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## Prevalence and causes of ocular disorders and visual impairment among preterm children in Ethiopia

Journal:	<i>BMJ Paediatrics Open</i>
Manuscript ID	bmjpo-2023-002317
Article Type:	Original research
Date Submitted by the Author:	05-Oct-2023
Complete List of Authors:	SHERIEF, SADIK; Addis Ababa University, Department of Ophthalmology; SickKids Research Institute Muhe, Lulu M; Addis Ababa University College of Health Sciences Mekasha, Amha; Addis Ababa University, Department of Pediatrics and Child Health Demtse, Asrat; Addis Ababa University College of Health Sciences, Paediatrics and Child Health Ali, Asim; The Hospital for Sick Children, Ophthalmology and Vision Sciences
Keywords:	Infant, Neonatology, Ophthalmology

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# Prevalence and causes of ocular disorders and visual impairment among preterm children in Ethiopia

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Short Title: Ocular disorders in Preterms

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Submitted as an Original Research article to: [BMJ Paediatrics Open](#)

Abstract word count (300 maximum): 235 words

Manuscript word count (4000 maximum): 3,433 words

Tables and Figures (maximum 5): 4 Tables

**Reference Count: 54**

**Submitted to:** *BMJ Paediatrics Open*

**Key words:** Preterm children; Low birth weight; Visual Impairment; Refractive error; Strabismus; Retinopathy of prematurity; Risk factors of visual impairment; Sub-Saharan Africa; Ethiopia.

## ABSTRACT

### Objective

The aim of this study was to determine the prevalence, causes of ocular disorders and visual impairment among preterm children previously admitted to neonatal intensive care units in Addis Ababa, Ethiopia.

### Methods and Analysis

A prospective screening survey was conducted from Feb. to June 2019 at the pediatric eye clinic of Menelik II Hospital. Children who were preterm at birth and who attended the eye clinic were included in the study. Data on demographic and neonatal characteristics, neonatal and maternal co-morbidities, and ocular disorders were collected. Odds ratio and univariate analysis were used to identify predictors of ocular diseases and visual impairment.

### Results

There were 222 children included in the study with a mean age at presentation of 2.62 years (range 2.08- 6.38 years), mean GA 34.11 weeks (range 30-36) weeks, and mean birthweight 1941.72g (range 953-3500g). Nearly 2/3 had ocular disorders with refractive error (51.8%), strabismus (11.3%), and history of ROP (7.2%) being more common. One-fourth of the children had visual impairment, and the prevalence of amblyopia was 40.1%. Uncorrected refractive errors, strabismus, and ROP were causes for visual impairment.

### Conclusion

Visual impairment and amblyopia are common in Ethiopia. There is a need to develop a screening protocol for ocular disorders for preterm children to enhance early detection and prevention of childhood visual impairment.

**Keywords:** Preterm children; Low birth weight; Visual Impairment; Refractive error; Strabismus; Retinopathy of prematurity; Risk factors of visual impairment; Sub-Saharan Africa; Ethiopia.

## Key Messages

### What is already known about this subject?

- In many low- and middle-income countries, the survival of preterm infants has improved as neonatal systems have improved.
- Preterm children are at a higher risk of developing ocular disorders, visual impairment, and amblyopia than term children.

### What this study adds

- The magnitude and causes of ocular morbidity among preterm children are not well studied in sub-Saharan African countries. This study, conducted among preterm children admitted to two NICUs in a sub-Saharan country, shows that preterm infants develop a higher rate of visual impairment and amblyopia.

### How this study might affect research, practice or policy

- The findings of this study provide some evidence for screening for ocular diseases in preterm children, but further studies are needed.

## INTRODUCTION

Global, regional, and national estimates of preterm birth (defined as childbirth at less than 37 completed weeks) using the 2019 Global Burden of Disease study showed 15.22 million preterm births (1). In the Global Burden of Disease Study, 3.1% of all disability-adjusted life-years were attributed to preterm birth, similar to the burden of HIV or malaria (2). More than 95% of preterm births are occurring in developing countries. Globally the estimated preterm birth rate is 11.1%. Over 60% of preterm births occur in Sub-Saharan Africa and South Asia (1). Ethiopia belongs to the top 15 countries that contribute to two-thirds of the world's preterm babies with a preterm rate of 14.1% out of 481 deliveries (3).

From six months of pregnancy to term is considered the most active period for ocular development (4). Improved neonatal care has increased the survival rates of extremely preterm infants with birth weights (BW) of 1,000 g or gestational age (GA) of 28 weeks; at the same time, retinopathy of prematurity (ROP) has become a significant threat to visual function (5-7). Preterm children are reported to have an increased incidence of visual impairment because of perinatal lesions in the brain (8-10).

It has been noted that both preterm birth and retinopathy of prematurity (ROP) have an effect on the developing visual system, leading to decreased visual acuity, decreased contrast sensitivity, and an increase in color vision deficiencies (11-16). Population-based studies suggest that ophthalmic impairments remain common in very low birth weight infants (11,16,17). Effects of prematurity on ocular and neurological development include retinopathy of prematurity (ROP), refractive error, strabismus, cerebral visual impairment, color vision deficits, reduced contrast sensitivity (CS), visual field defects, and decreased visual acuity (16). According to population studies, the incidence of ROP, whether moderate or severe, for infants born at less than 1500–1700 g ranges from 22–49% (17-19).

In a cohort study, children with lower birth weights had significantly worse near and distance visual acuity at ages 10 to 12 years compared to full-term infants (10). Additionally, infants born prematurely without ROP are more likely to have myopia and anisometropia than infants born at term because preterm babies are more likely to experience refractive errors (20). An increased incidence of strabismus has also been reported in children born prematurely,

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2  
3 regardless of the presence of ROP (21-24).  
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5 Research on ocular morbidities among preterm infants in sub-Saharan African nations is  
6 limited. Before 2020, blindness from ROP was not reported in Ethiopia, including studies in  
7 schools for the blind (25, 26).  
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10 To determine the top causes of illness and mortality in preterm infants admitted to  
11 neonatal intensive units (NICUs) in Ethiopia, an Ethiopian Study of Illness in Preterms (SIP)  
12 study was conducted based on standardized diagnostic protocols. This study is part of the SIP  
13 study focusing on ocular morbidities among preterms. The present study aimed to identify ocular  
14 disorders in a population of preterm children with and without ROP.  
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## 20 **METHODS**

### 21 **Study design and subjects**

22 The SIP Study is a prospective study conducted to determine the top causes of illness and  
23 mortality in preterm infants admitted to hospitals in Ethiopia based on standardized diagnostic  
24 protocols (27). The study participants of this current study are from the SIP study from Feb –  
25 June, 2019. The research was performed in accordance with the Declaration of Helsinki and was  
26 approved by the Institute Ethics Committee of Addis Ababa University ((Ref No. 003/2016). All  
27 parents or legal guardians provided informed consent before the examination. Patients or the  
28 public weren't involved in our research's design, conduct, reporting, or dissemination plans.  
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### 36 **Study setting**

37 For the SIP study, standard protocols were developed to undertake a physical examination and  
38 laboratory investigation, in particular microbiology, radiologic, and ultrasound examinations.  
39 There were initial and follow-up examinations to detect the progress of the preterm infant. Addis  
40 Ababa University, Gondar University, Jimma University, and St. Paul Millennium Medical  
41 College were included in the SIP study. However, for this ocular morbidity aspect of the SIP  
42 study, preterms from Addis Ababa, Tikur Anbessa Hospital, Gandhi Hospital, and St. Paul  
43 Millennium Medical College were included in the research.  
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### 50 **Recruitment methods**

51 Inclusion criteria were (1) GA < 37 weeks and (2) participation in the SIP study. The preterm  
52 children were identified from the SIP database. Parents of all preterm infants received a phone  
53 call invitation to participate in our investigation.  
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### Assessment of prenatal and postnatal history

History data were assessed from each child's recorded file for the enrolled children. The following data were extracted: antenatal risk factors: maternal age, in vitro fertilization, antenatal corticosteroids, preeclampsia/eclampsia, diabetes, HIV/AIDS, chorioamnionitis, mode of delivery, and multiple births. Neonatal factors included sex, GA, BW, resuscitation in the delivery room, respiratory distress syndrome (RDS), duration of invasive/noninvasive mechanical ventilation and oxygen therapy, intracranial hemorrhage, patent ductus arteriosus (PDA), neonatal sepsis, necrotizing enterocolitis (NEC), number of blood transfusions, and bronchopulmonary dysplasia (BPD). There were no regular ROP screening programmes within the NICUs of the hospitals where the patients were admitted. There was no referral system from the NICUs to Ophthalmology clinic, except if the parents noted a concern. In addition, all parents were interviewed using a standardized protocol to request information concerning medical history of the child and parents, including ocular and general morbidities.

### Definitions

Gestational age was determined using last menstrual period [LMP], Ballard and Dubowitz scores and ultrasound assessment. Studies in Papua New Guinea have shown good concordance (0.878, 0.914, and 0.886, respectively) compared to antenatal ultrasound as the gold standard (28). LMP in a low-resource setting such as Bangladesh was found to be a more reliable measure of gestational age than previously thought for the estimation of postnatal gestational age of preterm infants (29).

Preterm infants were further classified as late and moderate preterm (32 to < 37 weeks), very preterm (28 to <32 weeks), and extremely preterm (less than 28 weeks). Glasses were prescribed if there was myopia >1.0D, astigmatism >1.0D, or hypermetropia >+2.0D.

### Eye examination

All examinations were performed by the PI and lead author (STS), a pediatric ophthalmologist. Testing of best-corrected visual acuity was performed with Lea symbols until school enrolment, and after that, ETDRS was used in all subjects. In cases of visual acuity below 6/60, depending on the children's age, Lea symbols or Landolt rings were used at a distance of 1 m. Values were converted for analysis into the logarithm of the minimum angle of resolution (logMAR) (30).

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3 Cyclopentolate (0.5%) eye drops were administered three times at 10-min intervals, after which  
4 cycloplegic refraction and keratometry were analyzed with an autorefractor (Nidek ARK-1s  
5 keratometer, Japan). The spherical equivalent (refractive error) was calculated by adding the  
6 spherical value and half of the cylindrical value. Anisometropia was defined as a difference  
7 between the patients' eyes of  $\geq 1.5$  diopters of spherical equivalent. Orthoptic examination for  
8 strabismus included the cover-uncover test and alternate cover test, the Hirschberg Test and  
9 examination of fixation behavior, as well as the presence or absence of nystagmus after having  
10 corrected refractive errors. If a child presented with heterotropia, an alternating prism cover test  
11 was added to measure the angle of deviation in prism diopters.

12 Strabismus was defined as constant or intermittent heterotropia of any dimension at a distance  
13 and/or near fixation after correcting refractive error. Classification of strabismus was categorized  
14 depending on deviation from the primary position (esotropia or exotropia). An anterior segment  
15 examination was done using slit lamp biomicroscopy. A dilated posterior segment examination  
16 was conducted using indirect ophthalmoscopy with a 28-diopter lens. Retinopathy of prematurity  
17 was diagnosed retrospectively from the patients' chart.

### 30 31 **Statistical analyses**

32 Statistical analysis was undertaken using IBM SPSS 21.0 (SPSS Inc., Chicago, USA).

33 Continuous variables were expressed as the mean  $\pm$  standard deviation (SD) or as the median  
34 when appropriate. Categorical variables were expressed as proportions. The chi-square test was  
35 used to analyze the association between categorical variables. Associations between ocular  
36 morbidities and continuous and categorical variables were computed using Fisher's exact test  
37 and Pearson chi-square ( $\chi^2$ ) test, respectively. Continuous variables were compared using  
38 ANOVA. Values of  $p < 0.05$  were considered statistically significant.

39 Two statistical models were used for risk factor analysis. First, separate univariate logistic  
40 regression analysis was performed with the presence of ocular morbidities as a dependent  
41 variable and documented potential risk factors for ocular morbidities as independent variables.  
42 Second, variables that were significant at the 0.25 level in univariable analysis were used in the  
43 multivariable mode. The goodness of fit of the final model was assessed using the Hosmer and  
44 Lemeshow test (31). Adjusted odds ratios are reported with 95% confidence-intervals; a p-value  
45 of  $< 0.05$  was considered statistically significant.

## RESULTS

During the study period 222 infants (146 from Saint Paul Hospital and 76 from TASH) were included in this study.

### Characteristics of the study population

Slightly more females than males were screened (52.7% and 47.3%, respectively). The majority of the study participants (n=156, 70.3%) were less than 3 years of age and the mean age at presentation was  $2.62 \pm 0.49$  years (range 2.08- 6.38). One hundred and twenty-three of the 222 children (55.4%) had a GA  $\leq 34$  weeks and 43 (19.4%) had a BW  $\leq 1500$ g. Birthweight ranged from 953-3500g with a mean of 1941.72g (SD 445.49); GA ranged from 30-36 weeks, with a mean of 34.11 weeks (SD 1.47). One hundred and twenty-three children (55.4%) were delivered vaginally, and 80 (36.1%) had multiple gestations. Forty-eight children (21.7%) were born to mothers with pregnancy-induced hypertension, and eight (3.7%) mothers tested positive for HIV (Table 1).

The mean BWs of children from SPH and TASH NICUs were  $1888.5 \pm 403.6$  (953-3000) g and  $2043.94 \pm 503.74$  (1125-3500) g, respectively; mean GAs were  $34.14 \pm 1.49$  (30-36) weeks and  $34.08 \pm 1.44$  (30-36) weeks, respectively. Differences in these parameters were not statistically significant (Table 2).

**Table 1 Characteristics of premature children and mothers screened for ocular disorders**

Variable		Total	Male		Female	
		N	N	%	N	%
Birthweight	≤1500 gm	43	20	46.5%	23	53.5%
	>1500gm	179	85	47.5%	94	52.5%
Gestational age	≤34 weeks	122	60	49.2%	62	50.8%
	> 34 weeks	100	45	45%	55	55%
Multiple gestation	Yes	80	42	52.5%	38	47.5%
	No	142	63	44.4%	79	55.6%
Oxygen supplementation	Yes	97	47	48.5%	50	51.5%
	No	125	58	46.4%	67	53.6%
Infantile morbidity	Sepsis	6	2	33.3%	4	66.7%
	IVH	2	0	0%	2	100%
	BPD and Sepsis	1	1	100%	0	0%
	None	213	102	47.9%	111	52.1%
Mode of delivery	Vaginal delivery	123	53	43.1%	70	56.9%
	Cesarean section	99	52	52.5%	47	47.5%
Multiparity	Yes	47	18	38.3%	29	61.7%
	No	175	63	34.3%	59	65.7%
Maternal morbidity	PIH	44	22	50%	22	50%
	HIV	5	2	40%	3	60%
	HIV & PIH	3	3	100%	0	0%
	DM	2	0	0%	2	100%
	DM & PIH	1	0	0%	1	100%
	TORCH	1	1	100%	0	0%
	None	166	77	46.4%	89	53.6%
NICU location	SPH	146	65	44.5%	81	55.5%
	TASH	76	40	52.6%	36	47.4%

**Legend:** BPD- Bronchopulmonary Dysplasia; DM- Diabetes Mellitus; HIV-IVH-Intraventricular Hemorrhage; PIH- Pregnancy-Induced Hypertension; SPH- Saint Paul Hospital; TASH-Tikur Anbessa Specialized Hospital; TORCH- Toxoplasmosis, Rubella, Cytomegalovirus, Herpes simplex, and HIV

### Ocular morbidities and risk factors

Overall, 145 (65.3%) of the children had ocular disorders at the presentation, of which 92 (63.4%) had isolated ocular diseases (69 refractive error, 13 nasolacrimal duct obstruction, five strabismus, and five ROP). The mean age at presentation of children with ocular disorders was  $2.7 \pm 0.5$  (2.1- 6.4) years, and there were more females with a male to female ratio of 1:1.27. None of the eyes examined had anomalies of the anterior segment or lens.

