The Value of Screening for Amblyopia Revisited

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Core Messages

- Vision screening for children may be considered in terms of detection of amblyopia, strabismus and/or refractive error. Variations exist within and between countries regarding vision screening for children in terms of programme content, referral criteria and personnel. Recommendations state preschool vision screening programmes be conducted by orthoptists or by professionals trained and supported by orthoptists.
- The justifications of vision screening for children include an increased risk of blindness to the healthy eye as result of injury of disease in adults with amblyopia. An increased risk of blindness is present as the non-amblyopic eye of an amblyope may become diseased or injured.
- A recent report found that screening for amblyopia could not be considered as cost-effective, but acknowledged that much uncertainty exists surrounding the short and long-term implications of the condition(s). Further research is needed to provide such evidence.
- Treatment of amblyopia associated with refractive error should incorporate a period of observation with glasses-wear alone to allow for "refractive adaptation" (also known as "optical treatment of amblyopia"). Improvements in visual acuity can occur up to and beyond 20 weeks after glasses are prescribed. Most improvement occurs in weeks 4 to 12. In some cases further amblyopia therapy may not be required.
- Children who undergo amblyopia therapy at an early age have been found to respond more quickly to occlusion than older children, and require less occlusion in total. There is evidence to suggest that successful treatment of children aged over 7 years can be achieved in cases of anisometropic, strabismic and mixed aetiology amblyopia.
- Atropine has been found to be as effective as patching in the treatment of both moderate and severe amblyopia.
- Recurrence of amblyopia may occur following treatment, with reported rates of 7% to 27%. Factors influencing recurrence include age of the child at cessation of treatment, VA at the time of cessation of treatment and the type of amblyopia that is present.
- Reported health related quality of life (HRQoL) implications of amblyopia include the impact of the condition upon stereoacuity; fine motor skills; reading speed; and interpersonal relationships.
- The reported HRQoL implications of strabismus are related to physical appearance, particularly upon self-image and interpersonal relationships. Surgical correction of strabismus has been reported to improve HRQoL.

Amblyopia

Amblyopia is a sensory anomaly defined as defective unilateral or bilateral visual acuity (VA). There are a number of classifications of amblyopia based on the aetiological cause(s). The reported prevalence of amblyopia varies widely, from 1-5%. Differences in prevalence can be attributed due to the population studied (e.g. ethnicity), and whether the study sample was taken from a clinical cohort (where a greater prevalence would be expected) or a population-based study. However, the most important factor which can account for differences in reported prevalence rates is that of amblyopia definition. Over recent years a definition of amblyopia based upon a difference in VA of two or more Snellen or logMAR lines between eyes has been adopted. However, there is no universally accepted definition of amblyopia in terms of VA deficit. Studies that report upon amblyopia prevalence, diagnosis and/or treatment must be interpreted carefully, and often cannot be directly compared. Nonetheless, amblyopia is considered to be a common condition which occurs in childhood, and if left untreated will remain present throughout adult life. This chapter will explore what is meant by screening; detection of amblyopia and strabismus through screening programmes; amblyopia treatment; and consequences of amblyopia and its treatment (both in the long and short-term).

1.1 What is Screening?

The purpose of screening is to identify persons as being at greater or lesser risk of developing, or having, a particular condition. The United Kingdom (UK) National Screening Committee (NSC) defined screening as "a public health service in which members of a defined population, who do not necessarily perceive that they are at risk of, or are already affected by, a disease or its complications, are asked a question or offered a test to identify those individuals who are more likely to be helped than harmed by further tests or treatment to reduce the risk of a disease or its complications"[1]. There are recognised criteria for screening relating to the condition itself; diagnosis; treatment and cost. These are summarised in Table 1.

1.1.2 Screening for amblyopia, strabismus and/or refractive errors

Screening for amblyopia, strabismus and/or refractive errors has long been an emotive and contentious issue. Differences in health care provision from one country to another can make it difficult to draw inferences on the possible benefits and risks associated with the implementation or withdrawal of such programmes. For example, differences exist between the United Kingdom (UK) and the United States of America (USA). Within the UK, vision screening of children was developed as part of the child health surveillance programmes established during the 1960's and 1970's. The appropriateness of such programmes was called into question following a systematic review of their effectiveness[2]. In 2003, the Health For All Children Report (also known as Hall 4) recommended changes in the way children are monitored and referred for suspected amblyopia and strabismus[3], and the Child Health Promotion Programme (CHPP) recommended all children to be screened for visual impairment between four and five years of age by an orthoptist-led service[4]. This recommendation has been adopted regionally in the UK, although not universally.

Within the USA there is also widespread differences regarding preschool vision screening guidelines, policies and procedures. Recommendations from the American Academy of Ophthalmology (AAO), American Association for Pediatric Ophthalmology and Strabismus (AAPOS) and the American Academy of Pediatrics

(AAP) are that vision screening should be performed on children between the ages of three and three and a half years of age[5]. Despite the existence of such recommendations, current practice within the USA is totally non-standardised, with much variability by state and locality. This was highlighted by Ciner et al[6] who recommended that specific components of a preschool vision screening programme ought to be considered; including the tests to be conducted, parental education of the condition, and recording and referral criteria.

Over recent years there has been a call to make any recommendations for vision screening for children more evidenced-based, and advances in the literature regarding screening test accuracy and treatment of amblyopia will only serve to facilitate this. However, the implementation of any recommendations is often driven by political rather than clinical factors.

1.1.2.1 Screening for amblyopia

The purpose of preschool vision screening for amblyopia is to detect children with unilateral or bilateral amblyopia. Accurate detection of amblyopia is primarily achieved through VA testing. The value of conducting other tests for the purpose of screening for amblyopia alone is minimal; some would argue additional tests could be included in the screening programme to detect amblyogenic factors (e.g. strabismus or refractive error).

1.1.2.2 Screening for strabismus

The purpose or value for preschool vision screening for strabismus alone could be questioned. It may be argued that the detection of large, cosmetically apparent strabismus would be observed by parents or guardians and/or health care practitioners. Once noted, appropriate referral to an ophthalmologist would be initiated. Therefore the justification of preschool vision screening for large-angled strabismus may not be valid. The detection of small-angle strabismus however, is not as easy and requires expert testing from orthoptists and ophthalmologists. The value of such detection remains under debate. If the strabismus is so small that it is not cosmetically obvious, then it is unlikely that surgical treatment for the condition would be undertaken. To that end, the value of screening may be questioned. An argument for screening could be that the presence of a small-angle strabismus is an amblyogenic factor: amblyopia may not be present at the time of screening, however the existence of the strabismus would be suggestive that amblyopia is likely to develop within the critical period of vision development.

