Visual development and visual defects in children with Down's syndrome

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The very last job in preparing this thesis was to count the total number of tests I performed. It was overwhelming how many names were attached to a picture and a situation. I would like to thank all these children and their families. Without their great contribution this work would not have been possible.

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Summary

This thesis investigated the refractive, accommodative and colour vision status of young people with Down's syndrome (DS). Seven separate studies were conducted. Participants were recruited from the Cardiff Down's Syndrome Vision Research Unit.

Abnormal refractive development was reported from an early age, and continued through the first 15 years of life. The normal emmetropisation process was re-aligned to leave subjects with hypermetropic errors, with a wide variation in refractive error, at all ages. There was a specific development of oblique astigmatism with age, which may be associated with the reduced palpebral aperture. Parental refractive status was not found to influence that of their children with DS, although such a relationship was found with their typically developing siblings. The cause of the refractive errors was axial in nature in children with DS. However, general physical growth did not have an active influence in shaping these errors.

Bifocal spectacles were found to be a successful treatment for reduced accommodation in children with DS. From the study cohort, over 40% of the children were able to effectively discard bifocal wear after gaining accurate accommodation.

Children with DS demonstrated their ability to engage in subjective colour vision testing, given that appropriate tests were used. The design of the Mollon-Reffin 'Minimalist' (M-R) colour vision test was found most suitable. This test showed high sensitivity and specificity in comparison to other clinical tests. Using the M-R test, the prevalence of colour vision defects in DS was found to be comparable to that of the general population.

The studies have generated optometric guidelines for the clinical care of people with DS which emphasise the importance of frequent routine clinical examination of this population due to the unpredictive nature of their refractive error development. Examination from an early age will allow for the early detection, and prompt management, of visual problems. Bifocal prescription is highly encouraged for those with reduced accommodation, with cessation of wear being decided from on-going assessment of the patient's accommodation after bifocal prescription.

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Chapter One : General introduction

Chapter One: General introduction

It is known that children with Down's syndrome (DS) are at a higher risk of developing ocular and visual disorders than typically developing children. Studying vision and visual development in these children has been the subject of interest of the Cardiff Down's Syndrome Vision Research Unit for many years. The present study aims to continue this longitudinal monitoring of the children in terms of refraction, accommodation and vision, concentrating on the distribution and development of refractive errors, their relationship between the children and their family members, and their relationship to axial length and body height, accommodation response to bifocal wear and the nature of colour vision in children with DS. This is with the overall aim of enhancing clinical guidelines for testing children with DS, maximising the predictive power of eye care practitioners and improving the relevance of clinical tests included in a routine vision assessment, ultimately leading to enhanced lifestyle and education for individuals with DS.

DS is a genetic disorder that was first described by the British doctor John Langdon Down in 1866 and named after him. It is caused by the presence of all or part of an extra chromosome 21. This disorder can be caused in four different ways: Trisomy 21, Mosaicism, Robertson translocation and duplication of a portion of chromosome 21. The incidence of DS is approximately one per 800 live births with no distinction between different ethnic groups and living standards, with males being at a slightly higher risk than females. However, maternal age induces a large risk for the occurrence of the disorder in the embryo, giving a higher risk for children of older mothers. Some individuals with DS can be recognised by having distinctive physical characteristics. Cognitive development is influenced by DS. It is believed to be the

most frequent genetic cause of learning disabilities. However, Intelligence Quotient (IQ) scores and disability levels are variable among individuals. Moreover, persons with DS can suffer from several health problems that are associated with the syndrome. Generally, they are more prone to diseases and infections. In addition, vision can be markedly affected in these persons.

This chapter will present a general background about DS, reviewing the history of the exploration of the syndrome and describing it, in addition to describing the latest research. In particular, it will contain information about the history of DS, genetic basis of the syndrome, physical and cognitive characteristics, incidence, general health and, most importantly, visual characteristics.

1.1 History of Down's syndrome

'Mongolian idiots', 'Kalmuck idiots' and 'unfinished children' are names that were used in the past to describe individuals with DS. Several publications suggested a degree of awareness of the syndrome by recording physical characteristics of some patients that strongly suggest the presence of DS.

According to Smith and Berg (1976), several people such as Esquirol in 1838 and Seguin in 1846, who were medical practitioners, described individual cases in the medical literature that are suggestive of the presence of DS. However, it was not until 1866 that Langdon Down published a paper in the London Hospital Reports describing and identifying the syndrome. Down (1866) was the first to categorise individuals with DS and differentiate them from individuals with other sorts of learning disabilities. He described their physical characteristics, mentioned the occurrence of their learning disabilities and even suggested that it was a congenital condition. He named them 'Mongol idiots' due to some facial similarities between

them and the Blumenbach's Mongolian race such as the presence of the epicanthal folds. Later in the nineteenth century many papers were published about DS. According to Smith and Berg (1976), several scientists were interested in the subject and each scientist concentrated on a specific aspect related to the syndrome. For example, during 1876, Mitchell had a special interest in the relationship between the presence of DS and maternal age, while Oliver studied the eyes in 1891 and so on. It was believed that the syndrome was caused by abnormalities that occur in the thyroid gland according a review of the history of the syndrome by Smith and Berg (1976). However, it was not until the twentieth century that Lejeune and his colleagues discovered the presence of the extra chromosome, in 1959, starting a new era in truly understanding the aetiology of DS (Catalano, 1990).

Research about different aspects of the syndrome continues around the globe both to further understand the nature of the syndrome, and to improve people's quality of life.

1.2 Genetic basis of Down's syndrome

DS is a genetic disorder that occurs before birth. There are four known mechanisms by which DS occurs. However, DS cannot be prevented and is congenital in all of the four types. The four types of DS are: Trisomy 21, Mosaicism, Robertson translocation and duplication of a portion of chromosome 21. Each of these methods causes DS when it takes place in an embryo. Nevertheless, the characteristic and extent of the effects of the syndrome are hugely diverse, not only between different types of DS, but also between different individuals having the same type of DS.

Chromosome 21

There has been extensive research to explore the critical regions of chromosome 21 that cause the disorders associated with DS. Studies have resulted in defining what is believed to be the DS critical region on chromosome 21 (Peterson et al., 1994). Miller and Therman (2001) summarised the results of various studies in a simple, yet informative way. Table 1.1 illustrates the critical regions of chromosome 21 that are thought to be responsible for the occurrence of some characteristics that are closely associated with Down's syndrome, as described by Miller and Therman (2001).

Gene	Abnormality	Effect
The superoxide dismuyase (SOD) gene	Over expression	Inability to detoxify reactive oxygen Bone marrow and thymus defects development
The Human Minibrain (MNB) gene	Mutations of the Drosophila homologue	Learning and memory disabilities.
ETS_2	Over expression	Development of skeletal abnormalities.

Table 1.1: Three different genes in the DS critical regions, their abnormality and their contribution to the DS phenotype (from Miller and Therman, 2001).

In addition, the results of many other studies have attempted to elucidate the DS critical region by defining the information of the specific genes and how it differs in the presence of DS. A study by Arron *et al.* (2006) indicated that an overdose of some particular gene products occur in individuals with DS, and this leads to the formation of the phenotypes of DS.

1.2.1 Trisomy 21

Trisomy 21 is the most common type of DS accounting for approximately 95% of DS cases (Selikowitz, 1997). It is described in many textbooks as resulting from having an extra copy of chromosome 21 gained from either the egg or the sperm of one of the parents; originating from an abnormality in the cell division before fertilisation.

In a typical gametogenesis, a cell in the testicle or the ovary divides to form two new cells with each cell having half of the original number of chromosomes. However, the egg or sperm receives an extra copy of chromosome 21 in the case of trisomy 21. This extra copy does not separate from the other one during the cell division; a process that is called meiotic non-disjunction. As a result, the embryo ends up with 47 chromosomes rather than the typical 46 chromosomes. All the cells in the body are affected if the syndrome occurs by this means. Hence, physical characteristics are likely to appear in individuals with trisomy 21. Maternal age is thought to influence the occurrence of trisomy 21. However, trisomy 21 is not a familial trait.

1.2.2 Mosaicism

Mosaicism is very rare. According to Selikowitz (1997), it accounts for approximately 1% of DS cases. It was named mosaicism because, unlike trisomy 21, not all of the body cells are affected. People with this type of DS have a mixture of normal cells and cells with an extra chromosome 21. There are 2 ways by which mosaicism DS can occur. One way is a non-disjunction event in a normal embryo. This leads to a fraction of the cells having trisomy 21. The other way occurs when some of the cells in a DS embryo return to the normal chromosomal arrangement after

undergoing non-disjunction. Physical features of DS are likely to be absent in these individuals, but this depends on the affected cells. Many cases of mosaicism may be undiagnosed for this reason. Moreover, Selikowitz (1997) suggested that development and function are closer to the normal range in these cases and that, rarely, it can occur without intellectual disabilities.

1.2.3 Robertson translocation

This occurs in about 4% of DS cases as reported by Selikowitz (1997). The difference in this type is that there is an extra chromosome 21, but it is attached to another chromosome. Parental age is not a risk factor in this type. However, inheritance could be the reason for having the syndrome.

This type of DS can occur in two different ways: it can either occur as an isolated error at the time of the formation of the egg or the sperm, or it could result from one parent being a carrier of the syndrome. This is the only case in which DS is a familial syndrome.

1.2.4 Duplication of a portion of chromosome 21

This type of DS is extremely rare. As the name suggests, it occurs by duplication of only a region of chromosome 21. This leads to extra copies of some of the genes in chromosome 21 rather than the whole chromosome. Physical and intellectual characteristics depend on the duplicated region, according to Petersen *et al.* (1990). It is suggested that if the duplicated region contained genes that are responsible for a specific characteristic, this particular characteristic can occur in the individual.

1.3 Characteristics

DS is commonly associated with some distinctive physical features such as the flat nasal bridge, protruding tongue, short neck and epicanthal folds. Delayed cognitive development and learning disability are also a stereotype that is linked to the syndrome.

1.3.1 Physical characteristics

"The hair is not black, as in the real Mongol, but of a brownish colour, straight and scanty. The face is flat and broad, and destitute of prominence. The cheeks are roundish, and extended laterally. The eyes are obliquely placed, and the internal canthi more than normally distant from one another. The palpebral fissure is very narrow. The forehead is wrinkled transversely from the constant assistance which the levatores palpebrarum derive from the occipito-frontalis muscle in the opening of the eyes. The lips are large and thick with transverse fissures. The tongue is long, thick, and is much roughened. The nose is small. The skin has a slight dirty yellowish tinge, and is deficient in elasticity, giving the appearance of being too large for the body." (Down, 1866)

This is the first published description of the DS phenotype, in Down's own words, and describes the majority of the physical features. These characteristics can occur in a person in full or in part, taking into account the four types of DS and their impact on the physical appearance of a person. Many of these characteristics could exist in any typically developing person. Hence, they are not the main basis for diagnosing a person as having DS. However, Devlin and Morrison (2004) suggested

that one or more features are very likely to be found in an individual with DS. Nevertheless, variability between individuals is very likely.

Further research followed Down's observations and studied these characteristics in greater details. Some strongly prominent characteristics are a large protruding tongue, abnormal teeth shape, short broad neck, single palmar crease, and thick broad feet (Smith and Berg, 1976; Selikowitz, 1997; Schepis *et al.*, 2002; Azman *et al.*, 2007). The focus in this chapter is placed on the face and head anatomy due to their relevance for the optometry profession.

Starting with the head, one of the main features to notice is that the back of the head is usually flat in comparison to that of a typically developing person (Fischer-Brandies *et al.*, 1986; Quintanilla *et al.*, 2002). The face tends to have a generally round profile and the hair is commonly soft and straight (Selikowitz, 1997).

Looking at the eyes superficially, one can notice the epicanthic folds, which is one of the main reasons the syndrome was called Mongol idiots, due to the frequent occurrence of folds in the Mongolian race. Arora *et al.* (2003) found these to be one of the commonest ophthalmic features in children with DS. Da Cunha and Moreira (1996) found epicanthic folds in 61% of their subjects. The palpebral fissure has a slightly distinctive slant in DS. Smith and Berg (1976) described them to be an outstanding feature, being very commonly oblique and narrow laterally. Brushfield's spots, which are white small spots on the periphery of the iris, are considered a relatively frequent feature of DS. Berk *et al.* (1996) observed these in 36.3% of their participants. Although Smith and Berg (1976) have suggested that these spots are a very useful diagnostic sign, they also stated that the spots need to be carefully diagnosed and differentiated from those that are commonly found in typically developing newborns. Moreover, the interpupillary distance tends to be shorter in

individuals with DS than it is in typically developing individuals in relation to the width of the head (Kerwood *et al.*, 1954; Woodhouse *et al.*, 1994).

A very noticeable feature is the flat nasal bridge this population tends to have (Ahmed *et al.*, 2005). Moreover, Ferrario *et al.* (2004) observed the dimensions of the nose in DS and described it as shorter vertically and wider horizontally, compared to members of the general population.

The ears are characterised to be reduced in size in DS. According to Sforza *et al.* (2004), the dimensions of the ears are significantly smaller in size compared to control subjects. Smith and Berg (1976) suggested that the most noteworthy ear features are the angular overlapping helix and the small ear lobe commonly observed in people with DS.

In summary, there are several physical characteristics that tend to be associated with DS. However, any one or group of these characteristics could appear in a typically developing individual, and although one or more of those characteristics are likely to occur in DS, some individuals with the syndrome may not have any of these signs, such as in those with mosaicism. This strongly indicates the importance of prenatal screening tests when there is a risk of DS pregnancy. Some of the available diagnostic techniques are amniocentesis, chorionic villus sampling (CVS), and percutaneous umbilical blood sampling.

1.3.2 Cognitive characteristics

DS is considered the major genetic cause of learning disabilities (Roizen, 2002). It is recognised that individuals with DS have intellectual disabilities as well as motor disabilities. Communication skills and intelligence both tend to be lower than average and delayed in DS, which ultimately contributes to enhanced learning

disabilities in those individuals. However, learning disability is very variable between different individuals with the syndrome. Moreover, physical characteristics and speech abilities often have an enormous influence on the perceived idea about the intellectual abilities of a person. Although the learning disability in DS is not medically treatable, it can be improved remarkably with appropriate rehabilitation and educational support and techniques.

1.3.2.1 Cognitive development

Many studies are suggestive of the presence of defects in long- and short-term memory in individuals with DS. Moreover, the Intelligence Quotient (IQ) scores for these individuals are generally reduced compared to the general population.

In a recent study, and in agreement with many previous studies, Jarrold *et al.* (2007) found the long-term memory to be reduced in children with DS for recalling verbal and visual information. Similarly, Vicari and Carlesimo (2006) found the short-term memory span to be shorter than it is in the general population. Moreover, Brock and Jarrold (2005) suggested that defective verbal short-term memory is very selective to DS.

The cognitive development of a child with DS appears to be very close to normal during infancy (Brown *et al.*, 1990; Glenn *et al.*, 2001). Many studies have investigated the IQ and found it to be lower in children with DS compared to controls (Bennett *et al.*, 1979; Carr, 1988; Turner and Alborz, 2003). However, Brown *et al.* (1990) also found that IQ and Social Quotient (SQ) results tend to decline during the life of an individual with DS after taking into account the chronologic age at each stage. Though, Volman *et al.* (2007) suggested that the restrictions in functional

activities in young children with DS are mainly caused by their level of motor abilities rather than their level of performance mental abilities.

Generally, it can be said that memory and level of intelligence are reduced in individuals with DS compared to their typically developing peers.

1.3.2.2 Communication skills

One of the main noticeable aspects in the development of a child with DS is the delay in communication skills. The abilities to use facial expressions, gestures, speech, to read and to write are of extreme importance for the development of communication skills in a person. The development of these skills occurs in different phases.

The first stage during which children start developing their communication skills is called the pre-linguistic stage. According to Roberts *et al.* (2007), this is when a child uses vocal voice, gesture and facial expressions for the purpose of communication. They stated that this stage lasts until the age of 12 to 18 months in typically developing children. Stoel-Gammon (2001) suggested, after a literature review, that most studies agreed that the pre-linguistic period in children with DS is nearly similar to that of typically developing children, but Lynch *et al.* (1995) found that canonical babbling, speech-like vocalisation, is delayed by approximately two months in children with DS compared to control children. Moreover, Roberts *et al.* (2007) suggested that the phonology stage could last for several years in children with DS before they start developing speech. Additionally, they advised that it is possible for an individual with DS to never develop speech. Similarly, Yoder and Warren (2004) found that language development tended to be hindered by the presence of DS.

After the pre-linguistic stage, a child starts to develop language, which occurs in four different stages (Roberts *et al.*, 2007): phonology, semantics, syntax and pragmatics (Table 1.2).

Stage	Definition
Phonology	The ability to form speech-like sounds and to join these sounds to produce words.
Semantics	When the child becomes able to understand the meanings of words and build comprehension of vocabulary and concepts about objects and events.
Syntax	When the child develops the ability of combining words into phrases and sentences.
Pragmatics	When a child develops the ability to use the language for communication.

Table 1.2: The four stages of language development (from Roberts *et al.*, 2007)

There is a substantial delay in phonological development in children with DS when compared to typically developing children (Smith and Stoel-Gammon, 1983). Moreover, Stoel-Gammon (1997) highlighted that the onset of meaningful words production is delayed in children with DS and that even after the transition to this stage, their speech is still most likely to be meaningless. However, this is very variable amongst the children. Stray-Gunderson (1986) found that the onset of speech ranged from 9 months to 7 years in their subjects with DS. The semantic stage is also delayed in children with DS in comparison to typically developing children (Miolo *et al.*, 2005). As in all stages of speech, the syntax stage is defective in children with DS. A study by Vicari *et al.* (2002) showed that sentence reproduction, vocabulary and verbal comprehension are all reduced in children with DS compared to mental age matched controls. It was also illustrated by Chapman *et al.* (1991) that this stage is

inferior in development than is the previous stage which restrains the development of vocabulary. The pragmatic stage, which is when the child becomes able to use their language to communicate, is also hindered in DS. Vicari *et al.* (2002) found that children with DS produce higher numbers of incomplete sentences and have lower abilities to repeat phrases.

Reading and writing are both considered to be delayed in individuals with DS. The results of Turner and Alborz (2003) suggested that reading, writing and numeracy skills are generally poorer in children with DS compared to the general population. These skills are essential as communication skills as well as educational skills.

Speech, reading and writing are very important in communication. They have a large impact on the perceived impression about the cognitive abilities of a person. Generally, they are considered to be delayed or defective in children with DS compared to typically developing children.

1.3.2.3 Enhancement

It is known that the extent of intellectual disabilities is incredibly variable amongst individuals with DS. There are several existing ways of enhancing the intelligence and social skills of these individuals. After understanding the intellectual abilities of children with DS, special improving techniques may be employed to enhance their cognitive development. This could be either from an educational or a daily life perspective.

Reduced memory span, reduced IQ scores and poor communication skills form a challenge in education. However, several methods could improve these abilities and improve education (Connolly, 1978). In a study by Bennett *et al.* (1979), attending a continuous stimulation programme at an early age accounted for increased

IQ scores in some children. Moreover, Libb *et al.* (1983) suggested that the parental level of education and socio-economics has a control over the intelligence and behavioural aspects of a child with DS, being better when the influencers are higher. The results of Neser *et al.* (1989) suggested that attending playgroups or preschool centres is superior to home care for the purpose of improving developmental functioning in children with DS. It was shown by Brown *et al.* (1990) that even though the IQ and Social Quotient (SQ) scores tend to decrease in all individuals with DS with age, the decline tends to be greater for those individuals residing at home compared to those who live in an institutional setting and related that to the amount of activities often provided for residents of such institutes which augment their independence. Furthermore, Irwin (1989) found that early intervention programmes could enhance reading abilities as well as numeracy skills in children with DS. Memory, on the other hand, can be improved in children with DS. Perez Sanchez *et al.* (2006) found that memory training could increase the memory capacity of children with DS.

It was found by several studies that children with DS tend to be more visual learners. Chapman (2006) found that their expressive language could be enhanced dramatically when supported with pictures. After performing several tests to rate the effects of visual context, sentence voice and auditory-verbal short-term memory on language comprehension, Miolo *et al.* (2005) found that the children with DS performed the best when pictures were used. This strengthens the point that children with DS are visual learners and this scheme should be adapted in education.

To sum up, it could be said that the extent of learning disabilities is variable in children with DS. Early intervention, socialising, parental education and memory training can enhance their learning disabilities. While learning, those children tend to

depend on their vision rather than hearing. Thus, this knowledge could be employed by parents and educationalists to give a better opportunity for education. However, the high prevalence of visual problems could give the children an additional handicap to learning if the deficits are not recognised and managed appropriately. Thus, a study of vision and visual defects in children with DS takes on a particular importance.

1.4 Prevalence, incidence and maternal age effect

1.4.1 Incidence and prevalence

DS is one of the most common of all malformation syndromes (Gorlin *et al.*, 2001). According to Malini and Ramachandra (2006), the occurrence of DS ranges from 0.9 to 2 per 1000 live births. Several studies have attempted to provide accurate statistical data regarding the incidence and prevalence of the syndrome but found a variance in the data dependent on the region and the year in which the study was conducted. In addition, it was found that the incidence is increasing over the years.

Table 1.3 summarises the findings of many studies that looked at prevalence and incidence of DS in different areas and different points of time. These results show a degree of variability. This diversity in the prevalence of the syndrome is due to several factors. For example, Devlin and Morrison (2004) suggested that the difference in result in their study may be due to the more accurate inclusion of mosaic DS and due to the continuous increase in maternal age during pregnancy over time (See section *1.4.2*).

Study	Year	Area	Prevalence Per 1000 births
Olsen *et al.* (1996)	1992	New York State	1.02
Iliyasu *et al.* (2002)	1996	Glasgow	1.24
Huang *et al.* (1998)	1997	England & Wales	1.84
Tagliabue *et al.* (2007)	1999	Italy	0.83
Devlin and Morrison (2004)	2001	Northern Ireland	1.679
Wahab *et al.* (2006)	2005	Qatar	1.95 (incidence)

Table 1.3: Prevalence and incidence of DS.

From literature, the prevalence of DS appears to be increasing over the years. Huang *et al.* (1998) found that the prevalence of the syndrome increased from 1.44 in 1990 to 1.84 per 1000 in 1997. Moreover, O'Nuallain *et al.* (2007) suggested that the prevalence boosted from 2.41 per 1000 during the decade 1981-1990 to 2.98 per 1000 during the following decade 1991-2000. Both studies related the increase directly to the increase in age during pregnancy of the carrying mother. Similarly, Olsen *et al.* (1996) found the prevalence of live births of children with DS to have increased over the years and suggested that it is due to the increase of pregnancy rate amongst women over the age of 30 years.

The ratio of males to females born with DS is slightly higher towards the males' side (Verma and Hug, 1987; Mikkelsen *et al.*, 1990). Additionally, Devlin and Morrison (2004) confirmed this information by finding that the rate of incidence of the syndrome is 54.8% males and 46.2% females. Similarly, Wahab *et al.* (2006) and Dzurova and Pikhart (2005) found DS to be slightly more common in males than in females in three different populations.

1.4.2 Maternal age effect

Maternal age is directly linked to the risk of carrying a child with DS; as a whole, children born to older mothers are at greater risk of having DS (Gaulden,

1992). Hook (1981) and Hook *et al.* (1983) found that the rate of all clinically significant abnormalities including DS is approximately 5 per 1,000 at the age of 35 years, 15 per 1,000 at age 40 years, and 50 per 1,000 at age 45 years.

Although an increased maternal age is an ultimate risk factor of having a child with DS, the majority of children with DS are born to younger-aged mothers. Owens *et al.* (1983) found that 29 years is the mean maternal age of DS births during 1979. It was found by Dzurova and Pikhart (2005) that the majority of children with DS are born to mothers under the age of 35 years. In agreement, Hoshi *et al.* (1999) found that most DS births were amongst mothers in the age range between 30 to 34 years old. This is mainly due to the fact that the highest proportions of total births in most parts of the world are of women under the age of 35, maybe due to the higher fertility level amongst females in this age group.

In addition, Malini and Ramachandra (2006) suggested that maternal grandmother age could be a risk factor of having a child with DS. They suggested that females who are born to mothers over 30 years of age during pregnancy have a 30% increase in the risk of conceiving a child with DS.

Conversely, paternal age seems not to influence the rate of conceiving a child with DS, according to de Michelena *et al.* (1993). Erickson (1979) stated that there can be an influence on the child due to increased paternal age, but if it exists, it is a very small effect. On the other hand, Dzurova and Pikhart (2005) found an association between paternal age and DS stating that older fathers are at higher risk of conceiving a child with DS. However, they suggested that the influence is not as strong as that of maternal age.

In summary, although increased maternal age is the ultimate factor in having a child with DS, most children, including those with DS, are born to younger mothers. Paternal age does not seem to effectively influence the incidence of DS.

1.5 Health problems

Several health problems are commonly associated with DS. Some of these problems are fatal. However, due to the improvement in healthcare, the life expectancy of individuals with DS has increased enormously. A brief review of the major health problems associated with the syndrome is presented below.

Congenital heart problems are commonly found in newborns with DS, an incidence of 51.7% (Wahab *et al.*, 2006) to 61.3% (Abbag, 2006). The most common type is ventricular septal defect, accounting for 33.3% of the heart problems (Abbag, 2006). Leukaemia is amongst the health risks of this population (Sullivan et al., 2007). Many studies such as Selikowitz (1992) and Hilton *et al.* (1999) proposed that upper, as well as lower, respiratory tract infections are very common amongst individuals with DS. Diabetes mellitus, especially Type one, occurs at a significantly higher prevalence than in the general population (Anwar *et al.*, 1998). Another common health problem is thyroid dysfunction, whether hypo- or hyper-thyroidism (Ali *et al.*, 2002). Generally, patients with DS are more prone to infections due to their subordinate immune system (Ugazio *et al.*, 1990). Roizen (2002) highlighted that children with DS could develop some orthopaedic problems such as atlantoaxial subluxation, partial dislocation of the upper spine, hip dislocation, patellar instability, flat feet and juvenile rheumatoid arthritis. Moreover, Roizen (2002) suggests that gastrointestinal malformations are found in approximately 5% of children with DS.

Johannsen *et al.* (1996) found that epilepsy tends to occur at higher rates in this population. Dementia and Alzheimer's disease occurs in adults with DS at a very early age compared to the general population (Brugge *et al.*, 1994; Holland *et al.*, 1998).

Hearing problems are very common among children with DS. Selikowitz (1992) diagnosed over one half of his subjects as having ear problems, with 11% of those suffering from hearing loss. Motor functions are delayed according to Palisano *et al.* (2001). They stated that motor development requires time and rehabilitation.

Life expectancy of individuals with DS has increased significantly over the last few decades. Penrose (1949) found life expectancy to be approximately 12 years. In contrast, Glasson *et al.* (2002) suggested that the estimated life expectancy of individuals with DS was reaching that of the general population of Australia when it reached approximately 60 years. Moreover, they found the death rate to be significantly lower amongst individuals born between 1991 and 2000 compared to previous decades. This indicates, in agreement with Bittles *et al.* (2007), the importance of adequate health care provision to this slice of the population, which, with no doubts, has improved significantly between 1940s and present.

1.6 Visual and ocular characteristics

Children with DS are known to have various problems related to their eyes and vision. Previous research has described the visual characteristics and problems in these children. As in typically developing children, some of these problems can be resolved with appropriate optometric care, or in some cases drugs or surgery might be necessary. A general, yet brief, background will be presented describing the most common visual and ocular problems that children with DS can suffer from. A more

detailed review of the literature concerning refractive errors, accommodation and bifocals and colour vision will be presented thereafter.

1.6.1 Visual acuity

One of the major visual problems is the reduced visual acuity in children with DS. During early infancy, the development of visual acuity in children with DS does not differ to that of their typically developing peers, but it tends to fall lower than normal after the age of two years (Woodhouse *et al.*, 1996). According to Courage *et al.* (1994) and Woodhouse *et al.* (1996), the visual acuity of children with DS is generally below the normal range when compared to typically developing children even with full optical correction in place. Moreover, John *et al.* (2004) confirmed that visual acuity is reduced in comparison with typically developing children not only when measured with behavioural tests, but also when using Visual Evoked Potential (VEP) techniques, which assured the presence of a genuine visual acuity defect. Similar results were reported with Vernier acuity (Little *et al.*, 2009a). Amblyopia, reduced vision in one eye compared to the other without a pathological reason to account for the reduction, is fairly common in children with DS, with a prevalence of 22% (Tsiaras *et al.*, 1999) and 26% (da Cunha and Moreira, 1996).

1.6.2 Refractive error

Another important problem that characterises children with DS is refractive error. Woodhouse *et al.* (1997) described the range of refractive error in DS to be much larger than it is in the general population. Typically developing children tend to grow out of their congenital refractive errors; a process called emmetropisation (Gordon and Donzis, 1985; Gwiazda *et al.*, 1993). However, it was found that

refractive error, power and range, typically increases with age in children with DS, which suggests a failure of the emmetropisation process (Woodhouse *et al.*, 1997; Haugen *et al.*, 2001b; Cregg *et al.*, 2003).

Hypermetropia is more common than myopia in children with DS (da Cunha and Moreira, 1996; Woodhouse *et al.*, 1997). More recently, in agreement with previous studies, Stephen *et al.* (2007) found significant refractive error to be very common amongst children with DS, especially hypermetropia and astigmatism. Although hypermetropia was found to be the chief refractive error, it was found in the same studies that myopia is usually very high when it occurs in children with DS (Woodhouse *et al.*, 1997). Astigmatism is another common feature of the refractive status in children with DS. Woodhouse *et al.* (1997) reported that the incidence of astigmatism in children with DS is higher than it is in normally developing children. Haugen *et al.* (2001b) also found astigmatism in 57% of their subjects and suggested that with-the-rule astigmatism is the most common direction.

1.6.3 Accommodation

Accommodation, the ability of a person to focus accurately for near and distant objects, is commonly reduced in individuals with DS. Haugen *et al.* (2004) stated that defective accommodation is very common amongst individuals with DS. Woodhouse *et al.* (1993) found it to be reduced in as many as 80% of children with DS and that it tends to further reduce with age (Woodhouse *et al.*, 2000). Subsequently, Cregg *et al.* (2001) showed that reduced accommodation is associated with DS regardless of the refractive status of the eye. However, they stated that the greater the hypermetropic refractive error, the greater the under-accommodation, yet spectacle correction does not improve the under-accommodation. In a more recent

study by Stewart *et al.* (2005), it was found that children with DS with reduced accommodation benefit from bifocals. Their results showed that accommodation improved significantly with bifocal wear.

1.6.4 Colour vision

Some studies suggested that defective colour vision prevalence is higher in persons with DS than it is in members of the general population. Perez-Carpinell *et al.* (1994) found defective colour vision in approximately 23% of their subjects using the Ishihara test and the Davico anomaloscope. However, other studies deny this. Stratford and Mills (1984) suggested that the nature of colour vision of children with DS is similar to that of typically developing children. Nevertheless, Suttle and Lloyd (2005) found abnormal chromatic VEP responses in adults with DS. However, they suggested that these abnormalities could not be detected when assessed clinically with behavioural colour vision tests; City University Colour Vision Test and Colour Vision Test Made Easy.

1.6.5 Strabismus

Strabismus is believed to be highly associated with DS. Cregg *et al.* (2003) found 29% of their subjects to have strabismus and that they all had esotropia. Similarly, Haugen and Hovding (2001) reported strabismus in 42% of their subjects with 84% of those having esotropia. Despite the fact that strabismus is often associated with high refractive errors in typically developing children, commonly esotropia with hypermetropia (Abrahamsson *et al.*, 1992), Cregg *et al.* (2003) found that strabismus occurrence in DS does not depend on the refractive status of the child.

Tsiaras *et al.* (1999) found that, in addition to high refractive error and anisometropia, strabismus was associated with reduced visual acuity and amblyopia.

1.6.6 Other characteristics

Contrast sensitivity, a very important aspect of vision, is reduced in children with DS, although there is a slight improvement with age (Courage *et al.*, 1997). In a more recent study, John *et al.* (2004) observed lower contrast sensitivity values for children with DS compared to typically developing controls using both behavioural tests and VEP techniques. Moreover, they found the values to be reduced in DS even after excluding the children with ocular anomalies.

Nystagmus is a fairly frequent condition in children with DS. Wagner *et al.* (1990) found the incidence to be 30% in children with DS, with the vast majority of their subjects who had nystagmus having no ocular pathology to account for the nystagmus. This agrees with the findings of Gonzalez Viejo *et al.* (1996) who reported a 28% incidence in their subjects. This figure differed slightly from da Cunha and Moreira (1996) who found an incidence of 18%.

Corneal abnormalities are more likely to occur in children with DS than in typically developing children. Evereklioglu *et al.* (2002) found the central corneal thickness to be significantly lower in children with DS compared to normally developing controls, being under 500 micrometers for children with DS and higher than 500 micrometers for the control group. Moreover, Vincent *et al.* (2005) found corneal curvature to be generally steeper in DS than it is in controls. Keratoconus, which can result from a thinner and steeper cornea, was found to occur most frequently in individuals with DS compared to other chromosomal abnormalities (Walsh, 1981). Shapiro and France (1985) and Haugen *et al.* (2004) also found

keratoconus in many of their subjects. However, keratoconus does not tend to occur during childhood in DS. Corneal power was found to be higher in children with DS when compared to age matched controls. (Ji, 2006; Little *et al.*, 2009b).

Brushfield's spots are a typical feature of the iris in children with DS. The incidence is as high as 86% according to Gnad and Rett (1979). Jaeger (1980) observed Brushfield's spots in 59% of their subjects with DS compared to only 10% in control children. In addition, they found it to be associated with the iris colour, with a much higher incidence in those with a less pigmented iris. Moreover, Jaeger (1980) proposed that iris stromal thinning is characteristic to DS with an incidence of 34% compared to only 8% in controls. However, the study stated that it is associated with ageing.

Crystalline lens opacities occur more frequently in children with DS. Caputo *et al.* (1989) found 11% of their subjects to have cataracts and da Cunha and Moreira (1996) found cataract in 13% of their subjects. Of course, this can be surgically removed, and, at a rate of 58.8%, the results of Koraszewska-Matuszewska *et al.* (1994) suggest that there is a good chance of gaining improvement in visual acuity after cataract surgery in children with DS.

The optical power of the lens appears to be lower in children with DS compared to typically developing children (Haugen *et al.*, 2001a; Ji, 2006).

The characteristics of the fundus in DS are slightly different to what is commonly seen in typically developing individuals. Ahmad and Pruett (1976) noticed an increased number of retinal blood vessels compared to the numbers commonly found in the general population. Moreover, Sherk and Williams (1979) found that the number of large blood vessels crossing the optic disc margin is higher in DS than observed in persons without the syndrome. Similarly, Jaeger (1980) counted the

number of retinal blood vessels crossing the disc margins in subjects with DS and in controls and found that the number ranged from 13 to 25 in DS compared to 10 to 19 in controls. Berk *et al.* (1996) also found an increased number of retinal vessels crossing the optic nerve head in 38.1% of their study sample. Moreover, Ahmad and Pruett (1976) reported reduced amount of fundus pigmentation regardless of the iris colour.

Blepharitis and conjunctivitis are two fairly common eye problems in children with DS. 30% of the children described by da Cunha and Moreira (1996), had blepharitis. Another common problem that occurs in children with DS is obstruction of the lacrimal system. Da Cunha and Moreira (1996) reported a prevalence of 30% and Kim *et al.* (2002) reported a prevalence of 17%.

Glaucoma is thought to be of higher incidence in children with DS. Liza-Sharmini *et al.* (2006) found glaucoma in 6.7% of the children they examined.

1.7 The present study

Despite the wide current knowledge with regards to eyes and vision in children with DS, several aspects are still not fully understood. Thus, the general aim of this study is to evaluate, understand and explore several aspects of visual development and visual defects in these children. This will consequently help in improving their lifestyles, as well as their educational gains and performance.

With the aim of adding some pieces to the "puzzle" of vision in children with DS, this study explores three main areas. First of all, to understand the aetiology of refractive error in children with DS by studying the development and distribution of refractive error in children with DS, discovering the relationship between their refractive errors and that of their family members, and determining the relationship

between axial length, refractive error and body height in the children. Secondly, the long-term effect of wearing bifocals in children with DS and its contribution to the accuracy of accommodation. Finally, to evaluate colour vision in children with DS. The findings are intended to effectively enhance lifestyle and educational performance and to define clinical optometric guidelines. An in-depth literature review of each aspect of the study will be presented in the relevant chapters.

Chapter Two: General Methods

Chapter Two: General methods

This chapter provides a thorough description of several aspects of the different studies presented in this thesis. It will concentrate on the study population, recruitment criteria and general testing techniques that have been used for data collection. In addition, it will provide a thorough explanation of the choices of data presentation modes.

2.1 Study population

2.1.1 Recruitment

The study population were members of the Cardiff Down's Syndrome Vision Research Unit that was established in 1991. In general, all children who are diagnosed with Trisomy 21 are eligible to join the cohort. However, for analysis purposes, the children were divided into two main categories; original recruits and newer recruits.

The original recruits were children who joined the cohort without awareness of any eye or vision problems. Some of these children were recruited between the years 1991-1994. They were identified in collaboration with the Cytogenetics Department at the University Hospital of Wales (Woodhouse *et al.*, 1996). Part of the original cohort members were recruited for a specific study; the bifocal trial. These children were identified through educational psychologists without regard to known eye problems (Stewart, 2003). The rest of the children in the original cohort joined the study under direct parental request without awareness or concerns about any eye or vision problems, mainly due to the reputation of the Special Assessment Clinic within Cardiff University Eye Clinic. The majority of these children reside in Wales and have a diversity of social backgrounds. The categorising criteria allows for the assumption that this population is representative of children with DS in general.

The newer recruits, recruited during 2007-2009, are those who attended Cardiff University Eye Clinic seeking eye care due to the presence of, or parental concerns regarding, eye or vision problems, or were referred to the clinic by NHS practitioners; mainly ophthalmologists and paediatricians. This creates a potentially biased population of children and young adults. Hence, suitability for inclusion was subject to the nature and the aim of each individual study. Justification for the selection criteria will be presented in each chapter separately.

Ethics Committee approval was granted for the ongoing study and all parents of the original recruits gave written consent for the children's data to be included in the studies. Ethics approval to use the data of children with Down's syndrome who are referred to the University Eye Clinic by NHS practitioners, the newer recruits, was also granted from the Research Ethics Committee for Wales. Similarly, consent was obtained from the children's parent(s) for inclusion in the studies. The study protocol allowed for the use of all prospective and retrospective clinical results to be included in the unit's research. A copy of the full study protocol as well as the consent forms can be seen in Appendix I.

2.1.2 Morphology of Study Population

There were 234 participants, 146 of whom were male and 88 were female. The following table (Table 2.1) provides a simple description of the study population.

	No. of subjects	♂	♀
Original Recruits **% within original recruits**	182 (100%)	113 (62.1%)	69 (37.9%)
Newer Recruits **% within newer recruits**	52 (100%)	33 (63.5%)	19 (36.5%)
Total **% of total**	**234** **(100%)**	**146** **(62.4%)**	**88** **(37.6%)**

Table 2.1: Numbers and percentages of recruits in the Cardiff Down's Syndrome Vision Research Unit.

The Cardiff Down's Syndrome Vision Research Unit was established in 1991 with 54 subjects recruited between 1991 and 1994; and recruitment has continued up to the present. The ages of subjects varied from 1.33 to 25.15 years as of 15th September 2009. Figure 2.1 describes the age distribution within the sample, separating the original from the newer recruits. The length of time each participant has been a member in our studies is very variable. Figure 2.2 describes the length of time participants have contributed to the Unit's studies.

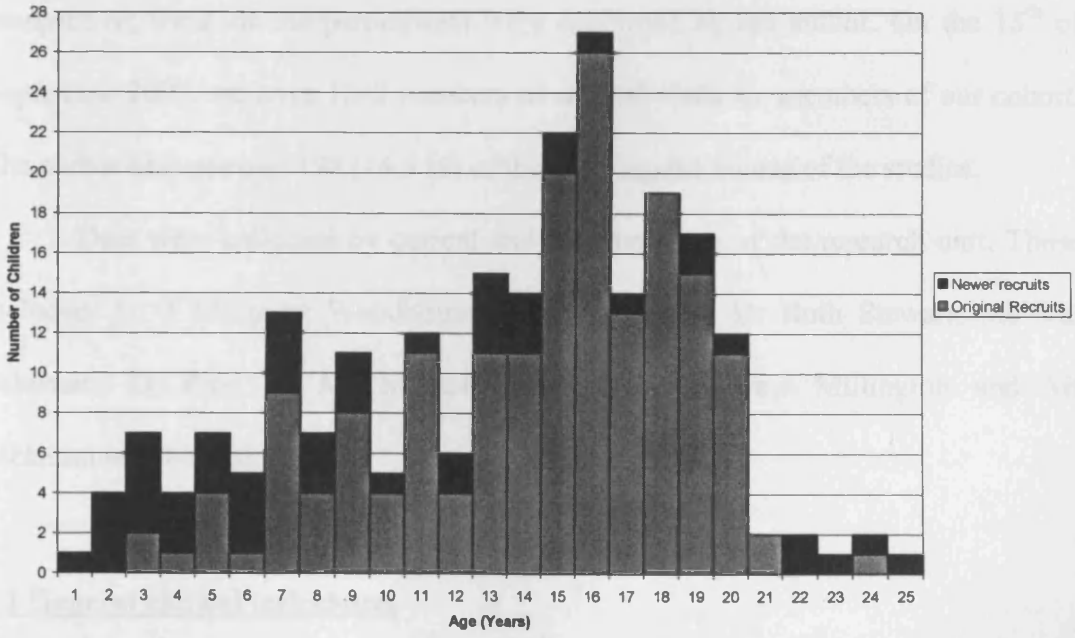


Figure 2.1: Age distribution of members of the Cardiff cohort. Light grey = original recruits; Dark grey = newer recruits (correct in September 2009)

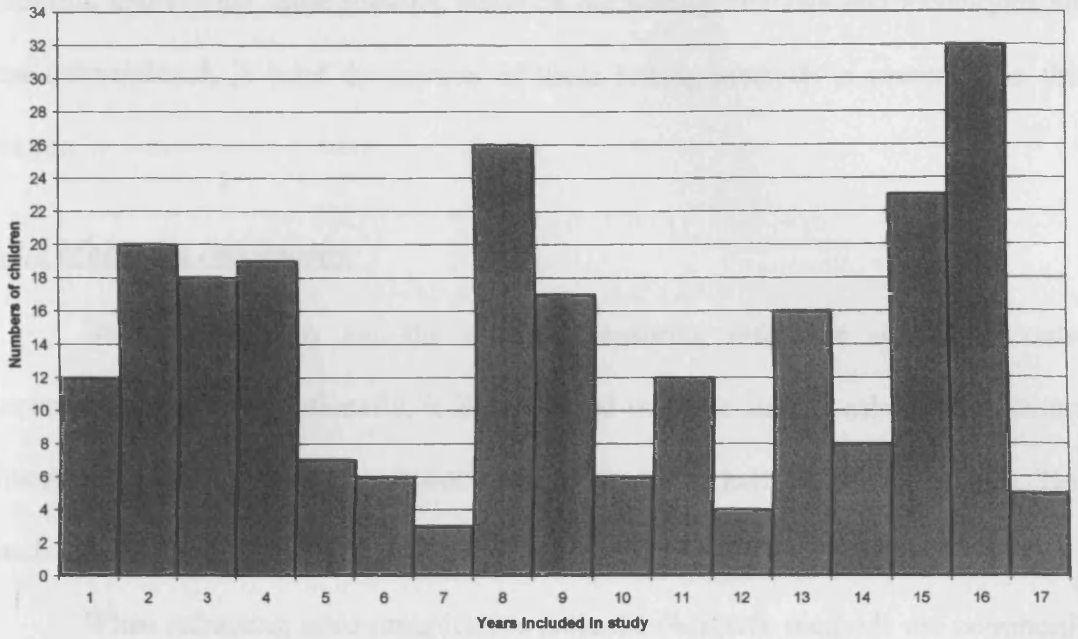


Figure 2.2: Number of years the 234 participants have been included in the Unit's studies (correct in September 2009)

As some parts of these studies were retrospective, the author has used all of the clinical records to extract relevant data. However, some of the studies are prospective; some of the participants were examined by the author. On the 15th of September 2009, we have 1362 numbers of clinical visits for members of our cohort. The author has assessed 198 (14.5 %) of them during the course of the studies.

