Temporal trends in the epidemiology of childhood severe visual impairment and blindness in the U.K.

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SYNOPSIS

By comparing two national surveillance studies, we report broadly stable incidence with a concomitant decrease in associated mortality since the millennium. Childhood visual disability represents an increasingly complex population at risk, with persisting inequalities.

ABSTRACT

Background/Aims
Understanding temporal trends in childhood visual disability is necessary for planning and evaluating clinical services and health policies. We investigate the changing epidemiology of severe visual impairment (SVI) and blindness (BL) in children in the U.K in the 21st century.

Methods
Comparative analysis of two national population-based epidemiological studies of incident childhood SVI/BL (ICD-10 definition; visual acuity worse than 1.0 LogMAR in the better eye) we carry out comparative analysis of studies conducted in 2000 and 2015 using identical methods.

Results
Overall annual and cumulative incidence rates remained broadly stable in 2015 at 0.38 per 10,000 (95%CI: 0.34-0.41) for 0-15 year olds and 5.65 per 10,000 (5.16-6.18) by 16 years, respectively, and with annual incidence in infancy (3.52 per 10,000, 3.13-3.97) remaining considerably higher than any other age. Mortality amongst children diagnosed in infancy declined (from 61.4 to 25.6 per 1000), despite an increase (from 77% to 84%, p=0.037) in the overall proportion with significant non-ophthalmic impairments/disorders. The relative contribution of all the main groups of disorders increased over time, most notably cerebral visual impairment (from 50% to 61%). Aetiological factors operating prenatally continued to predominate, with an increased relative contribution of hereditary conditions in all children (from 35% to 57% p<0.001). The substantially elevated rates for any ethnic minority group and those born preterm were unchanged, with amplification of increased rates associated with low birth weight.

Conclusion
The changing landscape of healthcare and increased survival of affected children, is reflected in increasing clinical complexity and heterogeneity of all-cause SVI/BL alongside declining mortality.

Keywords: Incidence, childhood blindness, visual disability

Abbreviations: U.K: United Kingdom, SVI/BL: Severe visual impairment and blindness: BCVIS: British Childhood Visual Impairment and Blindness Study

INTRODUCTION

Impaired vision in childhood significantly impacts on development, educational experience and attainment, and all activities of everyday life,[1–3] setting affected individuals and their families on different trajectories to those with good vision in all domains and throughout their lives. The personal and societal burden of childhood visual impairment in terms of 'sighted years lost' and the associated opportunity and financial costs is disproportionately greater than adult onset impairment.[4]

Like many countries, the United Kingdom (UK) lacks a national intelligence system drawing detailed clinical data from multiple sources for epidemiological monitoring of childhood visual disability. Whilst a system for certification of those with sight impairment is long-standing, this is neither mandatory nor collects the detailed clinical data required for investigating temporal trends in incidence and aetiology. Thus, the U.K. lacks the capability to identify with agility emerging risk factors, rapidly evaluate the impact of primary, secondary or tertiary preventive strategies, and nimbly develop services and policies in response to temporal trends.

To address this data gap, two national studies of incident severe visual impairment and blindness in childhood were conducted in the UK in 2000 (British Childhood Visual Impairment and Blindness Study, BCVIS1[5] and in 2015 (BCVIS2).[6] Identical case definitions (using the WHO international taxonomy) of severe visual impairment (SVI) or blindness (BL) (ie visual acuity worse than 1.0 LogMAR (or 6/60 Snellen) in the better seeing eye),[7] case ascertainment and standardised data collection methods were used. We used these sources to investigate changes in the epidemiology of childhood SVI/BL in the UK during a 15 year period since 2000, i.e. the second new generation of children in the 21st Century.

METHODS

Both BCVIS1 and 2 ascertained all children/young people aged under 16 years newly diagnosed with severe visual impairment and blindness (SVI/BL) in a 12 month period in the U.K, respectively in 2000[5] and 2015.[6] The findings of BCVIS2; the incidence and short term outcomes of children up to 18 years of age with full-spectrum visual impairment (including moderate visual impairment (VI) in addition to SVI/BL), have been reported previously[6] and here we only use data from that study about participants with SVI/BL. Eligible children were identified simultaneously but independently by consultant ('attending') ophthalmologists and paediatricians through the British Ophthalmological (BOSU) and the British Paediatric Surveillance Units (BPSU) respectively, the long-established national active surveillance schemes for rare disease in ophthalmology and paediatrics/child health respectively as described elsewhere.[8,9] Both schemes utilise a monthly reporting system whereby clinicians notify researchers of newly diagnosed eligible cases and report data using standardised questionnaires. All independent (attending) ophthalmologists and paediatricians in the UK participate in the respective schemes. Ascertainment through both, simultaneously but independently, maximised unbiased ascertainment. The design, analysis and reporting of the studies is consistent with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline (https://www.strobe-statement.org). The studies were approved by independent research ethics committees or RECs (BCVIS2 study by the Bloomsbury REC and BCVIS1 study by the Great Ormond Street Hospital REC). The use of confidential patient data without consent was approved by the UK Health Research Authority Confidentiality Advisory Group (reference 14/CAG/1028).