1.1.2.3 Screening for refractive error

Screening for refractive error alone is not commonplace. The justification would be that the presence of significant refractive error may impact upon educational progress and daily living. The existence of unequal refractive error (anisometropia) could be deemed an amblyogenic risk factor. Indeed, the correction of any clinically significant refractive error during the critical period of vision development supports the notion of preschool vision screening.

1.1.2.4 Screening for other ocular conditions

Any form of preschool vision screening is likely to result in detection of other ocular conditions. These may include ocular pathologies such as cataract or retinoblastoma; or may be related to motility, such as Duane's or Brown's syndrome. Whilst such

conditions are of great clinical importance, not least because of their association with systemic health problems, the justification of screening for detection of these conditions alone cannot be justified. To screen for such conditions in isolation is neither practical nor appropriate. The economic benefit of adding such conditions to a screening programme for amblyopia and/or strabismus is negligible.

1.1.3 Difference between a screening and diagnostic test

There is difference between a screening test and a diagnostic test. As the name implies, a screening test is used to identify and eliminate those with a given problem(s); there is no requirement for it to quantify the extent of any deficit or problem, or indeed for it to provide any information for diagnosis. A diagnostic test provides information which can be used to help make a clinical diagnosis, and/or influence the management plan of the condition. A diagnostic test often quantifies the extent or severity of the condition. For example, photoscreening is used to detect refractive error (screening test); however the results would not be used to diagnose the extent of the refractive error present or indeed for the prescription of glasses. This would be achieved through refraction (diagnostic test).

1.1.4 Justification for screening for amblyopia and/or strabismus

The justification of preschool vision screening for amblyopia and/or strabismus remains a controversial issue. Referring to the NSC criteria of screening, the condition to be screened should be an important clinical condition. The evidence relating to the condition's importance and impact relate primarily to the consequence of amblyopia and/or strabismus in the short or long term. It has been recognised that there is a detrimental effect of having reduced vision in one eye (as is the case with unilateral amblyopia). Brown et al[7] stated that in the presence of ocular disease, yet good VA in both eyes, subjects reported to have a higher health related quality of life (HRQoL) than those with good VA in only one eye.

One of the arguments regarding the consequence of amblyopia refers to the risk of blindness to the healthy eye as a result of injury or disease. Rahi et al[8] reported upon the findings of the British Ophthalmological Surveillance Unit (BOSU), a national surveillance scheme for the study of rare ophthalmological disorders or events. Over a two-year period the number of individuals with unilateral amblyopia with a newly acquired loss of vision in the non-amblyopic eye was recorded. The authors were able to report upon the total population lifetime risk and annual rate of permanent visual impairment or blindness attributable to loss of vision in the non-amblyopic eye. In addition, the projected lifetime risk and annual rate of permanent visual impairment or blindness attributable to loss of vision in the non-amblyopic eye in individuals with amblyopia were reported. It was found that the lifetime risk of visual impairment increased substantially from the ages 15-64 years and by 95 years of age (incidence per 100,000 total UK population, 5.67 [4.33-7.01 CI] compared to 32.98, [29.06-36.89 CI]). This can be attributed to the increased prevalence of other ocular disorders that occur with increasing age (such as cataract and age-related macular degeneration). The authors stated that every year as a result of disease affecting the non-amblyopic eye, at least 185 people in the UK with unilateral amblyopia have vision loss to a level that is associated with detriment to quality of life. It is possible that the incidence rates are greater than this, with only the minimum estimates of the risk of visual impairment after disease in the non-amblyopic eye being reported. The authors stated that the lifetime risk of serious vision loss for an individual with

amblyopia was substantial and in the region of 1.2-3.3%. This was supported by Chua and Mitchell[9], who found that people with amblyopia had almost three times the risk of visual impairment in their better seeing eye compared to people without amblyopia.

More recently, Van Leeuwen et al[10] examined the excess risk of bilateral visual impairment among individuals with amblyopia as part of the Rotterdam study (a population-based prospective cohort study of the frequency and determinants of common cardiovascular, locomotor, neurological and ophthalmological diseases). They found that the estimated lifetime risk of bilateral visual impairment is almost doubled in those who also have a diagnosis of amblyopia. The authors reported that the number of individuals needed to treat to prevent one case of binocular visual impairment is 12.5.

When vision loss in the non-amblyopic eye in the presence of amblyopia does occur (through injury or disease), the effect upon the individual is often devastating. There have been reported cases of plasticity in the visual system, even in adulthood, whereby improvements in VA in the amblyopic eye have been observed[11].

Another argument for the notion of preschool vision screening for amblyopia and/or strabismus is the impact of having either condition upon quality of life. This will be examined in more detail towards the end of the chapter.

1.1.5 Recent reports examining preschool vision screening

The scarcity of evidence which would allow decision makers in the UK NHS to fund screening programmes with confidence that it is an efficient use of limited health care resources has made screening for amblyopia problematic. To be cost effective a programme has to demonstrate that it is first clinically effective. Issues of how disinvestment in existing technologies or health care programmes is carried out is becoming increasingly important in the UK health care setting, as new evidence based technologies are mandated by the National Institute for Health and Clinical Excellence (NICE). Decisions concerning which programmes can be continue to be funded from the health care budgets which are under increasing pressure due to the mandated programmes from NICE are being made in local areas. The problems associated with older established programmes relate mainly to the reality that often these were implemented many years ago when evidence was limited, or they were never subject to the level of scrutiny that is currently expected for any new technology or programme. The recent review of screening for amblyopia is one such area.

In 2008, the Health Technology Assessment report on preschool vision screening was updated, examining both the clinical and cost-effectiveness of screening programmes for amblyopia and strabismus in children up to the ages of four to five years[12].
A systematic review of the literature examining the clinical and cost effectiveness of screening children for amblyopia and strabismus before the age of five years was undertaken. Cost effectiveness and expected value of perfect information (EVPI) modelling was reported. EVPI modelling is used in cost-effectiveness analysis to attempt to establish the benefits of undertaking research which would reduce the costs of uncertainty. The cost of uncertainty in this case is that the wrong disinvestment decision could be made.

