Impact of persisting amblyopia on socio–economic, health and well–being outcomes in adult life: findings from the UK Biobank study

Running title: The value of childhood vision screening

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Precis: Implementation of universal child vision screening has reduced but far from eliminated the risk of incompletely treated amblyopia. It has mitigated some of the direct vision–mediated functional impact of amblyopia but the psychological impact of diagnosis or treatment of amblyopia requires attention.

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Abstract

Objectives: To investigate associations between persisting amblyopia into adulthood and 'real–life' impacts and inform the current debate about the value of childhood vision screening programmes.

Methods: Associations between persisting amblyopia and diverse socio–economic, health, and well–being outcomes were investigated in multivariable adjusted (sex, age, ethnicity, deprivation) regression models, using 126,400 40 to 70–year–old participants of the UK Biobank study with complete ophthalmic data. Analysis by age–group (cohort–1: 60–70 years, 2: 50–59 years, 3: 40–49 years) assessed temporal trends.

Results: Of 3,395 (3%) with confirmed amblyopia, overall 77% (2,627) had persisting amblyopia, declining from 78% in cohort 1 to 73% in cohort 3. Odds of persisting amblyopia was 5.91 (5.24–6.66) and 2.49 (2.21–2.81) times greater in cohort–1 and cohort–2, respectively, relative to cohort–3. Odds were also higher for more socio–economically deprived groups and for any "Other than White" ethnicity. Reduced participation in sport, adverse general and mental health and well–being were all independently associated with persisting amblyopia, with strongest associations in the youngest cohorts. Associations with lower educational attainment and economic outcomes were only evident in the oldest cohort.

Conclusions: The overall frequency of persisting amblyopia has declined during the time in which universal child vision screening became established in the UK. Nevertheless, most adults treated for amblyopia in childhood have persisting vision deficits. There was no evidence that persisting amblyopia has vision–mediated effects on educational, employment, or economic outcomes. The observed adverse outcomes were largely those not directly mediated by vision. Patients undergoing treatment should be counselled about long–term outcomes.

Keywords: screening; long–term outcomes; public health policy; amblyopia

Highlights

- Whole population child vision screening is now well established in most countries to detect and enable early treatment of amblyopia, but its value is being questioned in the absence of a robust evidence base about the 'real–life' impact of living with persisting amblyopia.
- We found the risk of persisting amblyopia has declined in the UK since the introduction of universal childhood vision screening but the majority of those treated in childhood nevertheless have persisting reduced vision (incompletely treated amblyopia) into adult life. There were no associations with social outcomes directly dependent on vision. Associations with adverse mental health and well–being outcomes were strongest in the youngest cohort who would have benefitted from universal screening.
- Our study reaffirms the dearth of evidence to support the contention that living with amblyopia confers a direct vision–mediated impact on key domains of life. It does identify that the psycho–social impact of amblyopia may require attention in clinical management. Further research is warranted to understand why affected individuals, who have normal vision in one eye, report poorer health and well–being.

Introduction

Amblyopia (*'blunt sight'*) is a potentially reversible neurodevelopmental condition which causes impaired sight, typically in one eye. It arises when normal visual maturation processes are altered, commonly due to refractive error or strabismus, during the critical period of neuro–development in early childhood.[1,2,3] Affecting at least 3% of most populations, it is the most common condition managed in paediatric ophthalmology and a key paradigm for human neural plasticity. Treatment is undertaken in childhood whilst the visual system is malleable. Treatment mainstays remain occlusion ('patching') or optical penalisation (drugs causing defocus) of the *non–amblyopic eye* to 'stimulate' the amblyopic eye, but new binocular approaches are being investigated.[4–6] Whilst most individuals achieve significant improvements in acuity, 'gained' acuity declines over time in around a quarter of children after stopping treatment.[7] Many children do not achieve normal vision.[1,2] Thus, amblyopia can be expected to '*persist'*[8] into adult life in a significant proportion of treated individuals. However population–based estimates for this are lacking, which limits the ability to counsel patients at the start of treatment.

Universal childhood vision screening programmes targeting amblyopia exist worldwide.[1,2,9–11] One justification is prevention of vision impairment later in life in the uncommon event of disease or injury affecting the *non–amblyopic* eye, rendering reliance on the amblyopic eye.[12–14] The more important question is what is the 'real–life' impact of living with amblyopia *per se* i.e. vision not restored to normal despite treatment and no disease/injury to the non–amblyopic eye.[8, 15–17] There is remarkably limited evidence about this. Thus the debate continues about the public health value of universal childhood screening due to this paucity of robust evidence about long–term benefits of child vision screening on health or other outcomes later in life.[1,2,9,10,18] The equipoise necessary for randomised controlled trials comparing *no* screening with extant programmes is lacking. Other approaches are required. We report an investigation of the associations between '*persisting amblyopia'*[8] and social, economic, general and mental health and well–being outcomes in adult life, alongside an assessment of whether cohort effects in

these associations are evident during the period in which childhood vision screening became widely established in the United Kingdom.

Methods

Participants and Data Collection

We utilised data from 133,353 participants aged 40 years or more in the UK Biobank[19] study, eligible for an enhanced ophthalmic examination, comprising individuals whose childhoods span the period during which universal childhood vision screening became established in the UK. Participants reported their medical history, including amblyopia and other eye conditions and treatment for them, as well as lifestyle and environment. Data collection started in 2006–10 with subsequent ongoing data collection cycles. Data collected to the end of 2017 were used in the present study, to maximise use of available data from physical examinations, surveys and medical record linkage. Details of the enhanced ophthalmic examination, other physical assessments and biological samples is available at https://www.ukbiobank.ac.uk/. Record linkage for all participants to the UK's National Health Service health administrative dataset (HES)[20] comprising all hospital admissions and attendances, using standardised pre–codes for conditions and treatments, provided additional objective data on ophthalmic diagnoses. This dataset allowed evaluation of the socio–demographic factors associated with persisting amblyopia to identify potential confounders for the main analysis. The breadth of social, economic, health and well–being outcomes measured in *all* participants allowed an investigation of key long–term outcomes across the spectrum of life domains.

