in children with epilepsy and other chronic health conditions: National estimates of prevalence and risk factors. *Epilepsy Behav.* **103**, 106828 (2020).
96. Friend, A. J., Feltbower, R. G., Hughes, E. J., Dye, K. P. & Glaser, A. W. Mental health of long-term survivors of childhood and young adult cancer: A systematic review. *Int. J. cancer* **143**, 1279–1286 (2018).
97. Barkmann, C. & Schulte-Markwort, M. Prevalence of emotional and behavioural disorders in German children and adolescents: a meta-analysis. *J. Epidemiol. Community Health* **66**, 194–203 (2012).
98. Duarte, C. *et al.* Child mental health in Latin America: present and future epidemiologic research. *Int. J. Psychiatry Med.* **33**, 203–222 (2003).
99. Dalsgaard, S. *et al.* Incidence Rates and Cumulative Incidences of the Full Spectrum of Diagnosed Mental Disorders in Childhood and Adolescence. *JAMA psychiatry* **77**, 155–164 (2020).
100. Koch, S. V, Andersson, M., Hvelplund, C. & Skovgaard, A. M. Mental disorders in referred 0-3-year-old children: a population-based study of incidence, comorbidity and perinatal risk factors. *Eur. Child Adolesc. Psychiatry* (2020) doi:10.1007/s00787-020-01616-2.
101. Thapar, A., Cooper, M. & Rutter, M. Neurodevelopmental disorders. *The lancet. Psychiatry* **4**, 339–346 (2017).
102. Luo, L., Feng, B., Yang, S., Zhang, N. & Qiu, S. Clinical characteristics of moderate-severe obsessive-compulsive disorder in children and adolescents in China. *J. Int. Med. Res.* **48**, 300060520922679 (2020).
103. Pinhas, L., Morris, A., Crosby, R. D. & Katzman, D. K. Incidence and age-specific presentation of restrictive eating disorders in children: a Canadian Paediatric Surveillance Program study. *Arch. Pediatr. Adolesc. Med.* **165**, 895–899 (2011).
104. van Eeden, A. E., Oldehinkel, A. J., van Hoeken, D. & Hoek, H. W. Risk factors in preadolescent boys and girls for the development of eating pathology in young adulthood. *Int. J. Eat. Disord.* (2021) doi:10.1002/eat.23496.
105. Kessler, R. C. *et al.* Age of onset of mental disorders: a review of recent literature. *Curr. Opin. Psychiatry* **20**, 359–364 (2007).
106. Razaz, N. *et al.* Incidence of Mood or Anxiety Disorders in Children of Parents with

Multiple Sclerosis. *Paediatr. Perinat. Epidemiol.* **30**, 356–366 (2016).

107. Bøe, T. *et al.* Socioeconomic status and child mental health: the role of parental emotional well-being and parenting practices. *J. Abnorm. Child Psychol.* **42**, 705–715 (2014).
108. Reiss, F. Socioeconomic inequalities and mental health problems in children and adolescents: a systematic review. *Soc. Sci. Med.* **90**, 24–31 (2013).
109. Al-Bakri, M., Bach-Holm, D., Larsen, D. A., Siersma, V. & Kessel, L. Socio-economic status in families affected by childhood cataract. *Acta Ophthalmol.* (2021) doi:10.1111/aos.14768.
110. Loepke, A. W. & Soriano, S. G. An assessment of the effects of general anesthetics on developing brain structure and neurocognitive function. *Anesth. Analg.* **106**, 1681–1707 (2008).
111. Backeljauw, B., Holland, S. K., Altaye, M. & Loepke, A. W. Cognition and Brain Structure Following Early Childhood Surgery With Anesthesia. *Pediatrics* **136**, e1-12 (2015).
112. Sun, L. Early childhood general anaesthesia exposure and neurocognitive development. *Br. J. Anaesth.* **105 Suppl**, i61-8 (2010).
113. Flick, R. P. *et al.* Cognitive and behavioral outcomes after early exposure to anesthesia and surgery. *Pediatrics* **128**, e1053-61 (2011).
114. Zhang, Q., Peng, Y. & Wang, Y. Long-duration general anesthesia influences the intelligence of school age children. *BMC Anesthesiol.* **17**, 170 (2017).
115. Plager, D. A., Lynn, M. J., Buckley, E. G., Wilson, M. E. & Lambert, S. R. Complications in the first 5 years following cataract surgery in infants with and without intraocular lens implantation in the Infant Aphakia Treatment Study. *Am. J. Ophthalmol.* **158**, 892–898 (2014).
116. Loudon, S. E. *et al.* Psychological causes of non-compliance with electronically monitored occlusion therapy for amblyopia. *Br. J. Ophthalmol.* **93**, 1499–1503 (2009).
117. Hrisos, S., Clarke, M. P. & Wright, C. M. The emotional impact of amblyopia treatment in preschool children: randomized controlled trial. *Ophthalmology* **111**, 1550–1556 (2004).
118. Pillas, D. *et al.* Social inequalities in early childhood health and development: a European-wide systematic review. *Pediatr. Res.* **76**, 418–424 (2014).
119. Solebo, A. L., Teoh, L. & Rahi, J. Epidemiology of blindness in children. *Arch. Dis. Child.* **102**, 853–857 (2017).

120. Bourdieu, P. *"The Forms of Capital." in Handbook of theory and research for the sociology of education, edited by J. G. Richardson. New York: Greenwood Press*. (1986).
121. Zablotsky, B. *et al.* Prevalence and Trends of Developmental Disabilities among Children in the United States: 2009-2017. *Pediatrics* **144**, (2019).
122. Wang, J. *et al.* Barriers, Costs, and Attitudes Toward Pediatric Cataract Surgery at Two Large Facilities in China and India. *Ophthalmic Epidemiol.* **26**, 47–54 (2019).
123. Tjiam, A. M. *et al.* Sociocultural and psychological determinants in migrants for noncompliance with occlusion therapy for amblyopia. *Graefes Arch. Clin. Exp. Ophthalmol.* **249**, 1893–1899 (2011).
124. Dandona, R. & Dandona, L. Socioeconomic status and blindness. *Br. J. Ophthalmol.* **85**, 1484–1488 (2001).
125. Sen, P. *et al.* Causes of delayed presentation of pediatric cataract: A questionnaire-based prospective study at a tertiary eye care center in central rural India. *Indian J. Ophthalmol.* **68**, 603–607 (2020).
126. Goldberg, D. P. *et al.* Multiple somatic symptoms in primary care: A field study for ICD-11 PHC, WHO's revised classification of mental disorders in primary care settings. *J. Psychosom. Res.* **91**, 48–54 (2016).
127. Lin, Z.-L. *et al.* Increased prevalence of parent ratings of ADHD symptoms among children with bilateral congenital cataracts. *Int. J. Ophthalmol.* **12**, 1323–1329 (2019).
128. Chak, M. & Rahi, J. S. The health-related quality of life of children with congenital cataract: findings of the British Congenital Cataract Study. *Br. J. Ophthalmol.* **91**, 922–926 (2007).
129. Hansen, M. M., Bach-Holm, D. & Kessel, L. Visual outcomes after surgery for childhood cataracts. *Acta Ophthalmol.* aos.14403 (2020) doi:10.1111/aos.14403.
130. Sildorf, S. M. *et al.* Poor Metabolic Control in Children and Adolescents With Type 1 Diabetes and Psychiatric Comorbidity. *Diabetes Care* **41**, 2289–2296 (2018).
131. Jin, J., Sklar, G. E., Min Sen Oh, V. & Chuen Li, S. Factors affecting therapeutic compliance: A review from the patient's perspective. *Ther. Clin. Risk Manag.* **4**, 269–286 (2008).
132. Roohafza, H. *et al.* Stress as a risk factor for noncompliance with treatment regimens in patients with diabetes and hypertension. *ARYA Atheroscler.* **12**, 166–171 (2016).
133. DiMatteo, M. R., Lepper, H. S. & Croghan, T. W. Depression is a risk factor for noncompliance with medical treatment: meta-analysis of the effects of anxiety and

depression on patient adherence. *Arch. Intern. Med.* **160**, 2101–2107 (2000).

134. Shrivastava, A., Johnston, M. & Bureau, Y. Stigma of Mental Illness-2: Non-compliance and Intervention. *Mens Sana Monogr.* **10**, 85–97 (2012).

135. Goodman, R. The Strengths and Difficulties Questionnaire: a research note. *J. Child Psychol. Psychiatry.* **38**, 581–586 (1997).

Appendix: Papers I-III

Paper I

Children with congenital and childhood cataract require frequent follow-up visits and examinations in general anaesthesia: considerations for the strain on families

Paper II

Socio-economic status in families affected by childhood cataract

Paper III

Increased incidence of mental disorders in children with cataract – findings from a population-based study

PAPER I

Acta Ophthalmologica

Children with congenital and childhood cataract require frequent follow-up visits and examinations in general anaesthesia: considerations for the strain on families

Moug Al-Bakri,[1] Birgit Sander,[1] Daniella Bach-Holm,[1] Dorte Ancher Larsen,[2] Hanne Jensen[1] and Line Kessel[1]

[1]Department of Ophthalmology, Rigshospitalet-Glostrup, Glostrup, Denmark
[2]Department of Ophthalmology, Aarhus Kommunehospital, Aarhus, Denmark

ABSTRACT.

Background: **Children with cataract require frequent monitoring to detect complications, adjust refractive correction and treat amblyopia. This is time consuming for the families. The aim of the study was to evaluate how often children with cataract are seen as outpatients or under general anaesthesia during the first 7 years of life.**

Methods: **We performed a retrospective chart review of all children with congenital and childhood cataract born between 2000 primo and 2017 seen at our institution. The cumulated number of outpatient visits and examinations and/or surgeries in general anaesthesia was extracted for age 1, 3, 5 and 7 years.**

Results: **Children who had cataract surgery were seen significantly more often than children without surgery. During the first year of life, children with bilateral surgery had a median of nine outpatient visits, children with unilateral cataract had 11 and children without surgery had five outpatient visits. At 7 years of age, half of the children operated bilaterally before 1 year of age had undergone at least five procedures/examinations in general anaesthesia versus 1/4 of those with unilateral surgery and none of those without surgery. Children were seen less frequently with advancing age.**

Conclusion: **The management, treatment and follow-up of children with cataract are demanding, requiring frequent hospital visits and repeated examinations and/or surgical procedures in general anaesthesia over many years, but mainly during the first year of life. Surgical patients are more complex and require closer follow-up. This message is important to convey to the parents at the onset of the disease.**

Key words: anaesthesia – cataract – childhood cataract – congenital – family strain – family stress

Acta Ophthalmol.

doi: 10.1111/aos.14081

Introduction

Congenital cataract is a lens opacity present at birth. The management of childhood cataracts is tedious and often difficult, requiring frequent follow-up over many years. Attending the regular follow-up examination at hospitals and the often repeated need for examinations and/or surgical procedures in general anaesthesia is demanding to the families, and making the right decisions already at the preoperative evaluation is essential and requires well-informed parents (Yorston 2004). A successful outcome after surgery for childhood cataracts requires a dedicated team effort involving parents, paediatric ophthalmologists, paediatric ophthalmic surgeons, paediatricians, anaesthesiologists, technicians, orthoptists, low vision rehabilitation specialists and community health workers. Children undergoing cataract surgery must be followed regularly because of a high risk of secondary glaucoma, visual axis opacification, amblyopia and changing refractive errors as the eye grows (Lim et al. 2017). It is very important to ensure that the family understands the prognosis and duration of treatment since they are going to be responsible for implementing most of it (Yorston 2004). Consequently, it is of interest to investigate how much time families of children with congenital cataract spend on hospital visits for outpatient follow-up and examinations and/or surgical procedures in general anaesthesia.

Materials and Methods

We included all patients born between 2000 and primo 2017 seen at Rigshospitalet-Glostrup with congenital or

childhood cataracts. We excluded patients who had undergone surgery outside our institution. We included children with all types of cataracts including traumatic cataracts. Only patients with lenticular opacities were included in the study. Patients with other types of lens anomalies, including subluxation, posterior lenticonus and persistent prepupillary membranes without lenticular opacities, were excluded. Both children with isolated cataracts, and children with cataracts in combination with ocular malformations (e.g. Peters anomaly) or syndromes were included. Hospital charts were reviewed and the number of outpatient visits and examinations/surgical procedures performed under general anaesthesia were recorded and cumulated for the ages of 1, 3, 5 and 7. Seven years of age was chosen as the final follow-up time since amblyopia treatment was usually stopped or markedly tapered after the age of 7, and because children older than seven usually were able to undergo small procedures (e.g. Yttrium Aluminium Garnet (YAG) laser membranectomy for visual axis opacification) without general anaesthesia. Examination in general anaesthesia in our study refers to when children only underwent examination without any surgical procedures. Surgical procedures under general anaesthesia were always accompanied by a thorough examination – examinations in combination with a surgical procedure were grouped according to the surgical procedure.

Indication for surgery was a visually disturbing cataract covering the pupillary area in the undilated eye. In some cases, visually disturbing unilateral cataracts were not operated if the risk associated with surgery exceeded the benefit of the procedure (e.g. severely microphthalmic eyes with little potential for visual recovery judged by visually evoked potentials, at the treating clinician′s discretion or late diagnosis of unilateral cataract with no hope of reversing deprivation amblyopia). Bilateral surgeries were typically performed 1–2 weeks apart in two different surgical settings, but some children had simultaneous bilateral cataract surgery.

Children were followed pre- and postoperatively by a paediatric ophthalmologist, an orthoptist and low vision specialist rehabilitation optometrist as required. In cases where cataract surgery was performed, the child was followed by a paediatric cataract surgeon prior to surgery and for the first month following surgery. When the child required follow-up by a multidisciplinary team, the outpatient visits were coordinated on the same date if at all possible to minimize the time consumption and days off work for the families.