Following a review of the literature a natural history model was constructed, which described the incidence and progression of amblyopia to age 7 years. As is customary a separate model which extrapolated the costs and effects of amblyopia over an individual's remaining lifetime was also constructed. These models were incorporated into a separate screening model which represented the potential impact of treatment. The expected health outcome for the individual was defined as the expected number of cases remaining in a population of 7 year olds. That is those children for whom treatment was either unsuccessful or who had failed to be detected.

A post-screening model was constructed to estimate the long term effects of childhood amblyopia on a cohort of individuals who would have bilateral or unilateral vision loss over a 93 year time horizon. The costs associated with the screening programme and the benefits (expressed as utility weights) were applied to both vision loss across the model's time horizon allowed us to give the estimated costs and consequences of amblyopia.

The model population was informed by the literature reviews. It was identified during the data extraction process that there was a significant lack of quantitative data available which could be used in the model. This problem was addressed by having a pragmatic approach to estimate the transitions in the model for which amblyogenic factors translated into a number of visual acuity states. A number of experts who were able to confirm or reject the plausibility of the assumptions that were made were consulted. It was not possible to use any empirical data which could have informed the effectiveness of treatment for amblyogenic factors. It was assumed that by removing the risk factor for refractive error the outcome would be 100% effective. Strabismus treatment is acknowledged to be less successful therefore the outcomes for removing the amblyogenic risk was considered to be between 0 and 30%.

Carlton et al[12] reported that the available evidence did not support the screening programme for amblyopia and amblyogenic factors. Economic evaluation showed that screening for amblyopia and strabismus in children could not be considered as a cost-effective use of resources. Analysis of the cost effectiveness using the available research data found that screening was not cost-effectiveness at currently accepted quality adjusted life years (QALY) values. (QALYs are used in cost-utility studies, and consider both the duration of health states and their impact on HRQoL[13]). However, the lack of evidence highlighted a need for further research into the impact of amblyopia and amblyogenic factors in the long-term. The lack of evidence surrounding the long term impact of amblyopia increased the level of uncertainty in the model. By making a number of assumptions on utility loss (that is, the impact upon quality of life) the model demonstrated that screening could become highly cost effective. EVPI modelling showed that the value of eliminating uncertainty ranges between £17,000 to over £100,000 per QALY. That is, the impact of amblyopia upon a person's quality of life (in the short or long-term) is still unknown, and guesstimates of such impact lead only to more uncertainty.

These findings may not provide the ideal result for decision makers as the answers are not clear cut. Cost-effectiveness alone should not be the deciding factor in the provision of preschool vision screening. For example, the issue of equity may also need to be considered. This is particularly relevant in communities where there may be a greater prevalence of amblyopia or strabismus which are failed to be detected or

acted upon by parental observation alone. The figures reported above linking the cost per QALY are those which are applied to new technologies. The QALY threshold for disinvestment is undefined at present.

The German Institute for Quality and Efficiency in Healthcare (IQWIG) is an independent scientific institute that investigates the benefits and harms of medical interventions. In producing reports upon the assessment of an intervention (such as screening) IQWIG adhere to strict inclusion and exclusion criteria in the reviewing of existing literature surrounding the given subject. In 2008, IQWIG assessed the benefits of screening for visual impairment in children up to the age of 6 years[14]. They concluded that "no robust conclusions" could be directly inferred from the studies identified in their review. To that end, the notion of preschool vision screening could neither be supported nor rejected.

Summary for the clinician

- The purpose of screening is to identify persons as being at greater or lesser risk of developing, or having, a particular condition. Screening should be considered in terms of the condition, diagnosis, treatment and the screening programme itself.
- Vision screening for children may be considered in terms of detection of amblyopia, strabismus and/or refractive error. Variations exist within and between countries regarding vision screening for children in terms of programme content, referral criteria and personnel.
- The justifications of vision screening for children include an increased risk of blindness to the healthy eye as result of injury of disease in adults with amblyopia.
- An increased risk of blindness is present as the non-amblyopic eye of an amblyope may become diseased or injured.
- Recent reports indicate that further evidence is required to support the notion of preschool vision screening despite seminal research examining diagnosis, treatment and consequence of amblyopia, strabismus and/or refractive error.

1.2 Screening tests for amblyopia, strabismus and/or refractive error

The accurate detection of amblyopia, strabismus and/or refractive error undoubtedly forms a critical factor in the reported success of any preschool vision screening programme. However, much variation exists both within and between countries as to the content of vision screening programmes. This includes the age at which the child is screened; referral criteria of the screening programme; and indeed the personnel administering the tests that form the screening programme. Due to such differences it is often difficult to make direct comparisons between studies which report upon vision screening success. Much has been contributed to the literature over recent years, largely through the work of the Vision in Preschoolers Study (VIP). VIP is a multi-centre study, conducted in the USA, whose purpose is to evaluate whether there are tests, or combinations of tests, that can be used effectively in preschool vision testing.

The effectiveness of a screening test in detecting a condition is considered in terms of sensitivity, specificity and positive and negative predictive values. Sensitivity is defined as the proportion of individuals with the target condition in a population who are correctly identified by a screening test. Specificity is the proportion of individuals free of the target condition in a population who are correctly identified by a screening test. Positive predictive values describe the proportion of individuals with a positive result who have a target condition; and negative predictive value is the proportion of individuals who test negative who do not have a target condition.

1.2.1 Vision tests

The use of crowded logMAR acuity is the gold-standard VA measure in adults both within clinical and research settings. This is also becoming the case with VA measurement in children. Steps have been made to identify normative values of paediatric VA using different vision tests, protocols of testing, and repeatability of testing [15-19]. The preference as to which vision test that is to be included in a screening programme is not always clear. Often a number of vision tests may be included within the one screening programme to incorporate factors such as a child's comprehension and ability to perform a test. It is outside the scope of this chapter to report upon the relative sensitivity and specificity of each vision test. However, it should be noted that the cut-off points used for referral within a screening programme should be directly related to the specific vision tests used within that screening programme. That is, it should not be generic, with an arbitrary referral point (such as 0.2 logMAR or worse). A VA level that is achieved using one vision test may be different to that achieved using an alternative vision test. The referral criteria should be stipulated for each vision test that could be used within the screening programme.

