Title page

Title: Epidemiology of visual impairment, sight-threatening or treatment-requiring diabetic eye disease in children and young people in the UK: findings from DECS.

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Precis

The burden of childhood diabetic eye disease in the United Kingdom is too low to be the sole justification for routine universal retinal examination as a secondary preventive strategy against visual impairment.

Abstract

Background: We investigated the incidence and causes of sight-threatening diabetes-related eye disease in children living with diabetes in the UK, to inform the national eye screening programme and enable monitoring of trends.

Methods: Prospective active national surveillance via the British Ophthalmic Surveillance Unit (BOSU). Eligible cases were children aged 18 years or younger, with Type 1 or 2 diabetes, newly diagnosed between January 2015 and February 2017 with sight-threatening diabetic eye disease.

Results: Eight children were reported. The annual incidence of all sight-threatening diabetes-related eye disease requiring referral to an ophthalmologist amongst children living with diabetes (n=8) in the UK was 1.21 per 10,000 persons-per-year (95%CI, 0.52-2.39), and was largely attributable to cataract (n=5) 0.76 per 10,000 persons-per-year (95%CI, 0.25-1.77). The incidence of sight-threatening diabetic retinopathy (n=3) among those eligible for screening (12 to 18 year olds living with diabetes) was 1.18 per 10,000 persons-per-year (95%CI, 0.24-3.46). No subjects eligible for certification as visually impaired/blindness were reported.

Conclusions: Secondary prevention of visual disability due to retinopathy is currently the sole purpose of national eye screening programmes globally. However the rarity of treatment-requiring retinopathy in children/young people living with diabetes, alongside growing concerns about sub-optimal screening uptake, merit new consideration of the utility of screening for primary prevention of diabetes-related morbidity by using the screening event and findings as a catalyst for better diabetes self-management.

(224/250 words)

Introduction

The growing population of children and young people developing and living with diabetes is a global health challenge.[1] The rate of new diagnosis of type 1 diabetes is currently about 24.5/100,000 children aged 0-14 in the UK.[2] European incidence rates of type 1 diabetes were predicted to double between 2005-2020. Whilst currently a minority of children living with diabetes in the UK have type 2 diabetes,[2] this is becoming more common, particularly in Black and Asian ethnic groups.[2] Diabetic (glycaemic) control is suboptimal in a large proportion of children living with diabetes, with more than 15% of children and young people with type 1 diabetes being in the highest risk group for complications (HbA1c >9.5%).[2] Children and young people with type 1 or 2 diabetes from deprived areas or from non-white ethnicity had poorer HbA1c level than their counterparts did.[2] Thus, there is a serious prospect of large and increasing numbers of children affected by sight-threatening diabetes-related eye disease in the UK and other similar populations. Despite this, there is limited contemporary epidemiological data on childhood diabetes-related eye disease.[3]

In common with other countries, the aim of the UK's National Diabetic Eye Screening Programme (NDESP) is secondary prevention of visual disability due to diabetes by detection of sight-threatening diabetic retinopathy sufficiently early to allow prompt referral to an ophthalmologist for further assessment and treatment to avoid permanent visual loss.[4] Diabetic cataract is not a target disorder of NDESP. UK national guidelines recommend that retinopathy screening of children/young people living with type 1 or 2 diabetes should start at 12 years of age regardless of duration or type duration of diabetes,[5] concording broadly with national policies in other similar settings.[6,7] The NDESP is currently delivered through more than 60 stand-alone local programmes which were established with adults, whose diabetes is primarily managed in primary care.[8]

Despite being the key metric for evaluating any retinopathy screening programme and for planning ophthalmic services for children/young people with diabetes-related eye disease, the incidence and causes of sight-threatening or treatment requiring diabetes-related eye disease and of visual impairment/blindness due to diabetes amongst children/young people living with diabetes are currently unknown. We report the first such national incidence study.

Materials and methods

The UK National Health Service (NHS) is unique in many respects and particularly by providing universal healthcare which is free at the point of use and accessible to all patients regardless of age, socio-economic status, ethnicity or any other personal characteristic. In keeping with best practice in research on rare disorders/health events,[9,10] we used whole population, active surveillance to identify eligible subjects. Specifically, cases were identified by all senior (consultant or associate specialist i.e. independent) ophthalmologists working in the NHS across the four UK nations (England, Scotland, Wales, and Northern Ireland) who each month reported eligible cases or confirmed they had no cases to report through the British Ophthalmic Surveillance Unit (BOSU).[11] This is the UK's long-established national public health ophthalmic active surveillance scheme for rare eye conditions, paralleling systems in other specialties in the UK and internationally.

