Fetal Alcohol Spectrum Disorders in Children and Young Adults

with an emphasis on ophthalmology

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To my beloved mother, Siv Gyllencreutz

To see a World in a Grain of Sand
And a Heaven in a Wild Flower,
Hold Infinity in the palm of your hand
And Eternity in an hour.

William Blake

ABSTRACT

Introduction: Fetal alcohol spectrum disorders (FASD) are a group of disorders caused by prenatal alcohol exposure (PAE). The most severe and most studied FASD condition is fetal alcohol syndrome. Other conditions include partial fetal alcohol syndrome and alcohol-related neurodevelopmental disorder. Longitudinal reports based on individuals with FASD are few, especially ophthalmological studies. **Aims and Methods**: The overall aim of this thesis was to describe the long-term consequences of FASD; both in general *(Paper I)* and with an emphasis on ophthalmological findings *(Paper II–IV)*. A total of 71 children adopted from eastern Europe to Sweden were examined by a multidisciplinary team in 2000–2001; 37 of them (13 female [f], median age 8 years [y]) were diagnosed with FASD. Of these 37, 36 were reassessed in 2014–2019 (13 f, median age 22y). A social, medical, psychiatric, psychological, and an ophthalmological evaluation, which included visual acuity, refraction, binocular function, motility, slit lamp examination, optical coherence tomography, structured history-taking of visual perception, and questionnaires regarding quality of life (QoL) were performed. A group of 29 healthy young adults (20 f, median age 25 y) were recruited as controls in *Paper III* and *IV*. **Results**: *Paper I*: 14/36 had attended special education, 20/36 were dependent on social welfare or disability pension, 22/32 showed gross motor coordination abnormalities, 29/32 had psychiatric co-morbidity, and 7/32 had attempted suicide. Mean intelligence quotient was low in both childhood (86) and young adulthood (68) (n=29). *Paper II*: Ophthalmological findings such as astigmatism (14/30), strabismus (13/30), and optic nerve abnormalities (11/30) were common. Findings from childhood persisted into young adulthood. *Paper III*: The peripapillary and macular nerve fiber layers were thinner in the FASD group than in the controls. *Paper IV*: Visual perception problems were more common in the FASD group, and self-reported health-related and vision-related QoL scores were lower than in the controls. **Conclusion**: These long-term follow-up studies show that the young adults with FASD in our cohort have general health problems including psychiatric disorders, impaired cognitive function, poor QoL, and ophthalmological conditions such as astigmatism, strabismus, structural abnormalities, and VPPs. The long-lasting effects of PAE must be considered when evaluating young adults with complex health issues. Given the high frequency of ophthalmological aberrations, an ophthalmological evaluation of individuals with FASD is important in both childhood and early adulthood.

Keywords: Fetal Alcohol Syndrome, Optic Nerve, Optical Coherence Tomography, Strabismus, Vision, Visual Perception, Quality of Life

Fetala alkoholspektrumstörningar hos barn och unga vuxna

med tonvikt på ögon och synfunktion

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SAMMANFATTNING

Introduktion: Fetala alkoholspektrumstörningar (FASD) är en övergripande term för funktionsstörningar som orsakas av att fostrets utsatts för alkohol i mammans mage. Någon gräns för hur mycket alkohol ett foster tål har inte kunnat fastställas. Det allvarligaste och mest studerade tillståndet är fetalt alkoholsyndrom (FAS). Denna avhandling omfattar individer med såväl FAS som partiellt fetalt alkoholsyndrom (PFAS) och alkoholrelaterade utvecklingsneurologiska avvikelser (ARND). FASD har tidigare främst studerats hos barn. Det finns få långtidsuppföljningar, särskilt uppföljningar i vilka det gjorts ögonundersökningar.

Syften och Metoder: Huvudsyftet med avhandlingen var att beskriva de långsiktiga konsekvenserna vid FASD, generellt och med inriktning mot ögon och synfunktion. En grupp om 71 barn deltog år 2000–2001 i en studie med anledning av deras adoption från Östeuropa till Västsverige. I samband med detta bedömdes 37 av dem ha FASD, de var då mellan 5 och 11 år gamla. Dessa 37 är nu unga vuxna och tillfrågades om att deltaga i en uppföljning vilken genomfördes 2014–2019, deltagarna var då mellan 19 och 28 år gamla. Genom att använda resultaten från undersökningar gjorda av en tvärvetenskaplig forskargrupp bestående av barnneurolog, neuropsykolog, psykiater, ögonläkare och ortoptist studerades hälsan hos denna grupp av unga vuxna med FASD. Avhandlingen omfattar fyra olika delarbeten. Jämförelser har gjorts gentemot såväl undersökningsfynden hos samma individer i barndomen som mot en kontrollgrupp bestående av 29 unga vuxna i samma åldersspann men utan FASD.

Resultat: Av de 37 individer som i barndomen bedömdes ha FASD bidrog 36 individer med information i någon utsträckning i uppföljningen. Fjorton av dessa 36 hade gått i särskola. En hög andel (20/36) fick sin försörjning genom bidrag. Många (29/32) hade någon form av psykisk åkomma, 7 av 32 hade försökt att ta sitt liv. IQ-nivån var förhållandevis lägre i ung vuxen ålder jämfört med i barndomen. Därtill var individerna med FAS både som barn och som unga vuxna korta och hade ett litet huvudomfång. Ögonundersökning visade att ögonavvikelser (så som skelning och avvikande synnerv) som hittades vid undersökningen i barndomen kvarstod upp i ung vuxen ålder. Näthinnan och synnerven studerades och resultaten från de unga vuxna med FASD jämfördes med samma strukturer hos kontrollgruppen. Mätningarna visade att de unga vuxna med FASD som grupp hade lika stora synnerver men ett tunnare lager av nervfibrer än de unga vuxna i kontrollgruppen. Visuella perceptionsproblem och livskvalitet hos unga vuxna med och utan FASD undersöktes. Visuella perceptionsproblem kan vara att ha svårt att känna igen ansikten och föremål, att orientera sig i nya omgivningar och att bedöma höjdskillnader och avstånd. Denna typ av problem var betydligt vanligare i FASD-gruppen (16 av 30) jämfört med i kontrollgruppen (1 av 29) och därtill var den självrapporterade livskvaliteten i FASD-gruppen lägre.

Slutsatser: Unga vuxna med FASD är en heterogen grupp och omfattar individer med en varierande symtombild. I vår undersökningsgrupp kvarstod tillväxthämningen upp i ung vuxen ålder, psykiska besvär var vanligt och sju personer hade försökt ta sitt liv. Majoriteten av de unga vuxna med FASD hade något som avvek från det normala när en grundlig ögonundersökning genomfördes. En del ögonavvikelser funna i barndomen hos denna grupp kvarstod upp i tidig vuxenålder. Ögats nervfiberlager hos FASD-gruppen var tunnare än hos kontrollerna och förekomsten av visuella perceptionsproblem var betydligt högre. Vid undersökning av unga vuxna med komplexa hälsoproblem utan känd orsak bör alkoholexponering under graviditet finnas i åtanke. Effekterna av alkoholexponering under fosterlivet kräver djupgående studier och dessa studier behöver omfatta många individer för att minska risken att sålla fram samband som beror på slumpen. Med tanke på att avvikande fynd vid ögonundersökning är vanligt hos både barn och unga vuxna med FASD så är en noggrann och riktad ögonundersökning viktig i båda åldersgrupperna.

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LIST OF PAPERS

This thesis is based on the following studies, which are referred to in the text by their Roman numerals.

I. Landgren V, Svensson L, **Gyllencreutz E**, Aring E, Andersson Grönlund M, Landgren M.
Fetal alcohol spectrum disorders from childhood to adulthood: a Swedish population-based naturalistic cohort study of adoptees from eastern Europe.
BMJ Open. 2019;9(10):e032407.
doi:10.1136/bmjopen-2019-032407

II. **Gyllencreutz E**, Aring E, Landgren V, Svensson L, Landgren M, Andersson Grönlund M.
Ophthalmologic Findings in Fetal Alcohol Spectrum Disorders - A Cohort Study from Childhood to Adulthood.
Am J Ophthalmol. 2020;214:14-20.
doi:10.1016/j.ajo.2019.12.016

III. **Gyllencreutz E**, Aring E, Landgren V, Landgren M, Andersson Grönlund M.
Thinner retinal nerve fibre layer in young adults with foetal alcohol spectrum disorders.
Br J Ophthalmol. 2020 Jul 3: bjophthalmol-2020-316506.
doi:10.1136/bjophthalmol-2020-316506

IV. **Gyllencreutz E**, Aring E, Landgren V, Landgren M, Andersson Grönlund M.
Visual perception problems and quality of life in young adults with foetal alcohol spectrum disorders.
Submitted 2020.

CONTENTS

ABBREVIATIONS

ADHD	attention deficit hyperactivity disorder
ARND	alcohol-related neurodevelopmental disorder
CVI	cerebral visual impairment
D	diopter
FAS	fetal alcohol syndrome
FASD	fetal alcohol spectrum disorders
GA	gestational age
HRQoL	health-related quality of life
ICD	inner canthal distance
IQ	intelligence quotient
LGN	lateral geniculate nucleus
LogMAR	logarithm of the minimal angle of resolution
OCT	optical coherence tomography
ONH	optic nerve hypoplasia
PAE	prenatal alcohol exposure
PFAS	partial fetal alcohol syndrome
PFL	palpebral fissure length
SE	spherical equivalent
VA	visual acuity
VPPs	visual perception problems
VRQoL	vision-related quality of life

DEFINITIONS

Accommodation	The ability to change the refractive power of the lens to create a sharp image on the retina at various distances.
Anisometropia	A difference in refraction between the eyes.
Astigmatism	Refractive error due to unequal refractive power in the two main meridians of the eye.
Emmetropia	Absence of refractive errors when the eye is relaxed.
Esophoria	Latent convergent strabismus. When performing the alternating cover test, the eyes deviate from a position on the medial side (nose side) toward the center.
Esotropia	Manifest convergent strabismus. The eye deviates medially (towards the nose).
Exophoria	Latent divergent strabismus. When performing the alternating cover test, the eyes move from a position on the lateral side (ear side) towards the center.
Exotropia	Manifest divergent strabismus. The eye deviates laterally (towards the ear).
Hyperopia	Refractive error in which the rays of light are focused behind the retina.
Heterotropia	Manifest strabismus.
Heterophoria	Latent strabismus.
Lateral geniculate nucleus	A nucleus in the thalamus which has a profound function in the visual pathways working as a relay center.
Myopia	Refractive error in which the rays of light are focused in front of the retina.

Optic atrophy	Congenital or acquired loss of optic nerve fibers. The optic disc appears pale.
Optic nerve hypoplasia	A congenital disorder characterized by abnormal configuration of the optic nerve. The main sign is a subnormal diameter of the optic nerve head.
Premature birth	Infant born before gestational week 37.
Refraction	The ability of the eye to refract light.
Strabismus	A misalignment of the eyes. The condition can be manifest (heterotropia) or latent (heterophoria). Heterotropia might be intermittent and/or can alternate between the eyes. In concomitant strabismus, the angle of deviation is constant regardless which direction the eyes are looking. In incomitant strabismus the angle of deviation differs in different directions.
Synapse	A structure in the nerve system where signals are transferred from one neuron to another through electrical or chemical signals.
Teratogens	Substances that may cause functional and/or physical defects in a fetus exposed to them.
Thalamus	A gray matter structure situated in the center of the brain.
Visual acuity	The measurement used when evaluating the ability to recognize small details with precision.

1 INTRODUCTION

Fetal alcohol spectrum disorders (FASD) are a group of disorders caused by prenatal alcohol exposure (PAE). The characteristic clinical syndrome in children with PAE has been named fetal alcohol syndrome (FAS).[1] Over the years, FAS has been included in the broader term FASD, which also covers partial fetal alcohol syndrome (PFAS), alcohol-related neurodevelopmental disorder (ARND), and alcohol-related birth defect (ARBD). Today there are several different guidelines used when diagnosing FASD, but the key features of FAS (growth deficiency, facial dysmorphology, and neurobehavioral impairment) are generally the same. FASD are a global health concern[2] with a prevalence range that is wide, largely unknown, and maybe underestimated. The highest prevalences of FAS have been noted in South Africa (585/10 000) and Croatia (115/10 000),[2] but calculation of prevalence is not unproblematic.[3]

The potential harmful effect of PAE on fetuses has long been known,[4–5] but there are few follow-up studies examining its long-term consequences, and even fewer studies taking its effects on the ophthalmological system into account. PAE may cause brain injury including damage to the visual pathways and the optic nerve, but the exact amount of alcohol necessary to cause this damage is hard to establish.[6–7]

Previous studies have reported a high frequency of ophthalmological aberrations such as refractive errors, strabismus and optic nerve hypoplasia (ONH) in individuals with FASD.[6,8–13] However, most studies are small and there are few longitudinal studies focusing on ophthalmology.

Genetic differences between individuals as well as the possible effects of other teratogens make this field of science hard to study, and the stigma still surrounding addiction problems could further obstruct the ability to collect reliable data. In addition, not all FASD sub-diagnoses have codes in the 10th revision of the International Classification of Diseases (ICD-10). The diagnostic code Q86.0 is used when the criteria for FAS are fulfilled, but there is no ICD code for PFAS or ARND. The shortage of ICD codes as well as lack of diagnostic consensus are aggravating factors in epidemiological studies of FASD. Nevertheless, it is of major public health interest to further understand the adult outcome of FASD. To be able to create adequate clinical guidelines, deeper knowledge of FASD is needed.

A basic knowledge of embryology and teratology as well as knowledge of important molecular pathways vulnerable to PAE is necessary for

understanding the role of ophthalmology in children and young adults with FASD.

1.1 EMBRYOLOGY AND MATURATION OF THE VISUAL SYSTEM

The beginning of a new human life comes when a sperm fuses with an egg. However, the start of the pregnancy is calculated from the first day of the last menstruation, which usually occurs two weeks before the ovulation that results in fertilization (**Figure 1**). The future development of the fetus is determined by both intrinsic (genetic) and extrinsic (environmental) factors,[14] and this delicate and complex process is vulnerable in many ways.

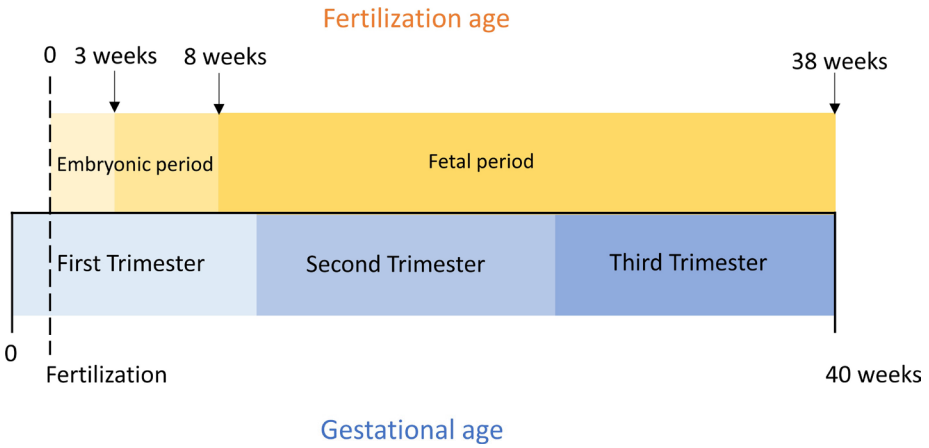

Figure 1. *Fertilization age versus gestational age.*
Illustration: Emelie Gyllencreutz.