1.2.2 Cover-uncover test

The cover-uncover test is used to detect the presence of strabismus, and is deemed to be the gold standard for detecting strabismus. However there are few studies which report upon the sensitivity and specificity of the test itself. Williams et al[20] were able to report the sensitivity and specificity of the cover-uncover test on children who had been screened at the ages of 8, 12, 18, 25, 31 and 37 months. At 37 months, the sensitivity of the test was calculated to be 75% (95% CI, 0.577 to 0.899%), with a specificity of 100%.

The VIP study also assessed the effectiveness of the cover-uncover test in detecting strabismus, amblyopia, reduced VA and refractive error[21]. The results are

summarised in Table 2. The results of this study indicated that the cover-uncover test is more sensitive at detecting the presence of strabismus compared to detecting the presence of amblyopia, refractive error or reduced VA.

1.2.3 Stereoacuity

The inclusion of stereoacuity tests within preschool vision screening programmes could be considered as a contentious issue. VIP[22] stated that most guidelines recommend a test of stereopsis. However, if a child was found to have normal VA, no strabismus, and no clinically significant refractive error yet failed to demonstrate adequate evidence of stereoacuity, should they be referred for further investigation? A number of stereotests are available for use as part of a preschool vision screening programme, however normative paediatric values of stereopsis have not been identified for some of these tests. In the absence of such data the appropriateness of inclusion of such tests could be questioned. Stereotests which involve a pass/fail response could be deemed as more appropriate for the purpose of screening for vision problems.

The VIP has reported upon the testability of two different stereotests used to screen for vision disorders, the Random Dot E and the Stereo Smile test[21;23]. The results reported by condition type are summarised in Table 3. The results indicated that both stereotests are more accurate at detecting the presence of amblyopia and strabismus compared to that of reduced VA or refractive error.

In a further study, VIP examined the sensitivity of the same stereotests when the specificity was set at 0.94. The results are summarised in Table 4, and show that the Stereo Smile test was more accurate than the Random Dot E in detecting most target conditions of screening.

1.2.4 Photoscreening and/or autorefraction

The use of photoscreeners and/or autorefractors in preschool vision screening is extremely varied. Within the USA they are commonplace, and the variety of different makes and models make summarising literature extremely difficult. The use of such instruments within UK preschool vision screening programmes is much less frequent. When considering the appropriateness of photoscreeners and/or autorefractors in preschool vision screening it is important to recognise their accuracy when compared to a gold-standard (usually a refraction performed under full cycloplegia). There are notable advantages and disadvantages of photoscreening when compared to autorefraction. One of the main differences is that of cost. After the initial expense of purchase, there is minimal additional cost to autorefraction. Photoscreening however requires printing of the image, and depending upon who is administering the test, interpretation of the results. The implications of both these factors lead to a higher overall expense when incorporated into a vision screening programme.

It should also be noted that the primary aim of the use of a photoscreener or autorefractor is the detection of refractive error. That is, it may detect an amblyogenic factor, but not amblyopia itself. Similarly, the presence of strabismus may also be detected, although understandably the sensitivity and specificity rates of these are considerably lower than those of detecting refractive error.

It is beyond the scope of this chapter to review and appraise literature describing specific photorefractors and/or autorefractors. Important points to note when considering such articles include; the study population (including age, ethnicity and whether general or clinical); test setting (e.g. environment); sensitivity and specificity of the test; the personnel conducting the test; and whether any comparison is made to the gold standard (in this case full refraction under cycloplegia).

1.2.5 What to do with those who are unable to perform screening tests?

Successful testing of children is largely dependent upon the child's cooperation and compliance. The decision about whether to refer those children who are unable to perform screening tests is difficult. Some would argue that such children ought to be referred for further investigation, for the reason that they are unable to perform the screening tests due to the presence of an ocular condition. Others would say that this may not be the case, and that cooperation may be the true issue. The prevalence of ocular conditions amongst children who were unable to perform preschool screening tests has been investigated and it was found that preschool children who were unable to perform the screening test were at a higher risk of higher amblyopia, strabismus, significant refractive error, or unexplained low VA compared to children who had passed the screening test[24]. This led the authors to recommend that these children ought to be referred or retested at a later date possibly with a different test. The impact of recall and re-testing, or automatic referral will undoubtedly affect the overall clinical and cost-effectiveness of any preschool vision programme.

1.2.6 Who should administer the screening programme?

Within the UK it is recommended that preschool vision screening programmes be conducted by orthoptists or by professionals trained and supported by orthoptists[3;4]. In the USA preschool vision screening is usually conducted by nurses and lay people. The use of lay people to administer screening tests does have advantages, particularly when considering the economic burden of a screening programme. Lay screeners are a cheaper alternative to eye care professionals, such as orthoptists, optometrists or ophthalmologists.

Concerns regarding training and assessment of lay screeners have been raised; are lay screeners as accurate as eye care professionals in detecting amblyopia, strabismus and/or refractive error? This question was addressed by VIP, who assessed the performance of lay screeners in administering preschool vision screening tests compared to nurse screeners[25]. In this study, the screening tests conducted included assessment of refractive error, VA, and stereoacuity. Two hand-held autorefractors were used to detect the presence of refractive error. VA was assessed at two different testing distances; a linear test was performed at 10ft, and a single, crowded test administered at 5ft. The results of the study demonstrated that although nurse screeners appeared to slightly higher sensitivities in the assessment of refractive error and presence of stereoacuity compared to lay screeners, the differences were not statistically significant.

However when examining the results of VA testing, the authors reported that nurse screeners achieved significantly higher sensitivity than lay screeners with the linear VA test. Whilst the authors make no recommendations for future screening protocol strategies, their results could be interpreted in two ways. The lack of statistically significant differences in detection of refractive error or stereoacuity with tests

administered by lay screeners could support the use of such personnel in vision screening programmes. However, the differences observed in VA testing between lay screeners and nurse screeners could suggest that nurse screeners would be more effective in detecting vision anomalies. Differences in screening programmes between countries will undoubtedly continue to exist, however recommendations as to who should conduct screening based upon personnel costs alone may not be appropriate.

Summary for the Clinician

- Content of vision screening programmes vary widely. Most involve assessment of visual acuity for which a large number of tests are available. The gold standard is a crowded logMAR based test. Referral criteria should be specific for the test used.
- The use of photoscreeners and/or autorefractors in vision screening programmes is not universal. The use of photoscreeners and/or autorefractors will have an impact upon the cost-effectiveness of screening.
- The inclusion of stereotests in preschool vision screening programmes could be questioned.
- Recommendations state preschool vision screening programmes be conducted by orthoptists or by professionals trained and supported by orthoptists.

