ARTICLE

Prevalence of and Early-Life Influences on Childhood Strabismus

Findings From the Millennium Cohort Study

Sophia Pathai, MRCOphth, MSc; Phillippa M. Cumberland, BA, MSc; Jugnoo S. Rahi, PhD, FRCOphth

Background: Strabismus is a common disorder of largely unknown cause reported to occur more frequently in children with neurodevelopmental conditions and in children born prematurely or of low birth weight. Population-based investigation of other potential early-life influences has been limited.

Objective: To investigate the prevalence of and the early-life risk factors associated with childhood strabismus.

Design: Cross-sectional analytical study of a nationally representative sample of children participating in the Millennium Cohort Study.

Setting: United Kingdom.

Participants: A population-based sample of 14 980 children aged 3 years.

Main Outcome Measures: Parental report of "isolated" strabismus and "neurodevelopmental" strabismus (ie, in the context of neurologic disorders), considered separately.

Results: Three hundred forty-three children had strabismus (of whom 20 [5.8%] had neurodevelopmental/neurologic disorders), giving a total weighted prevalence of 2.1% (95% confidence interval, 1.8%-2.4%). In multivariable analysis, the risk of isolated strabismus was reduced in children of nonwhite maternal ethnicity and was increased in those born after an assisted or cesarean delivery and in those who were of low birth weight and preterm (in particular, late preterm). An increased risk of neurodevelopmental strabismus was independently associated with maternal smoking into later pregnancy, maternal illnesses in pregnancy, and decreasing birth weight for gestational age and sex. Socioeconomic status was associated with isolated (inverse relationship) and neurodevelopmental (U-shaped relationship) strabismus.

Conclusions: Several early-life social and biological factors are associated with strabismus, with differences in patterns between isolated and neurodevelopmental forms. Further collaborative research could explore this hypothesis to identify modifiable risk factors.

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STRABISMUS IS A COMMON DISorder in children that is associated with amblyopia and refractive error.[1-4] Compared with the general population, it has been reported to occur with increased frequency in children with neurodevelopmental conditions and in those born prematurely or of low birth weight.[5-7]

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The prevalence of childhood strabismus has been reported to be 1.5% to 5.3% in the United Kingdom (UK).[2,8] Evidence is conflicting regarding whether the incidence of infantile esotropia (the common form of early-onset convergent strabismus) is decreasing,[9,10] but if it is, this would suggest secular trends in (unknown) environmental risk factors, that is, nongenetic biological, social, and lifestyle influences. There has been limited population-based etiologic research on strabismus and limited attention given to distinguishing "isolated" forms from "neurodevelopmental" forms (ie, strabismus in the context of neurodevelopmental or neurologic disorders). Despite the increased frequency of strabismus in children born prematurely or of low birth weight, investigation of other possible relevant early-life influences, which might help identify mechanisms or modifiable risk factors or understand trends in frequency, has been limited. We report the findings of an investigation of the prevalence of and early-life risk factors associated with strabismus in the Millennium Cohort, a contemporary national cohort of children born in the UK.

Author Affiliations: Medical Research Council Centre of Epidemiology for Child Health, Institute of Child Health (Mss Pathai and Cumberland and Dr Rahi), and Institute of Ophthalmology (Dr Rahi), University College London, London, England.

METHODS

STUDY POPULATION

The Millennium Cohort Study (MCS) is a prospective cohort study set up to investigate the social, family, and health-related circumstances of children born at the start of the new century.[11] Families were invited to participate in the first survey (MCS1) if they were eligible for the universal state child benefit and resided in the UK when their child was aged 9 months. A total of 18 818 children, 72% of those invited, were recruited starting in September 2000 in England and Wales and in December 2000 in Scotland and Northern Ireland. A disproportionately stratified cluster sampling design was used to overrepresent children living in the 3 smallest countries of the UK (Scotland, Northern Ireland, and Wales), those at high or low levels of child poverty (based on the Child Poverty Index), and those from ethnic minority wards (>30% of residents from an ethnic minority group, ethnicity based on 1991 UK census categorization).[12] Approximately 80% of the eligible households that participated in MCS1 also took part in the second survey (MCS2), undertaken when the children were aged 3 years (**Figure**).[13] Data collection was completed in 2005 and became available for analysis in 2006. The attrition was greater between the MCS1 and MCS2 surveys in Northern Ireland, in disadvantaged areas, and in ethnic minority wards in England.[12,14] The present study drew on 14 980 children (from 14 766 households) who participated in both MCS1 and MCS2 and for whom ophthalmic data (described in the "Data on Strabismus and Eye Conditions" subsection) were available.