Case definition and data collection

The 'case' definition comprised a new diagnosis of SVI/BL during the study periods, using the WHO classification of SVI/BL based on acuity or a qualitative equivalent for children whose age or developmental status prevented formal acuity testing.[7] Surveillance identified any child newly diagnosed with SVI/BL, irrespective of age. Detailed clinical and sociodemographic data were

collected using standardised collection instruments completed by the reporting clinician at diagnosis, and at one year follow up and included ethnicity and socio-economic deprivation using the standard approach of residential postcode or 'zipcode' derived Index of Multiple Deprivation[10]. This is a commonly used measure of material of relative deprivation in epidemiological research in the UK, which assesses 7 domains, including housing, income, education and health, and ranks geographically defined small neighbourhoods (average of 1,500 residents) nationally from most to least deprived.

Analysis

Using the vision of each reported child at 1 year follow, only those with confirmed *permanent* SVI/BL a year following initial notification were included in the analyses. Population denominators for children aged <16 years in the constituent four nations (England, Northern Ireland, Wales and Scotland) were sourced from the UK Office of National Statistics (ONS).[11] Age-group specific incidence rates for SVI/BL, relative rates and 95% confidence intervals were calculated. The infant mortality was calculated using the number of children diagnosed with SVI/BL under the age of one as the denominator. Disorders resulting in SVI/BL were categorised using the WHO international dual taxonomy, which groups disorders by 'anatomical' sites affected, and causal factors by the *timing* of action of the aetiological factor (i.e. prenatal, perinatal/neonatal, childhood or unknown).[7] More than one ophthalmic 'site' can be assigned to each child, as required. Some children in BCVIS1 have multiple aetiological factors (were counted more than once) so in order to allow statistical comparison to BCVIS2 we have restricted analyses to children with a single aetiology. Differences between BCVIS1 and BCVIS2 (two independent samples) in the relative contribution of different aetiological factors were calculated using the two-sample test of proportions. The two-sample test for proportions could not be used to assess changes in the contribution of ophthalmic disorders due to multiple counts, so only the difference in proportions is

presented. Incidence and relative rates were calculated using person-time analysis.[12] Statistical analyses were undertaken in STATA 15.[13]

RESULTS

Characteristics of the study populations

The study samples comprised 420 SVI/BL children (45.5% female, 71.1% white) in the BCVIS1 study (2000) and 466 SVI/BL children (44.3% female, 61.5% white) in BCVIS2 (2015). The proportion of children with significant non-ophthalmic disorder or impairment - SVI/BL 'plus' for brevity - was 78.1% in BCVIS1 and 83.8% in BCVIS2, (p=0.037, difference in proportions test).

Incidence of childhood severe visual impairment and blindness

As shown in Table 1, overall annual and cumulative incidence rates in 2015 were broadly unchanged from those in 2000. Annual incidence in infancy specifically was also unchanged (Relative rate (RR): 0.87, 95% CI: 0.74 – 1.03) and remained substantially higher than at any other age.
Incidence in 5-15 year olds has increased since 2000 (IRR: 1.63, 95% CI: 1.14- 2.36), however incidence in this group is still the lowest compared to any other group, as was the case in 2000.

In 2015, incidence remained considerably higher amongst children from any ethnic minority group, as shown in Table 2. The already higher relative rates for children of low birthweight (in a 'dose response gradient') doubled from 2000 to 2015, from a relative rate (RR) of 9.2 (95% CI 6.4 – 13.3) to RR 18.8 (95% CI 13.0 - 27.4) for those with birthweight <1500g compared to ≥2500g. Substantially higher rates for those born prematurely were observed in 2015: compared to those born at ≥37 weeks gestation, the relative rate for those born at 32-36 weeks gestation was 3.8 (95% CI 2.8-5.1) and 14.5 (95% CI 8.7-24.2) at <28 weeks gestation.

Children in the worst quintile for deprivation (IMD score) in the UK remained over-represented, comprising 34.7% of the cohort in 2015 and 40.9% in 2000 (p=0.062, 95% CI for difference: 0.32 to -12.7).

Table 1. Cumulative and annual age-specific incidence of SVI/BL in the UK in 2000 and 2015

	Age at SVI/BL diagnosis			
Annual age specific incidence per 10,000 (95% CI)	**<1 year**	**1-4 years**	**5-15 years**	**All (0-15 years)**
2000 (reference)	**4.04** (3.56-4.52)	**0.32** (0.28-0.38)	**0.06** (0.04-0.08)	**0·35 (0·31–0·38)**
2015	**3.52** (3.13-3.97)	**0.34** (0.29-0.41)	**0.10** (0.08-0.12)	**0.38 (0.34-0.41)**
Incidence rate ratio (IRR) or relative rate (95% CI)	**0.87** (0.74 – 1.03)	**1.09** (0.82 – 1.46)	**1.63** (1.14-2.36)	**1.09 (0.95-1.24)**
Cumulative incidence per 10,000 (95% confidence intervals)	**By 1 year**	**By 5 years**	**By 16 years**	
2000	**4.04** (3.56-4.52)	**5.30** (4.76-5.84)	**5.90** (5.33-6.47)	
2015	**3.52** (3.13-3.97)	**4.90** (4.43-5.41)	**5.65** (5.16-6.18)	

