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Essays on the impact of vision impairment in Portugal

4th Doctoral Programme of Public Health

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This thesis is presented as part of the requirements for the Degree of Doctor of Public Health, under supervision of Professor Rui Manuel Candeias Santana and Professor António Filipe Macedo

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Preface

This thesis was developed under the supervision of Professor Rui Santana (Escola Nacional de Saúde Pública, Universidade Nova de Lisboa) and Professor António Filipe Macedo (Department of Medicine and Optometry Linnaeus, University Kalmar). Professor Amândio Rocha-Sousa (Department of Organs of Senses, Faculty of Medicine, University of Porto) completed the tutorial commission.

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Ophthalmology Departments from Hospital de Braga, Centro Hospitalar do Alto Ave, Centro Hospitalar de São João and Hospital de Santa Maria Maior -Barcelos helped in the selection and recruitment of the participants included in this thesis therefore I must express my gratitude for their support.

The interviews made to the study participants were developed and conducted by a group of researchers hired in the research project financed by Fundação para a Ciência e Tecnologia namely: Laura Hernandez-Moreno, Joana Cima, Pedro Lima e Ana Patrícia Marques that worked under the supervision of Professor António Filipe Macedo.

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Part of this work has been presented in ARVO 2014 annual meeting, Orlando, Florida; ARVO 2015 annual meeting, Denver, Colorado; 8th European public health conference, Milan, Italy; European Society for Low Vision Conference 2015, Oxford, United Kingdom; Encontro Nacional de estudantes de doutoramento em saúde pública, Porto, Portugal and at Colóquio de Oftalmologia 2016, Jornadas de Investigação, Cascais, Portugal.

Part of this work was also presented in two public seminars promoted by the Coordination of the Doctoral Program of the Escola Nacional de Saúde Pública, Universidade Nova de Lisboa. The suggestions and comments received during this meeting were very useful to improve this thesis.

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During this journey I have received the support and encouragement of many people.

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Last but not the least I am very grateful to my wonderful family, my husband and my two lovely daughters for all the support, the incentive and for their love and care. I could not have done this without them.

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List of abbreviations

95%CI	95% Confident Interval
ADL	Activities of Daily Living
AI	Activity Inventory
AMD	Age-related Macular Degeneration
anti-VEGF	Antivascular Endothelial Growth Factor
DALYS	Disability Adjusted Life Years
DRG	Diagnosis Related Group
EMA	European Medicines Agency
FDA	Food and Drug Administration
GDP	Gross Domestic Product
HRQoL	Health Related Quality of Life
IADL	Instrumental Activities of Daily Living
ICD 9 - CM	International classification of diseases 9th revision Clinical Modification
IOP	Intraocular Pressure
Ipar	Immediate participants
IRR	Incidence Rate Ratio
LogMAR	Logarithm of the Minimum Angle of Resolution
LPar	Late participants
NHS	National Health Service
Npar	Non-participants
PCVIP study	Prevalence and Cost of Visual Impairment in Portugal study
PPP	Purchasing Power Parities
QALYS	Quality Adjusted Life Years
RWP	Reduced Workforce Participation
SD	Standard Deviation
UI	Uncertainty interval
VA	Visual Acuity
VI	Vision Impairment
WHO	World Health Organization

Summary

Background: Visual impairment is a major public health problem as it affects 252. 2 million persons worldwide. In 2015 36 million people were blind and 216.6 million people had moderate to severe visual impairment. With the aging population, the number of people with VI will increase dramatically, leading to a much heavier disease and economic burden in the coming future.

Purpose: The purpose of thesis was to investigate and characterize the impact of vision impairment in selected aspects of the healthcare system and the society. To accomplish this purpose five research papers were developed. Three papers are considered the main studies and investigated: 1) The access to a new anti-VEGF treatment for retinal diseases; 2) The use of informal care and its determinants in persons with vision impairment; 3) Productivity losses in persons with vision impairment and its predictors. In addition, two complementary studies were conducted to: 4) Investigate patient-reported outcome measures using a condition-specific instrument (activity inventory) and a generic health-utilities instrument (EQ5D); 5) Investigate the profile of the participants in the face-to-face interviews that were conducted as part of the main studies.

Methods: Two different data sources were used to perform the investigations reported in the research papers. A national database of inpatient and day cases episodes was used to investigate access to anti – VEGF treatments. Data from the Prevalence and Costs of Visual Impairment in Portugal: a Hospital Based Study (PCVIP-study) were used to investigate informal care, productivity losses, to characterize patient-reported outcome measures and to investigate the profile of the participants. Different strategies were used to select our participants/cases and to collect information.

Descriptive statistics was used to summarize socio-demographic and clinical characteristics of the participants. Chi-square tests were used to compare the composition of groups. T-tests were used to compare normally distribute variables and the Mann-Whitney–test or Kruskal-Wallis were used for other non-parametric comparisons between groups. Spearman Correlation was used to determine the association between variables. Generalised linear modelling was used to investigate determinants of the geographical diffusion of anti-VEGF. Logistic regression was used to determine explanatory factors associated with the use of informal care and to determine explanatory factors of productivity losses. Linear regression was used to determine factors associated with the amount of informal care.

Results: The diffusion and consequently the access to new eye care treatment was found to be large but unequally distributed and associated with availability of healthcare delivery services. The reduced number of treatments found in some counties is worrisome since it can lead to an increased number of people becoming visually impaired due to treatable causes. We also found that vision impairment in Portugal has substantial socioeconomic implication since it affects individual's autonomy levels that are associated with an intensive use of informal care. It also affects individual's participation in society, namely employment status and health related quality of life that led to significant productivity losses.

Conclusion: Vision impairment in Portugal has a wide ranging impact. Many of the causes of vision loss could be reversible and preventable with currently available healthcare technology. Eye care has a range of proved, low risk, high success and cost effective health interventions so the key element is to guarantee that these interventions are available and reaches all the persons that can benefit from it.

Key words: vision impairment, access to eye care, visual ability, informal care, productivity losses

Resumo

Enquadramento: A deficiência visual é um importante problema de saúde pública que afeta 252,2 milhões de pessoas no mundo. Em 2015 existiam globalmente 36 milhões de pessoas cegas e 216,6 milhões de pessoas com deficiência visual severa a moderada. Dado o envelhecimento da população estima-se que o número de pessoas com deficiência visual irá aumentar dramaticamente provocando uma maior carga de doença e um maior impacto económico no futuro.

Objetivos: Com a realização desta tese pretendeu-se investigar e caracterizar o impacto da deficiência visual em aspetos selecionados do sistema de saúde e da sociedade. Para alcançar este objetivo foram desenvolvidos cinco artigos de investigação. Considerou-se que três artigos constituíam a componente principal do trabalho realizado investigando: 1) O acesso de doentes com doenças da retina a um novo tratamento com anti-VEGF; 2) A utilização de cuidados informais em pessoas com deficiência visual e os fatores associados a essa utilização; 3) Perdas de produtividade e os seus determinantes em pessoas com deficiência visual. Foram ainda desenvolvidos mais dois artigos complementares que pretendiam: 4) Investigar medidas de resultados auto-reportadas utilizando um questionário específico para a deficiência visual (activity inventory) e um questionário genérico (EQ5D);5) Investigar o perfil dos indivíduos que aceitaram participaram nas entrevistas realizadas no âmbito dos estudos apresentados nos artigos principais.

Metodologia: Foram utilizadas duas bases de dados. A base de dados nacional de morbilidade hospitalar foi utilizada para investigar o acesso a tratamentos com anti-VEGF. Dados do estudo sobre a Prevalência e custos da baixa visão em Portugal foram utilizados para os artigos referentes aos cuidados informais, perdas de produtividade, análise de medidas auto-reportadas e análise do perfil dos entrevistados. Utilizaram-se diferentes estratégias para selecionar os casos e para a recolha de informação.

Utilizou-se estatística descritiva para sintetizar a informação sociodemográfica e clínica. Utilizou-se testes de chi-quadrado para comparar a composição de grupos. Utilizou-se testes T para comparar variáveis com distribuição normal e testes não-paramétricos nomeadamente teste de Mann-Whitney e teste de Kruskal-Wallis para comparar grupos. Para analisar os determinantes associados à difusão dos tratamentos anti-VEGF recorreu-se a modelos lineares generalizados. Utilizou-se modelos de regressão logística para investigar fatores associados à utilização de cuidados informais e às perdas de produtividade. Recorreu-se a modelos de regressão linear para determinar fatores associados à intensidade de utilização de cuidados informais.

Resultados: Verificou-se que a difusão e consequentemente o acesso a um novo tratamento ocular foi significativo, distribuído de forma desigual e associado à disponibilidade de prestadores de cuidados de saúde. O número reduzido de tratamentos encontrado em alguns concelhos é problemático na medida em que pode conduzir a um aumento do número de indivíduos com deficiência visual por causas tratáveis. Verificou-se também que a deficiência visual tem repercussões significativas a nível socioeconómico dado que afeta o nível de autonomia dos indivíduos que está por sua vez associado à necessidade de cuidados informais. Afeta também a participação dos indivíduos na sociedade, afetando, a situação no mercado de trabalho e a qualidade de vida produzindo perdas de produtividades avultadas.

Conclusão: A deficiência visual em Portugal produz um impacto diverso e significativo. Muitas das causas de perda de visão podem ser preveníeis ou tratadas através da tecnologia existente. Os cuidados de saúde oculares dispõem de um conjunto de intervenções de saúde baseadas na evidência, custo-efetivas e de baixo risco pelo que a medida mais importante a tomar é a de garantir que estas intervenções estão disponíveis e alcançam todas as pessoas que delas podem beneficiar.

Palavras-chave: deficiência visual, acesso a cuidados oculares, funcionalidade visual, cuidados informais, perdas de produtividade

Chapter 1 – Introduction

Vision impairment (VI) is a public health problem with substantial burden worldwide. The number of people with VI is likely to increase due to the aging population and that can lead to a deeper impact of the condition for individuals and societies.

Studies measuring the impact from an economic and societal perspectives are important to alleviate the burden of VI and here we name a few reasons. The first reason is that these studies inform policy makers and decision-makers on the relative impact of this condition at the population level. The second reason is because they assist in the projections of future health care costs. A third reason is explained by the importance of these studies to support measures to improve patient outcomes and patient care. The last reason that we would like to mention is that studies measuring the impact of VI from an economic and societal perspectives are important to contribute and support resource allocation decisions that are unavoidable and crucial to reduce the burden of VI.

The purpose of thesis was to investigate and characterize the impact of vision impairment in selected aspects of the healthcare system and the society.

The thesis is organized in 7 chapters. It begins with the present chapter were the subject is introduced and the structured of the thesis is presented. The next chapter starts with the definition of VI, presents the latest prevalence estimates and characterizes the main causes of VI. Then an overview of the impact of vision impairment in the perspective of the individual, healthcare system and society is presented. The third chapter describes the objectives of this thesis and the fourth chapter provides a description of the research methods. The fifth chapter report the results and includes 5 manuscripts that have been published or are under review. In 5.1 we report results from an analysis of the access to a new eye care treatment (anti-VEGF); In 5.2 we report estimates of the use of informal care and its determinants in this population; in 5.3 we estimate and characterize productivity losses in persons with vision impairment. In addition to these 3 papers with me, the PhD candidate, as first author I also contributed to two more papers. Section 5.4 report results of a study comparing patient-reported outcome measures using a condition-specific instrument (activity inventory) with a generic health-utilities instrument (EQ5D) and section 5.5 reports the findings of an analysis of the participants and non-participants profiles and the levels of participation in face-to-face interviews. The sixth chapter provides the key findings, a discussion of the work performed, limitations and suggestion to future work. The final chapter provides the conclusion of the thesis.

Research findings of this thesis has been previously published as:

Marques AP, Macedo AF, Perelman J, Aguiar P, Rocha-Sousa A, Santana R. Diffusion of anti-VEGF injections in the Portuguese National Health System. BMJ Open 2015;5:e009006.doi:10.1136/bmjopen-2015-009006

Marques AP, Macedo AF, Hernandez-Moreno L, Ramos PL, Butt T, Rubin G, Santana R. Portuguese visual impairment study group (PORVIS-group). The use of informal care by people with vision impairment. PLoS One. 2018 Jun 7;13(6):e0198631. doi: 10.1371/journal.pone.019863

Macedo AF, Ramos PL, Hernandez-Moreno L, Cima J, Baptista AM, **Marques AP**, Massof R, Santana R. Visual and health outcomes, measured with the activity inventory and the EQ-5D, in visual impairment. Acta Ophthalmologica. 2017 Mar 30. doi:10.1111/aos.13430

Ramos PL, Santana R, Moreno LH, **Marques AP**, Freitas C, Rocha-Sousa A, Macedo AF; Portuguese visual impairment study group. Predicting participation of people with impaired vision in epidemiological studies. BMC Ophthalmology. 2018 Sep 4;18(1):236. doi: 10.1186/s12886-018-0889-9

Additionally, the following manuscript was submitted to Ophthalmic Epidemiology, and it is currently under revision:

Marques AP, Macedo AF. Ramos P. Moreno L. Butt T. Rubin G. Santana R.Productivity losses and their explanatory factors amongst people with impaired vision. – Submitted in July in 2018.

Chapter 2 – Background

This chapter starts with the definition of VI, presents the latest prevalence estimates and characterizes the main causes of VI. Then an overview of the impact of vision impairment in the perspective of the individual, healthcare system and society is presented. Adopting the perspective of the individuals we describe how VI affects daily living activities, how is associated with depression and anxiety and how it is related to risk of falls and fractures. Adopting the perspective of the healthcare system we describe the healthcare resource utilization of visually impaired persons, we review the determinants of access to healthcare services and describe the factors that influence the adoption of new healthcare treatments. The societal impact of VI is characterized by the economic impact of vision impairment and its main components.

2.1- Definition of Vision Impairment

To better understand the concepts of visual acuity and visual field here is given a superficial and oversimplified description of the eye and the visual system. As shown in Figure 1 the visual system has many levels of information processing but the first organ that process physical stimuli is the eye. For our purpose we consider the eye analogous to a camera that focus the external world trough optics on a light-sensitive element (the retina).

The retina is an elaborate neural structure that actively analyses the image that is focused on it. The signal travels from the retinal to the brain trough a complex neural pathway and then, in the brain, a representation of the retinal image is perceive (1). Visual function includes a series of aspects of the visual system that can be quantified and that includes visual acuity, visual field, contrast sensitivity, colour vision, binocular function, visual search, glare and light adaption (2, 3). In this thesis is important to understand in some detail the first two concepts: visual acuity and visual field.

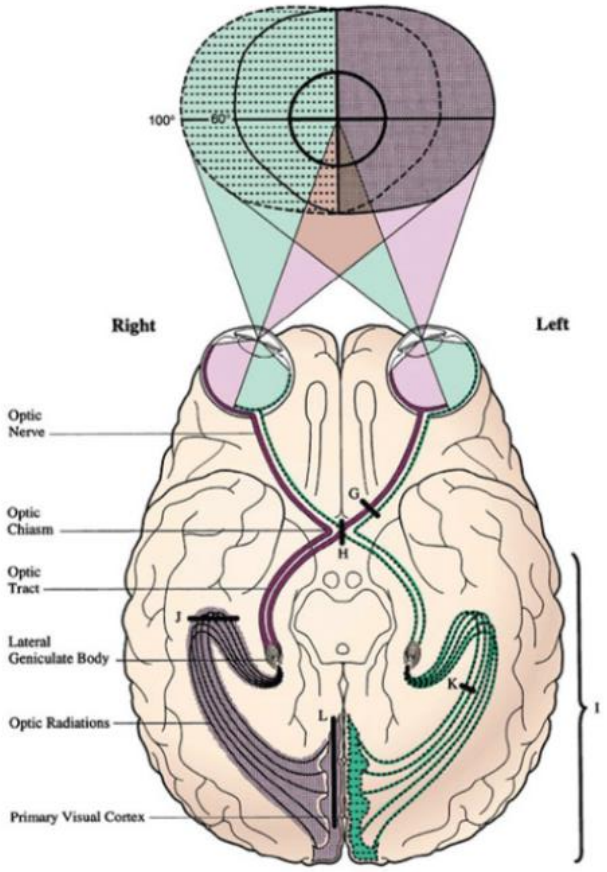

Figure 1 - A schematic view of the visual system. The image shows the eye as the first organ of the system receiving input from the external stimuli (physical world). The extend of the physical word that can be seen with both eyes open is shown by the almost elliptical shaped line surrounding the coloured green and brown half-parts. The centre of the ellipse is depicting the fixation point were the lines of sight of both eyes converge. The size extent of the ellipse defines the visual field, that is, the amount of physical world stimuli that can be perceived around the fixation point without moving the eyes. The extent of the field is variable according with the lighting conditions, but as the image shows can be up to 100 degrees to each side of the fixation point in the horizontal meridian (1)

Visual acuity referrers to the ability of the visual system to resolve spatial details of objects (see details as separate parts) that correspond to a known visual angle. Acuity is typically measured by asking a person to resolve the details of visual symbols called optotypes forming an acuity chart as shown in Figure 2-A. As the person reads down in an acuity chart, the optotypes become smaller and their details become finer a point is reached where the details of the optotypes can no longer be resolved, this limit of resolution define the limit of visual acuity. Visual acuity can be expressed using what is known as the Snellen fraction e.g. 6/6 (20/20), 6/24 (20/80), etc., in which the numerator is the testing distance, usually expressed in metres (or in feet), and the denominator is the distance (in the same units as the numerator) at which the smallest Snellen letter

read by the eye has an angular size of 5 minutes-arc. The reference of 5 minutes-arc is used because letters are formed of 5 elements of 1 minute-arc each and that is expected to be the limit of resolution of a normal eye. Acuity scales have been designed in such a way that when an individual can see a line with letters marked with 20/20 (distances in feet) or 6/6 (distances in meters) its acuity is considered normal. When acuity is, for example, 6/18 (or 0.33 when we compute the fraction, we have acuity in what is called the decimal scale) it is considered to be below the normal limits. In simple terms this fraction tells us that the individual needs to be at a testing distance of 6 meters to be able to read a letter that should be visible to him / her at 18 meters (denominator).

The visual field is defined as the extend of the physical world with visual stimuli (visual field does not matter in the absence of stimuli such as in a complete dark room) that can be perceived around the point of fixation without moving the gaze. A typical visual field is shown in Figure 2-B and the extent of a binocular visual field (when keeping both eyes open) is expected to be more than 180 degrees.

A B

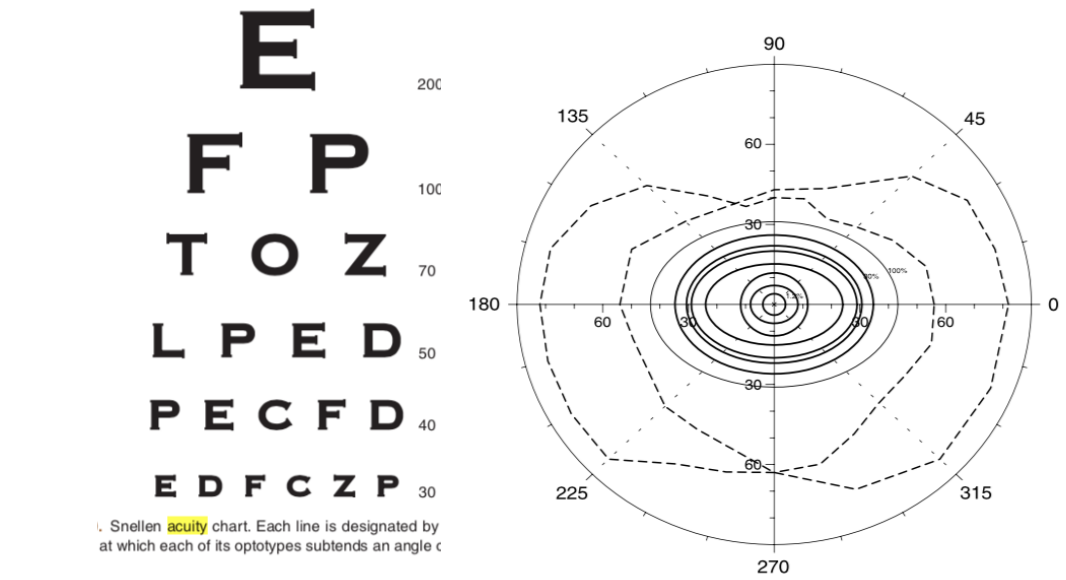

Figure 2 - A - Snellen acuity chart. Each line is designated by its foot-size (small numbers of the right-hand side, which is the distance at which each of its optotypes subtends an visual angle of 5-minute arc. Is important to mention that acuity can be measured with other type of symbols that do not require ability to recognize letters. Adopted from:(1) B – Binocular visual fields of stimuli recognition (heavy lines) and stimuli detection (doted lines) for a healthy subject. To understand the concept of visual field that is going to be discussed in this thesis the relevant limits are defined by the doted lines and they can be called isopters defining the limit of the visual field for each eye. The right doted isopter represents the visual field of the right eye and the left doted isopter represents the limit of the visual field for the left eye. The monocular vertical extent of the visual field is approximately 100 degrees and the horizontal extent is approximately 140 degrees (4)

Vision loss can be defined as a measurable reduction of visual acuity or visual field and that can lead to vision impairment. In the 10th revision of the World Health Organization (WHO) International Statistical Classification of Diseases, Injuries and Causes of Death vision impairment has been divided in 'low vision' and 'blindness'. 'Low vision' is defined as visual acuity of less than 6/18 but equal to or better than 3/60, or a corresponding visual field loss to less than 20°, in the better eye with presenting visual acuity. 'Blindness' is defined as visual acuity of less than 3/60, or a corresponding visual field loss to less than 10°, in the better eye with the best possible correction. 'Visual impairment' or 'vision impairment' includes both low vision and blindness (5, 6). A person with vision impairment is one who has impairment of visual functioning even after treatment and/or standard refractive correction. However, people who are visually impaired retain some vision, even if is only light perception, and that allows them to a certain extent planning and/or execution of tasks that rely on vision. Because of that a few levels of vision impairment have been defined and are summarized in Table 1.

Table 1 - Vision impairment definition - 2010

Categories	**Notation Type**	**Presenting distance visual acuity**	
		Worse than:	**Equal to or better than:**
0 Mild or no Visual Impairment	6 metre notation*		6/18
	Decimal notation**		3/10 (0.3)
	U.S.A notation***		20/70
1 Moderate visual impairment	6 metre notation	6/18	6/60
	Decimal notation	3/10 (0.3)	1/10 (0.1)
	U.S.A * notation	20/70	20/200
2 Severe visual impairment	6 metre notation	6/60	3/60
	Decimal notation	1/10 (0.1)	1/20 (0.05)
	U.S.A * notation	20/200	20/400
3 Blindness	6 metre notation	3/60	1/60****
	Decimal notation	1/20 (0.05)	1/50 (0.02)
	U.S.A * notation	20/400	5/300 (20/1200)
4 Blindness	6 metre notation	1/60*	Light perception
	Decimal notation	1/50 (0.02)	
	U.S.A * notation	5/300 (20/1200)	
5 Blindness	No light perception		
9	Undetermined or unspecified		

* commonly used in United Kingdom; ** commonly used in Europe; **** commonly used in United States of America **** or count of fingers at 1 metre

Source: Adapted from (5).

At this stage is also important to define 4 concepts that are often used as synonyms, but, whilst related, they are expected to express different aspects of vision loss. The 4 concepts that need to be defined are: (1) disorder or injury, (2) impairment, (3) disability or loss of ability and (4) handicap. The separation between these concepts has been recommended by the International Council of Ophthalmology and is summarised in Table 2. Two of the aspects refer to the organ system, the first aspect is that of anatomical and structural changes. Defects are described as diseases, disorders or injuries. The second aspect is that of functional changes at the organ level. Defects are described as impairments. The other two aspects refer to the individual. One aspect describes the skills and abilities of the individual. Defects are described as ability loss. The last aspect points to the social and economic consequences (7). Defects are described as handicaps and as lack of participation. This separation into: disorder or injury, impairment, disability or loss of ability and handicap is important to understand this thesis because it covers aspects of vision impairment very briefly and most of the investigations have been about the consequences of vision impairment, in particular, social and economic consequences of VI.

When trying to understand impairment from its consequences it also important to distinguish visual functions from functional vision. The term “visual functions” is used to refer to the concept of impairment. Visual functions such as visual acuity and visual field can be assessed quantitatively, and they are usually measured for each eye separately. In contrast, abilities such as reading, orientation and mobility refer to the person, not to the eye. Although some aspects, such as reading speed, can be readily quantified, other aspects, such as reading enjoyment are highly subjective. Because of this it was need to define also the term "functional vision" and this is used to refer to these visual abilities, as they are needed for the proper performance of activities of daily living (2, 8-10). This separation is also needed because two persons with similar levels of visual functions can show distinct levels of functional vision.

Table 2 - Aspects of vision loss according with the recommendations of the International Council of Ophthalmology

	THE ORGAN		THE PERSON	
ASPECTS:	Structural change, at the organ level	Functional change at the Organ level	Skills, Abilities (ADL) of the individual	Social, Economic Consequences
Neutral terms:	Health Condition	Organ Function	Skills, Abilities	Social Participation
Loss, Limitation:	Disorder, Injury	Impairment	Ability Loss (Dis-ability)	Handicap
Application to VISION:	Eye Health	**"Visual Functions"** measured quantitatively	**"Functional Vision"** described qualitatively	Vision-related Quality of Life
		Categorized as ranges of **"Vision Loss"**		
Performance Tests:		Performance on eye tests *E.g.: Visual Acuity*	Performance on ADL skills *E.g.: Reading ability*	Performance on job-related and social tasks
Ambiguous terms:		Disability = impairment as in "Americans with Disabilities Act" (ADA)	Dis-ability = ability loss as in "Disabled Veterans"	Disability = economic as in "Being on disability"

Source: Colenbrander (7)

There has been some debate in the literature if vision impairment should be defined according to presenting visual acuity or best corrected visual acuity. Presenting visual acuity is the acuity measured regardless the amount of refractive error that may be incorrected. Resnikoff et al. *(11)* defines "*presenting vision as the visual acuity in the better eye using currently available refractive correction, if any*" and best corrected vision "*as the visual acuity in the better eye achieved by subjects tested with pinhole or refraction".* To understand why presenting vs best corrected acuity can create polemic when quantifying the number people with vision impairment lets consider an example. An individual with a relatively common refractive error such as 4 dioptres of uncorrected myopia in both eyes would almost for sure have acuity below 6/18 and therefore would be classified as visually impaired if presenting acuity is considered. In contrast, this individual would reach 6/6 vision when wearing correcting lenses. Many studies at regional or global level have concluded that uncorrected refractive error account for a high number of cases with mild to moderate levels of VI (11-14) and that forced authorities to redefining the rules to determine the number of people with vision impairment.

Since 2010 the ICD-10 - World Health Organization (WHO) version uses presenting vision when determining the number of people with VI. This has been adopted following recommendation by the Resolution of the International Council of Ophthalmology and the Recommendations of the WHO Consultation on "Development

of Standards for Characterization of Vision Loss and Visual Functioning". This new recommendations emphasize that the use of “best corrected” vision misses or excludes a large proportion of persons with VI, including blindness, due to uncorrected refractive error (7, 15, 16).

VI caused by uncorrected refracted errors may occur due to the lack of awareness of this problem from the family, community or public health services, insufficient or inadequate screening services and/or provision of affordable corrective lenses, lack of continuity of eye care, delays in access to specialist eye care among other reasons (11, 17). In terms of consequences it may lead to many short or long term penalties, both in children and in adults, such as loss of opportunities in education or employment, income losses and quality of life losses (11, 17, 18). Therefore, another way to classify VI is to distinguish *uncorrectable* VI, the amount of vision impairment that remains after appropriate treatment or intervention, from *uncorrected* or avoidable vision impairment defined as the amount of vision impairment that could be improved by currently available treatments (19, 20).

Vision impairment has been defined based on visual acuity and visual field, amongst other reasons, for legal purposes. For example, in case of accidents insurance companies need to establish compensations to be paid to people that will face permanent vision impairment that will, eventually create disability and/or handicap. Although, the legal limit to what is considered vision impairment is different in different nations. For instance the legal definition of blindness in the United States of America, Australia and Portugal is visual acuity worse than 0.1 decimal (20/200 or 6/60) whereas for WHO blindness correspond to a visual acuity worse than 0.05 decimal (20/400 or 3/60) (17). The existence of different levels for what is considered vision impairment can cause difficulties when comparing, for example, the prevalence of VI.

In summary, the different definitions of vision impairment make prevalence numbers somewhat difficult to discuss and compare. In addition, there are other methodological options adopted by researchers that need to be considered too such as the type of visual acuity scale, data collection methods (e.g. self-reported acuity or measured acuity or registered in medical records), the age range considered (e.g. all the population, children only, adults above 40 years old or adults above 65 years old) or the method used to extrapolate and infer unknown prevalence (16, 21). The next section covers relevant aspects of prevalence of vision impairment in Portugal and in other parts of the world.

2.2 - Prevalence of Vision Impairment and Blindness

The most recent estimate of the number of visually impaired at a global scale was reported in 2017 by Bourne et al. (22) on behalf of the Vision Loss Expert Group. The Vision Loss Expert Group is an international group of mainly ophthalmologists and optometrists that has convened with WHO to assist with the development of epidemiological estimates for blindness and vision impairment that would be included in the Global Burden of Disease study. In this latest report blindness was defined as presenting visual acuity in the better eye worse than 3/60, moderate to severe vision impairment was defined as presenting visual acuity in the better eye worse than 6/18 to 3/60 inclusive and mild vision impairment was defined as presenting visual acuity in the better eye worse than 6/12 to 6/18 inclusive. Based on these definitions Bourne et al. (22) reported that globally in 2015: 36 million people were blind (prevalence ratio of 0.49% 80% UI 0.18-0.89 UI – uncertainty interval); 216.6 million people had moderate to severe visual impairment (prevalence ratio of 2.95%: 80% UI 1.34-4.89) and 188.5 million had mild visual impairment (prevalence ratio of 2.57%: 80% UI 0.88-4.77).

Figure 3 illustrates prevalence ratios in the world. Accordingly with this illustration the burden of VI was not uniformly distributed throughout the world. South and East Asia regions have the highest prevalence whereas the lowest prevalence is reported in most European countries (Portugal included), Australia, United States of America and Canada. The lowest prevalence ratios are in the interval of 1% to 1.5%.

Figure 3 - Vision impairment prevalence ratio for moderate to severe vision impairment in the World - 2015. Each country is painted with a colour that represents the estimated prevalence ratio. The legend gives us the correspondence between the colours and the prevalence ratios. There are 8 different prevalence ratio intervals ranging from 1% to >4.5% (23)

VI is strongly associated with age and because of that the authors of the most recently reported data reported, in addition to age standardized prevalence ratios, prevalence to population aged 50 years and older. Those results are summarized in Table 3. In the population aged 50 years in 2015 there were 31 million blind people (86% of all age blind population), 172·3 million people with moderate and severe vision impairment (80% of all age moderate to severe visually impaired population), 140·3 million people with mild vision impairment (74% of all age mild visually impaired population) in the world (20). It is important to mention that in many cases prevalence values have been extrapolated or inferred as is the case of Portugal. To our knowledge there is a lack of exact numbers about the prevalence of VI in Portugal and the authors used data from other countries in the same global burden of disease region. Portugal is included in the Western Europe global burden of disease region which includes a total of 21 countries. In Western Europe region only 10 countries had prevalence data. The estimates for Portugal show a prevalence of blindness, moderate and severe visual impairment that is in general inferior to the global values. Although, the uncertainty interval, for example, for moderate and severe VI ranges from 0.58 to 2.22 which indicates that these estimates are a very gross picture of the situation in Portugal and further studies are necessary.

Table 3 - Blindness and Moderate and Severe Visual Impairment age standardised prevalence ratios and uncertain interval for aged ≥50 years and all ages in Portugal and in the world

Age standardised prevalence ratios in 2015		**World**	**Portugal**
People aged ≥50 years old	Population (Nr. in million)	1,638.00	4.25
	Blind (%)	1.87% (80% UI; 0.67-3.39)	0.54% (80% UI; 0.25-0.88)
	Moderate and Severe Visual Impairment (%)	10.47% (80% UI; 4.93-17.13)	5.06% (80% UI; 2.3-8.61)
All ages	Population (Nr. in million)	7,338.00	10.34
	Blind (%)	0.48% (80% UI; 0.17-0.87)	0.13% (80% UI; 0.06-0.21)
	Moderate and Severe Visual Impairment (%)	2.9% (80% UI; 1.31-4.8)	1.3% (80% UI; 0.58-2.22)

Source: Adapted from: Bourne et al (22)

2.2.1 - Trends of Blindness and Visual Impairment

Since 2002 there have been several reports on global prevalence estimates using different definitions of VI. Results of 6 recently published studies are summarized in Table 4. Best corrected visual acuity was only reported in two of the six studies whereas presenting visual acuity was reported in five studies. It is important to point that the numbers reported are crude prevalence using best corrected visual acuity and presenting visual acuity. This reflects the Resolution of the International Council of Ophthalmology issued in 2002 (7) and the Recommendations of the WHO Consultation on "Development of Standards for Characterization of Vision Loss and Visual Functioning" issued in 2003 (15) that led to a modification on the WHO definition of blindness and visual impairment in 2010. The estimates and the trend summarized are variable because of a spectrum of reasons that are mentioned below.

Table 4 - Summary table of estimated number and crude prevalence of blind, moderate and severe visual impairment and mild visual impairment between 2002-2015

Year			**2002[1*]**	**2002[2*]**	**2004[3*]**	**2010[4*]**	**2010[5**]**	**2015[6]**
Global population (Nr. in million)			6,276.7	6,276.7	6,429.8	6,895.9	n.a	7,338
Blind	Best Corrected VA	Nr.	36.86	n.a	n.a	38.18	n.a	n.a
		%	0.59	n.a	n.a	0.55	n.a	n.a
	Presenting VA	Nr.	n.a	42.01	45.08	39.37	32.4	36
		%	n.a	0.67	0.7	0.57	0.5	0.49
MSVI	Best Corrected VA	Nr.	124.26	n.a	n.a	142.69	n.a	n.a
		%	1.98	n.a	n.a	2.07	n.a	n.a
	Presenting VA	Nr.	n.a	217.19	269.24	246.02	191	216.6
		%	n.a	3.46	4.19	3.57	2.8	2.95
Mild VI	Best Corrected VA	Nr.	n.a	n.a	n.a	n.a	n.a	n.a
		%	n.a	n.a	n.a	n.a	n.a	n.a
	Presenting VA	Nr.	n.a	n.a	n.a	n.a	155	188.5
		%	n.a	n.a	n.a	n.a	2.4	2.57

1 Resnikoff et al (2004); 2 Dandona e Dandona (2006); 3 Resnikoff et al (2008); 4 Pascolini e Mariotti (2012); 5 Stevens et al (2013); 6 Bourne et al (2017).* Blindness: VA<0.05 decimal (20/400 or 3/60); MSVI Moderate and Severe Visual Impairment: VA<0.3 (20/60 or 6/18)> 0.05 decimal (20/400 or 3/60); Mild visual impairment VA<0.5 (20/40 0r 6/12)> 0.3 (20/60 or 6/18)

Source: Adapted from: Resnikoff and Keys (16)

Estimates based on best corrected visual acuity (VA) give us a smaller prevalence when compared with presenting visual acuity estimates. Accordingly with Resnikoff and Keys (16) this is explain by the fact that when corrected VA is considered that leads to

an underestimation of the prevalence caused by, for example, uncorrected refractive error. Mild vision impairment was only reported in two recent studies. These reports wanted to expand global estimate by including a mild category that incorporates presenting visual acuity less than 0.5 decimal (20/40 or 6/12) but higher than 0.3 decimal (20/70 or 6/18) in the better seeing eye. Stevens et al. (24) reports the smallest prevalence even when compared with Pascolini and Mariotti (25) which reports results for the same year. Accordingly with Stevens et al. (24) their estimate is within the same uncertainty range as Pascolini and Mariotti (25) in most world region. The main difference is in China where Pascolini and Mariotti (25) estimated 8.2 million blind people and 67.2 million people with low vision in 2010 versus 5.4 million blind people and 32.4 million people with low vision. The differences between this two studies rely on data collection methods. In a big and heterogeneous country like China extrapolating data from a smaller sample may increase uncertainty level (24, 25).

An additional source of uncertainty and eventual lack of agreement between studies is the way authors deal with missing data. Pascolini and Mariotti (25) used economic status to extrapolate data, Stevens et al. (24) used country´s development status whereas Dandona and Dandona (26) extrapolated data based on epidemiological, socioeconomic, ecological and eye care services characteristics.

Other explanation to these differences is related with the time frame of the surveys and papers included in each study. In Dandona and Dandona (26) studies used to estimate prevalence range from 1980 to 2003 in Stevens et al. (24) range from 1980 to 2012 and Pascolini and Mariotti (25) range from 2001 to 2008.

In short, trends are difficult to interpret due to limited comparability between global estimates over the years. Nevertheless, estimates on blindness seems to have a relatively clear pattern with blindness decreasing from 0.67 in 2002 to 0.49 in 2015 when using presenting distance visual acuity definition. For moderate to severe VI the best way to analyse trends is to consider studies that used only comparable data as Stevens et al. (24) and Bourne et al.(22) did. In both studies global age-standardized all-age prevalence ratio of blindness and moderate to severe VI decreased worldwide. However, because of the rapid increase in the older adult population, the number of people with blindness and with moderate to severe VI did not decrease. Bourne et al.(22) project that in 2020 the number of people suffering with blindness reach 38.5 million and the number of people suffering with moderate to severe VI can reach 237·1 million. For 2050 the projection is 114.6 million people with blindness and 587.6 million people with moderate and severe VI (22).

2.3 - Causes of Vision Impairment and Blindness

The most recent estimate of the causes of vision impairment and blindness at a global scale was reported in 2017 by Flaxman et al. (27) on behalf of the Vision Loss Expert Group of the Global Burden of Disease Study. In this systematic review and meta-analysis the authors use the definition of vision impairment proposed by WHO which is based on visual acuity for distance (27). Figure 4 shows the main causes of blindness, defined as presenting visual acuity of less than 3/60 in the better eye and Figure 5 shows the main causes of vision impairment, excluding blindness, for population aged 50 years or more, both represent the global causes of impairment.

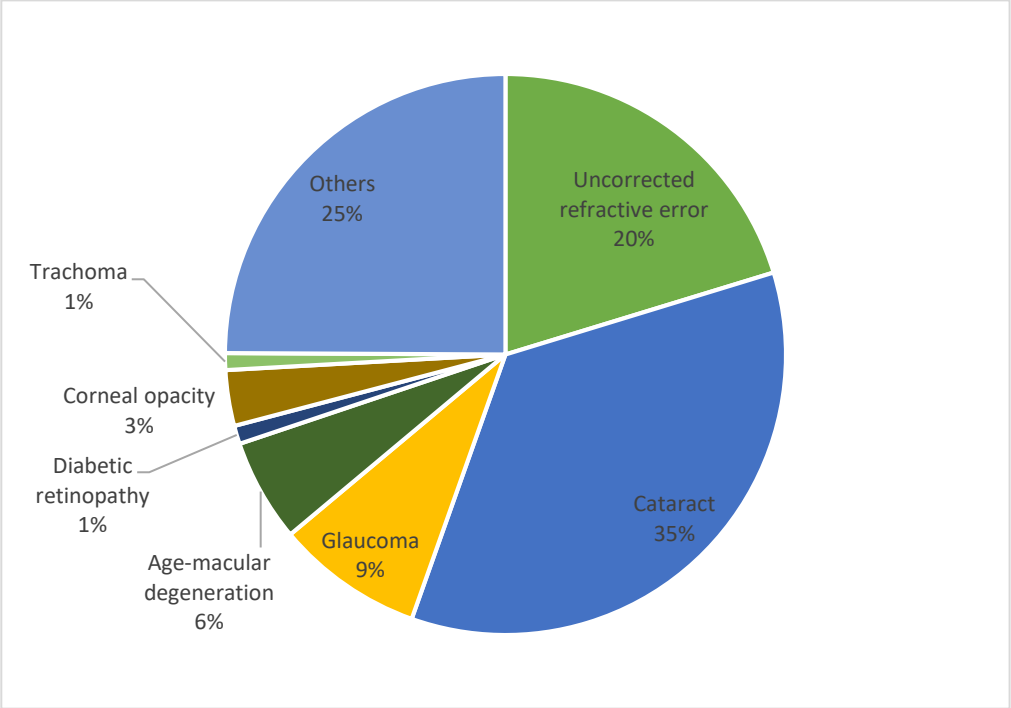

Figure 4 - Global causes of blindness among adults 50 years and older in 2015. Adapted from Flaxman et al. (27).

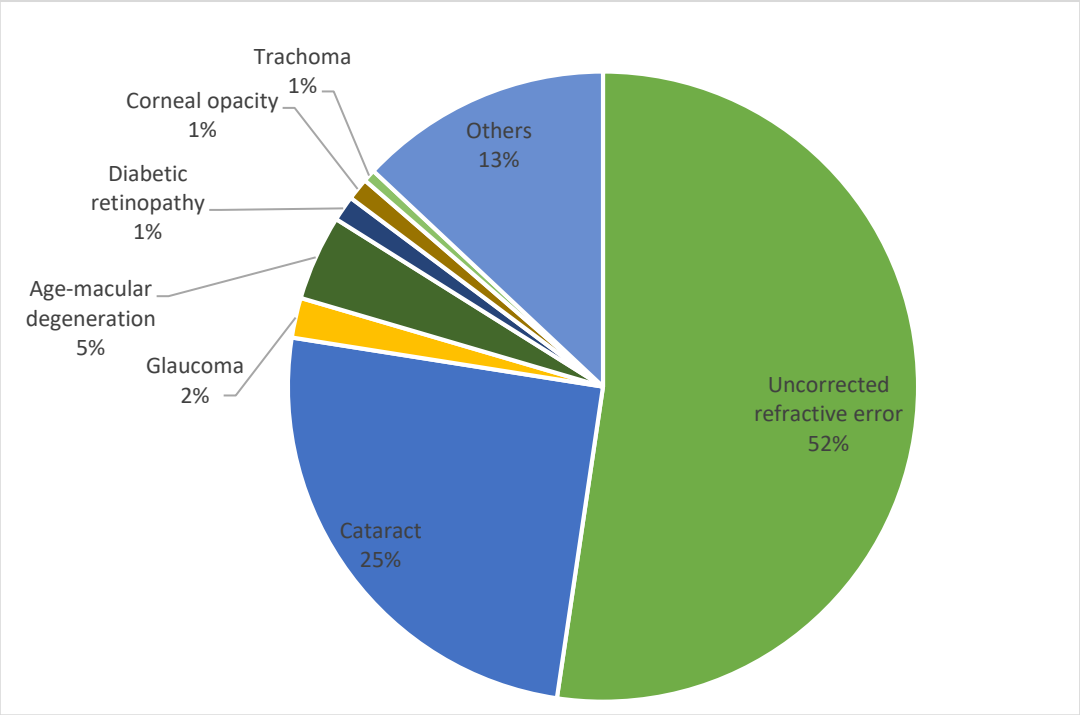

Figure 5 – Global causes of vision impairment among adults 50 years and older in 2015. Adapted from Flaxman et al. (27).

The two images show that the top causes of vision impairment, including blindness, in 2015 were cataract, uncorrected refractive error, glaucoma, age-related macular degeneration, corneal opacity, trachoma and diabetic retinopathy. Cataract together with uncorrected refractive error account for 55% of blindness and 77% of other levels of vision impairment in adults aged 50 years and older in 2015 in the world. A brief description of the main causes of vision impairment, including, blindness, is given in Table 5.