Number of outpatient visits and examinations/procedures in general anaesthesia were calculated only for visits at the Eye Department. Some children were also followed by other departments, for example, paediatric departments, those visits and examinations under anaesthesia plus procedures in general anaesthesia performed for non-ocular causes were not evaluated as we did not have sufficiently reliable historical data for this.

A large proportion of children with cataracts were not operated because the cataract was not deemed visually significant, for example, small anterior polar cataracts, or vision was not expected to improve after surgery, for example, posterior polar cataract with or without persistent foetal vasculature with severe deprivation amblyopia.

The study was approved by the Danish Data Protection Agency (RH-2016-336; I-Suite # 05070), and the Danish Patient Safety Authority (3-3013-1935/1/NAAN). According to the Committee on Health Research Ethics in the Capital Region of Denmark ethical board review was not required. The study followed the tenets of the Helsinki Declaration.

Statistical method

Statistical analyses were performed using SIGMAPLOT® (version 13.0, Systat Software, Inc., San Jose, CA, USA) and The SAS® (version 9.4, SAS Institute, Cary, NC, USA). If the number of outpatient visits and number of procedures and/or examinations in general anaesthesia were not normally distributed, non-parametric tests were used. p-values ≤ 0.05 were considered statistically significant. Data are summed in relation to the child's age at operation examination in the groups: $0 \leq 1$, $1 \leq 3$, $3 \leq 5$ and $5 \leq 7$ years. Also, cumulated data are shown for ages $0 \leq 1$, $0 \leq 3$, $0 \leq 5$ and $0 \leq 7$ years. Categorical data were analysed with chi-squared. For the data relating to birth year (Fig. 2) linear regression and a linear regression model was applied.

Results

We included 227 children (116 boys and 111 girls) born between 2000 and primo 2017 and followed at our institution since the diagnosis of congenital or childhood cataracts. Of the 79 children who had bilateral cataract extraction, 51 were operated during the first year of life. Correspondingly, 44 out of 69 children with unilateral surgery had surgery in the first year of life. 79 children were not operated. A relatively high number of children were operated for unilateral cataract late between the age of 3–5 years ($n = 15$) and 5–7 years ($n = 6$). This was in part due to traumatic cataracts ($n = 3$) or secondary cataracts related to uveitis or postradiation therapy ($n = 4$) but the majority of cases were discovered as part of the preschool visual screening programme ($n = 14$). A large number of the children who were not operated were diagnosed late in childhood between 3 and 7 years of age.

Outpatient visits

Generally, children who had been operated for cataract were seen more frequently than children who were not operated, see Table 1. Unoperated children diagnosed $0 \leq 5$ years of age had significantly fewer outpatient visits for the first 5 years of life than children operated for bilateral or unilateral cataracts at all follow-up time points ($p < 0.0001$, non-parametric test). It was 5, 8 and 14 in median for $0 < 1$, $0 < 3$ and $0 < 5$ respectively and 9/11, 15/14 and 20/21 for bilateral/unilateral in corresponding years. For children diagnosed after the age of 5, there were too few observations to allow for statistical testing.

For those children who were diagnosed before 1 year of age, children with bilateral surgery were seen a median of nine times during their first year of life and accumulated median of 27 times by their 7th year. Correspondingly, children with unilateral surgery diagnosed before 1 year of life were seen a median of 11 times during the first year of life and cumulated 28 times during

the first 7 years of life and children who were not operated were seen five (median) times in their first year of life and cumulated 16 times for the first 7 years of life. Children diagnosed in early infancy had more frequent outpatient visits than those diagnosed later.

The need for regular follow ups tapered over the years, see Table 1. For children diagnosed before 1 year of age and who underwent bilateral surgery, the median number of days between outpatient visits increased from 23 days during the first year of life, to 69 at age 3 years, 85 at age 5 years and 95 at age 7 years. For children diagnosed before 1 year of age with unilateral surgery the corresponding median number of days between visits were 19 days at 1 year, 68 at 3 years, 85 at 5 years and 72 at 7 years. There was no significant difference between children with unilateral or bilateral surgery but children without surgery were seen at significantly longer intervals for the first 3 years of life ($p < 0.001$). For the first year of life, 60.8% ($n/N = 31/51$) of children with bilateral surgery were seen more than once per month and only 3.9% ($n/N = 2/51$) were seen in longer intervals than every second month. For children with unilateral surgery, 81.8% ($n/N = 36/44$) of children were seen more than once per month and 4.6% ($n/N = 2/44$) were seen less frequent than every second week during the first year of life. Only 13.9% of the children without surgery were seen at 1-month intervals or shorter in the first year of life ($n/N = 11/79$).

Examinations and surgical procedures in general anaesthesia

The need for repeated surgical procedures or examinations in general anaesthesia during the first year of life was significantly higher for children with bilateral cataract surgery compared to children with unilateral cataract or no surgery, see Table 2. A need for thorough

Table 1. Cumulated number of outpatient visits.

Cumulated interval Age at diagnosis	0 ≤ 1 year of life	0 ≤ 3 years of life	0 ≤ 5 years of life	0 ≤ 7 years of life
≤1 years				
Bilateral surgery	9 (3–42) [51]	15 (6–52) [42]	20 (0–67) [36]	27 (3–60) [23]
Unilateral surgery	11 (2–36) [44]	14 (2–52) [33]	21 (5–57) [25]	28 (8–57) [19]
No surgery	5 (1–14) [33]	8 (3–20) [20]	14 (9–33) [10]	16 (12–44) [4]
>1 year to ≤3 years				
Bilateral surgery	–	10 (1–18) [14]	17 (11–26) [8]	25 (18–40) [4]
Unilateral surgery	–	9 (2–26) [11]	19 (8–32) [8]	23 (15–44) [6]
No surgery	–	4 (2–12) [13]	9 (5–19) [5]	15 (13–16) [3]
>3 years to ≤5 years				
Bilateral surgery	–	–	14 (6–30) [12]	21 (15–36) [8]
Unilateral surgery	–	–	16 (8–30) [8]	25 (18–33) [8]
No surgery	–	–	5 (2–14) [15]	9 (3–16) [5]
>5 years to ≤7 years				
Bilateral surgery	–	–	–	12 (10–13) [2]
Unilateral surgery	–	–	–	9 (0–19) [6]
No surgery	–	–	–	5 (3–23) [18]

Numbers are given in median (range) and [number of children].

Table 2. Cumulated number of examinations/surgeries in general anesthesia.

Cumulated interval Age at diagnosis	0 ≤ 1 year of life	0 ≤ 3 years of life	0 ≤ 5 years of life	0 ≤ 7 years of life
≤1 years				
Bilateral surgery	3 (1–9) [51]	4 (1–12) [42]	4 (1–12) [36]	5 (1–11) [23]
Unilateral surgery	2 (0–6) [44]	2 (0–6) [33]	0 (0–7) [25]	3 (0–8) [19]
No surgery	0 (0–0) [33]	0 (0–3) [20]	0 (0–3) [10]	2 (0–3) [4]
>1 year to ≤3 years				
Bilateral surgery	–	3 (0–5) [14]	3 (2–5) [8]	3 (3–5) [4]
Unilateral surgery	–	1 (1–5) [11]	2 (2–5) [8]	2 (2–5) [6]
No surgery	–	0 (0–3) [13]	0 (0–1) [5]	0 (0–0) [3]
>3 years to ≤ 5 years				
Bilateral surgery	–	–	2 (2–4) [12]	2 (2–4) [8]
Unilateral surgery	–	–	2 (2–10) [8]	2 (1–6) [8]
No surgery	–	–	0 (0–0) [15]	0 (0–1) [5]
>5 years to ≤7 years				
Bilateral surgery	–	–	–	3 (2–3) [2]
Unilateral surgery	–	–	–	1 (1–3) [6]
No surgery	–	–	–	0 (0–3) [18]

Numbers are given in median (range) and [number of children].

examination was the most frequent cause for general anaesthesia followed by cataract and glaucoma surgery, see Fig. 1. Surgery for visual axis opacifications and other types of surgeries were performed in smaller numbers (16%). Other surgeries included a total of 23 surgical procedures performed on 12 children ranging from pupilloplastic surgery (n = 1), removal of anterior synechia (n = 2) over removal of a subluxated intraocular lens (IOL) (n = 1), subtenon depot of steroid for otherwise uncontrolled uveitis related to juvenile arthritis (one child, two injections), repeat fluorescein angiography and panretinal photocoagulation in a child with Eales disease (one child, two procedures) to more severe cases of unilateral cataract with persistent hyaloid artery ultimately resulting in several surgical procedures to treat a retinal detachment (n = 1 child) and unilateral cataract caused by persistent hyaloid artery resulting in glaucoma and removal of a blind, painful eye (n = 1 child). In addition, four children with traumatic cataracts required repeat surgical procedures to control the condition with three of those children developing a retinal detachment in the aftermath of the trauma.

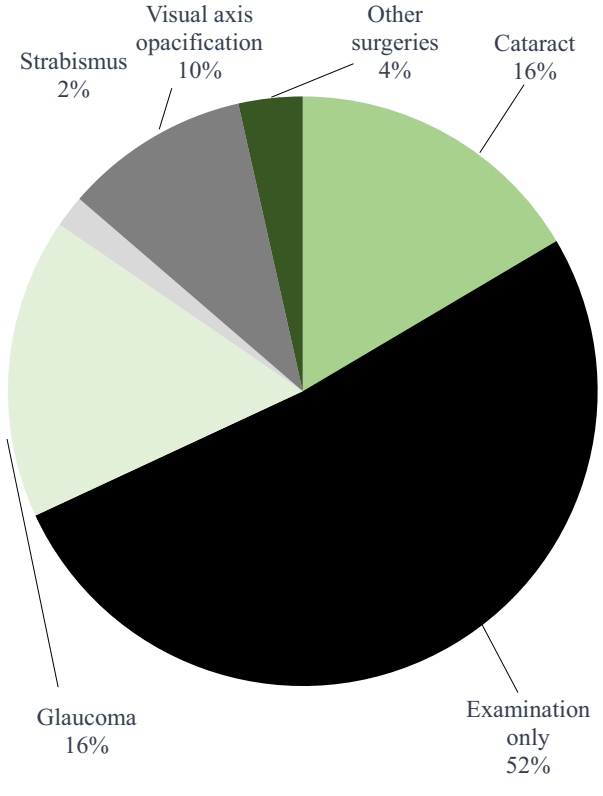


Fig. 1. Pie chart demonstrating the causes for general anaesthesia in children with congenital or childhood cataracts diagnosed ≤1 year of age. The expression 'examination only' was used when the sole cause of anaesthesia was a need for thorough examination. An examination was always performed when the child was in general anaesthesia for a surgical procedure, but those examinations are not included in the number of examinations reported in the pie chart. Cataract surgery includes all universal anaesthesia settings with the purpose of performing cataract surgery.

There were no significant differences between children with IOL or aphakia with respect to the number of examinations and procedures in general anaesthesia, see Table 3.

To examine if the need for examinations and surgical procedures in general anaesthesia changed over the years as more handheld examination devices, for example, Icare tonometer, became available (from 2007 in our institution) the number of general anaesthesia procedures for a subgroup of children who were diagnosed and operated ≤1 year of age, as shown in Fig. 2, was examined in relation to year of birth. Data were summed for each of the age groups $0 \leq 1$, $1 \leq 3$ and $3 \leq 5$ years. The number of general

Table 3. Cumulated number of outpatient visits and examinations/procedures in general anaesthesia for children diagnosed before 1 year of age depending on whether they had intraocular lens implant at the time of surgery or not.

	0 ≤ 1 year of life	0 ≤ 3 years of life	0 ≤ 5 years of life	0 ≤ 7 years of life
Bilateral surgery, outpatient visits				
All patients	9 (3–42) [51]	16 (6–52) [42]	20 (0–67) [36]	27 (3–60) [23]
Patients with aphakia	11 (4–42) [38]	16 (6–52) [33]	20 (0–67) [28]	36 (4–60) [17]
Patients with IOL	7 (3–19) [13]	10 (6–29) [9]	16 (1–32) [8]	22 (3–47) [6]
Bilateral surgery, procedures/examinations in general anaesthesia				
All patients	3 (1–9) [51]	4 (1–12) [42]	4 (1–12) [36]	5 (1–11) [23]
Patients with aphakia	4 (1–9) [38]	4 (1–12) [33]	5 (1–12) [28]	5 (1–11) [17]
Patients with IOL	3 (1–3) [13]	3 (1–5) [9]	2 (0–5) [8]	2 (0–6) [6]
Unilateral surgery, outpatient visits				
All patients	11 (2–36) [44]	14 (2–52) [33]	21 (5–57) [25]	28 (8–57) [19]
Patients with aphakia	12 (4–36) [18]	17 (8–52) [12]	19 (11–57) [11]	38 (11–57) [8]
Patients with IOL	11 (2–19) [26]	14 (2–27) [21]	23 (5–43) [14]	27 (8–44) [11]
Unilateral surgery, procedures/examinations in general anaesthesia				
All patients	2 (0–6) [44]	2 (0–6) [33]	0 (0–7) [25]	3 (0–8) [19]
Patients with aphakia	2 (0–6) [18]	3 (0–6) [12]	3 (0–7) [11]	5 (1–8) [8]
Patients with IOL	2 (0–5) [26]	2 (0–4) [21]	3 (0–6) [14]	3 (0–6) [11]

Numbers are given in median (range) and [number of children].

