Amblyopia treatment outcomes after preschool screening v school entry screening: observational data from a prospective cohort study

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Background/aims: Preschool screening for amblyopia has controversially been abandoned in some localities within the United Kingdom, on the basis that there is no clear evidence of benefit to support its continuation. Data collected within a birth cohort study were used to examine visual outcomes at 7 1/2 years in children who did or did not receive preschool vision screening.

Methods: Monocular logMAR visual acuity with and without a pinhole was assessed by orthoptists. Contemporary records were used to identify children who had been offered and/or received preschool screening.

Results: Of 6081 children, 24.9% had been offered preschool screening and 16.7% had attended. The prevalence of amblyopia was approximately 43% lower in the children who received preschool screening than in those who did not (1.1% v 2.0%, p = 0.05). The mean acuity in the worse seeing eye after patching treatment was better for amblyopic children who received preschool screening than for those who did not; 0.14 v 0.20 logMAR (p <0.001). These effects did not persist in an intention to screen analysis.

Conclusions: Preschool screening at 37 months was associated with an improved treatment outcome for individuals with amblyopia. However, the improvement was clinically small and disappeared when considering all children offered screening rather than only those who received it. Further research is needed into improving the effectiveness of vision screening for preschool children, while in the interim these data do not conflict with current recommendations for school entry screening by orthoptists.

METHODS

Setting and participants

The Avon Longitudinal Study of Parents and Children (ALSPAC or “Children of the Nineties”) project is a longitudinal study following the health and development of children born in a geographically defined area (which was formerly Avon), between 1 April 1991 and 31 December 1992. Approximately 14 000 children were recruited, an estimated 85% of those eligible. Since the age of 7 1/2, all participating children have been invited to yearly examination sessions where a variety of collaborators from different disciplines have assessed them. This paper uses data from all children who attended the examination at the age of 7 1/2 years and who were part of a “natural experiment,” in which children from some districts in the study area were offered screening at 37 months, whereas children from other districts were not. Data are not presented for a randomly selected subgroup, who were involved in the RCT and whose results are presented separately.

Vision screening services in the study area

One of the three health districts in the ALSPAC study area provides preschool orthoptic vision screening; the others do not. One institution provides hospital eye services (HES) for the whole study area. The HES clinic lists for the preschool vision screening clinics in the relevant years were copied, stripped of identifiers except for a code number, and linked with the main ALSPAC database. These clinic lists identified

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The orthoptic preschool screening examination includes a monocular vision test (Kay's pictures or Sheridan Gardiner singles), a cover test, and an assessment of binocularity using a 20 dioptre prism or a test of stereopsis, or both. Failure of any part of this examination results in referral to the HES, after a retest if poor cooperation is suspected. All children in the study area are offered vision screening in the school reception class (age 4–5 years).

Outcome data
Vision testing at 7½ was carried out by orthoptists who had not been involved in the preschool screening clinics and were unaware of the child's screening history. They tested monocular logMAR acuity with ETDRS charts, using a standardised protocol and giving credit for each letter identified correctly. Children were tested in their “habitual” state (that is, with spectacles if worn) and in the state of “habitual plus pinhole,” the latter as a proxy for full refractive correction with spectacles. Autorefraction and a cover test were also carried out. A randomly selected 3% of all children attending were invited back within 6 weeks for a repeat examination, for which the testers had no records of their previous visit, to provide quality control data.

Any child with a strabismus or visual acuity in either eye of 0.2 or worse (approximately 6/9 or worse on a Snellen chart) was invited to a separate research clinic where an experienced optometrist checked their refraction under cycloplegia and examined their fundi.

Power of the study and statistical methods
The primary outcomes were the prevalence of amblyopia at 7½ years and the results of treatment for amblyopia (visual acuity in the worse seeing eye), in children who had actually received orthoptic preschool vision screening, compared with the children who had not. Further comparisons were carried out comparing those children who were offered orthoptic preschool vision screening with those who weren’t (intention to screen approach). Calculated post hoc, the numbers of children who provided outcome data (of whom approximately one third actually attended the preschool vision screening clinics) gave this study 80% power (using a two tailed p <0.05) to detect a drop in the prevalence of amblyopia of 62.5%—for example, from 2.0% down to 0.75%, with a corresponding odds ratio of approximately 0.35.