Table 5 – Brief description of common causes of blindness and other levels of vision impairment

Age-related macular degeneration (AMD)	
Affected structure	Macula
Definition, risk factors and general actions for treatment	AMD is a degenerative eye disease that causes damage to the macula. AMD can be divided into two stages: early AMD, characterized by sub-retinal pigmented epithelium deposits (drusen) and pigmentary changes, and advanced AMD (28). Advanced AMD has atrophic and neovascular forms. Although neovascular AMD comprises only 10% of the burden of the disease, it is responsible for 90% of severe vision loss years. Increasing age and history of smoking are considered risk factors of AMD. Anti-VEGF therapy for neovascular AMD has substantially changed the management of the disease. These drugs are injected into the vitreous chamber to reduce neovascular formation in the macula (29, 30)
Cataracts	
Affected structure	Lens of the eye
Definition, risk factors and general actions for treatment	A cataract is a clouding of the lens. This cloudiness may decrease vision and may lead to eventual blindness if left untreated. Cataracts often develop slowly and without pain, so vision can be affected without a person realizing it. Cataract prevalence increases with age. In addition to age the risk of cataract increases also with history of smoking and diabetes mellitus. Cataract treatment includes lens removal by surgery which may be followed by lens replacement (31, 32)
Diabetic retinopathy	
Affected structure	Blood vessels in retina
Definition, risk factors and general actions for treatment	Diabetic retinopathy is a common complication of diabetes mellitus. It is characterized by “signs of retinal ischemia (micro aneurysms, haemorrhages, cotton woolspots, intraretinal microvascular abnormalities, venous calibre abnormalities, and neovascularization) and/or signs of increased retinal vascular permeability. Vision loss can occur from different ways including macular edema, neovascularization that leads to vitreous haemorrhage and/or retinal detachment. It can be prevented by aggressive control of hyperglycemia and hypertension. The most important risk factor is duration of diabetes. Poor glycaemic control, insulin use, and elevated blood pressure are other important risk factors. Eye injections are used to control macula edema and laser treatment for growth of new blood vessels (32, 33)
Glaucoma	
Affected structure	Optic Nerve
Definition, risk factors and general actions for treatment	Glaucoma is an ocular disease that causes optic nerve damage which leads to peripheral vision loss and in some cases to vision loss. There are two major types of glaucoma: primary open angle glaucoma and angle closure glaucoma. Primary open angle glaucoma is the most common type. Elevated intraocular pressure (IOP) is one of the clinical symptoms associated with loss of visual function although not every patient experience IOP. The diagnosis is based on evaluating, IOP, optic nerve and retinal nerve changes and by performing visual tests, in particular, vision field tests to assess peripheral vision loss. High intraocular pressure, thin central corneal thickness, positive family history, increasing age, corticosteroid use, and possibly myopia and diabetes are risk factors or associations for development of glaucoma. Treatment includes medication to control IOP and surgery (31).
Refractive errors	
Affected structure	Cornea, lens or eye shape
Definition, risk factors and general actions for treatment	State in which “the optical system of the non-accommodating eye fails to bring parallel rays of light to focus on fovea”. Myopia and hyperopia consist on refractive errors where the optical system brings parallel rays of light into focus anterior and posterior of the fovea respectively. This results in blurred vision. Myopia is much more prevalent in younger age and higher education level. Risk of hyperopia appears to increase with age, less education, and is most prevalent in white men. It can be relieved by the use of glasses, contact lenses or refractive surgery (32, 34).

The main causes for blindness in the population aged 50 years or more in Western Europe are shown in Figure 6. Figure 7 shows the main causes for other vision impairment levels for the same region and age range. In Western Europe, where Portugal is included, in 2015 cataract and uncorrected refractive error combined contribute to 36% of blindness and 65% of other levels of vision impairment for those aged 50 years and older (27).For vision impairment alone, uncorrected refractive error, reversible with spectacle correction, represents 50% of total cases in adults aged 50 years and older. For blindness, and also in Western Europe cataract, reversible with surgery, accounts for 21% of cases in the same age range and year. Cataracts is followed by Age-related macular degeneration (AMD) and glaucoma that are responsible for 15% and 14% respectively of blindness cases whereas uncorrected refractive error accounts for 13%.

There are differences in the distribution of causes of blindness and other levels of vision impairment in the world (27).The proportion of blindness and other levels of vision impairment caused by cataract was smaller in high income regions and in Europe than in some sub regions of Asia and sub-Saharan Africa (27). It ranges from less than 22% in Western Europe and high income regions of North America and Asia Pacific and higher than 44% in Central, West and East sub-Saharan Africa for blindness and less than 15% in Western and Eastern Europe and in high income regions of North America and Asia Pacific and higher than 34% in Central sub-Saharan Africa for other levels of vision impairment, respectively. Uncorrected refractive error has a larger proportion of blindness and other levels of vision impairment in south Asia than in other regions of the world. It is responsible for 36% of the cases of blindness and 66% of other levels of vision impairment in this sub-region of the world. In Europe and high income North America uncorrected refractive error is responsible for 13% of blindness and about 50% of other levels of vision impairment.

The proportion of vision impairment (including blindness) attributed to AMD in Europe and high income North America ranges from 19.5% to 15.4% for blindness and from 13.4% to 10.7% for other levels of vision impairment. AMD causes a lower proportion of cases of blindness and other levels of vision impairment is the rest of the world, 5.93% and 4.38% respectively (27). Glaucoma follows a similar pattern as AMD with a higher proportion of cases for blindness and other levels of vision impairment in Europe and high income North America than in other world sub regions (27). In Europe and North America 13.5% of cases of blindness and 3.6% for other levels of vision impairment are due to Glaucoma whereas at a global scale the values are 8.5% and 2.1% respectively.

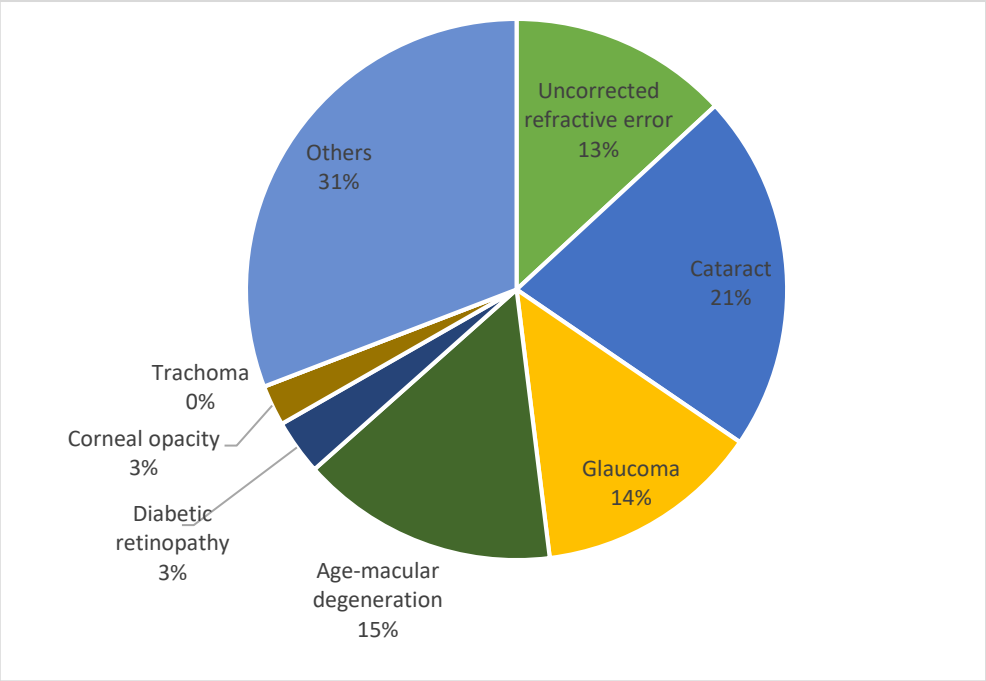

Figure 6 – Causes of blindness among adults 50 years and older in 2015 – Western Europe. Adapted from Flaxman et al. (27)

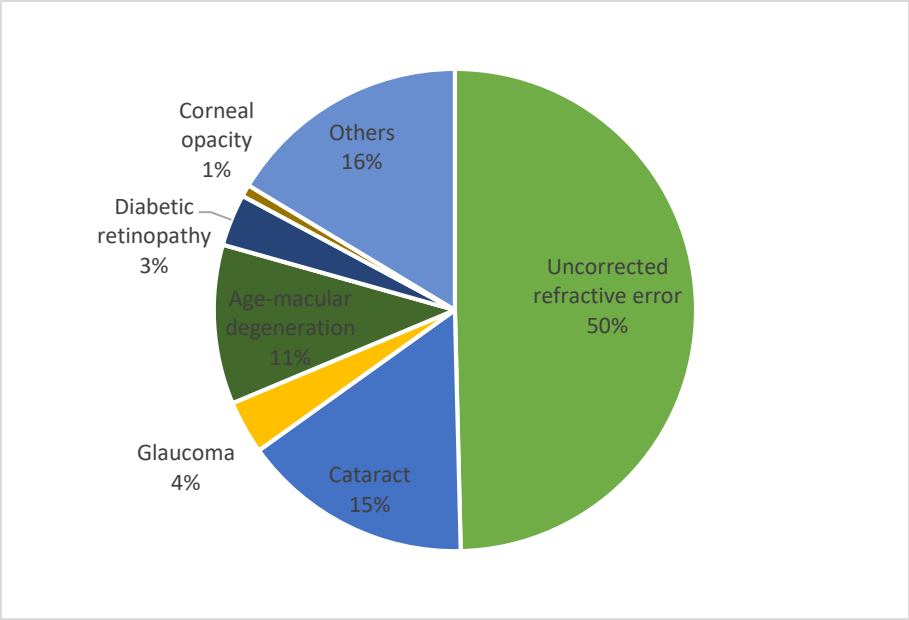

Figure 7 - Causes of vision impairment among adults 50 years and older in 2015 - Western Europe. Adapted from Flaxman et al. (27)

2.4 - Impact of vision impairment on individuals, healthcare system and society

Vision impairment (VI) can lead to a large spectrum of difficulties. VI is associated with difficulties performing activities of daily living (35-37), mobility and autonomy (38-40), depression and anxiety (41, 42), social isolation (40, 43), decreased quality of life (44-46), a high number of falls, injuries and trauma related with falls and injuries (47, 48), a high risk of car accident (31, 40), a higher levels of dependency (35), high need of informal and formal care (49-51), an increase risk of healthcare resource use (52, 53), leading to an economic burden for individuals, healthcare system and society.

This subsection provides an overview of the main impacts of VI. It describes how VI affects daily living activities, how is associated with depression and anxiety and how it is related to risk of falls and fractures. The impact of VI on healthcare systems is characterized in terms of healthcare resource utilization, what are the determinants of access of visually impaired persons to healthcare services and how is the adoption of new healthcare treatments. The societal implications of VI is characterized by the economic impact of vision impairment and its main components.

2.4.1 - Impact of vision impairment on individuals

2.4.1.1 Impact of vision impairment on daily living activities

The activities and performance of daily living activities of persons with vision impairment are likely to be affect by their disability (35-37, 54). For example, when compared with participants without vision problems, older people with vision impairment were 3 times more likely to report walking difficulties, 3.3 times more likely to report problems getting outside, 4.3 times more likely to report difficulties managing money and 4.9 times more likely to report difficulties to use a telephone (54). Visual acuity, contrast sensitivity and visual field losses are associated with difficulties in performance of everyday activities including, walking around, inserting a plug or dialling a telephone or visually intensive tasks like reading speed or face recognition (35-37). Likewise, different levels of visual acuity and contrast sensitivity are associated with different levels of difficulties depending on the task. Figure 8-A shows an example of a relationship between contrast sensitivity and the score of speed of inserting a plug. Figure 8-B illustrates an example of a linear relationship between presenting visual acuity measured in logMAR and the number of faces recognized during a face recognition test.

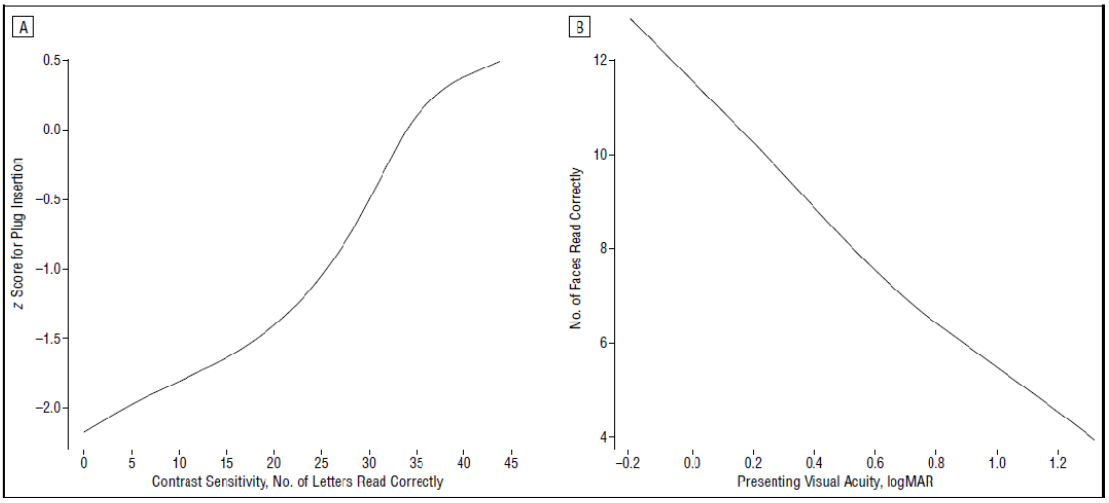

Figure 8 - A, Smoothed graph of the relationship between contrast sensitivity in the better eye and the score of inserting a plug. B, Smoothed graph of the relationship betweem visual acuity in the better eye and the number of faces read correctly on the face recognition test (35)

Different eye diseases affect visual function (see section 2.1) differently leading to typical limitations in functional vision with different impacts on daily living activities (55, 56). For example, reduction in contrast sensitivity and visual field in old adults with glaucoma is associated with weaker limb strength, lower self-reported physical activity and lower overall functional status score (57). People with cataracts have reduced visual acuity and contrast sensitivity that has been associated with difficulties performing several activities like reading, inserting a key in a lock or reading a medicine bottle (37).

The type of activities or tasks are relevant when assessing the impact of vision impairment on everyday life activities. Some studies have divided everyday life activities into two groups: Activities of daily living (ADL) and Instrumental activities of daily living (IADL). ADL are usually defined as basic tasks of everyday life including bathing, dressing, brushing teeth, and eating while, IADL are more complex tasks including cooking, using the telephone or computer, shopping, household maintenance and managing medication. Berger et al. (56) reported that IADL are more challenging and required better visual acuities than ADL activities. ADLs and IADLs require also different skills and are associated differently with patient characteristics such as age, gender, marital status, race, income level and comorbidities. Haymes et al. (55) also concluded that visual functions had a higher correlation with performance with IADL such as, reading, writing and using the telephone, than with basic ADL like dressing and eating. Many of the reported results took into consideration other variables that may influence the ability to perform everyday life activities besides vision impairment including age, gender, presence of comorbidities, depression among others (35, 56).

Reduced performances in activities of daily living and instrumental activities of daily living may have a number of consequences in everyday life such as increased frustration and embarrassment and shortened feeling of personal competency. In addition, limitations in daily living activities affect negatively the independence of visually impaired persons and result in a higher need of family and community support as well as a higher use of long term care facilities (51, 58).

2.4.1.2 Impact of vision impairment on depression and anxiety

Vision loss is a disabling, disturbing and stressful consequence of aging for many elderly individuals (59, 60). It is associated with, declining ability to live independently, to depression and social isolation (35, 40). Depression has also been associated with reduced ability to perform daily living activities, diminished capability to socialize and reduced quality of life. Untreated depression has been linked to limitation in everyday activities, to various systematic diseases including metabolic disorders, cardiovascular diseases (61) imunoendocrine dysregulation, increased risk of death and higher need of long term care (62, 63).

Vision loss is one of the most common chronic condition associated with depression in old age, with both increased odds ratio and relative risk (64). According to a meta-analysis, comparing depression between participants with and without vision loss, there is an association between depression in old age and poor vision. Figure 9 shows the results of pooling 15 studies, 12 studies comparing subjects with and without good vision and three studies comparing incidence rates of depression between subjects with poor and good vision, and presents a pooled odds ratio of 1.94 (95% CI: 1.68 – 2.25) and a relative risk of 2.39 (95% CI: 1.23 – 4.6) respectively (64). More recently the association between vision loss and depression was also demonstrated and generalized in individuals with 20 years of age and older (65). The prevalence of depression and depressive symptoms among eye diseases was also estimated an the overall pooled prevalence was 25% (1502/6589; 95%CI: 0.20-0.3) ranging from 5.4% to 57.4% (61). It can be said that the prevalence of depression amongst people with impaired vision is comparable to the prevalence found in life threatening diseases like cancer and cerebrovascular disease.

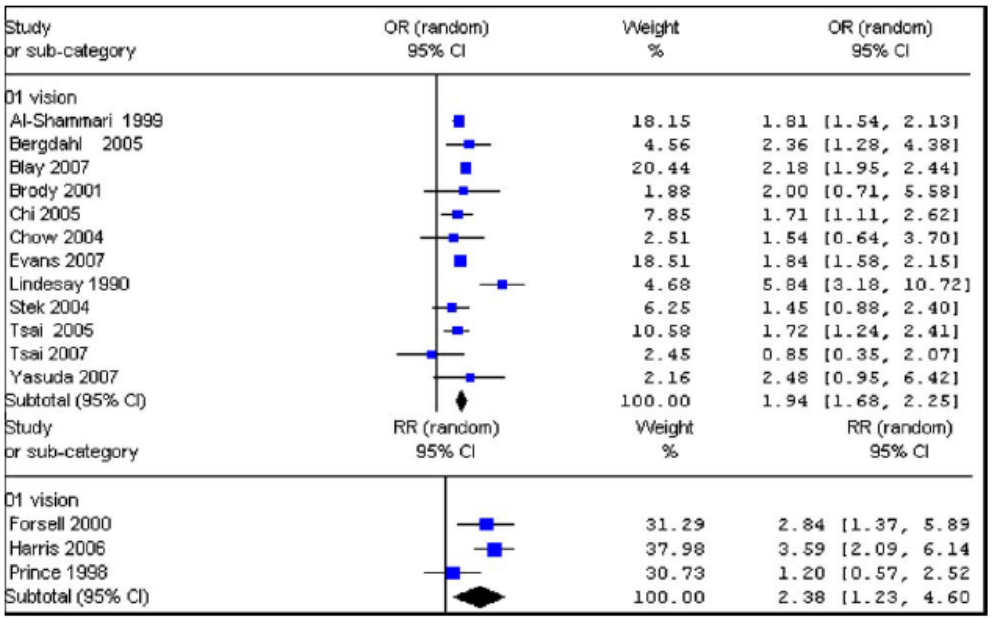

Figure 9 - Forest plot of Odds Ratio and Relative Risk from 15 studies comparing the prevalence and incidence rates of depression in persons 65 years old and more with poor and good vision (64)

Depression may occur at any level of vision impairment (62, 66) and even patients with minimal vision loss are at risk for depression (67). For example Goldstein et al. (67) reported that from 764 patients recruited at low vision rehabilitation clinics 22% were depressed, 23% were experiencing anxiety even though 65% had mild to moderate vision impairment. Brody et al.(62) also demonstrated that visual acuity had little correlation with the severity of depressive symptoms. Accordingly to the authors this finding could be related to the fact that depression associated with AMD may occur earlier in the course of AMD and at low levels of vision loss and not only in those with very poor vision. Moreover, Rovner et al. (68) in a prospective study concluded that as depressive symptoms increased over time and there was a corresponding decline in the performance of vision related activities, regardless of visual acuity. Another study demonstrated that vision- specific distress including, amongst others, feelings like loneliness and isolation, anxiety about the future and worries that eyesight gets worse were the predictors of depressive symptoms. The emotional consequences of vision loss seems a critical factor for depression independently of the severity and duration of vision impairment (69). In addition, Tournier et al. (70) also suggested that severity of vision impairment may not be associated with risk of depression. In summary, vision impairment is a risk factor for depression but depression may be an avoidable consequence of vision loss.

2.4.1.3 Vision impairment and risk of falls and fractures

Vision impairment has been shown to be associated with an increased risk of falls and different types of fractures in multiple studies. Falls are part of the snowball effect triggered by vision impairment putting pressure on health care services. For example, falls can lead to increased needs of medical interventions and long term care due to trauma. In the Framingham Eye Study participants with moderate VI had an increased risk of subsequent fractures over a 10-year period (Risk Ratio, RR 1.5) (71). Dargent - Molina et al. (72) in a large multicentre prospective study (EPIDO) with women aged 75 years or older reported that the risk of hip fracture increased with visual acuity 3-4/10 in decimal scale (Risk Ratio of 1.9) (95% CI 1.1 to 3.1) and was even higher in subjects with visual acuity equal or bellow 2/10 (decimal scale) with a Risk Ratio of 2.0 (95% CI 1.1 to 3.7). These values are summarized in Table 6. In another study with older white women the risk of hip fracture was considered multifactorial. Both poor depth perception and reduced perceive contrast sensitivity were independent predictors of hip fracture (73). In this study participants who had five or more risk factors had an incidence of hip fracture of 19 per 1000 woman-year whereas women who had two or fewer risk factors had an incidence of only 1.1 per 1000 woman year (73).

Table 6 - Relative risk of fall related factors including visual acuity presented in decimal scale

Explanatory variables	**Relative Risk (RR)**	**95% C.I. for RR**	
		Lower	Upper
Visual acuity (vs >7/10)			
5-7/10	1.5	0.9	2.4
3-4/10	1.9	1.1	3.1
<= 2/10	2.0	1.1	3.7

Source: Adapted from: Dargent – Molina et al. (72)

Functional limitations and physical performance appear to mediate these relationship between impaired vision and recurrent falling (74). Patino et al. (75) showed that central visual impairment (defined as visual acuity > 20/40) and peripheral visual impairment (defined as mean deviation < -2 dB) were independently associated with increased risk of falls and falls with injuries in Latino participants aged 40 years or older. The study found that individuals with central moderate to severe visual impairment (visual acuity < =20/80) were 2.36 more likely to report a fall and 2.76 more likely to report a fall with injuries when compared with participants without central visual impairment. Similarly those with moderate to severe impairment (mean deviation < =6 dB in worse eye) where 1.42 times as likely to report falls and 1.40 times as likely to

report falls with injury, compared with individuals without any peripheral visual impairment (75). Reduced contrast sensitivity and visual acuity were also associated with an increase rate of falls and with injurious in a prospective study conducted in older adults with age macular degeneration (48). Falls caused by deficits in central and peripheral vision can be explained by many factors such as incorrect judgments about distance or spatial information such as a shadow or a ground surface and reduced postural stability (72, 74, 75). Visual inputs are also important to help individuals to coordinate and plan movements and to maintain balance (47, 76).

Older adults who fall are at greater risk of hospital admission and nursing home placement (58, 77). Compared with younger controls, older adults have a higher injury related mortality rate, poorer diagnosis, more complications and subsequently higher health care costs (39, 78-80). Hip fracture is one of the most serious injury caused by falls. The majority of patients with a hip fracture do not return to the level of activity of daily living experienced before the fracture. Psychological difficulties associated with a fall may cause loss of self-confidence, activity avoidance or self-imposed restrictions on physical activities (47). In short, falls are common amongst the elderly with VI and that can cause serious injuries such as fractures which increase physical and psychological difficulties.

2.4.1.4 Vision impairment and its association with comorbid conditions

Comorbidities in visually impaired individuals are common but the knowledge about its implications is sparse (81, 82). The causal pathway between comorbid conditions is also unclear, for instance, diabetes and stroke are likely to contribute to vision loss while others, like depression and falls, may result from severe vision loss (83). People with several chronic conditions such as diabetes and cardiovascular conditions, may have cumulative risk of vision loss due to vascular, neurodegenerative, biochemical or inflammatory conditions (82). Cataracts have been related to arthritis and diabetes. Diabetic retinopathy is a consequence of diabetes, hypertension and hypercholesterolemia which may indicate cumulative effects of comorbid conditions (82). Crews et al. (83) estimated the frequency of nine conditions (breathing problems, diabetes, hearing problems, heart problems, hypertension, depression, joint problems, lower back pain and stroke) in older people with comorbidities and with visual impairment concluding that older adults with vision impairment had a high prevalence of comorbid conditions.

Comorbidities are associated with further barriers to remain active and maintain social participation. Comorbidities create difficulties to walk and climbing steps,

shopping, socializing, accelerate the declining of perceived health and increase disabilities caused by VI (62, 83, 84).

2.4.2 - Consequences of vision impairment for the healthcare system

2.4.2.1 Vision impairment: hospital resource use and long-term care

Hospital resource use is higher in persons with vision impairment when compared with persons without vision impairment (52, 53, 85-88). For example, Crewe et al. (86) reported that, when compared with age-matched controls, blind people went to the hospital more frequently, more often to the emergency department. Visually impaired persons also have longer lengths hospital stays compared to persons without VI (53, 89). As summarize in Table 7 an additional 2.4 days to the average length of stay was reported in patients with vision impairment after controlling for age, sex, payer type, disease, disorders and ophthalmological procedures (89). Authors speculate that problems in room orientation, confusion in finding the bathroom or safely walking in corridors and additional difficulties in managing new prescriptions may delayed discharge (89). In addition, Crewe et al. (86) and Wang et al. (90) demonstrated that blind individuals had a higher number of emergency department utilization or costs when compared with controls.

Table 7 - Hospital Average Lengh of Stay (ALOS) for patients with and without vision impairment. Vision impairment was identified using ICD9 CM codes

	No Visual Impairment		**Visual Impairment**		**ALOS Difference (days)**
	Number	**ALOS (days)**	**Number**	**ALOS (days)**	
Actual Number	21456586	8.2	5764	13.4	5.2
Case Mix-Adjusted *	1961094	8.6	5739	11.4	2.8
Multivariate analysis adjusted**	Not Available	Not Available	Not Available	Not Available	2.4

*Case mix adjusted to provided matching disease categories in both populations
** Multivariate analysis adjusted for age, sex, payer type, disease, disorders and ophthalmological procedures

Source: Adapted from: Morse et al. (89)

Long term care needs such as nursing home placement, home help or skilled nursing facilities use is higher in persons with impaired vision (52). Javitt et al.(52) and Bramley et al.(91) reported an increased odds of utilization of skilled nursing facilities and long term care admission in persons with any degree of progressive vision loss. For

example, progression from normal vision to blindness is associated with 2.5 to 3 increased odds of utilization compared with persons without VI (52). Bilateral VI was associated with an increased risk of nursing home placement over 6 years following baseline examinations in an Australian population (51). An increased odds of admission to a nursing home has also been found in participants with VI in an population-based study conducted in the United States of America (Beaver Dam eye study) (92).

Some studies reported an excess cost both for eye-related resource utilization and non-eye related resource utilization in patients with vision impairment (52, 90). These studies reported that non-eye related medical care was significant in the total excess costs of vision impairment when comparing participants with and without visual impairment. Furthermore, Javitt et al. (52) showed that those progressing from a normal vision state at baseline incur higher non-eye costs than those who remain in the same level. Cost distribution by type of care varied also across severity of VI (90, 91). Figure 10 provides an example of mean total and component annual health care costs per patient and by vision impairment categories. In this example costs increased with the degree of vision loss, ranging from $8157 for no vision loss to $18670 for blindness and inpatient care was the major component of costs. In another study, excess cost of blindness were driven by inpatient care whereas for moderate to severe visually impaired patients outpatient care was the main cost component (90). Other studies demonstrated that the excess costs of vision impairment decreased from the first year to the second year after diagnose. This may result from a large amount of resources used initially in eye-related conditions or complications from vision loss, such as falls or depression, which may stabilize after patients become adjusted to the condition (90, 93).

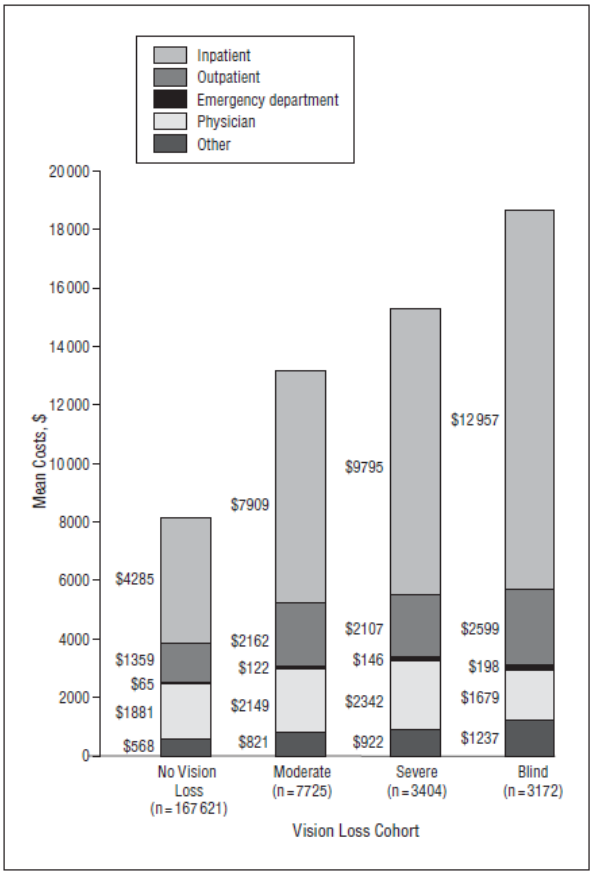

Figure 10- Mean total and component annual health care costs per patient and by vision impairment categories. Vision impairment is categorized in 4 categories based on their worst degree of vision loss during follow-up using 57 ICD-9-CM codes: no vision loss, moderate vision loss (ICD-9-CM codes 369.6-369.9), severe vision loss (ICD-9-CM codes 369.1-369.4), and blindness (ICD-9-CM codes 369.0-369.08) (91)

The main focus of all the studies mentioned previously was to analyse the use of hospital resources between those with and without vision impairment. Therefore, these studies were based on realized access of eye care rather than “potential” access. By focusing on realized access none of these studies assessed if resource utilization was adequate to meet health needs of this population, if there are visually impaired individuals who are not getting eye care, or if there is underutilization or overutilization of those who are in the healthcare system. These aspects will be briefly reviewed further in section 2.4.2.3.

2.4.2.2 Vision impairment, comorbid condition and its association with resource utilization

Vision loss can have a magnifying and acceleration effect on comorbid conditions leading to increased health care needs and costs (52, 83). Multiple comorbidities are associated with high mortality, have a negative impact on quality of life and increase the

use of inpatient and ambulatory healthcare services (84, 94). This may be driven by complications, complexity to define treatment strategies and higher risk of readmissions. As severity of VI increases, resource consumption, adverse consequences and intensity of care may also increase (91). For example, the coexisting of ocular conditions, including primary open-angle glaucoma and cataracts, and other comorbidities, such as hypertension and diabetes, is associated with higher eye treatment costs in patients with AMD as summarize in Table 8 (95).

Table 8 - Adjusted estimates from the multiple linear regression model for other eye diseases and comorbidities with Medicare costs for any eye-related visit during 1995 to 1999. Subjects were Medicare beneficiaries with AMD and controls were Medicare beneficiaries with no AMD. Cost ratios were calculated by exponentiation of regression coefficient estimates

	Cost ratio	**95% CI**		**P Value**
		Lower	**Upper**	
Primary Open-angle glaucoma	2.12	2.04	2.20	< 0.001
Cataracts	1.67	1.63	1.71	< 0.001
Hypertension	1.04	1.01	1.06	0.001
Cardiovascular disease	1.22	1.07	1.13	< 0.001
Diabetes	1.10	1.18	1.26	< 0.001
Hyperlipidemia	1.08	1.05	1.11	< 0.001

Source: Adapted from: Coleman et al.(95)

VI may complicate the management of other comorbidities and comorbidities may also affect the management of ocular diseases leading to a closed-loop feedback. Individuals with VI may experience difficulties to properly administrate medications, prepare healthy meals, use of medical devices to measure and control hypertension or glycaemia as well as, for instance, foot checks in diabetics. Transportation to and from medical appointments may also be more difficult to visually impaired individuals (19) and caregivers capacity to support patients getting to several medical appointments and treatments in different places and different times may also be more limited (96). From other perspective, comorbidities may also influence the capacity to cope with VI. Comorbidities may affect vision rehabilitation outcomes and adherence to treatments, may amplify communication barriers, delay treatments and follow-up medical appointments (96). For example, the exacerbation of a chronic disease like asthma may increase difficulties on breathing and therefore reduce the capacity of a patient to engage vision rehabilitation sessions. In addition, administration of eye drops can be more difficult for patients with cognitive impairments, limited movements of the neck, arthritis or neuropathy in the hands (19, 97). Therefore, some aspects of eye care may be challenging due to comorbidities. At the same time, comorbidities may become worse due to limitations to its management imposed by impaired vision.

2.4.2.3 Vision impairment and access to eye care

Eye diseases and subsequent vision loss poses a big challenge to healthcare systems and are a public health concern since most vision loss may be avoidable (27, 98-100). Even though there are available many cost-effective interventions for prevention, treatment and control of major eye diseases access to eye care remains problematic in many countries (100-103). For instance Vela et al. (100) reporting eye care utilization in 70 countries concluded that only 18% of older adults have seen an eye care professional in the last year. As summarized in Table 9 eye care utilization rates ranged from less than 10% to higher than 40% depending on the income status of the country. In addition, several studies reported geographical variability in rates of eye care use within developed countries (103-105) while others have reported low compliance of examination routines defined in clinical guidelines even in risk groups like patients with diabetes (100, 106-108). Adequate access to care is essential to reduce vision related morbidity and mortality and to improve health related quality of life (109).

Table 9 - Use of glasses or contacts lenses and eye care utilization in low, middle, and high income countries

	Overall	**LIC**	**LMIC**	**UMIC**	**HIC**
Within last 12 months	18%	10%	24%	22%	37%
1-2 years ago	16%	9%	21%	20%	27%
3-4 years ago	9%	5%	11%	12%	13%
5 years ago	3%	3%	4%	3%	3%
More than 5 years ago	16%	12%	20%	17%	15%
Never	38%	61%	20%	26%	5%

LIC = low income countries (Bangladesh, Burkina Faso, Chad, Comoros, Congo, Cote d'Ivoire, Ethiopia, Ghana, India, Kenya, Lao, Malawi, Mali, Mauritania,Myanmar, Nepal, Pakistan, Senegal, Vietnam, Zambia, Zimbabwe)

LMIC = lower middle income countries (Bosnia Herzegovina, Brazil, China, Dominican Republic, Ecuador, Georgia, Guatemala, Kazakhstan, Morocco, Namibia,Paraguay, Philippines, Russian Federation, South Africa, Sri Lanka, Swaziland, Tunisia, Ukraine)

UMIC = upper middle income countries (Croatia, Czech Republic, Estonia, Hungary, Latvia, Malaysia, Mauritius, Mexico, Slovakia, Uruguay)

HIC = high income countries (Slovenia, Spain, United Arab Emirates)

Source: Adapted from: Vela et al. (100)

Access is a multidimensional concept which may be defined as "those dimensions which describe the potential and actual entry of a given population into the healthcare system" (110). In this definition potential and actual (or realized) access are two different parts of access. Potential access refers to the probability of using health care services while realized access refers to the effective use of health care services. Accordingly with Andersen's Behavioural Model of health services access is driven by contextual and individual characteristics including both predisposing, enabling and need factors (111). A modified model was applied in the context of access to eye care by Zhang et al. (102) to review the theoretical and empirical literature on access to eye care. In this modified model "predisposing individual characteristics exist before the onset of vision problems,

enabling characteristics are the potential financial and medical resources available to allow use of eye care" and need factors may include perceived need (by the patient) and evaluated need (professional assessment of need of medical care). Table 10 summarize examples of factors associated with access separating individual and contextual characteristics.

Table 10 - Predisposing, enabling and need factors associated with access to eye care aggregated into individual and contextual level

Predisposing factors	Enabling factors	Need factors
Individual level		
Age, gender, marital status, education, occupation, race/ethnicity	Income/wealth, health insurance coverage, continuity and regular sources of care	General health, disability status, comorbidities, vision problems and eye diseases.
Contextual level		
Community sociodemographic characteristics such age and sex distribution, education and employment level	Community income and health care system factors like health insurance "carve outs" for eye care, number of eye care professionals	Population health index

Source: Adapted from: Zhang et al. (102)

Predisposing individual factors such as age, gender, race or ethnicity, education and income has been consistently associated with differences in access to care (101). Women are more likely to attend eye care services than men (101, 112). Utilization of eye care services has been reported to increase with age (87, 113, 114). Race or ethnicity has also been associated with access with non-whites being less likely to have an eye examination compared with whites (87, 101, 107). Individuals with higher education and higher incomes are more likely to use eye care services (101, 104, 115).

Disparity in access to health care related to differences in socioeconomic status is widely recognized. Low socioeconomic status has been consistently related with lower access and poorer outcomes (106). Income and health insurance are among the socioeconomic determinants related to socioeconomic status. Regarding health insurance coverage, many studies have reported a positive association between insurance coverage and access to eye care services (103, 106, 116). Nevertheless, a study from Australia showed that despite the existence of universal health insurance nearly half of patients with diabetes did not receive screening or follow-up for diabetic screening (103). Other studies reported that the lack of private health insurance beyond governmental health coverage emerged as barriers to the access of eye services (103, 116, 117). Table 11 summarizes the results of a study that shows that patients with public

and private insurance had three times the odds (OR 3.39, 95% CI 1.82– 6.31) of having their vision tested compared with those with only public insurance.

Table 11 - Effects of insurance status on having vision tested in patient age 65 years old or older

Insurance status	**Odds ratio**	**95% CI**	
		Lower	**Upper**
None	N/A	N/A	N/A
Public only	1		
Private only	2.6	0.9	7.5
Public and private	3.39	1.82	6.31
Public with Medicare supplement	1.78	1.14	2.77

Source: Adapted from: Puent et al. (116)

Differences in patterns of utilisation seemed also to be associated with availability of eye care services with lower utilisation rates found in rural areas (103). Sloan et al. (114) reported that the probability of having an eye exam was higher with greater geographic density of eye care professionals and that different provider organizational models and different levels of integration between providers also affect access to eye care services. Lee et al. (108) referred that difficulties finding an eye care provider, transportation problems and caregiver time constraints may have act as barrier in access to eye care. That may play a major role in the compliance of clinical guidelines related to annual eye care examinations in people with diabetes and chronic eye diseases (108). Rural areas are more likely to have shortage of eye care professionals and that may decrease healthcare utilization, cause longer waiting lists and increased transportations costs for patients (101). Transportation problems or lack of social support have been extensively reported as important factors that act as barriers to access eye care (98, 109, 115, 118).

Need factors measured by, general health factors such as diabetes and hypertension and eye health factors like visual impairment, diabetic retinopathy, glaucoma, cataract, history of cataract surgery and retinal vein occlusion were found to be important determinants to increase usage of eye care services (87, 101, 113). Although, it is relevant to emphasize that evidence shows that there is a lack of compliance of clinical guidelines for preventive care and follow-up care even amongst people with sight threatening eye and systemic health conditions with lower access than recommended. For example, accordingly with Zhang et al. (101) and Spencer et al. (109) persons with vision and eye problems and persons with diabetes were the ones who were more likely to need visual aids and the ones who most often could not afford it.

Figure 11 shows an example where a group of high risk patients have a higher percentage of persons who cannot afford eyeglasses.

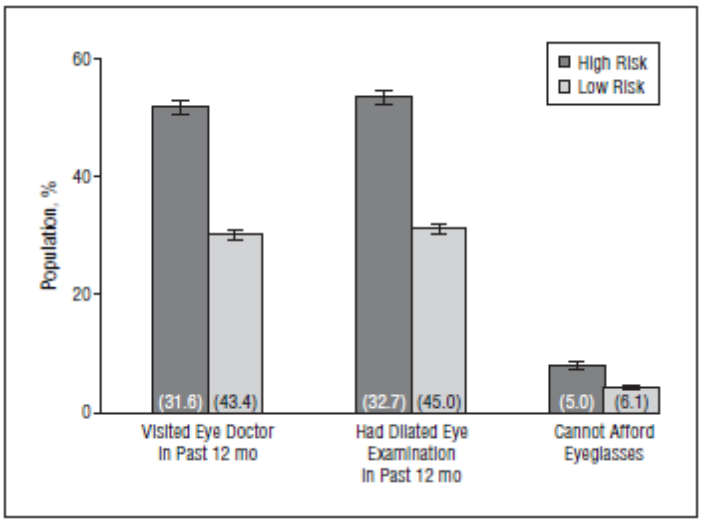

Figure 11 - Estimated eye care use among adults at high risk for serious vision loss (include patients with diabetes, those having self-reported vision or eye problems, or those aged 65 years and older) vs those at low risk of vision loss. The percentage refers to those who visited an eye doctor in the past 12 months, had a dilated eye examination in the past 12 months, or cannot afford eyeglasses when needed. Numbers in parentheses represent the number of millions of persons to which the percentage applies for the high-risk and low-risk subpopulations; error bars represent 95% confidence intervals (101)

Perceived benefit of eye care services by patients may also influence the decision to seek eye care. People frequently cited “no need to go” or “can´t afford prescription drugs, co-payment or eyeglasses” “no insurance coverage” as reasons for not seeking eye care (98, 101, 118). Furthermore the asymptomatic nature of many eye diseases in their early and treatable stage may also influence the decision of patients to postpone eye care (119).

Interestingly, some authors associated gender disparities in access to eye care with distinct attitudes with health. Women seems to have “greater awareness of symptoms, lower threshold of symptoms before seeking care and social support and differences in comfort levels in seeking care” so different perception of need and therefore different health service use (112).

Eye care providers reporting their impressions of older patients attitudes about vision care mentioned as barriers to eye care: the lack of awareness of the importance of preventive care, routine examination and prescript treatments by patient as well as the patients perception that other medical problems have higher priority than eye

problems (101). The lack of awareness and knowledge about health and diseases has been related to health illiteracy that may also be associated to education level. For instance health illiteracy measured by inadequate knowledge about basic symptoms, risk factors and available treatments has been presented as one of the explanatory factors of the less likelihood to receive routine comprehensive eye examinations in minority groups such as African Americans and Latinos (87, 98, 119).

2.4.2.4 Vision impairment and access to new treatments

Access to eye care services remains as a topic of special concern for a few reasons. The firs reason is related to the growing demand for vision and eye care mainly due to an ageing population with multimorbidity that needs to be under clinical observation, to be treated or to be rehabilitated. Furthermore the adoption and development of new healthcare technologies that will emerge from advances in medical science will also result in greater use of eye care and that may increase pressure in healthcare system capacity and therefore influence access to eye care. For instance, antivascular endothelial growth factor (anti-VEGF), licensed and clinically available in the last decade, have change the management of age macular degeneration that was largely untreatable before the introduction of this new medicine posing considerable resource allocation issues to the healthcare system (120).

The adoption and diffusion of new healthcare technology is a complex process shaped by a multiplicity of determinants performing at the professional, organizational and regulatory level (121, 122). Professional and organizational level has been associated to the timing and pattern of diffusion. Regulatory levels, more specifically, the mechanism to assess reimbursement at a national level as well as the payment system to providers may also play a substantial role affecting provider's behaviour (121, 122). Few studies have analysed the cross-country variations in the diffusion of healthcare technology considering differences in national regulatory policies, such as coverage, reimbursement and pricing, and payment mechanism to professionals or to organizations (122, 123). Among the determinants associated to the adoption and diffusion of new healthcare technology more commonly reported there are: the features of the technology; the attitudes and skills of the healthcare professionals; the features of the organizations and the features of the regulatory system specially the reimbursement of healthcare providers (124, 125).

The perceived benefit of the innovation and its relative advantage compared with existing technology have a major influence on the acceptance and diffusion of a new

and innovative technology in the health care services (125, 126). For instance Stein et al.(120) reported that the lack of a more effective treatment for age macular degeneration was one of the key element to the rapid diffusion rate of anti-VEGF in the United States. Health care professionals are more likely to adopt a new technology if they think it can help them, if it is relevant to the patient they treat and if the innovation is appealing to use (127, 128). The more knowledge health care professionals have about a new technology the more likely they are to adopt it (129).