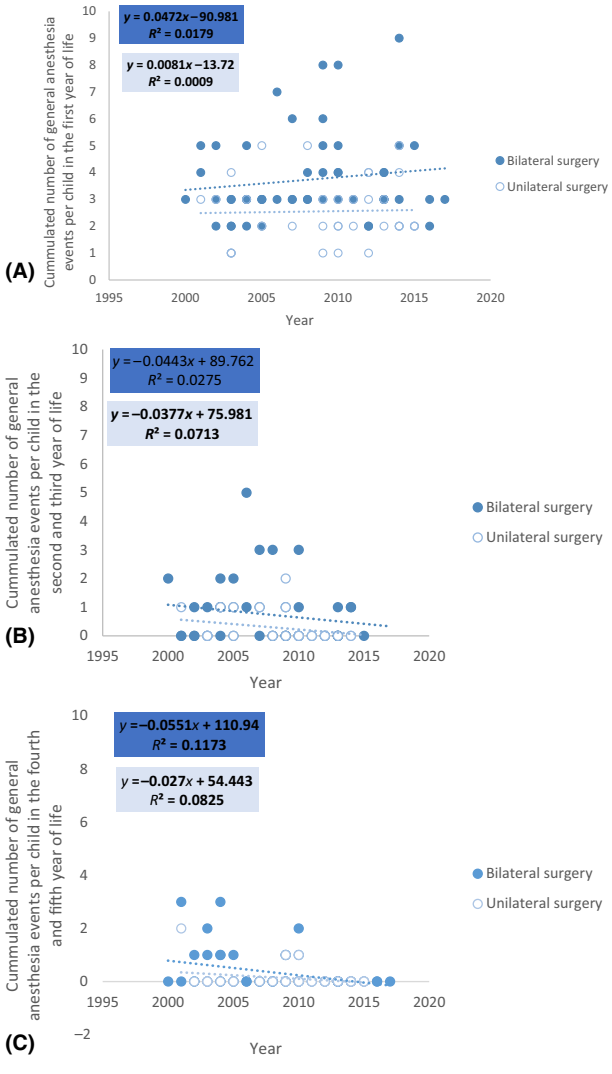


Fig. 2. Distribution of the number of general anaesthesia events per child diagnosed and operated ≤1 year of age according to year of birth. Linear tendency lines for the bilateral and unilateral groups are added. (A) Follow-up for the first year of life. (B) Follow-up in the second and third year of life. (C) Follow-up in the fourth and fifth year of life. Icare tonometer was introduced in our clinic in 2007.

anaesthesia events was consistently higher in bilateral patients compared to unilateral at all time periods. For the first year of life (Fig. 2 top) the number of examinations increased for children with bilateral cataracts and was stable for children with unilateral cataract from 2000 to 2017. For the age groups $1 \leq 3$ and $3 \leq 5$ years the need for general anaesthesia decreased with time both for bilateral and unilateral children and a large proportion had no general anaesthesia procedures at all, in particular if they were born in more recent years.

Discussion

We performed a retrospective chart review of all children with congenital cataract born between 2000 and primo 2017 seen and operated at our institution. We found that children who underwent surgery early in life had the highest number of outpatient visits and that some would need check-ups as regularly as every month throughout childhood. Especially, the first year in life was burdened by frequent outpatient visits with as many as 1/4 of children with bilateral surgery and 1/3 of children with unilateral surgery needing check-ups at least every second week. The need for monitoring tapered as expected over the years and was less for children who were diagnosed with cataract later in childhood.

Around 1/3 of the children were diagnosed late between 3 and 7 years of age, compared to children receiving the diagnosis earlier in life, for example, the first year of life. Half of those were not operated. To prevent implication and progression of the disease, we need to detect and operate children with congenital cataract early in life. In Denmark, children are screened for congenital cataract using a pencil light only by the general practitioner at 5 weeks of age instead of incorporating screening in maternity wards and well-baby clinics by examining red light reflexes as in Sweden (Magnusson et al. 2013). Visual screening is performed at 3, 4 and 5 years of age by a general practitioner and when the child begins school (age 6) by a school nurse. Although it is not possible to determine with certainty that cataract diagnosed later in childhood was already present at birth, a large number of those diagnosed late had posterior subcapsular cataracts with or without persistent foetal vasculature. These numbers seem to suggest that children are diagnosed as a consequence of visual screening rather than the 5-week screening. It has previously been documented that children are diagnosed later in Denmark compared to neighbouring Sweden.

The Infant Aphakia Treatment Study found that additional intraocular surgeries were performed more frequently in the IOL group (Plager et al. 2014). We found no significant differences between children with IOL or aphakia with respect to the number of outpatient visits or examinations in general anaesthesia. In our institution, surgeries with IOL implantations were usually performed in children over the age of 6 months while children below 6 months of age were typically left aphakic. Thus, in our study children operated early in life were generally aphakic and children operated later in life generally had an IOL. Complications, for example, visual axis opacification and glaucoma, is often considered to be more common in children operated at an early age. It may also be that complicated eyes are left aphakic, and these eyes may require a closer follow-up.

In other words, the difference between ours and other studies may be related to age differences as to which groups received IOLs or were left aphakic rather than the effect of implanting an IOL or not on the number of procedures and examinations in general anaesthesia in children with IOL.

It may not be risk-free having infants undergoing general anaesthesia (Loepke & Soriano 2008). Therefore, the benefits of thorough examinations in general anaesthesia need to be balanced with the risk of repeat anaesthesias. Some studies suggest that general anaesthesia in early childhood often affects the intelligence, growth and wellbeing (Loepke & Soriano 2008; Sun 2010; Backeljauw et al. 2015). The general anaesthesia events should be limited to must be performed only when needed (Hackel et al. 1999). The most common cause for general anaesthesia was a need for thorough examinations. The majority of operated children in our cohort had surgery within the first year of life. Small children may be more difficult to examine and since early treatment of complications is mandatory, repeated anaesthesia may be warranted. Over the years, more handheld examinations devices have become available, and we found that the need for anaesthesia was reduced from 2000 to 2017 in children older than 1 year, while the need was stable in the first year of life.

Conclusion

Children who had surgery for congenital and childhood cataracts had more hospital visits and more procedures or examinations with anaesthesia regardless of whether surgery was uni- or bilateral or whether an IOL was implanted.

The families do need to be prepared for a long course with many visits and some interventions.

Some children were seen monthly for their first 7 years.

We found that families may benefit from counselling at the time of diagnosis on the need for frequent hospital visits. This is especially the case with children of vulnerable families with unilateral cataract where the prognosis is poor and repeat examinations and surgery are frequent.

References

Backeljauw B, Holland SK, Altaye M & Loepke AW (2015): Cognition and brain structure following early childhood surgery with anesthesia. Pediatrics **136**: e1–e12.

Hackel A, Badgwell JM, Binding RR et al. (1999): Guidelines for the pediatric perioperative anesthesia environment. American Academy of Pediatrics. Section on Anesthesiology. Pediatrics **103**: 512–515.

Lim ME, Buckley EG & Prakalapakorn SG (2017): Update on congenital cataract surgery management. Curr Opin Ophthalmol **28**: 87–92.

Loepke AW & Soriano SG (2008): An assessment of the effects of general anesthetics on developing brain structure and neurocognitive function. Anesth Analg **106**: 1681–1707.

Magnusson G, Bizjajeva S, Haargaard B, Lundstrom M, Nystrom A & Tornqvist K (2013): Congenital cataract screening in maternity wards is effective: evaluation of the paediatric cataract register of Sweden. Acta Paediatr **102**: 263–267.

Plager DA, Lynn MJ, Buckley EG, Wilson ME, Lambert SR; Infant Aphakia Treatment Study Group (2014): Complications in the first 5 years following cataract surgery in infants with and without intraocular lens implantation in the Infant Aphakia Treatment Study. Am J Ophthalmol **158**: 892–898.

Sun L (2010): Early childhood general anaesthesia exposure and neurocognitive development. Br J Anaesth **105**(Suppl 1): i61–i68.

Yorston D (2004): Surgery for congenital cataract. Community Eye Health **17**: 23–25.

Received on December 18th, 2018.
Accepted on February 10th, 2019.

Correspondence:
Moug Al-Bakri, MD
Rigshospitalet-Glostrup
Valdemar Hansens Vej 3
2600 Glostrup
Denmark
Tel: +45 21 36 36 71
Fax: +45 38 63 46 69
E-mail: moug.adil.yaser.al-bakri@regionh.dk

The study received financial support from Øjenforeningen (Fight for Sight Denmark) and Carl and Nicoline Larsen´s Fund, Synoptik Foundation and Øjenfonden. The funding bodies had no influence on conception, design or reporting of the study.

PAPER II

Acta Ophthalmologica

Socio-economic status in families affected by childhood cataract

Moug Al-Bakri,[1] Daniella Bach-Holm,[1,2] Dorte Ancher Larsen,[3] Volkert Siersma[4] and Line Kessel[1,2]

[1]Department of Ophthalmology, Rigshospitalet-Glostrup, Glostrup, Denmark
[2]Department of Clinical Medicine, University of Copenhagen, Copenhagen, Denmark
[3]Department of Ophthalmology, Aarhus University Hospital, Aarhus, Denmark
[4]The Research Unit for General Practice and Section of General Practice, Department of Public Health, University of Copenhagen, Copenhagen, Denmark

ABSTRACT.

Purpose: **To investigate the socio-economic status of families affected by childhood cataract and to assess how the socio-economic status is affected by cataract diagnosis.**

Materials and methods: **Children born between 2000 and 2017, seen between the age 0 and 10 years in the same period at Rigshospitalet or Aarhus University Hospital for cataract (N = 485), were included and compared to a matched children group without cataract (N = 4358). Socio-economic status was evaluated by the parents' income, employment, education, marital status and family structure.**

Results: **Parents of children with cataract were more likely to have a low yearly income (OR = 1.60, 95% CI (1.12–2.27)), be out of work (OR = 1.74, 95% CI (1.34–2.26)) and have basic education as the highest attained education (OR = 1.64, 95% CI (1.27–2.13)) prior to diagnosis. This social gradient was not affected by the diagnosis. In addition, a higher number of children with cataract lived in multi-family residencies (13.8% versus 8% in group of children without cataract) and they had a greater number of siblings (6.2% had ≥4 siblings versus 2.1% in group of children without cataract).**

Conclusion: **Families affected by childhood cataract have a lower socio-economic status and educational background even before cataract is diagnosed but the diagnosis does not aggravate the differences between these families and the background population. The lower socio-economic status and parental educational background should be taken into consideration in the management of these families.**

Key words: childhood cataract – congenital cataract – socio-economic status

Acta Ophthalmol.

doi: 10.1111/aos.14768

Introduction

Congenital and childhood cataracts affect not only the child but also the immediate family. Having a child with congenital cataract often puts serious strain on the family as they have to handle the burden of disease with many years of hospital follow-up, visual stimulation and patching for amblyopia (Yorston 2004; Al-Bakri et al. 2019). This may affect the family's socio-economic status as parents are forced to care for their child rather than to be at work. It is therefore relevant to examine the socio-economic conditions of families affected by childhood cataract. Socio-economically disadvantaged individuals often face a higher risk of disease and healthcare access inequalities (Bourdieu 1986; Pillas et al. 2014; Zablotsky et al., 2019).

Several studies examine the socio-economic status of families to children with visual impairment/blindness and systemic diseases (Dandona & Dandona 2001; Cumberland et al. 2010; Pillas et al. 2014; Bountziouka et al. 2017; Solebo et al.2017). But to the best of the authors' knowledge, no study has been conducted to examine childhood cataract/congenital cataract and socio-economic status.

The first aim of this study was to evaluate the social gradient in congenital and childhood cataract by examining the socio-economic status of the families prior to cataract diagnosis. The second aim was to evaluate whether the socio-economic status of the families was affected by the diagnosis.

Materials and Methods

A registry study was conducted by reviewing the socio-economic status of the families to children with congenital or childhood cataract diagnosed between the age of 0–10 years and born between 1 January 2000 and 31 December 2017. We included children seen at

Rigshospitalet and Aarhus University Hospital. Management of childhood cataract is a highly specialized function in Denmark with the two centres performing all surgeries. For each child affected by cataract, 10 control children from the background population without cataract were included and matched on age at the time of the child's diagnosis, sex, country of birth and municipality (Fig. 1).

Socio-economic information on parents was obtained from the Danish National Administrative Databases (Statistics Denmark). These databases include among many other data records on income, health care, birth, work, education, civil status, place of residence for each resident of Denmark. In Denmark, each resident has a unique identification number (Central Person Registry, CPR number). The CPR makes it possible to track all residents of Denmark and to link children and parents.

The study was approved by the Danish Data Protection Agency (RH-2016-336; I-Suite # 05070), and the Danish Patient Safety Authority (3-3013-1935/1/NAAN). According to the Committee on Health Research Ethics in the Capital Region of Denmark, ethical board review was not required as the study was a registry study and did not include patient examinations. The study followed the tenets of the Helsinki Declaration.

Geographic area of birth

For each child, country of birth was registered. Children not born in Denmark were grouped according to geographical birth area: Europe, Middle East, Africa and Far East.

Parental income

Household financial resources were inventoried as the disposable personal income (DPI) per adult over the full calendar year. The DPI is the amount of money that households have available for spending and saving after taxes have been accounted for. The mean DPI in Denmark in 2018 was 227194 DKK/year (Denmark 2020). For cohabiting parents, we used the average DPI in the household; for separated parents and parents living apart, we used the highest DPI. We analysed the income by two dichotomizations: ≤99 999 DKK/year versus ≥100 000 DKK/year and ≤499 999 DKK/year versus ≥500 000 DKK/year.

Parental employment status

The employment status of a family was inventoried as the employment status of the parents at the beginning of the calendar year. The family was classified as unemployed if both parents were unemployed. Parents were defined as unemployed if they were registered as unemployed for up to six months, received unemployment benefits, had retired early or if they were students.

Parental highest attained education

The educational background of families was defined as the highest attained education between the parents. Education was grouped into primary education (up to 9th grade), high school, vocational (technical) education, short-term higher education programmes (e.g. diploma programmes), medium-term higher education programmes (e.g. professional bachelor programmes such as nursing and teaching), and bachelor and long-term higher education programmes (e.g. bachelor programmes at universities, graduate programmes and PhD programmes). We analysed the education by two dichotomizations, *basic education*, where parents had completed the compulsory 9 years of schooling versus education higher than basic education, and *advanced education,* where parents had completed a university degree education (bachelor and long-term higher education) versus education lower than advanced education.