Data were collected by current and past members of the research unit. These included: Dr J Margaret Woodhouse, Dr Mary Cregg, Dr Ruth Stewart, Ms Val Pakeman, Dr Ping Ji, Mr Michael George, Mr Andrew Millington and Mr Mohammad Al-Bagdady.

2.2 General clinical techniques

Most of the studies depended on data that can be obtained during a thorough optometric examination. As the research is aimed at children with various degrees of learning disabilities, consistency in testing methods was not possible at all times. In

addition, and for the same reasons, some of the testing methods and techniques are less conventional. A brief description of these testing methods is presented in this section.

2.2.1 Mohindra retinoscopy

Static retinoscopy has the aim of measuring refractive error with static accommodation. Conventionally, it is performed with the subject asked to fixate at a distant target to relax accommodation (usually the green half of the duochrome). This method is simple to perform with co-operative subjects.

When refracting uncommunicative patients, objective methods are commonly employed. There are two main 'objective' techniques for measuring refractive error in young children and in adults with learning disabilities; cycloplegic retinoscopy and Mohindra retinoscopy. In general, cycloplegic retinoscopy is performing retinoscopy after the instillation of cycloplegic drugs to force accommodation relaxation; this is considered the Gold Standard. Mohindra retinoscopy uses total darkness to achieve fixed accommodation.

Mohindra retinoscopy is the refraction technique adopted in our clinic for determining the refractive errors of children and adults with learning disabilities. The technique is fully described in Mohindra (1977). Near retinoscopy is performed in total darkness, while the person is fixating the dimmed retinoscope beam. Darkness is aimed at relaxing accommodation. The pupil reactions, being dilated, as well as observing a moderately stable refractive error, are indicators for relaxed accommodation. An adjustment factor of +1.25 D was suggested by Mohindra (1977), which is subtracted from the refraction result. This accounted for a +2.00 D working distance and -0.75 D of residual accommodation. However, this was changed by Saunders and Westall (1992) to +0.75 D for children aged 2 years or younger and

+1.00D for older children to achieve more comparable results to cycloplegic retinoscopy.

The main reason for using this technique is the absence of cycloplegic drop use in order to maintain the clinic as a *child friendly* environment and to allow for further visual tests to be carried out thereafter. This has always helped in maintaining the patient's cooperation throughout testing periods. However, the technique is criticised in that it may not fully relax accommodation, especially since the fixating target is at a near distance and this may lead to the under-estimation of the presence of a refractive error (e.g. child accommodating to overcome hypermetropia). Cycloplegic retinoscopy is considered the Gold Standard and is the widely accepted method of refracting young children because, of course, accommodation is fully controlled due to the drug use. Although some studies, such as Wesson *et al.* (1990), found significant differences between the two techniques especially for infants, Saunders and Westall (1992) showed agreement between the results of Mohindra and cycloplegic retinoscopy especially after changing the adjustment factor. More importantly, Woodhouse *et al.* (1996) showed that both techniques give equivalent results when performed with children with DS.

2.2.2 Modified Nott dynamic retinoscopy

The most common clinical method of assessing accommodation is the push-up technique using the RAF rule. Another way is by using auto-refractors. However, both methods require a subjective response expected from the patient for accuracy. Dynamic Retinoscopy (DR) is an objective method of assessing the accuracy of the accommodative abilities of a person. In general, DR assesses the accommodation response by observing the retinoscope reflex movement while the patient is observing

an object at a known distance. With the retinoscope aligned with the observed object, a neutral reflex indicates accurate accommodation, a 'with' movement indicates under-accommodation (lag) and an 'against' movement indicates over-accommodation (lead). There are two common methods of measuring the accommodative response with DR; the monocular estimate method (MEM) and Nott retinoscopy. In MEM, monocular accommodative response is examined under binocular conditions. The examiner estimates the retinoscope reflex and briefly introduces spherical lenses to neutralise any movement. The lenses need to be presented rapidly to avoid interfering with the accommodative response of the patient. When a 'with' movement is observed, a positive lens is required to neutralise the movement, and the patient is said to be under-accommodating by the dioptric amount of the lens used to neutralise the retinoscope reflex. In Nott retinoscopy, neutralisation is achieved by moving the retinoscope to find the neutral retinoscope reflex while the patient is observing the accommodative target. When the neutral point is closer to the patient than the target, then the patient is over-accommodating, and when it is further from the accommodative target, then the patient is under-accommodating. The amount of lag or lead is then calculated as the dioptric power of the distance between the accommodative stimulus and the accommodative response (neutral point).

The modified Nott DR simply differs to the original Nott version by the target used. As described in (Woodhouse *et al,*. 1993), an internally illuminated cube, with black and white line-pictures drawn on the outside of the cube walls, is used as the target. This cube is mounted on a metric ruler to allow for accurate measurements (Figure 2.3).

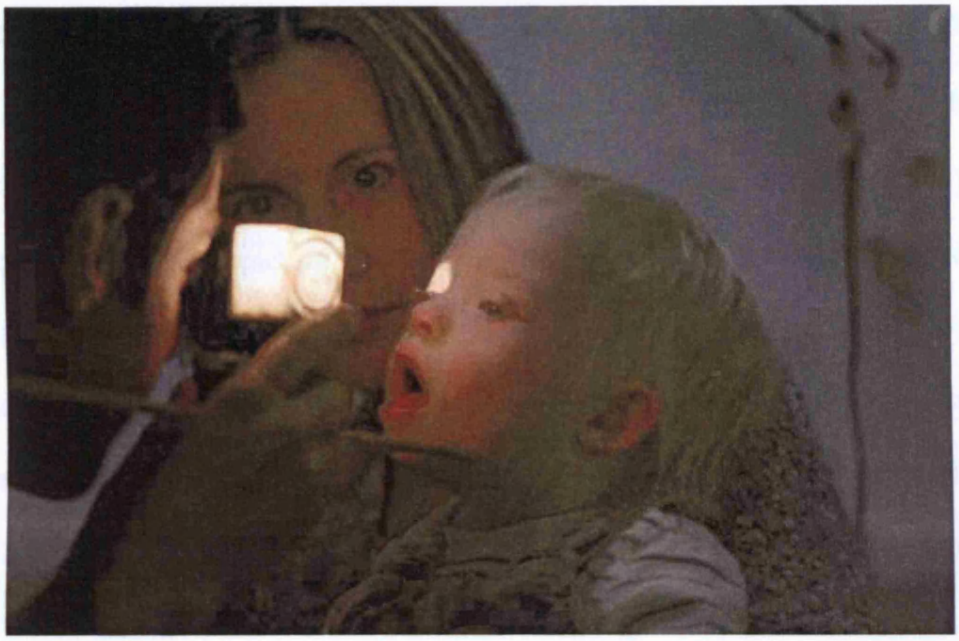


Figure 2.3: Modified Nott dynamic retinoscopy (Child: Lucas Shatliff, Photo by: Mike O'Carroll)

An advantage of this technique over MEM is that the use of lenses in MEM may act as a distraction for the child. Also, changing corrective lenses can disrupt constancy in the accommodative response (Leat and Gargon, 1996). The illuminated cube aids in triggering the child's attention to the target especially when performed in a darkened room. Moreover, the use of *child-friendly* drawings keeps the child's attention for longer which triggers accommodation (e.g. the child can be asked to *count the stripes on the clown's jumper* or to *find the mouse in the picture*).

The Modified Nott DR technique was assessed for validity and repeatability against the "push-up" technique and against the Shin-Nippon SRW-5000 auto-refractor and was found to be a repeatable valid method of DR (Woodhouse *et al.*, 1993; McClelland and Saunders, 2003). However, there are several criticisms of dynamic retinoscopy, the most important of which regards the effect that the testing angle can induce on the measurement. Since the retinoscope is held next to the accommodative target, an off-axis error would be expected. However, given that the

width of the cube is 35 mm, the degree of off-axis will therefore be approximately 10° at 10 cm, 7° at 16.7 and 5° at 25 cm. The maximum off-axis extent (when the child looks at the far side of the cube) would be 20°. According to Jackson *et al.* (2004), there is an increasing myopic shift with increasing eccentricity, of −0.02 dioptre, −0.59 dioptre, −0.45 dioptre, −0.64 dioptre, and −0.98 dioptre at 0 degrees, 5 degrees, 10 degrees, 15 degrees, and 20 degrees of eccentricity, respectively. This amount of off-axis error can be significantly important when refracting a person for prescription purposes. However, such a subtle difference is not essentially important in evaluating accommodative abilities.

Other criticisms might be directed towards the nature of detail in the target; with regards to the children's ability to resolve the detail, as well as the effect of variation in optical resolution of the detail on the accommodative measurements at different distances. However, it was shown that a difference in target resolution does not have an effect on the accommodation measurement and that the detail size in a modified Nott dynamic retinoscopy target is within the near acuity level of children with DS (Woodhouse *et al.*, 2000).

2.2.3 Visual acuity testing

Visual acuity was measured with various tests, to account for the age and intellectual ability of each child. Mainly, Cardiff Acuity Test, Kay picture test (LogMAR version) and Keeler LogMAR letters were used. All of the three tests involve a separate presentation of each visual acuity level. Unlike a conventional visual acuity chart, confidence level is less likely to be lost due to the inability of resolving all of the targets. This is because, in all three tests, each level of visual acuity is presented on a separate card. A thorough description on the use of each of these tests is available in their testing manuals. Keeler logMAR letters and Kay

picture test were always performed at 3 meters. Cardiff Acuity Test was performed at either 1 meter or 50 centimetres, based on the attention span of the child. Generally, the Cardiff Acuity Test was used with the younger, non-communicative children, while the other two tests were used with those who were able to communicate. The Kay picture test and Keeler LogMAR letters have been shown to give equivalent results with very high reliability in comparison with conventional acuity testing methods (McGraw *et al.*, 2000; Jones *et al.*, 2003; Elliott and Firth, 2009).

In general, communicative participants were presented with the matching cards of Kay pictures and Keeler LogMAR letters and were asked to choose. Once the choice was made, the practitioner asked the child to identify all of the letters or pictures to check whether the child recognised all of the optotypes. If this was successful, the test was explained to the child and performed at 3 meters. If the child did not identify the letters or pictures, they were encouraged to match. Acuity was recorded in Snellen terms for 3 meters. For patients with lower abilities, due to younger age for example, Cardiff Acuity Test was performed. Preferential looking technique was used with some children, while others pointed to the location of the target. Visual acuity was recorded as its Snellen equivalent at 6 meters.

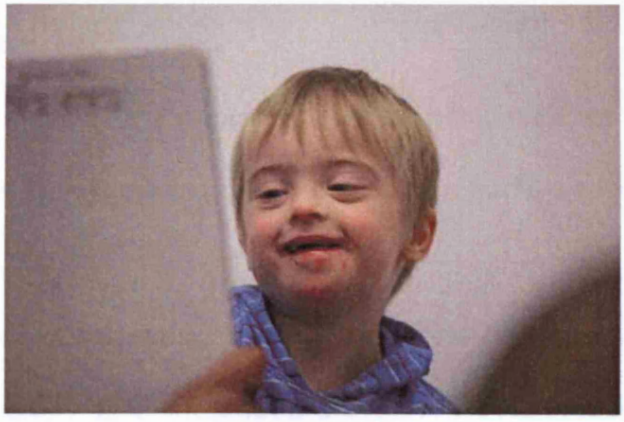


Figure 2.4: Cardiff Acuity Test. (Child: Joshua Tod, Photo by: Mike O'Carroll)

2.3 Data expression

2.3.1 Power vectors

For the description of refractive errors, Mean Spherical Equivalent (MSE) is the traditional method of representation in research. This is calculated by combining the dioptric amount of spherical error with half of the dioptric amount of the cylindrical error. Although the astigmatic power is somewhat represented, the direction and the actual amount of astigmatism cannot be appreciated. For example, the mean spherical equivalent of the prescription +2.50DS/+1.00DCx90 is +3.00D; this will also be the mean spherical equivalent for the prescription +1.00DS/+4.00DCx180. Power vectors are a method of representation of refractive error that accounts for the spherical error as well as the amount of astigmatism and its direction. It was proposed by Thibos *et al.*, (1997). There are three power vector components; M, J_0 and J_{45}. M equals the spherical equivalent of the refractive error, J_0 is similar to the construct of the Jackson cross-cylender (JCC) with its axis at 90° and 180°, and the J_{45} is with the axis at 45° and 135°. The formulae that Thibos *et al,* (1997) presented are as follows:

$$M = S + C/2$$

$$J_0 = (C/2)\cos(2\alpha)$$

$$J_{45} = (C/2)\sin(2\alpha)$$

Where; S = the spherical component of the refractive error

C = the cylindrical component of the refractive error

This method of presenting refractive error was employed in all of the studies included in this thesis that concentrate on refractive error as the main subject.

However, when refractive error was used only as a minor aspect of comparison/description, mean spherical equivalent was used.

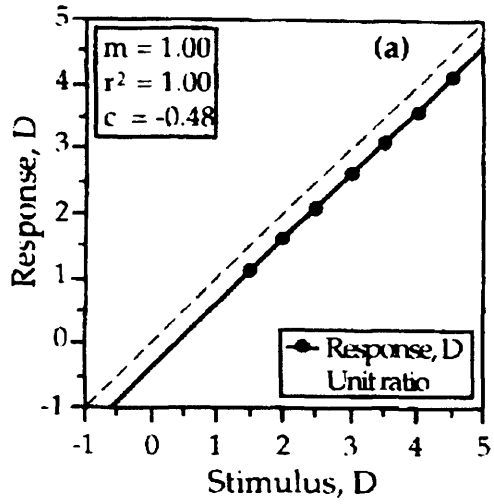
2.3.2 Accommodative error index

The accommodative error index (AEI) is a single-figure index that characterises the response-stimulus line, which indicates the ability of a stimulus to maintain a steady-state response, as described by Chauhan and Charman (1995) who first proposed it. Conventionally, accommodative responses are presented in a graph with the x-axis representing stimulus and the y-axis representing response. The slope, the intercept and the Pearson correlation coefficient are the aspects that define this line. However, each in isolation is problematic in describing the accommodative response. The AEI describes the difference between the ideal response, when response equals stimulus, and the measured response. It also considers the linearity of an individual's accommodative response to different stimuli. A formula was generated to obtain this. However, there are two formulae. The first formula is indicated as formula (a). It is only used when the two curves, the ideal response and the measured response, do not intersect within the field of the testing stimuli. The second formula, which is shown as formula (b), is correct when the lines do intersect. Graphs to illustrate both formulae are also added here and are taken from the original Chauhan and Charman (1995) paper that first introduced and described the AEI.

Calculation of AEI:

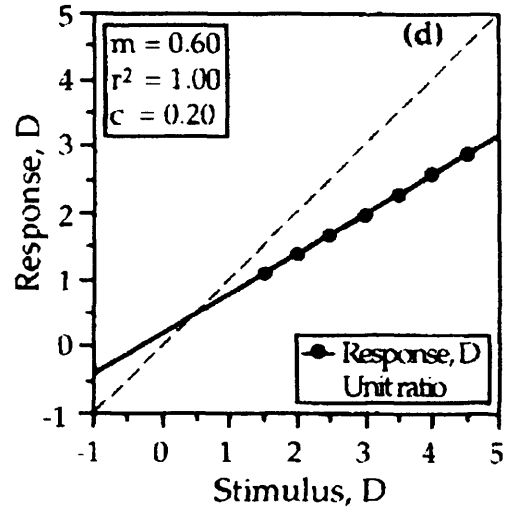
a) When the perfect response line and the measured response line do not intersect.

$$I = \frac{|\,(1-m)\,[(x_2 + x_1)/\,2] - c\,|}{r^2}$$



b) When the perfect response line and the measured response line do intersect.

$$I = \frac{\{[(1-m)\,/\,2(\,x_2 - x_1\,)]\,[\,x_1^2 + x_2^2\,-\,[(\,2c\,(\,x_1 + x_2\,))\,/\,(\,1 - m\,)] + [\,2c^2\,/\,(1-m)^2]\}}{r^2}$$



Where:

m = slope of response line

c = intercept of response line

r^2 = correlation coefficient

x_1 = lowest stimulus used

x_2 = highest stimulus used

Dashed line = perfect response line

Solid line = best fit regression line through a set of data points.

2.3.3 Additional methods

Additional methods were used in different experiments throughout this thesis. These are described individually within the relevant chapters.

Chapter Three: Development and distribution of refractive errors in children with Down's syndrome

Chapter Three: Development and distribution of refractive errors in children with Down's syndrome

3.1 Introduction

Refractive error is caused by a failure of the optics of the eye to correctly focus light from a distant object of regard and results in blurred vision. A person who does not have a refractive error is called emmetropic. This means that the light is accurately focused by the cornea and the crystalline lens on the retina. There are three types of refractive error: myopia, hypermetropia and astigmatism. Myopia, or short sight, occurs when the light is focused in front of the retina. Hypermetropia, or long-sight, occurs when the light is focused behind the retina. In astigmatism, the eye has two different refractive powers along two different meridians (usually perpendicular to each other). Generally, we are all born with an infantile refractive error that often reduces rapidly during the first years of life towards emmetropia. A minority, whose refractive error does not stop at emmetropia, require the aid of an optical correction either temporarily during their childhood or early adulthood, or permanently. This is thought to be influenced by genetics and lifestyle, as well as developmental factors.

The story is entirely different in children with Down's syndrome (DS). Refractive errors are much more likely to accompany these children from birth, during childhood and all the way towards adulthood. The distribution and development pattern of these refractive errors are not well established in the literature and the causes of such errors are not yet fully understood.

3.1.1 Emmetropisation in typically developing children

Emmetropisation is the term used to describe the reduction and ultimate removal of infantile refractive errors during the first few years of life. This occurs due

to active and passive factors. The active factor is the visual feedback that controls the growth of the eye, and the passive factor is the physical growth of the eye which leads to a weaker refractive power (Troilo and Wallman, 1991).

Most studies state that infants are born with a relatively high refractive error, mainly hypermetropia, with very variable values between subjects. Both the amount of refractive error and the variability between children tend to decline with increasing age (Saunders *et al.*, 1995; Mayer *et al.*, 2001; Kuo *et al.*, 2003). The only exception to this is Gwiazda *et al.* (1993) who found the mean refractive error to be slightly myopic during the first 6 months of life. Data from all of the above studies show the process of emmetropisation illustrated as a decline in refractive error, and as a narrowing of the variability in refractive errors between children with increasing age; with the highest rate of change occurring during the first 12 months. For example, Gwiazda *et al.* (1993) showed that an average refractive error of approximately +0.5 dioptres was achieved by 1 year of age and is stable until 8 years of age, with the standard deviation of refractive errors reaching a minimum at 6 years of age (Figure 3.1).

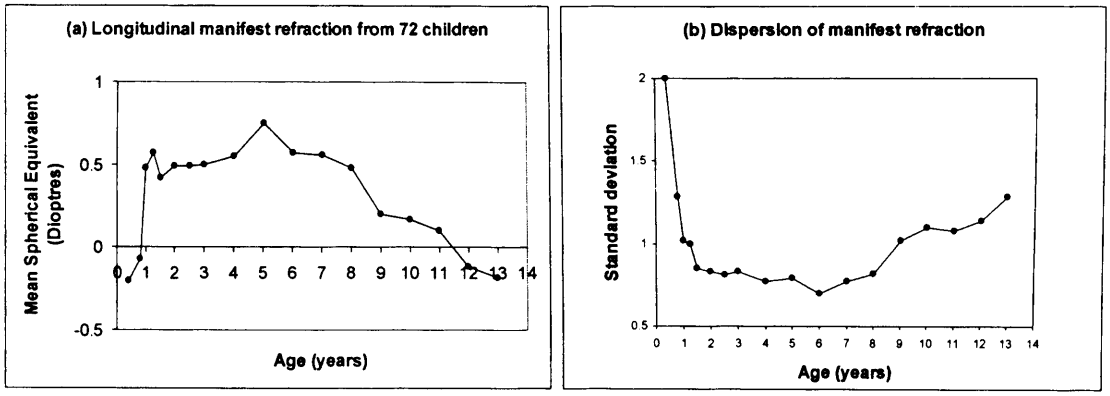


Figure 3.1: (a) Mean spherical equivalent from 72 children from birth to 13 years. (b) Dispersion of manifest refractions in (a), as measured by standard deviation. (Replicated graphs from Gwiazda *et al.* (1993))

In addition, a high proportion of infants and young children were found to have a significant astigmatic refractive error, which tends to reduce during early childhood (Ehrlich *et al.*, 1995; Saunders *et al.*, 1995; Kuo *et al.*, 2003). The axis of astigmatism tends to be against-the-rule in infancy. A minority retain, or develop, significant astigmatism as they grow older, and the axis of this astigmatism tends to be with-the-rule (Dobson *et al.*, 1984).

Most of the studies on the development of refractive error and emmetropisation agree that the initial refractive power has an influence on the rate of emmetropisation and on the end point after the process is complete. Saunders *et al.* (1995) suggested that the greater the hypermetropia present during the first 6 months of life, the greater the rate of change in power towards emmetropia and similarly, the greater the astigmatic power, the more rapid the reduction rate of that power. With myopic infantile refractive error, Gwiazda *et al.* (1993) showed that a relatively large portion of children with myopic infantile refractive error emmetropise towards slight hypermetropia, but that they eventually return to their original myopic refractive error by puberty, especially when either against-the-rule or no astigmatism is present. While these trends in refractive error can give great predictive power for clinicians, the age of stabilised refractive error cannot be accurately predicted.

To sum up, the emmetropisation process is not only a reduction in refractive error, but also a narrowing of the distribution of refractive error in children. It can be said that this process is complete by the age of 5-6 years and that very slight residual hypermetropia is mainly what is considered "emmetropia".

3.1.2 Emmetropisation in children with Down's syndrome

It is known that children and adults with DS typically have higher refractive errors compared to that of the general population, and it has been suggested that a

failure in the emmetropisation process is the main reason for such an anomaly (Woodhouse *et al.*, 1997). Little is known regarding the typical emmetropisation process and even less is known about emmetropisation in children with DS.

Refractive errors are higher in individuals with DS compared to that of the general population (da Cunha and Moreira, 1996; Woodhouse *et al.*, 1997). The failure of the emmetropisation process is a good justification for such erroneous refractive development (Doyle *et al.*, 1998; Haugen *et al.*, 2001b; Cregg *et al.*, 2003). This is characterised as the presence of refractive errors that are higher than the average for typically developing children of the same age, accompanied by a widening of the range of refractive error with age for each study population. The distribution of refractive error is similar to those of typically developing children during infancy, but starts to significantly differ by the second year of life, leaving the majority of typically developing children emmetropic, while ammetropia exemplifies most of those with DS (Woodhouse *et al.*, 1997). Many studies have highlighted the development of a large refractive error, or the persistence of the infantile refractive error, which occurs in the eyes of children with DS, rather than the reduction in the error towards emmetropia that occurs in typically developing individuals. However, there is a noticeable clinical presence of relatively similar amounts of hypermetropia amongst young teenagers with DS in our population, the same population described by Woodhouse *et al* (1997). This may suggest a late narrowing in the distribution of refractive errors that may be likened to a delayed *emmetropisation* with a different end result. Having in mind that a slight hypermetropia of approximately +1.00 Dioptres is the *actual* emmetropia amongst the population, despite it being 0 Dioptres *theoretically*; can a higher hypermetropia be considered the *emmetropia* in individuals with DS?

3.1.3 The aim

The aim of this study was to define the pattern of development and distribution of refractive errors in children and young adults with DS compared with that of the general population from previously published studies. The clinical observation of relatively comparable moderate to high hypermetropia in older children with DS suggests the presence of an emmetropisation process, only delayed and shifted towards higher hypermetropia.

The results will help in understanding the process of emmetropisation and its occurrence in children with DS; whether it completely stops or is being delayed. Most previous studies only focused on small age groups of children with DS (Woodhouse *et al.*, 1997; Doyle *et al.*, 1998; Cregg *et al.*, 2003). Therefore, there is a need for studies that focus on a wider age-range of children. The study will add to the current understanding of the visual development and the aetiology of refractive errors in children with DS and help to increase predictive power regarding refractive status in clinical settings by giving more detailed information about the development of refractive error during childhood and the early teenage years.

3.2 Methods

3.2.1 Study population

All of the original recruits from the Cardiff Down's Syndrome Vision Research Unit were included in this study. 182 participants were in the database during the term of this study. The group should be representative of children with DS in general, due to the selection criteria on recruitment. Children were either identified at birth by the Cytogenetics Department of the University Hospital of Wales or by educational psychologists, without any awareness of visual problems (Woodhouse *et al.*, 1996; Stewart, 2003), or have joined the study at parental request without the

knowledge of visual problems. Data from all participants were included in the analysis.

3.2.2 Study design

This study was largely retrospective in nature. Several reasons were behind this choice: firstly, shorter data collection time; secondly, the low cost; and thirdly, the nature of the Cardiff Down's syndrome study protocol under which children are seen for full optometric examinations and relevant information can then be extracted for research purposes. The full protocol can be found in Appendix I. The study consisted of two parts: a cross-sectional study of refractive error distribution across 15 age groups, and a longitudinal study of refractive error change with age for individual participants.

3.2.3 Data collection

Children were seen at 6 month intervals up to school age, and at 1 year intervals thereafter; unless additional visits were necessary due to clinical decisions or poor child co-operation. Refractive error and age were collected from the clinical records of all children. All refractions were written in plus cylinder form. Refractive errors were presented as vector components for analysis M, J_0 and J_{45} which allows for the expression of the sphere, the cylinder and its axis (see section *2.3.1*) (Thibos *et al.*, 1997).

The presence/absence of significant astigmatism was noted and children within each age group were divided into 4 categories; with-the-rule astigmatism, against-the-rule astigmatism, oblique astigmatism and no astigmatism. Significant astigmatism was defined as a difference of 1.00 dioptres or more between the two meridians. Cylindrical axis was classified as with-the-rule when the plus cylinder axis

was at 90° ± 15°; against-the-rule when the axis was between 180° ± 15°; and oblique for all other axes (Gwiazda *et al.*, 1993).

Due to the frequent absence of any significant difference in refractive error between the two eyes in children with DS, only data from the right eye was used in most cases (Haugen *et al.*, 2001a). However, data from the fixing eye was used in the presence of strabismus or the least ametropic eye in anisometropia (defined as a spherical difference of 1.00 dioptre or more between the two eyes). Refractive errors were always measured using Mohindra near retinoscopy technique (see section *2.2.1*).

3.2.4 Data analysis

The children were divided into fifteen yearly age groups ranging from 1 to 15 year olds. Each age group included all children at the given age ± 6 months. For example, the 1 year old group included all children aged from 0.5 to 1.49 years. Data of each child were only used once within an age group. When a child was seen more than once within one year, data was collected from the visit during which the age was closest to the integer of the relevant age group.

The mean and standard deviation of the three vector components of refractive error (M, J_0 and J_{45}) were calculated for each age group. The distributions of the three components were assessed for normality using the Kolmogorov-Smirnov test and were found not to be normally distributed (reasons for normality test choice can be found in Appendix II). Hence, non-parametric statistical tests were used for analysis. The cross-sectional nature of this study, with different numbers of participants in each age group, made data transformation to enhance normality and allow the use of parametric statistical tests a non-viable option. A Kruskal-Wallis one-way analysis of variance test was performed to test for difference in refractive error distribution across the age groups. The Kruskal-Wallis test is designed for comparisons between

independent samples. Because our age groups were not entirely independent, the result of the Kruskal-Wallis may be questionable. Therefore, Friedman's two-way analysis of variance was also conducted to compare M, J_0 and J_{45} between groups, and a Wilcoxon signed-ranks test used to compare the three aspects between each pair of groups individually. Reasons for test choices are presented in Appendix III.

Line graphs representing the distribution of the mean spherical equivalent of refractive error and the standard deviation of the mean across age groups were plotted. A box plot was also constructed to show refractive errors data, medians, as they were not parametric. Scatter plots showing astigmatic refractive error (power vector components J_0 and J_{45}) were produced for each age group.

The percentages of children in each category of astigmatism (with-the-rule, against-the-rule, oblique and no astigmatism) were calculated for each age group. A Chi-Squared test was performed to examine differences in presence of significant astigmatic axis distribution across the 15 age groups. A bar graph representing these data was constructed.

Individual longitudinal data were collected and analysed separately in order to assess the change of refractive error with age. Minimum inclusion criteria were the presence of clinical data for each participant in the age range of 0.5 to 1.5 years and in the age range of 14.5 to 15.5 years. This allowed for the occurrence of possible refractive changes that tend to start appearing after the age of 8 years (Gwiazda *et al.*, 1993). Scatter plots of spherical equivalent (power vector component M) against age were plotted for all of the individual children longitudinally, and polynomial trend lines were calculated and included for each child. These plots included all available clinical visits for each participant.

Refractive errors were collected from the clinical records of each child at age 1 and at age 15 years. Vector components of refractive error were calculated and the presence/absence of significant astigmatism (≥1.00D) was noted. The three vector components were compared between the two visits for each child. Paired sample t-tests and Wilcoxon Signed-Rank tests were used for comparison of refractive error, and a Chi-Squared test was used to compare the distribution of the four categories of astigmatism between the two visits.

Data was analysed using the SPSS data editor version 16.0 (SPSS Inc., Chicago, IL, USA), and graphs were constructed using SPSS data editor and Microsoft Excel.

3.3 Results

3.3.1 Study population

All of the children in the original cohort were included in this study (n=182), 113 were boys and 69 were girls. The vast majority of participants were of white Caucasian background, residing in Wales. A total of 730 refractions were included. However, the number of participants was not consistent between the age groups, principally because the majority of our participants were younger children. The numbers of participants and mean age within each age group are presented in Table 3.1.

Twenty-three children had strabismus; divergent strabismus was reported for one case, and convergent strabismus was reported for the remaining 22 children. Of these with strabismus, 3 fixed with their left eye, all of which had a convergent strabismus. Nine children had anisometropia without strabismus, 6 of these preferred to fixate with the left eye. Two children had anisometropia with strabismus; both had

a convergent strabismus and fixed with the left eye. Data were obtained from the fixing eye in strabismus, and the least ametropic eye in anisometropia without strabismus. Right eye data were otherwise used.

For the longitudinal study, 6 subjects matched the inclusion criteria, 4 of which were boys and 2 were girls. Data from the left eye was used for one participant due to anisometropia. The total number of refractions for each subject varied between 13 and 26 visits (mean = 18.16).

Age group	Number of participants	Mean age (Years)
1	70	1.04
2	78	1.94
3	66	2.97
4	60	4
5	58	5.01
6	60	5.98
7	49	6.97
8	54	7.98
9	49	9.06
10	44	10.03
11	38	10.95
12	39	12.01
13	25	13.01
14	20	13.95
15	20	14.98

Table 3.1: Numbers and mean age of participants within each age group

3.3.2 Distribution of refractive error across age groups (cross-sectional)

3.3.2.1 Mean spherical equivalent

Figure 3.2 shows the mean of the spherical equivalent refractive errors for each of the 15 groups. The children are hypermetropic, in general, with a mean refractive error of + 2.32 Dioptres (D) in the 1 year old age group. The hypermetropia increased by +0.74D by the age of 8 years, leaving this age group with a mean refractive error of +3.09D. This was followed by a slow decrease of -1.49D, leaving the 15 year old age group with a mean refractive error of +1.60D. In general, the mean spherical equivalent steadily increased towards higher hypermetropia with increasing age in the first seven age groups. This was followed by a slow decrease towards less hypermetropia. Figure 3.3 shows the standard deviation of the mean refractive errors across the 15 age groups. It was lowest in the 1 year olds and highest in the 10 year olds. A noticeable gradual increase in standard deviation took place between the age of 1 and 4 years. It was followed by a slow decrease that formed a low point at the age of 8 years. It can be seen that there is no specific pattern thereafter.

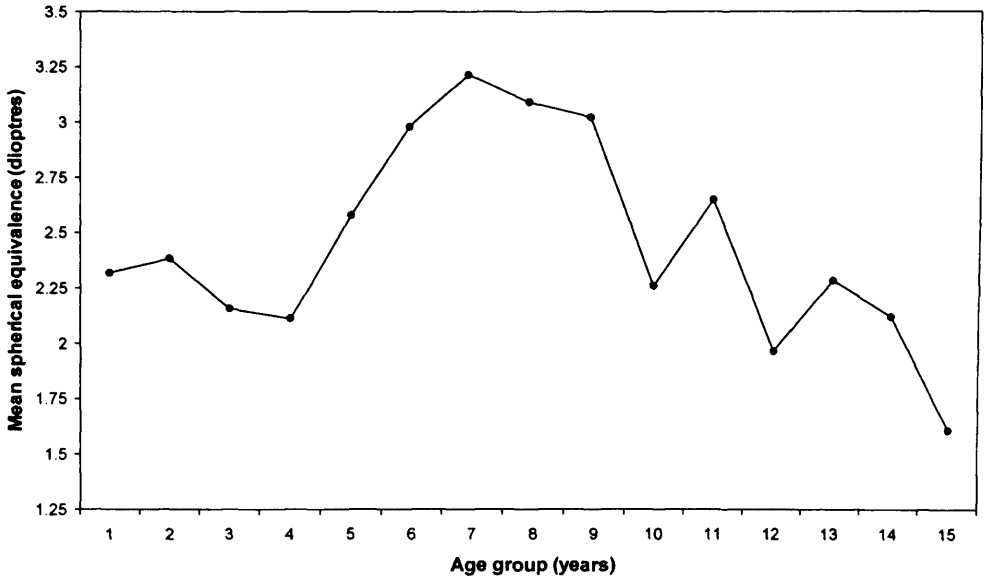


Figure 3.2: Mean spherical equivalent of refractive error across the 15 age groups. Data points represent means.

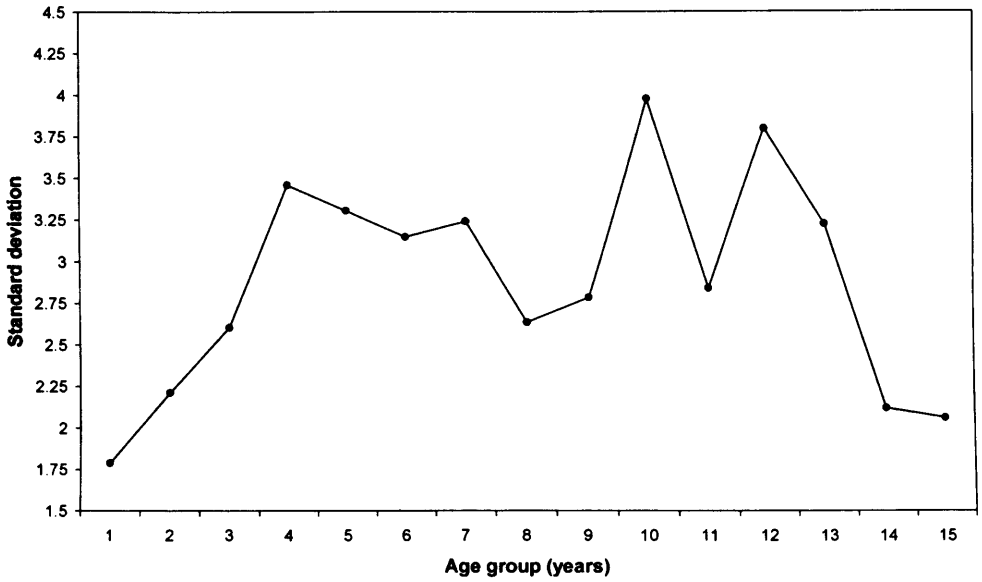


Figure 3.3: Standard deviation of the mean spherical equivalent of refractive error across the 15 age groups

A Kruskal-Wallis test found no statistically significant difference in spherical equivalent refractive error distribution between the 15 age groups (p = 0.28). Because the data was not entirely independent, related-samples statistical tests were also conducted. The results of the Friedman Test suggest that there were no significant differences in the M vector scores across the 15 age-groups, $\chi^2 = 16.79$, $p > 0.05$. Individual Wilcoxon Signed Rank Tests confirmed the finding showing no significant difference in M vector between age-groups ($p>0.05$ for all comparisons).

Since the data were non parametric, a box-plot was constructed (Figure 3.4). The median shows a similar pattern to the mean in Figure 3.2. The hypermetropia slightly increased with increasing age groups up to 9-year-olds followed by a small decrease thereafter.

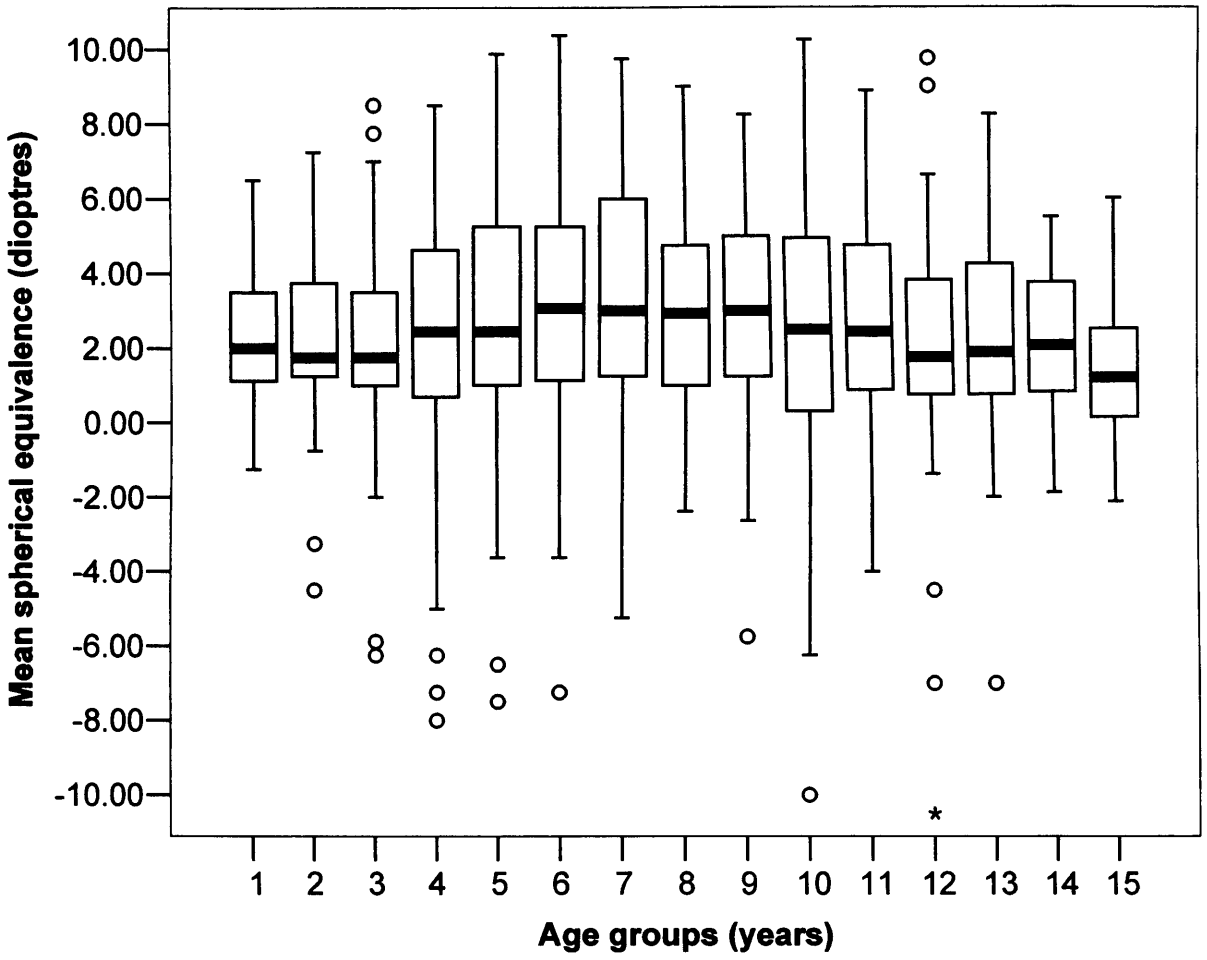


Figure 3.4: Mean spherical equivalence of refractive error across the 15 age-groups. Medians for the total number of children in each age group.

3.3.2.2 Astigmatism

Figure 3.5(a-o) shows the distribution of the astigmatic components of refractive error. They describe the distribution of the power vector components J_0 and J_{45} for each age group. The J_0 component represents the Jackson cross-cylinder (JCC), with its axes at 90° and 180°, and the J_{45} component represents the JCC with its axes at 45° and 135°. The plus cylinder is at 90° when J_0 value is positive and it is at 180° when the value is negative. Similarly, the plus cylinder axis is at 135° when J_{45} value

is positive and it is at 45° when the value is negative. A value of zero indicates the absence of astigmatism (Thibos *et al.*, 1997).

