Visual Function, Ocular Morphology and Growth – Children Born Moderate-to-Late Preterm

LINA RAFFA, MD, FEBO

Department of Clinical Neuroscience
Institute of Neuroscience and Physiology
The Sahlgrenska Academy at the University of Gothenburg,
Gothenburg, Sweden

UNIVERSITY OF GOTHENBURG

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lina_raffa@yahoo.com

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"Seek knowledge from the cradle to the grave"

Prophet Mohammed (PBUH)

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ABSTRACT

Introduction: In the past, researchers have closely studied both systemic and ophthalmological complications associated with extreme preterm birth. Moderate-to-late preterm (MLP) infants have become the fastest-growing subgroup of preterm infants in the last decade, accounting for 84% of all preterm births. Evidence is currently emerging that even near-term birth predisposes those children to a higher risk of mortality and morbidity than term infants. Effects of extreme prematurity on ocular development are known to include retinopathy of prematurity (ROP), refractive errors, strabismus, low visual performance, decreased contrast sensitivity, visual field defects, colour vision deficits and abnormal cognitive development. To date, very few studies have focused on the ophthalmological aspects of this particular subset of MLP children. The aim of the project was to investigate the development of ocular morphology and visual function in children born MLP, relating them to auxological data and comparing them with their full-term counterparts.

Methods: In a prospective population-based study conducted in 2002-2004, 247 potentially eligible children (110 girls and 137 boys) born MLP (gestational age (GA) 32-36 weeks) participated in the neonatal study. None of the participating children had a previous history of ROP. At 5.5, 8 and 12 years of age, 78, 50 and 22 children respectively who were still included in the study took part in sub-studies that focused on orthoptic evaluation, ocular morphology, visual function and electrophysiology in relation to auxological data in both MLP and sex- and age-matched controls.

Results: Based on our findings, being born MLP is associated with increased ocular morbidity and may require greater ophthalmic surveillance than full-term counterparts. Auxological data at birth, especially birth weight, seems to be an important risk indicator when establishing an ophthalmological diagnosis in preschool MLP children, and visual acuity outcome was positively correlated to GA. Good catch-up growth favoured proper development of ocular growth and morphology. Our results show that macular morphology, visual evoked potential (VEP) and full-field electroretinography (ff-ERG) responses are also affected in the MLP group at 12 years of age.

Conclusion: It has been confirmed in our study that preterm birth, even just in the moderate to late phase, represents a continuum of risks associated with visual system morbidities. These findings have potentially important implications for the follow-up of premature children and therefore require confirmation in large population-based studies that encompass these MLP premature children.

Keywords: Auxological data, Electroretinography, IGF-I, Moderate-to-late preterm, Ocular growth, Optical coherence tomography, Retinal nerve fibre layer, Visual evoked potential, Visual function.

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SAMMANFATTNING PÅ SVENSKA

Introduktion: Forskare har studerat både systemiska och oftalmologiska komplikationer i samband med extremt tidig födsel. Måttligt prematurfödda spädbarn (Moderate-to-late preterm -MLP) har blivit den snabbast växande undergrupp av för tidigt födda barn under det senaste decenniet, och motsvarar 84% av alla prematura födslar. Nya forskningsresultat tyder på att även barn födda måttligt för tidigt är predisponerade för en ökad risk för dödlighet och sjuklighet jämfört med fullgångna barn. Effekter av mycket för tidig födelse avseende utveckling av ögon och synfunktion är kända. Det inkluderar prematuritetsretinopati (ROP), brytningsfel, skelning, minskad kontrastkänslighet, försämrad synskärpa, synfältsdefekter, påverkat färgseende och onormal kognitiv utveckling. Hittills har mycket få studier fokuserat på oftalmologiska aspekter av denna speciella undergrupp av barn födda måttligt för tidigt. Syftet med projektet var att undersöka och följa utvecklingen av ögonmorfologi och synfunktion hos barn födda MLP; relatera dem till auxologiska data vid födsel respektive vid olika åldrar och jämföra dem med fullgångna kontroller.

Metoder: I en prospektiv populationsbaserad studie i Göteborgsområdet, 247 potentiellt möjliga barn (110 flickor och 137 pojkar) födda MLP (gestationsålder 32-36 veckor) under åren 2002-2004 tackade ja till den neonatala delen av studien. Ingen av de deltagande barnen hade tidigare anamnes av ROP. Barnen följdes upp vid 5.5, 8 och 12 års ålder, och då deltog 78, 50 och 22 barn respektive med fokus på ortoptisk utvärdering, ögonmorfologi, synfunktion och elektrofysiologi i förhållande till auxologiska data i båda MLP och köns- och åldersmatchade kontroller.

Resultat: Att födas måttligt för tidigt visade sig vara förknippat med ökad ögon sjuklighet och kräver således en noggrannare kontroll av ögon och synfunktion jämfört med fullgångna barn. Auxologiska uppgifter vid födseln, särskilt födelsevikt, tycks vara en viktig riskindikator för en ögondiagnos hos måttligt för tidigt födda förskolebarn. Resultaten av synskärpa var positivt korrelerad till födelsevecka. God ”catch-up” avseende tillväxten tycks gynna utveckling av ögontillväxt och morfologi. Våra resultat visar också att morfologi i området för gula fläcken (makula) och funktionsutfall mätta med visual evoked potential (VEP) och full-fälts elektroretinogram (ff-ERG) var påverkade hos de måttligt för tidigt födda barnen vid 12 års ålder.

Slutsats: Våra resultat visar på att prematuritet, även i måttlig till sen fas, representerar ett kontinuum av risker i samband med sjuklighet inte enbart systemisk, utan även i öga och synsystem. Dessa fynd har potentiellt viktiga konsekvenser för uppföljning av måttligt för tidigt födda barn och kräver därför ytterligare studier för att få en bättre förståelse för mekanismerna bakom dessa processer.

LIST OF PAPERS

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

I. Lina H. Raffa, Ann Hellström, Eva Aring, Susann Andersson, Marita Andersson Grönlund. Ocular dimensions in relation to auxological data in a sample of Swedish children aged 4–15 years. *Acta Ophthalmol.* 2014 Nov; 92 (7): 682-8. doi: 10.1111/aos.12310. Epub 2014 Jan 22.

II. Lina Raffa, Eva Aring, Jovanna Dahlgren, Ann-Katrine Karlsson, Marita Andersson Grönlund. Ophthalmological findings in relation to auxological data in moderate-to-late preterm preschool children. *Acta Ophthalmol*. 2015 Nov; 93(7):635-41. doi: 10.1111/aos.12763.

III. Lina H. Raffa, Jovanna Dahlgren, Ann Hellström, Marita Andersson Grönlund. Ocular morphology and visual function in relation to general growth in moderate-to-late preterm school-aged children. *Acta Ophthalmol.* 2016 May. doi: 10.1111/aos.13085.

IV. Lina H. Raffa, Josefin Nilsson, Jovanna Dahlgren, Marita Andersson Grönlund. Electrophysiological changes in 12-year-old children born moderate-to-late preterm: Reduced VEP amplitude and altered ERG response in MLP children. *Submitted 2016*.

CONTENT

ABBREVIATIONS

ACD	Anterior chamber depth
AGA	Appropriate for gestational age
BW	Birth weight
BL	Birth length
BHCF	Birth head circumference
BMI	Body mass index
CI	Confidence interval
CP	Cerebral palsy
CCT	Central corneal thickness
CT	Cover test
D	Diopter
DA	Dark adapted
DTL	Dawson-Trick-Litzkow
EEG	Electroencephalogram
EOM	Extraocular muscle
ERG	Electroretinography
ETDRS	Early treatment diabetic retinopathy study
GA	Gestational age
HCF	Head circumference
ICD	Intercanthal distance

IGF-I	Insulin-like Growth Factor I
IOP	Intraocular pressure
ISCEV	International Society for Clinical Electrophysiology of Vision
IUGR	Intrauterine growth retardation
LA	Light-adapted
LE	Left eye
LT	Lens thickness
LogMAR	Logarithm of the minimal angle of resolution
MLP	Moderate-to-late preterm
NICU	Neonatal intensive care unit
NPA	Near point of accommodation
NPC	Near point of convergence
n.s.	non-significant
OCT	Optical coherence tomography
ODA	Optic disc area
pD	Prism diopter
PFL	Palpebral fissure length
RAF	Royal air force
RDS	Respiratory distress syndrome
RE	Right eye
ROP	Retinopathy of prematurity

RNFL	Retinal nerve fibre layer
RST	Retinal size tool
PPHN	Persistent pulmonary hypertension
PRVEP	Pattern reversal visual evoked potential
SD	Standard deviation
SDS	Standard deviation score
SE	Spherical equivalent
SGA	Small for gestational age
TAL	Total axial length
TTN	Transient tachypnoea of new-born
VA	Visual acuity
VD	Vitreous depth
VEP	Visual evoked potential
VPP	Visuo-perceptual problems
WHO	World health organization

DEFINITIONS IN SHORT

Accommodation	Ability of the eye to change the refractive power of the lens and automatically focus objects at various distances on the retina.
Amblyopia	Also known as lazy eye, is decreased vision in one or both eyes due to abnormal development of vision in infancy or childhood.
Anisometropia	Difference in refraction between the two eyes. Generally a difference in power of one diopter or more of spherical equivalence is the accepted threshold for labelling the condition.
Astigmatism	Refractive error as a result of unequal optical power in the two major meridians of the cornea, which are at right angles to each other.
Cover test (CT)	The main method of detecting strabismus. Each eye is covered, while the examiner looks for movement in the non-covered eye in order to reveal any manifest strabismus.
Diopter (D)	Unit of measurement of the power of a lens.
Esophoria	Latent convergent strabismus, kept in check by the fusion mechanism in binocular viewing.
Esotropia	Convergent strabismus (i.e. one eye deviates towards the nose).
Exophoria	Latent divergent strabismus, kept in check by the fusion mechanism in binocular viewing.
Exotropia	Divergent strabismus (i.e. one eye deviates away from the nose).
Emmetropia	Absence of refractive error (light is focused exactly on the fovea).
Heterophoria	Latent ocular misalignment, kept in check by the fusion mechanism in ocular viewing.
Heterotropia	Manifest deviation not kept in check by fusion.
Hyperopia	Refractive error causing the light to focus behind the retina.

Myopia	Refractive error casing the light to focus in front of the retina.
Ocular Motility	Ability to use the extraocular muscles (EOM) to move the eye in different directions.
Premature birth	Infants born before 37 weeks of gestation, late preterm are those born between 34 and 36 weeks of gestation, moderately preterm are those born between 32 and 34 weeks of gestation.
Stereo acuity	Ability to perceive a three-dimensional depth, which requires adequate fusion of the images from both eyes.
Strabismus	Misalignment of the visual axes.

1 INTRODUCTION

The World Health Organization (WHO) defines prematurity as birth before 37 weeks of gestation (Blencowe et al. 2012). Moderate preterm infants are defined as those born between weeks (+days) 32+0 and 33+6 of gestation, and late preterm in weeks (+days) 34+0 and 36+6 weeks of gestation (Shapiro-Mendoza & Lackritz 2012). Previously, researchers have closely studied both systemic (D'Onofrio et al. 2013) and ophthalmological complications (Holmstrom et al. 1998) associated with extreme preterm birth (<32 weeks of gestation). Moderate-to-late preterm (MLP) infants have become the fastest-growing subgroup of preterm infants in the last decade (Verklan 2009), accounting for 84% of all preterm births (Shapiro-Mendoza & Lackritz 2012). Preterm birth is a significant global burden, with 15.1 million babies born before 37 weeks of pregnancy every year across the world, representing one in 10 babies (Howson et al. 2013). This subset of children is becoming the focus of some researchers following the realisation of the highly increased morbidities that is associated with MLP birth, including, in the short term, respiratory morbidities, temperature and glucose dysregulation, feeding difficulties, intracranial haemorrhages, periventricular leukomalacia and infections, in addition to the long-term outcomes including neurodevelopmental, neurobehavioral sequelae and hospital readmissions (Natarajan & Shankaran 2016). Evidence is currently emerging that even near-term birth predisposes those children to a higher risk of mortality than term infants (Engle et al. 2007). To date, very few studies have focused on the ophthalmological aspects of this particular subset of children (Robaei et al. 2006; Nilsson et al. 2011).

It is well known that premature babies are at an increased risk of damage to the visual system, as well as to the cognitive and motor systems (Holmstrom et al. 1998; Holmstrom et al. 1999; O'Connor et al. 2007; Volpe 2009). Growth retardation in utero can have subsequent negative consequences on the adult's health in the form of e.g. hormonal and metabolic effects. Premature infants include both those whose weight is appropriate for gestational age (AGA) and those who have a low weight and/or length relative to gestational age, small for gestational age (SGA). In terms of visual function in children born preterm, several studies describe retinopathy of prematurity (ROP) with morphological retinal changes (neural and vascular), increased risk of refractive errors, strabismus, as well as visuo-perceptual problems (Hellstrom et al. 1997; Hard et al. 2000; Hellgren et al. 2016). Recently, it has been reported that there is a relationship between birth weight (BW) and refraction at birth in both term and premature infants, with weight being a better predictor for refraction than gestational age (GA) (Varghese et

al. 2009). A study from New Zealand showed an increased risk of strabismus and subnormal visual maturation in moderate to low birth weight compared with infants of normal birth weight (Robaei et al. 2006). Studies of the growth factor IGF-I (insulin-like growth factor I) have shown that premature birth, regardless of whether an infant is born SGA or AGA, is associated with low plasma IGF-I levels in mid-childhood, suggesting partial growth hormone resistance (Cutfield et al. 2004; Mericq et al. 2005).

Researchers at the Eye clinic at the Queen Silvia Children's Hospital in Gothenburg, Sweden, have studied for many years how various factors such as growth retardation, brain damage and premature birth influence development of the eye and visual functions. Eye structures can be directly inspected and abnormalities in the eye and visual pathway can be measured using simple, non-invasive and non-painful methods. The central retinal fundus can be photographed, and objective measurement of the optic nerve, macula, nerve fibre layer and retinal vessels can be performed using a specific quantitative digital image analysis (Strömland et al. 1995; Bartling et al. 2008) and Optical Coherence Tomography (OCT). The function of the retina and visual pathways can be recorded using visual evoked potential (VEP) and full-field electroretinography (ff-ERG). The eye can thus be used as a sensitive indicator of prenatal and perinatal effects on the neural and vascular tissues.

Refraction in human infants is usually hyperopic, gradually developing toward emmetropia over the first years of life (Baldwin 1990). Most infants born hyperopic become emmetropic by age 6 to 8 years. Lewis and Maurer (Lewis & Maurer 2005) indicated that grating acuity is adult-like by 4-6 years, and letter acuity by 6 years of age. Daw (Daw 1997) stated that adult-like levels of 30 cycles per degree are reached by 3 years, and clinically, it is assumed that visual acuity (VA) is similar to an adult value of 1.0 by 5 years. This has led the authors to study the MLP children with emphasis on emmetropisation, stereoacuity and visual function by the ages of 5.5 and 8 years. Considerable maturation of the fovea, macular retinal layers (Yuodelis & Hendrickson 1986) and blood vessels (Provis 2001) begins 24 to 27 weeks after conception and continues until early childhood (Yuodelis & Hendrickson 1986) and as a result it was safe to consider examining the children with respect to retinal morphology and visual function by the ages of 8 and 12 years.