CI: confidence interval

Table 2. Annual incidence rates per 10,000 of SVI/BL (0-15 years old) by sex, ethnic group, birthweight, gestation and relative rates (95% confidence intervals)

	2000 (n=420)					**2015** (n=466)				
	SVI/BL cases	**IR**[a]	95%CI	**RR**[b]	95%CI	SVI/BL cases	**IR**[a]	95%CI	**RR**[b]	95%CI
Sex	n=419					n=465				
Female	190 (45%)	**0.3**	0.28–0.37	Reference		206 (44%)	**0.29**	0.25 – 0.33	Reference	
Male	229 (55%)	**0.4**	0.32–0.42	**0.9**	0.7 – 1.1	259 (56%)	**0.34**	0.31 – 0.39	**1.2**	1.0– 1.4
Ethnicity	n=386					n=408				
White	272 (70%)	**0.2**	0.21–0.26	Reference		251 (63%)	**0.2**	0.18 – 0.23	Reference	
South Asian[c]	69 (18%)	**1.2**	0.92–1.49	**5.1**	3.9 – 6.7	103 (25%)	**1.0**	0.85 – 1.3	**5.0**	4.0 – 6.2
Pakistani or Bangladeshi	48 (12%)	**1.6**	1.1–2.1	**6.7**	4.9 – 9.1	74 (18%)	**1.1**	0.91 – 1.4	**5.6**	4.3 – 7.2
Indian	13 (3%)	**0.5**	0.2–0.8	**2.1**	1.2 – 3.6	14 (3%)	**0.4**	0.24 – 0.68	**1.9**	1.1 – 3.3
Black	18 (5%)	**0.5**	0.3–0.8	**2.3**	1.4 – 3.7	20 (5%)	**0.3**	0.20 – 0.49	**1.5**	0.96 – 2.4
Other	27 (7%)	**0.7**	0.4–0.9	**2.9**	1.9 – 4.3	13 (3%)	**0.8**	0.44 – 1.3	**3.7**	2.1 – 6.4
Mixed	NA					21 (5%)	**0.3**	0.20 – 0.48	**1.5**	1.0 – 2.4
Gestational age						n=342				
≥ 37 weeks	NA			-	-	242 (71%)	**3.5**	3.1 – 4.0	Reference	

32-36 weeks	NA			-	-	64 (19%)	**13.3**	10.4 – 16.9	**3.8**	2.8 – 5.1
28-31 weeks	NA			-	-	19 (6%)	**32.1**	20.5 – 50.3	**9.1**	5.6 – 14.8
<28 weeks	NA			-	-	17 (5%)	**51.1**	31.7 – 82.1	**14.5**	8.7 – 24.2
Birthweight[d]	n=267					n=244				
Normal ≥2.5kg	191 (72%)	**4.3**	3.7 – 4.8	Reference		160 (66%)	**2.3**	2.0 – 2.7	Reference	
2.49-1.5kg	44 (16%)	**10.2**	7.0 – 13.3	**2.4**	1.7 – 3.3	50 (20%)	**11.2**	8.5 – 14.8	**4.8**	3.5 – 6.6
<1.5kg	32 (12%)	**39.4**	25.8 – 53.1	**9.2**	6.4 – 13.3	34 (14%)	**43.9**	31.2 – 61.7	**18.8**	13.0 – 27.4

[a] IR: Annual Incidence rate per 10,000

[b] RR: Relative rate

[c] includes children with 'South Asian - Other'

[d] excludes Northern Ireland as denominator not available

NA: data not available for BCVIS1

95%CI: 95% confidence intervals

Underlying ophthalmic conditions/disorders

The proportion of children with multiple ophthalmic conditions increased substantially over time from 23.6% to 57.3% in 2015 ($p<0.0001$, 95% CI for difference: 27.7 – 39.8%), as reflected in the increased proportions of almost all specific ophthalmic conditions or 'sites' (Table 3). An 11.2% increase in the overall proportion of children with disorders affecting the visual pathways and brain was seen between 2000 and 2015, largely driven by the increased overall proportion of children with structural brain abnormalities or with hypoxic ischaemic encephalopathy (Table 3). The proportion of congenital eye anomalies (affecting whole globe/anterior segment/cornea) also increased. Disorders of the retina, largely inherited retinal dystrophies and albinism, continued to account for around 30% of children, without a significant change in the proportion of children with retinopathy of prematurity (4.1% in 2015).

