



Guggenheim, J. A., Williams, C. E. M., & UK Biobank Eye and Vision Consortium (2016). Childhood febrile illness and the risk of myopia in UK Biobank participants. *Eye*, 30(4), 608-614.
<https://doi.org/10.1038/eye.2016.7>

Peer reviewed version

Link to published version (if available):
[10.1038/eye.2016.7](https://doi.org/10.1038/eye.2016.7)

[Link to publication record in Explore Bristol Research](#)
PDF-document

This is the author accepted manuscript (AAM). The final published version (version of record) is available online via Springer Nature at <https://www.nature.com/articles/eye20167>. Please refer to any applicable terms of use of the publisher.

University of Bristol - Explore Bristol Research

General rights

This document is made available in accordance with publisher policies. Please cite only the published version using the reference above. Full terms of use are available:
<http://www.bristol.ac.uk/pure/about/ebr-terms>

Childhood febrile illness and the risk of myopia in UK Biobank participants

Authors:

Jeremy A. Guggenheim¹, Cathy Williams², and The UK Biobank Eye and Vision Consortium³

Affiliations:

1. School of Optometry & Vision Sciences, Cardiff University, Cardiff, UK.
2. School of Social and Community Medicine, University of Bristol, Bristol, UK.
3. <http://www.ukbiobankeyeconsortium.org.uk>

Address for correspondence:

Professor Jeremy A. Guggenheim
School of Optometry & Vision Sciences
Cardiff University
Maindy Road, Cardiff, CF24 4HQ, UK
Tel. +44 2920874904
Email. GuggenheimJ1@cardiff.ac.uk

Financial support: The work was funded by a NIHR Career Development Fellowship CDF-2009-02-35 (CW), an internal award Z0GM from the Hong Kong Polytechnic University (JAG) and a Wellcome Trust ISSF Populations Pilot Award (grant 508353/509506). The funding organizations had no role in the design or conduct of this research.

Conflict of Interest: No conflicting relationship exists for any author.

Running head: Febrile illness and the risk of myopia

Word count: 2,321

Abstract

Purpose: Historical reports suggest febrile illness during childhood is a risk factor for myopia. The establishment of the UK Biobank provided a unique opportunity to investigate this relationship.

Methods: We studied a sample of UK Biobank participants of White ethnicity aged 40-69 years-old who underwent autorefraction (N=91,592) and were classified as myopic (≤ -0.75 Dioptres [D]), highly-myopic (≤ -6.00 D) or non-myopic (> -0.75 D). Self-reported age-at-diagnosis of past medical conditions was ascertained during an interview with a nurse at a Biobank assessment centre. Logistic regression analysis was used to calculate the odds ratio (OR) for myopia or high myopia associated with a diagnosis prior to age 17 years of each of nine febrile illnesses, after adjusting for potential confounders (age, sex, highest educational qualification, and birth order).

Results: Rubella, mumps and pertussis were associated with myopia: rubella, OR=1.38, 95% CI 1.03 to 1.85, P=0.030; mumps, OR=1.32, 95% CI 1.07 to 1.64, P=0.010; pertussis, OR=1.39, 95% CI 1.03 to 1.87, P=0.029. Measles, rubella and pertussis were associated with high myopia: Measles, OR=1.48, 95% CI 1.07 to 2.07, P=0.019; rubella, OR=1.94, 95% CI 1.12 to 3.35, P=0.017; pertussis, OR=2.15, 95% CI 1.24 to 3.71, P=0.006.

The evidence did not support an interaction between education and febrile illness in explaining the above risks.

Conclusion: A history of childhood measles, rubella or pertussis was associated with high myopia, while a history of childhood rubella, mumps or pertussis was associated with any myopia. The reason for these associations are unclear.

Introduction

Myopia is a multifactorial disorder, with risk factors that include specific genetic variants¹⁻³, prolonged nearwork^{4,5}, time spent outdoors^{6,7}, maternal age^{8,9}, and birth order^{9,10}. Rare genetic and environmental causes of severe myopia have also been documented¹¹⁻¹⁶. Nevertheless, most of the variance of refractive error in the population remains unaccounted for, and thus additional risk factors for myopia are likely to exist¹⁷⁻²⁰.

Historically, childhood febrile illness has been proposed as a predisposing factor for myopia development. For instance, Duke Elder²¹ states, "It has long been observed that myopia has a habit of appearing or increasing in periods of ill-health or after disease: the common belief that it starts in youth with measles or some such childish febrile illness is not without truth." However, apart from a small study by Hirsch²² examining the age of contracting measles in myopic versus non-myopic school children, little research into this question has been carried out in recent decades. We examined this question in participants participating in the UK Biobank project.

Methods

Participants

The UK Biobank recruited 502,649 subjects aged 37–73 years, during 2006–2010. Participants attended one of 22 assessment centres located in England, Scotland or Wales, at which they completed a touch-key questionnaire, had a face-to-face interview with a trained nurse, and underwent anthropomorphic and other assessments. Later stages of the recruitment process included an ophthalmic component. All assessments adhered to standardised protocols. Ethical approval was obtained from the National Health Service (NHS) National Research Ethics Service (Ref 11/NW/0382) and all participants provided informed consent.

Febrile illness history was ascertained during the face-to-face interview, when participants self-reported cancer and non-cancer illnesses, including the date of diagnosis by a doctor. The available illness response terms included: pneumonia, encephalitis, meningitis, rheumatic fever, measles, rubella, mumps, diphtheria, and pertussis. Ethnicity, educational/professional qualifications and birth order were recorded during the touch-key questionnaire session. For participants who underwent the ophthalmic assessment, refractive error in each eye was measured by non-cycloplegic autorefraction using a Tomey RC5000 autorefractor (Tomey GmbH, Erlangen, Germany) after participants removed their habitual spectacles or contact lenses.

Classification of variables

Participants were classified as affected if they self-reported a diagnosis of the febrile illnesses before the age of 17 years (this age threshold having been chosen as encompassing the period of childhood when myopia most often develops²³). Ethnicity was classified as either “White” (self-report of British, Irish, or any other white background) or “Other” (self-report of Indian, Pakistani, African, Chinese, mixed-race, or “prefer not to answer”). Birth order was calculated as one plus the number of older siblings, or set as missing if the number of older siblings reported was greater than the total number of siblings reported. Birth orders of 4 and above were combined into a single group, due to small numbers. The Biobank touch-key questionnaire categorized highest educational or professional qualification into 7 groups: College or University degree; A-levels/AS-levels; O-levels; CSEs or equivalent; NVQ or HND or HNC or equivalent; other professional qualifications, eg: nursing, teaching; none. This scheme was reduced to 4 categories – (1) None; (2) O-levels or CSEs; (3) A-levels, NVQ, HND, HNC or other professional qualification; (4) Degree – which were chosen to reflect approximately equal years of academic education. Autorefractor data for participants were excluded from further analysis if the instrument labelled the reading as “low reliability” or “lower reliability”. The refractive error of a participant was taken as the average spherical equivalent (spherical power plus half the cylinder power) of their fellow eyes. If data were only available for one eye, then the spherical equivalent for that eye was used. Participants with a refractive error ≤ -0.75 D and ≤ -6.00 D were classified as myopic and highly myopic, respectively⁸.

