Universidade do Minho
Escola de Ciências

Pedro Alexandre Fernandes de Lima Ramos

Studying prevalence using capture-recapture methods: visual impairment in Portugal

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Doctoral Thesis in Mathematics

Work supervised by:

Prof. Doutora Inês Pereira Silva Cunfa Sousa

Prof. Doutor António Filipe Teixeira Macedo

Prof. Doutor Amândio Rocha-Sousa

DECLARAÇÃO

Nome: Pedro Alexandre Fernandes de Lima Ramos

Endereço Eletrónico: pedro.limaramos@lnu.se Telefone: 964557011

Número do cartão de cidadão: 11652588

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Studying prevalence using capture-recapture methods: visual impairment in Portugal

Orientadores:

Prof. Doutora Inês Pereira Silva Cunfa Sousa

Prof. Auxiliar do Departamento de Matemática e Aplicações

Universidade do Minho

Prof. Doutor António Filipe Teixeira Macedo

Prof. Associado do Departamento de Medicina e Optometria

Universidade de Linnaeus, Kalmar, Suécia

Prof. Doutor Amândio Rocha-Sousa

Prof. Associado da Faculdade de Medicina

Universidade do Porto

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STATMENT OF INTEGRITY

I hereby declare having conducted my thesis with integrity. I confirm that I have not used plagiarism or any form of falsification of results in the process of the thesis elaboration.

I further declare that I have fully acknowledged the Code of Ethical Conduct of the University of Minho.

Universidade do Minho, 30 of July 2021

Signature____

TITLE

Applying capture-recapture models to estimate the prevalence of visual impairment in Portugal

ABSTRACT

Visual impairment (VI) due to eye diseases remains a significant health problem worldwide and, also, in Europe. There are an estimated 15 million people suffering from moderate or severe visual impairment in Western Europe. VI has a significant impact on the quality of life by reducing functional status and interfering with the ability of the subject to maintain independence in a safe manner. Prevalence of VI needs to be estimated regularly so that the progress of the vision health of a population can be evaluated and monitored. In addition, it is important to ascertain the causes behind VI so that health programs can be designed to lower its prevalence. There is currently a lack of epidemiological information about the prevalence and causes of VI in Portugal. Therefore, the aim of this thesis was to determine the prevalence of VI in a large region Portugal using data from lists of cases of VI.

Capture-recapture models have been applied in several disciplines, as biomedical sciences, epidemiology or ecology, to estimate the size of populations. In particular, they have been used to estimate the prevalence of several diseases or conditions. Developing these inferential models is of great importance to avoid the high costs and unreasonable time spending of cross-sectional studies. However, applying capture-recapture models is challenging, as they are very sensitive to list dependence and possible capture rates heterogeneity among subgroups of the population. In particular, applying these models to human population samples is additionally challenging, as in most epidemiologic studies only a small number of lists are available. There are two main differences between human and wildlife populations. First, human population lists generally have not a well-defined time order. Second, in wildlife studies there are often more trapping samples than in human population studies. In most epidemiologic surveys, only two to four lists are available. This can be problematic and is an additional difficulty when applying capture-recapture models in the context of human populations.

The main objective of this work was to estimate the prevalence of VI using capture-recapture models. We estimated a crude prevalence of 1.97%,95%CI=[1.56,2.54] to the Northwest of Portugal in the time period between 2014 and 2015, specifically at the regions of Minho and Douro Litoral. Almost 2 of every 100 inhabitants of the Portuguese Northwest suffer from visual impairment. This prevalence value is in line with the values in some countries, particularly with Spain. Diabetic Retinopathy was the main cause (31%), followed by Cataract (15%), Age-related Macular Degeneration (14%) and Glaucoma (10%). This thesis provides a significant contribution to the understanding of the CR methodology in human populations and for the knowledge of the epidemiological information about VI in Portugal.

Key words: Capture-recapture models; human populations; prevalence; visual impairment.

TITULO

Estudo de prevalência usando métodos capture-recapture: deficiência visual em Portugal

RESUMO

A deficiência visual devido a doenças oculares continua a ser um problema de saúde significativo na Europa. Na Europa Ocidental, estima-se que 15 milhões de pessoas sofrem de deficiência visual moderada ou grave A deficiência visual tem um impacto significativo na qualidade de vida, reduzindo o estado funcional e interferindo na capacidade do sujeito em manter a sua independência de forma segura. Portanto, é importante que a sua prevalência seja estimada regularmente para que o progresso da saúde visual de uma população possa ser avaliado e monitorado. Além disso, é importante determinar as suas causas para que programas de saúde possam ser elaborados para reduzir a prevalência. De momento, há uma ausência de informação epidemiológica relativamente à prevalência e às causas da deficiência visual em Portugal. O principal objetivo desta tese é precisamente fornecer essa informação.

Os modelos capture-recapture têm sido aplicados em diversas disciplinas, como ciências biomédicas, epidemiologia ou ecologia, para estimar a dimensão de populações. Em particular, têm sido usados para estimar a prevalência de várias doenças ou condições. O desenvolvimento destes modelos inferenciais é de grande importância para evitar os altos custos e o desmesurado dispêndio de tempo dos estudos cross-sectional. No entanto, a aplicação de modelos capture-recapture é um desafio, pois são muito sensíveis às dependências entre listas e possível heterogeneidade de probabilidades de captura entre subgrupos da população. Em particular, a aplicação destes modelos a populações humanas é um desafio adicional, pois na maioria dos estudos epidemiológicos apenas um pequeno número de listas está disponível. Existem duas diferenças principais entre as populações humanas e as de vida selvagem. Primeiro, as listas de populações humanas geralmente não têm uma ordem temporal bem definida. Em segundo lugar,nos estudos de vida selvagem, frequentemente existem mais listas do que em estudos de populações humanas. Na maioria dos estudos epidemiológicos, apenas duas a quatro listas estão disponíveis. Tal pode ser problemático e é uma dificuldade adicional na aplicação de modelos de capture-recapture no contexto de populações humanas. O objetivo principal deste trabalho foi estimar a prevalência da deficiência visual usando modelos de capture-recapture. Estimamos uma prevalência bruta de 1.97%,95%CI=[1.56,2.54] para o Noroeste de Portugal no período entre 2014 e 2015, especificamente nas regiões do Minho e Douro Litoral. Quase 2 em cada 100 habitantes do Noroeste Português sofrem de deficiência visual. Este valor de prevalência está em linha com os valores de alguns países, em particular da Espanha. A retinopatia diabética foi a principal causa (31%), seguida por catarata (15%), degeneração macular relacionada à idade (14%) e glaucoma (10%).

Key words: Modelos Capture-recapture; populações humanas; prevalência; deficiência visual.

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CHAPTER I INTRODUCTION

This chapter is divided into 4 main sections. Section 1.1 provides a context to this thesis, briefly explains the importance of the topic, and states the general aim and specific goals of this thesis. Section 1.2 and Section 1.3 explain the concept of prevalence and how it can be computed according to the study design or sources of data. The sections also describes the convenience of using capture-recapture methods to compute prevalence. As the main objective of this doctoral project was to estimate the prevalence of visual impairment (VI) in Portugal using capture-recapture models, Section 1.4 provides a brief description of VI as well as the recent studies reporting prevalence values of VI in European countries. In Section 1.5 the construction of lists is described with detail as well as the capture-recapture models we applied. Some techniques to assess list dependences and capture rates heterogeneity among subgroups of the population are also described in this section. Throughout all the chapter Papers 1,2,3 and 4 are described and the connection between the paper and the contents of the thesis is explained.

1.1. Aim and goals of this thesis

Temporal and spatial estimations of disease occurrence are fundamental for disease monitoring and health care planning. This kind of information can be obtained by studying the prevalence and/or the incidence of the disease in the population. The classic methods to determine prevalence are cross-sectional studies in the population. However, these studies are expensive because they imply, for example, screening a significantly large sample of the population.[1-3]. In many diseases the total ascertainment (the process of attempting to ascertain all cases in a population) [4] relies on registries. Registries aim to collect information about all new cases of the disease under study and often rely on a regular collection of data from specialists (in hospitals or elsewhere) but some cases are typically not reported [5]. A method that can be used to calculate the number of disease cases that are missed by imperfect registers is the capture-recapture (CR) method. This method is useful when incomplete information from registers or surveys is available and an estimate of unregistered cases is necessary [6, 7]. The technique can also be used to estimate the size of populations that are difficult to find and count, or populations that are in motion and cannot be counted all at one time [1].

This method has been successfully used in some studies in the ophthalmic literature. It was used to study the prevalence of congenital cataracts in the UK [8, 9], the prevalence of visual impairment caused by diabetes [10], the prevalence of nystagmus [11] and, more recently, it was used by Crew *et al.* in Australia to determine the prevalence of severe visual impairment [12]. The world health organization defined as objective 1 in its action plan 2014-2019 the knowledge of the prevalence and causes of visual impairment [13]. However, at the time of starting this project in year 2017, there was a lack of knowledge about the prevalence and causes of visual impairment in the Portuguese population.

At the start of this project there was information from the prevalence and costs of visual impairment in Portugal (PCVIP-study), from health authorities and blind associations. This information could be used with CR methods to estimate the prevalence of VI in Portugal without the need of cross-sectional studies of the population. Although, given the constraints imposed by the assumptions necessary for the validity of the CR method, a significant amount of theoretical analysis was needed before the final results can be obtained.

The general aim of this thesis was to use capture-recapture methods to estimate prevalence and causes of visual impairment (VI) in a region of Portugal.

To achieve this aim, the following specific goals were established:

Goal 1 was to explore the theoretical basis of CR methods from the literature and beyond in order to face experimental data with superior knowledge of the mathematical concepts behind the estimators used.

Goal 2 was to investigate the quality of the experimental lists available, in order to study the prevalence of visual impairment.

Goal 3 was to apply several capture-recapture models to a final dataset and obtain an estimate for the prevalence of visual impairment in the Northwest of Portugal. Several mathematical approaches were tested, including Bayesian methods [14].

The results of this PhD project intended not only provide estimates for the prevalence of visual impairment in Portugal but also develop a deep knowledge about the CR methods, with implications for prevalence and incidence calculations, study design and maintenance/development of disease registers, in particular for vision related impairment.

During this project, we wrote four papers in which I am the first author. They are included in CHAPTER II. I also collaborated in other papers, these papers are included in this thesis as Appendixes, a brief context of my contribution is given before each paper.

1.2. Fundamental concepts of epidemiology

Biostatistics is the application of statistics to biological data [15]. Epidemiology is an area of knowledge concerned with the number of persons affected by a condition or disease in a defined population. In other words, epidemiology can be defined as “The quantitative study of the distribution, determinants and control of diseases in populations” [16]. Epidemiology studies the distribution and determinants of health-related states or events in specified populations [17]. It also uses this information to reduce illness and promote health and wellbeing [18]. The number of persons affected by a particular condition or disease is important because it allows authorities to make decisions about public health policies. With updated epidemiological information is possible to limit, control or minimise the impact of the disease, to allocate resources, to monitor public health actions, to determine the best treatment options and to forecast the consequence of diseases in the population [19, 20]. Two typical metrics produced by epidemiologic studies are prevalence and/or incidence of disease.

1.3. Prevalence and incidence

Prevalence can be defined as “the proportion of a population or sub-population that has a particular disease at a particular point in time”[16]. There are there ways to report prevalence: crude prevalence, category-specific prevalence and standardized prevalence. Crude prevalence accounts for the total burden of a health condition or disease to a community. It is the number of cases divided by the population at risk. However, some studies may be interested in the prevalence of a disease or condition within an age range. Others may be interested at a specific disease that only affects certain groups. For example, only people with diabetes are at risk of developing Diabetic Retinopathy. Therefore, it may be more important to estimate the prevalence of Diabetic Retinopathy among people with diabetes than among the entire population. Those are two examples of Category-specific prevalence. Standardized prevalence is normally used to compare health outcomes between populations that have different age distributions. The most commonly reported is likely to be crude rates and is eventually informative at local level, but the standardized prevalence is the most informative when comparing prevalence amongst populations.

The incidence of a disease can be defined as "the number of new cases arising in a given period of time in a specified group of people (population)". To estimate incidence three numbers are needed. The time period being studied. The dimension of the population at risk during the time period, the denominator. The number of new cases also during the time period, the numerator. The individuals already with the disease or condition of interest at the beginning of the study are not included. Incidence measures the risk that a subject will get the disease during a time period.

1.3.1. Study designs

In epidemiology there are several types of study designs. Cross-sectional studies (surveys) take a representative sample from the population, large enough to estimate the prevalence of the disease with accuracy. Cross-sectional studies are the most reliable strategy to quantify the number of cases of a particular condition or disease in a population [21]. This method is reliable but has the disadvantage of being very expensive, time consuming and labour intensive. There are reports in the literature of studies that stopped due to budget and time constraints [22]. In many instances, this method represents a cost that is disproportional to the benefits of gathering the information in particular when studying rare conditions or events in the general population [23, 24]. A good example is the epidemiology of pterygium in Victoria (Australia) that surveyed 5147 persons and found only 6 cases of pterygium surgery [25]. Other weakness of this type of studies is that the data was gathered at one time which implies that they cannot be used to prove that a risk factor causes a disease or condition of interest, that is, causality cannot be proven [23].