DATA COLLECTION

Information on birth and pregnancy was collected in MCS1 when the children were aged 9 months. For MCS2, data were obtained in the home; interviews with primary caretakers and their partners were conducted by trained fieldworkers. Information was collected on socioeconomic status (SES), household composition, and the health and development of the child.

DATA ON STRABISMUS AND EYE CONDITIONS

The scope and design of the MCS1 and MCS2 surveys precluded a formal ophthalmic clinical examination of the children. Thus, specific questionnaire items were used (following appropriate procedures for development, field testing, and refinement), to elicit information about vision and ophthalmic problems. Open- and closed-ended questions were used to elicit the diagnosis of strabismus and other eye conditions (http://www.cls.ioe.ac.uk/studies.asp?section=0001000200010015). Responses on all eye conditions (specified or open ended) were categorized using a coding system that incorporated a taxonomy applied previously in research on childhood blindness[15,16] in the UK and based on a World Health Organization classification for developing countries.

All parental responses on eye conditions using common synonyms for strabismus, for example, "turn," "eyes crossing," "glide," "overaction," "squint," "eye wanders," "one eye looks/turns inward/outward," "cast," and "cross-eyed," were considered positive spontaneous parental responses for strabismus. Each report of strabismus was categorized as "validated" if at least 1 of the following items of corroborating information was present: (1) report of any treatment for strabismus, for example, operation, occlusion, or glasses; (2) additional parental report of other relevant eye disorders, for example, hypermetropia or amblyopia; (3) report of eyesight and vision problems at MCS1 and strabismus at MCS2; and (4) concurrent but independent report of a long-standing eye condition or any other relevant condition, for example, cerebral palsy with developmental delay. All strabismus reports were categorized as either "isolated" or "neurodevelopmental" strabismus. Those labeled neurodevelopmental were strabismus reports in children with a coexistent history of systemic neurodevelopmental conditions, such as cerebral palsy and Down syndrome.

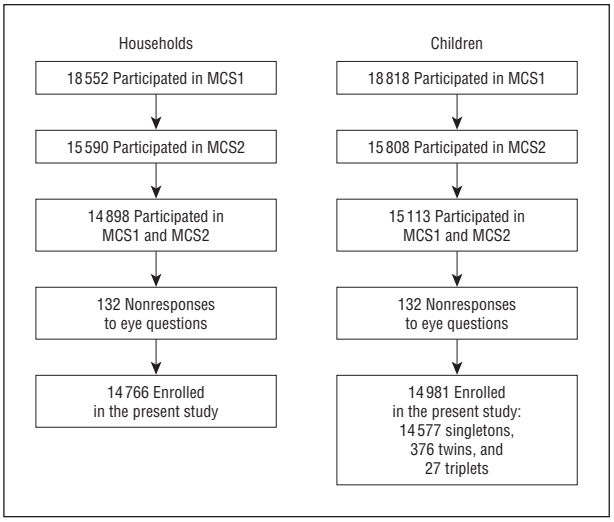

Figure. Millennium Cohort Study (MCS) structure and participant flow.

Parents also reported any long-term condition diagnosed by a health care professional that their child had had for at least 3 months and that was expected to continue for at least the next 3 months. Long-standing illnesses were categorized using the *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision (ICD-10),* taxonomy.[17] Reports on developmental status were elicited using 3 indicators (ability to walk on level ground and on steps and ability to be understood in his or her own language).