1.3 Treatment of amblyopia

The clinical management of amblyopia is determined following careful consideration on a case-per-case basis, taking into account a number of factors including the type of amblyopia present; the patient's age; and the level of VA in the amblyopic eye. Nonetheless, advances in evidence-based medicine have led to a number of recognised studies which have reinforced or altered clinical practice in the management of this condition. The Pediatric Eye Disease Investigator Group (PEDIG), based in the USA, is a multi-centre group dedicated to clinical research in strabismus, amblyopia and other eye disorders affecting children. Funded by the National Eye Institute (NEI), this group have investigated many aspects of the clinical course of amblyopia and its treatment. The Monitored Occlusion Treatment of Amblyopia Study Cooperative (MOTAS Cooperative) is a multidisciplinary group of ophthalmologists, orthoptists, basic scientists and statisticians dedicated to investigating amblyopia treatment. Based in London (UK), it is funded by the charities Guide Dogs for the Blind Association, and Fight for Sight. They have conducted two clinical trials to identify the response of amblyopia to occlusion therapy. Data from both the studies conducted by PEDIG and the MOTAS Cooperative have contributed to our understanding of the management of amblyopia.

1.3.1 Type of treatment

Amblyopia is treated by obscuring the image from the good eye to promote use of the amblyopic eye. This can be achieved through occlusion treatment (patching or pharmacological occlusion, in the form of atropine); or through optical penalisation. There are notable advantages and disadvantages to different treatment modalities in terms of compliance, ease of administration and visual acuity outcome. Comparison of studies investigating the effectiveness of treatment of amblyopia is hindered, due to differing definitions of both "amblyopia" and "treatment success". In addition, clinicians have long recognised that the amount of treatment prescribed and the amount of treatment actually undertaken may differ. Objective measurement of the amount of occlusion worn has been made possible with the introduction of occlusion dose monitors (ODM). ODMs were developed and validated by the Monitored Occlusion Treatment for Amblyopia Study (MOTAS) Cooperative (UK), and since then have been used to examine whether there is a dose-response to occlusion therapy.

1.3.2 Refractive adaptation

One of the main concepts that has arisen over the recent years in amblyopia treatment is that of refractive adaptation (or "optical treatment of amblyopia" as it is sometimes known[26]). There has been increasing evidence to suggest that the treatment of amblyopia in the presence of refractive error should incorporate observation of VA following the prescription of glasses alone[26-29]. These studies report increases in VA in subjects such that some did not require any additional treatment for their amblyopia. Prior to such studies, it was uncertain whether observed improvements in VA achieved were as a result of amblyopia therapy (i.e. occlusion) or due to glasses-wear alone.

It is becoming increasingly clear that refractive adaptation is a recognised period in amblyopia therapy. The time taken to reach this period however remains under debate. The MOTAS studies utilised a period of 18-weeks observation[27-29]; however the PEDIG reported 83% of their study group demonstrated stability of improvement in VA before 15 weeks, however one patient improved for 30 weeks[26]. Improvements

in VA have been described to occur after 20 weeks, but not considerably, with the majority of improvement having occurred in weeks 4 to 12[30].

One of the arguments supporting the notion of vision screening is the detection of bilateral refractive error. Wallace et al[31], as part of the PEDIG study, examined the improvements in VA in children with bilateral refractive amblyopia aged between 3 and 10 years. They reported that correction of refractive error improved VA, with only 12% of the cohort requiring additional amblyopia therapy in the form of occlusion or atropine.

1.3.3 Conventional occlusion

Patching treatment is often initiated as the first-line approach in amblyopia therapy. One advantage of patching treatment is that the effects are reversible; in that once the patch is removed the non-amblyopic eye is favoured, which is not the case with pharmacological occlusion. Since the acknowledgement of refractive adaptation it has been necessary to confirm that occlusion therapy is also effective in the management of amblyopia. PEDIG compared the effect of daily patching versus a control group of amblyopes in children aged 3 to 7 years, following a period of refractive adaptation. An improvement in VA was observed in both groups after 5-weeks, and as expected a greater improvement reported in the patched group[32].

The MOTAS Cooperative have investigated the amount of occlusion required to improve VA and explore the dose-response relationship in amblyopia therapy[28]. They found that most children required between 150-250 hours of occlusion, irrespective of the type of amblyopia present. Specific characteristics were observed to affect the response, such as the age of the patient; where older children required a greater amount of occlusion to achieve similar gains in VA compared to their younger counterparts. Younger children have been observed to respond more quickly and with less occlusion than older children; however the final level of VA achieved is similar for all ages[29].

Traditionally clinicians have recommended near visual activities whilst occlusion therapy is undertaken, however there has been little research to justify such advice. The PEDIG investigated whether performing such activities influenced the improvement in VA outcome when treating amblyopia in conjunction with occlusion therapy[33]. No statistical evidence to support the notion that near visual activities improved VA outcome in their study group was found. It should be noted that the study group were prescribed only 2 hours of patching per day, and that the authors make no inference as to whether the results would be similar in subjects patched for a greater or lesser time.

1.3.4 Pharmacological occlusion

Pharmacological occlusion (i.e. atropine) has notable benefits; it could be argued that it carries with it less of a social stigma compared to the wearing of an eye patch. One disadvantage of pharmacological occlusion is that the effects are not readily reversible; it can take several weeks for the effects of atropine to wear off. Concerns also exist regarding its efficacy as a treatment modality, with some clinicians believing it to be a less effective treatment when compared to conventional occlusion. Studies conducted by PEDIG examined the effectiveness of conventional occlusion versus pharmacological occlusion in the treatment of moderate amblyopia (20/40 to 20/80)[34]

and severe amblyopia (20/100 to 20/400)[35]. Either treatment modality was found to be appropriate with similar improvements in VA in either group. The decision towards which therapy should be adopted may now be based on other factors. One such factor may be the instillation of the atropine itself. The effect of different atropine regimens in the treatment of moderate amblyopia (20/40 to 20/80) was investigated. Comparisons were made between the observed effect of daily atropine instillation to that of weekend-only atropine instillation[36]. Both groups were observed to show improvements in VA of similar magnitudes. It could be argued that the need for daily atropine instillation is redundant, thereby improving the therapeutic experience for the child. This in itself may encourage parents and/or clinicians to adopt this treatment modality.