An alternative to population-based studies is to use registers. Registers are databases where patients or physicians can enrol cases with a particular condition that needs to be registered and they are frequently used to determine prevalence through what is sometimes defined as "case counting". Registers are extensively used to monitor conditions such as cancer, diabetes or tuberculosis [26-28]. The disadvantages include, for example, voluntary registration (in most cases), information dispersed through several registers and misdiagnosis. Case counting has been found to be an ineffective strategy to estimate prevalence of conditions in the general population because many persons fail to register [29, 30].

There are also case-control studies in which a group of individuals with the condition of interest, the group of cases, is compared with other group with subjects without the condition of interest, the group with the controls. These studies are cheap and appropriated to investigate rare diseases. However, they do not catch temporality and therefore they are unable to measure incidence [21]. Cohort studies are longitudinal studies able to estimate incidence and the correlation disease/risk factors. In the beginning of the study participants are divided into two groups, the ones who were exposed to a risk factor for the disease or condition under investigation and the ones who were not. All participants are subsequently followed during the time period of the study and it is registered whether or not they developed the disease. Incidence can be calculated and at the end of the study the number of exposed participants who have developed the disease is compared with the number of non-exposed participants who have not developed the disease. In this way, we can assess if the exposure is a risk fact for developing the disease. Cohort studies are fit to analyse rare conditions, they can establish causality and they have a temporal dimension. However, they are very sensitive to the loss to follow-up situation [24]. Other study design widely used are randomised controlled trials. One group of individuals undergo an intervention and another group does not. The intervention can be a drug, a vaccine, among others. This type of studies is suited to assess if an intervention is effective but tends to be expensive [21].

A methodology that has been shown to be useful in ascertaining the total number of cases using incomplete information from registers is capture-recapture. The situations in which CR methods can be most useful are, for example, when it is too expensive to perform a screening of the entire population or when a condition is very rare (or both). One aim of this PhD was, precisely, to explore the fundamental aspects of this methodology and to apply capture-recapture models to estimate the prevalence of visual impairment in Portugal.

1.4. Definition and causes of vision impairment

According to the World Health Organization (WHO) there are four levels of visual function: mild or normal vision, moderate visual impairment, severe visual impairment and blindness [31]. Moderate visual impairment and severe visual impairment can be combined into one group defined as “low vision". Moderate visual impairment, severe visual impairment and blindness represents all visual impairment. The WHO categories are based on the visual acuity of the better seeing eye. Regarding the category Mild or no visual impairment, vision acuity (VA) is equal to or better than 6/18 in the better eye using Snellen chart measurements. Moderate visual impairment, $6/60 \leq VA < 6/18$. Severe visual impairment, $3/60 \leq VA < 6/60$. Blindness, $VA < 3/60$. Throughout our project, we aim to estimate the prevalence of visual impairment (VI) and we define it as low vision together with blindness.

Visual impairment has a significant impact on the quality of life by reducing functional status and interfering with the ability of the subject to maintain independence in a safe manner [32-37]. Therefore, it is important that the prevalence of VI is estimated regularly so that the progress of the vision health of a population can be evaluated and monitored. Also, it is important to ascertain the causes behind VI so that health programmes can be designed to lower its prevalence [38].

In the year of 2020, in Western Europe, it has been estimated that there were 15 400 000 (95% CI, 13 900 000–16 900 000) people with moderate or severe visual impairment [39]. However, the prevalence of VI and the methodology for the estimation varies significantly from country to country. For example, a population-based conducted in Denmark in 2016 defined VI as best corrected visual acuity worse than 20/40 in the better-seeing eye. The study involved people aged 20 to 94 years and found a prevalence of 0.4% (95% CI, 0.2–0.7) [40]. A population-based cohort study in Germany concerning adults aged 35 to 74 produced a prevalence value of 0.37% (95% CI, 0.28–0.49) for visual impairment, defined as visual acuity (VA) below 0.3 in the better eye [38]. In Iceland, using a random sample of citizens of Reikjavik aged 50 or more years, a prevalence of 0.96% (95% CI, 0.37−1.55) for bilateral visual impairment was reported [41]. A very different estimation with significantly different values was performed in France in 2005, with 57959 individuals with blindness (0.1%) and 1116862 (1.94%) with low vision, that is, a prevalence of VI of 1.95% [42]. In Spain, it was reported a prevalence for near visual impairment of 1.89% (males, 1.36%; females, 2.40%) and 1.89% for distance visual impairment (males, 1.40%; females, 2.34%) [43]. In 2007 and for the population aged 50 years or older, a study from Hungary reported a prevalence of 0.5% (95% CI, 0.2–0.7) for severe visual impairment and 5.1% (95% CI, 4.3–5.9) for moderate visual impairment [44]. These numbers are difficult to compare due to different age categories included and methods used; although, they point to differences between European nations. However, the prevalence in countries of South Europe seems to be higher than the prevalence in Northern European countries and lower than the prevalence in Eastern European countries.

Differences in prevalence of VI in Europe may also be due to differences in disease prevalence. The causes of visual impairment and blindness in most countries in Western Europe are mainly related with diseases associated with age. For example, 70% of all cases of blindness in Germany are due to diseases of old age [45]. In Scotland, for example, the five leading causes of visual impairment, in decreasing frequency, were reported to be: age-related macular degeneration, glaucoma, diabetic retinopathy, myopic degeneration, and optic atrophy [46]. In the Netherlands, it was reported that the five main causes of visual impairment in adults aging more than 55 years old is, in decreasing frequency, were: cataract, age-related macular degeneration, cataract in combination with another cause, myopic macular degeneration and rare causes [47]. In the UK, North London, to people aging more than 65 years old, the main reported causes were cataract, age-related macular degeneration, refractive error and glaucoma [48]. In Italy, from a cohort of 860 persons aged 45 to 69, the main reported causes were cataract, myopia, age-related macular degeneration and diabetic retinopathy [49]. In Bulgaria, the five leading causes of visual impairment in adults were reported to be cataract, age-related macular degeneration, glaucoma, optic atrophy and diabetic retinopathy [50]. In Slovakia, cataract, myopia, glaucoma, diabetic retinopathy and age-related macular degeneration [50]. Concerning children, a study in UK reported that the main causes for severe visual impairment were, in decreasing frequency, cerebral/visual pathways, Retina problems, optic nerve, cataract and glaucoma [51].

1.5. Methods

The design of our study was influenced by the results of Paper 1, in which the profile of the subjects who accept to take part in epidemiologic studies as well as the profile of those who decline to participate were investigated.

Epidemiologic studies involve collecting data from large number of individuals. However, participation rates in such studies, particularly in industrialized 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[52]. 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 [53, 54]. In order to produce reliable outcomes, it is important to consider possible problems arising during the recruitment process and, if possible, control for factors that lead to reduced participation. Some studies have shown that participation rates are influenced by: education (participation increasing with the level of education [55-57]) , gender (women tend to participate more than men [58-60]) and marital status (married people participating more than others [61]). Another factor that has been found to influence participation is general health, as given by the index of comorbidities [57, 62]. 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 [58, 59], whilst others found higher participation rates among young people [55]. 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 [57]. However, in addition to the characteristics of the target group, recruiting strategies can also influence rates of participation. 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) tends to increase credibility [63]. Personalized letters and reply paid envelopes are also known to improve response rates [64]. Other researchers investigated the primary reasons to take part in epidemiologic studies and concluded that participation is, amongst others, driven by moral reasons [63, 65].

Regarding Paper 1, 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. 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. 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". Participants were divided into 2 sub-groups: "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.

Our goal in Paper 1 was to determine the probability of participation as a function of personal characteristics, including severity of vision loss. We wanted to distinguish between the profiles of a participant and a non-participant. We also 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 [66, 67].

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. From the 325 participants, 241 were immediate participants and 84 were late participants. We used logistic regressions with a 10-fold cross-validation [68]. We split 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 generate the final theoretical model which was tested against the real participation results for the 600 cases. 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. This enable us to distinguish between participants (immediate or late) and non-participants. In order to distinguish between immediate and late participants we first used the J48 classifier to define optimal cut points [69, 70]. We used the software Weka 3.8 [71]. Then, we applied chi-square tests and Fisher exact test [72].

1.5.1. Data sources

After contacting several institutions (primary care centre – ACES) in the region of interest of the study we were given access to data concerning subjects issued with medical certificates of visual impairment from the Primary Care Centre of Braga and the Primary Care Centre of Barcelos. From those records, a list with cases from Primary Care Centres was constructed (L1). We also have had access to the records of a blind association named ACAPO, concerning the areas of Braga, Viana do Castelo and Porto.

A second list with cases from ACAPO was constructed (L2). 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 [73]. The study gathered demographic, clinical, and economic information of people with VI. Participants were recruited among patients routinely attending ophthalmologists' appointments at four Portuguese public hospitals, Hospital of Braga, Hospital of

Guimarães, Hospital of Barcelos and Hospital of São João, the last one at the city of Porto. The inclusion criteria were: patients with VA in the better eye of 0.5 decimal (0.30logMAR) or worse and/or visual field less than 20 degrees. The study was designed considering the recommendations of the Vancouver Economic Burden of Vision Loss Group [74]. From the general database generated by the PCVIP study, a list with cases from all Hospitals with visual acuity below 0.3 decimal in the better-seeing eye was filtered (L3).

All the data in these three lists captures information regarding visual impairment in the Northwest of Portugal in the time period between 2014 and 2015, specifically at the regions of Minho and Douro Litoral. These are the lists used in Paper 4. From these lists we filtered the cases of subjects inhabiting the Municipality of Braga. The resulting lists were used in Paper 2, to give an example, and in Paper 3, to perform simulations. In Paper 3 though the list of the Hospital was L2 and the list of ACAPO was L3.

1.5.2. List matching and data filtering

All lists had variables that allowed assessment of repeated cases. Information available included: initials, date of birth, sex, municipality and visual acuity. The list of the Hospitals also had information about the cause of VI. A unique identity string was constructed for each individual in all lists by concatenating the initials of the name, date of birth and sex. For example, an identity string of a subject at a given list could be JS130519802, meaning that the subject first and last name initials were JS, with birth date 13/05/1980 and that the subject was a female. By matching the identity strings of the three lists, it was possible to ascertain the number of individuals present in all three lists and the number of individuals present at any combination of two lists. Upon these values several models were applied.

In Paper 4 we estimated the prevalence of VI in the Northwest of Portugal. The list from Primary Care Centres (L1) had a total of 208 cases (52% females) with a mean age of 60 years old (SD=18.93). The list with the cases from ACAPO (L2) had 878 cases (43% females) with a mean age of 54 years old (SD=18.0). The list of the Hospitals (L3) had 4272 cases (58% females) with a mean age of 74 years old (SD=18.0). Figure 1 shows the Venn diagram representing the intersection between the identity strings of the three lists.

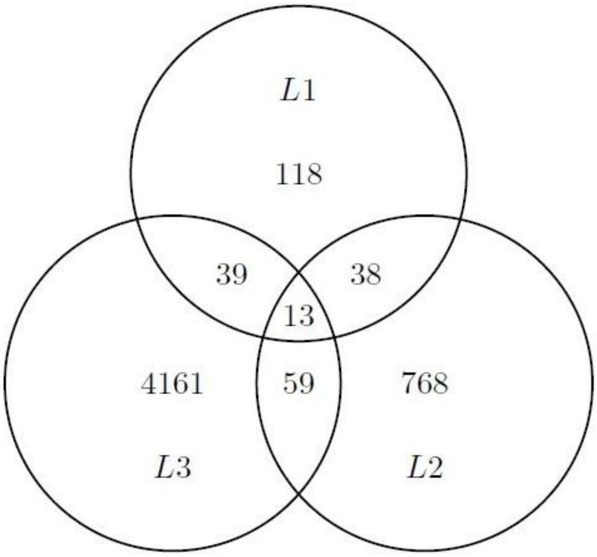


Figure 1: Venn diagram representing the overlap between the three lists.

In Papers 2 and 3, two methodologic papers, we used lists with fewer cases, from which possible values arise for the prevalence of visual impairment in the Municipality of Braga.

1.5.3. Capture-recapture methods

This section describes the main models used in Papers 2 and 3. CR methods were originally developed and used in ecology, but have been applied to characterize prevalence in human populations since 1949 [2]. CR methods use lists from registers (or other reliable sources) of which the completeness is unknown. In health applications, lists can be obtained from hospitals, laboratories, insurers, social service agencies, religious institutions, schools and others. Cases are identified from multiple sources, where a source is defined as any location or origin where a case is reported. All cases from each source make up a list. Lists of cases obtained from 2 or more registers (or sources) can be combined and used to estimate the number of unregistered cases.