Statistical analysis

Participants aged less than 40 years, older than 69 years, or who reported non-White ethnicity were excluded, since the numbers reporting a febrile illness were very low in age groups or ethnic groups outside this range. Those reporting a history of cataract, cataract surgery, corneal graft surgery, laser eye surgery, serious eye trauma, or having undergone retinal/vitreotomy surgery were also excluded. For each febrile illness in turn, logistic regression was used to examine the association between affection status (independent variable) and myopia (dependent variable) or high myopia (dependent variable). For the analyses of high myopia, participants with mild/moderate myopia (> -6.00 D and ≤ -0.75 D) were excluded. Univariate analyses were followed by multivariate analyses that included the potential confounders, age, sex, birth order, and highest educational qualification. Initially, logistic regression analyses were carried out with the *glm* function of R^[24], separately for 10 age bins of interval 3 years (40-42, 43-45, ... 67-69 years) and the resulting log odds ratios combined using the *rma* random effects meta-analysis function from the R *metafor* package²⁵. Analyses were carried out for the entire sample aged 40-69 years old using age as a categorical variable with 10 levels, each corresponding to a 3-year age bin.

Results

Participant demographics

Of the 502,656 individuals whose data were released for analysis, 114,741 (22.8%) had autorefractor readings for at least one eye. Participants were excluded if they were outside the age range 40-69 (N=602), were of non-White ethnicity (N=12,588), or reported a history of cataract or other eye disorder (N=8,220). Covariate information (birth order, highest educational qualification, or age-at-onset of febrile illness) was missing for 1739 (1.9%) of the participants, leaving 91,592 available for analysis. The mean \pm SD age was 56.9 \pm 7.9 years, the prevalence of myopia and high myopia was 30.3% and 3.9%, respectively, and the median (interquartile range) of refractive error was 0.14 D (-1.23 to 1.12 D). Table 1 presents the demographic characteristics of the study sample.

Age-dependence of illnesses

The nine febrile illnesses showed varying patterns of self-reported age at diagnosis (Figure 1). With the exception of encephalitis, the illnesses exhibited a peak onset during childhood. Pneumonia and meningitis were notable in showing secondary peaks in older and middle age, respectively. Again with the exception of encephalitis, there was a trend towards a reducing prevalence of each illness in participants born in more recent decades (Figure 2). The number of participants affected varied markedly between illnesses (Figure 1, Table 1).

Association between febrile illness and myopia (Table 2)

In an attempt to limit any excessive influence from isolated epidemic outbreaks, analyses were initially conducted separately for each of ten age strata (40-42, 43-45, 46-48, ... 67-69 years) and the results combined using a random effects meta-analysis²⁶. This approach was designed to down-weight associations occurring only sporadically, for example during a disease epidemic that affected individuals in one particular year, compared to associations that occurred consistently across age strata. However, no evidence of heterogeneity across age strata was found ($P \geq 0.25$ for Cochrane's Q test, for all illnesses). In further support of consistency across age strata, the meta-analysis odds ratios were found to be similar to those for analyses of the full 40-69 year age spectrum. Hence, only the latter results are reported.

Pneumonia, Meningitis, and Rheumatic fever. There was no indication that any of these three febrile illnesses was associated with myopia. *Measles.* Prior to adjustment for potential confounders, measles had a modest, positive association with myopia (OR=1.27, 95% C.I. 1.08 to 1.50, P=0.003). However, adjusting for confounders reduced the strength and magnitude of the association (OR=1.14, P=0.12). *Rubella.* A larger,

positive association (OR=1.55, P=0.002) was observed between rubella and myopia, which was moderately attenuated after adjusting for potential confounders (OR=1.38, 95% C.I. 1.03–1.84, P=0.030). *Mumps*. Mumps showed a similar pattern of association with myopia to that of rubella (unadjusted OR=1.50, P<0.001; adjusted OR=1.32, 95% C.I. 1.07–1.64, P=0.010). *Pertussis*. Before adjusting for potential confounders there was a modest positive association between pertussis and myopia (OR=1.40, 95% C.I. 1.05 to 1.87, P=0.023), which was not attenuated in the adjusted analysis (OR=1.39, 95% C.I. 1.03 to 1.87, P=0.029). *Encephalitis and Diphtheria*. There were too few cases of encephalitis and diphtheria to obtain reliable risk estimates.

Association between febrile illness and high myopia (Table 3)

Pneumonia, Rheumatic fever and Mumps. These three febrile illnesses were not convincingly associated with high myopia, although there was suggestive evidence of an association with mumps in the unadjusted analysis (OR=1.59, 95% C.I. 1.00 to 2.51, P=0.049). *Measles*. The evidence linking measles to high myopia was stronger than that linking it to any level of myopia. A moderate positive association was observed between high myopia and measles prior to adjustment for potential confounders (OR =1.71, P=0.001); adjustment for potential confounders partially reduced the estimated effect size (OR=1.48, 95% C.I. 1.07 to 2.07, P=0.019). *Rubella and Pertussis*. There was support for an association between rubella and high myopia (adjusted OR=1.94, 95% C.I. 1.12 to 3.35, P=0.017) and between pertussis and high myopia (adjusted OR=2.15, 95% C.I. 1.24 to 3.71, P=0.006). These estimates were similar to those prior to adjustment for potential confounders. *Encephalitis, Meningitis, and Diphtheria*. There were too few participants diagnosed with these illnesses to calculate reliable risk estimates.

Discussion

In White UK Biobank participants aged 40-69 years, a self-reported history of rubella, mumps or pertussis during childhood was associated with an approximately 30% increased risk of myopia in adulthood. A history of measles, rubella or pertussis was associated with a 50-110% increased risk of high myopia.

The mechanism previously proposed to explain a causal association between febrile illness and myopia is a change in the biomechanical properties of the sclera after the illness²¹. Intriguingly, measles, mumps and rubella are all single strand RNA viruses that have very high mutation rates compared to DNA viruses, therefore the immunological and inflammatory responses to these infective agents may be relevant to their association with myopia. In contrast, *Bordetella pertussis*, the gram-negative bacterium responsible for pertussis secretes a range of toxins, one of which – Adenylate Cyclase Toxin (ACT) – increases levels of intracellular cAMP in host cells, which could conceivably be related to myopia susceptibility through a cAMP-

dependent mechanism²⁷⁻²⁹. Alternatively, and more generally, it also seems plausible that children recovering from a febrile illness might spend prolonged periods of time indoors and reading, compared to their unaffected peers, both of which have been associated with incident myopia⁷. However, it is unclear why such an effect would occur for certain febrile illnesses yet not for others. Other potential explanations for the observed associations between febrile illnesses and myopia are reverse causality and confounding.

Reverse causality, i.e. children with myopia having an increased risk of developing a febrile illness, seems plausible: for instance, myopic children have been reported to spend less time playing outdoors³⁰ and being indoors for longer than average may increase a child's risk of infection. However, if true, this relationship would again be expected to confer a higher risk of all communicable illnesses, not just those found to be associated here. Of the potential confounders examined, age, highest educational qualification, and birth order were all strongly correlated with myopia (all $P < 0.001$). Furthermore, highest educational qualification was associated with self-reported history of measles, rubella, and mumps (Chi-squared test; all $P < 0.001$) though not pneumonia and pertussis. These interrelationships reflect the wide age span of the UK Biobank participants, along with increased myopia prevalence, years spent in education, and reduced prevalence of febrile illnesses in younger generations. Confounding due to unmeasured variables thus appears feasible. The risk of myopia or high myopia associated with a history of febrile illness varied across age strata and to a greater extent across educational strata (Supplementary Tables S1–S6). The difference in effect size across educational qualification strata was most apparent for mumps in relation to the risk of myopia, and for rubella in relation to the risk of high myopia. For instance, the OR for myopia associated with a history of mumps varied from **OR=1.17 (95% C.I. 0.87 to 1.57)** for those in the top educational qualification category, to **OR=1.90 (95% C.I. 1.26 to 2.88)** for those in the second-highest category (Table S1). Likewise, the OR for high myopia associated with a history of rubella varied from OR=1.29 (95% C.I. 0.55 to 3.03) to OR=4.95 (95% C.I. 2.26 to 10.86) for those in the top and second-highest educational strata, respectively (Table S3). To formally examine the presence of confounding, we tested for an age \times febrile illness interaction, or an educational qualification \times febrile illness interaction. However these tests did not support the presence of an interaction. Under-reporting or over-reporting of a childhood febrile illness in more highly educated participants may have contributed to the observed differences in effect size across educational strata. However, arguing against this cause, the pattern of effect size across educational followed an inverted U-shape, i.e. the risk of myopia or high myopia associated with febrile illness was greatest in participants with an intermediate educational qualification (specifically, the second-highest category) rather than in the highest or lowest category.