EARLY-LIFE FACTORS

A priori, we were interested in factors known to influence general health and growth in childhood and in those previously postulated to be associated with strabismus. Socioeconomic factors comprised highest occupational class of the household, housing tenure, and income of the highest earner in the household. Maternal factors (at the birth of the cohort member) comprised maternal age, ethnic group, maternal place of birth, educational level, smoking (number of cigarettes and duration) and alcohol consumption during pregnancy, and history and type of problems in pregnancy. Perinatal and early postnatal factors comprised complications during labor, type of delivery, admission to a special care baby unit, and illnesses at birth or during the first week of life. Specific child factors comprised birth weight (<2.5 kg indicated low birth weight; 2.5-4.2 kg, normal birth weight; or >4.2 kg, high birth weight), gestational age (term was >37 weeks; late preterm, 34 to ≤37 weeks; and preterm, <34 weeks),[18] and birth weight for gestational age and sex (tertiles of standardized *z* scores). A further composite variable combining birth weight and gestational age in 4 mutually exclusive categories was created to allow a more detailed multivariable analysis of prenatal growth in relation to maturity: 2.5 kg or more and 37 weeks or longer, less than 2.5 kg and 37 weeks or longer, 2.5 kg or more and shorter than 37 weeks, and less than 2.5 kg and shorter than 37 weeks.

STATISTICAL ANALYSIS

Appropriate sampling and nonresponse weights were applied to obtain unbiased estimates of effect, with robust standard errors. Thus, unless indicated, weighted percentages are reported for estimates of proportion of the population, for example, the prevalence. Because of a small amount of missing data, denominators vary and are reported individually.

Univariable multinomial regression was used to investigate whether "validated" parental reports of strabismus and reports on those without corroborating evidence ("unvalidated") differed compared with those without strabismus for any of the early-life factors of interest. We analyzed separately children with isolated and neurodevelopmental strabismus, comparing each group with those without strabismus. To investigate associations of early-life factors with strabismus, we first undertook univariable multinomial regression analyses and estimated risk ratios. We then undertook multivariable analysis, using backward stepwise regression, in which early-life factors were included if in the univariable analysis they had altered the risk ratio estimate by more than 10% or if they were independently associated at a 5% significance level. The most clinically relevant or statistically significant factors of any highly correlated factors identified from the univariable analysis were included in multivariate models (eg, the combined birth weight and gestational age variable rather than birth weight, gestational age, and admission to a special care baby unit). All regression analyses were adjusted to account for multiple-birth children.

The MCS data were obtained from the UK Data Archive, University of Essex (Essex, England), and all analyses were performed using "svy" commands in Stata version 10.0IC (StataCorp LP, College Station, Texas). The MCS1 and MCS2 were approved by the South West and London Multi-Centre Research Ethics Committees, respectively, with individual informed consent to participation.

RESULTS

A total of 14 980 children were included in the study, 99.1% of the 15 113 children in both MCS1 and MCS2 whose caretakers responded to the question on eyesight and vision (Figure). Of these children, 7372 (49.4%) were girls.

Of 343 strabismus reports (prevalence, 2.1%; 95% confidence interval, 1.8%-2.4%), 323 were isolated strabismus and 20 were neurodevelopmental strabismus. Of these, 52.3% (181 of 343) of the isolated and all of the neurodevelopmental strabismus reports could be validated. No significant differences were noted between associations with early-life factors of interest by validation status compared with those without strabismus (data not shown). Thus, the analysis was undertaken, and the results are presented for validated and nonvalidated reports combined.

Four hundred three of the children in the MCS (2.8%) were born from a multiple birth (188 twin pairs and 9 sets of triplets). Fourteen of these children, 13 (3.3%) of whom were from twin pairs, had isolated strabismus (prevalence, 2.4%; 95% confidence interval, 0.4%-4.4% in multiple births), and 1 twin had neurodevelopmental strabismus. Of 26 children with reported cerebral palsy, 4 (15.4%) had strabismus, as did 3 of 10 children with Down syndrome (30.0%) and 5 of 55 with reported mental and behavioral disorders (9.1%). The remaining cases of strabismus in the context of a neurodevelopmental condition were reported to have disparate nervous system disorders (*ICD-10* chapter VI) or congenital malformations and chromosomal abnormalities (*ICD-10* chapter XVII) (eTable; http://www.archpediatrics.com). Fifty-six children (16.3%) with isolated strabismus had other systemic comorbidities, for example, 21 (37.5%) had respiratory disorders, 7 (12.6%) had digestive system disorders, and 6 (13.7%) had skin disorders. The developmental status of children with isolated strabismus was comparable with that of those without strabismus, whereas children with neurodevelopmental strabismus had impaired developmental indicators.