Case definition

Participants were classified as having amblyopia ('amblyopes') using all available data (ophthalmic assessment, HES linkage, or self–reported treatment) to validate their *self–report* of childhood amblyopia (i.e. ≤16yrs old). We used a hierarchical approach comprising presence of: i) strabismus ii) significant anisometropia (difference of at least +1.00/-1.00D between eyes), iii) significant astigmatism (cylinder power ≥1.00D), iv) significant refractive error per se (i.e. -3.00D/+3.00D or more extreme), v) less severe

refractive error but visual impairment without any other underlying eye disease (such as stimulus deprivation amblyopia or cataract), vi) current emmetropia (absence of refractive error, -0.99D to +0.99D) but self–reported glasses worn for hypermetropia in childhood and at least mild visual impairment but no other eye disease. In addition, those with amblyopia who did *not* self–report this (e.g. due to recall) were identified through record linkage to treatment codes using HES data. Thus *'persisting unilateral amblyopia'*[8] was defined as residual unilateral acuity deficit despite treatment in childhood. To assess specifically the impact of *'persisting unilateral amblyopia'*[8] the analysis of outcomes excluded participants with any other eye disease and those with current bilateral visual impairment or blindness (VI/SVI/BL using WHO taxonomy[21]), bilateral amblyopia or current near normal acuity (<0.06 logMAR). The comparator group comprised participants with bilateral normal visual acuity (i.e. 0.0 logMAR) and without primary refractive error (i.e. emmetropia) or any other eye disease or amblyogenic factors (using self–report, ophthalmic examination and HES data), representing the 'optimal' vision state and thus allowing the functional impact of persisting amblyopia to be clearly discernible. Those with presbyopia alone were not excluded from either group.

Outcomes in adult life

We used the diverse socio–economic, health and well–being outcomes collected in UK Biobank to ensure a wide–ranging view of the potential impact of persisting amblyopia, exploring both potential 'direct' and 'indirect' functional impact of amblyopia, where indirect indicates impact on outcomes through pathways that are not directly related to vision per se.

Social and economic outcomes comprised (appendix; Table 1S):

a) Educational attainment to assess direct functional impact of amblyopia on educational experience, categorised as a gradient towards lower attainment: University/college degree, A–levels/NVQ/HND/HNC/Other professional qualifications (i.e. school examinations at age 18 years or national vocational qualifications), O–levels/GCSEs/CSEs (i.e. school examinations by 16 years, the minimum statutory school–leaving age), no qualifications.

b) Self–reported current employment status to assess any functional impact of amblyopia on ability to work, categorised as a gradient towards lower working capacity: employed, retired, voluntary/unpaid work/student, looking after the household/family, unemployed and unable to work due to sickness or disability.

c) Personal economic status using the conventional measure of current housing tenure: owned, rented, or sheltered accommodation/care home.

d) Participation/engagement with any social activities in leisure time using self–report of: none, sports club, other club/group including pub, religious group, adult education class.

Health and well–being outcomes comprised (appendix; Table 2S):

a) General health using four indicators to assess any direct or indirect impact of amblyopia: i) self–rated current health (excellent, good, fair or poor), ii) receipt of UK government financial benefit for those with disabling chronic conditions,[22] iii) any self–reported long–standing illness (LSI), disability or infirmity, and iv) frailty measured as at least one fall during previous year.

b) Current mental health to assess indirect impact of amblyopia, using three self–reported measures: i) often feeling lonely (yes/no), ii) ever seen a doctor for anxiety, stress or depression, iii) general happiness (six categories from extremely happy to extremely unhappy).

c) Current well–being using three self–reported measures of general satisfaction with i) health, ii) family life and iii) friendships (six categories from extremely satisfied to extremely dissatisfied).

Statistical analysis

Descriptive statistics are shown as frequencies (%) with 95% confidence interval (CI). Differences in distribution of outcomes between amblyopic and non–amblyopic participants were assessed using the chi–squared test. We used logistic regression models to investigate persisting amblyopia as a risk factor for social, health and well–being outcomes in adulthood as follows: binary (longstanding illness, falls in the previous year and loneliness), ordinal (educational attainment, employment status, poor health status, happiness and satisfaction with health/family life/friendships) and multinomial (housing tenure, disability

allowance, ever seen a doctor for depression/anxiety and participation in social activities). Sex (male/female), age (40–49, 50–59, 60–70 years), ethnicity (categorised as White or Other due to the small number (i.e. <3%) of all other ethnic groups combined in the amblyopia group), and social deprivation score (Townsend Index deprivation score at the time of recruitment; 1st quintile being most affluent[23]) were investigated as potential confounders in these models. We categorised participants into three age groups (cohorts) to distinguish pre– and post–screening eras, that initiated in the 1960s in UK,[11] allowing examination of any cohort effects in associations consistent with an impact of universal vision screening. Specifically, those aged 40 to 49 years would have undergone whole population screening and those aged 60 to 70 years would not. All participants had treatment once diagnosed.

We additionally adjusted analyses as follows: i) socio–economic and general health outcomes for presence of long–standing illness (LSI) and ii) life satisfaction outcomes for seeing a doctor for mental health issues and also for LSI. Since advanced age is associated with coexisting disadvantages, we also performed stratified analyses by age group. Goodness of fit was assessed with the likelihood ratio (LR) chi–square test. All tests were two–sided at 5% significance level and analyses were performed in Stata v15.0.

To validate our 'phenotyping' we compared frequency of amblyopia amongst UK Biobank participants born in 1958 with that previously reported in the 1958 British Birth Cohort study which used longitudinal clinical assessments to determine amblyopia status.[8]

Results

The analysis drew on 126,400 participants (Figure 1), invited to the enhanced ophthalmic examination from which we excluded those with incomplete or missing ophthalmic data necessary to confirm self–reported amblyopia (251) and those with other eye diseases (14,688). Whilst males and younger participants and those from any 'Other' (i.e. not 'White') ethnic groups or most socio–economically deprived groups were more likely to have missing data, differences were minimal.

Our sample comprised 3,394 confirmed amblyopes (80% of those who self–reported amblyopia formally validated using other data). Thus the overall frequency for confirmed amblyopia was 3.0% (3,394/111,461; 95%CI: 2.9% to 3.1%). It was lowest among those born after screening for amblyopia become widespread in the UK, specifically 2.5% (2.3% to 2.6%) for the 40 to 49 year age group; 3.1% (2.9% to 3.3%) for 50 to 59 years and 3.4% (3.2% to 3.5%) for 60 to 70 year olds.