Animal experiments on intrauterine growth-retarded (IUGR) rats have shown that VEP activity is altered compared with normal-weight animals (Sjöström 1985). Previous studies in infants have demonstrated pathological responses to electrophysiological studies in growth-retarded infants compared with

appropriately grown infants (Thordstein et al. 2004). Maturation of VEP responses in premature infants has been shown to be more related to children's corrected GA than to their post-natal age (Roy et al. 1995). Children with a history of ROP are reported to have reduced function of the central retina (macula) as measured by multifocal electroretinography (mf-ERG) (Fulton et al. 2005).We studied the electrophysiological changes in MLP children at the age of 12 years, when the visual system is believed to have fully matured in comparison to their full-term counterparts, as it has been noted that the rapid changes seen during infancy decrease gradually in latency in school-aged children (Brecelj 2003). However, it should also be born in mind that electrophysiological maturation might even continue into adulthood (Brecelj 2003).

This project pertains to a large proportion of children and youths growing up in Sweden today. According to the WHO, in almost all the countries with reliable data, preterm birth rates are increasing, with many survivors facing a lifetime of disability including learning, visual and hearing problems. Since brain growth and the visual system are not fully mature and thus susceptible to damage at a younger age, early prevention and treatment can have a positive effect later on in childhood. Employing methods for studying neuronal function and morphology will not only aid in providing a better understanding of the pathophysiology, but could also promote prevention, diagnosis and treatment.

1.1 Development of the Eye

Postnatal growth and emmetropisation

Refractive error is a result of discrepancy between optical refractive determinants of the eye i.e. corneal curvature, lens power and axial length. The new-born is usually hyperopic, and within two years refractive error decreases and becomes closer to emmetropia in a process called emmetropisation. Eye growth is rapid and reaches 90% of adult proportions by approximately the age of 4. As the cornea flattens it loses refractive power, which is balanced by increasing axial length (Creig S. Hoyt 2013). Whether this balance is guided by genetically-encoded mechanisms, environmental influences or growth factors levels, has been the subject of study for years.

Insulin-like growth factor-I during gestation is known to be crucial for the growth of most organs, but in the context of ocular affection, IGF-I is shown to influence myelination, brain development and synaptogenesis, as well as

angiogenesis (O'Kusky & Ye 2012). A study conducted on children with Silver-Russell syndrome (SRS) showed that these patients born extremely SGA and treated with growth hormone (GH) had significantly shorter total axial lengths than the controls despite a normal emmetropisation process (Grönlund et al. 2010). Parentin and Perissutti studied the effect of GH treatment on refraction and hypothesised that timely introduction could permit normal emmetropisation. The change in refraction could have been related to GH-induced somatic growth per se, or to the direct effect of GH/IGF-I (Parentin & Perissutti 2005). To our knowledge, no other group of researchers has studied the relationship between IGF-I levels and ocular growth.

Retinal anatomy and function

While funduscopic examination may reveal the fovea to appear mature soon after birth, detailed anatomic studies have shown that neither the migration of cone receptors to the foveal pit nor the movement of the ganglion cells away from the pit are complete during the first months of life. Retinal development starts in the early gestational period and by mid-gestation all retinal cells are present though very immature. It continues through the first years of life (James D. Reynolds 2011). Further development includes differentiation, migration and apoptosis of the retinal cells to form the adult retina. **Fig. 1** shows the different layers of the retina. A rapid development of the electroretinography (ERG) response of both the rods and cones take place during the first four months of life and continues slowly into early school age. This process is not fully complete until several years after birth. Healthy full-term infants have a more immature ff-ERG response from rods than cones, indicating that cones mature earlier than rods. The ff-ERG response in premature infants is very immature when recorded at 30 weeks of gestation, with low amplitudes and long implicit times for both rods and cones. The ff-ERG matures continuously and, when tested in preterm infants at 40 weeks of gestation, matches the level of full-terms tested just after birth. Electroretinography in former preterm school children has been studied only to a limited extent and mainly in children with a history of ROP (Harris et al. 2011; Akerblom et al. 2014). A normal ff-ERG response is illustrated in **Fig. 2**.

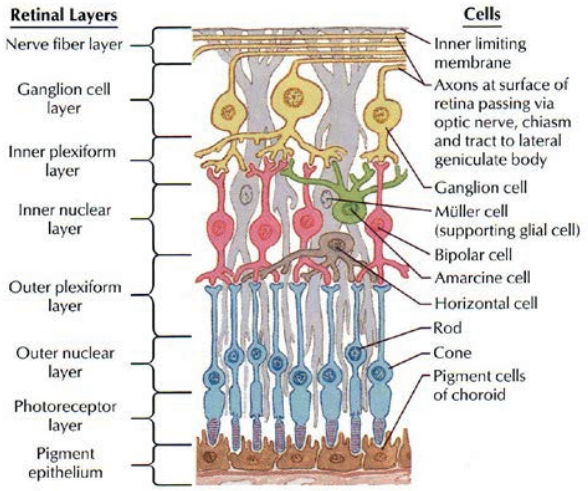


Figure 1. *Layers of the retina.*

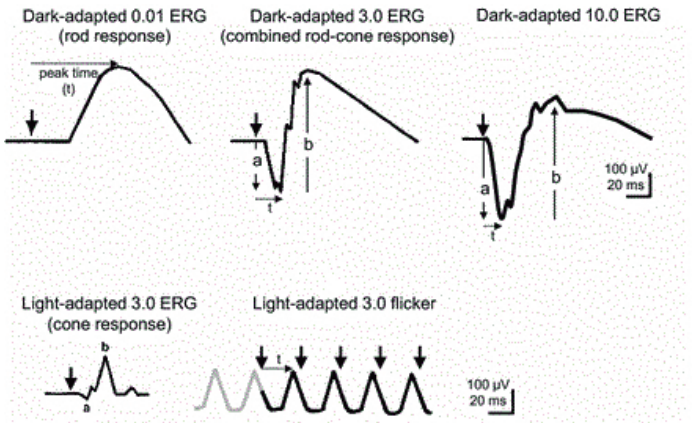


Figure 2. *Five standard electroretinography (ERG) tests with full-field stimulation.*

Optic nerve myelination and visual evoked potential response

Considerable visual development occurs in the third trimester and during the first year of life. Myelination of the optic nerve and tract is incomplete at term birth and continues up to 2 years postnatally (Magoon & Robb 1981). Although the number of cells in the primary visual cortex appears to be complete at birth, considerable increases in cell size, synaptic structure and dendritic density take place during the first six to eight years of life (Garey 1984). Visual function is dependent on VA, macular, optic nerve and primary

visual cortex functions. Visual evoked potentials are massed electrical signals generated by occipital cortical areas 17, 18 and 19 in response to visual stimulation. Pattern VEPs are elicited by abrupt contrast reversal. The transient pattern reversal VEP typically contains a small negative peak and a second negative peak as shown in **Fig. 3**. Visual responses have been documented in preterm infants as young as 24 weeks GA. The presence, amplitude and latency of pattern VEPs change with maturation and age. The presence of good pattern/reversal VEP response may be a good indicator of the integrity of cortical function (Aminoff 2012).

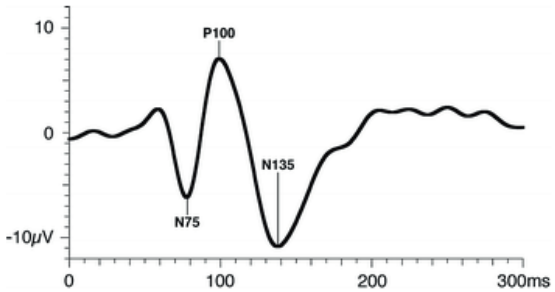


Figure 3. *A Normal pattern reversal VEP.*

1.2 Systemic Impact of Moderate-to-Late Preterm Birth

1.2.1 During infancy

There has been only infrequent study of MLP infants, and understanding of the developmental biology and mechanisms of disease in these infants is largely incomplete (Wang et al. 2004; Raju et al. 2006; Shapiro-Mendoza et al. 2006; Tomashek et al. 2006). Management strategies, therefore, are based on general principles, clinical experience and extrapolation from knowledge of very preterm and term infants. Even MLP infants are physiologically and metabolically immature (Kramer et al. 2000; Wang et al. 2004; Escobar et al. 2005; Oddie et al. 2005; Raju et al. 2006; Shapiro-Mendoza et al. 2006; Tomashek et al. 2006). As a consequence, MLP infants are at a greater risk than are term infants of developing medical complications that result in higher rates of mortality and morbidity during the birth hospitalisation (Kramer et al. 2000; Shapiro-Mendoza et al. 2006; Tomashek et al. 2006).

In the last decade, improved neonatal care has increased the survival of preterm infants (Richardson et al. 1998), but unfortunately, this surge in premature births can be associated with long-term medical sequelae (Moster et al. 2008). Nevertheless, some of the reported increase in morbidity among MLP infants may be attributable to observation and detection bias, since clinicians' thresholds for monitoring late-preterm infants for medical complications may be lower than their thresholds for term infants.

Moderate-to-late preterm birth infants have increased mortality when compared to term infants, and are at increased risk of complications including transient tachypnoea of new-born (TTN), respiratory distress syndrome (RDS), persistent pulmonary hypertension (PPHN), respiratory failure, temperature instability, jaundice, feeding difficulties and prolonged neonatal intensive care unit (NICU) stay (Gilbert et al. 2003; Ramachandrappa & Jain 2009; Verklan 2009). One study reported that new-born morbidity is seven times more likely in late preterm infants than in term infants (Shapiro-Mendoza et al. 2008). One study of all California singleton live births who survived to one year of age found that infants born at 34 to 36 weeks' gestation were 3 to 9 times more likely to require mechanical ventilation than infants born at 38 weeks' gestation (Gilbert et al. 2003; Wang et al. 2004; Escobar et al. 2005). Moderate-to-late preterm infants are also more likely than term infants to have longer initial hospital stays and to be admitted to the NICU (Gilbert et al. 2003). Mean cost per infant was highest for children who were born 24-31 weeks ($5,393) and higher for infants born 32-36 weeks ($1,578) compared with those born at term ($725) in Massachusetts (Clements et al. 2007). Relative risk of at least one extreme event in late preterm infants is increased compared with full-term infants, and remains high until 43 postmenstrual age (Hunt 2006). Late preterm neonatal mortality rates per 1,000 live births were 1.1,1.5 and 0.5 at 34, 35, and 36 weeks respectively, compared with 0.2 at 39 weeks (McIntire & Leveno 2008).

Health care professionals have recently identified a large segment of the morbidity associated with preterm birth as being mainly attributable to MLP infants (Verklan 2009). This may be because this group is the fastest-growing sector of all preterm births, or it may simply be that they were neglected, while research was focused mainly on the complications associated with extreme premature babies. Since the MLP group is not as protected as previously believed while also taking up significant resources, it would be cost-effective to conduct formal evaluations of the therapies and follow-up strategies employed in caring for this population.

1.2.2 During childhood and adolescence

It has now been revealed that MLP infants may even have long-term neurodevelopmental consequences secondary to their late prematurity (McIntire & Leveno 2008; Moster et al. 2008). Recently, moderate preterm birth has been shown to carry considerable risks for long-term disability, lower likelihood of completing a university education, lower net income, and receipt of social security benefits (Lindstrom et al. 2007; Moster et al. 2008).

Moderate-to-late preterm birth and even marginal preterm birth (GA 37-38 weeks) also carried significantly increased risks for disability and were responsible for 74% of the total disability associated with preterm birth (Lindstrom et al. 2007). Risk of developmental delay or disability was 36% higher among late preterm infants compared with term infants (Morse et al. 2009). Risk of suspension from kindergarten was 19% higher in late preterm infants (Morse et al. 2009). Furthermore, the presence of intelligence deficits, hyperactivity and learning disorders was reportedly more common among children with a modest low birth weight (Seidman et al. 1992; Breslau et al. 1994).

Woythaler et al (Woythaler et al. 2011) observed a higher frequency of delayed mental development at 2 years, and delayed psychomotor development in MLP compared to infants born at term. In Brazil, Santos et al. showed a higher frequency of inadequate growth at 2 years (Santos et al. 2009). Peacock et al. studied performance in regular preschool tests, comparing infants born between 32 and 37 weeks to full-term infants (Peacock et al. 2011). They found a lower frequency of good performance among preterm infants. Teune et al. found a greater risk of cerebral palsy (CP) and mental retardation (Teune et al. 2011). Moster et al. reported an increased risk of schizophrenia and a lower proportion of young individuals completing college/university (Moster et al. 2008). Teune et al. found a lower chance of completing high school (Teune et al. 2011).

1.3 Ophthalmological Aspects of Moderate-to-Late Preterm Birth

It is well known that premature babies are at high risk of developing eye complications. Until now, most studies have focused on extremely preterm infants born ≤ 32 weeks and those with extremely low birth weight (≤ 1,500 grams) because of their higher risks of mortality and serious morbidity (Ecsedy et al. 2007; Åkerblom et al. 2011; Wang et al. 2012; Åkerblom et al. 2012). Effects of extreme prematurity on ocular development are known to

include ROP, refractive error, strabismus, low visual performance, decreased contrast sensitivity, visual field defects, colour vision deficits and abnormal cognitive development (Holmstrom et al. 1998; Quinn, G. E. et al. 1998; Holmstrom et al. 1999; Cook et al. 2008; Haugen et al. 2012). However, the impact of prematurity on visual development is not limited to the most extremely preterm infants or those with extremely low birth weights (Robaei et al. 2006). Moreover, due to the increased activity and consequent vulnerability to injury of the foetal brain during the last trimester, it is important to investigate the neurologic and visual outcomes of MLP infants carefully (Adams-Chapman 2006). To date, little is known about the effects of moderate-to-late preterm birth on the ocular and visual system.

The refractive state of the human eye is dependent on the balance of changes in overall eye size and the refractive components. Additionally, the flattening of the cornea and the decreasing power of the crystalline lens balance axial elongation in a way that maintains elongation (Zadnik et al. 2004). Any disturbance in this balance or emmetropisation mechanism may result in refractive error (Saw et al. 2004). Environmental and genetic factors, premature birth per se and the development of ROP are all known to be associated with the development of myopia (Cook et al. 2008).

A literature review revealed an increased prevalence of behavioural and emotional problems in very low birth weight or preterm infants, with rates ranging from 25–55%, as opposed to 7% in controls (Hayes & Sharif 2009). Children born very preterm (<32 weeks) and without major neurodevelopmental sequelae have an increased prevalence of ophthalmic impairments at primary school age that are associated with visuo-perceptual, motor and cognitive defects (Hard et al. 2000; Cooke et al. 2004).

Researchers at the eye clinic at the Queen Silvia Children's Hospital in Gothenburg, Sweden, have a long history of studying the influence of various factors such as growth retardation, brain damage and preterm birth on the development of the eye and visual function (Grönlund et al. 2004; Grönlund et al. 2006; Martin et al. 2008). It has previously been found that a persistent reduction in serum levels of insulin-like growth factor-I (IGF-I) after birth is associated with subsequent poor angiogenic development (Hellström et al. 2003). Retinopathy of prematurity development was lower in infants that were placed in early aggressive parental nutrition inducing high IGF-I, as an inverse correlation is found between ROP and IGF-I levels (Can et al. 2013).

