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AN APPRAISAL OF CHILDHOOD VISION PROBLEMS:

EVALUATING RISK FACTORS AND THE

PSYCHOSOCIAL IMPACT OF STRABISMUS IN CHILDREN

A dissertation submitted in partial satisfaction of the requirements for the degree of Doctor of Philosophy

in

Public Health (Epidemiology)

by

Kimbach Tran Carpiuc

Committee in charge:

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Professor Barbara Brody
Professor Sheila Gahagan

San Diego State University

Professor Ming Ji
Professor Caroline A. Macera

2013

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The Dissertation of Kimbach Tran Carpiuc is approved, and it is acceptable in quality and form for publication on microfilm and electronically:

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University of California, San Diego

San Diego State University

2013

DEDICATION

For my parents, Van and Kim Cuc Tran, who left their home country 38 years ago for this one, in order to provide me with the promise of a better future. Thank you for instilling in me the importance of education, hard work, and perseverance through adversity, as well as for your support in pursuing my academic and professional goals.

For Dan, my love and best-friend, who has supported me throughout my entire academic journey, which began as an undergrad at UCSD in 1995, continued through grad school at Tulane and Georgetown, and come full-circle with its final conclusion (I promise) nearly two decades later at UCSD/SDSU. You have been my rock throughout this whole process. Thank you for the late nights which you stayed up to keep me company, helping me keep perspective and balance in my life, and your unending words of encouragement, hugs, and offers of chocolate and ice cream.

And especially for Bradley and Maddy, who changed my life with both of your arrivals. You are my inspirations, joy, and sunshine. You have taught me what it truly means to hope, have patience, and have peace in knowing that despite life's challenges, everything will turn out just fine. I am so thankful for the blessing and gift of being your mom.

EPIGRAPH

History will judge us by the difference
we make in the everyday lives of children.

Nelson Mandela

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LIST OF ABBREVIATIONS

A&SQ	Amblyopia and Strabismus Questionnaire
AAO	American Academy of Ophthalmology
AAPOS	Pediatric Ophthalmology and Strabismus
AS20	Adult-Strabismus Questionnaire
ATI	Amblyopia Treatment Index
BDI	Beck Depression Inventory
CHDS	Child Health and Development Studies
CVFQ	Children's Visual Function Questionnaire
FAD	Family Assessment Device
HRQoL	Health-related quality of life
HSC	Hopkins Symptom Checklist
IXTQ	Intermittent Exotropia Questionnaire
K-CBCL	Korean Child Behavior Checklist
MEPEDS	Multi-ethnic Pediatric Eye Disease Study
MeSH	Medical Subject Header
NEI-VFQ-25	National Eye Institute Visual Functioning Questionnaire
PARI	Parental Attitude Research Instrument
PAS	Pediatric Academic Societies
PedsQL	Pediatric Quality of Life Inventory
PSI	Parenting Stress Index
SF-20	20-Item Short Form Health Survey
STAI	State-Trait Anxiety Inventory
VQS	Vision Quality Scale
WHO	World Health Organization

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Chapter 2, in part is currently being prepared for submission for publication of the material. Carpiuc, Kimbach; Wingard, Deborah; Brody, Barbara; Macera, Caroline; Klonoff-Cohen, Hillary; Ji, Ming; and Gahagan, Sheila. The dissertation author was the primary investigator and author of this material.

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ABSTRACT OF THE DISSERTATION

AN APPRAISAL OF CHILDHOOD VISION PROBLEMS:

EVALUATING RISK FACTORS AND THE

PSYCHOSOCIAL IMPACT OF STRABISMUS IN CHILDREN

by

Kimbach Tran Carpiuc

Doctor of Philosophy in Public Health (Epidemiology)

University of California, San Diego, 2013
San Diego State Unviersity, 2013

Professor Deborah Wingard, Chair
Professor Hillary Klonoff-Cohen, Co-Chair

Strabismus is an anomaly of ocular alignment, resulting in a departure from the parallel nature of a normal gaze, and affects approximately 1-5% of the population. Left uncorrected, strabismus can result in amblyopia, a permanent vision loss in an otherwise normal eye. Although strabismus can happen at any age, the peak age of onset is around 3 years. Despite being a relatively common eye problem in young children, little attention has been given to strabismus in the published literature, with limited research exploring the etiology of strabismus. This dissertation was undertaken with the goal of better understanding factors associated with the development of strabismus, and to review

the psychosocial and health-related quality of life (HRQoL) implications of having strabismus in young children. Using data from the Child Health and Development Studies (CHDS), in-utero exposure to maternal smoking, alcohol, and coffee during pregnancy, as well as multiple perinatal factors, were explored as possible risk factors with the association of esotropia and exotropia, the most common forms of strabismus in children.

Overall, the risk of developing esotropia or exotropia were increased in children whose mothers smoked heavily during pregnancy compared to those who did not, after controlling for covariates. No association was found in children whose mothers consumed alcohol or coffee during pregnancy compared to those who did not drink; perinatal factors, including maternal hemorrhage before delivery, delivery position, type of delivery, fetal stress, head circumference, and baby cry time, were also not found to be significantly associated with an increased risk of strabismus in this study population. The literature review highlights concerns related to self-image, social and school phobias, mental-health problems, and interpersonal relationships in children with strabismus, as well as strabismus-related distress in caregivers. Studies involving children have only recently found their place in quality of life research, with few studies examining the impact of HRQoL from strabismus or its treatments.

The work of this dissertation adds to the small yet growing field of pediatric ophthalmology and strabismus. Additional research is needed to better understand the causes of strabismus, as well as the overall quality of life burden of strabismus in children.

CHAPTER 1

BACKGROUND AND SIGNIFICANCE

Strabismus – *noun* \strə-'biz-məs\:
Inability of one eye to attain binocular vision with the other
because of imbalance of the muscles of the eyeball

Etymology: New Latin, from Greek *strabismos* condition of squinting,
from *strabizein* to squint, from *strabos* squint-eyed;
akin to Greek *strephein* to twist

Merrium-Webster Dictionary

Background

Vision is a key facet in the life of a child. It plays an important role in children's development, having a great impact on the way they learn, interact, and interpret the world around them. Visual impairment, through decreased visual acuity, refractive errors, and/or alignment or stereoacuity problems, can significantly alter the neurological, physical, and emotional development of a child.

Left untreated, vision problems can lead to challenges with learning, work and productivity, impaired quality of life, as well as blindness.[1] Reduced vision may impair a child's ability and willingness to participate in academics, sports, and other social activities, thereby having a negative impact on school performance and limiting personal development.[2, 3]

Often commonly referred to as "squint", "cross-eyes", or "wandering eyes", strabismus can develop at any age, with the peak age of onset around 3 years.[4, 5] The prevalence of strabismus in children is approximately 1-5% of the population.[6, 7] Most large population-based studies indicate no difference in prevalence for strabismus between gender.[8-11] Left uncorrected, strabismus in children can result in amblyopia, a permanent vision loss in an otherwise normal eye.

Strabismus can occur in one or both eyes and in any direction, with horizontal deviations being the most common; esodeviations, where the eye turns inwards/nasally, or exodeviations, where the eye turns outwards/temporally. Vertical strabismus includes hyperdeviations, with *hyper-* generally referring to the eye more superior regardless of

which eye is fixing, and cyclotropia occurs when the ocular misalignment is torsional. Additional terminology is utilized to describe when strabismus is present without interruption of the visual axis (*-tropias*, or manifest strabismus) or whether it changes with the position of a gaze *(-phorias*, or latent strabismus). Manifest strabismus can also be constant or intermittent (occurring when an individual is ill or fatigued), and comitant (where deviations are all the same in all positions of gaze) or incomitant (where the deviations change). Moreover, strabismus can be monocular, always involving the same eye, or alternating, where both eyes may deviate.

The detection of strabismus can be conducted by pediatric healthcare providers using several clinical tests. Along with an overall physical examination to assess general health, neurologic status, and childhood development, the eye exam should include an assessment of ocular and family history, visual function, external inspection of the eyes and lids, ocular motility, pupilary reactivities, as well as the red reflex, corneal light reflex, and cover/uncover test.[12] Additional ophthalmological examinations, including cycloplegic refraction, or funduscopy/ophthalmoscopy may also be carried out where possible. The results of these tests can help better characterize the type of strabismus present in the child.

Specific therapies may vary depending on the subtype due to differences in etiology, though surgical procedures to correct ocular muscles are common.[13] Non-surgical therapies to correct and manage alignment and visual impairment may be addressed by eyeglasses,[14-16] occlusion or pharmacologic therapy (e.g,. miotic drops, botulinum toxin),[17-20] as well as vision training.[21] Guidelines and Policy Statements from

the American Academy of Ophthalmology (AAO) and American Association for Pediatric Ophthalmology and Strabismus (AAPOS) are available to help direct pediatric ophthalmologists in managing the patient with strabismus.[13]

Pediatric Ophthalmology and Strabismus research

Despite strabismus being a relatively common condition in children, overall little attention has been given to strabismus in the published literature. To illustrate, a search within the Pubmed/MEDLINE database was conducted with several chronic health conditions observed in children (**Figure 1-1**). For simplicity, the condition name with a Medical Subject Header (MeSH) term was combined also with a MeSH term for *child* to reveal a rough estimation on the number of studies for that condition available in the published literature. While not an exact measure, an additional term using *epidemiology* was added to highlight where possible epidemiological studies were carried out. Pediatric conditions included ADHD, arthritis, asthma, Autism Spectrum Disorder, cystic fibrosis, diabetes, epilepsy, cancer, leukemia, and obesity. As of July 2013, the number of total hits ranged from 9,722 for cystic fibrosis, to 179,654 for childhood cancer (overall), with all other conditions in the 15,000-32,500 range. Including the *epidemiology* term in the search resulted in 1,211 hits for cystic fibrosis to 34,877 for childhood cancer, with the other conditions resulting in 2,000-8,500 hits. Childhood strabismus resulted in a total of 6,086 total hits; including the epidemiology term, *only 458.*

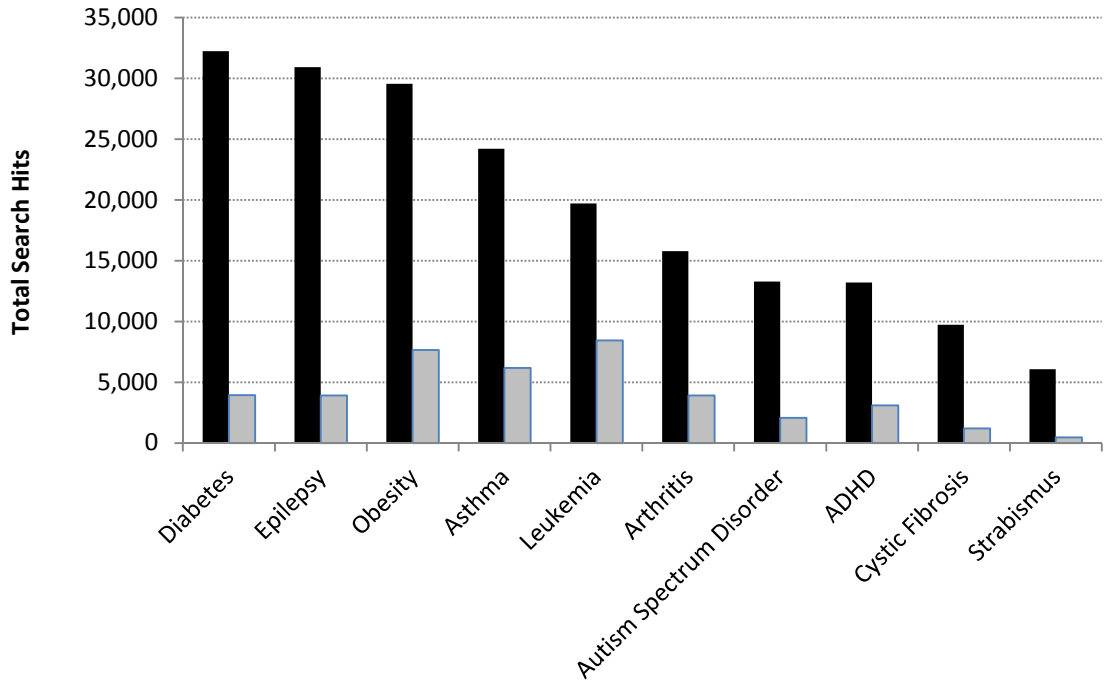


Figure 1-1. Search hit results of PubMed/MEDLINE database. Dark bars represent using the Medical Search Headings (MeSH), and include a MeSH term for "child" to differentiate from adult conditions. Light bars included an additional "epidemiology" term.

The limited number of studies published in childhood strabismus may be due, at least in part, to the relatively recent establishment of pediatric ophthalmology as a subspecialty. While surgery to treat strabismus has been reported as early as the late eighteenth century,[22] not until the mid 1900s did ophthalmology became an area of focus in pediatrics, not just in adults and geriatric patients.[23] The beginnings of pediatric ophthalmology is credited towards Frank D. Costenbender in 1943, an ophthalmologist who decided to dedicate his practice solely to the care of children under age eleven, and

Marshall M. Parks, his first trainee and mentee who identified a critical gap in the care of ophthalmology patients. Parks reports,

> During my training in 1946, it became apparent that ophthalmology was primarily a geriatric specialty. Both the attending and their trainings were obviously ill prepared for examining and treating infants and preschool children; nor was there any inclination manifest for improving their deficiency. Children were unwanted as patients. From this observation came my resolve to change that scenario.

Together, both Costenbender and Parks moved forward to establish the first ophthalmology fellowship training of any subspeciality at Children's Hospital in Washington D.C. (now the Children's National Medical Center), and by the late 1960s, enough pediatric fellows warranted an alumni association. While Costebender retired in 1970, Parks continued his efforts to advance the establishment and growth of the field, and has since been referred to as the "father of pediatric ophthalmology." With Parks as its founding member, the American Association for Pediatric Ophthalmology and Strabismus (AAPOS) was created as a national professional organization dedicated to advance the quality of care and management of ocular diseases in children. Since its inception, it has since grown from a few dozen members in 1975, to close to 1,500 members worldwide in 2013.[23, 24] The first issue of the official publication for the AAPOS, the *Journal of the American Association for Pediatric Ophthalmology and Strabismus*, appeared in 1997 and continues to provide expert clinical and research information on childhood eye diseases.

Yet despite its overall growth, many have noticed a declining interest in ophthalmology residents in pursuing pediatric ophthalmology and strabismus as a career following graduation.[6, 16, 19, 25] Despite having a positive view towards pediatric

ophthalmology, very few express interest in pursuing a fellowship.[25] In an analysis of the 2005 Ophthalmology Fellowship Match Report, compared to higher numbers of filled fellowships for corneal/external disease (72/79; 91.1% filled), retina (83/96; 86.5%), and glaucoma (43/56; 76.8%), only 24/44 (54.5%) of pediatric ophthalmology fellowship positions filled.[6, 25] Studies attempting to assess the attitudes from residents cite reasons related to the difficulty with working with children, as well as low compensation compared to other subspecialties.[6, 25] Only a fraction of the residents surveyed reported that being a pediatric ophthalmologist is prestigious.[25] With a growing population of children in the U.S. and worldwide, concern due to the lack of manpower and consequent efforts to recruit additional residents in the field of pediatric ophthalmology and strabismus may continue to rise in the future.[18, 25] While the number of pediatric and ophthalmology and strabismus clinicians are low, epidemiologists and other health researchers working in this specialized field are even more rare.