Ophthalmologists reported each month all individuals aged 18 years or younger with type 1 or 2 diabetes presenting to them and *newly diagnosed* with:

a) visually significant diabetic retinopathy (M1, R2, or any grade thought sufficient to require referral to hospital eye services for further assessment) or

b) diabetes-related cataract, or

c) visual impairment, severe impairment or blindness (WHO criteria, acuity worse than LogMAR 0.5 in better eye)[12] due to diabetic eye disease or

d) eligible for formal certification as visually impaired or blind in the UK(acuity worse than LogMAR 1.0).[13]

This case definition ensured that all subjects with a diagnosis of sight-threatening or treatment-requiring diabetic eye disease were captured i.e. those with *moderate or severe non-proliferative diabetic retinopathy who require referral to hospital eye services for further assessment, proliferative diabetic retinopathy and diabetic maculopathy, with treatment requiring cataract, or with incident permanent visual impairment due to diabetes.* Alternatively, respondents made a 'null' (no cases to report) return. Ophthalmologists undertook full expert standardised assessment including fundus examination after cycloplegia. Cataract due to any other cause was excluded based on history and clinical examination. Patients who were referred to the hospital eye service with a presumptive diagnosis of sight-threatening eye disease (i.e. a positive screening result), which was not confirmed by the ophthalmologist at HES, were considered ineligible for inclusion as they were not newly diagnosed with a sight-threatening diabetic eye disease.

Population surveillance was undertaken for 24 months to February 2017. Detailed clinical data (based on the expert clinical ophthalmic examination) were reported by ophthalmologists at notification and one year later using standardised pre-piloted forms developed for the study. The follow up data collection enabled progression and/or treatment of disease and final visual outcome to be ascertained. Returned proformas were scrutinised for inconsistencies or missing data and these were resolved through further correspondence with the reporting ophthalmologist. Potential duplicate reports were assessed using unique identifiers. As there is no UK register of children and young people living with diabetes, the population denominators for incidence rates were derived by synthesizing available prevalence data for the four UK nations corresponding to the first year of surveillance (i.e.

2015), giving a total population at risk of 33,000 children/young people under 18 years living with either type 1 or 2 diabetes in the UK.[14,15]

Asymptomatic but nevertheless sight-threatening retinopathy may go undetected in those under 12 years of age as they are not screened. Thus, the incidence of sight-threatening diabetic retinopathy may be underestimated if the whole population at risk is used as denominator. Therefore, we additionally estimated overall incidence of sight-threatening retinopathy and any ethnic variations using as the denominator the population eligible for retinopathy screening during the surveillance period ie children/young people aged 12 to 18 years reported by the National Paediatric Diabetes Audit (NPDA).[15] The NPDA 2015/2016 reported 66% of children living with type 1 diabetes eligible for screening actually underwent screening[15] we also estimated incidence using a denominator downward adjusted by 0.66. 95% Poisson confidence intervals (CIs) were calculated for all incidence estimates. Analysis was undertaken using R language and environment for statistical computing, version 3.5.1.

The study was approved by the NHS Research Ethics Committee London – Bloomsbury (Ref 14/LO/1810) and UK National Health Service Health Research Authority (Ref 95030) which also granted exemption from obtaining individual consent under Section 251 of NHS Act 2006. It conforms to the Declaration of Helsinki.

Results

Eight subjects living with diabetes newly diagnosed with any sight-threatening diabetes-related eye disease in the UK were reported in the 24-month study period. Although we had no way of formally evaluating completeness of ascertainment using capture-recapture analysis, it is notable that all cases reported via BOSU were eligible for inclusion.

No children/young people were reported with permanent visual impairment/severe visual impairment or blindness or eligible for formal certification in the UK as visually impaired or

blind.[13] All had type 1 diabetes, with duration shown in Table 1. The five subjects (4 females) with acute treatment-requiring bilateral cataract were White and of pubertal age. Visual symptoms due to cataract preceded the diagnosis of diabetes in three subjects (all girls) and all had HbA1c >14% at diagnosis. All three subjects with sight-threatening retinopathy lived in England (versus Scotland, Wales or Northern Ireland) and two were from minority ethnic groups. None required ophthalmic treatment for retinopathy during the surveillance period but all were permanently retained within ophthalmology services for close follow-up.