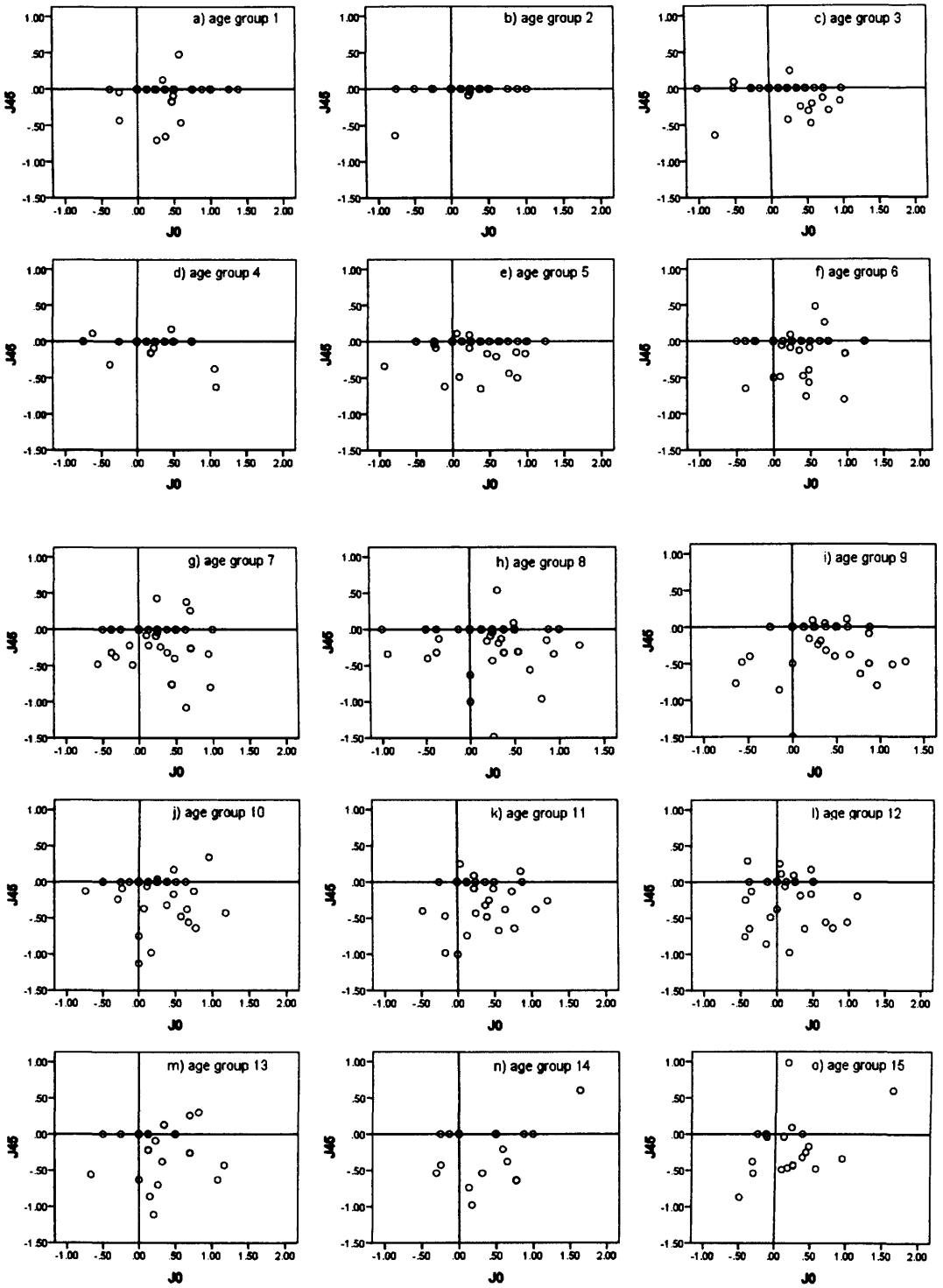


Figure 3.5: Distribution of astigmatism in each age group (1 to 15) using vector components J_0 and J_{45}. a +ve J_0 = JCC @ 90°, a -ve J_0 = JCC @ 180°. a +ve J_{45} = JCC @ 135°, a -ve J_{45} = JCC @ 45°.

Figures 3.5 a to o show that the majority of children in the younger age groups either did not have astigmatism or they had an astigmatic error along the 90° axis. However, the amount of astigmatism (J value) increased with increasing age, with the axis of astigmatism shifting towards 45°. This showed a high prevalence of oblique astigmatism, with most axes being between 45° and 90°; presented as data points having a positive J_0 value combined with a negative J_{45} value. Statistical analysis, using Kruskal-Wallis one-way analysis of variance, showed a significant difference in the distribution of astigmatism across the age groups for the J_{45} vector component (Oblique meridians) ($p < 0.001$). However, there was no statistically significant difference in the distribution of astigmatic errors along the J_0 vector component (Principle meridians) ($p = 0.14$). The outcomes of a Friedman Test and individual Wilcoxon Tests revealed the same result. They showed no statistical difference in J_0 across age groups ($p>0.05$ in all comparisons for both tests), while they showed a significant difference in J_{45} ($p<0.05$, Friedman Test). The Wilcoxon tests indicated that the difference occurred between 2-year-olds and all age groups that are older than 7 years of age, $p<0.05$ ($p>0.05$ in all other comparisons using Wicoxon Signed Rank Test).

Figure 3.6 shows the distribution of astigmatic refractive error across the 15 age groups. The presence of significant astigmatism (≥ 1.00D) increased dramatically with increasing age; 64.3% of 1 year olds had a spherical refractive error (no significant astigmatism) compared to only 30% of 15 year olds. More interestingly, the increase in the presence of astigmatic error was accompanied by the increasing occurrence of oblique astigmatism (7.1% of 1 year olds and 50% of 15 year olds). However, the prevalence of with-the-rule and against-the-rule astigmatism did not seem to be changing with age. A Chi-Square test revealed the presence of a

significant difference in the distribution of astigmatism categories across age groups ($p < 0.001$).

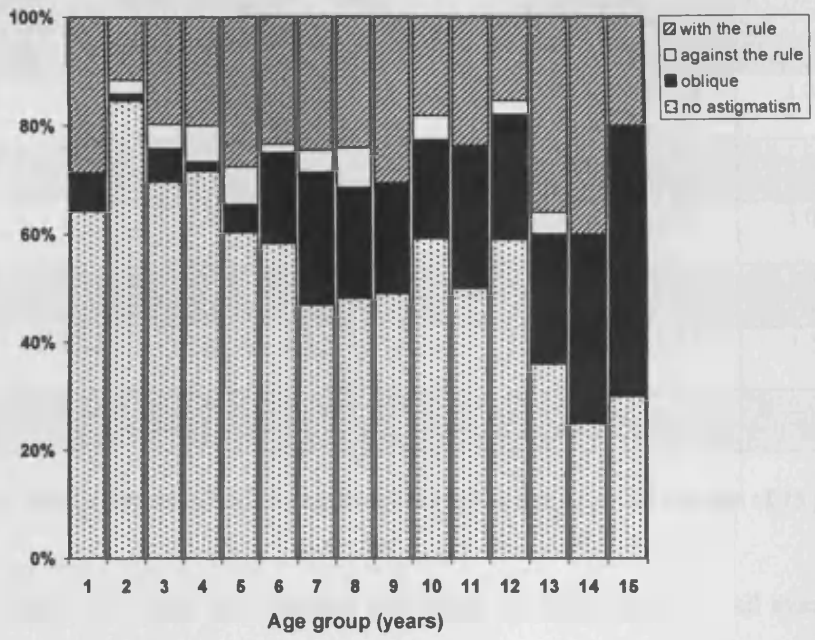


Figure 3.6: Distribution of Astigmatism categories across the 15 age groups

3.3.3 Development of Refractive Error (Longitudinal)

Table 3.2 shows data from 6 children who attended the clinic between the age of 1 year and the age of 15 years. Although the spherical refractive error (M vector) increased slightly in the majority of the children, a paired samples t-test and a Wilcoxon Signed-Rank test showed no statistically significant difference ($p = 0.49$, $p = 0.60$ respectively). Similarly, the amount of astigmatism increased substantially in the majority of the children, but statistical analysis did not find a significant change for the J_0 vector ($p = 0.31$, $p = 0.29$) and the J_{45} vector ($p = 0.96$, $p = 0.68$); p values are for t-test and Wilcoxon Signed-Rank test respectively. However, 5 out of the 6 children had no significant astigmatism (of 1.00 or more dioptres) at 1 year of age compared to only 1 of the 6 at age 15. Four of the children developed oblique astigmatism, all of whom did not have significant astigmatism at 1 year of age. A Chi-

Square test revealed a significant difference in astigmatism, presence and direction, between age 1 and age 15 ($p = 0.03$).

Subject No	Age (years)	Mean Sphere	Astigmatic Power	Axis	Age (years)	Mean Sphere	Astigmatic Power	Axis
1	1.35	+5.00	0.00	No Cyl	15.04	+3.125	2.00	Oblique
2	1.21	+4.25	0.00	No Cyl	14.9	+6.00	1.00	Oblique
3	1.15	+3.25	1.00	W-T-R	15.13	+2.25	1.00	W-T-R
4	1.32	+0.50	0.50	No Cyl	15.2	+1.375	0.75	No Cyl
5	1.02	+4.50	0.50	No Cyl	14.91	+5.25	1.50	Oblique
6	1.02	0.00	0.00	No Cyl	14.58	+2.50	2.00	Oblique

Table 3.2: Refraction details for 6 children during the age of 1 and the age of 15 years

Figure 3.7 shows the spherical equivalent refractive error for all available refractions for the 6 subjects. An Order 2 Polynomial trend line was added to illustrate the pattern of refractive development. It can be seen that the trend lines formed a "hill" for all but one of the children. The spherical equivalent increased slightly for all of the children and then decreased leaving 4 out of the 6 children with slightly higher hypermetropia at the age of 15 than they had at age 1. A slight decline in hypermetropia occurred for the remaining two children. However, the difference in refraction between age 1 and age 15 was not statistically significant. Line graphs for the individual subjects can be found in Appendix III.

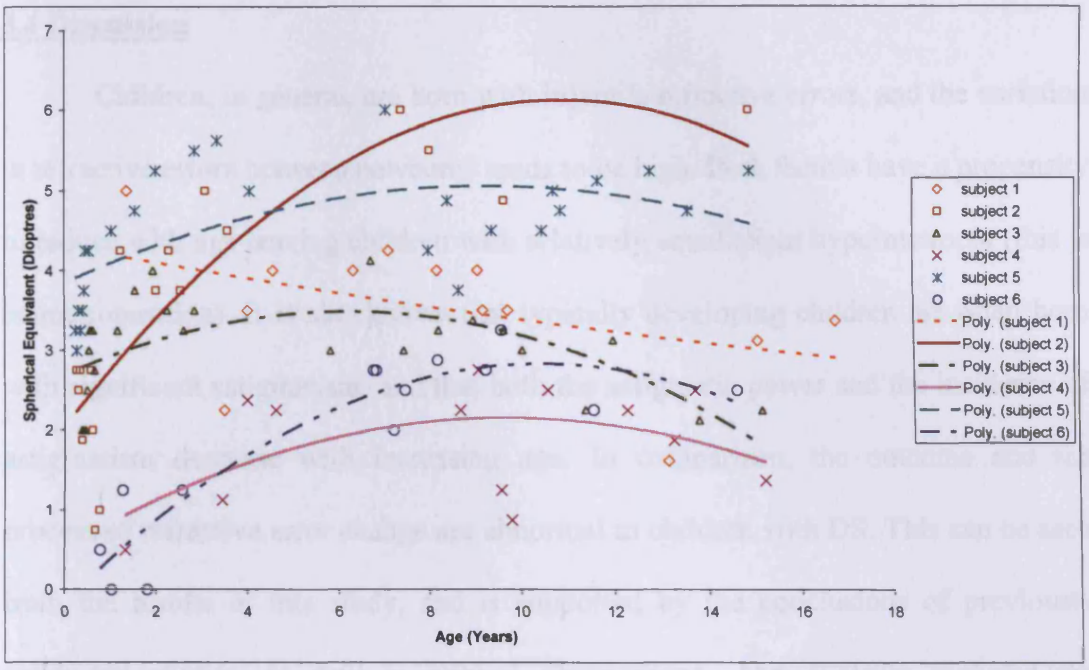


Figure 3.7: Spherical equivalent development with age for 6 children with DS. Dots represent spherical equivalent. Lines show Order 2 Polynomial trend line.

Figures 3.8 a and b demonstrate the distribution of astigmatism using the power vector components J_0 and J_{45} at age 1 and age 15, respectively. The amount of astigmatism increased and the axis shifted towards oblique astigmatism. It can also be seen that most of the shift in axis was discriminatory. The axis of astigmatism was between 90° and 45° in the right eye in most of those who developed astigmatism (the left eye was used for subject 1, hence the axis was between 90° and 135°).

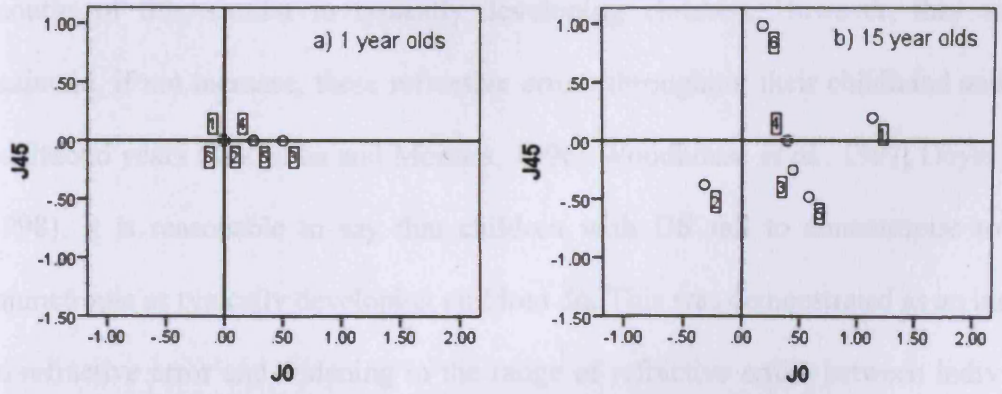


Figure 3.8: Distribution of astigmatism using vector components J0 and J45 in 6 children with DS at age 1 (a) and at age 15 (b)

3.4 Discussion

Children, in general, are born with infantile refractive errors, and the variation in refractive errors between newborns tends to be high. Both factors have a propensity to reduce with age leaving children with relatively equal slight hypermetropia (this is emmetropisation). It is also known that typically developing children are often born with significant astigmatism, and that both the astigmatic power and the incidence of astigmatism decrease with increasing age. In comparison, the outcome and the process of refractive error change are abnormal in children with DS. This can be seen from the results of this study, and is supported by the conclusions of previously conducted studies, as well as clinical observations. Abnormalities included the spherical component as well as the astigmatic component of refractive error.

3.4.1 Spherical component

In the present study, the overall trend of refractive error distribution amongst the 15 age groups revealed two main features. Firstly, the children tend to be hypermetropic with a wide variation in refractive error at all ages. Secondly, refractive error distribution does not differ significantly across different age-groups.

The vast majority of children with DS are hypermetropic during their early months of life; similar to typically developing children. However, they tend to maintain, if not increase, these refractive errors throughout their childhood and early adulthood years (da Cunha and Moreira, 1996; Woodhouse *et al.*, 1997; Doyle *et al.*, 1998). It is reasonable to say that children with DS fail to emmetropise towards emmetropia as typically developing children do. This was demonstrated as an increase in refractive error and widening in the range of refractive errors between individuals

(Doyle *et al.*, 1998; Haugen *et al.*, 2001b; Cregg *et al.*, 2003). However, all of these studies concentrated on a small age range of participants.

It has long been established that persons with DS generally have higher refractive errors compared to age matched controls and this was well reflected in our results. Despite the outcome of Haugen *et al.* (2001b) that suggested myopia to be more prevalent, our results suggest that children at all ages are likely to be hypermetropic. However, the pattern of refractive error distribution in children with DS actually shares some similarities to that of typically developing children, published by Gwiazda *et al.* (1993), when looking at the mean of the spherical equivalent of both groups. The amount of refractive error of both groups of children shifts towards higher hypermetropia during the first few years of life and declines thereafter towards lower hypermetropia or myopia by comparable amounts (Figure 3.9). The only difference is that children with DS take longer to achieve this "peak" before the refractive error starts to go in the direction of lower hypermetropia.

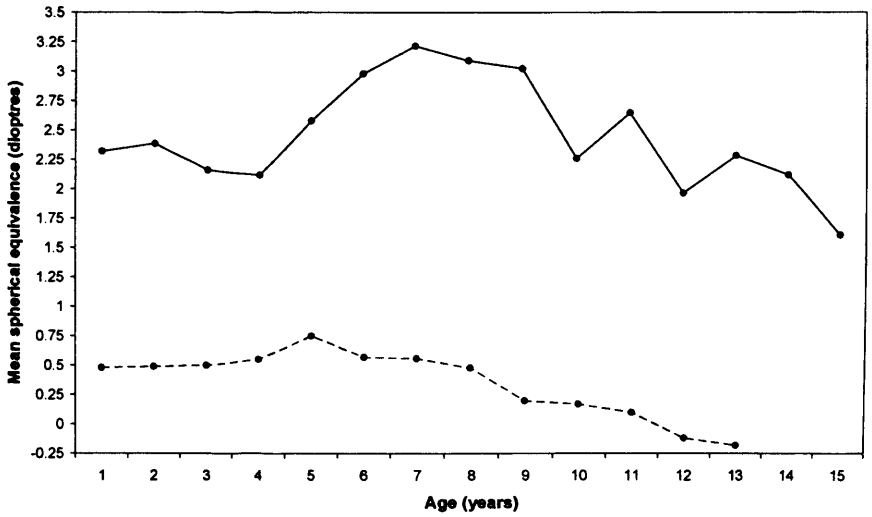


Figure 3.9: Mean spherical equivalent of refractive error, solid line; cross sectional data of children with DS. Dashed line; longitudinal data from Gwiazda *et al.*, (1993)

Nevertheless, a considerable difference appears when looking at the range of refractive errors in children with DS (Figure 3.10). Generally, the range of refractive errors is much wider in children with DS compared to typically developing children at all ages; a major feature that is suggestive of inactive emmetropisation and the reason for the absence of statistical significance in refractive error change with age in our results. This was previously established regarding refractive development in DS, and our result confirms this finding (Haugen *et al.*, 2001a).

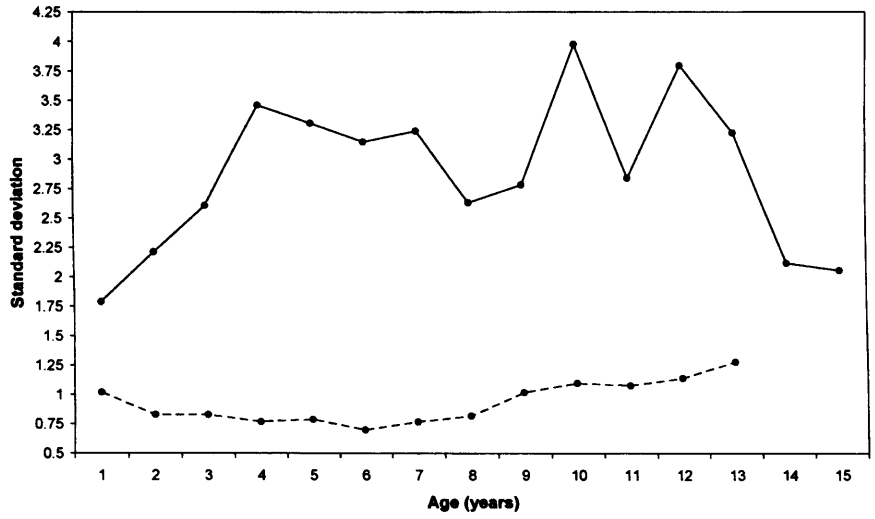


Figure 3.10: Standard deviation of the mean spherical equivalent of refractive error, solid line; cross sectional data for children with DS. Dashed line; longitudinal data from Gwiazda *et al.*, (1993)

Our results suggest that children with DS tend to fail to emmetropise in general. The range of refractive errors tend to decrease with age in typically developing children, the lowest being at 6 years of age, and variation starts to increase thereafter, reflecting the influence of genetic and lifestyle on refractive error (Guggenheim *et al.*, 2007). Hence, emmetropisation is thought to end by the age of approximately 6 years. In contrast, in children with DS the range of refractive errors was lowest in 1-year-olds and then started to increase thereafter. A longitudinal study

of refractive development, in which the same children were represented in each age group, would have been more informative. However, a defined pattern in spherical refractive error distributions across age groups was apparent during the first 8 years in our study population, both when looking at the mean and the median of refractive errors; the absence of a defined pattern after the age of 8 may be due to the reduced number of participants in the older age groups in our study. But since Gwiazda *et al.* (1993) showed widening in the range of refractive errors after completion of emmetropisation in typically developing children, it can be argued that emmetropisation, as we know it, takes effect only between the age of 4 and 8 in children with DS. This may be due to the slothful general growth rate in this population (Myrelid *et al.*, 2002). This, and the fact the most children are hypermetropic, also suggests that the reason for this abnormal emmetropisation is a shorter axial length, which was shown by Haugen *et al.* (2001a). Growth hormones, proved to enhance general growth in children with DS, are currently used with some children to augment their development (Anneren *et al.*, 1999; Pallotti *et al.*, 2002). When under-development of the eye is the reason for this abnormal development, growth hormones may prove useful for the purpose of enhancing normal refractive development. Of course, expert opinion should be consulted for the consideration of health-related aspects of the hormone intake.

Interestingly, refractive errors appeared stable, after the age of 4 years, when the children were observed individually (Appendix III). Although our data set is very small to draw a general conclusion, it reflected the outcome of Haugen *et al.* (2001b). They reported stable hypermetropia, of different levels, that is within 1.50D of change in the majority of their participants with DS.

3.4.2 Astigmatism:

Development of astigmatism has a defined pattern in children with DS that largely differs to that of typically developing children. It has been reported that significant astigmatism is more prevalent in individuals with DS than in their typically developing peers and that oblique astigmatism is widely present within the older children (Doyle *et al.*, 1998; Haugen *et al.*, 2001a). Our results showed consistency with previous studies. Unlike typically developing children, the incidence of astigmatism increases with age, and the power of astigmatism is also increasing. More interestingly, whereas a minority of typically developing children maintain with-the-rule astigmatism (Gwiazda *et al.*, 1984), the increase of astigmatism in DS is associated with a rising incidence of oblique astigmatism. This was confirmed by looking at individual children longitudinally, where those infants with spherical refraction were very likely to develop oblique astigmatism later in life. This increasing incidence and rise in the power of astigmatism in general may be caused by the effect of eyelids on the thinner corneas in children with DS. It is known that children with DS have an obliquely-slanted palpebral fissure and lower corneal thickness (Smith and Berg, 1976; Evereklioglu *et al.*, 2002). The significant presence of oblique astigmatism further supports this proposal; especially that the axis of astigmatism is highly correlated with the slanting of the palpebral fissure in typically developing individuals (Gracia *et al.*, 2003). This may relate to the increasing incidence of oblique astigmatism with age. The lower corneal thickness may augment the effect from the eyelids on the degree and axis of astigmatism. However, Little *et al.* (2009b) failed to show the expected relationship between corneal and total oblique astigmatism, either in children with DS or in typically developing controls. This may be explained by their small study population (n=24 children with DS).

3.5 Conclusions

The development and distribution of refractive error has its differences between children with DS and typically developing children. Whereas typically developing children grow out of their infantile refractive error towards emmetropia, children with DS tend to continue to be hypermetropic. Moreover, the range of refractive errors remains relatively high between individuals with DS at all ages. Interestingly, the nature of astigmatism development is unique.

The outcome of this study is very useful in aiding clinical planning for children with DS, and further supports spectacle prescription at an earlier age, since a child with DS tends to be hypermetropic with reduced accommodative abilities (Woodhouse *et al.*, 1993). The outcomes also suggest further research that would ultimately lead to a full understanding of refractive error development in children with DS. One factor that can influence refractive development is family history. The role of familial refractive errors in shaping this abnormal refractive development in DS was investigated and is presented in Chapter Four. It is also appealing to investigate the reasons behind the specific development of oblique astigmatism in this population.

Chapter Four: The relationship between the refractive errors of children with Down's syndrome and that of their parents and siblings

Chapter Four: The relationship between the refractive errors of children with Down's syndrome and that of their parents and siblings

4.1 Introduction

In similarity to many developmental characteristics, various studies have highlighted the possibility of inheritance in the aetiology of refractive error. This aspect has undergone extensive investigation, especially for myopia, since this is the most prevalent refractive error amongst typical adults. Understanding the aetiology of any characteristic often allows the exploration of ways to either enhance or prevent a particular trait. However, most studies have concentrated on the general population. The parent-child relationship with regards to refractive error has never been investigated in children with Down's syndrome (DS).

4.1.1 Refractive error inheritance in typically developing individuals

Refractive error inheritance has been a subject of study for many years. This has had the intention of predicting the development of the refractive status of a child, in turn leading to successful ophthalmic planning. The inheritance of myopia has undergone extensive research, due mainly to its strong presence as a refractive error in most populations, its increasing magnitude, and the risk of ocular morbidity it can induce (Midelfart *et al.*, 2002; Saw *et al.*, 2002; Kempen *et al.*, 2005). Myopia is found to be an inherited trait, as reflected by the strong correlation in parent-child refractive errors. The consistent finding is that a child with two myopic parents has a higher chance of becoming myopic than a child with only one myopic parent who has a higher chance than a child without any myopic parents (Zadnik *et al.*, 1994; Pacella

et al., 1999; Mutti *et al.*, 2002). Refractive errors were also found to correlate between siblings (Guggenheim *et al.*, 2007), and especially between twins (Hammond *et al.*, 2001; Dirani *et al.*, 2006). In addition, other blood relatives have been shown to have an active effect on the child's refractive error (Hui *et al.*, 1995). However, most of these studies also suggest that it was environmental and lifestyle effects which triggered the development of myopia, assuming that the habits, such as prolonged reading, may be the inherited factor rather than the myopia itself. For example, it has been found that myopic children tend to spend more time performing near tasks than their emmetropic peers (Mutti *et al.*, 2002).

Hypermetropia has not undergone the same level of investigation, perhaps due to the less prevalent occurrence within the general population (2-12% in school age children compared to 10-73% for myopia) (Zadnik *et al.*, 2003; He *et al.*, 2004; Ip *et al.*, 2008). However, Young *et al.* (2007) have suggested a possible genetic influence in hypermetropia, although, from their discussion, this mainly relates to very high hypermetropia. The results of Hammond *et al.* (2001) support this hypothesis by finding a strong correlation in the refractive errors (myopia, hypermetropia and astigmatism) of monozygotic and dizygotic twins.

4.1.2 Refractive error inheritance in children with Down's syndrome

There is currently no published research that has explored the relationship between the refractive errors of children with DS and that of their parents and siblings. As was noted in the previous chapter, children with DS have higher refractive errors than their typically developing peers. The genetic difference that characterise individuals with DS is most often the presence of an extra chromosome 21; a chromosome which, to date, has not been implicated in harbouring a genetic

locus involved in refractive error development (Young *et al.*, 2007). This indicates that a relationship may still exist between children with DS and their family members. In addition, the presence of a specific developmental pattern of refraction in the study population further supports this argument. However, because hypermetropia is present in most children with DS, perhaps due to the under-development that characterises individuals with DS, then, according to Cronk *et al.* (1988), myopic parents may give birth to a "less hypermetropic" child rather than a myopic one.

4.1.3 The aim

The aim of this study was to investigate the relationship between refractive errors of children with DS and that of their parents and siblings. The results will contribute to the definition of aetiology of refractive errors in persons with DS, and may also be useful for increasing the predictive power for eye care practitioners when following a child with DS.

4.2 Methods

4.2.1 Study population

All children with DS who attend to Cardiff University Eye Clinic were invited to join the study (n = 234); these included the original cohort members (n = 182) and the newer recruits (n = 52). The inclusion of this selected population will strengthen the results of this particular study, since these newer recruits may be biased towards having significant refractive errors, and the presence of such errors will aid in defining the relationship between their refractive errors and these of their parents and siblings. Parents and siblings of the children were invited to participate in the study.

In concordance with previous studies, the minimum age for inclusion was 10 years for children with DS and for their siblings. This is to allow for a completion of the emmetropisation process and to allow for the development of possible juvenile myopia in typically developing children (Gwiazda *et al.*, 1993; Gwiazda *et al.*, 2000; Mutti *et al.*, 2002). For consistency, the same age limit was chosen for children with DS. Parental consent was obtained for inclusion of their children's data and for inclusion of their personal data. Separate consents were also acquired from siblings over the age of 16 years for inclusion in the study.

4.2.2 Data collection

Initially, a questionnaire was distributed to all participants, either by post or during clinical consultation, to collect information regarding spectacle or contact lens wear, as well as refractive surgery, and eye care provider's contact details for parents and siblings of children with DS. An optional section of the questionnaire was assigned to collect information regarding biological relationships within the families, but only fully answered questionnaires were included in the analysis. A consent form allowing collection of refractive errors and monocular visual acuities from the participant's eye care provider was attached to the questionnaire.

A second questionnaire was sent to all of the eye care providers noted by our participants, with a photocopy of the participant's consent form attached, to collect refractive error, visual acuity and date of examination. Copies of both questionnaires and the consent form can be seen in Appendix IV. Any family members who indicated no optical correction wear and did not assign an eye care provider were assumed to be emmetropic, and a refractive error of 0 dioptres was assigned for data analysis.

Refraction details of children with DS were extracted from the latest visit in their clinical records at Cardiff University Eye Clinic. Refraction was performed by current and past members of the Cardiff Down's Syndrome Vision Research Unit, with Mohindra near retinoscopy as the method of choice (See *Chapter Two*)

4.2.3 Data analysis

4.2.3.1 Comparison between the refractive errors of children with DS and those of their parents and siblings

Only data of children aged 10 years or older during the time of analysis were included in the study. This was chosen to allow for the development of refractive error based on previous studies (Gwiazda *et al.*, 1993; Gwiazda *et al.*, 2000; Mutti *et al.*, 2002).

Data from the right eye were used unless the subject was anisometropic, strabismic or amblyopic when the dominant eye refraction was used. Anisometropia was defined as a difference of ±1.00 D in the spherical equivalent of refractive error between the two eyes. Amblyopia was defined as difference of two or more Snellen equivalent visual acuity lines between the two eyes.

Refractive error was divided into its power vector components; M, J_0 and J_{45} (Thibos *et al.*, 1997) and comparison between the refractive errors of children with DS and those of their parents was separately made for each vector component. To take account for the genetic input of both parents, each child's spherical equivalent was also compared to the average of the spherical equivalent for both parents (midparent refractive error). Children with DS were then separated according to gender and the analysis repeated to assess possible gender differences. Correspondingly, the three power vector components were compared between

children with DS and their siblings. One sibling from each family, over the age of 10, was randomly chosen to be included in the analysis.

A Spearmen's Rank Ordered Correlation was used to test all comparisons. Standard multiple-regression was used, in addition to Spearman's rho, to determine the relationship between the parents' average spherical equivalent and that of their children with DS and that of their typically developing children.

4.2.3.2 Comparison between Refractive error of siblings and parents.

For comparison purposes, power vector components of refractive error were compared between siblings of children with DS and each parent. Midparent refractive error was also compared to that of the siblings.

4.3 Results

4.3.1 Study population

Questionnaires were sent to 234 families, of which 105 were returned. One hundred and three questionnaires were forwarded to the indicated eye care practitioners (95 original and 8 newer recruits). Two cases were dismissed due to the non-biological relationship between the child and a family member. Of the 103, 92 were returned by the eye care practitioners. Questionnaires completed by parents of a child with DS under the age of 10 years during their latest assessment were eliminated from analysis. Therefore, the final number of questionnaires of children with DS aged 10 years or over available for analysis was 55; 35 of which were male and 20 were female. Their ages ranged from 10 to 18.6 years (mean=13.3).

Refractive error information was available from both parents of only 35 children, from the mother only for 44 children and from the father only for 42

children. Thirty-six of the children with DS had siblings, with 32 having siblings aged 10 years or older; 17 were male and 15 were female with their ages ranging from 11.2 and 32.7 years (mean = 19.1 years). However, for comparison between the midparent refractive error and sibling's refractive error, only 22 cases were eligible for inclusion, due to the unavailability of the refractive error for *both* parents for the other 10 cases. Data from the left eye were used with 4 children with DS and one parent, all due to anisometropia, with data from the right eye otherwise used.

4.3.2 Data analysis

Data were assessed for normality and the distributions were found to deviate from normal ($p < 0.005$, Shapiro-Wilk test). Since standard transformations (Blackie and Harris, 1997) were not effective in achieving normality and the dataset was too small to permit use of a normal deviates transformation (Blackie and Harris, 1997), non-parametric statistical tests were used to assess the relationship between variables. In particular, Spearman's Rank Order Correlations were performed. In addition, because the parents' average refractive error distribution did not seriously deviate from normality, linear multiple regression was employed to assess its relationship with that of their children with DS and with that of their typically developing children.

The mean spherical refractive error distribution curves for children with DS, their siblings and for the midparent refractive error can be seen in Figure 4.1. The mean and standard deviation of refractive errors was much higher in children with DS (mean = +2.75 D, s.d. = 4.11), compared with their siblings (mean = -1.13 D, s.d. = 1.02) and parents (mean= -0.01 D, s.d. = 1.51), reflecting the expected shift towards

hypermetropia and the wide range of refractive errors in children with DS at all ages (Woodhouse et al,. 1997; *Chapter Three*).

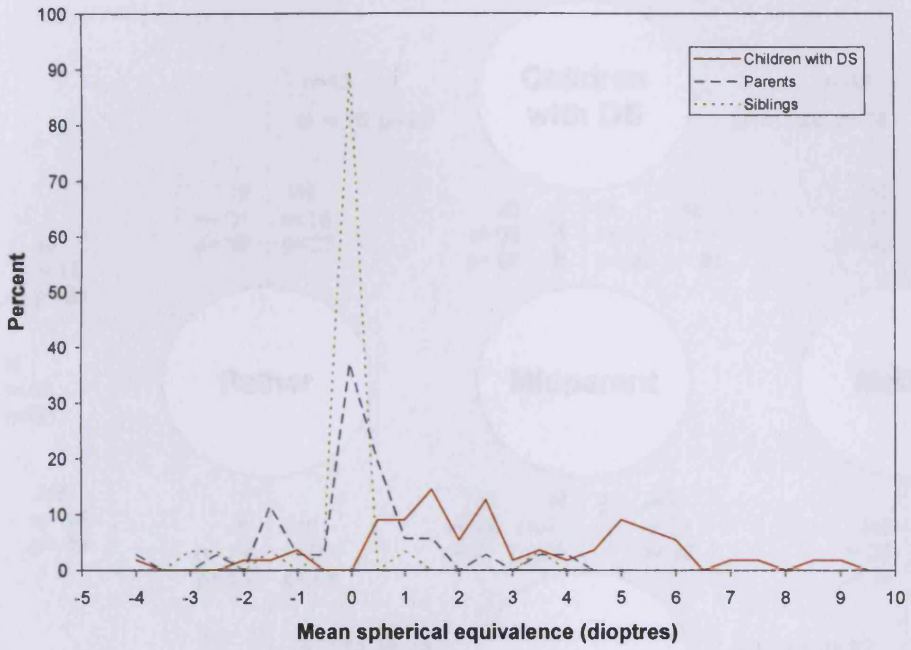


Figure 4.1: Distribution of mean spherical equivalent refractive error of children with DS, their parents and their siblings

Figure 4.2, summarising the results of the Spearman's rho correlations, shows that there are no statistically significant relationships between the refractive errors of children with DS and that of their parents, either separately or jointly as the midparent refractive error. In contrast, it reveals the presence of a significant positive relationship between the midparent refractive error (M) and that of their typically developing children [r=0.426, n=22, p = 0.048]. Specifically, it shows a higher significance level between the spherical equivalent of typically developing children and their mothers, than that with their fathers. The relationship between children with DS and their siblings is not significant. With regards to astigmatism, there was no

statistically significant relationship between the power vector components J_0 and J_{45} of children and parents.

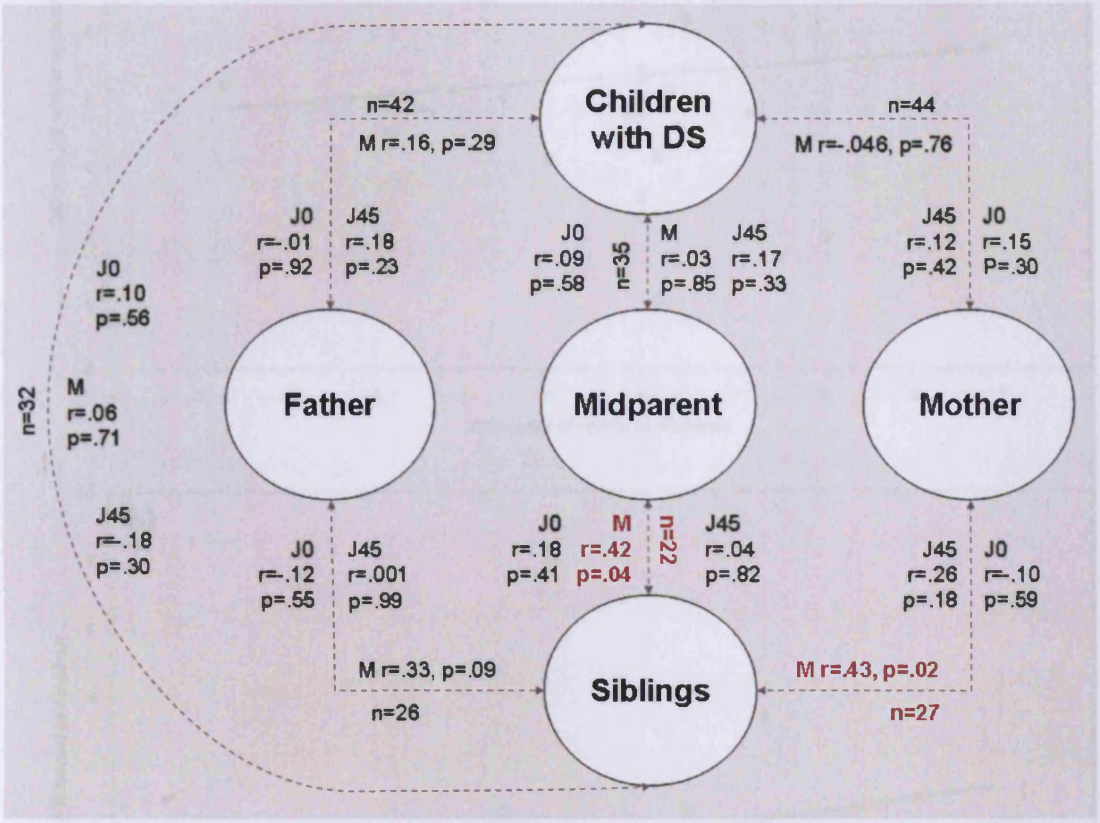


Figure 4.2: Summary of the results of Spearman's rho test indicating the number of subjects (n), the correlation coefficient (r) and the significant level (p) for each comparison.

The results of a standard multiple-regression further support these findings. There was no significant relationship between the spherical equivalent of children with DS and the midparent refractive error [beta = 0.075, B = 0.045; SE = 0.1, p = 0.67], while there was a statistically significant relationship between the refractive error of their siblings and their midparent refractive error [beta = 0.546, B = 0.842; SE = 0.285, p = 0.008].

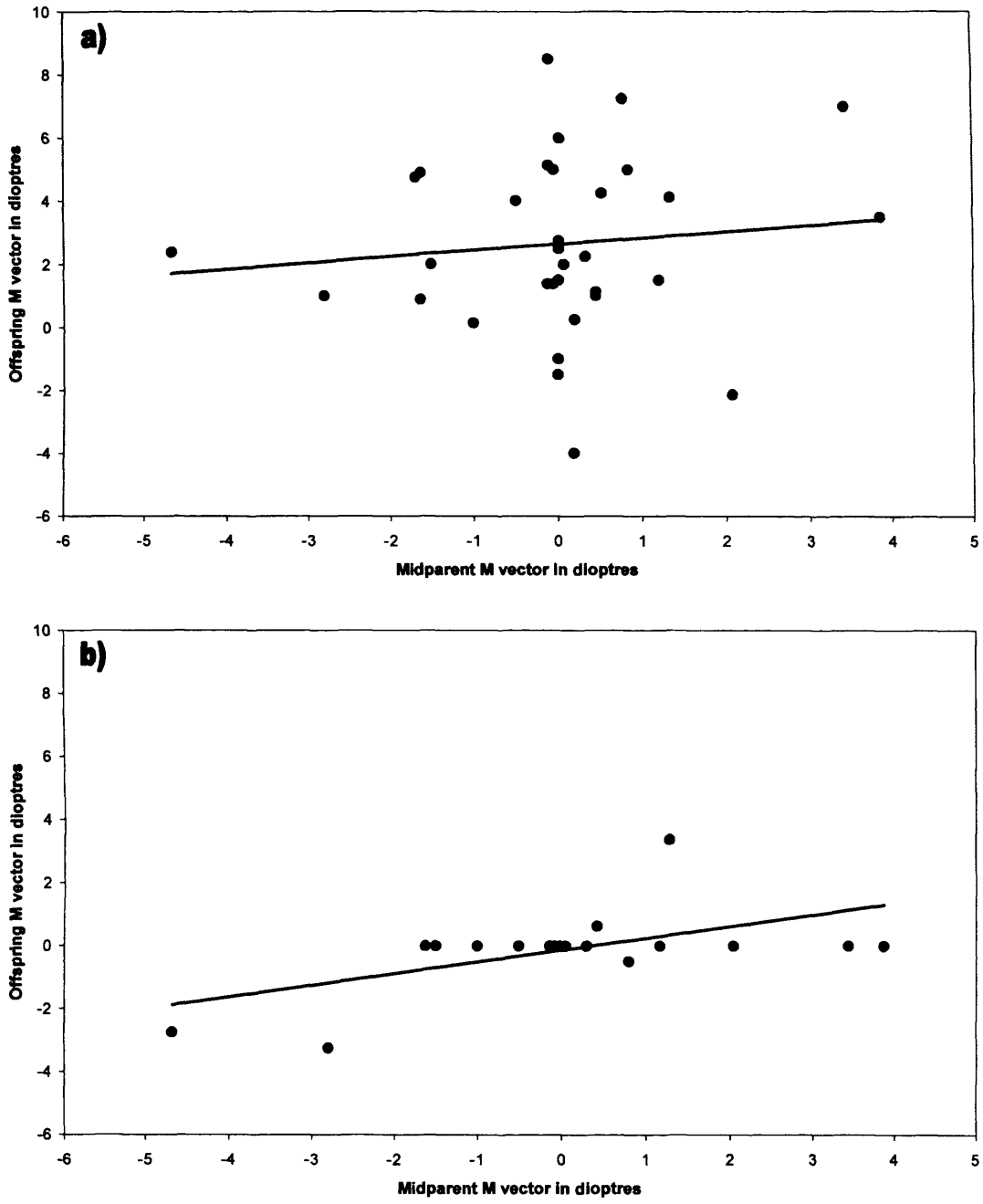


Figure 4.3: The relationship of the spherical refractive error between parents and children. a) children with DS against the average of both parents' prescription (n=35), b) typically developing siblings against the average of both parents' prescription (n=22).

Figure 4.3 a-b shows the comparisons between children and their parents in more detail, which emphasises the greater scatter in the data for children with DS compared to their typically developing siblings.