The visual acuity of each eye was taken as the better of “habitual” v “habitual plus pinhole.” Proportions were compared using the χ² test or Fisher’s exact test. Amblyopia was initially defined in advance in two ways, to allow comparisons with other studies; amblyopia A, where the interocular difference in acuity was 0.2 logMAR (two lines on the chart) or more, and amblyopia B—where the visual acuity in the amblyopic eye was worse than 0.3 logMAR (worse than 6/12). In order to allow a further post hoc direct comparison with a previous study of similar design, a definition of “6/9 or worse in one eye” (0.18 or worse logMAR) was also used—amblyopia C.

Continuous data were compared using analysis of variance or multivariate regression provided the data approximated to a normal distribution and Mann-Whitney if they did not. Data on potential confounding variables were taken from the main ALSPAC database. Results are proportions (95% CI), intraclass correlation coefficients (ICC, 95% CI), odds ratios (OR, 95% CI), or mean (SD) or median (interquartile range) visual acuities in logMAR units, unless otherwise stated.

Quality control for visual acuity data
All results are for the right eyes (very similar results were obtained for the left eyes).

The randomly selected 3% of children who were invited a second time provided the data used to estimate test and tester variability. There was a small learning effect in that on average, children who were retested did very slightly better on their second visit; the mean difference was 0.01 logMAR and 95% of differences were between −0.12 and 0.12. This mean difference is significantly larger than 0 (one sample t test, p = 0.018, t = −2.38, df = 210). The interobserver (tester) variability was estimated from the results from 163 children who were re-examined by a different orthoptist from the one they originally saw. The median (IQR) difference between pairs of different testers was 0.02 (−0.02 to 0.06) and 95% of differences were between −0.12 and 0.14 logMAR units. The corresponding mean ICC for all pairs of orthoptists was 0.76 (0.69 to 0.82), F = 4.3, df = 164. The intraobserver (test-retest) variability was estimated from the results of children who were re-examined by the same orthoptist; the median (IQR) difference between visits was −0.01 (−0.02 to 0.05) logMAR and 95% of differences were between −0.14 and 0.12 logMAR units. The corresponding mean ICC for all orthoptists was 0.86 (0.74 to 0.92), F = 7.0, df = 45.

In the separate clinic to which children with strabismus or acuity of 0.2 or less were invited, the differences between testing with pinhole and testing with a full correction (or none for emmetropes) were assessed. Results obtained using the pinhole tended to be slightly worse than those obtained using full correction; the median (IQR) difference was 0.04 (−0.02 to 0.12) logMAR and 95% of differences fell between −0.16 and 0.30 logMAR units. The corresponding ICC was 0.83 (0.75 to 0.88), F = 6.6, df = 294. Almost identical results were obtained when excluding the emmetropes and examining the data from only the 141 children who wore glasses that were found not to need changing by the optometrist.

RESULTS
Overall, 8042 children attended, 1917 of whom were involved in the RCT and have been reported separately. Of the remaining 6125, another 44 had known developmental delay, organic eye disease, or developmental syndromes and were excluded from this analysis, leaving 6081 children whose results are reported here. Of these, 1516 (24.9%) had been offered orthoptic preschool vision screening and 1019 (16.7%) had actually received it.

Differences between the two groups (children who received preschool screening v children who did not)
Factors other than exposure to preschool vision screening that were significantly associated with the worse eye acuity are shown in Table 1, together with their distribution in each of the two groups (received v did not receive screening). The children who received the preschool screening had on average older, better educated mothers who were less likely to have smoked during pregnancy than were children who did not receive it (that is, those who were invited but did not attend plus those not invited); maternal age at birth: p = 0.013; maternal smoking in the first trimester: p = 0.011 or second trimester: p = 0.018; highest level of education achieved by the mother: p <0.0001. There were no statistically significant differences in any other variables between the two groups.

The prevalence of amblyopia at 7½ years in children
Amblyopia at 7½ years was less common among children who had received orthoptic preschool screening, for all definitions of amblyopia. The raw data and odds ratios are shown in Table 2. Also shown are the results of adjustment for the potentially confounding variables shown in Table 1. Adjustment increased the confidence intervals for the ORs such that the reductions in amblyopia A and amblyopia C in the preschool screening group were no longer statistically borderline or significant respectively.
Results of patching treatment for children in each group
The mean (SD) logMAR acuities after patching treatment in the worse seeing eyes were better for children who had received preschool screening than for those who had not: 0.14 (0.18) v 0.20 (0.23), whereas the acuities in the worse seeing eyes for children who had no previous patching treatment were very similar: −0.01 (0.09) v −0.02 (0.08) in the two groups respectively (two factor ANOVA; p = 0.002 for preschool screening/not and p = 0.015 for an interaction between patched/not and preschool screening/not, which
indicates that the effect of preschool screening differs depending on whether the child was treated for amblyopia or not.