The process by which the fertilized egg divides in a controlled manner into a multicellular embryo requires specialization of the cells, a process called differentiation. Differentiation of the embryonal cells is regulated by means of inductive signaling which requires information from the genome of the cell. The cell nucleus contains almost all of the 3 billion deoxyribonucleic acid (DNA) base pairs of the human genome.[14]

The development of a human being takes about 38 weeks, which equals 40 gestational weeks. A child born before gestational week 37 is called preterm. The first three weeks post-fertilization cover the early development of the embryo, the following five weeks (week 4 to week 8) constitute the embryonic organogenesis, and the last 30 weeks are known as the fetal period (**Figure 1**).

Weeks 1–8 are divided into 23 stages called the Carnegie stages, each including a specific characteristic of the embryo.[15] In clinical practice, the pregnancy is subdivided into three trimesters. Most of the organs are formed in the first trimester, develop further in the second trimester, and gain their final structure in the third trimester.[16(p22)]

1.1.1 MAIN FEATURES AND EVENTS OF EMBRYOLOGY

Certain main features of embryogenesis are depicted in **Figure 2**. During the first week the sperm fertilizes the egg, creating a fertilized oocyte and thereafter a two-cell zygote. A morula of 4–16 cells is been formed by day 2 or 3. On day 5, when the morula contains about a hundred cells, a cavity with a clump of cells is formed and the cells are organized into a blastocyst.[17] At day 6 the blastocyst hatches, which is necessary for it to be able to invade the endometrium of the uterine wall. Implantation of the oocyte in the uterine wall usually starts at day 6 or 7 and is completed by day 12.

During the end of the second week a primitive streak is formed.[16(pp59–61)] During the third week, the gastrulation begins; this is a complex process in which the bilayer embryo reorganizes into an embryo with three germ layers through cell movements. There are three primary germ layers: the ectoderm (outer layer), mesoderm (middle layer), and endoderm (inner layer). At day 18 the neural plate, neural folds, and blood islands appear.[16(p70)] The first somites (embryonic limbs) and early heart tubes appear.

Around the beginning the fourth week (equal to the beginning of gestational week 6), the heart begins to beat. The optic grooves are formed along with the optic vesicle. At about this time, the appearance of the embryo changes, from a primitive vertebrate embryo like other species, to resemble a miniature human being. Throughout the development of the embryo, and even after birth, the head is proportionally big.

During the fifth week, the lens placode appears along with the lower limb buds, and the optic vesicle is separated from the surface ectoderm. The lens vesicle and nasal pits are formed.

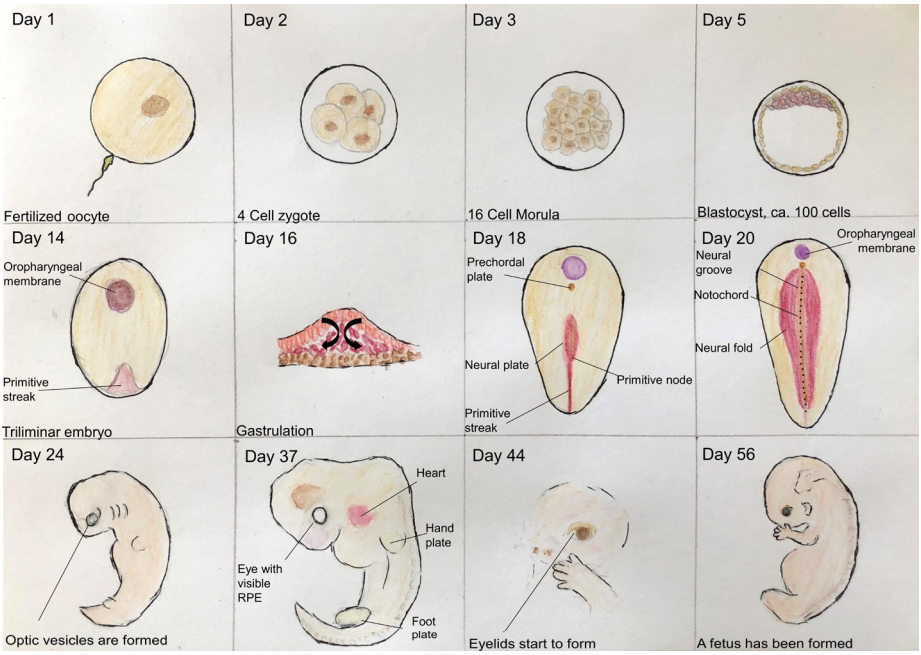

Figure 2. *Some important events during the first eight weeks of development of a human fetus.*[17] *Illustration: Emelie Gyllencreutz*

During the sixth week the hand plates, primary urogenital sinus, nasal pits, foot plates, and cerebral hemispheres develop, and the head enlarges rapidly. The retinal pigment is visible and is a derivate from the central nervous system. The eyelids, which along with the lacrimal glands, lens, and cornea originate from the head ectoderm, begin to form, and the development continues until the end of the eighth week when the eyelids fuse. Meanwhile, the nose, elbows, trunk, urogenital organs, fingers, toes, ears, and external genitalia continue to develop.

At day 56 (fertilization week 8, gestational week 10), the embryonic period ends and the fetal period begins. The organogenesis is completed, but all organs are immature and vulnerable.[15]

1.1.2 FUNDAMENTAL MOLECULAR PROCESSES IN EMBRYOLOGY

When the gastrulation is completed, a cephalocaudal axis is established, defined by the location of the primitive streak. The orientation of the embryo is determined by specific genes.

There are several main groups of molecules involved in the development of a fetus. Transcription factors are proteins with domains that bind to the DNA of important locations of specific genes.[16(p77)] Signaling molecules leave the cell to act on other cells, either neighboring ones or distant ones. One important group of signaling molecules are the so-called growth factors. For a signaling molecule to start a cascade of events it must bind to a receptor molecule; this complex then starts a signal transduction which transports the message to the nucleus of the responding cell.

One of the most important groups of transcription factors are the homeobox genes, called Hox genes, which are involved in the craniocaudal segmentation of the body. Another important family of transcription factors is the Pax gene family, which is involved in the development of the eyes.

For the organogenesis to proceed correctly, the structures must interact with one each other; this procedure is called induction.[14] In neural induction, the notochord interacts with the overlying ectoderm, thus determining the fate of the ectodermal cells. Embryonic induction has been known since the early 1900s.

The induction is mediated by signaling molecules. The hedgehog proteins such as sonic hedgehog (Shh) are involved in several important inductive interactions, including important pathways in the development of the eyes.[14] When sonic hedgehog binds to a receptor molecule, it stimulates the target cell to either produce new gene products or undergo new pathways of differentiation.

1.1.3 EMBRYOGENESIS AND DEVELOPMENT OF THE EYE

The eye is a fascinating and complex organ which requires several coordinated processes to develop properly. **Figure 3** depicts the mature structures of the eye, and the formation of the eye is described below.

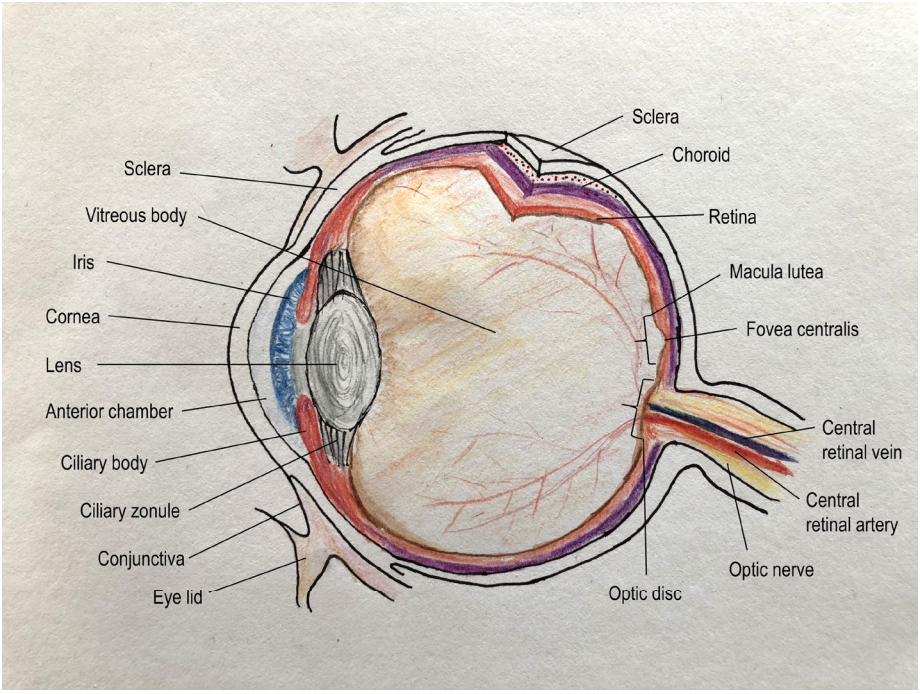

Figure 3. *Basic eye anatomy of a mature eye.*
Illustration: Emelie Gyllencreutz

A primordium is the earliest stage of a tissue or an organ. The eye originates from two different types of primordia: the optic vesicle and the lens placode. As these two are brought together, induction starts and eventually gives rise to the mature eye. The optic vesicle arises from the forebrain region of the anterior neural plate, whereas the lens placode originates from the surface ectoderm of the head (**Figure 4**). In the later stages of eye development, neural crest mesenchyme contributes to the formation of the cornea and sclera.[14] An adequate development of the eye requires both inductive signals to form the major components of the eye and coordinated differentiation of the

components forming the eye. These procedures make the eye one of the most complex organs in the embryogenesis.[16(pp262–276)]

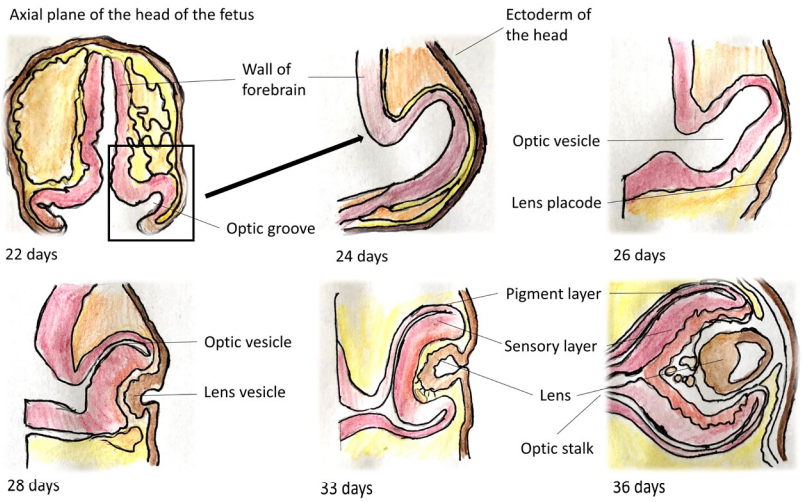

Figure 4. *Key features in the development of the human eyes. Illustration: Emelie Gyllencreutz*

The first signs of a developing eye are seen around day 20 after fertilization as the eye fields appear in the anterior part of the neural plate. The eye fields are areas expressing *PAX6*, a paired box gene which is crucial throughout early eye development as well as in some of the stages in the development of the retina and lens. Four weeks after fertilization, the optic groove deepens, and the optic vesicle is formed from the diencephalon (a part of the brain) through evagination of the lateral walls. The optic stalk, which eventually becomes the optic nerve, connects the optic vesicles with the brain. Simultaneously with the formation of the optic vesicle into the optic cup, the lens vesicle starts to develop through induction of ectoderm, eventually detaching from the surface epithelium from which it originates. The lens vesicle thereafter inducts the formation of the cornea from the overlying surface ectoderm.[16(pp262–276)]

The iris and the ciliary body develop from the lip of the optic cup. The outer pigmented part of the iris is continuous with the pigment epithelial layer of the retina. The stroma of the iris originates from the neural crest. The vitreous body consists of a gelatinous substance that fills the space between the neural retina and the lens. During the embryonic development, the vitreous body receives

its oxygen supply from the hyaloid artery and its branches. Most of the hyaloid artery, like its branches, regresses through apoptosis when the development of the eye progresses, but the most proximal part persists and forms the central artery of the retina and its branches.[16(p274)] However, sometimes an embryonal remnant of this artery is seen when examining eyes.

The choroid coat and the sclera are formed from mesenchymal cells, mostly from the neural crest. The innermost cells differentiate to a vascular tunic known as the choroid coat, whereas the outermost cells form the sclera, a white, dense structure of collagen.[16(p274)] When the development of the eye is normal, the choroid fissure closes and no trace of it is seen, but if this development is disturbed, a coloboma can appear. This lower midline defect might affect the iris, creating a keyhole-like pupil (**Figure 5**). It can also affect the whole midline close, creating a retinal coloboma and/or optic disc coloboma. Colobomas can be the result of a mutation of the gene *PAX2*,[16(pp262–276)] and might occur in individuals with FAS as well as in individuals with other conditions.

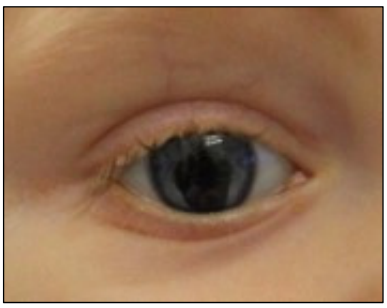

Figure 5. *The keyhole-like pupil is an iris coloboma, a midline defect in the iris due to incomplete midline closure.*

There are six main extraocular muscles, namely the medial rectus (MR), lateral rectus (LR), superior rectus (SR), inferior rectus (IR), superior oblique (SO), and inferior oblique (IO). All six are derivates from the head mesoderm.[14] Cranial nerve III (oculomotor nerve) innervates MR, SR, IR and IO. Cranial nerve IV (trochlear nerve) innervates SO and cranial nerve VI (abducens nerve) innervates LR. The levator palpebrae superioris, which is the muscle responsible for elevating the upper eyelid, has the same origin as the SR and is innervated by the superior division of the oculomotor nerve. If there is a failure in the development of these muscles and/or their innervation, the child is born with a congenital eyelid ptosis.[14]

Eyelid ptosis can occur in one or both eyes, it might occur isolated or in combination with other conditions, e.g., FAS.[18] During formation of the cornea and the lens, the optic cup undergoes profound changes. The epithelial cells of its inner layer thicken and start to differentiate into neurons and light receptor cells, finally forming the neural retina, whereas the outer layer remains thin and develops into the pigment layer of the retina. The sensory pathway in the neural retina includes three neurons. Firstly, the photoreceptors (rods and cones), which lie in the outer nuclear layer. The rods are responsible for low-light vision and peripheral vision, while the three different types of cones are together responsible for color vision and vision in daylight.[19] Secondly, the bipolar cells which are located in the inner nuclear layer. The bipolar cell synapses with a ganglion cell (the third neuron in the chain) in the inner plexiform layer. The ganglion cells handle contrast vision by means of their lateral connection to horizontal cells in the plexiform layer.[19] The bodies of the ganglion cells are in the ganglion cell layer, and their long processes build the innermost part of the nerve fiber layer on their way to the optic nerve which connects the eye with the brain. In the inner and outer plexiform layer there are horizontal cells and amacrine cells which contribute to creating high resolution images.[16(pp270–272)] In the inner nuclear layer, there are also Müller glial cells which serve as support cells for the neurons. The Müller glial cells originate from the neural crest and are important in the development of the retina.[20] The retinal layers are depicted in **Figure 6**.