Technologies that required additional resources like special lighting, extra training for healthcare professionals or special technical requirements like mandatory use of operating room may have slower rates of diffusion (130). Furthermore, innovations have a faster rate of adoption if it possess 4 attributes: simplicity, compatibility, triability and observability (126-128). Commonly, simple innovation spread faster than more complex ones. Innovations there are compatible with the values, standards, principles and past history of the adopters are adopted easily (126).Triability and observability also influence the spread of innovation and are related to the capacity to test the innovation in a small sample and to observe its implementation by other health care professionals respectively observability (127, 128).

Beyond the features of the technology the attitudes and skills of the healthcare professionals are another important factor to explain the adoption and diffusion of new healthcare technology. Berwick and Mathews based on the work of Roberts classified adopters into 5 categories: innovators, early adopters, early majority, late majority and laggards (127, 130). These categories were built taking into consideration the time of adoption and more specifically the mean and standard deviation (SD) of the time taken to adopt a new technology are shown in Figure 12(127). Innovators are those whose time to adopt is bellow two SD bellow the mean time of adoption and correspond to 2.5% of the population. Usually they are tolerant to the risk, always available to learn something new and fascinated by novelties. Early adopters correspond to 13% of population and are usually key opinion leaders that communicate with innovators and other key opinion leaders and are willing to take some risks to try new technology. Early majority correspond to 34% of population and are more risk-adverse than early adopters and incorporate innovations that are relevant to their local problems and learn mostly with people they know well. Late majority correspond to 34% of the population and professional included in this categories are more conservative than the early majority and only adopt a new health technology when it became standard of practice. The last category, laggards are the last to adopt a new technology and correspond to 16%.

Usually laggards are traditionalists and choose only technologies that are well established and that has been proven to be safe and produces good outcomes.

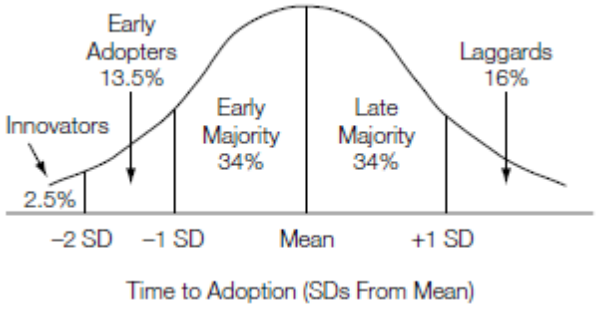

Figure 12 - Adopter categorization on the basis of innovativeness. There are five categories built taking into consideration the time of adoption and more specifically the mean and standard deviation of the time taken to adopt a new technology (127)

Among the determinants related to organizational features that influence the adoption and diffusion of new healthcare technology Fleuren et al. (128) reported that the organization capacity to implement innovation, availability of expertise and staff and the nature of collaboration between departments involved in the implementation of the innovation are some of the features more often reported to influence the diffusion of innovation. An organization will assimilate innovation more rapidly and easily if it encourages, promotes and support the spread of innovation, if it has risk tolerance to incorporate failures and unexpected costs, if it has available resources to try new technologies in terms of human resources, financial and technical capacity (126, 127). More specifically, studies on hospital characteristics have reported that specialization in intensive treatments is likely to influence the diffusion of new healthcare technology (131). In fact, there is evidence that the diffusion across regions and hospitals is not optimal and there are often under-and-overutilization of new healthcare technologies. Factors such as, teaching status, urban location, degree of specialization, multispecialty practice setting, hospital size (large hospitals compared with small hospitals) and the presence of competition influences positively the spread and rate of diffusion (131). For example teaching hospitals, higher volume hospitals, hospitals with high skill and better reputation physicians may have better capacity to disseminate information on new healthcare technologies.

The influence of the reimbursement system on the diffusion of healthcare technology is an ongoing debate with several approaches and different results. Fixed-global budget systems, especially if based on historical expenditures, are expected to slow down the spread of new technology (132). Diagnosis related groups (DRG) based hospital financing schemes, including DRG-based hospital case payment or DRG-based

budget allocation, also face challenges to adopt new technologies because hospitals are exposed to financial risks of having costs above the established price/budgets. There are two basic and consensual incentives related to DRG payment systems: incentive to reduce costs per admissions and increase number of admissions (133). So, if new technologies are associated with increased costs per admissions, there are impediments or disincentive for the hospital to adopt new technology until DRG system is updated to account for the additional costs imposed by the use of the new technology (122, 123). Accordingly with a recent study, financing systems with frequent updates and adjustments of their DRG system, including the introduction of new codes to incorporate current practice patterns or the adjustment of costs weights reflecting new treatment costs, are in a better position to introduce new healthcare technologies (134).

Diffusion is a cumulative process in which the rate and direction has been described as having an “S shape with an early slow phase affecting a very few adopters, a rapid middle phase with wide spread and a third phase with incomplete penetration in the end” (127). It is considered to be a passive, untargeted and unplanned spread of new technology and opposite of dissemination which is an active and planned spread of a new technology to a target audience (130).

This S curve as a “tipping point”, often around 15% to 20% adoption rate, after which it becomes difficult to stop the diffusion of the innovation. This 15% to 20% usually happens with innovators and early adopters, meaning that as the spread comes near to the early majority most certainly the others will follow. This dynamics explain that diffusion depends on how an organization deals with innovators and early adopters as well as the relationship between them, rather than with any other type of adopters (127).

2.4.3 - Impact of vision impairment to the society

2.4.3.1. Economic impact of vision impairment

The economic impact of vision impairment and blindness has been characterized in countries such as Australia, United States of America, France, Italy, Germany, Japan, Canada and in the United Kingdom (135-142). Table 12 shows the economic burden of vision impairment (blindness is included in vision impairment) estimates reported in these 8 countries. Reported costs were grouped in 6 categories:1) Direct medical costs that include mostly inpatient and outpatient care and all the resources used for diagnosis and treatment; 2) Formal care costs that include long-term care and nursing home costs, community care and paid assistance provided by professionals; 3) Other direct costs that

comprise costs related to vision aids and devices and home modifications. 4) Productivity costs that include absenteeism, loss of income, loss of work, lower workforce participation and in some studies lower productivity due to premature mortality; 5) Informal care costs that includes a monetary estimate of the hours spent by caregivers to help/care visually impaired persons; 6) Other indirect costs comprised mostly dead-weight loss generically defined as an excess financial burden on society caused by an illness or condition.

Cost values were transformed for better comparison across studies. Costs were inflated to 2013 using a country specific gross domestic product deflator and then converted to USD purchasing power parities (PPP). Purchasing power parities are the rates of currency conversion that make equal the purchasing power of different currencies by accounting for differences in price levels between countries.

Table 12 - Summary of reported economic burden of vision impairment in 8 countries, 2013 billion USD PPP

	Australia		USA		USA		France		Germany		Italy		Japan		Canada		United Kingdom	
	All ages		Pop. over 40 years		Pop. under 40 years		All ages		All ages		All ages		All ages		All ages		All ages	
	bn $	%	bn $	%	bn $	%	bn $	%	bn $	%	bn $	%	bn $	%	bn $	%	bn $	%
1. Direct medical costs	1.73	36%	19.48	46%	7.9	28%	n.r	0%	n.r	0%	n.r	0%	10.43	44%	7.83	55%	3.95	29%
2. Formal care costs	n.r	0%	13.18	31%	0.14	1%	2.69	20%	3.22	27%	2.22	14%	8.61	36%	n.r	0%	0.43	3%
3. Other Direct Costs	0.35	7%	0.07	0%	6.66	24%	0.62	5%	0.73	6%	2.36	14%	1.71	7%	0.28	2%	0.93	7%
(1)+(2)+(3)	2.09	44%	32.74	76%	14.71	53%	3.31	25%	3.95	33%	4.58	28%	20.75	87%	8.10	57%	5.31	39%
4. Productivity losses	1.69	35%	9.63	23%	12.41	44%	5.62	42%	3.16	27%	4.16	25%	0.70	3%	4.02	28%	3.92	29%
5. Informal care costs	0.80	17%	0.44	1%	0.61	2%	3.11	23%	3.88	33%	6.24	38%	0.71	3%	0.63	4%	3.69	27%
6. Other Indirect costs	0.20	4%	n.r	0%	0.19	1%	1.20	9%	0.91	8%	1.39	9%	1.57	7%	1.59	11%	0.59	4%
(4)+(5)+(6)	2.69	56%	10.07	24%	13.21	47%	9.93	75%	7.94	67%	11.79	72%	2.99	13%	6.24	43%	8.20	61%
Total Estimates	4.78	100%	42.81	100%	27.92	100%	13.24	100%	11.89	100%	16.37	100%	23.74	100%	14.34	100%	13.51	100%

n.r – not reported; bn – billion

Sources: Australia (135) ; USA (136, 137, 142) ; France, Germany and Italy; (138) Japan (139); Canada (140);United Kingdom (141) – adapted

Total estimates on the economic burden of vision impairment ranged from 42.81 billion US PPP in 2013, reported in the United States of America for persons over 40 years, to 4.78 billion US PPP in 2013 in Canada (Table 12). United States of America and Japan were the countries reporting the highest estimate of economic burden. In both countries direct medical costs, formal care and other direct costs accounted for the majority of costs representing over 50% in the United States of America and in Japan 87% of total estimates for each country.

In the United States of America and Australia direct medical costs of eye diseases and vision problems are considered one of the leading sources of medical expenditures. Eye care costs are seventh and fifth highest disease expenditure respectively (135, 142). In Australia only cardiovascular disease, musculoskeletal, injuries, mental disorders, cancer and dementia had higher direct medical costs than VI (135). In the United Sates direct medical costs for eye diseases were exceeded only by heart conditions, trauma, cancer, and mental health disorders (143).

In France, Italy and Germany direct medical costs were not reported therefore the sum of all direct costs was lower and represented less than in all of the other countries reported in Table 12. Interestingly in these countries as well as in the United Kingdom formal care costs had a lower contribution to total estimates than informal care costs. The highest difference was observed in Italy were informal care accounted for 38% of total estimates while formal care contributed only to 14% of costs (138). Australia and Canada did not report formal care (135, 140).

Productivity losses, informal care and other indirect costs were major contributors (corresponding to more than 50%) to total estimates in Australia, France, Italy, Germany and United Kingdom. In France productivity losses alone were responsible for 5.62 billion US PPP in 2013 representing 42% of total estimate in this country. In the United States of America productivity losses were much higher for persons under the age of 40 years reaching 44% of total estimate in this age-category. These results are in agreement with a systematic review that included not only cost of illness of vision impairment but also disease-specific studies like glaucoma or diabetic retinopathy. The authors of the review found that productivity losses and informal care were major contributors to the economic burden of vision impairment and blindness (144).

Loss of Quality Adjusted Life Years (QALYS) were also reported in the United States of America in population under the age 40 years (142) and older than 40 years (137). In the first case 215,173 quality adjusted life years were lost corresponding to an economic value of 10.93 billion US PPP in 2013. For adults with more than 40 years of

age, 209,202 quality adjusted life years were lost corresponding to an economic value of 12.55 billion US PPP in 2013. If QALYS were added to the values reported in Table 12 they would represent 28% and 23% of total estimates in the United States in population under the age 40 years and older than 40 years respectively.

Loss of well-being estimated with Disability Adjusted Life Years (DALYs) were reported in Australia, Japan, Canada and United Kingdom (135, 139-141). For instance, in Australia 41,187 DALYS were loss due to vision disorders of which 40.068 corresponded to Years of Life with Disability and 1119 to Years of Life Lost. Reports of DALYS and its conversion into a monetary value using the value of a statistic life available and transformed to USD PPP for 2013 in each country are shown in Table 13.

Table 13 - Loss of well-being in Australia, Japan, Canada and United Kingdom, 2013 expressed in DALYS and USD PPP

	Australia		Japan		Canada		United Kingdom	
	Nº/$	%	Nº/$	%	Nº/$	%	Nº/$	%
Monetary of Loss of Well Being (DALYS) (billion USD ppp)	4,58	49%	13,23	36%	10,61	43%	11,26	45%
Total Estimates	9,35	100%	36,97	100%	24,95	100%	24,77	100%
Loss of Well Being (DALYS)	41187		229085		77306		81033	
Per capita estimates (USD ppp)*	45161		48861		41564		22745	

Sources: Australia (135); Japan (139); Canada (140); United Kingdom (141); * per capita estimates from Australia and Japan were obtain from Roberts et al (139) and values from Canada and United Kingdom were obtain from Pezzullo et al. (141) – adapted

If values reported in Table 13 were added to the values reported in Table 12 loss of well-being would have a considerable impact on the economic burden corresponding in Australia to 4.58 billion US PPP (49% of total estimates), in Canada to 10.6 billion US PPP (43% of total estimates), in the United Kingdom to 11.3 billion US PPP (45% of total estimates) and in Japan 13.23 billion US PPP (36% of total estimates). Per capita costs including DALYS and all costs components reported in Table 13 ranged from 48,861 US PPP in Japan and 22,745 US PPP in the United Kingdom. However, attributing a monetary value on QALYS and DALYS is controversial (137, 145) and because of that often these impacts are reported as non-monetary measures (144).

Despite of the efforts made to ensure comparability between studies it is important to highlight that methods, sampled population and reported costs components varied widely between studies. For instance some studies reported costs for all population with vision impairment (140) while others restricted their analysis to adults aged 40 years and older (136). Additionally, estimates were made accordingly with medical treatments available at that time. This may have major implications on estimates. Koberlein et al. (144) emphasized that in their systematic review published in 2013 none of the reviewed studies included antivascular endothelial growth factor treatment. The authors assumed that it is likely that economic estimates made after the introduction of this treatment will report higher direct medical costs. In Table 12 only one study, reporting estimates from United Kingdom, included anti-VEGF treatment. Accordingly to the authors direct medical costs increased 39%, compared with a previous estimate reporting 2008 data in the country, mostly due to an increase of costs with anti-VEGF treatment (ranibizumab) as well as costs with outpatient care and other non-admitted expenditures (141). Additionally, productivity losses rised 49% mainly because there was a fall in the employment rate of people with vision impairment. In contrast, costs with formal care decreased from 2008 to 2013 most likely due to a decline in the number of people registered as visual impaired (including blindness) and due to cuts in social care budgets that have occurred in the United Kingdom during the analysed period (141). The authors reported also considerable differences in the prevalence of eye diseases. Prevalence of AMD, cataracts, glaucoma and diabetic retinopathy increased and the prevalence of under-corrected refractive error decreased.

There is only one economic estimate of vision impairment that reports direct costs, productivity costs and health burden for all world regions (146). In this global estimate a prevalence approach was adopted, vision impairment was defined using presenting visual acuity and all causes of vision impairment were considered, including uncorrected refractive errors. Costs and the health burden were estimated using published disease prevalence rates, mortality rates, health care expenditures and economic data including employment rates and gross domestic product (GDP) per capita (146). The total costs of VI globally was estimated in 2954 billion US$ in 2010 and 118 million DALYS. Direct costs were estimated in 2302 billion US$ in 2010 representing 78% of total estimates (146). Productivity losses in developed countries were estimated in 168.3 billion US$ and included lower employment rates for people with vision impairment and premature mortality. Informal care was estimated in 246 billion US$ and deadweight welfare loss in 238 billion US$.

In the global estimates of the burden of vision impairment, the lack of data for many countries required methodological assumptions that may have influenced the results. For instance, informal care estimates were calculated based on studies from Australia and the UK and under the assumption that all countries had similar formal care availability. These assumptions may have led to a conservative estimate of the informal care costs. Estimating productivity losses only in developed countries may have also contributed to a conservative estimate of productivity costs and for such a high percentage of direct costs in total estimates.

Overall reported estimates showed that, even in developed countries, vision impairment causes a considerable economic burden for affected individuals, for the healthcare system and for the society. It is also clear that countries updated estimates both on prevalence and costs are needed to better analyse the impacts of treatments and prevention strategies over time (141).

The introduction of new healthcare technology may also impact eye care use and costs (147). It is likely that costs component distribution (direct costs versus productivity costs) will change as well as costs distribution by causes of vision impairment. Efforts to screen for and treat for currently undiagnosed and untreatable eye disease may increase direct costs but, if effective, may improve vison outcomes, health related quality of life and potentially decrease DALYS, QALYS and productivity losses (137). Many eye care interventions have proven to be cost-effective so it is likely that higher costs may lead to better outcomes (148).

2.4.3.2. Productivity losses associated with vision impairment

Productivity losses are given a detailed description in this thesis because they were one of the topics investigated in this thesis. Productivity losses were reported by a specific eye condition, uncorrected refractive error (18), in a specific region, Europe (149), and in a sample of nine countries representing different global regions (150). These reports will be presented in the next paragraphs.

The global economic productivity losses associated with uncorrected refractive error were estimated using purchasing power parity gross domestic product losses attributable to individuals with vision impairment (18). For each country it was assumed that individual productivity losses of persons aged 16 and older were equal to a disability weight of 0.6 for persons with blindness and 0.282 for persons with other levels of vision impairment (moderate to severe visual impairment). Caregiver's productivity losses were also added to this estimation assuming a 10% productivity loss for the care of each person with blindness and a 5% productivity loss for the care of each person with other

levels of vision impairment. Productivity costs were adjusted accordingly with the labour force participation rate and employment rate of each country.

Globally productivity losses for uncorrected refractive error were estimated in 268.8 billion dollars representing 0.25% of GDP at the global level (18). The distribution of cases of uncorrected refractive error by regions, using prevalence data was obtained from Bourne et al (20), correlates positively with productivity costs estimates. In Europe and in particular subregion A, where Portugal is included, productivity losses were estimated in 38.9 billion dollars and represented 0.3% of the GDP of this subregion assuming a population-weighted regional labour force participation rate of 0.583 and a population-weighted regional employment rate of 0.88.

Productivity losses due to vision impairment were estimated in Europe only for individuals with 50 or more years (149) and were made using three models reported in the literature: 1) minimum wage; 2) gross national income; 3) purchasing power parity adjusted GDP. Productivity losses were assumed to be 100% for blind individuals and 30% for those with other levels of vision impairment (moderate to severe vision impairment) in the first two models and it was assumed that individuals worked only until 65 years old and then retired. In the third model losses were assumed to be 70% for blind individuals and 34.5% for those with moderate to severe vision impairment adjusted for general employment rates and labour force participation rate but including all individuals aged 50 years and above. The most conservative estimate was produced by the minimum wage model followed by the purchasing power parity adjusted gross domestic product model.

Productivity losses from blindness and other levels of vision impairment in Europe were estimated in 25.8 billion euros by the minimum wage model, in 31.1 billion euros by the purchasing power parity adjusted GDP model and in 56.5 billion euros by the gross national income model (149). These findings demonstrate, independently of the model used in estimation, that vision impairment has a significant economic impact in Europe despite the relatively low prevalence of blindness and moderate and severe vision impairment.

Productivity losses from blindness and other levels of vision impairment were estimated in a sample of nine countries representing different global regions and based on two economic models; 1) minimum wage model; 2) gross national income model (150). Productivity losses were defined as the loss of income incurred in individuals aged 50 years and above with blindness or other levels of visual impairment who were not able to work (100% productivity losses - blind individuals) or worked at reduced

productivity (30% productivity losses – individuals with moderate to severe VI) as a results of their vision impairment. With minimum wage model a more conservative estimate was obtained in the majority of countries and cost of blindness ranged from 0.1 billion in Honduras to 2.5 billion Us dollars in the United States of America while cost of moderate to severe visual impairment ranged from 0.1 to 5.3 million UD dollars in the same countries (150). With gross national income model cost of blindness ranged from 0.1 billion in Honduras to 7.8 billion Us dollars in the United States of America and cost of moderate to severe visual impairment ranged from 0.1 to 16.5 million UD dollars in the same countries (150). The authors concluded that although blindness and vision impairment occurs more frequently in developing countries, the economic burden is still high in developed countries like the United States and Japan (150).

Global estimates on productivity losses related to vision impairment have limitations. For instance, some studies have considered in their estimates persons age 16 and above (18), while others have restricted their analysis for persons within age range of 50 to 65 years old (149). Other studies assumed 100% productivity losses for blindness (149, 150) which can be considered a bit extreme in the majority of developed countries. Others studies, have used disability weights for moderate to severe visual impairment obtained from Global burden of disease (18, 141). For example Smith et al.(18) used values from Global burden Diseases of 2002 report (a disability weight of 0.282 for persons with moderate to severe visual impairment) while Pezullo et al. (141) used Global burden Diseases of 2004 and 2010 by applying for example a disability weight of 0.191 for persons with severe visual impairment accordingly to 2010 report. Eckert et al. (150) used a weight of 0.3 for persons with moderate to severe visual impairment. Recently, considerable debate as emerge surrounding disability weights updates since vision disorders weights have been declining over the years with arguments being used against the methodologies used to determine this weights (151, 152).

Methods used to attribute monetary value to productivity losses also influence estimates. In general, the minimum wage model gives a more conservative estimate which may lead to a substantial underestimation of the true cost of these conditions to the society. Estimates on productivity losses from different countries have shown great variability with productivity losses ranging from 0.2 billion US dollars in Honduras and 11.12 billion euros in Germany (149, 150). Apart from economic estimates, several studies involving persons with visual impairment have reported low rates of employment, high rates of unemployment, job loss and early retirement (153) and documented barriers and factors associated with reduced labour force participation in this population (154).

Accordingly to the literature there are three groups of variables namely demographic characteristics, socioeconomic status and aspects of disability and health that may influence the chances of impaired persons to be in the labour market (154).

Age and gender are among the demographic factors that may affect the probably of being employed in persons with disabilities. Men are more likely to be in paid employment than women as shown for instance in Sherrod et al. (155) possibly because women are more likely to choose social roles, like staying at home to take care of the house and family, or because women are less likely to engage in vocational training necessary to facilitate entering to the labour market or maintaining a job. The relationship between age and employment in persons with disability varies across studies. For instance, some studies have found that older individuals were more likely to lose their jobs or to stay longer as unemployed (156) had a lower rate of employment or reported to be early retired (ages between 50 and 64 years old) (154) while others demonstrated that visually impaired younger individuals (under 55 years old) were less likely to have a paid employment possibly because decided not to enter the labour market (155) or because are more likely to report being student (ages between 18 and 29 years old) (154) .

Amongst socioeconomic variables education level is considered an important factor positively associated with the probabilities of being employed. A study in the United Kingdom showed that visually impaired individuals with higher education level had a greater likelihood of being employed (above 50%) compared with visually impaired individuals less educated (154).

Severity of vision impairment, age of onset and the presence of additional comorbidities are reported as aspects of disability and health that may influence employment status in these population (154). Severity of vision impairment has been reported to negatively influence the odds of being in the labour market. Accordingly with a study in the United Kingdom, being registered as legally blind rather than having other levels of vision impairment (sometimes mention as partly sighted) reduced in 36% the probability of being at the labour market (154). In the same sample population later onset of vision impairment was also associated with lower rate of employment. Age of onset of vision impairment may also play an important role because it may influence the ability to cope vision loss and may also reduce the effects of support programs and rehabilitation services (35) .

2.5 - Summary of the background

Visual impairment is a major public health problem as it affects 252. 2 million persons worldwide (22, 99). In 2015 36 million people were blind and 216.6 million people had moderate to severe visual impairment. Globally blindness as a standardized prevalence rate for those with 50 years and above of 1.87% and moderate to severe vision impairment as a prevalence rate of 10.47% (22). In Portugal accordingly with Vision Loss Expert Group estimate blindness as a standardized prevalence for the same population of 0.54% and other levels of vision impairment (moderate to severe vision impairment) has a prevalence of 5.06% (22). The top causes of vision loss in Western Europe, the world region were Portugal is included, vision impairment (including blindness) are cataract, AMD, glaucoma, uncorrected refractive error and diabetic retinopathy (27).

Vision impairment has wide-ranging negative effects on health affecting visual, physical and mental health (41, 42, 47, 48). It also has major socioeconomic implications since it can affect individuals participation in society, individuals employment and personal income, autonomy levels and quality of life (38, 44, 46, 155). This increases the need of Informal care (49, 50). Informal care leads to loss of income and lower productivity in visually impaired individuals and in caregivers (146). If informal care is not provided, formal care assistance will eventually occur either in the form of home assistance or with inpatient services in long term care facilities (141).

Vision impairment has a wide impact on the healthcare system (52, 53, 89, 91). In addition to the amount of eye care provided, VI imposes extra resource utilization and costs related to complications of vision loss and its effects on comorbid conditions (52, 90). VI may effect or may be affect by comorbid conditions (52, 83). Access to eye care services remains as a topic of concern due to the population aging and the expansion of medical technologies posing significant pressure on healthcare delivery systems (120).

In the only worldwide economic estimate the total costs of VI was estimated in 2954 billion US$ in 2010. Direct costs were estimated in 2302 billion US$ in 2010. Productivity losses were only estimated in developed countries and ascended to 168.3 billion US$. Informal care costs were estimated in 246 million US$ (146). Productivity losses estimates have shown that although VI occurs more frequently in developing countries the economic burden is still high in developed countries like the United States, Japan and Germany (149, 150). Understanding the cost of vision impairment is necessary to know its socioeconomic impact, for making an economic argument and support economic evaluation about interventions to reduce the burden of these condition.

Chapter 3 – Aim of this thesis

Eye diseases and subsequent vision loss poses a big challenge to the healthcare system and are a public health major concern. Many of the cases of vision loss may be avoidable since there are available cost-effective intervention for prevention, treat and control of major eye diseases, although the access to these intervention remains problematic in many countries. Adequate access to care is essential to reduce vision related morbidity, to improve health related quality of life and to reduce social and economic impact caused by vision impairment. Losing vision at any age may have a wide-ranging impact. People with vision impairment have reduced independence, higher health costs and higher unmet health needs, lower wages and lower workforce participation, when compared with people without vision impairment. These consequences produces a widespread impact that goes beyond the affected individuals, producing also significant effects on the healthcare system and to the society.

The aim of this thesis was to investigate and characterize the impact of vision impairment in selected aspects of the healthcare system and the society. To do so we decided to investigate the access to a new eye treatment for retinal diseases – anti-VEGF, informal care use, and productivity losses in visually impaired people in Portugal.

Thesis specific objectives:

1. To assess the access to a new eye care treatment for retinal disease – anti-VEGF
2. To estimate and characterize the use of informal care by people with vision impairment
3. To estimate and characterize productivity losses in persons with vision impairment.

Chapter 4 – Research Methods

In this thesis are reported five research papers. Three papers are considered the main studies and investigated: 1) The access to a new anti-VEGF treatment for retinal diseases; 2) The use of informal care and its determinants in this population;3) Productivity losses in persons with vision impairment and their explanatory factors. In addition, two complementary papers are presented resulting from investigations necessary to develop the methodology and knowledge used in the main manuscripts. The first complementary paper included in this thesis investigated patient-reported outcome measures using a condition-specific instrument (activity inventory) with a generic health-utilities instrument (EQ5D) and the second investigated the profile of the participants in the face-to-face interviews that were conducted as part of the main studies. Four papers have been published and one is under review in a peer-review journal, the contents of these papers are given in chapter 5.

A summary of the papers and research methods involved is Table 14. The table provides a description of the, study perspective, aims, data source, setting, outcome measures, and statistical analysis. A more detail version of the research methods is provided in the methods sections of each paper presented that is given in chapter 5.

Table 14 - Summary of the research methods

Study perspective	Aim	Data source	Setting	Outcome measures	Statistical analysis
Study Designation: Diffusion of anti-VEGF injections in the Portuguese National Health System					
Healthcare system	Analyse the diffusion of anti-VEGFs injections in the Portuguese NHS	Administrative Inpatient and day cases episodes	Mainland Portuguese Public Hospitals	✓ Number of hospital episodes ✓ Number of patient treated ✓ Yearly rates of hospital episodes	✓ Mean, minimum and maximum values of the rates of hospital episodes per 100.000 population to analyse the diffusion of treatments across areas was evaluated with ✓ Relative variation coefficient to measure the dispersion of the diffusion ✓ Generalized linear modelling more precisely Generalized Estimating Equations (GEE) to investigate the determinants of geographical diffusion of anti-VEGF treatments
Study Designation: The use of informal care by people with vision impairment					
Societal	Estimate the use of informal care and its determinants	PCVIP Study	4 hospitals in the north of Portugal	✓ Use of informal care ✓ Number of hours of informal care ✓ Opportunity costs of informal care Use of informal care	✓ Chi-square tests to compare groups. ✓ T-tests to compare visual ability between groups ✓ Mann-Whitney–test or Kruskal-Wallis for non-parametric comparisons between groups. ✓ Spearman Correlation to determine association between variables ✓ Logistic regression to determine explanatory factors associated with the use of informal care ✓ Linear regression to determine factors associated with the amount of informal care needed (intensity of care).
Study Designation: Productivity losses and their explanatory factors amongst people with impaired vision					
Societal	Estimate and characterize productivity losses	PCVIP Study	4 hospitals in the north of Portugal	✓ Workforce participation ✓ Absenteeism ✓ Productivity costs	✓ Chi-square tests to test differences between participants working and not-working. ✓ Independent t-tests to compare visual ability and Mann-Whitney tests were performed to compare visual acuity in the better eye and in the worse eye and HRQoL ✓ Logistic regression was used to determine explanatory factors associated with participation in the labour market

Study perspective	Aim	Data source	Setting	Outcome measures	Statistical analysis
Study Designation: Visual and health outcomes, measured with the activity inventory and the EQ-5D, in visual impairment					
Methodological	Compare PROMS[a] using a condition-specific instrument (activity inventory) and a generic health-utilities instrument (EQ5D)	PCVIP Study	4 hospitals in the north of Portugal	✓ Visual ability ✓ EQ5D score	✓ ANOVA for multiple comparisons ✓ t-test to compare groups ✓ Kruskal-Wallis or Mann-Whitney U tests for comparisons when variables failed normality tests. ✓ Pearson correlations and Spearman's rank-order correlation to test associations between variables ✓ Linear regression to investigate if final scores of Activity Inventory and Eq5D were associated with the same factors
Study Designation: Predicting participation of people with impaired vision in epidemiological studies					
Methodological	Investigate study participants and non-participants profiles and the levels of participation in face-to-face interviews	PCVIP Study	4 hospitals in the north of Portugal	✓ Participation in epidemiologic studies	✓ Chi-square tests to compare groups. ✓ Multiple logistic regression to determine the effect of independent variables in participation rates.

[a]PROMS- Patient Report Outcome Measures

As mentioned in Table 14, we used two different data sources to perform the investigations reported in the reported manuscripts. A national database of inpatient and day cases episodes from public hospitals in mainland Portugal provided by Administração Central do Sistema de Saúde was used to investigate access to anti – VEGF injections. Anti-VEGF injections were considered a new treatment when the study was conducted. Data from the Prevalence and Costs of Visual Impairment in Portugal: a Hospital Based Study (PCVIP-study) were used to investigate informal care and productivity losses. In addition, data collected during this study was also used to characterize patient-reported outcome measures using two instruments and to investigate the profile of the participants in the study itself. A general description of these two data sources, participants/case selection and of the ethics procedures is provided in subtitles 4.1 and 4.2.

4.1- Administrative inpatient and day-cases database

To evaluate the access to anti – VEGF injections we used a national database of inpatient and day cases episodes admitted in Portuguese public hospitals from 2002 to 2012. This administrative database includes demographic, administrative and clinical information from all in-patient and day cases episodes performed in public hospitals. The basic unit of measurement of this database is the episode of care.

Demographic data includes: sex, date of birth, age and county of residence. We also had access to the admission and discharge dates, hospital department and services provided. Information about services provided includes, episode type (eg in-patient or day cases), admission type (e.g. elective or emergency admissions) and treatment type (e.g. medical or surgical). Diagnoses (principal and secondary) and procedures (maximum of ten) are classified according with the International Classification of Diseases 9th revision Clinical Modification (ICD-9-CM).

4.1.1 - Cases selection

We selected the cases (episodes) related to intravitreal injections for anti-VEGF treatments based on four procedures of ICD-9-CM codes: 1414, 1475, 1479, 149. Given that these procedures are not specific for intravitreal injections we have implemented two strategies to increase our precision: 1) years 2002-2006 were included as baseline as before 2006 intravitreal anti-VEGF treatments for ophthalmologic use were not licensed; and 2) we crossed information of age with principal diagnosis.

Baseline years provide the picture of the number of cases associated with the codes but not related with anti-VEGF treatment. We considered that AMD only affects people in the range of 50-59 years or above (157) and anti-VEGF are used for specific diagnosis, such as AMD or diabetic macular oedema. Since 2007 the number of patients older than 50 years have increased and represented 90% of cases. 75% of cases are concentrated in seven diagnoses that have indication for treatment with anti-VGEF and these are also the diagnoses responsible for the majority (around 80% of cases) of additionally cases observed after 2007 in age categories 20-39 40-49 and 50 years old and above. Patients below 19 years of age remain constant in absolute values during the analysed period and the proportion reduced from 3.6% in 2006 to 0.4% in 2012.

4.1.2 - Ethic procedures

Authorization to use these information was obtained from Escola Nacional de Saúde Pública, Universidade Nova de Lisboa. At inpatient and day-cases national database the cases are irreversibly anonymized. Patient identification numbers are subject to a recode procedure made by Administração Central do Sistema de Saúde that attributes an anonymous key identifier per patient per year therefore it is not possible to identify individuals. Only aggregate data at regional level, more specifically county of residence was considered in this study. County of residence was used to compute rates of hospital episodes per year (crude and standardized) and to create a dichotomous variable about the availability of an ophthalmology department in the hospital of the patient county of residence. Regional aggregate data are sufficiently large to guarantee individual privacy.

4.2 - PCVIP study

4.2.1 - Setting

The PCVIP-study was designed according to guidelines published by the Vancouver Economic Burden of Vision Loss Group (158) and was conducted in 4 public hospitals in the north of Portugal. The hospitals were selected accordingly with the level of differentiation of their ophthalmology departments (159).Two hospitals, Hospital de Santa Maria Maior – Barcelos and Centro Hospitalar do Alto Ave are classified as primary level hospitals providing only basic care services to all the inhabitants living in their catchment area. One hospital, Hospital de Braga is classified as a secondary level hospital that offers a wide range of eye care and is responsible to provide care both to

patients living in its direct catchment area as well indirect catchment area. Hospital de Braga receives the more complex patients referred by the two primary level hospitals also included in this study. A hospital, Centro Hospitalar de São João is a tertiary level hospital with a highly differentiated ophthalmology department which includes highly specialized staff and technical equipment and is responsible to provide eye care including rare diseases, ocular cancers, transplantation and paediatric glaucoma, cataract and premature retinopathy. This hospital as its own direct catchment area as well as an indirect catchment area that includes among others the secondary level hospital mentioned earlier. In total these hospital are expected to provide eye care to a total population of 2 million inhabitants belonging to 3 districts in the north of Portugal namely Porto, Braga and Viana do Castelo.

4.2.2 - Participants selection

4.2.2.1 Vision impairment definition

The definitions for vision impairment includes low vision and blindness. In this study we followed the definitions given in the International statistical classification of diseases, injuries and causes of death, 10th revision (ICD-10): H54 (5). Definitions are: i) low vision is defined as visual acuity of less than 6/18, but equal to or better than 3/60, or a corresponding visual field loss to less than 20 degrees in the better eye with presenting visual acuity (ICD-10 visual impairment categories 1 and 2); ii) blindness is defined as visual acuity of less than 3/60, or a corresponding visual field loss to less than 10 degrees in the better eye (ICD-10 visual impairment categories 3, 4 and 5) (5).

4.2.2.2 Participants selection description

Each week, members of the hospital staff with biomedical qualifications and hired for this purpose searched files of patients attending ophthalmology medical appointments for potential new cases of vision impairment. Records of all patients assisted at the site (Department of Ophthalmology) were analysed weekly during one calendar year. From clinical records we collected information about visual acuity, cause of vision loss (classified according with International Classification of Diseases 9th revision Clinical Modification), date of birth and gender. This information was registered in a secure platform that is online at www.pcdvp.org. A print screen of this platform is shown in Figure 13.

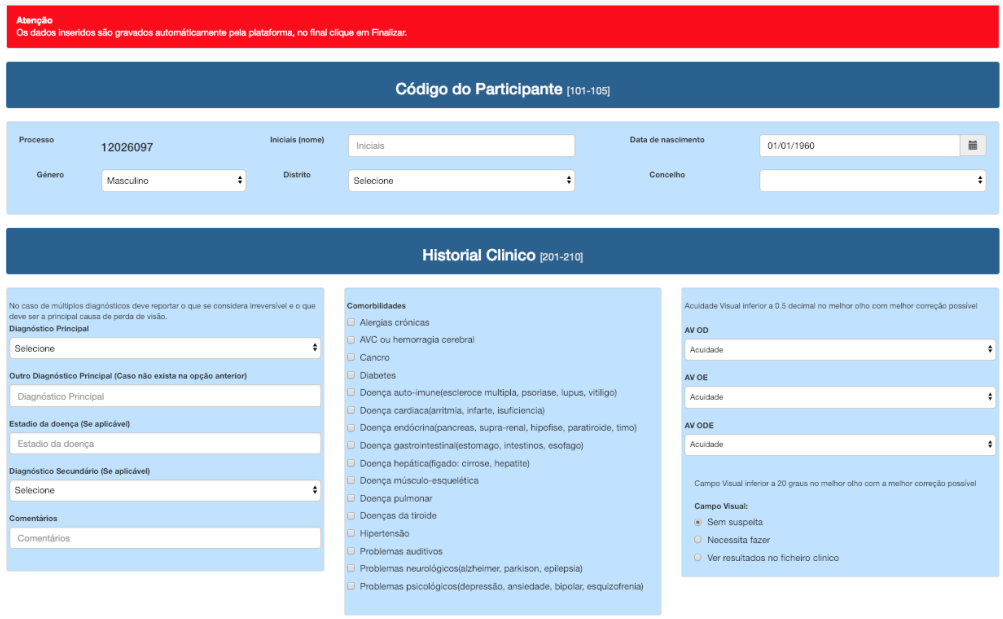

Figure 13 - PCVIP platform: print screen of tables were information about selected participants information was introduced

Contact was tried initially by letter with a reply-paid envelope addressed to Escola Nacional de Saúde Pública (National School of Public Health (ENSP), Lisbon). The envelope contained the information booklet and consent form. The consent form was expected to be returned to the ENSP. If the consent was not mailed back to ENSP in approximately 2 weeks, potential participants were contacted by telephone. If the letter did not reach the home address people were invited by telephone. Similar methodology has been adopted by other epidemiological studies conducted in Europe (EUREYE study group (160)). Refusals were not contacted again.

Those returning the consent form were considered participants and most were able to attend an interview that was scheduled at the hospital.

4.2.3 - Data collection methods

4.2.3.1 Visual acuity measured during face-to-face interviews

Distance visual acuity (VA) reassessment was made using an internally illuminated ETDRS chart (Lighthouse International. NY. USA) at 4. 2 or 1m according with the severity of their vision loss. The room lights where extinguished during measurements. Letter by letter scoring was employed to specify final measured acuity. The formula VA = 1.1–0.02xNL, where NL represents the number of letters read, was use to score patient's acuity with the ETDRS chart at distance.

4.2.3.2 Comorbidities assessment

Participants were asked to report comorbidities based on a list of 16 categories: cancer, diabetes, heart condition, hypertension, musculoskeletal disorder, pulmonary disease, stroke or brain haemorrhage, hearing impairment, thyroid condition, psychological problems, neurological problems, chronic allergies, gastrointestinal condition, liver disease, autoimmune disease and endocrine condition. The list of comorbidities was based on previous studies that analysed the association between vision impairment and self-reported comorbidities (8, 161-164).

4.2.3.3 Patient reported outcome measures

Participants were also asked to respond to a functional vision questionnaire to assess visual ability, the Activity Inventory and to respond to EUROQol-5D (EQ5D) in Portuguese to determine health related quality of life.

4.2.3.3.1 Assessment of Visual Ability

The Activity Inventory is an adaptive visual function questionnaire designed to provide an individualized assessment of difficulties of a visually impaired respondent when performing valued activities. Patients differ from one another in terms of the reported importance and difficulties to perform different activities. Disabilities, or activity limitations according to the World Health Organization's International Classification of Functioning, occur when a person reports abnormal difficulties in achieving important goals. Difficulties achieving a goal are said to depend on the difficulty experienced in the tasks that underlie each goal (165-168).

In the Activity Inventory participants are asked to rate goals in a four point scale that ranged from "not important" to "very important. Whenever goals are scaled different than "not important", participants are ask to rate the difficulty to perform tasks related to that goal in a five point scale that ranged from "impossible to do" to "not difficult" (168). Figure 14 shows a print screen of PCVIP platform to illustrate how Activity Inventory answers were register in our database. Participants rate the importance of each goal, but rate only the difficulty of the tasks that are related to the goals that were of some importance to them. Therefore, each participant respond to a relevant set of questions that is unique to her/him, meaning that for each participant we have done a personalized functional assessment. For minors, when necessary, parents or guardians served as proxies for the interview. An example of the content of the Activity Inventory is presented in Table 15.

Table 15 - Questions and answers categories of Goal 3 “choose your clothes and dress yourself” as an example of the type of words used in Activity Inventory

	Type of question	Answer categories
Goal importance	How important is it for you to be able to ***choose your clothes and dress yourself*** without the assistance of another person?	1=not important
		2=somewhat important
		3=moderately important
		4=very important
If the participant responded "not important" , the interviewer moved to the next Goal; If the Goal was rated with any other importance category, than the participant was asked to rate difficulty achieving the Goal		
Goal difficulty	How difficult is it for you to **choose your clothes and dress yourself** without the assistance of another person?	1=not difficult
		2=slightly difficult
		3=moderately difficult
		4=very difficult
		5= impossible to do

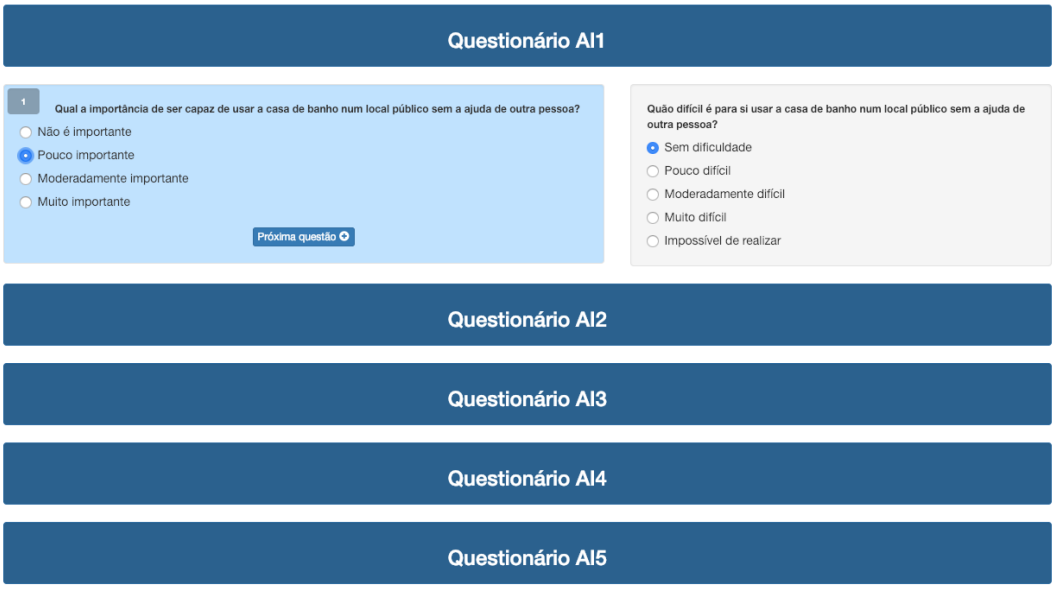

Figure 14 - PCVIP platform: print screen of tables were information about Activity Inventory was register

In our translated version of the Massof activity inventory participants were questioned about difficulties with 46 goals (presented in appendix 1) and the “difficulty” responses were Rasch analysed to produce a continuous measure of visual ability given by the variable ‘person measure’ (Program Winsteps. v3.9). Visual ability is considered a composite variable since incorporates both goal importance and task difficulties.