The mean GA was  $34.14 \pm 1.49$  (30-36) weeks, and BW was  $1927.27 \pm 429.19$  (953-3100) grams. Refractive errors were the leading type of ocular morbidity seen in 115/222 (51.8%), followed by NLDO (21.2%) (Table 2).

**Table 2. Types of ocular disorders among premature children screened**

Ocular disorders	n	%
Refractive error	115	51.8
Nasolacrimal duct obstruction	47	21.2
Strabismus	25	11.3
Retinopathy of prematurity	16	7.2
Others	5	2.3

**NB-** Some ocular disorders occur more than once.

### Refractive error

One hundred and fifteen (51.8) children had a refractive error, of which 55.5% (81/146) and 44.7% (34/76) of children enrolled from the SPH and TASH had refractive errors, respectively. The mean age at presentation was  $2.68 \pm 0.56$  (2.08-6.38) years, and the male-to-female ratio was 1:1.25. Thirty-nine (59%) of children aged  $> 3$  years developed refractive error in comparison with 76 (48.1%) of those aged  $< 3$  years.

The mean gestational age and birthweight of children with refractive errors was  $34.11 \pm 1.54$  (30-36) weeks and  $1892.34 \pm 414.55$  (1080-3100) grams, respectively. Myopia was the commonest type of refractive error, accounting for 78/115 (60.8%) of cases, followed by astigmatism (30, 26.1%) and hyperopia (15, 13.1%). Gender, GA, BW, oxygen supplementation, children, and maternal morbidity were not statistically associated with refractive error. (Table 3)

### Strabismus

Twenty-five children (11.3%) had strabismus (5 isolated, 20 in combination with refractive error, nystagmus, ROP, and nasolacrimal duct obstruction). The age at presentation was  $2.73 \pm 0.52$  (2.1-3.6) years, and the male-to-female ratio was 1.08:1.

The mean GA and BW were  $34.0 \pm 1.41$  (30-36) weeks and  $906.76 \pm 489.92$  (1140-3000), respectively. Regarding the types of strabismus, 13 cases had esotropia, and the remaining 12 patients had exotropia. There was no statistically significant association between GA, BW, and strabismus (Table 3). In this study, the prevalence of strabismus among children aged  $\geq 3$  years was 16.7% compared to 8.9% in those  $< 3$  years. However, older age was not statistically associated with strabismus.

### Retinopathy of prematurity

Previous history of ROP was noted in 16/22 (7.2%) of the children enrolled in this study. Most patients (12, 57%) with ROP were from SPH. Almost all of them (15/16) had a GA < 34 weeks, and the mean GA and BW of patients with ROP were 32.19±1.33 (30-35) weeks and 1596.25 ±483.64 (953-2600) grams, respectively. Nine patients with ROP had an associated refractive error (6 myopia and 3 astigmatism). Only one patient had an associated intermittent exotropia. In univariate analysis, ROP was statistically associated with low GA and low BW (Table 3). Multivariable logistic regression analysis was not conducted due to the small number of children with ROP.

**Table 3. Ocular disorders by sex, gestational age, and birthweight among premature children screened for ocular disorders**

Type of Disorder	Variables		Yes	No	Odds Ratio	p-Value
			n	n		
Refractive error	Sex	Male	51	54	0.78(0.46-1.33)	0.361
		Female	64	53		
	BWt	≤1500 gm	22	21	1.03(0.53-2.01)	0.926
		>1500gm	93	86		
	GA	≤34 weeks	62	60	1.09(0.64-1.85)	0.746
> 34 weeks		53	47			
Strabismus	Sex	Male	12	93	1.03(0.4501.37)	0.940
		Female	13	104		
	BWt	≤1500 gm	7	36	0.57(0.22-1.48)	0.246
		>1500gm	18	161		
	GA	≤34 weeks	14	108	0.95 (0.41-2.2)	0.911
> 34 weeks		11	89			
ROP	Sex	Male	6	99	0.65(0.22-1.85)	0.415
		Female	10	107		
	BWt	≤1500 gm	7	36	Reference	0.01
		>1500gm	9	170		
	GA	≤34 weeks	15	107	Reference	0.001
> 34 weeks		1	99			

**Legend:** BWt- Birth Weight ; GA-Gestational Age

### Visual impairment and ocular disorders

The mean VA of the right and left eyes was 0.22(SD 0.23) logMAR and 0.17 (SD 0.21) logMAR, respectively. The mean VA in the better and worse eyes was 0.17 (SD 0.22) logMAR

and 0.28 (SD 0.21) logMAR, respectively. In this study, 101 (45.9%) and 181 (81.5%) of the children had subnormal visual acuity ( $>\log\text{MAR } 0.1$ ) in the better and worst eyes, respectively. Nearly one-fourth (55, 24.8%) of children screened had visual impairment in the better eye. Of this group 51 (92.7%) had uncorrected refractive error alone (34/51) or with strabismus (10/51), ROP (6/51), or nystagmus (1/51). Eighty-nine (40.1%) patients had amblyopia, of which 59/89 (66.3%) had bilateral amblyopia from uncorrected refractive error. Isometric and anisometric amblyopia from uncorrected refractive error were the commonest causes of amblyopia, contributing to 49/89 (55%) and 20/89 (22.8%), respectively. Of the 16 cases with ROP, 12 (75%) had a visual impairment associated with other disorders like refractive error, strabismus, and nystagmus.

In univariate analysis, visual impairment in the better eye was statistically associated with ROP, uncorrected refractive error, and strabismus with p-values of 0.001, 0.001, and 0.004, respectively. Amblyopia was not statistically associated with low GA or low BW (Table 4).

**Table 4. The presence of visual impairment by types of ocular disorders among premature children screened for ocular disorders.**

Variables		Visual Impairment in the better eye		Odds Ratio 95% CI (Lower-Upper)	p-Value
		Yes	No		
Sex	Male	23	82	0.75(0.40-1.38)	0.348
	Female	32	85		
BWt	$\leq 1500$ gm	14	29	0.62(0.29-1.27)	0.188
	$> 1500$ gm	41	138		
GA	$\leq 34$ weeks	28	94	1.24(0.67-2.29)	0.294
	$> 34$ weeks	27	73		
Refractive error	Yes	48	67	10.24(4.37-23.97)	0.001
	No	7	100		
Strabismus	Yes	12	13	3.31 (1.41-7.77)	0.004
	No	43	154		

## DISCUSSION

The present prospective study examines the effects of prematurity on visual acuity and ocular disorder in children born preterm. In Sub-Saharan Africa, neonatal death has decreased by 40% since 1990 due to improved newborn care, likely leading to an increase in childhood ocular morbidity and blindness from diseases like ROP (32). Despite this positive progress, data on the extent of ocular diseases among the preterms in Sub-Saharan Africa are limited. Our study has demonstrated that the prevalence of ocular diseases and visual impairment in Ethiopian children born preterm is high. To our knowledge, this is the first study to assess the prevalence and causes of ocular disorders and visual impairment among children born preterm and admitted to NICUs. In Ethiopia, intensive neonatal care has expanded in many public and private hospital NICUs since 2013 (33), and neonatal mortality per thousand live births has declined modestly from 39 in 2000 to 33 in 2019(34). A prospective screening survey among neonates admitted to two NICUs in Ethiopia showed that 32.2% of the screened infants had any stage ROP (35). However, there is no regular ROP screening program in the country. A comparison of studies of ocular morbidity and visual impairment among preterm children is difficult as there are methodological variations such as differing age groups, inclusion or exclusion of ROP, stages of ROP, and cohort size. Even though genetic and visual experiences predominantly determine the prevalence of refractive error, studies have shown that low BW interrupts emmetropisation and increases the prevalence of refractive error (36). In our study, nearly half of the premature screened children (51.8%) had refractive error, which is comparable to a survey from Turkey (53.8%) (37) but higher than in Italy (42.3%) (38), and in cohorts of extremely preterm infants from Sweden (29.7%) (39) and Norway (10%) (40). In our study, the prevalence of myopia was 35.1%, which was higher than a cohort of preterm children at age 10–12 years from the UK (18.9%) (41), India (15.8%) (42), and Sweden (4.1%) (39). The prevalence of hyperopia in our study, 13.5%, is comparable with that reported in Turkey (14.3%) (37) and Sweden (17.1%) (39) but higher than the UK (6.6%) (41) and India (8.54%) (42). In the present study, 13.5% of the preterm children



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3 had clinically significant astigmatism, which was lower than that reported in Norway (21%) (40)  
4 and India (55.6%) (42) and higher than in Turkey (5.7%) (37) and Sweden (6.5%) (39). The  
5 higher proportion of myopia seen in our study, in comparison with studies from the UK (41),  
6 India (42) and Sweden (39), is supported by long-term studies which have confirmed the  
7 increased incidence of myopia following preterm birth (43).  
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9

10  
11 Manifest strabismus was seen in 11.3% of our cohort, which is comparable to studies  
12 from Norway (10%) (40), the UK (13.6%) (15), Sweden (13.5%) (20), and Australia (14%) (45),  
13 and lower than reported in Sweden (17%) (36), the UK and Ireland (24%) (46) and Germany  
14 (26%) (47). It is unclear at what age the different types of strabismus develop (36), and the age at  
15 onset of strabismus in low birthweight children is variable, from the first few months of life to  
16 many years later (11, 15, 16,21,22, 44). In our study, a higher prevalence of strabismus in those  
17 aged > 3 years was noted. This finding (16.7%) is comparable with a similar age group from  
18 Sweden (20). Regarding the type of strabismus, we detected similar proportions for esotropia and  
19 exotropia. This is similar to the other studies from Germany (47) and England (41). However,  
20 other investigations confirmed that esotropia was the most frequent type of strabismus (20, 39,  
21 48) The increased prevalence of strabismus in the low birthweight population is well-  
22 documented (21, 36, and 44). Such an association was not apparent in our study, as most of the  
23 children were considerably higher in weight and older than in the studies mentioned above.  
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26  
27 The prevalence of ROP in our study is 7.2%, lower than in other studies, from sub-  
28 Saharan African countries, including Ethiopia, which ranged from 15-41.7% (35, 49-51). The  
29 lower prevalence of ROP in our study can be explained by our data collection method, where we  
30 depend on the history of ROP either from the patient's parents or from old features of ROP.  
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33  
34 In the present study, 46% of the children had subnormal visual acuity (>logMAR 0.1) in  
35 the better eye, which is comparable with a population-based study from Norway (45.9%) (40).  
36 The figure is higher than what has been reported for prematurely-born children with BWs 1500–  
37 2000 g (15 %) from Denmark (9) and from Sweden 32 % (20). Birch et al. reported significantly  
38 lower visual acuities in low birthweight infants compared to those born full term (52). In our  
39 study, there was no statistically significant correlation between BCVA and BW or GA, similar to  
40 a study from Turkey (37). However, Dowdeswell et al. (53) found low levels of distance visual  
41 acuity in preterm children compared with full-term children. However, in our study, ocular  
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3 morbidities like strabismus, refractive error, and ROP were statistically associated with visual  
4 impairment.  
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7 In our study, the prevalence of amblyopia among premature children was 40.1%. The  
8 result in our study is much higher than other studies from Australia (7.3%) (45) and Turkey  
9 (7.7%) (37). Previous studies have shown that prematurity and low birthweight are two risk  
10 factors for amblyopia (41, 54). Nevertheless, amblyopia was not statistically associated with low  
11 GA and BW. Even if we did not find a statistical association between GA and BW with  
12 amblyopia, the prevalence among premature children is higher than in other studies; this  
13 indicates that more importance should be given to screening amblyopia risk factors for premature  
14 infants.  
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## 22 **CONCLUSION**

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25 In conclusion, the rates of ocular disorders, visual impairment, and amblyopia in these NICUs in  
26 Ethiopia were higher than in other studies. Refractive error, strabismus, and ROP were all  
27 significant risk factors for visual impairment. These findings underline the importance of early  
28 screening of premature infants for vision and amblyopia. As the two NICUs included in the  
29 survey are Ethiopia's main neonatal referral centers, it can be postulated that ocular morbidities,  
30 visual impairment, and amblyopia are emerging as potentially avoidable causes of childhood  
31 blindness among preterm children in Ethiopia. Developing preterm ocular-related screening  
32 protocols within the NICUs, strengthening the referral links between the NICUs and eye centers,  
33 and further detailed comparative studies between preterm and term children for ocular disorders  
34 are recommended.  
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43 The strengths of this study were the prospective controlled study design with a high number of  
44 participants, the multi-center design which increases the representativeness of our research, and  
45 the availability of medical information from all children and mothers, which allowed a very  
46 detailed examination and an adjustment for different possible confounding factors. The strict  
47 standardization reduced the probability of examiner-dependent variances.  
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3 Limitations of the study included the wide age range of the examined children, some of whom  
4 were at an early age and phase of refractive development, and other older children that can affect  
5 the physiologic refractive changes noted in normal health children. The other limitation is there  
6 is a chance that those infants with poor health outcomes did not take part in our study. In  
7 subsequent research, we will continue following up with these infants to determine future  
8 changes in their refractive error and strabismus.  
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### 14 **Lists of Abbreviations**

15 Bronchopulmonary dysplasia (BPD); Necrotizing enterocolitis (NEC); Neonatal Intensive Care  
16 Units (NICUs); Patent ductus arteriosus (PDA); Preterm birth (PTBs); Respiratory distress  
17 syndrome (RDS); Retinopathy of prematurity (ROP), Saint Paul Hospital (SPH) and Tikur  
18 Anbessa Specialized Hospitals (TASH).  
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## 24 **Declarations**

### 25 **Ethics Approval and Consent to Participate**

26 The study was conducted following the Helsinki Declaration and after it was approved by the  
27 Institute Ethics Committee of Addis Ababa University ((Ref No. 003/2016). All parents or legal  
28 guardians provided written informed consent before the examination.  
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### 34 **Availability of Data and Materials**

35 All data generated or analysed during this study are included in this published article  
36  
37

### 38 **Competing Interests**

39 The authors have no conflicts of interest.  
40

### 41 **Funding**

42 The SIP study was supported by BMG fund.  
43  
44

### 45 **Authors' Contributions**

46 Drafting of the manuscript: STS., LM., AM. , and AD. Revision of the manuscript for important  
47 intellectual content: STS., LM., AM., AD and AA. Conception and design of study: STS., LM.,  
48 AM. , and AD. Data acquisition, analysis, or interpretation of data: STS., LM., AM., AD., and  
49 AA. Approval of final manuscript to be published: STS., LM., AM., AD., and AA. All authors  
50 have read and approved the final version of the manuscript.  
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## Acknowledgements

The authors wish to acknowledge the assistance of the staff of the SIP project (Ahmed, Beleyu, Efrata, and Wagaye) for their support during data collection. Our special appreciation goes to Sr Martha H/Mariam and Sr. Medhanit from Menelik II pediatrics Ophthalmology clinic.