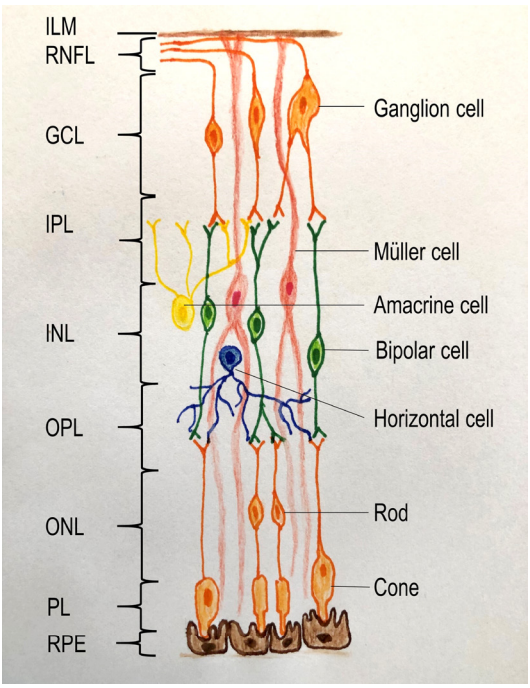

Figure 6. *Retinal layers: internal limiting membrane (ILM), retinal nerve fiber layer (RNFL), ganglion cell layer (GCL) with ganglion cells, inner plexiform layer (IPL), inner nuclear layer (INL), outer plexiform layer (OPL), outer nuclear layer (ONL), photoreceptor layer (PL), retinal pigment epithelium (RPE). Illustration: Emelie Gyllencreutz.*

1.1.4 MATURATION OF THE VISUAL SYSTEM

Visual acuity

Even though the most of structures of the eye are complete in a baby born at term, the visual function is not, since neither the visual acuity (VA) nor the interpretation of visual information conducted by the brain have reached their full potential. In other words, the visual system is immature. To develop a good VA, both eyes need to be exposed to visual stimuli. If the eye cannot create a clear picture on the retina, for example due to uncorrected refractive errors, strabismus, ptosis, or cataract, there is a risk of amblyopia; that is, decreased VA due to a disturbance of the visual system during its development.[21–22] The development of VA continues during childhood and young adulthood, and the younger the child the larger the risk of amblyopia. Most healthy, full-term children have developed a good VA by the time they are 7–9 years old.[23] VA continues to develop during young adulthood, peaks around the age of 25 years, and then declines.[24] To detect amblyopia in time for accurate intervention, screening systems are used in several countries, including Sweden.[25] Measurement of VA requires good concentration and cooperation, and so a poor VA result might reflect problems other than just an ophthalmological condition. Low VA has been reported in children with FASD.[9, 26–27]

Refraction

Refraction is the change of direction of a light wave entering in a medium from another medium. An eye with a perfect focusing power of the cornea and lens is called emmetropic. When the focusing power is too weak and/or the eye is too short, hyperopia occurs. Conversely, when the focusing power is too strong and/or the eye is too long, myopia occurs. Astigmatism occurs when the refractive power differs between the two principal meridians of the eye.[28(p63)] In an adult eye, the cornea holds two thirds of the refractive power while the lens is responsible for the remaining third. Among Caucasian children, hyperopia is the most common refraction at birth.[29] The disappearance of neonatal refractive errors during childhood is called emmetropization.[30] The short hyperopic eye grows, the axial length of the eye increases, and the hyperopia decreases.[23] Most individuals have eyes that are similar to each other, but some have eyes that differ. Different refraction between the eyes is called anisometropia, and a difference of 1 diopter (D) or more spherical equivalent (SE) between the eyes is usually considered clinically significant. Anisometropia and strabismus are common reasons for amblyopia. Refractive error as well as strabismus are common in children with FAS.[8–9,26]

Strabismus

Strabismus, also called heterotropia, is a misalignment of the eyes. When one eye deviates inwards the condition is called esotropia, and when it deviates outward it is called exotropia. Manifest strabismus is named heterotropia, whereas latent strabismus is called heterophoria. To fuse an object seen by the two eyes into a single image (binocular single vision), the object must be projected onto corresponding retinal points. A misalignment of the eyes results in diplopia unless one of the images is suppressed. Strabismus can be divided into concomitant strabismus, in which the angle of misalignment is constant regardless of direction of gaze, and incomitant strabismus, in which the misalignment differs depending on which eye is fixating an object or in which way the patient is gazing.[31] In incomitant strabismus (e.g. paralytic and mechanical strabismus) the muscle function and structure may be affected, whereas this is less likely in concomitant strabismus.[32] Strabismus is associated with several different syndromes as well as with prematurity. In a large proportion of children with FASD concomitant strabismus has been reported.[8,26,33]

Binocular vision

As the view of the world is slightly different between the right and the left eye, special mechanisms are needed to create binocular vision. Binocular single vision requires perfect coordination between the eyes (motor fusion) as well as the ability of the brain to combine slightly different monocular signals into a single image (sensory fusion). In addition, the VA must be good in both eyes. The ability to generate a three-dimensional image from a pair of two-dimensional retinal images is called stereopsis, and when measured it is called stereoacuity.[28(p746)] Stereoacuity is the ability to reliably distinguish the smallest disparity between images presented to the two eyes, and is considered a higher-order visual process as it requires complex cortical processing.[28(p35)] The visual function of an individual is determined not only by the formation of an intact eye but also by the correct development of the brain, as the interpretation of the images collected by the eyes takes place in the brain. Children with brain damage have a higher risk of developing strabismus, ocular motor problems, and visual perception problems (VPPs). Impaired stereoacuity has been reported in children with FASD.[27]

1.2 OPTIC NERVE HYPOPLASIA

Optic nerve hypoplasia (ONH) is a congenital disorder characterized by abnormal configuration of the optic nerve. Its main sign is a subnormal diameter of the optic nerve head,[34] but additional signs such as the shape of the disc, estimated number of axons, appearance of the cup, configuration of the surrounding retinal vessels, and presence of peripapillary abnormalities are also taken into consideration.[28(p565)] ONH can affect one or both optic nerves. In some cases it occurs in isolation, and in others as part of a syndrome. It is a complex disorder with multifactorial origin[35] that presents with a wide range of visual dysfunction, from slightly affected visual field[34] to severe bilateral visual impairment.[36] The condition is believed to be non-progressive, with a subnormal number of retinal ganglion cell axons.[28(pp564–567)]

The ganglion cells (**Figure 6**) are the first retinal cells to appear. The number of axons increases during embryogenesis to over 3.5 million in each eye, followed by apoptosis and a decrease to about 1.2 million in a full-term baby. Severely hypoplastic optic nerves are usually the result of an early injury (week 4–6 post fertilization), whereas mild forms of ONH might appear due to an insult later in the pregnancy. Myelination of the optic nerve begins at about 5 months of gestation. It starts posteriorly from the lateral geniculate nucleus (LGN) and reaches the lamina cribrosa — that is, the mesh-like structure in the sclera (**Figure 3**) through which the optic nerve exits the eye — when the baby is full-term.[28(pp564–567)]

The etiology of ONH has been suggested to be multifactorial. Young maternal age has been pointed out as a risk factor.[37] In addition, genetic factors have been identified, and genetic causes of ONH are possible.[38] It has been recognized that ONH can co-occur with neurodevelopmental disorders[35] and FAS,[8] as well as with pituitary hormone deficiencies.[37]

The prevalence has been estimated to be anywhere from 1.8 per 100,000 to 17.3 per 100,000.[35] Differences in the population studied as well as the definition of ONH might explain this wide prevalence range. In a thesis by Strömland on ocular abnormalities in FAS,[8] ONH was defined as $\leq$ -1 standard deviation (SD) compared with normal controls, corresponding to an optic disc area of 2.07 mm^2 or less, whereas Teär Fahnehjelm and colleagues used the cut off $\leq$ -2 SD,[35] corresponding to < 1.31 mm^2 optic disc area, in their reference group. The size of the optic disc can be measured using different methods such as measurements on fundus photos or automatic measurements from optical coherence tomography (OCT). It is important to note that when the OCT machine measures the optic disc parameters, they are determined at

the reference plane height of 120 µm from the retinal pigment epithelial plane, and so do not perfectly overlap measurements on fundus photographs of the optic disc.

When examined with fundoscopy, the hypoplastic disc is sometimes surrounded by a double ring (**Figure 7**). The yellowish double ring is composed of dysplastic retina and pigment epithelium.[28(pp564–567)] At a glance, this area could be mistaken for the optic rim and the optic disc for the optic cup.

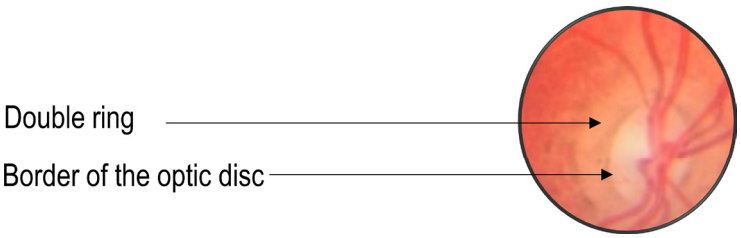

Figure 7. *A photo of an optic nerve with optic nerve hypoplasia with a typical double ring sign.*

1.3 CEREBRAL VISUAL IMPAIRMENT

Development of a fully functional visual system requires not only normally configured eyes with a clear cornea, lens, and vitreous body as well as functional cells of the retina and the optic nerve,[39] but also the ability of the brain to interpret the visual information sent to it.[40] In addition, the ocular motor system must work properly in order to induce correct fixation and movements of the eyes.[41] The photoreceptors of the retina collect visual information which is transferred by the optic nerve via the LGN, the superior colliculus, and the suprachiasmatic nucleus to the primary visual cortex (V1) and secondary visual cortex (V2). From there the information is transferred to specialized areas. The ventral stream passes through the V4 area to the inferotemporal cortex and is responsible for interpreting color and form ("what"). The dorsal stream is directed to the medial temporal area (V5) and to the dorsomedial area (V6), and is aligned to handle perception of motion and depth ("where").[19] The ventral stream includes several areas in the occipitotemporal cortex and temporal cortex, whereas the dorsal stream projects to areas of the parietal cortex (**Figure 8**).

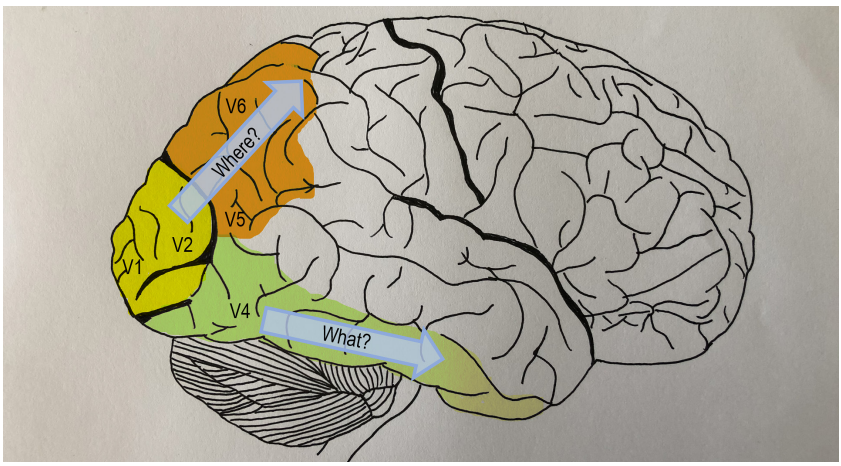

Figure 8. *Information from the eye is sent through the optic nerve via the lateral geniculate nucleus (LGN), the superior colliculus and the suprachiasmatic nucleus to the primary visual cortex (V1) and secondary visual cortex (V2). From there the information is transferred to specialized areas. The ventral stream passes through the V4 area to the inferotemporal cortex and is responsible for interpreting color and form ("what"). The dorsal stream travels to the medial temporal area (V5) and dorsomedial area (V6) and is aligned to handle perception of motion and depth ("where").*
Illustration: Emelie Gyllencreutz.

However, much like other biological phenomena, this dedication of a functional domain to a specific area of the brain is not absolute, and so a lesion in a specific area does not always erase the function for which the damaged part of the brain is responsible. The delicate system of visual information interpretation is vulnerable to brain damage. Disorders such as hydrocephalus, meningitis, encephalitis, and head trauma can affect the ability to interpret visual information, causing cerebral visual impairment (CVI). Brain damage occurring in gestational weeks 24–34 might give rise to periventricular white matter damage.[40] Periventricular leukomalacia (PVL) is a condition seen in preterm babies or babies born at term but who suffered from brain damage prenatally. Superior periventricular damage may cause bilateral lower visual field impairment.[40] Due to the ability of the brain to regenerate in unborn children, prenatal brain damage might cause visual field defects that differ from the visual field defects seen in adults with lesions in the same part of the brain. **Figure 9** shows the classic visual field defects connected to lesions in different parts of the brain.

Prenatal brain damage might cause visual impairment less obvious to the examiner than the classic defects seen in adults. Cerebral damage affecting the ventral stream causes difficulty in identifying faces, shapes, and forms, whereas damage affecting the dorsal stream causes problems with identifying objects in surroundings with an overload of information as well as problems with judging the correct height of, for example a stair step.[40] Using an escalator could be impossible. In addition, CVI can manifest as the inability to handle movement perception, or the inability to use visual memory.[40] Children with CVI might have reduced VA, but this does not occur in all cases. Visual field defects are difficult to identify in young children, and the range of normal visual maturation in children is wide; specific screening questions are therefore mandatory in cases when CVI is suspected.[42–44]

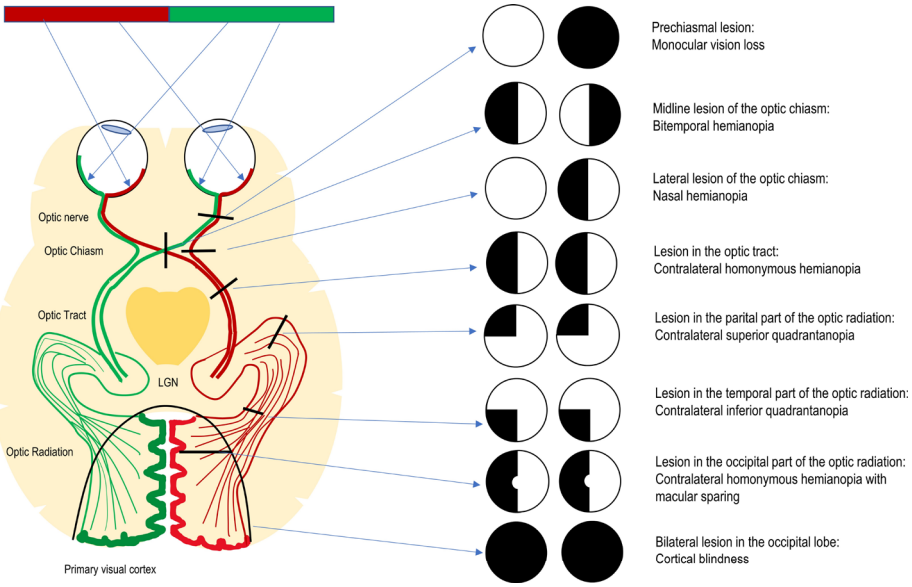

Figure 9. *Schematic picture of the visual pathways and the visual field defects that occurs depending on where a lesion is situated.*
LGN=lateral geniculate nucleus
Illustration: Emelie Gyllencreutz

VPPs, sometimes referred to as perceptual visual dysfunctions,[45] might occur in children with different types of acquired brain injury, such as cerebral palsy, and hydrocephalus.[40,45] There are different types of VPPs. In some cases, the problem is recognizing faces or objects, while in other cases orientation is challenging, and sometimes walking on uneven ground or finding objects in crowded surroundings is hard or impossible. Impaired motion perception has previously been reported in children with FAS.[46]

1.4 TERATOLOGY

The term teratology originates from the Greek word *teras*, which means monster, and so teratology literally means "the study of monsters". However, a more modern interpretation is "the study of congenital malformations".[47(p45)] Modern teratology has had two milestones: first, the discovery of malformations caused by the rubella virus in 1941,[48] and second, the devastating effects of thalidomide exposure on the developing fetus.[7,49]

Environmental agents that cause permanent morphological changes in the development of a fetus are called teratogens. Examples of teratogenic agents are drugs, infections, toxins, nutrients, and environmental agents such as fever and ionizing radiation. **Table 1** lists some well-known teratogenic agents.[47(pp45–53)] In some cases, the presence of a teratogenic agent causes the deformation (e.g. thalidomide) and in other cases the absence of the agent is problematic (e.g. folic acid shortage). The teratogen changes the development of an organ and alters the function and/or morphology.[47(pp45–53)] There are three important factors contributing to the consequences of exposure to a teratogenic agent: 1) the embryonal stage at which the fetus is exposed, 2) the dose of the teratogen agent, and 3) the genotype of the embryo and the mother along with the nutritional status of the mother. In particular, the timing of exposure is of great importance because of the constant changes in development; a teratogenic agent might have lethal effects in one stage of development and no effect in another stage. As randomized controlled studies on teratogen agents in human fetuses cannot be performed for ethical reasons, many drugs are not licensed for use in pregnancy. In addition, a substance might be teratogenic in humans but not in other animals.[50] The devastating effects of thalidomide are an example of this.