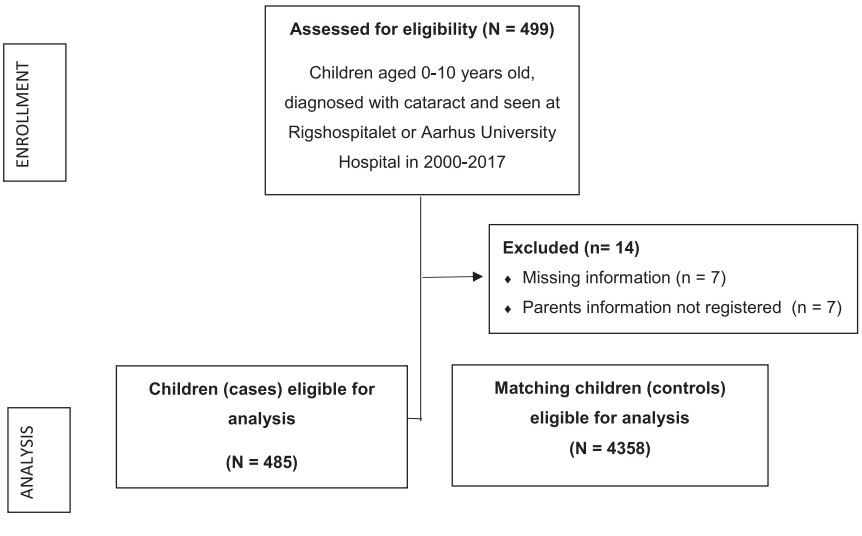


Fig. 1. Flow chart showing inclusion and exclusion of the study population.

Number of siblings

The number of children living in the household (with minimum one adult registered) was defined as the number of persons ≤24 years of age without children of their own.

Family structure

Civil status was grouped into single, married, cohabiting and multi-family residential based on the mother's household type. A household includes all persons living at the same address. Multi-family residential was used to describe when more than one family lived at the same address, for example grandparents with children and grandchildren. The civil status was further divided into two groups: single and not single (married, cohabiting couple & multi-family residential).

Statistical methods

Unadjusted comparisons of the demographic and socio-economic characteristics of the children and their families at baseline between children with and without cataract were performed by Pearson's chi-squared tests. The socio-economic variables were each assessed before diagnosis time, one and three years after the diagnosis was made. The differences in socio-economic variables were investigated in multi-variable logistic regression models using generalized estimating equation (GEE)

methods to adjust for the clustering inherent to the matching of children with cataract and children without cataract, and to the repeated assessments of each included child. The model was parameterized so that the assessments at the one- and three-year time-points were adjusted for differences already present in the year preceding the diagnosis. The assessments at the follow-up time-points one and three years after the diagnosis was made report on the developments in the socio-economic variable attributable to congenital cataract diagnosis. Results are reported both unadjusted and adjusted for: age, sex, municipality, season, calendar year and ethnicity. Statistical analyses were made using the R software package, V.3.4.1 (The R Foundation for Statistical Computing, http://www.r-project.org). The significance level was set at <0.05.

Results

We included 485 children with cataract (243 boys and 242 girls) and 4358 children without cataract (2177 boys and 2181 girls) matched by age at the time of cataract diagnosis, sex, municipality and geographical origin of birth. Baseline demographics of the study population is shown in Table 1. We did not find a significant difference in any of the parameters in Table 2 when comparing boys and girls, why the children were pooled in one group.

Geographic area of birth

Significantly more children with cataract were born outside Denmark compared to children without cataract (p-value = 0.01) with Middle East as the most frequent birth place (6.8% in group of children with cataract versus 4.3% in group of children without cataract) followed by Far East (2.1% in group of children with cataract versus 1.7% in group of children without cataract), Europe (1.9% in group of children with cataract versus 0.9% in group of children without cataract) and Africa (1.0% in group of children with cataract versus 0.6% in group of children without cataract) – see Table 1.

It was not possible to analyse for socio-economic differences between children from each birth place due to the small numbers in the different groups (Table 1). However, when pooling children with cataract in two groups (children born in European countries including Denmark and children born in Middle East, Africa and Far East), we found that the parents of the group of children from Middle East, Africa and Far East had lower education, lower income and were more often unemployed compared to the European group ($p < 0.05$). There was no significant difference in civil status.

Parental income

The prevalence of low parental income (≤99 999 DKK/year) was higher among children with cataract compared to children without cataract before the diagnosis was made (OR = 1.60, 95% CI (1.12–2.27), p-value = 0.03), see Table 2. The diagnosis of cataract was not seen to lower income further, see Table 2.

Parental employment status

We found a higher tendency towards more parents of children with cataract being outside the workforce prior to the cataract diagnosis (OR = 1.74, 95% CI (1.34–2.26), p-value < 0.0001). This remained unchanged one and three years after diagnosis, see Table 2.

Parental highest attained education

A significantly larger proportion of parents of children with cataract had ≤9 years of schooling (basic education) as the highest attained education prior to the cataract diagnosis was made (OR = 1.64, 95% CI (1.27–2.13), p-value = 0.003), see Table 2.

Number of siblings

More children with cataract came from families with a higher number of children (6.2% had ≥4 siblings versus 2.1% in group of children without cataract, p-value = 0.0005).

Family structure

More children with cataract lived in multi-family residencies compared to the group of children without cataract (13.8% versus 8%, p-value = 0.001). There was no difference in civil status of parents (p-value = 0.19), see Table 1.

Discussion

In this registry study, we compared the socio-economic status in families of children with cataract to a background population without childhood cataract matched by age at the time of cataract diagnosis. We found that families of children with cataract had lower income, lower parental educational levels, were more likely to be outside the workforce and to live in multi-family residencies with a higher number of children per family. In addition, more children with cataract were born outside Denmark. This points to striking socio-economic differences between families affected by childhood cataract and the background population. We found that the differences between families were present already before the cataract diagnosis was made and that the diagnosis did not aggravate the differences.

Growing up in social disadvantage may lead to overall health and developmental disadvantage for the rest of life (Kuh et al. 2003). A systematic review based on 201 studies provided strong evidence between multiple adverse social factors and poorer health/developmental outcomes through early childhood (Pillas et al. 2014). In our study, we found that parents of children with cataract had a 60% higher risk of having a low income compared to children without cataract. It is not uncommon for diseases to strike mainly in lower socio-economic groups; for example, children living in a household <200% of the federal poverty level are more likely to be diagnosed with developmental disability (Zablotsky et al., 2019). Eye diseases including hypermetropia and amblyopia are also more common in families from low socio-economic status (Williams et al. 2008; Cumberland et al. 2010).

Lower income is typically related to low rate of participation in the workforce and to lower educational level. We found that parents of children with cataract had a 74% higher risk of being unemployed prior to diagnosis compared to children without cataract. Unemployed parents are typically associated with poorer health and developmental disabilities in children which could be due to the parents' limited resources (Delpisheh et al. 2006). In some countries, low income or being

Table 1. Baseline characteristics of children with cataract and children without cataract

	Children with childhood cataract (N = 485)	Children without childhood cataract (N = 4358)	Missing	p-value*
Age at diagnosis†, *n* (%)				
0 years	229 (47.2)	2077 (47.7)	0	0.98
1–2 years	66 (13.6)	553 (12.7)		
3–4 years	68 (14.0)	632 (14.5)		
5–7 years	62 (12.8)	562 (12.9)		
>7 years	60 (12.4)	534 (12.3)		
Age (years), median (IQR)	1.22 (0.19–5.01)	1.18 (0.19–5.03)	0	0.99
Sex, *n* (%)				
Boy	243 (50.1)	2177 (50.0)	0	0.99
Girl	242 (49.9)	2181 (50.0)		
Geographical origin, *n* (%)				
Denmark	428 (88.2)	4030 (92.5)	0	0.01
Europe	9 (1.9)	38 (0.9)		
Middle East	33 (6.8)	189 (4.3)		
Africa	5 (1.0)	27 (0.6)		
Far East	10 (2.1)	74 (1.7)		
Number of siblings, *n* (%)				
No siblings	56 (11.5)	457 (10.5)	0	0.0005
1–2 siblings	314 (64.7)	3258 (74.8)		
3–4 siblings	85 (17.5)	553 (12.7)		
>4 siblings	30 (6.2)	90 (2.1)		
Number of siblings, median (IQR)	1 (0–5)	1 (0–4)	0	0.002
Parental Civil status, *n* (%)				
Single	52 (11.0)	519 (12.0)	42	0.001
Married	222 (47.1)	2182 (50.4)		
Cohabiting couple	132 (28.0)	1282 (29.6)		
Multi-family residential‡	65 (13.8)	347 (8.0)		
Parental average income§, *n* (%)				
<100 000 DKK	36 (7.6)	187 (4.3)	28	0.02
100 000–200 000 DKK	170 (35.7)	1520 (35.0)		
200 000–300 000 DKK	185 (38.9)	1830 (42.2)		
300 000–500 000 DKK	77 (16.2)	707 (16.3)		
>500 000 DKK	8 (1.7)	95 (2.2)		
Income (DKK), median (IQR)	211.275 (149.625–267.324)	221.345 (168.231–277.433)	28	0.02
Parental work status, *n* (%)				
Outside workforce	58 (12.0)	253 (5.8)	3	0.00002
One parent at work	100 (20.7)	880 (20.2)		
Both parents at work	325 (67.3)	3224 (74.0)		
Highest attained parental education, *n* (%)				
Primary education (up to 9th grade)	71 (15.1)	390 (9.0)	41	0.002
High school	18 (3.8)	175 (4.0)		
Vocational education	133 (28.3)	1313 (30.3)		
Short-term higher education	38 (8.1)	364 (8.4)		
Medium-term higher education	94 (20.0)	959 (22.1)		
Bachelor	102 (21.7)	1041 (24.0)		
Long-term higher education	14 (3.0)	90 (2.1)		

* p-Value: Pearson's chi-squared test for categorical variables, t-test for continuous variables.
† Age at diagnosis: Controls are matched by the age at diagnosis for patients.
‡ Multi-family residential: When one or more families are living with the examined family.
§ 1 Danish Krone corresponds to 0.13 Euro.

outside the workforce may reduce the access to health care services. In Denmark, healthcare expenditures are financed via the tax system and receiving health care is free of charge to individual patients. The level of healthcare provision is the same for all irrespective of income, insurance status or socio-economic status. This is in contrast with the United States where healthcare access inequalities was described in families with lower income (Zablotsky et al., 2019).

In our study, it was also remarkable to find that fewer parents of children with cataract had completed schooling beyond basic education. This was in agreement with findings from an American study where parents with less than high school education were more likely to have children with blindness (Zablotsky et al., 2019). In India, lower socio-economic status and lower education levels were important barriers to affect the care-seeking behaviour among parents to children with paediatric cataract (Wang et al. 2019). In a 5-year follow-up period, children with cataract from low socio-economic groups had poorer follow-up compared with the high socio-economic group due to lack of awareness (Chougule et al. 2018). Lower educational background may result in a poor

Table 2. Selected socio-economic indicators of the families to children with cataract and children without cataract at the time before the diagnosis and adjusted for baseline differences one year and three years after the diagnosis

	Children with childhood cataract (N = 485)				Children without childhood cataract (N = 4358)				Crude OR (95% CI)*	p-value	Adjusted OR (95% CI)†	p-value
	n	%	*n*	%	*N*	%	*n*	%				
Low Income	≤99 999 kr.		≥100 000 kr.		≤99 999 kr.		≥100 000 kr.					
Prediagnosis	36	7.6	440	92.4	187	4.3	4152	95.7	1.60 (1.12–2.27)	**0.01**	1.52 (1.05–2.20)	**0.03**
1 year after diagnosis	32	6.7	447	93.3	155	3.6	4202	96.4	1.06 (0.71–1.58)	0.79	1.05 (0.69–1.61)	0.80
3 years after diagnosis	21	5.2	380	94.8	92	2.5	3565	97.5	1.18 (0.71–1.96)	0.52	1.15 (0.68–1.92)	0.60
High Income	≤499 999 kr.		≥500 000 kr.		≤499 999 kr.		≥500 000 kr.					
Prediagnosis	468	98.3	8	1.7	4244	97.8	95	2.2	1.27 (0.61–2.65)	0.53	1.22 (0.58–2.56)	0.60
1 year after diagnosis	471	98.3	8	1.7	4262	97.8	95	2.2	1.00 (0.44–2.24)	0.99	1.00 (0.44–2.25)	1.00
3 years after diagnosis	388	96.8	13	3.2	3553	97.2	104	2.8	0.68 (0.30–1.56)	0.36	0.67 (0.28–1.56)	0.35
Civil status	Single		Cohabiting parents		Single		Cohabiting parents					
Prediagnosis	52	11.0	419	89.0	519	12.0	3811	88.0	0.90 (0.67–1.20)	0.47	0.82 (0.60–1.11)	0.19
1 year after diagnosis	49	11.2	388	88.8	477	11.9	3517	88.1	1.03 (0.81–1.30)	0.84	1.03 (0.81–1.32)	0.80
3 years after diagnosis	56	15.7	300	84.3	479	14.6	2801	85.4	1.20 (0.89–1.63)	0.24	1.23 (0.89–1.69)	0.21
Workforce	Outside		At work		Outside		At work					
Prediagnosis	58	12.0	425	88.0	253	5.8	4104	94.2	1.74 (1.34–2.26)	**< 0.0001**	1.81 (1.32–2.50)	**0.0003**
1 year after diagnosis	45	10.1	401	89.9	221	5.5	3786	94.5	0.87 (0.68–1.12)	0.29	0.85 (0.62–1.16)	0.30
3 years after diagnosis	38	10.4	327	89.6	172	5.2	3122	94.8	0.94 (0.69–1.28)	0.69	0.94 (0.64–1.37)	0.74
Highest attained education	Basic education		Higher		Basic education		Higher					
Prediagnosis	71	15.1	399	84.9	390	9.0	3942	91	1.64 (1.27–2.13)	**0.0002**	1.55 (1.16–2.08)	**0.003**
1 year after diagnosis	65	14.9	370	85.1	335	8.4	3663	91.6	1.06 (0.96–1.18)	0.27	1.07 (0.95–1.20)	0.27
3 years after diagnosis	47	13.1	311	86.9	250	7.6	3037	92.4	1.00 (0.82–1.23)	1.00	1.00 (0.80–1.26)	0.99
Highest attained education	Lower		Advanced education		Lower		Advanced education					
Prediagnosis	354	75.3	116	24.7	3201	73.9	1131	26.1	1.05 (0.86–1.30)	0.63	1.01 (0.82–1.26)	0.87
1 year after diagnosis	330	75.9	105	24.1	2944	73.6	1054	26.4	1.04 (0.98–1.11)	0.22	1.05 (0.98–1.12)	0.20
3 years after diagnosis	267	74.6	91	25.4	2407	73.2	880	26.8	1.00 (0.89–1.12)	0.93	1.00 (0.88–1.12)	0.93

* The OR at the first and third year after diagnosis refers to unchanged difference in the socio-economic status presented at the time before the diagnosis between children with cataract and children without cataract.
† Adjusted for age at diagnosis, sex, birth origin, diagnosis year, diagnosis season and number of siblings; categorized as indicated in Table 1.
Bold values denote statistical significance.

understanding of the risks associated with congenital or childhood cataract and it may impact how parents recognize symptoms of cataract or it's complications, for example glaucoma or visual axis opacification, and how parents cope and comply with the treatment and follow-up, for example compliance in amblyopia treatment (Tjiam et al. 2011).