Table 3. Relative proportion of each disorder causing childhood SVI/BL (aged 0-15 years) in 2000 and 2015, by ophthalmic site affected

Ophthalmic site affected[a]	**BCVIS1** (n=420)	**BCVIS2** (n=466)	**Difference in proportion**
Visual pathways & Cortex[a]	**208 (49.5%)**	**283 (60.7%)**	**11.2%**
Neurodegenerative	9 (2.1%)	21 (4.5%)	
Hypoxia/Ischaemia	52 (12.4%)	83 (17.8%)	
Infection	11 (2.6%)	18 (3.9%)	
Non-accidental Injury	1 (0.2%)	9 (1.9%)	
Structural	32 (7.6%)	85 (18.2%)	
Tumour	11 (2.6%)	16 (3.4%)	
Metabolic	1 (0.2%)	15 (3.2%)	
Unknown disorder	90 (21.4%)	46 (9.9%)	
Glaucoma[a] **(primary or secondary)**	**12 (2.9%)**	**30 (6.4%)**	**3.6%**
WGAS[a]	**28 (6.7%)**	**65 (13.9%)**	**7.3%**
Microphthalmos/Anopthalmos	21 (5.0%)	31 (6.7%)	
Microphthalmos	19	27	
Anophthalmos	2	4	
Coloboma (multiple-site)	6 (1.4%)	8 (1.7%)	
Anterior Segment Dysgenesis	5 (1.2%)	19 (4.1%)	

Buphthalmos		4 (0.9%)	
Disorganised globe		7 (1.5%)	
Phthisis	1 (0.2%)	4 (0.9%)	
Cornea[a]	**7 (1.7%)**	**38 (8.2%)**	**6.5%**
Opacity	1 (0.2%)	25 (5.4%)	
Other	6 (1.4%)	13 (2.8%)	
Lens[a]	**13 (3.1%)**	**40 (8.6%)**	**5.5%**
Cataract/ aphakia (or other)[b]	13 (3.1%)	40(8.6%)	
Uvea[a]	**11 (2.6%)**	**20 (4.3%)**	**1.7%**
Aniridia	4 (1.0%)	10 (2.1%)	
Uveitis	5 (1.2%)	2 (0.4%)	
Coloboma single site	2 (0.5%)	5 (1.1%)	
Other		2 (0.4%)	
Retina[a]	**125 (29.8%)**	**133 (28.5%)**	**-1.2%**
Retinopathy of Prematurity	13 (3.1%)	19 (4.1%)	
Retinal dystrophies	55 (13.1%)	53 (11.4%)	
Oculocutaneous albinism	18 (4.3%)	18 (3.9%)	
Retinal detachment	3 (0.7%)	29 (6.2%)	
Retinoblastoma	2 (0.5%)	3 (0.6%)	
Retinitis	5 (1.2%)	2 (0.4%)	
Other	19 (4.5%)	9 (1.9%)	
Coloboma single site	3 (0.7%)	2 (0.4%)	
Foveal hypoplasia		4 (0.9%)	
Vitreoretinal dysplasia		3 (0.6%)	
Optic Nerve[a]	**117 (27.9%)**	**141 (30.3%)**	**2.4%**
Hypoplasia	52 (12.4%)	77 (16.5%)	
Isolated	39	53	
SOD	13	24	
Atrophy	58 (13.8%)	56 (12.0%)	
primary	9	12	
secondary	47	44	
Neuritis/neuropathy	3 (0.7%)	6 (1.3%)	
Other	5 (1.2%)	4 (0.9%)	
Other[a]	**8 (1.9%)**	**2 (0.4%)**	**-1.5%**
Idiopathic nystagmus	2 (0.5%)	1 (0.2%)	
High refractive error	6 (1.4%)		
Blepharophimosis		1 (0.2%)	

[a]Children with multiple sites are counted more than once so subtotals exceed 100%

[b]Other lens disorders including: lens subluxation

Aetiological factors

Factors originating or acting prenatally accounted for around two thirds of all cases across both cohorts. However the proportion attributed specifically to hereditary/genetic conditions increased from 35.3% to 56.7% (p<0.001), as shown in Table 4. The relative contribution of childhood (post-neonatal) factors declined from 16.4% to 9.7% (p=0.003), mainly due to a reduction in infectious disease from 2.8% to 0.4% (p=0.005). Vitamin A deficiency causing blindness was only reported in 2015. Non-accidental injury continued to account for 2% of all SVI/BL in children.

All-cause mortality in the year following diagnosis of SVI/BL

The overall proportion of children dying within a year of diagnosis of visual disability decreased from 10.5% (95% CI: 7.7%-13.8%) in BCVIS1 to 5.6% (95% CI: 3.7%- 8.1%) in BCVIS2 (p=0.007) (Figure 1). The mortality rate in infancy (deaths in first year of life among those diagnosed as SVI/BL by age 1 year) decreased from 61.4 per 1000 (95% CI: 36.1-96.4) to 25.6 per 1000 (95% CI: 10.4-52.1) in 2015 (p=0.040, 95% CI for difference -7.0--0.2).