Intrauterine infections are aggravating factors for preterm birth as well as increased morbidity. In addition, it has been noted that the babies exposed to intrauterine infections might be small for gestational age (SGA).[51] Maternal malnutrition is associated with increased risk of coronary heart disease [52–53] and being SGA is linked to increased risk of chronic diseases.[54]

Table 1. *An incomplete list of different teratogenic agents.*[47,50]

Teratogenic agent	Effect
Drugs	
Thalidomide	A very potent teratogen which may cause major defects from exposure to a single 50 mg dose. The sensitive period occurs between day 20 and 36 after fertilization. Exposure at days 20–24 causes eye and ear abnormalities such as microphthalmia, coloboma, and abnormal pinnae whereas exposure at days 24–31 causes upper limb hypoplasia and exposure at days 27–33 causes lower limb hypoplasia.
Sodium valproate	Exposure may cause craniosynostosis, neural tube defect, cleft palate, atrial septal defect, and hypospadias.
Methotrexate	As this is an anti-folate drug it may cause neural tube defects (see discussion of folic acid, below).
Warfarin	Exposure may cause optic atrophy, limb hypoplasia, bone abnormalities, nasal hypoplasia, and neurological impairment.
Infections	
Rubella	Intrauterine infection may cause cataract, glaucoma, microphthalmos, retinopathy, microcephaly, sensorineural deafness, and cardiac defects.
Cytomegalovirus (CMV)	Intrauterine infection may cause growth retardation, microcephaly, progressive sensorineural deafness, and periventricular calcification.
Toxoplasmosis	Intrauterine infection may cause eye lesions, microphthalmos, microcephaly, hydrocephalus, intracerebral calcification, hearing loss, and neurological sequelae.
Varicella zoster virus	Intrauterine infection may cause limb hypoplasia, skin scarring, and visceral, neurological, and eye lesions.
Herpes simplex virus	Intrauterine infection may cause microphthalmia, microcephaly, and hydrocephalus.
Zika virus	Intrauterine infection may cause microcephaly, intracerebral calcification, and hypoplastic brainstem, cerebellum, and corpus callosum.
Syphilis	Intrauterine infection may cause sensorineural deafness, neurological sequelae, bone lesions, maxillary hypoplasia, and saddle nose.
Toxins	
Alcohol	Prenatal exposure may cause fetal alcohol syndrome, characterized by growth retardation, microcephaly, and facial dysmorphology (short palpebral fissures, hypoplastic midface, smooth philtrum, and thin upper lip). Birth defects such as heart defects, vertebral

	segmentation defects, and optic nerve hypoplasia may occur.
Heroin	Exposure has been correlated with growth retardation, prematurity, and perinatal death.
Mercury	Exposure may cause microcephaly and neurological symptoms.
Nutrients	
Vitamin A	Excessive intake may cause embryopathy such as microphthalmia, cleft palate and cardiac defects. Vitamin A is important in the regulation of gene expression as well as in the control of cellular differentiation and proliferation.
Folic acid	Deficiency in early pregnancy may cause neural tube defects. Folic acid is important for DNA synthesis.
Maternal conditions	
Diabetes mellitus	Diabetic embryopathy includes cardiac abnormalities, central nerve system abnormalities, and gastrointestinal malformations.
Phenylketonuria (PKU)	If a baby carried by a woman with PKU is exposed to high phenylalanine levels in the first trimester, there is a risk of microcephaly, heart defects, and growth retardation.

The negative effect of PAE has been brought to light throughout history, for instance during the gin scandal in the 18th century London.[5] In the beginning of the 20th century, animal studies on the toxic effect of PAE were performed,[55–56] but the two world wars put this research on hold. In 1957, French medical student Jacqueline Rouquette wrote her thesis on the topic: "Influence de la toxicomanie alcoolique parentale sur le développement physique & psychique des jeunes enfants" ("Influence of parental alcoholic drug addiction on the physical and psychological development of young children").[5] In 1967, French general practitioner Alexandre Lamache wrote a report on malformation in patients prenatally exposed to alcohol,[57] and a year later his compatriots Lemoine et al. published an article on the abnormalities of 127 children with PAE.[4] The term fetal alcohol syndrome and its distinct dysmorphology was coined by Jones et al. in 1973,[1] accompanied by a description of eight children with different ethnicities and the same dysmorphic features including growth retardation, microcephaly and the typical facial dysmorphology: short palpebral fissures, a hypoplastic midface, smooth philtrum, and a thin vermilion border of the upper lip (**Figure 10**). There are photo-based guidelines to use when to evaluate the degree of smooth philtrum and thin upper lip. Web links to lip/philtrum guides are available in **Appendix 1.**

With alcohol, as with other teratogens, the severity of exposure is dependent on the duration of the exposure as well as the dose and the timing. Not all children with PAE develop full-blown FAS; instead, they might fulfill the criteria of a diagnosis under the broader term FASD.

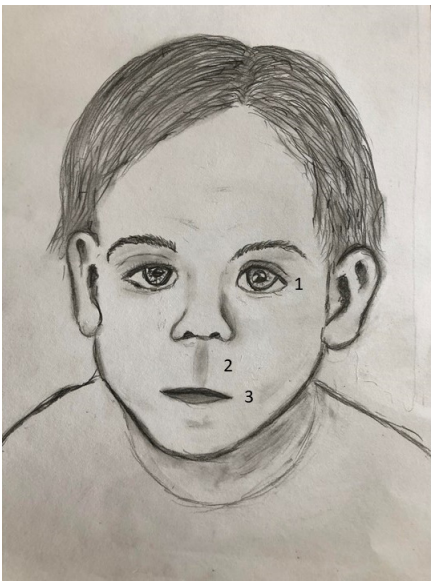

Figure 10. *A child with fetal alcohol syndrome. Note*
(1) the short palpebral length,
(2) the smooth philtrum, and
(3) the thin vermilion border of the upper lip. There is also a lid ptosis at the right eye.

Illustration: Freja Gyllencreutz.

1.5 FETAL ALCOHOL SPECTRUM DISORDERS

Since the recognition of FAS,[1] disorders likely caused by PAE have been gathered under the term FASD. All FASD diagnoses are dependent on fulfilling diagnostic criteria based on observational studies of individuals with or without documented PAE. As mentioned in the section on teratology above, the effect of a teratogen depends on the timing of exposure, the dose of the teratogen agent, and the genotypes of the embryo and mother. The combination of these factors in exposed fetuses generates a wide spectrum of impairments and disorders. The diagnostic criteria are built on the most common features in children recognized with PAE. There are currently several similar but non-identical sets of diagnostic guidelines in use in different countries.[18,58–65] Since the different guidelines do not overlap completely,[66] ophthalmological findings in individuals with FASD must be interpreted with consideration of which diagnostic guidelines have been used. The two different diagnostic guidelines[59,61] used when diagnosing FASD in our cohort[11,26,67], are explained in **Table 2.** Our research group have found, the criteria for FASD developed by the IOM in 1996[58] and updated by Hoyme in 2005[61] and 2016[18] both useful and practical. In these guidelines the terms FAS, PFAS, ARND and ARBD are used. In FAS and PFAS the alcohol exposure might be confirmed or unknown, whereas ARND and ARBD require confirmed PAE. Even though many guidelines stress the importance of a multidisciplinary approach to FASD, the ophthalmological aspects of FASD are rarely mentioned; the one exception is the short palpebral fissure. Measurement of the palpebral fissure length (PFL)

is used when diagnosing FASD. In addition, the distance between the two eyes, the inner canthal distance (ICD), is measured (**Figure 11**). However, ICD is not a part of the diagnostic criteria.

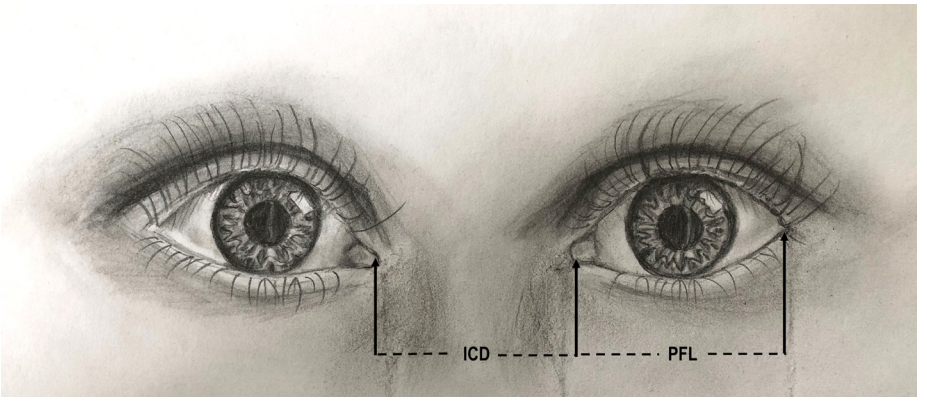

Figure 11. *Inner canthal distance (ICD), sometimes also referred to as the inter-canthal distance, is the distance between the inner canthi of the eyes. The palpebral fissure length (PFL) is the distance between the inner and outer canthus of an eye. These measurements are traditionally captured with a transparent ruler. Illustration: Emelie Gyllencreutz.*

The characteristics seen in FASD are not exclusive but can also be present in genetic syndromes such as Dubowitz syndrome, Noonan syndrome, and Williams syndrome[18] as well as neurodevelopmental disorders. Other causes of a child's features and behavior must therefore be ruled out before a FASD diagnosis is considered the most probable. A genetic evaluation is often recommended to identify known genetically determined syndromes. However, even a child with a genetic condition might have been exposed to alcohol prenatally.

Table 2. *A simplified overview of the two different guidelines used when diagnosing fetal alcohol syndrome (FAS) in childhood in our cohort.*[26,67–68]

	4-Digit Code, FAS 2004[59]	**Hoyme, FAS 2005**[61]
Alcohol	Confirmed or unknown	Confirmed or unknown
Growth	Prenatal and/or postnatal height or weight ≤3rd percentile	Prenatal and/or postnatal height or weight ≤10th percentile.
Dysmorphology	All three of the following at any age: 1. PFL ≤3rd percentile 2. Smooth philtrum* 3. Thin upper lip* *Rank 4 or 5	Two or more of the following: 1. PFL ≤10th percentile 2. Smooth philtrum* 3. Thin upper lip* *Rank 4 or 5
Central nerve system	At least one of the following: 1. Structural/neurological: (e.g., OFC ≤3rd percentile, abnormal structure, seizure disorder, hard signs) 2. Severe dysfunction: (three or more domains of function with impairment two or more SDs below the mean)	At least one of the following: Structural 1. OFC ≤10th percentile 2. Abnormal structure

FAS=fetal alcohol syndrome; OFC=occipital frontal circumference; PFL=palpebral fissure length; SD=standard deviation.

Web links to lip/philtrum guides are available in **Appendix 1**.

1.5.1 ANIMAL STUDIES ON PRENATAL ALCOHOL EXPOSURE

Studies on chick embryos in the 1930s[56] revealed the complexity of eye development. Removal of the prechordal plate in the chick embryos resulted in cyclopia, showing that a normal development of a single eye field into two separate eye fields is dependent on signals between different embryological structures. The signal system responsible for the creation of two separate eye fields is now known as the Shh pathway.[13,69]

In the early 1980s, Sulik and Johnston[70] reported the occurrence of microcephaly and microphthalmia in mouse fetuses that had been exposed to alcohol during the time of gastrulation **(Figure 2)**. The experiments revealed an obvious size reduction in the neural plate.[70] However, even embryos in the control group had eye abnormalities, albeit in a lower proportion. The authors concluded that the craniofacial features typical in FAS originate from an insult during gastrulation when the anterior part of the neural plate is formed.[70] A great number of animal studies have shown that the retina and the optic nerve are vulnerable to PAE. Alcohol can alter the normal patterns of how stem cells are recruited, delay the myelination,[71] and cause ONH and optic nerve atrophy.[6] Later, animal studies on the effect of PAE on the facial dysmorphology using magnetic resonance microscopy, have shown that both the incidence and the severity of ocular defects were markedly increased in mice exposed to alcohol at gestational day seven.[72]

The Shh pathway is considered a key target in clinical conditions that involve disruption of the early development of the eye. Shh is a signal molecule that is synthesized as a precursor protein. Through autocatalytic cleavage, a carboxyl terminal fragment (Shh-C) and an active amino terminal fragment (Shh-N) are produced. Shh-N mediates the signals and is modified twice to become the functionally active ligand Shh-Np.[13,73] Alcohol exposure during early eye development may reduce the Shh mRNA expression in chick embryos.[74] These results have been confirmed in a study on zebrafish embryos,[75] whereas a study using a mouse models of FAS did not find modification of the Shh mRNA.[76]

2 AIMS

The overall aim was to describe the long-term consequences of FASD, both in general and with an emphasis on ophthalmology.

Specific aims

Paper I

To describe the clinical characteristics in young adulthood of individuals with FASD who were adopted in childhood from eastern Europe to western Sweden.

Paper II

To examine whether visual and ocular findings in children with FASD persist into early adulthood.

Paper III

To investigate whether retinal thickness, retinal nerve fiber layer (RFNL), and optic disc area (ODA) measured with OCT differ between young adults with FASD and healthy controls.

Paper IV

To study the occurrence and persistence over time of VPPs in individuals with FASD and to compare VPPs, health- as well as vison-related quality of life (QoL) in young adults with FASD with these variables in healthy controls.