Etiology and Impact

To date, little is understood regarding the causes leading to poor neuromuscular control of the eye muscles. Though the underlying etiology for strabismus remains unclear, it is likely multifactorial, resulting from both genetic and environmental causes. The prevalence of strabismus is higher in families where a parent or sibling has strabismus, indicating a possible hereditary component.[26-28] Strabismus is also more prevalent in children with certain genetic, congenital, and/or neurologic conditions (e.g. Down's syndrome, Apert-Crouzon syndrome, Duane syndrome, and cerebral palsy).[29-33]

Prematurity and low-birth weight have also widely been established as risk factors for developing strabismus.[34-44]

As cases of strabismus peak in early childhood, possible environmental effects exist. However, few studies have looked at potential environmental factors for strabismus, particularly during the *in-utero* and perinatal period. While some studies have indicated an increased risk of strabismus with maternal cigarette smoking, [45-49] little evidence is available regarding alcohol and coffee, and no studies were identified exploring whether or not these influences are different between boys and girls. Moreover, while numerous studies have examined the risk of perinatal influences on the association of many childhood conditions ranging from infectious and respiratory diseases, cancer, diabetes, to body mass index, behavioral, neurological, and psychological disorders,[50-59] few have studied the potential risk of these factors on the development of childhood strabismus.

In recent years, a growing body of evidence examining the impact of strabismus upon an individual's physical and psychosocial well-being has emerged in the published literature. The implications of strabismus on a child are becoming more accepted and well-recognized, particularly in more visually obvious cases of strabismus, and include concerns with interpersonal relationships, self-image issues, social and school phobias, mental-health problems, as well as overall decreased HRQoL.[60-66] The implications of having strabismus in young children extend to their caregivers as well, with families often experiencing high levels of distress.[67-69] While studies reporting increased levels of HRQoL following surgery have been well-documented in adults with strabismus,[70-73]

research in children is less extensive, but evidence available also suggest positive benefits following surgery.[74-76]

CHDS

The Child Health and Development Studies (CHDS) are prospective longitudinal studies on the medical and social aspects of pregnancies and on the health and development of children. Data were collected on over 20,000 pregnancies from 1959 to 1967 and followed for pregnancy outcome. Key objectives of the CHDS since its inception has been to investigate the relationship of biologic, genetic, behavioral, and environmental factors in the parents – including events in pregnancy, labor, and delivery – to the development of the offspring. Today, CHDS scientists still carry out research to investigate how factors in early life influence later health outcomes as an adult in the children of the CHDS mothers (now adults), and their children.[77] The CHDS were initiated as a project funded by the National Institute of Child Health and Human Development designed to investigate the impact of early life experience on the growth and development of the child and to study the long term implications of experiences during pregnancy.

Overall significance

This dissertation aims to look at two key aspects of childhood strabismus, which are, in effect, an examination of both ends of the epidemiological spectrum: (1) to study possible causes of childhood strabismus, and (2) to quantify the impact and outcomes of strabismus in children. Results from these studies will add to the limited studies

conducted in pediatric ophthalmology and strabismus to help better understand the possible factors leading to disease, and to highlight the psychosocial concerns related to the child and the effects associated with treatments.

Dissertation Objectives

The aims of the studies examined in this dissertation are

1. To examine the risk of horizontal strabismus (i.e., esotropia and exotropia) associated with in-utero maternal exposure to smoking, alcohol, and coffee in a population-based sample of children;
2. To investigate the effects of maternal and child perinatal factors on the association of horizontal strabismus in a population-based sample of children; and
3. To review the published literature in order to characterize the perceptions of childhood strabismus from peers and adults, describe the psychosocial impact of strabismus in children and their families, examine instruments that have been developed and validated to measure vision-specific, HRQoL in children, and to assess how treatments for strabismus affect HRQoL in children with strabismus.

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CHAPTER 2

THE ASSOCIATION OF IN-UTERO MATERNAL SMOKING, ALCOHOL, AND COFFEE WITH CHILDHOOD HORIZONTAL STRABISMUS

Reducing the tremendous toll of
disease, disability, and death
caused by tobacco use in the United States
is an urgent need and shared responsibility.

How Tobacco Smoke Causes Disease,
A Report of the Surgeon General 2010

ABSTRACT

Purpose : The purpose of this study was to examine the association of horizontal strabismus with maternal exposure to smoking, alcohol, and coffee during pregnancy in a population-based sample of boys and girls. **Methods:** Data were analyzed for 14,050 women and their offspring participating in the Child Health and Development Studies (CHDS) between 1959 and 1966, a prospective study of pregnant women and the health and developmental outcomes of their children. Logistic regression models in children without severe anomalies were used to examine the independent association of maternal exposure to smoking, alcohol, or coffee during pregnancy with the development of esotropia or exotropia. **Results:** Overall, 309 boys and girls were found to have horizontal strabismus; 225 (1.6%) with esotropia, and 84 (0.6%) with exotropia. Boys born to mothers who smoked ≥20 cigarettes/day during pregnancy had an almost 3-fold increased risk of esotropia (OR=2.95, 95% confidence interval (CI): 1.59-5.46) compared to boys whose mothers did not smoke during pregnancy. Girls whose mothers smoked ≥20 cigarettes/day during pregnancy showed had an almost 2-fold increased risk for esotropia (OR= 1.88, 95% confidence interval (CI): 1.61-3.47) compared to girls whose mothers did not smoke during pregnancy. Maternal alcohol and coffee consumption during pregnancy were not associated with risk of esotropia or exotropia. **Conclusions:** Of maternal life-style behaviors during pregnancy, only heavy cigarette smoking during pregnancy was associated with an increased risk of horizontal strabismus. Consumption of alcohol or coffee was not associated with esotropia or exotropia.

INTRODUCTION

Vision plays an important role in children's development, having a great impact on the way they learn, interact, and interpret the world around them. Impairment, through decreased visual acuity, refractive errors, or alignment/stereoacuity problems, can significantly alter the neurological, physical, and emotional development of a child.[1] Left untreated, vision problems can lead to problems with learning, work/productivity, impaired quality of life, as well as blindness.[2] Reduced vision may impair a child's ability and willingness to participate in academics, sports, and other social activities, thereby having a negative impact on school performance and limiting personal development.[3, 4]

Strabismus is a misalignment of the eyes, which produces deviation from the parallel nature of a normal gaze, and affects approximately 1-5% of the population.[5, 6] The eyes (one or both) may turn outward, inward, up, or down, and are often known as "crossed-eyes" or "wandering eyes". Left uncorrected, strabismus can result in amblyopia, a permanent vision loss in an otherwise normal eye. Horizontal deviations of the eyes include two major types: esotropia (where the eyes converge), or exotropia (where the eyes diverge). Although strabismus can develop at any age, the peak age of onset is around 3 year.[7, 8] Most large population-based studies indicate no gender difference for strabismus.[9-12]

The etiology of strabismus is currently poorly understood, with few studies looking at potential risk factors for strabismus, particularly environmental (biological, social, and life-style) risk factors. The prevalence of strabismus is higher in families

where a parent or sibling has strabismus, indicating a possible genetic component.[13-15] Strabismus is also more prevalent in children with certain genetic or congenital conditions (e.g. Down's syndrome, Apert-Crouzon syndrome, Duane syndrome, and cerebral palsy).[16-20] Prematurity and low-birth weight have also widely been established as risk factors for developing strabismus.[21-31] Few studies have investigated the influence of *in-utero* maternal exposures to smoking, alcohol, and coffee on the development of strabismus,[32-36] and no studies have been identified examining whether or not these influences affect the risk differently between boys and girls.

Our study aimed to examine the association of horizontal strabismus (i.e., esotropia and exotropia) with maternal exposure to smoking, alcohol, and coffee in a population-based sample of children.

PATIENTS AND METHODS

Data Sources / Population

The Child Health and Development Studies (CHDS) are prospective longitudinal studies on the medical and social aspects of pregnancies and on the health and development of children. Data were collected on over 20,000 pregnancies from 1959 to 1967 and followed for pregnancy outcome. Key objectives of the CHDS since its inception has been to investigate the relationship of biologic, genetic, behavioral, and environmental factors in the parents – including events in pregnancy, labor, and delivery – to the development of the offspring. Today, CHDS scientists still carry out research to

investigate how factors in early life influence later health outcomes as an adult in the children of the CHDS mothers (now adults), and their children.[37] The CHDS were initiated as a project funded by the National Institute of Child Health and Human Development designed to investigate the impact of early life experience on the growth and development of the child and to study the long term implications of experiences during pregnancy. Families involved in the CHDS were members of the Oakland-East Bay Kaiser Foundation Health Plan during their pregnancy and interviewed on referral to the CHDS from prenatal service of the Kaiser clinic.

The sample population for this study is based on singleton live births surviving past the neonatal period in women who were available for interview during pregnancy. Excluding those with vertical strabismus (n=3), phorias (n=2), and unspecified strabismus type (n=27) resulted in an initial sample of 14,555 births. After further exclusion of those identified with any number of severe congenital anomalies (n=505), there remained 14,050 participants (7,118 boys and 6,932 girls) who are the focus of this report. The study protocol was approved by the Human Subjects Protections Program of the University of California, San Diego (La Jolla, California), and the Institutional Review Board of the Public Health Institute (Oakland, California). The original data collection predated the requirement for Institutional Review Board approval.

Procedures

Socio-demographic characteristics, reproductive and medical history, as well as smoking, coffee, and alcohol habits, were gathered from the women during pregnancy via in person interview. Information on smoking consumption were obtain through a

number of questions which inquired about current smoking status, number of cigarettes smoked per day, and whether the woman had quit smoking (and if so, when and why). During the interview at the time of the first prenatal visit, mothers were also asked about the smoking habits of the father.

For analyses, smoking consumption during pregnancy was categorized as non-smokers (including both never and former smokers), light (1-19 cigarettes per day), or heavy smokers (≥20 cigarettes per day). Maternal alcohol consumption was based on number of drinks of beer, wine, and hard liquor consumed in the past week and converted to drinks per day. Mothers were also queried about usual daily coffee consumption and categorized also as the number of cups drank per day.

All information on the children, including birthweight, was obtained from abstraction of the infant's medical record. Any medical visit made by a child to the clinic, hospital, or health plan facility were recorded in the patient's medical record, including any diagnoses, treatments, as well as clinical or laboratory examinations or tests. Data were collected on all children for a minimum of 5 years after birth. If strabismus was suspected and/or detected by the pediatrician, patients were referred to ophthalmology for diagnosis and follow-up. All information abstracted on abnormalities, including strabismus, were reviewed by at least two CHDS physicians independently, and coded based on seventh revision of the International Classification of Diseases assignment (World Health Organization, Geneva, Switzerland, 1967). Subsequent review of the abstracted medical charts noted any specific strabismus subtype identified in the record.

Data Analysis

Comparisons of demographic and socioeconomic characteristics were analyzed using two-sample independent t-tests for continuous variables and chi-square analyses for categorical variables. Logistic regression for rare events according to the Firth method, including gender-specific regression models, were used to examine the independent association of maternal exposure to smoking, alcohol, or coffee during pregnancy on the development of esotropia or exotropia. Based on the literature suggesting possible etiologic differences among strabismus subtypes, all regression analyses were conducted separately for children with esotropia and exotropia.

Several covariates were considered *a priori* based on the existing published literature on possible risk factors associated with developing strabismus as potential confounders. Variables with a significant association with esotropia or exotropia in univariate analyses, or those that created a greater than 10% change in the beta-estimate were included in the multivariate regression models. Tests of interaction between selected variables were completed by including an interaction term in the multivariate model, with product terms with at least marginally significant associations ($P \leq 0.1$) considered interactions of interest. A product term for infant gender and maternal smoking yielded a $P=0.10$ for esotropia; a non-significant association was found for exotropia. All estimates were adjusted for year of birth to account for cohort effects in follow-up in the study population. To avoid collinearity, a variable combining both infant birth weight and gestational age in mutually exclusive categories was created (≥2500 grams/≥37 weeks; <2500 grams/≥37 weeks; ≥2500 grams/<37 weeks; <2500

grams/<36 grams). Those who did not smoke, did not consume alcohol, and did not consume coffee were used as the reference group for risk calculations. Statistically significant risk factors for esotropia or exotropia were indicated by significance levels of $p<0.05$ and based on two-sided tests. Data were analyzed using SAS version 9.2 (SAS Institute Inc, Cary, NC).

RESULTS

Of the 14,050 boys and girls born in this study population, 309 were found to have horizontal strabismus; 225 (1.6%) with esotropia, and 84 (0.6%) with exotropia. The mean age of diagnosis for esotropia was 3.6 (±2.1) years, and 4.8 (±2.0) years for exotropia; the oldest child detected in the study population was 10.7 years. The mean age of the mothers was 27.3 ±5.8 years, with a diverse racial mix of 67% White, 25% Black, 4% Hispanic, and 7% Other (Asian, Native American, Mixed Race) women. **Table 2-1** indicates the smoking, alcohol, and coffee exposure characteristics of the study population. Approximately one-third of the women in the study reported smoking during pregnancy; of these, 40.7% were identified as heavy smokers consuming greater than 20 cigarettes per day. Nearly half of women reported that their spouses smoked; 20.9% consumed 1-19 cigarettes per day, and 27.7% were heavy smokers of ≥20 cigarettes per day. While the majority of women in the study did not drink during pregnancy, over 10% of pregnant mothers reported drinking four or more drinks per day. Coffee consumption was reported to be common in this study; 26.6% of mothers consumed 1-2 cups per day, 16.6% consumed 3-4 cups per day, and 17.3% drank ≥ 5 cups of coffee per day.

There were slightly more boys in this study than girls (50.7% vs 49.3%, respectively). Among girls, 1.7% (118/6932) were reported to have esotropia, and 0.63% (44/6932) exotropia, compared to 1.5% (107/7118) and 0.56% (40/7118) for esotropia and exotropia in boys, respectively. The ORs for the association of horizontal strabismus with maternal smoking during pregnancy are presented for three models: a model adjusted only for infant characteristics including year of birth, birthweight/gestational age, and infant gender (Model 1); a model with year of birth, birthweight/gestational age, infant gender, and maternal social and behavioral risk factors (Model 2); and a fully adjusted model with all the above covariates along with paternal factors (Model 3). Adjusted regression models indicated that compared to women who did not smoke, those who reported to be current smokers during pregnancy had a significant increased risk of esotropia in the offspring (**Table 2-2**) after adjusting for year of birth, birthweight/gestation age, and infant gender, as well as maternal factors including age, race, education, alcohol and coffee consumption, and paternal factors include age, education, and daily smoking (OR=1.75, 95% CI: 1.18-2.61), a finding that was not significant for those who were considered former smokers (OR=1.26, 95% CI: 0.79-2.00).

Increased risk of esotropia was different depending on the amount of cigarettes the mother smoked during pregnancy (*P* for homogeneity <0.001). After adjusting for covariates, no increased risk of esotropia was found for children of women who smoked 1-19 cigarettes/day, however those who smoked ≥20 cigarettes/day had a significant increased risk of esotropia (OR=2.31, 95% CI: 1.49-3.59) compared to those with

mothers who did not smoke during pregnancy. Maternal alcohol or coffee consumption during pregnancy was not found to be associated with the risk of esotropia in the children after adjustment for year of birth, birthweight/gestational age, and infant gender, as well as maternal and paternal factors.