Notably 77% (2,626/3,394; 95%CI: 76% to 79%) of all amblyopes had *persisting unilateral amblyopia.* This proportion was lowest in the youngest age group: 73% (495/677; 70% to 76%) for 40 to 49 years and 78% for 50 to 59 (914/1,166; 76% to 81%) and 78% for 60 to 70 years (1,217/1,551; 76% to 80%). Specifically, the frequency of *persisting unilateral amblyopia* among 3,390 UK Biobank participants born in 1958 was 2.3% (1.9% to 2.9%) compared to 4.8% (4.4% to 5.3%) for persisting unilateral *and* bilateral amblyopia *combined* in our prior study of the 1958 British Birth cohort[8], supporting the validity of our approach to 'phenotyping'.

The main analysis of associations with social, health and well–being outcomes drew on 2,392 participants with *persisting unilateral amblyopia*, for whom complete data were available on all outcomes. They were compared with 16,839 participants with bilateral normal visual acuity, emmetropia or presbyopia only and no other eye disease or amblyogenic factors. Table 1 shows older age (in a gradient spanning the eras before and after implementation of childhood vision screening) and being in the worst quintile of socio–economic deprivation were independently associated with increased odds of persisting unilateral amblyopia, whilst being male or of 'Other' (i.e. not 'White') ethnicity were associated with reduced odds. As these are also known to be associated with social, health and well–being outcomes, these variables were included as confounders in analysis described below.

Associations (adjusted) between persisting unilateral amblyopia and outcomes (Table 2)

Social and economic

In *fully* adjusted analysis, *persisting unilateral amblyopia* was *not* independently associated with higher odds of having limited working capacity/ability (1.13 (0.99; 1.28)) or lower current economic status

(measured by housing tenure) (1.19 (1.00; 1.40)). It was also *not* associated with lower educational attainment (1.06 (0.98; 1.15)). A subgroup analysis of those currently in paid employment showed no significant differences in gradient of occupation 'categories' between those with persisting amblyopia and normal vision (1.06 (0.97; 1.15)). The single association observed in this domain was the lower odds of participation/engagement in sports (0.78 (0.70; 0.88)). (*Social and Economic outcomes*; Table 2)

Health and well–being

Those with *persisting unilateral amblyopia* were more likely to have worse *current* general health, with consistency in independent associations with all four indicators (odds ratios in the adjusted models ranging from 1.29 to 1.46), three of which remained significant albeit attenuated by adjustment for long–standing illness. Equally consistent associations between amblyopia and poorer *current* mental health outcomes were observed (odds ratios in the adjusted models ranging from 1.21 to 1.26). Apart from the association with seeing a doctor for anxiety/depression, these also remained significant, although attenuated, after further adjustment for long–standing illness. There was some consistency in the independent associations between amblyopia and well–being measured as lower self–reported *satisfaction* with health, with relationships with family, or relationships with friends (odds ratios in the adjusted models ranging from 1.12 to 1.25). However the association with lower satisfaction with health was not significant after additional adjustment for long–standing illness whereas the associations with family life and friendships became stronger after this adjustment. (*Health and Well–being outcomes*; Table 2)

Temporal trends in associations of persisting amblyopia (Table3)

The effect size of associations between persisting amblyopia and outcomes varied by age group (cohort), as shown in Table 3. Associations with lower socio–economic status (housing tenure) (1.44 (1.08; 1.94)) and limited working capacity/ability (1.30 (1.08; 1.57)) were now evident but *only* in the oldest cohort. This cohort can be reasonably assumed *not* to have undergone childhood vision screening and thus may have undergone treatment late resulting in poorer vision from childhood onwards. By contrast associations with three of the four measures of adverse general health were seen in all three cohorts, with the largest

effect size for two of these in the youngest cohort. Interestingly the association with receiving disability–related financial assistance was only evident in the oldest cohort. Conversely associations with the three adverse mental health outcomes were only observed in the younger cohorts, with the magnitude of the effect size depending on the cohort and the outcome. Associations with the three adverse well–being outcomes were more prominent amongst the youngest cohort, who would have experienced early detection and treatment through vision screening.

Discussion

This novel investigation shows that more than three quarters of UK adults aged 40 years or more who were treated for amblyopia as children, have a *persisting* vision deficit as adults. The risk of having this *persisting amblyopia* is independently greater for older adults, those socio–economically deprived backgrounds and lower for men and those of any ethnicity other than White. Overall *persisting amblyopia* is associated with adverse general health, mental health and well–being outcomes. There was no association between adverse educational, occupational or economic outcomes and persisting amblyopia, despite these outcomes being the ones most directly impacted by reduced vision. There was some variation in size and strength of these associations by age group which defined the three time periods during the decades in which childhood vision screening for amblyopia was introduced, became more common and was finally well–established in the UK.

We used the UK Biobank study in the absence of any alternative longitudinal study of sufficient size which includes formal ophthalmic assessments participants. Whilst the scale and detail afforded by Biobank is unrivalled[19] there are nevertheless potential limitations to our study. Whilst our overall sample was large, because amblyopia is not common, it is possible that some important true associations were missed, despite a number of associations observed with effect size of around 15%. It is also theoretically possible that the 'statistically significant' associations were observed by chance alone. The accuracy of our hierarchical process for 'ruling in' and 'ruling out' amblyopia using clinical measures alongside health services data on diagnoses and treatment to minimise the impact of recall bias and to validate self–report

and is supported by similarities in frequency reported previously in other British population–based studies.[8,24] We used history of strabismus/strabismus treatment in our hierarchical 'phenotyping' of persisting/residual amblyopia. Due to the size of our sample we did not undertake subgroup analysis of strabismic versus anisometropic or mixed amblyopia so we are unable to comment on whether the observed associations with health and well–being differ between these groups. The formal ophthalmic assessment and linkage to HES data allowed identification of an appropriate comparator group with normal vision and no history of any eye disease.

As this is an observational study, none of the observed associations can be assumed to reflect a causal relationship. Reverse causality can be ruled out as amblyopia is a childhood disorder and all the outcomes were assessed in adult life and at the same time point. We used broad age groups to examine changes over time as screening was first introduced and eventually became established universally in the UK. Other significant societal changes occurred over these decades which would have affected the lives of participants as both children and adults, for example in terms of social structures, expectations or 'norms'. Therefore any variations in associations by age group cannot be attributed solely or mainly to the introduction of universal child vision screening. Finally the UK Biobank study does not comprise a truly random subsample of the general population, and studies using this resource cannot offer population prevalence. However, the associations we report are internally valid, and in keeping with other studies using this resource,[25] we suggest the findings are generalizable to similar populations.