3 METHODS

PARTICIPANTS

The individuals with FASD in *Paper I–IV* were all drawn from a cohort of adoptees from eastern Europe.[11,26,67–68] During 1993–1997, 99 children born in 1990–1995 were adopted from Poland, Romania, Estonia, and Latvia to western Sweden. Of these, 71 agreed to participate in a population-based study performed in 2000–2002 (**Figure 12**). The children underwent a comprehensive investigation by a multidisciplinary team including pediatric ophthalmology, orthoptics, neuropediatrics, and child neuropsychology.[11,26,67–68] In this cohort, 37 children were diagnosed with FAS (n=21), PFAS (n=10), or ARND (n=6) according to the criteria described by Hoyme.[61]

Two follow-ups were carried out (**Figure 12**). During the first follow-up period in 2014–2015, 16 of the young adults with FAS were examined by Marita Andersson Grönlund (MAG), Eva Aring (EA), Leif Svensson (LS), and Magnus Landgren (ML). The second follow-up period was performed in 2017–2019. All 21 young adults with FAS were invited once again, along with the young adults with PFAS and ARND, to participate in an even more comprehensive examination which covered questionnaires regarding QoL in addition to the previously performed examinations *(Paper IV*). Moreover, this second follow-up also included a control group of young adults without FASD, who served as controls in *Paper III* and *IV*. The controls were recruited consecutively and consisted of young adults living in the county of Västra Götaland, Sweden. Individuals 18–30 years were eligible, and exclusion criteria in the control group were epilepsy, syndromes of any kind, and prematurity.

During the second follow-up period, the participants were examined by Emelie Gyllencreutz, Valdemar Landgren, EA, and LS under supervision by MAG and ML.

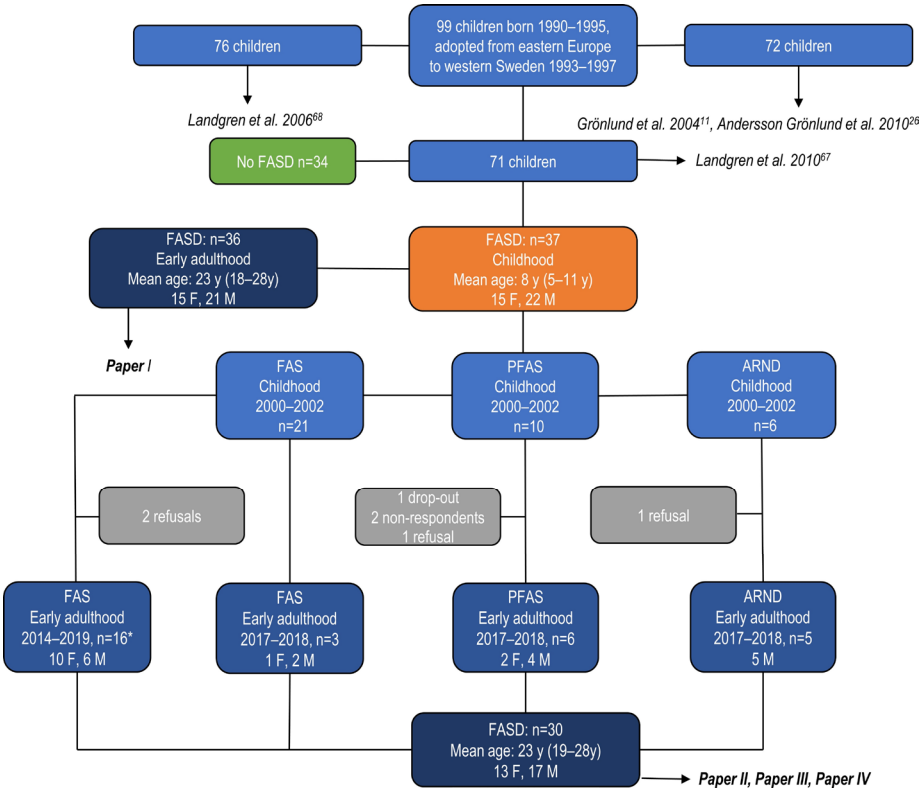

Figure 12. *Flowchart describing the cohort from which the participants with fetal alcohol spectrum disorders (FASD) were drawn.*
** Six participants with FAS were examined twice.*
F=female, M=male

3.1 PAPER I

This paper was concerned with the characteristics of a group of young adults diagnosed with FASD in childhood and reassessed in early adulthood by the same multidisciplinary team (**Figure 12**). The participants underwent five different evaluations at follow-up. The first of these was a social evaluation covering the current social situation as well as educational attainment. The information was collected by phone, primarily from the parents of the young adults. The second was a medical evaluation including auscultation of the heart and lungs, a neurological examination, and measurements of weight, height, body mass index (BMI), blood pressure, and occipitofrontal circumference (OCF). Values were converted into appropriate standard deviations (SD) and percentile scores. A lip/philtrum guide was used to score the upper lip and the philtrum.[18,61] The third was a psychiatric evaluation using the Mini International Neuropsychiatric Interview 6.0.0 (MINI),[77] the Adult Attention Deficit Hyperactivity Disorder (ADHD) Self-Report Scale 1.1,[78] and the Clinical Global Impressions—Severity (CGI-S) instrument.[79] The fourth evaluation was ophthalmological. Data on palpebral fissure length (PFL) and inner canthal distance (ICD) are presented in *Paper I* along with a summary of the ophthalmological findings, and the detailed information from the ophthalmological evaluation is presented in *Paper II–IV*. The fifth and final evaluation was a psychological evaluation using Leiter-Revised (Leiter-R) non-verbal tests including an intelligence quotient (IQ) test of fluid reasoning and visualization as well as the Leiter-R Attention and Memory battery.[80] The non-verbal test was used because the median age at adoption was relatively high (2.8 years), 12/71 children in the cohort were 4 years or older when adopted to Sweden, and not all of the children spoke Swedish fluently at the baseline examination. To be able to compare the results from childhood with the results at follow-up, the same test was used.

3.2 PAPER II

In this paper, best corrected VA (BCVA), refraction, stereoacuity, strabismus, and the anterior and posterior segment were examined in young adults with FASD, and the results were compared with the results from the baseline examination in childhood.[11,26] Monocular and binocular BCVA were measured using a digital KM chart at 3 meters,[81] and refraction was obtained using autorefractors from Topcon (A6300/KR8800; Topcon Corporation, Tokyo, Japan) and measured without cycloplegia in young adulthood. Astigmatism ≥1.0 D was considered significant as well as spherical equivalents (SE) of hyperopia ≥2.5 D SE, myopia ≥0.5 D SE, and anisometropia ≥1.0 D SE were considered significant. A cover test was performed to diagnose strabismus at near and/or at distance. Stereoacuity was measured using a TNO test[82] if possible. Lang stereo test or Titmus stereo test was used if the young adult could not perform the TNO test. Evaluations of the optic fundus were conducted using indirect ophthalmoscopy as well as retrospective review of fundus photographs. Data from the baseline examination in childhood were available in a database covering all details from the ophthalmological examination as well as data on the participants' medical and psychological status. Preterm birth was defined as gestational age of <37 weeks, and SGA was defined as birth weight and/or birth length ≤2 standard deviation score (SDS) lower than mean for gestational age and sex.[83]

3.3 PAPER III

As a part of the ophthalmological examination performed at the follow-up of the individuals with FASD, OCT data of the macula and the optic disc were obtained, and compared with the results from the controls. Data on monocular BCVA and non-cycloplegic refraction were collected from all participants. ONH was defined as a small optic disc with or without a double-ring sign, pallor, or segmental irregularities of the optic disc. Data on IQ was drawn from the examination presented in *Paper I*.

Spectral domain OCT of the optic disc and the macula was performed using Topcon 3D-OCT 2000 software (Topcon Corporation, Tokyo, Japan). Optic disc parameters and peripapillary retinal nerve fiber layer (RNFL) were measured with the 3D disc 6.0x6.0 mm scan mode. The 3D macular 6.0x6.0 mm scan mode was used to measure the macular RNFL and retinal thickness

in nine areas (**Figure 13**) defined by the Early Treatment Diabetic Retinopathy Study (ETDRS).[84]

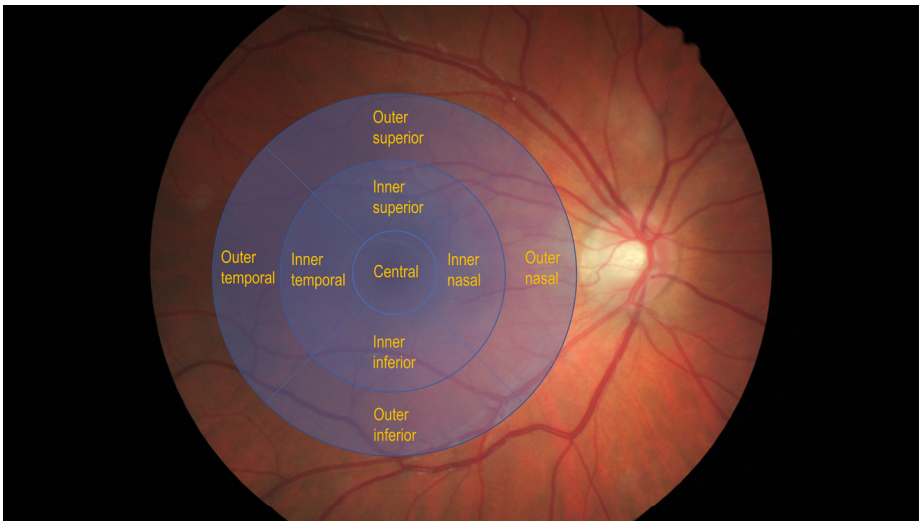

Figure 13. *The nine areas of the central fundus. These areas were first defined in the Early Treatment Diabetic Retinopathy Study.*[84]

3.4 PAPER IV

In *Paper IV*, VPPs and QoL were evaluated in the FASD group and in controls. The controls are described in *Paper III*. BCVA was measured using a digital KM chart at distance and at near. VPPs were investigated using twelve questions from a structured history-taking model.[40,85–86] The questions were divided into five areas: recognition (questions 1–4), orientation (questions 5–7), depth perception (question 8), movement perception (questions 9–10), and simultaneous perception (questions 11–12) (**Appendix 2**). To avoid over-reporting of VPPs, only clearly affirmative answers such as "yes, always" and "yes, often" were counted as possible VPPs whereas "yes, sometimes" and "no" were considered not to represent VPPs.

QoL was divided into health-related QoL (HRQoL) and vision-related QoL (VRQoL). The Pediatric Quality of Life Inventory™-4.0 (PedsQL)[87] was used to investigate HRQoL whereas a Swedish version[88] of the National Eye Institute (NEI) 25-item Visual Function Questionnaire (VFQ-25)[89] was used to

investigate VRQoL. PedsQL has three scoring dimensions: total (23 items), psychosocial (15 items), physical (8 items). The classical test theory of VFQ-25 has 12 dimensions: general health (1 item), general vision (1 item), ocular pain (2 items), near activities (3 items), distance activities (3 items), social functioning (2 items), mental health (4 items), role difficulties (2 items), dependency (3 items), driving (3 items), color vision (1 item), peripheral vision (1 item). PedsQL has recently been validated in children 8–18 years with vision impairment.[90]

All participants with FASD from the adoption cohort were invited to participate in the study on QoL, but not all of them were willing to participate. The QoL data from the FASD group were therefore somewhat smaller (n=20) than the data on VPPs (n=30).

3.5 STATISTICAL METHODS

3.5.1 PAPER I

Frequencies, medians, minimums (min), maximums (max), means, standard deviation (SD), Z-scores, and standard deviation scores (SDSs) were calculated for descriptive purposes. A paired samples test was performed when comparing continuous data and the Kruskal-Wallis test was used to detect subgroup differences. All analyses were calculated using version 22 of SPSS (IBM Corp.)

3.5.2 PAPER II

Medians, min, max, means and SD were calculated for descriptive purposes. McNemar's exact test was used to analyze paired data of binary type, the Wilcoxon signed rank test was used for continuous data, and Fisher's exact test was used for categorical comparisons. To calculate confidence interval of the mean change from childhood to adulthood a linear non-parametric permutation test for paired observations was used for continuous variables. The analyses were performed using version 25 of SPSS Statistics (IBM Corporation, Armonk, New York, USA), the confidence interval was calculated by using SAS Software version 9.4. P-values <0.05 were considered statistically significant.

3.5.3 PAPER III

Medians, min, max, means and SD were calculated for descriptive purposes. The Mann–Whitney U-test was used to compare the FASD group with the controls. Fisher's exact test was used for categorical comparisons. The confidence interval for the mean difference between groups is based on Fishers non-Parametric permutation test. Spearman's rho was used when calculating correlations. Version 26 of SPSS Statistics (IBM Corporation, Somers New York, USA) was used when analyzing the data with exception from Fisher's exact test which was performed using QuickCalcs from GraphPad (https://www.graphpad.com/quickcalcs/ contingenecy1/), the confidence interval is calculated by using SAS Software version 9.4. P-values <0.05 were considered statistically significant.

3.5.4 PAPER IV

Medians, min, max, means and SD were calculated for descriptive purposes. Version 26 of SPSS Statistics (IBM Corporation, Somers, New York, USA) was used in all analyses apart from the confidence intervals (CI), where version 19.4.0 of MedCalc (MedCalc Software Ltd, Ostend, Belgium; https://www.medcalc.org/; 2020) was used. Fisher's exact test was used when comparing categorical variables between the groups, and McNemar's test was used when comparing paired data on VPPs. P-values <0.05 were considered statistically significant, and 95% CIs were calculated for the main findings when statistically possible. The Mann–Whitney U-test was used to compare the QoL data and the VA data between the FASD group and controls. PedsQL-4.0 scores were analyzed using the scaling and scoring manual by Varni,[87] and VFQ-25 scores were analyzed using the classical test theory from the NEI[89] as well as item response theory using Rasch analysis.[91]

3.6 ETHICAL CONSIDERATIONS

The research was approved by the Regional Ethical Committee at the Medical Faculty, Sahlgrenska Academy at Gothenburg University, Gothenburg, Sweden (approval no: 704-11 and 294-17).

The participants with FASD in this thesis had all been adopted from eastern Europe. One young woman dropped out with the explanation that everything connected to her adoption made her anxious and uncomfortable. She was invited to meet with our neuropsychologist, but preferred an appointment with her regular psychologist in her hometown.

4 RESULTS

4.1 PAPER I

Data on social circumstances were available for 36 (15 female, 21 male; mean age 22 years) out of the 37 individuals (97%) in the FASD cohort. Fourteen had attended special education, nine had completed primary school (9 years), eleven had completed secondary school (12 years), and the last two had attempted university studies but were not able to complete them. Out of the 36 young adults with FASD, eleven were working, ten lived on social welfare, and ten had a disability pension. Nine (six women and three men) had been victims of sexual abuse and four of physical assault. Two men reported convictions for violence and drug-related theft.

The medical evaluation was completed by 32 participants, 24 (75%) of whom had somatic health issues such as sleep disturbance (n=15), headache (n=11), pain other than headache (n=10), and stomach disturbance (n=6). Ten had a BMI ≥25, nine had high blood pressure, and seven were tobacco smokers. In total, psychotropic medications such as ADHD medication and antidepressants were used by 16 participants (46%). Anthropometric measurements showed that the participants were still of short stature. Mean SDS at baseline examination and at follow-up is shown in **Table 3**. Over 70% of the participants had a lip/philtrum rank (**Appendix 1**) ≥4 **(Table 2**) both in childhood and in young adulthood.