Children with DS were divided into two groups according to gender, and Spearman's Rank Order Coefficient analyses were conducted. No statistically significant relationship was found between the refractive error components (power vectors M, J_0 and J_{45}) of children with DS and those of each parent separately. A similar result was found when the mean spherical equivalent (M) of children with DS was compared to the midparent refractive error, or to the average of that of their siblings ($p > 0.05$ in all cases).

4.3.2.1 Re-analysis after eliminating subjects without a valid refraction result

In this section, only participants that were provided with a valid refraction result from a qualified eye care practitioner were analysed. After eliminating subjects without a valid refraction result, the results of a Spearman's rho further confirmed the previous results. The results can be seen in Table 4.1. It confirmed the absence of a statistically significant relationship between children with DS and each parent separately, and both parents jointly. It was not possible to reassess the relationship between typically developing siblings and parents due to the loss in numbers.

Comparison	Number of cases (n)	Correlation coefficient (r)	Significance level (p)
Child-Mother	32	-0.048	0.795
Child-Father	16	0.446	0.084
Child-Parents' average	10	0.511	0.132

Table 4.1: The result of a Spearman's rho for comparisons between the spherical equivalent of children with DS and that of their parent's separately, and jointly as an average.

4.4 Discussion

It is well established that refractive errors are highly correlated between family members, reflecting the strong influence of genetics (Zadnik *et al.*, 1994; Pacella *et al.*, 1999; Hammond *et al.*, 2001; Mutti *et al.*, 2002; Dirani *et al.*, 2006; Guggenheim *et al.*, 2007), and the results from this study are consistent with the literature, when looking at typically developing children and their parents. However, this study also indicates that no such relationship exists between children with DS and their parents.

Parental refractive status does not seem to influence that of their children with DS. This raises some further questions regarding the aetiology of refractive errors in individuals with DS.

The results demonstrated the hypermetropic shift in the refractive errors of individuals with DS shown in *Chapter Three*, which is similar to previously published results (Woodhouse *et al.*, 1997; Doyle *et al.*, 1998; Akinci *et al.*, 2009). The hypermetropia is principally caused by a shorter ocular axial length, termed as axial hypermetropia (Doyle *et al.*, 1998; Cegarra *et al.*, 2001). It is understood that children with DS suffer from delay in growth and general development (Myrelid *et al.*, 2002), so the high prevalence of hypermetropia may be related to the developmental delay in children with DS. Although growth is known to be generally hindered in individuals with DS, the delay in development may not be consistent amongst all children with the syndrome. This may be the reason behind the increasing variability in refractive error with age in children with DS, which may, in turn, have a masking effect on the relationship between parental refractive error and their children with DS. Regardless of the reasons behind the absence of this relationship, it can be concluded that the refractive state of the parents cannot actively influence the refractive development of a child with DS.

There were two major weaknesses in the study design that mean that the results must be interpreted with a degree of caution. Firstly, the sample size of the study was low, which means that a weak correlation being present between parents and children with DS may still be possible. Due to the complex sampling distribution of correlation coefficients, the sample size required to firmly establish a midparent-offspring relationship for parents and children with DS would need to be about an order of magnitude greater (Lynch and Walsh, 1997). A second weakness was that subjects who did not have a known refractive error were assigned a trait value of zero dioptres. This assumption, though likely to be frequently correct, probably led to greater scatter in the data for subjects with moderate/high undiagnosed hypermetropia, and reduced scatter for subjects close to emmetropia. However, because the expected relationship between typically developing children and their parents was found in the study – and with a lower sample size than that available for the same comparison for children with DS – there is evidence for the general validity of the findings. However, the two weaknesses mentioned above were likely to have been the cause of this midparent-offspring correlation for refractive error in typically developing children being higher than that usually reported (Guggenheim *et al.*, 2003). In addition, these weaknesses may also be the cause of the absence in relationship of astigmatism.

To summarise, refractive errors in DS are not influenced by those of their parents and they differ to those of their typically developing siblings. This may be due to a delayed and variable general growth rate amongst children with DS that may obstruct the general rule of refractive error inheritance. The inability to predict the refractive development of a child with DS based on their parental refractive status stresses the importance of regular routine optometric examination to assess possible

changes in refraction and provide the appropriate updated treatment and advice. It is known that refractive error correlates significantly with the axial length of the eye in children, for both typically developing children and children with DS (Doyle *et al.*, 1998; Cegarra *et al.*, 2001). It is also known that overall height is lower in children with DS than in age-matched controls in many populations (Myrelid *et al.*, 2002; Styles *et al.*, 2002). The combined analysis from these results and the published literature suggests that the refractive error shift towards higher hypermetropia is triggered by a shorter axial length, and that the refractive error relationship was absent between children with DS and their family members due to the inconsistency in the developmental delay amongst the children. If the axial length is hypothesised to be related to the stature of children with DS, then children who are shorter will have a shorter axial length and, therefore, higher hypermetropia. This relationship was investigated and is presented in *Chapter Five*. The confirmation of this hypothesis will help explain the aetiology of refractive errors in children with DS.

Chapter Five: The relationship between ocular axial length, refractive error and body height in children with Down's syndrome

Chapter Five: The relationship between ocular axial length, refractive error and body height in children with Down's syndrome.

5.1 Introduction

Familial refractive errors do not influence those of children with Down's syndrome (DS) (*Chapter Four*). We proposed that the reason for such refraction development is the variation in general development rate amongst the children. The anatomical reasons that account for refractive error development are well established and it is widely accepted that ocular axial length forms an important basis for refractive error formation. It is consistently presented that there is a link between ocular axial length, refractive error and body height in typically developing individuals. Should such a relationship exist in individuals with DS, the abnormal refractive development of this population might be better understood. The literature that links these three aspects will be presented for both individuals with, and without, DS.

5.1.1 The relationship between refractive errors, ocular axial length and body height in typically developing individuals

Many studies confirm an anatomical relationship between ocular axial length and refractive errors; finding larger axial lengths for myopic eyes and shorter axial length for hypermetropic eyes, with the axial length being larger for higher myopia and shorter for higher hypermetropia (Cegarra *et al.*, 2001; Ojaimi *et al.*, 2005b). This suggests that axial length is the basis of refractive error (Strang *et al.*, 1998; Warrier *et al.*, 2008). Such a relationship also exists within the lifetime of an individual, confirming the axial length basis of refractive error. During emmetropisation,

reduction of infantile hypermetropia is associated with increasing axial length, which is thought to be the prime factor in emmetropisation (Mutti *et al.*, 2005).

During this increase in axial length, and during emmetropisation, the child's height is surely increasing too. After completion of the emmetropisation process, and when there is no significant change in refractive errors, ocular axial length was found to be correlated with body height and weight, rather than with age, in children (Selovic *et al.*, 2005). Similar results have been documented for adults (Wu *et al.*, 2007).

Evidently, the relationship between refractive error and height is not as solid as that between axial length and refractive error, or that between height and axial length. Wu *et al.* (2007) confirmed the presence of a significant, but weak, correlation between refractive error and height, with taller persons having higher myopia than the shorter ones. Other studies did not find such a relationship (Ojaimi *et al.*, 2005a)

The above information presents an association between the three components; refractive error, axial length and body height. The rule of thumb that can be extracted is that, for typically developing individuals at least, the eyes of shorter individuals have a tendency to be of shorter axial length, this in turn causes the eye to be hypermetropic. In contrast, taller individuals tend to have longer ocular axial lengths, which in turn cause axial myopia.

5.1.2 The relationship between refractive errors, ocular axial length and body height in children with DS

It is very noticeable that individuals with DS are generally shorter than individuals without the syndrome (Styles *et al.*, 2002). We also know that most of these children are hypermetropic, and that a major reason for hypermetropia, in

general, is a reduced ocular axial length (i.e. shorter eye) (Woodhouse *et al.*, 1997; Strang *et al.*, 1998; Cegarra *et al.*, 2001). It has been confirmed that individuals with DS have a relatively short ocular axial length (Haugen *et al.*, 2001a). Haugen's group found that the average ocular axial length of teenagers with DS is significantly shorter than that of typically developing controls; however, they failed to find a difference in refractive errors between the two groups. In addition, the refractive error distribution of their sample was unlike that of other studies, including that of our study population (See *Chapter Three*). Nevertheless, a similar relationship was found in another formerly published study, with the refractive error distribution of the study population being very similar to that of ours (Doyle *et al.*, 1998), but unfortunately, the average ocular axial length of the participants was not published.

The differences in height, axial length and refractive error distributions between individuals with DS and individuals without the syndrome are indicative of the likelihood of a relationship existing between refractive error, ocular axial length and body height in this population, similar to that in typically developing individuals. Relationship between axial length and refractive errors was established in teenagers with DS and was found to be comparable to that of the general population (Doyle *et al.*, 1998; Haugen *et al.*, 2001a). However, the relationship between axial length and height and between refractive error and height has not yet been confirmed.

5.1.3 The aim

Our ultimate aim was to understand the reasons behind the abnormal refractive error development in children with DS. It is noticeable that the refractive error distribution is identical to that of typically developing children during infancy, and only differs later during childhood. We also know that the general physical

development in these children follows the same rule; which further supports the following hypothesis. If the relationships between refractive error, body height and ocular axial length exist, the reason for the abnormal refractive development could be attributed to child's hindered general development. This should be characterized by shorter ocular axial length and body height for those with hypermetropia compared to emmetropic or myopic individuals with DS. The findings will help to determine the reasons behind the atypical refractive development in children with DS. This will consequently help in directing research towards approaches for prevention of such development.

5.2 Methods

5.2.1 Study population

Members of the Cardiff Down's Syndrome Vision Research Unit, both original and newer recruits, were invited to participate in this study. The invitation included all of those who attended for a routine eye examination during the course of this particular study.

5.2.2 Procedures

5.2.2.1 Refractive errors

Refractive errors were determined as a part of the clinical consultation using Mohindra near retinoscopy (see *Chapter Two*). Mean spherical equivalent was calculated and used for analysis.

5.2.2.2 Ocular axial length

This was measured using a non-invasive technique; in particular, the IOL Master (Carl Zeiss Meditec). This instrument measures the axial length by using signals from the tear film and the retinal pigment epithelium and presents the results in millimetres (IOLMaster, 2001).

Children were asked to place their head on the instrument's chin rest and were encouraged to gaze at the fixation target. The machine was focused by the examiner and the measurement was made. Static gaze was achieved by encouraging the child to describe the fixation target and answer some questions about it (e.g. *What colour is the light? Can you tell me if it changes in colour?*). Measurements were only accepted when the Signal/Noise ratio (SNR) was equal to or more than 2.0 (IOLMaster, 2001; Olsen and Thorwest, 2005).

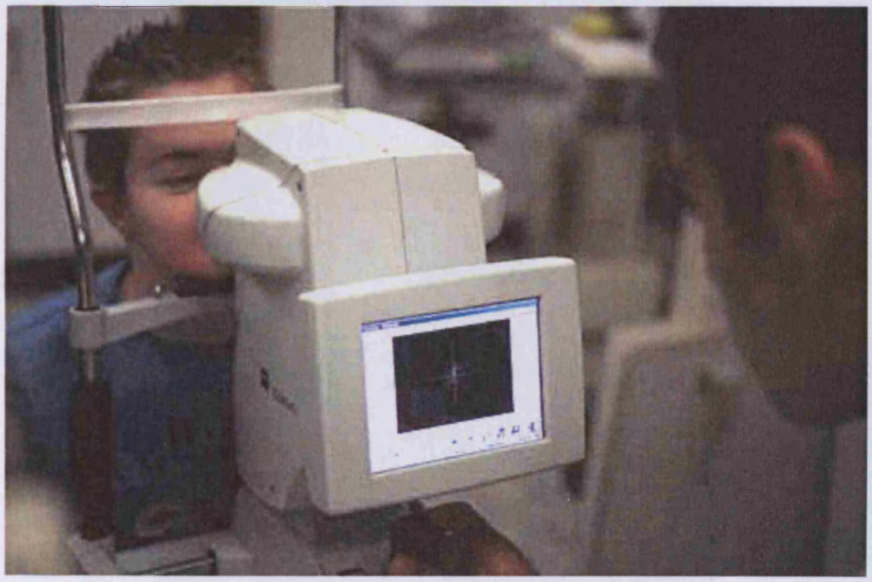


Figure 5.1: Axial length measurment using the IOL Master (Carl Zeiss Meditec) (*Photo by*: Mike O'Carroll, *Child*: Thomas Markwell)

5.2.2.3 Body height

The children's height was measured using a metric chart. They were asked to remove their footwear to obtain an accurate measurement. To control for age and gender, the Down's syndrome growth charts were used. These are charts that were specifically generated by the UK Down's Syndrome Medical Interest Group (DSMIG) based on cross-sectional data from healthy children with DS living throughout the UK and Republic of Ireland (Styles *et al.*, 2002). The outcome was presented as height centiles; a measure that indicate the height of a person in comparison to the age-norm and according to gender. A copy of a detailed example of a DS centile chart can be found in Appendix V.

Figure 5.2: Height measurement (*Photo by:* Mike O'Carroll, *Child:* Emily Morgan) – Note that Emily is lifting her heels; this result was excluded and the measurement was repeated

5.2.3 Order of procedures

The order at which the children performed these tests was in the same order for each participant. Refractive errors were measured first as part of the clinical assessment; axial length measurement was then attempted after the completion of the clinical consultation. When this was successful, the child's height was measured.

5.2.4 Comparisons

The following table summarises the desired comparisons and provides the reasons for each comparison.

Comparison	Reason
MSE and AL	To confirm the axial basis of refractive error
AL and Height*	To assess the effect of relative height on axial length and refractive error
MSE and Height*	
AL and Height**	To assess the effect of physical growth on axial length and refractive error
MSE and Height**	
Age and Height**	To determine whether change in axial length and/or refractive error are related to a difference in age or a difference in body height
Age and AL	
Age and MSE	

Table 5.1: A summary of the comparisons between the variables. MSE; mean spherical equivalent, AL; ocular axial length, * height in centiles, **height in cm

5.3 Results

5.3.1 Study population

Measurements were attempted on a total of 20 participants. Refractive errors were obtainable for all participants. A satisfactory axial length measurement was not

possible for 4 participants and, correspondingly, height was not measured for these 4. This was because the participants did not fixate for a sufficient length of time which halted the collection of an axial length measure with an SNR of 2.0 or higher. The results of these participants were eliminated from analysis. The age range of the 16 participants included in the analyses was 7.73 to 19.15 years (mean = 13.87 years, s.d. = 3.1). Five of these participants were female and 11 were male.

5.3.2 Refractive error

The mean spherical equivalent of the participants ranged from -7.25 to +6.63 dioptres (mean = +0.77D, s.d. = 3.56) for the right eye. The range was identical for the left eye (mean = +0.91D, s.d. = 3.60). The refractive errors of both eyes were strongly correlated (Spearman's rho, $r = 0.995$, $p < 0.001$).

5.3.3 Ocular axial length

The ocular axial length for the right eye was in the range of 20.74 to 28.49 mm (mean = 22.95 mm, s.d. = 2.01), and between 21.30 and 29.1 mm for the left eye (mean = 23.33 mm, s.d. = 2.22). Similar to refractive error, there was a strong significant correlation between the axial length of both eyes (Spearman's rho, $r = 0.961$, $p < 0.001$).

5.3.4 Body height

Absolute body height was in the range of 110 to 162 cm. However, since age and gender have implications on the children's height, DS specific centile charts were used and the children's height fell between the 2nd and the 99.6th centile (mean =

56.1th, s.d. = 36.57). This indicated that our population are representative of a population of children with DS.

5.3.5 Correlations

Because the correlation was strong between the two eyes with regards to mean spherical equivalent and axial length, only data from the right eye were used. Data were tested for normality using the Shapiro-Wilk test. Mean sphere, age and absolute height were normally distributed (Shapiro-Wilk, p = 0.12; p = 0.97; p = 0.43 respectively), however, axial length and centile distributions deviated from normal (Shapiro-Wilk, p = 0.027; p = 0.02, respectively). Therefore, non-parametric statistical tests were performed, particularly Spearman's Rank Order Correlations. In correlations, significance levels are thought to be of less value especially with small study populations. Hence, the percentage of variance was also calculated. This figure explains the amount of variance each 2 variables share (Pallant, 2007). The correlation coefficient and the percentage of variance for each comparison are presented in Table 5.2. Normative data from previously published studies are also included.

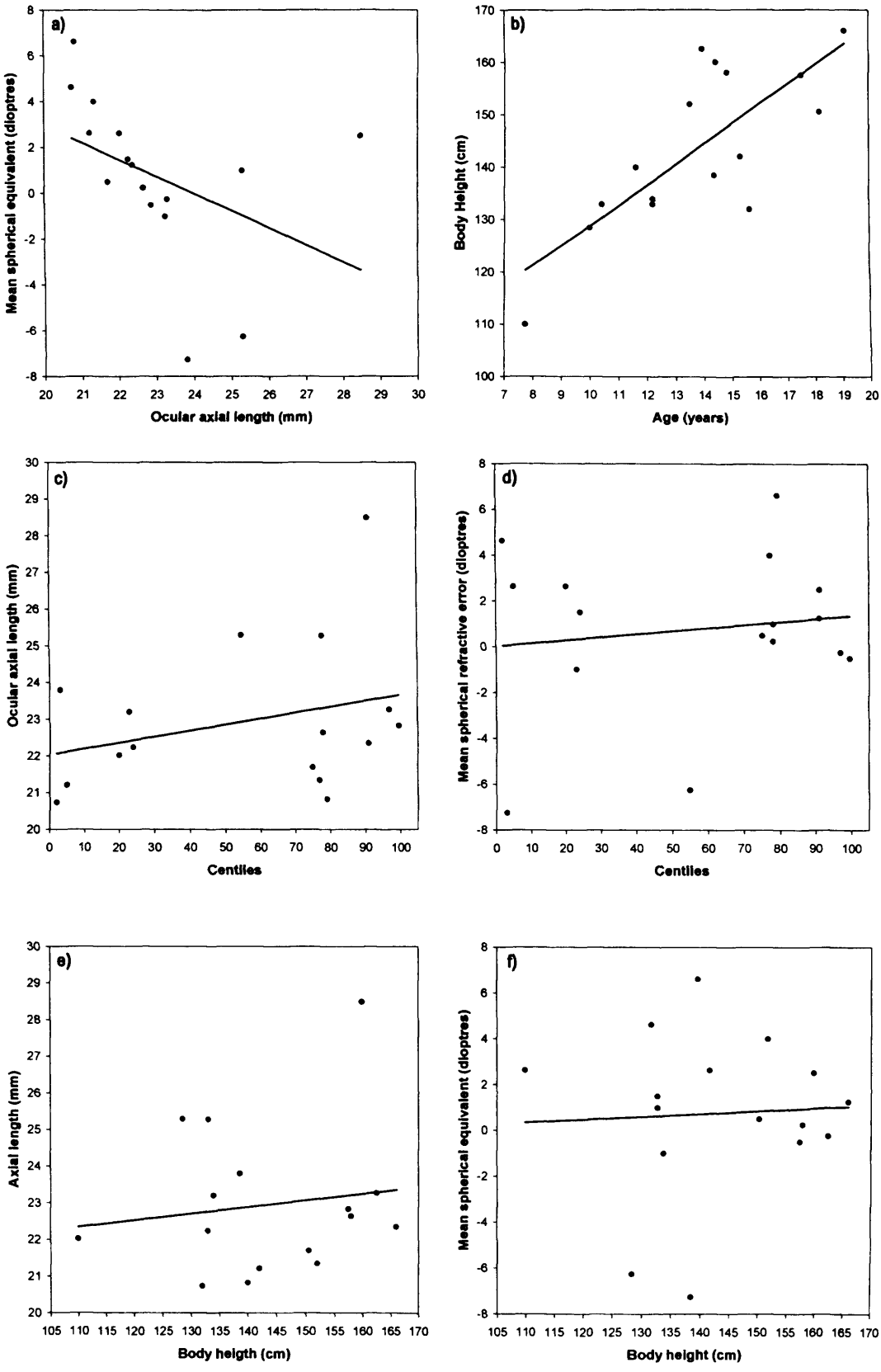
	Centile	Height	Age	Axial length
Mean sphere	-0.116 (1.3%) -0.031*[1]	-0.074 (0.54%)	-0.031 (0.09%)	-0.723* (52.27%) -0.438*[3]
Axial length	0.322 (10.36%)	0.119 (1.41%) 0.252*[2]	-0.226 (5.10%) 0.082*[2]	——
Height	0.723* (52.27%)	——	0.639* (40.83%)	0.119 (1.41%) 0.252*[2]

Table 5.2: Data from the Spearman's rho correlation coefficient. *Correlation is significant at the 0.01 level (2-tailed). Percentages in brackets are percentage of variance. Data in red are comparative data for typically developing children from the following studies: 1 Saw et al (2002a), 2 Ojaimi et al (2005a) and 3 Ojaimi et al (2005b)

The strong negative correlation between the mean spherical equivalent and the ocular axial length indicates that participants with longer eyes had more myopia / less hypermetropia in comparison to those with shorter axial length. The percentage of variance indicates that axial length help explain 52.27% of the refractive error cases. Figure 5.3a shows the relationship between axial length and spherical equivalent in more detail. It shows a dramatic shift of mean sphere towards myopia with increasing axial length. However, neither the children's centiles, nor their absolute height correlated significantly with either their mean sphere or their axial length. Clearly, there is a moderate positive relationship between the child's centile and their axial length (i.e. taller children had larger axial length) and a weak negative one with their refractive errors (i.e. taller children were less hypermetropic / more myopic). Although both are not statistically significant, it is suggested that the absence of statistical significance can be neglected in small sample sizes (Pallant, 2007). Moreover, the percentage of variance shows that centile explained the axial length in 10.36% of the participants, but explained refractive errors of only 1.3% of the participants. Similarly, age and axial length correlated negatively, but not

significantly. Nevertheless, there was a strongly significant positive correlation between the absolute height and the age of the participants, with a respectable percentage of variance.

It can be seen from the results of the Spearman's rho that age and absolute height were strongly correlated. However, neither correlated significantly with ocular axial length, with both showing minimal variance (Figure 5.3b). A graphical display of the relationship between the children's centile and their ocular axial length (Figure 5.3c) and their mean spherical equivalent (Figure 5.3d) shows a weak relationship between the variables. There is a wide spread of the data points in both graphs. Figure 5.3 e and g show the relationship between axial length and height, and between axial length and age, respectively. There is a very noticeable, expected, increase in height with age. However, both figure 5.3 e and g show a very minimal change of axial length with either height or age. The same applied to the effect of body height and age on the mean spherical equivalent (Figure 5.3 f and h).



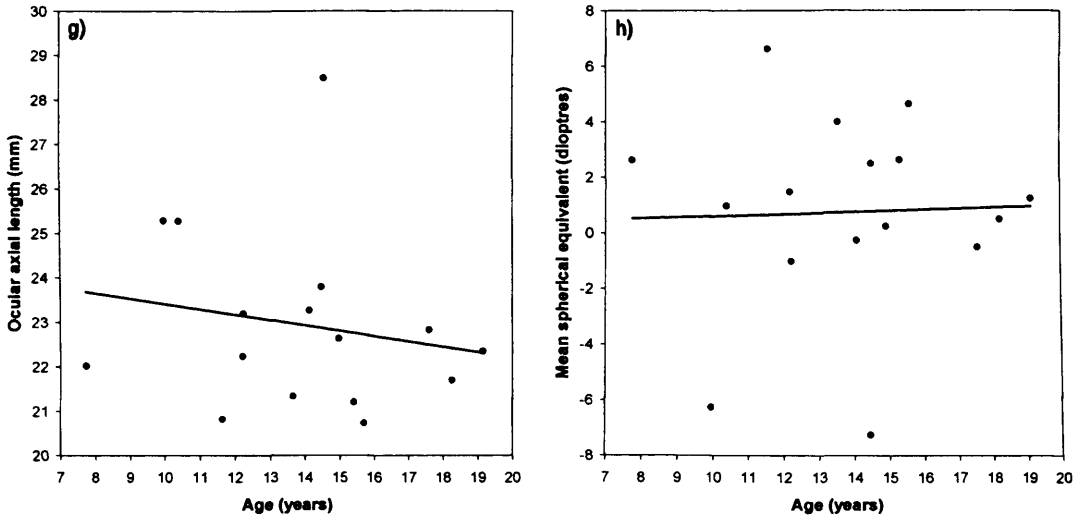


Figure 5.3 (a-h): Scatter plots for comparisons between the different parameters for 16 children with DS. Linear trend-line (correlations in figure (a) and (b) are statistically significant)

5.4 Discussion

Ocular axial length is a major determinant of refractive error in persons with DS. However, neither relative height nor physical growth seems to actively affect the axial length or refractive error of these individuals.

Ocular axial length is considered a good predictor of refractive errors in people with or without DS. The results of this study were consistent with the literature regarding this finding (Doyle *et al.*, 1998; Haugen *et al.*, 2001a).

In typically developing individuals, it has been shown that axial length increases with age and height, indirectly causing a reduction in the infantile hypermetropia as a part of the emmetropisation process. Mutti et al (2005) followed infants longitudinally between 3 and 9 months of age. They reported an increase in the mean of ocular axial length from 19.03 mm at 3 months to 20.33 mm at 9 months. This was accompanied by refractive error decrease from a mean of +2.16D at 3 months to +1.36D at 9 months of age. This increase was found to be most dramatic up to the age of 9 years, with the increase continuing at a slower pace afterwards (Zadnik

et al., 2003; Zadnik *et al.*, 2004; Mutti *et al.*, 2005). In our population of children with DS, axial length did not correlate with the age of participants in spite of the strong association between their body height and age. This may suggest that, despite the continuing in general growth, eye growth appears to stop earlier than the overall growth.

When adjusted for age and gender, the relative height (centiles) did not show any relationship to either refractive error or axial length. The literature is inconsistent regarding this point in typically developing individuals (see section *5.1.1*). The results from this study showed a moderate positive relationship between axial length and the relative height (i.e. centile) of children with DS, with a reasonable percentage of variance. However, this relationship did not reach statistical significance. Although there is an argument regarding the importance of statistical significance in a small sample size such as ours, we chose to dismiss this result to avoid ambiguities. Also, there is a similar relationship between the axial length and the absolute body height (in cm) in the children; which was stronger than that of axial length and age. This replicated what occurs in typically developing children (Selovic *et al.*, 2005). However, the absence of statistical significance in our results can defy the validity of such results. This indicates that absolute or relative heights (i.e. in cm and in centiles respectively), are very poor predictors of refractive error in DS.

The study had some weaknesses. First of all, the sample size was very small. This may have been the prime cause for the absence of statistical significance in most comparisons. However, even with a small sample, the expected relationship between axial length and refractive error was confirmed. It is noteworthy that the participant with the longest eye was hypermetropic despite the strong negative correlation between axial length and refractive error in the group as a whole. There are factors

other than axial length that contribute in determining refractive error. These factors include corneal power, anterior chamber depth and crystalline lens power and thickness, with axial length as the main determinant (Mutti *et al.*, 2005). Compared to typically developing individuals, crystalline lens power is significantly weaker and corneal power is stronger in people with DS compared to controls (Haugen *et al.*, 2001a; Little *et al.*, 2009b). This study did not account for their contribution to refractive error formation because axial length was found to implement the highest effect on refraction in DS and in controls (Doyle *et al.*, 1998; Haugen *et al.*, 2001a; Mutti *et al.*, 2005). In addition, Little *et al* (2009b) found no significant relationship between corneal and refractive power in children with DS or in controls. However, consideration of these factors may have explained the outliers. Another weakness is the variation in the participants' age. Although height was adjusted for age and gender, ideally, a study population consisting of uniformly aged participants would have enabled a more accurate assessment of the relationship between body height and refractive error, and between body height and axial length. This was not achievable due to the short duration of the study. An implication of such a problem is the possible unknown effect of refractive error development, although it can be argued that this factor can be ignored due to the absence of real age-related change in refraction between such age groups (See *Chapter Three*), and due to the absence of such a relationship in these particular participants (See *Figure 5.3h*).

To conclude, the amount and quality of general growth cannot predict refractive error and, if it does, it has a minimal effect on axial length development in individuals with DS. However, axial length is a strong determinant of refractive error in these individuals. Their refractive error distribution is generally shifted towards hypermetropia. This is accompanied by a generally shorter axial length in comparison

to typically developing individuals. The relationship between the two explains the strong presence of hypermetropia. However, the absence of a relationship between body height and either axial length or refractive error leaves the variation in refractive error distribution in this population unexplained.

Chapter Six: Accommodation accuracy in children with Down's syndrome wearing bifocal spectacles

Chapter Six: Accommodation accuracy in children with Down's syndrome wearing bifocal spectacles

The outcome of this study resulted in the following publication – (Appendix VI):

Al-Bagdady M, Stewart RE, Watts P, Murphy PJ and Woodhouse JM (2009) Bifocals and Down's Syndrome: Correction or Treatment? *Ophthal Physiol Opt.* 29: 416-421

6.1 Introduction

Bifocal spectacles are commonly prescribed as an optical correction for reduced accommodation in presbyopic adults. They are rarely prescribed for children, mainly to control strabismus or to aid near vision in aphakic children. The majority of children with Down's syndrome (DS) are known to have a genuinely reduced ability to focus accurately on near targets; instead, they focus behind the subject of interest. Bifocal spectacles have shown great success in aiding near vision for these children in a clinical trial. As a result, it is now standard practice in our and other clinics to prescribe bifocals for children with DS who have reduced accommodation.

6.1.1 Accommodation

Accommodation, as described in many textbooks such as Goss and West (2002), is the course of action the eye takes to bring near objects into focus to create a clear retinal image by increasing the optical power of the eye's lens. There are several theories behind the mechanism of accommodation, with the Helmholtz theory as the most accepted theory today. This theory states that when viewing a distant object, the ciliary muscle is in its relaxed state, which causes the lens zonules and the suspensory ligaments to pull on the edges of the lens making the lens flatter. This process is aided by the tension from the pressure that the vitreous and aqueous humours apply outwards onto the sclera. In contrast, when viewing a near target, the ciliary body

contracts causing the lens zonules and the suspensory ligaments to relax, allowing the lens to also relax into a convex shape.

The amplitude of accommodation is a measure of the largest power increase which a person can produce in response to a near target to maintain a clear retinal image. This is measured in dioptres (D) and tends to be high during childhood, declining slowly throughout life until the onset of presbyopia, loss of elasticity of the lens, which commonly occurs between 45 to 55 years of age.

Accuracy of accommodation, the ability to focus accurately at a given distance, is also considered to be exact in children (Rouse *et al.*, 1984; McClelland and Saunders, 2004). The accuracy of accommodation decreases with age resulting in a declining ability to accommodate accurately at closer objects with age due to presbyopia (Leat and Gargon, 1996).

6.1.2 Accommodation in children with Down's syndrome

The amplitude of accommodation, and the accommodative response, are considered to be generally adequate in typically developing children, regardless of their refractive error (Mantyjarvi, 1987; Nakatsuka *et al.*, 2005). Hence, they are not commonly examined during a routine eye examination until the onset of presbyopia. However, the situation is different in children with DS. Approximately 80% of children with DS suffer from reduced accommodation accuracy leading the children to focus behind the subject of interest, which is described as lag of accommodation (Woodhouse *et al.*, 1993). Moreover, this lag tends to further increase with age (Woodhouse *et al.*, 2000). Woodhouse *et al.* (1993) suggested that reduced focusing abilities could be tolerated by myopic children with DS, due to the natural close focus of the myopic eye. However, most children with Down's syndrome are

hypermetropic, and Cregg *et al.* (2001) suggested that accommodation is reduced in children with Down's syndrome regardless of their refractive error. In addition, they stated that accommodation tends to further reduce with increasing hypermetropia. Recently, Stewart *et al.* (2007) confirmed the relationship between hypermetropia and reduced accommodation in children with DS and also suggested an association between strabismus and reduced accommodation, both of which are common in children with DS.

6.1.3 Bifocals and children with Down's syndrome

Cregg *et al.* (2001) stated that the amount of accommodative response which children with DS produced did not reflect their maximum amplitude of accommodation. Single vision spectacles cannot adequately improve the children's under-accommodation (Cregg *et al.*, 2001; Nandakumar and Leat, 2009b). Stewart *et al.* (2005) carried out a bifocal trial with these children and found that they, as in a presbyopic adult, improved the image focus when looking through the near add. Therefore, bifocals are now prescribed routinely in Cardiff University Eye Clinic for children with inaccurate accommodation. Furthermore, Stewart *et al.* (2005) found that, unlike presbyopic individuals, accommodation improved, during at least one occasion, while the child was looking through *and over the top* of the bifocal segment. Clinical and parental observation revealed that the children tend to use their bifocal near add less often over time by making an effort to look at near objects via the distance portion of the lens. This was confirmed by clinically observed accurate accommodation amongst these children. This may indicate the possibility of prescribing bifocal spectacles as an active treatment rather than a permanent correction for the defective accommodation often experienced by children with DS.

6.1.4 The aim

The aim of this study was to determine the effect of bifocal spectacle wear amongst children and young adults with DS suffering from reduced accommodative abilities, to provide further guidelines on the prescription and follow-up for bifocal lens wearing individuals with DS, and with the goal of changing the current opinion of using bifocal spectacles from a simple optical correction for reduced accommodation to a treatment for the deficit.

6.2 Methods

6.2.1 Study population

All of the children in the Cardiff Down's Syndrome Vision Research Unit, who attended Cardiff University Eye Clinic regularly and were prescribed bifocal spectacles, were invited for participation (original cohort = 47, newer recruits = 12; total n = 59). The inclusion of the newer recruits, who are biased towards having significant refractive errors and reduced accommodation, did not affect the results of this study because reduced accommodation is the only criterion for inclusion in the study. Prescription and dispensing of bifocals was determined purely on the presence of clinically confirmed reduced accommodation. Distance vision was fully corrected and a bifocal add of +2.50 D was prescribed for all of the children presenting with an accommodative lag that was higher than that of typically developing children, as described by McClelland and Saunders (2004). The fixed amount of near add was determined previously by Stewart (2003), after taking into account the habitual working distance and the average accommodative lag of children with DS. Accommodation measurements for this study were performed by JM Woodhouse, M Al-Bagdady and RE Stewart. Bifocals were prescribed for some children before the

commencement of this study and during its course for others. In compliance with the study protocol, measurements were conducted during the children's routine eye examinations.

6.2.2 Procedures

Accommodative accuracy was measured routinely in children from the cohort using a Modified Nott dynamic retinoscopy technique, which has been fully described and validated by previous studies (Woodhouse *et al.*, 1993; McClelland and Saunders, 2003) (See section *2.2.2*). Accommodation was measured at three distances; 10, 16.7 and 25 centimetres, i.e. 10, 6 and 4 Dioptres, respectively. The target consisted of an internally illuminated cube with *child friendly* black line-pictures drawn on the outer walls of the cube. The size of the cube was 35 mm. The size of the detail ranged from 0.4 mm to 5.2 mm; angular substense ranged from 0.23° to 2.96° when the cube was at 10 cm from the eye, and from 0.09° to 1.18° when the target was at 25 cm from the eye (Cregg *et al.*, 2001). This variation showed no effect on accommodative response in children with DS (Woodhouse *et al.*, 2000). Both studies, as well as the present study, used the same cube with the same cohort of children. Accommodation was measured while the child looked at the target both through the bifocal reading segment, and through the distance part of the bifocal lens. Accommodative response at the three distances was used to calculate the accommodative lag before, during and after wearing bifocals. Data for all of the children who were prescribed bifocals were recorded for the visit when bifocals were first prescribed (baseline visit) and for either their latest visit or the visit when bifocals were discarded (for those who developed accurate accommodation). Accommodation was also noted for the latest follow-up visits for those who returned to single vision spectacle wear, in order to evaluate the

sustainability of accurate accommodation after the bifocal treatment. The age of the participants, the gender, visual acuity, the presence of strabismus and the refractive error (mean sphere, right eye) were also recorded for the day of prescription of bifocals. Visual acuity was measured by age and ability appropriate clinical tests. These were Kay Pictures (LogMAR version) or Keeler LogMAR letter test; both used at 3 meters. Jones *et al.* (2003) has shown equivalence between the two tests in typical children. Refractive error was measured using Mohindra near retinoscopy (See *Chapter Two*). Data analysis was performed using the SPSS data editor version 16.0 (SPSS Inc., Chicago, USA) and the graphs were produced using Microsoft Excel.

6.2.2.1 Accommodative responses before and after wearing bifocal spectacles

The following protocol was used to determine *accurate* and *improved* accommodation through *both* the bifocal segment and the distance portion of the bifocal (or through single vision lenses). Accommodation was considered *accurate* when the lag was less than or equal to the following values in at least 2 of the 3 distances: 2.50D lag at 10D demand, 0.74D lag at 6D demand and 0.30D lag at 4D demand. These values are the age-related norms of school children aged 4 to 15 years (McClelland and Saunders, 2004). *Improvement* in accommodation was defined as a reduction of lag for at least 2 of the 3 distances by 1.34D at 10D demand, 1.09D at 6D demand and 0.56D at 4D demand *when the child looked through the distance part of the lens*. These criteria were determined by considering the repeatability of the technique (which determined the presence of a 'real' change in accommodation) (McClelland and Saunders, 2003). Age, gender, visual acuity, refractive errors and the presence of strabismus were compared between children with improved accommodation and those who did not show improvement. These factors were also

compared between those who achieved *accurate* accommodation and those whose accommodation showed *improvement only* according to the previously described criteria.

6.2.2.2 Accommodative responses before wearing bifocal spectacles

The development of the accommodative responses of the children before wearing the bifocals was evaluated. The accommodative lag of the children whose accommodation had improved was collected from their clinical records from the earliest eye examination at which their accommodation was measured, and then compared to that measured on the day of bifocal prescription. Accommodative Error Index (AEI) was used to present these data. This allowed for the inclusion of a higher number of participants as accommodation measurements were not available for the three testing distances at both visits in some instances (e.g. accommodation measurement available at 10D and 6D at the first visit and at 6D and 4D at bifocal prescription visit). Using the criterion described earlier (Section *6.2.2.1*) comparisons between the two visits cannot be made. On the other hand, AEI can be calculated using values from the regression line between the two available points at each visit and therefore allows for a comparison between the accommodative responses during the two visits (See section *2.3.2*).

6.2.2.3 Accommodative responses after returning to single vision spectacles wear

Children with accurate accommodation were returned to single vision spectacles when appropriate (i.e. when there was a significant distance refractive error). Their accommodation was recorded during a follow-up visit to evaluate the

sustainability of accurate accommodation after returning to single vision wear. The same criteria were used to determine change in accommodation (See section *6.2.2.1*).

6.2.2.4 Handling missing data

Accommodative responses were measured at three distances. In line with Stewart *et al.* (2005), when AEI was used and accommodation measurement was not available for one out of the three distances, AEI was calculated using values taken from a regression line between the two available points. The unavailability of the data was either due to poor compliance of the subject or the accommodative response being off the scale of the ruler, which hindered accurate measurement. In previous studies, such as Stewart *et al.* (2005), AEI was calculated only when the correlation coefficient (r^2) $\geq$ 0.80. However, this could not be applied to this study due to the small number of subjects. Instead, when two of the three measurements were off the scale of the ruler, the definitions of *improvement* in accommodation and *accurate* accommodation, described previously, were used to analyse the data.

For the purpose of graphical demonstration, when accommodative lag was off the scale of the ruler, it was recorded as if it was at the end of the measuring ruler. For example, accommodative lag was assumed to be 9D when the demand was 10D and the child's focus point was off the scale of the ruler, given that the ruler length is 1 meter. This resulted in a slight under-estimation of the child's actual accommodative lag in the graphs.

6.3 Results

6.3.1 Study population

The total number of participants who were prescribed bifocals was 59. Seventeen children were excluded due to the non-availability of accommodation measurement after the day of bifocal prescription. This was because the children were not due to attend for an eye examination before the deadline of this study (n = 16) or gave poor co-operation during the follow up visit (n = 1). The final number of participants was 42, of which 29 were male. The age ranged between 4.66 and 14.64 years on the day of bifocal prescription (mean = 8.73, s.d. = 2.60). Accommodation measurement was obtainable for all 42 subjects through the distance portion of the lens and through the bifocal segment.

6.3.2 Accommodation through the near bifocal add

Accommodation was *accurate* in 40 subjects (95.2%) when looking through the near add of the bifocals. (In some cases, this was not the latest visit, but the latest at which the child brought their bifocal spectacles). The remaining 2 subjects showed *improvement* in accommodation through the near add.

6.3.3 Accommodation through the distance vision lens

Table 6.1 shows the accommodative lag of all participants during the visit of bifocal prescription and during the child's latest visit with bifocal spectacles. All of the accommodation measurements presented were taken when the child looked through the *distance* portion of the lens.

Twenty-nine out of 42 children (69.04%) showed an improvement in accommodation through the distance portion of the lens; Figure 6.1 shows the mean

accommodative lag during the baseline visit and during the latest visit for the 29 children with improved accommodation. It can be seen that the average of the accommodative lag for these 29 reached the age norms at all three distances during the latest visit (although not all individuals reached the age norms). Data for the 13 children whose accommodation did not show improvement according to our criteria are presented in Figure 6.2.