ISOLATED STRABISMUS

Many of the early-life factors of previous interest were significantly associated with isolated strabismus in univariate analysis (**Table 1**). Children with mothers from a nonwhite ethnic group and those with mothers not born in the UK were less likely to have isolated strabismus, whereas decreasing SES, heavy maternal smoking, and high maternal alcohol consumption in pregnancy were associated with increased risk. Maternal illnesses during pregnancy, intrapartum complications, assisted or cesarean delivery, admission to a special care baby unit, and neonatal illness during the first week of life were all associated with increased risk. Finally, low birth weight and decreasing gestational age (preterm, <34 weeks, and late preterm, 34 to <37 weeks) increased the risk of isolated strabismus.

However, in the multivariable analysis, nonwhite maternal ethnicity was associated with reduced risk of isolated strabismus, whereas decreasing family SES, being born by assisted delivery, and being of low birth weight and preterm (but with a trend suggestive of prematurity having a greater influence than birth weight per se) were all associated with an increased risk of isolated strabismus (Table 1).

NEURODEVELOPMENTAL STRABISMUS

Despite few children in this group, several early-life factors were associated with neurodevelopmental strabismus in univariate analysis (**Table 2**.) There was a U-shaped relationship with household SES, whereas maternal smoking beyond the first trimester, maternal illness during pregnancy, low birth weight, decreasing gestational age and decreasing birth weight for gestational age and sex, and perinatal and neonatal illnesses were all associated with an increased risk of neurodevelopmental strabismus.

In multivariable analysis, extremes of household SES, maternal smoking in pregnancy beyond the first trimester, maternal illnesses during pregnancy (in particular diabetes mellitus), and decreasing birth weight for gestational age and sex (intrauterine growth retardation) were all independently associated with an increased likelihood of neurodevelopmental strabismus (Table 2).

Table 1. Associations of Isolated Strabismus With Social, Maternal (Perinatal and Postnatal), and Child Factors