One essential aspect is that each list needs to include accurate identifiers such as first and last name, date-of-birth, sex or others in order to build an identity string to each individual. By matching the identity strings of all lists, it is possible to ascertain the number of individuals present in all lists as well as the number of individuals present at any combination of lists. It is this last information that allows the ascertainment of the size of the hidden population, that is, the number of unregistered cases, and therefore the estimation of the prevalence of the disease or condition of interest.

Capture-recapture was first used when ecologists were trying to estimate the number of fish in a lake. Assuming that we want to estimate the total number of fish (N) in a lake, a sample A with n_1 fish is captured, fish are marked and then released back to the lake - the marked rate in the population is given by the $\frac{n_1}{N}$. Next, a sample B with n_2 fish is captured and from those n_2, there are m fish that are marked from the first capture. Thus, the recapture rate is given by the fraction $\frac{m}{n_2}$. If samples A and B are independent, then the marked rate in the population should be approximately equal to the recapture rate, that is, the equality

$$\frac{n_1}{N} = \frac{m}{n_2}$$

is likely to occur [75].

This equation yields the Petersen estimator of the population size ($\widehat{N}$):

$$\widehat{N} = \frac{n_1 n_2}{m}$$

The Petersen estimator can also be used in human populations. The captured samples are lists and the probability of an individual being captured in a certain list is often defined as *ascertainment probability*.

1.5.4. Concept of independence and heterogeneity

Typically, there are two sources of variability that may affect the probability of capture of a unit in a list: - behavioural variability, that is, the inclusion of a subject in one list has a direct causal effect on his/hers inclusion in other lists and heterogeneity - due to specific characteristics of each unit, that is, observable or unobservable features of each subject may have an impact on his/hers capture probability [76]. If the capture probability at any list does not depend on whether the individual is present at other lists, then there is, according to some authors, local independence [75]. Heterogeneity can be observed in clusters if capture probabilities differ among a finite number of classes of individuals [77]. Those classes can be males and females, juveniles and adults, among others It can also be observed individually if a different rate of capture for each individual is observed [77].

Positive local dependence occurs when individuals captured in a list A are more likely to be also in list B than those not in list A. When this occurs then the two fractions given above are unequal, $\frac{n_1}{N} < \frac{m}{n_2}$, which is equivalent to $N > \frac{n_1 n_2}{m}$. Therefore, in this case, the Petersen formula underestimates the true size of the population. In contrast, if the two lists have local negative dependence, then $\frac{n_1}{N} > \frac{m}{n_2}$, which yields $N < \frac{n_1 n_2}{m}$. In this case there will be an overestimation of the true size of the population.

The Petersen estimator is subject to bias if n_{11} is small or zero [78]. Therefore in 1951 Chapman modified the Petersen estimator, which resulted in the Chapman estimator:

$$\widehat{N} = \frac{(n_{10} + n_{11} + 1)(n_{01} + n_{11} + 1)}{n_{11} + 1} - 1$$

Chapman showed that if $n_{10} + n_{01} + 2n_{11} \geq N$ the previous estimator is an exactly unbiased estimator of N [79]. If $n_{10} + n_{01} + 2n_{11} < N$, then the bias of the Chapman estimator is less than 2% if $\frac{(n_{10}+n_{11})(n_{01}+n_{11})}{N} > 4$ [80]. However, N is unknown but if $n_{11} > 7$ then there is a 95% chance that $\frac{(n_{10}+n_{11})(n_{01}+n_{11})}{N} > 4$ and the bias of Chapman estimator is negligible [81, 82].

1.5.5. Several types of capture-recapture models

Log-linear models determine the expected value of n_{ijk}, that is, the expected value to the number of individuals with capture history $(i\ j\ k)$. It uses the Poisson distribution to model the count of a contingency table computed from the lists (each list has two categories, captured and not captured). It models the logarithm of the expected value of each observable cell of such contingency table. If there are three lists and there is local dependence amongst the three and local dependence between any possible pair of lists, then the log-linear model is given by:

$$\log E(n_{ijk}) = u_0 + u_1 I(i=1) + u_2 I(j=1) + u_3 I(k=1) + u_{12} I(i=j=1) + u_{13} I(i=k=1) + u_{23} I(j=k=1) + u_{123} I(i=j=k=1)$$

As a matter of example, in the equation above $I(i=1)$ stands for the function that assigns 1 to capture history $(1\ j\ k)$ and 0 to all the others. Log-linear models estimate the logarithm of the expected value for the number of individuals with capture history $(i\ j\ k)$, that is, $\log E(n_{ijk})$. For example, the parameter u_{12} models the dependence between lists 1 and 2, and u_{13} the dependence among lists 1 and 3 and so on [83].

Consider now that only lists 1 and 3 are dependent. If we want to compute the expected number of individuals with capture history $(1\ 0\ 1)$, that is, $E(n_{101})$, then we use the formula:

$$\log E(n_{101}) = u_0 + u_1 + u_3 + u_{13} \Leftrightarrow E(n_{101}) = e^{u_0+u_1+u_3+u_{13}}$$

The values of all parameters (in this case, u_0 , u_1, u_3 , u_{13}) can be obtained, for example, by using the R package Rcapture [84, 85]. This package can be used to estimate the abundance and other demographic parameters for closed and open populations using log-linear models. By comparing the difference between the estimated value of individuals with a capture history $(1\ 0\ 1)$ and the actual number of subjects with that capture-history, the bias of the model can be computed. By doing the same to all observed capture-histories, the deviance of the model can be calculated. The deviance of the model measures its quality in terms of how well its predictions fit the experimental data. Data is the set of vectors with all observed capture-histories, low deviance values correspond to better model fittings.

The main objective though is to compute an estimation of the size of the population N (e.g. the number of people with vision impairment) and to do that we need to determine the expected number of subjects that are missing from our available lists. That is, we need to estimate the number of individuals with a capture history $(0\ 0\ 0)$ and that is given by the expression:

$$\log E(n_{000}) = u_0 \Leftrightarrow E(n_{000}) = e^{u_0}$$

The number of individuals with capture history (0 0 0) is then added to the number of individuals that have been captured on the lists:

$$\widehat{N} = n_{100} + n_{010} + n_{001} + n_{111} + e^{u_0}$$

When, for example, there is an interaction between lists 1 and 2 and between lists 1 and 3, then equation 1 would yield the $(12, 13)$ log-linear model:

$$\begin{aligned}\log E(n_{ijk}) = u_0 + u_1 I(i=1) + u_2 I(j=1) + u_3 I(k=1) + u_{12} I(i=j=1) \\ + u_{13} I(i=k=1)\end{aligned}$$

Usually, models are denoted as $M_{subscripts}$ and the subscripts are $t\ b, h$ [83]. Models allowing capture probabilities for a fixed population unit to vary between lists are indexed by t, with t standing for time. Models with local list dependence, the behavioural effect, are indexed by b. Models that deal with heterogeneity are indexed by h. Therefore, in the more general structure, we have M_{tbh} models; M_{bh} or M_b models and other combinations are also possible [75]. There is also the M_0 model, in which there is no local list dependence, no heterogeneity and the capture probability is the same to all individuals throughout the entire capture time [86, 87]. In short, models can allow capture probabilities to vary by time, individual, response to capture and combinations of the previous [3].

Some models include covariates to explain the different capture probabilities among individuals due to heterogeneity [88-90]. For example, the probability of capture in a certain list for an individual may depend on covariates such as gender, age or the severity of a disease.

Other models compute capture probabilities conditioned on each possible partial capture history [91-93]. Capture occasions do not even need to be ordered along a time horizon [94]. Let us consider a discrete capture-recapture experiment in which a closed population is sampled r times. The units of such population are assumed to act independently. The units are associated with a capture history. Data can be represented as an $\mathrm{N} \times \mathrm{r}$ binary matrix $\mathrm{X} = [x_{ij}]$, with $\mathrm{x}_{ij} = 1$ if the $i-th$ unit is captured at list j and $\mathrm{x_{ij}} = 0$ otherwise. If $\Omega = \{0,1\}$, then $\Omega^r = \{0,1\}^r$ is the set of all possible capture histories. Capture probabilities are conditioned on each possible partial capture history as follows

$$\begin{cases} p_1() = Pr(x_{i1} = 1) \\ p_j\left(x_{i1}, \dots, x_{i(j-1)}\right) = Pr\left(x_{ij} = 1 | x_{i1}, \dots, x_{i(j-1)}\right) \quad \forall j > 1, \forall\left(x_{i1}, \dots, x_{i(j-1)}\right) \in \Omega^{j-1}. \\ \end{cases}$$

For example, $p_3(1,0)$ represents the probability of a unit to be captured at the list 3 given that was captured at list 1 and not captured at list 2. This is a saturated model. Constrained versions based on conditional probabilities constraints are constructed. The number of parameters is reduced by doing a partition of the set H of all possible partial capture histories. All past partial capture histories of the same equivalence class originate the same future capture probability. The size of the population N is the only parameter of interest, all the other parameters are considered nuisance parameters. The most popular approach in capture-recapture analysis to make inference on N is used. The unconditional likelihood is factorized in two factors. The first is the conditional likelihood, corresponding to the observed units. That is, the joint probability of observing the capture histories of all observed units conditionally on the fact that they are eventually observed. The second factor is the binomial likelihood, a residual term. The estimation of N follows two steps: maximization of the conditional likelihood deriving an estimation for all nuisance parameters; maximizing the binomial likelihood as a function of N only, plugging in the estimates of all the other nuisance parameters calculated in the first step. We used this model in Paper 3.

An important estimator, used, for example, by the previous model, is the Horvitz-Thompson estimator [95]. Suppose that a system identifies a case with a probability $(1 - p_0)$. Then, the population size is $N = Np_0 + N(1 - p_0)$. Note that $N(1 - p_0)$ is the number of observed cases, n_{obsv}, or, according to the previous notation, M. So, the previous equation can be written as $N = n_{obsv} + Np_0$, which leads to the Horvitz-Thompson estimator

$$\hat{n}_{HTE} = \frac{n_{obsv}}{(1 - \hat{p}_0)}$$

The Horvitz-Thompson estimator can also be derived as the maximum likelihood estimator of the number of trials in a binomial experiment when the probability of success is known, and it is equal to $1 - \hat{p}_0$.

There are two main differences between human and wildlife populations. First, human population lists generally have not a well-defined time order. Second, in wildlife studies there are often more trapping samples than in human population studies. In most epidemiologic surveys only two to four lists are available [75]. Some authors though argue that the use of more than three lists does not substantially alter the confidence of the results and that multiple human population lists should be condensed into three lists for the use of capture-recapture models [96].

1.5.6. Techniques to assess list dependence and heterogeneity of capture rates between individuals

Similarly to what other researchers have been investigating [91, 97], in Paper 3, we regarded each capture occurrence of unit i at list j as a binary outcome whose probability of success can be modelled by a linear logistic regression with an explanatory variable $z_{ij} = q(x_{i1}, \ldots, x_{ij-1})$ associated to the partial capture history. That is,

$$log\left(\frac{Pr(x_{ij}=1|x_{i1},\ldots,x_{i(j-1)})}{\left(1-Pr(x_{ij}=1|x_{i1},\ldots,x_{i(j-1)})\right)}\right) = \alpha + \beta z_{ij} \quad \forall i, j$$

where $\boldsymbol{z_{ij}}$ is a suitable numeric summary of partial capture history.

Contrarily to Fegatelli et al. [91], we defined $\boldsymbol{z_{ij}}$ not as continuous but as a factor. It assigns one value to each possible partial capture history. In this way, this covariate groups the sequences of progressive individual partial capture histories.

If $n_{obsv} + 1 \leq i \leq N$, then $z_{ij} = 0$, $\forall j$. If we set a function z and a value to N, then the unconditional likelihood function obtained from a linear logistic model fitted using $N \times t$ binary observations with the corresponding numerical covariates z_{ij} is

$$L(N, \alpha, \beta) = \binom{N}{n_{obsv}} \left[\prod_{i=1}^{N} \prod_{j=1}^{t} \left(\frac{exp(\alpha + \beta z_{ij})}{1 + exp(\alpha + \beta z_{ij})} \right)^{x_{ij}} \left(1 - \frac{exp(\alpha + \beta z_{ij})}{1 + exp(\alpha + \beta z_{ij})} \right)^{1 - x_{ij}} \right].$$

For each value $N \in [n_{obsv} + 1, N_{upper}]$, N_{upper} a reasonable upper limit to N, a logistic regression was performed, the previous equation was applied and

$\hat{L}(N) = L(N, \hat{\alpha}(N), \hat{\beta}(N))$ was calculated.

A sequence of logistic regressions was performed, which was computationally demanding and time-consuming. The value of N that maximizes the unconditional likelihood function is the estimate for the population size. That is, the maximum likelihood estimate for N is

$$\widehat{N} = arg \max_{N \in [n_{obsv}+1, N_{upper}]} (\hat{L}(N)).$$

For example, to the scenario in which there is only one dependence between lists, L_2 and L_3, Hospital and ACAPO respectively, we defined the memory-related summary z as represented in Table 1

Table 1: Covariate z *for the scenario in which there is only one list dependence,* L_2 L_3

Partial capture history	$\boldsymbol{z}$
()	0
(0)	0
(1)	0
(1 0)	0
(0 1)	1
(1 1)	1
(0 0)	0

For example, a subject is captured in list L_2. That capture will produce a value 1 in the binary variable Y. If that subject was captured in L_1, then his partial capture history is (1) and this will produce a value 0 in the variable z. The index of 1 in the binary variable Y is the same as the index of 0 in the variable z.