Table 3. *Anthropometric measurements in childhood and early adulthood in participants with fetal alcohol spectrum disorders (FASD) and fetal alcohol syndrome (FAS).*

	Childhood SDS mean	**Early adulthood** SDS mean
FASD	n=28	n=28
Weight	-0.9	-0.4
Height	-1.0	-1.4
Head circumference	-1.5	-1.0
FAS	n=19	n=19
Weight	-1.4	-0.8
Height	-1.3	-1.7
Head circumference	-2.5	-1.9

SDS=standard deviation score

A psychiatric evaluation was performed both in childhood and in early adulthood (**Table 4**). ADHD, autism, and obsessive-compulsive disorder (OCD) were present in both childhood and young adulthood, while the other diagnoses altered between the two study periods. Clinical Global Impression—Severity score[79] was used at follow-up; one participant was considered normal, five were ranked as borderline to mildly ill, six as moderately to markedly ill, and 21 as severely to extremely ill. The score is explained in **Appendix 3**.

Table 4. *DSM-IV diagnoses in childhood and in early adulthood among the participants with fetal alcohol spectrum disorders.*

	Childhood n=37 n (%)	**Early adulthood** n=33 n (%)
Any psychiatric disorder	30 (81)	29 (88)
Attention deficit hyperactivity disorder	23 (62)	23 (70)
Autism	2 (5)	4 (12)
Obsessive compulsive disorder	1 (3)	2 (6)
Oppositional defiant disorder	16 (43)	N/A
Developmental coordination disorder	15 (41)	N/A
Tic disorder	5 (14)	N/A
Conduct disorder	2 (5)	N/A
Any anxiety disorder	N/A	17 (52)
Social phobia	N/A	8 (24)
Panic disorder	N/A	7 (21)
Generalized anxiety disorder	N/A	7 (21)
Agoraphobia	N/A	5 (15)
Any depressive episode	N/A	14 (42)
Self-harm	N/A	8 (24)
Suicide attempt	N/A	7 (21)
Substance use disorder	N/A	4 (12)
Manic or hypomanic episode	N/A	3 (9)
Antisocial personality disorder	N/A	2 (6)
Eating disorder	N/A	2 (6)
Psychotic disorder	N/A	1 (3)

N/A=not available

The ophthalmological evaluation revealed that 29 of 30 (97%) had ophthalmological findings, with a wide range in severity. ICD and PFL were measured as a part of the examination (**Table 5**). PFL is included in the FASD diagnostic criteria. PFL≤10th percentile was found in 23/29 (79%) in childhood

and in 14/29 (48%) in early adulthood, which represented a significant decrease (p=0.012).

Table 5. *Palpebral fissure length (PFL) and inner canthal distance (ICD) in childhood and early adulthood in a group of individuals with fetal alcohol spectrum disorders (FASD) adopted from eastern Europe to Sweden.*

	Childhood n=29	**Early adulthood** n=29
PFL, mm		
Right eye		
mean (SD)	25 (2)	29 (3)
median (min; max)	25 (21; 29)	29 (24; 32)
mean z-score (SD)	-1.5 (0.8)	-1.4 (1.7)
Left eye		
mean (SD)	25 (2)	29 (3)
median (min; max)	25 (21; 29)	29 (24; 32)
mean z-score (SD)	-1.5 (0.8)	-1.4 (1.7)
ICD, mm		
mean (SD)	29 (3)	31 (3)
median (min; max)	29 (24; 35)	32 (26; 37)
mean z-score (SD)	-0.3 (1.2)	0.3 (1.2)
ICD≥5–10 mm>PFL* n (%)	13 (45)	10 (34)

*ICD≥5–10mm>PFL is defined as a difference of ≥5 mm between the ICD and the smallest PFL in the same individual.

The psychological evaluation consisted of IQ and Leiter-R scores regarding social and cognitive abilities rated by the psychologist. The results are summarized in **Table 6**.

Table 6. *Intelligence quotient in the participants with fetal alcohol spectrum disorders.*

	Childhood n=29	**Early adulthood** n=29
Intelligence quotient		
mean (SD)	86 (15)	68 (21)
median (min; max)	87 (50; 107)	62 (36; 121)

SD=standard deviation, min=minimum, max=maximum

4.2 PAPER II

This paper was concerned with the ophthalmological outcome from the follow-up examination of the FASD group from the adoption cohort. In all, 30 (17 male, 13 female) young adults with FASD (FAS=19, PFAS=6, ARND=5) from the original cohort participated (**Figure 12**). The mean age was 23 years (19–28 years), and the mean follow-up time was 15 years (13–18 years). Six participants with FAS were examined in both 2014 and 2017–2019. The results from 2017–2019 were used in the analysis. **Table 7–9** summarizes the results from the examination. Astigmatism, anisometropia, abnormal or negative stereoacuity, strabismus, and morphological aberrations persisted into young adulthood.

Table 7. *Visual acuity and refractive errors in 30 individuals with fetal alcohol spectrum disorders.*

	Childhood n=30	**Early adulthood** n=30	**Change from childhood to adulthood**	
BCVA at distance decimal notation	median (min; max)	median (min; max)		**p-value**
Right eye	0.65 (0.1; 1.0)	0.9 (0.01; 1.3)		**0.001**
Left eye	0.65 (0.1; 1.0)	1.0 (0.1; 1.3)		**<0.0001**
BCVA at distance logMAR	mean (SD) median (min; max) (95% CI for mean)	mean (SD) median (min; max) (95% CI for mean)	mean (SD) median (min; max) (95% CI for mean)	
Right eye	0.3 (0.3) 0.2 (0.0; 1.0) (0.2; 0.4)	0.2 (0.5) 0.05 (-0.10; 2.0) (0.03; 0.4)	-0.04 (0.4) -0.10 (-0.6; 1.2) (-0.2; 0.09)	**0.048***
Left eye	0.3 (0.3) 0.2 (0.0; 1.0) (0.2; 0.4)	0.1 (0.2) 0.0 (-0.10; 1.0) (0.04; 0.2)	-0.2 (0.2) -0.10 (-0.6; 0.1) (-0.2; -0.09)	**<0.0001**
Refraction D SE	mean (SD) median (min; max) (95% CI for mean)	mean (SD) median (min; max) (95% CI for mean)	mean (SD) median (min; max) (95% CI for mean)	
Right eye	+0.7 (3) +0.9 (-8.8; +4.8) (-0.3; 1.7)	-1.0 (3.0) -0.3 (-12; +2.8) (-2.2; 0.06)	-1.7 (1.4) -1.4 (-4.6; 0.4) (-2.2; -1.2)	**<0.0001**
Left eye	+1.1 (2.4) +1.3 (-9.4; +5.3) (-0.2; 2.0)	-0.8 (2.9) -0.3 (-13.3; +2.6) (-1.9; + 0.3)	-1.9 (1.5) -1.6 (-6.4; 0.3) (-2.5; -1.4)	**<0.0001**

BCVA=best corrected visual acuity; D=diopter; logMAR=Logarithm of the Minimum Angle of Resolution; SE=spherical equivalent.
The Fisher non-parametric permutation test for paired observations failed to approximate the p-value so Wilcoxon signed rank test was used instead.

Table 8. *Ophthalmological data on 30 individuals with fetal alcohol spectrum disorders in childhood and in early adulthood.*

	Childhood n=30	**Early adulthood** n=30	**Change from childhood to adulthood**		**p-value**
Refractive errors n (%)					
Hyperopia ≥2.5 D SE	7 (23)	3 (10)	Decrease Equal Increase	4 (13.3%) 26 (86.7%) 0 (0.0%)	0.13
Myopia ≥0.50 D SE	4 (13)	13 (43)	Decrease Equal Increase	0 (0.0%) 21 (70.0%) 9 (30.0%)	**0.004**
Astigmatism ≥1 D	13 (40)	14 (47)	Decrease Equal Increase	4 (13.3%) 21 (70.0%) 5 (16.7%)	1.00
Anisometropia ≥1 D SE	7 (23)	8 (27)	Decrease Equal Increase	5 (16.7%) 19 (63.3%) 6 (20.0%)	1.00
No refractive error	14 (47)	9 (30)	Decrease Equal Increase	8 (26.7%) 19 (63.3%) 3 (10.0%)	0.23
Stereoacuity n (%)					
≤60″	10 (33)	8 (27)	Decrease Equal Increase	2 (6.7%) 28 (93.3%) 0 (0.0%)	0.50
>60″ (but not negative)	10 (33)	12 (40)	Decrease Equal Increase	1 (3.3%) 26 (86.7%) 3 (10.0%)	0.63
Negative	10 (33)	10 (33)	Decrease Equal Increase	1 (3.3%) 28 (93.3%) 1 (3.3%)	1.00
Strabismus n (%)					
Heterotropia at distance	11 (37)	13 (43)	Decrease Equal Increase	0 (0.0%) 28 (93.3%) 2 (6.7%)	0.50
Heterotropia at near	12 (40)	13 (43)	Decrease Equal Increase	1 (3.3%) 27 (90.0%) 2 (6.7%)	1.00
Heterophoria at distance	3 (10)	6 (20)	Decrease Equal Increase	0 (0.0%) 27 (90.0%) 3 (10.0%)	0.25
Heterophoria at near	5 (17)	9 (30)	Decrease Equal Increase	3 (10.0%) 20 (66.7%) 3 (10.0%)	0.34

″=arc second**;** D=diopter; SE=spherical equivalent.

Table 9. *Data on ophthalmological morphology of 30 individuals with fetal alcohol spectrum disorders.*

	Childhood n=30	**Early adulthood** n=30	**Change from childhood to adulthood**		**p-value**
Morphology n (%)					
Ptosis	2 (7)	2 (7)	Decrease Equal Increase	0 (0.0%) 30 (100.0%) 0 (0.0%)	1.00
Epicanthus	4 (13)	0	Decrease Equal Increase	4 (13.3%) 26 (86.7%) 0 (0.0%)	0.13
Tortuosity of retinal vessels	8 (27)	11 (37)	Decrease Equal Increase	1 (3.3%) 25 (83.3%) 4 (13.3%)	0.38
Optic nerve hypoplasia	3 (10)	4 (13)	Decrease Equal Increase	0 (0.0%) 29 (96.7%) 1 (3.3%)	1.00
Optic nerve abnormality, other than ONH*	6 (20)	7 (23)	Decrease Equal Increase	1 (3.3%) 27 (90.0%) 2 (6.7%)	1.00

ONH=optic nerve hypoplasia
*Optic nerve abnormalities include optic discs with unsharp edges, atypical configuration, and damaged rim.

In three cases the gestational age was unknown. Twelve of the remaining 27 participants were born preterm (gestational week 31–36), and ten of these (83%) had refractive errors while eight (67%) had strabismus and/or subnormal stereoacuity. Among the 15 born at term, nine (60%) had refractive errors and eight (53%) had strabismus and/or subnormal stereoacuity. A post hoc analysis of the impact of prematurity within the FASD cohort showed no significant differences concerning refractive errors (p=0.24) or strabismus/subnormal stereovision (p=0.70) when comparing those born preterm with those born at term.

4.3 PAPER III

In this paper both young adults with FASD and controls were examined. Although 31 young adults with FASD initially agreed to participate (**Figure 12**), one woman dropped out; hence OCT examinations of the macula and the optic disc were performed in 30 participants with FASD. In 26 young adults with FASD (FAS=18, PFAS=6, ARND=2), the examinations generated reliable data for analysis for at least one eye. Most of the controls were medical students. With only one exception, the rest of the controls were university students from other educational programs. None of the participants in the control group was adopted. The controls were examined in 2018–2019. One control was excluded due to preterm birth and two participants due to a high degree of myopia (≥6 D SE), leaving 27 controls for analysis. **Figure 14** shows a cross-sectional image of the macula from one of the controls and the retinal layers that could be visualized.

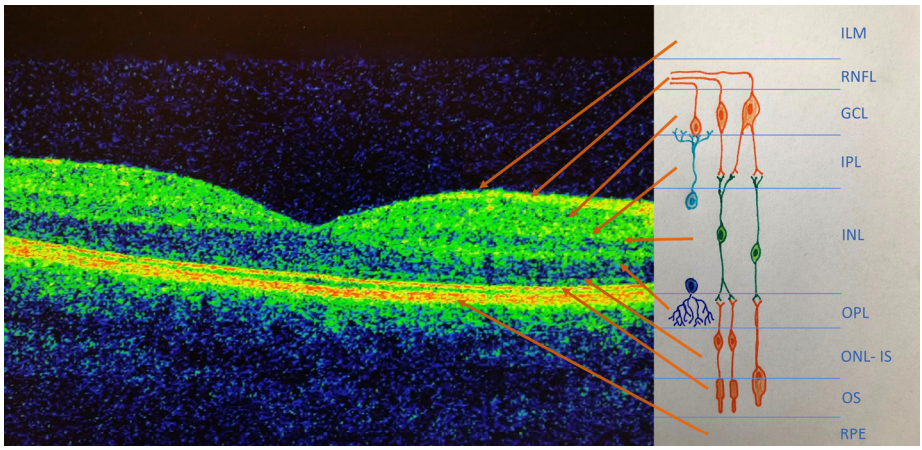

Figure 14. *A cross-sectional optical coherence tomography (OCT) scan of the retina with the fovea in the center and a schematic image of the retinal layers: internal limiting membrane (ILM), retinal nerve fiber layer (RNFL), ganglion cell layer (GCL) with ganglion cells, inner plexiform layer (IPL), inner nuclear layer (INL), outer plexiform layer (OPL), outer nuclear layer — inner segment (ONL-IS), outer segment (OS), and retinal pigment epithelium (RPE). Illustration and OCT scan: Emelie Gyllencreutz.*

Data on demographics, VA, refraction, and morphology are summarized in **Table 10**.

Table 10. *Demographic and ophthalmological data on 26 individuals with fetal alcohol spectrum disorders (FASD) and 27 controls.*

	FASD n=26	**Controls** n=27	**p-value**
Demographic data			
Female, n (%)	12 (46)	18 (68)	0.17
Male, n (%)	14 (54)	9 (32)	
Age in years			
Mean (SD)	24 (2.5)	25 (2.0)	0.17
Median (min; max)	23 (19; 27)	25 (21; 29)	
Born preterm*, n	10	0	
Ophthalmological data			
BCVA			
RE decimal fraction			
Median (min; max)	0.9 (0.05; 1.3) n=25†	1.1 (0.9; 1.3)	**0.003**
LE decimal fraction			
Median (min; max)	1.0 (0.1; 1.3)	1.1 (0.8; 1.6)	**0.001**
RE logMAR			
Mean (SD)	0.1 (0.5)	-0.03 (0.05)	
Median (min; max)	0.05 (1.3; -0.10) n=25†	0.00 (0.05; -0.1)	**0.003**
LE logMAR			
Mean (SD)	0.1 (0.2)	-0.04 (0.07)	
Median (min; max)	0.00 (1.0; -0.01)	0.00 (0.1; -0.20)	**0.001**
Refraction, D SE			
RE			
Mean (SD)	-0.9 (2.8)	-1.3 (2.0)	
Median (min; max)	-0.3 (-3.9; +2.6) n=25†	-0.5 (-4.5; +1.0)	0.20
LE			
Mean (SD)	-0.8 (2.9)	-1.3 (2.0)	
Median (min; max)	-0.3 (-4.1 to +1.6)	-0.6 (-4.1 to +1.3)	0.07
Morphology, n (%)			
ONH‡ in either eye	4 (15)	0	0.051

BCVA=best corrected visual acuity; D=diopter; logMAR=logarithm of the minimum angle of resolution; ONH=optic nerve hypoplasia; SE=spherical equivalent.
*Gestational week 31–36.
†One male participant contributed only with the LE, as the RE had myopia >6D SE.
‡ONH was defined clinically as a small optic disc, with or without a double-ring sign.