At our department, it has previously been found that VEP latencies did not differ in SGA children compared with AGA children in the MLP children studied (Nilsson et al. 2011), supporting previous studies (Scherjon et al.

1996) suggesting a catch-up in neurophysiological maturation during the first year of life compared with controls.

The increased survival of prematurely born infants poses a long-term problem in terms of increased incidence of ophthalmological problems such as strabismus, amblyopia and refractive errors (Schalij-Delfos et al. 2000). These findings have potentially important implications for the follow-up of MLP preterm-born children, and therefore require confirmation in large population-based studies encompassing these preterm children.

2 AIMS

Overall aim

- Identifying visual function, eye morphology and growth in children born MLP (SGA and AGA), comparing the findings to their full-term counterparts and relating the data to other growth parameters and IGF-I levels.
- Identifying "normal" variations of the eye and vision (function and morphology) in children aged 4-15 years in relation to auxological data.

Paper I

The purpose was to characterise normal growth patterns of ocular components and to relate them to auxological data in a sample of Swedish children aged 4–15 years.

Paper II

To evaluate ophthalmological findings in preschool children born MLP (SGA and AGA) and relate the findings to auxological data and IGF-I levels at birth and at 5.5 years of age.

Paper III

To study ocular morphology and visual function in relation to other growth parameters in children born MLP at 8 years of age.

Paper IV

To study electrophysiological changes in relation to fundus morphology in children born MLP at 12 years of age.

Research Questions

1. Is there a difference in the eye and visual function between children born MLP (SGA and AGA) and healthy term infants?
2. Do children born MLP have normal eye growth and hence normal refraction development (emmetropisation) at the age of eight years? How is their eye growth and visual maturation in relation to the other growth parameters?
3. Is there a difference in retinal function and morphology between children born MLP and healthy full-term children?
4. What is the relationship between circulating IGF-I levels and ocular and visual maturation?
5. What is the "normal" variation in ophthalmologic variables in healthy term infants at 4-15 years of age in relation to other growth parameters?

3 PATIENTS AND METHODS

3.1 Patients

Paper I

At the Department of Paediatric Ophthalmology at the Queen Silvia Children's Hospital, Gothenburg, Sweden, a total of 143 children (67 girls; 76 boys) were evaluated with regard to ophthalmological and auxological variables. The children were selected from four different schools and three day-care centres in the Gothenburg area to represent a city centre, a suburban, and a rural area in order to reflect the socioeconomic mix of the area from which the cohort study was drawn. Inclusion criteria were age between 4 and 15 years, birth in Sweden, and residence in the Västra Götaland region, Sweden. Any history of ocular or serious health diseases were regarded as exclusion criteria. The aim was to recruit at least five girls and five boys from each year of age. A detailed description of the population, including medical, ethnic and socio-economic background, as well as ophthalmologic findings, (Grönlund et al. 2006), in addition to the orthoptic evaluation (Aring et al. 2005) and fixation (Aring et al. 2007), has previously been presented.

Papers II-IV

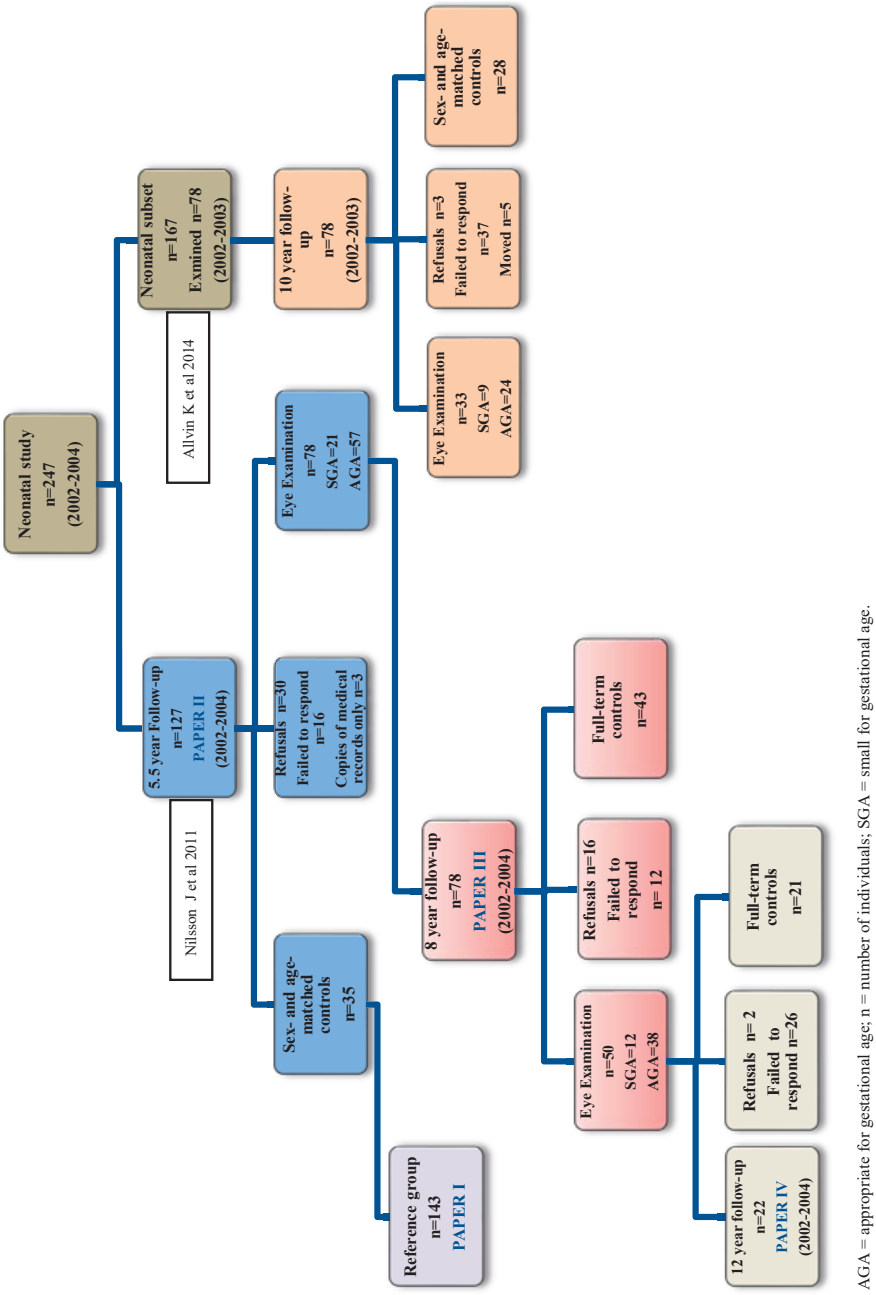
In an ongoing, prospective, population-based study, all children born MLP (GA 32 weeks+0 days to 36 weeks+ 6 days) between 2002 and 2004 in either of the two available maternity wards in Gothenburg, Sweden (Östra and Mölndal University Hospitals) were invited, through their parents or guardians, to participate **(Fig. 4).** Children with syndromes, chromosome abnormalities, severe malformations or mothers with severe chronic diseases were not included. None of the participating children had any previous history of ROP. Guardians of 247 potentially eligible children (110 girls and 137 boys) agreed to allow them to join the neonatal study. At 5.5 years of age, all children still included in the study (n=127) were invited to participate in an ophthalmological investigation. Of these 127 MLP children, 78 MLP children with a GA of 32–36 weeks (34 girls; mean age 5.7 years; 21 SGA and 57 AGA children) agreed, with their guardians' permission, to take part in this sub-study focussing on VEP studies (Nilsson et al. 2011) and detailed eye examinations including orthoptic evaluation, which have been related to the different growth parameters obtained at birth and at 5.5 years of age

(*Paper II*). The data was compared with age- and sex-matched controls born full term from our reference group in *Paper I* (n=35).

At 8 years of age, all children included in the ophthalmological part of the study (n=78) at 5.5 years (*Paper II*) (Raffa et al. 2015) were invited to participate in this sub-study focusing on eye growth, refraction development and retinal morphology in relation to other growth parameters. Of these 78 MLP children, 50 (29 boys, 21 girls) with a mean ± standard deviation (SD) GA of 35±1.5 weeks and mean birth weight (BW) of 2299±469 g agreed, with their guardians' permission, to take part in the study (*Paper III*). Examinations were carried out on 12 children born SGA (7 boys, 5 girls; mean±SD GA = 34±1.4 weeks; BW 1843±420 g) and on 38 children born AGA (22 boys, 16 girls; mean GA±SD = 35±1.5 weeks, and BW = 2443±388 g). Forty-three children were recruited by invitation through local schools in different areas of Gothenburg to serve as controls. Inclusion criteria for the control group included children born at term aged 8 from these randomly chosen local schools with no previous history of ocular or systemic diseases.

All 50 examined in the previous study at 8 years of age (*Paper III*) (Raffa et al. 2016) were invited, through their parents or guardians, to participate in the last sub-study (*Paper IV*). Examinations were carried out on 22 children (11 boys, 11 girls; mean±SD GA 34.5±1.7 weeks; BW 2266±482 g) who agreed to participate. Twenty-one children were recruited from local Gothenburg schools to serve as controls. Inclusion criteria for the control group included children born at term (GA≥37 weeks) with no previous history of ocular or systemic diseases.

Figure 4. *Flowchart showing a summary of children's participation in this study.*



AGA = appropriate for gestational age; n = number of individuals; SGA = small for gestational age.

3.2 Methods

Paediatric Examinations

3.2.1 Auxological data

Weight, length and head circumference (HCF) at birth and at time of assessment were measured in accordance with a standard protocol and converted into standard deviation scores (SDSs) based on Swedish reference values (Niklasson et al. 1991). Body mass index (BMI) was computed as weight (kg) divided by height squared (m^2).

3.2.2 IGF-I data

IGF-I was analysed using the new automated immunoassay (IDS-iSYS; Immunodiagnostics Systems) and transformed to SDS at birth (Bidlingmaier et al. 2014), 5.5, 8 and 10 years of age (Lofqvist et al. 2001). Calculating the delta IGF-I, values from cord serum IGF-I at birth were subtracted from the serum values at time of investigation.

Ophthalmic Examinations

3.2.3 Visual Acuity tests for far and near fixation

Visual acuity was tested using a linear KM-Boks chart. If a child could not manage to read the KM-Boks chart, an HOTV chart was used (Moutakis et al. 2004). Distance vision was tested monocularly at a distance of 3 m, and near vision was tested binocularly at a distance of 0.33 m. Values were noted in Snellen decimal format and converted to logarithm of minimal angle of resolution (logMAR) (**Appendix 1**). Amblyopia was defined as a difference in VA between the eyes in at least two lines with VA in the amblyopic eye ≤0.2 logMAR that could not be explained by structural abnormalities in the eye. Subnormal VA was defined as VA<0.2 logMAR in either eye.

3.2.4 Refraction under cycloplegia

This was performed using an autorefractor (Topcon A6300; Topcon Corporation, Tokyo, Japan) following a single instillation of a mixture of cyclopentolate (0.85%) and phenylephrine (1.5%). Significant refractive errors were defined as a spherical equivalent (SE) of myopia ≥0.5 dioptres

(D) or hyperopia ≥2.0 D. Astigmatism was assessed at a level of ≥1.0 D and anisometropia at ≥1.0 D SE.

In addition to the examinations mentioned above, the following tests were performed on the children:

Paper I

3.2.5 Assessment of ocular dimensions

The inner canthal distance (ICD) and right and left palpebral fissure lengths (PFL) were measured in mm using a ruler (Hall et al. 1989). Canthal index was calculated as ICD x 100/outer canthal distance as a percentage (Taylor & Hoyt 2005). Total ocular axial length (TAL), anterior chamber depth (ACD), lens thickness (LT), and vitreous depth (VD) were measured by means of ultrasound biometry (Paxis Version 2.01; BIOVISION, Clermont Ferrand, France). The mean value of ten measurements of each eye was recorded where possible.

3.2.6 Photography of the ocular fundus for qualitative image analysis

The children underwent cycloplegia and ocular fundus photographs were obtained using a Topcon 50-VT fundus camera (Topcon Corporation, Tokyo, Japan). Only well-focused pictures were accepted. The optic disc was identified as the inner margins of the nerve tissue excluding the white scleral rings. The cups were identified manually by contour and pallor in both eyes. The optic disc area (ODA) and cup areas were measured by marking their outlines with a cursor. The projected areas were analysed using a specifically designed computer-assisted digital mapping system (Strömland et al. 1995). Cup-disc ratios and the neuro-retinal rim were calculated.

Paper II

3.2.7 Orthoptic evaluation

Strabismus and motility

Heterotropia was diagnosed using a cover test with fixation at a distance of 3 m and 0.33 m respectively, and was defined as a permanently or intermittently manifested deviation. The angle was measured in prism dioptres (pD) using alternate and prism cover tests. The cover test (CT) was

performed at 3.0 and 0.3 m. During the Hirschberg test and the CT, any anomalous head postures and presence of nystagmus were noted. The nomenclature was eso-, exo-, hypo- and hypertropia (Von Noorden & Campos 2002). Motility (versions and ductions) was tested using a penlight in the nine positions of gaze. Significant misalignment was defined as heterotropia at any distance, or exophoria (-) as values below the 5th percentile in the control group, and esophoria (+) as values above the 95th percentile. Cut-off values at distance -5 prism diopters (PD) to +3PD and at near -11PD to +7PD (Aring et al. 2005).

Stereo acuity testing

The TNO test was used to evaluate stereo acuity (Von Noorden & Campos 2002). For the TNO test, stereo acuity was defined as the smallest level of disparity at which both test figures were correctly identified, and it was considered reduced if it was more than 60 seconds of arc (Aring et al. 2005).

Near point of convergence

The Royal Air Force (RAF) ruler was used to measure the near point of convergence (NPC). A mean value of three measurements was recorded. The near limit is 6 cm (Von Noorden & Campos 2002).

Near point of accommodation

The near point of accommodation (NPA) was measured binocularly in D as the target was brought toward the patient with the RAF ruler, using the push-up test (Scheiman & Wick 2008).The cut-off limit was set at 20 D according to Duane's standard curve of accommodation (Duane 1922). A mean value of three measurements was recorded.

3.2.8 Examination of the anterior segment, media, and ocular fundus

Examination of the anterior segment of the eye was performed using a slit lamp, and the ocular fundus was examined by means of indirect ophthalmoscopy. Fundus photographs were taken and inspected by the observers for optic nerve, macular or vessel pathologies.

3.2.9 History of visual perception

A structured history-taking was conducted with respect to visuo-perceptual problems (VPPs) in five different areas, these being recognition, orientation, perception of depth and motion, and simultaneous perception (Dutton et al. 1996). The history-taking was based on 12 selected questions regarding visual perceptual cognitive problems translated into Swedish. Whereas questions 1-4 dealt with recognition, questions 5-7 addressed orientation, question 8 asked about perception of depth, questions 9 and 10 about perception of motion and questions 11 and 12 about simultaneous perception (**Appendix 2**).