There are no studies with which we can *directly* compare our findings relating to frequency and potential impact of amblyopia persisting into adult life. Indeed there is a striking paucity of investigations of the long–term 'real–life' impact of amblyopia *per se*.[12] This is hampering health economic evaluations[14] and underpins the ongoing debate about the value of universal childhood vision screening.[18] The extensive literature on children describes deficits in specific visual functions in amblyopia, *but* does not explain whether and how such discernible deficits of the disorder itself translate into any 'real–life' adverse outcomes of daily living.[8,14,16,17, 26, 27] Instead it evidences the adverse psychosocial impact of *treatment,* for

example of occlusion and/or spectacle wear.[28] It is possible to speculate that this may in part explain the associations with mental health and 'life satisfaction' scores in the younger cohorts observed in our study, as discussed below. This is difficult to disentangle as a study of outcomes in those diagnosed with amblyopia but intentionally not treated would be unethical. The direct *functional* impact of amblyopia, mediated through reduced vision and/or impaired stereopsis, is arguably the most relevant issue in the debate about universal screening. Associations between amblyopia and impaired fine motor skills and reading speed in childhood[29] have been reported. It is therefore striking that adverse educational attainment was not associated with persisting amblyopia in our study. This mirrors prior research.[8,17,30] We also found no associations with adverse employment or economic outcomes. Instead our findings paint a picture of current disadvantage across general and mental health and well–being domains reported by adults with persisting amblyopia, even though they have normal vision in their non–amblyopic eye. This has not been observed in prior research.[8,15,17]

We investigated whether different age groups (cohorts) had different patterns of associations as a way of indirectly assessing the impact of the establishment of universal child vision screening aimed at achieving earlier treatment and better outcomes. It is often argued that amblyopia can impact on employment and participation in specific social activities because impaired visual function. We did not find an association between reduced capacity to work/not being employed and presence of persisting amblyopia. Nor was there evidence of differences with regards to actual occupation, including jobs that are considered to require good vision in both eyes.[31] Our finding aligns with prior research[8] and we suggest might be explained by adjustment to a long–standing visual deficit originating in childhood versus acutely losing vision through injury or disease. One explanation for the association, seen only in the younger cohorts, of reduced participation in sports–based, but not other social activities, is a lifetime's awareness of reduced depth–vision or concern about injuring the non–amblyopic eye, rather than solely or mainly actual *ability* to participate. Similarly the association with lower 'life satisfaction' scores in the younger cohorts may reflect the challenges and possibly disappointment of living with a residual deficit in vision despite

treatment or living with an 'invisible' disability. The association with increased risk of falls is not surprising but the associations with other markers of poorer general health are unexpected and are also consistent across the cohorts. Evidence [32] of the significant impact that even mildly impaired vision in *both* eyes can have when *acquired* in adult life is attributable to vision mediated impact on tasks of daily living that require good vision in both eyes. Our findings demonstrate for the first time at population level that, despite having normal vision in one eye, living with *persisting unilateral amblyopia* can be associated with worse self–rated health and well–being. One possible explanation is a gap between the *expectations* of affected individuals of the effectiveness of screening and treatment and the *reality* of their own visual outcome, which would align with the established disability paradox theory.[33]

Although a variety of standalone programmes had existed before, child vision screening in the UK was first implemented formally into child health surveillance programmes during the 1960s. One impetus for creating the formal universal programme that exists today[34] was the recognition that amblyopic children from socio–economically disadvantaged families were likely to present later and have worse outcomes.[35] Our finding that women, those in the most socio–economically deprived quintile and of White ethnicity were at greater risk of having persisting amblyopia identifies that some groups may benefit from closer attention during treatment. It also points to the potential impact of universal screening in addressing inequalities. Conventionally amblyopia treatment ceases and children are discharged from care once they reach visual maturity i.e. no further gain can be expected. This inevitably means a dearth of data about long–term stability of attained visual function. Nevertheless, prevailing clinical thinking is that around three quarters of all children will *retain t*he gains in acuity achieved through treatment[7] although it is projected that two thirds of treated children will not achieve normal vision.[36] However three quarters of all people with treated amblyopia in our study had a *residual acuity deficit* in adult life, which supports attrition of visual function over the life course, i.e. after the time window of the 'critical period' of visual maturation has closed. This lack of *guaranteed* long–term stability of treatment outcomes is relevant because a key justification of childhood vision screening is as a means of ensuring the amblyopic eye

serves usefully as a 'back up'.[37] This would therefore prevent subsequent *bilateral* visual impairment, should disease or injury affect the non–amblyopic eye, and in turn prevent the attendant impacts on health status,[8,33] risk of falls,[38] depression,[39] and well–being.[9,40] Thus our finding of a remarkably high frequency of residual amblyopia highlights that further efforts are required to optimise existing treatment or develop new approaches to ensure long–term stability of gained vision.[5,6] Whilst interest in neural plasticity in adult life[6] has stimulated some interest in addressing residual amblyopia *per se*, this should be viewed as an adjunct, tapping into a reserve of 'potential vision', rather an alternative to treatment during childhood.[29] The importance of primary treatment in childhood is underlined by evidence that improvement in visual acuity in the *amblyopic* eye after loss of sight due to disease or injury in the non–amblyopic eye is more likely in those who have previously undergone amblyopia treatment.[13]

Conclusion

Our study demonstrates that the overall frequency and the odds of having *persisting* (residual) *unilateral amblyopia* as an adult have declined since the introduction of formal vision screening in the UK. It offers no evidence to support the notion that persisting amblyopia has significant vision–mediated effects on educational, employment or economic outcomes. But it does identify unexpected associations with adverse self–rated health and well–being. Persisting amblyopia may have different impacts than might be assumed and this warrants further investigation. In the meantime, our study shows why clinicians should consider the expectations of their patients diagnosed with amblyopia and to counsel them and their families about expected long–term outcomes after treatment.

Declarations

Ethics approval/ consent to participate: The Biobank Study was approved by the National Health Service National Research Ethics Service (Ref 11/NW/0382) and all participants gave written informed consent to participation and linkage to HES data.

