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Impact of Persisting Amblyopia on Socioeconomic, Health, and Well-Being Outcomes in Adult Life: Findings From the UK Biobank

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ABSTRACT

Objectives: This study aimed to investigate associations between persisting amblyopia into adulthood and its "real-life" impacts and inform the current debate about the value of childhood vision screening programs.

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

Results: Of 3395 (3%) participants with confirmed amblyopia, overall 77% (2627) had persisting amblyopia, declining from 78% in cohort 1 to 73% in cohort 3. The odds of persisting amblyopia were 5.91 (5.24-6.66) and 2.49 (2.21-2.81) times greater in cohort 1 and cohort 2, respectively, than cohort 3. The odds were also higher for more socioeconomically deprived groups and for white ethnicity. Reduced participation in sport, adverse general and mental health, and well-being were all independently associated with persisting amblyopia, with the strongest associations in the youngest cohorts. Associations with lower educational attainment and economic outcomes were only evident in the oldest cohort.

Conclusions: There has been a decline in the overall frequency of persisting amblyopia since the introduction of universal child vision screening in the United Kingdom. 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-related, or economic outcomes. The observed adverse outcomes were largely those not directly mediated by vision. Patients undergoing treatment should be counseled about long-term outcomes.

Keywords: amblyopia, long-term outcomes, public health policy, screening.

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Introduction

Amblyopia ("blunt sight") is a potentially reversible neurodevelopmental condition that causes impaired sight, typically in 1 eye. It arises when normal visual maturation processes are altered, commonly because of refractive error or strabismus, during the critical period of neurodevelopment in early childhood.[1-3] Affecting at least 3% of most populations, it is the most common condition managed in pediatric ophthalmology and a key paradigm for human neural plasticity. Treatment is undertaken in childhood when the visual system is malleable. Treatment mainstays remain occlusion ("patching") or optical penalization (drugs causing defocus) of the nonamblyopic eye to "stimulate" the amblyopic eye, but new binocular approaches are being investigated.[4-6] Although 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. Nevertheless, population-based estimates for this are lacking, which limits the ability to counsel patients at the start of treatment.

Universal childhood vision screening programs targeting amblyopia exist worldwide.[1,2,9-11] One justification is the prevention of vision impairment later in life in the uncommon event of disease or injury affecting the nonamblyopic 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, that is, vision not restored to normal despite treatment and no disease/injury to the nonamblyopic eye.[8,15-17] There is remarkably limited evidence about this. Thus, the debate continues about the public health value of universal childhood screening because of 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 randomized controlled trials comparing no screening with extant programs is lacking. Other approaches

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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 used data from 133 353 participants aged 40 years or older in the UK Biobank[19], eligible for an enhanced ophthalmic examination, comprising individuals whose childhoods spanned the period during which universal childhood vision screening became established in the United Kingdom. Participants reported their medical history, including amblyopia and other eye conditions and treatment for them, as well as lifestyle and environment. Data were collected from 2006 to 2010 with subsequent ongoing data collection cycles. Data collected toward the end of 2017 were used in this study to maximize the use of available data from physical examinations, surveys, and medical record linkage. Details of the enhanced ophthalmic examination, other physical assessments, and biological samples are available at the UK Biobank website (https://www.ukbiobank.ac.uk/). Record linkage for all participants to the United Kingdom's National Health Service health administrative data set (Hospital Episode Statistics [HES])[20] comprising all hospital admissions and attendances, using standardized precodes for conditions and treatments, provided additional objective data on ophthalmic diagnoses. These data allowed the evaluation of the sociodemographic 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 (ie, ≤16 years). We used a hierarchical approach comprising the presence of the following: (1) strabismus, (2) significant anisometropia (difference of at least +1.00 D/−1.00 D between eyes), (3) significant astigmatism (cylinder power ≥ 1.00 D), (4) significant refractive error per se (ie, −3.00 D/+3.00 D or more extreme), (5) less severe refractive error but visual impairment without any other underlying eye disease (such as stimulus deprivation amblyopia or cataract), and (6) current emmetropia (absence of refractive error, −0.99 D to +0.99 D) but self-reported glasses worn for hypermetropia in childhood and at least mild visual impairment with no other eye disease. In addition, those with amblyopia who did not self-report this (eg, because of 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 World Health Organization taxonomy[21]), bilateral amblyopia, or current near normal acuity (<0.06 logMAR). The comparator group comprised participants with bilateral normal visual acuity (ie, 0.0 logMAR) and without primary refractive error (ie, 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 socioeconomic, health, and well-being outcomes collected in the 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 the following:

See Appendix Table 1 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2021.05.010.