Paper III

3.2.10 Ocular dimensions

The ICD and the right and left PFLs were measured in mm using a ruler (Hall et al. 1989). Canthal Index was calculated as ICDx100/outer canthal distance as a percentage. Total ocular axial length was measured by means of ultrasound biometry (IOL master, 500 Zeiss Meditec, Jena, Germany). The mean value of 10 measurements (when possible) of each eye was recorded.

3.2.11 Intraocular pressure

Intraocular pressure (IOP) was measured using a handheld tonometer (TA0li, I care, Finland Oy, Espoo, Finland) which is automated to take the average of six readings. Readings with high deviations were discarded and repeated.

3.2.12 Central corneal thickness

Central corneal thickness (CCT) was measured twice – firstly using a handheld ultrasound pachymeter (Pocket Class II; Quantel Medical Inc, Clermont-Ferrand, France) with the mean of five measurements being taken in each eye, and secondly using the Spectral Domain (SD)-OCT machine.

3.2.13 Fundus photography

Ocular fundus photographs were obtained using the fundus camera (Nonmyd-7 Kowa, Tokyo, Japan) and were taken in cycloplegia. Digital fundus photographs were fed into the RetinaSizeTool (RST) program (Bartling et al. 2008). Optic disc area, neuroretinal rim area and cup area were analysed by

manually marking the outlines of the optic disc and cup in addition to the fovea, yielding the projected area results (Bartling et al. 2008).

Paper III-IV

3.2.14 Optical coherence tomography variables

Retinal and papillary nerve fibre layer thickness and retinal thickness were measured by analysing images taken with the SD-OCT, using 3D-OCT 1000 software from Topcon, Tokyo, Japan, to obtain the average thickness of 9 early treatment diabetic retinopathy study (ETDRS) sectors (i.e. sectors A1 to A9: central (C), inner superior (IS), outer superior (OS), inner inferior (II), outer inferior (OI), inner nasal (II), outer nasal (ON), inner temporal (IT), and outer temporal (OT)), and the retinal nerve fibre layer (RNFL) thickness, foveal minimum, and total macular volume in the sectors A1 to A9 **(Fig. 5).** The children were asked to fixate on the internal target and the scans automatically provided the aforementioned results. Imaging of dilated fundi was obtained in a dim room, with the highest quality image selected for analysis. The software also calculated average thickness for each RNFL macular segment in the 9 ETDRS sectors. The papillary RNFL thickness was measured in four sectors (superior (S), inferior (I), nasal (N) and temporal (T)) and an average thickness was automatically calculated.

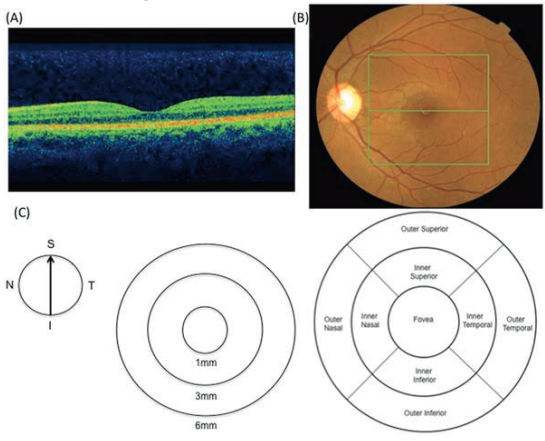


Figure 5. *Example of macular thickness measurements obtained using the Topcon SD-Optical coherence tomography(OCT) system. OCT image of a healthy subject (A) Fundus photograph of a healthy subject; the box indicates a 6×6 mm scanning area using 3D macular protocol (B). Image of standard early treatment diabetic retinopathy study (ETDRS) map (C), showing map diameters centred on fovea (left) and 9 standard ETDRS regions (right).*

Paper IV

3.2.15 Visual evoked potential

Pattern-reversal VEPs (PRVEPs) with a stimulus rate of 2 Hz were recorded using the Espion E2 system (Diagnosys LLC, Cambridge, UK) (Odom et al. 2010). In accordance with the international 10–20 electroencephalogram (EEG) system, three silver⁄silver chloride electrodes were placed at O1, Oz and O2. The reference electrode was placed at the mid-frontal region (Fz) and a ground electrode on an earlobe. Electrode impedance was kept below 5 kΩ if possible, however, <10 kΩ was accepted for less cooperative patients. Patients sat in front of the video-monitor screen at a distance of one meter. The check sizes subtended visual angles of 60 min of arc. The artefact rejection filter was set at ±200-μV amplitude, with the amplifier bandpass filter set at 0.625–100 Hz. The recording window was 250 ms post stimulus. Two trials for each binocular, right eye (RE) and left eye (LE) stimulation were recorded. In mesopic lighting with un-dilated pupils, binocular recordings were always performed first; for the second run, RE or LE stimulation was chosen arbitrarily. If cooperation was sufficient, a minimum of 64 reversals were collected for each trial. If attention failed, fewer reversals were accepted for each trial.

3.2.16 Full-field electroretinography

Patients were dark-adapted for 30 min and sequentially tested monocularly in RE only. Using the Espion E2 (Diagnosys LLC, Cambridge, UK), ff- ERG was performed according to the International Society for Clinical Electrophysiology of Vision (ISCEV) standards, except for a shorter light adaptation period (5 min instead of 10 min) (McCulloch et al. 2015). Prior to testing, pupils were fully dilated using cyclopentolate (0.85%) + phenylephrine (1.5%). Dawson-Trick-Litzkow (DTL) fibre electrodes placed in the lower cul-de-sac were used for recordings after topical anaesthetic (0.5% tetracaine hydrochloride) was applied. Each DTL fibre was anchored near the inner canthus and outer canthus. The reference electrode was a silver/silver chloride EEG electrode that was placed on the centre of the forehead, with the ground placed on the right ear lobe. The protocol included three stimuli under dark-adapted (DA) conditions: rod response (0.01 cd.s/m^2), followed by DA combined rod-cone response (3.0 cd.s/m^2), and a stronger flash (10.0 cd.s/m^2). Thereafter, eyes were light-adapted (LA) for 5 min using a white background light of 30 cd/m^2. Cone single flash and 30-Hz flicker responses (flash intensity of 3.0 cd.s/m^2; background of 30 cd/m^2) were then recorded. Responses were individually checked to avoid artefacts.

4 STATISTICAL ANALYSIS

Means, medians, SDs, SDSs, ranges and 95% confidence intervals (95% CIs) were calculated for descriptive purposes. Statistical analyses were performed using Microsoft Excel, SPSS Statistics (IBM Corporation, Somers, NY, USA) and SAS 9.2 (*Papers I-IV*). For comparison between groups, Fisher's Exact test was used for dichotomous variables (*Paper II*), with the Mann-Whitney U test (*Papers I-IV*) and the Kruskal Wallis test (*Papers II-III*) used for continuous variables. The Jonckheere-Terpstra test was used for comparison between ordered categorical and continuous variables (*Paper I*). The Wilcoxon signed-rank test was used for continuous variables for comparison over time (*Papers I-IV*). Relative risks were provided with their 95% CI. The reference group in *Paper II* was selected one individual –at a time by minimising the maximal *t* values between the MLP group and a reference group of healthy Swedish preschool aged children, over the variables age and sex (Pocock & Simon 1975). Correlation analyses were performed using Spearman's partial-rank correlation analysis, including adjustment for age and/or sex (*Papers I-IV*). The 95% CIs for the correlation coefficients were estimated by using Fisher's z-transformation (*Paper III*). Multiple logistic regressions were also used in order to study the relationship between gender, specified as dependant variable in the model, and TAL and age, specified as independent variables (*Paper I*). Univariable and stepwise logistic regression analyses were performed in order to determine the effects of auxological data and GA on ophthalmological findings (*Paper II*). Since age at examination differed between preterm and full-term children in *Papers III and IV*, parameters were analysed using logistic regression tests adjusting for age and sex. The calculated expected false negative results according to the Eklund-Seeger formula alpha / (1-alpha)*(N-n (alpha)), where alpha=0.05 and N=number of tests, were calculated for selected parameters (*Paper IV*). All tests were two-tailed and conducted at 0.05 significance levels (*Papers I-IV*). When testing IGF-I levels at 5.5,8 and 10 years of age, logistic regression was used to adjust for IGF-I levels at birth.

5 RESULTS

5.1 Auxological data

Table 1 summarises auxological data (weight, height, head circumference and BMI) at birth and/or at the time of assessment according to different age groups in a sample of Swedish children aged 4–15 years (n=143) (*Paper I*). **Table 2** summarizes demographics including gender, age, GA, and auxological data (weight, length, HCF at birth and at assessment, and BMI) in both the MLP children and the control groups (*Papers II-IV*).

Table 1. *Demographic data for a sample of Swedish children aged 4–15 years (n=143) at birth and at the time of assessment according to different age groups (Paper I). Except where indicated otherwise, values are given as means (range).*

Variable at birth **Median (range)**	**4–6 years** **n = 35***	**7–9 years** **n = 42***	**10–12 years** **n = 35***	**13–15 years** **n = 31***
Weight, g	3542 (2760; 4970)	3516 (2730; 4650)	3617 (2190; 4760)	3689 (1540; 4890)
Weight SDS	-0.0014 (-2.2; 4.1)	0.065 (-1.7; 1.8)	0.112 (-2.5; 2.2)	0.36 (-4.0; 2.7)
Length, cm	50.6 (46.0; 54.0)	50.9 (46.0; 57.0)	50.6 (46.0; 56.0)	50.5 (40.0; 54.5)
Length SDS	0.007 (-2.0; 2.83)	0.29 (-2.4; 3.0)	-0.02 (-1.8; 2.5)	0.03 (-4.2; 1.9)
Head circumference, cm	34.6 (31.0; 37.0)	34.9 (33.0; 38.2)	35.1 (32.0; 38.5)	35.1 (31.0; 38.0)
Head circumference SDS	-0.01 (-3.0; 2.4)	0.17 (-1.4; 2.5)	0.23 (-2; 3.0)	0.31 (-1.8; 2.0)
Variable at the time of assessment **Median (range)**	**4–6 years** **n = 35***	**7–9 years** **n = 42***	**10–12 years** **n = 35***	**13–15 years** **n = 31***
Weight, kg	21.8 (15.3; 30.2) (n = 33)	28.3 (21.0; 44.5) (n = 36)	41.7 (26.0; 59.0) (n = 34)	54.9 (35.6; 74.6) (n = 28)
Weight SDS	0.70 (-1.34; 3.04) (n = 33)	0.38 (-1.99; 3.50) (n = 36)	0.72 (-1.68; 2.76) (n = 34)	0.40 (-1.62; 2.09) (n = 28)
Height, cm	114.9 (98.5; 130.0) (n = 33)	131.4 (121.8; 151.7) (n = 36)	150.7 (129.7; 174.7) (n = 34)	162.8 (141.2; 175.5) (n = 27)
Height SDS	0.27 (-1.78; 2.24) (n = 33)	0.28 (-1.34; 3.12) (n = 36)	1.00 (-1.65; 3.92) (n = 34)	1.19 (-1.93; 2.67) (n = 27)
Head circumference, cm	52.0 (48.8; 54.0) (n = 33)	53.3 (50.0; 56.3) (n = 33)	55.1 (51.7; 59.5) (n = 32)	55.4 (53.3; 59.9) (n = 28)
BMI **Mean (SD)**	16.4 (1.7) (n = 33)	16.2 (2.1) (n = 36)	18.2 (2.2) (n = 34)	20.6 (2.6) (n = 27)

*Where numbers differ from the total number of children in the group, they are given separately for each category.
BMI = Body mass index; cm = centimetre; g = gram; kg =kilogram; SD = standard deviation; SDS = standard deviation score.

Table 2. *Demographic data for moderately-to-late preterm (MLP) children and their full-term controls (Paper II-IV).*

Characteristics	MLP group Paper II	Control group Paper II	MLP group Paper III	Control group Paper III	MLP group Paper IV	Control group Paper IV
Total children (n)	78	35	50	43	22	21
Mean age years (range)	5.7 (5.0–6.4)	5.68 (4.1–7.4)	8.01 (7.2–8.6)	8.30 (7.2–9.0)	11.6 (10.8–12.2)	11.2 (10.1–11.9)
Gender						
Female, n (%)	34 (44%)	17 (49%)	21 (42%)	17 (40%)	11 (50%)	9 (42.9%)
Male, n (%)	44 (56%)	18 (51%)	29 (58%)	26 (60%)	11 (50%)	12 (57.1%)
Birth parameters						
Mean birth weight, g (SD)	2302 (518)	3594 (535)	2299 (469)	3607 (657)	2266 (482)	3683 (654)
Mean birth length, cm (SD)	45.14 (3.3)	50.9 (2.01)	45.0 (3.2)	50.8 (2.4)	45 (2.9)	50.6 (3.2)
Mean birth HCF cm (SD)	31.9 (1.94)	34.79 (1.63)	32.0 (1.9)	35.5 (1.4)	31.7 (2)	36.9 (2.8)
Mean GA weeks (range)	34.65 (32-36)	39.71 (37-42)	34.6 (32–36)	39.5 (37–43)	34.5 (32–36)	39.4 (35–43)
Parameters at assessment						
Mean weight kg (SD)	20.16 (3.14)	16.36 (1.73)	28.5 (5.2)	30.4 (5.1)	N/A	N/A
Mean height cm (SD)	115.3 (5.4)	115.8 (8.9)	132.3 (6.5)	133.5 (5.9)	N/A	N/A
Mean HCF cm (SD)	51.75 (1.76)	52.17 (1.33)	53.3 (1.7)	53.3 (1.5)	N/A	N/A
Mean BMI kg/m^2 (SD)	15.09 (1.52)	16.36 (1.73)	16.2 (2.2)	17.0 (1.9)	N/A	N/A

BMI = body mass index; cm = centimetre; GA = gestational age; g = gram; HCF = head circumference; kg = kilogram; m = metre; MLP = moderate-to-late preterm; N/A = not applicable; SD = standard deviation.