Rasch analysis is used to estimate the magnitude of an attribute shared by a set of items. The inputs of rash analysis are ordinal rates given to a group of items in a

questionnaire by a group of respondents. The outputs are estimated measures of both the items and the respondents (169). In Activity Inventory rash analysis takes ordinal ratings assigned to the tasks and estimates the relative abilities of the persons that rated the items. We use the term 'visual ability' to define the overall ability of each person to perform activities that depend on vision (8).

4.2.3.3.2 Assessment of Health-Related Quality of Life

Participants also responded to EUROQol-5D (EQ5D) to determine health related quality of life (presented in appendix 2). The EQ-5D is a generic preference-based measure of health that has five domains: mobility, self-care, usual activities, pain or discomfort, anxiety and depression. Each dimension is rated on a three-point scale with categories "no problems", "some problems", or "extreme problems", producing a descriptive health profile. A respondent´s health state is then defined by combining the levels on each of the five dimensions which will provide a 243= (3^5) health profile´s. For every patient a single health state value, or utility, can be calculated. These health sate values are set on a scale ranging from 0 to 1 corresponding to death and perfect health respectively. Negative values correspond to a health state worse than death. Respondents' health profiles were valued using valuations derived from the general population in Portugal (170). Figure 15 shows a print screen of PCVIP platform to illustrate how EQ5D answers were register in our database.

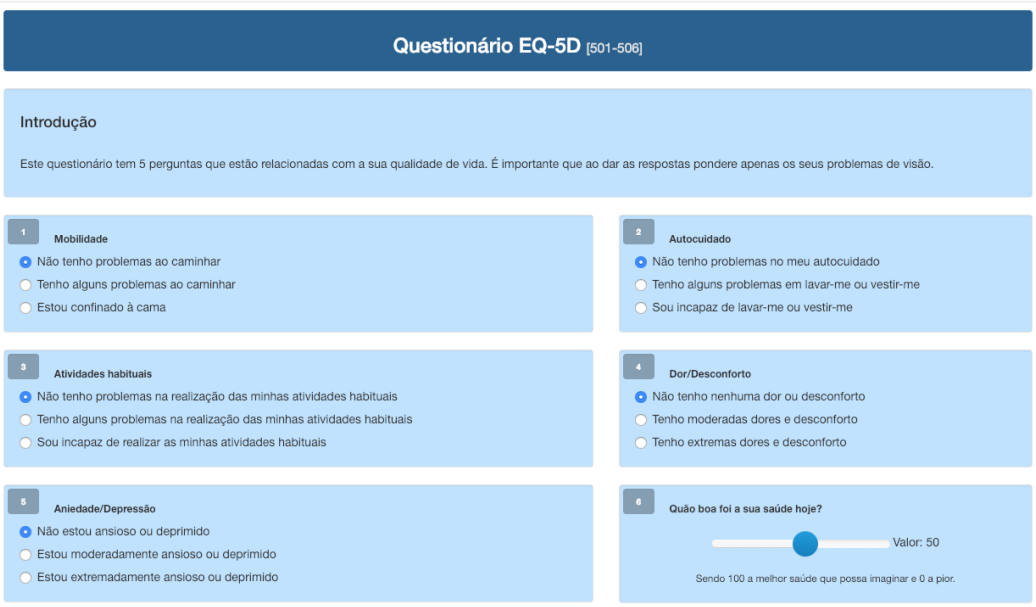

Figure 15 - PCVIP platform: print screen of tables were information about EQ5D was register

4.2.3.4 Informal care and productivity losses questionnaires

We used the questionnaire method, administered by trained members of the research team, to collect data about informal care needs, absenteeism, and workforce participation. Informal care use and absenteeism were asked with a 2 week recall time period as propose by Severens et al (171) with the view to minimised recall biases.

The questionnaire was drawn from previously validated instruments (172, 173) it underwent pilot testing and revisions to clarify wording, and to simplify data recording and to remove redundant items. The final version of the questionnaire is summarized in Table 16.

Table 16 - Questions used to collect information about sociodemographic information, informal care need and absenteeism. Absenteeism questions were applicable to participants in the working age range (17-64 years). In all questions, there was 1 option with: do not know or do not want to answer

Categories	Questions	Options
Sociodemographic information	1. What is your marital status?	a) Single b) Married or living as married c) Divorced or separated d) Widowed e) Other (please specify)
	2. What is the highest level of education you completed?	a) Up to university 3rd cycle (PhD) b) Up to university 2nd cycle (Master) c) Up to university 1st cycle (undergraduate) d) Up to 12 years of education e) Up to 9 years of education f) Up to 6 years of education g) Up to 4 year of education
	3. What best describes your living environment?	a) Live alone b) Live with spouse (including children) c) Live with parents d) Live with children (sons/daughters) e) Live with other relatives f) Live with others
	4. What is your employment status?	a) In full-time work b) In part-time work c) Currently seeking work d) Homemaker e) Retired f) Early retired g) Student h) Other (please specify)
	5. Please provide an estimate of your month household income from all sources (after tax and other deductions and including your partner/spouse)	a) less than €485* b) between € 485 and €1000 c) above €1000 *this is the national minimum monthly wage
Informal Care Need	6. Over the last two weeks have you been helped and/or cared for by a relative or friend because you have poor vision?	a) Yes (please continue to question 6.1) No

Categories	Questions	Options
	6.1. Over the last two weeks how many relatives/friends have helped and/or cared you?	Number of caregivers
	6.2. Over the last two weeks how many hours were spend by caregivers to support you?	Number of hours
	6.3 What would that person normally have been doing as the main activity if they had not been helping and or caring you?	a) Paid Job b) Currently seeking work c) Homemaker d) Retired e) Student f) Other (please specify)
Absenteeism*	For those reporting employment (part-time or full-time) we asked 2 questions 6. Over the last two weeks how many hours per week do you spend working?	Number of Hours
	7. Over the last two weeks how many days have been absent from work owing to your visual condition?	Number of days
	For those reporting two weeks of absenteeism in the last two weeks we asked 7.1 How long were you in sick leave?	a) less than three months b) three months or more

4.2.3.5 Cost categories and cost calculation

4.2.3.5.1 Informal care cost assessment

Informal care costs represent a monetary estimate of the hours spend by caregivers to help/care visually impaired persons. The number of reported hours were extrapolated from the 2 weeks recall period included in the questionnaire to 12 months. To estimate the economic impact of informal care we used the opportunity costs in which time spent providing informal care is valued based on competing use, in this case paid labour. This method is commonly used to do these economic estimates including in eye care studies (174, 175). Total informal care costs were calculated by multiplying the number of annual hours by the average Portuguese hourly pay rate of full time employees in the year 2014 (€6.63). This value is within the interval €4.10 to €19.18 reported by Costa et al (176).

4.2.3.5.2 Productivity losses assessment

Absenteeism was measured by the number of absent workdays due to health. Total annual absenteeism costs were calculated by converting reported working days

missed due to visual impairment into hours and then valuated with the average hourly pay rate obtain by the three categories of income level also reported by the participants. In category 1 (less than €485) we considered the maximum value €485, in category 2 (between € 485 and €1000) we considered the mean value €742,5 and in category 3 = above €1000 we considered the minimum value €1000. We extrapolated the 2 weeks recall period to an annual level multiplying by 24 working weeks adjusting for annual leave and public holidays. Absenteeism was divided into short term and long term absenteeism. Long term absenteeism includes all the individuals that reported being absent for more than three months. All the other cases were considered short term absenteeism.

Reduce workforce participation refers to the loss of production caused by visual impaired persons who are out of the labour market. It was calculated for participants who were aged more than 17 and less than 64 years old (working age) and reported being early retired due to visual impairment or unemployed. It was only included the excess number of unemployed calculated by the difference between unemployment rate of active population adjusted by sex and age of 2014 in Portugal reported by Eurostat, presented in Table 17, and the unemployment rate by sex and age observed is this sample.

Table 17 - Unemployment by sex and age (% of active population) - annual average, 2014

Unemployment rate	Total	Male	Female
Portugal	14,10%	13,80%	14,50%
Less than 25 years old	34,70%	33,90%	35,50%
25-74 years old	12,50%	12,20%	12,80%

Source: Eurostat. (177)

These two figures were, in turn applied against the average Portuguese monthly wage adjusted by sex and education level shown in Table 18. There was also other participants that were out of the labour market categorized as homemaker and others (which includes students and other reasons not specified) that were not considered in this estimation because it can be a choice of the individual and therefore cannot be attributable to visual impairment.

Table 18 - Monthly wage adjusted by sex and education for year 2014 used to calculate productivity costs due to reduced workforce participation rate

Education level	Male	Female
Did not attend school	731,60 €	604,40 €
4 years of education	858,60 €	639,60 €
6 years of education	878,70 €	653,70 €
9 years of education	954,60 €	728,80 €
12 years of education	1.267,40 €	923,80 €
University undergrad or more	2.259,20 €	1.580,00 €

Source: CITE (178)

4.2.4 - Ethic procedures

The present study was conducted in accordance with the tenets of the Declaration of Helsinki, reviewed and approved by the ethical commission for Life Sciences and Health of the University of Minho, by Comissão Nacional de Protecção de Dados (Authorization Nr. 5982/2014 presented in appendix 3) and by the hospitals ethics committees. Written informed consent was obtained from all participants participating in face-to-face interviews. Data was kept in a secure platform, confidentiality was assured by removing personal identification; thus, data can be considered anonymised.

Chapter 5 – Research Findings

This section is organized in two parts: main research findings and additional research findings.

In the main research findings there are included three papers that aimed to investigate and characterize the impact of vision impairment in selected aspects of the healthcare system and the society.

Adopting the healthcare system perspective we have studied the temporal and geographical diffusion of a new eye care treatment, anti-VEGF injections to better understand how was the access and diffusion of a new eye treatment in the Portuguese national health system. This paper was published in October 2015 by BMJ Open.

Adopting the societal perspective we conducted a study to estimate the use of informal care and its determinants in visually impaired individuals. This paper was published in June 2018 by Plos One. We also developed a study to estimate and characterize productivity costs in persons with vision impairment. This paper was submitted in July 2018 to Ophthalmic Epidemiology

In the additional research findings are included two methodological papers. During the recruitment of participants and data collection phases two methodological papers were developed: 1) to compare two of the instruments used to characterize participant's characteristics and 2) to analyse participants and non-participants profiles.

The paper comparing visual and health outcomes measured with activity inventory and EQ5D was published in March 2017 by Acta Ophthalmologica. The first author of this paper was Professor Antonio Filipe Macedo. As expressed in the first author declaration presented in Appendix 4A my collaboration in this paper is associated with data collection, results analyses and providing help writing and reviewing the manuscript.

The paper predicting participation of people with impaired vision in epidemiological studies was published in August 2018 by BMC Ophthalmology. The first author of this paper was the Researcher Pedro Lima Ramos. As expressed in the print version of the paper and in the first author declaration presented in Appendix 4B my collaboration in this paper is associated with data collection, results analyses and providing help writing and reviewing the manuscript.

5.1 – Main research findings

5.1.1- Diffusion of anti-VEGF injections in a National Health System

Material in this Chapter has been published in:

Marques AP, Macedo AF, Perelman J, Aguiar P, Rocha-Sousa A, Santana R.

Diffusion of anti-VEGF injections in the Portuguese National Health System. BMJ Open. 2015 Nov 23;5(11):e009006

doi: 10.1136/bmjopen-2015-009006

Abstract

Purpose: To analyse the temporal and geographical diffusion of antivascular endothelial growth factor (anti-VEGF) interventions and its determinants in a National Health Service (NHS).

Setting: NHS Portuguese Hospitals

Participants: All inpatient and day cases related to eye diseases at all Portuguese public hospitals for the period 2002-2012 were selected on the basis of four International Classification of Diseases 9th revision. Clinical Modification (ICD-9-CM) codes for procedures: 1414, 1475, 1479 and 149.

Primary and secondary outcome measures: We measured anti-VEGF treatment rates by year and county. The determinants of the geographical diffusion were investigated using generalized linear modelling.

Results: We analysed all hospital discharges from all NHS hospitals in Portugal (98 408 hospital discharges corresponding to 57 984 patients). National rates of hospitals episodes for the codes for procedures used were low before anti-VEGF approval in 2007 (less than 12% of hospital discharges). Between 2007 and 2012, the rates of hospital episodes related to the introduction of anti-VEGF injections increased by 27% per year. Patients from areas without ophthalmology departments received fewer treatments than those from areas with ophthalmology departments. The availability of an ophthalmology department in the county increased the rates of hospital episodes by 243% and a 100-persons greater density per square kilometre raised the rates by 11%.

Conclusions: Our study shows a large but unequal diffusion of anti-VEGF treatments, despite the universal coverage and very low co-payments. The technological innovation in ophthalmology may thus produce unexpected inequalities, related to financial constraints unless the implementation of innovative techniques is planned and regulated

Introduction

Age Related Macular Degeneration (AMD) is a chronic, progressive disease and the most common cause of visual impairment in developed countries in patients older than 65 years (28, 105, 147, 179-182). AMD requires lifelong observation and interventions (183). AMD can be divided into two stages: early AMD, characterized by sub-retinal pigmented epithelium deposits (drusen) and pigmentary changes and advanced AMD (28). Advanced AMD has atrophic and neovascular forms. Although neovascular AMD comprises only 10% of the burden of the disease, it is responsible for 90% of severe vision loss years (105, 184-187). Vision loss leads to reduced quality of life and autonomy and is associated with large costs for health systems and the society (48, 185, 188, 189).

Before the introduction of antivascular endothelial growth factor (anti-VEGF) treatments, AMD was largely untreatable (29). Anti-VEGF therapy for neovascular AMD has substantially changed the management of the disease (29, 30). These drugs are injected into the vitreous chamber to reduce neovascular formation in the macula (179). Currently the most common anti-VEGF therapies in Portugal are: 1) Ranibizumab (Lucentis, Novartis) which was licensed for the treatment of neovascular AMD by the Food and Drug Administration (FDA) in 2006 and by the European Medicines Agency (EMA) in 2007. In Portugal ranibizumab has been covered by the National Health Service (NHS) since 2008. Ranibizumab is the most widely used approved anti-VEGF drug in Europe (105, 180, 190); 2) Bevacizumab (Avastin, Roche) was licensed in 2004 by the FDA, and by EMA in 2005 for the treatment of metastatic colorectal cancer. It has been widely used for the treatment of neovascular AMD as an off-label alternative (29); 3) Pegaptanib sodium (Macugen, Eyetech/Pfizer) was approved by FDA 2004 and by EMA in 2006 for the treatment of neovascular AMD. It is less commonly used in clinical practice as it is not as effective as ranibizumab or bevacizumab (179, 191). In Portugal this therapy was approved but not marketed; 4) Aflibercept (Eylea, Bayer) was approved for wet AMD treatment by FDA in 2011 and by the EMA in 2012. Aflibercept is covered by the Portuguese NHS since 2014.

Several clinical trials have shown that intravitreal injections prevent vision loss in the majority of patients and, in some cases, significantly improve vision (29, 192-194) with low numbers of serious adverse effects (183). Subsequently, anti-VEGF therapy has become the standard clinical option to treat AMD patients (190, 192). In 2011, anti-VEGF therapy was also introduced as treatment for diabetic macular oedema and central retinal vein occlusion years (105, 190, 195).

New therapies such as anti-VEGF injections improve the clinical course of diseases but represent substantial expenditures for healthcare systems (120). To face rising costs of healthcare, copayments have been introduced during the period of this study in public Portuguese hospitals. If not exempt due to special circumstances, such as being disabled, patient receiving anti-VEGF injections have to pay typically €7.5 per appointment with their physician at the hospital. In a context of economic recession and tight public budgets the introduction and diffusion of these treatments can face substantial barriers (196). Despite the strong equity commitment of the Portuguese NHS, one of the expected barriers is likely to be geographical due to unequal distribution of resources across areas.

The aim of this study was to examine the diffusion of anti-VEGF drugs in the Portuguese NHS by analysing the temporal and geographical diffusion patterns and its determinants. We conducted a longitudinal study in order to measure the evolution of hospital episodes related to anti-VEGF treatments per county from 2002 to 2012.

Methods

Data sources and extraction strategies

We used an administrative database that includes demographic, administrative and clinical information from all in-patient and day case episodes performed at all Portuguese NHS hospitals during the years 2002 to 2012. Authorization to use these information was obtained from Institutional Review Board from Escola Nacional de Saúde Pública/Universidade Nova de Lisboa. In order to select the episodes related to intravitreal injections for anti-VEGF treatments, we used the following International Classification of Diseases 9th revision. Clinical Modification (ICD-9-CM) codes for procedures: 1414, 1475, 1479, 149. These codes have been commonly used in the literature but they are likely to capture other treatments such as injectable antibiotic or corticosteroids (105). Cases were excluded even if the diagnosis was likely to be associated with anti-VEGF treatment but the code pf procedures was outside the selected group specified above. For example, for the five diagnoses shown in figure 2, there were 13.750 cases excluded from further analysis due to this filter. Effects to our estimation caused by the poor specificity of the code were reduced using two methods: 1) years 2002-2006 were included as baseline as before 2006 intravitreal anti-VEGF treatments for ophthalmologic use were not licensed; and 2) we crossed information of age with principal diagnosis. Baseline years provide the picture of the number of cases associated with the codes but not related with anti-VEGF treatment. We considered that AMD only affects people in the range of 50-59 years or above (157) and anti-VEGF are used for specific diagnosis such as AMD or diabetic macular oedema. Supplementary

tables shown in appendix 5 show how this information was used in our methods. For the period studied, the only approved anti-VEGF drugs for use in public hospitals were Ranibizumab (Lucentis. Novartis) and Bevacizumab (Avastin).

We used the indicators bellow:

- The absolute values of the number of hospital episodes per year. Episodes were then disaggregated by: 1) sex, 2) age of the patients (under/over 60 years old), 3) principal diagnosis.
- The number of patient treated per year. To calculate the number of patients, we considered one treatment per person per year, regardless of the number of episodes of care (number of treatments) that occurred in each year.
- The yearly rates of hospital episodes per 100.000 population [(number of episodes per year/annual average resident population per year) x 100.000].

The age-standardized rates of hospital episodes per 100 000 population by counties per year [(number of episodes by county and year/annual average resident population per county and year)x 100.000] using general demographic information published by Statistics Portugal (197). County of residence was obtained from the administrative database used in the study. We used the direct method of standardization as described by Beaghole et al. (198) for standard Portuguese population. The age-standardisation was necessary to control the effect of age heterogeneity across populations living in different counties. Mainland Portugal is divided into 248 counties that correspond to local prefectures with specific administrative and political competences defined by the central government.

Study analysis

We first evaluated the diffusion of treatments across areas using the mean, minimum and maximum values of the rates of hospital episodes per 100.000 population in 2002. 2006 and 2012. The relative variation coefficient was used to measure the dispersion of the diffusion.

Three time points were selected because they corresponded to: 2002 – the first year included in this study, 2006- the year before the approval of intravitreal injections with anti-VEGF by EMA and 2012 because it was the latest available information when this study started.

To investigate the determinants of geographical diffusion of anti-VEGF treatments we used generalized linear modelling. Considering the longitudinal nature of the data and its non-normal distribution we used Generalized Estimating Equations (GEE) (199). The dependent variable was defined as the yearly rate of hospital episodes per county

per 100.000 population. We defined as independent variables: 1) the years during which the geographical diffusion was analysed (a linear trend); 2) a dichotomous variable to indicate the year where the drug was authorized in the European Union by EMA (Anti-VEGF therapy availability: 0-not available; 1–available; 3) a dichotomous variable to indicate the availability of an ophthalmology department in the hospital of the patients' county of residence (Ophthalmology department availability: 0-no ophthalmology department; 1–ophthalmology department) and 4) population density (population per squared kilometre) in the county. Information about the availability of ophthalmology departments was obtained in October 2014 from the Health Ministry official website. The referral pathway for ophthalmology starts with the general practitioner (GP) according to the local referral guidelines. The circuit of the treatment does not interfere with our calculations because we compute treatment ratios based in the country of origin of the patient and this is independent of the hospital where treatment was administered. The model was defined as gamma log link distribution regression model as the rate was expected to be positively skewed with an autoregressive first order matrix representing time dependence within repeated subject (200). A total of 278 counties were considered as "subjects" with repeated measures. Year and dichotomous variable "anti-VEGF availability" were defined as within subject independent variables. Dichotomous variable "Ophthalmology department availability" and "population density rates" were defined as between subject variables. The analysis was performed using IBM SPSS Statistics 21.0.

Results

The final sample included 98.408 hospital episodes. Figure 16 shows that the total number of episodes increased from 1.815 in 2002 to 25.106 in 2012. This corresponds to a mean annual increase of 32%.

In 2012, the number of treated patients was six times higher than in 2002, corresponding to a mean annual increase of 24%. The ratio number episodes/number patients was 1.16 in 2002, 1.17 in 2006 and 2.1 in 2012. The most relevant demographic information was the percentage of patients treated who were older than 60 years of age. The figures changed from about 60% in 2002 to 80% in 2012.

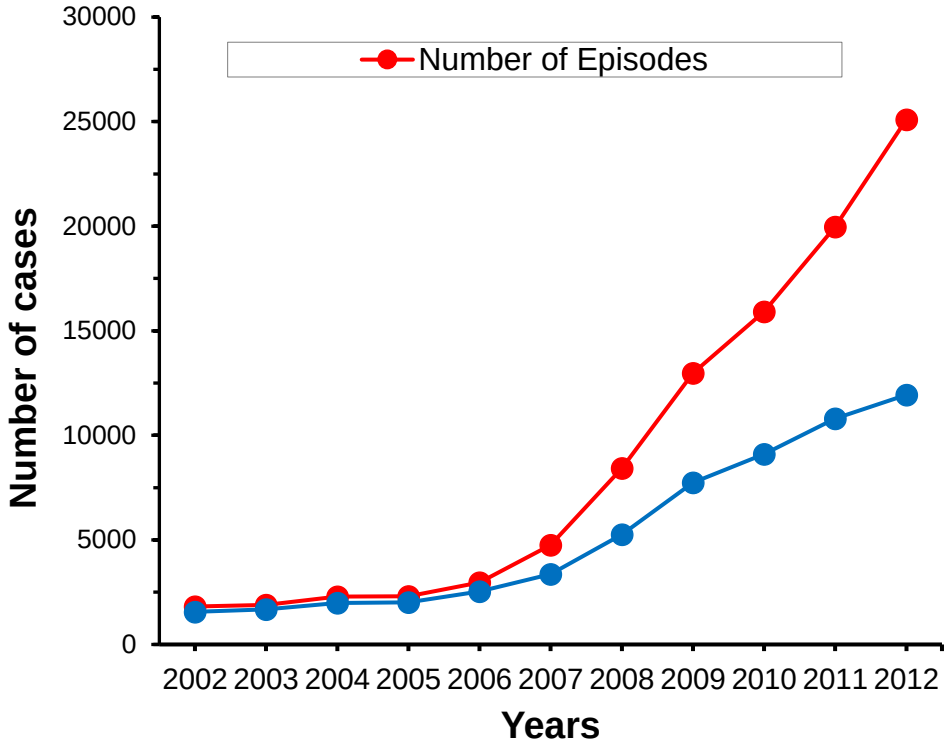

Figure 16 - Annual number of hospital episodes of antivascular endothelial growth factor (antiVEGF) treatments and annual number of treated patients from 2002 to 2012

Figure 17 shows the five principal diagnoses responsible for the episodes detected. The figure is expected to provide a picture of the growth of the number of episodes per year and number of patients treated per diagnoses. The most common diagnosis was exudative age -related macular degeneration, followed by diabetic macular oedema (diabetes with ophthalmic complications), oedema of the retina, retinal neovascularization and non-specific AMD. The cumulative percentage of episodes associated with these five diagnoses was 73% in 2012, in contrast with only 16% in 2002. These values corresponded to an increase in the yearly rates of hospital episodes per 100.000 individuals from 17.4 in 2002 to 238.77 in 2012.

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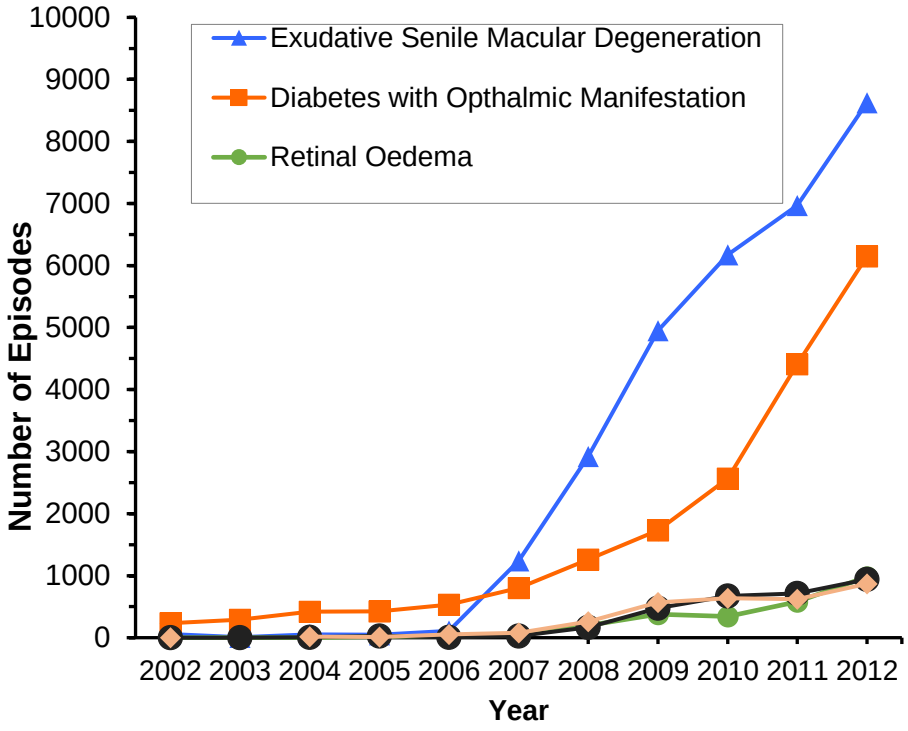

Figure 17 - Number of hospital episodes associated with the top five diagnoses by year

Table 19 gives a summary of the mean, minimum and maximum values in 3 specific years of the rates of hospital episodes per 100.000 population. Both maximum and minimum rate values increased over time. The relative variation coefficient varied from 200% in 2002, to 204% in 2006 and 209% in 2012. The relative coefficient of variation indicates that rates per county have a great dispersion and that this dispersion did not reduce over time. The first quintile always contains rates equal to zero, which means that there are counties without events. In 2002 there were 58 counties in the first quintile (without episodes). The number of counties without episodes reduced over time to 33 in 2006 and 3 in 2012. All the mean values per quintile rose in the period analysed.

Table 19 - Age-standardized rates of hospital episodes per 100.000 populations per county in the year 2002. 2006 and 2012. Values show quintiles mean, minimum and maximum values

Quintile	2002			2006			2012		
	Mean	Min	Max	Mean	Min	Max	Mean	Min	Max
1st	0	0	0	0.0001	0	0.0002	0.0013	0	0.0024
2nd	0.0002	0.0001	0.0003	0.0003	0.0002	0.0005	0.0037	0.0024	0.0051
3rd	0.0005	0.0004	0.0008	0.0009	0.0006	0.0013	0.0069	0.0051	0.0091
4th	0.0012	0.0008	0.0017	0.0019	0.0013	0.0026	0.0148	0.0093	0.0221
5th	0.0048	0.0017	0.0231	0.008	0.0026	0.0459	0.0764	0.0222	0.3745
Total	0.0013	0	0.0231	0.0022	0	0.0459	0.0208	0	0.3745

Results of the regression analysis are summarized in Table 20. In agreement with the initial prediction and consistent with the introduction of the new treatment with anti-VEGF, the model shows a significant effect of the variable "year", $p<0.0001$. For each additional year the rate of hospital episodes increased by 28%. The rate was significantly higher after the EMA approval; in Table 20 results for "Anti-VEGF therapy availability". $p<0.0001$. With the approval of this treatment the rates of hospital episodes increased by 27%. The availability of an ophthalmology department in the hospital of the county (in Table 20 results for "Ophthalmology department availability") significantly increased the rates of hospital episodes by 243% p <0.0001 (compared with counties without). The positive association between the variable "Ophthalmology department availability" and our dependent variable indicates that anti-VEGF treatments were more frequent to patients living near hospitals with ophthalmology departments, which are typically located in areas of median/high population density. There was a positive association between the dependent variable and population density. An increase of 100 persons per square kilometre raised the rates of hospital episodes by 11%. This results show that patients living in rural areas were less frequently treated.

Table 20 - Results of the Generalized Estimating Equation for the rate of hospital episodes per 100.000 population per year and independent variables were: year. Anti-VEGF therapy availability (separating years before and after the drug was authorized by EMEA) Ophthalmology department availability (representing the availability of ophthalmology departments in the hospital of county residence) and population density (population per square Kilometre in the county);

Parameter	**IRR***	**p- value**	**95%CI****	
			Lower	**Upper**
Year (from 2002 to 2012)	1.281	<0.001	1.263	1.299
Anti-VEGF therapy availability (0- not available; 1 – available)	1.270	<0.001	1.183	1.362
Ophthalmology department availability (0 - no ophthalmology dept; 1 – ophthalmology dept)	3.430	<0.001	2.566	4.583
Density rate (per 100 persons)	1.113	<0.001	1.095	1.132

Total number of counties is 278.
*Incidence Rate Ratio
**Wald chi-square test of significance (95% Confidence Interval)

Discussion

With this study we wanted to investigate the diffusion of anti-VEGF treatments for eye disease in Portugal looking for possible determinates and/or barriers. We performed this investigation by characterizing the temporal and geographical distribution of anti-

VEGF treatments using codes for specific type of procedures from all episodes performed in public hospitals. Our results show that the number of episodes for the codes analysed was low before the introduction of anti-VEGF treatments. The numbers of episodes rose significantly since the treatment was introduced in the country in 2007. The most relevant finding was that patients from small areas without ophthalmology departments near their residence received fewer treatments as revealed by the geographical distribution of episodes. The unequal distribution is puzzling, given the equity-oriented nature of the Portuguese NHS.

We consider three possible barriers for the equitable anti-VEGF diffusion related to legal, technical and financial factors. Following the EMA approval of this treatment in 2007 and the NHS coverage decision in 2008, the treatment became legally available at all ophthalmology departments in Portugal. One can thus say that the legal problem was sorted out. However, technical conditions were imposed for the use of this treatment that included extra training for doctors and that the procedure needed to be performed in the operation theatre (190). These technical requirements possibly created financial and service capacity pressures on ophthalmology departments (105, 181). Indeed, higher rates of treatment were observed mostly in areas around big cities and specialized centres. Smaller hospitals may have taken longer to adopt this treatment due to budget limitations or technical conditions. It should also be mentioned that anti-VEGF therapy was first introduced to treat AMD, and then expended to diabetic macular oedema and central retinal vein occlusion treatment. This certainly increased the rate of hospital episodes, but the effect is expected to be similar in all counties.

Regarding financial barriers, we can speculate about two main budget limitations that reduced the speed of diffusion of anti-VEGF treatments. The first financial challenge is the cost of the treatment of approximately €1.913 per episode, a figure similar to the United States (196, 201). In Portugal, hospitals receive a global budget from the government that covers the cost of all drugs and medical devices (190). During the period included in this study, the financing methodology used to allocate resources to the Portuguese NHS hospitals has been subject to several changes. This included the introduction of different unit payment and new incentive programs that rely on quality and cost indicators. These changes to hospital budgets and pressure for cost-containment may have reduced the availability of anti-VEGF treatments in small hospitals concentrating patients in big centres with limited capacity. A second financial barrier for hospitals is the fact that the intravitreal injections need to be administered in an operating room by an ophthalmologist. Typically, patients receive three injections in the first 3 months, followed by monthly visits for assessment and further injections as necessary

(194). These surgical procedures and monthly appointments impose high demands on hospitals (staff and facilities). In a period of tight budgets expansions in the medical staff or facilities are difficult to implement. These problems have been recently reported by Marko Hawlina, a retinal specialist form Slovenia, quoting results of a survey of the European Union of Medical Specialists (202). Thus, some hospitals may have delayed the start of these treatments or they may still not be available.

The reasons outlined above have implications for the geographical diffusion of the treatment leading to inequalities. Patients referred from distant cities or rural areas may have delayed access to treatments. The lower rate of treatments in patients living in areas of low population density may also indicate that these patients are more likely to miss follow-up appointments. Travelling distances may be a barrier to attending appointments as reported by other studies (203-205). These evidence are causes of concern because vision loss caused by eye diseases for which anti-VEGF treatments are indicated cannot be restored. That is, reduced number of treatments might lead to an increased number of people becoming visually impaired due to treatable causes.

During this study we found some limitations: the lack of specific codes for anti-VEGF injections, the inability to follow patients across different years, the exclusion of the activity in the private sector and the absence of individual data. Limitations caused by non-specific codes have been described in methods. The inability to follow patients across years might have had an impact on the ratio of episodes/patient that we found. Nevertheless, the county of residence remained unchanged across years ensuring temporal and geographical accuracy of treatment diffusion. Other studies analysing equivalent temporal periods also report treatments ratios under 3 per year. These authors explained the low ratios by a higher concentration of patients treated as required (105). Numbers from private treatments were likely to be small because this treatment is expensive and patients tend to look for care in the National Health System where treatment is free. The lack of individual data limited our analysis of socio-economic determinants such as patient income or education level or other clinical conditions that could restrict the prescription of anti-VEGF therapy. However, with the available data we were able to construct a complex and multivariable model to explain the geographical diffusion and time variation based on a nationally representative database with many types of hospital settings and geographic areas; this would have been difficult to perform with a limited sample number of cases.

In brief, the use of anti-VEGF drugs in ophthalmology marked the beginning of effective treatments for age related eye diseases that can lead to severe visual

impairment. This study shows that the number of intravitreal procedures increased substantially since anti-VEGF treatments were approved in Portugal, but that the diffusion was inequitably distributed. Local restrictions to the temporal and geographical diffusion seem mostly imposed by financial aspects. These financial constraints may arise not only from cuts in budgets in the health care system but also from difficulties for families to fund travel costs. With the aging of the population and the expected growth in conditions, such as diabetic retinopathy and age-related macular degeneration, the demand for these treatments is likely to increase (147). The combination of these factors will maintain pressure on ophthalmology departments delivering eye care. Health authorities need to consider the equitable distribution when planning human and material resources for ophthalmology departments.

5.1.2 - The use of informal care by people with vision impairment

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PLOS ONE

RESEARCH ARTICLE

The use of informal care by people with vision impairment

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Abstract

Purpose: To estimate and characterize the use of informal care by people with vision impairment in Portugal.

Methods: A total of 546 visually impaired individuals were recruited from Portuguese hospitals. Clinical information was obtained from records, socio-demographic details and informal care use was collected during face-to-face interviews. In addition, participants responded to a functional vision questionnaire (activity inventory) to assess their visual ability. Logistic regression was used to determine independent factors associated with informal care use and linear regression was used to determine independent predictors of intensity of informal care use.

Results: Informal care was reported by 39.6% of the participants. The probability of reporting informal care was higher in non-married, those with comorbidities, with lower visual ability and worse visual acuity. The median number of caregivers' hours per year was 390 (mean = 470; 95%CI=488-407), which represent a median opportunity cost of €2.586. Visual ability was the only independent predictor of the number of hours of informal care received.

Conclusions: Informal care was frequently used by individuals with impaired vision. Improving visual ability of people with impaired vision when performing valued activities may reduce the burden of visual loss at personal and societal level. This can eventually be achieved with person-centred visual rehabilitation.

Introduction

Vision impairment puts a burden on individuals, families and society. People with impaired vision require more informal care to perform activities of daily living, have more difficulties with mobility, have increased risk of falls and are more likely to require long term care than persons without vision impairment (47, 48, 51, 206).

Informal care is generally defined as "help provided to older and dependent persons by non-professional individuals such as, a spouse, parent, other relative, neighbour or friend, in a wide variety of activities and with no payment associated" (207, 208). Some factors such as age, type of activities, type of disability and severity level can influence the demand for informal care (207, 209). In addition, it can be influenced by socio-cultural aspects such as familiar structures, levels of income per capita and availability of formal long-term care systems (207)

In 2007 the Portuguese minister of health implemented a national network of integrated care to provide health and social support including long term care. Visually impaired persons may have access to the national network of integrated care when they meet the access criteria. Nevertheless, the access is difficult due to the limited capacity of the network and in some cases, due to the co-payment associated. Therefore, in Portugal, long-term care for people with impaired vision remains mostly informal, that is, provided by relatives or friends.

Informal care tends to be a major contributor to the total costs of vision impairment (144). Some studies investigated informal care costs in people with impaired vision due to specific eyes diseases such as Age-Related Macular Degeneration or Diabetic Retinopathy (175, 210, 211) considering, in a few instances, self-reported difficulties (175, 210). However, one study relied in presumed visual acuity (210) and other failed to investigate the effect of self-reported difficulties in informal care (175). Other authors reported the use of informal care by people with impaired vision but did not used structured and validated questionnaires to assess limitations with daily activities. Although, some took in consideration limitation to mobility imposed by vision impairment (49, 50). In general, self-reported difficulties have been overlooked in past studies so investigating this topic and further research is needed to characterize the use of informal care and its predictors in this population.

The aims of this study were to estimate and characterize informal care use in persons with impaired vision in Portugal and to investigate the association between

informal care, clinical and socio-demographic aspects. We used a bottom-up approach and administered validated questionnaires to a sample of people with impaired vision.

Methods

Study design, setting and participant selection

Participants were recruited from 4 public hospitals with ophthalmology departments in the north of Portugal between July-2014 and January-2016. Outpatients at these hospitals with a latest recorded visual acuity of 0.30 logMAR (6/12) or worse in the better seeing eye were invited to take part in face-to-face interviews. Patients were invited by letter posted using the hospital mail service, the logo of the hospital was printed on the envelope and letters were sent directly to the patients 'address. All documents were printed in font Arial – 16 point. The mail envelope include a letter of invitation signed by a physician from the local hospital, an information booklet and a consent form. Despite some letters were returned to sender due to incorrect address, we estimate at least 3000 reached at the patient´s home, 546 returned a signed consent form on a reply-paid envelope addressed to Escola Nacional de Saúde Pública, Lisboa (National School of Public Health. Lisbon) with an updated phone number. After acceptance participants were contacted and an interview was scheduled at the hospital.

Causes of visual impairment, principal diagnosis and secondary diagnosis, were retrieved from clinical records and classified according with the ICD9 CM (International Classification of Diseases 9th Clinical Modification) codes. The information was registered in a secure platform that is online at www.pcdvp.org.

This study has been designed according to guidelines published by the Vancouver Economic Burden of Vision Loss Group (158). The study was conducted in accordance with the tenets of the Declaration of Helsinki, reviewed and approved by the ethical committee for Life Sciences and Health of the University of Minho and local ethics committees at Centro Hospitalar São João, Hospital de Braga, Centro Hospitalar do Alto Ave and Hospital de Santa Maria Maior. Written informed consent was obtained from all participants. Further details about the study have been described in our previous publications (212).

Clinical measurements during face-to-face interviews

Patients answered a functional vision questionnaire, the Activity Inventory (AI), to assess visual ability. The AI is an adaptive visual function questionnaire designed to provide an individualized assessment of difficulties of a visually impaired respondent

when performing valued activities. Disabilities, or activity limitations according to the World Health Organization's International Classification of Functioning, occur when an individual reports abnormal difficulties in achieving important goals. Difficulties achieving a goal are said to depend on the difficulty experienced in the tasks that underlie each goal (165-168). In our translated version of the Massof activity inventory patients were questioned about difficulties with 46 goals and the "difficulty" responses were Rasch analysed to produce a continuous measure of visual ability given by the variable 'person measure' (Program Winsteps. v3.9) (167, 213). We use the term 'visual ability' to define the overall ability to perform activities that depend on vision (8).

Participants also reported comorbidities based on a list of 16 categories as described in Appendix 6. Visual acuity with the habitual correction was re-assessed in both eyes separately using an internally illuminated ETDRS chart (Lighthouse International. NY. USA) at 4. 2 or 1 meter – the measuring distance was adjusted according with the severity of the expected vision loss. The room lights where extinguished during measurements. Letter by letter scoring was employed to specify final measured acuity (212).

Informal care questionnaire and cost estimation

A questionnaire to collect information about informal care was administered by trained researchers. We asked information about the use of informal care within a 2-week recall time period. This period has been proposed by others to minimise recall biases (171, 172). The questionnaire was drawn from previously validated instruments (172, 173), it underwent pilot testing and revisions to clarify wording, to simplify data recording and to remove redundant items. The final version of the questionnaire is summarized in Table 21.

Table 21 - The table summarises the questions used to collect information about sociodemographic information and the use of informal care. In all questions, there was one option with: do not know or do not want to answer (not shown in the table for simplicity).

Cat	Questions	Options
Sociodemographic	1. What is your marital status?	a) Single b) Married or living as married c) Divorced or separated d) Widowed e) Other (please specify)
	2. What best describes your living environment?	a) Live alone b) Live with spouse (including children) c) Live with parents d) Live with children (sons / daughters) e) Live with other relatives f) Live with others
Informal Care Need	3. Over the last two weeks have you been helped and/or cared for by a relative or friend because you have poor vision?	b) Yes (ask question 3.1)
		c) No
	3.1. Over the last two weeks how many relatives or friends provided you care?	Number of caregivers
	3.2. Over the last two weeks how many hours were spend by caregivers to help you?	Number of hours
	3.3 What is the main occupation of the persons providing you care?	a) Paid job b) Currently seeking work c) Homemaker d) Retired e) Student f) Other (please specify)

Informal care costs represent a monetary estimate of the hours spend by informal caregivers to help visually impaired persons. To estimate the economic impact of informal care we used the *opportunity costs* in which time spent providing informal care is valued based on competing time use, in this case paid labour. This method is commonly used for these estimates including in eye care and rehabilitation studies (174, 175, 207, 214). The number of reported hours were extrapolated from 2 weeks to 12 months. Total informal care costs were calculated by multiplying the number of annual hours by the mean Portuguese hourly wage rate of full time employees in the year 2014 (€6.63). This value is within the interval €4.10 to €19.18 reported by Costa et al (176).

Statistical analysis

Descriptive statistics was used to summarize socio-demographic and clinical characteristics of the participants. Participants were divided into 4 age categories: (1) 39 years or younger; (2) 40-64 years; (3) 65-79 years; (4)80 years and older. Causes of visual impairment were divided in 11 categories (see Table 22). Visual acuity was used either as continuous variable or categorical variable whichever was deemed more appropriate.

Chi-square tests were used to compare the composition of groups. T-tests were used to compare visual ability between groups and the Mann-Whitney–test or Kruskal-Wallis was used for other non-parametric comparisons between groups. Spearman Correlation was used to determine the association between variables.

Logistic regression was used to determine explanatory factors associated with the use of informal care. Linear regression was used to determine factors associated with the amount of informal care needed (intensity of care). A description of the models is provided in Appendix 7. Statistical analysis was performed with SPSS Statistics (IBM SPSS Statistics v.23).

Results

A total of 546 participants were included in this study, from those 216 (39.6%) reported informal care needs. The sample comprised a high percentage of old individuals, 50% (n=275) were older than 65 years. The most common causes of visual impairment were: diabetic retinopathy, age-related macular degeneration (AMD), glaucoma and other retinal disorders and detachments. Participants were divided in 2 groups: “users” and “non-users” to identify sociodemographic and clinical independent predictors of the use of informal care. We compared the distribution of cases, between groups, according with several categories. These results are summarized in Table 22. The proportion of women and participants with comorbidities was higher in the users group. The percentage of married individuals was higher in the non-users group.

Table 22 - The socio-demographic and clinical characteristics of study participants (n=546).