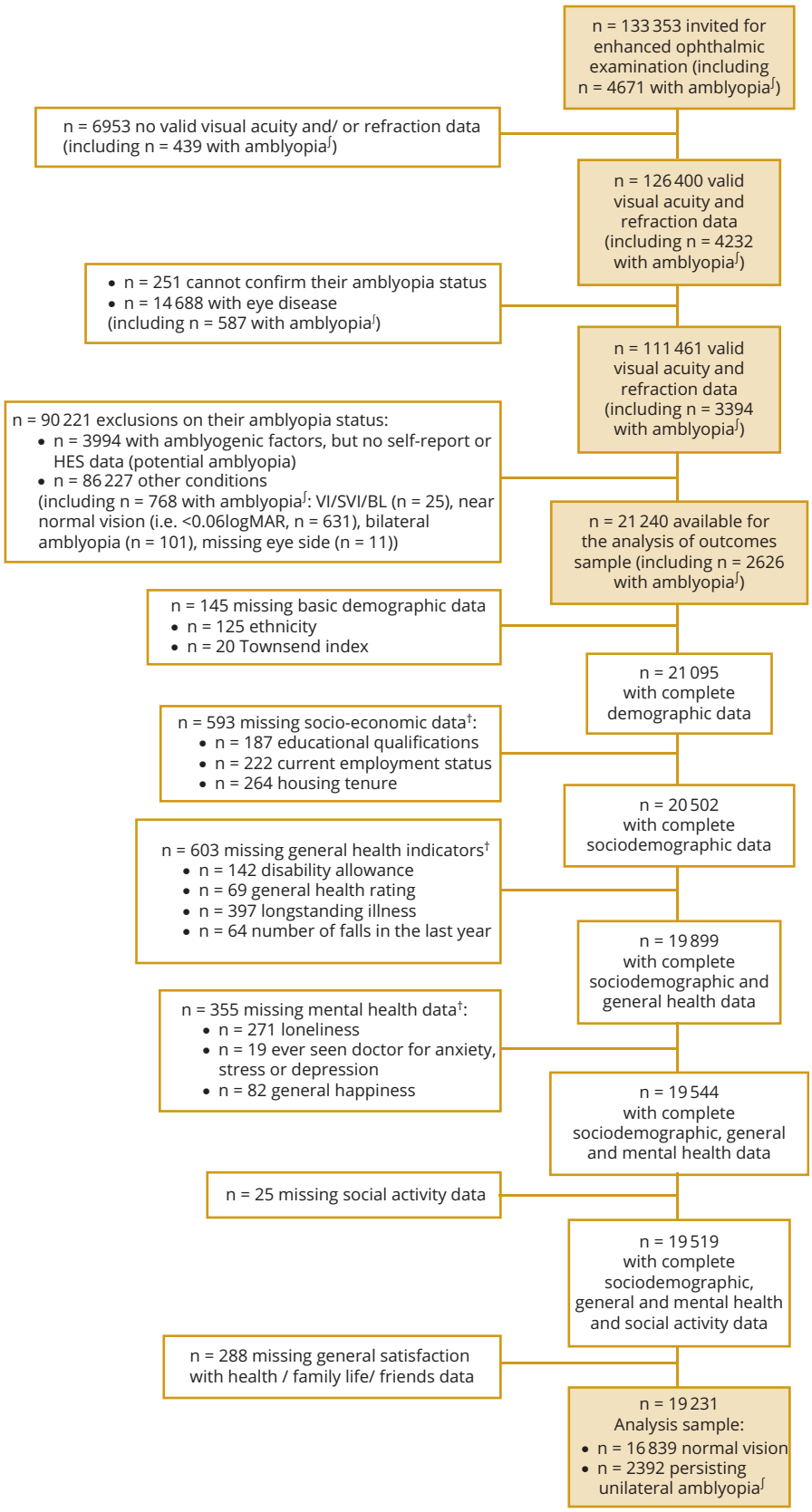
1. Educational attainment to assess direct functional impact of amblyopia on educational experience, categorized as a gradient toward lower attainment based on university/college degree, A-Levels/NVQ/HND/HNC/other professional qualifications (ie, school examinations at the age of 18 years or national vocational qualifications), O-Levels/GCSEs/CSEs (ie, school examinations by 16 years, the minimum statutory school-leaving age), or no qualifications.
2. Self-reported current employment status to assess any functional impact of amblyopia on ability to work, categorized as a gradient toward lower working capacity based on employed, retired, voluntary/unpaid work/student; looking after the household/family; and unemployed or unable to work because of sickness or disability.
3. Personal economic status using the conventional measure of current housing tenure, defined as owned, rented, or sheltered accommodation/care home.
4. Participation/engagement with any social activities in leisure time using self-reporting of the following: none, sports club, other club/group including pub, religious group, or adult education class.