Repeating this analysis for children who were or were not strabismic at 7½ revealed that for the “straight amblyopia” subgroup who had been patched in the past, receiving preschool screening was associated with a significantly better mean (SD) outcome than not receiving it: 0.06 (0.12) respectively (p = 0.009). For the children who were strabismic at 7½ and had been previously patched, there was no such association with preschool screening: 0.27 (0.20) v 0.29 (0.24) for the screened v unscreened children respectively (p = 0.21). For the “straight amblyopia” subgroup, these mean values correspond to 92.9% v 86.3% (Fisher’s exact test: p = 0.44) of children attaining driving vision (6/12 or better) in their treated eyes in the preschool screened v no preschool screened groups respectively. For the strabismic amblyopes the corresponding figures are 62.5% v 58.9% (Fisher’s exact test p = 0.58) for the preschool screened v not preschool screened.

**Adjustment for potentially confounding variables**

All the variables in Table 1 were used in a forward stepwise multivariate regression analysis, together with “received preschool screening (yes/no)” as the exposure of interest. The results were almost identical to the original analysis, even after adjustment for family history, sex, mother’s highest educational achievement, birth weight, and duration of breastfeeding: 0.15 (95% CI 0.11 to 0.18) in the preschool screening group compared with 0.22 (95% CI 0.20 to 0.23) in the no preschool screening group (p < 0.0001).

**Analysis according to “offered screening or not”**

The coverage of the preschool programme was 67.2% (1019 children attending, out of 1516 who were invited). Amblyopia was still less common in the children offered preschool orthoptic screening, but not statistically significantly so. The prevalences of amblyopia definitions A, B, and C in the two groups (not offered v offered) were 2.0% v 1.4% (p = 0.14), 1.3% v 1.2% (p = 0.59), and 3.4% v 2.4% (p = 0.08), respectively. There was no difference between the groups (offered preschool screening v not offered) in the mean acuities achieved after patching treatment. The mean acuity in the worse seeing eye was 0.20 (0.23) for children not offered preschool screening v 0.18 (0.22) for children who were offered preschool screening (p = 0.217). For the “straight amblyopia” subgroup, there were similar results: 0.10 (0.13) in the “offered preschool screening” group v 0.12 (0.19) in the “not offered screening” group (p = 0.11).

After adjustment for family history, sex, mother’s highest educational achievement, birth weight and duration of breastfeeding, the overall estimated mean results were very similar.

**DISCUSSION**

These data support the hypothesis that preschool screening for amblyopia leads to better acuity after treatment for affected children. The magnitude and statistical significance of this effect on vision in the worse seeing eye persisted despite adjustment for a number of potentially confounding variables, suggesting it was not because of other differences between the children. However the magnitude of this improvement is clinically small (mean difference between preschool screened v not was ~ 3 letters on a logMAR chart). This study was only able to detect quite a large drop in prevalence (by 62%) as statistically significant, so our consistent finding of a 45% drop in the screened children is of either borderline or no statistical significance given the numbers of children in this study, yet it does fit with the robust finding of a small improvement in visual acuity after treatment in the same children. The reduction in effectiveness seen in the intention to screen analysis illustrates that, in practice, obtaining only 67% coverage of the population at risk attenuated any benefit attributable to the screening to levels undetectable in a study of this size. The only other prospective UK based study comparing orthoptic preschool screening v none, found a similar lack of effect on the prevalence of amblyopia (definition C) using an intention to screen approach; however, they did not consider children who did or did not attend separately. The coverage of the population achieved in this area was moderately good compared to other UK programmes; however, the serious effects of incomplete or poor compliance with screening or treatment on the effectiveness of preschool screening have already been highlighted in another UK study.

The nested RCT carried out alongside the present study, however, found that offering intensive vision screening before 37 months was associated with clinically more important improvements in outcome (a reduction in the prevalence of amblyopia by two thirds, and an average of one line better vision for the amblyopic eyes in children who had been treated) compared with screening at 37 months. Taken together, our two studies (the nested RCT and this “natural experiment”) support the hypotheses, firstly, that treatment for amblyopia does improve visual acuity and, secondly, that on average, the results of treatment after screening are better for screening before 37 months than after 37 months, and slightly better again after screening at 37 months than at school entry, especially for children with straight eyed amblyopia. This may be the result of age related changes in the plasticity of the visual system, or in compliance or in other undescribed factors.