Factor	Total, No. (%) (N=14 960)	Strabismus, No. (n=323)	Risk Ratio (95% CI)	
			Univariable Analyses[a]	Multivariable Model[b]
Social				
Household socioeconomic status				
Professional/managerial	5462 (39)	86	0.7 (0.5-1.0)	0.7 (0.5-1.0)
Intermediate-technical	3943 (27)	87	1 [Reference]	1 [Reference]
Semiroutine/never worked/long-term unemployed	5555 (34)	150	1.2 (0.8-1.7)	1.3 (0.9-1.8)
Tenure				
Own house/have mortgage	9831 (66)	168	1 [Reference]	NA
Rent accommodation/other	5128 (34)	155	1.6 (1.2-2.1)	NA
Maternal				
Age, y				
<21	1621 (12)	42	1.1 (0.7-1.6)	NA
21-34	10 790 (72)	232	1 [Reference]	NA
≥35	2510 (16)	49	0.9 (0.7-1.3)	NA
Ethnic group				
White	12 746 (89)	295	1 [Reference]	1 [Reference]
South Asian	1316 (6)	15	0.6 (0.3-1.1)	0.5 (0.3-1.0)
Black, African, or Caribbean	434 (2.5)	3	0.2 (0.1-0.6)	0.2 (0.1-0.6)
Other	402 (2.5)	8	0.6 (0.3-1.2)	0.6 (0.3-1.1)
Main respondent born in the UK				
Yes	13 034 (89)	302	1 [Reference]	NA
No	1925 (11)	21	0.5 (0.3-0.8)	NA
Smoking in pregnancy				
Never smoked	9977 (66)	195	1 [Reference]	NA
Former smoker	1734 (12)	30	0.9 (0.5-1.4)	NA
Gave up in first trimester	1955 (13)	51	1.3 (0.9-1.9)	NA
≤10 cigarettes per day after first trimester	569 (4)	20	1.4 (0.8-2.4)	NA
>10 cigarettes per day after first trimester	722 (5)	27	2.0 (1.2-3.2)	NA
Alcohol consumption in pregnancy				
Nondrinker	12 563 (82)	271	1 [Reference]	NA
Up to 4 U/wk	2027 (15)	36	0.9 (0.6-1.3)	NA
>4 U/wk	370 (3)	16	1.9 (1.0-3.3)	NA
Main type of problem/illness during pregnancy				
None	9227 (60)	173	1 [Reference]	NA
Bleeding	1284 (9)	32	1.3 (0.9-2.1)	NA
Persistent vomiting	657 (4)	19	1.9 (1.2-3.2)	NA
Raised blood pressure	833 (6)	27	1.5 (0.9-2.5)	NA
Diabetes mellitus	161 (1)	5	2.1 (0.8-5.7)	NA
Other: baby related	1161 (8)	26	1.0 (0.6-1.6)	NA
Other: maternal related	1635 (11)	41	1.6 (1.1-2.3)	NA
Main complications during labor				
No complications	10 111 (67)	202	1 [Reference]	NA
Abnormal lie/duration	2165 (15)	55	1.5 (1.1-2.1)	NA
Fetal distress	1645 (12)	36	1.2 (0.8-1.8)	NA
Other	1008 (7)	30	1.6 (1.0-2.5)	NA
Delivery type				
Normal	10 086 (68)	190	1 [Reference]	1 [Reference]
Assisted	1510 (10)	44	1.7 (1.1-2.4)	1.7 (1.2-2.5)
Cesarean	3336 (22)	89	1.5 (1.1-2.1)	1.4 (1.0-2.0)
Child				
Birth weight, kg				
>4.2	865 (6)	12	0.6 (0.3-1.2)	NA
2.5-4.2	12 928 (87)	269	1 [Reference]	NA
<2.5	1127 (7)	40	2.2 (1.5-3.1)	NA
Gestational age, wk				
>37	13 652 (91)	270	1 [Reference]	NA
34 to ≤37	941 (6.5)	37	2.2 (1.5-3.3)	NA
<34	367 (2.5)	16	3.0 (1.7-5.4)	NA
Birth weight for gestational age and sex, *z* score tertiles				
High	4998 (34)	103	0.9 (0.7-1.3)	NA
Mid	4955 (34)	112	1 [Reference]	NA
Low	4970 (33)	108	1.0 (0.8-1.3)	NA
Birth weight, kg, and gestational age, wk				
≥2.5 and ≥37	13 195 (88)	262	1 [Reference]	1 [Reference]
<2.5 and ≥37	418 (3)	7	1.2 (0.5-2.6)	1.2 (0.5-2.8)
≥2.5 and <37	598 (4)	19	1.8 (1.0-3.0)	1.7 (1.0-2.9)
<2.5 and <37	709 (5)	33	3.1 (2.0-4.7)	2.8 (1.9-4.3)
Admission to a special care baby unit				
No	13 557 (91)	273	1 [Reference]	NA
Yes	1401 (9)	49	2.0 (1.4-2.9)	NA
Problems at birth/first week				
None	11 189 (74)	200	1 [Reference]	NA
Breathing difficulty	1121 (8)	42	2.6 (1.8-3.6)	NA
Jaundice/infection	1269 (9)	44	1.9 (1.3-2.8)	NA
Other	1352 (9)	37	1.6 (1.0-2.5)	NA

Abbreviations: CI, confidence interval; NA, not applicable; UK, United Kingdom.

[a] In univariable analyses, missing data were as follows: maternal factors—age (n=39), ethnicity (n=62), country of origin (n=1), and tenure (n=1); pregnancy/labor factors—maternal smoking (n=3), type of illness (n=2), type of delivery (n=28), complications in labor (n=31), and admission to a special care baby unit (n=2); and postnatal factors—birth weight (n=40), problems in the first week (n=29).

[b] All the estimates were adjusted for the other factors in the multivariable model and for the inclusion of multiple-birth children (n=14 865; 319 with strabismus).