N took all multiple of 5 values between 850 and 4300. For example, for $N = 1500$, we will have $1500 - 842 = 658$ $(0,0,0)$ capture histories, wich adds $658 \times 3 = 1974$ values of 0 to the binary variable Y as well as 1974 values of 0 to the behavioral explanarory variable z.

In fact, the first 0 of a capture history $(0,0,0)$ has associated the partial capture history $()$ and $z(()) = 0$. The second 0 of a capture history $(0,0,0)$ has associated the partial capture history (0) and $z((0)) = 0$. The third 0 of a capture history $(0,0,0)$ has associated the partial capture history $(0 \ \ 0)$ and $z((0 \ \ 0)) = 0$. Finally, a logistic regression is apllied to Y and z. This regression models the capture probabilty of any subject at any list as a function of his/hers partial capture history assuming there is only one list dependence, L_2 and L_3.

Table 2: Covariates z assuming list dependences scenarios; pch stands for partial capture history

List dependence scenarios	**Covariate** z
$L_1, \quad L_2$	$z = \begin{cases} 1 & if \ pch = (1) \\ 0 & otherwise \end{cases}$
$L_1, \quad L_3$	$z = \begin{cases} 1 & ifpch = (10) \ or \ pch = (1 \ \ 1) \\ 0 & otherwise \end{cases}$
$L_2, \quad L_3$	$z = \begin{cases} 1 & if \ pch = (0 \ \ 1) \ or \ pch = (1 \ \ 1) \\ 0 & otherwise \end{cases}$
$L_1, \ L_2$ and $L_2, \ L_3$	$z = \begin{cases} 2 & if \ pch = (0 \ \ 1) \ or \ pch = (1 \ \ 1) \\ 1 & if \ pch = (1) \\ 0 & otherwise \end{cases}$
$L_1, \ L_2$ and $L_1, \ L_3$	$z = \begin{cases} 2 & if \ pch = (1 \ \ 0) \ or \ pch = (1 \ \ 1) \\ 1 & if \ pch = (1) \\ 0 & otherwise \end{cases}$
$L_1, \ L_3$ and $L_2, \ L_3$	$z = \begin{cases} 3 & if \ pch = (1 \ \ 1) \\ 2 & if \ pch = (0 \ \ 1) \\ 1 & if \ pch = (1 \ \ 0) \\ 0 & otherwise \end{cases}$

For each multiple of 5 value of N between 850 and 4300, a binary variable Y and a behavioural explanatory variable z, defined as in Table 2, were built and a logistic regression was applied. For each regression the log-likelihood was calculated. The population size $\widehat{N}$ assigned with the regression with the highest likelihood value is the maximum likelihood population size estimate within the $L_2,\ L_3$ list dependence scenario.

We did the same for other covariates assuming other list dependences scenarios, represented in the Table 2. The covariate was considered a factor, $z = 0$ the class of reference, β_1 the coefficient of $z = 1$, β_2 the coefficient of $z = 2$, β_3 the coefficient of $z = 3$.

Our simulation performed 4146 logistic regressions, 691 regressions for each covariate establishing a list dependence scenario. The results are represented in *Figure 2* .

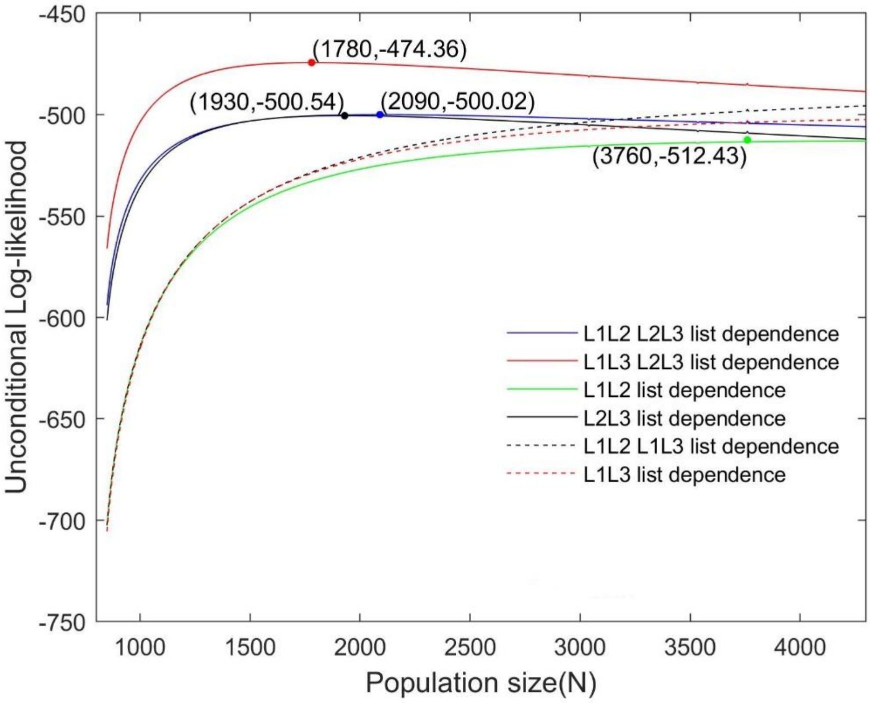


Figure 2: Unconditional log-likelihood varying with the population size to several list dependence scenarios.

Regardless of the value of N, the unconditional log-likelihood of the list dependence scenario L_1, L_3 and $L_2,\ L_3$ is always greater than the unconditional log-likelihood of all other scenarios. It reaches the peak at $\widehat{N} = 1780$. The scenario $L_1,\ L_2$ and $L_2,\ L_3$ reaches its maximum at $\widehat{N} = 2090$, L_2, L_3 at $\widehat{N} = 1930$, $L_1,\ L_2$ at $\widehat{N} = 3760$. The scenario $L_1,\ L_3$ as well as the scenario $L_1,\ L_2$ and L_1, L_3 either diverge or reach the peak for values of N greater than 4300, which is an unrealistic situation.

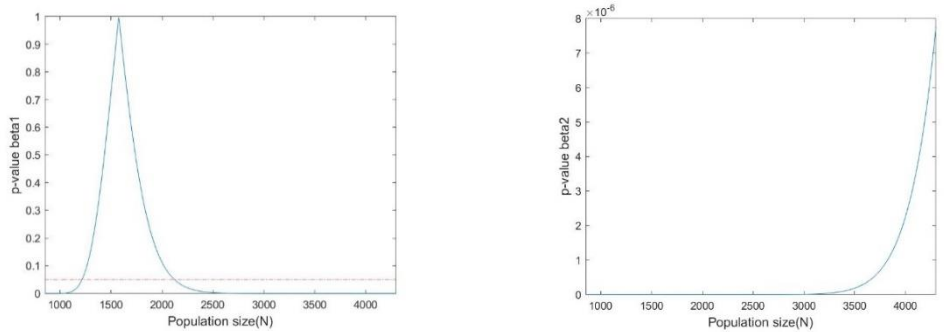
The logistic regressions associated with the four highlighted peak points were analysed in detail and the results are in Table 3.

Table 3: Logistic regressions associated with the four maximum likelihood estimates of N

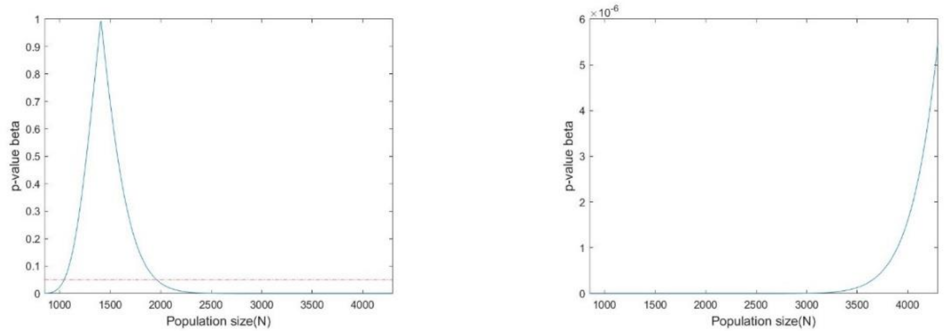
Scenarios	**LogLiK**	**AIC**	α	**p-value** α	β	**p-value** β
$L_1,\ L_3$ and $L_2,\ L_3$	-474.4	4647	-1.44	$< 2e$-16	$\beta_1 = -17.13$	0.98
					$\beta_2 = -17.13$	0.95
					$\beta_3 =$20.00	0.90
$L_1,\ L_2$ and $L_2,\ L_3$	-500	5118.6	-1.67	$< 2e$-16	$\beta_1 = 0.40$	0.0625
					$\beta_2 = -2.31$	5.74e-13
$L_2,\ L_3$	-500.5	4945.2	-1.56	$< 2e$-16	-2.43	3.81e-14
$L_1,\ L_2$	-512.4	6359.6	-2.44	$< 2e$-16	1.16	4.44e-08

The scenario $L_1,\ L_3$ and $L_2,\ L_3$ has the best Log-likelihood curve. However, its logistic regression with maximum likelihood only has the intercept as statistically significant. The logistic regression with maximum likelihood of the scenario $L_1,\ L_2$ and $L_2,\ L_3$ has the coefficient of the class $z = 2$ as statistically significant while the level $z = 1$ almost reaches such status. This information suggests that the levels $z = 0$ and $z = 1$ should be merged, which would lead to the covariate of the $L_2,\ L_3$ scenario. Both the $L_2,\ L_3$ scenario and the $L_1,\ L_2$ scenario have statistically significant covariate coefficients. In the $L_2,\ L_3$ scenario though, such p-value is lower as well as the AIC. The goodness of fit test indicates that this model fits the data well, $p = Pr(\chi^2_{5788} \geq 4941.2) \approx 1$.

Figure 3 represents the p-value for the nullity of the coefficient of z varying with the population size within the last three scenarios. As it can be observed, regarding the list dependence scenario $L_1,\ L_2$ and $L_2,\ L_3$, the p-value for the nullity of the coefficient of $z = 1$ is above 0.05 to values of N approximately between 1200 and 2100. Regarding the scenario $L_1,\ L_2$, the p-value also is not always significant. On the contrary, within the scenario $L_2,\ L_3$, the p-value is always significant no matter the value of N and always with extremely low values. The variable establishing this list dependence scenario is always statistically significant predicting capture probabilities regardless of the value of N.



a) List dependence $L_1L_2\ L_2L_3$ b) List dependence $L_1L_2\ L_2L_3$



c) List dependence L_1L_2 d) List dependence L_2L_3

Figure 3: The p-value for the nullity of the coefficient of z *varying with the population size.*

All considered, the $L_2,\ L_3$ list dependence scenario is perhaps the most likely. By choosing the logistic regression with maximum likelihood assuming this scenario, we were consequently led to one conclusion when applying its odds ratios. The odds of being captured if your partial capture history is $(0\ \ 1)$ or $(1\ \ 1)$ are $exp(2.43) = 11.36$ lower than the odds of being captured if your partial capture history is $(1\ \ 0)$ or $(0\ \ 0)$. In other words, the odds of being captured in L_3 are 11.36 lower if an individual is also in L_2.

Ignoring the heterogeneity of capture rates between subjects when it does exist may result in the underestimation of the size of the population [98]. Heterogeneity can be observed in clusters if capture probabilities differ among a finite number of classes of individuals. Those classes can be males and females, juveniles and adults, among others. It can also be observed individually if a different rate of capture for each individual is observed [77].

The approach consisting of modelling heterogeneity in clusters by finite mixture models has been applied by some authors [98-100]. The finite mixture model or latent-class model has the characteristic that the heterogeneity distribution is discrete. The mixing distribution can be interpreted as the heterogeneity distribution. To model individual heterogeneity some continuous models for the heterogeneity distribution have been proposed, as the beta-binomial.

To investigate the possibility of existence of heterogeneity through clusters, we applied in Paper 3 binomial mixtures [98, 99] to model the counting distribution, that is, the distribution of the variable that counts how many times a case has been identified by the registration system.

By counting the number of times every case is captured several parameters can be calculated. The number of cases that were captured exactly 1 time is n_1, the number of cases captured exactly 2 times is n_2 and so on till the number of cases captured exactly t times n_t, with t the number of lists. Modelling the counting distribution with a mixture of binomials, yields

$$f(y, Q, \Theta) = \sum_{j=1}^{k} q_j \binom{t}{y} \theta_j^y \left(1 - \theta_j\right)^{t-y},$$

with k the number of clusters, $y = 0,1,\dots,t$, $\Theta = \{\theta_1,\dots,\theta_k\}$ and $Q = \{q_1,\dots,q_k\}$, Q the mixing distribution.