Children with cataract came from families with a significantly higher number of siblings. We did not find a difference in parental marital status, but more cataract children lived in multi-family residences. Some of differences in family structure observed in this study could possibly be explained by a larger proportion of children with cataract being born outside Denmark as immigrants may have other family structures (Landale et al. 2011). Others have found that the risk of visual impairment is higher among ethnic minority group (Cumberland et al. 2010).

Strengths and limitations

Our study was a registry study based on information collected consecutively and regularly by Statistics Denmark that has access to a large amount of data on the Danish population. Our study provided representative and nearly complete data for the target population with limited risk for selection, attrition and no-response bias. The study has a large sample size and because the data were updated and collected yearly, we were able to distinguish between the social gradient present before cataract was diagnosed and the separate effect of cataract after diagnosis. To ensure that socio-economic differences were not caused by low maternal income due to maternity leave, the cataract children were matched to children without cataract according to the age at time of diagnosis.

Conversely, this study also has some limitations. We intended a study design where children with cataract were matched to children from the background population matched by age, municipality and birth origin. However, it proved impossible to match by birth origin as children with cataract were born outside Denmark much more often than it was possible to find children without cataract born outside Denmark and living in the same municipality. Thus, we adjusted for that in our analysis. We evaluated the socio-economic status up to three years after cataract diagnosis. A longer perspective would have been welcome, but it was not possible because 25% of cataract cases were diagnosed so recently that they would be recorded as missing data at a five-year follow-up time-point.

Conclusion

We found that Danish families affected by childhood cataract were more likely to be part of a low-income population with the parents being outside the

workforce and with a low parental educational level but with a larger number of siblings. This socio-economic difference was present before cataract was diagnosed and it persisted after the diagnosis. Deprived families with lower educational level may require individualized support in clinical settings, for example longer consultation time to process the information provided, shorter follow-up visit intervals in order to have tighter control on treatment, for example amblyopia therapy, and in general offer holistic consultations, ensuring the best possible course for the children and their families. The society may pay attention to those challenges in public health in order to minimize the socio-economic costs and inequality.

References

Al-Bakri M, Sander B, Bach-Holm D, Larsen DA, Jensen H & Kessel L (2019): Children with congenital and childhood cataract require frequent follow-up visits and examinations in general anaesthesia: considerations for the strain on families. Acta Ophthalmol **97**: 778–783.

Bountziouka V, Cumberland PM & Rahi JS (2017): Trends in visual health inequalities in childhood through associations of visual function with sex and social position across 3 UK birth cohorts. JAMA Ophthalmol **135**: 954.

Bourdieu P (1986): The forms of capital. In: Richardson JG (ed.) Handbook of theory and research for the sociology of education. New York, NY: Greenwood Press. 241–258.

Chougule P, Murat S, Mohamed A & Kekunnaya R (2018): Follow-up patterns and associated risk factors after paediatric cataract surgery: observation over a 5-year period. Br J Ophthalmol **102**: 1550–1555.

Cumberland PM, Pathai S & Rahi JS (2010): Prevalence of eye disease in early childhood and associated factors: findings from the millennium cohort study. Ophthalmology **117**: 2183–2184.

Dandona R & Dandona L (2001): Socioeconomic status and blindness. Br J Ophthalmol **85**: 1484–1488.

Delpisheh A, Kelly Y, Rizwan S & Brabin BJ (2006): Socio-economic status, smoking during pregnancy and birth outcomes: an analysis of cross-sectional community studies in Liverpool (1993–2001). J Child Health Care **10**: 140–148.

Denmark S. (2020): Income in Denmark. Available at: https://www.dst.dk/en/Statistik/emner/arbejde-indkomst-og-formue/indkomster. (Accessed on 1 Dec 2020).

Kuh D, Ben-Shlomo Y, Lynch J, Hallqvist J & Power C (2003): Life course epidemiology. J Epidemiol Community Health **57**: 778–783.

Landale NS, Thomas KJA & Van Hook J (2011): The living arrangements of children of immigrants. Futur Child **21**: 43–70.

Pillas D, Marmot M, Naicker K, Goldblatt P, Morrison J & Pikhart H (2014): Social inequalities in early childhood health and development: a European-wide systematic review. Pediatr Res **76**: 418–424.

Solebo AL, Teoh L & Rahi J (2017): Epidemiology of blindness in children. Arch Dis Child **102**: 853–857.

Tjiam AM, Akcan H, Ziylan F, Vukovic E, Loudon SE, Looman CWN, Passchier J & Simonsz HJ (2011): Sociocultural and psychological determinants in migrants for noncompliance with occlusion therapy for amblyopia. Graefes Arch Clin Exp Ophthalmol **249**: 1893–1899.

Wang J, Jin L, Lu Q et al. (2019): Barriers, costs, and attitudes toward pediatric cataract surgery at two large facilities in China and India. Ophthalmic Epidemiol **26**: 47–54.

Williams C, Northstone K, Howard M, Harvey I, Harrad RA & Sparrow JM (2008): Prevalence and risk factors for common vision problems in children: data from the ALSPAC study. Br J Ophthalmol **92**: 959–964.

Yorston D (2004): Surgery for congenital cataract. Community eye Heal **17**: 23–25.

Zablotsky B, Black LI, Maenner MJ et al. (2019): Prevalence and trends of developmental disabilities among children in the United States: 2009–2017. Pediatrics **144**: 2009–2017.

Received on July 19th, 2020.
Accepted on December 27th, 2020.

Correspondence:
Moug Al-Bakri, MD
Department of Ophthalmology
Rigshospitalet-Glostrup
Valdemar Hansens Vej 3
2600 Glostrup
Denmark
Tel: +45 21 36 36 71
Fax: +45 38 63 46 69
Email: mougalbakri@yahoo.com

The study received financial support from Øjenforeningen (Fight for Sight Denmark) and Carl and Nicoline Larsen's Fund, Synoptik Foundation and Øjenfonden. The funding bodies had no influence on conception, design or reporting of the study.

PAPER III

Increased incidence of mental disorders in children with cataract – findings from a population-based study

Authors: *Moug Al-Bakri[1] MD, Anne Mette Skovgaard MD, DM Sci [2], Daniella Bach-Holm[1,3] MD, PhD, Dorte Ancher Larsen[4]MD, Volkert Siersma[5] PhD, Line Kessel[1,3] MD, PhD*

Institutions:

1) Department of Ophthalmology, Rigshospitalet, Copenhagen, Denmark.
2) National Institute of Public Health, University of Southern Denmark, Copenhagen, Denmark.
3) Department of Clinical Medicine, University of Copenhagen, Copenhagen, Denmark
4) Department of Ophthalmology, Aarhus University Hospital, Aarhus, Denmark.
5) The Research Unit for General Practice and Section of General Practice, Department of Public Health, University of Copenhagen, Copenhagen, Denmark

Corresponding author: Moug Al-Bakri. Rigshospitalet-Glostrup. Valdemar Hansens Vej 3. 2600 Glostrup. Denmark. E-mail: moug.al-bakri@regionh.dk. Phone: +45 21 36 36 71.

Key words: Congenital cataract, childhood cataract, mental disorders, neurodevelopmental disorders, autism spectrum disorders, ADHD, anxiety, developmental delay.

KEY POINTS

Question: Is there a higher incidence of mental disorders among children with cataract?

Findings: This cohort study based on 485 children with cataract and 4358 without cataract found a two-fold increase in incidence of mental disorders

Meaning: Our findings highlight the need for clinical attention to mental health and neurodevelopment in children with cataract as an integrated part of the management along with refractive and visual rehabilitation.

ABSTRACT

Importance: Childhood cataract is a chronic disease with marked impact on the child and family. Little is known about the risk of mental disorders in this group of children which lead to this study.

Objective: To examine the incidence of mental disorders in children with cataract compared to sex- and age-matched children without cataract, taking somatic disease in the child, parental socio-economic status and psychiatric morbidity into account.

Design: Nationwide cohort study evaluating mental health based on entries in comprehensive national databases.

Setting: The two university hospitals in Denmark managing children ≤6 years of age with cataract in (Rigshospitalet, Copenhagen and Aarhus University Hospital, Aarhus).

Participants: Children born from January 1, 2000 to December 31, 2017 and diagnosed with cataract before 10 years of age (N=485) were included and compared to a sex- and age-matched background population (N=4358). Children with missing data were excluded (N=14).

Main Outcomes and Measures: We evaluated the risk of mental disorders in cataract group compared to controls using logistic regressions models.

Results: The incidence of any mental disorder (21.8%) was higher in children with cataract and somatic comorbidities compared to children with isolated cataract (8.4%). The incidence of mental disorders was nearly doubled in children with cataract compared to controls (OR = 1.83 95% CI (1.28 – 3.63)). The risk of anxiety disorders was quadrupled (OR = 4.10, 95% CI (1.90 - 8.84)) and the risk of developmental delay was doubled (OR = 2.66, 95% CI (1.45 - 4.90)). The risk was significantly higher in children diagnosed with cataract in the first 3 years of life compared to

controls (OR = 2.36, 95% CI (1.53 - 3.64)), whereas difference was found for those diagnosed later in childhood.

Conclusions and Relevance: The risk of mental disorders, in particular anxiety and neurodevelopmental delay, is markedly increased in children with cataract and even more so in those diagnosed within the first three years of life. Psychiatric screening instruments may be integrated in the management of these children.

INTRODUCTION

Clinical and research evidence point to an increased risk of mental health problems and disorders in children and adolescents suffering from chronic diseases [1–4]. Thus, attention deficit/hyperactivity disorders (ADHD) and autism spectrum disorders (ASD) are more frequent among children with cerebral palsy [5], and anxiety and depression have been found in one of four children with epilepsy [6]. In children with diabetes type I, an increased risk of anxiety, mood disorders and eating disorders have been shown in the years following disease onset [7].

Childhood cataract is a significant cause of visual disability in infancy and early childhood, affecting approximately 200,000 children worldwide [8]. It is a chronic condition requiring intensive management [9]. Visually disturbing cataracts can be removed by surgery [10] but prolonged and intensive visual and optical rehabilitation is required [11,12]. Childhood cataract can occur isolated or can be seen in combination with somatic comorbidities [13] that may be associated with neurodevelopmental disorders [14–20]. Most cases of childhood cataract occur in early childhood [21], which is also the period of onset of several childhood mental disorders, in particular neurodevelopmental disorders [22]. Children with cataract are more likely to come from a socio-economically disadvantaged background [23] which may further increase the risk of pediatric child mental disorders [24,25] .

Two questionnaire studies based parental reporting found a higher risk of conduct problems, learning problems, psychosomatic, impulsiveness/hyperactivity and anxiety problems in children with cataract compared to children with normal vision [26] and a lower level of psychosocial health in children with cataract which was similar to the psychosocial health level of children with other severe somatic diseases like rheumatological disease and cancers [27].

The aim of the present study was to examine the risk of mental disorders in children with childhood cataract compared to children without cataract, using Danish population registries and taking into account potential confounders such as parental socio-economic status, family psychiatric load and the children's somatic comorbidity.

MATERIALS AND METHODS

Study population

We included patients born from January 1, 2000 to December 31, 2017, who were diagnosed with cataract before age 10 years at one of the two hospitals that manage all children with cataract in Denmark: Rigshospitalet, Copenhagen and Aarhus University Hospital, Aarhus. In Denmark, each person has a unique identification number (CPR number). The CPR number is used in national administrative registries which makes it possible to link data from individuals accurately between registries. In addition, children are linked to their parents by the CPR number.

Control population

For each child with cataract, a sample of 10 children without cataract matched by age, sex and municipality were sampled from the general Danish population by Statistics Denmark [28].

Data from national population registries

We used data from the following national registries: *National Patient Registry*, NPR, which contains information about diagnostic and procedural ICD-10 codes on all contacts to public hospitals, as in- or out-patient and including emergency settings. The *Population Registry* was used to access information about child sex, geographical birth origin and parental socio-economic status.

Information regarding parental work status was extracted from *AKM registry (work classification module)*. Parental civil status was obtained from *BEF registry* (population registry) and information on parental income was obtained from the *income registry.* In addition, we extracted information on parental mental disorders from NPR. See **Supplementary Table 1** for details. Any variables with <5 observations cannot be tabulated according to the policy of Statistics Denmark.