Strengths, weaknesses and limitations of the study

This study benefitted from a large sample size and standardised, systematic methods of data collection. Weaknesses were that the febrile illnesses were self-reported – usually decades after their onset – rather than being collected from medical records, that no attempt was made to validate the sensitivity and specificity of the febrile illness self-reports, the large age span of the sample (which increased the risk of confounding effects), and the inability of the study design to distinguish causal from non-causal associations.

The non-random nature of the Biobank recruitment process means that these results may not generalise to the whole UK population. In addition, the rarity of most febrile illnesses in countries that are currently experiencing a high incidence of myopia makes it unlikely that febrile illness is an important contributor to the current myopia epidemic.

In summary, the findings of this study support a previously-reported association between measles and high myopia²² and further suggest that childhood rubella, mumps and pertussis are also associated with myopia and/or high myopia. There was no evidence that meningitis or rheumatic fever were associated with myopia. Further work will be required to discover the causal relationships underlying these associations.

Acknowledgements

This research has been conducted using the UK Biobank Resource (<https://www.ukbiobank.ac.uk/>).

References

1. Verhoeven VJM, Hysi PG, Wojciechowski R, Fan Q, Guggenheim JA, Hohn R, *et al.* Genome-wide meta-analyses of multiancestry cohorts identify multiple new susceptibility loci for refractive error and myopia. 2013; **45**: 314-318.
2. Kiefer AK, Tung JY, Do CB, Hinds DA, Mountain JL, Francke U, *et al.* Genome-wide analysis points to roles for extracellular matrix remodeling, the visual cycle, and neuronal development in myopia. 2013; **9**: e1003299.
3. Wojciechowski R, Hysi PG. Focusing In on the complex genetics of myopia. 2013; **9**: e1003442.
4. Zylbermann R, Landau D, Berson D. The influence of study habits on myopia in jewish teenagers. *J Ped Ophthalmol Strab* 1993; **30**: 319-322.
5. French AN, Morgan IG, Mitchell P, Rose KA. Risk factors for incident myopia in Australian schoolchildren: The Sydney Adolescent Vascular and Eye Study. 2013; **120**: 2100–2108.
6. Jones-Jordan LA, Mitchell GL, Cotter SA, Kleinstein RN, Manny RE, Mutti DO, *et al.* Visual activity prior to and following the onset of juvenile myopia. *Invest Ophthalmol Vis Sci* 2011; **52**: 1841–1850.
7. Guggenheim JA, Northstone K, McMahon G, Ness AR, Deere K, Mattocks C, *et al.* Time outdoors and physical activity as predictors of incident myopia in childhood: A prospective cohort study. 2012; **53**: 2856-2865.
8. Rahi JS, Cumberland PM, Peckham CS. Myopia over the lifecourse: Prevalence and early life influences in the 1958 British Birth Cohort. *Ophthalmol* 2011; **118**: 797-804.
9. Rudnicka AR, Owen CG, Richards M, Wadsworth ME, Strachan DP. Effect of breastfeeding and sociodemographic factors on visual outcome in childhood and adolescence. *Am J Clin Nutr* 2008; **87**: 1392-1399.
10. Guggenheim JA, McMahon G, Northstone K, Mandel Y, Kaiserman I, Stone R, *et al.* Birth order and myopia. 2013; **20**: 375-384.
11. O'Leary DJ, Millodot M. Eyelid closure causes myopia in humans. *Experimentia* 1979; **35**: 1478-1479.
12. McClements M, Davies WIL, Michaelides M, Young T, Neitz M, MacLaren RE, *et al.* Variations in opsin coding sequences cause X-linked Cone Dysfunction Syndrome with myopia and dichromacy. 2013; **54**: 1361-1369.
13. Mordechai S, Gradstein L, Pasanen A, Ofir R, El Amour K, Levy J, *et al.* High myopia caused by a mutation in LEPREL1, encoding prolyl 3-hydroxylase 2. *Am J Hum Genet* 2011; **89**: 438-445.
14. Shi Y, Li Y, Zhang D, Zhang H, Lu F, Liu X, *et al.* Exome Sequencing Identifies ZNF644 Mutations in High Myopia. *PLoS Genet* 2011; **7**: e1002084.
15. Tran-Viet K-N, Powell C, Barathi Veluchamy A, Klemm T, Maurer-Stroh S, Limviphuvadh V, *et al.* Mutations in SCO2 are associated with autosomal-dominant high-grade myopia. 2013; **92**: 820-826.
16. Zhao F, Wu J, Xue A, Su Y, Wang X, Lu X, *et al.* Exome sequencing reveals CCDC111 mutation associated with high myopia. 2013; **132**: 913-921.
17. Foster PJ, Jiang Y. Epidemiology of myopia. 2014; **28**: 202–208.
18. Flitcroft DI. Emmetropisation and the aetiology of refractive errors. 2014; **28**: 169–179.
19. Morgan IG, Ohno-Matsui K, Saw SM. Myopia. *Lancet* 2012; **379**: 1739-1748.
20. Pan CW, Ramamurthy D, Saw SM. Worldwide prevalence and risk factors for myopia. *Ophthalmic Physiol Opt* 2012; **32**: 3-16.

21. Duke-Elder S. *Text-book of Ophthalmology*. St. Louis: C. V. Mosby, 1949.
22. Hirsch MJ. The relationship between measles and myopia. *Am J Optom Arch Am Acad Optom* 1957; **34**: 289-297.
23. Scheiman M, Zhang Q, Gwiazda J, Hyman L, Harb E, Weissberg E, *et al*. Visual activity and its association with myopia stabilisation. 2014; **34**: 353-361.
24. R Development Core Team. *R: A language and environment for statistical computing*. Vienna, Austria: R Foundation for Statistical Computing, 2008.
25. Viechtbauer W. Conducting Meta-Analyses in R with the metafor package. 2010; **36**: 1-48.
26. Berkey CS, Hoaglin DC, Mosteller F, Colditz GA. A random-effects regression model for meta-analysis. 1995; **14**: 395-411.
27. Chen W, Zhou X, Li C, Qu J, Zeng C. PDE4B is a high myopia susceptibility gene likely by down regulating collagen synthesis in sclera. 2011; **Meeting Abstract**: E493F.
28. Tao Y, Pan M, Liu S, Fang F, Lu R, Lu C, *et al*. cAMP level modulates scleral collagen remodeling, a critical step in the development of myopia. 2013; **8**: e71441.
29. Feldkaemper M, Schaeffel F. An updated view on the role of dopamine in myopia. 2013; **114**: 106–119.
30. Deere K, Williams C, Leary S, Mattocks C, Ness A, Blair SN, *et al*. Myopia and later physical activity in adolescence: a prospective study. *Br J Sports Med* 2009; **43**: 542-524.