For exotropia, only children who had mothers who smoked during pregnancy had an increased risk of exotropia in models that adjusted for year of birth, birthweight/gestational age, infant gender, and maternal factors (**Table 2-3**). Similar results to esotropia were observed for the amount consumed during pregnancy; only children whose mothers were heavy smokers (≥20 cigarettes/day) were found to have an increased risk of exotropia (OR=2.13, 95% CI: 1.12-4.07) compared to children of nonsmokers after adjusting for all covariates, which was not significant in women who smoked 1-19 cigarettes/day. After adjustment for other covariates, daily maternal alcohol and coffee consumption was not associated with an increased risk of exotropia in the children.

To examine whether differences in risk varied by gender of the offspring, results of the fully adjusted gender-specific regression models by smoking consumption are shown in **Figure 2-1** for esotropia. Children who were born to women who smoked heavily during pregnancy were significantly associated with a risk of developing esotropia, an association which appears higher in boys than in girls. Boys born to mothers who smoked ≥20 cigarettes/day during pregnancy had an almost 3-fold increased risk of esotropia (OR=2.95, 95% CI: 1.59-5.46) compared to boys whose mothers did not smoke during pregnancy. Girls whose mothers smoked ≥20 cigarettes/day during

pregnancy were associated with a nearly 2-fold increased risk for esotropia (OR=1.88, 95% CI: 1.61-3.47) compared to girls whose mothers did not smoke during pregnancy. In children whose mothers smoked 1-19 cigarettes/day, no significant increase in risk of esotropia was found for either boys or girls after adjustment for covariates. For children with exotropia, after stratifying by gender, the risk of exotropia was diminished and not statistically significant for either boys or girls of mothers who smoked either 1-19 or ≥20 cigarettes/day after adjusting for covariates (**Figure 2-2**).

DISCUSSION

In this large, diverse population-based cohort, esotropia (1.6%) was two-times more common than esotropia (0.6%) in the children diagnosed with strabismus, which is consistent with data that have indicated esotropia as the most common form of pediatric ocular deviations in Western countries.[6, 8] Overall, the risk of developing horizontal strabismus in this study were increased in children whose mothers smoked heavily (≥20 cigarettes/day) during pregnancy compared to those who did not smoke during pregnancy, after controlling for covariates. No significant association was found in children whose mothers consumed alcohol or coffee during pregnancy compared to those who did not drink. While the gender by maternal smoking interaction was not significant at the 0.05 level (P=0.1), results suggest possible differences in risk between boys and girls and the development of esotropia of mothers who smoked heavily during pregnancy, a finding that has not been previously reported in the literature. In this cohort of women from the Bay Area, the risk of esotropia appears higher in boys than in girls of women who smoked heavily during their pregnancy, an association not observed for exotropia.

While our primary analysis did not include children with severe abnormalities, (such as Down's or Duane's syndrome, which has been associated with an increased risk of strabismus), supplementary analyses which including the children with congenital abnormalities noted similar findings.

This study is in-line with previous findings from other population-based cohorts that have evaluated maternal cigarette smoking as a risk factor for strabismus, however our study has several strengths and differences over previous studies.[33-36] In addition to evaluating differences between boys and girls in the development of esotropia and exotropia, a particular strength was that exposure ascertainment to smoking, alcohol, and coffee occurred when information indicating that these exposures during pregnancy could lead to negative health outcomes in the offspring had not yet been established.[38-40] In contrast to current widespread knowledge regarding potential deleterious effects of smoking and drinking during pregnancy, women interviewed during the time of this study were not aware of these associations, which reduce the chance of reporting bias related to social stigma of these behaviors during pregnancy.

The ability to account for environmental smoke by adjusting for the amount of smoking by the husband was another strength of this study, which was not widely reported in other studies. In our study, 60% of the husbands were considered smokers during the time of interview. Even in women who did not smoke during pregnancy, half of the husbands were identified as smokers, representing a significant amount of second-hand smoke even in the women who did not smoke; 23% smoked 1-19 cigarettes/day, and 27% were heavy smokers at ≥20 cigarettes/day. While smoking levels for both

mothers and fathers were based on maternal report, these self-reported levels have been considered very reliable based on older studies from the CHDS comparing self-reported smoking levels to serum cotinine samples.[40-42]

Participation and attrition can generally be a problem in large, population-based prospective studies, even with intensive follow-up of the children. However, the participation rate among pregnant women in the CHDS was considered to be high, and mothers/children lost to follow-up were low. Less than 0.5% of eligible women refused to participate, and loss to follow-up was less than 8%. The CHDS include subjects that are ethnically and socioeconomically diverse, in contrast to other studies where the population is more homogenous.[12, 35, 36]

The effect of alcohol consumption during pregnancy on the risk of strabismus in the offspring has been explored briefly with inconsistent results. In one study, light to moderate drinking during pregnancy was associated with a significant decreased risk in strabismus in the offspring compared to those who did not drink, whereas heavy drinking did not affect the risk of strabismus.[36] Other studies have found no association.[34, 43] While a decreased risk in esotropia and exotropia was also observed for those who drank 4-7 drinks/day or ≥8 drinks/day during pregnancy in this study, the results were not statistically significant. Coffee consumption during pregnancy was not found to be associated with the risk of esotropia or exotropia in this study, even after adjustment for covariates, as was found in one other study that has examined maternal coffee consumption during pregnancy.[36]

Epidemiological research in recent years has indicated that experiences and exposures during fetal life may have long-lasting effects on the child and also into adult life. Large, population-based cohort studies like the CHDS have been key in studying diseases examining childhood outcomes, however like any epidemiology study, are not without limitations. The main drawback of conducting these studies is the dependence on available records, where diagnostic/evaluation assessments may be poorly recorded, considered outdated, or data that are simple not available. In this study, data on parental history of strabismus was not available, which limited the ability to account for genetic factors on the association of esotropia or exotropia. Additionally, data from the abstracted medical records did not always distinguish on the specific subtypes of strabismus, therefore analyses could only be conducted on the primary direction of the tropia. Despite the overall sample and cohort design, the small percentage of children with exotropia, especially when stratified by gender, may limit the power to detect small effects. Moreover, missing data on variables resulting in observations that were excluded in the regression analyses may also results in a potential loss of statistical power. However, subjects whose data were missing were similar in socio-demographic information to those that were included in the final regression models, except that those with missing data were more likely to be mothers who were on average, slightly older. While this is unlikely to cause serious bias to the results, it cannot be overlooked.

The mechanism of how in-utero exposure to cigarette smoke is linked to the development of strabismus is currently unknown, but may be related to fetal exposure to toxins in cigarettes that may result in physiological changes in the child. With the fetus

exposed via the placenta, direct toxicity to greater than 2,500 substances found in cigarettes, including carbon monoxide, ammonia, hydrogen cyanide, arsenic, vinyl chloride, and nicotine, may result in changes in the developing fetus.[44, 45] The genetic material of the fetus may also be directly damaged via maternal smoking. In a study comparing cytogenetic data between smokers and non-smokers, significant differences in structural chromosomal abnormalities, namely increased chromosomal instability of amniocytes, was observed in women who smoked regularly and during pregnancy compared to women who did not smoke (12.1% vs 3.5%, respectively).[46]

Hypoxia in the fetus from maternal smoking has also been related to several adverse outcomes resulting from abnormal structural changes to the placenta and consequent compromised fetal oxygen exchange and delivery.[47-49] Other mechanisms suggest impaired fetal oxygen delivery from the formation of carboxyhemoglobin in both maternal and fetal blood due to carbon monoxide exposure. Fetal hypoxia, when severe enough, can also be teratogenic.

The effect of maternal smoking exposure during pregnancy on low birth weight and small for gestational babies has been well-studied in the literature.[42, 50-54] Women who smoke are more likely to have infants that are of low birth weight (<2500 grams) or small for gestational age, which appears to increase with increasing consumption to smoking. Maternal cigarette smoking on the risk of strabismus, however, did not seem to be mediated by the effect of smoking on fetal growth, as the association was observed after controlling for birthweight/gestational age.

The effect of maternal smoking during the post-natal and early childhood years was not measured in this study, though it is likely that pre-natal smoking is a biomarker of childhood exposure to smoking as well. Studies have been reported suggesting that exposure to environmental tobacco smoke during the postnatal period may result in effects on cognitive, auditory processing, and other neurodevelopmental aspects of development in young children.[55-57] Future studies on the association of cigarette smoking with strabismus should attempt to separate the influences of in-utero exposure to cigarette smoking from post-natal exposure to environmental tobacco smoke (ETS) as well.

The variation in the prevalence of abnormalities according to gender has been reported, with boys generally having a higher prevalence overall than girls.[58-62] While severe abnormalities were excluded in the analysis for this study population, it is possible that other minor defects in development or abnormalities between boys and girls remain. Why gender deviations occur remain unclear, but depending on the abnormalities, may be related to urogenital morphogenesis or differences in sex hormones during fetal development (if occurring after gonadal differentiation), or possibly include errors in expression of X or Y-linked genes.[58] Additionally, other environmental mechanisms may be at play, as strabismus also presents in periods post infancy.

Distinct characteristics of esotropia and exotropia suggest that etiologies for their respective development differ. Esotropia tends to have an earlier onset in infancy and early childhood and tends to present as a more constant condition than exotropia. The innate divergence amplitudes tend to be weaker, resulting in poorer control of esotropia,

compared to a stronger fusional convergence with a stronger amplitude, which may explain why exotropia presents more intermittently.[63, 64] Because exotropia is usually acquired at a later onset time than esotropia, the impact of influences from in-utero and postnatal environmental risk factors on the developing fetus may differ for the two subtypes depending on the timing of the exposures. Additionally, while data on family history of strabismus was not available for the current study, recent evidence from twin studies suggest that genetic factors may be specific to the etiology of esodeviations of strabismus only, and negligible with no corresponding heritability for exodeviations.[65] These ideas provide additional evidence supporting distinct etiologies between esotropia and exotropia, and may also help suggest reasons for the differences seen in the current study.

Despite the known adverse effects of exposure to cigarette smoking on maternal and child health outcomes,[32, 58, 66] an estimated one-third to one-fourth of American women of reproductive age smoke cigarettes,[67, 68] with the prevalence of smoking during pregnancy reported to be approximately 14% in the United States,[68] well above the recommended 1.6% target set by the Healthy People 2020 objectives.[69] Moreover, studies using biochemical markers suggest studies based on self-reported smoking habits are likely to be underreported.[70-72] As such, the results of this study continue to support the need for smoking cessation recommendations during pregnancy.

In conclusion, this population-based study of childhood horizontal strabismus adds to the growing evidence of maternal smoking as a significant risk factor for esotropia and exotropia. We present new data suggesting that boys exposed to maternal

smoking may be at greater risk for esotropia than girls. Additional studies are needed to further evaluate the association between gender and horizontal strabismus in children.

Chapter 2, in part, was presented as a poster at the Pediatric Academic Societies (PAS) Annual Meeting in Washington, D.C. on May 4, 2013. The dissertation author was the first author of this poster: Carpiuc, Kimbach; Wingard, Deborah; Brody, Barbara; Macera, Caroline ; Klonoff-Cohen, Hillary; Ji, Ming; and Gahagan, Sheila. *Risk for Esotropia Increased in Boys Whose Mothers Smoked During Pregnancy.* Abstract 1503.19.

Chapter 2, in part is currently being prepared for submission for publication of the material. Carpiuc, Kimbach; Wingard, Deborah; Brody, Barbara; Macera, Caroline ; Klonoff-Cohen, Hillary; Ji, Ming; and Gahagan, Sheila. The dissertation author was the primary investigator and author of this material.

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Table 2-1. Distribution of smoking, alcohol, and coffee exposure of pregnant mothers: Child Health and Development Studies, Northern California Bay Area, 1959-1967

Characteristic	N	%
Maternal smoking during pregnancy		
None	9006	64.1
Light (1-19 cigarettes/day)	2781	19.8
Heavy (≥20 cigarettes/day)	1938	13.8
Paternal smoking during pregnancy		
None	4470	31.8
Light (1-19 cigarettes/day)	2942	20.9
Heavy (≥20 cigarettes/day)	3888	27.7
Maternal alcohol consumption during pregnancy		
None or <1/week	9257	65.9
1-3 drinks/day	1382	9.8
4-7 drinks/day	917	6.5
≥8 drinks/day	625	4.4
Maternal coffee consumption		
None or <1 week	3375	24.0
1-2 cups/day	3735	26.6
3-4 cups/day	2338	16.6
≥ 5 cups/day	2436	17.3

% totals may not add up to 100% due to missing data

Table 2-2. Multivariate analyses on risk for esotropia among 14,050 Bay Area children born 1959-1967, according to in-utero exposure to maternal risk factors

	Model 1		Model 2		Model 3	
Risk Factor	OR	(95% CI)	OR	(95% CI)	OR	(95% CI)
Maternal smoking status	n=13,724		n=11,844		n=9,414	
Never	1.00	[ref] ---	1.00	[ref] ---	1.00	[ref] ---
Former	1.26	(0.86-1.85)	1.19	(0.79-1.79)	1.26	(0.79-1.99)
Current	1.63	(1.22-2.18)	1.43	(1.02-2.02)	1.75	(1.18-2.61)
		P=0.004		*P*=0.116		*P*=0.020
Maternal cigarettes during pregnancy, cigs/day	n=13,642		n=11,824		n=9,363	
0	1.00	[ref] ---	1.00	[ref] ---	1.00	[ref] ---
1-19	1.10	(0.78-1.57)	1.05	(0.71-1.56)	1.23	(0.79-1.92)
≥20	2.16	(1.57-2.97)	1.84	(1.26-2.70)	2.31	(1.49-3.59)
		P<0.0001		*P*=0.005		*P*=0.001
Maternal alcohol consumption during pregnancy, drinks/day	n=12,105		n=11,824		n=9,363	
None or <1/week	1.00	[ref] ---	1.00	[ref] ---	1.00	[ref] ---
1-3	1.07	(0.68-1.67)	0.82	(0.52-1.29)	0.91	(0.56-1.48)
4-7	1.17	(0.70-1.96)	0.75	(0.43-1.30)	0.75	(0.40-1.40)
≥8	1.09	(0.58-2.05)	0.71	(0.37-1.36)	0.59	(0.27-1.25)
		P=0.926		*P*=0.528		*P*=0.486
Maternal coffee consumption, cups/day	n=12,206		n=11,824		n=9,363	
None or <1/week	1.00	[ref] ---	1.00	[ref] ---	1.00	[ref] ---
1-2	1.12	(0.76-1.66)	1.02	(0.67-1.52)	0.93	(0.60-1.45)
3-4	1.37	(0.90-2.08)	1.12	(0.73-1.74)	0.94	(0.58-1.54)
≥5	1.67	(1.12-2.49)	1.09	(0.69-1.70)	1.04	(0.63-1.71)
		P=0.057		*P*=0.953		*P*=0.961

Model 1: Adjusted for year of birth, birthweight/gestational age, infant gender
Model 2: Model 1 + maternal factors (maternal age, race, education, daily smoke, alcohol consumption, coffee consumption)
Model 3: Model 2 + paternal factors (paternal age, daily smoke, education)