Subject Number	Age on Prescription (Years)	Accommodative Lag (Dioptres)			Age on Follow-up (Years)	Accommodative Lag (Dioptres)		
		10D	6D	4D		10D	6D	4D
Subjects that developed *accurate* accommodation								
1	13.73	6.00	OS	OS	15.49	0	0	0
2	7.87	2.31	1.12	1.06	10.04	0	0	0.55
3	9.42	4.44	2.43	1.62	12.32	1.67	0	0.15
4	9.15	4.44	2.43	1.50	11.74	0	0.12	1.06
5	7.41	5.65	3.67	2.00	15.42	0	0	0
6	9.65	6.43	3.62	2.39	12.32	2.31	0.44	0
7	10.54	3.75	1.65	0.30	13.67	1.67	0.12	0.30
8	7.80	3.33	2.30	1.50	9.84	3.75	0	0
9	8.20	2.86	2.15	0.67	12.58	0	0.12	0
10	14.33	OS	OS	OS	17.99	NA	0	0
11	6.28	6.77	3.87	2.34	11.62	0	0	0
12	5.85	7.44	3.83	2.70	13.64	1.67	0.12	0
13	10.63	4.45	2.00	0.97	15.90	1.67	1.00	0
14	5.92	3.34	2.55	1.83	10.50	0	0	0
15	6.50	6.30	3.67	1.92	10.35	0	0.44	0
16	4.66	5.24	2.77	2.11	5.78	0	0	0
17	14.64	3.33	1.24	0.67	15.65	0	0	0
Subjects with *improved only* accommodation								
18	9.26	OS	OS	OS	11.87	3.34	1.45	0
19	9.27	6.67	4.44	OS	16.64	4.45	2.30	1.23
20	13.79	6.97	3.78	2.08	15.27	1.67	1.24	0.55
21	8.10	OS	3.83	OS	10.36	4.12	1.45	1.14
22	4.96	4.12	3.14	1.92	8.31	1.67	1.24	0.77
23	13.81	5.00	3.67	OS	15.93	3.34	0.12	NA
24	12.59	7.62	4.11	2.51	17.33	4.74	1.45	0.77
25	6.88	6.88	4.15	2.65	8.36	4.74	2.77	1.92
26	6.69	6.15	2.77	1.62	11.64	1.67	1.24	1.06
27	9.17	5.65	3.14	2.04	12.70	3.75	1.24	1.30
28	6.62	6.30	3.62	2.39	11.65	4.12	2.43	1.06
29	6.22	4.74	2.15	0.67	8.04	2.86	1.00	0.43
Subject with no *improvement* in accommodation								
30	7.14	6.67	3.73	OS	9.27	8.21	OS	OS
31	9.42	2.31	2	1.83	13.13	2.86	1.83	1.06
32	11.34	3.75	2.88	1.56	13.70	1.67	2.67	1.67
33	8.03	4.44	2.67	1.92	13.12	7.50	3.78	2
34	6.25	6.30	2.30	1.67	9.11	6.67	3.50	OS
35	6.02	4.12	2.88	1.78	8.45	5.65	3.50	OS
36	9.44	3.75	1.24	0.88	11.93	6.43	2.43	1.22
37	7.67	4.12	2.67	1.83	8.67	5.65	2.43	1.61
38	7.51	5.65	2.55	1.92	9.93	6	3.06	1.22
39	7.02	3.75	0.44	0.43	14.36	3.34	1	0
40	9.35	3.55	2.15	1.37	14.19	4.44	2.15	1.37
41	9.55	3.10	2.67	1.37	11.52	5.24	2.77	1.92
42	8.07	3.75	1.83	2.08	13.82	3.75	2.29	1.37

Table 6.1: Accommodative lag with fully corrected distance vision for the total number of subjects during initial assessment and follow up. (OS = off scale; N/A = accommodation was not measured)

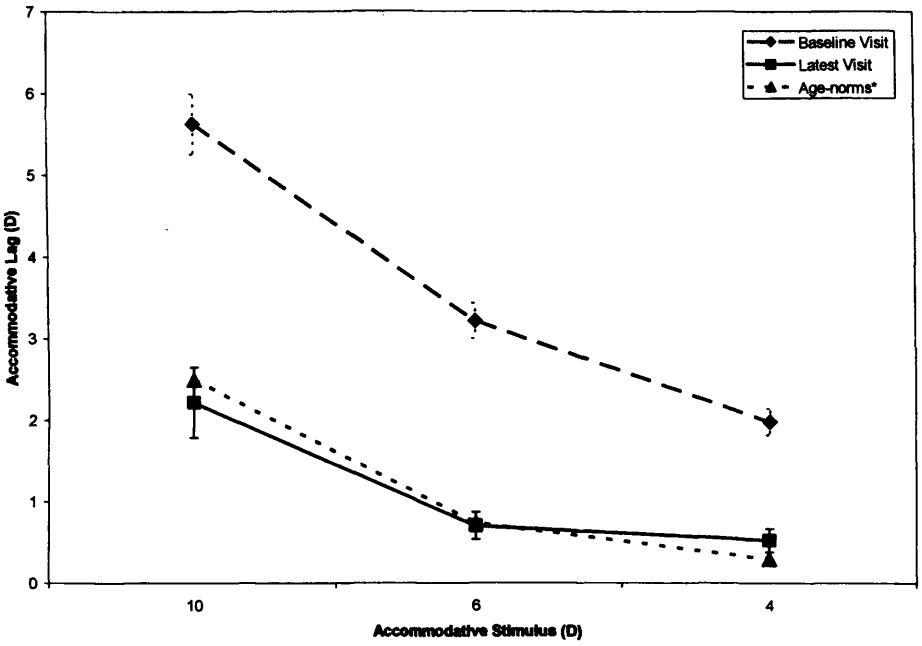


Figure 6.1: Accommodative lag during baseline visit and during follow up visit for children with improved accommodation (n=29). Data points indicate the mean accommodative lag at each testing distance in dioptres and error bars represents standard error. *Age norms for accommodative lag for school age children (McClelland and Saunders, 2004).

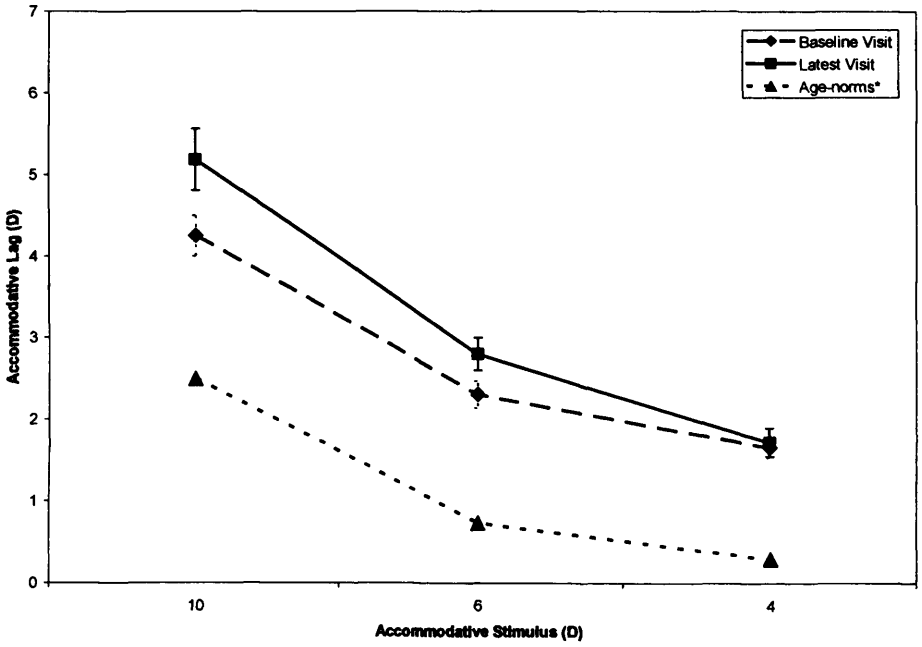


Figure 6.2: Accommodative lag during baseline visit and during follow up visit for children with no accommodation improvement (n=14). Data points indicate the mean accommodative lag at each testing distance in dioptres and error bars represents standard error. *Age norms for accommodative lag for school age children (McClelland and Saunders, 2004).

Seventeen out of the 29 children with improved accommodation had accurate accommodation and all were returned to single vision wear, *if needed*. This accounts for 40.47% of the overall number of children included in this study. Follow-up intervals for all children varied between 1 and 8 years between bifocal prescription and latest visit with bifocals (Mean = 3.5 years).

Table 6.2 shows the follow-up interval for children with improved accommodation, distinguishing those who developed accurate accommodation from those who only improved their accommodation, and for those whose accommodation did not show any improvement.

Group		Number of children	Follow up interval (mean, SD)
Children with *Improved* accommodation	*Accurate* accommodation	17	3.56, 2.08
	Improvement only	12	3.39, 1.80
Children with *no improvement*		13	3.41, 1.81

Table 6.2: The mean and standard deviation of the duration between bifocal prescription and the latest visit for all groups of children (in years)

6.3.4 Accommodation after ceasing bifocal wear

Six participants were seen for a follow-up assessment after returning to single vision spectacle wear. All of these participants showed sustained accurate accommodation. Follow-up time ranged from 1.53 to 5.29 years (Mean = 3.69 years).

6.3.5 Effect of age on accommodation before the commencement of bifocal wear

The accommodative lag of the children whose accommodation had improved after bifocal wear was collected from their clinical records, from the earliest eye examination at which their accommodation was measured, and compared to that measured during the visit when bifocals were prescribed. Data were available for 16

children only. The remaining 13 children joined the study with a specific parental interest in bifocals. For these, reduced accommodation was confirmed and bifocal spectacles were prescribed at first consultation.

In the previous section, repeatability of dynamic retinoscopy was used to determine improvement in accommodation. However, Accommodative Error Index (AEI) was used for this section to maximise the number of participants (see section *2.3.2*). When calculating AEI, the correlation coefficient (r^2) was < 0.80 for only 1 (r^2 = 0.64) out of the 16 subjects, but was included in the results due to the small sample size. A paired-samples t-test to evaluate the accommodative responses of children before going into bifocals showed no statistically significant difference between the accommodative response during the first accommodation measure (mean = 4.25D, s.d. = 1.14) and the responses measured on the day the bifocals were prescribed (mean = 3.83D, s.d. = 0.67), [t(14) = 1.206, Sig. (2-tailed) = 0.248]. This analysis included 15 out of the 16 children. The remaining subject was not eligible for inclusion in the analysis due to the accommodative response being off the scale of the ruler for two of the three distances. This child, ID 21 (See *Table 6.1*), did not show any accommodation improvement before bifocals were worn. The child's accommodative lag was 4.12D, 1.84D and 1.15D when measured at 10D, 6.7D and 4D, respectively, during the first visit. The lag of accommodation had increased when measured on the bifocal prescription date leaving the subject focusing beyond the length of the ruler, when looking at the 10D target and 4D target. However, the response was 3.83D for the 6.00D target.

The range of time difference between the two accommodation measurements for the 16 children was 0.15 to 9.61 years (mean = 5.27 years, s.d. = 2.87). Figure 6.3

shows the accommodative lag of the 16 children at the 2 visits. It is clear that there was no accommodation improvement with age before bifocals were worn.

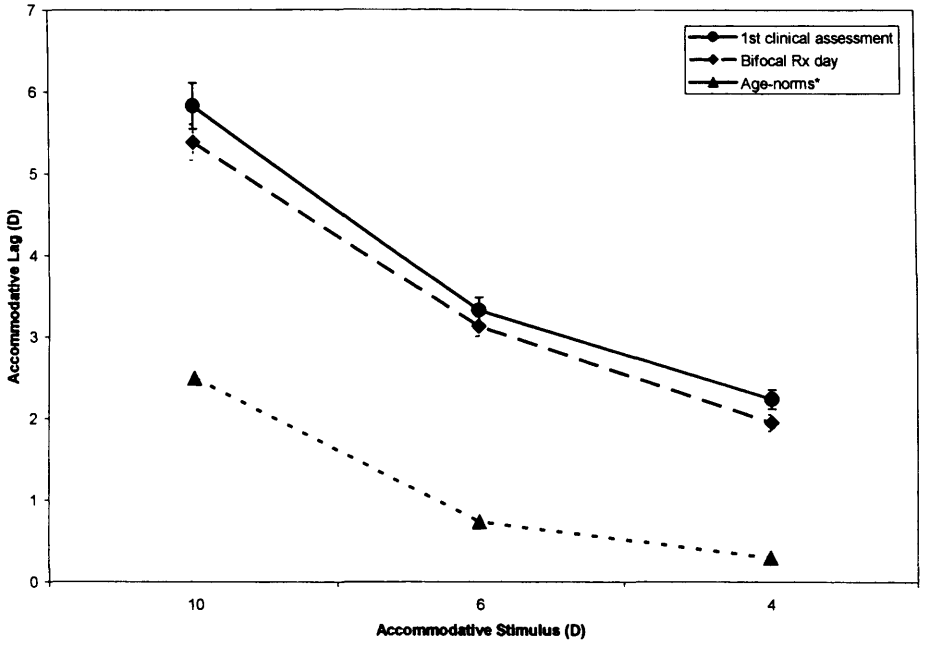


Figure 6.3: Accommodative lag during 1st clinical assessment and bifocal prescription visit for 16 children with improved accommodation. Data points indicate the mean accommodative lag at each testing distance in dioptres and error bars represents standard error. *Age norms for accommodative lag for school age children (McClelland and Saunders, 2004).

6.3.6 Comparisons between the two groups of children

Age, gender, visual acuity, refractive error and presence of strabismus, all on the day of bifocal prescription, were compared between children with improved accommodation and those with no improvement. The results of an independent samples t-test indicate no significant difference between the 2 groups in age [t(40)= 0.857, Sig. (2-tailed)= 0.396], refractive error [t(40)= -1.011, Sig. (2-tailed)= 0.318], or in visual acuity [t(40)= -0.362, Sig. (2-tailed)= 0.719]. The results of Chi-squared tests showed no significant difference in the presence of strabismus ($p = 0.41$) or in gender ($p = 0.46$) between the 2 groups.

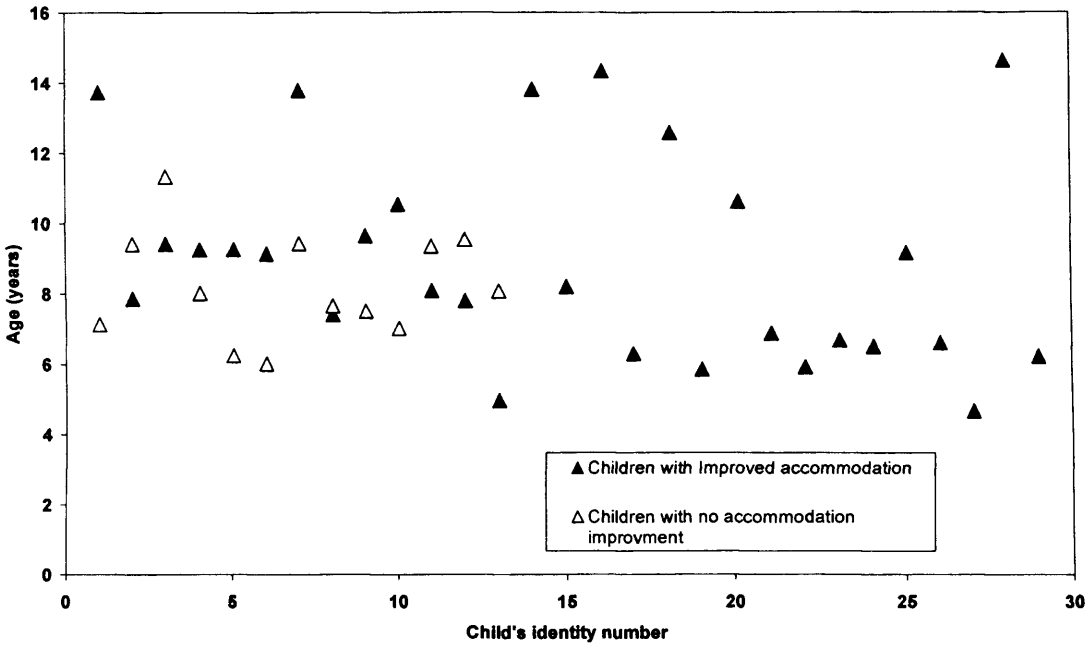


Figure 6.4: Age distribution of children with improved accommodation after bifocal wear (filled triangles, n=29), and children with no improved accommodation (n=13)

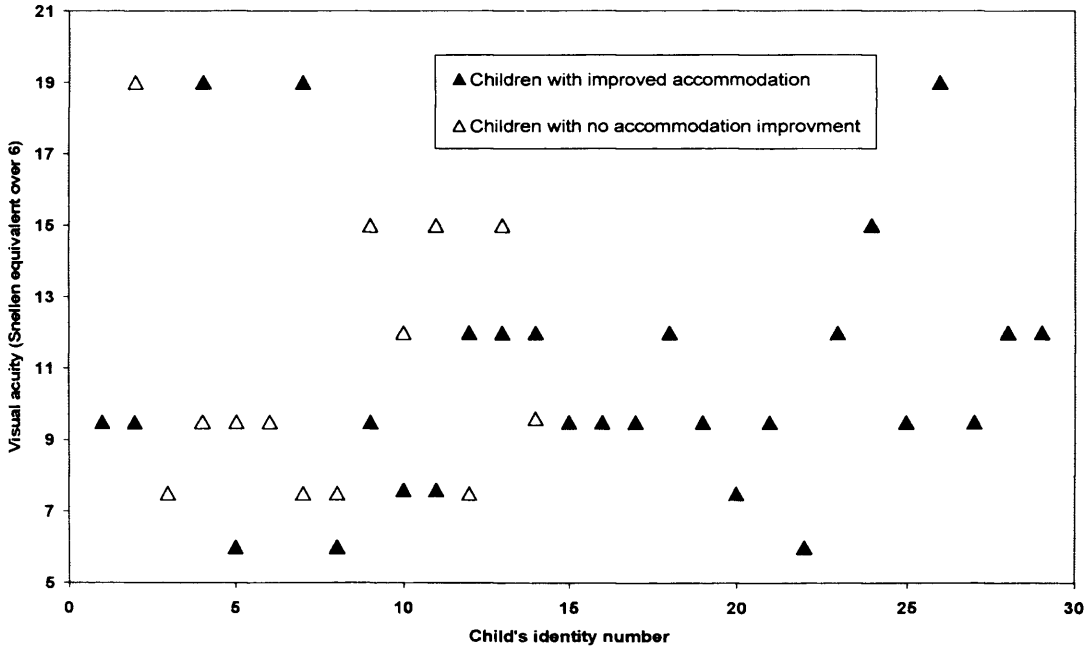


Figure 6.5: Visual acuity distribution of children with improved accommodation (filled triangles, n=29), and children with no accommodation improvement (n=13)

Figure 6.4 shows the age distribution of each group of children on the day of bifocal prescription and figure 6.5 shows their visual acuity distributions. The figures show that both parameters are equally variable in the 2 groups of children.

Children with improved accommodation were divided into 2 sub-groups; children with *accurate* accommodation and children with *improvement only*. The previous analysis was repeated and the results of an independent samples t-test showed the absence of a statistically significant difference in age [t(27) = 0.027, Sig. (2-tailed) = 0.978] or refractive error [t(27) = -0.147, Sig. (2-tailed) = 0.884]. However, it revealed that those who achieved accurate accommodation had better visual acuity (mean = 6/9.35) than those with improved-only accommodation (mean = 6/12.46) on the day of bifocal prescription [t(27) = -2.512, Sig. (2-tailed) = 0.018]. The results of a Pearson Chi-square test indicated that boys had a significantly higher chance of gaining accurate accommodation than girls. Fifteen out of the 17 children who gained accurate accommodation were boys (p = 0.002). However, there was no statistically significant difference in the presence of strabismus between the two groups (p = 0.35).

6.4 Discussion

Accommodation through the bifocal segment was accurate in 95% of the participants, and improved over the top of the bifocal segment in the majority of the children while wearing bifocal spectacles. Other factors that may influence accommodation, such as strabismus or refractive error cannot account for the improvement in accommodation. Over 40% of all children prescribed bifocals achieved accurate accommodation when looking over the top of the bifocal. These children have returned to single vision spectacle wear and all of these reassessed, so

far, have sustained accurate accommodation. Hence, bifocal spectacle wear can be temporary and can be considered a 'treatment' for the reduced accommodation often experienced by children with DS. It remains to be seen, when children have worn bifocals for longer, whether more children will be able to return to single vision spectacle wear. It also remains to be seen whether children returning to single vision wear can maintain accurate accommodation over the long term.

Accommodation is reduced in most children with DS (Woodhouse *et al.*, 1993; Cregg *et al.*, 2001; Haugen *et al.*, 2001b) and this is confirmed by the high accommodative lag of the children before wearing the bifocals (see *Figure 6.3*). Reduced accommodation is mainly associated with the presence of hypermetropia and strabismus (Stewart *et al.*, 2007), both of which are very common amongst children with DS. This higher incidence of strabismus in DS raises issues regarding the accommodative status of this population. Accommodation usually increases with convergent strabismus (vergence accommodation) (Fincham and Walton, 1957; Bobier et al., 2000). Rather, there may be an abnormal link between the two; it is hypothesised that strabismus may have occurred at higher rates in DS due to their weak accommodation (Haugen and Hovding, 2001). They suggest that children apply higher accommodative effort in an attempt to compensate for the accommodation weakness, which causes convergence, in a process similar to that followed by some uncorrected typically developing hypermetropic children. However, neither refractive error nor presence of strabismus affected the chances of benefiting from the bifocal treatment. This encourages the prescription of bifocals at younger age. This may prevent the occurrence of strabismus in under-accommodators, which in turn may prevent amblyopia and anisometropia and may encourage better emmetropisation (Mutti *et al.*, 2009). Accommodation remains reduced in children with DS even when

the distance refractive error is fully corrected by the means of single vision spectacles (Cregg *et al.*, 2001; Nandakumar and Leat, 2009b). The finding that the accommodative lag is consistent indicates that the prescription of separate single vision spectacles, for near and for distance, might not improve the children's own accommodative responses, and it also challenges their benefit as an optical correction for near targets. In addition, single vision spectacles for near are not suitable because children need clear images at distance and near simultaneously for schoolwork. Bifocal spectacles are a very successful method of improving near focusing in children with DS both through the near add and through the distance portion of the lens (Stewart *et al.*, 2005). There is excellent tolerance and acceptance from the children, their carers and their educators, and no adverse reactions were reported (Stewart *et al.*, 2005).

Reduced accommodation results in a blurred near image which can reduce near visual acuity considerably. This was confirmed by Nandakumar and Leat (2009b) and supports the improvement in academic achievement parents and educators often reported after bifocal prescription. This aspect was confirmed by Nandakumar and Leat (2009a). This was shown as a reduction in time when performing writing and reading tasks accompanied with a rise in scores.

Age, cognitive abilities and target size cannot account for any improvement in accommodation in children with DS (Woodhouse *et al.*, 2000). This, in addition to the diversity of the children's ages on bifocal prescription, suggests that the likelihood of improvement in accommodation is not affected by the age of the child on the commencement of bifocal wear. Accommodation did not improve adequately before bifocals were prescribed in our sample. Thus, the improvement in accommodation appears solely due to the bifocal wear. There is no demonstrable difference between

the children who improve in accommodation and these who do not, so at present this improvement is unexplained. However, there seems to be a higher chance of gaining accurate accommodation for children with better distance visual acuity.

Figure 6.1 shows that the mean accommodative lag of children with DS who showed accommodation improvement reached that of typically developing children (McClelland and Saunders, 2004). There is, however, variation in accommodative lag in both typically developing children and children with DS with improvement in accommodation, so that not all children within the normal range would be described as accurate according to our criteria. Therefore reaching accurate accommodation is not a necessity to accomplish a parallel accommodative ability to that of typically developing children. However, reaching accurate accommodation was associated with better visual acuity. Children with better visual acuity have a higher chance of gaining accurate accommodation, or at least arrive at it faster than those who only showed improvement in accommodation. The clearer retinal image may be the force that drives this improvement in accommodation. Also, gaining *accurate* accommodation showed a very high association with gender, with the vast majority of those with accurate accommodation being boys. This difference in behaviour between genders is currently unexplained.

There were two weaknesses in this study that prohibited the provision of guidelines regarding the duration of bifocal wear before accurate accommodation can be expected. Table 6.2 provides the length of time between prescription and latest visit for those whose accommodation improved. This is however of limited value because the children were only seen during their routine eye examination, when measurements of accommodation were obtained. The onset of accurate accommodation could have occurred prior to a clinical appointment. Another

limitation was the unavailability of information regarding daily bifocal wearing time. This may have influenced the chances of gaining improvement in accommodation and/or the speed at which children gained accurate accommodation. Both limitations resulted because bifocals were initially prescribed as permanent optical correction without awareness of possible improvement in accommodation (Stewart *et al.*, 2005).

The improvement in accommodation demonstrates that the accommodative deficit in children is unlikely to be mechanical in origin (i.e. it is not presbyopia). The original deficit and the improvement must have a neural basis, as yet not understood. The presence of reduced accommodation in children with DS at a very early stage of their life may account for the abnormal refractive development in these children (Haugen *et al.*, 2001b). This implies that the prescription of bifocals at an early age might help to prevent this abnormal development, since a clearer retinal image will be possible at both near and distance.

In conclusion, bifocal spectacles can be prescribed to children with DS as an active *treatment* for their reduced accommodative responses, with a success rate of nearly 70%. Furthermore, for at least 40% of children there is the possibility of ultimately discarding bifocal wear. In addition, the age and gender of the child as well as their visual acuity, the presence of strabismus and the type of refractive error does not affect their chances of gaining improvement in accommodation. Of those with improved accommodation, males with reasonably good visual acuity seem to be more likely to achieve accurate accommodation. The children in this study were all aged 4 years or older at first prescription of bifocal, and this was initially intended to aid school work. The success rate and benefits of bifocals for younger children are yet to be determined.

Chapter Seven: Colour vision in children and young adults with Down's syndrome

Chapter Seven: Colour vision in children and young adults with Down's syndrome

7.1 Introduction

Defective colour vision is relatively rare. However, its occurrence can result in limitations in occupational and lifestyle choices. More importantly, it can hinder education in children with learning disabilities. This chapter presents a brief review of the most accepted colour vision theory, describes colour vision defects and presents their occurrence within the population. Also, a summary of the most common clinical test methods for colour vision is presented. Although this chapter's aim is to explore the nature of colour vision in individuals with DS, it is important to take the previous information in consideration.

7.1.1 Colour vision theories

Colour vision can be described as the ability to discriminate between objects according to the wavelength of the light they reflect or emit. The human visual range is between the wavelengths of 380 nm and 780 nm (Birch, 1998). However, there are several colour vision theories that have been reported over the centuries, starting with Sir Isaac Newton who first discovered that white light is composed of several colours in the seventeenth century. Several scientists attempted to understand the concept of colour vision and their studies resulted in two main theories; the trichromatic theory and the opponency theory. These are the most accepted theories to date.

Briefly, the most current understanding of the trichromatic theory suggests the presence of three distinct types of photoreceptors, cones, in the human eye. Each of these contains a different photopigment that responds best to a specific wavelength of

light; Long, Medium and Short wavelengths (or red, green and blue light, respectively). Spectral sensitivity curves are measurable for each type of cone and those curves overlap to allow the perception of a range of colours and not only the three primary ones. Evidence for this theory has been provided by several studies. For example, Marks *et al.* (1964) identified three cone pigments. In addition, Nathans *et al.* (1986a) and Nathans *et al.* (1986b) identified gene codes for short, medium and long wavelength cones. However, several aspects are not explained by the trichromatic theory. For example, the theory cannot clarify simultaneous colour contrast or successive colour contrast.

The opponent colour theory is based on subjective colour appearance. The theory states that there are four primary colours (red, green, yellow and blue) and that they are arranged in opponent pairs with red being opposed with green, and yellow being opposed with blue. In addition, there is a third channel in which white is opposed with black. Opponent cells can be either excited or inhibited according to the perceived signal. Evidence for this theory was gained after the observance of opponent colour processes by electrical recordings in many studies (Svaetichin, 1956; De Valois *et al.*, 1966; Gouras, 1968; De Monasterio and Gouras, 1975; Zrenner and Gouras, 1981).

Although both theories are able to answer some of the questions related to the theory of colour vision, each is not viable as a *stand-alone* theory to explain the nature of colour vision. Later studies showed that colour vision is processed in different zones within the visual pathway and that both theories are valid to occur at different stages of the pathway. It is now believed that the trichromatic theory occurs at the stage of photoreceptors in the retina, cones in particular, and colour opponency occurs at the stage of the ganglion cells.

7.1.2 Colour vision defects

Knowing that normal colour vision is the ability to discriminate and distinguish all of the colours in the visible spectrum range, defective colour vision is then failing to do so. It is believed that colour vision defects result from the lack or malfunction of one or more of the three photopigments, or by discolouration of the optical media. Defects can be congenital or acquired and they are of several types. It is very difficult to generalise the causes of acquired defects due to their wide variability. Hence a thorough review of congenital defects will be presented and a short section will be dedicated to present the main reasons for acquiring a colour vision defect. The following information is widely accepted and reported in most textbooks and current reviews such as (Kaiser and Boynton, 1996; Birch, 1998; Neitz and Neitz, 2000; Melamud *et al.*, 2004).

7.1.2.1 Congenital colour vision defects

A) Monochromatic colour vision

In this defect type, colour vision is absent and individuals usually observe differences in brightness rather than in colour. This condition is also called achromatopsia. There are two types of monochromatic defects. Firstly, the typical, or rod, monochromacy occurs when the cones are dysfunctional. This is often associated with reduced visual acuity, photophobia and nystagmus. The second type is called atypical, or cone, monochromacy. According to Melamud *et al.* (2004), individuals with this defect have only one functioning type of photopigments; blue. However, rods dominate vision due to the very small number of blue cones in the retina. Visual acuity reduction is also associated with this type; however it is less severe than in the previous type. Nystagmus and photophobia are also frequently reported in association

with this defect. Rod monochromacy (typical) is considered to be autosomal recessive (Kohl *et al.*, 1998). Cone monochromacy (atypical) is X-linked recessive (Spivey, 1965; Nathans *et al.*, 1989). It is not yet possible to differentiate between the two types with the current common clinical tests (Melamud *et al.*, 2004)

B) Dichromatic colour vision

People with dichromatic colour vision, dichromats, have two functional cone pigments out of the three due to either the loss of one of the photopigment's gene or the non-expression of that gene (Neitz and Neitz, 2000). Dichromats match any colour by using only the two functioning pigments, objects that require the presence of the missing pigment are observed as white, black or gray. There are three types of dichromatic colour vision, and differentiation between the types depends on the missing photopigment. It is possible to differentiate between them clinically. The genetic bases of these defects are presented in Table 7.1:

- ***Protanopia:*** lack of the long wavelength sensitive photopigment (or red gene).
- ***Deuteranopia:*** lack of the medium wavelength sensitive photopigment (or green gene).
- ***Tritanopia:*** lack of the short wavelength sensitive photopigment (or blue gene).

C) Anomalous trichromacy

Individuals with this type have the three photopigments. However, one of them has abnormal absorption characteristics. Hence, the defective photopigment is used in abnormally higher quantities to match white. Severity is variable between

individuals. There are three types of anomalous trichromacy depending on which photopigment is present with abnormalities. Clinical segregation between the types is possible and the genetic bases are shown in Table 7.1.

- ***Protanomaly:*** There is abnormality in the long wavelength sensitive photopigments that results in reduced sensitivity to red light. Protanomalous people are thought to have normal green pigment and normal blue pigment while lacking all of the red pigment. They are thought to have a different 'green-like' pigment instead. Its sensitivity is highest in the region of the spectrum that lies between red and green (Neitz and Neitz, 2000).
- ***Deuteranomaly:*** The abnormality lies in the medium wavelength sensitive photopigment which leads to decreased sensitivity to green light. Deuteranomalous people lack the green pigment and have a pigment that is sensitive to wavelengths that are longer than those that stimulate the green pigment but shorter than those that stimulates the red pigment (Neitz and Neitz, 2000).
- ***Tritanomaly:*** Tritanomalous individuals have reduced sensitivity to blue light. They have an abnormality in the short wavelength sensitive photopigment.

D) Terminology

The terms protan, deutan and tritan are widely accepted and used to describe both dichromatism and anomalous trichromatism. This is mainly because the majority of clinical colour vision tests cannot differentiate between the two. Protan and deutan are described as red-green defects, while tritan is used to describe blue-yellow defects (Birch, 1998).

7.1.2.2 Acquired colour vision defects

The causes of acquired colour vision defects vary considerably. In general, they occur later in life either as a result of aging or environmentally induced effects and are sometimes progressive. They can be a result of optic nerve, macula or visual cortex lesions, or they can result from optical media changes. They can also be induced by drug intake or prolonged exposure to specific wavelengths of light. For this reason, these defects are evenly distributed between males and females. Some causes for acquired defects are cataracts, diabetes, burns and injuries. Some medications can induce a colour vision defect as a side-effect. Alzheimer's disease is also thought to be associated with colour vision defects (Birch, 1998; Kessel *et al.*, 1999; Pache *et al.*, 2003). Classification of acquired defects is very similar to that of congenital defects. However, the difference lies in the names. They are Type I, Type II and Type III; or red, green and blue-yellow respectively.

7.1.3 Inheritance and incidence

Most colour vision defects are said to be inherited and thus congenital. Therefore, incidences vary according to sex. Moreover, each type has a different incidence rate between the two sexes.

Colour vision defects are mostly carried on the X chromosome following the Mendelian inheritance mechanism. This naturally makes males at a greater risk than females. However, some defects can be autosomal. As a general rule, most studies agree that protan and deutan defects are X-linked while tritan defects as well as monochromacy are inherited in an autosomal fashion. Table 7.1 shows the inherited colour vision defects stating their inheritance mechanism and providing the incidence/prevalence of each of the defects.

Colour vision defect		Inheritance mode	Location	Approximate Incidence (%)	
				Male	Female
Monochromatism	Rod monochromatism	Autosomal recessive	Chromosome 2	0.005*	0.005*
	Blue cone monochromatism	X-linked	Chromosome X		
Dichromatic colour vision	Protanopia	X-linked	Chromosome X	1	0.02
	Deuteranopia	X-linked	Chromosome X	1	0.01
	Tritanopia	Autosomal dominant	Chromosome 7	0.005	0.005
Anomalous trichromatic colour vision	Protanomaly	X-linked	Chromosome X	1	0.02
	Deuteranomaly	X-linked	Chromosome X	5	0.4
	Tritanomaly	Autosomal dominant	Chromosome 7	unknown	unknown

Table 7.1: Colour vision defects, their inheritance, location and frequency (Neitz and Neitz,. 2000; Melamud *et al*,. 2004) *it is impossible to distinguish between rod and cone monochromatism clinically which may have had an effect on the presenting incidence level.

7.1.4 Colour vision testing

There are numerous colour vision tests available for clinical practice. They are all developed for the purpose of assessing human colour vision; however they differ in design and outcome. They fall into four main categories; anomaloscopes, pseudo-isochromatic plate tests, arrangement tests and lantern tests.

In the aim of standardising colour vision tests, the Committee Internationale de l'Eclairage (CIE) recognised a system that can be used as a reference to present accurate colour measurement. It represents trichromatic colour matching characteristics of a normal observer on a two dimensional diagram. It provides information about colour space and lines of confusion within this space. This information can then be used by test designers to produce colour vision tests (Melamud *et al.*, 2004).

A) Anomaloscopes

Anomaloscopes are instruments that use colour matching for testing colour vision. The first anomaloscope was the Nagel anomaloscope. It is considered the Gold Standard to which all tests are compared. Based on the same principle, several other anomaloscopes have been developed. They are aimed to diagnose and classify colour vision defects. They are the only colour vision tests with an ability to distinguish between dichromats and anomalous trichromats. Earlier models are based on the Rayleigh equation that can only diagnose red-green defects. Several designs were developed following the design of the Nagel anomaloscope such as the Neitz anomaloscope, the Pickford-Nicolson and the HMC anomaloscope (Oculus). Some of the later designs included the Moreland equation; which tests for blue colour vision defects.

The Neitz anomaloscope is considered a very good substitution of the Nagel anomaloscope (Birch, 1998). Anomaloscope sensitivity in the detection of tritan defects has not been established in the literature. They require a high level of cooperation and hence, their suitability for testing children is arguable.

B) Pseudo-isochromatic plate tests

There is a variety of pseudo-isochromatic plate tests available. They all require the patient's ability to name or recognise objects on a test card. Generally, they require minimal illustration and results are easily interpreted, however they must be performed under precise viewing conditions, such as lighting and viewing distance, to obtain accurate results. They are primarily designed for screening purposes. The most famous test is the Ishihara which has good agreement with the Neitz anomaloscope and is considered the clinical test of choice with very high sensitivity and specificity,

and an ability to grade severity to an extent (Birch, 1997b; Block *et al.*, 2004; Seshadri *et al.*, 2005). Nevertheless, it can only detect red-green defects. Other plate tests are able to detect tritan defects, such as the new Richmond Hardy, Rand and Rittler test (HRR). The HRR test is of a very similar design to the Ishihara. It was proven that its ability to detect red-green defects is superior to that of the Ishihara, and in addition, it is able to detect and grade tritan defects (Bailey *et al.*, 2004; Cole *et al.*, 2006). Therefore, it can be used to substitute or to complement Ishihara. The Colour Vision Testing Made Easy™ (CVTME) is another pseudo-isochromatic plate test that also shows high sensitivity and specificity and is primarily aimed for testing young children and persons with learning disabilities (Cotter *et al.*, 1999). The CVTME cannot detect tritan defects.

C) Arrangement tests

Arrangement tests typically consist of a number of coloured caps. These caps are all of fixed chroma and value, while they differ in hue. The task expected from the patient is to arrange these caps in what they perceive as a natural order. These tests are designed to evaluate colour discrimination and describe colour discrimination loss. Their outcome can classify patients as colour normal, deutans, protans or tritans. Severity of colour discrimination loss can also be evaluated. Similar to pseudo-isochromatic plates, viewing conditions are crucial for accuracy.

The main arrangement tests are those developed by Dean Farnsworth; The Farnsworth-Munsell 100 Hue Test (100-hue) and the Farnsworth Panel D-15 Test (D-15). They are both based on the same principle. The FM 100-Hue test evaluates hue discrimination in colour vision normals and assesses the chromatic discrimination loss

in congenital and acquired colour defects. It identifies the defect type (as protan, deutan or tritan) and determines the severity of the defect (Farnsworth, 1943).

The D-15 test is derived from the 100-hue test except it uses larger steps in hue between the caps. It consumes less time, though it can only reliably detect severe discrimination loss (Cole *et al.*, 2006). The Lanthony Desaturated Panel D-15 Test (Desaturated D-15) was developed to complement the D-15 test. It is of the same design, whilst the coloured caps are paler and lighter. This was intended to increase its ability to detect mild discrimination loss. Several other tests have also been developed to function in the same fashion. For example, the Panel 16 Colour Vision Test is very similar to the D-15 test only that it enjoys a larger colour surface on the caps. This was mainly to interest children.

The City University Colour Vision Test (City Test) is a plate test that was derived from the D-15 test. It differs in the task required by the patient. It can classify subjects in the same way as other plate tests. Nevertheless, it was shown to be poor in detecting protan and deutan defects and differentiating between them (Birch, 1997a). Consequently, it is advised to be used in conjunction with another test such as the Ishihara. It is especially useful for detecting tritan defects (Heron *et al.*, 1994).

D) Lantern tests

Lantern tests are essentially intended for occupational competency purposes. Therefore, they are not useful tools for colour vision diagnosis or chromatic discrimination assessment. Specifically, they are designed to assess a person's ability to identify specific coloured light signals. Examples of lantern tests are the Holmes Write Type A, Beyne and Spectrolux. These tests do not provide a diagnosis and result varies considerably between the three tests (Squire *et al.*, 2005).

E) Test batteries

Since most tests are either superior at diagnosing red-green defects or blue defects, it is widely acceptable to use test batteries for colour vision diagnosis. Such approaches are commonly employed in clinical settings as well as research settings. For example, Ishihara is the clinical test of choice for detection of red-green defects. Its inability to detect tritan defects has encouraged the use of other complementary tests, such as the City test or the HRR to screen for tritan defects, both of which were shown to be effective for such purpose (Heron *et al.*, 1994; Cole *et al.*, 2006). Conversely, the City Test is thought to be less effective than the Ishihara for red-green defect diagnosis (Birch, 1997a).

7.1.5 Colour vision in Down's syndrome

There is an interesting conflict is in the literature concerning colour vision in individuals with DS. While some studies claim a high association of colour vision defects with DS, others deny this statement. Most studies have concluded that the prevalence of colour vision defects in individuals with Down's syndrome is higher than found in the general population when assessed clinically; 23-48% (Stratford and Mills, 1984; Perez-Carpinell *et al.*, 1994; Rocco *et al.*, 1997). The most recent study also found that lower colour discrimination abilities were present in DS when assessed with chromatic VEPs, even when these were not clinically observable (Suttle and Lloyd, 2005).

There are several reasons why colour vision defects in DS should be studied further. First of all, congenital colour vision defects are not carried on chromosome 21 (Birch, 1998). Secondly, adults with DS might present with other reasons for abnormal colour vision such as Alzheimer's disease or opacities in the ocular media;

i.e. the defect will be acquired and not congenital in these instances (Perez-Carpinell *et al.*, 1994; Rocco *et al.*, 1997). Thirdly, and more importantly, previous studies did not account for the learning disabilities present in association with DS. This was demonstrated by the tests and procedures used to evaluate colour vision. Moreover, most of these studies agreed on the difficulty of the segregation between the presence of a genuine colour vision defect and a simple misunderstanding of the test concept.

Persons with DS are at higher risk of eye and vision problems compared to their typically developing peers. It is known that children with DS are 'visual learners'. Speech development is more efficient when supported with pictures (Miolo *et al.*, 2005; Chapman, 2006). Hence, abnormalities in visual perception would have a higher impact on the learning process in DS compared to typically developing children.

Colours are widely employed in education; especially during the first years of school. This is always associated with the assumption by teachers and course planners that the children have normal colour vision. It is known that, at least in children with visual impairment, poor visual function can directly effect cognitive skills development (Anderson *et al.*, 1984). Therefore, the presence of an undiagnosed colour vision defect can enormously decrease the confidence level for learning in a child with learning disabilities. For this reason, and with the presence of such contradictions in the literature, a definite answer is much needed.

7.1.6 The aim

The ultimate aim of this study was to evaluate colour vision in a population of children and young adults with DS.

In Cardiff University Eye Clinic, children with DS have been regularly seen since the establishment of the cohort in 1992. The fact that the children are seen regularly by the same practitioners enables the building of a relationship with the child and his/her family which helps the child to enjoy having the eye test.

A study to find the most suitable colour vision test for children with learning disabilities, out of the available tests, is logically the first step towards understanding colour vision in this population. The Mollon-Reffin 'Minimalist' colour vision test was chosen and validated. Subsequently, a study of colour vision in a population of children and young adults with DS was conducted.

7.2 General methods

First of all, the test procedures for the colour vision tests used in the study are described below.

7.2.1 Colour vision tests procedures

7.2.1.1 The Mollon-Reffin 'Minimalist' colour vision test (M-R)

The M-R test was intended to detect and grade colour vision defects (Mollon and Reffin, 1994). It consists of 3 sets of coloured caps; each coincides with the protan, deutan or tritan confusion line. There are 5 caps in the protan set and 6 caps in each of the other two. Each set contains caps of the same hue, but of different saturations. The caps in each set are numbered from 1 to 5 or 6. The lower numbers indicate lower saturation of the cap. There are also 9 grey caps that differ in brightness and one orange demonstration cap that does not lie on any of the confusion lines (i.e. visible regardless of the colour vision status of a person).The test can be seen in Figure 7.1.