Figure 1. Violin plots showing age at diagnosis of febrile illnesses as a function of age at recruitment. Each panel shows the median (black circle), interquartile range (white rectangle) and the frequency distribution (smoothed histogram with brown shading, mirrored vertically; width proportional to number of affected participants in that age category) of the age at diagnosis, by category of age at recruitment. The total number of cases across all three age categories is indicated (N). The analysis was restricted to White participants aged 40-69 with valid autorefraction information (N=91,592).

Figure 2. Histograms showing the year in which participants self-reported a diagnosis of febrile illness. Year at diagnosis was calculated as year of birth + age at diagnosis.

Table 1. Subjects demographics

Variable	Group	N	(%)	N	(%)
Myopia	Myopic	27,752	(30.3%)		
	Non-myopic	63,840	(69.7%)		
High myopia	Highly myopic	3,586	(5.3%)		
	Non-myopic	63,840	(94.7%)		
Sex	Male	42,039	(45.9%)		
	Female	49,553	(54.1%)		
Ethnicity	White	91,592	(100.0%)		
Birth order	1	43,009	(47.0%)		
	2	27,779	(30.3%)		
	3	11,663	(12.7%)		
	4+	9,141	(10.0%)		
Highest qualification	University degree	32,048	(35.0%)		
	A-levels or similar*	21,226	(23.2%)		
	O-levels or CSEs	24,774	(27.0%)		
	None	13,544	(14.8%)		
Febrile illness	Age-at-onset	Any age		Prior to 17 yrs	
	Pneumonia	993	(1.1%)	400	(0.4%)
	Encephalitis	54	(0.1%)	10	(0.0%)
	Meningitis	303	(0.3%)	142	(0.2%)
	Rheumatic fever	206	(0.2%)	183	(0.2%)
	Measles	657	(0.7%)	649	(0.7%)
	Rubella	230	(0.3%)	196	(0.2%)
	Mumps	418	(0.5%)	371	(0.4%)
	Diphtheria	32	(0.0%)	31	(0.0%)
	Pertussis	207	(0.2%)	193	(0.2%)

*Includes: NVQ, HND, HNC and other professional qualifications.

Table 2. Association between febrile illness prior to age 17 and myopia (N=91,592).

Illness	Univariate analysis			Multivariate analysis*		
	OR	95% C.I.	P-value	OR	95% C.I.	P-value
Pneumonia	1.083	(0.877 to 1.337)	0.458	1.157	(0.933 to 1.434)	0.184
Meningitis	0.840	(0.579 to 1.219)	0.359	0.808	(0.554 to 1.179)	0.269
Rheumatic fever	1.014	(0.740 to 1.390)	0.929	1.148	(0.832 to 1.584)	0.401
Measles	1.274	(1.084 to 1.496)	0.003	1.139	(0.966 to 1.342)	0.121
Rubella	1.555	(1.168 to 2.069)	0.002	1.380	(1.033 to 1.845)	0.030
Mumps	1.495	(1.214 to 1.842)	<0.001	1.322	(1.069 to 1.635)	0.010
Pertussis	1.400	(1.047 to 1.874)	0.023	1.392	(1.034 to 1.874)	0.029

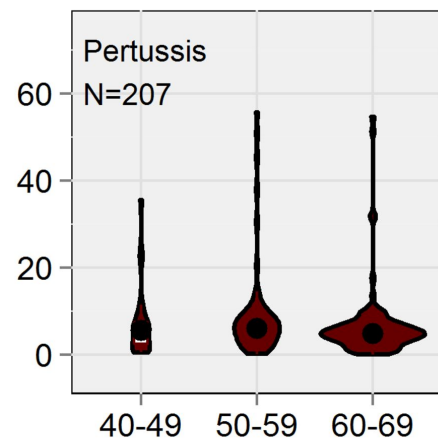
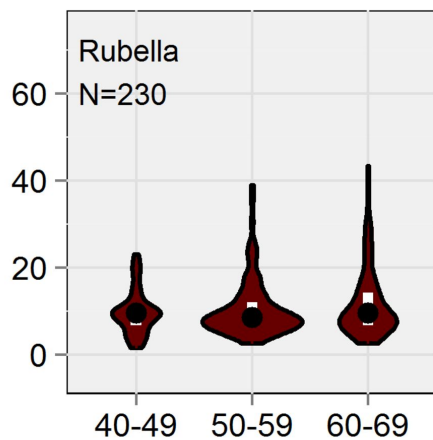
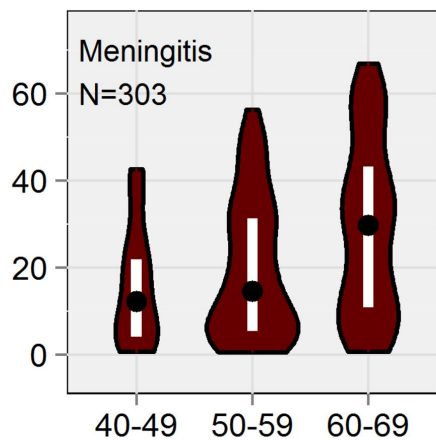
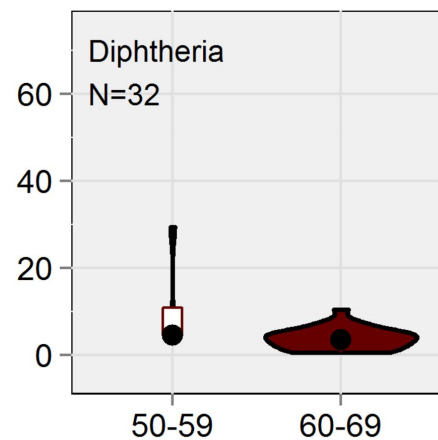
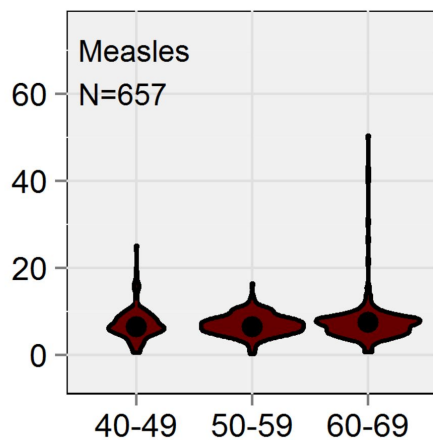
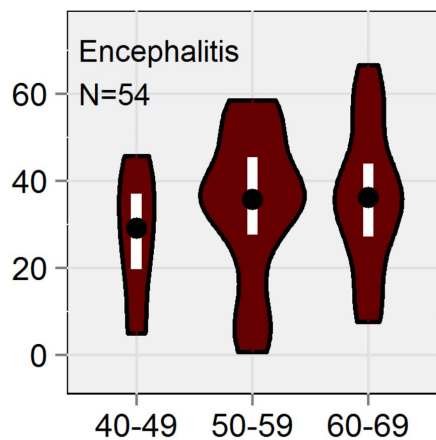
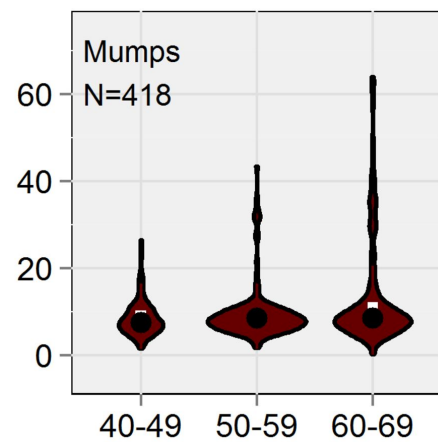
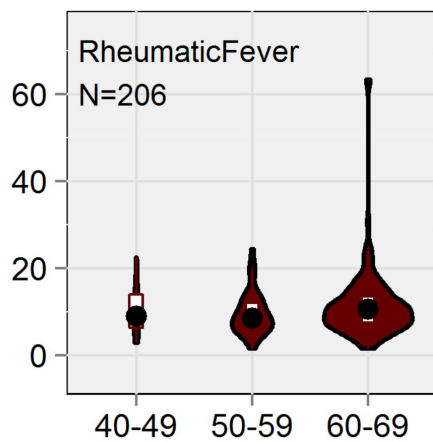
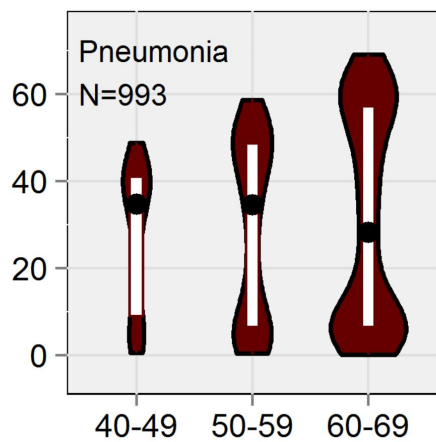
*Adjusted for age, sex, highest educational qualification, and birth order.