In the FASD group, accurate OCT measurements of the optic disc was harder to achieve than OCT of the macula, mainly because of fixation difficulties. Reliable data of the optic disc was finally acquired in 22 right eyes and 25 left

eyes, despite several attempt to receive a high-quality examination of both eyes in all participants.

The results from the measurement of the optic disc and the macular topography are depicted in **Figure 15** and **Table 11** and those from of the macula in **Figures 16–19.** The OCT measurements showed that both the total peripapillary RNFL and the macular RNFL in a majority of the ETDRS areas were thinner in the FASD group than in the controls, and that the macular volume was somewhat smaller in the FASD group than in controls.

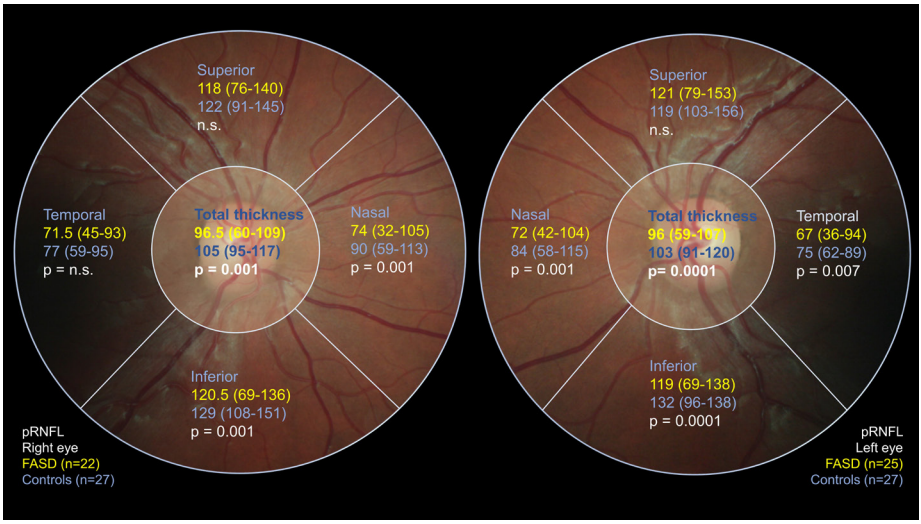

Figure 15. *Optical coherence tomography measurements depicting the median (min–max) of the peripapillary retinal nerve fiber layer in micrometers in both eyes.*

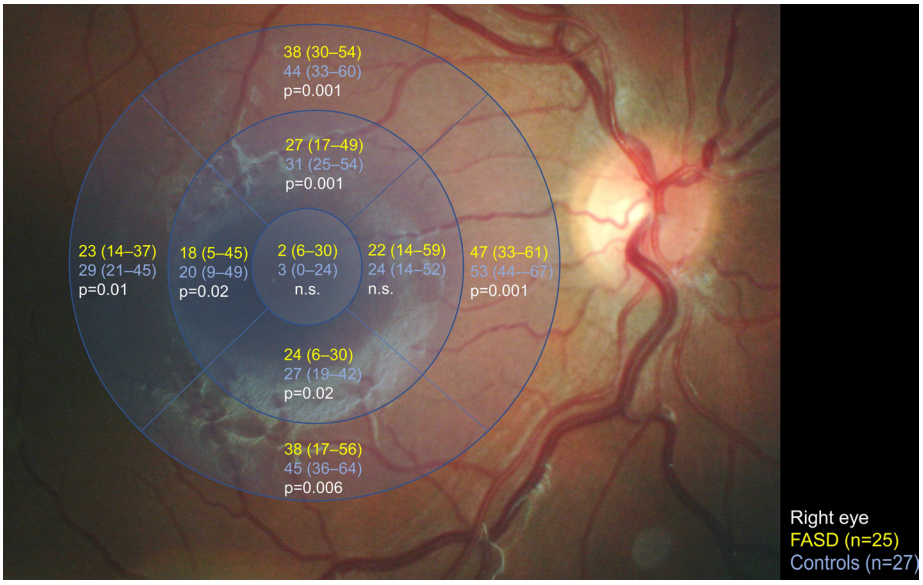

Figure 16. *Optical coherence tomography measurement of the retinal nerve fiber layer from the right eyes. Median (min–max) in micrometers.*

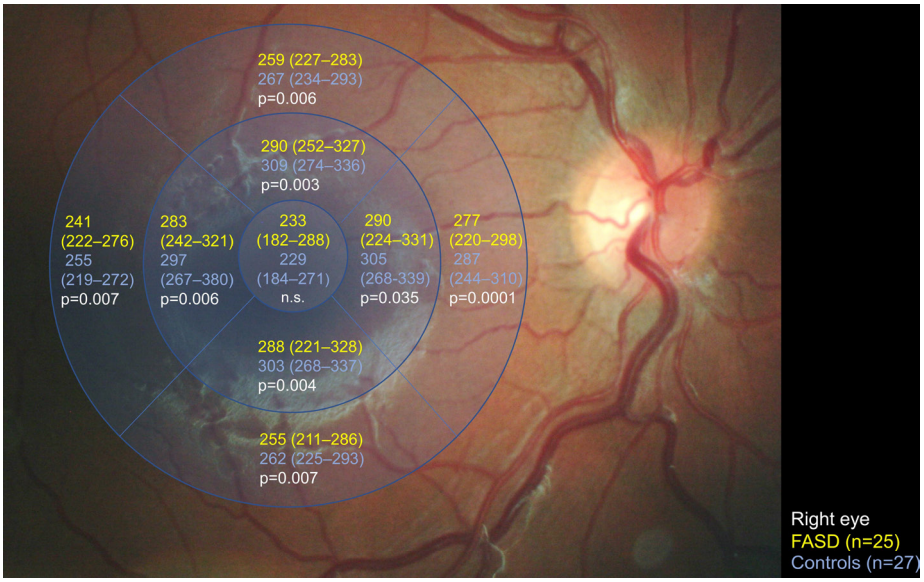

Figure 17. *Optical coherence tomography measurement of the retinal thickness from the right eyes. Median (min–max) in micrometers.*

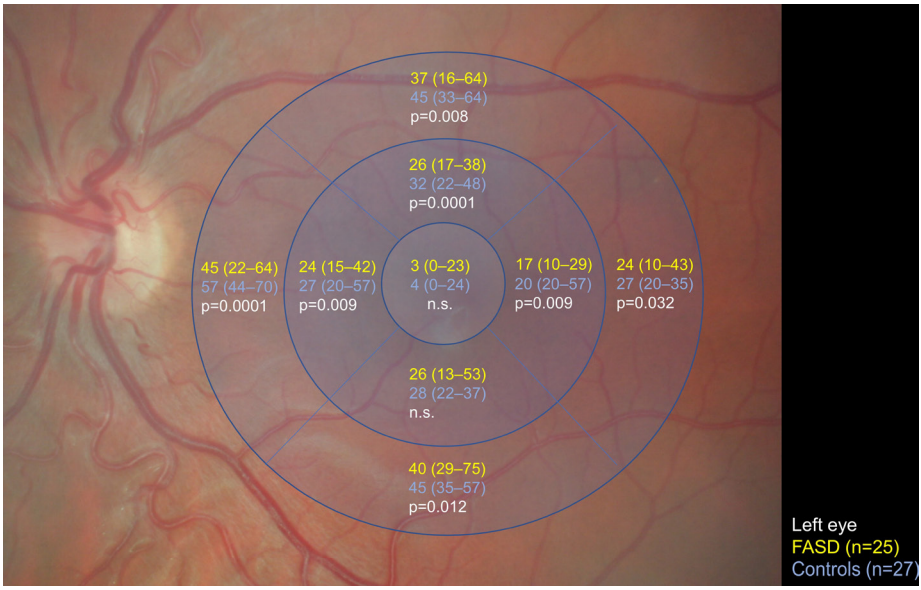

Figure 18. *Optical coherence tomography measurement of the retinal nerve fiber layer from the left eyes. Median (min–max) in micrometers.*

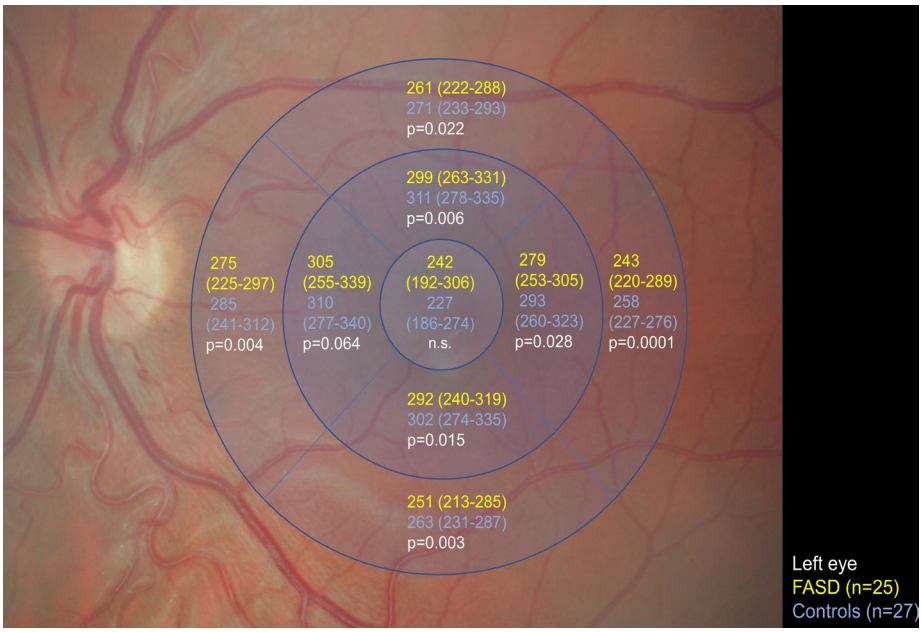

Figure 19. *Optical coherence tomography measurement of the retinal thickness from the left eyes. Median (min–max) in micrometers.*

Table 11. *Optical coherence tomography measurements of the macula and optic disc.*

Optical coherence tomography	**FASD** n=26*	**Controls** n=27	**p-value**
Macular topography	Median (min–max)	Median (min–max)	
Foveal minimum, RE, µm	196 (155–290) n=25	186 (166–238)	0.2
Foveal minimum, LE, µm	203 (164–314)	186 (160–229)	0.06
Macular volume, RE, mm^3	7.5 (6.3–8.3) n=25	7.8 (6.8–8.4)	**0.003**
Macular volume, LE, mm^3	7.5 (6.4–8.4)	7.9 (6.8–8.5)	**0.009**
Optic disc parameters	Median (min–max)	Median (min–max)	
ODA, RE, mm^2	2.2 (1.4–2.8) n=22	2.2 (1.7–3.3)	1.0
ODA, LE, mm^2	2.2 (1.3–2.9) n=25	2.2 (1.7–3.2)	0.4
Rim area, RE, mm^2	1.6 (1.0–2.2) n=22	1.8 (0.8–2.8)	0.4
Rim area, LE, mm^2	1.6 (1.0–2.9) n=25	1.6 (0.6–2.9)	0.5
Cup area, RE, mm^2	0.5 (0.0–1.2) n=22	0.5 (0.0–1.8)	0.3
Cup area, LE, mm^2	0.4 (0.0–1.3) n=25	0.5 (0.0–2.)	0.7
Optic disc symmetry, %	87 (40–97) n=22	87 (65–94)	0.8

*Where the number differs from the total number of participants in the group, this is given separately when applicable.
One female contributed only with her right eye and one male only with his left eye.
FASD=fetal alcohol spectrum disorders; LE=left eye; ODA=optic disc area; RE=right eye.

4.4 PAPER IV

Paper IV describes the occurrence and persistence over time of VPPs in individuals with FASD and compares VPPs, health- as well as vison-related quality of life (QoL) in young adults with FASD with these variables in healthy controls. The demographic and ophthalmological data are summarized in **Table 12**.

Table 12. *Demographic and ophthalmological data in 30 individuals with fetal alcohol spectrum disorders (FASD) and 29 healthy controls.*

	FASD n=30*	**Controls** n=29	**p-value**
Demographic data			
Female, n (%)	13 (43)	20 (69)	0.12
Male, n (%)	17 (57)	9 (31)	0.12
Age in years			
Mean (SD)	23 (2.7)	25 (2.0)	0.08
Median (min; max)	22 (19; 28)	25 (21; 29)	
FAS, n	19	0	
PFAS, n	6	0	
ARND, n	5	0	
Born preterm†, n (%)	10 (37) n=27	0	
Ophthalmological data			
BCVA, binocular,			
At distance, logMAR			
Mean (SD)	0.03 (0.11)	-0.07 (0.06)	
Median (min; max)	0.00 (0.30; 0.10)	-0.11 (0.00; -0.20)	**0.0001**
At near, logMAR			
Mean (SD)	0.05 (0.08)	0.00 (0.00)	
Median (min; max)	0.00 (0.30; 0.0)	0.0 (0.00; 0.00)	**0.0001**
At distance, decimal fraction			
Median (min; max)	1.0 (0.5; 1.25)	1.0 (1.0; 1.6)	**0.0001**
At near, decimal fraction			
Median (min; max)	1.0 (0.5; 1.0)	1.0 (1.0; 1.0)	**0.0001**

ARND=alcohol-related neurodevelopmental disorder; BCVA=best corrected visual acuity; FAS=fetal alcohol syndrome; logMAR=logarithm of the minimum angle of resolution; PFAS=partial fetal alcohol syndrome.
*Where the number differs from the total number of participants in the group, this is given separately when applicable.
†Gestational week <37. In three cases in the FASD group, gestational age was unknown.

VPPs were reported more frequently in the FASD group (16/30) compared with in the control group (1/29), p=0.0001 **(Figure 20).**

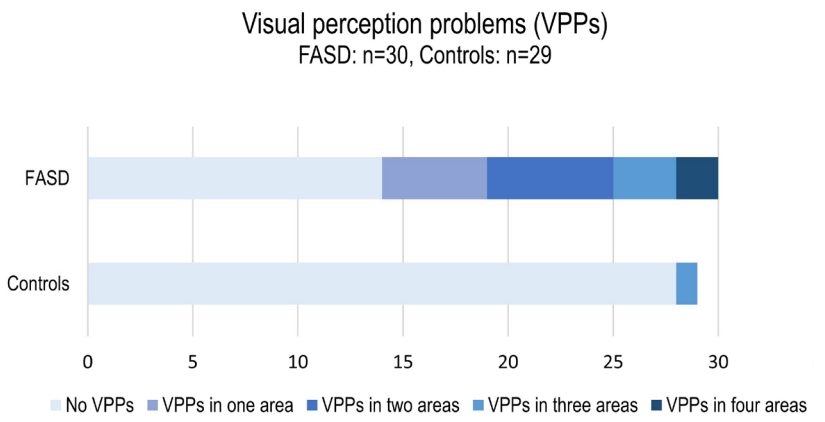

Figure 20. *Visual perception problems (VPPs) among 30 individuals with fetal alcohol spectrum disorders (FASD) and 29 controls. Sixteen in the FASD group in a median of one area (range 1–4) and one in the control group reported having VPPs. None of the participants reported problems in all five areas.*

The most frequently affected area was simultaneous perception; ten participants in the FASD group reported problems in this area. Among the eight reporting depth perception problems, five had strabismus. The number of participants reporting problems in the different areas is depicted in **Figure 21.**

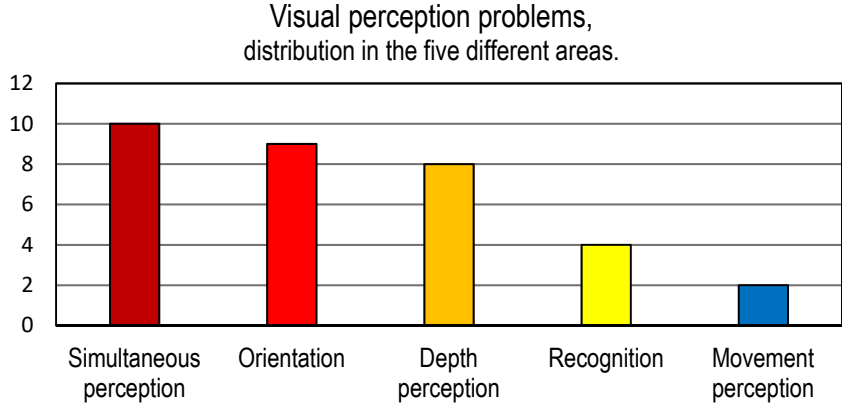

Figure 21. *Sixteen participants with fetal alcohol spectrum disorders. The most affected area was the one that involved problems with simultaneous perception (n=10). Problems with orientation and depth perception were also common.*

Data on VPPs reported in childhood as well as in young adulthood were available for 27 participants with FASD. Of the eight who reported VPPs in childhood, five also reported VPPs at follow-up. Three participants reported VPPs only in childhood (only in one area) and ten participants reported VPPs in young adulthood but had not reported VPPs in the childhood investigation. Thus, VPPs were found in childhood as well as in early adulthood.