Mental disorders

Presence and type of mental disorders diagnosed during the first 10 years of life were assessed using the ICD-10 diagnostic codes (F00-F99 and R41.8, R62.0, R62.9) listed in the NPR. The latter codes for unspecific developmental delays are commonly used among Danish pediatricians and child psychiatrists to categorize unspecific developmental delay in younger children who often have more subtle and unspecific symptoms of developmental delays compared to older children [29]. In accordance with the latest version of the international classification schemes [30,31] and recent research in the field [7,32], we grouped the mental disorders in neurodevelopmental and other mental disorders:

Neurodevelopmental disorders: intellectual disability (F70–F79), specific developmental disorders (F80–F83), autism spectrum disorders (ASD) (F84), unspecified developmental disorders (F88–F89), hyperkinetic disorder (F90), and unspecific developmental delay (R41.8, R62.0, R62.9).

Other mental disorders: psychoactive substance misuse (F10–F19), psychotic disorders (F20–F29), mood disorders (F30–F39), anxiety, dissociative, stress-related and somatoform disorders (F40–F48), eating disorders (F50), sleep disorders and medication abuse (F51-59), personality disorders (F60–F69), and other mental or behavioral disorders (F91–F99).

The term *"any mental disorders"* included all above-mentioned diagnostic codes.

Notably, a child could be diagnosed with two or more different mental disorders. But each child could be counted only once in the analysis of overall incidence of any mental disorder. When exploring the risk of specific psychiatric disorders, each child could figure in more than one subgroup if they had more than one diagnosis, but only once in each category.

Somatic comorbidities

Since childhood cataract is often found in association with systemic disease or as part of a syndrome, we sub-grouped the cataract population into 1) children with isolated cataract and 2) children with cataract and severe somatic comorbidities, see **Supplementary Table 2** for details.

Confounders

Some somatic comorbidities were potential confounders (disease confounders) as either the disease itself or its treatment may increase the risk of cataract as well as mental disorders. This group included: interstitial lung disease (J84.9 + J84.8 + J84.1) due to treatment with high doses of prednisolone [33,34], congenital rubella syndrome (P35.0 + B06.0 + B06.8 + B06.9) [15–17], congenital cytomegalovirus infection (B25.0 + B25.1 + B25.2 + B25.8 + B25.9 + P35.1) [15,18], degenerative disease of the nervous system (G31 + G31.1 + G31.9) [35,36] and cancer in brain or meninges due to radiation therapy (C70-72.9 + C76.0 + C69) [37–39], microcephaly (Q02.9), megalencephaly (Q04.5), Smith-Lemli-Opitz' syndrome (Q87.1I), trisomy 21 (Q90.0-90.2), Down's syndrome (Q90 + Q90.9) and autosomal trisomies (Q92-92.9).

153 Children with cataract have previously been shown to be more likely to come from socio-
154 economically disadvantaged families [23] and many pediatric mental disorders are more prevalent in
155 families of lower socio-economic status [24,25]. Hence, in addition to disease confounders, the
156 statistical analyses were also adjusted for the geographical birth location of the child, parental
157 socio-economic status (income, employment and civil status). Definition of these variables were
158 described previously in detail [23] and are available in **Supplementary Table 3**.
159
160 As parental mental disorders may predispose to child mental disorder [40] we adjusted for any mental
161 disorders diagnosed at hospital (F00-F99) in one or both parents.
162
163 ***Statistical method***
164 The association between childhood cataract and mental disorders was assessed using odds ratio
165 (OR) with 95% confidence interval (95% CI) in unadjusted analyses and in conditional logistic
166 regression models including age at onset of cataract, sex and the abovementioned confounders.
167 Adjusted and unadjusted analyses were repeated separately in each of the two cataract onset age
168 groups; 0-3 years and 4-10 years, a test for interaction was added. Statistical analyses were made
169 using the R software package, V.3.4.1 (The R Foundation for Statistical Computing, http://www.r-
170 project.org). The significance level was set at < 0.05.
171
172 ***Approvals***
173 The study was approved by the Danish Data Protection Agency (RH-2016-336; I-Suite # 05070),
174 and the Danish Patient Safety Authority (3-3013-1935/1/NAAN). According to the Committee on
175 Health Research Ethics in the Capital Region of Denmark, ethical board review was not required
176 (decision number: 16038234). The study followed the tenets of the Helsinki Declaration.

RESULTS

We included 485 children (243 boys and 242 girls) with childhood cataract and an age- and sex-matched control group (N = 4358, 2177 boys and 2181 girls) drawn from the background population. Baseline characteristics of the study population are listed in **Table 1**. No difference in the parental mental health was found between the two groups. Severe somatic comorbidities in the cataract group are listed in **Supplementary Table 2**.

The incidence of any mental disorders (21.8%), neurodevelopmental disorders (15.4%) and other mental disorders (9.0%) was significantly higher in children with cataract who have somatic comorbidities compared to children with isolated cataract (any mental disorders: 8.4%, neurodevelopmental disorders: 5.8% and other mental disorders: 2.3%), see **Table 2**.

Children with cataract were twice as likely to have a mental disorder as children without cataract, 10.5% (n = 51/485) and 5.2% (n = 225/4358), respectively, with OR = 1.83, 95% CI (1.28 – 2.63), p-value = 0.0009 in analyses adjusted for geographical birth origin, somatic disease confounders, socio-economic status and parental mental disorders. A particular high incidence of mental disorders was seen in children diagnosed with cataract during their first 3 years of life (10.7%, n = 35/327), compared to age-matched children without cataract (4.1%, n = 118/2912), OR = 2.36, 95% CI (1.53 - 3.64), p-value = 0.0001, whereas we did not find a significantly increased risk in children diagnosed with cataract after three years of age compared to an age-matched cohort, see **Table 3**.

The risk of neurodevelopmental disorders was doubled in the cataract group, OR = 2.05, 95% CI (1.35 – 3.11), p-value = 0.0007 after adjustment for confounders, see **Table 4**. The most frequent

neurodevelopmental disorder was developmental delay (4.5%, n = 22/485) followed by autism spectrum disorders (ASD, 2.3%, n = 11/485) and attention deficit/hyperactivity disorders (ADHD, 1.2%, n = 6/485). The risk of developmental delay was higher in the cataract group than in the control group, OR = 2.66, 95% CI (1.45 - 4.90), p-value = 0.0017, whereas we did not find a significantly increased risk of ASD (OR = 1.62 95%CI (0.78 – 3.39), p-value = 0.192) or ADHD (OR = 1.31, 95% CI (0.50 – 3.46), p-value = 0.581) in the children with cataract compared to children without cataract.

Children with cataract also had an overall higher risk of having a mental disorder of not primary neuro-developmental origin; in crude analyses (OR = 1.73, 95% CI (1.04 - 2.89), p-value = 0.036), and in analyses adjusting for several confounders (OR = 1.69, 95% CI (1.0 - 2.87), p-value = 0.052). The risk of anxiety disorders was quadrupled in children with cataract (2.1%, n = 10/485), OR = 4.10, 95% CI (1.90 - 8.84), p-value= 0.0003. In addition, an increased risk of eating disorders was observed, OR = 4.19, 95% CI (0.72 - 24.44), p-value = 0.111.

DICUSSION

This is the first study to explore a broad range of mental disorders in children with cataract comparing the incidence in these children with the age- and sex-matched background population based on diagnoses made by medical doctors. We used nationwide population registries to account for the potential influences of a range of confounders including somatic comorbidities, the socio-economic status of the family, and parental mental disorders. The risk of anxiety disorders was increased more than fourfold, and the risk of neurodevelopmental delay was increased twofold in children with cataract. The risk was highest among children diagnosed with cataract before 3 years

of age. In addition, the risk of any mental disorders was highest in the group of children who had cataract in combination with systemic disease.

Whereas the increased risk of neurodevelopmental disorders in children with cataract was expected, the fourfold risk of anxiety disorders was a remarkable finding but in line with finding from studies of other chronic diseases in childhood, e.g. epilepsy [6] and diabetes type I [7]. Children with cataract are exposed to repeated examinations under anesthesia, hospital appointments and restraining, e.g. with amblyopia patching [11,41] and they may suffer from visual impairment associated with cataract, which influence social interactions, e.g. response to facial expressions [8,42,43]. It is already well known that blind and visually impaired young people face an increased risk of depression and anxiety [44–46]. Importantly, our incidence of anxiety disorders may be underestimated as anxiety often presents during adolescence [22] and we only included children up to the age of 10 years.

For comparison, only a limited number of studies have been published in which mental health problems and disorders have been investigated in children with cataract. A Chinese study of 119 3-8-years-old children with cataract used the Conners Parent Rating Scale and found a doubling in the incidence of conduct problems, learning problems, psychosomatic, impulsiveness/hyperactivity, and anxiety problems compared to 143 children without cataract [26]. This study is in consistent with our findings based on diagnoses made by medical doctors using the ICD-10 criteria. In a previously study of Danish children with cataract, we found that the subjective visual function related to academic achievements was rated as poor [47] which is in line with the parental assessment of learning problems in the Chinese study. In contrast to the Chinese study, we did not find a statistically significant higher incidence of impulsiveness/hyperactivity related diagnoses. Our study was based on mental disorders diagnosed in a hospital setting where only the most seriously

affected children exceed the threshold for referral. A study of 41 British 5-19 years aged children with congenital cataracts found a lower psychosocial health level in these children compared to children with other systemic diseases [27] which supports our findings.

Severe somatic disease may be directly linked to both development of cataract and presence of mental disease [14–20]. We found a doubling of the risk of unspecific developmental delay disorder in children with cataract also in analyses adjusting for diseases with known neuro-developmental comorbidity and diseases in which the treatment involves potential adverse neuro-developmental exposures [33,34,37–39].

Our findings highlight the psychological burden on children living with chronic somatic disease. In some situations, the psychological load may influence treatment outcome, as shown in studies of children and adolescents with Type 1 Diabetes Mellitus [32,48,49]. Management of childhood cataract often include patching of the better seeing eye to improve vision in the poorer seeing eye (amblyopia treatment) [13]. Compliance is essential for visual outcome in amblyopia treatment. Treatment of amblyopia can be associated with a high degree of distress, increased stigma and logistical problems for children and parents [50–52]. We were not able to discern whether amblyopia therapy contributed to the increased risk of anxiety in our cataract population, but attention should be paid to the mental vulnerability of the child and treatment adjusted based on a holistic perspective.

Strengths and limitations

The major strength of this population-based registry study is its nationwide character with no attrition bias. Mental disorders were diagnosed by medical doctors in hospital settings in accordance

with ICD-10 diagnostic criteria. To ensure that the interaction of other confounders was minimized, we adjusted for relevant variables such as geographical birth origin, disease confounders, parental socio-economic status and parental mental disorders. Conversely, this study also has some limitations. There may be risk of selection bias since children seen and treated by child psychiatrists working in private practice are not always reported into NPR, which may result in an underestimated true incidence of mental disorders. On the contrary, referral bias must be considered, because children with cataract are treated in hospital settings and therefore have higher odds of being referred and diagnosed with a mental disorder. On the other hand, some families may also decline referral as they already have to deal with cataract, or they may interpret the child's behavior as related to the eye disease.

CONCLUSION & PERSPECTIVES

In this nationally representative sample, we found a markedly higher incidence of developmental disorders and anxiety among children with cataract compared to the background pediatric population. The associations between childhood cataract and mental disorders remained significant even after adjusting for relevant factors such as disease confounders and parental socio-economic status and psychiatric disease. Increased awareness of the mental health burden associated with childhood cataract is important. Routine screening of mental health, e.g. using the Strengths and Difficulties Questionnaire (SDQ) [53], could guide the support to these children taking into account their mental health as well as overall quality of life, in the visual and optical rehabilitation.

ACKNOWLEDGEMENTS

The study received financial support from Øjenforeningen (Fight for Sight Denmark) and Carl and Nicoline Larsen´s Fund, Synoptik Foundation and Øjenfonden. The funding bodies had no influence on conception, design or reporting of the study. None of the authors have any conflicts of interests to declare.

REFERENCE

1. Hysing M, Elgen I, Gillberg C, Lie SA, Lundervold AJ. Chronic physical illness and mental health in children. Results from a large-scale population study. *J Child Psychol Psychiatry*. 2007;48(8):785-792. doi:10.1111/j.1469-7610.2007.01755.x

2. Glazebrook C, Hollis C, Heussler H, Goodman R, Coates L. Detecting emotional and behavioural problems in paediatric clinics. *Child Care Health Dev*. 2003;29(2):141-149. doi:10.1046/j.1365-2214.2003.00324.x

3. Butler A, Van Lieshout RJ, Lipman EL, et al. Mental disorder in children with physical conditions: a pilot study. *BMJ Open*. 2018;8(1):e019011. doi:10.1136/bmjopen-2017-019011

4. Sztein DM, Lane WG. Examination of the Comorbidity of Mental Illness and Somatic Conditions in Hospitalized Children in the United States Using the Kids' Inpatient Database, 2009. *Hosp Pediatr*. 2016;6(3):126-134. doi:10.1542/hpeds.2015-0117

5. Craig F, Savino R, Trabacca A. A systematic review of comorbidity between cerebral palsy, autism spectrum disorders and Attention Deficit Hyperactivity Disorder. *Eur J Paediatr Neurol EJPN Off J Eur Paediatr Neurol Soc*. 2019;23(1):31-42. doi:10.1016/j.ejpn.2018.10.005

6. LaGrant B, Marquis BO, Berg AT, Grinspan ZM. Depression and anxiety in children with epilepsy and other chronic health conditions: National estimates of prevalence and risk factors. *Epilepsy Behav*. 2020;103(Pt A):106828. doi:10.1016/j.yebeh.2019.106828

7. Dybdal D, Tolstrup JS, Sildorf SM, et al. Increasing risk of psychiatric morbidity after childhood onset type 1 diabetes: a population-based cohort study. *Diabetologia*. 2018;61(4):831-838. doi:10.1007/s00125-017-4517-7

8. Foster A, Gilbert C, Rahi J. Epidemiology of cataract in childhood: a global perspective. *J Cataract Refract Surg*. 1997;23 Suppl 1:601-604. doi:10.1016/s0886-3350(97)80040-5

9. Al-Bakri M, Sander B, Bach-Holm D, Larsen DA, Jensen H, Kessel L. Children with congenital and childhood cataract require frequent follow-up visits and examinations in general anaesthesia: considerations for the strain on families. *Acta Ophthalmol*. March 2019. doi:10.1111/aos.14081

10. Jamieson JRBG and R V. Clinical embryology and development of the eye. In: *Taylor and Hoyt's Pediatric Ophthalmology and Strabismus*. Elsevier Inc.; 2017:17-24.