The annual incidence of **any** sight-threatening diabetes-related eye disease (n=8) in children/young people living with diabetes in the UK was 1.21 per 10,000 persons-per-year (95%CI, 0.52 to 2.39). This was largely accounted for by the UK incidence of treatment-requiring cataract of 0.76 per 10,000 persons-per-year, 95%CI, 0.25 to 1.77). The incidence of sight-threatening diabetic retinopathy among all children and young people living with diabetes aged 18 years or under in UK was 0.45 per 10,000 persons-per-year (95%CI, 0.09 to 1.33).

Specifically the incidence of sight-threatening diabetic retinopathy in children aged 12 to 18 years (i.e. eligible for screening) and living with type 1 diabetes in England (n=12,659) was 1.18 per 10,000 persons-per-year (95%CI, 0.24 to 3.46). This rate was higher in those from ethic minority groups (5.85; 95%CI, 0.71 to 21.13 per 10,000 persons-per year) than amongst the majority White group (0.46; 95%CI, 0.01 to 2.54 per 10,000 persons-per-year). After adjusting the denominator by attendance to eye screening, (0.66- NPDA), the incidence was 1.80 per 10,000 persons-per-year (95%CI, 0.37 to 5.25). As NPDA did not report attendance to screening by ethnicity, such adjusted analysis by ethnicity was precluded. As all subjects had type 1 diabetes, no calculation of incidence rates for those living with type 2 diabetes was possible.

Discussion

From a national whole population surveillance study, we report the incidence of *any* ophthalmologist confirmed sight-threatening or treatment-requiring diabetic eye disease in children/young people living with diabetes aged ≤ 18 years in the UK to be very low. Notably, treatment requiring cataract was more common than diabetic retinopathy. There were no individuals who were eligible for formal certification as being permanently visually impaired or blind according to WHO criteria.

Our approach to identifying eligible cases from the population at risk is known to be the optimal method for national studies of rare disease.[9,10] Case ascertainment via BOSU, a unique and well-established ophthalmic public health active surveillance scheme comprising all consultant ophthalmologists in the UK, has ensured unbiased high ascertainment in prior studies of eye disease in children.[16] Our study was well publicised and strongly supported by a collaborative research network (the Diabetic Eye Disease in Childhood Study Group comprising >150 clinicians managing children with diabetes in the UK)[17], predisposing to high ascertainment. Incident visual impairment and treatment-requiring cataract are symptomatic. Sight-threatening diabetic retinopathy is the de facto key clinical outcome in the NDESP in the UK. It is extremely unlikely, therefore, that any eligible cases would *not* have been referred to reporting ophthalmologists. However we are unable to formally estimate ascertainment using capture-recapture analysis,[18] in the absence of any alternative independent data source. We deliberately employed an inclusive reporting case definition so as to ensure we captured significant i.e. ophthalmology referral-warranted retinopathy and cataract. We have no evidence of lower ascertainment of cases not requiring treatment versus those requiring treatment but this is a theoretical possibility. Surveillance duration of 12 months is conventional in BOSU studies but we undertook surveillance for 24 months. Our study resources did not permit a longer period but in any case, given the rarity of the incident

events, an extremely long study would be required to achieve a larger study sample. Thus although we believe our study sample is unbiased, its size precluded some investigations of interest *a priori* – for example by type of diabetes and level of glycaemic control – and limited analysis by age and ethnicity. As there is currently no live register of people living with diabetes in the UK, which could provide precise denominators, we had to estimate the population denominators for our analysis from available sources of prevalence data in which data quality and granularity vary by nation within the UK. However, the impact of inaccuracies is highly unlikely to be significant, given the small numerators. Whilst we consider ascertainment of eligible cases to be high for the reasons of universal health care provision and a reporting base comprising all ophthalmologists in the UK, it is important to reflect on the fact that no children/young people with type 2 diabetes were identified in our study. This may due to chance alone, differences in natural history of eye disease between type 1 and type 2 diabetes and/or differences in screening attendance patterns. In particular onset of type 2 diabetes in childhood generally occurs later then type 1 diabetes,[19] and cataract occurs as a result of the pathophysiological changes of acute hyperglycaemia which is more typical of type 1 diabetes.[20] In the UK, type 2 diabetes is more common in children/young people of minority ethnic groups and those living in more deprived areas.[2,21] In the USA, these same groups have lower attendance at eye screening.[22] Furthermore, amongst young adults with childhood-onset diabetes in the USA, retinopathy is more frequent in type 2 than type 1 diabetes.[19] It may be that similar variations in both retinopathy prevalence by type of diabetes and screening attendance by socio-demographic factors may exist in the UK. There is no way of 'ruling out' the possibility of a very small number of incident cases of sight-threatening diabetic retinopathy in children/young people with either type 1 or 2 diabetes during the period of our surveillance who did not come to the attention of ophthalmologists because they did not attend screening during the surveillance period.