Table 3. Association between febrile illness prior to age 17 and high myopia (N=67,426).

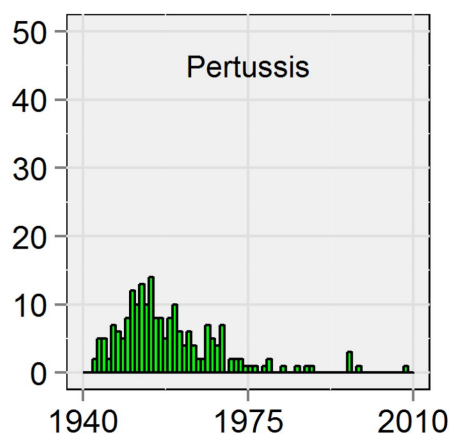
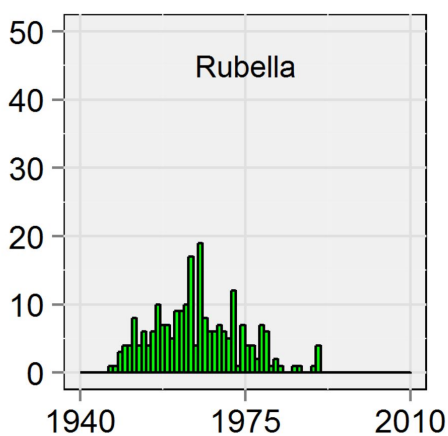
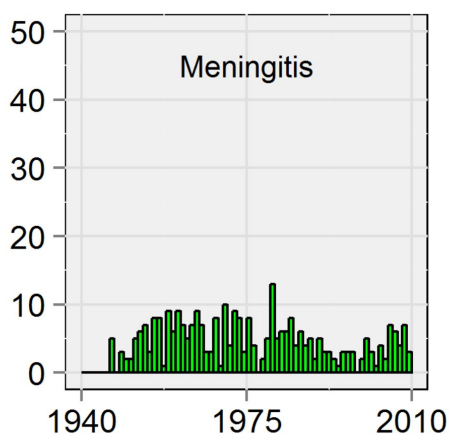
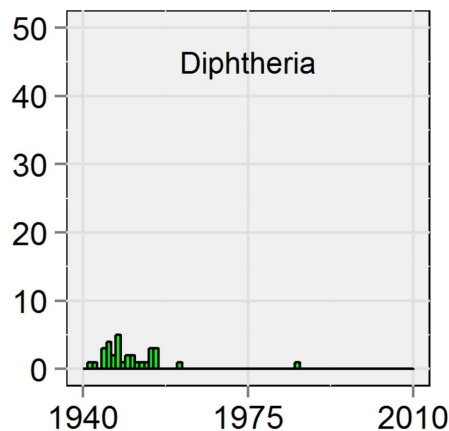
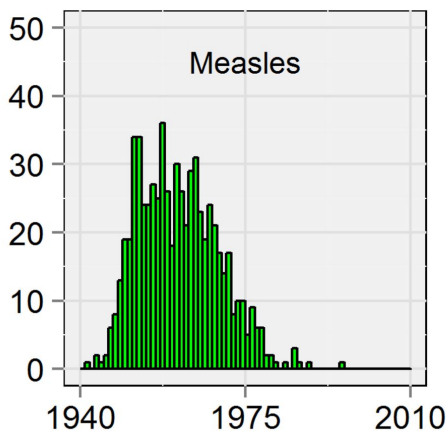
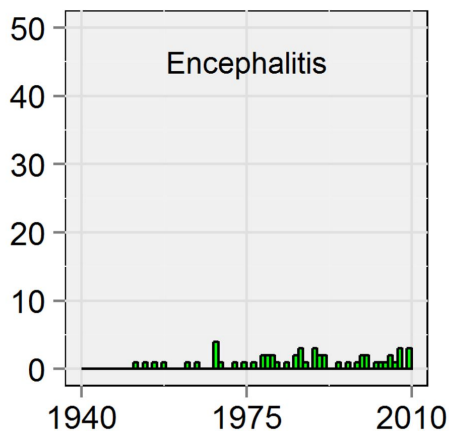
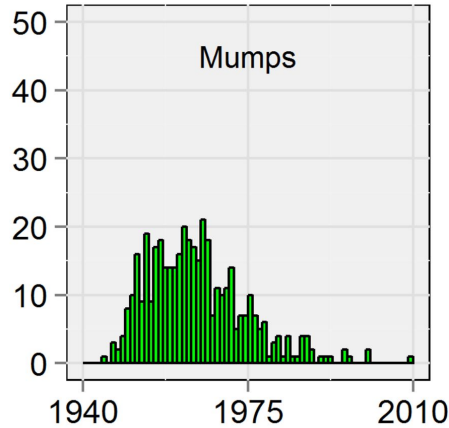
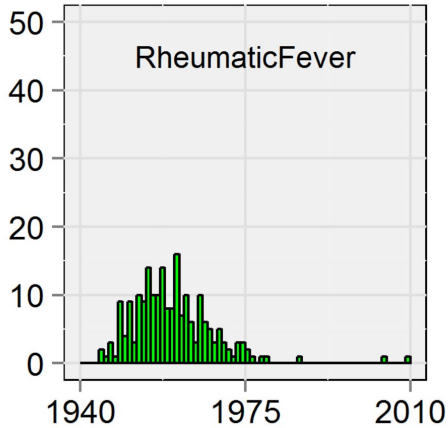
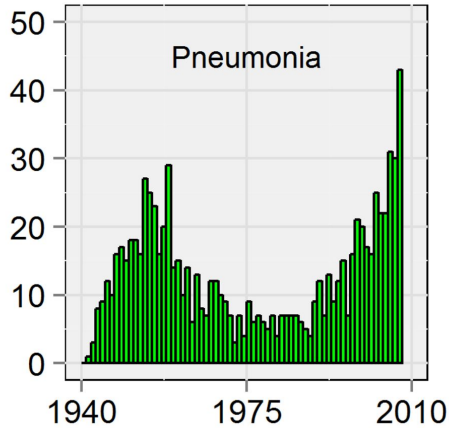
Illness	Univariate analysis			Multivariate analysis*		
	OR	95% C.I.	P-value	OR	95% C.I.	P-value
Pneumonia	1.377	(0.882 to 2.149)	0.159	1.551	(0.987 to 2.436)	0.057
Rheumatic fever	0.700	(0.287 to 1.712)	0.435	0.835	(0.339 to 2.059)	0.696
Measles	1.712	(1.235 to 2.372)	0.001	1.484	(1.067 to 2.065)	0.019
Rubella	2.288	(1.335 to 3.920)	0.003	1.941	(1.124 to 3.349)	0.017
Mumps	1.586	(1.002 to 2.508)	0.049	1.325	(0.834 to 2.107)	0.234
Pertussis	2.230	(1.303 to 3.819)	0.003	2.147	(1.242 to 3.711)	0.006

*Adjusted for age, sex, highest educational qualification, and birth order.