5.2 IGF-I data

Figure 6 illustrates IGF-I levels in children born MLP who were tested at different age groups. **Figure 7** shows the difference in IGF-I levels in children born SGA versus AGA. A statistically significant difference was found at birth ($p < 0.0001$) however when adjusting for this difference, no significant differences were noted between these two groups at 5.5, 8 and 10 years of age. IGF-I levels at birth positively correlated with birth weight (BW) ($p<0.0001$, $r=0.57$), birth length (BL) ($p=0.0008$, $r=0.47$) and HCF at birth ($p=0.0006$, $r=0.48$). Delta IGF-I was found to correlate only with BW ($p=0.041$, $r=-0.32$). Growth auxological data expressed in SDS are represented in **Table 3.**

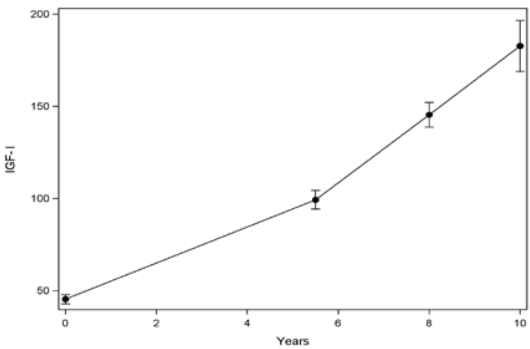


Figure 6. *Line graph demonstrating mean insulin-like growth factor (IGF-I) levels ± standard error of the mean (SEM) in MLP children examined at birth, 5.5, 8 and 10 years of age.*

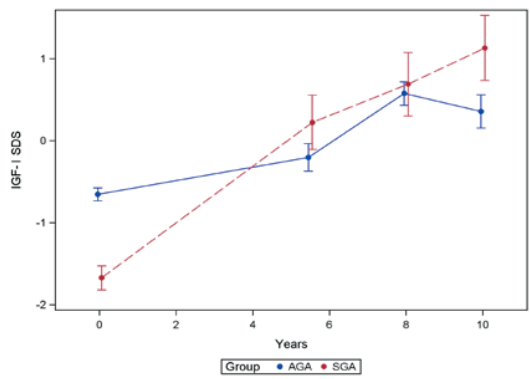


Figure 7. *Line graph demonstrating mean ±standard error of the mean(SEM) for insulin-like growth factor-I (IGF-I) standard deviation scores (SDS) in MLP children divided into appropriate for gestational age (AGA) and small for gestational age (SGA) tested at birth,5.5, 8 and 10 years of age.*

Table 3. *Growth pattern in terms of auxological data and insulin-like growth factor levels in a cohort of MLP children examined at birth, 5.5, 8 and 10 years of age.*

Growth	New-born n=78*	5.5 years n=78*	8 years n=50*	10 years n=13*
Weight, SDS				
Mean (SD)	-0.83 (1.7)	-0.43(1.15)	0.34 (1.32)	0.61 (1.14)
Length/Height,				
SDS Mean (SD)	-0.83 (1.46)	-0.09 (1.12)	0.22 (1.2)	0.62 (0.85)
IGF-I levels				
Mean (SD)	43.69 (23.68)	99.38 (39.5)	145.4 (43.5)	228.25 (91)
Median (range)	40 (5;99)	90 (45;221)	138.5 (71;263)	189 (142;476)
	n=78	n=61	n=42	n=12
Delta IGF-I level				
Mean (SD)	N/A	55.54 (45.8)	105.2 (46.3)	200.25 (91.55)
Median (range)		46 (-31;170)	94 (19;228)	176.5 (109;441)
		n=61	n=42	n=12

*Where numbers differ from the total number of children in the group, they are given separately for each category.
IGF-I = insulin-like growth factor-I; N/A = not applicable; SD = standard deviation; SDS = standard deviation score.

5.3 Ophthalmological findings at examination Paper I

Total axial length and ACD of the RE increased from 22.2±0.7 mm to 22.9±0.9 mm and from 3.7±0.24 mm to 3.9±0.2 mm respectively, between 4–6 years and 13–15 years of age ($p = 0.0005$ and $p = 0.0012$ respectively). The LT of RE decreased by an average of 0.14 mm between 4 and 15 years, and the average VD of RE increased from 15.0±0.6 mm at 4–6 years of age to 15.7±0.8 mm at age 13–15 years ($p = 0.0122$ and $p = 0.0051$ respectively). The increase in LT thinning and vitreous chamber deepening is statistically significant but not as significant as the change in ACD, which is much larger and with an increase in age. Boys had TALs that were on average 0.7 mm longer compared with girls ($p<0.0001$).

Papers II-III

Overall ophthalmological findings included subnormal VA, refractive errors, eyeglass wear, abnormal stereo acuity, decreased accommodation and convergence, heterotropia and heterophoria, ocular motility disturbances, optic nerve anomalies and/or nystagmus. Ophthalmological findings were noted in 82.5% of MLP children and 45.7% of controls (p=0.0004) (*Paper II*). Presence of ophthalmological abnormalities in relation to auxological variables are shown in **Table 4.** There was no statistically significant difference between the measurements of MLP and controls with regard to CCT pachymeter/OCT or IOP. However, a significant difference was found when comparing CCT measured using the different devices in all children combined (555 ± 26 µm vs 571 ± 37 µm; RE P = 0.0003; LE P = 0.003) (*Paper III*).

Table 4. *Presence of ophthalmological abnormalities in relation to auxological variables in 78 MLP children and 35 full-term controls.*

Variable	Ophthalmological abnormality No n=33* Mean (SD) Median (range)	Ophthalmological abnormality Yes n=80* Mean (SD) Median (range)	Univariable logistic regression P-value	Odds ratio (95% CI)	Stepwise logistic regression P-value
Birth weight, g	3119 (796) 3080 (945; 4970)	2530 (732) 2455 (1035; 4330)	0.0007	0.90 (0.85-0.96)**	0.0003
Birth length, cm	48.6 (4.2) 48.0 (33.0; 56.0)	46.2 (3.7) 47.0 (35.0; 53.0)	0.0065	0.84 (0.74-0.95)	0.0042
Head circumference at birth, cm	33.8 (2.0) 34.0 (28.0; 38.2)	32.3 (2.2) 32.5 (25.8; 37.0) n=79	0.0022	0.71 (0.58-0.89)	0.0014
Gestational age, wk	37.6 (2.5) 38.0 (32.0; 42.0)	35.7 (2.7) 35.5 (32.0; 42.0)	0.0010	0.77 (0.65-0.90)	0.0004
Weight at 5 yrs, kg	21.2 (3.1) 20.7 (13.8; 27.0)	20.5 (3.6) 19.8 (15.1; 33.8) n=75	0.38	0.95 (0.85 – 1.07)	
Height at 5 yrs, cm	116.0 (7.5) 114.6 (98.5; 131.0)	115.2 (6.3) 115.0 (101.2; 129.8) n=75	0.57	0.98 (0.92 – 1.05)	
Head circumference at 5 yrs, cm	52.3 (1.7) 52.5 (49.0; 55.2) n=32	51.7 (1.6) 52.0 (47.5; 55.2) n=73	0.082	0.79 (0.60 – 1.03)	

*Where numbers differ from the number of children in the group, they are given separately for each category. ** For birth weight, OR (95% CI) is presented per 100g increase.
cm = centimetre; CI = confidence interval; GA = gestational age; g = gram; kg = kilogram; wk = week, SD = standard deviation.

5.3.1 Visual acuity

Paper I

Table 5 presents the median VA at distance (decimal and logMAR) in the better eye in the study sample according to age group. The median distance VA of the better eye for the whole population was 1.0 (0.0 logMAR) (range 0.5 to 1.25; 0.3–0.1 logMAR). No statistical significance was found between VA and auxological variables after adjusting for age and gender.

Table 5. *Median visual acuity (VA) at distance in the better eye, mean refraction in right eye (RE) and left eye (LE) and number of children found on measurement to be hyperopic (≥2.0 D SE), myopic (≥0.5 D SE) and anisometropic (≥1.0 D SE), as well as children who were astigmatic (≥1 D) in the study sample of Swedish children (n=143), according to age group (Paper I).*

Ophthalmological variables	4-6 years n=35	7-9 years n=42	10-12 years n=35	13-15 years n=31
VA in better eye				
Decimal median (range)	0.9 (0.5;1.25)	1.0 (0.8;1.25)	1.25 (0.9;1.25)	1.25 (1.0;1.25)
LogMAR median (range)	0.05 (0.3;-0.1)	0.0 (0.1;-0.1)	-0.1 (0.05;-0.1)	-0.1 (0.0;-0.1)
Refractive error				
n (%)	6 (17%)	5 (11.9%)	8 (22.9%)	11 (3.5%)
Myopia (≥0.5 D SE)				
n (%)	0 (0%)	0 (0%)	3 (8.6%)	6 (19.4%)
Hyperopia (≥2.0 D SE)				
n (%)	5 (14.2%)	4 (9.5%)	1 (2.9%)	3 (9.7%)
Astigmatism (≥1.0 D)				
n (%)	3 (8.6%)	3 (7.1%)	4 (11.4%)	2 (6.5%)
Anisometropia (≥1.0 D SE) ***n (%)***	1 (2.9%)	0 (0%)	2 (5.7%)	1 (3.2%)

D = dioptre; LogMAR = logarithm of the minimal angle of resolution; SE = spherical equivalent; VA = visual acuity.

Papers II-IV

The VA (decimal and logMAR) of the better eye for MLP children and controls are given in **Table 6**. There were no statistically significant differences between the MLP and control groups for VA after adjusting for age and sex (*Papers II-IV*). There were no significant differences between the RE and LE regarding VA (*Papers II -IV*). In the MLP group, VA of the best eye correlated with GA (p=0.04; r=0.23), HCF at birth (p=0.049; r=0.22) and

HCF at 5 years of age (p=0.02; r=0.27) (*Paper II*). However, VA logMAR did not correlate to any auxological data or OCT parameters at 8 years of age (*Paper III*).

Table 6. *Comparison of visual acuity (VA), refraction and refractive errors in moderate-to-late preterm (MLP) children and their full-term controls (Papers II-IV).*

Ophthalmo-logical variables	MLP n=78 PAPER II	Controls n=35	p-value	MLP n=50 PAPER III	Controls n=43	p-value	MLP n=22 PAPER IV	Controls n=21	p-value
VA best eye at distance, decimal Median (range) logMAR , mean (SD)	1.0 (0.3;1.25) 0.096 (0.11)	1.0 (0.5;1.25) 0.097 (0.12)	n.s	1.25 (0.65;1.25) -0.05 (0.07)	1.25 (0.65;1.25) -0.06 (0.07)	n.s	1.30 (0.8; 1.6) -0.095 (0.1)	1.3 (1.3; 2.0) -0.133 (0.06)	n.s
VA binocular at near	1.0 (0.3;1.0) 0.113 (0.11)	1.0 (0.3;1.0) 0.11 (0.12)	n.s	1.0 (0.5;1.0) 0.02 (0.06)	1.0 (0.4;1.0) 0.02 (0.07)	n.s	1.0 (0.65;1.0) 0.029 (0.05)	1.0 (1.0;1.0) 0.0 (0.0)	n.s
Refraction SE RE (D) Mean (SD) Median (range)	1.78 (1.29) 1.4 (0.5; 7.25)	1.23(1.08) 1.00 (-0.13; 6.63)	0.013	1.74(1.5) 1.25(0.25; 8.5)	1.4 (0.85) 1.25 (0; 4.75)	n.s	1.47 (1.71) 1.0 (-0.25 ; 7.75)	0.94 (0.68) 1.0 (-0.5 ; 2.25)	n.s
Refraction SE LE (D) Mean (SD) Median (range)	1.77 (1.34) 1.4 (-0.5; 7.13)	1.33 (1.33) 1.13 (-0.38; 8.08)	0.018	1.72 (1.38) 1.25 (0.0; 8.0)	1.48 (1.06) 1.25 (-0.25; 6.5)	n.s	1.48 (1.79) 1.0 (-0.25; 7.75)	0.91 (0.69) 1.0 (-0.5;2.0)	n.s
Refractive errors Myopia (≥0.5 D SE) n (%)	0	0	n.s.	0	0	n.s	0	0	n.s
Hyperopia (≥2.0 D SE) n (%)	26 (33.3%)	5 (14.3%)	n.s.	14 (28 %)	7 (16.3%)	n.s	4 (18.2%)	0 (0%)	n.s
Astigmatism (≥1.0 D) n (%)	11 (14.1%)	3 (8.6%)	n.s.	7 (14%)	1 (2.3 %)	n.s.	4 (18.2%)	1 (4.8%)	n.s

D = dioptre; logMAR = log of the minimal angle of resolution; LE = left eye; MLP = moderate-to-late preterm; n.s. = non-significant; RE = right eye; SD = standard deviation; SE = spherical equivalent; VA = visual acuity.

5.3.2 Refraction and refractive errors Paper I

Table 5 shows the number of children with refractive errors in the study sample according to age group. The mean SE for RE in the study was +0.83 (SD 1.06; range -2.13 to +6.63) and for LE +0.89 (SD 1.23; range -2.75 to +8.08).

Papers II-IV

Refraction and refractive errors are shown in **Table 6**. Refraction in the RE and LE of the SGA and AGA groups differed from that of the control group (p=0.013 and p=0.018, respectively) in *Paper II,* however that difference had disappeared by the age of 8 and 12 in the MLP group (*Paper III-IV*). There were no significant differences between the RE and LE regarding SE (*Papers II-IV*). Refractive errors were not found to be significantly different between MLP and control children examined at 5.5, 8 and 12 years of age (*Papers II-IV).*

5.3.3 Ocular dimensions

Papers I and III

Children born more mature, with male predilection, were found to have deeper anterior and vitreous chamber depths, longer axial lengths and thinner crystalline lens thickness (*Paper I*). There was no statistically significant difference between the measurements of MLP and controls with regard to TAL at 8 years of age. (*Paper III*). Correlations were found between TAL and refraction after adjustment for confounding variables in Caucasian children (p=0.0048, r=-0.29) and at 8 years of age in MLP children (p<0.0001, r=-0.58 RE; p<0.0001, r=-0.57 LE) (*Papers I and III*). In the study of 8-year-old MLP children, TAL correlated also to VA logMAR (p=0.018, r=-0.37 RE; p=0.0082 r=-0.41 LE) and HCF at assessment (p=0.0032, r=0.51 RE; p=0.0078, r=0.47 LE) after adjusting for age and sex (*Paper III*). Total axial length correlated significantly to length at assessment in girls (p = 0.0084) and GA (p = 0.0226) after adjusting for age in both genders (*Paper I*).

Palpebral fissure lengths were found to be significantly longer and the ICD shorter in the MLP group compared to the control group (*Paper III*). Intercanthal distance was found to be shorter in girls in the MLP group (p=0.017) (*Paper III*). The canthal index was found to correlate to GA (p=0.02, r=-0.33) in MLP children at 8 years of age, whereas our previous study of normative data found a correlation between ICD and BL (p = 0.03), height, weight, BMI and HCF (p = 0.0008, p = 0.0007, p = 0.037, and p = 0.04 respectively) at time of assessment after adjusting for age (*Paper I*).

5.3.4 Orthoptic evaluation Paper II

Results of orthoptic evaluation are shown in **Table 7**. There was a statistically significant difference between the study groups with regards to motility (p=0.034) and heterophoria at distance (p=0.006). Significant misalignment was not found to be more prevalent in MLP children than in controls; however, children born SGA had more misalignment than the AGA group (p=0.027). All children had normal head posture and no nystagmus was found. No difference was found between the study groups in terms of stereo acuity performance (**Table 7).** All four children with absent stereo acuity and one of the 11 children with subnormal stereo acuity had heterotropia in the MLP group at 5.5 years of age. The NPC was more than 6 cm in three (3.8%) of the MLP children (3 [8.6%] controls; p=n.s.), and accommodation was reduced according to age in 16.7% of the MLP children **(Table 7).** Mean±SD NPA for the MLP children was 19±2.3 D.