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19 **TABLES LEGEND**

20 **Table 1 Characteristics of premature children and mothers screened for ocular disorders**

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22 **Table 2. Types of ocular disorders among premature children screened**

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25 **Table 3. Ocular disorders by sex, gestational age, and birthweight among premature**  
26 **children screened for ocular disorders**

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29 **Table 4. The presence of visual impairment by types of ocular disorders among premature**  
30 **children screened for ocular disorders.**  
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# BMJ Paediatrics Open

## Prevalence and causes of ocular disorders and visual impairment among preterm children in Ethiopia

Journal:	<i>BMJ Paediatrics Open</i>
Manuscript ID	bmjpo-2023-002317.R1
Article Type:	Original research
Date Submitted by the Author:	31-Oct-2023
Complete List of Authors:	SHERIEF, SADIK; Addis Ababa University, Department of Ophthalmology; SickKids Research Institute Muhe, Lulu M; Addis Ababa University College of Health Sciences Mekasha, Amha; Addis Ababa University, Department of Pediatrics and Child Health Demtse, Asrat; Addis Ababa University College of Health Sciences, Paediatrics and Child Health Ali, Asim; The Hospital for Sick Children, Ophthalmology and Vision Sciences
Keywords:	Infant, Neonatology, Ophthalmology

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4 **1 Prevalence and causes of ocular disorders and visual impairment among**  
5 **2 preterm children in Ethiopia**  
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9 4 Sadik Taju Sherief <sup>1,2</sup>, Lulu Muhe <sup>3</sup> Amha Mekasha <sup>3</sup>, Asrat Demtse <sup>3</sup>, and Asim Ali<sup>4</sup>

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38  
39 24 **Submitted as an Original Research article to: BMJ Paediatrics Open**

40  
41 25 **Abstract word count (300 maximum): 235 words**

42  
43 26 **Manuscript word count (4000 maximum): 3,433 words**

44  
45 27 **Tables and Figures (maximum 5): 4 Tables**

46  
47 28 **Reference Count: 54**  
48

49 30 **Submitted to: *BMJ Paediatrics Open***

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51 31 **Key words:** Preterm children; Low birth weight; Visual Impairment; Refractive error;

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53 32 Strabismus; Retinopathy of prematurity; Risk factors of visual impairment; Sub-Saharan Africa;

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## 35 **ABSTRACT**

### 37 **Objective**

38 The aim of this study was to determine the prevalence, causes of ocular disorders and visual  
39 impairment among preterm children previously admitted to neonatal intensive care units in Addis  
40 Ababa, Ethiopia.

### 41 **Methods and Analysis**

42 A prospective screening survey was conducted from Feb. to June 2019 at the pediatric eye clinic  
43 of Menelik II Hospital. Children who were preterm at birth and who attended the eye clinic were  
44 included in the study. Data on demographic and neonatal characteristics, neonatal and maternal  
45 co-morbidities, and ocular disorders were collected. Odds ratio and univariate analysis were used  
46 to identify predictors of ocular diseases and visual impairment.

### 47 **Results**

48 There were 222 children included in the study with a mean age at presentation of 2.62 years  
49 (range 2.08- 6.38 years), mean GA 34.11 weeks (range 30-36) weeks, and mean birthweight  
50 1941.72g (range 953-3500g). Nearly 2/3 had ocular disorders with refractive error (51.8%),  
51 strabismus (11.3%), and history of ROP (7.2%) being more common. One-fourth of the children  
52 had visual impairment, and the prevalence of amblyopia was 40.1%. Uncorrected refractive  
53 errors, strabismus, and ROP were causes for visual impairment.

### 54 **Conclusion**

55 Visual impairment and amblyopia are common in Ethiopia. There is a need to develop a  
56 screening protocol for ocular disorders for preterm children to enhance early detection and  
57 prevention of childhood visual impairment.

58 **Keywords:** Preterm children; Low birth weight; Visual Impairment; Refractive error;  
59 Strabismus; Retinopathy of prematurity; Risk factors of visual impairment; Sub-Saharan Africa;  
60 Ethiopia.

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3 69 **Key Messages**  
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7 71 **What is already known about this subject?**  
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- 9 72 • In many low- and middle-income countries, the survival of preterm infants has improved as  
10 73 neonatal systems have improved.  
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12 74 • Preterm children are at a higher risk of developing ocular disorders, visual impairment, and  
13 75 amblyopia than term children.  
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18 77 **What this study adds**  
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- 20 78 • The magnitude and causes of ocular morbidity among preterm children are not well studied  
21 79 in sub-Saharan African countries. This study, conducted among preterm children admitted to  
22 80 two NICUs in a sub-Saharan country, shows that preterm infants develop a higher rate of  
23 81 visual impairment and amblyopia.  
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28 83 **How this study might affect research, practice or policy**  
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- 30 84 • The findings of this study provide some evidence for screening for ocular diseases in preterm  
31 85 children, but further studies are needed.  
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## 95 INTRODUCTION

96 Global, regional, and national estimates of preterm birth (defined as childbirth at less than  
97 37 completed weeks) using the 2019 Global Burden of Disease study showed 15.22 million  
98 preterm births (1). In the Global Burden of Disease Study, 3.1% of all disability-adjusted life-  
99 years were attributed to preterm birth, similar to the burden of HIV or malaria (2). More than  
100 95% of preterm births are occurring in developing countries. Globally the estimated preterm  
101 birth rate is 11.1%. Over 60% of preterm births occur in Sub-Saharan Africa and South Asia (1).  
102 Ethiopia belongs to the top 15 countries that contribute to two-thirds of the world's preterm  
103 babies with a preterm rate of 14.1% out of 481 deliveries (3).

104 From six months of pregnancy to term is considered the most active period for ocular  
105 development (4). Improved neonatal care has increased the survival rates of extremely preterm  
106 infants with birth weights (BW) of 1,000 g or gestational age (GA) of 28 weeks; at the same  
107 time, retinopathy of prematurity (ROP) has become a significant threat to visual function (5-7).  
108 Preterm children are reported to have an increased incidence of visual impairment because of  
109 perinatal lesions in the brain (8-10).

110 It has been noted that both preterm birth and retinopathy of prematurity (ROP) have an  
111 effect on the developing visual system, leading to decreased visual acuity, decreased contrast  
112 sensitivity, and an increase in color vision deficiencies (11-16). Population-based studies suggest  
113 that ophthalmic impairments remain common in very low birth weight infants (11,16,17). Effects  
114 of prematurity on ocular and neurological development include retinopathy of prematurity  
115 (ROP), refractive error, strabismus, cerebral visual impairment, color vision deficits, reduced  
116 contrast sensitivity (CS), visual field defects, and decreased visual acuity (16). According to  
117 population studies, the incidence of ROP, whether moderate or severe, for infants born at less  
118 than 1500–1700 g ranges from 22–49% (17-19).

119 In a cohort study, children with lower birth weights had significantly worse near and  
120 distance visual acuity at ages 10 to 12 years compared to full-term infants (10). Additionally,  
121 infants born prematurely without ROP are more likely to have myopia and anisometropia than  
122 infants born at term because preterm babies are more likely to experience refractive errors (20).  
123 An increased incidence of strabismus has also been reported in children born prematurely,

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2  
3 124 regardless of the presence of ROP (21-24).  
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5 125 Research on ocular morbidities among preterm infants in sub-Saharan African nations is  
6  
7 126 limited. Before 2020, blindness from ROP was not reported in Ethiopia, including studies in  
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9 127 schools for the blind (25, 26).

10 128 To determine the top causes of illness and mortality in preterm infants admitted to  
11  
12 129 neonatal intensive units (NICUs) in Ethiopia, an Ethiopian Study of Illness in Preterms (SIP)  
13  
14 130 study was conducted based on standardized diagnostic protocols. This study is part of the SIP  
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16 131 study focusing on ocular morbidities among preterms. The present study aimed to identify ocular  
17  
18 132 disorders in a population of preterm children with and without ROP.  
19

20 133

## 21 134 **METHODS**

### 22 135 **Study design and subjects**

23  
24 136 The SIP Study is a prospective study conducted to determine the top causes of illness and  
25  
26 137 mortality in preterm infants admitted to hospitals in Ethiopia based on standardized diagnostic  
27  
28 138 protocols (27). The study participants of this current study are from the SIP study from Feb –  
29  
30 139 June, 2019. The research was performed in accordance with the Declaration of Helsinki and was  
31  
32 140 approved by the Institute Ethics Committee of Addis Ababa University ((Ref No. 003/2016). All  
33  
34 141 parents or legal guardians provided informed consent before the examination. Patients or the  
35  
36 142 public weren't involved in our research's design, conduct, reporting, or dissemination plans.

### 37 143 **Study setting**

38 144 For the SIP study, standard protocols were developed to undertake a physical examination and  
39  
40 145 laboratory investigation, in particular microbiology, radiologic, and ultrasound examinations.  
41  
42 146 There were initial and follow-up examinations to detect the progress of the preterm infant. Addis  
43  
44 147 Ababa University, Gondar University, Jimma University, and St. Paul Millennium Medical  
45  
46 148 College were included in the SIP study. However, for this ocular morbidity aspect of the SIP  
47  
48 149 study, preterms from Addis Ababa, Tikur Anbessa Hospital, Gandhi Hospital, and St. Paul  
49  
50 150 Millennium Medical College were included in the research.

### 51 151 **Recruitment methods**

52 152 Inclusion criteria were (1) GA < 37 weeks and (2) participation in the SIP study. The preterm  
53  
54 153 children were identified from the SIP database. Parents of all preterm infants received a phone  
55  
56 154 call invitation to participate in our investigation.  
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### 157 **Assessment of prenatal and postnatal history**

158 History data were assessed from each child's recorded file for the enrolled children. The  
159 following data were extracted: antenatal risk factors: maternal age, in vitro fertilization, antenatal  
160 corticosteroids, preeclampsia/eclampsia, diabetes, HIV/AIDS, chorioamnionitis, mode of  
161 delivery, and multiple births. Neonatal factors included sex, GA, BW, resuscitation in the  
162 delivery room, respiratory distress syndrome (RDS), duration of invasive/noninvasive  
163 mechanical ventilation and oxygen therapy, intracranial hemorrhage, patent ductus arteriosus  
164 (PDA), neonatal sepsis, necrotizing enterocolitis (NEC), number of blood transfusions, and  
165 bronchopulmonary dysplasia (BPD). There were no regular ROP screening programmes within  
166 the NICUs of the hospitals where the patients were admitted. There was no referral system from  
167 the NICUs to Ophthalmology clinic, except if the parents noted a concern. In addition, all parents  
168 were interviewed using a standardized protocol to request information concerning medical  
169 history of the child and parents, including ocular and general morbidities.

### 170 **Definitions**

171 Gestational age was determined using last menstrual period [LPM], Ballard and Dubowitz scores  
172 and ultrasound assessment. Studies in Papua New Guinea have shown good concordance (0.878,  
173 0.914, and 0.886, respectively) compared to antenatal ultrasound as the gold standard (28). LMP  
174 in a low-resource setting such as Bangladesh was found to be a more reliable measure of  
175 gestational age than previously thought for the estimation of postnatal gestational age of preterm  
176 infants (29).

177 Preterm infants were further classified as late and moderate preterm (32 to < 37 weeks), very  
178 preterm (28 to <32 weeks), and extremely preterm (less than 28 weeks). Glasses were prescribed  
179 if there was myopia >1.0D, astigmatism >1.0D, or hypermetropia >+2.0D.

### 180 **Eye examination**

181 All examinations were performed by the PI and lead author (STS), a pediatric ophthalmologist.  
182 Testing of best-corrected visual acuity was performed with Lea symbols until school enrolment,  
183 and after that, ETDRS was used in all subjects. In cases of visual acuity below 6/60, depending  
184 on the children's age, Lea symbols or Landolt rings were used at a distance of 1 m. Values were  
185 converted for analysis into the logarithm of the minimum angle of resolution (logMAR) (30).

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3 186 Cyclopentolate (0.5%) eye drops were administered three times at 10-min intervals, after which  
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5 187 cycloplegic refraction and keratometry were analyzed with an autorefractor (Nidek ARK-1s  
6  
7 188 keratometer, Japan). The spherical equivalent (refractive error) was calculated by adding the  
8  
9 189 spherical value and half of the cylindrical value. Anisometropia was defined as a difference  
10  
11 190 between the patients' eyes of  $\geq 1.5$  diopters of spherical equivalent. Orthoptic examination for  
12  
13 191 strabismus included the cover-uncover test and alternate cover test, the Hirschberg Test and  
14  
15 192 examination of fixation behavior, as well as the presence or absence of nystagmus after having  
16  
17 193 corrected refractive errors. If a child presented with heterotropia, an alternating prism cover test  
18  
19 194 was added to measure the angle of deviation in prism diopters.  
20  
21 195 Strabismus was defined as constant or intermittent heterotropia of any dimension at a distance  
22  
23 196 and/or near fixation after correcting refractive error. Classification of strabismus was categorized  
24  
25 197 depending on deviation from the primary position (esotropia or exotropia). An anterior segment  
26  
27 198 examination was done using slit lamp biomicroscopy. A dilated posterior segment examination  
28  
29 199 was conducted using indirect ophthalmoscopy with a 28-diopter lens. Retinopathy of prematurity  
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31 200 was diagnosed retrospectively from the patients' chart.

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33 201  
34 202 Data analyzed using IBM SPSS 21.0 (SPSS Inc., Chicago, USA). Continuous variables were  
35  
36 203 expressed as the mean  $\pm$  standard deviation (SD) or as the median when appropriate. Categorical  
37  
38 204 variables were expressed as proportions. The chi-square test was used to analyze the association  
39  
40 205 between categorical variables. Associations between ocular morbidities and continuous and  
41  
42 206 categorical variables were computed using Fisher's exact test and Pearson chi-square ( $\chi^2$ ) test,  
43  
44 207 respectively. Continuous variables were compared using ANOVA. Values of  $p < 0.05$  were  
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46 208 considered statistically significant.  
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## 216 RESULTS

217 During the study period 222 infants (146 from Saint Paul Hospital and 76 from TASH)  
218 were included in this study.

### 219 Characteristics of the study population

220 Slightly more females than males were screened (52.7% and 47.3%, respectively). The majority  
221 of the study participants (n=156, 70.3%) were less than 3 years of age and the mean age at  
222 presentation was  $2.62 \pm 0.49$  years (range 2.08- 6.38). One hundred and twenty-three of the 222  
223 children (55.4%) had a GA  $\leq 34$  weeks and 43 (19.4%) had a BW  $\leq 1500$ g. Birthweight ranged  
224 from 953-3500g with a mean of 1941.72g (SD 445.49); GA ranged from 30-36 weeks, with a  
225 mean of 34.11 weeks (SD 1.47). One hundred and twenty-three children (55.4%) were delivered  
226 vaginally, and 80 (36.1%) had multiple gestations. Forty-eight children (21.7%) were born to  
227 mothers with pregnancy-induced hypertension, and eight (3.7%) mothers tested positive for HIV  
228 (Table 1).

229  
230 The mean BWs of children from SPH and TASH NICUs were  $1888.5 \pm 403.6$  (953-3000) g and  
231  $2043.94 \pm 503.74$  (1125-3500) g, respectively; mean GAs were  $34.14 \pm 1.49$  (30-36) weeks and  
232  $34.08 \pm 1.44$  (30-36) weeks, respectively. Differences in these parameters were not statistically  
233 significant (Table 2).