	Informal Care				
	Users n = 216		Non-users n = 330		Group comparison
	n	(%)	n	(%)	
Gender					Chi-square=6.3; **p=0.012**
- Female	120	56%	147	45%	
- Male	96	44%	183	55%	
Age categories (years)					Chi-square=1.36; p=0.714
- 39 years or younger	16	7%	32	10%	
- 40 to 64	92	43%	131	40%	
- 65 to 79	85	39%	136	41%	
- 80 or more	23	11%	31	9%	
Marital status					Chi-Square=4.3; **p=0.037**
- Not Married	91	42%	110	33%	
- Married	125	58%	220	67%	
Living arrangement					Chi-square=0.13; p=0.724
- Live alone	25	12%	35	11%	
- Live with others	191	88%	295	89%	
Cause of Visual impairment (principal diagnosis)					Chi-square=12.9; p=0.228
- Diabetic Retinopathy	82	38%	115	35%	
- AMD	20	9%	44	13%	
- Glaucoma	27	13%	32	10%	
- Other Retinal Disorders and Detachments	25	12%	27	8%	
- Cornea	13	6%	28	8%	
- High Myopia	13	6%	28	8%	
- Cataracts	4	2%	15	5%	
- Disorders of Choroid	9	4%	8	2%	
- Optic Nerve Disorders	9	4%	10	3%	
- Disorders of Globe	5	2%	4	1%	
- Others	9	4%	19	6%	
Secondary diagnosis					Chi-square=1.7; p=0.194
- Yes	117	54%	160	48%	
- No	99	46%	170	52%	
Other Comorbidities					Chi-square=6.0; **p=0.014**
- Yes	164	76%	218	66%	
- No	52	24%	112	34%	

Table 23 summarizes and compares visual ability and visual acuity in informal care users and non-users. Visual ability and visual acuity (both in the better eye and in the worse eye) were lower in the users group.

Table 23 - Visual ability (person measures) and distance visual acuity of users and non-users of informal care in the sample. SD = standard deviation; IQR = Inter-quartile range

	Informal care				**Group Comparison**	
	Users		**Non-users**			
Visual ability (logits)						
Mean (SD)	-0.51 (1.48)		1.6 (2.01)		t-test=14.1; **p<0.001**	
Median (IQR)	-0.52 (1.83)		1.42 (2.95)			
Visual acuity (logMAR**)**						
	Better eye	Worse eye	Better eye	Worse eye	Better eye	Worse eye
Mean (SD)	0.87 (0.61)	1.55 (0.82)	0.47 (0.32)	0.97 (0.72)	z-test=9.11; **p<0.001**	z-test=8.74; **p<0.001**

Table 24 summarizes the results of a logistic regression to determine predictors of the use of informal care. Marital status, comorbidities, visual acuity, and visual ability were independent predictors of the use of informal care. When the odds ratio (OR) reported in Table 24 is less than 1, the reciprocal is used here in the text for consistency of interpretation. Non-married individuals were 1.85 times more likely to use informal care. Individuals with comorbidities were 2.17 times more likely to use informal care than those without. An additional unit of visual acuity in the better eye increases the odds of using informal care 3.2 times (1 unit of visual acuity =1 LogMAR; higher values of acuity correspond to higher level of impairment). One unit reduction in visual ability increase the odds of using informal care 2.22 times (1 unit of visual ability = 1logit; lower values of visual ability are associated with increased difficulty to perform tasks that rely on vision). The deviance chi-squared goodness (residual deviance = 463.706; 524 degrees-of-freedom) of fit test confirmed an excellent fit of the model. p=0.96.

Table 24 - Explanatory variables of informal care usage. In the first column, brackets show the reference categories.

Explanatory variables	**Odds Ratio**	**95% C.I. for Odds Ratio**		**p-value**
		Lower	**Upper**	
Gender (Male *versus* Female)	0.87	0.55	1.38	0.545
Marital Status (not Married *versus* Married)	1.85	1.14	2.99	0.013
Presence of other comorbidities (No *versus* Yes)	0.46	0.27	0.77	0.003
Visual Acuity	3.2	1.71	6	<0.001
Visual Ability	0.45	0.37	0.55	<0.001

Among those who needed informal care, 60% reported having only one caregiver and the main activity of the caregivers was homemaker (the person whose principal role is to do housework and other domestic concerns). The median number of caregiver hours was 390 hours per year and the mean number of caregivers' hours was 470 hours per year (95%CI=488.1-406.6) which represent a median cost of €2,585.7 per year. Therefore, in our sample of 206 cases (10 out of the initial 216 cases were considered outliers) that would correspond to 92,144 hours of informal care per year, resulting in an annual cost of €610,915.0.

The number of caregivers' hours was statistically different between categories of vision impairment (Kruskal-Wallis=10.86; p-value=0.012). Categories: 1) visual acuity from 0.3 logMAR to 0.5 logMAR; 2) visual acuity from 0.51 logMAR to 1.0 logMAR; 3) visual acuity from 1.02 logMAR to 1.3 logMAR and 4) visual acuity from 1.32 logMAR and 3.0 logMAR. The pairwise comparison showed that participants in categories 1 and 2 needed less informal care than participants in categories 3 and 4 (Mann-Whitney U=3200; p=0.002). These results show that the use of informal care tends to increase with the severity of vision impairment. Differences between groups according with gender, causes of visual impairment, presence of comorbidities, marital status and living arrangement were not statistically significant.

There was a negative association between visual ability and the amount of informal care used, Spearman´s rho = -0.381($p<0.001$). This means that lower visual ability was associated with increased use of informal care (intensity). Table 25 summarizes results of the multiple linear regression analysis used to investigate predictors of the intensity of use of informal care. Visual ability was the only statistically significant independent predictor ($p<0.001$). These results show that one-unit change in visual ability corresponds, per year, to a variation of 67 hours in the intensity of informal care. The model also includes as explanatory variables age, gender and severity of visual impairment (2 categories) that were not statistically significant. The R-squared of the model was 0.157.

Table 25 - Explanatory variables of intensity of use of informal care. In the first column brackets show the reference categories.

Explanatory variables	Unstandardized Coefficients		p-value
	B	Std. Error	
Visual ability	-66.99	14.81	<0.001
Age	0.93	1.28	0.468
Gender (male)	48.70	38.64	0.209
Severity of Visual Impairment (visual acuity in the better eye above 1 logMAR)	74.79	46.75	0.111

Discussion

In this study, we quantified and characterized the use of informal care in a sample of 546 visually impaired individuals. Informal care was reported by 39.6% of the participants requiring, each, a median of 390 hours of informal per year. Based on the median values, that corresponds to an estimated 92.000 hours per year for our 216 users. The use of informal care was influenced by marital status, comorbidities, visual ability and acuity. The intensity of use of informal care was negatively associated with visual acuity. However, lower visual ability was the only predictor of higher informal care utilisation intensity after controlling for age, gender and severity of vision impairment.

The percentage of informal care users found in our study is similar to other studies (49, 210). Some authors reported that 39.3% of participants with best corrected visual acuity worse than 20/40 (or 41 letters in the ETDRS chart) use community or family support (49). Others found that 36% of AMD patients use paid or unpaid assistance (210). The estimated intensity of use (amount of caregiver hours) per-week per individual in our sample was 9 hours. This value is between the 4.7 and the 17.4 reported in other studies (210, 211).

The use of informal care was affected by marital status and comorbidities but not by gender. Non-married participants were more likely to report informal care, this may be because they cannot rely on their partners and the need to ask for help is more clearly defined for them. Those married not reporting may be because, although they rely in their partners for some tasks, they see any help received as a natural gesture of mutual help between members of a couple. It is also intuitive that those with other comorbidities face further difficulties in their daily life and therefore are more likely to require informal care. In a univariate analysis gender seemed to be a predictor but that effect disappeared in the logistic regression. This result is in contrast with some studies reporting that women are more likely to use informal care (49, 50). It is know that informal care can be

influenced by many factors and, in particular, by the organization of the society (207). Therefore, our results need to be interpreted in the Portuguese context and can be eventually applicable to similar societies (215).

Visual ability was the only independent predictor of the intensity of use of informal care after adjusting for age, gender and severity of vision impairment. The association between visual ability and informal care shows a link between self-reported task difficulties and the amount of help needed. Others reported an effect of visual acuity; however, these studies did not considered self-reported levels of visual ability (50, 175, 216, 217). We recognize that visual acuity gives a partial measure of visual performance and that the inclusion of a broader spectrum of visual tests, such as contrast sensitivity or visual field, could provide a better understanding of the association between visual performance and informal care. This would be particularly true in cases of impaired vision caused by diseases such as retinitis pigmentosa in which acuity is preserved but severe functional limitations are imposed by restricted visual fields. In line with our results, Wang et al. (49) found an increase in intensity with increased self-reported walking difficulties. Keefe et al (214) reported that people with impaired vision need help for vision-dependent activities such as driving, reading documents and support for independent activities outside home. These are the tasks covered by the activity inventory to determine visual ability. In short, visual rehabilitation tailored to increase visual ability is likely to reduce simultaneously the use of informal care and its intensity. These findings suggest that the use of instruments such as the AI during clinical assessment would help to target resources at those with the greatest caring needs.

One of the methodological dilemmas of this study was how to collect information about informal care. We used a questionnaire, the most common method, with a short recall time period to minimize recall bias (174, 207). Informal care is a frequent event and is known that, contrary to unusual events such as an inpatient stay at a hospital, short recall periods increase the accuracy of the reports (171, 218). Some participants may, accidentally, extend or reduce recall periods or we might have collected data during seasonal changes in the needs of informal care; however, this factors are unlikely to lead to systematic error in our estimation (218). Other factors, such as treatments or disease changes can alter visual acuity – a 2 week recall period may be beneficial to capture the informal care needed according with the acuity that we measured. Nevertheless, using a short recall period may result in an underestimation of the use of informal (171). Keeping a diary would minimize this limitation but would be significantly more expensive and time consuming (207, 219). In addition, the amount of missing data and the complexity of the information available may increase substantially with a diary (220, 221).

Thus, the method adopted can eventually lead to a conservative estimation of informal care usage. Conversely, to estimate the economic impact of informal care we used opportunity costs which can inflate the costs because it includes 6 caregivers that were retired. The method and value used in our study was used previously in various analysis (174, 175, 207, 214) and is within the interval used in studies using the opportunity cost method (176, 207). Therefore, it seems appropriate and ensures comparability with others studies (175, 214).

Our participants were recruited at hospitals and therefore our sample includes only patients seeking eye care. Considering that informal eye care is used by patients who are under treatment or have stable eye diseases (207, 209, 214) we believe that the results reported can be generalized to all the Portuguese population with vision impairment. However, information about the characteristics of the Portuguese population with impaired vision is lacking and therefore there is no evidence to confirm this generalization. In addition, we compared the profile of patients who responded our questionnaire and those that declined participation and found some differences. For instance, we found that participation in our study was influenced by gender, distance to the hospital, number of years of education, number of visits to the hospital per year, marital status and visual acuity. This means that the profile of our participants was different from those declining participation.

In summary, this study provides a comprehensive analysis of use of informal care in persons with impaired vision. In the context of the reviewed literature, this study is the first to show a strong link between self-reported ability and the use of informal care in large multi-centre study in an European country. Visual ability was a predictor of the use of informal care and the intensity of care. Therefore, visual rehabilitation interventions, alongside with usual eye care may reduce the economic burden of visual loss at personal and societal level.

5.1.3 - Productivity losses and their explanatory factors amongst people with impaired vision

Material in this Chapter has been submitted to Ophthalmic Epidemiology:

Marques AP, Macedo AF, Ramos P, Moreno L, Butt T, Rubin G, Santana R.
Productivity losses and their explanatory factors amongst people with impaired vision.

Abstract

Purpose: To estimate productivity losses amongst people with impaired vision in Portugal and to investigate explanatory factors associated with participation in the labour market.

Methods: A total of 546 visually impaired individuals participated in face-to-face interviews. Participants were asked about their workforce participation (employment status questionnaire), health-related quality of life - HRQoL (EQ-5D) and about visual ability (Activity Inventory). Logistic regression was used to determine independent factors associated with participation in the labour market.

Results: Fifty percent (50%) of the participants were retired. 47% were within working age and 3% were students. The labour force participation rate was 28% and the unemployment rate was 21% to the working age sample and 13% and 10% respectively for the total sample. For the sub-group within the working age productivity losses were estimated at €1.51 million per year (mean €5496 per participant.) The largest contributor for losses was reduced workforce participation estimated from 159 early retired or unemployed participants. After controlling for visual acuity and ability, younger individuals, with more years of education, without comorbidities and high HRQoL had higher chances of being employed.

Conclusions: Vision impairment can cause disability and that can lead to significant productivity losses. The probability of being employed was associated with education. HRQoL and comorbidities. We speculate that promoting education and health through effective visual rehabilitation programs may be crucial to increase access to the labour market. These findings need to be considered when acting to reduce the burden of vision loss at individual and societal level.

Introduction

People with impaired vision are likely to have disability because reduced vision imposes barriers to acquisition and development of skills and abilities (10, 35, 55, 222-224). Disability caused by vision impairment limits the ability to perform valued activities for example driving (225) or reading documents without the help of special devices or software (225, 226). In addition to the direct impact on health related quality of life through the impact on people's ability to perform activities of daily living and self-care, difficulties to perform vision related tasks can also cause extra stress and anxiety in persons with impaired vision (227). These events may not only impact on health, but also alter the chances to find and retain jobs, reduce the range of jobs in which people with impaired vision can work (227-230), or may lead individuals to never look for a job or leave workforce prematurely leading to lower productivity among people with impaired vision (230). Being able to have a paid job is important to most individuals living in society. For example, work provides opportunities for maintaining or increasing one's financial independence enables relationships and social inclusion and increases quality of life (231, 232). It is therefore important to understand the causes of reduced employment amongst people with impaired vision for both the financial and health burden for the individual and for the society.

From the economic perspective, the burden for the society is captured by productivity costs. Productivity costs can be defined as "costs associated with production loss and replacement costs due to illness, disability and death of productive persons, both paid and unpaid" (233). Productivity costs can incorporate several components leading to different concepts and calculations. In this work, we consider two components: absenteeism and reduced workforce participation. These are considered two of the most relevant components of productivity costs and major contributors to the total costs of vision impairment. (144) Working with limitations due to illness, or presenteeism, is a further component of impaired productivity. However there is no consensus on the measurement of presenteeism meaning that it is rarely included in economic calculations of productivity costs (234).

For those in the labour market absenteeism can be defined as the number of workdays lost due to health related issues (235). For those in working age, but out of the labour market, reduced workforce participation can be defined as production missed due to the premature exit of the labour market (136). Some studies found high productivity

costs and high rates of unemployment, job loss and early retirement amongst persons with vision impairment (144, 150, 153-155, 236).

From our perspective, the information available from studies published in the past decade has some limitations in two aspects: 1) the samples studied were too restricted and 2) the explanatory factors used lacked accuracy. For example, one study used self-reported vision impairment (236),other used exclusively blind individuals (153) and other used an unclear definition of vision impairment (154). When explaining productivity costs past studies also left out one or both of two relevant measures: patient-reported levels of visual ability and the impact of vision loss in quality of life (153-155, 236). We argue that employment has an impact on both productivity and health and therefore it is important to include measures of patient-reported HRQoL when investigating productivity. The type of patient-reported measures referred are likely to influence the ability to look for jobs and to retain them. Therefore we decided to include them when studying productivity costs.

The aim of this study was to estimate productivity costs and investigate their explanatory factors in people with vision impairment. We collected information about employment status and analysed socio-demographic factors, patient-reported measures and clinical aspects that can be explicative of employment.

Methods

Study design, setting and participant selection

Participants were recruited from 4 public hospitals with an area of influence of nearly 2 million inhabitants divided into 3 regions in Portugal: Porto, Braga and Viana do Castelo. Patients attending medical appointments at the department of ophthalmology in these hospitals with latest recorded visual acuity of 0.30 logMAR or worse were invited to take part in face-to-face interviews. Principal diagnosis, designated by causes of vision impairment, and secondary diagnosis, were retrieved from clinical records and classified according with the International Classification of Diseases 9th Clinical Modification codes (ICD9 CM). From clinical records we have also collected information about gender, date of birth and systemic diseases. The information was registered in secure platform that is online at www.pcdvp.org.

The study was conducted in accordance with the tenets of the Declaration of Helsinki, approved by the local ethics committees of the participant hospitals and by the ethical committee for Life Sciences and Health of the University of Minho. Written

informed consent was obtained from all participants. More details about the study have been described in our previous publications (212, 237).

Clinical and quality of life measurements during face-to-face interviews

During face-to-face interviews patients were asked to respond to the EuroQol EQ-5D 3 level (EQ5D-3L) to classify their perceived health-related quality of life (HRQoL). The EQ-5D is a generic preference-based measure of HRQoL that has five domains: mobility, self-care, usual activities, pain or discomfort, anxiety and depression (presented in Appendix 2). Each dimension is rated on a three-point scale with categories "no problems." "some problems." or "extreme problems." producing a descriptive health profile. Respondents' health states were converted to health utility scores using valuations derived from the general population in Portugal (170).

Additionally, patients responded to a vision function questionnaire, the Activity Inventory (AI), to measure their visual ability. The AI is an adaptive visual function questionnaire designed to provide an individualized assessment of difficulties of a respondent with impaired vision when performing valued activities (presented in Appendix 1). Participants are asked to rate goals which dependent on the difficulty experienced in the tasks that underlie each goal (165-168). Responses are then Rasch analysed to produce a continuous measure of visual ability given by the variable 'person measure' (Program Winsteps. v3.9). The term 'visual ability' defines the overall ability to perform activities that depend on vision (8).

During the interview, visual acuity was (re)measured using an internally illuminated ETDRS chart (Lighthouse International. NY. USA) at 4. 2 or 1m according with the severity of the (expected) vision loss. Letter by letter scoring was employed to specify the final measured acuity (212).

Comorbidities were also reported by participants and/or extracted from the clinical records and classified according with the 16 categories listed in Appendix 6.

Productivity losses questionnaire

We used a questionnaire administered by trained researchers and collected information about absenteeism and workforce participation. The questionnaire was drawn from previously validated instruments (172, 173). We conducted a pilot test to simplify data recording, to remove redundant items and to clarify words and questions. The questionnaire was written and administrated in Portuguese. Table 26 summarizes a translated version of the questionnaire.

Table 26 - Questions used to collect information about sociodemographic information and absenteeism. Absenteeism questions were applicable to participants in the working age range (17-64 years). In all questions there was 1 option with: do not know or do not want to answer

Cat	Questions	Options
Sociodemographic information	1. What is your marital status?	a) Single b) Married or living as married c) Divorced or separated d) Widowed e) Other (please specify)
	2. How many years of education do you have?	a) Up to university 3rd cycle (PhD) b) Up to university 2nd cycle (Master) c) Up to university 1stcycle (undergraduate) d) Up to 12 years of education e) Up to 9 years of education f) Up to 6 years of education g) Up to 4 year of education
	3. What best describes your living environment?	a) Live alone b) Live with spouse c) Live with parents d) Live with child e) Live with other relatives f) Live with others
	4. What is your employment status?	a) In full-time work b) In part-time work c) Currently seeking work d) Homemaker e) Retired f) Early retired g) Student h) Other (please specify)
	5. Please provide an estimate of your month household income from all sources (after tax and other deductions and including your partner/spouse)?	a) less than €485* b) between € 485 and €1000 c) above €1000 *this is the national minimum monthly wage in the year we started to collect data
Absenteeism*	For those reporting employment (part-time or full-time) we asked 2 questions 6. Over the last two weeks how many hours per week do you spend working?	Number of Hours
	7. Over the last two weeks how many days have been absent from work owing to your visual condition?	Number of days
	- For those reporting two weeks of absenteeism in the last two weeks we asked 7.1 How long were you in sick leave?	a) less than three months b) three months or more

The societal perspective was adopted to estimate productivity costs. Productivity costs encompass: absenteeism and reduction in workforce participation.

Absenteeism was measured by the number of absent workdays due to health problems. The annual costs of absenteeism were calculated by converting the reported working days missed due to vision impairment into hours and then valued using the average hourly pay rate obtained by the three categories of income level reported by the participant. We extrapolated the 2-week recall period to an annual level multiplying by 24 working weeks adjusting for annual leave and public holidays. Absenteeism was divided into short term absenteeism and long term absenteeism. Long term absenteeism includes all the individuals that reported being absent for more than three consecutive months. All the other cases were considered short term absenteeism.

Reduced workforce participation (RWP) refers to the loss of production caused by having people with impaired vision out of the labour market. In Portugal, individuals (men or women) outside the age-range 17-64 are considered to be in mandatory education (less than 17) or retired (more than 65) (238, 239). RWP was calculated for participants within the working age 17-64 years that reported early retirement or unemployment due to impaired vision. It was calculated as the excess unemployment compared to the unemployment rate adjusted by sex and age of active population in Portugal in 2014 (reported by Eurostat) and the unemployment rate observed by sex and age in our sample. These two figures were in turn applied against the mean Portuguese monthly wage adjusted by sex and education level. More details about these assumptions are shown in Appendix 8. Some participants were out of the labour market categorized as homemaker and others (which includes students and other reasons not specified) that were not considered in this estimation because it can be a choice of the individual and therefore cannot be attributable to vision impairment.

Statistical analysis

Descriptive statistics regarding sociodemographic and clinical participant characteristics were analysed. Participants were divided into 4 age categories: (1) 17-39 years. (2) 40-64 years and (3) 65-79 years; (4) 80 years or older. Causes of vision impairment were divided into 8 categories.

Chi-square tests were used to test differences between participants working and non-working. Categorical binary variables included gender, secondary diagnosis and comorbidities. Independent t-tests were performed to compare visual ability and Mann-Whitney tests were performed to compare visual acuity in the better eye and in the worse eye and HRQoL.

Logistic regression was used to determine explanatory factors associated with participation in the labour market. The dependent variable was employment status in working age participants (non-working = 0; working =1). Independent predictors were: age (categories: 40-64 years=0; 17-39 years=1); Education (categories: less than12 years of education = 0; 12 years of education or more=1), comorbidities (categories: No = 0; Yes =1), visual ability (continuous predictor provided by the AI), visual acuity in better eye (continuous predictor using a logMAR scale) and HRQoL (continuous predictor provided by the EQ-5D). The graphic method was used to validate assumptions of the model for residuals independence and to identify extreme cases that were removed from the model (whenever it increases the goodness of fit of the model). Multicollinearity was analysed with variance inflation factor (VIF). Statistical analyses were conducted with SPSS Statistics (IBM SPSS Statistics v.23. for Windows).

Results

From the 546 participants. 47% (n=254) were within the working age. 50% were retired and 3% were students. Of those within working age 28% (n=71) were working full-time or part-time and 72% were not working because required early retirement (n=105), were unemployed (n=54), were homemakers (n=14), were students (n=4) or for reasons not specified (n=6). The labour force participation rate was 28% and the unemployment rate was 21% for those within the working age and 13% and 10% respectively for the all sample. Diabetic retinopathy, high myopia and diseases of the cornea were the major causes of vision impairment amongst participants within working age. We divided the group within working age in two subgroups: “working” and “non-working” and compared the characteristics of the groups. These results are summarized in Table 27.

The group of participants working had a higher proportion of individuals within the age group 17-39 years (p=0.023), a higher proportion of participation with up to 9 years of education or more (p=0.007) and a lower proportion of participants with other comorbidities (p=0.037) when compared with the non-working group. There were difference in causes of vision impairment between groups (p=0.003). The working group had a smaller proportion of patients with diabetic retinopathy and a higher proportion of patients with high myopia, diseases of the cornea and AMD.

Table 27 - The socio-demographic and clinical characteristics of study participants within the working age (n=254)

	Working age participants				
	Working n = 71		Non-working n = 183		Group comparison
	n	(%)	n	(%)	
Gender					Chi-Square=3.9; p=0.052
Female	28	39%	97	53%	
Male	43	61%	86	47%	
Age categories (years)					Chi-Square=5.2; p=0.023
17 to 39	14	20%	17	9%	
40 to 64	57	80%	166	91%	
Education level					Chi-Square=14.1; p=0.007
Do not Know/Do not answer	0	0%	12	7%	
Up to university 1st cycle (undergraduate) or more	9	13%	6	3%	
Up to 12 years of education	9	13%	19	10%	
Up to 9 years of education	16	23%	32	17%	
Up to 4 years of education	37	51%	114	62%	
Marital status					Chi-Square=1.1; p=0.301
Not Married	20	28%	64	35%	
Married	51	72%	119	65%	
Living arrangement					Chi-Square=1.5; p=0.219
Live alone	3	4%	16	9%	
Live with others	68	96%	167	91%	
Cause of Visual impairment (principal diagnosis)					Chi-Square=21.6; p=0.003
Diabetic retinopathy	16	23%	77	42%	
Other Retinal Disorders	7	10%	16	9%	
Cornea	13	18%	16	9%	
High Myopia	13	18%	16	9%	
Glaucoma	3	4%	15	8%	
Optic Nerve Disorders	2	3%	10	6%	
AMD	8	11%	6	3%	
Others	9	13%	27	14%	
Secondary eye diagnosis					Chi-Square=1.5; p=0.214
Yes	28	39%	88	48%	
No	43	61%	95	52%	
Other Comorbidities					Chi-Square=4.4; p=0.037
Yes	39	55%	126	69%	
No	32	45%	57	31%	

Table 28 summarizes visual ability, visual acuity and HRQoL in both groups, working and non-working. The median visual acuity in the better eye was higher in the non-working group (z-test= -2.03; p=0.042) meaning higher severity of vision impairment. The non-working group reported lower health-related quality of life (z-test= -4.17; p<0.001) and lower visual ability (t-test= -45.04; p<0.001) compared to the working group.

Table 28 - Visual ability, distance visual acuity and health related quality of life characteristics of the participants within working age (n=254)

	Working age					
	Working		**Not-working**		**Group Comparison**	
Visual ability (Activity Inventory)						
Mean (SD)	1.78 (1.8)		0.55 (2.0)		t-test=-45.04; p<0.001	
Median (IQR)	1.91 (2.89)		0.30 (2.43)			
Visual acuity (logMAR)[a]						
	Better eye	Worse eye	Better eye	Worse eye	Better eye	Worse eye
Mean (SD)	0.52 (0.43)	1 (0.77)	0.69 (0.58)	1.2 (0.84)	z-test=2.03; p=0.042	z-test=1.83; p=0.067
Median (IQR)	0.42 (0.40)	0.82 (0.80)	0.52 (0.60)	1 (1.10)		
Health Related Quality of Life (EQ5D Score)						
Mean (SD)	0.65 (0.29)		0.48 (0.28)		z-test=-4.17; p<0.001	
Median (IQR)	0.66 (0.55)		0.45 (0.38)			

[a] In a logMAR acuity scale higher values of acuity correspond to higher level of impairment

Absenteeism was reported by 28 individuals out of 71 (39%). In total 22.296 hours of work were lost over 1 year, which represents a productivity costs of 102 thousand EUs based on the average hourly pay rate obtained by the income level reported by the participants. Long term absenteeism (absent for more than 3 consecutive months) reported by 8 individuals accounted for 15.840 hours of work lost. 71% of hours of work lost and 65% of the absenteeism costs. The distribution of costs of absenteeism was skewed to the right with a median of €1.635 and a mean of €3.646 (95%CI = [5.125; 2.167]).

RWP was estimated for 159 participants, early retired or unemployed, and represented an annual cost of 1.4 million EUs with a median of €9.151 and a mean of €8.855 (95% CI= [9.517; 8.194]) per participant.

Results of the logistic regression with predictors of participation in the labour market are summarize in Table 29. HRQoL (p-value<0.001), age (p-value=0.013), education (p-value=0.027) and comorbidities (p-value=0.004) were independent predictors of employment status.

A change of 1 unit of HRQoL measured by EQ-5D score is associated with odds of being in the labour market of 162.6. Since the EQ-5D score maximum value is 1, our results show that a change of 0.1 unit of health utility increase correspond to odds of being in the labour market of 16.3. The odds of being employed for individuals within the age 17-39 years was 3.9 higher than for individuals in the category 40-64 years. The

odds of being employed for individuals with 12 or more years of education was 2.7 higher than for individuals with less than 12 years of education. The odds of being employed for individuals with comorbidities were lower than for those without comorbidities. The deviance goodness of fit test confirmed an excellent fit of the model to the data (p-value = 0.99).

Table 29 - Explanatory variables of participation in the labour market (n=222)

Variable	**Interval**	**Working Vs Not Working** **Odds Ratio (OR)**	**95% C.I. for OR**		Sig.
			Lower	**Upper**	
Age categories					
17-39 years	40-64 years	3.93	1.33	11.61	0.013
Education level					
12 years of education or more	less than 12 years of education	2.86	1.13	7.25	0.027
Other Comorbidities					
Comorbidities	No Comorbidities	0.29	0.12	0.67	0.004
Visual acuity		0.35	0.08	1.53	0.163
Visual ability		0.96	0.72	1.29	0.795
Health Related Quality of life		162.6	17.49	1511.87	<0.001

Figure 18 shows the probability of participation in the labour market as a function of HRQoL (EQ-5D utility score) for 2 scenarios: best-case and worst-case, details of the computations are given in Appendix 9. The best-case scenario includes participants within the age 17-39 years, 12 years of education or more, no comorbidities and visual ability set as constant equal to the mean value of the group. Five curves were computed according to 5 categories of vision impairment. With acuity in logMAR, categories were: 1) No VI= [-0.3.0.3]; 2) Minor VI=[0.32.0.5]; 3) Moderate VI=[0.5.1.0]; 4) Severe VI=[1.02.1.3]; 5) Profound VI or blind=[1.32. 3.0]. The worst-case scenario is defined as participants within the age 40-64 years, less than 12 years of education, comorbidities and visual ability set as constant equal to the mean value of the group.

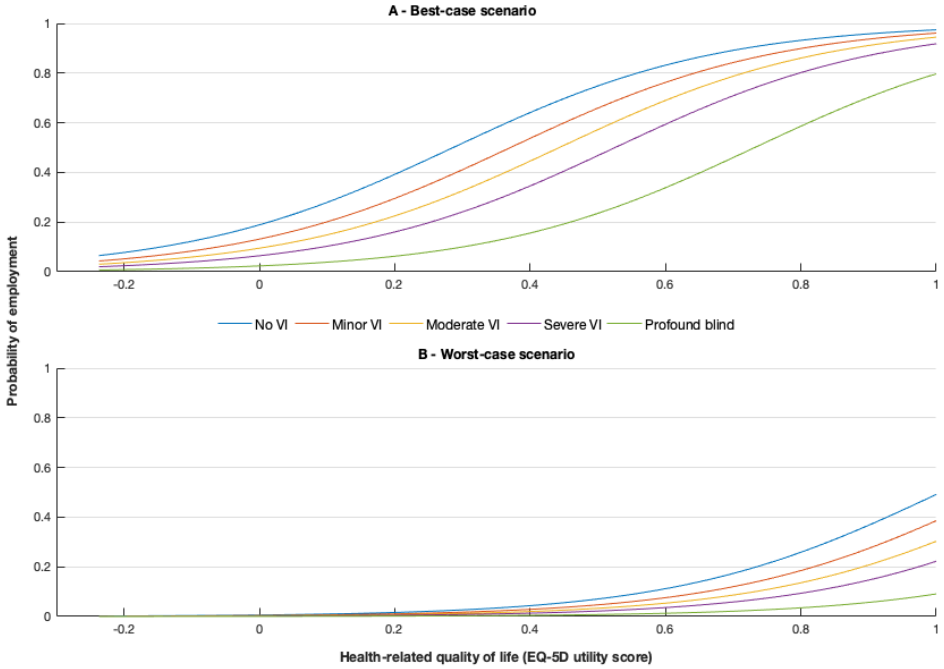

Figure 18 - Predictive probability of participation in the labour market as a function of health-related quality of life divided into 5 categories of vision impairment. A) best-case scenario, B) worst-case scenario. Best case scenario includes: participants within the age 17-39 years, 12 years of education or more, no comorbidities and setting visual ability as constant equal to the mean value of the group. Worst case scenario includes: participants within the age 40-64 years, less than 12 years of education, with comorbidities and visual ability the same as in the best scenario

In both scenarios higher levels of HRQoL and better acuity increased the probabilities of being employed. For example, with a health utility of 0.6 given by the EQ-5D utility score, in the best-case scenario, more than 34% of the participants would be employed against 1% in the worst-case scenario. In the worst-case scenario the probabilities of being employed ranged from 0 to 0.4. The maximum value of 0.4 was observed in participants included in category 1 (No VI) and with the highest possible score for level of HRQoL. In the best-case scenario, the probabilities of being employed ranged from 0.1 to 0.97. Here, the probability of participants in category 5 (Profound VI or blind) to be employed can reach more than 0.8. This is in contrast with the worst-case scenario in which persons with these levels of impairment would have a probability of employment around 0.07.

Discussion

In this study we quantified and characterized productivity losses in a sample of 546 persons with impaired vision, 47% were within the working age and from those 28%

were working. Productivity losses would correspond to an estimated €1.51 million per year for this sample (median of €4.399 and mean of €5.495 (95% CI=[5.292; 6.598] per participant). The largest portion of losses were due to RWP estimated from a sample of 159 individuals that were either unemployed or early retired due to vision impairment. The logistic regression model, controlling for visual acuity and visual ability, showed that individuals within the age range of 17-39 years, 12 or more years of education, no comorbidities and reporting higher HRQoL had higher probability of employment.

Our rate employment of 28% was smaller than expected when we compared with the 38% employment rate for people with disabilities reported by Eurostat in 2015 and even smaller when compared with the 68% employment rate for people without disabilities (64% in Portugal) (177, 240). However, the report of Eurostat is unspecific about the type of disability. In a Portuguese report considering only participants from the Portuguese blind association (ACAPO) the percentage of employed participants was 33% which is in line with our findings (241). Our employment results are also in line with results reported by others. Rein found a gap of 41% in employment rates between people with impaired vision and the general population (136). In our sample the gap between people with impaired vision and the employment rates of the active population in the country was 36%.

Several studies, adopting a top-down approach, reported RWP as the major contributor to productivity costs (136, 139). Through our bottom-up approach RWP also emerged as the main driver of productivity costs. Similar to our results, Cruess and colleagues, which adopted a top- down approach, also reported absenteeism costs that were substantial lower than RWP costs (140).

Younger and more educated people with impaired vision are more likely to be employed. We found that the probability of being employed was higher in the age group 17-39 years. These results are in line with the findings of previous studies showing that job loss occurs more frequently at older ages and that the duration of unemployment is longer for older individuals (156, 242). In our sample individuals with education of 12 years or more had higher odds of being employed compared with less educated individuals which is consistent with the findings of other studies (154, 243). Therefore, we speculate that education is an important modifiable factor that can increase the level of participation in the labour market amongst people with vision impairment.

The severity of vision impairment, as measured by visual acuity, and the proportion of individuals with other comorbidities was higher in the non-working group. Others found that more severe impairment and the presence of comorbidities were

associated with a lower probability of employment (154, 243, 244). However, in our study, in the logistic regression analysis only the presence of comorbidities showed statistically significant effect in employment status. Visual acuity had an odds ratio of 0.35 (p-value=0.163), which points to a tendency to individuals with lower visual acuity (higher values in logMAR scale) having lower chances of participation in the labour market. While this effect was not significant, the trend is similar to the previous findings.

We included patient-reported measures in our regression analysis to explain the employment status. The EQ-5D used to assess health-related quality of life includes questions about anxiety and depression and pain and discomfort which are known factors associated with the ability to work (245-247). Visual ability measured by the AI allowed us to incorporate also difficulties performing vision related tasks (168). Whilst the effect of visual ability was not statistically significant we found that EQ5D utility score was a strong predictor of employment and therefore of RWP. This possibility was also being raised in other studies who tried to predict absenteeism and presenteeism using EQ5D (248). Given this strong effect of the EQ5D utility score we performed the simulation with the equations given in Appendix 9 and obtained the scenarios shown in Figure 18. The results of the scenarios show that by increasing the perceived HRQoL the levels of participation can change for the same level of vision impairment. We cannot infer causality from this association and, indeed, the effect of HRQoL on employment may run in both directions: higher HRQoL may improve the chance of employment and higher employment may improve HRQoL. Regardless of causality, the benefits of enabling those with low vision to participate in the workforce are likely to lead to both productivity and health benefits. These findings should be taken in consideration when planning initiatives to promote inclusion of people with impaired vision in the labour market. This also shows how important is to monitor and prevent other health related aspects of people with impaired vision.

We must acknowledge that the relationship between HRQoL and productivity losses is a controversial topic in economic evaluation (243, 249). Some authors consider that taking productivity loss as costs and quality of life as an outcome can be double counting because these two measures may capture the same reality (158, 250). Whilst this issue is important when interpreting estimates of productivity losses incorporated in cost-effectiveness studies our study was not designed to provide contributions for this discussion and it is addressed in detail elsewhere (251-253).

A possible limitation of our study is lack of indicators about presenteeism which is defined as reduced productivity at work. A recent systematic review of the economic

burden of visual impairment found that in 5 studies that estimated indirect costs and productivity losses only 1 included presenteeism (144). There is no consensus on the best instruments to reliably measure presenteeism and empirical research showed that the use of different instruments can lead to large differences in outcomes (235, 254). Accordingly to the references used by Cruess (140) if we assumed an estimated of 15.7% for reduced productivity at work our estimate of productivity costs (considering absenteeism and reduction in workforce participation) would increase in less than 8%, so the impact of presenteeism in our sample may not be substantial.

Vision impairment can cause disability and that can lead to significant productivity losses. In our sample the main driver of these losses was reduced work participation. The probability of having impaired vision and being employed was associated with modifiable factors such as: education, HRQoL and comorbidities. We speculate that promoting education and health amongst persons with impaired vision through effective rehabilitation programs may be crucial to increase their access to the labour market, which can lead to productivity and health benefits. Our results provide information that can be used by decision makers to reduce the burden of vision loss at individual and societal levels.

5.2 - Additional research findings

Material in this Chapter has been published Acta Ophthalmologica and BMC Ophthalmology.

5.2.1 - Visual and health outcomes, measured with the activity inventory and the EQ5D, in visual impairment

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Visual and health outcomes, measured with the activity inventory and the EQ-5D, in visual impairment

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Abstract

Purpose: Generic instruments to assess health utilities can be used to express the burden of health problems in widely used indexes. That is in contrast with what can be obtained with condition-specific instruments, outcomes are very specific and difficult to compare across conditions. The purpose of this study was to assess health and visual outcomes and its determinants in patients with visual impairment (VI) using the EQ-5D-3L and the Activity-inventory (AI).

Methods: Participants were recruited in different hospitals during the PCVIP-study. A total of 134 patients with acuity 0.30 logMAR or less in the better eye were interviewed. The AI includes 46 goals split between three objectives: social functioning, recreation and daily living, was used to measure visual ability. The EQ-5D consists of five questions covering one domain each and was used to provide a measure of health states. Responses to each domain were combined to produce a single individual index.

Results: The AI and the EQ-5D-3L showed enough discriminatory power between VI levels ($p<.001$) and their results were strongly correlated $r(134)=.825$, ($p<.001$). Explanatory factors for visual ability were level of VI in better eye, age and gender, $R2=.43$, ($p<.001$). Explanatory factors for the EQ-5D-3L were level of VI in the better eye, comorbidities and gender, $R2=.36$, ($p<.001$).

Conclusions: Our results showed that the EQ-5D-3L is useful when characterizing the burden of VI and to compute, when necessary, quality-adjusted-life-years (QALY) changes due to VI. However, is important to consider that the EQ-5D-3L uses a coarse response scale, assesses a limited spectrum of domains and is influenced by comorbidities. This might limit its responsiveness to small changes in visual ability.

Introduction

Patient reported outcome measures are fundamental for evaluation of health technologies or interventions (255). To perform a complete assessment of the benefits of a health intervention, it is necessary to provide evidence of the effect of intervention on patients' health status and/or health related quality of life. The type of instrument used to measure outcomes of health interventions must be designed to serve the specific requirements of the study question or the proposed application. Instruments to assess patient reported outcome measures can be divided into several categories, however, the divisions should not be regarded as rigid or mutually exclusive (256). The present study compares the performance of two categories of these measures, health utility and functional ability measures, in visually impaired patients.

Health utility measures express preferences or values attached to individual health states as a single number. Instruments commonly used to collect data on utilities include the EuroQol-EQ-5D (227, 257-259), the SF-6D (164, 259), the Geriatric Depression Scale (260) and other rating scale questionnaires. Health utilities typically are estimated from time trade-off (261) or standard gamble methods (262), or from one of several stated-preference methods (e.g., discrete choice (263), pairwise comparison (264), best-worst scaling (265), or iterative bidding games (266)). Health utilities are used to provide estimates of the overall value of health states to the individual and/or to society and are used in cost-utility analyses.

To simplify data collection, all likely combinations of ratings of the five items in the EQ-5D-3L, each of which represents a different health state, have been mapped to community-based health utilities by a representative sample of the community population using a time trade-off method (170). Therefore, the EQ-5D-3L can be administered as a rating scale questionnaire and a utility tariff, corresponding to the pattern of responses to the 5 items, can be looked up in a table (or estimated from an algorithm). The assigned utility values then can be used to estimate quality-adjusted life-years (QALYs) (267). However, it often has been suggested that the EQ-5D-3L can have unreliable and unresponsive outcomes in the case of visual disorders (162, 268).

The intent of health utilities is to have the scale referring only to the value of health states and not be disease-specific. The EQ-5D-3L, like most instruments, do not include items responsive to the effects of vision disorders when assessing health states. In the past, there have been attempts to develop separate vision-related utilities (45), but that

approach has been criticized because it overestimates the utility of vision relative to that of overall health (269, 270).

Condition-specific (individualised) health state assessment instruments have item content targeted to specific symptoms and/or quality of life consequences, with many allowing respondents to select relevant items and/or rate the importance of each item (256). Self-report instruments used to assess visual functioning include the National Eye Institute Visual Functioning Questionnaire (NEI-VFQ) (271), the Impact of Vision Impairment Questionnaire (IVI) (272), and the Activity Inventory (AI) (166-168). In our study the AI was adopted to estimate person measures, mostly because it has been developed and used specifically for individuals with low vision and we had access to the item calibration file (8, 166, 167). The advantage of using an instrument calibrated with hundreds of low vision individuals is that the interaction between person's "ability" and item's "difficulty" can be modulated. A strength of such individualised self-report instruments is that they address the concerns of individual patients rather than impose community standards that may not be well-informed or well-targeted to the patient population of interest. Although sometimes criticized by strict methodologists, in the case of assessing the effect of visual impairment or the impact of low vision rehabilitation, it often is necessary to administer self-report visual functioning assessment instruments by interview because of the patients' vision limitations.

Given the high and growing prevalence and incidence of visual impairments from age-related eye diseases, policy makers need evidence about the burden of visual impairment in order to develop effective and inclusive public health strategies (273). For example, with the aging of the population and elevated risks of adverse health events, it is necessary to know the impact of vision impairment on health states and the cost-utility of low vision rehabilitation. In many European countries, Portugal in particular, these two topics remain poorly studied. A recent exhaustive critical review of the relevant literature concluded that more cost-effectiveness studies are necessary in order to understand the effectiveness of current low vision rehabilitation practices (273). Without evidence of cost-effectiveness of interventions intended to tackle the burden of visual impairment, two scenarios are likely: i) decision makers will reduce the availability of resources for this purpose or ii) allocated resources might be poorly managed due to undefined priorities. Therefore, for the correct evaluation of the burden of visual impairment it would be desirable to use generic instruments to make estimated patient preferences directly comparable to other health state preferences.

The use of generic instruments to access health preferences of visually impaired people remains uncommon, but seems necessary. For example, Malkin and colleagues recently conducted one of the few studies to use a generic health state instrument, the EQ-5D-3L, to assess both the health utility of visual impairment and the impact of low vision rehabilitation (162). The authors concluded that the EQ-5D-3L was unresponsive to low vision rehabilitation, a conclusion supported by the results summarized by Tosh and colleagues who concluded that the EQ-5D-3L might have limited ability to distinguish between groups of patients, stratified by acuity, suffering from age-related macular degeneration or diabetic retinopathy (162, 268). These studies demonstrate that the use of health utility measures with visually impaired patients requires further investigation, in particular to determine which factors other than visual acuity can influence health utilities in visually impaired people.

The purpose of our study was to investigate if the EQ-5D-3L and the AI have equivalent ability to discriminate between visual impairment categories and which factors can affect those measures. We hypothesize that generic (EQ-5D-3L) and condition-specific (AI) instruments have different abilities to discriminate between levels of visual and that each instrument is influenced by a different set of visual and non-visual factors.