Table 2-3. Multivariate analyses on risk for exotropia among 14,050 Bay Area children born 1959-1967, according to in-utero exposure to maternal risk factors

	Model 1		Model 2		Model 3	
Risk Factor	OR	(95% CI)	OR	(95% CI)	OR	(95% CI)
Maternal smoking status	n=13,586		n=11,772		n=9,626	
Never	1.00	[ref] ---	1.00	[ref] ---	1.00	[ref] ---
Former	1.48	(0.80-2.73)	1.49	(0.79-2.82)	1.31	(0.66-2.55)
Current	1.91	(1.19-3.06)	1.87	(1.10-3.18)	1.60	(0.90-2.81)
		P=0.028		*P*=0.070		*P*=0.274
Maternal cigarettes during pregnancy, cigs/day	n=13,504		n=11,712		n=9,279	
0	1.00	[ref] ---	1.00	[ref] ---	1.00	[ref] ---
1-19	1.35	(0.78-2.32)	1.36	(0.76-2.42)	1.31	(0.70-2.44)
≥20	2.43	(1.46-4.05)	2.33	(1.30-4.18)	2.14	(1.12-4.07)
		P=0.003		*P*=0.017		*P*=0.067
Maternal alcohol consumption during pregnancy, drinks/day	n=11,911		n=11,712		n=9,279	
None or <1/week	1.00	[ref] ---	1.00	[ref] ---	1.00	[ref] ---
1-3	1.21	(0.63-2.33)	0.96	(0.50-1.88)	1.07	(0.53-2.14)
4-7	0.95	(0.40-2.26)	0.74	(0.31-1.77)	0.79	(0.30-2.05)
≥8	0.64	(0.18-2.23)	0.44	(0.12-1.56)	0.56	(0.16-1398)
		P=0.818		*P*=0.581		*P*=0.776
Maternal coffee consumption, cups/day	n=12,092		n=11,712		n=9,279	
None or <1/week	1.00	[ref] ---	1.00	[ref] ---	1.00	[ref] ---
1-2	0.95	(0.51-1.79)	0.94	(0.50-1.76)	0.78	(0.40-1.54)
3-4	1.35	(0.70-2.60)	1.18	(0.60-2.33)	0.98	(0.47-2.02)
≥5	1.97	(1.09-3.55)	1.46	(0.75-2.84)	1.33	(0.67-2.66)
		P=0.056		*P*=0.550		*P*=0.514

Model 1: Adjusted for year of birth, birthweight/gestational age, infant gender
Model 2: Model 1 + maternal factors (maternal age, race, education, daily smoke, alcohol consumption, coffee consumption)
Model 3: Model 2 + paternal factors (paternal age, daily smoke, education)

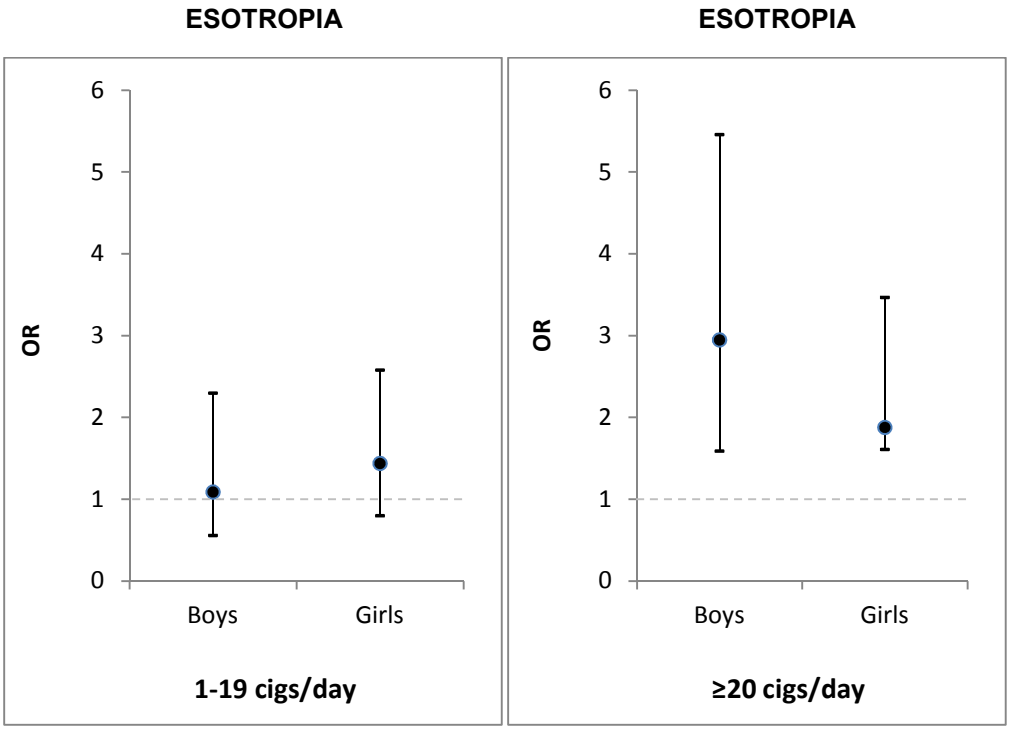


Figure 2-1. Multivariate ORs for maternal smoking during pregnancy and esotropia by gender and cigarettes smoked per day in a cohort of 7118 boys and 6932 girls from the Child Health and Development Studies compared to women who did not smoke during pregnancy. All models adjusted for infant year of birth, infant birthweight/gestational age, maternal age, race, education, alcohol consumption, coffee consumption, paternal age, daily smoke, and education.

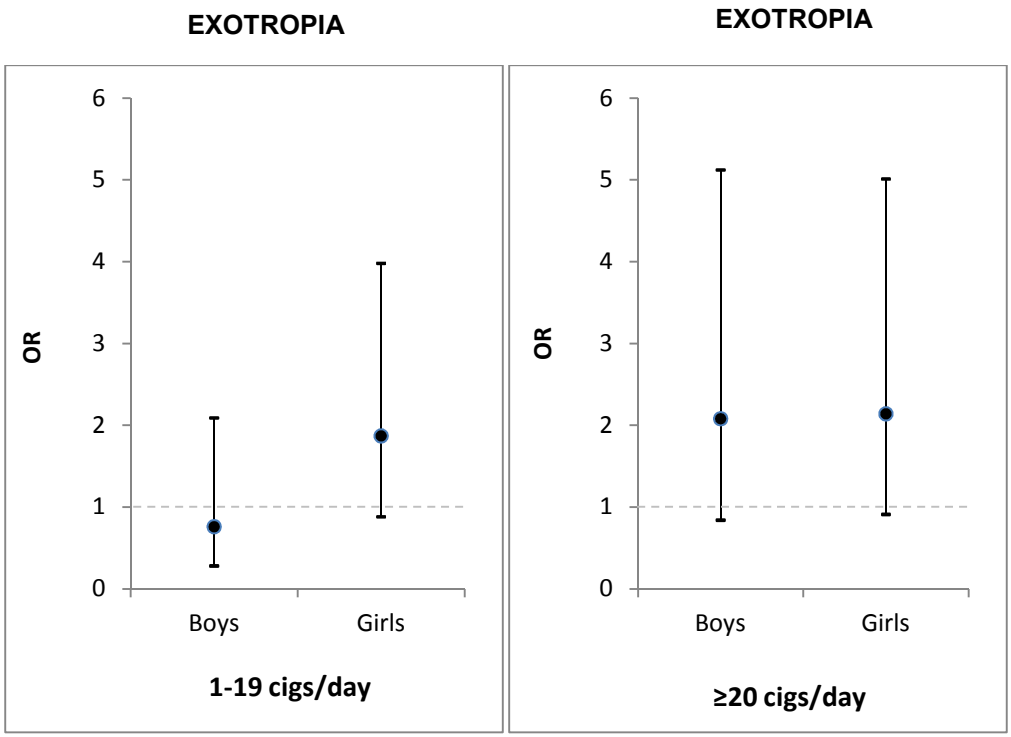


Figure 2-2. Multivariate ORs for maternal smoking during pregnancy and exotropia by gender and cigarettes smoked per day in a cohort of 7118 boys and 6932 girls from the Child Health and Development Studies compared to women who did not smoke during pregnancy. All models adjusted for infant year of birth, infant birthweight/gestational age, maternal age, race, education, alcohol consumption, coffee consumption, paternal age, daily smoke, and education.

CHAPTER 3

PERINATAL FACTORS FOR ESOTROPIA AND EXOTROPIA IN CHILDREN

Every child begins the world again.

Henry David Thoreau

ABSTRACT

Purpose : To examine perinatal factors for possible association with horizontal strabismus in a population-based cohort of children.

Methods: Data for 14,050 pregnant women and their children enrolled in the Child Health and Development Studies (CHDS) between 1959 to 1965 were analyzed for pregnancy and child developmental outcomes. Logistic regression models in children without severe anomalies were used to estimate the association of perinatal factors with esotropia and exotropia.

Results: A total of 309 boys and girls were found to have horizontal strabismus ; 225 (1.6%) with esotropia, and 84 (0.6%) with exotropia. After multivariate adjustment, the risk of esotropia and exotropia was not shown to be associated with perinatal risk factors, including delivery position, type of delivery, head circumference, fetal stress, or baby cry time.

Conclusions: Maternal complications before and during delivery, as well as fetal stress, may play no role in the development of esotropia or exotropia. Additional studies are warranted to better understand whether in-utero influences may impact the genotype of the growing fetus, and whether other environmental factors are linked to the development of strabismus in early childhood.

INTRODUCTION

Strabismus is a misalignment of the eyes, which produces deviation from the parallel nature of a normal gaze, and affects approximately 1-5% of the population.[1, 2] The eyes (one or both) may turn outward, inward, up, or down, and has often been referred to as "squint", "crossed-eyes", or "wandering eyes". The two major types of strabismus which affect the eyes horizontally include esotropia (where the eyes converge), or exotropia (where the eyes diverge).

The etiology of strabismus is currently poorly understood, with only a few studies looking at potential risk factors for strabismus, particularly environmental (biological, social, and life-style influences) risk factors. The prevalence of strabismus is higher in families where a parent or sibling has strabismus, indicating a possible genetic component.[3-5] Strabismus is also more prevalent in children with certain genetic, neurodevelopmental, or congenital conditions (e.g. Down's syndrome, Apert-Crouzon syndrome, Duane syndrome, and cerebral palsy).[6-10] Prematurity and low-birth weight have also widely been established as risk factors for developing strabismus.[11-24] Several studies have also indicated that maternal smoking has been associated with an increased risk as strabismus.[22, 23, 25-27] Few studies have investigated other perinatal risk factors for strabismus, with mixed results.[22, 23, 26]

Our study aimed to investigate the effects of maternal and child perinatal factors with the association with horizontal strabismus in a population-based sample of children.

PATIENTS AND METHODS

The Child Health and Development Studies (CHDS) are prospective longitudinal studies on the medical and social aspects of pregnancies and on the health and development of children. Data were collected on over 20,000 pregnant women from 1959 to 1967 and followed for pregnancy outcome. Key objectives of the CHDS since its inception has been to investigate the relationship of biologic, genetic, behavioral, and environmental factors in the parents – including events in pregnancy, labor, and delivery – to the development of the offspring.

The sample population for this study is based on singleton live births surviving past the neonatal period, excluding those identified with vertical strabismus (n=3), phorias (n=2), or types with unspecified direction (n=27). The present analyses focuses on children who did not have any severe congenital anomalies, resulting in 14,050 subjects for this study.

Data collection

Socio-demographic characteristics, reproductive and medical history, as well as smoking habits, were gathered from the women during pregnancy via in person interview. Information on pregnancy outcome, labor and delivery, newborn status, as well as any postpartum complications were abstracted from the medical records of the mother, including any notes or transcripts recorded by the medical staff during delivery. A variable indicating the condition/cry time of the infant at birth was used rather than the APGAR score, which was more consistently recorded at the time the data was collected.

Environmental exposure to cigarette smoking consumption were obtained through a number of questions which inquired about current smoking status, number of cigarettes smoked per day, as well as maternal-reported smoking habits of the father.

All information on the children, including birth weight and head circumference at birth, was obtained from abstraction of the infant's medical record. Any medical visit made by a child to either clinic, hospital, or health plan facility were recorded in the patient's medical record, including any diagnoses, treatments, as well as clinical or laboratory examinations or tests. Data were collected on all children for a minimum of 5 years after birth. If strabismus was suspected and/or detected by the pediatrician, patients were referred to ophthalmology for diagnosis and follow-up. All information abstracted on abnormalities, including strabismus, were reviewed by at least two CHDS physicians independently, and coded based on the seventh revision of the International Classification of Diseases assignment (World Health Organization, Geneva, Switzerland, 1967). Subsequent review of the abstracted medical charts noted any specific strabismus subtype identified in the record.

Data Analysis

Logistic regression for rare events using the Firth method was used to examine the independent association of the perinatal risk factors on strabismus. Due to differences in the characteristics and possible etiology of the two major subtypes of strabismus, all regression analyses were also conducted separately for children with esotropia and exotropia. Several covariates were considered a priori based on the existing published literature on possible risk factors associated with developing strabismus. Variables with

a significant association with esotropia or exotropia in univariate analyses, or those that created a greater than 10% change in the beta-estimate were included in the multivariate regression models.

All estimates were adjusted for year of birth to account for cohort effects in follow-up in the study population. To avoid collinearity, a variable combining both infant birth weight and gestational age in mutually exclusive categories was created (≥2500 grams/≥37 weeks; <2500 grams/≥37 weeks; ≥2500 grams/<37 weeks; <2500 grams/<36 grams). Statistically significant risk factors for esotropia or exotropia were indicated by a significance levels of $p<0.05$ and based on two-sided tests. Data were analyzed using SAS version 9.2 (SAS Institute Inc, Cary, NC).

RESULTS

A sample of 14,050 boys and girls were included in this study; of these, 7118 (49.3%) were girls. Of the 309 children in the study found to have horizontal deviations, 225 (1.6%) had esotropia, and 84 (0.6%) exotropia. The mean age of diagnosis for esotropia was 3.6 (±2.1) years, and 4.8 (±2.0) years for exotropia; the oldest child detected in the study population was 10.7 years. The mean age of the mothers was 27.3 ±5.8 years, with a diverse racial mix of 67% White, 25% Black, 4% Hispanic, and 7% Other (Asian, Native American, Mixed Race) women.

The majority (95.2%) of all babies in this cohort sample were delivered vaginally. Of these, 94.8% were delivered in the vertex position. While most babies and mothers did not report major complications during labor and delivery, 7.2% of babies experienced

fetal stress (indicated by cord prolapse, rupture of the uterus, fever before delivery, meconium staining amniotic fluid, or had an unusual/irregular fetal heart-rate), 1.7% of babies cried initially five minutes or more after delivery, and 2.7% of mothers hemorrhaged before delivery. Very few women (0.7%) had labor induced due to toxemia. Most babies were delivered at term, however some babies (7.6%) were born prematurely prior to 37 weeks of pregnancy; 2.3% of babies were born before 34 weeks. The mean birth weight was 3349 g (± 505 g), with approximately 4.4% of babies born extremely low birth weight (<2500 g). The mean head circumference of babies was 34.2 cm (±1.5 cm), with only 1.7% of infants born with a head circumference ≥37 cm.