Supposing that $f(y, Q, \Theta)$ is a suitable distributional model for the counting distribution of the number of times Y a case was captured, the Horvitz-Thompson estimator becomes

$$\hat{n}_{HTE} = \frac{n_{obsv}}{1 - f(0, Q, \Theta)}.$$

In order to calculate the maximum likelihood estimation of Q and Θ we applied the EM algorithm. We used the popular algorithmic framework for mixtures of distributions [99], described below.

Step 0 Choose some initial value for $Q^{(0)}$; $j = 0$.

Step 1 Choose some initial value for $\Theta^{(0)}$;

Step 2 Compute $\hat{n}^{(j+1)} = \frac{n_{obsv}}{1-f\left(0,Q^j,\Theta^j\right)}$ and $\hat{n}_0{}^{(j+1)} = \hat{n}^{(j+1)} - n_{obsv}$;

Step 3 Use the complete frequency table $\hat{n}_0{}^{(j+1)}, n_1, \dots, n_t$ to compute a new maximum likelihood estimator $Q^{(j+1)}$;

Step 4 $j = j + 1$; go back to Step 2.

In Step 3 the non-parametric maximum likelihood estimation of the mixing distribution Q needs itself to be algorithmically calculated. The EM steps for mixtures are well known. First, define $e_{il}^{j} = \frac{f\left(i,\theta_l^j\right)q_l^j}{f(i,Q^j)}$ and let $n_0 = \hat{n}_0{}^{(j+1)}$. Then:

Step 3.1 $q_l^{(j+1)} = \frac{1}{\hat{n}^{(j+1)}}\sum_{i=0}^{t} n_i e_{il}^{(j)}$;

Step 3.2 Find solution $\theta_l^{(j+1)}$ for the $l-th$ component scoring equation in θ_l

$$\sum_{i=0}^{t} n_i e_{il}^{(j)} \frac{\partial}{\partial\theta_l} f(i,\theta_l)$$

for $l = 1,\dots,k$. The solution of the previous equation for the binomial density is

$$\theta_l^{(j+1)} = \frac{\sum_{i=0}^{t} i\, n_i e_{il}^{(j)}}{\sum_{i=0}^{t} n_i t\, e_{il}^{(j)}}.$$

In Paper 3, after applying this algorithm to our data, we concluded that the situation with only one cluster $k = 1$ produced the best log-likelihood value and the only credible value for $\widehat{N}$. This suggests that heterogeneity through clusters is unlikely.

We investigated the possibility of individual heterogeneity with another type of model that considers the individual capture probability θ as being drawn from a continuous probability distribution on the interval $(0,\ 1)$. If the distribution of θ has probability density function (pdf) $g(\theta)$, then the probability of an individual being captured y times becomes

$$\pi_y = \int_0^1 \binom{t}{y} \theta_j^y \left(1-\theta_j\right)^{t-y} g(\theta) d\theta, \qquad y = 0,1,\dots,t.$$

We considered $g(\theta)$ to be the pdf of a beta distribution $Beta(\alpha,\beta)$, $\alpha,\beta > 0$. It follows that

$$\pi_y = f(y|t,\alpha,\beta) = \frac{\Gamma(\alpha\beta)}{\Gamma(\alpha)\Gamma(\beta)} \frac{\Gamma(\alpha+y)\Gamma(t-y+\beta)}{\Gamma(t+\alpha+\beta)}, \qquad y = 0,1,\dots,t.$$

This is the so-called beta-binomial distribution. The multinomial likelihood function as well as the estimation of N, α and β, through maximum likelihood calculations can be seen in [77]. In Paper 3, by applying this model to our data, we obtained values for the population size with magnitudes of millions. Therefore, when we estimated the population size on the assumption that individual heterogeneity exists, we obtained values even more unrealistic than when we consider heterogeneity through the existence of clusters. We concluded that individual heterogeneity is also unlikely. The capture probability of a subject at a given list is only a function of whether or not he/she is present on the other lists.

CHAPTER II ARTICLES AS FIRST AUTHOR

This chapter presents four papers that form the core contents of this thesis because I am the first author, the papers are presented according to their date of submission.

Section 2.1 corresponds to Paper 1 that gives the design of the study Prevalence of Costs os Visual Impairment in Portugal – The PCVIP study. This paper is a comprehensive description of the methodology used to gather data about the people with visual impairment attending hospital appointment in 4 hospitals in the region of interest of our study. Information from the hospitals was later used as the fundamental list to determine prevalence and causes of visual impairment in Portugal. These are the results published in Section 2.4.

Section 2.2 corresponds to Paper 2, that is a comprehensive review of the literature about the methodology of capture -recapture. This review fits into goal 1 of this thesis. The review was important to clarify definitions, explore the theoretical concepts of the method capture-recapture and to start to link the methodology to the type of ophthalmological data that we wanted to work with. Writing this review with collaborators from other parts of the world and having the work per reviewed was a fundamental step to be confident to use it with the data available to compute prevalence of vision impairment in Portugal.

Section 2.3 corresponds to Paper 3, the need to work on these theoretical concepts arose during the writing of the literature review. In this paper, we aim to explore other more sophisticated techniques and inferential tools to understand and model list dependence and heterogeneity, as briefly given in sub-sections 1.5.4 to 1.5.6 .

Section 2.4 corresponds to Paper 4 and in this paper, we report the prevalence of causes of vision impairment in Northwest Portugal. This publication was the ultimate objective of this thesis but, has described above, before computing these results it was necessary to work in different fronts (2.1 to 2.3) to be confident to perform the calculations reported.

2.1. Paper 1: Predicting participation of people with impaired vision in epidemiological studies

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RESEARCH ARTICLE **Open Access**

Predicting participation of people with impaired vision in epidemiological studies

Pedro Lima Ramos[1,2], Rui Santana[3], Laura Hernandez Moreno[1], Ana Patricia Marques[3], Cristina Freitas[4], Amandio Rocha-Sousa[5,6], Antonio Filipe Macedo[1,2*] and The Portuguese visual impairment study group

Abstract

Background: The characteristics of the target group and the design of an epidemiologic study, in particular the recruiting methods, can influence participation. People with vision impairment 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. Therefore, participation of people with impaired vision in studies is less predictable than predicting participation for the general population.

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.

Keywords: Study participation, Epidemiologic studies, Study design, Vision impairment, Recruitment strategies

Background

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 [1]. 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 [2–5]. 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

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* Correspondence: a.macedo@ucl.ac.uk
[1] Low Vision and Visual Rehabilitation Lab, Department and Center of Physics – Optometry and Vision Science, University of Minho, Braga, Portugal
[2] Department of Medicine and Optometry, Linnaeus University, 39182 Kalmar, Sweden
Full list of author information is available at the end of the article

influenced by: education (participation increasing with the level of education [6–8]), gender (women tend to participate more than men [9–11]) and marital status (married people participating more than others [12]). Another factor that has been found to influence participation is general health, as given by the index of comorbidities [8]. 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 [9, 10], whilst others found higher participation rates among young people [6]. 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 [8]. 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 [13]. 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 [14]. Other researchers investigated the primary reasons to take part in epidemiologic studies and concluded that participation is, amongst others, driven by moral reasons [13, 15]. 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 [16].

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 [17]. However, this group was more interested in health service barriers for parents with children with VI [17].

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 [18–21].

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 [16, 22]. 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 http://www.pcdvp.org/login.php. 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 [23]. 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 [24].

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 = 63,752, 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 [25].

Table 1 Summary of the distribution of 600 subjects included in the analysis. Among 600, 325 are participants [a] (immediate or late) and 275 non-participants randomly selected from 1577 total non-participants

Characteristic	*n* (%)	Participation YES/NO	Participation (%)	*p*-value (χ^2)
Gender				< 0.001
Male	339 (56.6)	225/114	66.4	
Female	261 (43.4)	100/161	38.3	
Age group				0.00535
< 20 yrs	14 (2.3)	12/2	85.7	
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	82 (13.7)	52/30	63.4	
60 to < 70 yrs	137 (22.8)	80/57	58.4	
≥ 70 yrs	288 (48.0)	114/174	39.6	
Number of Hospital Appointments per year (AHATTEND)				< 0.001
Low - AHA (≤4×/yr)	173 (28.8)	52/121	30.1	
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)				< 0.001
Married	261 (43.5)	110/151	42.1	
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)				< 0.001
0	42 (7.0)	26/16	61.9	
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)				0.4336
Adult Macular Degeneration	76 (16.0)	31/45	40.8	
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] Participants as mentioned here include immediate and late participants

The median DISTH (in kilometres) for the complete sample was 9.6 km (IQR = 24.2), for participants was 1 km (IQR = 15.1) and for non-participants was 19.4 km (IQR = 38.7); this difference was statistically significant (Mann-Whitney, U = 24,416, $p < 0.001$). Other socio-demographic and VI-related data are summarized in Tables 1 and 2.

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

Table 2 Summary of the distribution of all cases ($n = 600$) according to participation

Characteristic	Participants ($n = 325$)		Non-participants ($n = 275$) n (%)	p-value (χ^2)
	Immediate ($n = 241$) n (%)	Late ($n = 84$) n (%)		
Gender				< 0.001
Male	183 (75.9)	42 (50)	114 (41.4)	
Female	58 (24.1)	42 (50)	161 (58.6)	
Age group				0.00535
< 20 yrs	10 (4.1)	2 (2.4)	2 (0.7)	
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				< 0.001
Low - AHA (≤4×/yr)	42 (17.4)	10 (11.9)	121 (44)	
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				< 0.001
Married	75 (31.1)	35 (41.7)	151 (54.9)	
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)				< 0.001
0	18 (7.5)	8 (9.5)	16 (5.8)	
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(*)				0.4336
Age-related Macular Degeneration	18 (7.5)	13 (15.5)	45 (16.4)	
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			

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 [26].

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 Additional file 1: Table S1).

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 Additional file 1: Table S1). For the final model, non-significant variables were removed and other levels or categories were defined as summarized in Additional file 2: Table S2. We now give an example to explain the rational. In the initial model, Additional file 1: Table S1, 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", Additional file 2: Table S2. 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.

Table 3 Multivariable logistic regression model used to predict the probability of participation

Variables/Characteristic	Beta coefficient (SE)	Odds Ratio (95% CI)	*p*-value
Gender			< 0.001
Female vs. Male	−1.27 (0.24)	0.28 (2.23–5.71)	
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 - in times-per-year (AHATTEND)			< 0.001
≥ 10×/yr vs < 10×/yr	1.64 (0.24)	5.18 (3.24–8.69)	
Marital Status (MST)			< 0.001
Living together vs. Others (married, single or widowed)	3.26 (0.46)	26.14 (10.62–64.4)	
Divorced vs. Others (married, single or widowed)	2.74 (0.56)	15.44 (5.15–46.27)	
Visual acuity (VA)			< 0.001
Intermediate (0.2–0.4) vs. extreme (0, 0.1 or 0.5)	1.10 (0.23)	3.02 (1.92–4.74)	

SE standard error, *CI* Confidence Interval

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 3. 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).

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:

$$\begin{aligned} \textit{Linear predictor} = {} & -1.71 - 1.27\left(\textit{If Gender} = {}''\textit{female}''\right) \\ & -0.02\,\textit{DISTH} + 0.21\,\textit{EDU} \\ & +1.64\left(\textit{If AHATTEND} = {}''\textit{frequent}''\right) \\ & +3.26\left(\textit{If MST} = {}''\textit{co–habiting}''\right) \\ & +2.74\left(\textit{If MST} = {}''\text{divorced}''\right) \\ & +1.1\left(\textit{If VA} = {}''\text{extreme}''\right) \end{aligned} \tag{1}$$

$$\textit{Participation probability} = \frac{e^{\textit{linear predictor}}}{1 + e^{\textit{linear predictor}}} \tag{2}$$

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 3. 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 3 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.

Table 4 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 and 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

According with the final model, the worst profile regarding the probability of participation, was being female attending the hospital 10× or less a year, married, single or widowed, with VA 0.2–0.4. The best profile was being male; attending the hospital 10× or more a year, living in a non-marital partnership, and VA ≤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 Fig. 1.

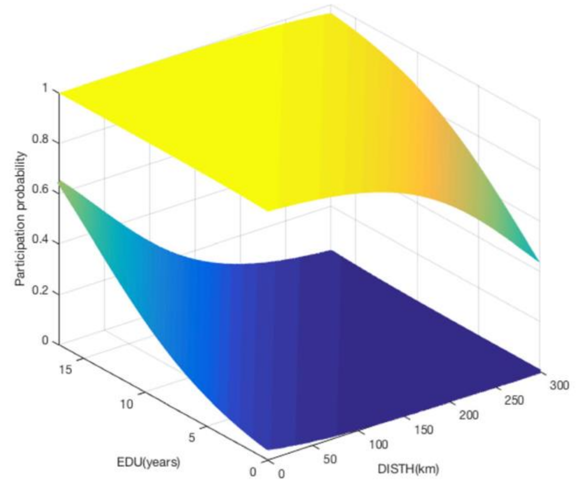

Fig. 1 Variation of the probability of participation predicted by our model according with the continuous variables DISTH and EDU. The two surfaces represent the most favourable and less favourable participation profiles defined according with the categorical variables used. The top yellow surface represents 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 0-150 km, the participation probability reduces slowly. That is, the distance residence-hospital is almost irrelevant within the range 0-150 km. For distance values greater than 150 km the probability of participation decreases sharply. When living over 150 km 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-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 when is below 100 km.