METHODS

Participant recruitment and data collection

Participants were recruited in three public hospitals as a part of a study of prevalence and costs of visual impairment in Portugal (PCVIP-study). Outpatients at these hospitals with visual acuity, measured with latest refractive correction prescribed, in the better seeing eye of 0.30 logMAR or lower were invited to take part in face-to-face interviews. Visual acuity was assessed using an internally illuminated ETDRS chart (Lighthouse International, NY, USA) at 4, 2 or 1m according with the severity of their vision loss. The room lights where extinguished during measurements. Letter by letter scoring was employed to specify final measured acuity (274).

During interviews participants were asked about 16 systemic health problems detailed in Appendix 6 that are consistent with those assessed in other studies (96, 275). Demographic information and other descriptive information for our sample of 134 participants is summarized in Table 31. All questionnaires were administered during the interview and responses recorded in our digital platform for further extraction and analysis.

The present study was conducted in accordance with the tenets of the Declaration of Helsinki, reviewed and approved by the ethical commission for Life Sciences and Health of the University of Minho and hospitals ethics committees. Written informed consent was obtained from all participants.

Functional reserve given by the Activity Inventory

The Activity Inventory (AI) is an adaptive visual function questionnaire designed to provide an individualized assessment of difficulties of a visually impaired respondent when performing valued activities. The AI consists of a hierarchal structure in which specific cognitive and motor vision-dependent tasks (e.g., pouring or mixing without spilling) underlie more global goals (e.g., preparing meals). Disabilities, or activity limitations according to the World Health Organization's International Classification of Functioning, occur when an individual reports abnormal difficulties in achieving important goals (165). Difficulties achieving a goal are said to depend on the difficulty experienced in the tasks that underlie each goal (166). The investigators translated the AI into Portuguese (213). In the Portuguese version 46 goals divided among three objectives (social functioning, recreation and daily living) were used. Respondents first rated the importance of each goal with four possible responses ranging from "not important" to "very important". Goals rated "not important" were skipped, for goals rated "slightly important" or above participants were asked to rate the goal's difficulty on a five-point scale ranging from "not difficult" to "impossible to do". The "difficulty" responses were Rasch analysed to produce a continuous measure of visual ability given by the variable *'person measure'* (Program Winsteps, v3.9). We use the term '*visual ability*' to define the overall ability to perform activities that depend on vision. Visual ability is likely to be affected by other conditions apart from visual impairment such are chronic pain, fatigue or depression (161).

Utility Values given by the EQ-5D-3L

The EQ-5D-3L is a generic instrument for preference-based measures of health and is expected to provide a measure of health status (257, 276). The EQ-5D-3L consists of five questions, each describing a different health state domain. The five domains are mobility (D1), self-care (D2), usual activities (D3), pain or discomfort (D4) and anxiety or depression (D5). Difficulties in each domain are classified using a 3-point scale: 1= "no problems", 2= "some problems" and 3= "extreme problems or unable". A respondent's overall health state is then defined by a vector representing the level for each domain; the combination of answers to 5 domains can generate 243 (3^5) unique vectors

representing overall heath states. For example, the heath state vector [11111] would be generated by someone who does not have difficulty in any domain, whilst [32211] would be the responses of someone unable to move, some problems in self-care and usual activities and no problems in the last two domains. Each response vector is then transformed to a health utility using the EQ-5D-3L index for which 0 corresponds to a state over which immediate death is preferred and 1 corresponds to the state of "perfect health". A negative value would correspond to a health state "worse than dead". Utility index values used here were obtained from Ferreira and colleagues who published community tariffs for the EQ-5D-3L in the Portuguese population (170). During the questionnaire administration, clear instructions were given to consider difficulties associated with visual impairment.

Categories of visual impairment

Visual impairment was categorized according to the guidelines of the International Council of Ophthalmology using visual acuity intervals on a logMAR scale (7). In a logMAR scale, acuity can be calculated by adding the number of letters read considering a score of 0.02 per correct letter. For example, in an ETDRS chart designed to measure distance VA at 4m, the top line corresponds to acuity 1.0 logMAR. Letters can be used to compute acuity using the formula: VA=1.1–0.02xNL, where NL represents the number of letters read (Table 30).

Table 30 - Definition of level of visual impairment used to divide participants into groups

Category Description	**Lower limit (Visual Acuity)**	**Upper limit (Visual Acuity)**	**Category Number**
No visual impairment	0.30 logMAR (0.5 decimal)	-0.30 logMAR	0
Minor VI	0.50 logMAR (0.32 decimal)	0.32 logMAR	1
Moderate VI	1.00 logMAR(0.10 decimal)	0.52 logMAR	2
Severe VI	1.30 logMAR (0.05 decimal)	1.02 logMAR	3
Profound VI/Blind	3.0 logMAR (0.00 decimal)	1.32 logMAR	

Data analysis

Variables were tested for normality using the Kolmogorov-Smirnov test. ANOVA was used for multiple comparisons and t-test was used to compare two distributions when the variables were normally distributed. Kruskal-Wallis or Mann-Whitney U tests were used for comparisons when variables failed normality tests. The null hypothesis

was rejected for alpha values less than 0.05, when necessary Bonferroni correction was applied (0.05/number-of-comparisons). Associations between variables were tested with Pearson correlations when both variables were continuous and Spearman's rank-order correlation when any of the variables was ordinal. Descriptions of correlations ranged from "very weak" (0.0-0.19) to "very strong" (0.8-1) using Swinscow's classifications (277). Vision specific tools for quantifying visual ability and generic utility measures need to be compared with caution. But comparisons have been tried in the past because they are necessary to gather information about the overall impact of vision loss in health (164, 278). To investigate whether final scores of our instruments were associated with the same factors we conducted a regression analysis using as explanatory factors: age, gender, visual impairment level in the better and in the worse eye and number of comorbidities. We included the level of visual impairment in the worse eye because a study from Finger and colleagues in 2013 has shown that this could be relevant to explain reported health states and we wanted to test this in both instruments used (279).

RESULTS

The ratio of male to female participants was 0.97. The median age of participants was 65.5 years (IQR: 55.7-74.2), five participants were less than 18 years old. For minors, when necessary, parents or guardians served as proxies for the interview. The median acuity in the better eye for the sample was 0.54 logMAR (IQR: 0.38-0.85) and was 1.02 logMAR (IQR: 0.64-1.68) for the worse eye, a more detailed summary is given in Table 31.

Table 31 - Demographic characteristics of the participants and descriptive statistics

Variable	N	EQ5Dindex mean [SD]	Visual ability (logits) mean [SD]	VA better (logMAR) median [IQR]	VA worse (logMAR) median [IQR]
Gender					
Male	66 [49%]	0.518 [0.281]	0.45 [2.03]	0.63 [0.31]	1.30 [0.84]
Female	68 [51%]	0.368 [0.322]	-0.09 [1.92]	0.75 [0.58]	1.24 [0.76]
P value	----	0.005	0.11	0.77	0.73
Age (years)					
Below 40	10 [8%]	0.509 [0.297]	0.24 [1.38]	0.81 [0.56]	1.16 [0.78]
41-80	116 [86%]	0.433 [0.321]	0.22 [2.07]	0.69 [0.47]	1.25 [0.81]
Above 80	8 [6%]	0.491 [0.138]	-0.59 [1.02]	0.54 [0.26]	1.68 [0.72]
P value	----	0.69	0.53	0.51	0.20
Level of VI Better Eye					
1	60 [45%]	0.596 [0.281]	1.34 [1.85]	0.37 [0.06]	0.88 [0.63]
2	50 [37%]	0.393 [0.270]	-0.20 [1.29]	0.69 [0.13]	1.27 [0.65]
3	24 [18%]	0.160 [0.220]	-1.96 [1.38]	1.50 [0.52]	2.26 [0.58]
P value	----	<0.001	<0.001	<0.001	<0.001
Level of VI Worse Eye					
1	20 [15%]	0.669 [0.261]	1.85 [1.76]	0.35 [0.04]	0.40 [0.06]
2	46 [34%]	0.511 [0.301]	0.80 [1.63]	0.50 [0.15]	0.76 [0.15]
3	68 [51%]	0.329 [0.282]	-0.74 [1.79]	0.92 [0.55]	1.87 [0.69]
P value	----	<0.001	<0.001	0.001	<0.001
Cause of VI					
DR	54(40)	0.410 [0.309]	-0.26 [1.71]	0.74 [0.47]	1.33 [0.81]
Other RD	30(22%)	0.421 [0.341]	0.57 [2.33]	0.66 [0.35]	1.32 [0.83]
AMD	15(11%)	0.529 [0.296]	0.38 [1.83]	0.50 [0.26]	1.23 [0.74]
Glaucoma	10(7%)	0.310 [0.258]	-0.53 [1.68]	0.66 [0.31]	1.32 [0.88]
Corneal disease	8(6%)	0.490 [0.322]	0.15 [2.23]	0.58 [0.37]	1.25 [0.97]
Cortical/ON	13(10%)	0.495 [0.299]	0.59 [2.27]	1.03 [0.81]	1.16 [0.81]
Cataract	4(3%)	0.719 [0.162]	2.21 [1.21]	0.34 [0.04]	0.69 [0.34]
P value	----	0.22	0.08	0.019	0.56
Number of comorbidities					
0-3	100 [75%]	0.479 [0.294]	0.28 [1.85]	0.68 [0.39]	1.28 [0.76]
3-6	34 [25%]	0.333 [0.334]	-0.13 [2.36]	0.73 [0.65]	1.37 [0.90]
P value	----	0.017	0.30	0.31	0.85

Results of visual ability scores

Rasch analysis of AI difficulty ratings generates a single interval-scaled value for each person, the “person measure”, for which higher values correspond to higher levels of visual ability. The mean visual ability person measure across all participants was 0.17 logit (SD=1.99). Table 31 provides a summary of these results and the distribution of visual ability person measures for different age groups is shown in Figure 19.

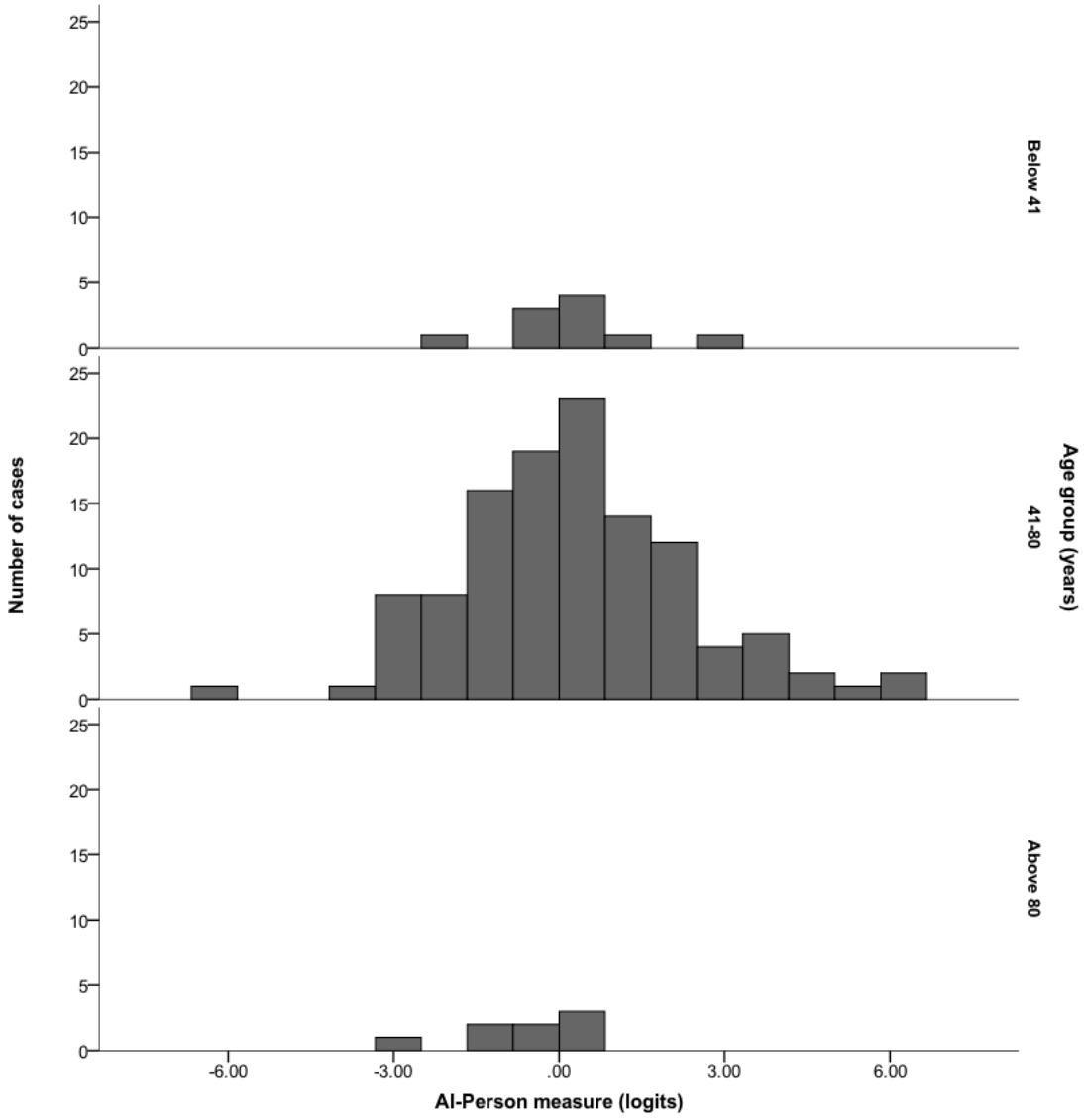

Figure 19 - Histogram showing the distribution of visual ability person measure per age in the all sample

A three-dimensional scatter plot of visual ability person measures as a function of logMAR acuity in the better and in the worse eye is shown in Figure 20. The difference between visual ability person measures for different groups, defined by the visual acuity in the better eye, was statistically significant, $F(2,131)=39.57$, ($p<0.001$; Bonferroni correction applied). Similar results for other factors are summarized in Table 31. For visual impairment groups 1 and 2 the mean difference between visual ability person measures was 1.54 logits ($p<0.001$); for groups 1 and 3 the mean difference was 3.30 logits ($p<0.001$); and for groups 2 and 3 the mean difference was 1.76 logits ($p<0.001$). There was a moderate negative correlation between logMAR acuity in the better seeing eye and visual ability person measures, $r(134)=-0.573$ ($p<0.001$). This result shows that

higher levels of visual impairment given by acuity were associated with lower visual ability person measures.

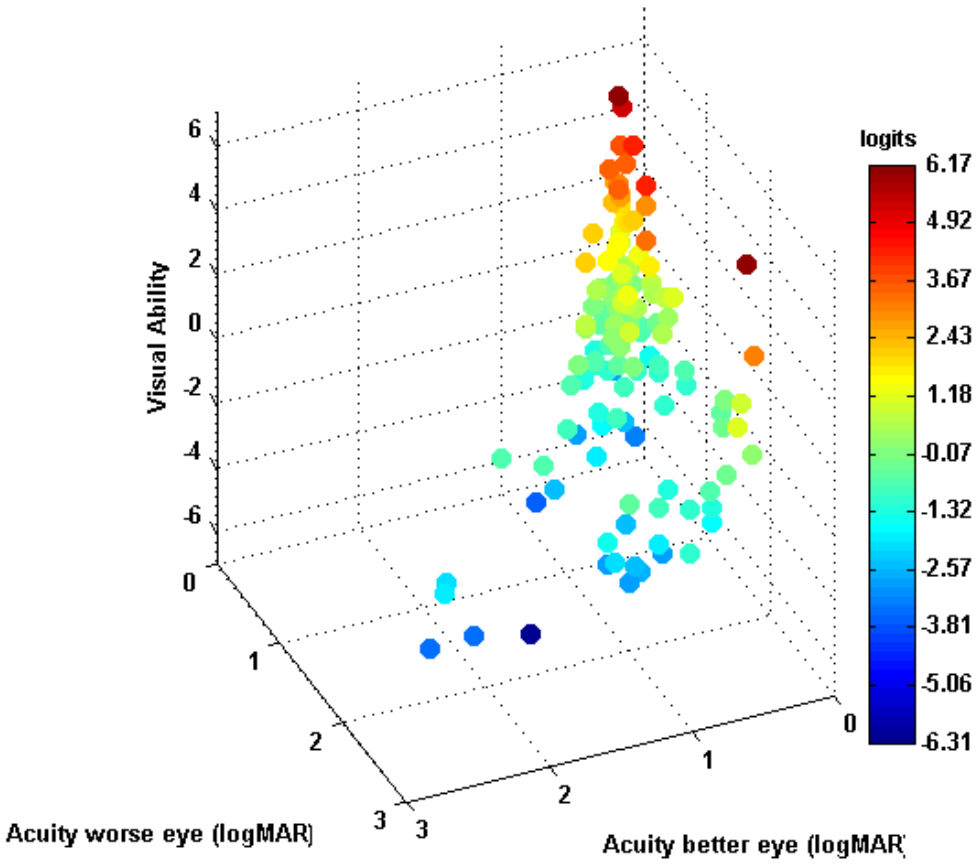

Figure 20 - Scatter plot showing the distribution of visual ability according with acuity in the better and worse eye

Results for health states

The most commonly observed health state vectors for the EQ-5D-3L were [11111] (index of 1.000) and [22222] (index of 0.288), reported by 14 participants each. The 10 most common health state vectors are summarized in Appendix.10 The mean EQ-5D-3L index for the entire sample was 0.442 (SD=0.311), comparisons between groups are given in Table 31. A 3-D scatter plot of the EQ-5D-3L index as a function of logMAR visual acuity in the better eye and the number of comorbidities is shown in Figure 21. The differences between EQ-5D-3L index for different visual impairment groups, based on the acuity of the better eye, tested with ANOVA, was statistically significant, $F(2,131)=24.05$ ($p<0.001$). Post hoc tests revealed that for visual impairment groups 1

and 2 the mean difference was 0.203 (p<0.001), for groups 1 and 3 the mean difference was 0.436 (p<0.001) and the mean difference between groups 2 and 3 was 0.233 (p=0.001). There was a moderate negative correlation between logMAR acuity in the better eye and EQ-5D-3L index, r(134)=-0.506 (p<0.001). Higher values of logMAR (i.e., lower visual acuities) are associated with lower EQ-5D-3L index. A partial correlation between age (controlling for acuity in the better eye) and EQ-5D-3L index also was observed, r(131)=-0.183 (p=0.035). The negative correlation indicates that the index tends to reduce with age.

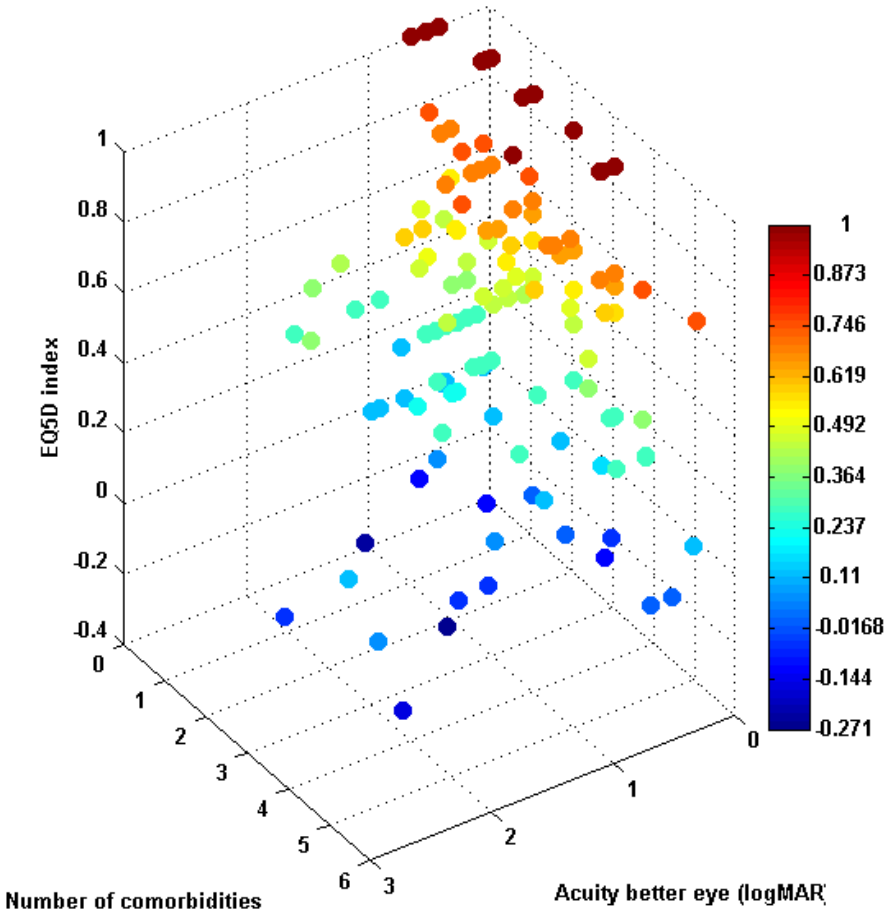

Figure 21 - Scatter plot showing the distribution of EQ5D according with acuity in the better eye and number of comorbidities

Comparison between instruments

We observed a strong correlation between the EQ-5D-3L index and visual ability person measures, r(134)=0.779 (p<0.001).

Factors associated with visual ability person measures

Multiple linear regression analysis showed that gender, age, level of VI in the better eye and in the worse eye are significant independent predictors of visual ability

person measures. Basic descriptive statistics and regression coefficients are summarized in Table 32; the four predictors account for 45% of the variance in visual ability person measures. Those with higher visual acuity in the better eye have higher visual ability. The typical difference between visual impairment groups (stratified by acuity in the better eye) was approximately 1.4 logits (unstandardized beta coefficients in Table 32). Level of visual impairment in the worse eye, does not achieve statistical significance in our model (p=0.053).

Table 32 - Factors associated with visual ability scores (person measures) in a multivariate regression model with forward selection of variables

Predictor	**Un-standardized beta coefficients**	***p* value**	**Standard error**
Intercept	1.978	<0.001	0.256
Gender			
male[a]	---		
female	-0.691	0.009	0.264
Age			
Below 80[a]	---		
Above 80	-1.495	0.010	0.576
VI better eye			
1[a]	---		
2	-1.397	<0.001	0.307
3	-2.940	<0.001	0.442
VI worse eye			
1[a]	---		
2[b]	---		
3	-0.622	0.053	0.318

[a] reference category; [b] result collapsed with the reference category; Excluded variables: comorbidities; Multiple R-squared: 0.45; Adjusted R-squared: 0.43; F(5,128) = 21.1; p-value < 0.001.

Factors associated with EQ-5D-3L index

Multiple linear regression analysis showed that gender, level of VI in the better eye and number of comorbidities are significant independent predictors of EQ-5D-3L results. Basic descriptive statistics and regression coefficients are summarized in Table 33; the 3 predictors account for 36% of the variance in the EQ-5D-3L index. In agreement with the visual ability person measures, those with higher acuity in the better eye had shown higher EQ-5D-3L scores. The difference between sequential groups of VI would be approximately 0.2. Females and those with 4 or more comorbidities have lower EQ-5D-3L scores.

Table 33 - Factors associated with EQ5D in a multivariate regression model with forward selection of variable

Predictor	Un-standardized beta coefficients	*p* value	Standard error
Intercept	0.726	<0.001	0.042
Gender			
male[a]	---		
female	-0.140	0.001	0.043
VI better eye			
1[a]	---		
2	-0.242	<0.001	0.048
3	-0.439	<0.001	0.060
Comorbidity			
0-3[a]	---		
3-6	-0.175	<0.001	0.050

[a] reference category; Excluded variables: age, level of VI worse eye; Multiple R-squared: 0.38; Adjusted R-squared: 0.36; F(4,129) = 20.01; p-value <0.001;

Figure 22 shows response patterns for the EQ-5D-3L domains when the group with 0-3 comorbidities was compared with the group with 4-6 comorbidities; the number of people with “no problems” was reduced in all domains. With 4-6 comorbidities, the number of cases with some problems increased in D1 (mobility) and D4 (pain and discomfort). Also, with 4-6 comorbidities, there was an increased percentage of extreme problem for all but D1. The contrast is particularly visible in D3 (usual activities) and D5 (anxiety and depression).

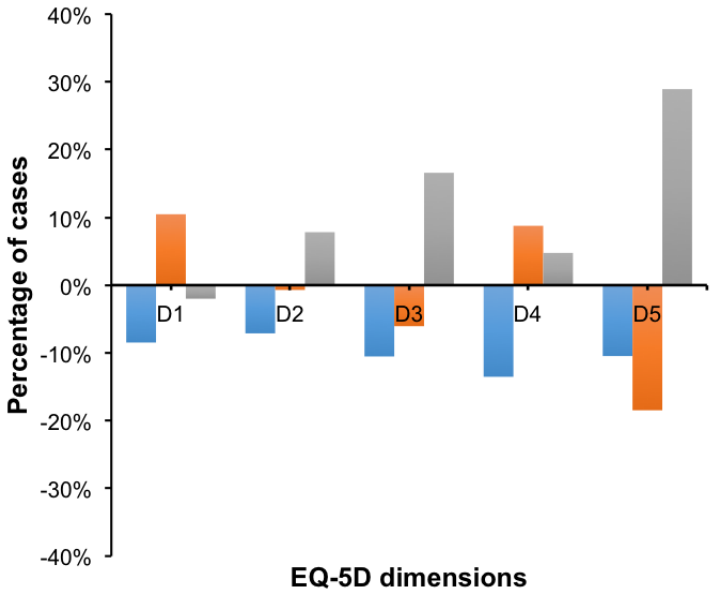

Figure 22 - Change in the percentage of participants reporting no problems (blue bars), some problems (orange bars) or extreme problems (grey bars) when comparing the group with 0– 3 comorbidities with the group 4–6 comorbidities in each of the five domains of the five domains of EQ-5D. D1 (mobility);D2 (self-care); D3 (usual activities);D4 (pain and discomfort); D5 (anxiety and depression)

DISCUSSION

This study was conducted to determine which factors affect patient-reported measures of health utilities, estimated from EQ-5D-3L responses, and of visual ability, estimated from difficulty ratings of activity goals in the activity inventory. Both measures were related positively to visual impairment in the better eye. Regression analysis suggests that EQ-5D-3L utility index is associated with both, visual impairment level in the better eye and the number of reported comorbidities. Visual ability measures are associated with age and visual impairment in the better eye. Both utility and ability measures are associated with gender. These results are in agreement with the initial hypothesis that expected a different set of predictors for each of the two measures. However, contrary to initial expectations, results from both instruments were associated with visual impairment in the better eye.

Our results indicate that the EQ-5D-3L index is responsive to visual impairments. In that sense, our results agree with previous observations by other investigators using the EQ-5D-3L (84, 227) and other health utilities instruments (278, 280). In contrast with our results, a study by Lloyd and colleagues found inconsistent associations of utilities with visual acuity in patients with diabetic retinopathy (281). Lloyd obtained lower scores

for patients with acuity 6/12 to 6/18 than for patients with acuity 6/24 to 6/36. As suggested by Tosh et al., the association of EQ-5D-3L utility indices with visual impairments might depend on the visual disorder studied (268). However, our study included a range of disorder diagnoses and we found no evidence of disorder diagnosis dependence. van Nispen and colleagues have found index results slightly higher than ours in an observational study applying the EQ-5D-3L in mixed causes of VI (84). Differences between our results and van Nispen's might be explained by the distribution of causes of VI, level of acuity in the better eye and age. The main cause of VI in their study was age related macular degeneration and in our study it was diabetic retinopathy. Also, our IQR of acuities was wider and our participants overall were younger compared to the van Nispen et al. study (median age of 65 years for our study vs 78 years for their study). As reported by others, younger subjects with visual impairment might feel, for example, more often anxious or depressed (227, 282). As shown in Appendix 10, 19 of our participants reported "severe depression or anxiety" and that was never reported in the van Nispen et al. study's top ten health states. Another additional explanation for the difference between studies is that lower EQ-5D-3L utility indices are expected in Portugal than in the Netherlands because of differences in community calibrations. Ferreira and colleagues found that there is discrepancy between the EQ-5D-3L index in Portugal and other countries. Ferreira found mean absolute differences ranging from 0.090, compared with Spain, to 0.251, compared with the USA (170).

Gender and the numbers of comorbidities were predictors of the EQ-5D-3L index. The effect of gender that we found in our multiple regression is not commonly observed; however, Langelaan et al. did report significance of gender (227) and that is in line with what has been found in the general population in some countries (283). Comorbidities also had an effect in the EQ-5D-3L; although, during the questionnaire administration clear instructions were given to consider difficulties caused only by VI. Generic questionnaires use broad questions and they are likely to capture effects of other health problems. Some studies have shown that people after stroke tend to report lower EQ-5D-3L scores than people with VI (227). In our case, sometimes these two conditions (VI and stroke) were present in the same participant. As shown in Figure 22, there are noticeable changes in response patterns when comparing people with 4 or more comorbidities with people with 3 or less. The lack of control for type and number of comorbidities can be a problem when applying the EQ-5D-3L. Vision impairment has the potential to influence EQ-5D-3L responses only to 4 of the 5 domains: anxiety-depression, mobility, self-care, and usual activities. Given the coarseness of the response scale, it is likely that vision impairment must be strong to affect the response.

Effects of co-morbidities combine with visual impairment effects to produce the final response.

In agreement with previous studies utility results were independent of the cause of VI and age (84, 278, 280). However, we observed a partial correlation (controlling to acuity in the better eye) between EQ-5D-3L index and age that pointed to some effect of age in this index. Langelaan and colleagues reported lower scores for people less than 41 years compared with people aged 41 years or older. They attributed their result to problems in social inclusion faced by young people with VI such as finding a job (227) . Contrary to Langelann's explanation, we consider plausible that lower scores with increasing age would be due to unemployment or early retirement that increase difficulties in dealing with vision loss (284, 285). Our results indicate that the EQ-5D-3L is an instrument that can be used to assess the impact of VI and to compute other important measures such as quality-adjusted life-years (QALY). However, its application requires caution because visual impairment can affect domains that are not currently included in the questionnaire such as sleep quality or concentration (286, 287).

Results of the Activity Inventory provide a comprehensive assessment of the impact of VI. Our results for the AI are in agreement with what other authors found for patients with VI due to various causes (8, 288) or VI caused by specific eye diseases such as diabetic retinopathy (289). The effect of age on visual ability obtained with the AI has been found before and has been explained by the overall physical functioning decline explained by aging (8). In addition, the sensitivity of the AI to the effect of VI in the worse eye is a further explanation why lower visual ability scores were obtained in the older group. Vision in the worse eye of participants with 81 years or older was typically very poor, range 0.8-2.7 logMAR, whilst for the other age groups was slightly higher, range 0.32-2.7 logMAR. It is understandable that when vision in one eye is reduced the visual field tends to be also compromised; severe VI in the second eye is likely to increase activity limitations such as mobility due to constriction of the visual field (279). This effect seems to be captured by our results because a detrimental effect of the level of VI in the worse eye in visual ability was only observed when VI in the worse eye was 3 (severe VI or blindness).

We acknowledge that a higher number of participants would have been ideal to have, for example, more subjects in the group with 81 years or more. Another advantage of a bigger sample would be a more detailed analysis by type of eye disease and type of comorbidity. A limitation that might reduce our explanatory power is that factors associated with scores do not follow a rectangular distribution.

To conclude, our results show that the EQ-5D-3L is useful when characterizing the burden of VI and, when necessary, to compute QALY associated with visual impairment. Given the coarseness of the response scale of the EQ-5D-3L, the limited spectrum of domains assessed (286) and the influence of comorbidities it might be of limited use in vision rehabilitation (162). Further studies are necessary to investigate if the new versions of the instrument are able to improve these limitations.

5.2.2 - Predicting participation of people with impaired vision in epidemiological studies

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Predicting participation of people with impaired vision in epidemiological studies

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Abstract

Purpose: The characteristics of the target group and the design of an epidemiologic study, in particular the recruiting methods, can influence participation. The aim of this study was to investigate participation rates and its determinants in epidemiologic studies involving participants with impaired vision.

Methods: Participants were recruited in the context of a study of prevalence and costs of visual impairment in Portugal (PCVIP-study). Participants were recruited from 4 Portuguese public hospitals. Inclusion criteria were: acuity in the better eye from 0.5 decimal (0.30logMAR) or worse and/or visual field of less than 20 degrees. Recruitment involved sending invitation letters and follow-up phone calls. A multiple logistic regression model was used to assess determinants of participation. The J48 classifier, chi-square and Fisher's exact tests were applied to investigate the possible differences between subjects in our sample.

Results: Individual cases were divided into 3 groups: immediate, late and non-participants. A participation rate of 20% was obtained (15% immediate, 5% late). Factors positively associated with participation included years of education, annual hospital attendance, and intermediate visual acuity. Females and greater distance to the hospital were inversely associated with participation.

Conclusion: In our study, a letter followed by a phone call was efficient to recruit a significant number of participants from a larger group of people with impaired vision. However, the improvement in participation observed after the phone call might not be cost-effective. People with low levels of education and women were more difficult to recruit. These findings need to be considered to avoid studies whose results are biased by gender or socio-economic inequalities of their participants. Young subjects and those at intermediate stages of vision impairment, or equivalent conditions, may need more persuasion than other profiles.

Introduction

Epidemiologic studies involve collecting data from large number of individuals. However, participation rates in such studies, particularly in industrialised countries, have been falling in the past 3 or 4 decades. A study in Finland showed a decline in response rates from 84% (men) and 85% (women) in 1978 to 59% (men) and 71% (women) in 2002 (290). High participation is necessary to ensure, for example, that the participating group is a representative sample of the population. When recruiting fails, statistical power of the results is reduced and conclusions may be distorted (291-294). In order to produce reliable outcomes, researchers need to consider possible problems arising during the recruitment process and, if possible, control for factors that lead to reduced participation.

During recruitment general and study-specific challenges arise according with the topic and the target population. Some studies have shown that participation rates are influenced by: education (participation increasing with the level of education) (295-297) gender (women tend to participate more than men) (298-300) and marital status (married people participating more than others) (301). Another factor that has been found to influence participation is general health, as given by the index of comorbidities (297). There are other aspects such as age in which results are less consistent, with some studies showing that older people are more likely to participate (298, 299), whilst others found higher participation rates among young people (295). Less commonly reported determinants include, for example, ethnicity. In a study by Patel et al. black, asian and other ethnic minorities were less likely to participate (297). However, in addition to the characteristics of the target group, recruiting strategies can also influence rates of participation.

Previous studies have shown that researchers, when contacting prospective participants, must sound trustworthy and must take into account the motivations of the subject. Slegers and Glass recommend the use of public phone numbers and clear references stating that the study is being carried out by a public institution (when this is the case), in order to increase credibility (302). They also recommend emphasizing that others invited have already responded to the study call and to provide open, clear and honest information from the onset (e.g. regarding monetary compensation or possible expenses). Personalised letters and reply paid envelopes are also known to improve response rates (303). Other researchers investigated the primary reasons to take part in epidemiologic studies and concluded that participation is, amongst others, driven by moral reasons (302, 304). In contrast, the actual effort required to participate has been identified has a barrier. Participation rates are expected to have a negative correlation

with the amount of effort that participation requires (305). The findings mentioned so far have been reported for studies in general; however, there is a lack of information about the profile of people with eye diseases and/or vision impairment (VI) who participate in epidemiological studies. Although, there is one study by Rahi et al. which investigated the engagement of families with children with VI (306). However, this group was more interested in health service barriers for parents with children with VI (306).

Studies involving directly people with VI have unique characteristics because those invited are often elderly and totally or partially dependent on help to complete daily activities such as travelling to study sites. This makes participation more unpredictable than for many of the studies referred. The purpose of the project from where this study originates was to determine the causes of vision impairment amongst patients attending outpatient eye clinics. In parallel we also wanted to conduct a cross-sectional study about the impact of VI and other clinical and social aspects (212, 237, 307, 308).

Our goal with this study was to determine the probability of participation as a function of personal characteristics, including severity of vision loss. We conducted a detailed investigation to distinguish between those who accepted the invitation to take part immediately from those who needed further contact before agreeing to participate. According to the “continuum of resistance” model, the more contacts a subject requires in order to take part in a study, the more similarities he/she shares with non-participants (305, 309). The participation model was tested in our sample by comparing those that agreed to participate with non-participants.

We hypothesized that: i) the lower the acuity is the less likely participation is; ii) participation is independent of the cause of VI; iii) participation is affected by the distance residence-hospital; iv) education increases participation; v) age and gender affect participation; vi) annual hospital attendance increases participation.

To our knowledge this is the first study to investigate participation rates and its determinants in research involving people with VI. By studying participant’s profiles, we hope to provide a significant contribution to the scientific community when planning studies involving people with VI and similar conditions.

Methods

Study design

The prevalence and costs of visual impairment in Portugal (PCVIP-study) was a hospital-based study whose aim was to determine, prevalence, causes and costs of VI in Portugal. The study gathered demographic, clinical, and economic information of

people with VI. Participants for this report were recruited at 4 Portuguese public hospitals; patients with VI attending outpatient appointments at each of the hospitals for a period of 12 months were invited to participate in the study. The inclusion criteria were: patients with visual acuity (VA) in the better eye of 0.5 decimal (0.30logMAR) or worse and/or visual field less than 20 degrees. Cases were entered in a database by qualified and trained clinical staff. The database is online at www.pcdvp.org. The study protocol required inviting patients to attend an in-hospital appointment with the research team for face-to-face interviews and additional visual measurements. The study was designed considering the recommendations of the Vancouver Economic Burden of Vision Loss Group (158). Basic demographic information was collected from administrative databases at the hospital. Information included: subject´s initials, date-of-birth, gender, and place of residence (*"concelho"*, in Portuguese, equivalent to district in many countries).

Participants

Letters were posted using the hospital mail service, the logo of the hospital was printed on the envelope and letters were sent directly to the patients' address. All documents were printed in font Arial- 16 point. The mail envelope included a letter of invitation signed by a physician from the local hospital (1 page), an information booklet (3 pages), a consent form (1 page) and a reply- paid envelope addressed to Escola Nacional de Saúde Publica, Lisboa (National School of Public Health, Lisbon). Information was printed on both sides of the paper; consent forms were printed on the reverse side of the invitation letter. In addition to information about investigators, institutions, contact details and clinicians involved in the study the letter contained a clear and isolated sentence (in Portuguese) with the instruction: *"If you agree to take part in this study, please tick the boxes in the flipside of this sheet, sign at the bottom of the page and provide a valid contact number for us to book your appointment at the hospital".*

If a response was not received within 2 weeks, a follow-up phone call was made. Calls were made by an experienced hospital staff member trained and informed about the study with instructions to ask the following questions: i) *did you receive our letter?* ii) *If yes, can I provide any further information about the study and the letter?* iii) *Would you be interested in taking part in this study?* If the person declined the invitation to participate, they were asked questions about: 1) years of education; 2) marital status; 3) annual hospital attendance.

For positive respondents, an appointment was booked at the hospital where they normally receive eye care and the same information was obtained. Those that agreed to

take part in the study are defined as “participants” and those that declined after all attempts are defined as “non-participants”. Those that dropped out after initially agreeing were not included in either of these categories. Participants were divided into 2 sub-grougps: “immediate participants” - those who sent the reply paid envelope with the consent form without being contacted by phone, and “late participants” - those who agreed to take part in the study only after they were contacted by telephone.

Data analysis

A database was built with information about: age, gender, distance between residence and hospital where the participant was recruited (DISTH), years of education (EDU), marital status (MST), visual acuity in the better eye (VA), annual hospital attendance (AHATTEND), cause of vision impairment (CAUSE-VI), Charlson comorbidities index (CCI). Information about causes of vision impairment and comorbidities to compute CCI was retrieved from medical records. The CCI measures to which extent an individual is affected by comorbidities (310).

Univariate differences in participation rates according to the independent categorical variables were assessed using chi-square tests. DISTH, EDU and CCI are, unless otherwise stated, continuous variables and the remainder are categorical. Multiple logistic regression (R data analysis software, v3.2.4 for Windows) was used to determine the effect of independent variables in participation rates. The final model was built upon a database with 600 individuals and the fit quality was firstly measured also within such database. That is, the sample was both the training data and the testing data. In addition, an internal validation of this model was performed, a 10-fold cross-validation using the logistic classifier of Weka 3.8.

Results

For the current study a group of 2130 individuals were contacted by letter. Of the initial 2130 letters sent, 31 were returned to sender and 349 individuals agreed to participate immediately (17% of 2099). Of these, 49 individuals eventually dropped out of the study for health reasons or transportation difficulties (the study only covered travel expenses up to 15 euro), this resulted in 300 immediate participants (15% of 2050).

Phone calls were made to 1750 non-respondents in order to invite them to participate; 89 were unreachable by phone. From the 1661 contacted by telephone 84 (5%) agreed to take part. Therefore, the final number of participants was 384 (20%) out of 1961 that could be successful reached by letter and/or phone call.

In total, 600 individuals (260 females or 43%) with a mean age of 66 years (SD=16.7) were included in this sample. In our analysis 325 (54%) were participants and 275 (46%) were non-participants. Non-participants analysed are a random sample of the total (1577) selected from successive cases in our list with all the required information. From the 384 participants only 325 were included in this report because the remaining 59 were waiting for the interview.

The median CCI for the entire sample was 0.6 (IQR=1.8), amongst participants was 0.8 (IQR=1.75), for non-participants was 0.5 (IQR=1.5); this difference was not statistically significant (Mann-Whitney, U=1110, p=0.45).

The median EDU in years for the complete sample was 4 (IQR=3), for participants was 4 (IQR=5), for non-participants was 4 years (IQR=1); this difference was statistically significant (Mann-Whitney, U=63752, p-value < 0.001).The number of years of education can be considered low but is expected for the age and geographical location of the participants (197).

The median DISTH (in kilometres) for the complete sample was 9.6km (IQR=24.2), for participants was 1km (IQR=15.1) and for non-participants was 19.4 km (IQR=38.7); this difference was statistically significant (Mann-Whitney, U=24416, p<0.001). Other socio-demographic and VI-related data are summarized in Table 34 and Table 35.