1.3.5 Optical penalisation

Another treatment option in the management of amblyopia is that of optical penalisation. This is where lenses are used to induce a defocused image of the non-amblyopic eye. Tejedor and Ogallar[37] directly compared the effects of atropine versus optical penalisation in the treatment of mild to moderate amblyopia (VA of at least 20/60). This small study found greater improvements in VA in the atropine group after six months of therapy, which may be attributed to the child peeking over or around the glasses and thereby not achieving the desired affect of the optical penalisation. Although optical penalisation remains a useful treatment option in specific clinical situations, it is often not considered an appropriate first-line choice of therapy in the management of amblyopia.

1.3.6 Effective treatment of amblyopia in older children (over the age of 7 years)

There has been strong evidence that treatment for amblyopia is more effective prior to the age of 7 years. Despite this, amblyopia therapy has been reported to be successful in older children with either anisometropic[38-42] and/or strabismic amblyopia[40-42]. Treatment of strabismic amblyopia in the older child should be pursued with caution, as there is a notable risk of reducing the density of suppression, and thereby inducing intractable diplopia in these patients. A number of studies which reported upon improvements in VA in older children with strabismic or mixed aetiology amblyopia following treatment do not report whether the density of suppression had been measured, or if any other side-effects had been observed[40-42]. Despite there being some evidence to suggest that successful treatment of amblyopia in the older child is possible, earlier intervention is more advantageous, and to that end supports the notion of preschool vision screening.

1.3.7 Treatment compliance

The successful management of amblyopia is intrinsically linked to treatment compliance and adherence to therapy. This in itself is multi-factorial in nature. The development and application of ODMs has meant that reasons for non-compliance can be more thoroughly investigated. In particular, ODMs have highlighted the discrepancy between the amount of occlusion prescribed and the amount administered. Clinicians have long recognised that the amount of occlusion carried out often falls short of their recommended treatment plan. Stewart et al[29] reported upon the effect of six hours a day occlusion compared to 12 hours a day occlusion in the treatment of strabismic and/or anisometropia amblyopia. They found that the amount of occlusion received was 66% and 50% of their prescribed six and 12 hours a day, respectively. Such information ought to be taken into account when prescribing occlusion therapy

Loudon et al[43] examined some of the limiting factors of occlusion therapy for amblyopia and reported parental fluency in the national language and level of education were both predictors of low compliance. Parental understanding of the condition and treatment has also been reported as being an important factor in the successful management of amblyopia.

Adherence to treatment must be considered not only in terms of the child complying with therapy, but in the parent/guardian administering the treatment as advocated by the ophthalmologist and/or orthoptist. Searle et al[44] found two variables that were significant predictors of compliance with occlusion therapy. They reported that self-efficacy (the belief in the ability to patch their child) was positively associated with treatment compliance. The parental belief that occlusion therapy prohibits the child's activities was negatively associated with treatment compliance.

1.3.8 Other treatment options for amblyopia

The use of photorefractive keratectomy (PRK) for the treatment of anisometropia in children has not been fully investigated and concerns exist surrounding the long-term response to refractive surgery in terms of VA and corneal status. However, it could be postulated that if the amblyopic risk factor of high anisometropia is removed early then the possibility of development of dense amblyopia would be reduced. Paysse et al[45] reported the results of a small study of children with high anisometropia, and found improvements in both VA and stereopsis following treatment. However, compliance with amblyopia therapy remained unaffected in this study group following treatment. The use of refractive surgery in children is not commonplace and there remains a need for a large randomised clinical trial to fully investigate the possible benefits of this form of treatment.

1.3.9 Recurrence of amblyopia following therapy

Recurrence of amblyopia has been observed in patients following the cessation of treatment, with rates varying widely. Some recent studies have sought to identify factors which may influence whether recurrence is likely to occur[46-49]. These include; age of termination of treatment; VA at the time of cessation of treatment; and which type of amblyopia is present. Recurrence in amblyopia was noted in 7% to 27%, with a low reported recurrence in children who underwent treatment after the age of 7 years[49]. Age of the child at the cessation of treatment does appear to be a factor, with recurrence inversely correlated with patient age[46].

Summary for the Clinician

- Treatment of amblyopia associated with refractive error should incorporate a period of observation with glasses-wear alone to allow for "refractive adaptation" or "optical treatment of amblyopia". Improvements in VA can occur up to and beyond 20 weeks after glasses are prescribed, but most improvement occurs in weeks 4 to 12. In some cases further amblyopia therapy may not be required.
- There is evidence to suggest that children who undergo amblyopia therapy at an early age respond more quickly to occlusion than older children, and require less occlusion in total.
- Pharmacological occlusion, in the form of atropine, has been found to be as effective as conventional occlusion (patching) in the treatment of both moderate and severe amblyopia. Weekend-only atropine instillation has been shown to produce

similar improvements in VA as daily atropine instillation in the treatment of moderate amblyopia.

- There is evidence to suggest that successful treatment of children aged over 7 years can be achieved in cases of anisometropic, strabismic and mixed aetiology amblyopia.
- The development of ODM has informed not only the occlusion-dose response of amblyopia treatment, but also reasons for poor treatment compliance. Parental understanding of the condition and belief in therapy may influence treatment outcome.
- Recurrence of amblyopia may occur following treatment, with reported rates of 7% to 27%. Factors influencing recurrence include age of the child at cessation of treatment, VA at the time of cessation of treatment and which type of amblyopia is present.

1.4 Quality of life

When considering the application of any screening programme, thought should be made regarding the impact of testing for the target condition; the impact the target condition has upon a person; and the impact subsequent treatment of that target condition may have upon a person. One of the ways in which the health impact of a disease or condition can be assessed is through measures of quality of life, or health-related quality of life (HRQoL). Over recent years there has been a growing body of evidence which has examined the impact of amblyopia and/or strabismus upon a person's physical and emotional well-being.

1.4.1 The impact of amblyopia upon HRQoL

There have been a number of studies which have investigated the impact of amblyopia upon HRQoL. These have examined the effect of amblyopia upon stereoacuity and motor skills[50;51]; reading speed ability[52]; educational attainment[9]; and emotional well-being[44;53-58].