Several socio-demographic factors were considered potential confounders for esotropia and exotropia, including maternal age, race, and education, as well as paternal age and education. Maternal and paternal smoking during pregnancy was also found to be associated with horizontal deviations of strabismus, and therefore included in multivariate models.

Following multivariate analyses controlling for socio-demographic variables, year of birth, birth weight/gestational age, infant gender, and parental smoking, no other perinatal characteristics were found to be significantly associated with an increased risk in esotropia or exotropia in this study population (**Table 3-1**).

DISCUSSION

In this population-based study of potential perinatal risk factors for esotropia and esotropia, head circumference, fetal stress, maternal hemorrhage before delivery, type of delivery, baby position during delivery, and baby cry time were not associated with an

increased risk for esotropia or exotropia after controlling for socio-demographic factors and parental smoking behavior during pregnancy.

While a myriad of studies have examined the risk of perinatal influences on the association of many childhood condition ranging from infectious and respiratory diseases, cancer, diabetes, to body mass index, behavioral, neurological, and psychological disorders,[28-37] few have studied the potential risk of these factors on the development of childhood strabismus. Very few have found an association with factors surrounding fetal stress or maternal complications during delivery to be associated with esotropia or exotropia.

In an analysis examining various characteristics in Danish children, neonatal asphyxia, caesarean delivery, and large head circumference were associated with an elevated risk of developing strabismus, however in further analysis which excluded children with congenital abnormalities, only large head circumference (≥38 cm) was found to be an independent risk factor for overall strabismus, after adjusting for birth weight and birth year.[27] In another study conducted in U.S. children born from 1959 to 1965, significant factors for both esotropia or exotropia in univariate analyses included nonspecific maternal uttering bleeding during the third trimester, duration of second stage of labor, APGAR scores, and respiratory abnormalities.[22] Nonspecific uterine bleeding during pregnancy, presentation at delivery, placental abrution or previa was also significantly associated with esotropia in univariate analyses. However, the authors did not portray results of these perinatal factors in multivariate analyses to account for potentially confounding variables. Results from the Millennium Cohort in the U.K. also

suggest several perinatal factors associated with an increased risk of isolated strabismus (maternal illnesses during pregnancy, abnormal fetal lie or duration, assisted or cesarean delivery, admission to special care baby unit, neonatal illness during first week of life), however only being born by assisted delivery remained significant in multivariate models.[26]

Several studies have reported an increased risk of strabismus associated with in-utero exposure to maternal smoking,[22, 23, 25-27] suggesting that development of strabismus may be at least in part associated with some environmental factors during the prenatal period. Yet while the overall causes of strabismus remain unclear, the results of this study and other published studies support the notion that perinatal and early postnatal factors are not likely to influence the association of esotropia or exotropia, particularly in children with strabismus unrelated to congenital abnormalities from neurodevelopmental conditions. With the exception of neonatal factors such as low birth weight and decreasing gestational age, which has previously been associated with childhood strabismus, [11-24] other factors related to events surrounding the time of birth have not been widely established. The etiology of strabismus, while currently not well understood, seems multifactorial with both environmental and genetic risk factors. A family history of strabismus has been associated with an increased risk for strabismus,[38-41] which may be specific to esodeviations and independent of refractive errors.[42] Other studies indicate possible etiologic differences between strabismus and latent phorias. Unfortunately, data on parental history of strabismus was not available for this current

study, which limited the ability to account for genetic factors in the current study population.

Pregnancy and childbirth can have a large influence on the physical, emotional, and quality of life well-being of mothers and their children. While the majority of women do not have complications during pregnancy or delivery, many mothers may still worry about whether or not factors surrounding these events may result in birth defects in their children. The results of this study do not support the association of maternal complications during pregnancy and delivery or signs related to fetal stress, on an increased risk of strabismus.

Epidemiological studies are necessary to evaluate the role of factors present around the time of birth in the association of strabismus in early childhood. Evidence from this population-based study suggest that maternal complications before and during delivery, as well as fetal stress from the baby, play no role in the development of esotropia or exotropia. Additional studies are warranted to better understand how in-utero influences may impact the genotype of the growing fetus, or whether other environmental factors are linked to the development of strabismus in early childhood.

Chapter 3, in part is currently being prepared for submission for publication of the material. Carpiuc, Kimbach; Wingard, Deborah; Brody, Barbara; Macera, Caroline ; Klonoff-Cohen; Ji, Ming; and Gahagan, Sheila. The dissertation author was the primary investigator and author of this material.

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Table 3-1. Risk of strabismus among Bay Area children born 1959-1967, according to perinatal risk factors*

Risk Factor	TOTAL HORIZONTAL STRABISMUS	
	Odds Ratio	95% CI
Head Circumference		
<33 cm	0.94	0.63-1.39
33-<35 cm	1.0 [ref]	---
35-<36 cm	0.83	0.60-1.16
≥ 37 cm	1.70	0.80-3.61
		P=0.317
Position		
Vertex	1.0 [ref]	---
Breech	1.49	0.81-2.72
Other[1]	0.33	0.02-5.42
		P=0.321
Fetal Stress[2]		
No	1.0 [ref]	---
Yes	1.15	0.73-1.80
		P=0.545
Maternal hemorrhage before delivery		
No	1.0 [ref]	---
Yes	1.24	0.63-2.42
		P=0.535
Type of delivery		
Vaginal	1.0 [ref]	---
Caesarean Section	0.82	0.41-1.63
		P=0.565
Baby Cry/Respiration		
Cried ≤5 minutes	1.0 [ref]	---
Cried >5 minutes	1.45	0.62-3.43
		P=0.393

* Adjusted for year of birth, birthweight/gestational age, infant gender, maternal age, race, education, paternal age, education, maternal and paternal smoking

[1] Compound, face, brow, or transverse position
[2] Cord prolapse, rupture of uterus, fever before delivery, meconium staining amniotic fluid, or unusual/irregular fetal heart rate

Table 3-2. Risk of esotropia and exotropia among Bay Area children born 1959-1967, according to perinatal risk factors*

Risk Factor	ESOTROPIA		EXOTROPIA	
	Odds Ratio	95% CI	Odds Ratio	95% CI
Head Circumference				
<33 cm	0.96	0.61-1.52	0.93	0.47-1.84
33-<35 cm	1.0 [ref]	---	1.0 [ref]	---
35-<36 cm	0.93	0.64-1.35	0.62	0.32-1.20
≥ 37 cm	1.99	0.89-4.48	1.27	0.26-6.32
		P=0.362		*P*=0.538
Position				
Vertex	1.0 [ref]	---	1.0 [ref]	---
Breech	1.30	0.62-2.71	2.29	0.90-5.84
Other[1]	0.43	0.03-6.97	1.40	0.09-21.35
		P=0.658		*P*=0.221
Fetal Stress[2]				
No	1.0 [ref]	---	1.0 [ref]	---
Yes	1.12	0.66-1.89	1.33	0.61-2.93
		P=0.678		*p*=0.474
Maternal hemorrhage before delivery				
No	1.0 [ref]	---	1.0 [ref]	---
Yes	1.12	0.50-2.49	1.81	0.62-5.27
		P=0.791		*P*=0.276
Type of delivery				
Vaginal	1.0 [ref]	---	1.0 [ref]	---
Caesarean Section	0.84	0.38-1.84	0.94	0.28-3.20
		P=0.662		*P*=0.336
Baby Cry/Respiration				
Cried ≤5 minutes	1.0 [ref]	---	1.0 [ref]	---
Cried >5 minutes	1.64	0.64-4.22	1.44	0.30-6.98
		P=0.305		*P*=0.651

* Adjusted for year of birth, birthweight/gestational age, infant gender, maternal age, race, education, paternal age, education, maternal and paternal smoking

[1] Compound, face, brow, or transverse position
[2] Cord prolapse, rupture of uterus, fever before delivery, meconium staining amniotic fluid, or unusual/irregular fetal heart rate

CHAPTER 4

THE PSYCHOSOCIAL AND HEALTH-RELATED QUALITY OF LIFE IMPACT OF STRABISMUS IN CHILDREN: A REVIEW OF THE LITERATURE

The part can never be well unless the whole is well.

Plato

ABSTRACT

Strabismus is characterized by a misalignment of the eyes, resulting in poor visual functioning due to by abnormal binocular vision and depth perception problems. Not only does strabismus affect physical functioning, but may also negatively impact the psychosocial well-being of a child, especially those with visibly noticeable or severe cases of strabismus. While safe and effective therapeutic options for strabismus exist, how these interventions affect the health-related quality of life (HRQoL) in children with strabismus has not been widely studied. The purpose of this review is to summarize the available evidence to characterize the social stigma and negative perceptions of childhood, describe the psychosocial implications related to strabismus in children and the effect on their families, examine the instruments that have been developed to measure vision-specific, HRQoL, and assess how interventions for strabismus impact the HRQoL burden of children.

INTRODUCTION

Strabismus is an anomaly of ocular alignment, resulting in a departure from the parallel nature of a normal gaze. Sometimes commonly referred to as "squint", "cross-eyes", or "wandering eyes", strabismus affects approximately 1-5% of the population.[1, 2] Left uncorrected, strabismus in children can result in amblyopia, a permanent vision loss in an otherwise normal eye. Strabismus can occur in one or both eyes and in any direction, with horizontal deviations (i.e., esotropia, where the eyes converge, and exotropia, where the eyes diverge) being the most common. Although the condition can develop at any age, the peak age of onset is around 3 years.[3, 4]

Vision problems related to the misalignment of the eyes include diplopia, lack of depth perception, and frequently concomitant refractive errors. Treatment goals for strabismus are thus aimed to improve ocular alignment, preserve or restore stereopsis and binocular vision, prevent amblyopia, and produce a more orthotropic ("normal") appearance.[5] Specific therapies may vary depending on the subtype due to differences in etiology, though surgical procedures to correct ocular muscles are common.[6] Non-surgical therapies to correct and manage alignment and visual impairment may be addressed by eyeglasses,[7-9] occlusion or pharmacologic therapy (e.g,. miotic drops, botulinum toxin),[10-13] as well as vision training.[14]

Aside from the physical and possible cognitive effects of strabismus,[15] evidence from the literature indicates that strabismus can have a negative impact on the social and emotional well-being of a child and their caregivers. This review aims to highlight the published literature in order to characterize the perceptions of strabismus from peers and

adults, describe the psychosocial impact of strabismus in children and their families, examine instruments that have been developed and validated to measure vision-specific, health-related quality of life (HRQoL), and assess how treatments for strabismus affect HRQoL.

STRABISMUS-RELATED PERCEPTIONS AND SOCIAL BIAS

Children with chronic illnesses are likely to experience lower self-esteem than their healthy peers, especially those whose condition are related to a visible defect.[16] Children with visual defects are at increased risk to be bullied by their peers.[13] Anecdotal evidence from case-studies report that children with strabismus are subjected to insensitive comments and ridicule from other children and adults, resulting in poor self-image, self-esteem, and impaired relationships.[17, 18] The following papers described in this section explore the social stigma that strabismus has on young children in larger study populations.[19-25] Using modified dolls or digitally-altered photographs, investigators created experiments using a simulated environment to determine whether or not there are pre-conceived perceptions from peers and adults, the age in which negative attitudes emerged, and whether a difference in perception between those with esotropia or exotropia exist.

Despite slight differences in study design and methodology, several studies indicate that negative attitudes towards strabismus can occur in children as young as 5 years old.[19, 22, 24] In a study U.S. by Paysse *et al* (2001), the eyes of three identical dolls

were modified to create one esotropic, one exotropic, and one orthotropic (eyes with normal alignment) doll. Thirty-four children ages 3-7 years were then placed in a room and privately observed regarding preferences and behaviors towards the dolls.[19] Children ages 3 to 4 ¼ did not notice a difference in the dolls and those ages 4 ½ to 5 ¼ expressed that the eyes were "different", but did not show a preference of one doll over the other. However, by age 5 ¾, children in the study gave a negative description of the dolls with strabismus when asked.

Lukman *et al* (2011a) also investigated whether biases were present in children aged 5-6 years in Kuala Lumpur, and whether that could lead to social-alienating behaviors related to strabismus.[22] Digital-altered images of children with exotropia (where the prevalence is higher than that of esotropia in Malaysia) were paired with images of children with orthotropia. A total of 129 kindergarteners were asked to chose the image they liked and would share their favorite toy with. The children expressed an overall preference for those with orthotropic eyes, and a preference for giving the toys to the peers with orthotropic eyes. Further analysis indicated that children tended to give toys to the faces that they preferred. Another study by Lukman *et al* also investigated whether social biases towards children with strabismus persisted in 157 children aged 8-12.[23] Results again indicated that children were less willing to sit next to a child with noticeable exotropia, however the magnitude of the effect was weaker in older study subjects, perhaps due to increasing awareness of social desirability response bias as children mature.

Mojon-Azzi and colleagues in Switzerland also present data that support the findings by Paysse *et al* and Lukamn *et al* that negative attitudes towards strabismus emerges around age 6.[24] Digitally-altered images of "twins" were created, which were identical except for the color of their shirt and position of their eyes, and shown to 118 children aged 3-8 as six pairs of photographs. For each twin pair, the children were asked to select one of the twins to invite to a birthday party. Results indicated that children age 4-6 noticed a difference between an orthotropic and a strabismic eye, however it was not viewed negatively in that age group. Children with noticeable strabismus were less likely to be accepted by peers aged 6 and older, and the older the child, the less number of children with strabismus they would theoretically invite in this study.

In contrast, results from Johns *et al* (2005) were not in line with other studies that indicated a negative social bias towards children with strabismus.[21] Digitally-altered photographs were created of children age 3-8 with varying magnitudes of strabismus, hairstyles, shirt color, and gender; two different books with 15 pairs of images (one orthotropic child, and another child with strabismus) were created. One hundred children were asked to select a playmate from each pair. The authors found that the distribution was almost even between those that were orthotropic and those with strabismus. Moreover, no significant difference was found between direction of strabismus, nor numbers of playmates chosen for each magnitude of strabismus. Playmate selection was not predicted by age in this study population. While there were limited responses, those that provided comments supported the concept that other items were more important than

eye alignment in selecting a playmate, such as perceived personality through clothing and hair styles.

The possible negative social bias against children with strabismus does not appear to be unique to their peer age group. Uretman *et al* (2003) investigated the perceptions of 30 elementary school teachers in Turkey on children with noticeable strabismus using digitally-altered photographs of children aged 8-10 with esotropic, exotropic, and orthotropic eyes.[20] The teachers were assessed with a scaled 10-item list of personal characteristics (intelligence, health, trustworthiness, hard-work capacity, happiness, cuteness, hesitancy, aggressiveness, activeness, and sentimentally) and five additional questions related to their initial impressions created by the pictures. The teachers rated the personal characteristics more negatively for children with strabismus in all 10 characteristics; which was significantly lower for health, capacity for hard-work, and happiness. Results also indicated that teachers perceived that it would be harder for children with strabismus to be accepted in a peer social group, and that children with esotropia were rated more negatively than those with exotropia.

Children in another study by Mojon-Azzi *et al* (2011) also viewed esotropia more negatively than exotropia, although the perception of strabismus by adults in the study was not influenced by the direction of strabismus. [25] However, both adults and children perceived a right eye deviation to be more disturbing than a left eye deviation.