Table 7. *Comparison of selected ophthalmological variables in moderate-to-late preterm (MLP) children divided into small for gestational age (SGA) and appropriate for gestational age (AGA), and their full-term age- and sex-matched controls (Paper II).*

Ophthalmological variables n (%)	MLP children n=78	SGA children n=21	AGA children n=57	Controls n=35	p-value*
Strabismus					
Heterotropia n (%)	4 (5.1%)	2 (9.5%)	2 (3.5%)	2 (5.7%)	n.s.
Heterophoria at distance n (%)	8 (10.3%)	6 (28.6%)	2 (3.5%)	4 (11.4%)	**0.006**
Heterophoria at near n (%)	25 (32.1%)	7 (33%)	18 (31.6%)	8 (22.9%)	n.s.
Reduced motility n (%)	13 (16.7%)	4 (19.0%)	9 (15.8%)	0 (0.0%)	**0.034**
Stereo acuity (>60″) n (%)	13 (16.7%)	2 (9.5%)	11 (19.3%)	2 (5.7%)	n.s.
NPC (>6 cm) n (%)	3 (3.8%)	1 (4.8%)	2 (3.5%)	3 (8.6%)	n.s.
NPA (<20 D) n (%)	13 (16.7%)	3 (14.3%)	10 (17.5%)	NA	NA

* The Kruskal-Wallis test was used for comparison between the three study groups – SGA, AGA and controls. AGA = appropriate for gestational age; D = dioptre; MLP = moderate-to-late preterm; NA = not applicable; NPA = near point of accommodation; NPC = near point of convergence; n.s. = non-significant; SGA = small for gestational age.

5.3.5 Relative risk of selected ocular outcomes in association with exposure to MLP birth

Paper II

Moderate-to-late preterm birth showed a 2.4-fold increased prevalence of refractive errors on univariate analysis compared with full-term children (RR 2.39: 95% CI 1.10-5.20; p=0.02).

5.3.6 Fundus morphology/digital image analysis

Papers I and III

The optic disc parameters (ODA, neuroretinal rim area, and cup area) and cup-disc ratios of the different age groups in *Paper I* are described in **Table 8**, and of the MLP children at 8 years of age in **Table 9**. No statistically significant difference was found between RE and LE regarding optic disc, cup or rim areas (*Papers I and III*). No statistically significant difference was found in any optic disc variable between MLPs and controls (*Paper III*). There was no significant difference between boys and girls on analysis of optic disc parameters in *Paper I* or *Paper III* **(Table 10)**.

The ODA was not found to be statistically correlated to auxological parameters at birth, including GA, or at assessment, or to VA, SE, TAL, ICD or PFL after adjustment for age in healthy school-aged children (*Paper I*). In *Paper III*, the ODA was found to be statistically correlated to BL (RE p=n.s.; LE p=0.028, r=0.36), weight (RE p=0.044, r=0.36; LE p=0.013, r=0.45) and height at assessment (RE p=0.044, r=0.36; LE p=0.027, r=0.4) in 8-year old children born MLP. Optic cup area was negatively correlated to delta IGF-I levels (RE p=0.022, r=-0.4; LE p=n.s.). Optic rim area was correlated to weight at assessment (RE p=n.s.; LE p=0.0053, r=0.50) and BMI (RE p= n.s.; LE p=0.015, r=0.44). Cup disc and rim disc ratios were correlated to HCF at birth (RE p=0.046, r=0.32; LE p=0.049, r=0.32) and (RE p=0.039, r=0.33; LE p=0.048, r=0.32) respectively. Girls had significantly smaller cup-disc ratios compared to boys, however, no overall RNFL difference between genders was found except for the nasal sector.

Table 8. *Optic disc parameters (optic disc area (ODA), cup area, neuroretinal rim area, and cup/disc ratio) in the right and left eye, by age, in a sample of Swedish children aged 4–15 years (n=143). Values are given as means (standard deviation (SD)).*

Variable mean (SD)	4–6 years n = 35*	7–9 years n = 42*	10–12 years n = 35*	13–15 years n = 31*	P value
ODA, RE, mm^2	2.51 (0.38) (n = 18)	2.41 (0.43) (n = 27)	2.36 (0.38) (n = 32)	2.19 (0.35) (n = 27)	**0.008**
ODA, LE, mm^2	2.46 (0.49) (n = 19)	2.28 (0.51) (n = 26)	2.34 (0.43) (n = 31)	2.19 (0.38) (n = 26)	0.16
Cup area, RE, mm^2	0.22 (0.25) (n = 18)	0.30 (0.33) (n = 27)	0.24 (0.27) (n = 32)	0.20 (0.24) (n = 27)	n.s.
Cup area, LE, mm^2	0.17 (0.24) (n = 19)	0.24 (0.27) (n = 26)	0.24 (0.29) (n = 31)	0.18 (0.26) (n = 26)	n.s.
Rim area, RE, mm^2	2.29 (0.30) (n = 18)	2.11 (0.38) (n = 27)	2.12 (0.37) (n = 32)	1.99 (0.34) (n = 27)	**0.01**
Rim area, LE, mm^2	2.29 (0.38) (n = 19)	2.04 (0.45) (n = 26)	2.09 (0.36) (n = 31)	2.01 (0.36) (n = 26)	0.12
Cup-disc ratio, RE	0.08 (0.09) (n = 18)	0.12 (0.12) (n = 27)	0.10 (0.10) (n = 32)	0.09 (0.10) (n = 27)	n.s.
Cup-disc ratio, LE	0.06 (0.08) (n = 19)	0.10 (0.11) (n = 26)	0.10 (0.11) (n = 31)	0.08 (0.10) (n = 26)	n.s.

*Where numbers differ from the total number of children in the group, they are given separately for each category.
LE = left eye; mm^2 = square millimetre; n.s. = non-significant; ODA = optic disc area; RE= right eye; SD = standard deviation.

Table 9. *Optic disc parameters (optic disc area (ODA), cup area, neuroretinal rim area, and cup/disc ratio) in right and left eyes of moderate-to-late preterm (MLP) and control groups (Paper III).*

Variable	MLP PAPER III n=41*	Control PAPER III n= 40*	P value
ODA, RE, mm^2 Mean (SD)	2.33 (0.34)	2.38 (0.45)	n.s.
ODA, LE, mm^2Mean (SD)	2.38 (0.42) (n=40)	2.44 (0.48)	n.s.
Cup area, RE, mm^2 Mean (SD)	0.46 (1.17)	0.52 (0.19)	n.s.
Cup area, LE, mm^2 Mean (SD)	0.48 (1.17) (n=40)	0.54 (1.18)	n.s.
Rim area, RE, mm^2 Mean (SD)	1.87 (0.33)	1.85 (0.33)	n.s.
Rim area, LE, mm^2 Mean (SD)	1.9 (0.35) (n=40)	1.9 (0.36)	n.s.
Cup-disc ratio, RE Mean (SD)	0.2 (0.07)	0.22 (0.05)	n.s.
Cup-disc ratio, LE Mean (SD)	0.2 (0.06) (n=40)	0.22 (0.04)	n.s.

*Where numbers differ from the total number of children in the group, they are given separately for each category.
LE = left eye¸ mm^2 = square millimetre; MLP =moderate-to-late preterm; n.s. = non-significant; ODA = optic disc area; RE = right eye; SD = Standard deviation

Table 10. *Gender difference in optic disc parameters of moderate-to-late preterm (MLP) children (Paper III).*

Variable	Female Mean (SD) Median (range) N = 19*	Male Mean (SD) Median (range) N = 22*	P value
ODA RE	2.22 (0.32) 2.26 (1.47; 2.79)	2.42 (0.33) 2.52 (1.88; 3.21)	n.s.
Cup RE	0.45 (0.17) 0.45 (0.16; 0.81)	0.47 (0.16) 0.52 (0.23; 0.82) n=21	n.s.
Rim RE	1.77 (0.26) 1.81 (1.30; 2.15)	1.96 (0.37) 1.96 (1.37; 2.90)	n.s.
CDR RE	0.20 (0.07) 0.21 (0.09; 0.32)	0.20 (0.07) 0.20 (0.09; 0.32)	n.s.
ODA LE	2.29 (0.51) 2.31 (0.95; 3.42)	2.46 (0.32) 2.43 (1.8; 2.94) n=21	n.s.
Cup LE	0.47 (0.21) 0.47 (0.10; 0.92)	0.49 (0.13) 0.51 (0.21; 0.82) n=21	n.s.
Rim LE	1.81 (0.36) 1.89 (0.85; 2.51)	1.97 (0.32) 1.93 (1.36; 2.59) n=21	n.s.
CDR LE	0.20 (0.06) 0.2 (0.10; 0.30)	0.20 (0.06) 0.20 (0.09; 0.34) n=21	n.s.

*Where numbers differ from the total number of children in the group, they are given separately for each category. CDR = cup:disc ratio; LE = left eye; n.s. = non-significant; ODA = optic disc area; RE = right eye; SD = standard deviation.

5.3.7 OCT parameters
Paper III

Total macular volume was significantly less in the MLP group (RE 7.75±0.5mm³; LE 7.62±0.6mm³) than in controls (RE 8±0.3mm³, p=0.0042; LE 7.97±0.4mm³, p=0.0041). Foveal minimum, central retinal thickness and central macular RNFL were thicker than in controls; however this was significant only in RE (RE p=0.0017, LE p=0.10; RE p=0.0046, LE p=0.084; RE p=0.011, LE p=0.076, respectively). The 9 ETDRS macular sectors in the MLP and control groups are illustrated in **Fig. 8**. Macular volume correlated to refraction (SE) (RE p=0.04, r=0.41; LE p=0.017, r=0.46).

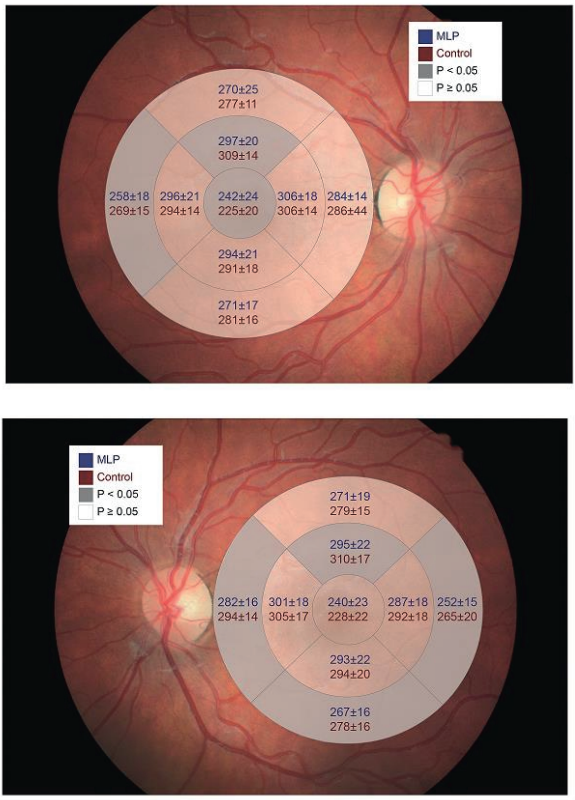


Figure 8. a-b. *Average Macular Thickness in the 9 ETDRS Areas, Expressed as Mean ± SD in 30 Moderate-to-Late Preterm (MLP) Children and 43 Controls. (a) Right Eyes; (b) Left Eyes.*

Paper IV

There was a significant difference between right and left values only in the outer temporal area in the ETDRS area and RNFL thickness in the temporal papillary region, which subsequently led the authors to present data on both eyes. Comparison of OCT variables in the same cohort of MLP children investigated at 8 years of age and subsequently at 12 years of age is shown in **Table 11**, as well as change over time of OCT parameters in the 14 MLP individuals measured at 8 and subsequently at 12 years of age (**Table 12**). Central retinal thickness correlated to IGF-I at assessment (RE p= 0.047, r=-0.47; LE p=0.024, r=-0.5) and delta IGF-I (RE p=0.029, r=-0.51; LE p=0.0065, r=-0.59). **Fig. 9** shows the fundus photograph and OCT image of an MLP child.

Table 11. *Optical coherence tomography (OCT) parameters in both moderate-to-late preterm (MLP) children and full-term controls examined at 8 and 12 years of age.*

Variable Mean (SD) Median (range)	MLP 8 years n=32	Control 8 years n=42	P value	MLP 12 years n=22	Control 12 years n=21	P value
Macular volume RE	7.75 (0.48) 7.75 (6.75; 9.11)	8.00 (0.30) 8.01 (7.39; 8.74)	**0.0042**	7.76 (0.32) 7.68 (7.33; 8.65)	7.65 (0.29) 7.66 (7.21; 8.29)	n.s.
Macular volume LE	7.62 (0.59) 7.65 (5.48; 8.86)	7.97 (0.35) 8.00 (7.08; 28.00)	**0.0041**	7.72 (0.30) 7.71 (7.20; 8.65)	7.65 (0.31) 7.65 (7.30; 8.36)	n.s.
Central retinal thickness RE	241.6 (23.5) 242.0 (202.0; 309.0)	225.4 (19.6) 227.0 (184.0; 279.0)	**0.0046**	239.7 (17.4) 240.5 (206.0; 282.0)	232.0 (18.1) 233.0 (201.0; 267.0)	n.s.
Central retinal thickness LE	239.6 (23.2) 238.5 (198.0; 292.0)	227.8 (22.0) 225.0 (190.0; 297.0)	n.s.	246.7 (22.0) 243.0 (208.0; 312.0)	233.3 (19.6) 231.0 (203.0; 270.0)	n.s.
Foveal minimum RE	207.7 (27.6) 201.5 (162.0; 290.0)	189.8 (18.1) 188.5 (163.0; 241.0)	**0.0017**	200.4 (23.6) 196.5 (165.0; 265.0)	191.8 (16.2) 192.0 (171.0; 220.0)	n.s.
Foveal minimum LE	205.5 (28.9) 199.0 (164.0; 294.0)	193.7 (25.1) 190.0 (158.0; 298.0)	n.s.	213.8 (33.5) 211.0 (176.0; 317.0)	192.8 (24.7) 188.0 (158.0; 271.0)	n.s.
RNFL central RE	14.9 (15.8) 6.0 (0.0; 52.0)	5.98 (9.53) 2.00 (0.00; 38.00)	**0.011**	3.82 (4.11) 2.50 (0.00; 12.00)	2.67 (2.31) 3.00 (0.00; 8.00)	n.s.
RNFL central LE	13.6 (16.6) 5.5 (0.0; 50.0)	7.81 (11.53) 3.50 (0.00; 50.00)	n.s.	8.29 (9.82) 4.00 (0.00; 29.00)	2.71 (2.65) 2.00 (0.00; 11.00)	n.s.

LE = left eye; MLP = moderate-to-late preterm; n.s. = non-significant; RE = right eye; RNFL = retinal nerve fibre layer; SD = standard deviation.