Availability of data and material: The MTA precludes direct data sharing. All derived data are deposited back to UK Biobank. Dissemination of the findings to study participants will be through the UK Biobank website.

Contributors: VB and PC contributed equally. VB analysed and interpreted the data, wrote the first draft of the manuscript, critically reviewed and revised the manuscript for important intellectual content, and approved the final version for submission; PC contributed to the concept of the study and data acquisition, supervised the data analysis, interpreted the data, critically reviewed and revised the manuscript for important intellectual content, and approved the final version for submission; JR contributed to the concept of the study and data acquisition, interpreted the data, critically reviewed and revised the manuscript for important intellectual content, approved the final version for submission, obtained funding and had the overall supervision of the study. All authors had full access to the data (including statistical reports and tables) in the study and can take responsibility for the integrity of the data and accuracy of the data analysis. JR, as corresponding author, affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained. JR had final responsibility for the decision to submit for publication.

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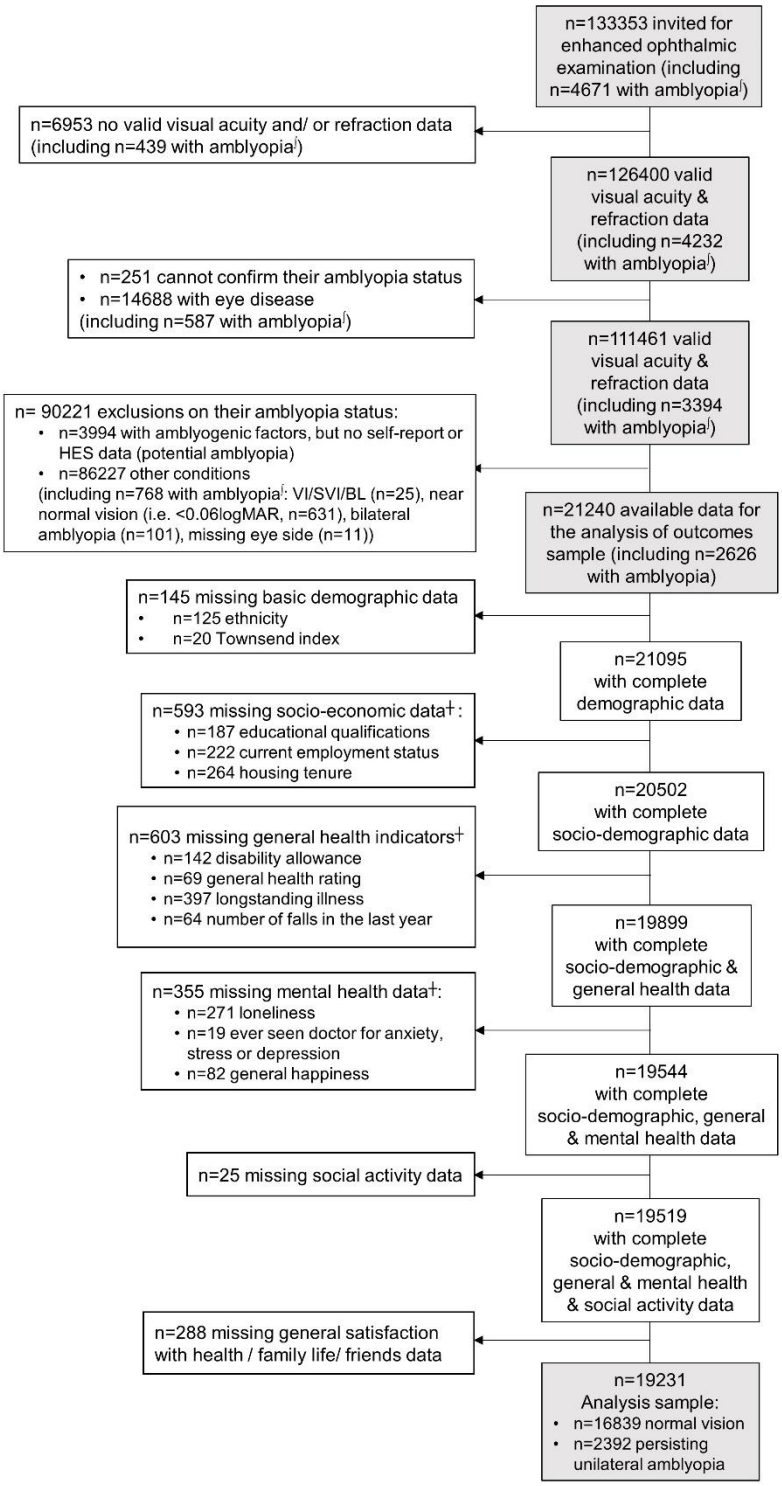
Figure 1: Flow of Participants in the study.



Legend

[ʃ]Either self–report amblyopia or identified through Hospital Episode Statistics (HES).

[+]Categories below not mutually exclusive.

Shaded boxes indicate key numbers referenced in the text.

Table 1: Associations (odds ratios (95% confidence intervals)) of socio–demographic characteristics with persisting unilateral amblyopia.

	Crude	P	LR-test (df); P	Adjusted[ʃ]	P	LR-test (df); P
Sex			1.08 (1); 0.30			1145 (8); <0.001
Female	1			1		
Male	0.96 (0.88; 1.04)	0.31		0.88 (0.81; 0.96)	0.005	
Age group			1034 (2); <0.001			
[40–49] yrs	1			1		
[50–59] yrs	2.55 (2.27; 2.88)	<0.001		2.49 (2.21; 2.81)	<0.001	
[60–70] yrs	6.11 (5.44; 6.87)	<0.001		5.91 (5.24; 6.66)	<0.001	
Ethnic background			163 (1); <0.001			
White	1			1		
Other	0.26 (0.20; 0.33)	<0.001		0.36 (0.27; 0.46)	<0.001	
Socioeconomic deprivation (Townsend quintiles)			9.11 (4); 0.06			
1st Quantile (least deprivation)	1			1		
2nd Quintile	1.02 (0.88; 1.17)	0.80		1.04 (0.90; 1.21)	0.56	
3rd Quintile	0.93 (0.81; 1.07)	0.32		1.02 (0.88; 1.19)	0.76	
4th Quintile	0.88 (0.76; 1.01)	0.06		1.05 (0.91; 1.21)	0.54	

5th Quintile (more deprivation)	1.04 (0.91; 1.19)	0.57	1.47 (1.27; 1.69)	<0.001

[∫] Model adjusted for all variables shown in table. For each model is given the likelihood ratio (LR) chi-square test along with the relevant degrees of freedom (df) and it's p-value.