11. Yorston D. Surgery for congenital cataract. *Community eye Heal*. 2004;17(50):23-25.

12. Khokhar SK, Pillay G, Dhull C, Agarwal E, Mahabir M, Aggarwal P. Pediatric cataract. *Indian J Ophthalmol*. 2017;65(12):1340-1349. doi:10.4103/ijo.IJO_1023_17

13. Lambert SR. Childhood cataracts. In: *Taylor and Hoyt's Pediatric Ophthalmology and Strabismus*. Fifth. Elsevier Inc.; 2017:346-361.

14. Harbord MG, Baraitser M, Wilson J. Microcephaly, mental retardation, cataracts, and hypogonadism in sibs: Martsolf's syndrome. *J Med Genet*. 1989;26(6):397-400. doi:10.1136/jmg.26.6.397

15. Robert W. Hered. Pediatric Opthalmology and Strabismus, section 6. In: *American Academy of Ophthalmology*. ; 2018:200-206.

16. Chess S, Fernandez P, Korn S. Behavioral consequences of congenital rubella. *J Pediatr*. 1978;93(4):699-703. doi:10.1016/s0022-3476(78)80921-4

17. Chauhan N, Sen MS, Jhanda S, Grover S. Psychiatric manifestations of congenital rubella syndrome: A case report and review of literature. *J Pediatr Neurosci*. 2016;11(2):137-139. doi:10.4103/1817-1745.187643

18. Gentile I, Zappulo E, Riccio MP, et al. Prevalence of Congenital Cytomegalovirus Infection Assessed Through Viral Genome Detection in Dried Blood Spots in Children with Autism Spectrum Disorders. *In Vivo*. 2017;31(3):467-473. doi:10.21873/invivo.11085

19. Shaw D, Bar S, Champion JD. The impact of developmental behavioral pediatrics in a population of children with Down syndrome. *J Pediatr Nurs*. 2020;57:38-42. doi:10.1016/j.pedn.2020.10.019

20. da Cunha RP, Moreira JB. Ocular findings in Down's syndrome. *Am J Ophthalmol*. 1996;122(2):236-244. doi:10.1016/s0002-9394(14)72015-x

21. Holmes JM, Leske DA, Burke JP, Hodge DO. Birth prevalence of visually significant infantile cataract in a defined U.S. population. *Ophthalmic Epidemiol*. 2003;10(2):67-74. doi:10.1076/opep.10.2.67.13894

22. Dalsgaard S, Thorsteinsson E, Trabjerg BB, et al. Incidence Rates and Cumulative Incidences of the Full Spectrum of Diagnosed Mental Disorders in Childhood and Adolescence. *JAMA psychiatry*. 2020;77(2):155-164. doi:10.1001/jamapsychiatry.2019.3523

23. Al-Bakri M, Bach-Holm D, Larsen DA, Siersma V, Kessel L. Socio-economic status in families affected by childhood cataract. *Acta Ophthalmol*. March 2021. doi:10.1111/aos.14768

24. Bøe T, Sivertsen B, Heiervang E, Goodman R, Lundervold AJ, Hysing M. Socioeconomic status and child mental health: the role of parental emotional well-being and parenting practices. *J Abnorm Child Psychol*. 2014;42(5):705-715. doi:10.1007/s10802-013-9818-9

25. Reiss F. Socioeconomic inequalities and mental health problems in children and adolescents: a systematic review. *Soc Sci Med*. 2013;90:24-31. doi:10.1016/j.socscimed.2013.04.026

26. Lin Z-L, Lin D-R, Chen J-J, et al. Increased prevalence of parent ratings of ADHD symptoms among children with bilateral congenital cataracts. *Int J Ophthalmol*. 2019;12(8):1323-1329. doi:10.18240/ijo.2019.08.14

27. Chak M, Rahi JS. The health-related quality of life of children with congenital cataract: findings of the British Congenital Cataract Study. *Br J Ophthalmol*. 2007;91(7):922-926. doi:10.1136/bjo.2006.109603

28. Denmark S. https://www.dst.dk/en#.

29. Koch S V, Andersson M, Hvelplund C, Skovgaard AM. Mental disorders in referred 0-3-year-old children: a population-based study of incidence, comorbidity and perinatal risk factors. *Eur Child Adolesc Psychiatry*. August 2020. doi:10.1007/s00787-020-01616-2

30. Thapar A, Cooper M, Rutter M. Neurodevelopmental disorders. *The lancet Psychiatry*. 2017;4(4):339-346. doi:10.1016/S2215-0366(16)30376-5

31. Thapar A RM. Neurodevelopmental disorders. In: *Child and Adolescent Psychiatry*. 6th ed. Oxford; 2018:31-40.

32. Sildorf SM, Breinegaard N, Lindkvist EB, et al. Poor Metabolic Control in Children and Adolescents With Type 1 Diabetes and Psychiatric Comorbidity. *Diabetes Care*. 2018;41(11):2289-2296. doi:10.2337/dc18-0609

33. Jobling AI, Augusteyn RC. What causes steroid cataracts? A review of steroid-induced posterior subcapsular cataracts. *Clin Exp Optom*. 2002;85(2):61-75. doi:10.1111/j.1444-0938.2002.tb03011.x

34. MacKenzie EM, Odontiadis J, Le Mellédo J-M, Prior TI, Baker GBI. The relevance of neuroactive steroids in schizophrenia, depression, and anxiety disorders. *Cell Mol Neurobiol*. 2007;27(5):541-574. doi:10.1007/s10571-006-9086-0

35. Eddy CM, Parkinson EG, Rickards HE. Changes in mental state and behaviour in Huntington's disease. *The lancet Psychiatry*. 2016;3(11):1079-1086. doi:10.1016/S2215-0366(16)30144-4

36. Muchowski PJ, Ramsden R, Nguyen Q, et al. Noninvasive measurement of protein aggregation by mutant huntingtin fragments or alpha-synuclein in the lens. *J Biol Chem*. 2008;283(10):6330-6336. doi:10.1074/jbc.M709678200

37. Chodick G, Sigurdson AJ, Kleinerman RA, et al. The Risk of Cataract among Survivors of Childhood and Adolescent Cancer: A Report from the Childhood Cancer Survivor Study. *Radiat Res*. 2016;185(4):366-374. doi:10.1667/RR14276.1

38. Willard VW, Berlin KS, Conklin HM, Merchant TE. Trajectories of psychosocial and cognitive functioning in pediatric patients with brain tumors treated with radiation therapy. *Neuro Oncol*. 2019;21(5):678-685. doi:10.1093/neuonc/noz010

39. Willard VW, Conklin HM, Wu S, Merchant TE. Prospective longitudinal evaluation of emotional and

behavioral functioning in pediatric patients with low-grade glioma treated with conformal radiation therapy. *J Neurooncol*. 2015;122(1):161-168. doi:10.1007/s11060-014-1696-7

40. Mattejat F, Remschmidt H. The children of mentally ill parents. *Dtsch Arztebl Int*. 2008;105(23):413-418. doi:10.3238/arztebl.2008.0413

41. Austerman J. ADHD and behavioral disorders: Assessment, management, and an update from DSM-5. *Cleve Clin J Med*. 2015;82(11 Suppl 1):S2-7. doi:10.3949/ccjm.82.s1.01

42. DeCarlo DK, Swanson M, McGwin G, Visscher K, Owsley C. ADHD and Vision Problems in the National Survey of Children's Health. *Optom Vis Sci Off Publ Am Acad Optom*. 2016;93(5):459-465. doi:10.1097/OPX.0000000000000823

43. Wrzesińska M, Kapias J, Nowakowska-Domagała K, Kocur J. Visual impairment and traits of autism in children. *Psychiatr Pol*. 2017;51(2):349-358. doi:10.12740/PP/OnlineFirst/61352

44. Lopes N, Dias LLDS, Ávila M, et al. Humanistic and Economic Burden of Blindness Associated with Retinal Disorders in a Brazilian Sample: A Cross-Sectional Study. *Adv Ther*. March 2021. doi:10.1007/s12325-021-01672-3

45. Augestad LB. Mental Health among Children and Young Adults with Visual Impairments: A Systematic Review. *J Vis Impair Blind*. 2017;111(5):411-425. doi:10.1177/0145482X1711100503

46. Ishtiaq R, Chaudhary MH, Rana MA, Jamil AR. Psychosocial implications of blindness and low vision in students of a school for children with blindness. *Pakistan J Med Sci*. 2016;32(2):431-434. doi:10.12669/pjms.322.8737

47. Hansen MM, Bach-Holm D, Kessel L. Visual outcomes after surgery for childhood cataracts. *Acta Ophthalmol*. March 2020:aos.14403. doi:10.1111/aos.14403

48. Jin J, Sklar GE, Min Sen Oh V, Chuen Li S. Factors affecting therapeutic compliance: A review from the patient's perspective. *Ther Clin Risk Manag*. 2008;4(1):269-286. doi:10.2147/tcrm.s1458

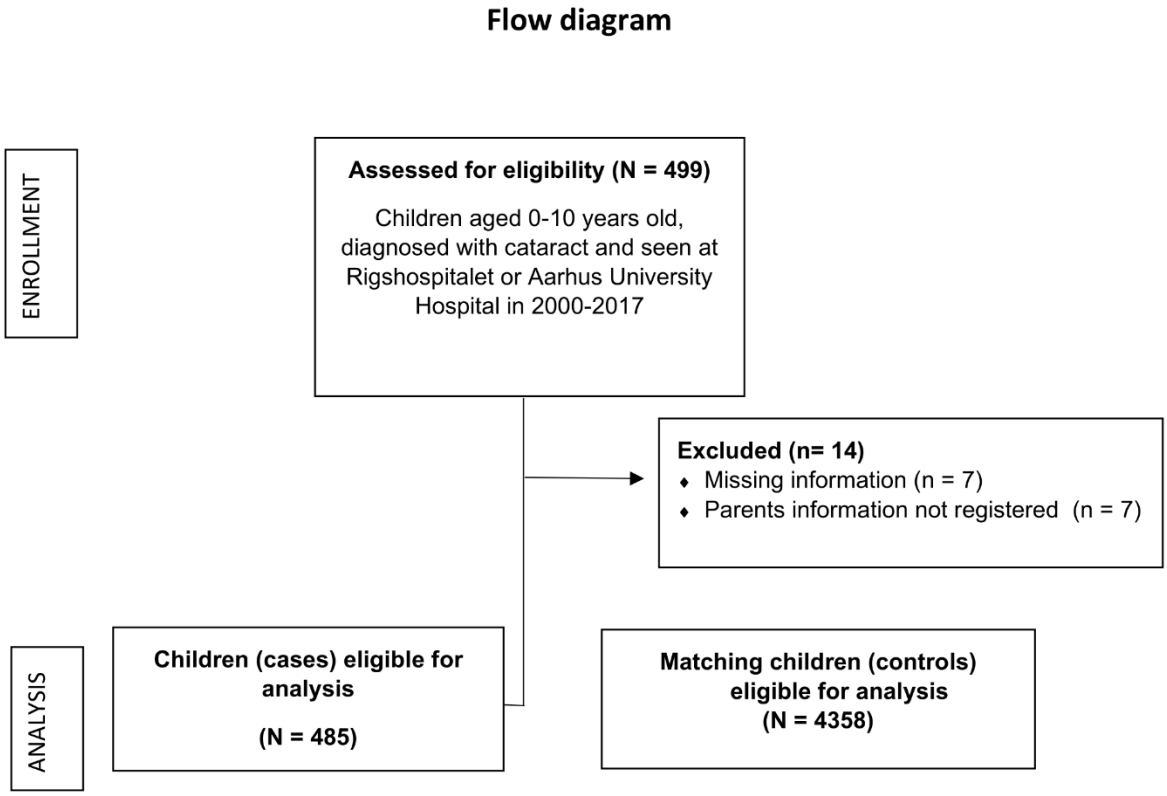
49. Roohafza H, Kabir A, Sadeghi M, et al. Stress as a risk factor for noncompliance with treatment regimens in patients with diabetes and hypertension. *ARYA Atheroscler*. 2016;12(4):166-171.

50. Loudon SE, Passchier J, Chaker L, et al. Psychological causes of non-compliance with electronically monitored occlusion therapy for amblyopia. *Br J Ophthalmol*. 2009;93(11):1499-1503. doi:10.1136/bjo.2008.149815

51. Hrisos S, Clarke MP, Wright CM. The emotional impact of amblyopia treatment in preschool children: randomized controlled trial. *Ophthalmology*. 2004;111(8):1550-1556. doi:10.1016/j.ophtha.2003.12.059

52. Dixon-Woods M, Awan M, Gottlob I. Why is compliance with occlusion therapy for amblyopia so hard? A qualitative study. *Arch Dis Child*. 2006;91(6):491-494. doi:10.1136/adc.2005.090373

53. Goodman R. The Strengths and Difficulties Questionnaire: a research note. *J Child Psychol Psychiatry*. 1997;38(5):581-586. doi:10.1111/j.1469-7610.1997.tb01545.x



420

421 **Figure 1**: Flow chart showing inclusion and exclusion of the study population.