All participants with FASD from the adoption cohort were invited to answer the questions on QoL, but not all of them were willing to participate in further investigations. HRQoL was assessed in 20 individuals (FAS: n=9, PFAS: n=6, ARND: n=5) and VRQoL in 19 (FAS: n=8, PFAS: n=6, ARND: n=5). All 29 individuals in the control group completed both questionnaires. The main findings are summarized in **Table 13**. The participants with FASD had significantly worse HRQoL and VRQoL compared with the controls.

Table 13. *Health-related and vision-related quality of life (QoL) in 20 young adults with fetal alcohol spectrum disorders (FASD) and 29 controls, investigated with the Pediatric Quality of Life Inventory™ (PedsQL) and the National Eye Institute 25-Item Visual Function Questionnaire (VFQ-25).*

	FASD Median score: min/max (95% CI)	**Controls** Median score: min/max (95% CI)	**p-value**
Health-related QoL (PedsQL)	(n=20)	(n=29)	
Total score	83: 63/98 (76–88)	91: 64/99 (90–95)	**0.0001**
Psychosocial	78: 50/98 (66–85)	90: 45/100 (87–93)	**0.003**
Physical	89: 75/100 (81–97)	100: 88/100 (100–100)	**0.0001**
Vision-related QoL (VFQ-25)	(n = 19)	(n = 29)	
Classical test theory			
General health	75: 0/100 (75–100)	100: 50/100 (100–100)	**0.001**
General vision	80: 20/100 (80–100)	100: 60/100 (100–100)	**0.003**
Item response theory - Rasch analysis			
Socio-emotional	100: 62/100 (81–100)	100: 74/100 (100–100)	**0.002**

CI=confidence interval
PedsQL and VFQ-25: High scores indicate good QoL.

5 DISCUSSION

The overall aim of this thesis was to investigate the characteristics and long-term outcome in young adults with FASD, in general and from an ophthalmological point of view. In our long-term follow-up studies, we have found that young adults with FASD are a vulnerable group of individuals with general health problems including psychiatric disorders, impaired cognitive function, poor QoL, and ophthalmological conditions such as astigmatism, strabismus, structural abnormalities, and VPPs. Our FASD cohort is a unique group of young adults who has been extensively examined by a research group with long experience of FASD evaluations.

In *Paper I* we found that the proportion fulfilling the anthropometric criteria for FASD decreased somewhat between childhood and young adulthood, though the lip/philtrum rank remained high. The proportion exhibiting short PFL decreased from 79% in childhood to 48% in early adulthood. However, the lack of validated scales for dysmorphological evaluation of FASD in adults, as well as the observer bias, must be taken into consideration when interpreting these results. A high proportion (88%) of the young adults in this cohort had psychiatric disorders of some kind, and that the rates of depression, anxiety disorders, and suicide attempts were similar to those found in other studies of young adults with FASD.[92–93] FASD have primarily been investigated in children, however there are some reports of adult outcome.[92–94] A thesis from 2016 on adults with FAS according to the Swedish register of patients concluded that these adults were less likely to be employed than individuals in a comparison group from the national register,[94] and that adults with PAE have problems with depression and are often victims of crime. Young adults with FASD are a vulnerable group in need of support and understanding from society, including the health care system. As FASD is not always externally detectable, special consideration may be needed from physicians as well as nurses and other health care workers when meeting young adults who do not act as might be expected.

In *Paper I* we also found that health issues such as epilepsy and motor abnormalities tended to persist or increase from childhood into early adulthood. This was also true for some of the ophthalmological findings presented in *Paper II*. Astigmatism, anisometropia, affected stereoacuity, strabismus, ptosis, tortuosity of the retinal vessels, and optic nerve abnormalities, remained unchanged on a group level with a mean follow-up time of 15 years. Our research group is the first to report the long-term ophthalmological outcome in individuals with FASD. The persistence of some

important ophthalmological variables might be valuable in the evaluation of young adults who have not been investigated for FASD in childhood. Especially as the facial features characteristic of FAS might diminish with age.[92] An ophthalmological examination might serve as an additional tool for FASD diagnosis in children as well as in young adults.

Paper III compared retina and optic disc measurements between the FASD group and controls. The participants with FASD had lower VA and thinner macular and peripapillary RNFL than the controls, this in agreement with a study from Spain in which participants with FAS had significantly thinner peripapillary RNFL compared with control subjects.[95] When comparing the results with another study that investigated different age groups, the RNFL in the FASD group was similar to individuals in the age span 70–85 years,[96] rather than to individuals of the same age. However, as another type of OCT was used in that study, this interpretation must be confirmed by other studies. Effects of PAE on the vascular structures of the brain has been investigated in animal models. It has been reported that PAE can affect vasoconstriction in fetal brain vessels.[97] Likewise, animal models should be interesting to use when investing the effect of PAE on the RNFL and the retinal vessels.

FAS was first evaluated from an ophthalmological perspective by Strömland who reported a high proportion of ONH.[6,8–9,98] In our cohort, ONH was not as frequently found. The diagnosis of ONH is somewhat problematic. Like other ophthalmological terms such as myopia, hyperopia, and amblyopia, the prevalence of ONH in studies is dependent on which definition is used. In the early works in the 1980's by Strömland, ONH was defined as ≤-1 SD from the normal mean size, measured on fundus photographs and this definition was in alignment with the clinical impression of ONH while examining the child with ophthalmoscopy.[8] However, the cut off used when to consider an optic disc as hypoplastic differ between studies. In the most recent prevalence study of ONH in Sweden, the cut off ≤ -2 SD was used.[35] In *Paper II* and *III*, the clinical impression of ONH was used when deciding whether an individual had ONH. In *Paper III* measurements on photographs using the retinal size tool program were performed.[99] As mentioned in the introduction, the size of the optic disc can be measured using different tools such as measurements on fundus photos and automatic measurements from OCT. Irrespectively of which method used, when ONH is found, FASD should be considered, keeping in mind that ONH is neither a mandatory ophthalmological finding in patients with FASD nor explicit for children with PAE.

In addition to ONH, increased tortuosity of the retinal vessels has been described in children with FAS. However, neither ONH nor increased tortuosity of the retinal vessels is exclusive to FAS; they are also found, for example, in children born preterm and are associated with retinopathy of prematurity (ROP).[100–102]

Ophthalmology is still a largely unexplored topic in FASD research. Not only have there been few publications on the ophthalmological aspects of FASD, most of the publications that do exist have small numbers of participants, making it hard to adjust for possible confounding factors such as prematurity, infections, and teratogens other than alcohol. The small sample size is a limitation also in the papers in this thesis and even though the results have not been adjusted for confounding factors, prematurity has been investigated with special interest. Alcohol is a well-known teratogen and alcohol consumption during pregnancy increases the risk of preterm birth.[103] Preterm birth is among other things associated with increased risk of refractive errors and strabismus. However, in the post hoc analysis of the participants in the present FASD group who presented with refractive errors and strabismus, no difference was found between those born at term and those born before GA 37 weeks. To be able to draw trustworthy conclusions regarding the ophthalmological aspects of FASD, larger studies are warranted in the future.

The occurrence of medical conditions in young adults with FASD has been described in a book chapter written by three members of the Canadian FASD patient network based on 541 responses from a survey sent to individuals with FASD living in Canada and the U.S. The mean age among those who answered was 27.5 years, and the majority (43.4%) of the respondents were 20–30 years old. They reported a large number of different health issues such as autism, ADHD, anxiety, cleft lip or palate, cerebral palsy, congenital heart defects, fused vertebrae in the neck, ptosis, refractive errors, and strabismus,[104] usually in much higher frequencies than the general population in Canada and the U.S. In the survey from Canada,[104] strabismus was reported in 36% of the respondents. The survey outline that ophthalmological abnormalities are present in individuals with FASD, and as the survey was initiated by individuals with FASD, ophthalmological diagnosis is likely something the patients consider important as these issues were included in the survey. The investigation of VPPs in *Paper IV* revealed that 27% of our cohort reported problems with depth perception compared with 31% among respondents to the Canadian survey.[104] In addition to VPPs, *Paper IV* also investigated QoL. The participants with FASD had significantly worse QoL compared with the controls, HRQoL as well as VRQoL. Low HRQoL might be explained by the high co-existence with psychiatric disorders. The fact that the participants in

the FASD cohort were adoptees might also explain the lower scores concerning HRQoL. However, all adoptees do not have worse mental health compared with non-adopted individuals.[105]

VRQoL was investigated using VFQ-25, a questionnaire and is widely used in investigations of VRQoL. If VRQoL should be investigated further, in-depth interviews might give even more accurate information of the actual VRQoL in young adults with FASD, especially as the questionnaire we used presupposed that the participants were literate, which was not the case in all FASD participants. Some of the participants could hardly write their first name with capital letters, and were not able to respond to questions such as "Do you have difficulty reading ordinary print in newspapers?"

Genetic predisposition might to some extent explain why PAE harms some fetuses more than others. Furthermore, the effects of PAE are highly dependent on when the fetus is exposed, for how long the exposure lasts, and finally the dose of alcohol. The most severe damage is usually noted in children born to mothers who used alcohol during the whole pregnancy. Binge drinking has proven to be the most damaging to the fetus.[106] Efforts have been made to study the direct effect of alcohol on ophthalmological abnormalities, but the results have been inconclusive and are difficult to rely on due to high degree of drop-outs.[107–108]

When comparing different studies on FASD, it is always important to consider the diagnostic criteria. The participants with FASD in this thesis were all examined in childhood, due to their adoption.[11,26,67–68] Even in the same cohort of adoptees, the outcome regarding diagnosis of FASD differed somewhat depending on which guidelines were used. The diversity between the different diagnostic guidelines has been discussed both in published articles[66,109] and at FASD conferences such as EUFASD 2018 in Berlin. From an ophthalmological perspective, the use of different diagnostic criteria is important to consider and the ophthalmological outcome might alter between different cohorts of FASD subjects. When applying the latest guidelines by Hoyme et al.,[18] four of the 37 participants in the FASD cohort did not fulfill a FASD diagnosis, one of them had a normal ophthalmological status whereas the remaining three presented with strabismus as well as with refractive errors. The disagreement between the guidelines by Hoyme et al. from 2005 and those from 2015 has been described in a study from South Africa.[110]

One challenge in the care of individuals with FASD is the fact that it might be a hidden disability. At patients' websites such as FAS-portalen,[111] one can read about the struggle of some parents to find help for their children with suspected FAS. Children with syndromic features but no explanatory genetic aberration need just as much care from society and the health care system as a child with a clear diagnosis. In addition, FAS might occur in combination with genetic syndromes. Unless the individual receives a diagnosis in childhood, a congenital reason for health issues later in life might not even be considered.

Hopefully, increased awareness of FASD might help individuals with FASD to receive the best health care possible, regardless of their age when first examined. A comprehensive ophthalmological investigation including an OCT examination as well as a structured history taking on VPPs might help us to find patients with FASD and to further understand the complexity of FASD.

6 CONCLUSIONS

- The young adults diagnosed with FASD in this cohort are a vulnerable group of individuals with ophthalmological, psychiatric, and intellectual disabilities.

- A detailed ophthalmological examination, including a structured history-taking regarding VPPs, is likely to reveal ophthalmological aberration in both children and young adults with FASD.

- PAE may harm the RNFL as well as other structures of the eye. In this cohort, the young adults with FASD had thinner peripapillary and macular RNFL as well as less macular volumes than controls without FASD.

- VPPs were common in this cohort of young adults with FASD and can persist into young adulthood. VPPs alone or in combination with other ophthalmological problems might cause impairment of VRQoL in individuals with FASD.

- Low HRQoL was found among the young adults with FASD in this cohort, which possibly might be explained by the high degree of psychiatric co-morbidity and/or the participants in the FASD group being adopted.

7 FUTURE PERSPECTIVES

The idea of using ophthalmological examination as an additional diagnostic tool has long been present in our research group. In an ongoing evaluation, a combination of different levels of visual acuity, refraction, strabismus/stereoacuity, and morphological abnormalities have been put together in a FASD eye code. This eye code is now being validated in a population of children suspected of having FASD and has previously been applied on children with ADHD, in children born moderate-to-late preterm without having ROP, and in children with Silver Russel syndrome.

Further ophthalmological investigations on FASD-patients would be of interest. For example, examining the retinal vessels using OCT angiography and oximetry. High blood pressure was measured in nine cases in our cohort, and being SGA is a known risk factor of developing high blood pressure as well as diabetes. PAE might be an additional risk factor and might affect the retinal vessels. Further interesting fields to investigate in individuals with FASD is the ocular movements, especially if measured with an eye tracker. Previous findings have suggested that the ocular motor control may be affected in children with FASD.[112] Finally, investigating VRQoL by means of in-depth interviews, might give us more detailed information on the importance of ophthalmology in FASD and the patients' experience of their ophthalmological conditions.

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APPENDIX

Appendix 1: Lip/philtrum guides

https://depts.washington.edu/fasdpn/htmls/lip-philtrum-guides.htm

https://pediatrics.aappublications.org/content/138/2/e20154256/tab-figures-data

Appendix 2: Questionnaire on visual perception problems

The questionnaire is available on page 67 (Appendix 2) in the thesis by Susann Andersson.
http://hdl.handle.net/2077/25493

Appendix 3: Supplementary data for Paper I

bmjopen-2019-032407supp001.pdf

bmjopen-2019-032407supp002.pdf

bmjopen-2019-032407supp003.pdf

Appendix 4: Visual acuity conversion table

Decimal notation	LogMAR	Snellen (foot)
0.01	2.00	20/2000
0.1	1.00	20/200
0.125	0.90	20/160
0.16	0.80	20/125
0.2	0.70	20/100
0.25	0.60	20/80
0.3	0.52	20/66
0.32	0.50	20/63
0.4	0.40	20/50
0.5	0.30	20/40
0.6	0.22	20/33
0.63	0.20	20/32
0.65	0.19	20/31
0.7	0.15	20/29
0.8	0.10	20/25
0.9	0.05	20/22
1.0	0.00	20/20
1.2	-0.08	20/17
1.25	-0.10	20/16
1.3	-0.11	20/15
1.6	-0.20	20/12.5
2.0	-0.30	20/10

LogMAR = log of the minimal angle of resolution