These observations must be considered with other matters such as the likelihood of screening the whole target population, the cost effectiveness of screening and treatment, and the individual and societal benefits to be expected from reducing the burden of amblyopia. Coverage of the whole population at risk ideally requires a coordinated approach.
between different aspects of the child health and surveillance network, such as developmental reviews, vaccinations, and other screening programmes, in order to be successful and to minimise resource expended and efforts required by the children’s families. Few cost effectiveness data are available for preschool screening programmes, although recent data from Germany have emphasised the importance of different prevalence rates for the target condition being sought and of the effectiveness of the screening tests, to overall costs.20–24 The benefits to society of effective detection and treatment for amblyopia include preventing incapacitating visual impairment if an individual with unilateral amblyopia loses their amblyopic eye. A recent study has recently reported that this will happen to approximately 33 amblyopic (using definition B) individuals per 100 000 total population, by the age of 95 years25 and that only 10% of these would be expected to gain useful vision in their previously amblyopic eye.26 There would therefore be considerable benefits to individuals with amblyopia and to the providers of the care and financial support they come to need, if their amblyopic eyes could be more effectively treated and so the risk of subsequent bilateral and socially significant or severe loss could be lessened.

The ALSPAC study population is largely representative of the UK population generally (as evidenced by comparing ALSPAC data with the 1991 census data), with the caveat that the cohort under-represents children from very deprived families, families of Asian extraction, and families where the mother was a teenager at the birth of her child. Our findings may therefore not be generalisable to children from these backgrounds. We used a proxy measure for “best corrected” acuity and therefore may have misclassified some children as amblyopic or not; however the quality control data suggest that on average agreement between the proxy measure and fully corrected acuity was good. The study was observational, therefore although the findings of better vision in treated children who had been screened were robust in a multivariate analysis with several potential confounders, other unaccounted for factors may also have affected the results. Overall, however, the findings from this study clearly suggest a small benefit in terms of final acuity after treatment for children who had amblyopia and were screened preschool, but on a population level this programme had little effect on the overall burden of amblyopia. This was even true for the straight eye subgroup who appeared to derive more benefit from screening than did the strabismic amblyopes. However, this study was not designed to investigate fully the effect of screening on children with subtypes of amblyopia and we do not have full data for all children regarding when they first received different types of treatment (that is, patching rather than glasses). There may therefore be further differential effects of age at screening or treatment for the different subtypes of amblyopia, investigation of which would require dedicated studies.

At the final assessment, the majority of children with amblyopia at 7½ were straight eyed, as were nearly all the amblyopes who had not had patching treatment previously. All the untreated children had been offered screening at school entry and therefore these children represent false negatives of school based screening, unless they developed their amblyopia after age 4–5 years. This seems unlikely as evidence suggests 6 years of age may be the upper age limit for developing amblyopia, which becomes increasingly less likely as a child’s age increases from infancy up to 6 years.25

There may be important improvements in outcome if children can be effectively screened earlier than was done here. Modelled data from our RCT,27 and from other studies, suggest that some forms of refractive screening may be more effective than acuity testing28–30 at detecting young children at risk of having amblyopia. The likely effectiveness of such techniques depends heavily on the accuracy of the device used and on the specificity (which dictates the number of false positives referred) of the programme.

The results of the present study do not conflict with the interim recommendations before the National Screening Committee, which are that the “best buy” at present, pending further evidence, is orthoptic screening for amblyopia at school entry.29–31 Coverage at this age is likely to be high and acuity testing by orthoptists is likely to be more accurate than by other professionals.31–32 However, the data in both the present study and our companion paper suggest that on average, better results are obtained after earlier treatment for amblyopia. More research is needed, therefore, to explore whether photorefractive or other technologies could be sufficiently accurate to be useful in a pragmatic programme screening for amblyopia children aged 2–3 years (that is, once ambylogenetic refractive error is likely to be more readily distinguishable from resolving, infantile refractive error33), which would then be expected to benefit from age associated improvements in treatment.

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CONTRIBUTORS

CW designed and managed the study with support from JMS, RAH, and IH; JG designed and manages the ALSPAC study; CW and KN analysed the data and all authors contributed to the manuscript; CW acts as guarantor.

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