The negative impact of strabismus on adults based on similar theoretical situations using digitally-altered photographs to create images of individuals with strabismus has been observed, further providing evidence that a social bias may continue

to persist into adulthood. One study reported that college students tended to judge individuals with strabismus more negatively across 11 descriptive personality characteristics than those without strabismus, specifically for esotropia.[5] Other studies have reported that strabismus can impact the ability of find a partner ,[26] as well as hindering an applicant's ability to obtain employment.[27, 28]

HEALTH-RELATED QUALITY OF LIFE (HRQoL) ASSESSMENTS FOR USE IN CHILDHOOD STRABISMUS

In the mid 1940s, the World Health Organization defined *health* as "a state of complete physical, mental and social well-being, not merely the absence of disease or infirmity".[29] Since then, concepts of quality of life, specifically health-related quality of life (HRQoL), have become increasingly used in clinical and outcomes research.[30] HRQoL is a broad, multi-dimensional construct used to describe the burden of a medical condition and/or the impact of treatments on a patient. HRQoL measures, or instruments, include domains related to physical, social, and role functioning, as well as psychological and overall general health, and are frequently used to help guide health care professions in clinical decision-making as well as policy and health economic assessments. While some studies may use HRQoL and psychosocial functioning interchangeably, for this review, HRQoL will refer to the more comprehensive assessment of health.

HRQoL measures can be generic, designed to be used across all medical conditions or diseases, interventions, and varied study populations, whereas specific

HRQoL measures are designed to focus on specific issues related to the particular health condition or population.[31] In ophthalmology, generic instruments, while useful to generate health profiles and utilities, may not be sensitive enough to detect specific characteristics manifested by specific conditions such as strabismus, and may be unresponsive to changes following therapeutic interventions. Specific HRQoL instruments, on the other hand, can be disease, population, function, and/or problem specific.

The development of valid HRQoL instruments is growing increasingly important for use in clinical research and management of chronic conditions, especially in assessing health status over time. While many HRQoL vision-related instruments have been identified in ophthalmology,[32-40] very few have been specific to strabismus. Questionnaires have historically been produced to quantify the impact of strabismus and/or their subsequent treatment on a patient for a specific study,[41-45] and while providing useful information to capture the experience of the patient, have not been rigorously developed. Only recently have strabismus-specific instruments been created and validated, including the Amblyopia and Strabismus Questionnaire (A&SQ),[46-49] Adult-Strabismus Questionnaire (AS-20),[50, 51] and the Intermittent Exotropia Questionnaire (IXTQ).[52, 53] Of these, only the IXTQ has been developed and validated for use in children.

Assessing HRQoL in children with strabismus has been not widely studied, partly due to methodological issues in developing vision-related or strabismus-specific HRQoL instruments in children. In general, HRQoL in children can be very difficult to measure

conceptually. Domains not only need to cover specific elements related to the child's illness, but also to their physical, social, and psychological development. In addition, a child's health status interacts with their development, especially in those with chronic conditions. Measures targeted towards children also need to be worded and constructed appropriately to reflect their developmental level of understanding and feasibility of use. While some studies have used instruments derived for adults (such as the widely established National Eye Institute Visual Functioning Questionnaire [NEI-VFQ-25]), not all items may not be appropriate for use in children. Moreover, challenges exist due to the need for a proxy responder in young children, as questions arise as to whether assessments made by parents and guardians are considered valid.

The number of vision-related instruments developed and validated specifically for measuring visual functioning in children are thus scarce: only the Children's Visual Function Questionnaire [54, 55] and the Vision Quality of Life Questionnaire [56] were found. With regards to generic HRQoL instruments, only the Pediatric Quality of Life Inventory (PedsQL) was found to be validated in a pediatric strabismus population. An overview of these instruments can be seen in **Table 4-1** and described briefly below.

The Children's Visual Function Questionnaire (CVFQ) was developed as a vision-specific quality of life instrument designed for use in young children age 7 and under.[54, 55] The questionnaire contains measurements to assess four quality of life domains: Competence, Personality, Family Impact, and Treatment Difficulty. Due to the young age of the children, the questionnaire is completed by proxy from a parent or guardian. Two age-specific versions of the CVFQ were generated, one for children <3

years and one for children aged 3-7 years, and contain 34 and 39 items, respectively. Respondents have the choice to choose from a 5-point Likert-type scale or mark "not applicable to my child" for each question. This was the only instrument that was found to that was able to assess vision-specific HRQoL in toddlers under age 3.

The Intermittent Exotropia Questionnaire (IXTQ) is a child-specific questionnaire developed based on concerns brought up from interviews of children with intermittent exotropia and their parents.[52, 53] Three versions of the questionnaire were derived: (1) a self-reported child version, to address the child's own HRQoL, (2) a proxy form parallel to the child questionnaire addressing the parent's perception of the child's HRQoL, and (3) a parent version to address the parent's own HRQoL. Moreover, separate questionnaires were developed for children aged 5-7 and 8-7 years. The final child and proxy versions contain 12 items, and the parent version 17 items, with Likert-type scales utilized for the responses. Initial validation has been carried out, with additional validation efforts planned, but looks to be a promising measure to assess the HRQoL related to intermittent exotropia in clinical and research settings.

The Pediatric Quality of Life Inventory™ (PedsQL) Version 4.0 is a well established and widely used instrument to assess HRQoL in children.[57-59] Not only has it been used in pediatric populations with both acute and chronic health conditions, but can also be used in healthy community and school populations. The PedQL contains a generic core measure, with many condition-specific modules developed to complement the Generic Core Scales for use in specific clinical populations. While no vision or strabismus-specific module has yet been developed, the PedsQL has recently been

explored for use in children with intermittent exotropia.[60, 61] The generic measure contains 23 items, and can be used for children ages 2-18 years. A child self-report form is available for children ages 5-7, 8-12, and 13-18 years, and a parent-proxy report available for children ages 2-4, 5-7, 8-12, and 13-18 years. A 5-point Likert-type scale was also used for responses.

The use of the IXTQ and the PedsQL was examined by Hatt *et al* (2010) in a population of 51 children to determine which instrument would best be able to detect HRQoL related to strabismus in children with intermittent exotropia.[61] The authors indicated that the Proxy IXTQ and Child IXTQ had a higher proportion of subnormal scores than the Proxy PedQL and Child PedsQL. In comparing median scores between children with strabismus vs healthy controls, patients with intermittent exotropia scored worse on the Proxy IXTQ ($P<0.0001$), Child IXTQ ($P=0.04$), and Proxy PedQL ($P=0.04$), however no significant difference was found between patients and controls on the Child PedsQL ($P=0.3$). Parents of children with intermittent exotropia have reported worse HRQoL than parents of health controls, which may be driven by a high degree of parental worry about strabismus.[53] It is possible that using the generic instrument may not be sensitive enough to detect differences in HRQoL scores that may be higher using self-reports. The IXTQ, particularly the Proxy IXTQ, may thus be a more useful clinical assessment in children with intermittent exotropia than using the PedsQL.

McKeon and colleagues developed the Vision Quality of Life Questionnaire to assess the impact of intermittent exotropia in both children and adults.[56] It includes both the 20-Item Short Form Health Survey (SF-20), a generic HRQoL measure, and the

Vision Quality Scale (VQS), developed by the authors to assess vision-specific issues. The questionnaire was mailed to children and adults between 8-46, and found to have acceptable internal consistency, as well as being able to discriminate vision function between patients with and without intermittent exotropia. This measure was intended to be self-reported, with no distinction is made for separate child and parent versions.

PSYCHOSOCIAL AND HRQOL BURDEN OF CHILDHOOD STRABISMUS

Due to recent development, not many vision-related or strabismus-specific instruments have been used in epidemiological or clinical research studies to assess the burden of childhood strabismus and/or its treatment. While the majority of studies in the published literature have used study-specific surveys or generic measures to assess the burden of strabismus in children, their families, or the impact from therapeutic interventions,[44, 62-68] some did use vision or strabismus-specific instruments to depict the experience by the children and their families (**Table 4-2**).[69-71]

In Children

While early documents have commented on the possible negative effects of strabismus in children with case-reports,[18, 72, 73] few studies have characterized the psychosocial implications of childhood strabismus in recent literature.[62-64, 69] These studies, while varied in study design and assessments, collectively report that children with uncorrected strabismus are more likely to experience adverse effects that include

concerns with interpersonal relationships, self-image issues, social and school phobias, mental-health problems, as well as overall decreased HRQoL compared to children that do not have strabismus. The ages varied widely in these studies, from parent-reports on children in preschoolers (aged 25-72 months),[69] elementary aged children,[64] to older teens and adults reporting on their own experience with strabismus from childhood.[62]

In a subjective assessment from 43 subjects with a history of childhood strabismus, Satterfield *et al* (1993) assessed the psychosocial impact of strabismus that was uncorrected or incompletely corrected past age 13 years.[62] Individuals self-reported on a 25 item questionnaire that addressed the medical background, previous eye/strabismus problems, treatment, as well as the effects of strabismus and treatment on friendship, ridicule, and self-esteem with regards to three age periods: childhood, teenage years, and as an adult. The Hopkins Symptom Checklist (HSC), a 58-item psychological inventory, was also completed to measure the general current psychological state of the subject on domains of somatization, obsession-compulsion, interpersonal sensitivity, depression, and anxiety. Patients reported that the presence of strabismus interfered with friendships, caused ridicule, and affected self-image, as well as having significantly higher levels of distress as measured by the HSC overall ($P<0.01$) than in age- and sex-matched normative controls. Results also indicated that problems occurring in childhood persisted as the subject got older, and may be more difficult to deal with in teenage and adult years.

Two studies found in the literature indicated that patients with strabismus may have a higher rate of mental-health issues than those without strabismus.[63, 64] In a

retrospective chart review of subjects residing in Olmsted County, Minnesota, a mental-health disorder was diagnosed for 41.3% of 407 individuals diagnosed with a history of childhood strabismus, compared to only 30.7% of birth-and gender-matched controls from the same population (P=0.002). Specifically, those with intermittent exotropia were significantly more likely to develop a psychiatric disorder than controls when monitored to age 20.3 years (OR=3.1, 95% CI: 1.9-5.1).[63] Investigators in Turkey, using self-reported assessments in children 8-13 years, also found significantly higher total scores using the Children's Depression Inventory (CDI) and Screen for Child Anxiety Related Emotional Disorders (SCARED) in 42 children with severe uncorrected strabismus compared to controls with refractive errors only, and specifically in areas of social phobia, separation anxiety, and school phobia using the SCARED assessment.[64]

Using the Pediatric Quality of Life Inventory (PedsQL), researchers from the Multi-ethnic Pediatric Eye Disease Study (MEPEDS) noted a significantly worse HRQOL in 121 preschool children aged 25-72 months with uncorrected strabismus compared to those without strabismus (n=4,097) in both physical and psychosocial domains, after controlling for age, gender, race, and family income (P<0.01). In this population-based study, psychosocial sub-domains, emotional and school functioning were significant (P<0.01), however, there was no significant difference in social functioning score between children with and without strabismus.[69] As the children in the MEDPEDS study were relatively young, the impact of strabismus on social interactions may change as the children grow older.

Among Parents

Chronic illnesses in children have been known to affect not only the child's physical and emotional well-being, but result in increased levels of parental stress that is associated with adverse psychological adjustment in their caregivers.[74] Family systems theory suggest that a problem or change in any member of the family affects the entire family, and consequently, any ramifications of a chronic illness in the child are felt throughout the whole family.[75] Thus, the psychosocial implications of having strabismus in young children are likely to extend to their families as well, though very few studies have been published to quantify the impact. Guardians of children with strabismus in urban and rural India indicated a high proportion of parents negatively affected by strabismus in children, with high proportions of families experiencing distress due to strabismus or other people's remarks, extreme worry, and difficulty to cope.[43] Two studies were identified that explored the quality of life differences in parents of children with strabismus compared to families without strabismus (**Table 4-2**).

A Turkish study by Akay *et al* (2005) found mothers of children with strabismus with higher depressive indices, poorer family relationships, and more problems in family functioning than in mothers of children without strabismus, as measured by the Beck Depression Inventory (BDI), State-Trait Anxiety Inventory (STAI), Parental Attitude Research Instrument (PARI), and Family Assessment Device (FAD).[65] Mothers had significantly higher depression scores (P=0.042), lower scores in democratic attitude encouraging a supportive and sharing relationship (P=0.0001), and higher rejection of maternal role (P=0.017) than mothers of healthy controls. Mothers of children with strabismus also had significantly poorer role functioning (P=0.034), affective

responsiveness (P=0.003), and general functioning (P=0.04) than mothers of children without strabismus. Another study assessing the impact of intermittent exotropia on the HRQoL of parents by Yamada *et al* (2011) found significantly lower scores in the overall composite, as well as all three subscales (function, psychosocial, and surgical) of the Parent Intermittent Exotropia Questionnaire (Parent IXTQ) than in parents in children with normal vision (all P<0.0001).[70] However, no significant differences were found in the scores for the Pediatric Quality of Life Family Impact Module (PedsQL FIM) scores.

Before and After Treatments

Several studies have reported on the positive effects in older teens and adults following therapy for strabismus, namely surgery.[41, 42, 44, 45, 76, 77] Significant improvements in physical and psychosocial health were seen, which was also observed in the few studies conducted in young children with strabismus. Three studies explored the impact from surgical interventions on the HRQoL in children with strabismus, [66, 68, 71] and one from occlusion therapy (**Table 4-3**).[67]

Children may derive clinical, psychosocial, and HRQoL benefits from surgery even if they do not always meet the endpoints for surgical success. Mruthyunjaya *et al* (1996) surveyed the parents of 77 children under age 6 to assess the parent's perceptions on the pre-operative, surgical, and post-operative experience of their child undergoing surgery.[68] Overall, the majority of parents were satisfied with the results of surgery; 85% parents noted that their satisfaction was "good" or "very good". Even though many patients (32/77, 41.6%) were deemed to have unsuccessful surgical outcomes (did not achieve alignment within 10Δ of orthotropia), 72% of parents of children with surgical

failures still reported “good” or “very good” satisfaction. Despite not meeting the objective endpoints for success, noted improvements in ocular alignment due to reduced deviation may have resulted in the high levels of parental satisfaction. A modest but significant correlation was observed between subjective satisfaction and objective alignment within 10Δ of orthotropia ($P<0.001$) as well as a change in alignment ($P=0.0009$). In small children under 4 years, 61% of parents reported improved eye contact, and 94% improved appearance. Approximately half of the children 4-6 years also were noted to have improved peer interactions and self-esteem.

Archer *et al* (2005) were also able to note positive psychosocial benefits in children following strabismus surgery. Using the RAND Health Insurance Study instrument, parents or guardians of 95 children (mean age 4.5 ± 3.3 years) were interviewed before and 2 months post-operatively on the impact of the surgery on their children. Significant improvements in HRQoL scores were observed for functional limitations, anxiety, depression, social relations, general health perceptions, current health, resistance/susceptibility, developmental satisfaction, and eye alignment concerns (all $P\leq0.01$). No significant difference was seen in the positive well-being, prior health, and parent -child closeness subscales. Three-fourths of the children achieved surgical successful endpoints (residual deviation of <10Δ), yet no significant difference between the improvement in HRQoL scores between children that had a successful surgery and those that did not were seen. Similar to the Mruthyunjaya study, parents may have perceived improvements in many HRQoL areas for changes in deviation that did not

reach the defined measure for surgical success. Moreover, a placebo effect with strabismus surgery cannot be ruled out.