Health and well-being outcomes comprised the following:

See Appendix Table 2 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2021.05.010.

1. General health using the following 4 indicators to assess any direct or indirect impact of amblyopia: (1) self-rated current health (excellent, good, fair, or poor); (2) receipt of UK government's financial benefits for those with disabling chronic conditions[22]; (3) any self-reported long-standing illness (LSI), disability, or infirmity; and (4) frailty measured as at least 1 fall during the previous year.
2. Current mental health to assess indirect impact of amblyopia using the following 3 self-reported measures: (1) often feeling lonely (yes/no); (2) ever seen a doctor for anxiety, stress, or depression; and (3) general happiness (6 categories from extremely happy to extremely unhappy).
3. Current well-being using the following 3 self-reported measures of general satisfaction: (1) with health, (2) with family life, and (3) with friendships (6 categories from extremely satisfied to extremely dissatisfied).

Figure 1. Flow of participants in the study.



BL indicates blindness; HES, Hospital Episode Statistics; SVI, severe visual impairment; VI, visual impairment.
∫Either self-reported amblyopia or identified through HES. †Categories below not mutually exclusive. Shaded boxes indicate key numbers referenced in the text.

Table 1. Associations (odds ratios [95% confidence intervals]) of sociodemographic characteristics with persisting unilateral amblyopia.

Covariates	Crude	*P*	LR test (*df*); *P*	Adjusted*	*P*	LR test (*df*); *P*
Sex			1.08 (1); .30			1145 (8); <.001
Female	1	-	-	1	-	-
Male	0.96 (0.88-1.04)	.31	-	0.88 (0.81-0.96)	.005	-
Age group, y			1034 (2); <.001			
40-49	1	-	-	1	-	-
50-59	2.55 (2.27-2.88)	<.001	-	2.49 (2.21-2.81)	<.001	-
60-70	6.11 (5.44-6.87)	<.001	-	5.91 (5.24-6.66)	<.001	-
Ethnic background			163 (1); <.001			
White	1	-	-	1	-	-
Other	0.26 (0.20-0.33)	<.001	-	0.36 (0.27-0.46)	<.001	-
Socioeconomic deprivation (Townsend quintiles)			9.11 (4); .06			
First quintile (least deprivation)	1	-	-	1	-	-
Second quintile	1.02 (0.88-1.17)	.80	-	1.04 (0.90-1.21)	.56	-
Third quintile	0.93 (0.81-1.07)	.32	-	1.02 (0.88-1.19)	.76	-
Fourth quintile	0.88 (0.76-1.01)	.06	-	1.05 (0.91-1.21)	.54	-
Fifth quintile (more deprivation)	1.04 (0.91-1.19)	.57	-	1.47 (1.27-1.69)	<.001	-

LR, likelihood ratio.
*Model adjusted for all variables shown in table. The LR chi-square test along with the relevant degrees of freedom (*df*) and its *P* value are given for each model.

Statistical Analysis

Descriptive statistics are shown as frequencies (%) with 95% confidence interval (CI). Differences in distribution of outcomes between amblyopic and nonamblyopic participants were assessed using the chi-square 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 (LSI, 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 (categorized as white or other because of the small number [ie, <3%] of all other ethnic groups combined in the amblyopia group), and social deprivation score (Townsend index deprivation score at the time of recruitment; first quintile being the most affluent[23]) were investigated as potential confounders in these models. We categorized participants into 3 age groups (cohorts) to distinguish prescreening and postscreening eras, which initiated in the 1960s in the United Kingdom,[11] allowing the examination of any cohort effects in associations consistent with an impact of universal vision screening. Specifically, those aged from 40 to 49 years would have undergone whole-population screening and those aged from 60 to 70 years would not. All participants had treatment once diagnosed.