1.4.2 Stereoacuity and motor skills in children with amblyopia

Stereoacuity and motor skills have been reported to be impaired in children with amblyopia. Webber et al[50] investigated the functional impact of amblyopia in children by assessing the fine motor skills of those with amblyopia compared to age-matched control subjects. It was noted that the subjects with amblyopia performed significantly poorer in most of the fine motor skills tests conducted as part of the study, particularly in the tasks related to time. The results were even more noticeable in those children with a diagnosis of amblyopia and strabismus. Hrisos et al[51] investigated the influence of VA and stereoacuity on the performance of preschool children undertaking tasks that required visuomotor skills and visuospatial ability. The authors reported that reduced monocular VA itself did not relate to any ability of task performance, but stereoacuity was found to affect task performance, with subjects with reduced steroacuity noted to have poorer responses to neurodevelopment tasks. Such studies support the notion that amblyopia is associated with negative implications to HRQoL.

1.4.3 Reading speed and reading ability in children with amblyopia

Reading speed and reading ability has been assessed in children with amblyopia. Stifter et al[52] reported that maximum reading speed was significantly reduced in those with the condition. Therefore they could be deemed to have a functional reading impairment when compared to normal sighted controls. It is recognised that reading ability is multifactorial in nature, and is influenced by comprehension. The study does not imply that children with unilateral amblyopia are poor readers under binocular conditions, for the binocular VA and reading acuity of the two groups were comparable.

1.4.4 Impact of amblyopia upon education

Chua and Mitchell[9], as part of the Blue Mountains Eye Study in Australia (a population based survey of people aged 49 years or older), examined the consequences of amblyopia on education, occupation and long term vision loss. In their study population, the presence of amblyopia was not found to be significantly associated with lifetime occupational class. However, fewer people with amblyopia were found to have completed higher university degrees. This finding was supported by Rahi et al[59] who reported upon findings of the 1958 British birth cohort with

respect to any association of amblyopia with diverse educational, health and social outcomes. The authors could find no statistical evidence between the presence of amblyopia and educational attainment or paid employment.

1.4.5 Emotional well-being and amblyopia

The psychosocial impact of amblyopia and its treatment has been explored from both the parental and child perspective[56]. Children have reported feelings of shame and negativity associated with amblyopia, particularly following the start of treatment. The initiation of therapy can draw adverse attention from others, and children have reported that they felt interrogated by others about their treatment (particularly if their treatment involved the wearing of glasses and a patch).

It is important to recognise that the impact of amblyopia therapy may be experienced not only by the child, but also by family members[54]. This could be result in impaired relationships between the child and parent/guardian, but also between siblings. Parents often state that their child may be more clingy or demanding when occlusion is worn; that the child's compliance with occlusion can lead to negative behavioural changes; or that their child appears to be less confident when wearing their patch or glasses[56].

The issue of peer victimisation and bullying associated with amblyopia has been recognised[55;56;58]. This may be in response to the wearing of glasses and/or occlusion therapy. Horwood et al[58] as part of the Avon Longitudinal Study of Parents and Children (ALSPAC) conducted in the UK, investigated whether wearing glasses, having manifest strabismus, or having a history of wearing an eye patch predisposed preadolescent children to being victimized more frequently at school. In this study, the outcome measure used to assess whether bullying had occurred was through a structured face-to-face interview, conducted with the child at the age of 8.5 years. Children were asked if they had experienced or used any forms of overt or relational bullying. The authors reported that those children who wore glasses or had a history of wearing an eye patch were 35% to 37% more likely to be victims of physical or verbal bullying (after adjustment for social class and maternal education).

Williams et al[55] argued the case for preschool vision screening in that those who had undertaken screening were likely to have concluded amblyopia therapy early (i.e. before school starts) and thus would avoid adverse reactions from their peers. They compared two groups that had been offered preschool vision screening at the age of three years to those who had not; and asked the children at age 8 years whether they had been bullied through a standard structured interview. The authors reported an almost 50% reduction in children who reported having been bullied in the group that had been offered preschool screening, compared to the group who had not.

Not all children undertaking amblyopia therapy find the treatment a negative experience. Indeed in a study by Choong et al[53], the authors found no significant changes in parental (carer's) stress or the child's psychosocial well-being between an occluded and non-occluded group. One factor which did result in changes in parental attitude towards the child was the issuing of glasses. A statistically significant difference was found, where carers felt more negative towards their child once glasses were prescribed. As glasses form an integral part of amblyopia therapy it could be

deemed that the results do in fact demonstrate psychosocial implications of amblyopia treatment, particularly from the carer's perspective.

Conflicting evidence exists in the adult population. Rahi et al[59] reported that adults with amblyopia were no more likely to be bullied (either at the age of 7 or 11 years); and could find no evidence for an association between the presence of amblyopia and participation in social activities in either childhood or adult life. The authors also stated that those with amblyopia were no more likely to report depression or psychological distress in adult life.

This finding was not supported by Packwood et al[57], who explored the psychosocial implications of growing up and living with amblyopia in a group of adult subjects. The authors reported that those with amblyopia experienced more distress in several areas of psychological well-being, including somatisation, obsession-compulsion, interpersonal sensitivity, anxiety and depression.

Taken in isolation, the impact of any one of the aforementioned problems may be minimally associated with detriment to HRQoL. However, the cumulative effect of impaired reading, motor skills and psychosocial impact of amblyopia, for example, might influence HRQoL to a greater degree.

1.4.6 The impact of strabismus upon HRQoL

The psychosocial implications of strabismus are more accepted and recognised, particularly in cases of cosmetically obvious strabismus. Detrimental implications of strabismus include a negative self-image, reduced self-confidence, low self-esteem and poor interpersonal relationships[60]. The presence of a cosmetically noticeable strabismus has also been reported to impact upon a person's ability to gain employment[61;62], and in a person's ability to attract a partner[63]. The presence of strabismus does not only affect those in adulthood. Uretman et al[64] determined that children with strabismus were perceived in a negative light by adults. The age at which the emergence of negative attitudes towards those with strabismus develops has been studied. Paysse et al[65] reported that at approximately six years of age, children begin to express a negative attitude towards strabismus.

In adults it has been documented that those with strabismus experience more social anxiety and use social avoidance strategies compared to the general population[66;67]. It could be argued therefore that surgical correction of strabismus serves to provide psychosocial benefits, and therefore improve HRQoL.

Improvements in quality of life following strabismus surgery are well-documented in adults[66-69], however its effect on children is not as extensively researched. Archer et al[70] reported upon a group of 98 children who underwent strabismus surgery (although it is unclear whether the purpose of surgery was purely cosmetic or functional in nature). The authors stated that following surgery there were significant improvements in a number of quality of life dimensions, including those of anxiety, social relations and developmental satisfaction (parental response). The results concur with those found in an adult population, and it can therefore be deemed that the psychosocial benefits reported in adults following strabismus surgery are also applicable to children.