Table 2: Associations of persisting unilateral amblyopia (versus normal vision) with social, economic, general and mental health and well–being outcomes.

	Odds ratio (95% confidence intervals)					
	Crude	P	Adjusted[ʃ]	P	Additionally adjusted for LSI	P
Outcomes						
Social and economic						
Education (gradient towards lower attainment)						
University/ college to no qualifications	1.23 (1.14; 1.33)	<0.001	1.06 (0.98; 1.15)	0.18	1.05 (0.97; 1.14)	0.27
Employment status (gradient towards limited working capacity/ ability)						
Employed to unable to work	1.21 (1.07; 1.36)	0.002	1.13 (0.99; 1.28)	0.06	1.07 (0.94; 1.22)	0.27
Economic status						
Housing tenure (rented vs owned)	0.92 (0.79; 1.07)	0.27	1.19 (1.00; 1.40)	0.05	1.14 (0.96; 1.34)	0.14
Social participation						
Participation in sports club vs none	0.76 (0.68; 0.85)	<0.001	0.78 (0.70; 0.88)	<0.001	0.80 (0.72; 0.90)	<0.001
Participation in social activities vs none	1.17 (1.06; 1.30)	0.002	1.04 (0.94; 1.16)	0.42	1.05 (0.95; 1.17)	0.34

Health and well–being						
General health						
Overall poorer self–rated health	1.27 (1.16; 1.38)	<0.001	1.29 (1.18; 1.41)	<0.001	1.18 (1.08; 1.29)	<0.001
Receipt of disability–related financial assistance	1.95 (1.61; 2.37)	<0.001	1.46 (1.19; 1.79)	<0.001	1.23 (1.00; 1.53)	0.05
Any long standing illness (LSI)	1.61 (1.47; 1.76)	<0.001	1.35 (1.23; 1.48)	<0.001	..	..
At least one fall over the last year	1.51 (1.36; 1.68)	<0.001	1.36 (1.22; 1.51)	<0.001	1.31 (1.17; 1.46)	<0.001
Mental health						
Feeling often lonely	1.16 (1.05; 1.30)	0.005	1.26 (1.12; 1.41)	<0.001	1.21 (1.09; 1.36)	0.001
Seen doctor for depression/ anxiety	1.25 (1.09; 1.43)	0.001	1.23 (1.06; 1.41)	0.005	1.14 (0.99; 1.32)	0.08
Overall feeling less happy	1.08 (1.00; 1.18)	0.06	1.21 (1.11; 1.31)	<0.001	1.17 (1.08; 1.28)	<0.001
Well–being						
Overall less satisfaction from						
Health	1.13 (1.04; 1.22)	0.004	1.16 (1.07; 1.26)	<0.001	1.07 (0.98; 1.16)	0.14
Family life	1.11 (1.03; 1.21)	0.007	1.25 (1.15; 1.36)	<0.001	1.23 (1.13; 1.34)	<0.001
Friendships	1.01 (0.93; 1.09)	0.82	1.12 (1.03; 1.22)	0.008	1.10 (1.01; 1.20)	0.02

[∫] Models adjusted for age, sex, ethnicity and deprivation. LSI: Long standing illness.

Table 3: Associations of persisting unilateral amblyopia (versus normal vision) with socio–economic, general and mental health and well–being outcomes, stratified by age group (cohort).

	Odds ratios (95% confidence intervals)					
	40–49 yrs	P	50–59 yrs	P	60–70 yrs	P
Outcomes						
Social and economic						
Education (gradient towards lower attainment)						
University/ college to no qualifications	0.95 (0.80; 1.13)	0.55	1.08 (0.95; 1.24)	0.25	1.08 (0.95; 1.22)	0.23
Employment status (gradient towards limited working capacity/ ability)						
Employed to unable to work	0.97 (0.71; 1.31)	0.83	1.06 (0.86; 1.31)	0.58	1.30 (1.08; 1.57)	0.005
Economic status						
Housing tenure (rented vs owned)	1.10 (0.81; 1.48)	0.55	1.00 (0.75; 1.34)	0.99	1.44 (1.08; 1.94)	0.01
Social participation						
Participation in sports club vs none	0.76 (0.60; 0.95)	0.02	0.74 (0.61; 0.89)	0.001	0.85 (0.71; 1.03)	0.10
Participation in other activities vs none	0.93 (0.74; 1.18)	0.55	1.04 (0.87; 1.23)	0.68	1.13 (0.96; 1.34)	0.14
Health and well–being						

General health						
Overall poorer self–rated health	1.27 (1.05; 1.54)	0.01	1.41 (1.22; 1.63)	<0.001	1.20 (1.04; 1.37)	0.01
Receipt of disability–related financial assistance	1.57 (0.91; 2.71)	0.10	1.17 (0.81; 1.70)	0.39	1.64 (1.24; 2.17)	0.001
Any long standing illness	1.53 (1.24; 1.89)	<0.001	1.30 (1.12; 1.53)	0.001	1.31 (1.14; 1.51)	<0.001
At least one fall over the last year	1.42 (1.11; 1.82)	0.005	1.35 (1.14; 1.61)	0.001	1.35 (1.14; 1.59)	<0.001
Mental health						
Feeling often lonely	1.14 (0.90; 1.44)	0.29	1.49 (1.25; 1.77)	<0.001	1.11 (0.92; 1.34)	0.26
Seen doctor for depression/ anxiety	1.31 (0.98; 1.76)	0.07	1.23 (0.97; 1.55)	0.08	1.20 (0.96; 1.49)	0.12
Overall feeling less happy	1.34 (1.11; 1.62)	0.002	1.22 (1.05; 1.41)	0.007	1.14 (1.00; 1.30)	0.06
Well–being						
Overall less satisfaction from						
Health	1.32 (1.10; 1.58)	0.003	1.11 (0.96; 1.27)	0.15	1.15 (1.01; 1.31)	0.04
Family life	1.34 (1.12; 1.60)	0.001	1.30 (1.14; 1.49)	<0.001	1.17 (1.03; 1.33)	0.02
Friendships	1.21 (1.01; 1.45)	0.04	1.18 (1.02; 1.35)	0.02	1.03 (0.90; 1.17)	0.70

[J] Models adjusted for age, sex, ethnicity and deprivation.