A small prospective study in China also demonstrated improvements in HRQoL in children undergoing surgery using a National Eye Institute Visual Functioning Questionnaire (NEI-FVQ-25), a widely established vision-related quality of life instrument that has not been previously used in children or adults with strabismus.[71] Significant improvements were noted following surgery in the overall, anxiety, and depression scores of the NEI-FVQ-25 as reported by parents for 60 strabismus children under age 15 years.

The psychosocial and HRQoL impact of one non-surgical intervention was found in the literature. Kim *et al* (2013) evaluated the behavioral and psychosocial effects of part-time occlusion therapy in 25 children aged 3-7 with intermittent exotropia in Korea.[67] Alternate or monocular patching was prescribed in 17 and 8 children, respectively, for 2-4 hours, depending on the age of the child. Following occlusion therapy, children in the study had significantly lower attention problems (P=0.012), as reported by the parents using the Korean Child Behavior Checklist (K-CBCL). The somatic problem domain was the only area found to be significantly correlated with compliance as assessed by the Amblyopia Treatment Index (ATI)(P=0.01), no other correlation was seen between the domains of the K-CBCL and the ATI instruments. Furthermore, no significant differences were observed in the Parenting Stress Index scores (PSI) pre- and post-occlusion therapy.

DISCUSSION

While the above studies presented in this review indicate significant differences in the psychosocial and broader HRQoL aspects of childhood strabismus, some caution should be noted before making definitive conclusions. The diverse populations, including differences in study subjects with regards to age, type, and magnitude of strabismus, methodological variation, as well as assessments and outcomes measured do not lend to direct comparisons between study samples. As strabismus does not affect a large population of children, the number of children and families able to be studied is usually small, with large, population-based studies scarce.

Available studies seem to note certain aspects of a child's HRQoL may improve following therapies for strabismus, however further research is necessary due to certain limitations presented by these studies. Studies examining the impact of surgery and occlusion therapy for strabismus were conducted in young children, thereby requiring proxy reporting by parents and caregivers. Additionally, the studies had relatively small samples, relied on a variety of assessments, including some that were not initially developed for the studied population (use of the NEI-FVQ-25, a measure indicated for adults, in children,[71] or the ATI for amblyopia, used for children with strabismus).[67] Non-response bias may have affected some of the results,[66,68] and the duration of therapy was not reported in the occlusion therapy study, [67] which would provide a better evaluation of the results. Despite these limitations, the available literature still provide worthwhile information on the psychosocial benefits of strabismus therapies, the challenges, and issues that may arise, such as non-compliance with patching.

The focus of this review was to examine the available evidence on the psychosocial and HRQoL impact of strabismus in children. Data regarding the effects of amblyopia are limited but are also becoming increasingly studied as well. While some children may have amblyopia that is caused by strabismus and have similar outcomes, this review aimed to look at only the impact of strabismus alone, and therefore did not include studies in children specifically with amblyopia. Unpublished studies, data presented only in scientific congresses, and articles not available in English were not included in this review. Overall, compared to other health conditions, the number of studies evaluating HRQoL in children with strabismus is still limited.

While many HRQoL measures exists for the adult population, studies involving children have only recently found their place in quality of life research. Although increased interest has been directed towards this special population, there are still a relatively small amount of outcome measures developed for children due to several conceptual and methodological issues. In addition, while attention continues to grow in this field for generic and some common or important disease-specific conditions, there is little consideration for childhood conditions that are more uncommon or are not life-threatening. Nonetheless, as with more common health conditions, health-related outcome measures to gauge functional and psychosocial status in childhood conditions such as strabismus are still extremely important, especially in assessing interventions. Using generic HRQoL measures may not be sensitive enough to characterize specific issues, and using established adult measures may not be developmentally appropriate.

One challenge in developing childhood assessments surrounds the issue of needing to use parents as proxy respondents. The agreement between parent and child-reported assessments are typically reported to low. Divergence between patient and parent-reported assessments in the strabismus population was also observed.[61] Many questions within quality of life research for assessments in children has been brought forth as a result of low to modest levels of agreement between parent and child.[76, 78] Can parents be reliable proxies? Are children able to accurately report their own health status? Who should be asked; which is more accurate? One view places more emphasis on the information as provided by the parents, as the validity of self-reports from children on their HRQoL is often questioned, for they may be too young or too sick to respond accurately. While the relationship between child and parent self-reports has not been widely studied, some reports have found them to be differentially sensitive for behavioral and psychological assessments. Some authors have noted that parents tend to report more overt, objective aspects of child's behavior, whereas children are better at reporting more covert, subjective feelings and experiences.[76, 79]

On the other hand, there is a growing consensus that the primary source of quality of life information should come from the patient,[78, 80-83] as parents may be confounded by their own emotional state regarding their child's illness. Others have suggested that young children would still be able to provide valuable information, as they may be able to judge their present functional status better than their caregivers.[84]

Historically, self-reports from children have been regarded with some skepticism in the medical community, yet relying solely on proxy reports may provide an incomplete

understanding of the patient's experiences. Instruments that generate information from both self- and parent-reports can be used to give a cohesive and comprehensive understanding of the patient's HRQoL.[76] Where possible, comparing and contrasting the reports from both patients and parents may elucidate other issues contributing to the overall quality of life in these families.

While differences in study methodologies and outcomes make interpretations regarding the body of evidence challenging, this review highlights the HRQoL and psychosocial burden in childhood strabismus, and the related stress that may be experienced by their caregivers. As the impact of strabismus can be long-lasting and can worsen with increasing age and severity, early intervention is critical whenever possible. Quantifying the effect of strabismus on HRQoL and psychosocial functioning is noteworthy to highlight the successful outcomes in order to advocate for positive peer-relationships and self-esteem in children with strabismus. Moreover, improved communication between clinicians and parents regarding strabismus, available therapies, and outcomes may also reduce the uncertainty and psychological distress experienced by their families.[85] Despite the difficulties of studying this patient population, future studies should aim to develop and utilize additional standardized, well-validated measures to assess and better understand the overall HRQoL burden of strabismus in children.

Chapter 4, in part is currently being prepared for submission for publication of the material. Carpiuc, Kimbach; Wingard, Deborah; Brody, Barbara; Macera, Caroline; Gahagan, Sheila; and Klonoff-Cohen, Hillary. The dissertation author was the primary investigator and author of this material.

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Table 4-1. Summary of validated HRQoL instruments for children with impaired visual function

Instrument	HRQoL measure	Age of use in children	Number of items	Domains or subscales	Mode of administration	Response scale
CVFQ [54, 55]	Vision-specific HRQoL	≤7 y	<3 y: 34 3-7 y: 39	Competence Personality Family Impact Treatment Difficulty	Written questionnaire; Parent-proxy	5-point Likert-type
IXTQ [52, 53, 61]	Strabismus-specific HRQoL (IXT)	5-17 y	Child: 12 Proxy: 12 Parent: 17	Global health General vision Competence Personality Family Impact Treatment	Written questionnaire; Self, proxy, or parent-report	5-7 y: 3-point Likert-type 8-17 y: 5- Likert-type Likert
PedsQL [57-61]	Generic HRQoL, validated in IXT	2-18 y	23	Physical functioning Emotional functioning Social functioning School functioning	Written questionnaire; Self-report , parent-proxy	5-point Likert-type
Vision Quality of Life Questionnaire [56]	Includes SF-20 (general HRQoL) and VFS (Vision-specific)	≥ 8 y	SF-20: 20 VFS: 9	Psychological well-being Health perception Role functioning Physical health Pain Visual function	Written questionnaire; Self-report	SF-20: 3, 5, and 6-point Likert-type VFS: 5 and 6-point Likert-type

CVFQ = Children's Visual Function Questionnaire; HRQoL = Health-related quality of life; IXT = intermittent exotropia; IXTQ = Intermittent Exotropia Questionnaire; PedsQL=Pediatric Quality of Life Inventory; SF-20 = 20-Item Short Form Health Survey; VFS = vision function scale

Table 4-2. Psychosocial and HRQoL implications of strabismus in children and families compared with children that do not have strabismus

Study	Subjects (n)	Age range	Strabismus type/ magnitude	Sample selection	Assessments (administered method)	Outcomes measured	Key results
Children							
Satterfield 1993 [62] *U.S.*	STR=43	15-81 y; mean age 38 y	ET=49%, XT=51%; mean 25 Δ	Computer search of patients aged ≥15 y seen in opht center with hx of uncorrected or incompletely corrected childhood strabismus after 13 y	Survey, HSC (self-report)	Interpersonal relationships, ridicule, self-image, psychological inventory (somatization, obsession-compulsion, interpersonal sensitivity, depression, anxiety)	63% felt STR interfered with school, work, play or sports as a child, and 84% as a teen, 85% as adult. Approximately half of subjects experienced ridicule due to STR, which persisted in adulthood. STR had a negative effect on self-image, which was more prevalent in teen years and adulthood than in childhood. Compared with age- and sex-matched HSC normative controls, those with STR had higher somatization, obsession-compulsion, interpersonal sensitivity, depression, and anxiety (P<0.01).
Mohney 2008 [63] *U.S.*	STR=407; controls= 407	<19 years; ET dx mean 3.9 y, monitored to mean 15.8 y; XT dx mean 7.8 y, monitored to mean 20.3 y	ET=65% XT=35%	Retrospective medical record review of children aged <19 y diagnosed with strabismus from 1985-1994	DSM-V codes, chart review	Diagnosis of mental illness, use of psychotropic medication, mental health ED or hospitalizations, suicide attempts, suicidal or homicidal ideation	Mental health disorder dx for 41.3% of pts with hx of STR, compared with 30.7% of birth- and gender-matched controls (P=0.002). Children with STR more likely to have a greater number of psychiatric disorders (P=0.003), use psychotropic medications (P=0.004), required psychiatric hospitalizations (P=0.04), and have suicidal ideation (P<0.0001). There was a significant difference in forms of STR; children with XT were 3.1x more likely to develop a psychiatric disorder than control (95% CI: 1.9-5.1). Children with ET did not have an increased risk than controls.
Wen 2011 [69] *U.S.*	STR=121; non-STR controls =4,097	6-72 mo, assessed only children ≥ 25 mo	1-9Δ=9%, 10-30 Δ=65%, >30Δ=17 %	Multi-ethnic, population-based study of preschool children	PedsQL (parent-report)	Generic HRQoL (Physical, emotional, social, and school functioning)	After controlling for age, gender, race, and family income, children with STR had significantly lower general HRQoL scores in both physical and psychosocial domains (P<0.01). In psychosocial sub-domains, emotional and school functioning were significant (P<0.01), however there were no significant difference in social functioning score between children with and without STR (p=0.06).
Cumurcu 2011 [64] *Turkey*	STR=42; refractive error controls= 47	8-13 y; STR mean 10.36 y; control mean 10.67 y	ET=61%, XT=38%; all >30Δ	Patients follow-up for strabismus in outpatient eye clinic	Kiddie-SADS-PL (structured interview), SCARED (self-report), CDI (self-report)	Social phobia, anxiety, depression	More patients with STR had depressive disorders and social phobias than controls, but samples were small to detect significance. CDI scores were higher for STR than controls (P=0.001). SCARED scores for STR were significantly higher for total score (P=0.004), social phobia (P=0.0001), separation anxiety (P =0.004), and school phobia (P=0.05) than in controls. No significant difference in panic or general anxiety.

Table 4-2. Psychosocial and HRQoL implications of strabismus in children and families compared with children that do not have strabismus, *Continued*

Study	Subjects (n)	Age range	Strabismus type/ magnitude	Sample selection	Assessments (administered method)	Outcomes measured	Key results
Families							
Akay 2005 [65] *Turkey*	STR=30; control s=31	STR children: 2-8 y, mean 6 y; mothers: 27-39 y, mean 31 y; control: 3-8 y, mean 6 y, mothers: 24-35 mean 31 y	ET=83% XT=17%	Random selection from the epidemiologic catchments area of University hospital	BDI, STAI, PARI, FAD (all interview)	Depression, anxiety, parental attitude/adjustment measure, family functioning	Mothers of children with STR have significantly higher depression scores (P=0.042), lower scores in democratic attitude (be an equalitarian and be in a friendship relationship with their child) (P=0.0001), and higher rejection of maternal role (P=0.017) than mothers of healthy controls. Mothers of children with strabismus had significantly higher scores in roles (P=0.034), in affective responsiveness (P=0.003), and in general functioning (P=0.04).
Yamada 2011 [70] *U.S.*	STR=59; control s=29	STR children: 3-16 y, median 7; control: 5-13 y, median 8 y	All IXT; median distance 25Δ, median near 16Δ	Prospectively recruited from outpatient clinic	Parent IXTQ, PedsQL FIM (self-report)	IXT HRQOL (functioning, psychosocial, surgical), general HRQOL (physical, emotional, social, cognitive functioning, communication, worry, daily activities, family relationships)	Parent IXTQ scores were worse in the IXT group than visually normal controls for the composite as well as function, psychosocial, and surgical subscales (P=0.0001), however were not significantly different in PedsQL FIM scores for the composite score or 8 subscales. Comparing proportions of subjects scoring below normal thresholds, more parents of children with IXT scored below normal with the Parent IXTQ than with the PedsQL FIM , P=0.008).

Δ = prism diopters; BDI = Beck Depression Inventory; CDI = Children's Depression Inventory; Dx = diagnosis; ED = emergency department; ET = esotropia; HSC = Hopkins Symptom Checklist; Hx = history; IXT = intermittent exotropia; Kiddie-SADS-PL=Schedule for Affective Disorders and Schizophrenia for School-Aged Children-Present and Lifetime Version; NR = not reported; opht = ophthalmology; Parent IXTQ = Parent Intermittent Exotropia Questionnaire; PARI = Parental Attitude Research Instrument; PedsQL FIM = Pediatric Quality of Life Inventory Family Impact Module; SCARED = Screen for Child Anxiety Related Emotional Disorders; STAI = State-Trait Anxiety Inventory; STB = strabismus; XT = exotropia; y = years

Table 4-3. Summary of studies assessing the impact of treatments for strabismus in children

Study	Subjects (n)	Age	Strabismus type	Intervention	Assessments (mode of administration)	Outcomes measured	Key results
Archer2005 [66] *U.S.*	98	Mean 4.5 (±3.3) y	ET=66% XT=28% VD=6%	Surgery	Modified RAND Health Insurance Questionnaire (Telephone, parent-proxy)	Function limitations, anxiety, depression, positive well-being, social relations, general health perceptions, current health perceptions, resistance/susceptibility, prior health, satisfaction with development, eye alignment concerns, parent-child closeness	Statistically significant differences in pre- and 2 months post-operative QoL scores seen in subscales of functional limitations, anxiety, depression, social relations, current health perceptions, resistance/susceptibility, satisfaction with development and eye alignment concerns (all $P \leq 0.01$). No difference in positive well-being, prior health, and parent-child closeness scales. 74% achieved deviation of <10Δ ("surgical success"). No difference in scores between those who had a successful outcome and those who did not.
Chai 2009 [71] *China*	STR=60, Healthy controls =60	<15 years HP: mean 8.3 (±2.8) y HT: mean 8.4 (±2.6) y	HP=50% HT=50%	Surgery	NEI-VFQ-25, HADS (Telephone, parent-proxy)	NEI-VFQ-25: General health, general vision, ophthalmological pain, near vision, distance vision, social function, mental problems, social role, dependency, color vision, peripheral vision; HADS: anxiety and depression in hospital setting	Those with HP or HT significantly worse domains of in all subscales of the NEI-VFQ-25 compared to age- and gender-matched health controls, though scores in domains of ophthalmological pain, social role, and color vision general health were not statistically different. Significant improvements seen for anxiety, depression, and NEI-VFQ-25 summary scale pre- and 2 months post-operatively for both heterotropia and heterophoria patients (all $P<0.05$).
Kim 2013 [67] *Korea*	25	Mean 4.7 y (range 3-7)	All IXT>15Δ	Occlusion therapy	K-CBCL, ATI, PSI (Parent-report)	K-CBCL: Withdrawal, somatic problems, depression/anxiety, social, thought, attention problems, delinquent & behavior; ATI: adverse effect, compliance, social stigma; PSI-parent: sense of competence, attachment, role restriction, depression, social isolation, spouse relationship, health; PSI-child: adaptability, mood, demandingness, acceptability, reinforces parents, hyperactivity / distractibility	After occlusion therapy, only attention was significantly decreased ($P=0.012$) as measured by the K-CBCL. Scores on the compliance item of the ATI were highest, indicating that parents have trouble getting the child to carry out therapy. Somatic problems (including fatigue, aches, nausea, vomiting, headaches, dizziness, and complaints about skin, stomach, and eye problems) assessed by the K-CBCL and compliance significantly correlated ($P=0.014$). No significant difference pre-and post-therapy were observed between change in PSI scores for any subscales for either the Parent of Child domains ($P=0.382$).