Table 4. Aetiological factors (by timing of action leading to SVI/BL) in BCVIS2 compared to BCVIS1 (aged 0-15 years)

	BCVIS1[a] n=397	**BCVIS2** n=466	**Difference in proportions test** (95% CI)
PRENATAL	**242 (61.0%)**	**309 (66.3%)**	p=0.10
Hereditary	**140 (35.3%)**	**264 (56.7%)**	p<0.001 (15.6 –28.5)
Autosomal dominant	6	24	
Autosomal recessive	89	69	
X-linked	12	9	
Chromosomal	5	21	
Maternal (mitochondrial)		7	
Sporadic/Uncertain	28	134	
Hypoxia/Ischaemia	**5 (1.3%)**	**11 (2.4%)**	p=0.23
Infection	9 (2.3%)	13 (2.8%)	p=0.63
CMV	3	2	
Group B Strep		5	
Toxoplasmosis		2	
Rubella	1	2	
HIV		1	
Varicella	1		
Unspecified	4		
Prenatal maternal drug use	**3 (0.8%)**	**2 (0.4%)**	p=0.53
Other	**1 (0.3%)**	**2 (0.4%)**	p=0.66
Unknown[b]	**84 (21.2%)**	**35 (7.5%)**	p<0.001 (9.0 – 18.3)
PERINATAL / NEONATAL	56 (14.1%)	75 (16.1%)	p=0.42
Hypoxia-ischaemia	**41 (10.3%)**	**52 (11.2%)**	p=0.7
Infection	**6 (1.5%)**	**16 (3.4%)**	p=0.07
Group B Streptococcus	3	8	
Herpes Simplex	2	1	
Other	1	7	

Unspecified meningitis	1	4 (1%)	
Non-accidental injury (NAI)	**1 (0.3%)**	**1 (0.2%)**	p=0.90
Other	**2 (0.5%)**	**10 (2.1%)**	p=0.04 (0.1 – 3.1)
Unknown[b]	**6 (1.5%)**	**12 (2.6%)**	p=0.28
UNDETERMINED (Prenatal or Perinatal)	**34 (8.6%**	**37 (7.9%)**	p=0.28
Visual pathways & cortex - **Hypoxia-ischaemia**		9	
Visual pathways & cortex - **Structural**		11	
Visual pathways & cortex - **Metabolic**		3	
Visual pathways & cortex - **Tumour**		1	
Visual pathways & cortex - **Unknown**		6	
CHILDHOOD (POST NEONATAL)	65 (16.4%)	45 (9.7%)	p=0.003 (2.2 –11.2)
Tumour	**23 (5.8%)**	**15 (3.2%)**	p=0.06
Infection	**11 (2.8%)**	**2 (0.4%)**	p=0.005 (0.62 – 4.1)
E coli	1		
Tuberculosis	1		
Staphylococcus	1		
Meningococcus	1		
Group B streptococcus	1	1	
Viral	2	1	
Epstein Barr virus (encephalitis)		1	
Bronchiolitis	1		
Unspecified	3		
Hypoxia-Ischaemia	**7 (1.8%)**	**11 (2.4%)**	p=0.54
Non-accidental injury (NAI)	**9 (2.3%)**	**8 (1.7%)**	p=0.56
Accidental injury	**3 (0.8%)**	**4 (0.9%)**	p=0.89
Systemic disorder	**5 (1.3%)**	**4 (0.9%)**	p=0.56
Vitamin A deficiency		**1 (0.2%)**	p=0.36
Other/ Unknown childhood	**7 (1.8%)**	**6 (1.3%)**	p=0.57

[a] Only children with a single aetiological site – to allow for side by side comparison and test of proportions

[b] Unknown = timing of action assigned but aetiology unknown

DISCUSSION

We report on the changing epidemiology of childhood blindness in the UK during the first decades of the 21st Century. Whilst overall incidence is broadly unchanged and mortality has declined, both clinical heterogeneity (multiple ophthalmic conditions) and aetiological complexity (diversity of factors) have increased substantially. Furthermore, with 84% of children with SVI/BL in 2015 having significant additional non-ophthalmic conditions/impairments, multi-morbidity is the now firmly the norm. Childhood blindness continues to be determined overwhelmingly by aetiological factors at play in prenatal or perinatal/neonatal life. Significant variations persist in rates of all-cause blindness by ethnicity and socio-economic status.

Our study was necessary because the UK lacks a comprehensive 'live' register of childhood blindness from which both temporal trends in incidence and aetiology can be examined. Whilst certification of sight impairment exists and for adults serves as a means of referral to governmental financial support, social care and specialist education provision, it is not statutory, entails limited collection of data, employs criteria different to the WHO international taxonomy and is not always coincident with diagnosis, making the system unsuitable for detailed epidemiological research. Additionally as the resulting data are sensitive to procedural changes, [14] it is challenging to interpret certification rates as a reflection of incidence alone. Thus the main strengths of our study are the utilisation of two nationally representative studies of clinician-confirmed cohorts of children newly diagnosed with SVI/BL with identical methods of case ascertainment and structured detailed data collection. Since we investigated an *outcome* rather than individual disorders, we cannot, by design, undertake statistical analysis to quantify associations with specific aetiological factors. Relative rates by key characteristics are reported. Whilst capture- recapture analysis to determine completeness of ascertainment was not possible (due to co-dependence of reporting sources). There is thus a

small theoretical possibility of incomplete or biased ascertainment. This is very unlikely to be to a significant degree given the long history of successful epidemiological studies conducted through BOSU and BPSU and the active involvement of a large collaborative study group comprising reporting clinicians and assistance by the study team with data collection at sentinel hospitals.[6] As this study was carried out in the context of universal coverage of the UK National Health Service,[6] it is very unlikely that any eligible children were not diagnosed through these pathways.