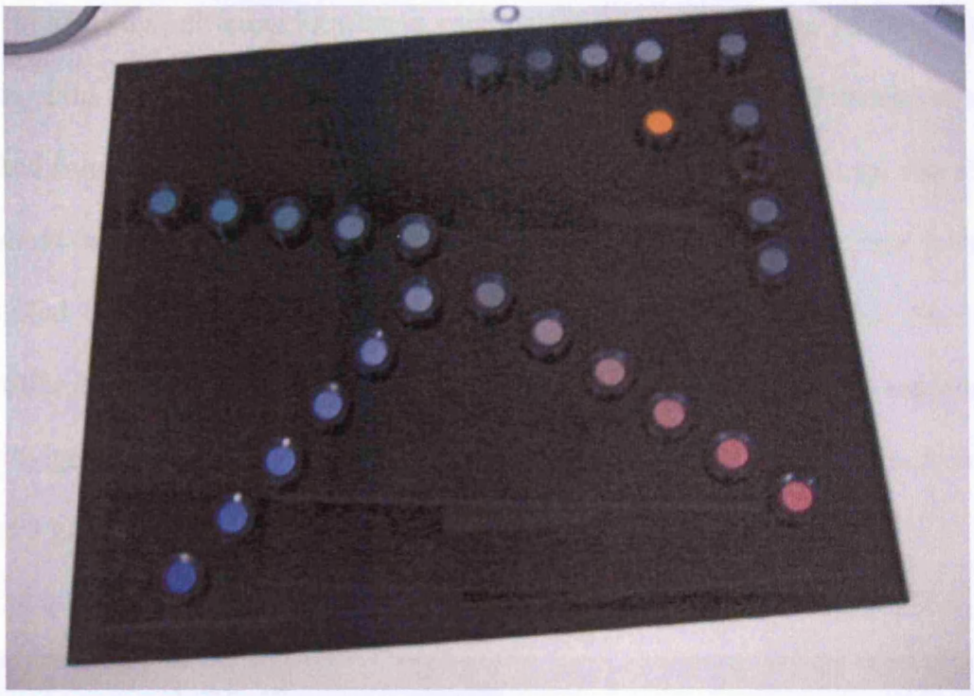


Figure 7.1: The Mollon-Reffin 'Minimalist' colour vision test.

A pre-test demonstration was performed first. The child was presented with 6 grey caps selected at random and the orange demonstration cap and asked to identify the coloured cap as instructed in the test manual. The grey caps act as distracters so that the caps cannot be identified by difference in brightness. When this task was successfully completed, the child was presented with the same number of grey caps in addition to cap number 3 of one of the confusion lines (medium saturation). When this was identified, it was replaced with cap number 2, and number 1 respectively (i.e. decreasing the saturation). When it is not seen, a cap with higher saturation was placed and the procedure was repeated. This was completed for the 3 sets of caps; deutan, protan and tritan. The task was initially presented to the child's carer to establish the appropriate terminology while the child was being entertained by another member of the research team. For example, some children were asked to *choose the different one*, whereas others were asked to *pick the wrong one*. The children were

given a paint brush and were instructed to point at their chosen cap. The coloured cap was 'hidden' in a different location at each presentation. A second attempt was given to the child if they failed to correctly identify the coloured cap. However, this was masked from the child; the examiner removed and returned the same cap. The child's threshold was considered as the cap with lowest saturation that was correctly identified in each line. Figure 7.2 shows the presentation of the test. The result identifies the children as colour normals, protan, deutan or tritan. A reduction in sensitivity to a specific area of the spectrum was demonstrated as a lower score in one of the 3 groups of caps.

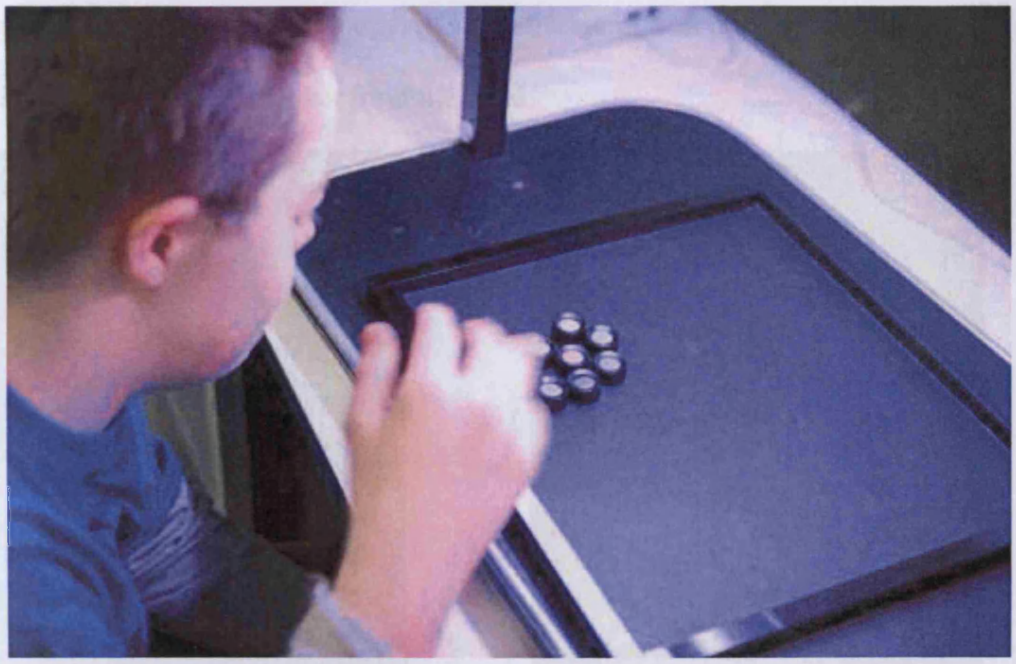


Figure 7.2: Illustration of the M-R testing procedure ***(Child: Thomas Markwell, photo by Mike O'Carroll)***

7.2.1.2 City University colour vision test (City)

The procedures of this test were performed as indicated in the manual. The test consists of two parts. The first part contains 4 pages that are intended for screening.

Each page consists of 4 sets of 3 coloured spots. Each set are either of the same colour or with one different coloured spot (see *Figure 7.3a*). The child is asked to answer the following questions. *Are the 3 spots similar or different?* If different, *which one?* The child's responses classified them as *colour normals*, *red-green defective* or *blue defective*. The second part of the test consists of 6 pages and a demonstration page. Each page contains 1 centred spot surrounded by 4 different coloured spots. The child was asked to identify the surrounding spot that is closest in colour to the central spot (see *Figure 7.3b*). This part of the test identifies subjects as colour normals, protans, deutans or tritans. In addition, it grades the presenting defect. Both parts of the test include a demonstration sample. The task was initially presented to the child's carer to determine appropriate terminology. A second attempt was not allowed in this test due to the inability to mask the act from the child.

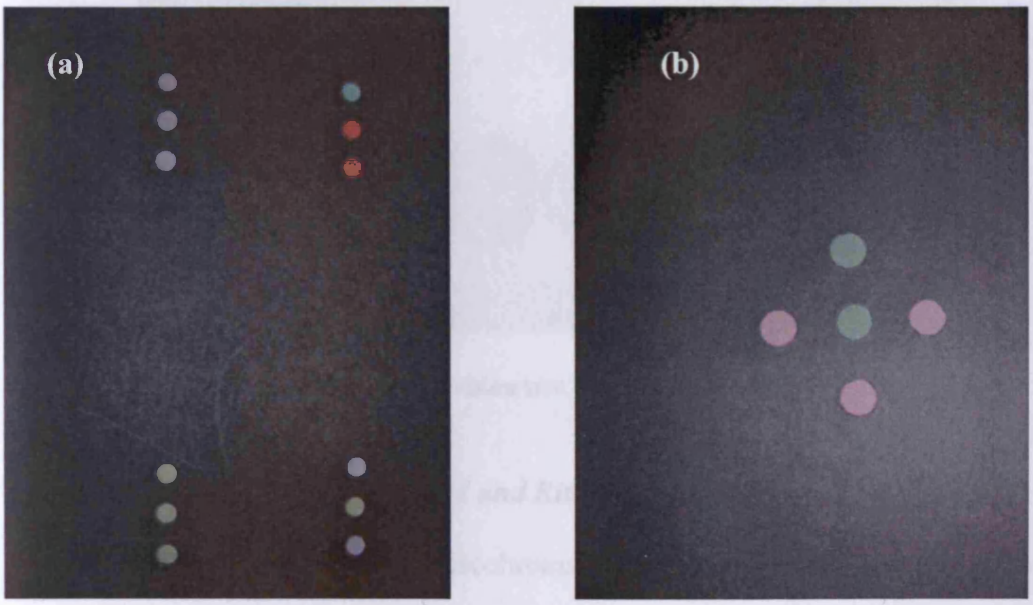


Figure 7.3: The City University colour vision test. (a) part 1, the demonstration set can be seen in the top right corner, (b) part 2, the demonstration page.

7.2.1.3 The Panel 16 colour vision test (PV-16)

The PV-16 test is an arrangement test that consists of 16 coloured caps including a reference one. The test can be seen in Figure 7.4. The 15 coloured caps

were mixed and randomly placed on a table. The child was then given the reference cap and was asked to locate the cap that looked *almost the same.* Once this was located, the child was asked to place it next to the reference cap. The same procedure was repeated while using the chosen cap as a reference. The child was asked to confirm their choice after each step. The children were allowed to rearrange the caps at any point if they wished. Similarly, carers were consulted for terminology prior to testing.

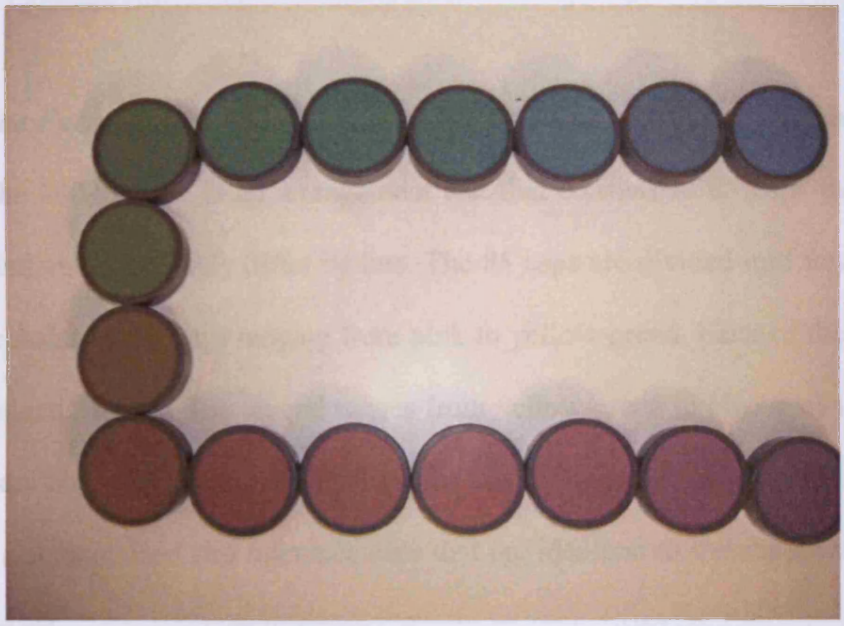


Figure 7.4: The PV-16 colour vision test. Pilot cap is the blue end of the series

7.2.1.4 The Richmond Hardy, Rand and Rittler colour vision test (HRR)

The HRR test is a pseudo-isochromatic plate test. It consists of 2 parts. The task required by the patient is consistent throughout the 2 parts. The child was asked to identify and locate geometrical shapes that may be present on a page. The test has 4 demonstration plates, 6 screening plates and 14 classifying/grading plates. Each plate may have up to 2 of 3 possible shapes (X, O and/or ►). The child was asked to indicate the presence or absence of any symbols on the plate, name them and locate

them with a paint brush. The screening plates are intended to screen for red-green and blue defects, and the classifying/grading plates are intended to identify and grade the defect. When the screening part was completed successfully, the classifying/grading part was not performed, as instructed in the test manual. The children's carers were consulted for suitable instructions terminology. A 'pass' in the four demonstration plates was mandatory for proceeding to the test. These were repeated until the child was confident with the testing procedures. Subsequently, the testing procedures complied with the test's instructions manual.

7.2.1.5 The Farnsworth-Munsell 100 Hue test (100-hue test) - used with adults only

The 100-hue test is an arrangement test that consists of 85 caps that unite in chroma and value, and only differ by hue. The 85 caps are divided into four sets. The first set consists of 22 caps ranging from pink to yellow-green. Each of the following sets contained 21 caps. The second ranges from yellow-green to blue-green. The third ranges from blue-green to purple-blue and the last set ranges from purple-blue to pink. Each set also contained two reference caps that are identical to the cap located at each end of the set.

To start, the caps of the first set were randomised on a table. The subject was given the box that contained the set with the reference caps located at each end. The participant was asked to arrange the caps in what they perceived as a natural order, ranging between the two reference caps. Subjects were allowed to start from either end of the set and they were allowed to rearrange the caps after locating them in the set box. Once the participant was happy with the arrangement, the whole procedure was repeated with following sets in a consequent fashion. Finally, the results were

recorded and analysed using the proposed method in the test manual (Farnsworth, 1957).

7.3 Choosing a suitable test for children with learning disabilities (with special reference to Down's syndrome)

7.3.1 Methods

7.3.1.1 Choice of tests

The criterion in test choice was to include all the tests that were specifically developed (or are suitable) for children and are able to detect protan, deutan and tritan colour vision defects. After a thorough review of the available colour vision tests, four colour vision tests were found to fulfil our criteria: the Mollon-Reffin "Minimalist" colour vision test (M-R), the City University colour vision test (City), the Panel 16 colour vision test (PV-16), and the Richmond Hardy, Rand and Rittler test (HRR).

7.3.1.2 Study population

All children with DS who attended the clinic for an eye examination during the course of this study were invited to participate (n = 34). All children were members of the Cardiff Down's Syndrome Vision Research Unit. This study included both groups of children; the original and the newer recruits. This is because the presence of visual disorders cannot impact on the results of this particular study.

7.3.1.3 Procedures

All of the four tests were initially attempted with all of the children in a random order. However, it was then decided to eliminate the HRR test. The reasons for this are presented in the results section.

7.3.1.4 Testing conditions

All of the tests were performed under an Illuminate C light source and at the required testing distance as indicated in the relevant test manual. Light level on the testing surface was 50.87 cd/m^2; measured using Minolta luminance meter LS-110 (Illumination level of 159.98 lux equivalent). The order in which the tests were attempted varied between children. Spectacle correction was worn during testing, when applicable. The parent/guardian's supervised involvement was encouraged when necessary.

7.3.1.5 Pass/Fail criteria

As this study was intended to assess the suitability of each test for children with learning disabilities, each child was rated on their performance throughout the test. Although passing the demonstration section is often considered as showing the child has a good understanding of the test, only the completion of a test was considered a success in this study. This was to allow for a more realistic clinical scenario demonstration. The reasons for failing the tests were recorded by the researchers.

7.3.2 Results

7.3.2.1 Study population

The HRR test was eliminated from the study after three attempts with 3 different children. None of the 3 children was able to pass the demonstration pages. Children were very competitive and insisted on finding all 3 of the symbols on all pages. This, in addition to the recommended presentation time (~ 4 seconds per page), was behind eliminating this test.

The M-R and the PV-16 tests were attempted on all of the 34 children. However, only 24 children agreed to attempt all of the three tests. The complete battery was not attempted with the remaining 10 children due to several reasons. Some children were tired and refused to participate prior to presenting one or more of the three tests. Others were not co-operative on the day. Therefore it was anticipated that the likelihood of understanding the instructions was low. As a result, the 24 children included are those who attempted to perform all three tests.

The age range of the 24 children was between 4.98 and 18.12 years (Mean = 12.69 years, s.d. = 3.69) at the time of their visit. Their mean corrected distance visual acuity was 6/10 (s.d. = 3.21).

7.3.2.2 Tests success rate

Of the 24 children, 22 were able to complete the M-R test, 11 completed the PV-16 and 5 completed the City test. This gives the M-R test a success rate of 91.6%. On the other hand, the City test had a success rate of only 20.8%. Around half of the children were able to complete the PV-16 test (45.8%). A table including individual results for each participant can be found in Appendix VII.

7.3.2.3 Reasons for failure

Reasons for failing the tests varied. They were classed into 2 categories. The first category was failure to understand the concept of the task required. This category included all of the children who did not successfully complete the demonstration section of a given test or showed incompetency while performing the test. The second category consisted of the children who lost interest to complete the test after completing the test's demonstration part successfully; identified as "lost interest".

These children either found the test repetitive and/or lengthy. Figure 7.5 shows the numbers of children in each category for each of the three tests.

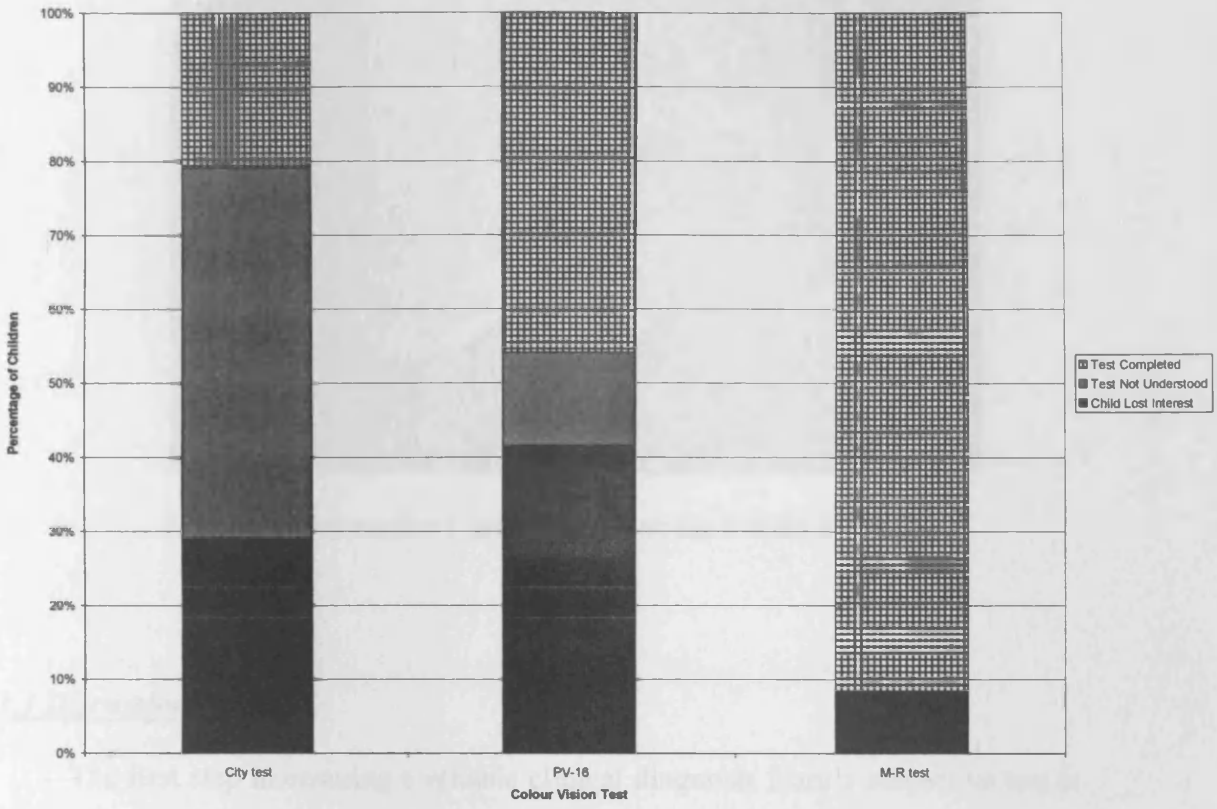


Figure 7.5: Performance of the 24 children in each of the three colour vision tests

Figure 7.5 shows that the majority of children did not understand the concept of the City test. Specifically, they found the concept of the second part of the test difficult to understand.

The reason for most of those who did not complete the PV-16 was losing interest in the test. A very specific reaction was noticed. Most children who lost interest found no further match for cap number 8. Some of the children verbally declared this while others decided to either stop the test or arrange the remaining caps in a random order. Figure 7.6 shows cap number 8 and the cap that is adjacent to it

(number 9), in the correct order, under Illuminate C light source. The 2 children who did not complete the M-R test found it repetitive and lost interest to complete the task.

Figure 7.6: Cap number 8 (left) and cap number 9 of the PV-16 test

7.3.3 Discussion

The first step in ensuring a reliable clinical diagnosis from a subjective test is to guarantee the participant's full understanding of the test concept. It was clear from our data that the concept of the M-R test was the most successful.

There was a great difference in the success rate of the three colour vision tests. This could be attributed to the test design. The M-R test has been shown to be successful with typically developing children as young as 3 years of age (Shute and Westall, 2000). This result may also apply to children with learning disabilities. The age of our youngest participant was 5 years; and it seems viable to assume that younger children may also be able to manage the test. Although individuals with DS tend to have variability in cognitive abilities regardless of age, the vast majority of those participating in this study were able to complete the M-R test. In contrast, most

children failed to complete the other tests. This strongly indicates that the previously published results regarding colour vision in DS were influenced by a failure to control for the learning disabilities associated with DS.

To summarise, it is reasonable to say that a test design such as that of the M-R is most suitable for individuals with learning disabilities, in particular DS. This was due to both the simplicity of the task and its entertaining nature. Also, an advantage of this test is the practitioner's ability to mask the result. This is extremely important to maintain the participant's confidence level. Although this test was assessed for suitability of young children and was found to be suitable, a validation study cannot be found in the literature (Shute and Westall, 2000). Therefore, the remaining sections of this chapter will report on a validation study of the M-R test.

7.4 Validation of the Mollon-Reffin 'Minimalist' Colour Vision test

7.4.1 Methods

7.4.1.1 Study population

For the purpose of validating the M-R test, posters for recruiting participants with normal colour vision and participants with colour vision defects were distributed across the Cardiff University campus. Email notifications were also circulated to all staff and students of the University. A copy of the advert is attached in Appendix VIII. Ethical approval for this study was obtained from the Research Ethics Committee for Wales and all participants gave written consents before taking part in the study. Copies of the participants information sheet and consent form can be found in Appendix VIII.

7.4.1.2 Determination of colour vision tests for comparison

Anomaloscopes are traditionally used for validation of new colour vision tests. However, this was not employed in this study for several reasons. Firstly, anomaloscopes provide a lengthy procedure for the participant; this may provide an obstacle in obtaining accurate results due to fatigue or misconception of instructions. Secondly, the only anomaloscope that can test for tritan defects is the HMC anomaloscope (Oculus), which provides a very lengthy and complicated task for the patient (Birch, 1998). As a result, a test battery was employed. The battery included the HRR, the 100-hue test, and the City test. Cole *et al.* (2006) suggested that when the pass/fail criterion for the HRR was adjusted (explained later), the sensitivity of the test became 1.0. However, the specificity dropped to 0.96; meaning that all individuals with defective colour vision can be correctly identified as having a colour vision defect while 4% of individuals with normal colour vision may be mis-diagnosed as having abnormalities. For this reason, the 100-hue test was employed. This test does not give pass/fail results; it gives a very good illustration of the colour discrimination abilities of a person. Age norms for error scores are well established and methods of interpretation of results are also existing in the literature (Farnsworth, 1957; Kinnear, 1970; Kinnear and Sahraie, 2002). Because the validity of the HRR was only tested for red-green defects, the City test was used for confirmation of tritan detection (Heron *et al.*, 1994).

Terminology

The sensitivity of a test indicates the percentage of people with a colour vision defect that can correctly be identified by the test as having a colour vision defect. The

specificity of a test indicates the percentage of people with normal colour vision that can correctly be identified as having normal colour vision by the test.

7.4.1.3 Procedures

Each participant was tested with the four colour vision tests in a random order. The procedures for all of the tests were performed as described earlier (See section *7.2.1*). In general, testing procedures followed the manufacturers' instructions. Results were also interpreted as instructed by the manual. However, the results of the HRR were interpreted differently for this study. Where the testing manual does not indicate a specific fail criterion, the fail criterion was adjusted to *two or more errors* in the screening plates to enhance sensitivity as proposed by (Cole *et al.*, 2006). As for classification of colour vision defects and grading their severity, the manufacturers' instructions were followed.

7.4.1.4 Determination of validity

In concordance with previous studies, validation was achieved by comparing three different parameters; the ability of the M-R test to detect the presence of a defect, its ability to classify the defect, and its accuracy in grading the defect in comparison to the other tests. The criteria for test choice for each comparison were determined according to the abilities of each of the tests in every field.

- ***Detection:*** Due to the high sensitivity and excellent specificity of the HRR test in detecting R-G colour vision defects, the results of the M-R were compared to it. However, for tritan detection the results of the City test were relied on due to its high ability for such purpose (Heron *et al.*, 1994; Landers *et al.*, 1998).

- ***Classification:*** The classification abilities of the HRR are 86% accurate, and a similar result was reported for the City test (Birch, 1997a; Cole *et al.*, 2006). Therefore, classification of the M-R was compared to that of the 100-hue test. Although this test demonstrates colour discrimination abilities and is not intended for colour vision defect detection, it was found to provide specific characteristic patterns for each of the defects; protan, deutan and tritan (Farnsworth, 1957).
- ***Severity grading:*** Severity grading of the M-R was compared to that of the HRR; which was shown to provide a valid scale (Cole *et al.*, 2006). All were compared to the error scores obtained by the 100-hue test.

7.4.2 Results

7.4.2.1 Study population

Adverts were designed to attract individuals with and without a known colour vision abnormality. The total number of responses was 44. The test battery was performed on all of the participants. The results of 2 participants were eliminated from analysis due to loss of concentration while performing one or more of the tests.

For the remaining 42 participants, age ranged between 21 and 59 years (mean = 30.6 years, s.d. = 9.23). Fifteen were female and 27 were male. Out of these 42; only 6 individuals participated with a known colour vision defect; 5 were male and 1 was female, age ranged between 22 and 59 years (mean = 33 years, s.d. = 15.4). Table 7.2 shows the individual results for each participant.

Subject ID	Gender	Age (years)	Colour vision test result				
			M-R	*HRR*	*City*	*FM-100 hue (plot interpretation)*	*Error score*
1	F	24	P_1, D_1, T_2	Normal	Normal	Normal	84
2	M	28	P_1, D_1, T_1	Normal	Normal	Normal	78
3	M	21	P_1, D_1, T_1	Normal	Normal	Normal	56
4	M	30	P_1, D_1, T_1	Normal	Normal	Normal	84
5	M	26	P_1, D_1, T_1	Normal	Normal	Normal	163
6	F	28	P_1, D_1, T_1	Normal	Normal	Normal	102
7	M	21	P_1, D_1, T_1	Normal	Normal	Normal	106
8	F	29	P_1, D_1, T_1	Normal	Normal	Normal	16
9	F	29	P_1, D_1, T_1	Normal	Normal	Normal	36
10	F	32	P_1, D_1, T_1	Normal	Normal	Normal	44
11	F	27	P_1, D_1, T_1	Normal	Normal	Normal	60
12	M	42	P_1, D_1, T_2	Normal	Normal	Normal	44
13	F	49	P_1, D_1, T_1	Normal	Normal	Normal	24
14	M	46	P_1, D_1, T_1	Normal	Normal	Normal	80
15	F	40	P_1, D_1, T_1	Normal	Normal	Normal	80
16	M	29	P_1, D_1, T_1	Normal	Normal	Normal	56
17	M	32	P_1, D_1, T_1	Normal	Normal	Normal	40
18	M	24	P_1, D_1, T_1	Normal	Normal	Normal	34
19	M	27	P_1, D_1, T_1	Normal	Normal	Normal	48
20	M	24	P_1, D_1, T_1	Normal	Normal	Normal	48
21	M	32	P_1, D_1, T_1	Normal	Normal	Normal	41
22	F	24	P_1, D_1, T_1	Normal	Normal	Normal	10
23	M	25	P_1, D_1, T_1	Normal	Normal	Normal	60
24	F	22	P_1, D_1, T_1	Normal	Normal	Normal	110
25	F	50	P_1, D_1, T_2	Normal	Normal	Normal	124
26	M	28	P_1, D_1, T_2	Normal	Normal	Normal	36
27	F	32	P_1, D_1, T_2	Normal	Normal	Normal	56
28	M	25	P_1, D_1, T_1	Normal	Normal	Normal	31
29	F	24	P_1, D_1, T_1	Normal	Normal	Normal	76
30	F	23	P_1, D_1, T_1	Normal	Normal	Normal	52
31	M	32	P_1, D_1, T_2	Normal	Normal	Normal	52
32	M	24	P_1, D_1, T_1	Normal	Normal	Normal	32
33	M	46	P_1, D_1, T_1	Normal	Normal	Normal	20
34	M	24	P_1, D_1, T_1	Normal	Normal	Normal	108
35	M	27	P_1, D_1, T_1	Normal	Normal	Normal	80
36	M	40	P_1, D_1, T_1	Normal	Normal	Normal	104
37	F	23	P_2, D_1, T_1	Mild Deutan	R-G (not classified)	Protan	96
38	M	22	P_1, D_5, T_1	Medium Deutan	Medium Deutan	Deutan	175
39	M	25	P_1, D_6, T_1	Medium Dutan	Medium Deutan	Deutan	203
40	M	59	P_4, D_2, T_1	Strong Protan	Medium Protan	Protan	144
41	M	24	P_1, D_2, T_2	Mild Deutan	Mild Deutan	Deutan	120
42	M	45	P_{none}, D_4, T_2	Medium Protan	Medium Protan	Protan	116

Table 7.2: Individual results for 42 adults using the four colour vision tests

7.4.2.2 Detection

All of the 6 participants with defective colour vision were correctly detected by all of the three tests; M-R, City and HRR. They were all diagnosed as having red-green colour vision defect by the City and the HRR tests; this was always paralleled by missing some of the protan/deutan caps on the M-R test. Similarly, all of those with normal colour vision were identified as having normal colour vision by the three tests. However, 6 out of the 36 participants with normal colour vision missed the lowest saturation tritan cap of the M-R test (T_1), while correctly identifying P_1 and D_1. Also, 2 of the 6 colour vision defective participants scored T_2. This result was expected after considering that, at least in older children, the T_1 cap was not correctly identified by 30% of the participants without the presence of a colour vision defect (Shute and Westall, 2000). However, none of the 42 participants scored lower than T_2 in the M-R test.

This gives the M-R test an identical sensitivity to the HRR test in detecting red-green defects; sensitivity of 1.0. A specificity of 0.96 is achievable by this test when a failure to identify the least saturated tritan cap (T_1) was ignored. Otherwise, the specificity of the test decreased to at least 0.83; this means that 17% of those with normal colour vision will be mis-diagnosed (when accounting for the 0.96 specificity of the HRR, the specificity of the M-R may further drop to 0.79).

7.4.2.3 Classification

The 4 tests agreed on the defect classification of 5 out of the 6 participants. For the remaining participant (ID 37), the M-R result, and the interpretation plot of the 100-hue tests showed agreement by classifying the participant as mild protan. However, the HRR diagnosed this subject as a deutan and the City test was not able to

classify the defect in this case. This participant made only one error on the HRR classifying plates and no errors on those of the City test. This indicated that they are likely to have a very mild anomalous trichromacy (Fletcher, 1998). In all of the cases, the result of the M-R test matched the interpretation of the plot produced by the 100-hue test. However, the tritan errors made with the M-R test (T_2) were not matched by any of the tests; including the 100-hue interpretation plot.

7.4.2.4 Severity grading

There was agreement between the tests in severity grading for 5 out of the 6 cases regardless of the type of defect. The remaining participant was graded as having a strong defect by the HRR test while the other tests graded his defect to be medium (ID 40).

In general, error scores of those with normal colour vision were significantly lower than for those with a colour vision defect. (mean = 63.2, s.d. = 33.9; mean = 142.3, s.d. = 40.2, respectively; $p < 0.001$, Independent samples t-test). For those with colour vision defects, there was a significant correlation between the degree of deutan error in the MR test and the 100-hue error score (Spearman's rho, $r^2 = 0.533$, $p < 0.001$). The same was found for the degree of protan errors (Spearman's rho, $r^2 = 0.311$, $p < 0.05$). No significant correlation was found for tritan errors. For example, subject 39 scored D_6 on the M-R test and had an error score of 203 on the FM 100-hue test, whereas subject 41 scored D_2 and had an error score of 120; both were present with 100-hue interpretation plots that reflected the degree of discrimination loss.

7.4.3 Discussion

The M-R test can be regarded as a valid test for detecting, classifying and grading colour vision defect for the purpose of this chapter. However, generalisation of this study's findings should be made with caution.

The ability of the M-R test for the detection of colour vision abnormalities was assessed previously with people with blue cone monochromatism and found to be useful (Michaelides *et al.*, 2005). Our results confirmed this finding and added that the test is capable of correctly classifying and grading colour vision defects. The ability of this test to detect the presence of a defect is as reliable as that of the HRR, which was proved to be better than the Ishihara for detecting red-green colour vision defects (Cole *et al.*, 2006). The results of M-R should be interpreted as instructed by the test's manual for this matter. However, for the detection of tritan defects it seems sensible to ignore the patient's mis-identification of the lowest saturation cap of the tritan line (T_1). Mild red-green colour vision defects can be detected by missing only the least saturated relevant cap in the M-R test. If this criterion is followed for the tritan line, we are at risk of diagnosing those with no tritan defect as having a mild one. In addition, when a red-green defect was detected, the result was reflected in the 100-hue interpretation plot, whereas this was not reflected in any of the cases that missed the least saturated tritan cap.

At least for red-green defects, the M-R was superior in classifying and grading these defects. It seems that patients with a medium or strong red-green defect are likely to make errors in both protan and deutan lines. However, they always make more errors in the line that correctly classified their defect.

Grading defects using the M-R test matches that of the 100-hue test. The stronger the defect of the person when assessed with the M-R test, the higher their 100-hue error score was found to be.

It was not possible to assess the M-R's ability to diagnose tritan defects due to the rarity of such defects. However, this test was essentially developed for detecting and grading acquired colour vision defects; and these are mainly tritan defects, and proved to be useful for such an aim (Mollon and Reffin, 1994; Maar *et al.*, 2001). A larger number of participants with colour vision defects would also have been desirable, but this was not achievable due to the rarity of colour vision defects in general. However, the results assure the validity of the M-R test despite the small sample size.

The sample size for this study was very low in comparison to other colour vision tests validation studies, especially for the group of participants with colour vision defects (n=6). In addition, sample size calculations for the validation of this test were performed, as described by Flahault *et al.*, (2005), and indicated a minimum number of 34 participants with colour vision defects and 391 controls to ensure precise sensitivity and specificity estimates (sample was calculated as described by Flahault *et al.*, (2005) given that the prevalence of colour vision defects is 8% and using an expected sensitivity of 0.95 and requiring lower 95% confidence limit to be >0.75). Therefore, this study cannot act as a satisfactory validation study for the M-R test and an enhanced study is required for this purpose. However, the outcome of this study should provide enough evidence of the general validity of the test, which allowed it use to evaluate colour vision in DS, the main purpose of this chapter.

To sum up, the M-R seems to be able to correctly identify and grade congenital colour vision defects, if the least saturated tritan cap is ignored. Therefore, this test was used to evaluate colour vision in individuals with DS.

7.5 Evaluation of colour vision in individuals with Down's syndrome

7.5.1 Methods

7.5.1.1 Study population

All children with DS attending Cardiff University Eye Clinic for a routine assessment during the course of this study were invited for participation. These included members of the original cohort and the newer recruits. The results of those who participated in the previous study (Section *7.3*) were included in this study.

7.5.1.2 Procedures

The procedure of the M-R test was performed with all of the participants as described earlier (See section *7.2.1.1*). Results were interpreted as instructed by the test manual. However, when a participant misidentified the T_1 cap and correctly identified T_2, they were not considered as having a tritan defect.

7.5.2 Results

7.5.2.1 Study population

The total number of participants was 39. Three of these were not co-operative and refused to complete the test reliably; hence their results were excluded. For the remaining 36, age ranged between 4.98 and 18.12 years (mean = 12.69 years, s.d. = 3.69). Twenty-three were male and 13 were female.

7.5.2.2 Test results

The results of the M-R for the 36 participants can be seen in Figure 7.7. The figure shows that 35/36 participants were able to identify the lowest saturated cap for the protan and for the deutan sets. One participant scored P_2 and another one scored D_2. None of the participants scored lower than these scores on the protan or the deutan lines. However, only 20 participants were able to correctly identify T_1. The remaining 16 had a score of T_2.

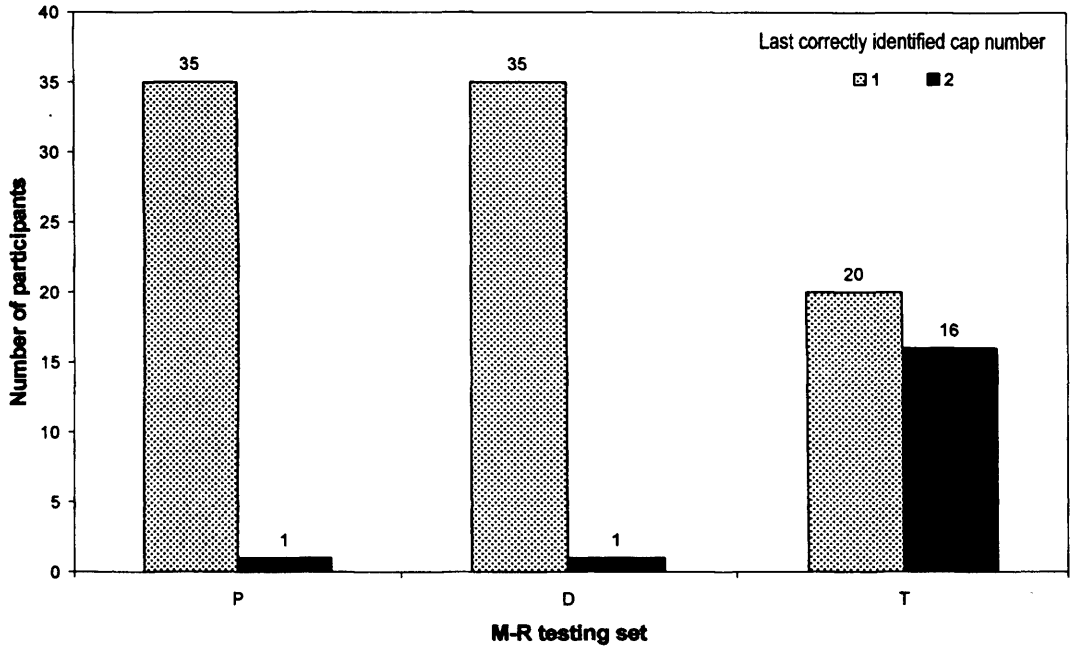


Figure 7.7: Results of the M-R test for the 36 children; light grey column represents the number of children who correctly identified the least saturated cap for each set; P, D and T; dark grey columns represents the number of children correctly identified cap numbered 2 as their threshold of each set.

To provide a breakdown of the results; 19/36 participants had a score of P_1, D_1 and T_1 (i.e. correctly identified the least saturated cap in each set). Fifteen participants had a score of P_1, D_1 and T_2 (i.e. they correctly identified the least saturated cap of the protan and the deutan lines and missed the tritan one). The remaining 2 participants

scored P_2, D_1 and T_1, and P_1, D_2 and T_2, respectively. It was established that T_1 may be mis-identified by colour vision normals; however, they are evidently able to detect T_2. Therefore, when ignoring T_1 the prevalence of colour vision defects amongst the study population is as presented in table 7.3.

	Number of participants (Percentage)		
	Male (out of 23)	Female (out of 13)	Total (out of 36)
Protan	1 (4.34%)	0	1 (2.78%)
Deutan	1 (4.34%)	0	1 (2.78%)
Tritan	0	0	0
Total	2 (8.97%)	0	2 (5.56%)

Table 7.3: Prevalence of colour vision defects in 36 individuals with DS

Only 2 participants had a colour vision defect; both of whom were male. One of the participants was a mild protan, he scored P_2 while correctly identified all of the caps in the other 2 sets. The second participant was a mild deutan with a score of P_1, D_2, and T_2.

7.5.3 Discussion

The prevalence of colour vision defects in DS seems to be similar to that of the general population. Males are at higher risk than females and red-green defects are more prevalent. The differences in results between this study and previously published studies may be attributed to several factors.

As a general rule, males are at higher risk of having a colour vision defect than females, and this is most likely to be a red-green defect. Our results confirms that this

also apply to individuals with DS. The prevalence found in this study slightly differed to that of the general population. 4.34% of males with DS were found to have a protan defect compared to 1% for typically developing males (Neitz and Neitz, 2000). For deutan defects, the result complied with the literature (4.34% for males DS and 5% for the general population). The difference in figures can be explained by the small number of participants in the study. Since the incidence of colour vision defects in females is much lower than it is in males, the absence of defects in females with DS in the study population can also be explained by the small study sample.

The results are contradictory to the available literature regarding colour vision defects prevalence in DS, which was found to range between 23% and 48% in previous studies (Perez-Carpinell *et al.*, 1994; Rocco *et al.*, 1997). In this study, prevalence was found that abides by the incidence of colour vision defects in the general population.

Several reasons may account for this difference. First of all, the test of choice may have affected the results. This study has demonstrated that not all tests can control for learning disabilities when testing colour vision (See section *7.3.2*). This may have resulted in the higher prevalence amongst the study population of Perez-Carpinell *et al.* (1994). They found 23% of teenagers with DS to have a colour vision defect; mainly in females using the Ishihara. Secondly, individuals with DS are at a risk of developing age-related diseases that can affect colour perception at an earlier stage compared to the general population; such as cataracts and Alzheimer's disease (Berk *et al.*, 1996; da Cunha and Moreira, 1996; Schupf *et al.*, 1998; Kessel *et al.*, 1999; Pache *et al.*, 2003). Since Rocco *et al.* (1997) studied an older group of individuals with DS (fourth and fifth decades), the higher prevalence of colour vision

defects may be a result of acquiring a defect, especially since 8 out of their 22 participants had cataracts.

Therefore, it appears that the prevalence of functional colour vision defects is not disrupted by the presence of DS, hence the same rate applies as in the general population.

7.6 Conclusions

The study has established that test choice is crucial for obtaining accurate results, and showed that children with DS are capable of performing the M-R test most successfully. The results have showed that the M-R test is a generally valid test for detecting, classifying and grading colour vision abnormalities. Also, the prevalence of defective colour vision appears to be similar in DS to the rest of the population.

Since the prevalence of defective colour vision does not differ in the presence of DS to that of the general population, routine clinical testing is not a requirement. However, as with typically developing patients, colour vision should be examined in every new patient with DS at first presentation. This is to allow for sufficient time to make adjustments and enhancement to educational plans at an early age in case of the presence of a colour vision defect to allow for better educational gains. Although colour vision defects are as prevalent in DS as they are in the general population, the presence of a defect may have a larger effect on the education of a child with DS than it would have on that of a typically developing child.

Chapter Eight: General conclusion

Chapter Eight: General conclusions

The findings of the Cardiff Down's Syndrome Vision Research Unit were primarily intended to widen the knowledge regarding visual development of individuals with DS, and to help shape clinical guidelines for optometric routine assessments in this population. Moreover, each finding provided more questions; hence, more research was generated based on the findings of the Unit. A summary of the main findings of the research unit is presented in this chapter. Greater focus is placed on the clinical implications of this thesis' results and the questions they may have raised.