Ascertainment of treatment requiring diabetic eye disease is likely to be high, as discussed below. Thus, we believe that through a single study, we have been able to provide a novel and reliable estimate of the burden of the sight-threatening and/or treatment requiring diabetes-related eye disease in children/young people living with diabetes under 18 years. This is important to planning services for children and young people living with diabetes.

Unfortunately, there are no *directly* comparable national studies of incident diabetes-related eye disease in children/young people against which we can assess our findings. Indeed sight-threatening eye disease has often been overlooked in research on childhood diabetes.[23] In the absence of a live register of children/young people living with diabetes in the UK from which outcomes could be routinely reported, it was necessary to undertake this study to investigate the contemporary epidemiology of sight-threatening and treatment-requiring diabetes-related eye disease. The National Diabetic Eye Screening Programme (NDESP) has until recently collected aggregated data from standalone local DESPs without specification by age and despite the recent move to reporting by broad age-group, the number of children/young people with an ophthalmologist-confirmed sight-threatening eye disease cannot be estimated from this source. Thus, the estimate of annual incidence of 4.7 per 1000/per year of 'referable' retinopathy in children and young people reported using screening data recorded between 2003 and 2012 from the Scottish, Welsh and Northern Irish programmes and a subset (approximately 5%) of screening programmes in the England, might overestimate the current national incidence of confirmed cases of sight-threatening eye disease.[24]

The UK's Paediatric National Diabetes Audit (NPDA) and National Diabetes Audit (for adults) do not include data from either local DESPs or from hospital ophthalmic services.

We found a greater number of children/young people affected by treatment-requiring cataract than sight-threatening diabetic retinopathy, mirroring findings in hospital-based/clinical

studies.[3] Screening for diabetes-related cataract is not warranted because of its symptomatic nature and the absence of any 'prophylactic' intervention. Our findings highlight the need for paediatricians and family doctors to be mindful of cataract in their patients with diabetes if acute onset visual disturbance occurs.[20] There may be merit in adding sudden visual disturbance to the characteristics of type 1 diabetes in children cited in the UK's National Institute of Health and Care (NICE),[25] or similar guidelines on diagnosis.

The very low incidence of sight-threatening retinopathy in childhood type 1 diabetes in our study concords with recent reports from other similar healthcare settings.[3,26] It is possible this rare outcome reflects recent advances in diabetes management, including continuous glucose monitoring and use of insulin pumps.[27] However, >70% of UK children living with diabetes are currently not achieving the International Society for Pediatric and Adolescent Diabetes (ISPAD) optimal control target (HbA1c<7.5%).[2] Thus low incidence may better reflect underlying natural history i.e. short duration of exposure to hyperglycaemia due to shorter duration of disease, rather than optimal glycaemic control. The fact that all subjects with referral-warranted retinopathy in our study were 14 years or older and none required ophthalmic treatment at the time of referral is notable, given the current UK recommendation that eye screening should start the age of 12 years.