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 4.

To build the categories defined in Table 4, 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 Fig. 2 - 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, for example, 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.

The decision about which demographic aspects would be compared was based on 3 criteria applied according with the sequence presented here: (1) specific hypothesis

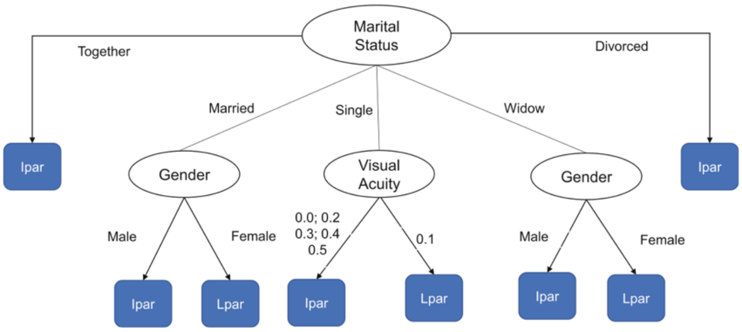

Fig. 2 Classification tree originated by the C4.5 / J48 algorithm predicting immediate and late participation

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 AGE_1 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 AGE_2, 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 AGE_2 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 EDU_1 within the group of those who are females, AGE_2 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 Fig. 3.

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 years 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 4. 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 AGE_1 was 20% (17 of 84) amongst Lpar and was 2% (5 of 275)

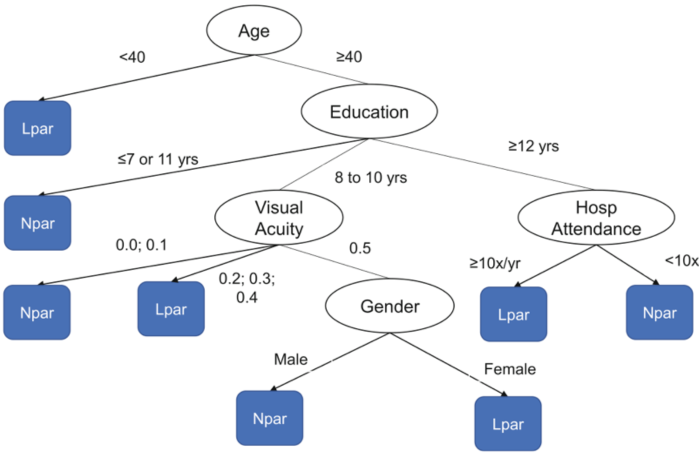

Fig. 3 Classification tree originated by the C4.5 / J48 algorithm predicting late participation and non-participation

amongst Npar (Fisher's exact test, $p < 0.001$). For those in the group AGE_3 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 $DISTH_1$ subjects within the group of those who are AGE_2 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 AGE_2 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 EDU_1 within the group of those who are AGE_3 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 AGE_2 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 AGE_3 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 AGE_1 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 AGE_2 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 AGE_3 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 that were willing to take part in interviews 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 [27]. 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 are in line with our initial hypotheses, 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 [16]. 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 [28]. 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 [29, 30].

The participation rate in our study was higher amongst men than women, which contrasts with some studies [9–11]. This is a result that needs further investigation but we acknowledge that this might be related to cultural factors because Correia et al. also found, in Portugal, higher participation amongst men [27]. 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 [12]. 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 [16]. In line with our results for education status, increased participation with the number of years of education has been reported in other studies [6–8]. 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 are likely to be due to the development of an acute civic awareness and/or familiarity with the hospital environment amongst those visiting the hospital more frequently.

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 [13, 15]. 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 [31, 32]. 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 [16, 22]. However, similar to results in other studies [33, 34], 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 [31, 32]. 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" [31–33, 35].

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.

Additional files

Additional file 1: Table S1. Initial regression model used. (DOCX 20 kb)

Additional file 2: Table S2. The table summarizes new categories that were defined after having run the first logistic regression. The categories were used for our final model. (DOCX 17 kb)

Additional file 3: Data used and analysed in this study. (XLSX 101 kb)

Abbreviations

AGE_1: Age less than 40 years; AGE_2: age between 40 and 69 years; AGE_3: age 70 or more years; AHA-frequent: number of annual hospital appointments 10 or more; AHA-rare: number of annual hospital appointments less than 10; AHATTEND: annual hospital attendance; AMD: age-related macular degeneration; CAUSE-VI: cause of visual impairment; CCI: Charlson comorbidities index; DISTH: distance from the residence to the hospital; $DISTH_1$: distance residence-hospital was less than 40 km; $DISTH_2$: distance residence-hospital was 40 km or more; 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; EDU: number of years of education; EDU_1: less than 12 years of education; EDU_2: 12 or more years of education; Ipar: immediate participants; Lpar: late participants; MST: marital status; Npar: non-participants; PCVIP-study: Prevalence and Costs of Visual Impairment in Portugal: a hospital based study; SD: standard deviation; SE: standard error; VA: visual acuity in the better eye; VI: vision impairment

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The members of "The Portuguese visual impairment study group" (PORVIS group) are:

- Amandio Rocha-Sousa (i)
- Marta Silva (i)
- Sara Perestrelo (i)
- João Tavares-Ferreira (i)
- Ana Marta Oliveira (i)
- Cristina Freitas (ii)
- Keissy Sousa (ii)
- Ricardo Leite (ii)
- José C Mendes (ii)
- Andreia B Soares (ii)
- Rui C Freitas (ii)
- Pedro Reimão (iii)
- Marco Vieira (iii)
- Joel Monteiro (iii)
- Natacha Moreno (iv)
- Gary Rubin (v)
- -Ana P Marques (vi)
- Rui Santana (vi)
- Laura Moreno (vii)
- Pedro L Ramos (vii)
- Antonio F Macedo (vii)

(i) From the Department of Surgery and Physiology; Faculty of Medicine; University of Porto and Department of Ophthalmology and Centro Hospitalar São João, Portugal
(ii) From the Department of Ophthalmology, Hospital de Braga, Portugal
(iii) From the Department of Ophthalmology, Centro Hospitalar de Alto Ave, Portugal
(iv) From the Department of Ophthalmology, Hospital Sta Maria Maior, Portugal
(v) From the UCL-Institute of Ophthalmology, United Kingdom
(vi) From the National School of Public Health, NOVA University of Lisbon, Portugal
(vii) From the Low Vision and Visual Rehabilitation Lab, Department and Center of Physics – Optometry and Vision Science, University of Minho, Portugal and Linnaeus University, Department of Medicine and Optometry, Sweden

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Availability of data and materials
All data used and analysed in this study are provide in Additional file 3.

Authors' contributions
AFM, RS, CF, ARS, designed the study; PLR, LHM, APM, CF, AFM, PORVIS group collected data and PLR, LHM, APM, AFM analyzed the results; all authors participated in reporting and evaluating the results. PLR and AFM wrote the first draft of the manuscript and all authors contributed to subsequent writing. All authors approved the current version of the manuscript.

Ethics approval and consent to participate
The study protocol was reviewed by the ethics committee for Life Sciences and Health of the University of Minho (REF: SECVS-084/2013) and was conducted in accordance with the principles of the Declaration of Helsinki. Written informed consent was obtained from individuals that agreed to participate in face-to-face interviews. The study was registered with the Portuguese data protection authority with the reference 9936/2013 and received approval number 5982/2014.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

Author details
[1]Low Vision and Visual Rehabilitation Lab, Department and Center of Physics – Optometry and Vision Science, University of Minho, Braga, Portugal. [2]Department of Medicine and Optometry, Linnaeus University, 39182 Kalmar, Sweden. [3]Centro de Investigação em Saúde Pública, Escola Nacional de Saúde Pública, Universidade NOVA de Lisboa, Lisbon, Portugal. [4]Department of Ophthalmology, Hospital de Braga, Braga, Portugal. [5]Department of Surgery and Physiology, Faculty of Medicine, University of Porto, Porto, Portugal. [6]Department of Ophthalmology, Centro Hospitalar São João, Porto, Portugal.

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2.2. Paper 2: A Review of Capture-recapture Methods and its Possibilities in Ophthalmology and Vision Sciences

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A Review of Capture-recapture Methods and Its Possibilities in Ophthalmology and Vision Sciences

Pedro Lima Ramos[a,b], Inês Sousa[c], Rui Santana[d], William H Morgan[e], Keith Gordon[f], Julie Crewe[e], Amândio Rocha-Sousa[g], and Antonio Filipe Macedo[a,b]

[a]Department of Medicine, Optometry Linnaeus University Kalmar, Kalmar, Sweden; [b]Department and Center of Physics—Optometry and Vision Science, University of Minho, Braga, Portugal; [c]Department of Mathematics and Applications and Center of Molecular and Environmental Biology, School of Sciences, University of Minho, Braga, Portugal; [d]National School of Public Health and Comprehensive Health Research Centre, Public Health Research Centre, NOVA University of Lisbon, Lisbon, Portugal; [e]Lions Eye Institute, Centre for Ophthalmology and Vision Science, University of Western Australia, Perth, Australia; [f]New Zealand Blind Foundation, Te Tūāpapa O Te Hunga Kāpō, Auckland, New Zealand; [g]Organs of Senses, Faculty of Medicine, University of Porto, Porto, Portugal

ABSTRACT
Epidemiological information is expected to be used to develop key aspects of eye care such as to control and minimise the impact of diseases, to allocate resources, to monitor public health actions, to determine the best treatment options and to forecast the consequence of diseases in populations. Epidemiological studies are expected to provide information about the prevalence and/or incidence of eye diseases or conditions. To determine prevalence is necessary to perform a cross-sectional screening of the population at risk to ascertain the number of cases.

The aim of this review is to describe and evaluate capture-recapture methods (or models) to ascertaining the number of individuals with a disease (e.g. diabetic retinopathy) or condition (e.g. vision impairment) in the population.

The review covers the fundamental aspects of capture-recapture methods that would enable non-experts in epidemiology to use it in ophthalmic studies. The review provides information about theoretical aspects of the method with examples of studies in ophthalmology in which it has been used. We also provide a problem/solution approach for limitations arising from the lists obtained from registers or other reliable sources.

We concluded that capture-recapture models can be considered reliable to estimate the total number of cases with eye conditions using incomplete information from registers. Accordingly, the method may be used to maintain updated epidemiological information about eye conditions helping to tackle the lack of surveillance information in many regions of the globe.

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Capture-recapture; Prevalence; Vision impairment; Ophthalmology; Optometry

Fundamental epidemiology

Epidemiology is an area of medicine concerned with the number of persons affected by a condition or disease in a defined population. In other words, epidemiology can be defined as "The quantitative study of the distribution, determinants and control of diseases in populations".[1,2] Epidemiologic studies provide, amongst other relevant numbers, information about the prevalence and/or incidence of diseases or conditions.

Prevalence can be defined as "*the proportion of a population, or sub-population, that has a particular disease at a particular point in time*".[3] For example, the Coimbra study reported the prevalence of AMD in the Portuguese population. In addition, the Coimbra AMD study also characterized risk factors for disease development.[4,5] Prevalence can be reported as crude prevalence (crude rates), category-specific prevalence and standardized prevalence.[3] Prevalence is commonly reported as a percentage, such as 1.5%, that is the number of cases per 100 people in the population.

Incidence can be defined *as "the number of new cases arising in a given period of time in a specified group of people (population)"*.[6] The incidence of a disease will depend on its aetiology, i.e., why it occurs. The incidence of diabetic retinopathy in Portugal,[7] incidence of tuberculosis[8] or incidence of prostate cancer[9] are examples of studies conducted in Portugal to monitor eye diseases or other relevant conditions. The prevalence of a disease depends not only on the incidence but also on the course of the disease, how long it lasts, whether it can be treated, and whether people die as a result of it.[6]

This review covers a method of ascertaining for the number of individuals with a disease (e.g. diabetic retinopathy) or condition (e.g. vision impairment)

CONTACT Antonio Filipe Macedo antonio.macedo@lnu.se Department of Medicine and Optometry, Linnaeus University, Kalmar, SE 39182, Sweden
Supplemental data for this article can be accessed here.

using capture-recapture methods. This method can be used to determine the prevalence and/or incidence, but in this review, we cover almost exclusively examples of prevalence with emphasis on the prevalence of vision impairment. Once affected by eye diseases that cause irreversible vision loss, individuals often have to live with the condition for the rest of their lives. Whilst the incidence of vision impairment may be low in developed countries, the prevalence is likely to rise due to the growing and aging population.[10]

Methods to determine the prevalence of eye conditions

There are several strategies to quantify the number of cases of a particular condition or disease in a population. However, the most reliable results are those obtained from a screening of the general population or cross-sectional studies.[2] In this case, a random and representative sample of the entire population or the target group, when the population of interest is a subgroup of the general population, must be screened for the condition by qualified researchers or clinicians. This method is reliable but has the disadvantage of being very expensive, time consuming and labour intensive. There are reports in the literature of studies that stopped due to budget and time constraints.[11] In many instances, this method represents a cost that is disproportional to the benefits of gathering the information in particular when studying rare conditions or events in the general population. A good example is the epidemiology of pterygium in Victoria (Australia) that surveyed 5147 persons and found only 6 cases of pterygium surgery.[12] Therefore, alternative methods can be and have been used.