Age at diagnosis of illness (years)



Age at recruitment (years)



Year at diagnosis of illness

Childhood febrile illness and the risk of myopia in UK Biobank participants

Authors:

Jeremy A. Guggenheim¹, Cathy Williams², and The UK Biobank Eye and Vision Consortium³

Affiliations:

1. School of Optometry & Vision Sciences, Cardiff University, Cardiff, UK.
2. School of Social and Community Medicine, University of Bristol, Bristol, UK.
3. <http://www.ukbiobankeyeconsortium.org.uk>

Address for correspondence:

Professor Jeremy A. Guggenheim
School of Optometry & Vision Sciences
Cardiff University
Maindy Road, Cardiff, CF24 4HQ, UK
Tel. +44 2920874904
Email. GuggenheimJ1@cardiff.ac.uk

Financial support: The work was funded by a NIHR Career Development Fellowship CDF-2009-02-35 (CW), an internal award Z0GM from the Hong Kong Polytechnic University (JAG) and a Wellcome Trust ISSF Populations Pilot Award (grant 508353/509506). The funding organizations had no role in the design or conduct of this research.

Conflict of Interest: No conflicting relationship exists for any author.

Running head: Febrile illness and the risk of myopia

Word count: 2,321

Abstract

Purpose: Historical reports suggest febrile illness during childhood is a risk factor for myopia. The establishment of the UK Biobank provided a unique opportunity to investigate this relationship.

Methods: We studied a sample of UK Biobank participants of White ethnicity aged 40-69 years-old who underwent autorefraction (N=91,592) and were classified as myopic (≤ -0.75 Dioptres [D]), highly-myopic (≤ -6.00 D) or non-myopic (> -0.75 D). Self-reported age-at-diagnosis of past medical conditions was ascertained during an interview with a nurse at a Biobank assessment centre. Logistic regression analysis was used to calculate the odds ratio (OR) for myopia or high myopia associated with a diagnosis prior to age 17 years of each of nine febrile illnesses, after adjusting for potential confounders (age, sex, highest educational qualification, and birth order).

Results: Rubella, mumps and pertussis were associated with myopia: rubella, OR=1.38, 95% CI 1.03 to 1.85, P=0.030; mumps, OR=1.32, 95% CI 1.07 to 1.64, P=0.010; pertussis, OR=1.39, 95% CI 1.03 to 1.87, P=0.029. Measles, rubella and pertussis were associated with high myopia: Measles, OR=1.48, 95% CI 1.07 to 2.07, P=0.019; rubella, OR=1.94, 95% CI 1.12 to 3.35, P=0.017; pertussis, OR=2.15, 95% CI 1.24 to 3.71, P=0.006. The evidence did not support an interaction between education and febrile illness in explaining the above risks.

Conclusion: A history of childhood measles, rubella or pertussis was associated with high myopia, while a history of childhood rubella, mumps or pertussis was associated with any myopia. The reason for these associations are unclear.

Introduction

Myopia is a multifactorial disorder, with risk factors that include specific genetic variants¹⁻³, prolonged nearwork^{4,5}, time spent outdoors^{6,7}, maternal age^{8,9}, and birth order^{9,10}. Rare genetic and environmental causes of severe myopia have also been documented¹¹⁻¹⁶. Nevertheless, most of the variance of refractive error in the population remains unaccounted for, and thus additional risk factors for myopia are likely to exist¹⁷⁻²⁰.

Historically, childhood febrile illness has been proposed as a predisposing factor for myopia development. For instance, Duke Elder²¹ states, "It has long been observed that myopia has a habit of appearing or increasing in periods of ill-health or after disease: the common belief that it starts in youth with measles or some such childish febrile illness is not without truth." However, apart from a small study by Hirsch²² examining the age of contracting measles in myopic versus non-myopic school children, little research into this question has been carried out in recent decades. We examined this question in participants participating in the UK Biobank project.

Methods

Participants

The UK Biobank recruited 502,649 subjects aged 37–73 years, during 2006–2010. Participants attended one of 22 assessment centres located in England, Scotland or Wales, at which they completed a touch-key questionnaire, had a face-to-face interview with a trained nurse, and underwent anthropomorphic and other assessments. Later stages of the recruitment process included an ophthalmic component. All assessments adhered to standardised protocols. Ethical approval was obtained from the National Health Service (NHS) National Research Ethics Service (Ref 11/NW/0382) and all participants provided informed consent.

Febrile illness history was ascertained during the face-to-face interview, when participants self-reported cancer and non-cancer illnesses, including the date of diagnosis by a doctor. The available illness response terms included: pneumonia, encephalitis, meningitis, rheumatic fever, measles, rubella, mumps, diphtheria, and pertussis. Ethnicity, educational/professional qualifications and birth order were recorded during the touch-key questionnaire session. For participants who underwent the ophthalmic assessment, refractive error in each eye was measured by non-cycloplegic autorefractometry using a Tomey RC5000 autorefractor (Tomey GmbH, Erlangen, Germany) after participants removed their habitual spectacles or contact lenses.

Classification of variables

Participants were classified as affected if they self-reported a diagnosis of the febrile illnesses before the age of 17 years (this age threshold having been chosen as encompassing the period of childhood when myopia most often develops²³). Ethnicity was classified as either “White” (self-report of British, Irish, or any other white background) or “Other” (self-report of Indian, Pakistani, African, Chinese, mixed-race, or “prefer not to answer”). Birth order was calculated as one plus the number of older siblings, or set as missing if the number of older siblings reported was greater than the total number of siblings reported. Birth orders of 4 and above were combined into a single group, due to small numbers. The Biobank touch-key questionnaire categorized highest educational or professional qualification into 7 groups: College or University degree; A-levels/AS-levels; O-levels; CSEs or equivalent; NVQ or HND or HNC or equivalent; other professional qualifications, eg: nursing, teaching; none. This scheme was reduced to 4 categories – (1) None; (2) O-levels or CSEs; (3) A-levels, NVQ, HND, HNC or other professional qualification; (4) Degree – which were chosen to reflect approximately equal years of academic education. Autorefractor data for participants were excluded from further analysis if the instrument labelled the reading as “low reliability” or “lower reliability”. The refractive error of a participant was taken as the average spherical equivalent (spherical power plus half the cylinder power) of their fellow eyes. If data were only available for one eye, then the spherical equivalent for that eye was used. Participants with a refractive error ≤ -0.75 D and ≤ -6.00 D were classified as myopic and highly myopic, respectively⁸.

Statistical analysis

Participants aged less than 40 years, older than 69 years, or who reported non-White ethnicity were excluded, since the numbers reporting a febrile illness were very low in age groups or ethnic groups outside this range. Those reporting a history of cataract, cataract surgery, corneal graft surgery, laser eye surgery, serious eye trauma, or having undergone retinal/vitreotomy surgery were also excluded. For each febrile illness in turn, logistic regression was used to examine the association between affection status (independent variable) and myopia (dependent variable) or high myopia (dependent variable). For the analyses of high myopia, participants with mild/moderate myopia (> -6.00 D and ≤ -0.75 D) were excluded. Univariate analyses were followed by multivariate analyses that included the potential confounders, age, sex, birth order, and highest educational qualification. Initially, logistic regression analyses were carried out with the *glm* function of R^[24], separately for 10 age bins of interval 3 years (40-42, 43-45, ... 67-69 years) and the resulting log odds ratios combined using the *rma* random effects meta-analysis function from the R *metafor* package²⁵. Analyses were carried out for the entire sample aged 40-69 years old using age as a categorical variable with 10 levels, each corresponding to a 3-year age bin.