We additionally adjusted analyses as follows: (1) socioeconomic and general health outcomes for presence of LSI and (2) life satisfaction outcomes for seeing a doctor for mental health issues and also for LSI. Because advanced age is associated with coexisting disadvantages, we also performed stratified analyses by age group. Goodness of fit was assessed with the likelihood-ratio chi-square test. All tests were 2 sided at 5% significance level, and analyses were performed in Stata Version 15.0 (StataCorp LLC, College Station, TX).

To validate our "phenotyping," we compared frequency of amblyopia among 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 (Fig. 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). Although males and younger participants and those from any "other" (ie, not white) ethnic groups or most socioeconomically deprived groups were more likely to have missing data, differences were minimal.

Our sample comprised 3394 confirmed amblyopes (80% of those who self-reported amblyopia formally validated using other data). Thus, the overall frequency for confirmed amblyopia was 3.0% (3394 of 111 461; 95% CI 2.9%-3.1%). It was the lowest among those born after screening for amblyopia became widespread in the United Kingdom, specifically 2.5% (95% CI 2.3%-2.6%) for the 40- to 49-year age group, 3.1% (95% CI 2.9%-3.3%) for 50- to 59-year age group, and 3.4% (95% CI 3.2%-3.5%) for 60- to 70-year age group.

Notably, 77% (2626 of 3394; 95% CI 76%-79%) of all amblyopes had persisting unilateral amblyopia. This proportion was the lowest in the youngest age group: 73% (495 of 677; 95% CI 70%-76%) for the 40- to 49-year age group, 78% (914 of 1166; 95% CI 76%-81%) for the 50- to 59-year age group, and 78% (1217 of 1551; 95% CI 76%-80%) for the 60- to 70-year age group. Specifically, the frequency of persisting unilateral amblyopia among 3390 UK Biobank participants born in 1958 was 2.3% (95% CI 1.9%-2.9%) compared with 4.8% (95% CI 4.4%-5.3%) for persisting unilateral and bilateral amblyopia combined in our previous 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 2392 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 that older age (in a gradient spanning eras before and after the implementation of childhood vision screening) and being in the worst quintile of socioeconomic deprivation were independently associated with increased odds of persisting unilateral amblyopia,

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

Covariates	Odds ratio (95% confidence intervals)					
	Crude	*P*	Adjusted*	*P*	Additionally adjusted for LSI	*P*
Outcomes						
Social and economic						
Education (gradient toward lower attainment)						
University/college to no qualifications	1.23 (1.14-1.33)	<.001	1.06 (0.98-1.15)	.18	1.05 (0.97-1.14)	.27
Employment status (gradient toward limited working capacity/ability)						
Employed to unable to work	1.21 (1.07-1.36)	.002	1.13 (0.99-1.28)	.06	1.07 (0.94-1.22)	.27
Economic status						
Housing tenure (rented vs owned)	0.92 (0.79-1.07)	.27	1.19 (1.00-1.40)	.05	1.14 (0.96-1.34)	.14
Social participation						
Participation in sports club vs none	0.76 (0.68-0.85)	<.001	0.78 (0.70-0.88)	<.001	0.80 (0.72-0.90)	<.001
Participation in social activities vs none	1.17 (1.06-1.30)	.002	1.04 (0.94-1.16)	.42	1.05 (0.95-1.17)	.34
Health and well-being						
General health						
Overall poorer self-rated health	1.27 (1.16-1.38)	<.001	1.29 (1.18-1.41)	<.001	1.18 (1.08-1.29)	<.001
Receipt of disability-related financial assistance	1.95 (1.61-2.37)	<.001	1.46 (1.19-1.79)	<.001	1.23 (1.00-1.53)	.05
Any LSI	1.61 (1.47-1.76)	<.001	1.35 (1.23-1.48)	<.001	-	-
At least 1 fall over the last year	1.51 (1.36-1.68)	<.001	1.36 (1.22-1.51)	<.001	1.31 (1.17-1.46)	<.001
Mental health						
Feeling often lonely	1.16 (1.05-1.30)	.005	1.26 (1.12-1.41)	<.001	1.21 (1.09-1.36)	.001
Seen doctor for depression/anxiety	1.25 (1.09-1.43)	.001	1.23 (1.06-1.41)	.005	1.14 (0.99-1.32)	.08
Overall feeling less happy	1.08 (1.00-1.18)	.06	1.21 (1.11-1.31)	<.001	1.17 (1.08-1.28)	<.001
Well-being						
Overall less satisfaction from						
Health	1.13 (1.04-1.22)	.004	1.16 (1.07-1.26)	<.001	1.07 (0.98-1.16)	.14
Family life	1.11 (1.03-1.21)	.007	1.25 (1.15-1.36)	<.001	1.23 (1.13-1.34)	<.001
Friendships	1.01 (0.93-1.09)	.82	1.12 (1.03-1.22)	.008	1.10 (1.01-1.20)	.02