We have previously reported vulnerabilities in ascertainment of eligible children/young people in the UK's National Diabetic Eye Screening Programme[17,28] which is delivered through more than 60 standalone programmes designed for, and managing predominantly, adults with type 2 diabetes. Screening outcome is communicated directly (in adult-orientated letters) to the child/young person and family. It is currently estimated that between a quarter and a third of eligible children/young people aged 12 to 18 years with type 1 diabetes in the UK do not attend an annual DR screening and attendance by those with type 2 is even lower.[2,15] Although there are no directly comparable reports from other settings, a recent

study of youths in one in a large managed care network in the USA reported that 65% of those with type 1 diabetes and 42% of those with type 2 diabetes had undergone an eye examination within 6 years of initial diagnosis.[22] The reasons are not known but can be anticipated to be complex, and in part to relate to changes in health-related behaviours in adolescence and transition to adult-centred care.[29,30] So whilst our finding of a low incidence of might be reassuring to patients and clinicians, it does serve to question whether the *sole* purpose of retinopathy screening of children and young people should continue to be *secondary prevention* of visual impairment, as currently recommended.[5] We hypothesise that an explicit discussion between the child/young person and their main managing clinician (in the UK usually a paediatrician) about their annual retinopathy screening result would afford the important opportunity to use a 'negative' result as reinforcement of good health behaviours as well as to reiterate the value of attending subsequent screening. In this context, our finding of a possible difference in incidence of sight-threatening diabetic retinopathy by ethnicity is of interest as it mirrors ethnic variation in retinopathy risk in adults.[31] Retinopathy screening attendance by adults in the UK varies by socio-demographic factors,[32,33] and this may also hold true for children but is currently unknown. Thus, there may be some particular groups who need additional support to maintain optimal glycaemic control which is the main protective factor against proliferative diabetic retinopathy.[34,35] We suggest that research is now warranted to investigate the potential *additional* value of retinopathy screening as *primary prevention* of sight-threatening sequelae of diabetes through facilitating optimal self-management and the changes to service configuration that would be required to deliver this.

The absence of any reports of incident visual impairment or blindness due to diabetes in our study concords with contemporary registry data on certifiable sight impairment in England and Wales.[36] However, there is no room for complacency. Given the growing population at risk and evidence of sub-optimal retinopathy screening attendance, further research is needed:

this includes evaluation of the utility of routinely collected health service data in understanding the evolving burden and natural history of diabetic eye disease in children/young people living with diabetes alongside the barriers and enablers to retinopathy screening they experience and the wider role of screening in their holistic care.

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Contributorship Statement

JSR is the guarantor, and agrees to be accountable for all aspects of the work. All authors contributed equally to study conceptualisation and design. MCIB and ALS collected the data. MCIB, ALS and JSR analysed the data. MCIB and ALS wrote the article. PMC and JSR critically revised and provided feedback on the manuscript. All authors and approved the final version of the manuscript.

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Table 1. Characteristics of children with sight-threatening or treatment-requiring diabetes-related eye disease reported through BOSU.

Diagnosis	Sex, age group* (years) & ethnicity	Context of presentation/ detection	Duration of type 1 diabetes	HbA1c (date)	Other systemic features	Ophthalmic management
Bilateral cataracts	Female, 11-13, White	Impaired vision (symptomatic)	Visual symptoms start 4 days before diabetes diagnosis.	14.9% (at diabetes diagnosis)	No	Cataract surgery
Bilateral cataracts	Male, 14-18, White	Impaired vision (symptomatic)	3 months	7.0% (3 months after referral)	Renal impairment, hypertension	Cataract surgery
Bilateral cataracts	Female, 11-13, White	Impaired vision (symptomatic)	Visual symptoms start 6 days before diabetes diagnosis.	17.1% (at diabetes diagnosis)	Psoriasis	Cataract surgery
Bilateral cataracts	Female, 11-13, White	Impaired vision (symptomatic)	15 months	7.0% (5 months after referral)	No	Cataract surgery
Bilateral cataracts	Female, 11-13, White	Impaired vision (symptomatic)	Visual symptoms start 15 days before diabetes diagnosis.	18.9% (at diabetes diagnosis)	Underweight (BMI 13)	Cataract surgery
Unilateral maculopathy	Male, 14-18, Mixed	DR screening (asymptomatic)	Unknown	Unknown	No	Follow-up in Hospital Eye Services
Severe NPDR	Female, 14-18, White	DR screening (asymptomatic)	16 years	11.8% (3 months after referral)	No	Follow-up in Hospital Eye Services
Severe NPDR	Male, 14-18, Asian	DR screening (asymptomatic)	Unknown	Unknown	No	Follow-up in Hospital Eye Services

NPDR: Non-Proliferative Diabetic Retinopathy; DR: Diabetic Retinopathy.

*Age groups versus exact age to avoid risk of identification with small sample.