Table 4-3. Summary of studies assessing the impact of treatments for strabismus in children, *Continued*

Study	Subjects (n)	Age	Strabismus type	Intervention	Assessments (mode of administration)	Outcomes measured	Key results
Mruthyunjaya 1996 [68] *U.S.*	77	<6 y	NR	Surgery	Parental survey (Telephone, parent-proxy)	Parent's satisfaction with strabismus treatment, relationship of treatment satisfaction with clinical outcomes	Overall satisfaction: 85% "good" or "very good". Correlations between subjective satisfaction and objective alignment within 10Δ of orthophoria significant (P<0.001). Coordination considered improved in 56%. In children <4 y, 61% parents report improved eye contact and 94% improved appearance. In children 4-6 y, 47% note improved peer interactions and 55% improved self-esteem. Satisfaction and positive outcomes reported even in cases deemed unsuccessful.

Δ = prism diopters; ATI = Amblyopia Treatment Index; ET = esotropia; HADS = Hospital Anxiety and Depression; HP = heterophoria; HT = heterotropia; IXT = intermittent exotropia; K-CBCL = Korean Child Behavior Checklist; NEI-VFQ-25 = National Eye Institute Visual Functioning Questionnaire; NR = not reported; PSI = Parenting Stress Index; STR = strabismus; VD = vertical deviation; XT = exotropia; y = years

CHAPTER 5

DISCUSSION AND CONCLUSIONS

The journey of a thousand miles begins with a single step.

Lao Tzu

Discussion

Strabismus is a relatively common vision problem in children with potentially debilitating effects, yet literature from large, population-based studies examining factors associated with the presence or development of strabismus are limited. Identification of strabismus in early childhood suggests that events occurring during the pre-natal and perinatal period might be important in understanding the pathogenesis of strabismus. Studies carried out in this field are important to guide health care providers involved in the care of pregnant women, as well as for pediatricians and ophthalmologists who treat and manage children with strabismus.

This dissertation was undertaken with the goal of better understanding possible factors associated with the development of strabismus, as well as to review the available literature on the psychosocial and HRQoL implications of having strabismus in young children, in order to add additional evidence to the current field of pediatric ophthalmology and strabismus.

Summary of findings

Study #1: The association of in-utero maternal smoking, alcohol, and coffee with childhood horizontal strabismus

Overall, the risk of developing esotropia or exotropia were increased in children whose mothers smoked heavily (≥20 cigarettes/day) during pregnancy compared to those who did not smoke during pregnancy, after controlling for covariates. Results using data from the CHDS, a large, population-based study indicate no significant association was

found in children whose mothers consumed alcohol or coffee during pregnancy compared to those who did not drink. This study is in-line with previous findings from other population-based cohorts that have evaluated maternal cigarette smoking as a risk factor for strabismus,[1-4] and adds to the inconsistent body of evidence with regards to alcohol. [4] [2, 5] Only one other study was identified that has examined maternal coffee consumption during pregnancy as a possible factor in the association with strabismus, which also found no association.[4]

Children who were born to women who smoked heavily during pregnancy in this study were significantly associated with a risk of developing esotropia, an association which appears higher in boys than in girls. Boys born to mothers who smoked ≥20 cigarettes/day during pregnancy had an almost 3-fold increased risk of esotropia (OR=2.95, 95% CI: 1.59-5.46) compared to boys whose mothers did not smoke during pregnancy. Girls whose mothers smoked ≥20 cigarettes/day during pregnancy were associated with a nearly 2-fold increased risk for esotropia (OR=1.88, 95% CI: 1.61-3.47) compared to girls whose mothers did not smoke during pregnancy.

While the gender and maternal smoking interaction was not statistically significant, additional studies are needed to evaluate this association, as variation in the prevalence of abnormalities according to gender have been reported, with boys generally having a higher prevalence overall than girls.[6-10] Moreover, distinct characteristics between esotropia and exotropia suggest that etiologies for their respective development differ, indicating the continued need to carry out large population studies with sufficient power to explore the association with various subtypes by gender.

Study #2: Perinatal factors for esotropia and exotropia in children

Data from the CHDS were also used to explore perinatal factors for esotropia and exotropia, including maternal and fetal complications before and during delivery, such as hemorrhage before delivery, delivery position, type of delivery, indicators for fetal stress, head circumference, and baby cry time. Following multivariate analyses controlling for socio-demographic variables, year of birth, birth weight/gestational age, infant gender, and parental smoking, no other perinatal characteristics were found to be significantly associated with an increased risk in esotropia or exotropia in this study population.

While the overall causes of strabismus remain unclear, the results of this study and other published studies support the notion that perinatal and early postnatal factors are not likely to influence the association of esotropia or exotropia, particularly in children with strabismus unrelated to congenital abnormalities from neurodevelopmental conditions. With the exception of neonatal factors such as low birth weight and decreasing gestational age, which has previously been associated with childhood strabismus, [1, 11-23] other factors related to events surrounding the time of birth have not been established.

Study #3: The psychosocial and health-related quality of life impact of strabismus in children: a review of the literature

The third study, as presented in Chapter 4, summarizes the published literature on the impact that strabismus has on the psychosocial well-being and health-related quality of life (HRQoL) in children. By examining the available evidence, the review collectively highlights the social stigma and negative perceptions of strabismus in

children by peers as well as adults, describes the psychosocial implications related to strabismus in children and the effect on their families, identifies the instruments that have been developed to measure vision-specific, HRQoL, and assesses how interventions for strabismus impact the HRQoL burden in children.

Anecdotal evidence from case-studies report that children with strabismus are subjected to insensitive comments and ridicule from other children and adults, resulting in poor self-image, self-esteem, and impaired relationships.[24, 25] Several psychological studies utilized modified dolls or digitally-altered photographs to create a simulated environment to determine whether or not there are pre-conceived perceptions from peers and adults.[26-32] Most studies indicated that negative attitudes towards strabismus seemed to emerge around the age of 6, which may result in decreased social interactions.[29-31] One study did not find a negative social bias towards children with strabismus, with results supporting the concept that other items were more important than eye alignment in selecting a playmate, such as perceived personality through clothing and hair styles.[26] Children with strabismus may be perceived negatively by adults as well.[33]

Few studies have characterized the psychosocial implications of childhood strabismus in recent literature. While varied in study design and assessments, these studies collectively report that children with strabismus are more likely to experience adverse effects that include concerns with interpersonal relationships, self-image issues, social and school phobias, mental-health problems, as well as overall decreased HRQoL compared to children that do not have strabismus.[33-36] Additionally, strabismus not only impacts the lives of the children with the visual impairment, but also increases distress and role functioning in their caregivers as well.[37, 38]

While many HRQoL measures exist for the adult population, studies involving children have only recently found their place in quality of life research. Although increased interest has been directed towards this special population, there are still a relatively small amount of outcome measures developed for children due to several conceptual and methodological issues. The number of vision-related instruments developed and validated specifically for measuring visual functioning in children were scarce,[39-41] indicating a significant gap in the needs of measuring HRQoL in children with strabismus. In addition, few studies were identified quantifying the impact of treatment on HRQoL, however overall results suggest significant improvements in physical and psychosocial health, especially with surgical interventions.

Strengths and Limitations

There are several strengths and limitations for using the CHDS data to examine the possible associations of in-utero and perinatal risk factors as reported in Chapters 2 and 3. One particular strength for using the CHDS dataset in studies looking as possible factors associated with childhood strabismus, is that exposure ascertainment to certain environmental factors, including cigarette smoke, alcohol, and coffee, occurred when information indicating that these exposures during pregnancy could lead to negative health outcomes in the offspring had not been established.[42-44] In contrast to current widespread knowledge regarding potential deleterious effects of smoking and drinking during pregnancy, women interviewed during the time of this study were not aware of these associations, which reduce the chance of reporting bias related to social stigma of

these behaviors. The ability to account for environmental smoking by adjusting for the amount of smoking by the husband was another strength in the study.

Participation and attrition can generally be a problem in large, population-based prospective studies, even with intensive follow-up of the children. However, the participation rate among pregnant women in the CHDS was considered to be high, and mothers/children lost to follow-up were low. Less than 0.5% of eligible women refused to participate, and loss to follow-up was less than 8%. The CHDS include subjects that are ethnically and socioeconomically diverse, in contrast to other studies where the population is more homogenous.[3, 4, 23]

The main drawback of using the CHDS was the dependence on available records, where diagnostic/evaluation assessments for strabismus was not well-recorded. Because the CHDS was not originally designed to study eye outcomes, reliance on medical records was necessary, yet detailed information regarding diagnosis was not consistently coded. Data on parental history of strabismus was not available, which limited the ability to account for genetic factors on the association of esotropia or exotropia. While data from the CHDS provide valuable information, it did not assess things which maternal and child health epidemiologists would consider important now (e.g., breastfeeding habits, pre-eclampsia, etc).

Additionally, data from the abstracted medical records did not always distinguish on the specific subtypes of strabismus, therefore analyses could only be conducted on the primary direction of the tropia. Despite the overall sample and cohort design, the small percentage of children with strabismus, especially when stratified by subtype and gender, may limit the power to detect small effects. Moreover, missing data on variables

resulting in observations that were excluded in the regression analyses may also results in a potential loss of statistical power.

The review of the psychosocial and HRQoL of strabismus in children was meant to highlight the currently available evidence in the literature, and therefore was not a systematic review with strict inclusion and exclusion criteria for the included publications. With the overall limited amount of articles, the information for most papers was presented, however the heterogeneity of the study population and methodology warrants caution with no definitive conclusions to be made. Additionally, due to limitations in resources, only one researcher was able to review the available literature. While a highly targeted search with carried out, which included manual cross-referenced citations of retrieved papers, search of abstracts from scientific and psychological conferences were not conducted. Additionally, unpublished studies and papers not in English were not included in the review, which may have resulted in a publication bias in the included studies.

Future Directions

Growing evidence suggests maternal exposures during pregnancy have long-lasting effects on the child. Additional epidemiological studies are needed in the field of pediatric ophthalmology, especially in childhood strabismus, to better understand the role of in-utero and perinatal factors with the association of strabismus. With the relatively low prevalence of strabismus in a population, large cohort studies with sufficient samples and adequate power are needed to analyze the different strabismus subtypes, and examine possible gender differences. As it is likely that the development of childhood strabismus

is multi-factorial, studies looking at both genetic and environmental factors need to be carried out to study how in-utero influences may impact the genotype of the growing fetus, or whether other environmental factors such as postnatal secondhand smoke exposure are linked to strabismus in early childhood.

As discussed in Chapter 2, despite the known adverse effects of exposure to cigarette smoking on maternal and child health outcomes,[6, 45, 46] an estimated one-third to one-fourth of American women of reproductive age smoke cigarettes,[47, 48] with the prevalence of smoking during pregnancy reported to be approximately 14% in the United States,[48] well above the recommended 1.6% target set by the Healthy People 2020 objectives.[49] Moreover, studies using biochemical markers suggest studies based on self-reported smoking habits are also likely to be underreported.[50-52] As such, the results of the first study continue to support the need for smoking cessation recommendations during pregnancy.

Although a large body of scientific evidence exists on the adverse effects of cigarette smoke exposure, there is still much to learn with regards to the understanding of how this exposure affects possible pathogenesis from a molecular and cellular level. As cigarette smoke contains an enormous amount of toxic substances, better delineation of the substances and how they impact the growing fetus should be studied. Assessing whether cigarette smoke causes damage at the DNA level during the critical period of brain and eye development would be worthwhile. Research is needed to better understand the biological mechanisms underlying possible differences in strabismus subtypes.

Despite the conceptual and methodological challenges of developing instruments to measure vision-specific, HRQoL in children, additional assessments to supplement the few instruments available are needed in order to better understand the overall HRQoL burden of strabismus, as well as to quantify the impact of interventions. Future research must take into account discrepancies in child vs parent reporting by utilizing multiple formats where possible. Research examining possible gender differences in the psychosocial impact of childhood strabismus would also be valuable to determine whether or not the implications of having strabismus vary between boys and girls, especially as body image and self-esteem is typical in adolescent development, particularly among girls. Moreover, because the negative implications of strabismus can persist into adult, early identification and correction is warranted, as is a more concerted effect to reduce strabismus-related social biases throughout the community. The economic benefits associated with treatment for strabismus in children has not been conducted, but deserve study as well.

Concluding Remarks

In 1949, ophthalmologist Stewart Duke-Elder made the following claims regarding the impact of strabismus:[33, 53]

> These psychological effects, indeed, may be very potent. A squint is an ugly thing and young people are pitiless and heartless to a degree. It is certainly the case that the cross-eyed child readily becomes the butt of its fellows at school and the ridicule so often showered upon him may warp his psychology with permanent results to an extent which is not always appreciated.

Without a doubt, children with strabismus not only suffer from the physical effects of strabismus, but as we have assessed as part of this dissertation, significant psychosocial

effects as well. Strabismus is not a cosmetic problem, therefore surgical interventions to treatment strabismus should not be considered cosmetic, but rather to restore normality.[54] Improvements in visual functioning are observed with early interventions, and though the literature is scarce, suggest improvements on the HRQoL burden as well. Although strabismus is not considered a life-threatening condition affecting children, it still has serious implications on the life and development of a child and warrants more attention in the research community.

Despite the growth in the field of pediatric ophthalmology over the past few decades, there are many unanswered questions regarding childhood strabismus. Many opportunities exist for pediatricians, ophthalmologists, and epidemiologists to add to the current knowledge of strabismus in children in order to better understand, manage, and improve the lives of the children and the families that it impacts.

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