Results

Participant demographics

Of the 502,656 individuals whose data were released for analysis, 114,741 (22.8%) had autorefractor readings for at least one eye. Participants were excluded if they were outside the age range 40-69 (N=602), were of non-White ethnicity (N=12,588), or reported a history of cataract or other eye disorder (N=8,220). Covariate information (birth order, highest educational qualification, or age-at-onset of febrile illness) was missing for 1739 (1.9%) of the participants, leaving 91,592 available for analysis. The mean \pm SD age was 56.9 \pm 7.9 years, the prevalence of myopia and high myopia was 30.3% and 3.9%, respectively, and the median (interquartile range) of refractive error was 0.14 D (-1.23 to 1.12 D). Table 1 presents the demographic characteristics of the study sample.

Age-dependence of illnesses

The nine febrile illnesses showed varying patterns of self-reported age at diagnosis (Figure 1). With the exception of encephalitis, the illnesses exhibited a peak onset during childhood. Pneumonia and meningitis were notable in showing secondary peaks in older and middle age, respectively. Again with the exception of encephalitis, there was a trend towards a reducing prevalence of each illness in participants born in more recent decades (Figure 2). The number of participants affected varied markedly between illnesses (Figure 1, Table 1).

Association between febrile illness and myopia (Table 2)

In an attempt to limit any excessive influence from isolated epidemic outbreaks, analyses were initially conducted separately for each of ten age strata (40-42, 43-45, 46-48, ... 67-69 years) and the results combined using a random effects meta-analysis²⁶. This approach was designed to down-weight associations occurring only sporadically, for example during a disease epidemic that affected individuals in one particular year, compared to associations that occurred consistently across age strata. However, no evidence of heterogeneity across age strata was found ($P \geq 0.25$ for Cochrane's Q test, for all illnesses). In further support of consistency across age strata, the meta-analysis odds ratios were found to be similar to those for analyses of the full 40-69 year age spectrum. Hence, only the latter results are reported.

Pneumonia, Meningitis, and Rheumatic fever. There was no indication that any of these three febrile illnesses was associated with myopia. *Measles.* Prior to adjustment for potential confounders, measles had a modest, positive association with myopia (OR=1.27, 95% C.I. 1.08 to 1.50, P=0.003). However, adjusting for confounders reduced the strength and magnitude of the association (OR=1.14, P=0.12). *Rubella.* A larger,

positive association (OR=1.55, P=0.002) was observed between rubella and myopia, which was moderately attenuated after adjusting for potential confounders (OR=1.38, 95% C.I. 1.03–1.84, P=0.030). *Mumps*. Mumps showed a similar pattern of association with myopia to that of rubella (unadjusted OR=1.50, P<0.001; adjusted OR=1.32, 95% C.I. 1.07–1.64, P=0.010). *Pertussis*. Before adjusting for potential confounders there was a modest positive association between pertussis and myopia (OR=1.40, 95% C.I. 1.05 to 1.87, P=0.023), which was not attenuated in the adjusted analysis (OR=1.39, 95% C.I. 1.03 to 1.87, P=0.029). *Encephalitis and Diphtheria*. There were too few cases of encephalitis and diphtheria to obtain reliable risk estimates.

Association between febrile illness and high myopia (Table 3)

Pneumonia, Rheumatic fever and Mumps. These three febrile illnesses were not convincingly associated with high myopia, although there was suggestive evidence of an association with mumps in the unadjusted analysis (OR=1.59, 95% C.I. 1.00 to 2.51, P=0.049). *Measles*. The evidence linking measles to high myopia was stronger than that linking it to any level of myopia. A moderate positive association was observed between high myopia and measles prior to adjustment for potential confounders (OR =1.71, P=0.001); adjustment for potential confounders partially reduced the estimated effect size (OR=1.48, 95% C.I. 1.07 to 2.07, P=0.019). *Rubella and Pertussis*. There was support for an association between rubella and high myopia (adjusted OR=1.94, 95% C.I. 1.12 to 3.35, P=0.017) and between pertussis and high myopia (adjusted OR=2.15, 95% C.I. 1.24 to 3.71, P=0.006). These estimates were similar to those prior to adjustment for potential confounders. *Encephalitis, Meningitis, and Diphtheria*. There were too few participants diagnosed with these illnesses to calculate reliable risk estimates.

Discussion

In White UK Biobank participants aged 40-69 years, a self-reported history of rubella, mumps or pertussis during childhood was associated with an approximately 30% increased risk of myopia in adulthood. A history of measles, rubella or pertussis was associated with a 50-110% increased risk of high myopia.

The mechanism previously proposed to explain a causal association between febrile illness and myopia is a change in the biomechanical properties of the sclera after the illness²¹. Intriguingly, measles, mumps and rubella are all single strand RNA viruses that have very high mutation rates compared to DNA viruses, therefore the immunological and inflammatory responses to these infective agents may be relevant to their association with myopia. In contrast, *Bordetella pertussis*, the gram-negative bacterium responsible for pertussis secretes a range of toxins, one of which – Adenylate Cyclase Toxin (ACT) – increases levels of intracellular cAMP in host cells, which could conceivably be related to myopia susceptibility through a cAMP-

dependent mechanism²⁷⁻²⁹. Alternatively, and more generally, it also seems plausible that children recovering from a febrile illness might spend prolonged periods of time indoors and reading, compared to their unaffected peers, both of which have been associated with incident myopia⁷. However, it is unclear why such an effect would occur for certain febrile illnesses yet not for others. Other potential explanations for the observed associations between febrile illnesses and myopia are reverse causality and confounding.

Reverse causality, i.e. children with myopia having an increased risk of developing a febrile illness, seems plausible: for instance, myopic children have been reported to spend less time playing outdoors³⁰ and being indoors for longer than average may increase a child's risk of infection. However, if true, this relationship would again be expected to confer a higher risk of all communicable illnesses, not just those found to be associated here. Of the potential confounders examined, age, highest educational qualification, and birth order were all strongly correlated with myopia (all $P < 0.001$). Furthermore, highest educational qualification was associated with self-reported history of measles, rubella, and mumps (Chi-squared test; all $P < 0.001$) though not pneumonia and pertussis. These interrelationships reflect the wide age span of the UK Biobank participants, along with increased myopia prevalence, years spent in education, and reduced prevalence of febrile illnesses in younger generations. Confounding due to unmeasured variables thus appears feasible. The risk of myopia or high myopia associated with a history of febrile illness varied across age strata and to a greater extent across educational strata (Supplementary Tables S1–S6). The difference in effect size across educational qualification strata was most apparent for mumps in relation to the risk of myopia, and for rubella in relation to the risk of high myopia. For instance, the OR for myopia associated with a history of mumps varied from OR=1.17 (95% C.I. 0.87 to 1.57) for those in the top educational qualification category, to OR=1.90 (95% C.I. 1.26 to 2.88) for those in the second-highest category (Table S1). Likewise, the OR for high myopia associated with a history of rubella varied from OR=1.29 (95% C.I. 0.55 to 3.03) to OR=4.95 (95% C.I. 2.26 to 10.86) for those in the top and second-highest educational strata, respectively (Table S3). To formally examine the presence of confounding, we tested for an age \times febrile illness interaction, or an educational qualification \times febrile illness interaction. However these tests did not support the presence of an interaction. Under-reporting or over-reporting of a childhood febrile illness in more highly educated participants may have contributed to the observed differences in effect size across educational strata. However, arguing against this cause, the pattern of effect size across educational followed an inverted U-shape, i.e. the risk of myopia or high myopia associated with febrile illness was greatest in participants with an intermediate educational qualification (specifically, the second-highest category) rather than in the highest or lowest category.