Table 2. Associations of Strabismus (Associated With Neurodevelopmental Conditions) With Social, Maternal (Perinatal and Postnatal), and Child Factors

Factor	Total, No. % (N=14 657)	Strabismus, No. (n=20)	Risk Ratio (95% CI)	
			Univariable Analyses[a]	Multivariable Model[b]
Social				
Household socioeconomic status				
Professional/managerial	5382 (39)	6	6.4 (1.6-25.0)	6.8 (1.7-28.0)
Intermediate-technical	3859 (26)	3	1 [Reference]	1 [Reference]
Semiroutine/never worked/ long-term unemployed	5416 (35)	11	7.6 (2.0-29.0)	6.8 (1.2-27.0)
Maternal				
Age, y				
<21	1581 (11)	2	0.8 (0.1-4.4)	NA
21-34	10 571 (72)	13	1 [Reference]	NA
≥35	2466 (17)	5	1.9 (0.6-6.2)	NA
Ethnic group				
White	12 468 (89)	17	1 [Reference]	NA
Nonwhite	2129 (11)	3	1.6 (0.4-6.5)	NA
Smoking in pregnancy				
Never smoked	9794 (66)	12	1 [Reference]	1 [Reference]
Former smoker	1706 (12)	2	0.2 (0.1-0.9)	0.2 (0.05-0.8)
Gave up in first trimester	1906 (13)	2	0.4 (0.1-1.6)	0.3 (0.07-1.3)
≤10 cigarettes per day after first trimester	551 (4)	2	3.1 (0.7-1.4)	2.8 (0.6-13.0)
>10 cigarettes per day after first trimester	697 (5)	2	2.1 (0.5-9.6)	1.7 (0.3-8.0)
Main type of problem/illness during pregnancy				
None	9061 (61)	7	1 [Reference]	1 [Reference]
Bleeding	1254 (9)	2	2.9 (0.6-15.0)	3.1 (0.6-16.0)
Persistent vomiting	639 (4)	1	0.6 (0.1-4.1)	0.6 (0.09-4.3)
Raised blood pressure	808 (6)	2	4.3 (0.6-30.0)	4.8 (0.7-33.0)
Diabetes mellitus	157 (1)	1	16.3 (2-136.0)	24 (2.8-202.0)
Other: baby related	1136 (8)	1	0.4 (0.1-3.3)	0.5 (0.06-3.6)
Other: maternal related	1600 (11)	6	5.4 (1.6-19.0)	5.5 (1.6-19.0)
Main complications during labor				
No complications	9921 (67)	12	1 [Reference]	NA
Abnormal lie/duration	2114 (15)	4	1.8 (0.5-6.2)	NA
Fetal distress	1612 (12)	3	0.7 (0.2-3.3)	NA
Other	979 (7)	1	0.2 (0.03-1.6)	NA
Child				
Birth weight, kg				
>2.5	13 526 (93)	14	1 [Reference]	NA
<2.5	1094 (7)	6	5.3 (1.9-15)	NA
Gestational age, wk				
>37	13 396 (91)	14	1 [Reference]	NA
34 to ≤37	906 (6.5)	2	2.9 (0.8-11.0)	NA
<34	355 (2.5)	4	8.1 (1.8-36.0)	NA
Birth weight for gestational age and sex, *z* score tertiles				
High	4898 (34)	3	0.6 (0.1-3.3)	0.6 (0.1-2.8)
Mid	4849 (34)	6	1 [Reference]	1 [Reference]
Low	4873 (32)	11	3.0 (1.0-9.2)	3.2 (1.0-9.8)
Admission to a special care baby unit				
No	13 299 (91)	15	1 [Reference]	NA
Yes	1357 (9)	5	1.8 (0.5-6.5)	NA
Problems at birth/first week				
None	10 998 (75)	9	1 [Reference]	NA
Breathing difficulty	1086 (8)	7	4.7 (1.4-16.0)	NA
Jaundice/infection	1228 (8)	3	1.9 (0.4-9.5)	NA
Other	1316 (9)	1	0.8 (0.1-6.0)	NA

Abbreviations: CI, confidence interval; NA, not applicable.
[a] In univariable analyses, missing data were as follows: maternal factors—age (n=39) and ethnicity (n=60); maternal smoking (n=3), type of illness (n=2), complications in labor (n=31) and admission to a special care baby unit (n=1); and postnatal factors—birth weight (n=37), problems in the first week (n=29).
[b] All the estimates were adjusted for other factors in the multivariable model and for the inclusion of multiple-birth children (n=14 594; 20 with strabismus).