On-line supplementary material

Table 1S: Distribution of demographic and socio-economic characteristics in the analysis sample (n=19,231).

	Normal vision (n=16,839)		Persisting unilateral amblyopia (n=2,392)		
	n	% (95% CI)	n	% (95% CI)	Chi^2 (df); p
Demographic					
Sex					1.076 (1); 0.31
Females	8,933	53 (52; 54)	1296	54 (52; 56)	
Males	7,906	47 (46; 48)	1096	46 (44; 48)	
Age					1100 (2); <0.0001
40-49	7,863	47 (46; 47)	445	19 (17; 20)	
50-59	5,743	34 (33; 35)	829	35 (33; 37)	
60-70	3,233	19 (19; 20)	1,118	47 (45; 49)	
Ethnicity					125.357 (1); <0.0001
White	15,237	90 (90; 91)	2,329	97 (97; 98)	
Non-white	1,602	10 (9; 10)	63	2.6 (2.1; 3.4)	
Townsend					9.044 (4); 0.06
1st Q	2,791	17 (16; 17)	409	17 (16; 19)	
2nd Q	3,217	19 (19; 20)	480	20 (19; 22)	
3rd Q	3,336	20 (19; 20)	455	19 (17; 21)	
4th Q	3,907	23 (23; 24)	501	21 (19; 23)	
5th Q	3,588	21 (21; 22)	547	23 (21; 25)	
Social and economic					
Education					117.164 (3); <0.0001
University/ college degree	6,315	38 (37; 38)	797	33 (31; 35)	
A-levels/ NVQ/ HND/ HNC/ Other professional qualifications	3,860	23 (22; 24)	600	25 (23; 27)	
O-levels/ GCSEs/ CSEs	5,220	31 (30; 32)	638	27 (25; 28)	
No qualification	1,444	8.6 (8.2; 9.0)	357	15 (14; 16)	
Employment status					134.322 (5); <0.0001
Employed	14,739	88 (87; 88)	2,032	85 (83; 86)	
Retired	460	2.7 (2.5; 3.0)	165	6.9 (5.9; 8.0)	
Student/ volunteer	156	0.9 (0.8; 1.1)	15	0.6 (0.4; 1.0)	
Household	712	4.2 (3.9; 4.5)	66	2.8 (2.2; 3.5)	

Unemployed	431	2.6 (2.3; 2.8)	49	2.0 (1.6; 2.7)	
Unable to work	341	2.1 (1.8; 2.2)	66	2.8 (2.2; 3.5)	
Economic status					11.675 (3); 0.009
(housing tenure)					
Ownership	15,070	89 (89; 90)	2,161	90 (89; 91)	
Rent	1,631	9.7 (9.2; 10)	215	9.0 (7.9; 10)	
Live in rent free	126	0.7 (0.6; 0.9)	10	0.4 (0.2; 0.8)	
Care home	12	0.1 (0.04; 0.1)	6	0.3 (0.1; 0.6)	
Social participation					66.319 (2); <0.0001
No social activity	5,026	30 (29; 31)	732	31 (29; 32)	
Participating in sports club (at least once/week)	6,007	36 (35; 36)	667	28 (26; 30)	
Participating in social activities (i.e. club Pub/ religious club/ educational classes)	5,806	34 (34; 35)	993	41 (40; 43)	

Table 2S: Distribution of general and mental health outcome and well-being characteristics in the analysis sample (n=19,231).

	Normal vision (n=16,839)		Persisting unilateral amblyopia (n=2,392)		
	n	% (95% CI)	n	% (95% CI)	Chi^2 (df); p
Health and well-being					
General health					
Overall self-rated health					33.985 (3); <0.0001
Excellent	2,839	17 (16; 17)	333	14 (13; 15)	
Good	10,137	60 (59; 61)	1,406	59 (57; 61)	
Fair	3,271	19 (19; 20)	531	22 (21; 24)	
Poor	592	4 (3; 4)	122	5 (4; 6)	
Receipt of disability-related financial assistance					47.934 (2); <0.0001
No allowance	16,331	97 (97; 97)	2,255	94 (93; 95)	
Disability allowance	386	2.3 (2.1; 2.5)	101	4.2 (3.5; 5.1)	
Other allowance	122	0.7 (0.6; 0.9)	36	2 (1; 2)	
Any long-standing illness					106.901 (1); <0.0001
No	12,502	74 (74; 75)	1,536	64 (62; 66)	
Yes	4,337	26 (25; 26)	856	36 (34; 38)	
Number of falls over the last year					62.584 (1); <0.0001
No falls	14,043	83 (83; 84)	1,838	77 (75; 78)	
At least one fall	2,796	17 (16; 17)	554	23 (22; 25)	
Mental Health					
Often feeling lonely					7.802 (1); 0.005
No	13,808	82 (81; 83)	1,905	80 (78; 81)	
Yes	3,031	18 (17; 19)	487	20 (19; 22)	
Seen doctor for depression/ anxiety					16.995 (2); <0.0001
No	11,297	67 (66; 68)	1,505	63 (61; 65)	