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248 **Table 1 Characteristics of premature children and mothers screened for ocular disorders**

Variable		Total		Female		
		N	N	%	N	%
<b>Birthweight</b>	<1500 gm	43	20	46.5%	23	53.5%
	>1500gm	179	85	47.5%	94	52.5%
<b>Gestational age</b>	≤34 weeks	122	60	49.2%	62	50.8%
	> 34 weeks	100	45	45%	55	55%
<b>Multiple gestation</b>	Yes	80	42	52.5%	38	47.5%
	No	142	63	44.4%	79	55.6%
<b>Oxygen supplementation</b>	Yes	97	47	48.5%	50	51.5%
	No	125	58	46.4%	67	53.6%
<b>Infantile morbidity</b>	Sepsis	6	2	33.3%	4	66.7%
	IVH	2	0	0%	2	100%
	BPD and Sepsis	1	1	100%	0	0%
	None	213	102	47.9%	111	52.1%
<b>Mode of delivery</b>	Vaginal delivery	123	53	43.1%	70	56.9%
	Cesarean section	99	52	52.5%	47	47.5%
<b>Multiparity</b>	Yes	47	18	38.3%	29	61.7%
	No	175	63	34.3%	59	65.7%
<b>Maternal morbidity</b>	PIH	44	22	50%	22	50%
	HIV	5	2	40%	3	60%
	HIV & PIH	3	3	100%	0	0%
	DM	2	0	0%	2	100%
	DM & PIH	1	0	0%	1	100%
	TORCH	1	1	100%	0	0%
	None	166	77	46.4%	89	53.6%
<b>NICU location</b>	SPH	146	65	44.5%	81	55.5%
	TASH	76	40	52.6%	36	47.4%

**Legend:** BPD- Bronchopulmonary Dysplasia; DM- Diabetes Mellitus; HIV-IVH-Intraventricular Hemorrhage; PIH- Pregnancy-Induced Hypertension; SPH- Saint Paul Hospital; TASH-Tikur Anbessa Specialized Hospital; TORCH- Toxoplasmosis, Rubella, Cytomegalovirus, Herpes simplex, and HIV

### 253 Ocular morbidities and risk factors

254 Overall, 145 (65.3%) of the children had ocular disorders at the presentation, of which 92  
255 (63.4%) had isolated ocular diseases (69 refractive error, 13 nasolacrimal duct obstruction, five  
256 strabismus, and five ROP). The mean age at presentation of children with ocular disorders was  
257 2.7±0.5 (2.1- 6.4) years, and there were more females with a male to female ratio of 1:1.27. None  
258 of the eyes examined had anomalies of the anterior segment or lens.

259 The mean GA was 34.14 ± 1.49 (30-36) weeks, and BW was 1927.27 ± 429.19 (953-3100)  
260 grams. Refractive errors were the leading type of ocular morbidity seen in 115/222 (51.8%),  
261 followed by NLDO (21.2%) (Table 2).

264 **Table 2. Types of ocular disorders among premature children screened**

Ocular disorders	n	%
Refractive error	115	51.8
Nasolacrimal duct obstruction	47	21.2
Strabismus	25	11.3
Retinopathy of prematurity	16	7.2
Others	5	2.3

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266 **NB-** Some ocular disorders occur more than once.

267  
268 **Refractive error**

269 One hundred and fifteen (51.8) children had a refractive error, of which 55.5% (81/146) and  
270 44.7% (34/76) of children enrolled from the SPH and TASH had refractive errors, respectively.  
271 The mean age at presentation was  $2.68 \pm 0.56$  (2.08-6.38) years, and the male-to-female ratio was  
272 1:1.25. Thirty-nine (59%) of children aged > 3 years developed refractive error in comparison  
273 with 76 (48.1%) of those aged < 3 years.

274 The mean gestational age and birthweight of children with refractive errors was  $34.11 \pm 1.54$  (30-  
275 36) weeks and  $1892.34 \pm 414.55$  (1080-3100) grams, respectively. Myopia was the commonest  
276 type of refractive error, accounting for 78/115 (60.8%) of cases, followed by astigmatism (30,  
277 26.1%) and hyperopia (15, 13.1%). Gender, GA, BW, oxygen supplementation, children, and  
278 maternal morbidity were not statistically associated with refractive error. (Table 3)

279 **Strabismus**

280 Twenty-five children (11.3%) had strabismus (5 isolated, 20 in combination with refractive error,  
281 nystagmus, ROP, and nasolacrimal duct obstruction). The age at presentation was  $2.73 \pm 0.52$   
282 (2.1-3.6) years, and the male-to-female ratio was 1.08:1.

283 The mean GA and BW were  $34.0 \pm 1.41$  (30-36) weeks and  $906.76 \pm 489.92$  (1140-3000),  
284 respectively. Regarding the types of strabismus, 13 cases had esotropia, and the remaining 12  
285 patients had exotropia. There was no statistically significant association between GA, BW, and  
286 strabismus (Table 3). In this study, the prevalence of strabismus among children aged  $\geq 3$  years  
287 was 16.7% compared to 8.9% in those < 3 years. However, older age was not statistically  
288 associated with strabismus.

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### 291 Retinopathy of prematurity

292 Previous history of ROP was noted in 16/22 (7.2%) of the children enrolled in this study. Most  
 293 patients (12, 57%) with ROP were from SPH. Almost all of them (15/16) had a GA < 34 weeks,  
 294 and the mean GA and BW of patients with ROP were 32.19±1.33 (30-35) weeks and 1596.25  
 295 ±483.64 (953-2600) grams, respectively. Nine patients with ROP had an associated refractive  
 296 error (6 myopia and 3 astigmatism). Only one patient had an associated intermittent exotropia.  
 297 In univariate analysis, ROP was statistically associated with low GA and low BW (Table 3).  
 298 Multivariable logistic regression analysis was not conducted due to the small number of children  
 299 with ROP.

300 **Table 3. Ocular disorders by sex, gestational age, and birthweight among premature**  
 301 **children screened for ocular disorders**

Type of Disorder	Variables		Yes	No	Odds Ratio	p-Value
			n	n		
Refractive error	Sex	Male	51	54	0.78(0.46-1.33)	0.361
		Female	64	53		
	BWt	≤1500 gm	22	21	1.03(0.53-2.01)	0.926
		>1500gm	93	86		
	GA	≤34 weeks	62	60	1.09(0.64-1.85)	0.746
> 34 weeks		53	47			
Strabismus	Sex	Male	12	93	1.03(0.4501.37)	0.940
		Female	13	104		
	BWt	≤1500 gm	7	36	0.57(0.22-1.48)	0.246
		>1500gm	18	161		
	GA	≤34 weeks	14	108	0.95 (0.41-2.2)	0.911
> 34 weeks		11	89			
ROP	Sex	Male	6	99	0.65(0.22-1.85)	0.415
		Female	10	107		
	BWt	≤1500 gm	7	36	Reference	0.01
		>1500gm	9	170		
	GA	≤34 weeks	15	107	Reference	0.001
> 34 weeks		1	99			

303 **Legend:** BWt- Birth Weight ; GA-Gestational Age

### 305 Visual impairment and ocular disorders

307 The mean VA of the right and left eyes was 0.22(SD 0.23) logMAR and 0.17 (SD 0.21)  
 308 logMAR, respectively. The mean VA in the better and worse eyes was 0.17 (SD 0.22) logMAR  
 309 and 0.28 (SD 0.21) logMAR, respectively. In this study, 101 (45.9%) and 181 (81.5%) of the  
 310 children had subnormal visual acuity (>logMAR 0.1) in the better and worst eyes, respectively.

311 Nearly one-fourth (55, 24.8%) of children screened had visual impairment in the better eye. Of  
 312 this group 51 (92.7%) had uncorrected refractive error alone (34/51) or with strabismus (10/51),  
 313 ROP (6/51), or nystagmus (1/51). Eighty-nine (40.1%) patients had amblyopia, of which 59/89  
 314 (66.3%) had bilateral amblyopia from uncorrected refractive error. Isometric and  
 315 anisometric amblyopia from uncorrected refractive error were the commonest causes of  
 316 amblyopia, contributing to 49/89 (55%) and 20/89 (22.8%), respectively. Of the 16 cases with  
 317 ROP, 12 (75%) had a visual impairment associated with other disorders like refractive error,  
 318 strabismus, and nystagmus.

319 In univariate analysis, visual impairment in the better eye was statistically associated with ROP,  
 320 uncorrected refractive error, and strabismus with p-values of 0.001, 0.001, and 0.004,  
 321 respectively. Amblyopia was not statistically associated with low GA or low BW (Table 4).

322 **Table 4. The presence of visual impairment by types of ocular disorders among premature**  
 323 **children screened for ocular disorders.**

Variables		Visual Impairment in the better eye		Odds Ratio 95% CI (Lower-Upper)	p-Value
		Yes	No		
Sex	Male	23	82	0.75(0.40-1.38)	0.348
	Female	32	85		
BWt	≤1500 gm	14	29	0.62(0.29-1.27)	0.188
	>1500gm	41	138		
GA	≤34 weeks	28	94	1.24(0.67-2.29)	0.294
	> 34 weeks	27	73		
Refractive error	Yes	48	67	10.24(4.37-23.97)	0.001
	No	7	100		
Strabismus	Yes	12	13	3.31 (1.41-7.77)	0.004
	No	43	154		

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## DISCUSSION

The present prospective study examines the effects of prematurity on visual acuity and ocular disorder in children born preterm. In Sub-Saharan Africa, neonatal death has decreased by 40% since 1990 due to improved newborn care, likely leading to an increase in childhood ocular morbidity and blindness from diseases like ROP (32). Despite this positive progress, data on the extent of ocular diseases among the preterms in Sub-Saharan Africa are limited. Our study has demonstrated that the prevalence of ocular diseases and visual impairment in Ethiopian children born preterm is high. To our knowledge, this is the first study to assess the prevalence and causes of ocular disorders and visual impairment among children born preterm and admitted to NICUs. In Ethiopia, intensive neonatal care has expanded in many public and private hospital NICUs since 2013 (33), and neonatal mortality per thousand live births has declined modestly from 39 in 2000 to 33 in 2019(34). A prospective screening survey among neonates admitted to two NICUs in Ethiopia showed that 32.2% of the screened infants had any stage ROP (35). However, there is no regular ROP screening program in the country. A comparison of studies of ocular morbidity and visual impairment among preterm children is difficult as there are methodological variations such as differing age groups, inclusion or exclusion of ROP, stages of ROP, and cohort size. Even though genetic and visual experiences predominantly determine the prevalence of refractive error, studies have shown that low BW interrupts emmetropisation and increases the prevalence of refractive error (36). In our study, nearly half of the premature screened children (51.8%) had refractive error, which is comparable to a survey from Turkey (53.8%) (37) but higher than in Italy (42.3%) (38), and in cohorts of extremely preterm infants from Sweden (29.7%) (39) and Norway (10%) (40). In our study, the prevalence of myopia was 35.1%, which was higher than a cohort of preterm children at age 10–12 years from the UK (18.9%) (41), India (15.8%) (42), and Sweden (4.1%) (39). The prevalence of hyperopia in our study, 13.5%, is comparable with that reported in Turkey (14.3%) (37) and Sweden (17.1%) (39) but higher than the UK (6.6%) (41) and India (8.54%) (42). In the present study, 13.5% of the preterm children had clinically significant astigmatism, which was lower than that reported in Norway (21%) (40) and India (55.6%) (42) and higher than in Turkey (5.7%) (37) and Sweden (6.5%) (39). The higher proportion of myopia seen in our study, in comparison with studies from the UK (41),



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3 360 India (42) and Sweden (39), is supported by long-term studies which have confirmed the  
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5 361 increased incidence of myopia following preterm birth (43).

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7 362 Manifest strabismus was seen in 11.3% of our cohort, which is comparable to studies  
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9 363 from Norway (10%) (40), the UK (13.6%) (15), Sweden (13.5%) (20), and Australia (14%) (45),  
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11 364 and lower than reported in Sweden (17%) (36), the UK and Ireland (24%) (46) and Germany  
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13 365 (26%) (47). It is unclear at what age the different types of strabismus develop (36), and the age at  
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15 366 onset of strabismus in low birthweight children is variable, from the first few months of life to  
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17 367 many years later (11, 15, 16,21,22, 44). In our study, a higher prevalence of strabismus in those  
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19 368 aged > 3 years was noted. This finding (16.7%) is comparable with a similar age group from  
20  
21 369 Sweden (20). Regarding the type of strabismus, we detected similar proportions for esotropia and  
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23 370 exotropia. This is similar to the other studies from Germany (47) and England (41). However,  
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25 371 other investigations confirmed that esotropia was the most frequent type of strabismus (20, 39,  
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27 372 48) The increased prevalence of strabismus in the low birthweight population is well-  
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29 373 documented (21, 36, and 44). Such an association was not apparent in our study, as most of the  
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31 374 children were considerably higher in weight and older than in the studies mentioned above.

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33 375 The prevalence of ROP in our study is 7.2%, lower than in other studies, from sub-  
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35 376 Saharan African countries, including Ethiopia, which ranged from 15-41.7% (35, 49-51). The  
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37 377 lower prevalence of ROP in our study can be explained by our data collection method, where we  
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39 378 depend on the history of ROP either from the patient's parents or from old features of ROP.

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41 379 In the present study, 46% of the children had subnormal visual acuity (>logMAR 0.1) in  
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43 380 the better eye, which is comparable with a population-based study from Norway (45.9%) (40).  
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45 381 The figure is higher than what has been reported for prematurely-born children with BWs 1500–  
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47 382 2000 g (15 %) from Denmark (9) and from Sweden 32 % (20). Birch et al. reported significantly  
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49 383 lower visual acuities in low birthweight infants compared to those born full term (52). In our  
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51 384 study, there was no statistically significant correlation between BCVA and BW or GA, similar to  
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53 385 a study from Turkey (37). However, Dowdeswell et al. (53) found low levels of distance visual  
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55 386 acuity in preterm children compared with full-term children. However, in our study, ocular  
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57 387 morbidities like strabismus, refractive error, and ROP were statistically associated with visual  
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59 388 impairment.

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389 In our study, the prevalence of amblyopia among premature children was 40.1%. The  
390 result in our study is much higher than other studies from Australia (7.3%) (45) and Turkey

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3 391 (7.7%) (37). Previous studies have shown that prematurity and low birthweight are two risk  
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5 392 factors for amblyopia (41, 54). Nevertheless, amblyopia was not statistically associated with low  
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7 393 GA and BW. Even if we did not find a statistical association between GA and BW with  
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9 394 amblyopia, the prevalence among premature children is higher than in other studies; this  
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11 395 indicates that more importance should be given to screening amblyopia risk factors for premature  
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13 396 infants.

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## 15 398 **CONCLUSION**

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19 400 In conclusion, the rates of ocular disorders, visual impairment, and amblyopia in these NICUs in  
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21 401 Ethiopia were higher than in other studies. Refractive error, strabismus, and ROP were all  
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23 402 significant risk factors for visual impairment. These findings underline the importance of early  
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25 403 screening of premature infants for vision and amblyopia. As the two NICUs included in the  
26  
27 404 survey are Ethiopia's main neonatal referral centers, it can be postulated that ocular morbidities,  
28  
29 405 visual impairment, and amblyopia are emerging as potentially avoidable causes of childhood  
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31 406 blindness among preterm children in Ethiopia. Developing preterm ocular-related screening  
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33 407 protocols within the NICUs, strengthening the referral links between the NICUs and eye centers,  
34  
35 408 and further detailed comparative studies between preterm and term children for ocular disorders  
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37 409 are recommended.

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39 410 The strengths of this study were the prospective controlled study design with a high number of  
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41 411 participants, the multi-center design which increases the representativeness of our research, and  
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43 412 the availability of medical information from all children and mothers, which allowed a very  
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45 413 detailed examination and an adjustment for different possible confounding factors. The strict  
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47 414 standardization reduced the probability of examiner-dependent variances.

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49 415 Limitations of the study included the wide age range of the examined children, some of whom  
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51 416 were at an early age and phase of refractive development, and other older children that can affect  
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53 417 the physiologic refractive changes noted in normal health children. The other limitation is there  
54  
55 418 is a chance that those infants with poor health outcomes did not take part in our study. In  
56  
57 419 subsequent research, we will continue following up with these infants to determine future  
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59 420 changes in their refractive error and strabismus.

60 421

## 422 **Lists of Abbreviations**

423 Bronchopulmonary dysplasia (BPD); Necrotizing enterocolitis (NEC); Neonatal Intensive Care  
424 Units (NICUs); Patent ductus arteriosus (PDA); Preterm birth (PTBs); Respiratory distress  
425 syndrome (RDS); Retinopathy of prematurity (ROP), Saint Paul Hospital (SPH) and Tikur  
426 Anbessa Specialized Hospitals (TASH).