An alternative to screening the population is to use population surveys. In this case information about the clinical condition of interest is self-reported. The most basic example of a survey with self-reported data is the national CENSUS that most countries conduct every 5 or 10 years. According to some authors, such a survey is not expected to provide data on the number of people with a disease of interest but is expected to tell how many are at risk of a disease in the general population.[2] However, self-reported information about disease suffers from several types of bias and leads to inaccurate estimates.[13] Common causes for this include the lack of knowledge about the condition and social desirability[14,15] but they are still being used in some instances.[16] An example of inaccurate self-reported information is the number of cases of vision-impaired individuals reached by CENSUS in Portugal.[17] In 2011, 892860 persons reported *"difficulties to see even when wearing optical correction"* and 27659 reported to be *"impossible to see"*. When taken together, that is, summing these two numbers and dividing the result by the number of individuals living in the country, this would lead to a crude prevalence of vision impairment in Portugal of approximately 9%. This crude prevalence would be extremely alarming but, fortunately, is unlikely to be true. Another alternative to population studies is to use registers.

Registers are databases where patients or physicians can enrol cases with a particular condition that needs to be registered and they are frequently used to determine prevalence through what is sometimes defined as "case counting". Registers are extensively used to monitor conditions such as cancer, diabetes or tuberculosis.[8,9,18] Registers are typically inexpensive and readily accessible when needed. The disadvantages include, for example, voluntary registration (in most cases), information dispersed through several registers and misdiagnosis. Case counting has been found to be an ineffective strategy to estimate the prevalence of conditions in the general population because many persons fail to register.[19,20] Although there are more elaborated ways to use registers, a methodology that has been shown to be useful in ascertaining the total number of cases using incomplete information from registers is capture-recapture (CR).

The aim of this review is to cover the fundamental aspects of this methodology that would enable non-experts in epidemiology to use it in ophthalmic studies. The structure that we adopted is expected to cover the fundamental theoretical aspects of the method and to provide examples of studies in ophthalmology in which the methodology has been used. We also provide a problem/solution approach for limitations arising, in particular, from the lists obtained from registers or other reliable sources.

The review is organized in small sections summarized here: section 3) section *capture-recapture methods* provides a brief historical perspective and a definition of CR methods; section 4) section *assumptions and requirements* describes what a researcher needs to know about the method before deciding on the use of this methodology to investigate prevalence (before collecting data); section 5) section *data analysis* describe what problems can arise during the process of combining information and analyse it (after collecting data); in section 6) section *computation of prevalence* we provide an example of the calculations of prevalence of vision impairment with three lists, in section *discussion and recommendations* we discuss the key messages of this review and section 8 section *literature review* gives a summary of the literature search.

Capture-recapture methods

CR methods were originally developed and used in ecology, but have been applied to characterize prevalence in human populations since 1949.[21] In ophthalmology, it has been used to determine the prevalence of a range of conditions including congenital cataracts and vision impairment.[22–31]

CR methods use lists from registers (or other reliable sources) of which the completeness is unknown. In health applications lists can be obtained from hospitals, laboratories, insurers, social service agencies, religious institutions, schools and others. Cases are identified from multiple sources, with a source defined as any location or origin where a case is reported. All cases from each source make up a list. Lists of cases obtained from two or more registers (or sources) can be combined and used to estimate the number of unregistered cases. A real-world example of this calculation is given in *section computation of prevalence*.

Estimating the total number of cases allows, in most circumstances, the estimate of prevalence or incidence of diseases in a population. The situations in which CR methods can be most useful are, for example, when it is too expensive to perform a screening of the entire population or when a condition is very rare (or both). There are basic requirements that need to be attained if the CR methods are to be utilized, requirements are described below.

Assumptions and requirements

To be used in CR, lists – defined as databases containing the profile of people with a condition of interest, need to be obtained at approximately the same time, or based on different sources that represent approximately the same population.[23] In addition, to obtain reliable results with CR methods certain assumptions need to be met: 1) the sources of lists are independent – this implies that the probability of a subject being in both list A and list B equals the product between the probability of being in A alone and the probability of being in B alone,[32] 2) the probability of association within each source (catchability) is equal for all individuals – the probability may vary from one list to another, or be constant overall,[32,33] 3) the population is closed (no births, deaths or migrants). These assumptions are restrictive and, when applied to medical conditions, are unlikely to be met.[32] Below we clarify some of the most important and, eventually, less intuitive concepts: list (in)dependence and closed populations and we also explain how to proceed when assumptions are not met.

List requirements

A list is a collection of units from a population and the act of generating a list is said to be a capture. A list in the context of human populations needs to include a minimum of demographic information about the people with the condition of interest. To be useful, the list most contained information entered in an organized and reliable way. Examples of lists are the databases of cases associated with tuberculosis or human immunodeficiency virus. In most European countries these are communicable diseases, meaning that health professionals are required to communicate them to central health authorities.[34,35] One essential aspect is that each list needs to include accurate identifiers such as first and last name, date-of-birth and sex. In the case of diseases, the diagnosis should ideally be confirmed by medically qualified professionals. All lists must have the same minimum amount of case-information that can be used to compare records during prevalence estimation using CR. Case-information is used to create a unique tag or a combination of tags that corresponds to a unique identifier for each subject. Tags are then used to determine the intersection of records in different lists (see sub-section *issues with tag-loss*).

Here we need to distinguish two types of list independence: a) the local independence and b) homogeneity across individuals. A detailed explanation of these concepts is provided below.

Local independence considers individuals as fixed and their presence in a list does not affect their probability of being included in other lists that are used. Mathematically speaking the local independence between lists implies that the event that unit i is in a certain list is independent of the event that unit i is in any combination of the other lists.[36] Local list independence is a theoretical concept that needs to be discussed by the investigators that know the origin of their lists. Although there are “diagnostic tools” for list independence that are discussed in sections *data analysis* and *computation of prevalence* with numerical examples. An intuitive example how to use this definition consists of separated lists from primary eye care providers (e.g. optometrists, consider this list A) and specialized eye care (e.g. eye care clinics at hospital, consider this list B). This procedure can lead to local dependence between lists because the sources of the lists refer to each other. That is, the fact that a patient is seen by an optometrist changes the probability of this patient to be in the eye clinic at the hospital. Patients seen by optometrists are more likely to be referred to the eye clinic at the hospital than if they did not look for eye care with the optometrist.

Local dependence between lists can be positive or negative.[2,37] Positive dependence means that individuals captured in the first capture, for example list A, are more likely to be captured in the second list, e.g. list B, than those that were not captured in list A. That is the type of dependence that should be expected in the example above (local optometrist and hospital eye clinic). This type of dependence can lead to an underestimation of the true size of the population.[34] In contrast, negative dependence exists when individuals captured in a list are less likely to be captured in other subsequent lists. In other words, if the presence of an individual in list A excludes or reduces the probability of him/her from being in list B, then this can be considered negative dependence. This type of dependence leads to an overestimation of the true size of the population.[33,36] From the previous example, if we consider list A taken from an eye clinic at hospital A and list B taken from an eye clinic at hospital B (assuming equal levels of specialization in both clinics), the presence of an individual in list A is likely to reduce the probability of that individual being in list B. That is, because the patient is already in treatment in one hospital it is unlikely that he or she is treated, for the same condition, in a second hospital. The examples given show that researches need to think carefully about the sources for their lists before they start to collect data. There are some solutions when assumptions of independence are not met and that is discussed in section *data analysis*.

The homogeneity across individuals means that the probability of capture in a list is independent of the individual characteristics of the subjects and is the same to all subjects.[38] In contrast, if there is heterogeneity, then the probability of capture in any sample is an attribute of the individual and may vary across the population. Subjects may vary in their capture probability according to age, sex, disease severity, social status and other factors.[39] Using the previous example, heterogeneity between individuals may exist if the probability of being registered at the eye clinic is a function of the individual's income and/or the distance between his home and the clinic.

In short, local dependence between lists means that probability of capture of a subject i in a list j depends on his past capture history. Heterogeneity means that the capture probability of a subject i in a list j depends on some specific attributes of the subject such as age, sex or income. These two concepts are linked to the concept of (equal) catchability. Equal catchability means that all individuals are equally likely to be chosen in each capture.[40] If local list independence fails, then the probability of capture in any list depends on the individual's prior history of capture and, therefore, the equal catchability assumption is violated. When homogeneity fails the probability of capture in any list is related with attributes of individuals and varies across the population, which makes the equal catchability assumption to be violated. If the assumption of equal catchability holds, then the two types of independence are verified.

Population requirements

One requirement of the traditional CR methods is that the population needs to be closed. That is, during the sampling period there will be no subjects coming in or out of the population (no migrations, births and no deaths).[41] Strictly speaking, this may be impossible to accomplish in human populations. Still, it is sometimes reasonable to admit that during the capture period the population is closed.[41,42] When the assumption of the closed population can be considered, methods described in sub-sections *analysing list dependence with the Petersen estimator and* using *log-linear models with dependent lists* can be used to determine the number of individuals with the condition of the interest in the population. If the population is open more elaborate and complicated methods are needed, those are briefly described in subsection *using log-linear models with dependent lists*. In this review, we provide only a superficial overview of complicated theoretical methods.

Data analysis

This section provides a list of procedures that need to be executed to assess if the lists and population meet the assumptions discussed in section *assumptions and requirements*. When assumptions are violated, we explain that and suggest some solutions. This section starts with the introduction of the Petersen estimator. This estimator can be used when there are only two lists, but it is also important to analyse dependence amongst pairs of lists when three or more are available. Then, we describe the use of log-linear models as an alternative when is desirable to use more than 2 lists or when the two available lists are dependent. Most studies use three lists and when more than 3 lists are available, the recommendations are to merge them.[43,44] The other three topics covered in this section are: 1) how to deal with open populations, 2) how to deal with poor information to identify subjects in lists (tag-loss) and 3) how to deal with false negatives or false positives.

Analysing list dependence with the Petersen estimator

The Petersen estimator is a formula that provides an estimate of size N of the population or, in other words, the unknown number of individuals affected by a disease (within a population) when two lists are available. To use the Petersen estimator (a) the population need to be considered closed, (b) the assumption of equal catchability holds (the capture probability may change throughout time, but within each capture, it is the same to all individuals) and (c) there are no problems with the individual's identifiers. If lists are dependent, the Petersen estimator should not be used. The bias in N induced by dependent lists can be significant.[22]

Now we explain the basis of the Petersen formula with an example from ecology using two samples (equivalent to 2 captures). Assume that we want to estimate the total number of fish (N) in a lake. A sample A with n_1 fish is captured, fish are marked and then released back to the lake – the marked rate in the population is given by the $\frac{n_1}{N}$. Next, a sample B with n_2 fish is captured and from those n_2, there are m fish that are marked from the first capture. Thus, the recapture rate is given by the fraction $\frac{m}{n_2}$. If samples A and B are independent, then the marked rate in the population should be approximately equal to the recapture rate, that is, the equality:

$$\frac{n_1}{N} = \frac{m}{n_2}$$

is likely to occur.[36]

This equation yields the Petersen estimator of the population size ($\hat{N}$):

$$\hat{N} = \frac{n_1 n_2}{m}$$

The Petersen estimator can also be used in human populations. The captured samples are lists and the probability of an individual being captured in a certain list is often defined as *ascertainment probability*. The Petersen formula is used in *computation of prevalence* with a numerical example.

In sub-section *list requirements* we explained that two lists may have local dependence and dependence may be positive or negative. Positive local dependence occurs when individuals captured in a list A are more likely to be also in list B than those not in list A. When this occurs then the two fractions given above are unequal, $\frac{n_1}{N} < \frac{m}{n_2}$, which is equivalent to $N > \frac{n_1 n_2}{m}$. Therefore, in this case, the Petersen formula underestimates the true size of the population. In contrast, if the two lists have local negative dependence, then $\frac{n_1}{N} > \frac{m}{n_2}$, which yields $N < \frac{n_1 n_2}{m}$. In this case, there will be an overestimation of the true size of the population.

At this point, it is important to refresh the concept of capture history using mathematics. Given two generic lists, the capture history y for a particular individual may be (i) y = (1,0) – individual is in list A but is not in list B, (ii) y = (0,1) – individual is not in list A but is in list B, (iii) y = (1,1) – individual is in list A and B, and (iv) y = (0,0) – individual is neither in list A nor in list B. What CR methods try to estimate is the number of individuals with a capture history (0,0), that is, the population not captured in either list.