	GP only	3,776	22 (22; 23)	593	25 (23; 27)	
	Psychiatrist	1,766	10 (10; 11)	294	12 (11; 14)	
Overall happiness						7.341 (5); 0.18
	Extremely happy	907	5.4 (5.1; 5.7)	113	4.7 (3.9; 5.6)	
	Very happy	6,405	38 (37; 39)	892	37 (35; 39)	
	Moderately happy	8,723	52 (51; 53)	1,248	52 (50; 54)	
	Moderately unhappy	668	4.0 (3.7; 4.3)	113	4.8 (4; 5.7)	
	Very unhappy	101	0.60 (0.49; 0.73)	18	0.75 (0.47; 1.19)	
	Extremely unhappy	35	0.21 (0.15; 0.29)	8	0.33 (0.17; 0.67)	
Well-being						
Overall satisfaction from health status						11.261 (5); 0.05
	Extremely happy	969	5.8 (5.4; 6.1)	126	5.3 (4.4; 6.2)	
	Very happy	5,744	34 (33; 35)	764	32 (30; 34)	
	Moderately happy	8,022	48 (47; 48)	1,168	49 (47; 51)	
	Moderately unhappy	1,543	9.2 (8.7; 9.6)	230	9.6 (8.5; 11)	
	Very unhappy	392	2.3 (2.1; 2.6)	71	3.0 (2.4; 3.7)	
	Extremely unhappy	169	1.0 (0.86; 1.2)	33	1.4 (0.98; 1.9)	
Overall satisfaction from family life						13.529 (5); 0.02
	Extremely happy	3,337	20 (19; 20)	437	18 (17; 20)	
	Very happy	7,474	44 (44; 45)	1,039	43 (41; 45)	
	Moderately happy	4,837	29 (28; 29)	725	30 (29; 32)	
	Moderately unhappy	851	5.1 (4.7; 5.4)	123	5.1 (4.3; 6.1)	
	Very unhappy	241	1.4 (1.3; 1.6)	43	1.8 (1.3; 2.4)	
	Extremely unhappy	99	0.59 (0.48; 0.72)	25	1.0 (0.71; 1.5)	
Overall satisfaction from friends						8.053 (5); 0.15
	Extremely happy	2,229	13 (13; 14)	297	12 (11; 14)	
	Very happy	8,611	51 (50; 52)	1,251	52 (50; 54)	
	Moderately happy	5,381	32 (31; 33)	756	32 (30; 34)	
	Moderately unhappy	518	3.1 (2.8; 3.3)	65	2.7 (2.1; 3.4)	
	Very unhappy	78	0.46 (0.37; 0.58)	16	0.67 (0.41; 1.1)	
	Extremely unhappy	22	0.13 (0.09; 0.20)	7	0.29 (0.14; 0.61)	

Table 3S: Likelihood ratio (LR) tests and degrees of freedom (df) for the associations of persisting unilateral amblyopia (versus normal vision) with social, economic, general and mental health and well–being outcomes (Table 2 in main paper).

	Crude		Adjusted[∫]		Additionally adjusted for LSI	
	LR-test (df)	P	LR-test (df)	P	LR-test (df)	P
Outcomes						
Social and economic						
Education (gradient towards lower attainment)	26.49 (1)	<0.001	306.75 (9)	<0.001	340.03 (10)	<0.001
Employment status (gradient towards limited working capacity/ ability)	9.30 (1)	0.002	310.91 (9)	<0.001	554.61 (10)	<0.001
Economic status	10.25 (3)	0.017	2449 (27)	<0.001	2554 (30)	<0.001
Social participation	67.27 (2)	<0.001	396.62 (18)	<0.001	507.34 (20)	<0.001
Health and well–being						
General health						
Overall poorer self–rated health	30.35 (1)	<0.001	404.95 (9)	<0.001	3326.92 (10)	<0.001
Receipt of disability–related financial assistance	40.59 (1)	<0.001	266.11 (9)	<0.001	1448.77 (10)	<0.001
Any long standing illness (LSI)	101.72 (1)	<0.001	456.99 (9)	<0.001	..	..
At least one fall over the last year	58.63 (1)	<0.001	250.19 (9)	<0.001	486.42 (10)	<0.001
Mental health						
Feeling often lonely	7.62 (1)	0.006	331.47 (9)	<0.001	499.32 (10)	<0.001

Seen doctor for depression/ anxiety	16.71 (2)	<0.001	826.13 (18)	<0.001	1366.68 (20)	<0.001
Overall feeling less happy	3.60 (1)	0.06	300.98 (9)	<0.001	477.17 (10)	<0.001
Well–being						
Overall less satisfaction from						
Health	8.23 (1)	0.004	155.14 (9)	<0.001	2388.95 (10)	<0.001
Family life	7.27 (1)	<0.001	318.17 (9)	<0.001	385.49 (10)	<0.001
Friendships	0.05 (1)	0.82	405.46 (9)	<0.001	458.93 (10)	<0.001

[∫]Models adjusted for age, sex, ethnicity and deprivation. LSI: Long standing illness.

Table 4S: Likelihood ratio (LR) tests and degrees of freedom (df) for the associations of persisting unilateral amblyopia (versus normal vision) with socio–economic, general and mental health and well–being outcomes, stratified by age group (cohort) (Table 3 in main paper).

	40–49 years		50–59 years		60–70 years	
	LR-test (df)	P	LR-test (df)	P	LR-test (df)	P
Outcomes						
Social and economic						
Education (gradient towards lower attainment)	56.25 (7)	<0.001	31.57 (7)	<0.001	37.64 (7)	<0.001
Employment status (gradient towards limited working capacity/ ability)	251.01 (7)	<0.001	111.66 (7)	<0.001	23.97 (7)	0.001
Economic status	1166.64 (21)	<0.001	614.16 (21)	<0.001	464.48 (21)	<0.001
Social participation	107.18 (14)	<0.001	96.45 (14)	<0.001	50.34 (14)	<0.001
Health and well–being						
General health						
Overall poorer self–rated health	190.25 (7)	<0.001	135.90 (7)	<0.001	93.97 (7)	<0.001
Receipt of disability–related financial assistance	68.98 (7)	<0.001	42.50 (7)	<0.001	82.63 (7)	<0.001
Any long standing illness	78.52 (7)	<0.001	56.98 (7)	<0.001	72.03 (7)	<0.001
At least one fall over the last year	43.89 (7)	<0.001	94.33 (7)	<0.001	65.99 (7)	<0.001
Mental health						
Feeling often lonely	120.13 (7)	<0.001	117.29 (7)	<0.001	72.20 (7)	<0.001
Seen doctor for depression/ anxiety	441.15 (14)	<0.001	243.72 (14)	<0.001	144.42 (14)	<0.001

	Overall feeling less happy	72.54 (7)	<0.001	70.09 (7)	<0.001	62.35 (7)	<0.001
Well–being							
	Overall less satisfaction from						
	Health	75.39 (7)	<0.001	57.83 (7)	<0.001	28.48 (7)	0.0002
	Family life	84.33 (7)	<0.001	88.67 (7)	<0.001	47.05 (7)	<0.001
	Friendships	163.10 (7)	<0.001	98.24 (7)	<0.001	79.40 (7)	<0.001

[Models adjusted for age, sex, ethnicity and deprivation.