The substantially greater proportion of children with multiple ophthalmic conditions ("ophthalmic multi-morbidity") in 2015 means temporal trends of relative contributions of individual disorders cannot be assessed statistically. This larger more complex sub-population of childhood SVI/BL, likely reflects a combination of changes in population at risk, in aetiological drivers, and in diagnostic and therapeutic interventions affecting child survival and/or visual outcomes. The greater relative contribution of diagnosed structural ocular anomalies may reflect improved diagnostic capability with innovations in ocular imaging. The smaller increases over time in the contributions of treatable conditions such as glaucoma and congenital cataract, reflects the co-occurrence of untreatable ophthalmic conditions. Although a comparison of two 'snapshot' studies only 15 years apart, our study also compares two 'generations' as a useful examination of key temporal changes in childhood blindness in an industrialised country setting in the early part of this century.

In the absence of any other national population-based studies of incident childhood blindness, direct comparison with existing literature is not possible. However, temporal trends reported from childhood blindness registers and health surveys[15][16] in other countries during the same time period align with our finding of unchanged incidence in the early 21st century, in contrast to a decline observed in the last decades of the 20th Century.[17] Trends in incidence of all-cause blindness reflect trends in disease risk (ie aetiological drivers of individual conditions) as well as risk of poor outcomes (ie progress in prevention and treatment of individual outcomes). Given this complexity, the persistence of strikingly increased rate for children from any ethnic minority

group and the overrepresentation of those from the most socio-economically deprived backgrounds are especially noteworthy. These inequalities remain unexplained, and echo inequalities in risk of vision impairment in adults in the UK[18]. Ethnicity and social position are linked in the UK, as in many multi-ethnic countries. However these are likely to be independent influences in all-cause childhood blindness, as social position at birth and during childhood are known to be independently associated with visual function[19]. Our findings of increased rates in *all* non-White ethic groups demonstrates that aetiological research on ethnicity and childhood blindness needs to have ambitions beyond the low hanging fruit of attributing increased risk purely to hereditary diseases resulting from consanguinity[20]. Further investigation is warranted of emerging evidence of socio-demographic patterning in access to and outcomes from ophthalmic and child healthcare against the backdrop of increasing childhood poverty,[21] which together with the COVID-19 pandemic is anticipated to lead widening of health and socio-demographic inequalities.[22] Systematic detailed monitoring of childhood blindness could provide a valuable 'pulse check' of the health of the public.

Our study demonstrates that clinical complexity and heterogeneity of childhood blindness can increase in a relatively short timespan. We suggest that childhood blindness in high income countries should now be conceptualised as multimorbidity in rare childhood disease. It is also an important exemplar of complex neuro-disability, underscoring the importance of fully implementing recommendations about multi-professional approaches and cross-sector care for children with significant vision impairment.[23] The substantial decline in mortality in this group is encouraging and broadly aligns with overall trends in national infant mortality rates attributed partly to continuing improvement in neonatal care for preterm babies resulting in increased survival beyond the first year of life.[24]

Our study quantifies a 'dose-response gradient' between all-cause blindness and gestation, embellishing understanding that recent improved survival and early outcomes overall for preterm children have also been accompanied by later adverse neurodevelopmental outcomes in some,[25] along with the recognition of adverse health outcomes associated with late or moderate preterm birth.[26] The doubling of the relative rates of blindness associated with low birth weight in our study is driven by a halving of rate amongst children of normal birth weight, and thus could be pointing to improved outcomes from some disorders that over time became more amenable to prevention or treatment. Consideration of visual function or vision impairment in longitudinal studies of children born preterm or with low birthweight is not yet the norm: our findings show the valuable insights this could afford as the number of these children increases globally. [27]

The increased relative contribution of cerebral visual impairment – the group of conditions affecting the brain and or visual pathways – from 50% to 61% in the UK aligns with recent[28]'[29] and prior trends reported from other high income countries[30][31], and the greater awareness of the heterogeneity of CVI and recent revised categorisation.[32] There is cause for optimism that neuroprotective interventions such as therapeutic hypothermia should improve vision outcomes in neonates and it is imperative this is assessed in research on established and emerging[33] therapies using the variety of techniques now available for assessing visual function in infants. Our findings also indicate that interventions against hypoxic brain injury outside infancy (13% of CVI in the 2015 cohort) will also be important. Tackling cerebral visual impairment is now the biggest challenge and the biggest opportunity for reducing the burden of childhood blindness in high income countries. The lessons learned will be increasingly important in the many low and middle income countries that are transitioning to the patterns of childhood blindness in high income countries as outcomes improve for children with fully preventable or treatable disorders.