1.4.7 Critique of HRQoL issues in amblyopia

Methods of determining the impact of amblyopia and/or strabismus upon HRQoL differ greatly from one study to another. Some report changes in psychosocial behaviour and well-being using a purpose designed questionnaire[60;62;63;67;71]. Whilst their findings are of great clinical importance it can be difficult to compare one study to another due to differences in methodologies.

One key component that must be considered when addressing the issue of HRQoL and amblyopia and/or strabismus, is that of the perspective from which the results are taken. That is, are the results taken from responses from the parent; the child; or from and adult with a history of amblyopia and/or strabismus. The findings of each study are equally valid, however it must be recognised that there may be levels of bias exerted depending upon which methodology is applied. For example, studies which report from the parental perspective[53;54;56;70] may in fact be capturing parental opinion regarding the condition and/or its treatment, rather than a true measure of HRQoL changes. Studies that involve adults with a history of amblyopia and/or strabismus[57] are asking subjects to recall childhood experiences. It is possible that adult experiences have since "tainted" the recall of such events; either exaggerating or diminishing the true changes in HRQoL experienced as a child. Perhaps studies which report from the child perspective[55;56;58] could be considered the most valid. They deliver insight into what is experienced at the time. However, they are not without their weaknesses. What they fail to do is inform as to whether the impact of amblyopia and/or strabismus (as a condition, or its treatment) is appreciated in the longer term, that is, into adulthood.

1.4.8 The impact of the condition or the impact of treatment?

It can be difficult to fully distinguish whether any reported detriment to HRQoL in amblyopia is due to the condition itself or its treatment. This is not a factor when considering strabismus. Strabismus (particularly that of large angle strabismus) is cosmetically noticeable and it is the impact that that has upon the person which can affect HRQoL. Therefore it can be said that any study which reports upon HRQoL and strabismus is reporting upon the effect the condition has upon a person's well-being. With amblyopia, this is not the case. The condition itself cannot be identified by peers. What is noted is the effect of treatment upon HRQoL, with the instigation of glasses or occlusion therapy. Studies which report upon changes in HRQoL in amblyopia frequently report upon the impact of the treatment upon quality of life rather than the condition itself[44;53-55;55-57]. Alternative studies do report upon the impact of amblyopia, however the measures of these studies are of adult-related issues (such as employment, educational attainment and risk of losing vision in the non-amblyopic eye)[9;59]. It is not possible to determine whether the same HRQoL changes which occur in childhood are appreciated in adulthood, because the measures used in the identified studies are so different. Nonetheless it can be concluded that there is evidence to suggest that there are HRQoL issues related to amblyopia and/or strabismus and its treatment.

Summary for the Clinician

- There have been a number of studies investigating HRQoL implications of amblyopia and/or strabismus over recent years. These have involved studies with children who have the condition, or adults who had previously undergone treatment.

- Studies have reported amblyopia to impact upon stereoacuity, fine motor skills and reading speed.
- The presence of amblyopia does not appear to have any impact upon educational attainment or paid employment in adult life.
- Amblyopia (more specifically amblyopia treatment) has been shown to impact negatively upon a child's emotional well-being; and may also affect relationships between the child and parent/guardian.
- The issue of bullying and amblyopia treatment requires further investigation. Some studies report children who had glasses or had a history of occlusion therapy were more likely to be victims of bullying. However, other studies refute this.
- Taken in isolation, the impact of any one of the aforementioned problems may be minimally associated with detriment to HRQoL. However, the cumulative effect of impaired reading, motor skills and psychosocial impact of amblyopia, for example, might influence HRQoL to a greater degree.
- The reported HRQoL implications of strabismus are related to physical appearance and the impact of strabismus upon self-image and interpersonal relationships. Surgical correction of strabismus has been reported to improve HRQoL.

Table 1 Summary of criteria for screening[72]

Category	Criteria
Condition	The condition should be an important health problem, whose epidemiology and natural history are understood. There should be a recognisable risk factor or early symptomatic stage.
Diagnosis	There should be a simple, safe, precise and validated screening test which is acceptable to the population. There should be an agreed policy on further investigation of individuals with a positive test result.
Treatment	There should be an effective treatment or intervention for those identified as having the disease or condition, with evidence of early treatment leading to better outcome than late treatment. There should be agreed evidence-based policies which individuals should be offered treatment.
Programme	There should be evidence from high quality randomised controlled trials (RCTs) that the screening programme is effective in reducing mortality or morbidity. There should be evidence that the complete screening programme (including the test, diagnostic procedures, and treatment) is clinically, socially and ethically acceptable. The benefit of the programme should outweigh the physical and psychological harm. The cost of the programme should be economically balanced in relation to expenditure on medical care as a whole (i.e. value for money).

Table 2 Sensitivity of cover-uncover test when specificity was set to 0.94[21]

Test	Amblyopia n=75 (95% CI)	Strabismus n=48 (95% CI)	Refractive error n=240 (95% CI)	Reduced VA n=132 (95% CI)
Cover-uncover	0.27 (0.17 to 0.37)	0.60 (0.46 to 0.74)	0.16 (0.11 to 0.21)	0.06 (0.02 to 0.10)

n = number of children

Table 3 Sensitivity of Random Dot E and Stereo Smile by condition type*[23]

Stereotest	Amblyopia	Reduced VA	Strabismus	Refractive error	Specificity
Year 1 n=796	n=75	n=132	n=48	n=240	
Random Dot E	0.63	0.38	0.60	0.47	0.90
Year 2 n=1037	n=88	n=114	n=62	n=299	
Stereo Smile	0.77	0.30	0.68	0.51	0.91

n = number of children * may have more than one condition

Table 4 Sensitivity of Random Dot E and Stereo Smile when specificity was set to 0.94*[21]

Test	Amblyopia (95% CI)	Strabismus (95% CI)	Refractive error (95% CI)	Reduced VA (95% CI)
Random Dot E	0.28 (0.18 to 0.38)	0.29 (0.16 to 0.42)	0.23 (0.18 to 0.23)	0.24 (0.17 to 0.31)
Stereo Smile	0.61 (0.51 to 0.71)	0.58 (0.46 to 0.70)	0.37 (0.32 to 0.42)	0.20 (0.13 to 0.27)

* may have more than one condition

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