427

## 428 **Research Ethics Approval**

429 This study involves human participants, and this research was approved by the ethics committee  
430 of Addis Ababa University Ethics Review Committee (Ref No. 003/2016) in line with the  
431 relevant national and institutional guidelines on care and clinical research. All parents or legal  
432 guardians gave written informed consent before participating in the study.

## 433 **Availability of Data and Materials**

434 All data generated or analysed during this study are included in this published article

## 435 **Competing Interests**

436 The authors have no conflicts of interest.

## 437 **Funding**

438 The SIP study was supported by the Bill & Melinda Gates Foundation (OPP1136965)

439

## 440 **Authors' Contributions**

441 Drafting of the manuscript: STS., LM., AM., and AD. Revision of the manuscript for important  
442 intellectual content: STS., LM., AM., AD and AA. Conception and design of study: STS., LM.,  
443 AM., and AD. Data acquisition, analysis, or interpretation of data: STS., LM., AM., AD., and  
444 AA. Approval of final manuscript to be published: STS., LM., AM., AD., and AA. All authors  
445 have read and approved the final version of the manuscript.

446

## 447 **Acknowledgements**

448 The authors wish to acknowledge the assistance of the staff of the SIP project (Ahmed, Beleyu, Efrata,  
449 and Wagaye) for their support during data collection. Our special appreciation goes to Sr Martha  
450 H/Mariam and Sr. Medhanit from Menelik II pediatrics Ophthalmology clinic.

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3 610 **TABLES LEGEND**  
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5 611 **Table 1 Characteristics of premature children and mothers screened for ocular disorders**  
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8 613 **Table 2. Types of ocular disorders among premature children screened**  
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11 615 **Table 3. Ocular disorders by sex, gestational age, and birthweight among premature**  
12 **children screened for ocular disorders**  
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15 617 **Table 4. The presence of visual impairment by types of ocular disorders among premature**  
16 **children screened for ocular disorders.**  
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# BMJ Paediatrics Open

## Prevalence and causes of ocular disorders and visual impairment among preterm children in Ethiopia

Journal:	<i>BMJ Paediatrics Open</i>
Manuscript ID	bmjpo-2023-002317.R2
Article Type:	Original research
Date Submitted by the Author:	05-Jan-2024
Complete List of Authors:	SHERIEF, SADIK; Addis Ababa University, Department of Ophthalmology; SickKids Research Institute Muhe, Lulu M; Addis Ababa University College of Health Sciences Mekasha, Amha; Addis Ababa University, Department of Pediatrics and Child Health Demtse, Asrat; Addis Ababa University College of Health Sciences, Paediatrics and Child Health Ali, Asim; The Hospital for Sick Children, Ophthalmology and Vision Sciences
Keywords:	Infant, Neonatology, Ophthalmology

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# Prevalence and causes of ocular disorders and visual impairment among preterm children in Ethiopia

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Short Title: Ocular disorders in Preterms

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Submitted as an Original Research article to: [BMJ Paediatrics Open](#)

Abstract word count (300 maximum): 235 words

Manuscript word count (4000 maximum): 3,433 words

Tables and Figures (maximum 5): 4 Tables

**Reference Count: 54**

**Submitted to:** *BMJ Paediatrics Open*

**Key words:** Preterm children; Low birth weight; Visual Impairment; Refractive error; Strabismus; Retinopathy of prematurity; Risk factors of visual impairment; Sub-Saharan Africa; Ethiopia.

## ABSTRACT

### Objective

The aim of this study was to determine the prevalence, causes of ocular disorders and visual impairment among preterm children previously admitted to neonatal intensive care units in Addis Ababa, Ethiopia.

### Methods and Analysis

A prospective screening survey was conducted from Feb. to June 2019 at the pediatric eye clinic of Menelik II Hospital. Children who were preterm at birth and who attended the eye clinic were included in the study. Data on demographic and neonatal characteristics, neonatal and maternal co-morbidities, and ocular disorders were collected. Odds ratio and univariate analysis were used to identify predictors of ocular diseases and visual impairment.

### Results

There were 222 children included in the study with a mean age at presentation of 2.62 years (range 2.08- 6.38 years), mean GA 34.11 weeks (range 30-36) weeks, and mean birthweight 1941.72g (range 953-3500g). Nearly 2/3 had ocular disorders with refractive error (51.8%), strabismus (11.3%), and history of ROP (7.2%) being more common. One-fourth of the children had visual impairment, and the prevalence of amblyopia was 40.1%. Uncorrected refractive errors, strabismus, and ROP were causes for visual impairment.

### Conclusion

Visual impairment and amblyopia are common in Ethiopia. There is a need to develop a screening protocol for ocular disorders for preterm children to enhance early detection and prevention of childhood visual impairment.

**Keywords:** Preterm children; Low birth weight; Visual Impairment; Refractive error; Strabismus; Retinopathy of prematurity; Risk factors of visual impairment; Sub-Saharan Africa; Ethiopia.

## Key Messages

### What is already known about this subject?

- In many low- and middle-income countries, the survival of preterm infants has improved as neonatal systems have improved.
- Preterm children are at a higher risk of developing ocular disorders, visual impairment, and amblyopia than term children.

### What this study adds

- The magnitude and causes of ocular morbidity among preterm children are not well studied in sub-Saharan African countries. This study, conducted among preterm children admitted to two NICUs in a sub-Saharan country, shows that preterm infants develop a higher rate of visual impairment and amblyopia.

### How this study might affect research, practice or policy

- The findings of this study provide some evidence for screening for ocular diseases in preterm children, but further studies are needed.
- A follow up prospective study commencing in 5 years' time would be of value as the number of surviving very low birth weight infants may significantly increase

## INTRODUCTION

Global, regional, and national estimates of preterm birth (defined as childbirth at less than 37 completed weeks) using the 2019 Global Burden of Disease study showed 15.22 million preterm births (1). In the Global Burden of Disease Study, 3.1% of all disability-adjusted life-years were attributed to preterm birth, similar to the burden of HIV or malaria (2). More than 95% of preterm births are occurring in developing countries. Globally the estimated preterm birth rate is 11.1%. Over 60% of preterm births occur in Sub-Saharan Africa and South Asia (1). Ethiopia belongs to the top 15 countries that contribute to two-thirds of the world's preterm babies with a preterm rate of 14.1% out of 481 deliveries (3).

From six months of pregnancy to term is considered the most active period for ocular development (4). Improved neonatal care has increased the survival rates of extremely preterm infants with birth weights (BW) of 1,000 g or gestational age (GA) of 28 weeks; at the same time, retinopathy of prematurity (ROP) has become a significant threat to visual function (5-7). Preterm children are reported to have an increased incidence of visual impairment because of perinatal lesions in the brain (8-10).

It has been noted that both preterm birth and retinopathy of prematurity (ROP) have an effect on the developing visual system, leading to decreased visual acuity, decreased contrast sensitivity, and an increase in color vision deficiencies (11-16). Population-based studies suggest that ophthalmic impairments remain common in very low birth weight infants (11,16,17). Effects of prematurity on ocular and neurological development include retinopathy of prematurity (ROP), refractive error, strabismus, cerebral visual impairment, color vision deficits, reduced contrast sensitivity (CS), visual field defects, and decreased visual acuity (16). According to population studies, the incidence of ROP, whether moderate or severe, for infants born at less than 1500–1700 g ranges from 22–49% (17-19).

In a cohort study, children with lower birth weights had significantly worse near and distance visual acuity at ages 10 to 12 years compared to full-term infants (10). Additionally, infants born prematurely without ROP are more likely to have myopia and anisometropia than infants born at term because preterm babies are more likely to experience refractive errors (20). An increased incidence of strabismus has also been reported in children born prematurely, regardless of the presence of ROP (21-24).

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3 Research on ocular morbidities among preterm infants in sub-Saharan African nations is  
4 limited. Before 2020, blindness from ROP was not reported in Ethiopia, including studies in  
5 schools for the blind (25, 26).  
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8 To determine the top causes of illness and mortality in preterm infants admitted to  
9 neonatal intensive units (NICUs) in Ethiopia, an Ethiopian Study of Illness in Preterms (SIP)  
10 study was conducted based on standardized diagnostic protocols. This study is part of the SIP  
11 study focusing on ocular morbidities among preterms. The present study aimed to identify ocular  
12 disorders in a population of preterm children with and without ROP.  
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## 18 **METHODS**

### 19 **Study design and subjects**

20 The SIP Study is a prospective study conducted to determine the top causes of illness and  
21 mortality in preterm infants admitted to hospitals in Ethiopia based on standardized diagnostic  
22 protocols (27). The study participants of this current study are from the SIP study from Feb –  
23 June, 2019. The research was performed in accordance with the Declaration of Helsinki and was  
24 approved by the Institute Ethics Committee of Addis Ababa University ((Ref No. 003/2016). All  
25 parents or legal guardians provided informed consent before the examination. Patients or the  
26 public weren't involved in our research's design, conduct, reporting, or dissemination plans.  
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### 34 **Study setting**

35 For the SIP study, standard protocols were developed to undertake a physical examination and  
36 laboratory investigation, in particular microbiology, radiologic, and ultrasound examinations.  
37 There were initial and follow-up examinations to detect the progress of the preterm infant. Addis  
38 Ababa University, Gondar University, Jimma University, and St. Paul Millennium Medical  
39 College were included in the SIP study. However, for this ocular morbidity aspect of the SIP  
40 study, preterms from Addis Ababa, Tikur Anbessa Hospital, Gandhi Hospital, and St. Paul  
41 Millennium Medical College were included in the research.  
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### 48 **Recruitment methods**

49 Inclusion criteria were (1) GA < 37 weeks and (2) participation in the SIP study. The preterm  
50 children were identified from the SIP database. Parents of all preterm infants received a phone  
51 call invitation to participate in our investigation.  
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### Assessment of prenatal and postnatal history

History data were assessed from each child's recorded file for the enrolled children. The following data were extracted: antenatal risk factors: maternal age, in vitro fertilization, antenatal corticosteroids, preeclampsia/eclampsia, diabetes, HIV/AIDS, chorioamnionitis, mode of delivery, and multiple births. Neonatal factors included sex, GA, BW, resuscitation in the delivery room, respiratory distress syndrome (RDS), duration of invasive/noninvasive mechanical ventilation and oxygen therapy, intracranial hemorrhage, patent ductus arteriosus (PDA), neonatal sepsis, necrotizing enterocolitis (NEC), number of blood transfusions, and bronchopulmonary dysplasia (BPD). There were no regular ROP screening programmes within the NICUs of the hospitals where the patients were admitted. There was no referral system from the NICUs to Ophthalmology clinic, except if the parents noted a concern. In addition, all parents were interviewed using a standardized protocol to request information concerning medical history of the child and parents, including ocular and general morbidities.

### Definitions

Gestational age was determined using last menstrual period [LPM], Ballard and Dubowitz scores and ultrasound assessment. Studies in Papua New Guinea have shown good concordance (0.878, 0.914, and 0.886, respectively) compared to antenatal ultrasound as the gold standard (28). LMP in a low-resource setting such as Bangladesh was found to be a more reliable measure of gestational age than previously thought for the estimation of postnatal gestational age of preterm infants (29).

Preterm infants were further classified as late and moderate preterm (32 to < 37 weeks), very preterm (28 to <32 weeks), and extremely preterm (less than 28 weeks). Glasses were prescribed if there was myopia >1.0D, astigmatism >1.0D, or hypermetropia >+2.0D.

### Eye examination

All examinations were performed by the PI and lead author (STS), a pediatric ophthalmologist. Testing of best-corrected visual acuity was performed with Lea symbols until school enrolment, and after that, ETDRS was used in all subjects. In cases of visual acuity below 6/60, depending on the children's age, Lea symbols or Landolt rings were used at a distance of 1 m. Values were converted for analysis into the logarithm of the minimum angle of resolution (logMAR) (30).

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3 Cyclopentolate (0.5%) eye drops were administered three times at 10-min intervals, after which  
4 cycloplegic refraction and keratometry were analyzed with an autorefractor (Nidek ARK-1s  
5 keratometer, Japan). The spherical equivalent (refractive error) was calculated by adding the  
6 spherical value and half of the cylindrical value. Anisometropia was defined as a difference  
7 between the patients' eyes of  $\geq 1.5$  diopters of spherical equivalent. Orthoptic examination for  
8 strabismus included the cover-uncover test and alternate cover test, the Hirschberg Test and  
9 examination of fixation behavior, as well as the presence or absence of nystagmus after having  
10 corrected refractive errors. If a child presented with heterotropia, an alternating prism cover test  
11 was added to measure the angle of deviation in prism diopters.

12 Strabismus was defined as constant or intermittent heterotropia of any dimension at a distance  
13 and/or near fixation after correcting refractive error. Classification of strabismus was categorized  
14 depending on deviation from the primary position (esotropia or exotropia). An anterior segment  
15 examination was done using slit lamp biomicroscopy. A dilated posterior segment examination  
16 was conducted using indirect ophthalmoscopy with a 28-diopter lens. Retinopathy of prematurity  
17 was diagnosed retrospectively from the patients' chart.

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31 Data analyzed using IBM SPSS 21.0 (SPSS Inc., Chicago, USA). Continuous variables were  
32 expressed as the mean  $\pm$  standard deviation (SD) or as the median when appropriate. Categorical  
33 variables were expressed as proportions. The chi-square test was used to analyze the association  
34 between categorical variables. Associations between ocular morbidities and continuous and  
35 categorical variables were computed using Fisher's exact test and Pearson chi-square ( $\chi^2$ ) test,  
36 respectively. Continuous variables were compared using ANOVA. Values of  $p < 0.05$  were  
37 considered statistically significant.  
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## RESULTS

During the study period 222 infants (146 from Saint Paul Hospital and 76 from TASH) were included in this study.

### Characteristics of the study population

Slightly more females than males were screened (52.7% and 47.3%, respectively). The majority of the study participants (n=156, 70.3%) were less than 3 years of age and the mean age at presentation was  $2.62 \pm 0.49$  years (range 2.08- 6.38). One hundred and twenty-three of the 222 children (55.4%) had a GA  $\leq 34$  weeks and 43 (19.4%) had a BW  $\leq 1500$ g. Birthweight ranged from 953-3500g with a mean of 1941.72g (SD 445.49); GA ranged from 30-36 weeks, with a mean of 34.11 weeks (SD 1.47). One hundred and twenty-three children (55.4%) were delivered vaginally, and 80 (36.1%) had multiple gestations. Forty-eight children (21.7%) were born to mothers with pregnancy-induced hypertension, and eight (3.7%) mothers tested positive for HIV (Table 1).

The mean BWs of children from SPH and TASH NICUs were  $1888.5 \pm 403.6$  (953-3000) g and  $2043.94 \pm 503.74$  (1125-3500) g, respectively; mean GAs were  $34.14 \pm 1.49$  (30-36) weeks and  $34.08 \pm 1.44$  (30-36) weeks, respectively. Differences in these parameters were not statistically significant (Table 2).