8.1 Findings of the Cardiff Down's Syndrome Vision Research Unit

The Unit provided a number of findings throughout the years, these findings added to the understanding of many aspects of visual and ocular development in children with DS. The key findings are presented in the list below with the findings of this thesis underlined. Some of these findings were presented in the following published articles and theses; (Woodhouse *et al.*, 1993; Woodhouse *et al.*, 1994; Woodhouse *et al.*, 1996; Woodhouse *et al.*, 1997; Bromham, 1999; Cregg, 1999; Woodhouse *et al.*, 2000; Cregg *et al.*, 2001; Bromham *et al.*, 2002; Cregg *et al.*, 2003; Stewart, 2003; John *et al.*, 2004; Stewart *et al.*, 2005; Ji, 2006; Stewart *et al.*, 2007; Al-Bagdady *et al.*, 2009)

Visual acuity

- 100% of children with DS have reduced visual acuity.
- Visual acuity is within the normal range for infants with DS compared to control children. It falls below normal after the age of 2 years.

- Reduction of visual acuity is not explained by refractive error or reduced accommodation; it is present even with the full optical correction.
- Visual acuity is reduced both when measured with behavioural tests and when measured using visual evoked potential (VEP) techniques.

Contrast sensitivity

- Contrast sensitivity is reduced both when measured with behavioural tests and when measured using VEP techniques

Refractive error

- 50.6% of children with DS have a significant refractive error (beyond the range -0.75 D to +3.00 D); 41.8% hypermetropia and 8.8% myopia.
- Amounts of refractive errors, and distribution, is similar to that of typically developing children during infancy. Unlike typically developing children, the amount increases and the distribution widens with age.
- Only 25% of children with DS emmetropise.
- All of the myopic children with DS had a congenital heart defect.
- Significant hypermetropia characterises the majority of children with DS at all ages.
- Variation in refractive error is very high in children with DS at all ages.
- The majority of children with DS develop oblique astigmatism during teenage years.
- Parental refractive errors do not actively influence these of children with DS.
- Refractive error in DS is axial in origin.
- General growth does not influence refractive error in children with DS.

Accommodation

- 80% of children with DS have reduced accommodation; accommodative lag.
- Accommodation is reduced regardless of refractive error.
- Accommodative lag increases with increasing hypermetropia.
- Single vision spectacle correction for hypermetropia does not improve accommodation.
- Children with DS with reduced accommodation are more likely to have hypermetropia and/or strabismus than are those with accurate accommodation.
- The children's accommodative lag does not reflect their maximum amplitude of accommodation.
- Age, testing target size and cognitive factors cannot explain poor accommodation in children with DS.
- Emmetropia during infancy is associated with accurate accommodation.
- Bifocal spectacles are beneficial as an optical correction for the reduced accommodation in children with DS.
- Bifocal spectacles are a successful treatment for reduced accommodation in children with DS.
- Accommodation improves in 69.04% of bifocal wearers.
- 40.4% of bifocal wearers are able to return to single vision wear.
- Children with better visual acuity are more likely to gain accurate accommodation after bifocal wear.
- Boys are more likely to gain accurate accommodation after bifocal wear.

Strabismus

- 29% of children with DS have strabismus, mainly esotropia.
- Strabismus in DS is not explained by hypermetropia or anisometropia.
- Presence of strabismus does not influence chances of gaining accommodation improvement after bifocal wear.

Nystagmus

- 14% of children with DS have nystagmus.
- All children with nystagmus had a congenital heart defect.

Colour vision

- Children with DS can successfully participate in colour vision testing providing the appropriate test is used.
- Prevalence of colour vision defects in children with DS is similar to that of the general population.

Ocular biometry

- Corneal power is high and lens power is low in children with DS compared to control children.
- Corneal thickness is lower in children with DS than in control children.
- Optic disc of children with DS is flat compared to controls.
- Number of retinal blood vessels is higher in children with DS than in control children.
- Body height has a very minimal influence on ocular axial length.

Other findings

- Development and validation of modified Nott dynamic retinoscopy.
- Validation of Mohindra near retinoscopy.
- Choice of test is crucial in determining accurate colour vision result.
- The Mollon-Reffin 'Minimalist' colour vision test is a valid test for detecting colour vision defect with a sensitivity of 1.0 and specificity of 0.96.
- Facial characteristics in DS differ to these of typically developing children, hence conventional frames needs special adjustment to achieve good quality fit.

8.2 Clinical implications and research questions

This thesis focused on three major aspects of vision in children with DS; refractive error, accommodation and colour vision, and each aspect will be discussed separately.

8.2.1 Refractive errors

There was an attempt to cover three areas of refractive error; the distribution and development of refractive errors in children with DS, the relationship between the refractive errors of the children and those of their family members, and the contribution of the child's height to their axial length and refractive errors. In typically developing individuals, all of these aspects help in understanding the shaping factors of refractive errors. In turn, this helps in enhancing the predictive power of optometrists and has contributed to current clinical practice. These 'guidelines' form strategic rules for prescribing optical correction for children and decide the frequency at which children should be assessed.

This thesis has confirmed the previous findings that children with DS are hypermetropic on average at all ages, and added that a pattern of refractive error progression occurs during childhood and early teenage years. However, there is a noticeable deficiency in the process and higher amounts and a wider range of refractive errors was found in comparison to typically developing children. In addition, the majority of children with DS tend to develop oblique astigmatism with a specific right/left favouritism (Haugen *et al.*, 2001b; Little *et al.*, 2009b).

Given the above information regarding the "emmetropisation" process in DS, it seemed reasonable to expect a genetic influence on the children's refractive errors. However, this was absent, or at least masked by an additional factor. The variation in refractive errors of the children was proposed to explain the absence of this relationship and it was hypothesised that variation in the quality of general growth accounted for the variation in axial length, and hence errors covering any familial influence. Consistent with the literature, refractive errors were found to be axial in nature in DS (Haugen *et al.*, 2001a). However, while relative height had a minimal effect on the axial length, it had no active effect on refractive error.

8.2.1.1 Clinical implications of refractive errors findings

The findings emphasise the relevance of the current clinical guidelines regarding optical correction, and the frequency of routine assessments for children and young adults with DS (DSMIG, 2006).

Because the emmetropisation process is not effective in the removal of infantile refractive error in children with DS, an earlier age of prescribing can be beneficial. This is recommended to be at the start of early education, at the latest, to minimise any educational loss due to poor vision. Certainly, earlier prescription may

be required in the presence of abnormally high refractive error, strabismus or anisometropia.

The cut-off point for prescribing at early age is +2.50D for hypermetropia, if accommodation is accurate, since this is the average refractive error for young children with DS. This cut-off point reduces as the children grow older. Prescribing at this level is to achieve a functional refractive error in children with DS that simulate that of their typically developing peers (see *Chapter Three*). With regards to low/moderate myopia, prescription should be sought when the error is detrimental to the child. This is more likely to be for older children; as near vision is the main interest for the younger ones.

Because parental refractive errors and the child's quality of growth have minimal effect, if any, on refractive errors, prediction is difficult. Hence, examination at early an age is crucial. Also, assessments are recommended to be more frequent than for typically developing children due to the unpredictability of refractive development. This is to allow for monitoring any possible changes in refraction and for prompt intervention.

8.2.1.2 Refractive errors: further questions

The findings regarding the development of the spherical component of refractive error confirmed the previous reports on the abnormal refractive development of children with DS. However, the development of a specific pattern of astigmatism in children with DS highly suggests alteration in corneal shape that is causing this astigmatism. The facts are:

- Children with DS tend to develop oblique astigmatism; this astigmatism is discriminatory being between 90° and 45° for the right eye (plus cylinder).

- Eyelids are obliquely slanted in children with DS (Smith and Berg, 1976).
- Children with DS have lower corneal thickness compared to controls (Haugen *et al.*, 2001a; Evereklioglu *et al.*, 2002)
- Axis of astigmatism and slanting of palpebral fissure correlates significantly in typically developing children (Gracia *et al.*, 2003).

Therefore, it can be hypothesised that the obliquity of the palpebral fissure is what determines the obliquity of the axis of astigmatism in children with DS. The fact that most of this astigmatism develops later during childhood suggests that it is mechanically induced via blinking. This should be characterised by a high correlation between the axis of astigmatism and the axis of the palpebral fissure slanting in children with DS. Although refractive status was not found to relate to corneal astigmatism, this may be attributed to the small study sample in Little *et al.* (2009b).

A higher number of children with DS need to be studied before any familial refractive connections can be ruled out. However, if such a relationship exists, it must be weak. Furthermore, larger number of children may show a relationship between ocular axial length and relative height in children with DS.

8.2.2 Accommodation

The reduced accommodation that characterises most children with DS is treatable in most cases. As expected from a previous trial (Stewart *et al.*, 2005), bifocal spectacles improved accommodation when measured through the near add and through the distance lens, which was confirmed in this study. Enhancement in the child's own accommodative abilities was documented and 40% of children were able to successfully discard bifocal wear.

the *newer recruits* (37% with reduced accommodation, compared to 80% in *original cohort* before bifocal prescription). This group of children were mainly younger children of parents who mainly self-refer and who may have higher awareness of factors that improve the cognitive abilities of children with DS. These enhancement techniques usually involve the encouragement of the child's sensory organs from a younger age (i.e. stimulating vision). Indirectly, this may educate children to use their accommodation, something that can be learned by bifocal wearers through having clear retinal image at distance and near. Studying the differences in the levels of visual activity and intelligence levels between those who showed improvement and those who did not may reveal the factor that segregated their responses to bifocal wear. Conversely, continuous monitoring of those with no accommodation improvement may show improvement of their accommodative abilities over time.

When looking at the children who gained accommodation improvement after bifocal wear, it is noticeable that some benefit more than others. More than half of these children were able to return to single vision spectacles, yet the other half did not. Of note was the better visual acuity and male gender of those who gained accurate accommodation. Better visual acuity can be a motive to increase the visual demand, which may be the force that teaches these children to use their accommodative abilities.

8.2.3 Colour vision

The test design is of particular importance for achieving an accurate result in colour vision testing. The Mollon-Reffin 'Minimalist' test is a valid and an extremely successful test for use with children with DS. This should be a motive to make this

test commercially available. Using this test, colour vision prevalence in DS was found to be similar to that reported for typically developing individuals.

8.2.3.1 Clinical implications of colour vision findings

It is of great importance to ensure the patient's understanding of the task when using colour vision tests, this surely applies to any subjective test to attain accurate results.

Because colour vision defects are not of higher prevalence amongst children with DS, routine assessment of colour vision is not a necessity. However, it is important to evaluate colour vision on first clinical examination of a child with DS. This is preferably at a very early age, essentially prior to commencement of education. Although prevalence of colour vision defects is similar to that of the general population, the impact of defects may markedly affect educational gains for this population, because they rely more heavily on vision for learning. Thus, early detection will allow for early intervention in the educational plan for children with colour vision abnormalities.

8.2.3.2 Colour vision: further questions

Given that the prevalence of congenital colour vision defects in children with DS is similar to that of the general population, it may be of value to assess colour vision in an older population of individuals with DS for acquired defects. This is because it is known that most age-related disorders occur earlier in individuals with DS and some of these disorders can be associated with colour vision abnormality, mainly Alzheimer's. This indicates the possible value of colour vision testing in adults with DS as an initial indicator of Alzheimer's disease. A great advantage since

dementia is difficult to identify in adults with learning disabilities. Furthermore, the involvement of tasks that require memory skills, which are poor in individuals with DS, increases the difficulty of segregation between dementia and learning disability (Jarrold *et al.*, 1999). Providentially, several studies assessed the presence of a colour vision defect in association with Alzheimer's disease in "non- Down's syndrome" patients (Pache *et al.*, 2003). Many studies concluded that tritan (blue) defect is associated with Alzheimer's patients (Cronin-Golomb *et al.*, 1993). This increases the value of assigning a "test of choice" for persons with learning difficulties.

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Appendices

Appendix I

Study Protocol

Participant's information sheet

Participant's consent form

Research Protocol: **Version 1**

Title: Vision and Visual Defects in Children with Down's Syndrome.

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Project Summary:

Children and adults with Down's syndrome are at much greater risk of eye and vision disorders than are members of the general population. We have been conducting a longitudinal study of eyes and vision in a large study group of children with Down's syndrome for over 15 years. Our findings so far have enabled us to draw up evidence based guidelines for how eye examinations are carried out and how eye defects are treated in children with Down's syndrome. For example, we now know that children with Down's syndrome are much less likely to grow out of the infantile errors that many children have (and that largely disappear in general population by the age of 4 years) and therefore need to wear spectacles at a much younger age. Most (over 75%) children with Down's syndrome find it difficult to focus accurately on near tasks and our studies show that bifocals offer a real benefit to the children. We now provide bifocals clinically.

We wish to continue the work and to recruit new children into the study. Our current study group has been recruited under ethical approval applicable at the time of recruitment, or under School of Optometry Ethics Committee approval, and does not, at the moment, include subjects who are NHS patients. Clinically, we see many children with Down's syndrome referred to us from NHS sources at the School of optometry & Vision Sciences, and we would like to extend the group to include these children. We would also like the study to include children seen through the NHS by Mr. Watts at UHW.

Our research plans are to evaluate:

- Development of vision and ocular/visual deficits in children with Down's syndrome
- The numbers of children with Down's syndrome prescribed bifocals, the success rate of bifocal wear, and the numbers able to return to single vision wear.
- The relationship between refractive error in children with Down's syndrome and that of their parents and siblings.

- The nature and development of refractive errors amongst children with Down's syndrome in relation to that of their typically developing peers.
- The prevalence of colour vision defects in children with Down's syndrome.
- The effect of nystagmus on visual acuity and refractive error amongst children with Down's syndrome.

The overall aim of the work is to improve clinical management of visual defects and to ensure that children with Down's syndrome make the best use of their vision and that learning is not impaired by uncorrected or unrecognized visual problems.

Introduction:

Children with Down's syndrome are known to have an intellectual disability that slows their learning ability. Because children with Down's syndrome have particular problems with speech and language, a characteristic of the children is that they are 'visual learners' (Miolo, Chapman and Sindberg, 2005; Chapman, 2006). Clearly, poor eyesight will hinder learning even further, and yet children with Down's syndrome are at greater risk than other children of eye and vision deficits. Hence, our aim is to understand the nature of eye and vision problems in children with Down's syndrome, to improve or optimise their eyesight and, in turn, to enhance their ability to learn. The findings of our longitudinal study of visual development in children with Down's syndrome have allowed for better understanding of the nature of visual defects in the children and, moreover, have aided effective clinical testing procedures as well as informing the management of visual defects in children with Down's syndrome.

The Cardiff University longitudinal study of visual development in children with Down's syndrome has resulted in and is still producing important findings. A summary of some can be seen here:

- The visual acuity of children with Down's syndrome does not reach the same level as it does in typically developing children of the same age beyond the age of two years even with the full optical correction in place(Woodhouse et al., 1996b; John et al., 2004).
- The emmetropisation process, which occurs normally in the general population, fails in children with Down's syndrome(Cregg et al., 2003). This prevents the children from growing out of their infantile refractive errors. Moreover, some children tend to progress to a larger refractive error and this could be hypermetropia or, much less likely, myopia.
- About 75% of children with Down's syndrome do not accommodate accurately for near objects and this is the case even with no or fully corrected refractive error (Woodhouse et al., 1993; Cregg et al., 2001). Children with Down's syndrome who have an accommodative deficit benefit from wearing bifocal spectacle lenses (Stewart, Woodhouse and Trojanowska, 2005). Moreover, some of the children

who wear bifocals learn to accommodate accurately throughout the distance portion of the bifocal lenses and are able to return to single vision spectacle wear.

In spite of these discoveries, several aspects about the eyes of individuals with Down's syndrome are still unknown:

- Although our studies have shown the benefit of bifocals for children with an accommodative deficit, we still do not understand the mechanism of the either the accommodative problem or its solution. Stewart et al (2004) showed that bifocals do not simply 'add' plus power to the children's accommodative state. Instead, when wearing bifocals, the children modify their own accommodative response to produce an accurate focus at all distances. This involves, for the closest distance tested (10cm), the children producing an extra 2.00D of accommodative effort. Similarly, children who wear bifocals can accommodate more accurately through the distance portion of the lens, than can children wearing single vision lenses to correct a distance refractive error; a further example of bifocal wear enabling children to improve their accommodative response. As a first step towards understanding the process, we wish to analyse the success rate of bifocals, the accommodative response of a large number of children, and the numbers able eventually to return to single vision lenses.

- Children with Down's syndrome are at a much higher risk of developing refractive errors than are typical children. In the general population, the heritability of myopia is well studied (Guggenheim et al. 2003; Mutti et al. 2002; Pacella et al. 1999; Krause et al. 1993). Hypermetropia, has not been studied as thoroughly as myopia (Hammond, 2001). However, most individuals with Down's syndrome are hypermetropic (Bailey et al. 1989; Castane et al. 1995; Woodhouse et al. 1997). According to Teikari et al. (1990), hypermetropia could be hereditary. Therefore, it is of importance to investigate the heritability of hypermetropia (as well as myopia) in Down's syndrome.

- From clinical observations, refractive errors in children with Down's syndrome seem to follow a certain pattern. The same applies to typically developing children. We would like to investigate the development of refractive error, in terms of time and power, in a large number of children with Down's syndrome and compare it to that of the general population (already established by many studies).

- There are doubts about whether children with Down's syndrome suffer from colour vision defects more frequently than other children. A small number of studies have been pursued to clarify this matter; however, to date no study has produced satisfactory results. For example, Perez-Carpinell, de Fez and Climent, (1994) suggested that individuals with Down's syndrome have defective colour vision. However, many of their subjects had ocular problems such as lens opacities, which could have an effect on the results of a colour vision test. Sinson

and Wetherick (1973), suggested that individuals with Down's syndrome have a defect in colour vision retention and not discrimination. Furthermore, some studies, such as Salvia and Ysseldyke (1972) were not confident about the ability of the subjects to understand and perform the tests correctly. A more recent study by Rocco, Cronin-Golomb and Lai, (1997) suggests the presence of impairment in colour discrimination for short wavelengths (blue hues) in adults with Down's syndrome and linked this to the early onset of Alzheimer's. None of above studies successfully controlled for the contribution of learning disability to the results.

- Nystagmus is a visual problem that can be impairing (Abadi and Bjerre, 2002). Children with Down's syndrome are more prone to nystagmus than are typically developing children (Wagner, Caputo and Reynolds, 1990). However, anecdotally, this problem tends to be neglected by educationalists, and simply considered as part of the syndrome. In typically developing children, nystagmus reduces visual acuity and it associates with higher refractive error of a specific pattern(Chung and Bedell, 1995; Sampath and Bedell, 2002). However, Down's syndrome is associated with reduced visual acuity and high refractive errors even in the absence of nystagmus (Woodhouse et al., 1996a; Cregg et al., 2003). We would like to investigate the effect of nystagmus on visual acuity and refractive error in children with Down's syndrome and find a way of eliminating its impact.

Study aims and objectives:

1. This study will continue to monitor the development of vision and the prevalence of ocular/visual deficits amongst children with Down's syndrome, as determined by conventional clinical eye examination procedures

2. The study will determine the success rate of wearing bifocals amongst children with Down's syndrome. This will add to the evidence base for the management of accommodative dysfunction by the simple and cost-effective technique of bifocal spectacle correction. Further, if appreciable numbers of children are able to return to single vision wear, it will introduce further clinical guidelines for follow-up.

3. An investigation of the relationship between the refractive error in children with Down's syndrome and that of their parents and siblings will add to our current knowledge of the aetiology of refractive errors. Clinically, it could allow practitioners better predicting power for the progress of refraction in a child with Down's syndrome from an earlier age.

4. Studying the pattern of refractive errors development in children with Down's syndrome would, as well, enable for better prediction of refraction development in a child with Down's syndrome. This will add to the guidelines for clinical practice by indicating

critical periods of the child's life at which refractive errors need to be monitored more frequently and when it is likely to stabilise. In addition, refraction norms for children with Down's syndrome will be established.

5. Colours are widely used in the first school years to aid in education. The presence of a colour vision defect in a child complicates colour discrimination and requires modification to methods and materials in the school environment. Teachers tend to assume the presence of normal colour vision in the children. If the likelihood of colour vision disturbances proves to be greater among children with Down's syndrome than the general population, then educators and eye care practitioners need to be alerted to the importance of colour vision testing. This may even raise an issue about the genetics of colour vision since it is believed that none of the known colour vision problems is carried on chromosome 21. If colour is normal in children, then an extension of the study into adulthood will be important. Confirmation of an adult blue defect would indicate the possibility of using colour vision testing as a diagnostic test for the onset of Alzheimer's disease in adults with Down's syndrome, since dementia is difficult to evaluate in individuals with such learning disabilities.

6. Nystagmus is a visually impairing condition that is present in children with Down's syndrome at higher rates than in their typically developing peers. From our experience, it is often neglected when present in a child with Down's syndrome. This hinders education and the identification of its effect on vision would help guidelines for management and rehabilitation. Identifying the effect of nystagmus on the refractive errors of children with Down's syndrome will enable us to further understand the etiology of refractive errors in Down's syndrome.

Investigational Plan

Overall design

Prospective and retrospective case studies, and comparison with a typical population when appropriate.

Study population:

The Cardiff Down's Syndrome Vision Research Unit currently has 182 children on the database. At 10th January 2008, ages ranged from 12 months to 19years 3months. These children were recruited either under previous ethical approval procedures, or have joined the study at direct parental request. All will remain within the study as long as parents and children wish.

In addition, Dr Woodhouse and Mr. Al-Bagdady see a number of children with Down's syndrome clinically, referred from NHS practitioners, specifically ophthalmologists and paediatricians. Some are referred for study purposes, having discussed this with their referring practitioner; others are referred for clinical optometric evaluation and management. Mr. Watts sees children with Down's syndrome as part of his clinical remit, and co-manages many with Dr. Woodhouse. No clinical data for these NHS patients have yet been entered into the study, and it is for the inclusion of these subjects that the present application is made.

For those parts of the study that require comparison with typically developing children (e.g. colour vision), control subjects will be recruited. Many control subjects will be siblings of the children with Down's syndrome, and indeed, siblings will be specifically recruited for corneal topography and refractive error. Other control subjects will be recruited through staff and students of Cardiff University, local schools often involved in School of Optometry and Vision Sciences studies, and current patients of the School clinic.

Recruitment procedures

Parents of children with Down's syndrome who attend the School clinic, or when appropriate, Mr. Watts' clinic, will be invited to enter their child (and siblings) in the study. Parents who specifically request inclusion in the study and make an appointment with that intention, will also be included.

Parents of control children will be contacted by letter.

Older children will be provided with their own information sheets and asked to sign their own consent form, although parental consent will be mandatory.

Child Protection Issues:

Dr. Woodhouse, PI, and Mr. Al-Bagdady have a current CRB certificate.

When children attend the School clinic for research purposes, the following rules apply:

> A parent or guardian is present for all examination procedures. In exceptional circumstances when the parent/guardian is temporarily absent (for example, taking a sibling to the toilet), procedures are halted and the child simply entertained, with at least one adult present in addition to the researcher.

Some control children (e.g. for colour vision testing) will be seen outside the University, on their own school premises. The following rules apply:

> Children attend in pairs. No child is alone with the researcher. Research takes place in a centrally placed room (e.g. staff room), near occupied rooms (e.g. school office) and the room door is open at all times. Parents are invited to be present.

Methodology:

1. **Longitudinal evaluation of ocular and visual status**: research will be clinically based including prospective data from regular eye examinations of the subjects as well as retrospective information saved in clinical records. Older children with stable refractive errors and stable visual status are seen annually. Younger children, those with new spectacle prescriptions (including bifocals), and/or changing visual status are seen more frequently.

In general, regular eye examinations will include all or parts of the following:

- Refraction, cycloplegic and non-cycloplegic as clinically warranted
- Ophthalmoscopy (direct or indirect)
- Accommodative functions by retinoscopy
- Assessment of visual status at distance and near with age-appropriate tests
- Ocular motility and alignment
- Stereopsis
- Colour vision (usually on one occasion only, since colour vision is not expected to change over time), using PV-16 test, City University Colour Vision Test and the Mollon-Reffin test (depending on the child's abilities)
- Slit lamp assessment when indicated
- Axial length measures by non-invasive procedures (IOLMaster)
- Corneal topography (since keratoconus has a high prevalence amongst young adults with Down's syndrome)
- Fundus photography when indicated

2. **Evaluating the success rate of wearing bifocal lenses:**

Data will be collected from clinical records. Children of school age are prescribed bifocals when the accommodation is consistently defective (on at least two consecutive occasions, with full correction for a distance refractive error). Children are provided with one pair of bifocals and one pair of single vision lenses and instructions are given that the bifocals are initially for school use only. A letter describing the purpose of bifocals is sent to the school. Children are instructed to change into single vision spectacles at the end of the school day if they wish, but if they prefer to wear the bifocals full-time, they are encouraged to do so. 'Success rates' will be evaluated by the numbers of children prescribed bifocal lenses, the numbers wearing in school and the numbers choosing to wear the spectacles full-time. Out of those children, the numbers able to accommodate accurately using the bifocals on subsequent visits and the numbers able to return to single vision wear will be recorded.

3. Relationship of refractive error between the children and their parents and siblings:

Refractive error data for the children with Down's syndrome is obtained as above. A questionnaire (appendix 1), aimed at collecting information about the parents and siblings concerning age, spectacle wear and opticians/optometrists details will be sent by post to all of the participating families of the Cardiff cohort. The refractive status of the parents and siblings will be obtained either by refracting them in clinic using autorefractors (for adults) or conventional retinoscopy procedures (for children) or by writing to their optometrist/opticians.

4. Development and distribution of refractive errors in children with Down's syndrome:

This will be done by following the development of refractive errors from the patient's clinical records, evaluating the periods at which refractive development is found to be rapid and the time when it stabilizes. The value of refractive errors during both periods will be considered. This will be then compared to that of the general population.

5. Investigating colour vision in children with Down's syndrome:

This will be done by using the PV-16 colour vision test, the City University colour vision test and the Mollon-Reffin test. Choice will be made according to the child's ability to perform the task required for the completion of the test. All tests are considered suitable for children. Control data will be collected under similar conditions (daylight bulb- Illuminant C) by school visits.

6. The effect of nystagmus on visual acuity and refractive errors in children with Down's syndrome:

Refractive errors and visual acuity measurements of all children with Down's syndrome who present with nystagmus will be collected from their clinical records and compared to those of children with Down's syndrome who do not have nystagmus. The presence or absence of nystagmus is indicated in the clinical records of each patient.

Data Management

Data for the study will be stored electronically in password-protected filespace available only to researchers involved in this project. Hard copies will be stored in a locked filing cabinet in the School clinic.

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Woodhouse J M, Pakeman V H, Saunders K J, Parker M, Fraser W I, Lobo S, and Sastry P (1996a) Visual acuity and accommodation in infants and young children with Down's syndrome. *Journal of Intellectual Disability Research* 40: 49-55.

Woodhouse J M, Pakeman V H, Saunders K J, Parker M, Fraser W I, Lobo S, and Sastry P (1996b) Visual acuity and accommodation in infants and young children with Down syndrome. *Journal of Intellectual Disability Research* 40: 49-55.

Vision in children with Down's syndrome

We would like to invite you and your child to take part in our study. Before you decide, you need to understand why the research is being done and what it would involve for you. Please take time to read the following information carefully. Talk to others about the study if you wish.

Why do we study vision and eyes in children with Down's syndrome?

Children with Down's syndrome are at much greater risk of eye and vision disorders than are typically developing children. Even when children wear glasses to correct long or short-sight, or even if they do not need glasses, children with Down's syndrome may have some visual difficulties. It is, therefore, very important that we understand the ways in which children's eyes develop and how we can best help them make the most of their vision.

Who are we?

At the Down's Syndrome Vision Research Unit, we have been studying visual development in children with Down's syndrome since 1992. We have a large group of enthusiastic and highly committed families taking part in our studies, many of whom have been with us since the beginning, and we see over 150 children regularly.

Why are we asking you to enrol your child in the study?

Because we are doing research, we need to collect information from many children and look for overall trends. We need your consent before we can use your child's information.

What would we do?

Most of our studies involve conventional eye-tests, measuring how well your child can see small or faint targets, measuring how well the eyes work together and so on – exactly what your local optometrist or hospital eye department will be doing. However, we do not use eye drops or any drugs.

What will you have to do?

You will not need to do anything and you will not need to bring your child specifically for our studies. We are only asking you to allow us to use the results of the eye examinations your child routinely has in our clinic. This means that you will only bring your child to routine appointments (as you usually do) where we will do the appropriate examinations and treatment as we usually do. The only difference is that we will use the outcomes in our research. If you do not routinely attend to our clinic for your eye tests, we may ask you to give us a separate consent to allow us obtain your eye test results from your local optometrist.

Why do we want to use the results of the parent's eye tests?

Some eye and vision defects are seemingly inherited like many other characteristics. This is confirmed by many studies in typically developing children; a good example is long- and short-sight. However, we don't know if such relationship exists for children with

Down's syndrome. Allowing us to use your test results will enable us to compare them to that of your child.

Vision in children with Down's syndrome

Will my child's information be confidential?
The information about you and your child remains completely confidential. When we publish research results (in journals or in talks etc.) we do not identify your child in any way.

We also occasionally carry out studies that involve different measures to a conventional eye test. In those cases, we ask for separate consent.

Will I know the results of the research?
Children who join our study are extremely valuable to us and we appreciate all of the effort that parents put in to take part. We keep families up to date with newsletters whenever we have any results to report (our parents are always the first to know the outcome of our research). We also organise information days and get-togethers occasionally.

Do I have to enrol my child?
Joining the study is voluntary, and you have the right to refuse joining. In any case, we respect your decision and it will not affect the standards of eye care you get from our clinic.

What happens if I want to withdraw my child from the study?
You are free to withdraw at any time, without giving a reason. However, any published results that included your child's data will be impossible to modify or discard. Nonetheless, if you decide to withdraw your child, we promises not to use his/her past and future results in any further studies that take place after the date during which we are informed of your decision.

We cannot promise the study will help you but the information we get from this study will help improve eye care for children with Down's syndrome.

If you are happy for your child to join the study, please sign the form overleaf.

For any questions, please feel free to ask any of the researches by contacting Mr Mohammad Al-Bagdady (+44 (0)29 2087 0247) or Dr Maggie Woodhouse whose contact details are provided below.

J. Margaret Woodhouse
Tel: +44 (0)29 2087 6522
Email: woodhouse@cf.ac.uk
http://www.cardiff.ac.uk/optom/DownsSyndromeGroup/Home.html

The work of the Down's Syndrome Vision Research Unit has been funded over the years by:
The Down's Syndrome Association, Mencap with the Community Fund, Mencap City Foundation, PPP Foundation, National Eye Research Centre, Welsh Assembly Government

Vision in children with Down's syndrome

I have read and understood the information about the study and had the opportunity to ask questions.

I understand that I may withdraw my child from the study at any time, and this will not affect the standard of care that my child receives.

Please tick as appropriate.

I consent to you using my previous eye test results for your research. ☐

I consent to you using my future eye test results for your research. ☐

I consent to you to use my child's previous eye test results for your research. ☐

I consent to you using my child's future eye test results for your research. ☐

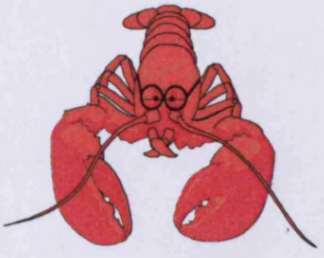
Child's name .....

Parent's name.....

Signature..... Date.....

I am happy to join your studies

Child's signature.....



Appendix II

Reasons for different normality tests

Power calculations

Normality tests

In order to decide on statistical test use for data analysis, the nature of the distribution of these data should be known. Parametric statistical tests have assumptions. One of these assumption is regarding the distribution of the sample, they assumes that the sample comes from a Gaussian *or normal* distribution. Generally, when this assumption is violated, non-parametric statistical methods are preferred.

There are different ways of testing the normality of a distribution, one of which is through statistical analysis. There are several tests and two of which were used in this thesis; the Kolmogorov-Smirnov (K-S) test and the Shapiro-Wilk (S-W) test.

Although the K-S test is useful for detecting deviation from normality in large samples, it is less powerful and therefore can miss non-normality in small sample sizes. The S-W test is a more powerful test that is useful for small to medium sample sizes (Conover, 1999; Gaten, 2000). However, statisticians often prefer the use of graphical methods to help in deciding upon the normality of a distribution.

In this thesis, the S-W test was used when the sample was small (less than 50), and the K-S was used otherwise (Gaten, 2000). In all cases, frequency distribution histograms were created to assess the normality of the distribution visually.

References

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Note - professional opinion was consulted regarding the information above prior to conducting statistical analysis

Power calculations

High numbers of participants are always desired in clinical research. However, cost and time can hinder this. Power calculations are used to determine the minimum number of participants needed for an experiment so that the result of statistical tests with a particular level of confidence can be accepted (95% is often used in clinical research).

Power calculations were not conducted in the studies of this thesis due to the limited control over sample size. Children could only be seen for research as part of their clinical consultation. In addition, limited funding prohibited reimbursing participants for their time and/or for travel expenses. When adult participants were recruited for colour vision test validation, it was not possible to create a cohort of people with colour vision defects within the timeframe of the study. Therefore, the maximum possible number of participants was always included.

Appendix III

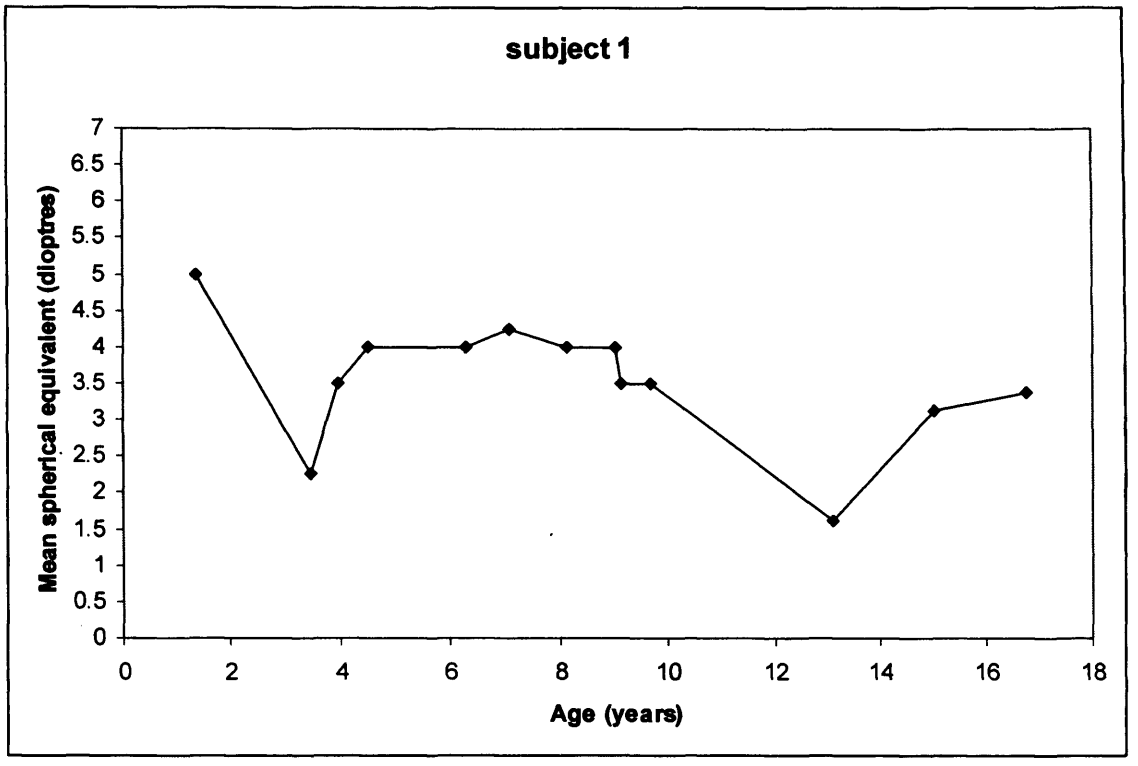
Choice of statistical tests for data analysis (Chapter Three)

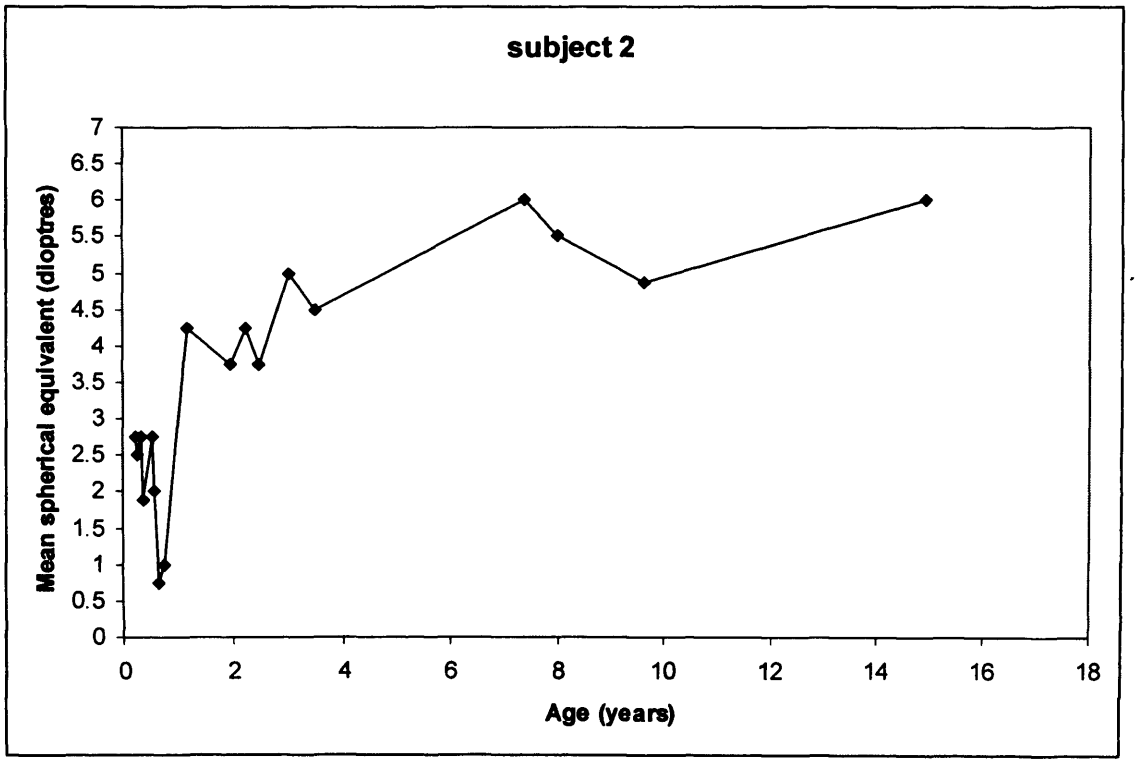
Individual line graphs for 6 participants showing longitudinal refractive error development over 15 years (Chapter Three)

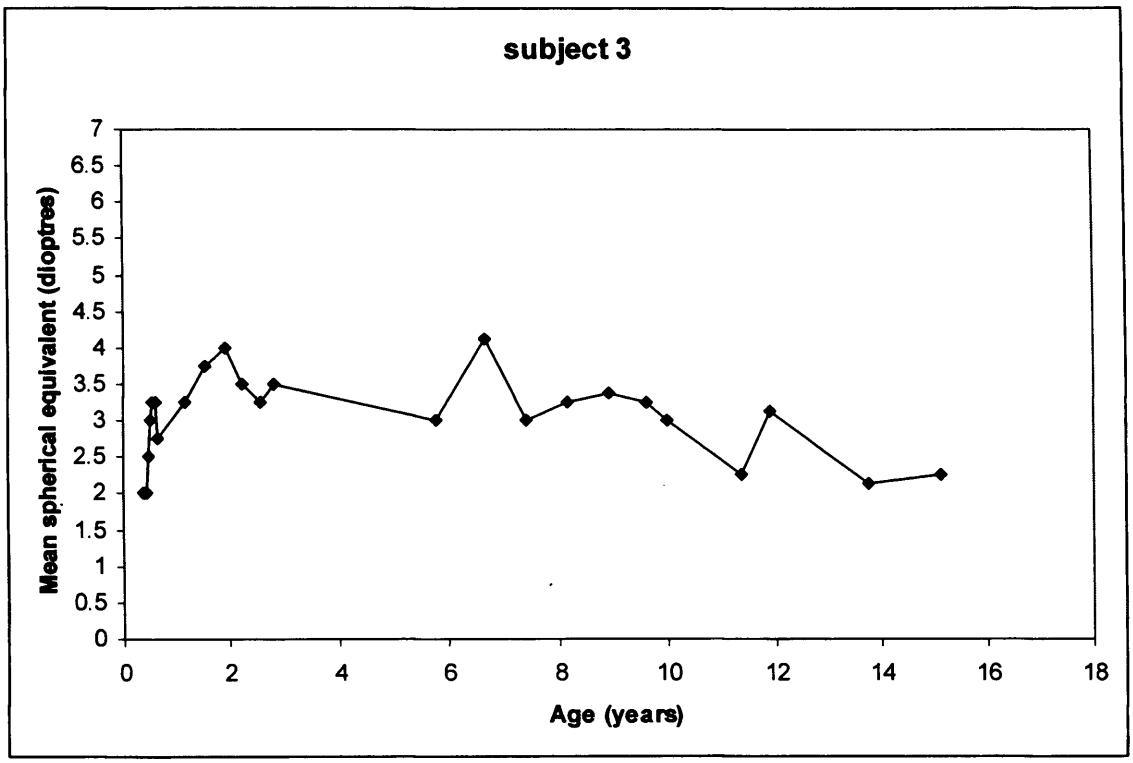
Choice of statistical tests for data analysis (Chapter Three)

- Data were not normally distributed, therefore non-parametric statistical tests were chosen.
- Most of the children were present in more than one age group. This has created a difficulty in deciding whither the samples were related or they were independent. Therefore, A Kruskal-Wallis was performed as some children were only present in one age group, and a Friedman test was performed as the data was not entirely independent.
- The Friedman Test requires the same number of participants in each group (related-samples). Therefore, the test was conducted with 20 randomly chosen participants from each age group and individual Wilcoxon signed-rank tests were performed on each pair of age-groups (e.g individual comparisons between *Age-group 1 and Age-group 2*, *Age-group 1 and Age-group 3* ... etc.). This aided in including more refractions and acted as a post-hoc to locate the position of a statistically significant difference in refractive error between the groups (Pallant, 2007).