Table 12. *Change over time of optical coherence tomography (OCT) parameters in 14 moderate-to-late preterm (MLP) individuals measured at both 8 and 12 years of age.*

Variable Mean (SD) Median (range)	MLP 8 yrs n=14*	MLP 12 yrs n=14*	Change from 8 yrs to 12 yrs n=14*
Macular volume **RE**	7.76 (0.54) 7.75 (6.75; 9.11) n=13	7.72 (0.33) 7.67 (7.33; 8.65) n=13	-0.04 (0.41) -0.110 (-0.46; 1.13) n=13
Macular volume **LE**	7.58 (0.80) 7.68 (5.48; 8.86)	7.70 (0.35) 7.68 (7.20; 8.65)	0.12 (0.61) -0.060 (-0.40; 1.72)
Central retinal thickness **RE**	245.6 (28.8) 242.0 (202.0; 309.0) n=13	244.1 (18.5) 245.0 (206.0; 282.0) n=13	-1.54 (20.09) 4.00 (-60.0; 18.0) n=13
Central retinal thickness **LE**	238.5 (24.3) 235.0 (199.0; 287.0)	247.1 (17.5) 244.0 (208.0; 285.0)	8.57 (17.26) 7.50 (-25.0; 46.0)
Foveal minimum **RE**	207.0 (33.5) 193.0 (162.0; 290.0) n=13	207.6 (24.8) 202.0 (165.0; 265.0) n=13	0.62 (29.02) 3.000 (-75.0; 46.0) n=13
Foveal minimum **LE**	205.3 (38.7) 195.0 (164.0; 294.0)	215.8 (24.7) 216.0 (176.0; 253.0)	10.5 (34.3) 9.0 (-60.0; 81.0)
RNFL central **RE**	15.2 (12.1) 12.0 (2.0; 37.0) n=13	4.62 (4.33) 3.00 (0.0; 12.0) n=13	-10.5 (12.2) -5.0 (-30.0; 6.0) n=13
RNFL central **LE**	16.9 (19.6) 9.0 (0.0; 50.0)	9.86 (10.20) 6.0 (0.0; 29.0)	-7.07 (14.63) -4.00 (-36.0; 17.0)

*Where numbers differ from the total number of children in the group, they are given separately for each category.
LE = left eye; MLP = moderate-to-late preterm; n.s. = non-significant; RE = right eye; RNFL = retinal nerve fibre layer; SD = standard deviation; yrs = years.

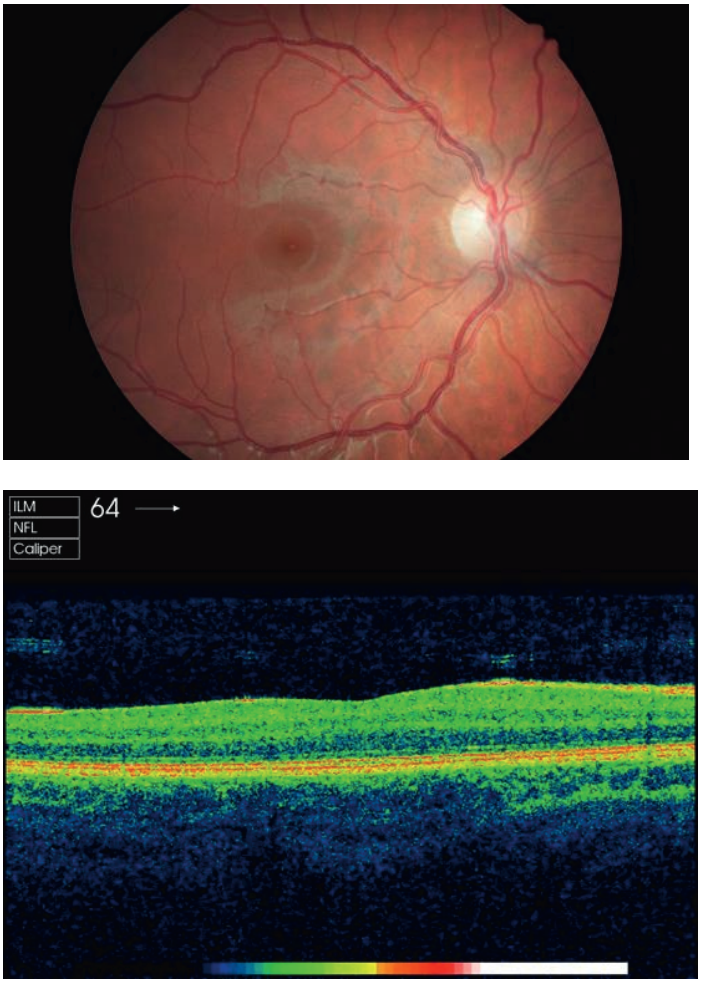


Figure 9. *Optical coherence tomography (OCT) image of the right eye (RE) of one of the thickest maculae in a moderate-to-late preterm (MLP) child. The child was born appropriate for gestational age (AGA) at 33 weeks and weighed 2035 g. Examination at 8 years of age showed visual acuity of 1.0 bilaterally (0.0 logMAR), spherical equivalence of +2.25 diopters (D) in RE and +2.50 D in left eye (LE), and total axial length of 21.87 mm RE and 21.83 mm LE. OCT findings revealed signs of a thickened fovea (foveal minimum 244 µm RE, central retinal thickness 277 µm, macular volume 7.75 mm³, central RNFL 16 µm) and somewhat flattened foveal depression with good retinal differentiation.*

5.3.8 History of visual perception problems Paper II

Structured history-taking regarding VPPs was performed in all MLP children. According to the structured interview, three (14.3%) SGA children and three (5.3%) AGA children compared with none of the controls (0%) showed signs of cognitive visual problems (p=n.s.) in one or more of the following areas: simultaneous perception (n=2), motion perception (n=2) and recognition (n=2), followed by depth perception (n=1) and orientation (n=1) (p=0.09) (p=n.s.).

Paper IV

5.3.9 Visual evoked potentials

Visual evoked potential amplitudes (P100) were decreased in the MLP group compared with controls (**Table 13**). No differences in PRVEPs latencies were found. After adjusting for age and gender, no correlations were found between any PRVEPs variable (amplitude and latency 60 P100) and VA, optic disc parameters, papillary RNFL, nor RNFL/retinal thickness of the inner circle of ETDRS macular zone. In addition, the amplitudes/latencies of PRVEPs did not correlate with birth anthropometric measurements or GA.

Table 13. *Pattern reversal visual evoked potentials (PRVEPs) variables in both moderate-to-late preterm (MLP) children and controls.*

PRVEPs Oz leads	MLP Mean (SD) n=19	Controls Mean (SD) n=21	p-value[a]
Amplitude (µV) RE	19.1 (7.2)	31.7 (13.1)	**0.0027**
Latency (ms) RE	104.7 (9.5)	105.6 (6.4)	n.s.
Amplitude (µV) LE	20.0 (6.9)	32.8 (11.1)	**0.0037**
Latency (ms) LE	104.9 (12.2)	105.3 (7.2)	n.s.

[a]values were calculated by logistic regression test adjusted for age and gender.
LE = left eye; µV = microvolt; ms = millisecond; MLP = moderate-to-late preterm; n.s. = non-significant; OZ = midline electrode; PRVEPs = pattern reversal visual evoked potentials; RE = right eye; SD = standard deviation.

5.3.10 Full-field electroretinography

The DA 3.0 b-wave amplitude was found to be higher and the LA 3.0 b-wave implicit time was significantly delayed and shorter for a-wave in the MLP group compared to controls. Central foveal thickness and foveal minimum did not correlate significantly with flicker's and LA 3.0's amplitudes and latencies. Gestational age correlated to LA 3.0 b-wave amplitudes ($p = 0.0076$, $r = 0.565$).

6 DISCUSSION

The aim of the project was to investigate the development of morphological and functional ophthalmological aspects in children born MLP, relating them to auxological data and comparing them with their full-term counterparts.

There was no difference in terms of distance VA between children born MLP and controls in our studies (*Papers II-IV*). Our 5.5 and 8-year-old studies of MLP children support the conclusion of Robaei et al., who stated that distant VA in the better eyes was not significantly different for children exposed and not exposed to modest prematurity (Robaei et al. 2006). In addition, GA and auxological data including HCF at birth and HCF at 5.5 years of age were positively correlated with VA outcome in MLP children (*Paper II*). These findings highlight the importance of head growth and the infant's catch-up growth during the first critical brain development period for proper development of the visual system and subsequently better visual outcome. More recently, infants born MLP were found to exhibit widespread brain white matter microstructure alterations at term equivalent age compared with term controls (Kelly et al. 2016). Structural MRI revealed smaller brain bi-parietal diameter, and smaller corpus callosum, basal ganglia, thalami and cerebellar measurements than full-term controls (Walsh et al. 2014). In addition, myelination of the posterior limb of the internal capsule was less developed and gyral maturation was delayed in these children. This might explain our finding that poorer VA correlates with smaller HCF. However, a similar correlation of these findings is lacking in the literature, to our knowledge. In disagreement with Robaei et al., who found similar refraction in the study groups (Robaei et al. 2006), refraction in RE and LE was slightly more hyperopic in MLP children than in controls in our study at 5.5 years of age (*Paper II*), however with emmetropisation at 8 years of age, this difference became insignificant between the study groups (*Paper III-IV*). We found that MLP children have a slightly higher risk of hyperopia (2.24-fold increase) than the children in the study performed by Robaei et al., which reported a 1.9-fold risk (Robaei et al. 2006) (*Paper II*). Nonetheless, a non-significant higher prevalence of refractive errors was observed at 8 years of age in the MLP group (*Paper III*). There is a fair degree of accordance between our results and Robaei's study indicating that modest prematurity was not associated with increased risk of myopia or significant hyperopia (Robaei et al. 2006). These findings are seemingly at odds with previous studies (Gallo et al. 1991; Robinson & O'Keefe 1993; Hebbandi et al. 1997; Quinn, Graham E et al. 1998; Larsson et al. 2003), which demonstrated an increased prevalence of myopia in premature children; however, most of

these studies tended to include children with previous ROP (Hebbandi et al. 1997; Quinn, Graham E et al. 1998; Larsson et al. 2003) or very premature children (Robinson & O'Keefe 1993; Quinn, Graham E et al. 1998). Our results also show that neither low BW nor prematurity was significantly correlated to refraction, which is consistent with other studies (*Paper I and III-IV*) (Robaei et al. 2006).

Saw et al. (2004) concluded that children who were born heavier (>4kg), had larger head size or length at birth or were born more mature had longer axial lengths and deeper vitreous chambers, and this has been confirmed in our study (*Paper I*). Based on population-based studies on adult subjects, our results support their findings where they showed a tendency towards shorter TAL (Wong et al. 2001; Shufelt et al. 2005; Atchison et al. 2008), shallower ACD (Wong et al. 2001; Shufelt et al. 2005), thicker lenses (Wong et al. 2001) and shallower VD (Wong et al. 2001; Shufelt et al. 2005; Atchison et al. 2008) in females compared to males. This suggests that differences in ocular size exist in childhood throughout adulthood, supporting the importance of taking this into consideration in our daily practice and establishing normal values for genders separately.

Intercanthal distance was found to correlate to GA in MLP children (*Paper III*) in addition to BL, as well as height, weight, BMI and HCF at assessment after adjusting for age in our previous study of normative data (*Paper I*). Measurement of ICD may be a useful or complementary indicator of growth, as it showed significant correlations to auxological data. In contrast, PFL did not correlate to any other auxological variable when adjusted to age (*Papers I and III*).

Our results show that increases in TAL seem to be associated with male gender, increased maturity at birth and increased height at assessment in girls (*Paper I*). Difference in TAL between genders should therefore be taken into account when taking paediatric ophthalmological measurements to evaluate patients with glaucoma or cataracts, for example. We should also account for prematurity when considering TAL growth, as this seems to differ depending on the size of the child. We have also studied the association between IGF-I levels and ocular growth. An association was found between low-serum IGF-I levels at assessment and central retinal thickness, as well as optic cup area and cup disc ratio. Thus high IGF-I levels were found to be associated with reduced central retinal thickness. Poor increase in IGF-I from birth to 8 years of age was correlated to central retinal thickness. An ongoing multicentre clinical trial, initiated by researchers at the Queen Sylvia Children's Hospital, is studying the effect of restoration of normal levels of IGF-I in extremely preterm neonates in preventing ROP (Hellström et al.

2003). A follow-up study in these infants is ongoing to examine the effects of IGF-I treatment on visual function and development.

In our study of 5.5-year-old MLP children, defective motility, heterophoria at distance and hyperopia were significantly more prevalent than in the controls (*Paper II*). There was no increased risk of strabismus in our cohort, as opposed to a 3.7-fold increase in association with exposure to moderate-to-late prematurity in another population-based study which also studied any strabismus at near or distance (Robaei et al. 2006). In our relatively small cohort of children born MLP, no differences in significant ocular alignment were found compared with full-term controls. However, in agreement with another study by Robaei et al., a non-significant trend for more misalignment was observed by the researchers in preterm children (Robaei et al. 2006). We found that children born SGA had significantly more misalignment than the AGA group. No significant difference was found between the study groups in terms of stereo acuity performance, unlike other studies that demonstrated decreased stereo acuity in preterm children (Robaei et al. 2006). In addition, no statistically significant difference was found in abnormal NPC between MLP and controls. Moreover, VPP as reported by history-taking was not found to occur more frequently in MLP children than in full-term controls (*Paper II*).

In addition, there was no difference between MLP and controls in respect of CCT (*Paper III*). The MLP study shows a statistically significant difference in CCT measured by means of OCT and ultrasound pachymeter in all the children combined. As with previous studies, ultrasound pachymeter seems to overestimate CCT in comparison to the CCT measured by OCT (Ishibazawa et al. 2011; Correa-Pérez et al. 2012), although further studies are needed to demonstrate the interchangeability and accuracy of these devices. This underlines the importance of using the same device when following children with glaucoma, for instance.

The MLP children had thicker central retinas as measured by OCT than those born at term. This agrees with other studies that confirmed thicker central maculae in preterm children. Åkerblom et al. studied 62 preterm children with GA of 32 weeks or less (Åkerblom et al. 2011) and Ecsedy et al.,(Ecsedy et al. 2007) and Park et al. (Park & Oh 2012) included children with moderate prematurity in addition to the extremely premature with and without ROP. To our knowledge, no such a study has as yet been conducted in this group of premature children without any history of ROP (*Paper III*). The same trend was also observed when the MLP children were re-examined at 12 years of age (*Paper IV*). We detected a positive correlation between macular volume and SE in the present study, indicating that an increased

macular volume was prone to higher refractive errors. However, no decrease in VA was observed. This concurs with previous studies, which found no relation between abnormal foveal morphology and reduction in VA (Recchia & Recchia 2007; Åkerblom et al. 2011; Park & Oh 2012).

The optic disc parameters showed no significant differences between the two study groups and when compared with normative data presented in *Paper I* (*Paper III*). However, a non-significant trend towards smaller optic disc areas was noticed in other reports (Wikstrand et al. 2010). Nevertheless, other researchers found a statistically significant difference between preterm children born at gestational week <32 and controls (Wikstrand et al. 2010). No gender difference was reported in our study of optic disc parameters in normal children (*Paper I*), which is in accordance with a previous report which documented the same finding (Hellström & Svensson 1998). However, girls were found to have non-significant smaller cups and rims compared to boys in the 8-year study of MLP (*Paper III*). Our results in *Paper I* appear to be at odds with the latter study, which found no change in the optic variables with increasing age (Hellström & Svensson 1998). Both ODA and rim area of RE and LEs have a tendency toward a decrease with increasing age in *Paper I,* however, only the RE show a statistical significance. This may be due to the fact that the means for RE and LE were used in the study by Hellström et al; by contrast, in the present study we decided to correlate the different variables separately in each eye. A tendency towards an increased cup-disc ratio with increasing age was reported (Carpel & Engstrom 1981) but by contrast, our analysis (*Paper I*) suggests a more static cup-disc ratio over time. Moreover, we found no correlation to any of the auxological data in our study of normative values, which is similar to a study carried out in Australia, which reports that BW did not influence the size of the optic disc in term infants (Kandasamy et al. 2012). However, in *Paper III*, larger optic disc was found to correlate to longer BL. Larger optic disc and neuroretinal rim areas were also found to correlate to heavier weight at time of assessment, and neuroretinal rim areas to higher BMI values. This suggests that good catch-up growth favours proper development of ocular fundus morphology. Papillary RNFL differences were noted to be non-significantly thinner in all four sectors. In discordance with other studies, nasal, superior and average disc RNFL were found to be decreased in preterm children however some of their children had severe ROP (Åkerblom et al. 2012; Park & Oh 2015).