LSI indicates long-standing illness.
*Models adjusted for age, sex, ethnicity, and deprivation. Likelihood ratio tests, and degrees of freedom for all the models are given in Appendix Table 3.

while being male or of "other" (ie, not white) ethnicity were associated with reduced odds. Because these are also known to be associated with social, health, and well-being outcomes, these variables were included as confounders in the analysis described below.

Associations (Adjusted) Between Persisting Unilateral Amblyopia and Outcomes

Crude and adjusted associations between persisting unilateral amblyopia and social, economic, health and well-being outcomes are shown in Table 2.

Social and economic

In the 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 included 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 4 indicators (odds ratios in the adjusted models ranging from 1.29 to 1.46), 3 of which remained significant albeit attenuated by adjustment for LSI. 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 LSI. There was some consistency in the independent associations between amblyopia and well-being measured as lower self-reported satisfaction with health, relationships with family, or relationships with friends (odds ratios in the adjusted models ranging from 1.12 to 1.25). Nevertheless, the association with lower satisfaction with health was not significant after additional adjustment for LSI, 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

The effect size of associations between persisting amblyopia and outcomes varied by age group (cohort), as shown in Table 3. Associations with lower socioeconomic 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 late treatment resulting in poorer vision from childhood onward. In contrast, associations with 3 of the 4 measures

Table 3. Associations* of persisting unilateral amblyopia (vs normal vision) with socioeconomic, general and mental health, and well-being outcomes, stratified by age group (cohort).

Covariates	Odds ratios (95% confidence intervals)					
	40-49 y	*P*	50-59 y	*P*	60-70 y	*P*
Outcomes						
Social and economic						
Education (gradient toward lower attainment)						
University/college to no qualifications	0.95 (0.80-1.13)	.55	1.08 (0.95-1.24)	.25	1.08 (0.95-1.22)	.23
Employment status (gradient toward limited working capacity/ability)						
Employed to unable to work	0.97 (0.71-1.31)	.83	1.06 (0.86-1.31)	.58	1.30 (1.08-1.57)	.005
Economic status						
Housing tenure (rented vs owned)	1.10 (0.81-1.48)	.55	1.00 (0.75-1.34)	.99	1.44 (1.08-1.94)	.01
Social participation						
Participation in sports club vs none	0.76 (0.60-0.95)	.02	0.74 (0.61-0.89)	.001	0.85 (0.71-1.03)	.10
Participation in other activities vs none	0.93 (0.74-1.18)	.55	1.04 (0.87-1.23)	.68	1.13 (0.96-1.34)	.14
Health and well-being						
General health						
Overall poorer self-rated health	1.27 (1.05-1.54)	.01	1.41 (1.22-1.63)	<.001	1.20 (1.04-1.37)	.01
Receipt of disability-related financial assistance	1.57 (0.91-2.71)	.10	1.17 (0.81-1.70)	.39	1.64 (1.24-2.17)	.001
Any long-standing illness	1.53 (1.24-1.89)	<.001	1.30 (1.12-1.53)	.001	1.31 (1.14-1.51)	<.001
At least 1 fall over the last year	1.42 (1.11-1.82)	.005	1.35 (1.14-1.61)	.001	1.35 (1.14-1.59)	<.001
Mental health						
Feeling often lonely	1.14 (0.90-1.44)	.29	1.49 (1.25-1.77)	<.001	1.11 (0.92-1.34)	.26
Seen doctor for depression/anxiety	1.31 (0.98-1.76)	.07	1.23 (0.97-1.55)	.08	1.20 (0.96-1.49)	.12
Overall feeling less happy	1.34 (1.11-1.62)	.002	1.22 (1.05-1.41)	.007	1.14 (1.00-1.30)	.06
Well-being						
Overall less satisfaction from						
Health	1.32 (1.10-1.58)	.003	1.11 (0.96-1.27)	.15	1.15 (1.01-1.31)	.04
Family life	1.34 (1.12-1.60)	.001	1.30 (1.14-1.49)	<.001	1.17 (1.03-1.33)	.02
Friendships	1.21 (1.01-1.45)	.04	1.18 (1.02-1.35)	.02	1.03 (0.90-1.17)	.70