Table 34 - Summary of the distribution of 600 subjects included in the analysis. Among 600, 325 are participants (immediate or late) and 275 non-participants randomly selected from 1577 total non-participants

Characteristic	n (%)	Participation YES/NO	Participation (%)	p-value (χ2)
Gender				
Male	339 (56.6)	225/114	66.4	<0.001
Female	261 (43.4)	100/161	38.3	
Age group				
<20 yrs	14 (2.3)	12/2	85.7	0.00535
20 to <30 yrs	8 (1.3)	6/2	75.0	
30 to <40 yrs	28 (4.7)	27/1	96.4	
40 to <50 yrs	43 (7.2)	34/9	79.1	
50 to <60 yrs	137 (22.8)	80/57	58.4	
60 to <70 yrs	82 (13.7)	52/30	63.4	
≥ 70 yrs	288 (48.0)	114/174	39.6	
Number of Hospital Appointments per year (AHATTEND)				
Low - AHA (≤ 4/ yr)	173 (28.8)	52/121	30.1	<0.001
Medium - AHA (5 to 9/ yr)	178 (29.7)	86/92	48.3	
High – AHA (≥ 10/ yr)	249 (41.5)	187/62	75.1	
Marital Status (MST)				
Married	261 (43.5)	110/151	42.1	<0.001
Living together	85 (14.2)	76/9	89.4	
Single	82 (13.7)	56/26	68.3	
Widow	131 (21.8)	48/83	36.6	
Divorced	41 (6.8)	35/6	85.4	
Visual Acuity- decimal scale (VA)				
0	42 (7.0)	26/16	61.9	<0.001
0.1	80 (13.3)	51/29	63.8	
0.2	105 (17.5)	43/62	40.9	
0.3	87 (14.5)	35/52	40.2	
0.4	129 (21.5)	63/66	48.8	
0.5	157 (26.2)	107/50	68.1	
Aetiology of visual impairment (CAUSE-VI)				
Adult Macular Degeneration	76 (16.0)	31/45	40.8	0.4336
Diabetic retinopathy	191 (40.1)	110/81	57.6	
Glaucoma	60 (12.6)	26/34	43.3	
Other	149 (31.3)	81/68	54.4	
Multiple or undefined	124			

[a] Participation here refers to any participation (immediate or late)

Table 35 - Summary of the distribution of all cases (n=600) according to participation

Characteristic	n (%)	Participation YES/NO	Participation (%)	p-value (χ^2)
Gender				
Male	183 (75.9)	42 (50)	114 (41.4)	<0.001
Female	58 (24.1)	42 (50)	161 (58.6)	
Age group				
<20 yrs	10 (4.1)	2 (2.4)	2 (0.7)	0.00535
20 to <30 yrs	2 (0.8)	4 (4.8)	2 (0.7)	
30 to <40 yrs	14 (5.8)	13 (15.5)	1 (0.4)	
40 to <50 yrs	27 (11.2)	7 (8.3)	9 (3.3)	
50 to <60 yrs	43 (17.8)	9 (10.7)	30 (10.9)	
60 to <70 yrs	64 (26.6)	16 (19)	57 (20.7)	
≥ 70 yrs	81 (33.7)	33 (39.3)	174 (63.3)	
Number of Hospital Appointments per year (AHATTEND)				
Low - AHA (≤ 4/ yr)	42 (17.4)	10 (11.9)	121 (44)	<0.001
Medium - AHA (5 to 9/ yr)	70 (29)	16 (19)	92 (33.5)	
High – AHA (≥ 10/ yr)	129 (53.6)	58 (69)	62 (22.5)	
Marital Status (MST)				
Married	75 (31.1)	35 (41.7)	151 (54.9)	<0.001
Living together	76 (31.5)	0 (0)	9 (3.3)	
Single	35 (14.5)	21 (25)	26 (9.5)	
Widow	25 (10.4)	23 (27.3)	83 (30.2)	
Divorced	30 (12.4)	5 (6)	6 (2.1)	
Visual Acuity- decimal scale (VA)				
0	18 (7.5)	8 (9.5)	16 (5.8)	<0.001
0.1	28 (11.6)	23 (27.4)	29 (10.5)	
0.2	33 (13.7)	10 (11.9)	62 (22.5)	
0.3	31 (12.9)	4 (4.8)	52 (18.9)	
0.4	47 (19.5)	16 (19)	66 (24)	
0.5	84 (34.8)	23 (27.4)	50 (18.3)	
Aetiology of visual impairment (CAUSE-VI)				
Adult Macular Degeneration	18 (7.5)	13 (15.5)	45 (16.4)	0.4336
Diabetic retinopathy	87 (36.1)	23 (27.4)	81 (29.5)	
Glaucoma	17 (7.1)	9 (10.7)	34 (12.4	
Other	58 (24.1)	23 (27.4)	68 (24.7)	
Multiple or undefined	124			

Factors predicting participation using a logistic regression model

All the results reported in this section compare participants (the group who agreed to take part in the study after an invitation letter **or** letter and a follow-up phone call) with the cases of non-participants (the group of cases that declined after both contacts). We used a diagnostic test for the multicollinearity of predictors, the variance inflation factor, calculated for each predictor. The highest inflation factor was 1.67 for AHATTEND. Which means that AHATTEND was slightly correlated with the other predictors; nevertheless, this value was below the critical value of 2.5 reported in the literature as the tolerable upper limit (311).

In an initial model, with a binary dependent variable that assigned a value of 1 to "participants" and 0 to "non-participants", some variables were independent predictors of participation (see appendix 11).

Amongst categorical predictors we found an effect for gender (males participated more, $p<0.001$), AHATTEND (participation for AHA-high was different from participation for AHA-low, $p <0.001$), MST (co-habiting, single or divorced individuals were more likely to participate than married individuals, $p<0.001$), VA (individuals with VA of 0.2 or 0.3 were less likely to participate than blind individuals, $p<0.001$) and CAUSE-VI (individuals with diabetic retinopathy were more likely to participate than individuals with AMD, $p=0.03$).

Amongst continuous predictors we found statistically significant effects for DISTH (participation reduced with increasing distance, $p <0.001$) and EDU (participation increased with the number of years of education, $p <0.001$).

The initial set of levels for each categorical variable were based on authors' experience (see appendix 11). For the final model, non-significant variables were removed and other levels or categories were defined as summarized in appendix 12. We now give an example to explain the rational. In the initial model, appendix 11**,** we observed that the effect of "Medium-AHA" in participation was not statistically different ($p=0.075$) from the reference category "Low-AHA", therefore we merged these 2 categories and re-classified cases as "AHA-rare", appendix 12. Cases classified as "High-AHA" in the first model were kept separately because there was a statistically significant effect of this category in the model ($p<0.001$). This category was renamed "AHA-frequent" to be consistent with the other category of the variable AHATTEND.

The variance inflation factor was recalculated for each predictor. The highest value obtained was 1.079 for MST, which means that multicollinearity can be ignored. Results for the final model are summarized in Table 36. All independent variables

considered had a significant effect on the dependent variable. The deviance chi-squared goodness of fit test confirmed an excellent fit of the model to the data (p-value= 0.99).

Table 36 - Multivariate logistic regression model used to predict the probability of participation

Variables/Characteristic	Beta coefficient (SE)	Odds Ratio (95% CI)	p-value
Gender			
Female vs. Male	-1.27 (0.24)	0.28 (2.23-5.71)	<0.001
Distance to clinic - km (DISTH)	-0.02 (0.004)	0.98 (1.01-1.03)	<0.001
Education – years (EDU)	0.21 (0.04)	1.23 (1.14-1.33)	<0.001
Annual number of hospital visits (AHATTEND)			
≥ 10 vs. <10	1.64 (0.24)	5.18 (3.24-8.69)	<0.001
Marital Status (MST)			
Living together vs. Others (married, single or widowed)	3.26 (0.46)	26.14 (10.62-64.4)	<0.001
Divorced vs. Others (married, single or widowed)	2.74 (0.56)	15.44 (5.15-46.27)	
Visual acuity (VA)			
Intermediate (0.2-0.4) vs. extreme (0, 0.1 or 0.5)	1.10 (0.23)	3.02 (1.92 -4.74)	<0.001

The likelihood of participation increased if individuals were male, had AHA-frequent, had VA-extreme, if they were co-habiting or were divorced, with more EDU and less DISTH. Formula 1 and Formula 2 summarize these results:

$$\begin{aligned} Linear\ predictor \\ &= -1.71 - 1.27\ (If\ Gender = "female") - 0.02DISTH\ + 0.21EDU \\ &+ 1.64\ (If\ AHATTEND = "frequent") + 3.26\ (If\ MST = "co-habiting") \\ &+ 2.74\ (If\ MST = \text{"divorced"}) \\ &+ 1.1\ (If\ VA = \text{"extreme"}) \end{aligned} \qquad [Formula\ 1]$$

$$Participation\ probability = \frac{e^{linear\ predictor}}{1 + e^{linear\ predictor}} \qquad [Formula\ 2]$$

A 10-fold (10 iterations) cross-validation of the prediction model was performed. Before the iteration the Weka 3.8 software splits the 600 cases into 10 subsamples (60 cases each). For each iteration, during the validation process, each sample was chosen, at random, once as “testing data”. The remainder 9 (540 cases) were used to generate temporary models. The 10 temporary models were then averaged to generated the final

theoretical model which was tested against the real participation results for the 600 cases. The coefficients of the resulting theoretical model were very similar to those summarized in Table 36. The theoretical model classified correctly 484 out of 600 cases, with a weighted average precision of 0.809, a weighted average F-Measure of 0.808 and a weighted average ROC area of 0.872. If taken together the results of the internal validation and the deviance chi-squared goodness of fit, we can say that the model fits the real data accurately.

Table 36 provides the odds ratios (ORs) for study participation. It can be observed that, for example, the odds of a man participating in the study was 3.57 times higher than the odds of a woman.

The model expressed in Formula 1 and Formula 2 was simulated using Matlab (v2014b, Matworks inc.). The simulation allows the visualization of the probability of participation estimated by the model for extreme cases.

According with the final model, the worst profile regarding the probability of participation, was being female attending the hospital 10x or less a year, married, single or widowed, with VA 0.2-0.4. The best profile was being male; attending the hospital 10x or more a year, living in a non-marital partnership, and VA $\leq$0.1 or 0.5. The model was implemented for these two situations as a function of the continuous variables distance residence-hospital (DISTH) and education in years (EDU), the results are shown in Figure 23.

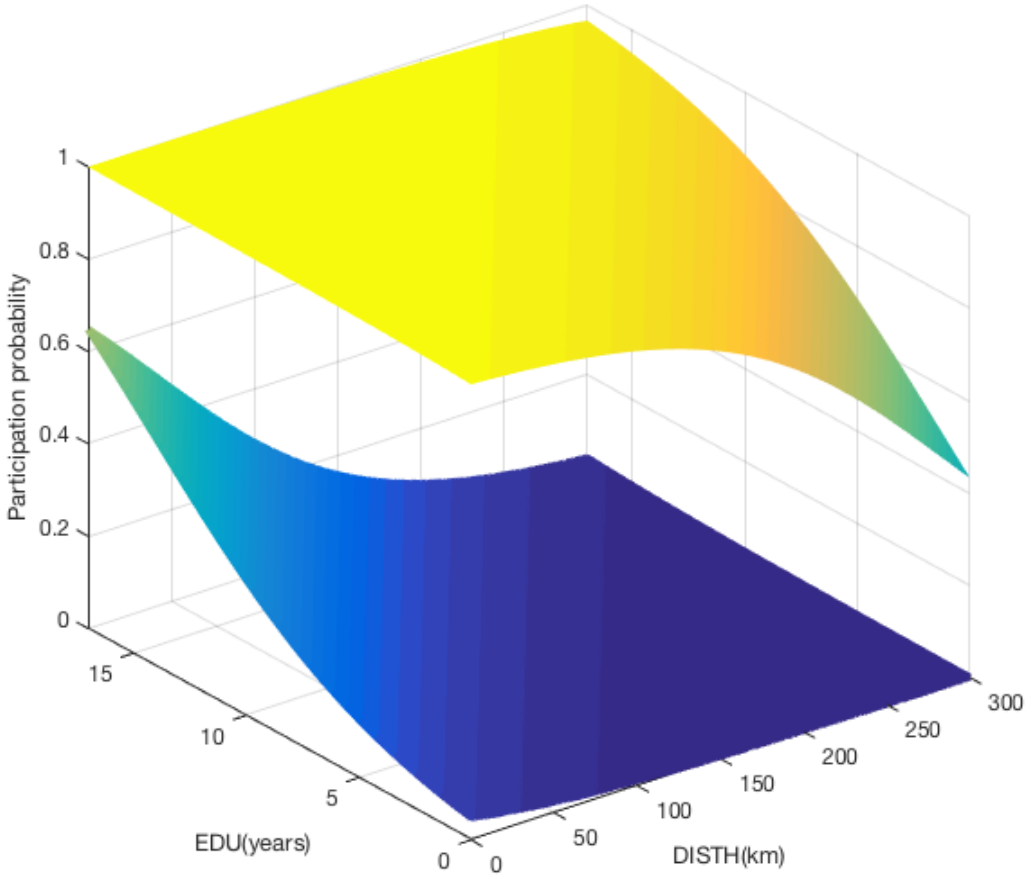

Figure 23 - Variation of the probability of participation predicted by our model according with the continuous variables DISTH and EDU. The two surfaces represent the most favourable and less favourable participation profiles defined according with the categorical variables used. The top yellow surface represents a male, with AHA-frequent, living together, with VA-extreme. The bottom blue surface represents a female, with AHA-rare, married single or widow, with VA-intermediate

In both cases the probability of participation increases when the distance residence-hospital decreases and education increases.

For the best profile and for distances 0-150km, the participation probability reduces slowly. That is, the distance residence-hospital is almost irrelevant within the range 0-150km. For distance values greater than 150km the probability of participation decreases sharply. When living over 150km away from the hospital, distance would be a big barrier for participation, in particular for those with less than 10 years of education.

Amongst individuals with the worst profile for participation, the distance-residence and hospital had little impact for those with less than 10 years of EDU; for EDU greater than 10 years the distance residence-hospital is an important factor for participation only when was below 100km.

The group with the best profile would always have a minimum participation probability of approximately 40% and the worst profile group a maximum participation probability of approximately 60%.

Comparison between immediate participants (Ipar) and late participants (Lpar)

Here we report results of a comparison between two sub-groups of participants (participants = Ipar+Lpar). Ipar = accepted to participate when invited by letter only; Lpar = accepted to participate after letter followed by a phone call.

We found that the percentage of Lpar+Ipar was significantly higher than Ipar only (McNemar's test, $p<0.001$). This shows that the number of participants increased significantly after the follow-up phone call. We investigated if there was a difference between Ipar and Lpar for the demographic aspects summarized in Table 37.

Table 37 - Categories used to analyse differences between immediate (Ipar) and late participants (Lpar) and between late and non-participants (Npar)

AGE	AGE_1 = age less than 40 years AGE_2 = age between 40-69 years AGE_3 = age 70 or more years
AHATTEND	AHA-rare = number of annual hospital appointments less than 10 AHA-frequent = number of annual hospital appointments 10 or more
EDU	EDU_1 = less than 12 years of education EDU_2 = 12 or more years of education
DISTH	$DISTH_1$ = if distance residence-hospital was less than 40 Km $DISTH_2$ = if distance residence-hospital was 40 Km or more
VA	VA-extreme; includes VA of 0.0 or 0.1 or 0.5 VA-intermediate; includes VA of 0.2 or 0.3 or 0.4
MST	1 = Married; 2 = Together; 3 = Single; 4 = Widow; 5 = Divorced
GENDER	1 = Male; 2 = Female

To build the categories defined in Table 37, first we investigated the existence of optimal cut points for the variables using the J48 classifier (Weka 3.8). The resultant decision tree is shown in Figure 24 in which the oval nodes represent random variables and rectangular nodes represent decisions or predictions. This classification model has a weighted average precision of 0.821, a weighted average F-Measure of 0.813 and a weighted average ROC area of 0.792. With this method we can predict that a widow man will be an immediate (Ipar) instead of a late (Lpar) participant. It also predicts that an individual that is single and has VA of 0.1 will be a Lpar instead of an Ipar.

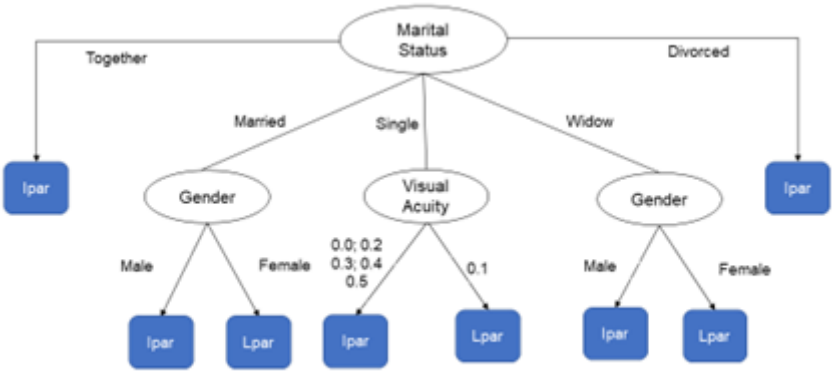

Figure 24 - Classification tree originated by the C4.5/J48 algorithm predicting immediate and late participation

The decision about which demographic aspects would be compared was based on 3 criteria applied according with the sequence presented here: (1) specific hypothesis that the researchers wanted to test, (2) the cut-off points resulting from the J48 classifier analysis and (3) the number of subjects in each category.

The percentage of males in the Ipar was 76% (183 of 241) and in the Lpar was 50% (42 of 84); the distribution by gender was different in both groups (chi-square=20.21, df=1, p<0.001).

The percentage of males in the AGE1 group was 12% (22 of 183) amongst Ipar and 40% (17 of 42) amongst Lpar (chi-square=19.3, df =1, p <0.001, after Bonferroni adjustment). For males with AGE2, the percentage was 56% (102 of 183) amongst Ipar and 31% (13 of 42) amongst Lpar (chi-square=7.3, df=1, p =0.006, after Bonferroni adjustment).

The percentage of participants with AHA-rare within the group of those who are males and AGE2 was 46% (47 of 102) amongst Ipar and 15% (2 of 13) amongst Lpar (Fisher´s exact test, p=0.04).

The percentage of participants with EDU1 within the group of those who are females, AGE2 and AHA-frequent was 95% (18 of 19) amongst Ipar and 60% (6 of 10) amongst Lpar (Fisher´s exact test, p=0.036).

Comparison between late participants (Lpar) and non-participants (Npar)

Here we report an analysis comparing Lpar with Npar (Npar = those decline participation after two invitations). We wanted to investigate if the the profile of Npar and Lpar was similar. If that was true the percentage of cases in each demographic category

should be similar in both sub-groups. This analysis is similar to the one performed in the previous section. The J48 classifier originated the decision tree shown in Figure 25**.**

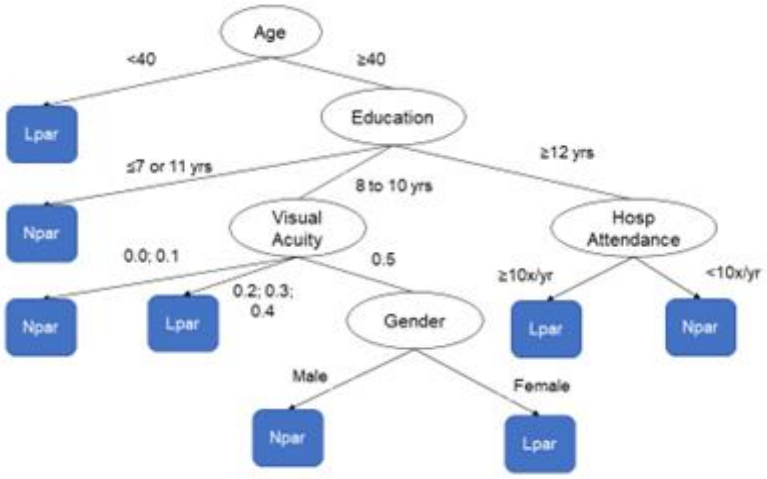

Figure 25 - Classification tree originated by the C4.5/J48 algorithm late participation and non-participation

This classification model has a weighted average precision of 0.801, a weighted average F-Measure of 0.803 and a weighted average ROC area of 0.688. The classifier predicts that someone younger than 40 that is not an Ipar will be a late participant (LPar) instead of a non-participant (NPar).The classification tree was used to define the levels summarized in Table 37. It was upon these levels that differences between Lpar and Npar were formally investigated.

The first finding was a difference in age between Lpar and Npar. The percentage of individuals with AGE1 was 20% (17 of 84) amongst Lpar and was 2% (5 of 275) amongst Npar (Fisher´s exact test, p<0.001). For those in the group AGE3 the proportion was 39% (33 of 84) amongst Lpar and 63% (174 of 275) amongst Npar (chi-square=12.82, df=1, p<0.001). The percentage of DISTH1 subjects within the group of those who are AGE2 was 97% (32 of 33) in Lpar and 78% (76 of 98) in Npar (Fisher´s exact test, p=0.009).

The percentage of individuals with EDU1 within the group AGE2 was 73% (24 of 33) in Lpar and 98% (96 of 98) in Npar (Fisher´s exact test, p<0.001). The percentage of individuals with EDU1 within the group of those who are AGE3 was 88% (29 of 33) in Lpar and 96% (167 of 174) amongst Npar (Fisher´s exact test, p=0.013).

The percentage of AHA-rare subjects within the group of those who are AGE2 was 9% (3 of 33) in the Lpar group and 45% (44 of 98) in the Npar group (Fisher´s exact test, p< 0.001).

The percentage of individuals AGE3 and AHA-rare was 18% (6 of 34) in the Lpar group and 45% (77 of 172) in the Npar group. (Fisher´s exact test, p=0.004).

The percentage of VA-extreme subjects within the group of those who are AGE1 was 76% (13 of 17) in Lpar and 20% (1 of 5) in Npar (Fisher´s exact test, p=0.039). The percentage of VA-extreme subjects within the group of those who are AGE2 was 61% (20 of 33) in Lpar and 35% (34 of 98) in Npar (chi-square=6.84, df=1, p=0.009). The percentage of VA-extreme subjects within the group of those who are AGE3 was 64% (21 of 33) in Lpar and 33% (58 of 174) in Npar (chi-square=9.44, df=1, p=0.002).

Non-participants were asked to specify reasons for non-participation and the most commonly mentioned reasons were:

- *"I am too debilitated to participate"*
- *"It is far away from my home"*
- *"There are no benefits in participating"*
- *"I have no one to go with me"*

Discussion

In this study we investigated participation rates in the PCVIP study and its determinants. We obtained an overall participation rate of 20%, low participation was anticipated given that the target group of the population were people with impaired vision. Some of the interested group were not able to participate because travel arrangements were too expensive compared with the compensation offered by our study. Despite this, the participation rate was comparable to other studies involving participation in phone interviews in the Portuguese population (312). Correia et al. were only able to interview 21.7% of those eligible for their study. When we analysed factors or determinants that are likely to affect participation rates in our study, we found that people at the extremes of VA (≤0.1 or less and 0.5) were more likely to participate than those with intermediate acuities (0.2-0.4). Participation was independent of age and cause of VI but influenced by gender (males were more likely to participate). People living together or divorced were more likely to participate than those in other categories of marital status. Participation reduced with increasing traveling distances to the hospital but increased with the number of years of education. A high frequency of hospital appointments was also favourable to participation. A decision to participate was independent of the Charlson comorbidities index.

The initial hypothesis regarding the effect of acuity was partially confirmed and we were also able to confirm that the cause of VI was not a determinant of participation. Other results were in line with our initial hypothesis, specifically, we confirmed an effect of education, distance to the hospital and frequency of hospital attendance as

determinants of participation in our study. Our model predicts that, for individuals with the best profile favouring participation, a minimum of 4 in 10 contacted would participate. For the worst profile, the maximum participation would be 6 out of 10. These profiles need to be considered when designing studies and planning recruitment.

Surprisingly subjects with severe vision loss, acuity 0.1 or less, were more likely to participate than those with better acuity, VA in the range 0.2-0.4. This finding seems to contradict the idea that the sustained willingness of individuals to participate can be inferred from the effort that participation requires (305). It would be expected, from the effort perspective, that someone with a worse acuity would have more difficulties participating than someone with better acuity. A possible explanation is that individuals at more advanced stages of their conditions may perceive a greater benefit in responding to study participation than those at less advanced stages. People at more advanced may have a stronger moral drive to help others in a similar situation (313). Another explanation for this result can be the level of adjustment to vision loss. Individuals with worse acuity might be better adjusted to vision loss whilst those in the medium range may still be in the process of adjusting and; therefore, less inclined to participate (284, 285).

The participation rate in our study was higher amongst men than women, which contrasts with some studies (298-300). This is a result that needs further investigation but we acknowledge that this might be related to cultural factors because Correia also found, in Portugal, higher participation amongst men (312). Another result that is in contrast to other studies was the higher participation amongst subjects that were divorced or single when compared with married individuals. In a study by Sahar and colleagues married people were more likely to participate than people with other marital status (301). We do not have a clear explanation for this result, but it could be related to the spectrum of relationships of the target group of the population.

Factors such as distance to the hospital, education or annual hospital attendance are important when planning recruitment. Individuals living further away from the hospital were less likely to participate. This result seems to be explained by the “principle of the effort” that predicts an inverse relationship between effort and participation probability (305). In line with our results for education status, increased participation with the number of years of education has been reported in other studies (295-297). The most likely reason for this is the ability to understand the purpose of the study and the contribution that studies can provide to the progress of knowledge. The participation odds for people visiting the hospital 10 or more times per year were higher than the participation odds of

those who attend the hospital less than 10 times per year. Differences found are likely to be due to the development of an acute civic awareness and/or familiarity with the hospital environment.

In this study we also looked at systematic differences between immediate and late participants. This analysis provides information regarding the spectrum of individuals in which a follow-up phone call can be effective. Overall, we can say that the phone call, as others have found, seems to be important in increasing the moral obligation to participate (302, 304). Our operators noted that a substantial number of individuals changed their minds and eventually decided to take part in the study after the importance of their participation has been emphasized. Compared with the initial letter, the follow-up call captured more women, more males younger than 40 years but fewer males within the age 40-69 years. Groups in which participation increased need more incentives or clarification than the groups that did not change in participation. Our results are in agreement with other studies showing that Lpar tend to be younger than Ipar (314, 315). Other differences between Ipar and Lpar that we found involve very small groups with specific characteristics that seem to show only scattered combinations of patterns of participation.

By comparing late participants (Lpar) with non-participants (Npar), we investigated if the model of “continuum of resistance” was valid in our sample. According with the “continuum of resistance” model the more contacts an individual requires to participate in a study the more similar he/she is to Npar (305, 309). However, similar to results in other studies (316, 317), we found many differences between the structure of the group of Lpar and Npar. In particular, the age distribution was different, Lpar were younger than Npar (314, 315). Overall, there were several differences between the structure of the group Lpar and Npar which somewhat contradicts what would be expected from the model “continuum of resistance” (314-316, 318).

A limitation of our study was the lack of information concerning the economic status of the subjects that could potentially clarify some of the unexplained findings. Another aspect that we believe would strengthen our results would be the inclusion of responses from more subjects in both groups. Amongst others reasons, some non-participants were excluded from the analysis because they were unable to answer our questions by telephone (for example due to dementia, staying in nursing homes, hospitalization) or the clinical information was of poor quality (to determine, for example, the Charlson comorbidities index). Therefore, the included cases may be slightly different from the general population of interest.

Conclusion

In conclusion, participation rates in our study were influenced by gender, distance to the hospital, number of years of education, annual hospital attendance, marital status and visual acuity. There were considerable differences between immediate participants and late participants and between late participants and non-participants. Individuals with low levels of education and women were more difficult to recruit. These facts need to be taken in consideration in order to avoid studies that are biased by gender or socio-economic inequalities of the participants. Young subjects and those at intermediate stages of vision impairment, or equivalent conditions, might need more persuasion than other profiles.

Chapter 6 – Discussion

The aim of this thesis was to investigate and characterize the impact of vision impairment in selected aspects of the healthcare system and the society. Our work investigated characteristics of vision impairment including barriers to access to care that can lead to an increase number of cases of vision loss. The work reported in this thesis can be considered as aspects of eye diseases and vision loss and their implications to the health system and the society.

The thesis is a compilation of study results that have been reported before as research papers. In one study, we studied the number of intravitreal procedures performed in Portugal during the period 2002 to 2012.That is, we investigate the raise in the number of intravitreal procedures as a proxy to understand the diffusion of anti-VEGF treatments. Anti-VEGF treatments are a revolutionary treatment in ophthalmology which reduced the number of people losing vision due to acquired eye diseases such as age related macular degeneration and diabetic macular oedema. In another paper we estimate the use of informal care and its determinants in people with impaired vision. We also investigated productivity losses in a sample of people with impaired vision. To support and complement our methodological options adopted in some of the papers in which I am the first author, the thesis also reports two papers in which we: 1) analysed the results produced by EQ5D and activity inventory to assess health and visual outcomes and 2) compared our study participant's profiles with non-participants. The key findings are summarized and discussed below.

6.1 - Key Findings and discussion

6.1.1 - Diffusion of anti-VEGF injections in a National Health System

In Chapter 5 section 1 we reported results of the study "Diffusion of anti-VEGF injections in the Portuguese National Health System". This study investigates how a sight saving treatment reached different regions in Portugal and was motivated by 1) expected problems with inequities concerning access to new treatments and 2) for the potential of this treatment to reduce the number of cases of vision impairment in Portugal. Ensuring equal access to eye care and reducing vision loss is a duty of the health care system; therefore, in this thesis we consider that this work explore the perspective of the health care system. In other words, this paper explores the role of the health care system when tacking the problem of sight treating disease that would lead to vision impairment. We performed a temporal and geographical analysis of the patterns of diffusion of antivascular endothelial growth factor (anti-VEGF) treatments in the Portuguese National

Health System. We analysed 98,408 hospital discharges from NHS Portuguese hospitals that corresponded to 57,984 patients and found that:

- The total number of episodes increased from 1815 in 2002 to 25106 in 2012.
- The yearly rates of hospital episodes per 100 000 population varied from 17.4 in 2002 to 238.77 in 2012.
- Between 2007 and 2012, the rates of hospital episodes related to the introduction of anti-VEGF injections increased by 27% per year.
- Patients from areas without ophthalmology departments received fewer treatments than those from areas with ophthalmology departments.
- The availability of an ophthalmology department in the county increased the rates of hospital episodes by 243%.
- A 100-persons greater density per square kilometre raised the rates of hospital episodes by 11%.
- Results show potential inequalities in eye care access that can lead to irreversible sight loss caused by treatable eye diseases.

A detailed discussion of our results has been given in section 5.1.1. In section 5.1.1 we considered three possible barriers for the equitable anti-VEGF diffusion related to legal, technical and financial factors. The EMA approval of this treatment in 2007 and the NHS coverage decision in 2008 fixed the legal barrier. Technical conditions regarding the need of extra training for doctors and the mandatory performance of this procedure at the operation theatre formed the technical barrier (190). These technical requirements possibly created financial and service capacity pressures on ophthalmology departments (105, 181). Higher rates of treatment were observed mostly in areas around big cities and specialized centres. Smaller hospitals may have taken longer to adopt this treatment due to budget limitations or technical conditions. Conversely, teaching hospitals, with urban location and the presence of competition may have helped the spread and rate of diffusion (131). Regarding financial barriers two main budget limitations may have reduced the speed of diffusion of anti-VEGF treatments. The first is related to the cost of the treatment, to changes in hospital budgets and pressure for cost-containment that may have reduced the availability of anti-VEGF treatments in small hospitals concentrating patients in big centres with limited capacity. A second financial barrier for hospitals is related to the fact that intravitreal injections need to be administered in an operating room by an ophthalmologist. Typically, patients receive three injections in the first 3 months, followed by monthly visits for assessment and further injections as necessary (194). These surgical procedures and monthly appointments impose high

demands on hospitals (staff and facilities). In a period of tight budgets expansions in the medical staff or facilities are difficult to implement. Thus, some hospitals may have delayed the start of these treatments or they may still not be available.

Our findings are causes of concern because vision loss caused by eye diseases for which anti-VEGF treatments are indicated cannot be restored. That is, reduced number of treatments might lead to an increased number of people becoming visually impaired due to treatable causes in Portugal.

6.1.2 - The use of informal care by people with vision impairment

We investigated informal care utilization amongst people with impaired vision using innovative approaches such as taking into consideration self-reported difficulties when performing daily living activities. The needs of informal care amongst people with VI are considered here as part of the impact of the condition in the society. Difficulties performing daily living activities have a huge impact on autonomy and can lead to an increased need of informal care. Our study fills into this lack of knowledge by including in our analyses a characterization of self-reported measures of visual ability obtained with an activity specific inventory. This has been used in combination with clinical measures such as visual acuity and socio-demographic characteristics that can influence the needs of informal care. We quantified and characterized the use of informal care in a sample of 546 visually impaired individuals, as detailed in section 5.1.2. In short, we found that:

- Informal care was reported by 39.6% of the participants requiring, each, a median of 390 hours (mean=470; 95% CI=488-407) of informal per year.
- In total we estimated 92.000 hours of informal care per year that corresponded to an opportunity annual cost of €610,915.
- Informal care was influenced by marital status, comorbidities, visual ability and acuity.
- The intensity of use of informal care was negatively associated with visual acuity and visual ability i.e. the ability to perform daily living activities that depend on vision.
- Visual ability was the only predictor of informal care utilisation intensity after controlling for age, gender and severity of vision impairment. With one-unit change in visual ability corresponding to a variation of 67 hours in the intensity of informal care per year.

- With this study we were the first to show a strong link between self-reported visual ability and informal care in a large multicentre study in a European country.

We concluded that visual ability, a measure of functional disability/dependency related to vision, was a predictor of the use of informal care and of its intensity. We suggested that visual rehabilitation alongside with usual eye care would help to alleviate the burden of vision impairment at this level.

A detailed discussion of our results can be found in section 5.1.2. In section 5.1.2 we have compared our estimates regarding the percentage of informal care users, the amount of hours of informal care and found that our findings were similar with other studies(49, 210, 211). Regarding the determinants of informal care use our results showed that the use of informal care was affected by marital status and comorbidities but not by gender. Non-married participants were more likely to report informal care presumably because they cannot rely on their partners and the need to ask for help is more clearly defined. Those with other comorbidities may also face further difficulties in their daily life and therefore are more likely to require informal care. In our study the users of informal care had a higher proportion of women compared with non-user and in the logistic regression women had a higher odd of needing informal care although this was not statistically significant. This result is in contrast with some studies reporting that women are more likely to use informal care (49, 50). As informal care can be influenced by many factors and, in particular, by the organization of the society (207) our results need to be interpreted in the Portuguese context and can be, eventually, applicable to similar societies (215).

Visual ability was the only independent predictor of the intensity of use of informal care after adjusting for age, gender and severity of vision impairment. This association shows a link between self-reported task difficulties and the amount of help needed. Others reported an effect of visual acuity; however, these studies did not considered self-reported levels of visual ability (50, 175, 216, 217). In line with our results, Wang et al. (49) found an increase in intensity with increased self-reported walking difficulties. Keefe et al. (214) reported that people with impaired vision need help for vision-dependent activities such as driving, reading documents and support for independent activities outside home. These are the tasks covered by the activity inventory to determine visual ability. We speculate that visual rehabilitation tailored to increase visual ability is likely to reduce simultaneously the use of informal care and its intensity.

6.1.3 - Productivity losses and their explanatory factors amongst people with impaired vision

We also investigated productivity losses caused by VI to characterize the impact of vision loss from a societal perspective. Results of this analysis have been reported in section 5.1.3. Again, there has been an effort to introduce innovative approaches. Previous studies analysed productivity losses associated with vision impairment with some limitations. We identified low samples and incomplete set of explanatory variables as the main limitations in the available literature. We believe that employment has an impact on both productivity and health and therefore we decided to include patient-reported outcomes measures when investigating productivity losses together with clinical and socio-demographic variables. We estimated and characterized productivity losses in a sample of 546 visually impaired individuals and found that:

- From 546 participants 47% were within the working age and from those 28% were working.
- Productivity losses were estimated in €1.51 million per year (median of €4.399 and mean of €5.495 (95% CI=[5.292; 6.598] per participant) in this sample.
- The largest portion of losses were due to reduced workforce participation estimated from a sample of 159 individuals that were either unemployed or early retired due to vision impairment.
- Individuals within the age range of 17-39 years, 12 or more years of education, no comorbidities and reporting higher health-related quality of life had higher probability of employment.
- There was a strong association between employment status and self-reported levels of health-related quality of life.

We have compared our estimates regarding rate of employment and workforce participation and concluded that our results were similar to previous reports (136, 139, 177, 240, 241). More details were given in section 5.1.3. Regarding the determinants of participation in the labour market our results show that, after controlling for visual ability and acuity, younger individuals without comorbidities, higher levels of education and high health-related quality of life had higher chances of being employed. Results about age and education were corroborated by several studies that demonstrated that younger and more educated individuals with impaired vision were more likely to be employed (154, 156, 242, 243). One possible explanation may be because job loss occurs more frequently at older ages and that the duration of unemployment is longer for older individuals (156, 242). Another explanation comes from the perception that many jobs

which are available to less qualified people require sight (154). Others studies have found that more severe impairment and the presence of comorbidities were associated with lower probability of employment (154, 243, 244). However, in our study, in the logistic regression analysis only the presence of comorbidities showed statistically significant effect in employment status. Visual acuity had an odds ratio of 0.35 (p-value=0.163), which points to a tendency to individuals with lower visual acuity (higher values in a logMAR scale) having lower chances of participation in the labour market. While this effect was not significant, the trend is similar to the previous findings. We have also included results from EQ5D and AI in our regression analysis to explain the employment status. The EQ-5D used to assess health-related quality of life includes questions about anxiety and depression and pain and discomfort which are known factors associated with the ability to work (245-247). Visual ability measured by the AI allowed us to incorporate also difficulties performing vision related tasks (168). Whilst the effect of visual ability was not statistically significant, we found that the EQ5D utility score was a strong predictor of employment and therefore of reduced workforce participation. This possibility was also being raised in other studies who tried to predict absenteeism and presenteeism using EQ5D (248).

6.1.4 - Complementary findings

In Chapter 5 section 2.1 we reported results of the study “Visual and health outcomes measured with the activity inventory and the EQ5D, in visual impairment”. This study analysed the outcomes produced by a condition-specific instrument, activity inventory (AI), and by a generic instrument, EQ5D to assess health and visual outcomes in patient with visual impairment and, in short, we found that:

- Both measures were related positively with visual acuity in the better eye. However, which measure had different association with other patient characteristics.
- EQ5D was also associated with gender and number of comorbidities while AI was also associated with age and gender.

In agreement with previous studies EQ5D was found to be responsive to VI (84, 227, 278). Van Nispen et al.(84) found slightly higher results applying EQ5D in mixed causes of VI. These slightly different results may be explained by a different distribution of causes of VI (more age macular degeneration than diabetic retinopathy compared with our sample), narrow inter-quartile range of visual acuity and older participants in their study. Another additional explanation is that EQ5D utility indices are expected to be lower

in Portugal compared to the Netherlands because of differences in community calibrations (170). Gender and the numbers of comorbidities were predictors of the EQ-5D scores. The effect of gender that we found in our multiple regression is not commonly observed; however, Langelaan et al. (227) did report significance of gender and that is in line with what has been found in the general population in some countries (283). Our results for the activity inventory are in agreement with what other authors found for patients with VI due to various causes (8, 288) or VI caused by specific eye diseases such as diabetic retinopathy (289). The effect of age on visual ability obtained with the AI has been found before and has been explained by the overall physical functioning decline explained by aging (8).

Because of these different association with other patient characteristics we concluded that EQ5D and AI produces complementary information about visually impaired individuals and therefore should be used in conjunction to assess the wider impact of vision impairment.

We have also compared our study participant's profiles with non-participants to investigate participation rates and its determinants. Results of this analysis have been reported in section 5.2.2. The main findings were:

- Participation was independent of age and cause of vision impairment but influenced by visual acuity, marital status, educational level, frequency of hospital attendance and traveling distances to the hospital.
- People at the extreme of visual acuity (0.1 or less or 0.5 in a decimal scale) were more likely to participate than those with intermediate visual acuities (0.2 to 0.4 in a decimal scale).
- Males were more likely to participate than women, people living together and divorced were more likely to participate than people included in any other marital status category (married, single or widowed).
- Participation increased with higher levels of education, higher frequency of hospital appointment but decreased with increasing traveling distances to the hospital.

Our results regarding visual acuity were in contrast with what we previously hypothesized. Participants with severe vision loss (visual acuity of 0.1 or less) were more likely to participate than those with visual acuity of 0.2 to 0.4. A possible explanation is that individuals at more severe stages may perceive a greater benefit and a higher moral obligation than those at less severe stages (313). Another explanation can be related to the level of adjustment to vision loss. Participants with worse acuity might be more

adjusted to vision loss than those in the middle range and that may explain lower participation in subject the middle range (284, 285). Our finding related to gender were in contrast with previous studies. Regarding gender we recognize that the results need further investigation although we speculate that this might be related to cultural factors since another study performed in Portugal also found higher participation in men (312). Individuals living further away from the hospital were less likely to participate. This result seems to be explained by the "principle of the effort" that predicts an inverse relationship between effort and participation probability (305). In line with our results for education status, increased participation with the number of years of education has been reported in other studies (295-297). The most likely reason for this is the ability to understand the purpose of the study and the contribution that studies can provide to the progress of knowledge.

6.2 - Strengths and limitations of this thesis

This section provides the strengths and methodological limitations of this thesis. The section is divided in two parts, in the first part we present in detail the advantages and disadvantages of our databases. In the second part we discuss some of the characteristics of the instruments used during face-to-face interviews and the methods used to valuate informal care providing an overview of their strengths and limitations.

6.2.1 - Strengths and limitations due to data collection strategies and databases used

To study the diffusion of a new eye treatment we used an administrative database with inpatient and day cases stays from all Portuguese public hospitals during period 2002-2012. This database has the benefit of gathering information through a consistent format and using ICD-9-CM to describe specific diagnoses and procedures. Portuguese public hospitals have the obligation to report inpatient and day cases in order to be paid for their services therefore this database is an abundant and standardized source of patient information.

Using administrative data allowed us to eliminate selection bias and enabled us to construct a complex and multivariable model to explain the geographical diffusion and time variation (319). We included all the procedures provided in public hospitals with different differentiation levels which increased generability of our findings because different clinical practice and different patient complexity are incorporated in our data. Because all patient identifiers such as name and address are removed from the database and an anonymized patient unique identification is given by the national agency that provides the data anonymization previously, confidentiality and patient anonymization is guaranteed. The disadvantages include the limitations of claims data, such as

incomplete, inaccurate, or missing data, the lack of specific billing codes for some procedures and the less sensitivity to evaluate the appropriateness of care (319). In our study it also implicated that we did not have access to some individual socioeconomic characteristics such as patient income or education level that could have been incorporated in our model. In addition, because this database is restricted to Portuguese Public hospitals, we could not include patients treated in the private sector although we believe that the number of patients that seek care in the private sector is small because the treatment is expensive and is available at public hospitals.

To collect information about informal care and productivity costs we used a questionnaire. Accordingly to Bhandari et al. (218) accuracy of self–reported data through questionnaires may be affected by three main factors: 1) recall time frame; 2) type of utilization;3) utilization frequency. We will discuss these factors since they support our option for a questionnaire with a 2-week time-frame to capture information about informal care use and productivity losses.

Recall time frame is define by the length of recall (eg. 1 week; 1 months or 1 year). Accuracy of recall may be influenced by telescoping and memory decay and poor accuracy of recall leads to inaccurate data and conclusions. Telescoping occurs when an individual lengthens the recall period beyond the timeframe in question and reverse telescoping occurs when individual shortens the recall period. Both telescoping and reserve telescoping applies to any time frame and does not produce a consistent bias (218). However, memory decay, defined as a failure to remember an event, always results on under-reporting. The shorter the recall period the more accurate individuals are at reporting use of healthcare services, absenteeism and worker productivity (218, 320). In particular, a shorter time frame between absence to work and the application of the questionnaire may result in a lower discrepancy between the real number of days missed from work and self-reported data (321).

Underreporting utilization is positively associated with increased frequency since people tend to fail to remember as frequency increases (320). Informal care may be frequent and occur on a daily basis and for that reason people tend to get use to that help and forget its frequency when they are asked to report the number of hours of care. We adopted a short recall time because asking the use of informal care in a shorter period may minimize underreporting.

The type of utilization and whether it is associated with stigma also influences the capacity to recall events. Usually, stigmatized care such as mental health visits are underreported. More important, salient visits such as inpatient hospitalization are more

likely to be reported accurately than typical and frequent visits such as visits to the primary care physician (218). Since informal care it is not a rare or salient event and, especially on old population, it is not associated with stigma. Therefore, we believe that the questionnaire is an adequate instrument to collect information.

An alternative method to collect data regarding informal care would be to use the diary. With the diary with would be possible to reduce recall time bias but this method is not exempt of disadvantages. Mainly it is necessary to have a higher budget to collect the information and the method is time intensive and can be straining for respondents (207, 219, 322). Being time consuming may bias the results in favour of less busy respondents (323). Additionally, there are also the risk of high levels of item missing data, complexity of data processing and analysis and dependence on participants motivation to repeatedly record their data (220) which can be even harder for people with impaired vision (221).

Regarding productivity losses and more specifically absenteeism, sick leave registers would be a reliable source of information to collect the number of days missed to work. However, the purpose of our study was to estimate the absenteeism in a group of participants that worked in many different locations and therefore this approach would unrealistic (171).

In short, based on these assumptions we decided to use the most common method, a questionnaire (174, 207) with a small recall time period to minimize recall bias. We have also conducted a pilot test to simplify data recording, to remove redundant items and to clarify words and questions in order to decrease potential biases.