**Table 1 Characteristics of premature children and mothers screened for ocular disorders**

Variable		Total		Female		
		N	N	%	N	%
<b>Birthweight</b>	<1500 gm	43	20	46.5%	23	53.5%
	>1500gm	179	85	47.5%	94	52.5%
<b>Gestational age</b>	≤34 weeks	122	60	49.2%	62	50.8%
	> 34 weeks	100	45	45%	55	55%
<b>Multiple gestation</b>	Yes	80	42	52.5%	38	47.5%
	No	142	63	44.4%	79	55.6%
<b>Oxygen supplementation</b>	Yes	97	47	48.5%	50	51.5%
	No	125	58	46.4%	67	53.6%
<b>Infantile morbidity</b>	Sepsis	6	2	33.3%	4	66.7%
	IVH	2	0	0%	2	100%
	BPD and Sepsis	1	1	100%	0	0%
	None	213	102	47.9%	111	52.1%
<b>Mode of delivery</b>	Vaginal delivery	123	53	43.1%	70	56.9%
	Cesarean section	99	52	52.5%	47	47.5%
<b>Multiparity</b>	Yes	47	18	38.3%	29	61.7%
	No	175	63	34.3%	59	65.7%
<b>Maternal morbidity</b>	PIH	44	22	50%	22	50%
	HIV	5	2	40%	3	60%
	HIV & PIH	3	3	100%	0	0%
	DM	2	0	0%	2	100%
	DM & PIH	1	0	0%	1	100%
	TORCH	1	1	100%	0	0%
	None	166	77	46.4%	89	53.6%
<b>NICU location</b>	SPH	146	65	44.5%	81	55.5%
	TASH	76	40	52.6%	36	47.4%

**Legend:** BPD- Bronchopulmonary Dysplasia; DM- Diabetes Mellitus; HIV-IVH-Intraventricular Hemorrhage; PIH- Pregnancy-Induced Hypertension; SPH- Saint Paul Hospital; TASH-Tikur Anbessa Specialized Hospital; TORCH- Toxoplasmosis, Rubella, Cytomegalovirus, Herpes simplex, and HIV

### Ocular morbidities and risk factors

Overall, 145 (65.3%) of the children had ocular disorders at the presentation, of which 92 (63.4%) had isolated ocular diseases (69 refractive error, 13 nasolacrimal duct obstruction, five strabismus, and five ROP). The mean age at presentation of children with ocular disorders was  $2.7 \pm 0.5$  (2.1- 6.4) years, and there were more females with a male to female ratio of 1:1.27. None of the eyes examined had anomalies of the anterior segment or lens.

The mean GA was  $34.14 \pm 1.49$  (30-36) weeks, and BW was  $1927.27 \pm 429.19$  (953-3100) grams. Refractive errors were the leading type of ocular morbidity seen in 115/222 (51.8%), followed by NLDO (21.2%) (Table 2).

**Table 2. Types of ocular disorders among premature children screened**

Ocular disorders	n	%
Refractive error	115	51.8
Nasolacrimal duct obstruction	47	21.2
Strabismus	25	11.3
Retinopathy of prematurity	16	7.2
Others	5	2.3

**NB-** Some ocular disorders occur more than once.

### Refractive error

One hundred and fifteen (51.8) children had a refractive error, of which 55.5% (81/146) and 44.7% (34/76) of children enrolled from the SPH and TASH had refractive errors, respectively. The mean age at presentation was  $2.68 \pm 0.56$  (2.08-6.38) years, and the male-to-female ratio was 1:1.25. Thirty-nine (59%) of children aged > 3 years developed refractive error in comparison with 76 (48.1%) of those aged < 3 years.

The mean gestational age and birthweight of children with refractive errors was  $34.11 \pm 1.54$  (30-36) weeks and  $1892.34 \pm 414.55$  (1080-3100) grams, respectively. Myopia was the commonest type of refractive error, accounting for 78/115 (60.8%) of cases, followed by astigmatism (30, 26.1%) and hyperopia (15, 13.1%). Gender, GA, BW, oxygen supplementation, children, and maternal morbidity were not statistically associated with refractive error. (Table 3)

### Strabismus

Twenty-five children (11.3%) had strabismus (5 isolated, 20 in combination with refractive error, nystagmus, ROP, and nasolacrimal duct obstruction). The age at presentation was  $2.73 \pm 0.52$  (2.1-3.6) years, and the male-to-female ratio was 1.08:1.

The mean GA and BW were  $34.0 \pm 1.41$  (30-36) weeks and  $906.76 \pm 489.92$  (1140-3000), respectively. Regarding the types of strabismus, 13 cases had esotropia, and the remaining 12 patients had exotropia. There was no statistically significant association between GA, BW, and strabismus (Table 3). In this study, the prevalence of strabismus among children aged  $\geq 3$  years was 16.7% compared to 8.9% in those < 3 years. However, older age was not statistically associated with strabismus.

### Retinopathy of prematurity

Previous history of ROP was noted in 16/22 (7.2%) of the children enrolled in this study. Most patients (12, 57%) with ROP were from SPH. Almost all of them (15/16) had a GA < 34 weeks, and the mean GA and BW of patients with ROP were 32.19±1.33 (30-35) weeks and 1596.25 ±483.64 (953-2600) grams, respectively. Nine patients with ROP had an associated refractive error (6 myopia and 3 astigmatism). Only one patient had an associated intermittent exotropia. In univariate analysis, ROP was statistically associated with low GA and low BW (Table 3). Multivariable logistic regression analysis was not conducted due to the small number of children with ROP.

**Table 3. Ocular disorders by sex, gestational age, and birthweight among premature children screened for ocular disorders**

Type of Disorder	Variables		Yes	No	Odds Ratio	p-Value
			n	n		
Refractive error	Sex	Male	51	54	0.78(0.46-1.33)	0.361
		Female	64	53		
	BWt	≤1500 gm	22	21	1.03(0.53-2.01)	0.926
		>1500gm	93	86		
	GA	≤34 weeks	62	60	1.09(0.64-1.85)	0.746
> 34 weeks		53	47			
Strabismus	Sex	Male	12	93	1.03(0.4501.37)	0.940
		Female	13	104		
	BWt	≤1500 gm	7	36	0.57(0.22-1.48)	0.246
		>1500gm	18	161		
	GA	≤34 weeks	14	108	0.95 (0.41-2.2)	0.911
> 34 weeks		11	89			
ROP	Sex	Male	6	99	0.65(0.22-1.85)	0.415
		Female	10	107		
	BWt	≤1500 gm	7	36	Reference	0.01
		>1500gm	9	170		
	GA	≤34 weeks	15	107	Reference	0.001
> 34 weeks		1	99			

**Legend:** BWt- Birth Weight ; GA-Gestational Age

### Visual impairment and ocular disorders

The mean VA of the right and left eyes was 0.22(SD 0.23) logMAR and 0.17 (SD 0.21) logMAR, respectively. The mean VA in the better and worse eyes was 0.17 (SD 0.22) logMAR and 0.28 (SD 0.21) logMAR, respectively. In this study, 101 (45.9%) and 181 (81.5%) of the children had subnormal visual acuity (>logMAR 0.1) in the better and worst eyes, respectively.

Nearly one-fourth (55, 24.8%) of children screened had visual impairment in the better eye. Of this group 51 (92.7%) had uncorrected refractive error alone (34/51) or with strabismus (10/51), ROP (6/51), or nystagmus (1/51). Eighty-nine (40.1%) patients had amblyopia, of which 59/89 (66.3%) had bilateral amblyopia from uncorrected refractive error. Isometric and anisometric amblyopia from uncorrected refractive error were the commonest causes of amblyopia, contributing to 49/89 (55%) and 20/89 (22.8%), respectively. Of the 16 cases with ROP, 12 (75%) had a visual impairment associated with other disorders like refractive error, strabismus, and nystagmus.

In univariate analysis, visual impairment in the better eye was statistically associated with ROP, uncorrected refractive error, and strabismus with p-values of 0.001, 0.001, and 0.004, respectively. Amblyopia was not statistically associated with low GA or low BW (Table 4).

**Table 4. The presence of visual impairment by types of ocular disorders among premature children screened for ocular disorders.**

Variables		Visual Impairment in the better eye		Odds Ratio 95% CI (Lower-Upper)	p-Value
		Yes	No		
Sex	Male	23	82	0.75(0.40-1.38)	0.348
	Female	32	85		
BWt	≤1500 gm	14	29	0.62(0.29-1.27)	0.188
	>1500gm	41	138		
GA	≤34 weeks	28	94	1.24(0.67-2.29)	0.294
	> 34 weeks	27	73		
Refractive error	Yes	48	67	10.24(4.37-23.97)	0.001
	No	7	100		
Strabismus	Yes	12	13	3.31 (1.41-7.77)	0.004
	No	43	154		

## DISCUSSION

The present prospective study examines the effects of prematurity on visual acuity and ocular disorder in children born preterm. In Sub-Saharan Africa, neonatal death has decreased by 40% since 1990 due to improved newborn care, likely leading to an increase in childhood ocular morbidity and blindness from diseases like ROP (32). Despite this positive progress, data on the extent of ocular diseases among the preterms in Sub-Saharan Africa are limited. Our study has demonstrated that the prevalence of ocular diseases and visual impairment in Ethiopian children born preterm is high. To our knowledge, this is the first study to assess the prevalence and causes of ocular disorders and visual impairment among children born preterm and admitted to NICUs. In Ethiopia, intensive neonatal care has expanded in many public and private hospital NICUs since 2013 (33), and neonatal mortality per thousand live births has declined modestly from 39 in 2000 to 33 in 2019(34). A prospective screening survey among neonates admitted to two NICUs in Ethiopia showed that 32.2% of the screened infants had any stage ROP (35). However, there is no regular ROP screening program in the country. A comparison of studies of ocular morbidity and visual impairment among preterm children is difficult as there are methodological variations such as differing age groups, inclusion or exclusion of ROP, stages of ROP, and cohort size. Even though genetic and visual experiences predominantly determine the prevalence of refractive error, studies have shown that low BW interrupts emmetropisation and increases the prevalence of refractive error (36). In our study, nearly half of the premature screened children (51.8%) had refractive error, which is comparable to a survey from Turkey (53.8%) (37) but higher than in Italy (42.3%) (38), and in cohorts of extremely preterm infants from Sweden (29.7%) (39) and Norway (10%) (40). In our study, the prevalence of myopia was 35.1%, which was higher than a cohort of preterm children at age 10–12 years from the UK (18.9%) (41), India (15.8%) (42), and Sweden (4.1%) (39). The prevalence of hyperopia in our study, 13.5%, is comparable with that reported in Turkey (14.3%) (37) and Sweden (17.1%) (39) but higher than the UK (6.6%) (41) and India (8.54%) (42). In the present study, 13.5% of the preterm children had clinically significant astigmatism, which was lower than that reported in Norway (21%) (40) and India (55.6%) (42) and higher than in Turkey (5.7%) (37) and Sweden (6.5%) (39). The higher proportion of myopia seen in our study, in comparison with studies from the UK (41),



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3 India (42) and Sweden (39), is supported by long-term studies which have confirmed the  
4 increased incidence of myopia following preterm birth (43).  
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7 Manifest strabismus was seen in 11.3% of our cohort, which is comparable to studies  
8 from Norway (10%) (40), the UK (13.6%) (15), Sweden (13.5%) (20), and Australia (14%) (45),  
9 and lower than reported in Sweden (17%) (36), the UK and Ireland (24%) (46) and Germany  
10 (26%) (47). It is unclear at what age the different types of strabismus develop (36), and the age at  
11 onset of strabismus in low birthweight children is variable, from the first few months of life to  
12 many years later (11, 15, 16,21,22, 44). In our study, a higher prevalence of strabismus in those  
13 aged > 3 years was noted. This finding (16.7%) is comparable with a similar age group from  
14 Sweden (20). Regarding the type of strabismus, we detected similar proportions for esotropia and  
15 exotropia. This is similar to the other studies from Germany (47) and England (41). However,  
16 other investigations confirmed that esotropia was the most frequent type of strabismus (20, 39,  
17 48) The increased prevalence of strabismus in the low birthweight population is well-  
18 documented (21, 36, and 44). Such an association was not apparent in our study, as most of the  
19 children were considerably higher in weight and older than in the studies mentioned above.  
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23 The prevalence of ROP in our study is 7.2%, lower than in other studies, from sub-  
24 Saharan African countries, including Ethiopia, which ranged from 15-41.7% (35, 49-51). The  
25 lower prevalence of ROP in our study can be explained by our data collection method, where we  
26 depend on the history of ROP either from the patient's parents or from old features of ROP.  
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30 In the present study, 46% of the children had subnormal visual acuity (>logMAR 0.1) in  
31 the better eye, which is comparable with a population-based study from Norway (45.9%) (40).  
32 The figure is higher than what has been reported for prematurely-born children with BWs 1500–  
33 2000 g (15 %) from Denmark (9) and from Sweden 32 % (20). Birch et al. reported significantly  
34 lower visual acuities in low birthweight infants compared to those born full term (52). In our  
35 study, there was no statistically significant correlation between BCVA and BW or GA, similar to  
36 a study from Turkey (37). However, Dowdeswell et al. (53) found low levels of distance visual  
37 acuity in preterm children compared with full-term children. However, in our study, ocular  
38 morbidities like strabismus, refractive error, and ROP were statistically associated with visual  
39 impairment.  
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54 In our study, the prevalence of amblyopia among premature children was 40.1%. The  
55 result in our study is much higher than other studies from Australia (7.3%) (45) and Turkey  
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3 (7.7%) (37). Previous studies have shown that prematurity and low birthweight are two risk  
4 factors for amblyopia (41, 54). Nevertheless, amblyopia was not statistically associated with low  
5 GA and BW. Even if we did not find a statistical association between GA and BW with  
6 amblyopia, the prevalence among premature children is higher than in other studies; this  
7 indicates that more importance should be given to screening amblyopia risk factors for premature  
8 infants.  
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14 The strengths of this study were the prospective controlled study design with a high  
15 number of participants, the multi-center design which increases the representativeness of our  
16 research, and the availability of medical information from all children and mothers, which  
17 allowed a very detailed examination and an adjustment for different possible confounding  
18 factors. The strict standardization reduced the probability of examiner-dependent variances.  
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Limitations of the study included the wide age range of the examined children, some of  
whom were at an early age and phase of refractive development, and other older children that  
can affect the physiologic refractive changes noted in normal health children. The other  
limitation is there is a chance that those infants with poor health outcomes did not take part in  
our study. In subsequent research, we will continue following up with these infants to determine  
future changes in their refractive error and strabismus.

## CONCLUSION

In conclusion, the rates of ocular disorders, visual impairment, and amblyopia in these NICUs in  
Ethiopia were higher than in other studies. Refractive error, strabismus, and ROP were all  
significant risk factors for visual impairment. These findings underline the importance of early  
screening of premature infants for vision and amblyopia. As the two NICUs included in the  
survey are Ethiopia's main neonatal referral centers, it can be postulated that ocular morbidities,  
visual impairment, and amblyopia are emerging as potentially avoidable causes of childhood  
blindness among preterm children in Ethiopia. Developing preterm ocular-related screening  
protocols within the NICUs, strengthening the referral links between the NICUs and eye centers,  
and further detailed comparative studies between preterm and term children for ocular disorders  
are recommended.

### **Lists of Abbreviations**

Bronchopulmonary dysplasia (BPD); Necrotizing enterocolitis (NEC); Neonatal Intensive Care Units (NICUs); Patent ductus arteriosus (PDA); Preterm birth (PTBs); Respiratory distress syndrome (RDS); Retinopathy of prematurity (ROP), Saint Paul Hospital (SPH) and Tikur Anbessa Specialized Hospitals (TASH).

### **Research Ethics Approval**

This study involves human participants, and this research was approved by the ethics committee of Addis Ababa University Ethics Review Committee (Ref No. 003/2016) in line with the relevant national and institutional guidelines on care and clinical research. All parents or legal guardians gave written informed consent before participating in the study.

### **Availability of Data and Materials**

All data generated or analysed during this study are included in this published article

### **Competing Interests**

The authors have no conflicts of interest.