422

423 **Table 1: Characteristics of the study population**

	Children with cataract	Children without cataract	p-value [a]	Missings
	N = 485	N = 4358		
Child's birth place, *n (%)*			0.001*	0
Denmark	428 (88.2)	4030 (92.5)		
Outside Denmark	57 (11.8)	328 (7.5)		
Disease confounders [b]			< 0.00001*	0
Yes	23 (4.7)	12 (0.3)		
No	462 (95.3)	4346 (99.7)		
Parental civil status, *n (%)*			0.598	42
Single	52 (10.7)	519 (11.9)		
Not single	419 (86.4)	3811 (87.4)		
Parental income [c] (DKK), *mean* (SD)	221230 (101047)	233355 (160947)	0.021*	28
Parental work status, *n (%)*			< 0.00001*	3
Outside work-force	58 (12.0)	253 (5.8)		
One or both parent(s) at work	425 (87.6)	4104 (94.2)		
Parental mental disorders			0.192	0
None	398 (82.1)	3467 (79.6)		
One or both parent(s)	87 (17.9)	891 (20.4)		

[a] P-value: Likelihood ratio test in a conditional logistic regression.

[b] Disease confounders: Congenital syndrome: microcephaly, megalencephaly, Smith-Lemi-Opitz' syndrome, trisomy 21, Down's syndrome, partial autosomal trisomy, Cytomegalovirus infection, interstitial lung disease, degenerative disease of the nervous system, congenital rubella infection, cancer in brain or meninges.

[c] 1 Danish Krone corresponds to 0.13 Euro.

424

425 **Table 2: Background characteristics of children with cataract (N=485)**

	Isolated cataract	**Cataract and severe somatic diseases**	**p-value** [a]
	N= 407	N=78	
Sex *Girls/Boys (%)*	197/210 (48.4/51.6)	45/33 (57.7/42.3)	0.168
Age at cataract diagnosis (year) *Median (IQR)*	1.4 (0.19 - 5.1)	0.6 (0.14 - 4.4)	0.344
Age at surgery (year) *Median (IQR)*	2.1 (0.3 - 4.9)	0.6 (0.2 - 4.0)	0.243
Operated/non-operated, n (%)	232/175 (57.0/43.0)	50/28 (64.1/35.9)	0.299
Any mental disorders [b]**, n (%)**	34 (8.4)	17 (21.8)	0.0008*
Neurodevelopmental disorder, n (%)	28 (5.8)	12 (15.4)	0.023*
Other mental disorders, n (%)	11 (2.3)	7 (9.0)	0.018*

[a] P-value: Pearson´s chi-squared test for categorical variables, t-test for continuous variables.

[b] Each child could be diagnosed with different mental disorders. The number of children with neurodevelopmental and other mental disorders does therefore not sum up to the number of children with any mental disorders.

426

427 **Table 3: Incidence of mental disorders among children with and without cataract**

	Children with cataract	Children without cataract	Unadjusted		Adjusted	
	N = 485	N = 4358	OR (95%CI)	p-value	OR (95%CI)	p-value
	n/N (%)					
Any mental disorders	51/485 (10.5)	225/4358 (5.2)	2.16 (1.57 - 2.78)	< 0.00001*	1.83 (1.28 - 2.63)	0.0009*
0-3 years [a]	35/327 (10.7)	118/2912 (4.1)	2.84 (1.91 - 4.22)	< 0.00001*	2.36 (1.53 - 3.64)	0.0001*
4-10 years [a]	16/158 (10.1)	107/1446 (7.4)	1.41 (0.81 - 2.45)	0.224	1.24 (0.66 - 2.30)	0.504
Neurodevelopmental disorders	40/485 (8.2)	148/4358 (3.4)	2.56 (1.78 - 3.67)	< 0.00001*	2.05 (1.35 - 3.11)	0.0007*
0-3 years [a]	28/327 (8.6)	77/2912 (2.6)	3.45 (2.20 - 5.40)	< 0.00001*	2.64 (1.59 - 4.4)	0.0002*
4-10 years [a]	12/158 (7.6)	71/1446 (4.9)	1.59 (0.84 – 3.00)	0.152	1.37 (0.68 – 2.76)	0.376
Other mental disorders	18/485 (3.7)	95/4358 (2.2)	1.73 (1.04 - 2.89)	0.036*	1.69 (1.0 - 2.87)	0.052
0-3 years [a]	12/327 (3.7)	50/2912 (1.7)	2.18 (1.15 - 4.14)	0.017*	2.22 (1.18 - 4.18)	0.014*
4-10 years [a]	6/158 (3.8)	45/1446 (3.1)	1.23 (0.52 – 2.98)	0.642	1.12 (0.40 – 2.85)	0.814

[a] Age at cataract onset

428

429 **Table 4: Incidence of the most prevalent mental disorders among children with and without cataract**

	Children with cataract	**Children without cataract**	**Unadjusted**		**Adjusted**	
	N = 485	N = 4358	OR (95%CI)	p-value	OR (95%CI)	p-value
	n/N (%)					
Neurodevelopmental disorders	40/485 (8.2)	148/4358 (3.4)	2.56 (1.78 - 3.67)	< 0.00001*	2.05 (1.35 - 3.11)	0.0007*
Autism spectrum disorders	11/485 (2.3)	55/4358 (1.3)	1.82 (0.94 - 3.49)	0.074	1.62 (0.78 - 3.39)	0.192
ADHD	6/485 (1.2)	43/4358 (1.0)	1.26 (0.53 - 2.97)	0.602	1.31 (0.50 - 3.46)	0.581
Unspecific developmental delay	22/485 (4.5)	54/4358 (1.2)	3.79 (2.29 - 6.28)	< 0.00001*	2.66 (1.45 - 4.90)	0.0017*
Other mental disorders [a]	18/485 (3.7)	95/4358 (2.2)	1.73 (1.04 - 2.89)	0.036*	1.69 (1.0 - 2.87)	0.052
Anxiety disorders	10/485 (2.1)	23/4358 (0.5)	3.97 (1.88 - 8.39)	0.0003*	4.10 (1.90 - 8.84)	0.0003*

Notably, a child could be diagnosed with two or more different mental disorders but counts once in the total number.

[a] Increased risk of eating disorders was found, but the number of children were too few to allow for publication according to rules of Statistics Denmark.

430

Supplementary Table 1: Description of variables used in the study

Name	*Registry*	*Description*	*Full name of registry*
Sex	BEF registry	Gender of the included population extracted from BEF registry (population registry)	BEF = Befolkning
Age at cataract onset	NPR + BEF registry	The date of cataract diagnosis was extracted from NPR (The National Patient Registry) and calculated based on birth date in BEF registry (population registry)	NPR = The National Patient Registry+ BEF = Befolkning
Geographical birth origin	BEF registry	Geographical birth origin is the place where the child was born extracted from BEF registry (population registry)	BEF = Befolkning
Children's mental disorders	PSYK_DIAG_ NPR	Children's mental disorders diagnosed at public hospitals extracted from NPR (The National Patient Registry)	Psyk_diag_NPR= The National Patient Registry with focus on psychiatric diagnoses
Children's systemic diseases	LPR_DIAG	Children's systemic disease diagnosed at public hospitals extracted from NPR (The National Patient Registry)	NPR = The National Patient Registry
Parental civil status	BEF registry	Parental civil status extracted from BEF registry (population registry)	BEF = Befolkning
Parental income	IND registry	Parental income extracted from IND registry (income registry)	IND = Indkomst
Parental work status	AKM registry	Information about parental work status extracted from AKM registry (work classification module)	AKM = Arbejdsklassifikationsmodulet
Parental mental disorders	PSYK_DIAG_ NPR	Parental mental disorders diagnosed at public hospitals extracted from NPR (The National Patient Registry)	Psyk_diag_NPR= The National Patient Registry with focus on psychiatric diagnoses

433 **Supplementary Table 2: Severe somatic diagnosis categories in children with cataract in the study**

Categories	ICD-10 Diagnoses	Number [a]
Congenital infections or conditions with immunosuppression	DB259 [b] (congenital cytomegalovirus infection) + DP350-351 [b] (congenital rubella syndrome + congenital cytomegalovirus infection) + DD849 (immunodeficiency) + DZ948C (bone marrow transplant) + DZ948C1 (bone marrow transplanted with allogeneic bone marrow)	8
Cancer in head and neck region	DC119 (nasopharyngeal cancer) + DC139 (cancer in hypopharynx) + DC301 (cancer in middle ear) + DC490 (cancer of connective tissue and soft tissue in head, face or neck) + DC694 [b] (cancer in ciliary body) + DD353 (benign tumor in craniopharyngeal duct) + DC720* (cancer in spinal cord) + DC760 [b] (cancer in head / face / neck without further spec. localization)	9
Blood related diseases	DD689 (coagulation disorder) + DD693 (idiopathic thrombocytopenic purpura) + DD699 (bleeding tendency) + DD709C (congenital neutropenia) + DC910 (acute lymphoblastic leukemia)	6
Endocrine and metabolic diseases	DE039 (hypothyroidism) + DE230 (decreased hormone secretion from pituitary gland) + DE740 (glycogen storage disorder) + DE740J (glycogenosis type I) + DE742 (disorder in galactose metabolism) + DE742B (galactosemia) + DE835 (disorder in calcium metabolism)	10
Neurological diseases	DG319 [b] (degenerative disease of the nervous system) + DG400 (focal idiopathic epilepsy) + DG402-404 (focal epilepsy with complex / gen. tonic-clonic seizure (GTCS)+generalized idiopathic epilepsy + epileptic encephalopathy) + DG409-10 (epilepsy + generalized tonic-clonic status epilepticus) + DG412 (non-convulsive complex partial status epilepticus) + DG418-419 (another form for status epilepticus + status epilepticus)	33
Cerebral palsy or plegia	DG800-803 (spastic tetraplegic cerebral palsy + spastic diplegic cerebral palsy + spastic hemiplegic cerebral palsy + dyskinetic cerebral palsy) + DG808 -809 (another form for cerebral palsy + mixed syndrome with cerebral palsy + cerebral palsy) + DG819 (hemiplegia) + DG824 (spastic tetraplegia)	31
Brain related diseases	DG919 (hydrocephalus) + DG939 (brain disease) + DG942 (hydrocephalus of other disease classified elsewhere) + DQ750 (Craniosynostosis) + DQ750D (trigonocephaly) + DQ753 (macrocephaly) + DI639 (stroke in the brain) + DQ029 [b] (microcephaly)+ DQ039-40 (congenital hydrocephalus + congenital malformation in corpus callosum) + DQ045 [b] (megalencephaly)	13
Cardiovascular diseases	DI420 (dilated cardiomyopathy) + DQ210-13 (ventricular septal defect + atrial septal defect + atrioventricular septal defect + tetralogy of Steno-Fallot) + DQ221 (congenital pulmonary valve stenosis) + DQ249-50 (congenital heart malformation + persistent ductus arteriosus)	17
Lung diseases	DJ841 [b] (second interstitial lung disease with fibrosis) + DJ848-849 [b] (another intersitial lung disease with fibrosis + intersitial lung disease) + DE840 (cystic fibrosis with lung manifestations) + DE849 (cystisc fibrosis)	9
Gastrointestinal diseases	DK316 (fistula from the stomach or duodenum) + DK 316B (gastrojejunal fistula) + DK316E (gastrointestinal fistula) + DQ410-11 (agenesis, atresia or congenital stenosis of duodenum + agenesis, atresia or congenital stenosis of jejunum) + DQ419 (agenesis, atresia or congenital stenosis of small intestine) + DQ438 (second congenital malformation of the intestinal tract) + DQ619-20 (cystic kidney disease + congenital hydronephrosis) + DQ649 (congenital malformation of urinary tract)	11
Rheumatic diseases	DM029 (reactive arthritis) + DM069 (rheumatoid arthritis) + DM080 (juvenile rheumatoid arthritis) + DM082-84 (juvenile arthritis with extra-articular manifestations + juvenile seronegative polyarthritis + pauciarticular juvenile arthritis) + DM089-90 (juvenile arthritis + psoriatic arthritis in children) + DM131 (monoarthritis)	17
Syndromes	DQ773 (chondrodysplasia punctata) + DQ788B (chondrodystrophia punctata) + DQ870 (syndromes with congenital malformations predominantly in face region) + DQ870H (Oro-Facial-Digital syndrome) + DQ870M (Waardenburg syndrome) + DQ871 (congenital malformation syndrome with dwarfism) + DQ871E (Prader-Willis syndrome) + DQ871I [b] (Smith-Lemli-Opitz' syndrome) + DQ873-75 (syndromes with congenital malformations with early height growth + Marfan syndrome + other congenital malformation syndrome with skeletal changes) + DQ878 (second congenital malformation syndrome) + DQ897A (multiple congenital malformations) + DQ899 (congenital malformation) + DQ900 [b] (trisomy 21) + DQ909 [b] (Down's syndrome) + DQ928 [b] (partial autosomal trisomy) + DQ999 (chromosome anomaly)	36

[a] A child could be diagnosed with different systemic diseases and therefore could figure in several systemic diagnoses.

[b] Disease confounders.

434

435 **Supplementary Table 3:**

Socio-economic variable	Definitions and classifications
The child's birth origin	Children born inside or outside Denmark.
Income	Household financial resources based on the disposable personal income (DPI)/adult over the full calendar year. The DPI is the amount of money that a household has available for saving and spending after it has been charged for taxes. For cohabiting parents: Average DPI in the household was used. For separated parents and parents living apart: The highest DPI was used.
Employment status	Family was defined as unemployed if both parents were registered as unemployed for up to six months, received unemployment benefits, had retired early or if they were students.
Civil status	The civil status was divided into two groups: single and not single (married, cohabiting couple & multi-family residential). Multi-family residential is when more than one family live at the same address.

436

437