*Models adjusted for age, sex, ethnicity, and deprivation. Likelihood ratio tests, and degrees of freedom for all the models are given in Appendix Table 4.

of adverse general health were seen in all 3 cohorts, with the largest effect size for 2 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 3 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 3 adverse well-being outcomes were more prominent among 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 older, 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 and those from socioeconomically 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 affected by reduced vision. There was some variation in size and strength of these associations by age group that defined the 3 periods during the decades in which childhood vision screening for amblyopia was introduced, became more common, and was finally well established in the United Kingdom.

We used the resource of UK Biobank in the absence of any alternative longitudinal study of sufficient size that included formal ophthalmic assessments by participants. Nevertheless, although the scale and detail afforded by Biobank are unrivaled,[19] there are potential limitations to our study. Although 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 minimize the impact of recall bias and to validate self-report is supported by similarities in frequency reported previously in other British population-based studies.[8,24] We used the history of strabismus/strabismus treatment in our hierarchical "phenotyping" of persisting/residual amblyopia. Because of the size of our sample, we did not undertake subgroup analysis of strabismic versus anisometropic or mixed amblyopia; therefore, 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 the identification of an appropriate comparator group with normal vision and no history of any eye disease.

Because this is an observational study, none of the observed associations can be assumed to reflect a causal relationship. Reverse causality can be ruled out because 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 United Kingdom. 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 does not comprise a truly random subsample of the general population, and studies using this resource cannot offer population prevalence. Nevertheless, the associations we report are internally valid, and given that the associations are in line 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 because a study of outcomes in those who received a diagnosis of 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. Therefore, it is striking that adverse educational attainment was not associated with persisting amblyopia in our study. This mirrors previous 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 nonamblyopic eye. This has not been observed in previous 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 affect employment and participation in specific social activities because of 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 regard to actual occupation, including jobs that are considered to require good vision in both eyes.[31] Our finding aligns with previous research,[8] and we suggest it 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 nonamblyopic 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 the disappointment of living with a residual deficit in vision despite treatment or living with an "invisible" disability. The association with an 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. To our knowledge, our findings demonstrate, for the first time at population level, that despite having normal vision in 1 eye, living with persisting unilateral amblyopia can be associated with worse self-rated health and well-being. One possible explanation is the gap between the expectations of affected individuals about the effectiveness of screening and treatment and the reality of their own visual outcome, which aligns with the established disability paradox theory.[33]

Although a variety of stand-alone programs had existed before, child vision screening in the United Kingdom was first implemented formally into child health surveillance programs during the 1960s. One impetus for creating the formal universal program that exists today[34] was the recognition that amblyopic children from socioeconomically disadvantaged families were likely to be noticed later and therefore have worse outcomes.[35] Our finding that women and those in the most socioeconomically deprived quintile and of white ethnicity were at a 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, that is, 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 the gains in acuity achieved through treatment[7] although it is projected that two-thirds of treated children will not achieve normal vision.[36] Nevertheless, 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, that is, 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] Therefore, this would prevent subsequent bilateral visual impairment, should disease or injury affect the nonamblyopic 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 optimize existing treatment or develop new approaches to ensure long-term stability of gained vision.[5,6] Although 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 the evidence that improvement in visual acuity in the amblyopic eye after loss of sight because of disease or injury in the nonamblyopic eye is more likely in those who have previously undergone amblyopia treatment.[13]

Conclusions

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 United Kingdom. It offers no evidence to support

the notion that persisting amblyopia has significant vision-mediated effects on educational, employment, or economic outcomes. Nevertheless, it identifies 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 who have received a diagnosis of amblyopia and to counsel them and their families about expected long-term outcomes after treatment.

Supplemental Material

Supplementary data associated with this article can be found in the online version at https://doi.org/10.1016/j.jval.2021.05.010.

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