### **Funding**

The SIP study was supported by the Bill & Melinda Gates Foundation (OPP1136965)

### **Authors' Contributions**

Drafting of the manuscript: STS., LM., AM., and AD. Revision of the manuscript for important intellectual content: STS., LM., AM., AD and AA. Conception and design of study: STS., LM., AM., and AD. Data acquisition, analysis, or interpretation of data: STS., LM., AM., AD., and AA. Approval of final manuscript to be published: STS., LM., AM., AD., and AA. All authors have read and approved the final version of the manuscript.

### **Acknowledgements**

The authors wish to acknowledge the assistance of the staff of the SIP project (Ahmed, Beleyu, Efrata, and Wagaye) for their support during data collection. Our special appreciation goes to Sr Martha H/Mariam and Sr. Medhanit from Menelik II pediatrics Ophthalmology clinic.

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**TABLES LEGEND**

**Table 1 Characteristics of premature children and mothers screened for ocular disorders**

**Table 2. Types of ocular disorders among premature children screened**

**Table 3. Ocular disorders by sex, gestational age, and birthweight among premature children screened for ocular disorders**

**Table 4. The presence of visual impairment by types of ocular disorders among premature children screened for ocular disorders.**

# BMJ Paediatrics Open

## Prevalence and causes of ocular disorders and visual impairment among preterm children in Ethiopia

Journal:	<i>BMJ Paediatrics Open</i>
Manuscript ID	bmjpo-2023-002317.R3
Article Type:	Original research
Date Submitted by the Author:	15-Jan-2024
Complete List of Authors:	SHERIEF, SADIK; Addis Ababa University, Department of Ophthalmology; SickKids Research Institute Muhe, Lulu M; Addis Ababa University College of Health Sciences Mekasha, Amha; Addis Ababa University, Department of Pediatrics and Child Health Demtse, Asrat; Addis Ababa University College of Health Sciences, Paediatrics and Child Health Ali, Asim; The Hospital for Sick Children, Ophthalmology and Vision Sciences; University of Toronto, Department of Ophthalmology and Vision Sciences
Keywords:	Infant, Neonatology, Ophthalmology

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# Prevalence and causes of ocular disorders and visual impairment among preterm children in Ethiopia

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Short Title: Ocular disorders in Preterms

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[Submitted as an Original Research article to: BMJ Paediatrics Open](#)

[Abstract word count \(300 maximum\): 235 words](#)

[Manuscript word count \(4000 maximum\): 3,433 words](#)

[Tables and Figures \(maximum 5\): 4 Tables](#)

**Reference Count: 54**

**Submitted to:** *BMJ Paediatrics Open*

**Key words:** Preterm children; Low birth weight; Visual Impairment; Refractive error; Strabismus; Retinopathy of prematurity; Risk factors of visual impairment; Sub-Saharan Africa; Ethiopia.

## ABSTRACT

### Objective

The aim of this study was to determine the prevalence, causes of ocular disorders and visual impairment among preterm children previously admitted to neonatal intensive care units in Addis Ababa, Ethiopia.

### Methods and Analysis

A prospective screening survey was conducted from February to June 2019 at the pediatric eye clinic of Menelik II Hospital. Children who were preterm at birth and who attended the eye clinic were included in the study. Data on demographic and neonatal characteristics, neonatal and maternal co-morbidities, and ocular disorders were collected. Odds ratio and univariate analysis were used to identify predictors of ocular diseases and visual impairment.

### Results

There were 222 children included in the study with a mean age at presentation of 2.62 years (range 2.08- 6.38 years), mean gestational age (GA) 34.11 weeks (range 30-36) weeks, and mean birthweight 1941.72g (range 953-3500g). Nearly 2/3 had ocular disorders with refractive error (51.8%), strabismus (11.3%), and history of retinopathy of prematurity (ROP) (7.2%) being more common. One-fourth of the children had visual impairment, and the prevalence of amblyopia was 40.1%. Uncorrected refractive errors, strabismus, and ROP were causes for visual impairment.

### Conclusion

Visual impairment and amblyopia are common in Ethiopia. There is a need to develop a screening protocol for ocular disorders for preterm children to enhance early detection and prevention of childhood visual impairment.

**Keywords:** Preterm children; Low birth weight; Visual Impairment; Refractive error; Strabismus; Retinopathy of prematurity; Risk factors of visual impairment; Sub-Saharan Africa; Ethiopia.

## Key Messages

### What is already known about this subject?

- In many low- and middle-income countries, the survival of preterm infants has improved as neonatal systems have improved.
- Preterm children are at a higher risk of developing ocular disorders, visual impairment, and amblyopia than term children.

### What this study adds

- The magnitude and causes of ocular morbidity among preterm children are not well studied in sub-Saharan African countries. This study of preterm children admitted to two neonatal intensive care units in a sub-Saharan country shows that preterm infants develop a higher rate of visual impairment and amblyopia.

### How this study might affect research, practice or policy

- The findings of this study provide some evidence for screening for ocular diseases in preterm children, but further studies are needed.
- A follow up prospective study commencing in 5 years' time would be of value as the number of surviving very low birth weight infants may significantly increase.

## INTRODUCTION

Global, regional, and national estimates of preterm birth (defined as childbirth at less than 37 completed weeks) using the 2019 Global Burden of Disease study showed 15.22 million preterm births (1). In the Global Burden of Disease Study, 3.1% of all disability-adjusted life-years were attributed to preterm birth, similar to the burden of HIV or malaria (2). More than 95% of preterm births are occurring in developing countries. Globally the estimated preterm birth rate is 11.1%. Over 60% of preterm births occur in Sub-Saharan Africa and South Asia (1). Ethiopia belongs in the top 15 countries that contribute to two-thirds of the world's preterm babies with a preterm rate of 14.1% out of 481 deliveries (3).

From six months of pregnancy to term is considered the most active period for ocular development (4). Improved neonatal care has increased the survival rates of extremely preterm infants with birth weights (BW) of 1,000g or gestational age (GA) of 28 weeks; at the same time, retinopathy of prematurity (ROP) has become a significant threat to visual function (5-7). Preterm children are reported to have an increased incidence of visual impairment because of perinatal lesions in the brain (8-10).

It has been noted that both preterm birth and ROP have an effect on the developing visual system, leading to decreased visual acuity, decreased contrast sensitivity, and an increase in color vision deficiencies (11-16). Population-based studies suggest that ophthalmic impairments remain common in very low birth weight infants (11,16,17). Effects of prematurity on ocular and neurological development include ROP, refractive error, strabismus, cerebral visual impairment, color vision deficits, reduced contrast sensitivity (CS), visual field defects, and decreased visual acuity (16). According to population studies, the incidence of ROP, whether moderate or severe, for infants born at less than 1500–1700g ranges from 22–49% (17-19).

In a cohort study, children with lower birth weights had significantly worse near and distance visual acuity at ages 10 to 12 years compared to full-term infants (10). Additionally, infants born prematurely without ROP are more likely to have myopia and anisometropia than infants born at term because preterm babies are more likely to experience refractive errors (20). An increased incidence of strabismus has also been reported in children born prematurely, regardless of the presence of ROP (21-24).

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3 Research on ocular morbidities among preterm infants in sub-Saharan African nations is  
4 limited. Before 2020, blindness from ROP was not reported in Ethiopia, including studies based  
5 on schools for the blind (25, 26).  
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8 To determine the top causes of illness and mortality in preterm infants admitted to  
9 neonatal intensive units (NICUs) in Ethiopia, an Ethiopian Study of Illness in Preterms (SIP)  
10 study was conducted based on standardized diagnostic protocols. This study is part of the SIP  
11 study focusing on ocular morbidities among preterms. The present study aimed to identify ocular  
12 disorders in a population of preterm children with and without ROP.  
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## 18 **METHODS**

### 19 **Study design and subjects**

20 The SIP Study is a prospective study conducted to determine the top causes of illness and  
21 mortality in preterm infants admitted to hospitals in Ethiopia based on standardized diagnostic  
22 protocols (27). The study participants of this current study are from the SIP study from Feb –  
23 June, 2019. The research was performed in accordance with the Declaration of Helsinki and was  
24 approved by the Institute Ethics Committee of Addis Ababa University ((Ref No. 003/2016). All  
25 parents or legal guardians provided informed consent before the examination. Patients or the  
26 public were not involved in research design, conduct, reporting, or dissemination plans.  
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### 34 **Study setting**

35 For the SIP study, standard protocols were developed to undertake a physical examination and  
36 laboratory investigation, in particular microbiology, radiologic, and ultrasound examinations.  
37 There were initial and follow-up examinations to detect the progress of the preterm infant. Addis  
38 Ababa University, Gondar University, Jimma University, and St. Paul Millennium Medical  
39 College were included in the SIP study. However, for this ocular morbidity aspect of the SIP  
40 study, only preterm children from Addis Ababa, Tikur Anbessa Hospital, Gandhi Hospital, and  
41 St. Paul Millennium Medical College were included.  
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### 48 **Recruitment methods**

49 Inclusion criteria were (1) GA < 37 weeks and (2) participation in the SIP study. The preterm  
50 children were identified from the SIP database. Parents of all preterm infants received a phone  
51 call invitation to participate in our investigation.  
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### Assessment of prenatal and postnatal history

History data were assessed from each child's recorded file for the enrolled children. The following antenatal risk factors were extracted: maternal age, in vitro fertilization, antenatal corticosteroids, preeclampsia/eclampsia, diabetes, HIV/AIDS, chorioamnionitis, mode of delivery, and multiple births. Neonatal factors extracted included sex, GA, BW, resuscitation in the delivery room, respiratory distress syndrome (RDS), duration of invasive/noninvasive mechanical ventilation and oxygen therapy, intracranial hemorrhage, patent ductus arteriosus (PDA), neonatal sepsis, necrotizing enterocolitis (NEC), number of blood transfusions, and bronchopulmonary dysplasia (BPD). There were no regular ROP screening programmes within the NICUs of the hospitals where the patients were admitted. There was no referral system from the NICUs to the Ophthalmology clinic, except if the parents noted a concern. In addition, all parents were interviewed using a standardized protocol to request information concerning medical history of the child and parents, including ocular and general morbidities.

### Definitions

Gestational age was determined using last menstrual period [LMP], Ballard and Dubowitz scores and ultrasound assessment. Studies in Papua New Guinea have shown good concordance (0.878, 0.914, and 0.886, respectively) compared to antenatal ultrasound as the gold standard (28). LMP in a low-resource setting such as Bangladesh was found to be a more reliable measure of gestational age than previously thought for the estimation of postnatal gestational age of preterm infants (29).

Preterm infants were further classified as late and moderate preterm (32 to < 37 weeks), very preterm (28 to <32 weeks), and extremely preterm (less than 28 weeks). Glasses were prescribed if there was myopia >1.0D, astigmatism >1.0D, or hypermetropia >+2.0D.

### Eye examination

All examinations were performed by the PI and lead author (STS), a pediatric ophthalmologist. Testing of best-corrected visual acuity was performed with Lea symbols until school enrolment, and after that, ETDRS was used in all subjects. In cases of visual acuity below 6/60, depending on the children's age, Lea symbols or Landolt rings were used at a distance of 1 m. Values were converted for analysis into the logarithm of the minimum angle of resolution (logMAR) (30).

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3 Cyclopentolate (0.5%) eye drops were administered three times at 10-min intervals, after which  
4 cycloplegic refraction and keratometry were analyzed with an autorefractor (Nidek ARK-1s  
5 keratometer, Japan). The spherical equivalent refractive error was calculated by adding the  
6 spherical value and half of the cylindrical value. Anisometropia was defined as a difference  
7 between the patients' eyes of  $\geq 1.5$  diopters of spherical equivalent. Orthoptic examination for  
8 strabismus included the cover-uncover test and alternate cover test, the Hirschberg Test and  
9 examination of fixation behavior, as well as the presence or absence of nystagmus after having  
10 corrected refractive errors. If a child presented with heterotropia, an alternating prism cover test  
11 was added to measure the angle of deviation in prism diopters.

12 Strabismus was defined as constant or intermittent heterotropia of any dimension at a distance  
13 and/or near fixation after correcting refractive error. Classification of strabismus was categorized  
14 depending on deviation from the primary position (esotropia or exotropia). An anterior segment  
15 examination was done using slit lamp biomicroscopy. A dilated posterior segment examination  
16 was conducted using indirect ophthalmoscopy with a 28-diopter lens. Retinopathy of prematurity  
17 was diagnosed retrospectively from the patients' chart.

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31 Data analyzed using IBM SPSS 21.0 (SPSS Inc., Chicago, USA). Continuous variables were  
32 expressed as the mean  $\pm$  standard deviation (SD) or as the median when appropriate. Categorical  
33 variables were expressed as proportions. The chi-square test was used to analyze the association  
34 between categorical variables. Associations between ocular morbidities and continuous and  
35 categorical variables were computed using Fisher's exact test and Pearson chi-square ( $\chi^2$ ) test,  
36 respectively. Continuous variables were compared using ANOVA. Values of  $p < 0.05$  were  
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## RESULTS

During the study period 222 infants (146 from Saint Paul Hospital and 76 from TASH) were included in this study.

### Characteristics of the study population

Slightly more females than males were screened (52.7% and 47.3%, respectively). The majority of the study participants (n=156, 70.3%) were less than 3 years of age and the mean age at presentation was  $2.62 \pm 0.49$  years (range 2.08- 6.38). One hundred and twenty-three of the 222 children (55.4%) had a GA  $\leq 34$  weeks and 43 (19.4%) had a BW  $\leq 1500$ g. Birthweight ranged from 953-3500g with a mean of 1941.72g (SD 445.49); GA ranged from 30-36 weeks, with a mean of 34.11 weeks (SD 1.47). One hundred and twenty-three children (55.4%) were delivered vaginally, and 80 (36.1%) had multiple gestations. Forty-eight children (21.7%) were born to mothers with pregnancy-induced hypertension, and eight (3.7%) mothers tested positive for HIV (Table 1).

The mean BWs of children from SPH and TASH NICUs were  $1888.5 \pm 403.6$  (953-3000) g and  $2043.94 \pm 503.74$  (1125-3500) g, respectively; mean GAs were  $34.14 \pm 1.49$  (30-36) weeks and  $34.08 \pm 1.44$  (30-36) weeks, respectively. Differences in these parameters were not statistically significant (Table 2).

**Table 1 Characteristics of premature children and mothers screened for ocular disorders**

Variable		Total		Female		
		N	N	%	N	%
Birthweight	≤ 1500g	43	20	46.5%	23	53.5%
	> 1500g	179	85	47.5%	94	52.5%
Gestational age	≤ 34 weeks	122	60	49.2%	62	50.8%
	> 34 weeks	100	45	45%	55	55%
Multiple gestation	Yes	80	42	52.5%	38	47.5%
	No	142	63	44.4%	79	55.6%
Oxygen supplementation	Yes	97	47	48.5%	50	51.5%
	No	125	58	46.4%	67	53.6%
Infantile morbidity	Sepsis	6	2	33.3%	4	66.7%
	IVH	2	0	0%	2	100%
	BPD and sepsis	1	1	100%	0	0%
	None	213	102	47.9%	111	52.1%
Mode of delivery	Vaginal delivery	123	53	43.1%	70	56.9%
	Cesarean section	99	52	52.5%	47	47.5%
Multiparity	Yes	47	18	38.3%	29	61.7%
	No	175	63	34.3%	59	65.7%
Maternal morbidity	PIH	44	22	50%	22	50%
	HIV	5	2	40%	3	60%
	HIV & PIH	3	3	100%	0	0%
	DM	2	0	0%	2	100%
	DM & PIH	1	0	0%	1	100%
	TORCH	1	1	100%	0	0%
	None	166	77	46.4%	89	53.6%
NICU location	SPH	146	65	44.5%	81	55.5%
	TASH	76	40	52.6%	36	47.4%

**Legend:** BPD- Bronchopulmonary Dysplasia; DM- Diabetes Mellitus; HIV-IVH-Intraventricular Hemorrhage; PIH- Pregnancy-Induced Hypertension; SPH- Saint Paul Hospital; TASH-Tikur Anbessa Specialized Hospital; TORCH- Toxoplasmosis, Rubella, Cytomegalovirus, Herpes simplex, and HIV

### Ocular morbidities and risk factors

Overall, 145 (65.3%) of the children had ocular disorders at the presentation, of which 92 (63.4%) had isolated ocular diseases (69 refractive error, 13 nasolacrimal duct obstruction, five strabismus, and five ROP). The mean age at presentation of children with ocular disorders was  $2.7 \pm 0.5$  (2.1- 6.4) years, and there were more females with a male to female ratio of 1:1.27. None of the eyes examined had anomalies of the anterior segment or lens.