Individual line graphs for 6 participants showing longitudinal refractive error development over 15 years (Chapter Three)



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Mean spherical equivalent (dioptres)
7
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4.5
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3
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12
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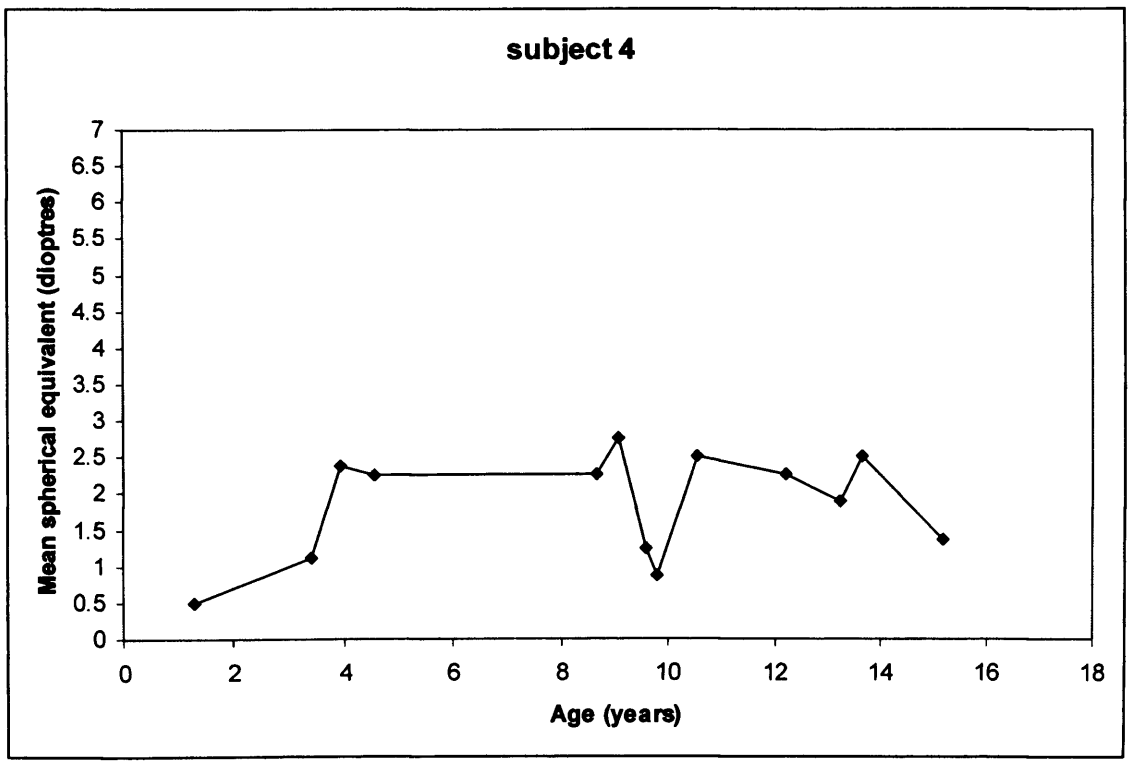
16
18
Age (years)


subject 4
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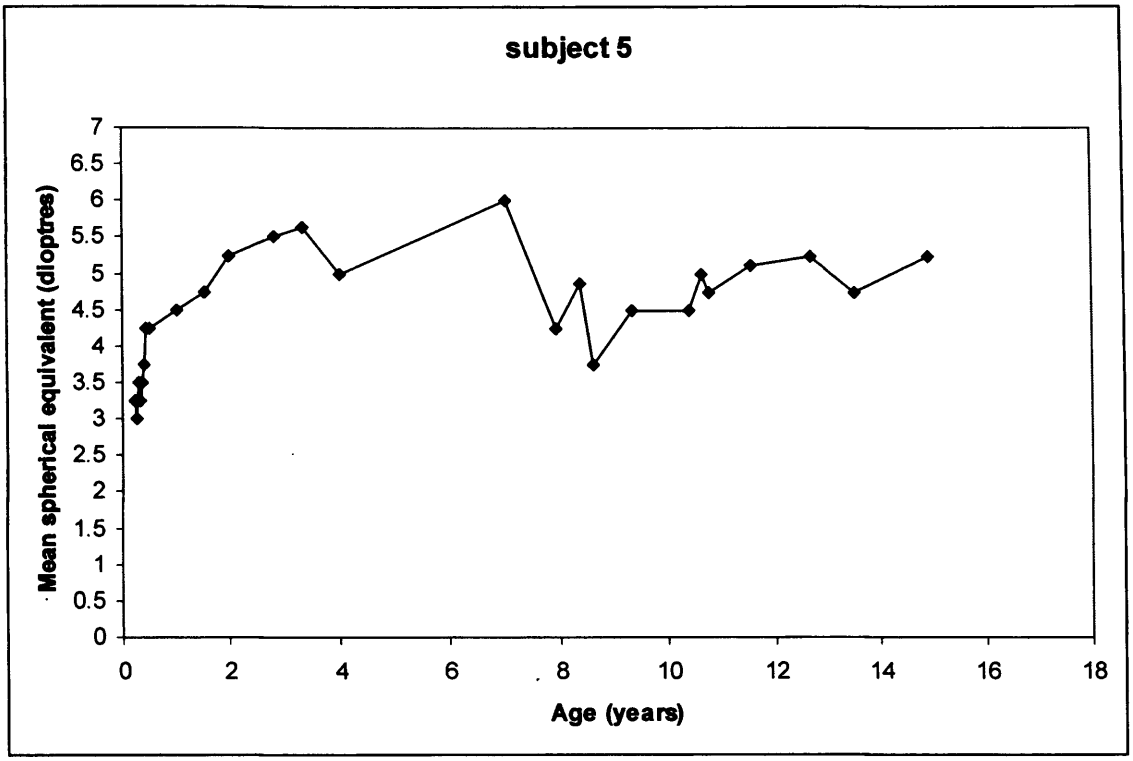
Age (years)


subject 5
Mean spherical equivalent (dioptres)
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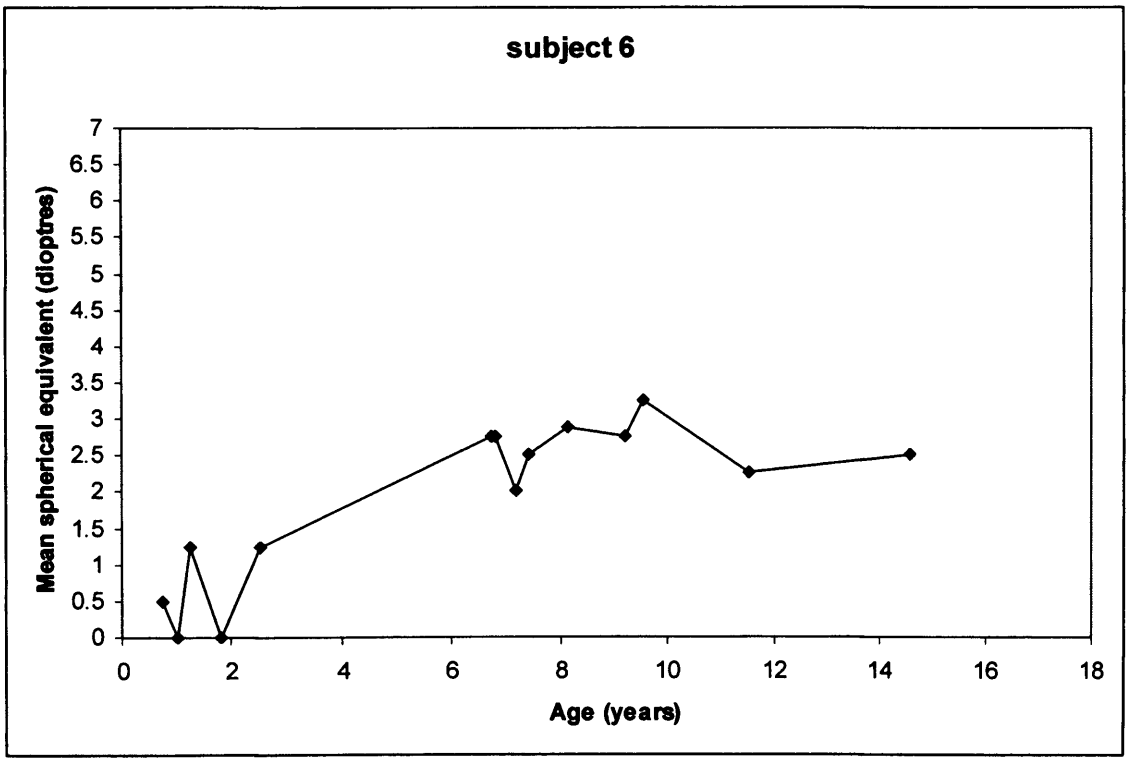
Age (years)


subject 6
Mean spherical equivalent (dioptres)
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6
8
10
12
14
16
18
Age (years)

Appendix IV

Familial refractive error collection (Chapter Four):

Invitation letter

Families' questionnaire

Consent form

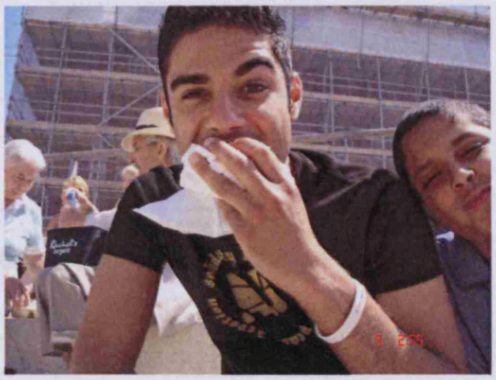
Optometrists' covering letter

Optometrists' questionnaire

Visual development in children with Down's syndrome

CARDIFF UNIVERSITY
PRIFYSGOL CAERDYDD

Dear



Thank you for your interest in joining the study. My name is Mohammad Al-Bagdady. I am a member of the Cardiff Down's Syndrome Vision Research Unit which was established in 1992 and still continuing a long-term monitoring of visual development in children with Down's syndrome.

We are currently collecting some new information that will be fundamental in identifying the relationship between the children's long or short-sight and that of their parents and siblings. I would be really grateful if you would help me by filling in the attached questionnaire and returning it in the enclosed envelope.

Please feel free to contact me if you have any questions either by phone (07884443173) or via email (al-bagdadym@cardiff.ac.uk)

Thank you for your time!

Yours sincerely,

Mohammad Al-Bagdady

Relationship between the long or short sight in children with Down's syndrome and that of their family

Please complete as fully as possible, but *feel free to leave blanks if you do not wish to provide the information*

Child's Name	Date of birth	Gender (M/F)	Wearing glasses/ Contact lenses*	Optometrist/ Optician details

Parents:

Name	Date of birth	Wearing glasses/Contact lenses*	Optometrist / Optician details
Birth Mother:			
Birth Father:			

Brothers and sisters:

Name	Date of birth	Gender (M/F)	Is Mother same as above YES/NO	Is Father same as above YES/NO	Wearing glasses/contact lenses*	Optometrist / Optician details

*Please indicate if wearing glasses/contact lenses or had refractive surgery or none of this.

Signatures from parent(s) and any sibling(s) aged 16 years and over are required in order to be able to access their clinical records. Please find the consent forms attached to this form and fill as necessary.

Thank You!

I consent to your contacting the optometrists/opticians listed overleaf to obtain details of refractive error (long or short-sight), visual acuity and prescription details.

Name: Date:

Signature:

I consent to your contacting the optometrists/opticians listed overleaf to obtain details of refractive error (long or short-sight), visual acuity and prescription details.

Name: Date:

Signature:

I consent to your contacting the optometrists/opticians listed overleaf to obtain details of refractive error (long or short-sight), visual acuity and prescription details.

Name: Date:

Signature:

I consent to your contacting the optometrists/opticians listed overleaf to obtain details of refractive error (long or short-sight), visual acuity and prescription details.

Name: Date:

Signature:

I consent to your contacting the optometrists/opticians listed overleaf to obtain details of refractive error (long or short-sight), visual acuity and prescription details.

Name: Date:

Signature:

Thank You!

Practice Name
Practice address
City
XX11 4XX

Dear Sir/Madam,

My name is Mohammad Al-Bagdady, a PhD student at Cardiff University School of Optometry and Vision Sciences. I am a member of the Cardiff Down's Syndrome Vision Research Unit which was established in 1992 and still continuing a long-term monitoring of visual development in children with Down's syndrome. We currently have a cohort of over 180 families who constantly participate in our studies.

We are now collecting some new information that will be fundamental in identifying the relationship between the children's refractive error and that of their parents and siblings. We have asked our members to provide us with their optometrist/optician details and we note one of our members attend to your clinic. I would be really grateful if you would help me by filling in the attached questionnaire and return it in the enclosed envelope. Information can also be sent by email if it is more convenient for you. Please note that a copy of the consent form is attached to this letter.

Please feel free to contact me if you have any questions either by phone (07884443173) or via email (al-bagdadym@cardiff.ac.uk)

Thank you for your time!

Yours,

Mohammad Al-Bagdady

Relationship between refractive error of children with Down's syndrome and that of their parents and siblings

Please complete as fully as possible.

Patient's name:
DoB:

Date of eye test: .....

Refractive Error	**Prescribed Distance Rx**	**Distance VA**	
R:	R:	R:	Binoc:
L:	L:	L:	

Name: .....

Date: .....

Signature: .....

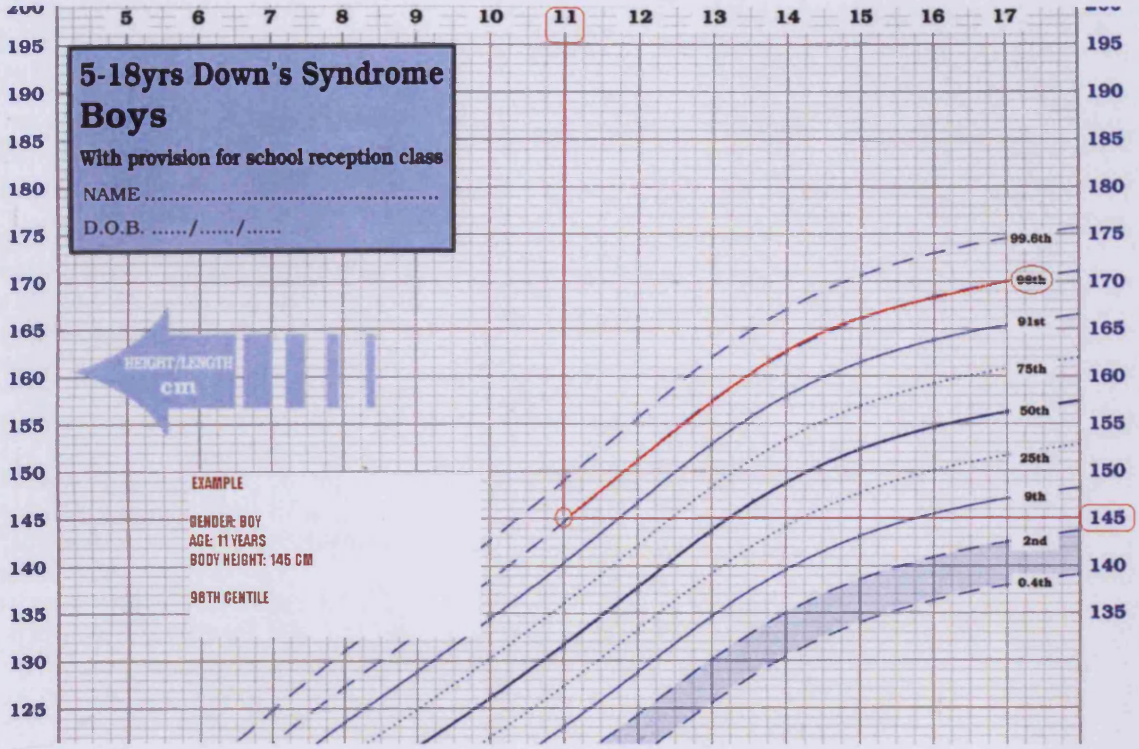
Thank You!

School of Optometry & Vision Sciences, Maindy Road, Cardiff University, Cardiff CF24 4LU

Appendix V

The Down's Syndrome Medical Interest Group (DSMIG) height centile chart (Chapter Five)

An example of the Down's syndrome growth charts



The example shows the method of determining the height centile for an 11 year old boy with DS with a height of 145 cm.

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Bifocals and Down's syndrome: correction or treatment?

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Abstract

Purpose: Accommodation is reduced in approximately 75% of children with Down's syndrome (DS). Bifocals have been shown to be beneficial and they are currently prescribed regularly. Clinical observations suggest the likelihood of improving accommodative ability after bifocal wear. The aim of the study is to evaluate the potential use of bifocals as a treatment for the reduced accommodation.

Methods: Clinical records of 40 children from the Cardiff Down's Syndrome Vision Research Unit, who were prescribed bifocals, were reviewed. Accommodation was noted before wearing the bifocals and during either their latest visit or when the children stopped using bifocals. Accommodation was reassessed during a follow up visit for the children who stopped wearing bifocals. Development of accommodation before bifocal commencement, age at bifocal prescription, gender, type of refractive error, visual acuity and the presence of strabismus were examined to evaluate their contribution to accommodation improvement.

Results: The accommodative ability of 65% (n = 26) of the children improved (through the distance part of the lens) after using the bifocals. More than half of those developed accurate accommodation without the use of bifocals (n = 14). Accommodative responses did not show any improvement with age before the children began wearing bifocals. Accurate accommodation was sustained after returning to single vision lenses in all examined children. The age distribution of the children on bifocal commencement was diverse. Presence of strabismus, refractive error type, visual acuity and gender did not have any effect on gaining improvement.

Conclusions: Bifocals are an effective correction for the reduced accommodation in children with DS and also act to improve accommodation with a success rate of 65%. Bifocal wear can therefore be temporary, i.e. a 'treatment' for the deficit, in at least one third of children.

Keywords: accommodation, bifocals, children, Down's syndrome

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A talk in the XIth Biennial Meeting of The Child Vision Research Society, London, June 2007
A talk in the British Congress for Optometry and Vision Sciences, N. Ireland, September 2007 that resulted in the publication of the abstract: Al-Bagdady M, Stewart RE and Woodhouse JM. The Success Rate of Wearing Bifocals in Children with Down's Syndrome. Ophthalmic and Physiological Optics. 2008; 28 (1): 101

Introduction

Accommodation is typically inaccurate in the majority of children with Down's syndrome (DS) (Woodhouse *et al.*, 1993; Cregg *et al.*, 2001; Haugen and Hövding, 2001). The children tend to under-accommodate, i.e. focus behind the object of interest. The deficit tends to further increase with age, and single vision spectacles do not improve it (Woodhouse *et al.*, 2000; Cregg *et al.*, 2001). Bifocal spectacles are known to aid presbyopic adults. A previous study showed that bifocals can be worn successfully by children with DS to improve accommodative accuracy through the bifocal segment (Stewart *et al.*, 2005). In the same study, accommoda-

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tion also improved, on average, through the distance part of the lens and was accurate for nine of the 17 children on at least one occasion. Accurate accommodation often manifested as less frequent use of the bifocal segment. However, it is still unknown whether occasional accurate accommodation is a sign of consistent improvement. Guidelines on bifocal prescription for the purpose of improving accommodative accuracy are not yet established.

The aim of the present study was to assess the change in accommodative accuracy as a result of wearing bifocal spectacles amongst children with DS and to evaluate the sustainability of accurate accommodation after the treatment. This will provide guidelines for bifocal prescription to children with DS and possibly alter the aim of bifocal prescription.

Methods

Study population

All the children from the Cardiff Down's Syndrome Vision Research Unit, who were prescribed bifocal spectacles, participated in this study (n = 40). Ages on first prescription of bifocals ranged from 4.96 years to 14.64 years. Prescription of bifocals was determined purely on measurement of accommodation for all children presenting with reduced accommodation. Distance vision was fully corrected and a bifocal add of +2.50 D was prescribed for all of the children presenting with accommodative lag that was higher than that of typically developing children shown by McClelland and Saunders (2004). Accommodation measurements for this study were performed by J. M. Woodhouse, M. Al-Bagdady and R. E. Stewart. The research followed the tenets of the Declaration of Helsinki. Ethics Committee approval was obtained for the study and all parents gave written consent for the children's data to be included in the study. The majority of our participants joined the cohort without awareness of any eye problems; they were identified at birth in collaboration with the Cytogenetics Department of the University Hospital of Wales (Woodhouse *et al.*, 1996). Children undergo regular ophthalmic examinations as part of the study protocol. Information for the present analysis was extracted from clinical records.

Methods

Accommodative accuracy is measured routinely in children from the cohort using Modified Nott dynamic retinoscopy technique which has been fully described and validated by previous studies (Woodhouse *et al.*, 1993; McClelland and Saunders, 2003). Accommodation was measured at three distances; 10, 16.7 and 25 cm, i.e. 10, 6 and 4 Dioptres, respectively. Accommodation was measured while the child looked at the target both through the bifocal segment and through the distance part of the lens. Accommodative lag at the three distances was used to calculate the accommodative responses before, while and after wearing bifocals. Data for all of the children who were prescribed bifocals, were recorded for the visit when bifocals were first prescribed (baseline visit) and for either their latest visit or the visit when bifocals were discarded (for those who developed accurate accommodation). Accommodation was also noted for the latest follow up visits for those who returned to single vision wear, in order to evaluate the sustainability of accurate accommodation after the bifocal treatment. The age of the participants, the gender, visual acuity, the presence of strabismus and the refractive error (mean sphere right eye) were also recorded for the day of prescription of bifocals. These factors were compared between those children with accurate accommodation who returned into single vision lens wear; those with improved accommodation who did not achieve accurate accommodation; and those who did not show improvement. Visual acuity was measured by age- and ability-appropriate clinical tests. These were the Kay Pictures (LogMAR version) or Keeler LogMAR letter test; both used at 3 m. Jones *et al.* (2003) have shown equivalence between the two tests in typical children. An independent sample t-test was used to compare visual acuity, refractive errors and age between the two groups. A chi-square test was used to compare the prevalence of strabismus, and gender, between the two groups. Data analysis was performed using the SPSS data editor version 12.0 (SPSS Inc., Chicago, IL, USA).

Accommodative responses whilst wearing bifocal spectacles. The following protocol was used to determine *accurate* and *improved* accommodation both through the bifocal segment and through the distance portion of the bifocal (or through single vision lenses). Accommodation was considered *accurate* when the lag was less than or equal to the following values in at least 2 of the 3 distances: 2.50 D lag at 10 D demand, 0.74 D lag at 6 D demand and 0.30 D lag at 4 D demand. These values are the age norms of school children aged 4–15 (McClelland and Saunders, 2004). *Improvement* in accommodation was defined as a reduction of lag for at least 2 of the 3 distances by 1.34 D at 10 D demand, 1.09 D at 6 D demand and 0.56 D at 4 D demand *when the child looked through the distance part of the lens.* These criteria were determined by considering the repeatability of the technique (which will determine the presence of a 'real' change in accommodation) (McClelland and Saunders, 2003).

Accommodative responses before wearing bifocal spectacles. The development of the accommodative responses of the children before wearing the bifocals was evaluated. The accommodative lag of the children whose accommodation had improved with bifocals was collected from their clinical records from the earliest eye examination at which their accommodation was measured, and then compared to that measured on the day of bifocal prescription. The same criteria as above were used in determining change in accommodation.

Accommodative responses after returning to single vision spectacles wear. Children with accurate accommodation were returned to single vision spectacles, when appropriate (i.e. when there was a significant distance refractive error). Their accommodation was recorded during a follow up visit to evaluate the sustainability of accurate accommodation after returning to single vision wear. The same criteria as above were used to determine accuracy of accommodation.

Results

Accommodation measurement was obtainable for all 40 subjects through the distance portion of the lens and through the bifocal segment. *Table 1* summarises the results. It shows the accommodative lag of all participants during the visit at which bifocals were prescribed, and during the child's latest visit with bifocal spectacles, whilst viewing through the distance portion of the lens.

Accommodation was accurate in 38 subjects (95%) when looking through the near add of the bifocals (in some cases, this was not the latest visit, but the latest at which the child brought their bifocal spectacles). However, the remaining two subjects showed improvement in accommodation through the near add.

Twenty-six out of 40 children (65%) showed an improvement in accommodation through the distance portion of the lens. *Figure 1* shows the mean accommodative lag during the baseline visit and during the latest visit for the 26 children with improved accommodation. It can be seen that accommodative lag for those 26 reached the age norms during the latest visit. Data for the 14 children whose accommodation did not show improvement according to our criteria are represented in *Figure 2*.

Moreover, 14 out of the 26 children with improved accommodation had accurate accommodation and all were returned to single vision wear if needed. This accounts for 35% of the overall number of children included in this study. Follow-up interval varied from 1 and 7.8 years between bifocal prescription and latest visit with bifocals (Mean = 3.41 years).

Of the 26 subjects whose accommodation improved, data on accommodation before the day of bifocal prescription were available for only 16 subjects. This is because the remaining 10 cases joined the cohort due to a specific interest by the parents in bifocals for their child: accommodative deficit was confirmed on examination and bifocals were prescribed at the first visit. Accommodation improved with age in only 2 of the 16 children before starting bifocal wear. The data for all 16 subjects during their first visit to our clinic and during the visit when bifocals were prescribed are shown in *Table 2*. Mean time interval between the two visits was 4.96 years (S.D. = 2.7).

Six participants have been seen to date for a follow up assessment after returning to single vision spectacle wear. All of these have shown sustained accurate accommodation. Follow up time ranged from 1.53 to 5.02 years (mean = 3.50 years).

For analysis, the children were divided into two groups; children with improved accommodation and children who did not show any improvement. An independent sample t-test showed no significant difference in age between the two groups on bifocal prescription day, $t(38) = 0.879$, $p = 0.385$ (two-tailed). There was no significant difference between the two groups in prevalence of strabismus [Asymp. Sig. (two-sided) = 0.307], visual acuity [$t(38) = 0.664$, Sig. (two-tailed) = 0.511], mean sphere refractive error [$t(38) = -0.922$, Sig. (two-tailed) = 0.362] and gender [Asymp. Sig. (two-sided) = 0.697]. Children with improved accommodation were divided into two subgroups; children with accurate accommodation and children with improvement only. Similarly, visual acuity [$t(24) = 1.734$, Sig. (two-tailed) = 0.096], age [$t(24) = -1.028$, $p = 0.314$ (two-tailed)], mean sphere refractive error [$t(24) = 0.771$, Sig. (two-tailed) = 0.448], presence of strabismus [Asymp. Sig. (two-sided) = 0.49] and gender [Asymp. Sig. (two-sided) = 0.019] were compared between the two groups. No statistically significant difference was found between the two groups in any aspect except gender: out of the 14 children who became accurate 12 were boys and 2 were girls.

Discussion

Accommodation through the bifocal segment was accurate in 95% of the subjects, and improved over the top of the bifocal segment in the majority of the children while wearing bifocal spectacles. Other factors that may influence accommodation, such as strabismus or refractive error cannot account for the improvement in accommodation. Over a third of all children prescribed bifocals achieved accurate accommodation when looking over the top of the bifocal. These children have returned to single vision spectacle wear and all of those reassessed so far have remained

Table 1. Accommodative lag with fully corrected distance vision for the total number of subjects during initial assessment and follow up

Subject number	Age on prescription (years)	Accommodative lag 10 D	6 D	4 D	Age on follow-up (years)	Accommodative lag 10 D	6 D	4 D
Subjects that developed accurate accommodation								
1	13.73	6	OS	OS	15.49	0	0	0
2	7.87	2.31	1.12	1.06	10.04	0	0	0.55
3	9.42	4.44	2.43	1.62	12.32	1.67	0	0.15
4	9.15	4.44	2.43	1.50	11.74	0	0	1.06
5	9.66	6.43	3.62	2.39	12.33	2.31	0.44	0
6	10.55	3.75	1.65	0.30	13.67	1.67	0.12	0.30
7	7.80	3.33	2.30	1.50	9.84	3.75	0	0
8	8.20	2.86	2.15	0.67	12.58	0	0	0
9	14.33	OS	OS	OS	17.99	NA	0	0
10	6.28	6.77	3.87	2.33	11.62	0	0	0
11	5.85	7.44	3.83	2.70	13.64	1.67	0.12	0
12	5.92	3.33	2.55	1.83	10.50	0	0	0
13	6.50	6.30	3.67	1.92	10.35	0	0.44	0
14	14.64	3.33	1.24	0.67	15.65	0	0	0
Subjects with *improved only* accommodation								
15	9.26	OS	OS	OS	11.87	3.33	1.45	0
16	9.42	6.67	4.44	OS	16.64	4.44	2.30	1.22
17	13.79	6.97	3.78	2.08	15.27	1.67	1.24	0.55
18	8.10	OS	3.83	OS	10.36	4.12	1.45	1.14
19	4.96	4.12	3.14	1.92	8.31	1.67	1.24	0.77
20	13.81	5	3.67	OS	15.93	3.33	0.12	NA
21	12.59	7.62	4.11	2.51	17.33	4.74	1.45	0.77
22	6.88	6.88	4.15	2.65	8.36	4.74	2.77	1.92
23	6.69	6.15	2.77	1.62	11.64	1.67	1.24	1.06
24	9.17	5.65	3.14	2.04	12.70	3.75	1.24	1.30
25	6.62	6.30	3.62	2.39	11.65	4.12	2.43	1.06
26	6.22	4.74	2.15	0.67	8.04	2.86	1	0.43
Subject with no improvement in accommodation								
27	7.14	6.67	3.73	OS	9.27	8.21	OS	OS
28	9.42	2.31	2	1.83	13.13	2.86	1.83	1.06
29	7.42	5.65	3.67	2	15.13	4.74	2.67	0.30
30	11.34	3.75	2.88	1.56	13.70	1.67	2.67	1.67
31	8.03	4.44	2.67	1.92	13.12	7.50	3.78	2
32	6.25	6.30	2.30	1.67	9.11	6.67	3.50	OS
33	6.02	4.12	2.88	1.78	8.45	5.65	3.50	OS
34	9.44	3.75	1.24	0.88	11.93	6.43	2.43	1.22
35	10.63	4.44	2	0.97	14.91	4.12	2.15	1.22
36	7.51	5.65	2.55	1.92	9.93	6	3.06	1.22
37	7.02	3.75	0.44	0.43	14.36	3.33	1	0
38	9.35	3.55	2.15	1.37	14.19	4.44	2.15	1.37
39	9.55	3.10	2.67	1.37	11.52	5.24	2.77	1.92
40	8.07	3.75	1.83	2.08	12.81	NA	1.65	1.56

OS = off scale; NA = accommodation was not measured.

accurate. Hence, bifocal spectacle wear can be temporary and can be considered a 'treatment' for the reduced accommodation often experienced by children with DS. It remains to be seen, when children have worn bifocals for longer, whether more of the children will be able to return to single vision spectacle wear: it also remains to be seen whether children returning to single vision wear can maintain accurate accommodation over the long term.

Accommodation is reduced in most children with DS (Woodhouse *et al.*, 1993; Cregg *et al.*, 2001; Haugen *et al.*, 2001) and this is confirmed by the high accommodative lag of the children before wearing the bifocals (*Figures 1 and 2*). Reduced accommodation is mainly associated with the presence of hypermetropia and strabismus (Stewart *et al.*, 2007), both of which are very common amongst children with DS. Accommodation remains reduced in children with DS even when the

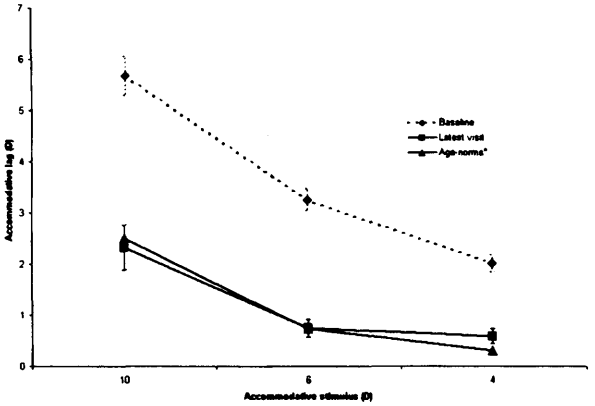

Figure 1. Accommodative lag during baseline visit and during follow up visit for children with improved accommodation ($n = 26$). Data points indicate the mean accommodative lag at each testing distance in dioptres and error bars represents standard error. *Age norms for accommodative lag for school age children (McClelland and Saunders, 2004).

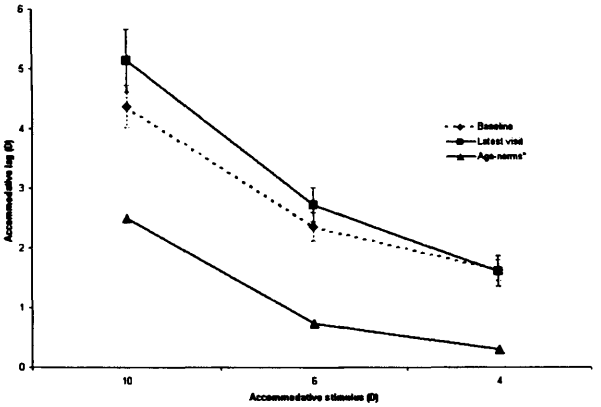

Figure 2. Accommodative lag during baseline visit and during follow up visit for children with no accommodation improvement ($n = 14$). Data points indicate the mean accommodative lag at each testing distance in dioptres and error bars represent standard error. *Age norms for accommodative lag for school age children (McClelland and Saunders, 2004).

distance refractive error is fully corrected by means of single vision spectacles (Cregg *et al.*, 2001). This indicates that the prescription of separate single vision spectacles, for near and for distance, might not improve the children's own accommodative responses, although they might be beneficial as an optical correction. In addition, the prescription of single vision spectacles for near is not suitable because children need clear images at distance and at near simultaneously for school. Bifocal spectacles are a very successful method of improving near focusing in children with DS both through the near add and through the distance portion of the lens (Stewart *et al.*, 2005). There was excellent tolerance and acceptance from the children and their carers and educators, and no adverse reactions were reported (Stewart *et al.*, 2005). Our results, *Figure 1*, showed that the mean accommodative lag of children with DS who showed accommodation improvement reached that of typically developing children (McClelland and Saunders, 2004). There is, however, variation in accommodative lag in both typically developing children and children with DS with improvement in accommodation,

Table 2. Accommodative lag with fully corrected distance vision for 16 subjects during first clinical assessment and on bifocal prescription day

Subject number	Age on 1st clinical examination (years)	Accommodative lag			Age on prescription (years)	Accommodative lag		
		10 D	6 D	4 D		10 D	6 D	4 D
Subjects with improvement in accommodation with age								
3	3.68	4.55	3.70	2.50	9.42	4.44	2.43	1.62
6	3.43	5.26	3.23	2.63	10.55	3.75	1.65	0.30
Subjects with no improvement in accommodation with age								
1	4.75	6.66	3.50	1.50	13.73	6	OS	OS
15	1.24	6.30	3.30	2.25	9.26	OS	OS	OS
16	9.27	3.33	1.56	OS	9.42	6.67	4.44	OS
4	3.47	5.88	2.78	1.54	9.15	4.44	2.43	1.50
17	5.56	2.78	1.61	1.25	13.79	6.97	3.78	2.08
5	5.03	1.96	1.64	1.39	9.66	6.43	3.62	2.39
18	1.60	4.12	1.83	1.14	8.10	OS	3.83	OS
7	2.05	3.03	3.22	2.08	7.80	3.33	2.30	1.50
20	5.56	3.85	2.13	1.69	13.81	5	3.67	OS
9	4.99	7.22	3.73	2.08	14.33	OS	OS	OS
10	2.22	5.88	3.84	OS	6.28	6.77	3.87	2.33
12	3.24	3.33	2.67	1.50	5.92	3.33	2.55	1.83
23	2.66	3.03	2.43	OS	6.69	6.15	2.77	1.62
24	6.79	5.88	3.44	2.50	9.17	5.65	3.14	2.04

OS = off scale.

so that not all children within the normal range would be described as accurate according to our criteria.

Age, cognitive abilities and target size cannot account for any improvement in accommodation in children with DS (Woodhouse *et al.*, 2000). This, in addition to the diversity of the children's ages on bifocal prescription, suggests that the likelihood of improvement in accommodation is not affected by the age of the child on the commencement of bifocal wear. Accommodation did not improve adequately before bifocals were prescribed in our sample. Thus, the improvement in accommodation appears solely due to the bifocal wear. There is no demonstrable difference between those children who improve in accommodation and those who do not, so at present this improvement is unexplained. However, boys seem to have a higher chance of gaining accurate accommodation and returning to single vision spectacles. This difference in behaviour between genders is currently unexplained. The improvement in accommodation demonstrates that the accommodative deficit in children is unlikely to be mechanical in origin (i.e. it is not presbyopia). The original deficit and the improvement must have a neural basis, as yet not understood. The presence of reduced accommodation in children with DS in a very early stage of their life may account for the abnormal refractive development in those children (Haugen *et al.*, 2001). This implies that the prescription of bifocals at an early age might help prevent this abnormal development since a clearer retinal image will be possible at both near and distance.

In conclusion, bifocal spectacles can be prescribed to children with DS as an active *treatment* for their reduced accommodation responses, with a success rate of over 60%. Furthermore, for over a third of children there is the possibility of ultimately discarding bifocal wear. In addition, the age and gender of the child as well as their visual acuity, the presence of strabismus and the type of refractive error does not affect their chances of gaining improvement in accommodation. The children in this study were all aged 4 years or older at first prescription of bifocal, and this was initially intended to aid school work. The success rate and benefits of bifocals for younger children are yet to be determined.

Conflicts of interest

No conflicting relationship exists for any author.

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Appendix VII

The performance of 24 children with DS using the City University colour vision test, the PV-16 and the Mollon-Reffin 'Minimalist' colour vision test (Chapter Seven).

ID	Performance City	PV-16	M-R	Age (Years)	Gender	VA (LogMAR)
1	Lost Interest	Pass	Pass	15.65	F	0.20
2	Lost Interest	Lost Interest	Pass	17.99	M	0.30
3	Not Understood	Not Understood	Pass	13.84	M	0.00
4	Lost Interest	Lost Interest	Pass	8.87	M	0.20
5	Lost Interest	Lost Interest	Pass	17.84	M	0.20
6	Not Understood	Pass	Pass	9.83	F	0.30
7	Lost Interest	Lost Interest	Pass	12.21	M	0.20
8	Pass	Lost Interest	Pass	16.5	M	0.20
9	Not Understood	Pass	Pass	14.63	M	0.00
10	Lost Interest	Lost Interest	Lost Interest	8.49	M	0.80
11	Not Understood	Pass	Pass	8.97	M	0.10
12	Pass	Pass	Pass	14.98	M	0.30
13	Pass	Pass	Pass	15.6	M	0.30
14	Not Understood	Not Understood	Pass	14.18	M	0.30
20	Not Understood	Lost Interest	Pass	9.25	F	0.00
21	Not Understood	Not Understood	Pass	4.98	M	0.60
22	Not Understood	Pass	Pass	12.81	M	0.30
23	Not Understood	Pass	Pass	17.33	M	0.10
24	Not Understood	Lost Interest	Pass	10.5	M	0.20
25	Not Understood	Pass	Pass	10.36	F	0.10
26	Lost Interest	Lost Interest	Lost Interest	7.71	M	0.20
27	Pass	Lost Interest	Pass	16.6	M	0.30
28	Pass	Pass	Pass	15.18	F	0.10
33	Not Understood	Pass	Pass	16.63	F	0.10
Total pass	**5**	**11**	**22**	**12.95±3.7 (mean±SD)**		**0.225±0.17 (mean±SD)**

Table: Characteristics and performance of all children in the 3 colour vision tests

Appendix VIII

Advertisement for recruitment of participants for the validation of the Mollon-Reffin 'Minimalist' colour vision test – Poster

Advertisement for recruitment of participants for the validation of the Mollon-Reffin 'Minimalist' colour vision test – Email

Participants' information sheet and consent form

Record sheet

Colour Vision Study!

- Do you have a colour vision defect?! If your answer is yes. then we need you!
- If you have 30 minutes to spare doing some colour vision tests (lets face it they are fun to do!), then you can help us in a study to validate a colour vision test for children!!!!
- If you think that you have a colour vision defect and not sure, you are welcome too!

For more information or to make an appointment, please get in touch!

Al-BagdadyM@cardiff.ac.uk
029 2087 0247

Do you ever argue over what colour the wall is? Or mix up your socks? Maybe you have a colour vision defect! We want you!

We are currently trying to validate a colour vision test! We are aiming to proof that this test is as sensitive in detecting colour vision problems as other available tests. This is because the task required by the patient while performing other colour vision tests is often difficult to administer and to perform by children with learning disabilities. Your role will only involve performing some clinical colour vision tests. It is estimated that the testing time will be approximately 20 minutes.

Waiting for your call!

Fyddwch chi byth yn dadlau ynghylch lliw'r wal? Neu'n cymysgu'ch sanau? Efallai bod diffyg ar eich gallu i weld lliwiau! Mae arnon ni'ch eisiau chi!

Rydyn ni'n ceisio dilysu prawf gweld lliwiau! Y nod yw profi bod y prawf yr un mor sensitif wrth ganfod problemau gweld lliwiau â'r profion eraill sydd ar gael. Gwnawn hyn am fod y dasg a gaiff y claf yn y profion eraill ar weld lliwiau yn aml yn anodd i blant ag anableddau dysgu ei gweinyddu a'i chyflawni. Eich rôl chi fydd gwneud dim mwy na chyflawni rhai profion clinigol ar weld lliwiau. Mae'n debyg y bydd hi'n cymryd rhyw 20 munud i wneud y prawf.

Ffoniwch ni!

Information sheet: Version 1.1 (21st July 2008)

Validation of the Mollon-Reffin 'Minimalist' Colour Vision Test

Dear Volunteer,

Thank you for answering our call! This project is aiming to evaluate a new test of colour vision, the Mollon-Reffin Minimalist Colour Vision Test compared to other available tests. The task required in performing colour vision tests is often difficult for children with learning disabilities. We are interested in the Mollon-Reffin test because it is simpler and likely to be readily understood by children. If we are able to show that this test is valid, we will then be able to go on to use it to evaluate colour vision in children with Down's syndrome, which is our particular interest. We therefore need adults with colour vision defects to help us to validate the test.

Taking part in this study will involve your performing some colour vision tests, generally by identifying colours and differences between colours. We estimate that the testing time will be approximately 15 minutes. You are free to withdraw from the study at any time with no consequences. All the results will be anonymous and will be presented in a PhD thesis as well as in journal papers.

Please fill in the information requested below and sign to verify that you understand all of the above and are keen on taking part in this study. If you would like to be informed of the results after the final analysis, please indicate appropriately on the form below. Please note that this will not be a substitute for an eye exam and so any problems with your eye sight should be addressed by a full eye exam at a local optician.

School of Optometry & Vision Sciences, Maindy Road, Cardiff University, Cardiff CF24 4LU

Information sheet: Version 1.1 (21st July 2008)

Validation of the Mollon-Reffin 'Minimalist' Colour Vision Test

I confirm that I have read all of the above information and have had the opportunity to ask questions before proceeding. I agree to take part in this study of colour vision.

Name: .....

I would like to be informed with the results of this study (Yes / No)

I would like to receive the information on the following (address/ email):

Signed: ..... Information on this paper is confidential.

Validity of the Mollon-Reffin 'Minimalist' colour vision test

Subject ID: .....

Name: ..... Gender: .....

Date of Birth: .....

Visual Acuity: ..... VA test: .....

Test/Order	Date/Time	Performance	Result
M-R			
City			
HRR			
F-M 100