Childhood blindness remains predominantly attributable to factors acting in the prenatal period. The increased contribution of hereditary or genetic conditions between 2000 and 2015 reflects progress in genomic technology and testing capability within the NHS as part of the UK's Rare Disease Strategy. This has already spurred impressive progress in novel therapies.[34]

The reduction in contribution of post-neonatal factors was driven largely by the decrease in infections. Blindness due to vitamin A deficiency in one child in 2015 is a salutary reminder that severe nutritional deficiencies can occur in children in high income countries even as effective public health strategies against this have been implemented in low and middle income countries. Non-accidental injury remained the underlying cause in 2% of children. These findings together serve simultaneously as a reminder of the successes of child public health, child protection and modern ophthalmic and paediatric clinical care in recent decades but also of the need to remain vigilant about its quality and coverage.

CONCLUSIONS

We report increasing complexity and heterogeneity of all-cause childhood blindness which mirrors broader changes in child health, child survival and ophthalmic management in the UK in the first part of the 21st Century. Incidence per se is unchanged, as are the striking variations by ethnicity and socio-economic position and the strong associations with prematurity and low birthweight. Our findings show that progress in prevention of childhood visual disability remains as much the domain of paediatrics and child health as of ophthalmology. This would be facilitated by adoption of childhood blindness as a sensitive and robust routinely measured indicator of the impact of global child health initiatives.[35]

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Competing Interests

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Data Availability Statement

Deidentified individual participant data will not be made available as ethics and governance approvals do not allow this.

Contributor statement

Prof. Rahi conceptualised the study and contributed to study design, data analysis, interpretation, drafting and revision.

Dr Solebo contributed to study design, data acquisition, data analysis, interpretation, drafting and revision.

Miss Teoh contributed to data acquisition, data analysis, interpretation, drafting and revision.

All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

REFERENCES

1 Tadić V, Hundt GL, Keeley S, *et al.* Seeing it my way: living with childhood onset visual disability. *Child Care Health Dev* 2015;**41**:239–48. doi:10.1111/cch.12158

2 Dale NJ, Tadić V, Sonksen P. Social communicative variation in 1-3-year-olds with severe visual impairment. *Child Care Health Dev* 2014;**40**:158–64. doi:10.1111/cch.12065

3 Bardin JA, Lewis S. A Survey of the academic engagement of students with visual impairments in general education classes. J. Vis. Impair. Blind. 2008;**102**:472–83. doi:10.1177/0145482x0810200804

4 Time to focus - The UK sight loss crisis and case for investment in research. 2019. https://www.fightforsight.org.uk/our-research/timetofocus/?utm_source=Fight+for+Sight&utm_campaign=bb818ef47a-EMAIL_CAMPAIGN_2019_10_04_10_04_COPY_01&utm_medium=email&utm_term=0_b7a82a2177-bb818ef47a-312866353

5 Rahi JS, Cable N. Severe visual impairment and blindness in children in the UK. *Lancet* 2003;**362**:1359–65. doi:10.1016/S0140-6736(03)14631-4

6 Teoh LJ, Solebo AL, Rahi JS, *et al.* Visual impairment, severe visual impairment, and blindness in children in Britain (BCVIS2): a national observational study. *Lancet Child Adolesc Heal* 2021;**5**:190–200. doi:10.1016/s2352-4642(20)30366-7

7 World Health Organisation (WHO). ICD-10 Version: 2016 - H54 Visual Impairment including blindness (binocular or monocular). https://icd.who.int/browse10/2016/en#/H54.0 (accessed 27 Apr 2020).

8 The Royal College of Ophthalmologists. The British Ophthalmological Surveillance Unit. https://www.rcophth.ac.uk/bosu-patient-participation/ (accessed 27 Apr 2020).

9 The Royal College of Paediatrics and Child Health. British Paediatric Surveillance Unit,. https://www.rcpch.ac.uk/work-we-do/bpsu (accessed 27 Apr 2020).

10 Ministry of Housing C& LG. English indices of deprivation 2019 - GOV.UK. https://www.gov.uk/government/statistics/english-indices-of-deprivation-2019 (accessed 27 Apr 2020).

11 United Kingdom population mid-year estimate - Office for National Statistics. https://www.ons.gov.uk/peoplepopulationandcommunity/populationandmigration/populationestimates/timeseries/ukpop/pop (accessed 27 Apr 2020).

12 Breslow NE, Day NE. Statistical methods in cancer research. Volume I - The analysis of case-control studies. *IARC Sci Publ* 1980;:5–338. doi:10.1016/0278-6915(83)90281-8

13 Stata Statistical Software: Release 17. College Station, TX: StataCorp LLC. https://www.stata.com/products/

14 Bunce C, Zekite A, Wormald R, *et al.* Is there evidence that the yearly numbers of children newly certified with sight impairment in England and Wales has increased between 1999/2000 and 2014/2015? A cross-sectional study. *BMJ Open* 2017;**7**. doi:10.1136/bmjopen-2017-016888

15 Mezer E, Chetrit A, Kalter-Leibovici O, *et al.* Trends in the incidence and causes of severe visual impairment and blindness in children from Israel. *J AAPOS* 2015;**19**:260-265.e1. doi:10.1016/j.jaapos.2015.04.002

16 McGuire DO, Tian LH, Yeargin-Allsopp M, *et al.* Prevalence of cerebral palsy, intellectual disability, hearing loss, and blindness, National Health Interview Survey, 2009–2016. *Disabil Health J* 2019;**12**:443–51. doi:10.1016/j.dhjo.2019.01.005

17 Bodeau-Livinec F, Surman G, Kaminski M, *et al.* Recent trends in visual impairment and blindness in the UK. *Arch Dis Child* 2007;**92**:1099–104.