The mean GA was  $34.14 \pm 1.49$  (30-36) weeks, and BW was  $1927.27 \pm 429.19$  (953-3100) g. Refractive errors were the leading type of ocular morbidity seen in 115/222 (51.8%), followed by NLDO (21.2%) (Table 2).

**Table 2. Types of ocular disorders among premature children screened**

Ocular disorders	n	%
Refractive error	115	51.8
Nasolacrimal duct obstruction	47	21.2
Strabismus	25	11.3
Retinopathy of prematurity	16	7.2
Others	5	2.3

**NB-** Some ocular disorders occurred more than once.

### Refractive error

One hundred and fifteen (51.8%) children had a refractive error, of which 55.5% (81/146) and 44.7% (34/76) of children enrolled from the SPH and TASH had refractive errors, respectively. The mean age at presentation was  $2.68 \pm 0.56$  (2.08-6.38) years, and the male-to-female ratio was 1:1.25. Thirty-nine (59%) of children aged > 3 years developed refractive error in comparison with 76 (48.1%) of those aged < 3 years.

The mean gestational age and birthweight of children with refractive errors was  $34.11 \pm 1.54$  (30-36) weeks and  $1892.34 \pm 414.55$  (1080-3100) g, respectively. Myopia was the commonest type of refractive error, accounting for 78/115 (60.8%) of cases, followed by astigmatism (30, 26.1%) and hyperopia (15, 13.1%). Gender, GA, BW, oxygen supplementation, children, and maternal morbidity were not statistically associated with refractive error. (Table 3)

### Strabismus

Twenty-five children (11.3%) had strabismus (5 isolated, 20 in combination with refractive error, nystagmus, ROP, and nasolacrimal duct obstruction). The age at presentation was  $2.73 \pm 0.52$  (2.1-3.6) years, and the male-to-female ratio was 1.08:1.

The mean GA and BW were  $34.0 \pm 1.41$  (30-36) weeks and  $1906.76 \pm 489.92$  (1140-3000) g, respectively. Thirteen children had esotropia, and the rest had exotropia. There was no statistically significant association between GA, BW, and strabismus (Table 3). In this study, the prevalence of strabismus among children aged  $\geq 3$  years was 16.7% compared to 8.9% in those < 3 years. However, older age was not statistically associated with strabismus.

### Retinopathy of prematurity

Previous history of ROP was noted in 16/222 (7.2%) of the children enrolled in this study. Most patients (12, 57%) with ROP were from SPH. Almost all of them (15/16) had a GA < 34 weeks, and the mean GA and BW of patients with ROP were 32.19±1.33 (30-35) weeks and 1596.25 ±483.64 (953-2600) g, respectively. Nine patients with ROP had an associated refractive error (6 myopia and 3 astigmatism). Only one patient had an associated intermittent exotropia.

In univariate analysis, ROP was statistically associated with low GA and low BW (Table 3).

Multivariable logistic regression analysis was not conducted due to the small number of children with ROP.

**Table 3. Ocular disorders by sex, gestational age, and birthweight among premature children screened for ocular disorders**

Type of Disorder	Variables		Yes	No	Odds Ratio	p-Value
			n	n		
Refractive error	Sex	Male	51	54	0.78(0.46-1.33)	0.361
		Female	64	53		
	BWt	≤1500 gm	22	21	1.03(0.53-2.01)	0.926
		>1500gm	93	86		
	GA	≤34 weeks	62	60	1.09(0.64-1.85)	0.746
> 34 weeks		53	47			
Strabismus	Sex	Male	12	93	1.03(0.4501.37)	0.940
		Female	13	104		
	BWt	≤1500 gm	7	36	0.57(0.22-1.48)	0.246
		>1500gm	18	161		
	GA	≤34 weeks	14	108	0.95 (0.41-2.2)	0.911
> 34 weeks		11	89			
ROP	Sex	Male	6	99	0.65(0.22-1.85)	0.415
		Female	10	107		
	BWt	≤1500 gm	7	36	0.27(0.09-0.78)	0.01
		>1500gm	9	170		
	GA	≤34 weeks	15	107	0.72 (0.09-0.56)	0.001
> 34 weeks		1	99			

**Legend:** BWt- Birth Weight ; GA-Gestational Age

### Visual impairment and ocular disorders

The mean VA of the right and left eyes was 0.22(SD 0.23) logMAR and 0.17 (SD 0.21) logMAR, respectively. The mean VA in the better and worse eyes was 0.17 (SD 0.22) logMAR and 0.28 (SD 0.21) logMAR, respectively. In this study, 101 (45.9%) and 181 (81.5%) of the children had subnormal visual acuity (>logMAR 0.1) in the better and worst eyes, respectively.

Nearly one-fourth (55, 24.8%) of children screened had visual impairment in the better eye. Of this group 51 (92.7%) had uncorrected refractive error alone (34/51) or with strabismus (10/51), ROP (6/51), or nystagmus (1/51). Eighty-nine (40.1%) patients had amblyopia, of which 59/89 (66.3%) had bilateral amblyopia from uncorrected refractive error. Isometric and anisometric amblyopia from uncorrected refractive error were the commonest causes of amblyopia, contributing to 49/89 (55%) and 20/89 (22.8%) of cases, respectively. Of the 16 cases with ROP, 12 (75%) had a visual impairment associated with other disorders like refractive error, strabismus, and nystagmus.

In univariate analysis, visual impairment in the better eye was statistically associated with ROP, uncorrected refractive error, and strabismus with p-values of 0.001, 0.001, and 0.004, respectively. Amblyopia was not statistically associated with low GA or low BW (Table 4).

**Table 4. The presence of visual impairment by types of ocular disorders among premature children screened for ocular disorders.**

Variables		Visual impairment in the better eye		Odds ratio 95% CI (Lower-Upper)	p-Value
		Yes	No		
<b>Sex</b>	Male	23	82	0.75(0.40-1.38)	0.348
	Female	32	85		
<b>BWt</b>	≤ 1500g	14	29	0.62(0.29-1.27)	0.188
	> 1500g	41	138		
<b>GA</b>	≤ 34 weeks	28	94	1.24(0.67-2.29)	0.294
	> 34 weeks	27	73		
<b>Refractive error</b>	Yes	48	67	10.24(4.37-23.97)	0.001
	No	7	100		
<b>Strabismus</b>	Yes	12	13	3.31 (1.41-7.77)	0.004
	No	43	154		

## DISCUSSION

The present prospective study examines the effects of prematurity on visual acuity and ocular disorder in children born preterm. In Sub-Saharan Africa, neonatal death has decreased by 40% since 1990 due to improved newborn care, likely leading to an increase in childhood ocular morbidity and blindness from diseases like ROP (32). Despite this positive progress, data on the extent of ocular diseases among the preterms in Sub-Saharan Africa are limited. Our study has demonstrated that the prevalence of ocular diseases and visual impairment in Ethiopian children born preterm is high. To our knowledge, this is the first study to assess the prevalence and causes of ocular disorders and visual impairment among children born preterm and admitted to NICUs.

In Ethiopia, intensive neonatal care has expanded in many public and private hospital NICUs since 2013 (33), and neonatal mortality per thousand live births has declined modestly from 39 in 2000 to 33 in 2019(34). A prospective screening survey among neonates admitted to two NICUs in Ethiopia showed that 32.2% of the screened infants had any stage ROP (35). However, there is no regular ROP screening program in the country. A comparison of studies of ocular morbidity and visual impairment among preterm children is difficult as there are methodological variations such as differing age groups, inclusion or exclusion of ROP, stages of ROP, and cohort size.

Even though genetic and visual experiences predominantly determine the prevalence of refractive error, studies have shown that low BW interrupts emmetropisation and increases the prevalence of refractive error (36). In our study, nearly half of the premature screened children (51.8%) had refractive error, which is comparable to a survey from Turkey (53.8%) (37) but higher than in Italy (42.3%) (38), and in cohorts of extremely preterm infants from Sweden (29.7%) (39) and Norway (10%) (40). In our study, the prevalence of myopia was 35.1%, which was higher than a cohort of preterm children at age 10–12 years from the UK (18.9%) (41), India (15.8%) (42), and Sweden (4.1%) (39). The prevalence of hyperopia in our study, 13.5%, is comparable with that reported in Turkey (14.3%) (37) and Sweden (17.1%) (39) but higher than the UK (6.6%) (41) and India (8.54%) (42). In the present study, 13.5% of the preterm children had clinically significant astigmatism, which was lower than that reported in Norway (21%) (40) and India (55.6%) (42) and higher than in Turkey (5.7%) (37) and Sweden (6.5%) (39). The higher proportion of myopia seen in our study, in comparison with studies from the UK (41),



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3 India (42) and Sweden (39), is supported by long-term studies which have confirmed the  
4 increased incidence of myopia following preterm birth (43).  
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7 Manifest strabismus was seen in 11.3% of our cohort, which is comparable to studies  
8 from Norway (10%) (40), the UK (13.6%) (15), Sweden (13.5%) (20), and Australia (14%) (45),  
9 and lower than reported in Sweden (17%) (36), the UK and Ireland (24%) (46) and Germany  
10 (26%) (47). It is unclear at what age the different types of strabismus develop (36), and the age at  
11 onset of strabismus in low birthweight children is variable, from the first few months of life to  
12 many years later (11, 15, 16,21,22, 44). In our study, a higher prevalence of strabismus in those  
13 aged > 3 years was noted. This finding (16.7%) is comparable with a similar age group from  
14 Sweden (20). Regarding the type of strabismus, we detected similar proportions for esotropia and  
15 exotropia. This is similar to the other studies from Germany (47) and England (41). However,  
16 other investigations confirmed that esotropia was the most frequent type of strabismus (20, 39,  
17 48) The increased prevalence of strabismus in the low birthweight population is well-  
18 documented (21, 36, and 44). Such an association was not apparent in our study, as most of the  
19 children were considerably higher in weight and older than in the studies mentioned above.  
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23 The prevalence of ROP in our study is 7.2%, lower than in other studies, from sub-  
24 Saharan African countries, including Ethiopia, which ranged from 15-41.7% (35, 49-51). The  
25 lower prevalence of ROP in our study can be explained by our data collection method, where we  
26 depend on the history of ROP either from the patient's parents or from old features of ROP.  
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30 In the present study, 46% of the children had subnormal visual acuity (>logMAR 0.1) in  
31 the better eye, which is comparable with a population-based study from Norway (45.9%) (40).  
32 The figure is higher than what has been reported for prematurely-born children with BWs 1500–  
33 2000 g (15 %) from Denmark (9) and from Sweden 32 % (20). Birch et al. reported significantly  
34 lower visual acuities in low birthweight infants compared to those born full term (52). In our  
35 study, there was no statistically significant correlation between BCVA and BW or GA, similar to  
36 a study from Turkey (37). However, Dowdeswell et al. (53) found low levels of distance visual  
37 acuity in preterm children compared with full-term children. However, in our study, ocular  
38 morbidities like strabismus, refractive error, and ROP were statistically associated with visual  
39 impairment.  
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54 In our study, the prevalence of amblyopia among premature children was 40.1%. The  
55 result in our study is much higher than other studies from Australia (7.3%) (45) and Turkey  
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3 (7.7%) (37). Previous studies have shown that prematurity and low birthweight are two risk  
4 factors for amblyopia (41, 54). Nevertheless, amblyopia was not statistically associated with low  
5 GA and BW. Even if we did not find a statistical association between GA and BW with  
6 amblyopia, the prevalence among premature children is higher than in other studies; this  
7 indicates that more importance should be given to screening amblyopia risk factors for premature  
8 infants.  
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14 The strengths of this study were the prospective controlled study design with a high  
15 number of participants, the multi-center design which increases the representativeness of our  
16 research, and the availability of medical information from all children and mothers, which  
17 allowed a very detailed examination and an adjustment for different possible confounding  
18 factors. The strict standardization reduced the probability of examiner-dependent variances.  
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Limitations of the study included the wide age range of the examined children, some of  
whom were at an early age and phase of refractive development, and other older children that  
can affect the physiologic refractive changes noted in normal health children. The other  
limitation is there is a chance that those infants with poor health outcomes did not take part in  
our study. In subsequent research, we will continue following up with these infants to determine  
future changes in their refractive error and strabismus.

## CONCLUSION

In conclusion, the rates of ocular disorders, visual impairment, and amblyopia in these NICUs in  
Ethiopia were higher than in other studies. Refractive error, strabismus, and ROP were all  
significant risk factors for visual impairment. These findings underline the importance of early  
screening of premature infants for vision and amblyopia. As the two NICUs included in the  
survey are Ethiopia's main neonatal referral centers, it can be postulated that ocular morbidities,  
visual impairment, and amblyopia are emerging as potentially avoidable causes of childhood  
blindness among preterm children in Ethiopia. Developing preterm ocular-related screening  
protocols within the NICUs, strengthening the referral links between the NICUs and eye centers,  
and further detailed comparative studies between preterm and term children for ocular disorders  
are recommended.

### **Lists of Abbreviations**

Bronchopulmonary dysplasia (BPD); Necrotizing enterocolitis (NEC); Neonatal Intensive Care Units (NICUs); Patent ductus arteriosus (PDA); Preterm birth (PTBs); Respiratory distress syndrome (RDS); Retinopathy of prematurity (ROP), Saint Paul Hospital (SPH) and Tikur Anbessa Specialized Hospitals (TASH).

### **Research Ethics Approval**

This study involves human participants, and this research was approved by the Addis Ababa University Ethics Review Committee (Ref No. 003/2016) in line with the relevant national and institutional guidelines on care and clinical research. All parents or legal guardians gave written informed consent before participating in the study.

### **Availability of Data and Materials**

All data generated or analysed during this study are included in this published article

### **Competing Interests**

The authors have no conflicts of interest.

### **Funding**

The SIP study was supported by the Bill & Melinda Gates Foundation (OPP1136965)

### **Authors' Contributions**

Drafting of the manuscript: STS., LM., AM., and AD. Revision of the manuscript for important intellectual content: STS., LM., AM., AD and AA. Conception and design of study: STS., LM., AM., and AD. Data acquisition, analysis, or interpretation of data: STS., LM., AM., AD., and AA. Approval of final manuscript to be published: STS., LM., AM., AD., and AA. All authors have read and approved the final version of the manuscript.

### **Acknowledgements**

The authors wish to acknowledge the assistance of the staff of the SIP project (Ahmed, Beleyu, Efrata, and Wagaye) for their support during data collection. Our special appreciation goes to Sr Martha H/Mariam and Sr. Medhanit Tesfaye from Menelik II pediatrics Ophthalmology clinic.

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3 **TABLE LEGEND**  
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5 **Table 1 Characteristics of premature children and mothers screened for ocular disorders**  
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7 **Table 2. Types of ocular disorders among premature children screened**  
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10 **Table 3. Ocular disorders by sex, gestational age, and birthweight among premature**  
11 **children screened for ocular disorders**  
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14 **Table 4. The presence of visual impairment by types of ocular disorders among premature**  
15 **children screened for ocular disorders.**  
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