Strengths, weaknesses and limitations of the study

This study benefitted from a large sample size and standardised, systematic methods of data collection. Weaknesses were that the febrile illnesses were self-reported – usually decades after their onset – rather than being collected from medical records, that no attempt was made to validate the sensitivity and specificity of the febrile illness self-reports, the large age span of the sample (which increased the risk of confounding effects), and the inability of the study design to distinguish causal from non-causal associations.

The non-random nature of the Biobank recruitment process means that these results may not generalise to the whole UK population. In addition, the rarity of most febrile illnesses in countries that are currently experiencing a high incidence of myopia makes it unlikely that febrile illness is an important contributor to the current myopia epidemic.

In summary, the findings of this study support a previously-reported association between measles and high myopia²² and further suggest that childhood rubella, mumps and pertussis are also associated with myopia and/or high myopia. There was no evidence that meningitis or rheumatic fever were associated with myopia. Further work will be required to discover the causal relationships underlying these associations.

Acknowledgements

This research has been conducted using the UK Biobank Resource (<https://www.ukbiobank.ac.uk/>).

References

1. Verhoeven VJM, Hysi PG, Wojciechowski R, Fan Q, Guggenheim JA, Hohn R, *et al.* Genome-wide meta-analyses of multiancestry cohorts identify multiple new susceptibility loci for refractive error and myopia. 2013; **45**: 314-318.
2. Kiefer AK, Tung JY, Do CB, Hinds DA, Mountain JL, Francke U, *et al.* Genome-wide analysis points to roles for extracellular matrix remodeling, the visual cycle, and neuronal development in myopia. 2013; **9**: e1003299.
3. Wojciechowski R, Hysi PG. Focusing In on the complex genetics of myopia. 2013; **9**: e1003442.
4. Zylbermann R, Landau D, Berson D. The influence of study habits on myopia in jewish teenagers. *J Ped Ophthalmol Strab* 1993; **30**: 319-322.
5. French AN, Morgan IG, Mitchell P, Rose KA. Risk factors for incident myopia in Australian schoolchildren: The Sydney Adolescent Vascular and Eye Study. 2013; **120**: 2100–2108.
6. Jones-Jordan LA, Mitchell GL, Cotter SA, Kleinstein RN, Manny RE, Mutti DO, *et al.* Visual activity prior to and following the onset of juvenile myopia. *Invest Ophthalmol Vis Sci* 2011; **52**: 1841–1850.
7. Guggenheim JA, Northstone K, McMahon G, Ness AR, Deere K, Mattocks C, *et al.* Time outdoors and physical activity as predictors of incident myopia in childhood: A prospective cohort study. 2012; **53**: 2856-2865.
8. Rahi JS, Cumberland PM, Peckham CS. Myopia over the lifecourse: Prevalence and early life influences in the 1958 British Birth Cohort. *Ophthalmol* 2011; **118**: 797-804.
9. Rudnicka AR, Owen CG, Richards M, Wadsworth ME, Strachan DP. Effect of breastfeeding and sociodemographic factors on visual outcome in childhood and adolescence. *Am J Clin Nutr* 2008; **87**: 1392-1399.
10. Guggenheim JA, McMahon G, Northstone K, Mandel Y, Kaiserman I, Stone R, *et al.* Birth order and myopia. 2013; **20**: 375-384.
11. O'Leary DJ, Millodot M. Eyelid closure causes myopia in humans. *Experimentia* 1979; **35**: 1478-1479.
12. McClements M, Davies WIL, Michaelides M, Young T, Neitz M, MacLaren RE, *et al.* Variations in opsin coding sequences cause X-linked Cone Dysfunction Syndrome with myopia and dichromacy. 2013; **54**: 1361-1369.
13. Mordechai S, Gradstein L, Pasanen A, Ofir R, El Amour K, Levy J, *et al.* High myopia caused by a mutation in LEPREL1, encoding prolyl 3-hydroxylase 2. *Am J Hum Genet* 2011; **89**: 438-445.
14. Shi Y, Li Y, Zhang D, Zhang H, Lu F, Liu X, *et al.* Exome Sequencing Identifies ZNF644 Mutations in High Myopia. *PLoS Genet* 2011; **7**: e1002084.
15. Tran-Viet K-N, Powell C, Barathi Veluchamy A, Klemm T, Maurer-Stroh S, Limvipuvadh V, *et al.* Mutations in SCO2 are associated with autosomal-dominant high-grade myopia. 2013; **92**: 820-826.
16. Zhao F, Wu J, Xue A, Su Y, Wang X, Lu X, *et al.* Exome sequencing reveals CCDC111 mutation associated with high myopia. 2013; **132**: 913-921.
17. Foster PJ, Jiang Y. Epidemiology of myopia. 2014; **28**: 202–208.
18. Flitcroft DI. Emmetropisation and the aetiology of refractive errors. 2014; **28**: 169–179.
19. Morgan IG, Ohno-Matsui K, Saw SM. Myopia. *Lancet* 2012; **379**: 1739-1748.
20. Pan CW, Ramamurthy D, Saw SM. Worldwide prevalence and risk factors for myopia. *Ophthalmic Physiol Opt* 2012; **32**: 3-16.

21. Duke-Elder S. *Text-book of Ophthalmology*. St. Louis: C. V. Mosby, 1949.
22. Hirsch MJ. The relationship between measles and myopia. *Am J Optom Arch Am Acad Optom* 1957; **34**: 289-297.
23. Scheiman M, Zhang Q, Gwiazda J, Hyman L, Harb E, Weissberg E, *et al*. Visual activity and its association with myopia stabilisation. 2014; **34**: 353-361.
24. R Development Core Team. *R: A language and environment for statistical computing*. Vienna, Austria: R Foundation for Statistical Computing, 2008.
25. Viechtbauer W. Conducting Meta-Analyses in R with the metafor package. 2010; **36**: 1-48.
26. Berkey CS, Hoaglin DC, Mosteller F, Colditz GA. A random-effects regression model for meta-analysis. 1995; **14**: 395-411.
27. Chen W, Zhou X, Li C, Qu J, Zeng C. PDE4B is a high myopia susceptibility gene likely by down regulating collagen synthesis in sclera. 2011; **Meeting Abstract**: E493F.
28. Tao Y, Pan M, Liu S, Fang F, Lu R, Lu C, *et al*. cAMP level modulates scleral collagen remodeling, a critical step in the development of myopia. 2013; **8**: e71441.
29. Feldkaemper M, Schaeffel F. An updated view on the role of dopamine in myopia. 2013; **114**: 106–119.
30. Deere K, Williams C, Leary S, Mattocks C, Ness A, Blair SN, *et al*. Myopia and later physical activity in adolescence: a prospective study. *Br J Sports Med* 2009; **43**: 542-524.

Figure 1. Violin plots showing age at diagnosis of febrile illnesses as a function of age at recruitment. Each panel shows the median (black circle), interquartile range (white rectangle) and the frequency distribution (smoothed histogram with brown shading, mirrored vertically; width proportional to number of affected participants in that age category) of the age at diagnosis, by category of age at recruitment. The total number of cases across all three age categories is indicated (N). The analysis was restricted to White participants aged 40-69 with valid autorefraction information (N=91,592).

Figure 2. Histograms showing the year in which participants self-reported a diagnosis of febrile illness. Year at diagnosis was calculated as year of birth + age at diagnosis.