Children born MLP with no history of ROP were found to have reduced P100 PRVEPs amplitudes. The results in the present study are in agreement with several studies which demonstrated decreased VEP amplitudes in preterm populations (Feng et al. 2011; Michalczuk et al. 2015). We report normal

latency which was found in the same cohort at 5.5 years (Nilsson et al. 2011), but disagrees with the previous reports demonstrating delayed latencies in their study groups at age 4-6 years (Feng et al. 2011) and 11 years (Michalczuk et al. 2015). However, essential differences exist between our studies, where their groups included extremely preterm children (Michalczuk et al. 2015), very low birth weight children (Michalczuk et al. 2015) and AGA children as a control group (Nilsson et al. 2011), as opposed to full terms in the present study. Compared with term-born peers, MLP infants are at double the risk of neurodevelopmental disability at 2 years of age, with most impairments observed in the cognitive domain, supporting the notion that even with MLP gestations, preterm birth may impede the normal trajectory of brain development (Johnson et al. 2015).

In the present study, the MLP group had higher DA 3.0 b-wave amplitudes than the controls, with similar implicit time and a-wave amplitude. Previous studies have shown mainly rod photoreceptor ERG-changes in pre-term children compared to full-term children. Fulton et al found rod photoreceptor dysfunction increasing with increasing severity of acute phase ROP compared with the full-term group (Fulton et al. 2001), and Åkerblom et al. demonstrated decreased a-wave amplitudes of the combined rod/cone response (rod 3.0, and rod 12.0) in the preterm group compared with the full-term group, but no differences in implicit times (Akerblom et al. 2014). In our study, LA 3.0 implicit time was significantly shorter for the a-wave and significantly delayed for the b-wave in the MLP group compared to controls. This disagrees with Åkerblom et al, who found no affection of the cone response in their preterm group; however, in their study, an exception to the standard protocol by ISCEV was made where no light adaptation was performed for the children to facilitate the procedure, as opposed to our 5 min light adaptation (Akerblom et al. 2014). Lower GA was associated with reduced cone response measured by ff-ERG (*Paper IV*).

7 CONSIDERATIONS

Paper I

This is one of only a few prospective studies that measure all major ocular, including optical, components in a moderately large, comprehensively-studied sample of children and adolescents aged 4–15 years, and relate ocular dimensions to auxological data both at birth and at assessment. Ninety-eight per cent of the children in the present study were white Europeans (Grönlund et al. 2006), which can be considered a strength, as it is an established fact that ocular dimensions differ between different ethnic groups (Saw et al. 2002; Ip et al. 2007; Twelker et al. 2009; Tariq et al. 2010; Knight et al. 2012). Therefore, our group of children can serve as a reference for Caucasian children. Nonetheless, the findings in our study need to be corroborated by findings in other ethnic groups.

Papers II-IV

These prospective, population-based studies had standardised examination protocols. The same examiners tested both MLP and control groups of children to decrease the risk of inter-examiner discrepancies. The first major limitation of these studies was that they included a relatively small sample size that might be more prone to random sampling error, however, one of the main strengths is their population-based design and use of standardised examination protocols, allowing relative generalisation to the preterm childhood population. In addition, complete perinatal data, full examination at birth and blood samples were taken as soon as the infants were included in the study. To our knowledge, no other group of researchers has studied the effect of IGF-I levels on ocular growth. A further strength is that MLP children have been followed since birth, with particular focus on visual outcome and full ophthalmologic examination. The MLP children examined may allow relative generalisation to the MLP population, as no differences were found compared with the neonatal original MLP population.

Paper III

To our knowledge, no study has previously focused on macular morphology in an 8-year follow-up in this subset of premature children. A possible limitation is the narrow representation of the population. The control group was recruited from only four different public schools in the area of Gothenburg. Children of mixed races were not excluded; however, the

number of these children was relatively low (16%) and equal between the two groups. In addition, the number of participant drop-outs over the years in our study is fairly high and may in itself contribute to a loss-to-follow-up bias.

Paper IV

The first major limitation of this study was that it included a relatively small sample size. The number of participant drop-outs over the years in this population-based longitudinal study is fairly high. However, our drop-out analysis revealed no difference in the birth parameters between this subgroup and the original group. A major strength is that, to our knowledge, no study has previously focused on electrophysiology compared to fundus structures on a purely moderate to late subset of preterm children with no history of ROP. In addition, the results were compared to full-term controls.

8 CONCLUSION

In conclusion, prematurity represents a continuum of adverse effects. Preterm birth is a significant global burden, with 15.1 million babies born before 37 weeks of pregnancy every year across the world, representing one in 10 babies (Howson et al. 2013). The increased survival of prematurely born infants poses a long-term problem in terms of increased incidence of ophthalmological problems such as strabismus and refractive errors. These findings have potentially important implications for the follow-up of premature children and therefore require confirmation in large population-based studies that encompass these premature children, since it has been confirmed in our study that prematurity, even in the moderate to late phase, represents a continuum of risks associated with visual system morbidities.

Paper I

Babies born more mature with a male predilection were found to have greater anterior and vitreous chamber depth, longer axial length, and thinner crystalline LT. The present study has shown different correlations that exist between the parameters of growth at birth and, specifically, ocular growth. These measurements and correlations may be very valuable in the evaluation of ocular dimensions in clinical paediatric ophthalmology, including evaluation of certain paediatric syndromes in children born preterm and/or SGA. In addition, the TAL measurements and their correlations will be particularly important in children undergoing intraocular lens implantation and also in paediatric glaucoma patients. These normative values will therefore be useful as a reference for ocular findings and their relationship to auxological data in Caucasian children aged 4–15 years. They will also be useful in future comparison of paediatric patients with other ocular pathologies.

Paper II

Based on our findings, even MLP children may be associated with increased ocular morbidity and may require greater ophthalmic surveillance than their full-term counterparts. Auxological data at birth, especially BW, was an important risk indicator when establishing an ophthalmological diagnosis in preschool MLP children, and VA outcome was positively correlated to GA.

Paper III

Children born MLP had similar VA, refraction, IOP, CCT and TAL compared with full terms, examined at the age of 8 years. Our results show that macular volume was significantly less in the MLP group than in controls examined at 8 years of age. Good catch-up growth and IGF-I levels seem to favour proper development of ocular growth and morphology. In addition, it is important to bear in mind in daily clinical practice that OCT is not interchangeable with ultrasound pachymetry for measuring CCT.

Paper IV

In conclusion, our results show that MLP birth may have a significant effect on pattern-reversal VEPs amplitudes without clear retinal structural changes. We also found significant differences for b-wave amplitude of mixed rod/cone response and implicit times for cone ERG-response, which are more difficult to interpret. Since none of our children born MLP had been treated for ROP, this may suggest that immaturity per se and not treatment for ROP might affect the retinal function, leading to both morphological and functional changes. Further studies are needed to better understand the association between these findings and visual functions in MLP children.

ETHICAL REVIEW AND CONSIDERATIONS

All studies were approved by the Ethics Committee at the Medical Faculty, Sahlgrenska Academy at Gothenburg University, Gothenburg, Sweden. The study protocols adhered to the tenets of the Helsinki Declaration. Written informed consent was obtained from the parents of all the children participating after they had been informed of the nature of the study.

The examinations included in the project are already well established and are used in everyday clinical practice. The risks are very small, being almost non-existent. Any discomfort that children may be exposed to is the effect of the eye drops given in conjunction with the ophthalmologic examination.
The children receive a detailed eye and eyesight investigation. If any treatable ailments are detected, the children receive treatment and are followed-up according to usual routines.

PROJECT ORGANISATION

Lina Raffa, MD, FEBO, Fellow in Paediatric Ophthalmology, PhD student, Department of Clinical Neuroscience, Institute of Neuroscience and Physiology, Sahlgrenska Academy at University of Gothenburg, Gothenburg, Sweden.

Marita Andersson Grönlund, MD, PhD, Associate Professor, Senior Lecturer and Senior Consultant in Paediatric Ophthalmology, Department of Clinical Neuroscience, Institute of Neuroscience and Physiology, Sahlgrenska Academy at University of Gothenburg, Gothenburg, Sweden. Principal PhD supervisor.

Jovanna Dahlgren, MD, PhD, Professor and Senior Consultant in Paediatrics, Department of Paediatrics, Institute of Clinical Sciences, Sahlgrenska Academy at the University of Gothenburg, Gothenburg, Sweden. Co-supervisor.

Ann Hellström, MD, PhD, Professor and Senior Consultant in Paediatric Ophthalmology, Department of Clinical Neuroscience, Institute of Neuroscience and Physiology, Sahlgrenska Academy at University of Gothenburg, Gothenburg, Sweden. Co-supervisor.

Josefin Nilsson, MD, PhD, Associate Professor in Clinical Neurophysiology, Department of Clinical Neurophysiology, Sahlgrenska University Hospital, Gothenburg, Sweden.

Susann Andersson, MD, PhD, Senior Consultant in Paediatric Ophthalmology, Department of Clinical Neuroscience, Institute of Neuroscience and Physiology, Sahlgrenska Academy at University of Gothenburg, Gothenburg, Sweden.

Eva Aring, orthoptist, PhD, Department of Clinical Neuroscience, Institute of Neuroscience and Physiology, Sahlgrenska Academy at University of Gothenburg, Gothenburg, Sweden.

Ann-Katrin Karlsson, nurse, Med.lic, Department of Paediatrics, Institute of Clinical Sciences, Sahlgrenska Academy at the University of Gothenburg, Gothenburg, Sweden.

Eva Rudholm, ophthalmology assistant, Department of Paediatric Ophthalmology, The Queen Silvia Children's Hospital, Sahlgrenska University Hospital, Gothenburg, Sweden.

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9 FUTURE PERSPECTIVES

Our data calls for further prospective birth cohort studies investigating the eye development in MLP children, as this group is susceptible to more ophthalmological complications than previously described. These children may need to be identified and followed-up ophthalmologically as moderate to late preterm births are common, seven times more likely to result in neonatal mortality and morbidity than births at 39 weeks,(McIntire & Leveno 2008; Shapiro-Mendoza et al. 2008) and remain at risk of developing a wide range of complications, not only in the neonatal period, but also in the long term (Saigal & Doyle 2008). Parents should be made aware of the various problems their infants can encounter. The care of these children should not be defined by the same policies and practices that govern full-term infants.

Planned project

Eye morphology and visual function in relation to growth and cardiovascular status in children born MLP at 10 years of age

Aim: To define the relationship between eye morphology and visual function on the one hand and growth and cardiovascular status on the other hand in children born MLP in comparison to full-term children.

BACKGROUND

From the same ongoing, population-based, prospective, longitudinal study of otherwise healthy, preterm children born at GA 32+0–36+6 weeks, 80 infants (35 girls, 45 boys) born at the two delivery wards at Sahlgrenska University Hospital, Gothenburg, Sweden, were consecutively enrolled between October 2002 and October 2003 **(Fig. 4)**. The purpose was to evaluate retinal vessel morphology of MLP infants during their first week of life in order to determine predictors of abnormal retinal vascularisation in new-borns considered to have no risk of developing ROP. Our hypothesis was that foetal growth restriction inhibits optimal vascular growth as a result of decreased angiogenetic growth factors and hypoxia. Of the 78 infants investigated, 27% had abnormal retinal vessel morphology; they had significantly lower birth weight, shorter birth length, and smaller head circumference. They also had significantly lower GA and IGF-I levels. A higher percentage of these infants were SGA, and maternal hypertension/preeclampsia rates were also higher.

Stepwise logistic regression showed that birth weight was the strongest predictor of abnormal retinal vascularisation (Allvin et al. 2014).

METHODS

The same children (n=33) as in this subset neonatal study **(Fig. 4)** are followed-up at 10-years of age with regard to auxological data, blood-pressure, IGF-I levels, fat-related hormones and insulin-sensitive markers (leptin and adiponectin) as well as to VA, refraction, fundus morphology (retinal vessels and optic disc) in order to find out if abnormal retinal vascularisation found in the neonatal study has any effect on these children later in life. Age- and sex-matched full-term children (n=28) have been selected to serve as controls. None of the participating children have previous history of ROP. All examinations have been performed and data analysis is ongoing.

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APPENDIX

Appendix 1 - Conversion Table for Representation of Visual Acuity

20 ft	6 m	Decimal	4 m	logMAR
20 / 630	6 / 190	0.032	4 / 125	+1.5
20 / 500	6 / 150	0.04	4 / 100	+1.4
20 / 400	6 / 120	0.05	4 / 80	+1.3
20 / 320	6 / 95	0.06	4 / 63	+1.2
20 / 250	6 / 75	0.08	4 / 50	+1.1
20 / 200	6 / 60	0.1	4 / 40	+1.0
20 / 160	6 / 48	0.125	4 / 32	+0.9
20 / 125	6 / 38	0.16	4 / 25	+0.8
20 / 100	6 / 30	0.2	4 / 20	+0.7
20 / 80	6 / 24	0.25	4 / 16	+0.6
20 / 63	6 / 19	0.32	4 / 12.5	+0.5
20 / 50	6 / 15	0.4	4 / 10	+0.4
20 / 40	6 / 12	0.5	4 / 8	+0.3
20 / 32	6 / 9.5	0.63	4 / 6.3	+0.2
20 / 25	6 / 7.5	0.8	4 / 5	+0.1
20 / 20	6 / 6	1.0	4 / 4	0
20 / 16	6 / 4.8	1.25	4 / 3.2	-0.1
20 / 12.5	6 / 3.8	1.6	4 / 2.5	-0.2
20 / 10	6 / 3	2.0	4 / 2	-0.3

ft = feet; logMAR = log of the minimal angle of resolution; m = metre.

Appendix 2 - Questionnaire: Visual Perceptual Problems

Recognition

1. Do you experience difficulties recognising people?
2. Do you experience difficulties recognising people in photos?
3. Do you experience difficulties recognising shapes?
4. Do you experience difficulties recognising colours?

Orientation

5. Do you have trouble finding your way around at home?
6. Do you have trouble finding your way around at school?
7. Do you have trouble finding your way around in new surroundings?

Depth perception

8. Do you have problems distinguishing a line from a step?

Movement perception

9. Do you have problems seeing a moving object?
10. Do you have problems seeing/finding an object while moving?

Simultaneous perception

11. Do you have problems finding an object on a patterned carpet?
12. Do you have problems finding objects in complex pictures?