18 Cumberland PM, Rahi JS. Visual function, social position, and health and life chances the UK Biobank study. *JAMA Ophthalmol* 2016;**134**:959–66. doi:10.1001/jamaophthalmol.2016.1778

19 Bountziouka V, Cumberland PM, Rahi JS. Trends in visual health inequalities in childhood

through associations of visual function with sex and social position across 3 UK birth cohorts. *JAMA Ophthalmol* 2017;**135**:954–61. doi:10.1001/jamaophthalmol.2017.2812

20 Sheridan E, Wright J, Small N, *et al.* Risk factors for congenital anomaly in a multiethnic birth cohort: An analysis of the Born in Bradford study. *Lancet* 2013;**382**:1350–9. doi:10.1016/S0140-6736(13)61132-0

21 Wickham S, Anwar E, Barr B, *et al.* Poverty and child health in the UK: Using evidence for action. Arch. Dis. Child. 2016;**101**:759–66. doi:10.1136/archdischild-2014-306746

22 Roberton T, Carter ED, Chou VB, *et al.* Early estimates of the indirect effects of the COVID-19 pandemic on maternal and child mortality in low-income and middle-income countries: a modelling study. *Lancet Glob Heal* 2020;**8**:e901–8. doi:10.1016/S2214-109X(20)30229-1

23 Oluonye N, Sargent J. Severe visual impairment: practical guidance for paediatricians. Paediatr. Child Heal. (United Kingdom). 2018;**28**:379–83. doi:10.1016/j.paed.2018.06.007

24 Santhakumaran S, Statnikov Y, Gray D, *et al.* Survival of very preterm infants admitted to neonatal care in England 2008-2014: time trends and regional variation. *Arch Dis Child Fetal Neonatal Ed* 2018;**103**:F208–15. doi:10.1136/archdischild-2017-312748

25 Cheong JLY, Anderson PJ, Burnett AC, *et al.* Changing neurodevelopment at 8 years in children born extremely preterm since the 1990s. Pediatrics. 2017;**139**. doi:10.1542/peds.2016-4086

26 Boyle EM, Poulsen G, Field DJ, *et al.* Effects of gestational age at birth on health outcomes at 3 and 5 years of age: Population based cohort study. *BMJ* 2012;**344**. doi:10.1136/bmj.e896

27 Blencowe H, Krasevec J, de Onis M, *et al.* National, regional, and worldwide estimates of low birthweight in 2015, with trends from 2000: a systematic analysis. *Lancet Glob Heal* 2019;**7**:e849–60. doi:10.1016/S2214-109X(18)30565-5

28 de Verdier K, Ulla E, Löfgren S, *et al.* Children with blindness – major causes, developmental outcomes and implications for habilitation and educational support: a two-decade, Swedish

population-based study. *Acta Ophthalmol* 2018;**96**:295–300. doi:10.1111/aos.13631

29 Chong CF, McGhee CNJ, Dai SH. Causes of childhood low vision and blindness in New Zealand. *Clin Exp Ophthalmol* 2019;**47**:165–70. doi:10.1111/ceo.13443

30 Hatton DD, Ivy SE, Boyer C. Severe visual impairments in infants and toddlers in the United States. *J Vis Impair Blind* 2013;**107**:325–36. doi:10.1177/0145482x1310700502

31 Kong L, Fry M, Al-Samarraie M, *et al.* An update on progress and the changing epidemiology of causes of childhood blindness worldwide. *J AAPOS* 2012;**16**:501–7. doi:10.1016/j.jaapos.2012.09.004

32 Sakki H, Bowman R, Sargent J, *et al.* Visual function subtyping in children with early-onset cerebral visual impairment. *Dev Med Child Neurol* 2020;:dmcn.14710. doi:10.1111/dmcn.14710

33 Juul SE, Comstock BA, Wadhawan R, *et al.* A randomized trial of erythropoietin for neuroprotection in preterm infants. *N Engl J Med* 2020;**382**:233–43. doi:10.1056/NEJMoa1907423

34 Voretigene neparvovec for treating inherited retinal dystrophies caused by RPE65 gene mutations. NICE Guid. https://www.nice.org.uk/guidance/hst11 (accessed 27 Apr 2020).

35 Clark H, Coll-Seck AM, Banerjee A, *et al.* A future for the world's children? A WHO–UNICEF–Lancet Commission. Lancet. 2020;**395**:605–58. doi:10.1016/S0140-6736(19)32540-1