COMMENT

These findings suggest that presently approximately 2 of every 100 children are affected by strabismus by age 3 years. More than 90% of these children have isolated strabismus rather than strabismus in the context of neurodevelopmental conditions. Early-life biological factors are associated, in differing patterns, with both forms of stra-

bismus. The observed associations of strabismus with maternal ethnicity and smoking and ill health during pregnancy, family SES, and prenatal growth in relation to maturity (birth weight for gestational age) highlight the scope and value of research efforts directed at understanding the prenatal and perinatal influences on strabismus.

This study has strengths in relation to the investigation of early-life influences on strabismus. These derive from the large size of the population-based sample on which it is based, with oversampling of ethnic minority groups and socially disadvantaged groups allowing investigation of these factors, combined with the collection of detailed and diverse data on key prenatal and perinatal factors soon after birth and independent of diagnosis of strabismus, minimizing recall and ascertainment biases. Despite the overall size and design of the cohort, the few children with strabismus in the context of a neurodevelopmental condition limits the power to detect small effects. Even so, different patterns of associations were observed for strabismus with and without a neurodevelopmental condition. Attrition between the MCS1 and MCS2 surveys may have led to an underestimation of the prevalence and strength of association of factors associated with strabismus, although weighted analysis was used.

The study context, within a broader study of health and disease, precluded a formal ophthalmic examination to confirm and refine the parental reports of strabismus used to define affected children, mirroring previous studies of strabismus embedded in population-based cohorts.[19] Although only just more than half of the reports could be formally validated by reference to other information (eg, on treatment) collected in the 2 surveys, no differences were noted between the validated and unvalidated reports for early-life factors of interest, which suggests that inclusion of unvalidated cases did not introduce significant bias into the study. Moreover, the resulting prevalence of strabismus reports is directly comparable with that found in other recent studies[2,3,8] in the UK based on clinical examination. This supports the view that it is likely that the unvalidated reports were real cases of strabismus. Previous investigations of the reliability of parental report in the MCS[11,14] lend support to the assumption that the validated cases of strabismus in the present study are real. It is, however, possible that some children with strabismus may not have been identified, for example, those with microstrabismus, which is not discernible without formal examination. In the absence of a clinical examination, we were unable to distinguish between different forms (which would be of interest), but the literature[20,21] on natural history suggests that most children with isolated strabismus by age 3 years in this study are likely to have had early-onset esotropia.

We recognize that we report a "minimum" estimate of prevalence of strabismus by age 3 years. This estimate is within the overall range (1.5%-5.3%) recently reported in the UK for the same age group.[2,3,8] Thus, we believe that this supports the notion that opportunities exist for population-based research on strabismus and possibly other pediatric eye disease in broader studies of health and disease that preclude formal ophthalmic examination by using parental report of ocular disease to identify potential cases that can be investigated in detail in further studies. This strategy for identifying subjects for further study is most likely to be appropriate when the condition is common.

We found a strong independent association between any nonwhite maternal ethnicity and a reduced likelihood of isolated strabismus; children born to African and Caribbean mothers were only one-fifth as likely to be affected as were children with white mothers, echoing previous reports of variation in the prevalence of strabismus (in particular early-onset esotropia) by country.[1] The nature and causes of this "protective" effect are unknown. It may be partly attributable to lower associated risk of related ocular conditions, in particular hypermetropia (farsightedness), which has been reported in the UK to be less likely in ethnic minority groups.[8] However, it is plausible that there are sociocultural and behavioral differences before and during pregnancy that affect as-yet undefined prenatal biological pathways that lead to isolated strabismus.

We found that SES was independently associated with isolated and neurodevelopmental strabismus in differing patterns. This serves to emphasize the importance of distinguishing between isolated and neurodevelopmental strabismus in etiologic research. The complex relationship between neurodevelopmental strabismus and extremes of SES, rather than a simple inverse relationship with isolated strabismus, as reported by others,[8,22] reiterates the importance of sociocultural, behavioral, and lifestyle influences before and during pregnancy. This identifies an important arena for future research, for example, the role of hormonal responses to socioeconomic circumstances during pregnancy.