6.2.2 - Other strengths and limitations of this thesis

To assess participant's ability to perform daily activities we used a functional vision questionnaire, the activity inventory. In this self-reported method participants are first questioned about the importance of performing a determined daily activity (goal importance). If the activity as at least some importance participants are asked to rate how difficult is it to perform that activity (tasks difficulties). In this type of inventory each participant responds to a relevant set of questions that is unique to her/him, meaning that each participant as personalized functional assessment. For minors, when necessary, parents served as proxies for the interview. Activity inventory can be describe as a custom-tailored questionnaire since is adapted to the individual preferences (166, 167).

In our study we wanted to include functional vision because two individuals with the same vision impairment level (for example defined by visual acuity) may have

different ability levels to perform daily activities. Furthermore, functional vision is a major determinant of whether a person can live independently and provides important information about the level of assistance that is needed if a visually impaired person is not fully independent (324). By collecting information about difficulties performing tasks that are considered of some importance to the individuals the AI is suitable to produce an personalized functional assessment, that can use be use to assess dependency level, to define an individualized rehabilitation plan, as well as to assess the outcomes of assessment of vision ability after rehabilitation. Therefore, we consider the inclusion of the AI an innovative approach characterizing, for example, informal care or productivity losses.

An alternative to self-reported methods would be observation. That implies, classify how participants performed a sample of daily living activities (direct method or performance based method) or we could have collected information by asking to someone close to the visually impaired individual how they rate participant's ability (indirect method or proxy report method). With direct performance observation we would capture real difficulties rather than perceived difficulties and reports from someone close to the visually impaired individual might be useful in cases of depression or cognitive impairment. By directly observing performance we could obtain a more precise estimative of ability and eliminate some issues related both to underestimate and overestimate of ability usually found respectively in depressed individuals or in healthy older individuals living in the community (324, 325). For example, a study on visual function in older adults found that about 10% of individuals had a considerable discrepancy between their self-reported reading difficulties and measured reading speed (326).

Direct methods are often time consuming and cost intensive. This approach requires specialized training to the observer, acquisition of materials to recreate the environment, special space for administering the performance test, designing an appropriate protocol, and may be considered intrusive from the patient perspective (327). Additionally, direct performance measures also possess their own limitations since no single "gold standard" exists to implement this data collection strategy (325). Interestingly, some authors have demonstrated that although direct performance measurement provide detailed information about individual's ability, both, direct measurements and self-reported measures, were found to be independent predictors of nursing home placement (327, 328). Some authors have also demonstrated that direct performance measurement are neither superior nor mutually exclusive compared to self-reported measures (329, 330). Direct performance measurement may measure different,

although related, attributes therefore provide complementary information (327, 329). Direct performance measurement may be more sensitive to detect slight ability decline in some older persons, while in some functional tasks the patient may detect an impeding problem earlier (329).

By asking someone close to the visually impaired individual rate their ability could also be influenced by, for example: i) an unconscious exaggeration of their caregiving role, an overprotective behaviour, ii) an overburdened feeling if dependency occur for a long time or if there is no other backup support, iii) a conscious process to gain sympathy or to encourage recommendation to a long term care/nursing home placement (324). Although a high level of agreement was found between self- reports and reports from others family/friends, for physical activities of daily living, instrumental activities of daily living and social functional (Interclass correlation coefficient above 0.6) at an aggregate level (summary measure), a consistent discrepancy was found at the item level (331). In general, reports from others indicate a higher level of disability when compared both to self-report as well as to direct performance observation (331).

To assess the existence of comorbid conditions we asked participants to report comorbidities based on a list of 16 categories that included, amongst others, diabetes, hypertension, cancer and heart conditions. The completeness of data obtained by this method depends on the patients' ability to remember their comorbidities (227). This ability is influenced by age, education level and memory capacity (332, 333). Young and highly educated people are likely to report comorbidities accurately, but that is more unlikely in old people or people with low education. Therefore, it is possible that in our study participants did not report comorbid conditions because the symptoms were absent and; therefore, they did not remember which results in a increased risk of under-report. Nevertheless, several studies showed data from interviews or questionnaires are a valid and practical source to collect this information (332, 333).

To estimate economic impact of informal care we used opportunity costs in which time losses are valued based on the value of competing time use for example, paid labour. The same approach was use by others authors in the field of vision impairment such as Keeffe et al. (214) and Schmier et al. (175) and in others diseases like Alzheimer´s (334) or Parkinson´s (335). An alternative method would be "proxy good method" (also known as the replacement cost method) in which the value of time spend on unpaid activities is based on a close market substitute, for example, the wage of a household helpers or a specialized nurse (336, 337). Although both methods are extensively used to value time, the opportunity costs method is used more often usually based on the average wage rate (174, 207). Keeffe et al. (214) used opportunity costs

method and informal care was valued with the average Australian hourly pay rate (A$ 11.25; US$ 8.73). In our study we used the average Portuguese hourly pay rate of full time employees in the year 2014 (EU$6.32) which accordingly with Costa et al (176) is within the interval used in studies reporting opportunity cost method that goes from EU$4.10 to EU$19.18. By using an average pay rate we valued time spent providing informal care equally regardless the occupational position or education level of the caregiver. That means that our method does not raise equity concerns that arises when different social values are attributed when care is provided by, for example, an health economist or by an administrative assistant (337). The method and value used to estimate informal care in our study was used previously and seemed appropriate and ensured comparability with others studies.

We also did not distinguish the number of hours spent providing care by the type of activities sacrificed: paid work, unpaid work, leisure time and we recognize that it is difficult to distinguish between normal housework and additional housework due to health problems of the care recipient. These issues may cause under or overestimates in our estimates. Without a proper distinction between normal housework and additional housework due to health problems the time spent on informal care may be overestimate (338). In contrast, if the caregiver and the patient live in the same household and have a social relationship (eg. spouse, parent, child) and/or if the starting point of informal care occurs gradually with the decline of patient autonomy. The way informal care is perceived by both, patients and caregivers, may be affected and this may result in an underestimation of informal care (323). We believe that both situations reported here may have occurred equally in our study therefore the impact in our estimates may be negligible.

6.3 - Implications of the findings of this thesis

With this thesis we concluded that vision impairment in Portugal has substantial socioeconomic implications since it affects individual's autonomy that leads to high use of informal care. It also affects individual's participation in society namely individual's employment status and health related quality of life which results in productivity losses. We also found that the diffusion of a new eye care treatment was large but unequally distributed and associated with availability of healthcare delivery services.

From a health policy and healthcare organizational delivery system viewpoint more actions are needed to reduce the burden of vision impairment in Portugal. The Portuguese healthcare system should improve the capacity to provide comprehensive care to this population investing in preventive, curative and rehabilitation care.

Preventive care including screenings, check-ups, providing information about risk factors and preventive measures to avoid risks should be reinforced. Many eye diseases that lead to vision loss are asymptomatic in the beginning therefore individuals may not be aware of the risks and of the alert signals (119). Screening programs to those at higher risks are needed. The number of participants with diabetic retinopathy in our sample shows that in Portugal there are many patients with diabetic retinopathy at young age (working age 17 to 64 years old), with visual acuity bellow 0.5 decimal that are not working. The cost-effectiveness of screening programs in eye diseases and in particularly in diabetic retinopathy is well documented in the literature (339, 340). Systematic screening for diabetic retinopathy versus "no screening" is cost-effective in terms of sight years preserved (340) so investing in screening programs is considered a good investment. However, screening programs will not produce benefits if detected cases are not monitored or treated in a timely and adequately way.

Access to medical treatments that restore and prevent vision loss should be provided. The unequal geographical distribution of anti-VEGF treatments found in Portugal seems to indicate that the access to these treatments is being provided at a suboptimal level. Because we considered that one possible barrier is related to financial factors, we advocate that it is not enough to evaluate the cost-effectiveness of a new healthcare technology to decide whether it should be reimbursed or not. A cost-effectiveness analysis (more specifically a cost utility analysis) tell us if the benefits (effects) are higher than the costs or more precisely tell us the cost per quality adjusted life years gain but, it is out of the scope of these analysis to determine the impact to healthcare system budget and sustainability. An assessment about the impacts to the healthcare system (in terms of budget and resources) is crucial to understand, if to

accommodate health innovation and improve population health, adjustments are required.

Adapting healthcare financing mechanism to better accommodate healthcare innovation is one possible measure. Healthcare financing mechanism may be used to distribute financial resources differently between providers. There are several options to incorporate instruments into hospital payment system to support the introduction of medical innovations. These options may be divided into short-term instruments and long-run mechanisms (134, 341). Short-term payment instruments should only be implemented in special cases, for instance when no other treatment option exists to treat a specific condition, for a limited period of time and under the supervision of continuing evaluation in terms of effects and type of cases treated (134). This instrument allows shared financial risk between healthcare providers and the financing agency (341). Long-run mechanism, a preferable option, are implemented through updates and adjustments in the DRG system. Frequent updates and adjustments of DRG system, including the introduction of new codes to incorporate current practice patterns or the adjustment of costs weights reflecting new treatment costs are important mechanisms to the introduction of new healthcare technologies and therefore to help to provide adequate access to patients who may benefit from this innovation (134, 342).

Planning the dissemination of healthcare innovation is also important to ensure that innovation is available to whom may most benefit. On the contrary, a passive, untargeted and unplanned spread of innovation may result in an unequal access to a new treatment. Monitoring the spread of innovation is crucial to guarantee that the dissemination is done based on the patient needs rather than on the healthcare organizational or professional characteristics and needs. Monitoring the spread of new treatment is crucial to ensure an equitable access. One of the aspects of this monitoring process should focus on the distribution of and access to eye care services in rural areas of Portugal since we found that patients living in rural areas had lowest levels of anti-VEGF treatments.

A comprehensive or integrated delivery of healthcare services is also important to this population. Vision impairment has substantial impacts on visual, physical and mental health (47, 48, 66). In our results we found that visual acuity and having comorbidities increased the chances of having a caregiver and that individuals with comorbidities had lower chances of being in the labour market. Therefore, besides eye diseases diagnosis, treatment and follow up it is necessary to take into consideration extra care needs related with complications associated to vision loss and with

comorbidities (52, 83).Vision impairment may affect the management of other comorbidities and comorbidities may also affect the management of ocular diseases that cause vision impairment.

Without an integrated vision care it will be more difficult to provide adequate care to the complex needs of individuals with vision impairment. The lack of continuity of eye care, the lack of awareness of this problem from the community or public health services, insufficient or inadequate screening services and/or provision of affordable care and delays in access to specialist eye care are some of the factors related to an increase number of cases of avoidable vision loss worldwide (11, 17).

Investing in vision rehabilitation is important to help all the patients with uncorrectable and unrestored vision loss to be as autonomous as possible. With this study we found that visual ability, i.e, patients ability to perform activities that depends on vision, was associated with having informal care, with the number of hours of informal care provided by caregivers and with employment status. Vision rehabilitation is useful whenever vision loss interferes with the activities of daily living, process of learning, social interaction and/or professional pursuits. Vision rehabilitation focus on the acquisition of alternative skills that will improve independence. Examples of interventions developed in vision rehabilitation programs include the orientation and mobility training, the provision of assistive devices (e.g. magnifying devices, haptic devices) and training to support assistive devices utilization, occupational therapy among others (273).

Because vision loss leads to many short or long term penalties that goes beyond the healthcare system namely loss of opportunities in education or employment, income losses and quality of life losses (11, 17, 18) actions to reduce vision loss impact should also include educational and labour market systems. In our study a higher education was associated with a higher chances of employment after controlling for age, visual acuity, visual ability, the presence of comorbidities and health related quality of life. The educational system and the labour market regulation should be adapted to the needs and ensure equal opportunities to visually impaired individuals.

In terms of clinical and administrative decisions, the focus is still the patient as an “isolated individual” (343) and the needs and preferences of others namely caregivers are easily ignored. This must change at the different levels of decision making. In terms of health policy, some initiatives for signalling informal care and registering caregivers have emerged in Portugal and worldwide. However, there is a lack of support programs for caregivers and a lack of initiatives to prevent undesired effects of providing informal care.

It is also important and necessary to increase awareness among health professionals and policy makers about the important contribution of informal care to the healthcare system and about the benefits of maintaining and supporting caregivers (209). For many patients, their families and the healthcare system, staying at home for as long as possible is the preferred alternative. Informal care may not only help to maintain the patient in the community, reducing the demand for home care but also facilitate an earlier discharge from hospitals both from inpatient acute episode or from outpatient surgery (337, 344-346). In this sense, promoting and supporting informal care is a win-win situation for the individuals, healthcare system and society.

6.4 - Future research

There are several challenges which need to be addressed in order to obtain a detailed evaluation of the impact of vision impairment.

In Portugal studies to estimate the prevalence and direct costs of vision impairment are needed. Even in a developed country vision loss imposes a tremendous cost therefore scientific evidence is essential to better define and implement policies and management plans, to rationalize and to direct health resources towards the areas that can reduce the burden of vision loss. Further research on prevalence and direct costs of vision impairment in Portugal should be conducted.

Regarding direct costs it is important that future studies includes ophthalmology and non-ophthalmology resource utilization and costs. Sight threatening disease are expected to be associated with direct medical ophthalmological cost. Non-ophthalmological costs in patients with vision impairment and blindness are also important to analyze since vision loss is associated with several clinical consequences and can be a comorbidity of chronic diseases, such as diabetes, arthritis and stroke. It is also important that direct costs studies include different care providers such as primary care facilities, hospitals and long-term care institutions.

Regarding informal care utilization further research should investigate the impact of vision impairment on caregivers. A wide body of research shows that informal care may require an intensive investment of time and effort for a long period of time depending on the characteristics of the patients such as age, type of activities provided, type of disability and severity level. Providing care may have a considerable impact on caregivers' time use (time for work, for leisure or social activities), finance, health and

wellbeing. By investigating the impact of informal care in caregivers it will be possible to have a more comprehensive characterization of the consequences of vision impairment.

Further research should also focus on the development of effective models of care provision that can provide for greater numbers of people with impaired vision. The increase number of visually impaired persons is driven not only from the ageing of the population but also from the emergence of new eye care technology and hopefully from more effective referral services. It will also be crucial to developed cost effectiveness studies to better understand which of these new models is more effective and produces the better outcome.

Chapter 7 – Conclusion

The research papers developed in this thesis tried to introduce innovative approaches to analyse the impact of vision impairment in the healthcare system and the society. By studying the access to a new anti-VEGF treatment, we have performed a unique analysis of temporal and geographical patterns of the diffusion of anti-VEGF treatment during one decade including all public hospitals in a National Health System. In our analyses of the determinants of informal care we introduced self-reported difficulties performing daily living activities measured by the Activity Inventory, in combination with clinical measures and socio-demographic characteristics, which was disregarded in previous studies. Previous studies analysed productivity losses associated with vision impairment with some limitations regarding the sample and the explanatory factors used to studied this association. We decided to include patient-reported health related quality of life when investigating participation in the labour market which no one, to the best of our knowledge, as done before.

We found that the diffusion and consequently the access to new eye care treatment was large but unequally distributed and associated with availability of healthcare delivery services. The reduced number of treatments found in some counties is worrisome since it can lead to an increased number of people becoming visually impaired due to treatable causes. We also found that vision impairment in Portugal has substantial socioeconomic implication since, it affects individual's autonomy levels that are associated with an intensive use of informal care. It also affects individual's participation in society, namely employment status and health related quality of life that led to significant productivity losses.

To conclude, much more can be done to reduce the burden of vision impairment in Portugal. It is never too much to say that, in many cases, vision loss may be preventable with the currently available healthcare technology. Eye care has a range of proved, low risk, high success and cost-effective interventions so the key element is to guarantee that these interventions are available and reaches all the persons that can benefit from them.

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Appendix 1

Table 1 – Activity Inventory goals designation, questions about importance and difficulties and answers categories

Number and Goal Designation		**Question to infer the importance -** How important is it for you to be able to …. without the assistance of another person?	**Answer categories**		**Question to infer the difficulties** - How difficult is it for you to …. without the assistance of another person?	**Answer categories**
1	Toileting	***use the restroom in a public place***	1= Not important, 2=Slightly important, 3=Moderately important, 4=Very important	If the participant responded "not important" , the interviewer moved to the next Goal; If the Goal was rated with any other importance category, than the participant was asked to rate difficulty achieving the Goal	***use the restroom in a public place***	1=Not difficult, 2=Slightly difficult, 3=Moderately difficult, 4=Very difficult, 5=Impossible to do
2	Personal hygiene	***groom yourself (shave, trim nails, apply makeup, etc.)***			***groom yourself (shave, trim nails, apply makeup, etc.)***	
3	Dressing	***choose your clothes and dress yourself***			***choose your clothes and dress yourself***	
4	Personal health care	***take care of your health***			***take care of your health***	
5	Eating	***eat your meals***			***eat your meals***	
6	Daily meal preparation	***prepare your daily meals***			***prepare your daily meals***	
7	Household tasks	***perform household tasks such as cleaning, laundry, or setting a thermostat***			***perform household tasks such as cleaning, laundry, or setting a thermostat***	
8	Personal Communication	***recognize people, see expressions, and make eye contact during personal communications***			***recognize people, see expressions, and make eye contact during personal communications***	
9	Correspondence	***read mail and write letters***			***read mail and write letters***	
10	Follow the news	***follow the news and keep up with current events***			***follow the news and keep up with current events***	
11	Follow a schedule	***read the time and follow a schedule***			***read the time and follow a schedule***	

12	Manage finance	***pay bills, balance accounts, or manage personal or household finances***			***pay bills, balance accounts, or manage personal or household finances***	
13	Shopping	***go shopping for food, clothes or other necessities***			***go shopping for food, clothes or other necessities***	
14	Child care	***care for young children***			***care for young children***	
15	Drive	***drive***			***drive***	
16	Adult care	***provide home care for an adult***			***provide home care for an adult***	
17	Pet care	***provide care for a pet***			***provide care for a pet***	
18	Use phone	***use a telephone***			***use a telephone***	
19	Go to parties	***attend parties or other functions***			***attend parties or other functions***	
20	Entertain guests	***entertain guests***			***entertain guests***	
21	Prepare food for guests	***cook or bake for social functions (for example, Thanksgiving or other holidays)***			***cook or bake for social functions (for example, Thanksgiving or other holidays)***	
22	Dining out	***dine out***			***dine out***	
23	Spectator events	***attend plays, concerts, movies, sporting events, etc***			***attend plays, concerts, movies, sporting events, etc***	
24	Attend meeting	***attend meetings of a club, church, civic group, etc.***			***attend meetings of a club, church, civic group, etc.***	
25	Play games	***play cards, board games, Bingo, or other games***			***play cards, board games, Bingo, or other games***	
26	Perform in public	***sing in a choir or play an instrument publicly, perform in plays, speak publicly or perform before a group***			***sing in a choir or play an instrument publicly, perform in plays, speak publicly or perform before a group***	
27	Attend church	***attend church or house of worship services***			***attend church or house of worship services***	
28	Dance	***dance socially***			***dance socially***	

29	Leisure entertain	***provide yourself with leisure entertainment***			***provide yourself with leisure entertainment***	
30	Do physical exercises	***exercise***			***exercise***	
31	Sewing or needle	***sew or do needlework***			***sew or do needlework***	
32	Woodwork	***do woodworking***			***do woodworking***	
33	Metalwork	***do metalwork***			***do metalwork***	
34	Paint or draw	***paint or draw***			***paint or draw***	
35	Recreational cooking and baking	***cook or bake for recreation***			***cook or bake for recreation***	
36	Electrical work	***do electrical work***			***do electrical work***	
37	Play music	***play a musical instrument***			***play a musical instrument***	
38	Sightseeing	***travel***			***travel***	
39	Fishing	***fish***			***fish***	
40	Outdoor activities	***perform outdoor recreational activities; i.e., boating, hiking, fishing, etc.***			***perform outdoor recreational activities; i.e., boating, hiking, fishing, etc.***	
41	Gardening and lawn care	***garden for pleasure or work in the yard"***			***garden for pleasure or work in the yard"***	
42	Play sports	***play sports; such as, golf, bowling, tennis, etc.***			***play sports; such as, golf, bowling, tennis, etc.***	
43	Use the computer	***use a computer***			***use a computer***	
44	Collect antiques	***collect things; i.e., antiques, stamps, coins, cards, dolls, etc.***			***collect things; i.e., antiques, stamps, coins, cards, dolls, etc.***	
45	Read newspaper	***read the newspaper***			***read the newspaper***	
46	Use camera	***do photography***			***do photography***	

Appendix 2

Table 1 – EQ5D – 3L

Please indicate which statements best describe your own health state today.
Mobility
I have no problems in walking about
I have some problems in walking about
I am confined to bed
Self-care
I have no problems with self-care
I have some problems washing or dressing my self
I am unable to wash or dress my self
Usual Activities
I have no problems with performing my usual activities
I have some problems with performing my usual activities
I am unable to perform my usual activities
Pain/Discomfort
I have no pain or discomfort
I have moderate pain or discomfort
I have extreme pain or discomfort
Anxiety/Depression
I am not anxious or depressed
I am moderately anxious or depressed
I am extremely anxious or depressed

Appendix 3

COMISSÃO NACIONAL
DE PROTECÇÃO DE DADOS

AUTORIZAÇÃO Nº 5982 /2014

I. Pedido

A **Universidade do Minho**, notificou à Comissão Nacional de Protecção de Dados (CNPD) um tratamento de dados pessoais com a finalidade de realização de um estudo observacional denominado *Prevalência e Custos da Deficiência em Portugal: Um Estudo Hospitalar.*

O objectivo do estudo é estimar o número de pessoas com deficiência visual e os custos associados à redução na visão na população da região Norte de Portugal recorrendo à caracterização da população que procura cuidados de saúde nos hospitais, desenvolvendo-se o trabalho em duas partes: i) durante 12 meses será determinada a prevalência da deficiência visual e ii) serão calculados os custos associados à perda visual.

Os dados serão recolhidos em cinco hospitais públicos no Norte de Portugal, nas duas maiores cidades, Porto e Braga e serão incluídos no estudo todos os doentes que forem atendidos nos departamentos de Oftalmologia e que apresentem parâmetros visuais de acordo com a definição de deficiência visual.

Os potenciais casos de deficiência visual serão contactados pelo hospital, por carta ou, caso não esta não seja respondida no prazo de duas semanas, por contacto telefónico.

Os doentes serão identificados pelas iniciais e pela data de nascimento, para evitar duplicações.

Caso decidam participar, os doentes deslocar-se-ão ao hospital para uma visita de duração aproximada de 90 minutos, na qual lhes serão aplicados os seguintes testes:

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medição da acuidade visual com a escala ETDRS longe e perto, medição da sensibilidade visual ao contraste; medição da velocidade de leitura, teste MNREAD; inventário das actividades da vida diária (comprometimento das tarefas diárias pelas dificuldades visuais); questionário sobre custos indiretos da redução da visão (ex.: aquisição de ajudas visuais do tipo lupa ou outros); questionário de utilidades-na-saúde (perguntas sobre o impacto da redução na visão, por exemplo, na mobilidade).

Através do contacto inicial será solicitado o consentimento informado aos titulares dos dados.

A segurança das informações é garantida pela manutenção dos dados em local de acesso reservado.

II. Da Análise

A CNPD já se pronunciou na sua Deliberação n.º 227/2007 sobre o enquadramento legal, os fundamentos de legitimidade, os princípios orientadores para o correto cumprimento da Lei n.º 67/98, de 26 de outubro (Lei de Proteção de Dados – LPD), bem como as condições gerais aplicáveis ao tratamento de dados pessoais para a finalidade de estudos de investigação na área da saúde.
Assim, enquadrando-se o caso em apreço no âmbito tipificado pela referida Deliberação, porque referentes à saúde e à vida privada, os dados recolhidos pela requerente têm a natureza de sensíveis, razão pela qual o respetivo tratamento só pode basear-se no consentimento expresso, esclarecido e livre dos titulares dos dados, nos termos do disposto no n.º 2 do artigo 7.º da LPD.

Entende-se por consentimento expresso qualquer manifestação de vontade, livre, específica e informada, nos termos da qual o titular aceita que os seus dados sejam objeto de tratamento, o qual deve ser obtido através de uma "declaração de consentimento informado " onde seja utilizada uma linguagem clara e acessível.

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Nos termos do artigo 10.º da LPD, a declaração de consentimento tem de conter a identificação do responsável pelo tratamento e a finalidade do tratamento, devendo ainda conter informação sobre a existência e as condições do direito de acesso e de retificação por parte do titular.

O fundamento de legitimidade é, então, o consentimento expresso do titular dos dados, que deve ser obtido junto dos potenciais participantes pelo médico assistente, que não transmitirá quaisquer dados pessoais, designadamente de contacto, à equipa responsável pelo estudo.
A declaração assinada pelo paciente deverá ser junta ao seu processo clínico, que deve ficar na posse do médico assistente.

Não havendo identificação direta dos participantes no caderno de recolha de dados, mas apenas a colocação de código composto pelas iniciais e data de nascimento, cuja chave apenas o médico assistente terá conhecimento e não transmitirá, considera-se que a informação tratada é recolhida de forma lícita (artigo 5.º, n.º1 al. a) da Lei n.º 67/98), para finalidades determinadas, explícitas e legítimas (cf. alínea b) do mesmo artigo) e não é excessiva.

III. Da Conclusão

Em face do exposto, a Comissão Nacional de Protecção de Dados (CNPD) autoriza o tratamento de dados pessoais *supra* apreciado, nos termos do n.º 2 do artigo 7.º, da alínea a) do n.º 1 do artigo 28.º e do n.º 1 do artigo 30.º da LPD, consignando-se o seguinte:

Responsável pelo tratamento: Universidade do Minho;
Finalidade: estudo observacional denominado *Prevalência e Custos da Deficiência em Portugal: Um Estudo Hospitalar.*

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Categoria de Dados pessoais tratados: data de nascimento; género; estado civil; grau de escolaridade; profissão e situação profissional; medição da acuidade visual com a escala ETDRS longe e perto, medição da sensibilidade visual ao contraste; medição da velocidade de leitura, teste MNREAD; inventário das actividades da vida diária (comprometimento das tarefas diárias pelas dificuldades visuais); questionário sobre custos indirectos da redução da visão (ex.: aquisição de ajudas visuais do tipo lupa ou outros); questionário de utilidades-na-saúde (perguntas sobre o impacto da redução na visão, por exemplo, na mobilidade).

Entidades a quem podem ser comunicados: Não há.

Formas de exercício do direito de acesso e retificação: Junto da responsável pelo tratamento dos dados.

Interconexões de tratamentos: Não há.

Transferências de dados para países terceiros: Não há.

Prazo de conservação dos dados: a chave de codificação deverá ser destruída um mês após o fim do estudo.

Lisboa, 1 de julho de 2014

Filipa Calvão (Presidente)

Appendix 4

Appendix 4A - First author declaration – Acta Ophthalmologica paper

Author's Declaration

I, the undersigned, hereby give authorization to my co-author Ana Patrícia Rego da Silva Santos Marques to include the journal article designated by ***"Visual and health outcomes, measured with the activity inventory and the EQ5D, in visual impairment"*** published in Acta Ophthalmologica in her PhD thesis. Ana Patrícia Rego da Silva Santos Marques collaborate in this article with data collection, results analyses and providing help writing and reviewing the manuscript.

Kalmar, 16 February 2019

First author signature: António Filipe Macedo

Appendix 4B - First author declaration – BMC Ophthalmology paper

Author's Declaration

I, the undersigned, hereby give authorization to my co-author Ana Patrícia Rego da Silva Santos Marques to include the journal article designated by ***"Predicting participation of people with impaired vision in epidemiological studies"*** published in BMC Ophthalmology in her PhD thesis. Ana Patrícia Rego da Silva Santos Marques collaborate in this article with data collection, results analyses and providing help writing and reviewing the manuscript.

Braga, 18 February 2019

First author signature:

Pedro Alexandre Fernandes de Lima Ramos

Appendix 5

Table 1 shows episodes distribution per age category and year. There is an increase in the absolute number of episodes for patients older than 50 years and percentage of patients with this age range also increases. In the age range 20-39 there is a reduction in the proportion of cases per year. It changes from 10.9% in 2002 to 2.7% in 2012 and the overall percentage for all years is 4.1%.

Age category 40-49 represents 5% of total cases (table 1). This age category also shows a decline in the proportion of cases per year although the mean average episodes per years increases from 210.5 in 2002/2007 to 744.4 in 2008/2012. The absolute number of cases increases but is associated with diagnosis compatible with anti-VEGF treatment as shown in Table 2.

Overall patients older than 50 years represent 90.0% of cases. Patients below 19 years of age remain constant in absolute values and the proportion reduced from 3.6% in 2006 to 0.4% in 2012.

Table 1 – Episodes per Year and Age Category. 2002-2012

Year/Age range	2002		2003		2004		2005		2006		2007		2008		2009		2010		2011		2012		Total	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
0-19	66	3.6%	44	2.3%	62	2.7%	38	1.6%	67	2.3%	45	0.9%	76	0.9%	94	0.7%	105	0.7%	102	0.5%	90	0.4%	789	0.8%
20-39	197	10.9%	208	11.0%	223	9.8%	200	8.7%	243	8.2%	275	5.8%	374	4.4%	468	3.6%	520	3.3%	654	3.3%	666	2.7%	4028	4.1%
40-49	171	9.4%	165	8.7%	192	8.4%	191	8.3%	242	8.2%	302	6.4%	437	5.2%	620	4.8%	758	4.8%	822	4.1%	1085	4.3%	4985	5.1%
> 50	1381	76.1%	1482	78.%	1808	79%	1876	81.%	2416	81.%	4128	87%	7535	90%	11793	91%	14535	92%	18387	92%	23265	93%	88606	90%
Total	1815	100%	1899	100%	2285	100%	2305	100%	2968	100%	4750	100%	8422	100%	12975	100%	15918	100%	19965	100%	25106	100%	98408	100%

Table 2 shows episodes distribution by diagnosis and age categories for two selected: years 2007 and 2012. These years were chosen because 2007 represents the year before the treatment was approved and 2012 because was the most recent year with complete information available. Diagnoses presented in this table represent 75% of episodes in 2012. Comparing 2007 with 2012 there is an increase of 391 episodes in the age range 20-39 years and 783 cases in the age range 40-49. The seven diagnosis in Table 2 correspond to 81% of extra cases found in in the age range 20-39 and to 76% of the extra cases found in the age range 40-49. The reminder cases were scattered by several diagnosis. The seven diagnoses below all have indication for treatment with anti-VGEF.

Table 2 – Episodes by Principal Diagnosis and Age Category. 2007 and 2012

Principal Diagnoses		2007					2012					2012 vs 2007				
ICD 9 CM	Designation	0-19	20-39	40-49	> 50	Total	0-19	20-39	40-49	> 50	Total	0-19	20-39	40-49	> 50	Total
36252	Exudative Senile Macular Degeneration	0	19	20	1200	1239	0	23	54	8549	8626	0	4	34	7349	7387
25050	Diabetes with Opthalmic Manifestation	0	13	46	740	799	2	117	335	5696	6150	2	104	289	4956	5351
36283	Retinal Oedema	0	4	4	39	47	2	32	53	895	982	2	28	49	856	935
36216	Retinal Nevascularization	6	5	2	14	27	0	94	121	726	941	-6	89	119	712	914
36250	Macular Degeneration Senile (unspecified)	0	0	4	77	81	0	12	10	847	869	0	12	6	770	788
36235	Retina Central Vein Occlusion	0	0	0	17	17	0	6	23	508	537	0	6	23	491	520
36236	Retina Veinous Tributary Occlusion	0	0	0	4	4	0	4	16	605	625	0	4	16	601	621
Others		39	234	226	2037	2536	86	378	473	5439	6376	47	144	247	3402	3840
Total		45	275	302	4128	4750	90	666	1085	23265	25106	45	391	783	19137	20356

Appendix 6

Table 1 – List of comorbidities

1. Cancer
2. Diabetes
3. Heart condition
4. Hypertension
5. Musculoskeletal disorder
6. Pulmonary disease
7. Stroke or brain haemorrhage
8. Hearing impairments
9. Thyroid condition
10. Psychological problems
11. Neurologic problems
12. Chronic allergies
13. Gastrointestinal condition
14. Liver disease
15. Autoimmune diseases
16. Endocrine condition

Appendix 7

Regression models description

Logistic regression - to find determinants of informal care utilisation. The dependent variable was informal care use (non-user=0; user=1) and the independent variables were: gender (dummy variable: Female= 0; Male =1), marital status (dummy variable: Married= 0; Not Married=1), presence of other comorbidities (more than one comorbidity =1; no comorbidities = 0), visual ability (measured by AI), visual acuity in better eye (logMAR scale). The graphic method was used to validate model assumption for residuals independence and to identify extreme cases that were removed from the model whenever it increased the goodness of fit of the model. Multicollinearity was analyzed with Variance Inflation Factor (VIF).

Multiple linear regression - to find predictors of informal care utilisation intensity. Depend variable was hours of informal care. Independent variables were visual ability, age, gender (dummy variable: Female= 0; Male =1), and severity of visual impairment transformed into a dummy variable (visual acuity in the better eye equal or below 1 logMAR = 0; visual acuity in the better eye above 1 logMAR = 1). The model assumption for normality and homoscedasticity of residuals were tested using the Kolmogorov-Smirnoff and the graphic method. Multicollinearity was analyzed with Variance Inflation Factor (VIF).

Appendix 8

Monthly wage adjusted by sex and education for year 2014

Monthly wage adjusted by sex and education for year 2014		
Education level	Male	Female
Did not attend school	731,60 €	604,40 €
4 years of education	858,60 €	639,60 €
6 years of education	878,70 €	653,70 €
9 years of education	954,60 €	728,80 €
12 years of education	1.267,40 €	923,80 €
University undergrad or more	2.259,20 €	1.580,00 €

Source: GEE/ME, Quadros de Pessoal Trabalhadores por conta de outrem

a tempo completo que trabalharam o horário completo no período de referência (outubro)

Available at: http://cite.gov.pt/pt/destaques/complementosDestqs/dis_imprensa.pdf

Unemployment by sex and age - annual average, 2014

Unemployment by sex and age (% of active population) - annual average, 2014			
	Total	Male	Female
PT	14,10%	13,80%	14,50%
less than 25 years old	34,70%	33,90%	35,50%
25-74 years old	12,50%	12,20%	12,80%

Source: Eurostat.v3.4.1-20170407-5840-PROD_EUROBASE

Available at: http://appsso.eurostat.ec.europa.eu/nui/show.do?dataset=une_rt_a&lang=en

Appendix 9

Logistic regression estimates the probability of the outcome occurring **given that the predictor assumes certain values**. In our case logistic regression was used to determine explanatory factors associated with participation in the labour market.

The dependent variable was **employment status in working age participants** (non-working = 0; working =1). The general equation of the linear predictor was:

$$\begin{aligned} &Linear\ predictor \\ &\quad = -3.838 - 0.039\ Visual\ Ability - 1.05\ Visual\ Acuity + 1.369\ Age\ categories - 1.25\ Comorbities\ categories \\ &\quad + 1.05\ Education\ categories + 5.091\ HRQL \end{aligned}$$

Where:

- Visual Ability is a continuous predictor given by the Activity Inventory
- Visual acuity in better eye is a continuous predictor using a logMAR scale
- Age is divided in two categories: 40-64 years=0; 17-39 years=1;
- Comorbidities is divided in two categories: No = 0; Yes =1;
- Education is divided in two categories: less than 12 years of education = 0; 12 years of education or more=1;
- Health related quality of life is a continuous predictor provided by the EQ5D utility score.

When a logistic regression is calculated, the regression coefficient (for example Visual ability) is the estimated increase in the log odds of the *outcome per unit increase* in the value of the *exposure.* In other words, the exponential function of the regression coefficient (*exponential* visual ability) is the odds ratio associated with a one-unit increase in the exposure.

So the probability of Working will be given by:

$$Probability\ (Working = 1) = \frac{exponetial^{linear\ predictor}}{(1 + exponential^{linear\ predictor})} + random\ error$$

Probability is the ratio between the number of events favourable to some outcome and the total number of events. It is constrained between zero and 1.To illustrate our logistic regression model we have built to 2 scenarios: best-case and worst-case. For both scenarios 5 curves were computed according to 5 categories of visual acuity in the better eye.

The best-case scenario includes participants within the age of 17-39 years, 12 years of education or more, no comorbidities and visual ability set as constant equal to the mean value of the group. Table 1 shows categorical variables and linear predictor equations computed for the 5 categories of visual acuity in the better eye for best-case scenario:

Table 1 – Best- case scenario computed for 5 categories of visual acuity in the better eye

Best-case scenario			
Categorical variables	**Linear predictor equation**	**Visual acuity in the better eye Categories**	**Linear predictor according with vision impairment categories**
Visual ability = Mean value of the group = 0.96 Age categories =17-39 years =1 Comorbidities= No = 0 Education= 12 years or more = 1	$linear\ predictor\ = \varepsilon = -3.838 - 0.039\ Visual\ ability - 1.05\ Visual\ Acuity + 1.369(Age\ categories = 1) + 1.05(\ Education\ categories = 1) + 5.091\ HRQL$	No VI: from -0.3 to 0.3 logMar Mid point **ACUITY=0**	$\varepsilon = -3.838 - 0.039 \times (0.96) + 1.369 + 1.05 + 5.091 HRQL$
		Minor VI: from 0.32 to 0.5 logMar Mid point **ACUITY=0.41**	$\varepsilon = -3.838 - 0.039 \times (0.96) - 1.05 \times (0.41) + 1.369 + 1.05 + 5.091 HRQL$
		Moderate VI: from 0.5 to 1.0 logMar Mid point **ACUITY=0.76**	$\varepsilon = -3.838 - 0.039 \times (0.96) - 1.05 \times (0.76) + 1.369 + 1.05 + 5.091 HRQL$
		Severe VI: from 1.02 to 1.3 Mid point **ACUITY=1.16**	$\varepsilon = -3.838 - 0.039 \times (0.96) - 1.05 \times (1.16) + 1.369 + 1.05 + 5.091 HRQL$
		Profound VI or blind: from 1.32 to 3.0 Mid point **ACUITY=2.16**	$\varepsilon = -3.838 - 0.039 \times (0.96) - 1.05 \times (2.16) + 1.369 + 1.05 + 5.091 HRQL$

For example if a patient as a HRQL of 0.6 and visual acuity classified as Profound VI or blind the probability of working will be given by:

$$Probability\ (Working\ status = 1) = \frac{exponential^{-3.838-0.039\times(0.96)-1.05\times(2.16)+1.369+1.05+5.091x(0.6)}}{(1 + exponential^{-3.838-0.039\times(0.96)-1.05\times(2.16)+1.369+1.05+5.091x(0.6)})} + random\ error$$

$$Probability\ (Working\ status = 1) = 0.339 + random\ error$$

A patient with age within 17 to 39 years old, with 12 years of education or more, no comorbidities and visual ability equal to 0.96, health related quality of life of 0.6 and visual acuity classified as profound VI or blind would have a probability of working of 0.339.

The worst-case scenario is defined as participants within the age 40-64 years, less than 12 years of education, comorbidities and visual ability set as constant equal to the mean value of the group. Table 2 shows categorical variables and linear predictor equations computed for the 5 categories of visual acuity in the better eye for Worst-case scenario:

Table 2 – Worst- case scenario computed for 5 categories of visual acuity in the better eye

Worst-case scenario			
Fixed Categorical variables	**Linear predictor equation**	**Visual acuity in the better eye Categories**	**Linear predictor according with vision impairment categories**
Visual ability = Mean value of the group = 0.96 Age categories= 40 - 64 years = 0 Comorbidities=Yes =1 Education= less than 12 years = 0	$\varepsilon = -3.838 - 0.039 Viual\ acuity - 1.05\ Visual\ ability - 1.25(Comorbidities = 1) + 5.091 HRQL$	No VI: from -0.3 to 0.3 logMar Mid point **ViLogmar=0**	$\varepsilon = -3.838 - 0.039 \times -1.25 + 5.091 HRQL$
		Minor VI: from 0.32 to 0.5 logMar Mid point **ViLogmar=0.41**	$\varepsilon = -3.838 - 0.039 \times (0.96) - 1.05\ \times (0.41) - 1.25 + 5.091 HRQL$
		Moderate VI: from 0.5 to 1.0 logMar	$\varepsilon = -3.838 - 0.039 \times (0.96) - 1.05\ \times (0.76) - 1.25 + 5.091 HRQL$

Worst-case scenario			
Fixed Categorical variables	**Linear predictor equation**	**Visual acuity in the better eye Categories**	**Linear predictor according with vision impairment categories**
		Mid point **VI LogMar=0.76**	
		Severe VI: from 1.02 to 1.3 Mid point **VI LogMar=1.16**	$\varepsilon = -3.838 - 0.039 \times (0.96) - 1.05 \times (1.16) - 1.25 + 5.091 HRQL$
		Profound VI or blind: from 1.32 to 3.0 Mid point **VI LogMar=2.16**	$\varepsilon = -3.838 - 0.039 \times (0.96) - 1.05 \times (2.16) - 1.25 + 5.091 HRQL$

For example if a patient as a HRQL of 0.6 and visual acuity classified as Profund VI or blind the probability of working will be given by:

$$Probability\ (Working\ status = 1) = \frac{exponential^{-3.838-0.039\times(0.96)-1.05\times(2.16)-1.25+5.09\,x\,(0.6)}}{(1 + exponetial^{-3.838-0.039\times(0.96)-1.05\times(2.16)-1.25+5.09\,x\,(0.6)})} + random\ error$$

$$Probability\ (Working\ status = 1) = 0.009 + random\ error$$

A patient with age within 40 to 64 years old, with less than 12 years of education, comorbidities and visual ability equal to 0.96 health related quality of life of 0.6 and visual acuity classified as profound VI or blind would have a probability of working of 0.009

Appendix 10

Health state	EQ-5D index	N of participants	Percentage
11111	1.000	14	10%
22222	0.288	14	10%
22223	0.129	10	7%
21223	0.287	9	7%
11112	0.767	7	5%
11121	0.694	7	5%
21222	0.446	7	5%
21221	0.482	6	4%
11122	0.657	5	4%
21111	0.695	5	4%

Appendix 11

Sup-Table 1 - Initial regression model used.

Variables	Beta estimate	Std.error	p-value
Intercept	-1.27	1.44	0.377
***Gender: Male**			
Female	-1.04	0.29	<0.001
***Age: <20**			
[20,30[	-0.76	1.73	0.66
[30,40[	2.12	1.62	0.189
[40,50[	0.36	1.33	0.328
[50,60[	0.67	1.29	0.604
[60,70[	-0.15	1.25	0.904
>=70	-0.22	1.24	0.859
DISTH (km)	-0.02	0.006	<0.001
EDU (years)	0.22	0.05	<0.001
***Low-AHA**			
Medium-AHA	0.65	0.37	0.075
High-AHA	2.16	0.36	<0.001
***MST: Married**			
Living together	3.12	0.6	<0.001
Single	0.25	0.49	<0.001
Widow	-0.14	0.34	0.678
Divorced	3	0.77	<0.001
***VA: 0**			
0.1	-0.74	0.6	0.218
0.2	-2.14	0.58	<0.001
0.3	-1.99	0.63	0.002
0.4	-0.94	0.54	0.084
0.5	-0.29	0.53	0.58
CCI	0.18	0.52	0.729
***Aetiologies: AMD**			
Diabetic retinopathy	0.88	0.41	0.031
Glaucoma	0.6	0.55	0.271
other	0.33	0.44	0.5

***Reference category**

Appendix 12

Sup-Table 1: The table summarizes new categories that were defined after having run the first logistic regression. The categories were used for our final model.

Variables	Categories (levels)
Gender	- Male - Female
DISTH (km)	- Continuous
EDU (years)	- Continuous
AHATTEND	- AHA-rare = number of hospital visits was less than 10 per year; - AHA-frequent = number of hospital visits was 10 or more per year;
MST	- Living together - Divorced - Others (married, single or widowed)
VA	- VA-extreme (includes VA of 0.0 or 0.1 or 0.5) - VA-intermediate (includes VA of 0.2 or 0.3 or 0.4)