Associations between strabismus and prematurity and low birth weight have been widely reported.[6,7,19,23,24] In the present multivariable analysis accounting simultaneously for a variety of early-life risk factors in an unselected population, we used a composite variable to dissect the role of maturity in relation to prenatal growth. Isolated strabismus was most strongly associated with being preterm and of low birth weight, echoing a recent study.[25] However, there was evidence of a greater role of immaturity than of prenatal growth, with the specific finding of increased risk of strabismus in children of late preterm birth. There is considerable interest in the outcomes, in particular neurodevelopmental and "subtle" functional outcomes, of late preterm children,[18,26,27] who account for most of the recent increase in preterm birth rates.[18] We suggest that the presence of strabismus might be included as a readily captured health outcome in future longitudinal studies of this group of children. Neurodevelopmental strabismus was associated with decreasing birth weight for gestational age (the few cases precluded the more detailed combined analysis of birth weight and gestation described for the isolated cases). Intrauterine growth retardation and subsequent "catch-up growth" are known to have an important influence, during the life course, on the risk of chronic disorders of adult life, such as diabetes mellitus and hypertension.[28,29] Thus, these findings point to prenatal factors that influence the maturation of biological systems[18,30] and growth itself as having important "upstream" roles in the pathogenesis of strabismus. Research collaborations between pedia-

tricians and ophthalmologists to investigate the etiology of strabismus may prove fruitful.

We found independent associations between neurodevelopmental strabismus and light and heavy smoking beyond the first trimester. However, we did not find an association between isolated strabismus and smoking, as reported variably by other researchers.[8,19,24,31] This may be because of the multivariable analysis, which adjusted for a range of confounding factors, in particular birth weight and gestation. Nevertheless, the present findings support the notion[24] that the most sensitive period for the effects of smoking is in the later stages of pregnancy, at a time of developing oculomotor control. Isolated strabismus was also independently associated with assisted delivery and neurodevelopmental strabismus with maternal illness during pregnancy. It is difficult to speculate on the nature of these associations, but they are noteworthy in highlighting the importance of factors that act in late pregnancy or perinatally.

By considering the associations for isolated and neurodevelopmental strabismus in the present study, the hypothesis that emerges is of prenatal programming of coordination and control of eye movements that is disturbed by an adverse intrauterine environment or events, especially in late pregnancy. There may be useful parallels to be drawn from research initiatives in other neurologic/neurodevelopmental pediatric disorders, in particular cerebral palsy, where motor control is affected.[32] Strabismus is a common childhood disorder throughout the world, and management of affected children accounts for a very high proportion of the pediatric workload in ophthalmology. The focus of most recent etiologic research has been eye-specific factors, for example, the relationship between strabismus and refractive error or amblyopia, although strabismus in the context of neurologic or neurodevelopmental disease has been recognized to differ. We suggest that there is a need to recast the paradigm, placing the development of strabismus into the context of prenatal health to enable more fruitful inquiry into mechanisms and, thus, to increase the possibilities for prevention.

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Correspondence: Jugnoo S. Rahi, PhD, FRCOphth, MRC Centre of Epidemiology for Child Health, Institute of Child Health, University College London, 30 Guilford St, London WC1N 1EH, England (j.rahi@ich.ucl.ac.uk).
Author Contributions: Mss Pathai and Cumberland had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. *Study concept and design:* Pathai and Rahi. *Acquisition of data:* Rahi. *Analysis and interpretation of data:* Pathai, Cumberland, and Rahi. *Drafting of the manuscript:* Pathai, Cumberland, and Rahi. *Critical revision of the manuscript for important intellectual content:* Rahi. *Statistical analysis:* Pathai and Cumberland. *Study supervision:* Cumberland and Rahi.
Members of the Millennium Cohort Study Child Health Group: Phillippa M. Cumberland, BA, MSc; Jugnoo S. Rahi, PhD; Carol Dezateux, PhD; Catherine Peckham, PhD; Catherine Law, PhD; Lucy Griffiths, PhD; Tim Cole, PhD; Helen Bedford, PhD; Carly Rich, MSc; Richard Pulsford, MSc; Flo Kinnafick, MSc; Jane Ahn, MA; and Sanja Stanojevic, PhD, Centre for Paediatric Epidemiology and Biostatistics, Institute of Child Health, University College London.
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Additional Information: Honorary Research Fellow (Ms Pathai); Ulverscroft Senior Research Associate in Biostatistics (Ms Cumberland); Reader in Ophthalmic Epidemiology/Honorary Consultant Ophthalmologist (Dr Rahi), for the Millennium Cohort Study Child Health Group.

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