In this scenario, $n_1 = n_{10} + n_{11}$, $n_2 = n_{11} + n_{01}$ and $m = n_{11}$. By replacing these values in the initial Petersen equation, $\hat{N} = \frac{n_1 n_2}{m}$, we obtain $\hat{N} = n_{10} + n_{11} + n_{01} + \frac{n_{10} n_{01}}{n_{11}}$. This is another expression to the Petersen estimator, in which n_{10} is the number of individuals with capture history $(1,0)$, n_{01} is the number of individuals with capture history $(0,1)$ and n_{11} the number of individuals with capture history $(1,1)$.

The Petersen estimator is subject to bias if n_{11} is small or zero.[45] Therefore, in 1951 Chapman modified the Petersen estimator, which resulted in the Chapman estimator:

$$\hat{N} = \frac{(n_{10} + n_{11} + 1)(n_{01} + n_{11} + 1)}{n_{11} + 1} - 1$$

Chapman showed that if $n_{10} + n_{01} + 2n_{11} \geq N$ the previous estimator is an exactly unbiased estimator of N.[46] If $n_{10} + n_{01} + 2n_{11} < N$, then the bias of the Chapman estimator is less than 2% if $\frac{(n_{10}+n_{11})(n_{01}+n_{11})}{N} > 4$.[47] However, N is unknown but if $n_{11} > 7$ then there is a 95% chance that $\frac{(n_{10}+n_{11})(n_{01}+n_{11})}{N} > 4$ and the bias of Chapman estimator is negligible.[48,49] In *computation of prevalence* we will use both the Petersen and the Chapman estimators.

In human populations, it is difficult to obtain two lists that are categorically independent[50]; however, they can be considered independent if the dependence is low.[34] There are several methods to assess which, if any, lists are dependent. For example, some authors defined the *"coefficient of covariation between samples"* that measures the degree of dependence among them.[36] There is also the odds ratio implemented with capture-recapture methods developed by Wittes et al.,[22,51] that estimates the increased probability of a case being reported in a first source when it is also reported in a second source. Often more than 2 lists are available which is good to CR methods, but when this happens the formulas given for Petersen and Chapman estimators cannot be used to estimate the size of the population (N). Although when using three or more lists, the Petersen estimator or the Chapman estimator can be used to detect dependency amongst pairs of lists. Discrepancies between estimates of N produced by different pairs of lists are indicative of positive or negative local dependences, numerical examples are given in sub-section scenario D. This method is considered intuitive and can be complemented by investigating the lists, the context surrounding them and how they were built, which can suggest the dependences amongst them. These last two intuitive approaches combined are used in *section computation of prevalence.*

Using log-linear models with dependent lists

When dependence between two lists is unavoidable and/or more than two are available, log-linear models can be used to estimate the size of the population (N). However, log-linear models are not the only closed models that allow unequal catchability.[36] An important aspect to consider in CR is the number of lists. When more than 3 lists are available, researchers should consider merging them because more than 3 lists lead to complicate models without increasing significantly the accuracy of its predictions.[43,52]

Log-linear models determine the expected value of n_{ijk}, that is, the expected value to the number of individuals with capture history (ijk). It uses the Poisson distribution to model the count of a contingency table computed from the lists (each list has two categories, captured and not captured).[53] It models the logarithm of the expected value of each observable cell of such contingency table. If there are three lists and there is local dependence amongst the three and local dependence between any possible pair of lists, then the log-linear model is given by equation 1:

$$\begin{aligned}\log E\left(n_{ijk}\right) = u_0 &+ u_1 I(i=1) + u_2 I(j=1) \\ &+ u_3 I(k=1) + u_{12} I(i=j=1) \\ &+ u_{13} I(i=k=1) \\ &+ u_{23} I(j=k=1) \\ &+ u_{123} I(i=j=k=1) \qquad (1)\end{aligned}$$

As a matter of example, in the equation above $I(i=1)$ stands for the function that assigns 1 to capture history $(1jk)$ and 0 to all the others. Log-linear models estimate the logarithm of the expected value for the number of individuals with capture history (ijk), that is, $\log E\left(n_{ijk}\right)$. For example, the parameter u_{12} models the dependence between lists 1 and 2, and u_{13} the dependence among lists 1 and 3 and so on.[33]

Consider now that only lists 1 and 3 are dependent. If we want to compute the expected number of individuals with capture history (101), that is, $E(n_{101})$, then we use the formula:

$$\begin{aligned}\log E(n_{101}) = u_0 + u_1 + u_3 + u_{13} \Leftrightarrow E(n_{101}) \\ = e^{u_0+u_1+u_3+u_{13}}\end{aligned}$$

The values of all parameters (in this case, u_0, u_1, u_3, u_{13}) can be obtained, for example, by using the R package Rcapture.[54,55] This package can be used to estimate the abundance and other demographic parameters for closed and open populations using log-linear models. By comparing the difference between the estimated value of individuals with a capture history (101) and the actual number of subjects with that capture-history, the bias of the model can be computed. By doing the same to all observed capture-histories, the deviance of the model can be computed. The deviance of the model measures its quality in terms of how well its predictions fit the experimental data. Data is the set of vectors with all observed capture-histories, low deviance values correspond to better model fittings.

The main objective though is to compute an estimation of the size of the population N (e.g. the number of people with vision impairment) and to do that we need to determine the expected number of subjects that are missing from our available lists. That is, we need to estimate the number of individuals with a capture history (000) and that is given by the expression:

$$\log E(n_{000}) = u_0 \Leftrightarrow E(n_{000}) = e^{u_0}$$

The number of individuals with capture history (0 0 0) is then added to the number of individuals that have been captured on the lists:

$$\hat{N} = n_{100} + n_{010} + n_{001} + n_{111} + e^{u_0}$$

When there is an interaction between lists 1 and 2 and between lists 1 and 3, then equation 1 would yield the $(12, 13)$ log-linear model:

$$\begin{aligned}\log E\left(n_{ijk}\right) = u_0 &+ u_1 I(i=1) + u_2 I(j=1) \\ &+ u_3 I(k=1) + u_{12} I(i=j=1) \\ &+ u_{13} I(i=k=1).\end{aligned}$$

There are more models, but they are not covered in this review. Usually, models are denoted as $M_{subscripts}$ and the subscripts are t, b, h.[33] Models allowing capture probabilities for a fixed population unit to vary between lists are indexed by t, with t standing for time. Models with local list dependence, the behavioural effect, are indexed by b. Models that deal with heterogeneity are indexed by h. Therefore, in the more general structure, we have M_{tbh} models; M_{bh} or M_b models and other combinations are also possible.[33,36] There is also the M_0 model, in which there is no local list dependence, no heterogeneity and the capture probability is the same to all individuals throughout the entire capture time.[38,40]

Some models include covariates to explain the different capture probabilities among individuals due to heterogeneity.[37,56,57] For example, the probability of capture in a certain list for an individual may depend on covariates such as sex age or the severity of a disease. One possible solution consists of stratifying the data according to the values of the covariates, estimating the total number of population units within each stratum and finally combining these estimates.[56] There are also finite mixture models and random-effect models for heterogeneous closed populations.[58]

The Bayesian approach to capture-recapture has also been proposed by some authors and we provide here a brief explanation and an example.[40,59,60] The Bayesian approach works by taking into account previous estimates of the population size N, in which N is considered a random variable with a certain distribution. For example, it can be considered that $N = N_1$ with probability $p = p_1$, $N = N_2$ with probability $p = p_2$, $N = N_3$ with probability $p = p_3$ and so forth. This will be the prior probability distribution for N. Then, observations are collected, that is, a capture is produced. Such empirical information is used to update the prior probability distribution of N into a posterior probability distribution of N. This posterior information will be used as prior information to the subsequent capture and it will be again updated, originating a new posterior distribution to N. These iterations go on for the desired number of times. The actual observed data changes our expectations concerning the values of certain population parameters.[61]

In some cases the population is open and, in those cases, capture-recapture models for open population need to be used. For instance, there is a method that has been proposed by Roberts and Brewer that allows for the control of admissions and departures of subjects.[62] In this method, and based upon CENSUS information, there are variables modulating for probabilities of elements departing or being admitted to the population. Another solution are the Cormack-Jolly-Seber models that apply Hidden Markov Models.[63] Here, in addition to the capture probabilities (or ascertainment probabilities as it is referred to in human populations), there are also the survival probabilities, that is, the probability of an individual to remain part of the population in some time period between captures. The CR models are expressed as state-space models in which the survival process is distinguished from the detection process. It requires a significant dedication and is mathematically demanding; readers interested to know more about those are referred to the cited literature.

Issues with "tag-loss"

It is always advisable to use data with good personal identifiers allowing the linkage of individuals from different registers (lists). Sometimes this is not possible and we have what can be defined as "tag-loss". Tag-loss is the name given to the event that some individuals are poorly identified and has its origin in ecology when captured animals lose their tags.

The event of losing a tag, in human CR studies, means that the subject's identification has errors due to poor records caused by, for example, mistyping. Let us suppose that we have the following record in list 1: initials "JA", birth date "13/06/1957", sex "male". If male is represented by the number 1 and female by the number 2, then we can create an identifier string for this record as "JA130619571". Now in list 2: initials "HA", birth date "13/06/1957", sex "male". This originates the identifier string "HA130619571". Let us assume that the first initial in list 2 was mistyped ("H" instead of "J") and initials should be "JA" in both cases. In this scenario, these two separated records refer to the same subject and this subject should be accounted as a double capture – in list 1 and in list 2. However, because of the typo, it will be counted twice, that is, as a separated record in each list. This is an example of tag-loss with false-negative matching. When this happens, it frequently leads to the significant bias of estimation.[60,64] False-positive matching, that is, distinct individuals being considered as the same is less likely.

Most CR methods as the Petersen estimator and log-linear models assume that no tags are lost and that all tags are correctly identified. When researchers suspect of tag-loss they can use some strategies to reduce bias in their estimation. One way to circumvent this problem is to use several combinations of the information provided. For example, to perform an initial match by last name, post code and sex and a second match by first and last initial, date of birth and sex, or other combinations. Still, tag-loss can always occur leading to errors in the estimate of the population size and its variance.[65,66]

When tag-loss cannot be avoided, there are models that can incorporate this effect. For example, Wang and colleagues proposed a Bayesian model that can deal with tag-loss by using prior information about the population.[60,67,68] In this model, true and observed values are considered. For instance, the number of re-sightings in one list will be replaced with two values: the observed number of re-sightings on the list and the true number of re-sightings on the list. Concerning only the true number of re-sightings, there is no tag-loss effect. The discrepancy between observed data and real data is considered to be due to tag-loss and the true or latent data can be estimated with Bayesian models.

False positives and false negatives

Lists obtained from registers or clinical files can have false positives and false negatives or misdiagnosis. A false positive (Fp) for CR exists when someone is included on the list without having the expected diagnosis.[34] For example, when studying the prevalence of vision impairment, someone with good vision that is listed is a false positive. A false negative (Fn) is someone with vision impairment that is listed as having good vision (or not listed in the vision-impaired records).

Let us consider a scenario in which list A is prone to have Fp and list B in which Fp or Fn are inexistent. An individual x that is a Fp in list A can cause that either n_{10} (number of cases in list A only) or n_{11} (number of cases in both lists) are inflated one unit. However, despite individual x could be captured in list B, he or she is not listed – which classifies x as a Fp in list A only. In this scenario n_{01} (number of cases in list B only) and n_{11} are correct. However, n_{10} is inflated because includes one Fp. When we put these numbers in the Petersen estimator $= n_{10} + n_{11} + n_{01} + \frac{n_{10}n_{01}}{n_{11}}$, the first and last addends have higher values than they should have and the total number of cases, given by N, will be overestimated.

When we have a Fn in list A, the effect in the population estimation will depend on whether the subject was diagnosed in the source of list B. If individual x is an Fn in list A, then n_{10} (number of cases in list A only) or n_{11} (number of cases in both lists) are reduced by one unit. If x is included in list B, then he was correctly diagnosed and therefore n_{11} is reduced by one unit and n_{01} is inflated by one unit. In this case, the sum $n_{10} + n_{11} + n_{01}$ will be correct, but the quantity $\frac{n_{10}n_{01}}{n_{11}}$ will be overestimated. Therefore, $N = n_{10} + n_{11} + n_{01} + \frac{n_{10}n_{01}}{n_{11}}$ is overestimated. Finally, if x is not diagnosed at the source of B, then only n_{10} will be reduced by one unit, and consequently, N is underestimated. In summary, Fp lead to the overestimation of the population and Fn can lead to overestimation or underestimation of the population.

Computation of prevalence

In this section we provide an example of how to estimate the number of persons with vision impairment (VI) in the general population of a Portuguese municipality using CR methods. The study was conducted in the Municipality of Braga, Portugal, that has 181494 habitants.[69] After excluding non-residents, we obtained three lists formed of people with VI: 133 subjects issued with medical certificates of VI from a Primary Care Centre or PCC (L1); 556 subjects from Hospital of Braga or HoB (L2) and a 232 subjects from the blind association, ACAPO (L3).

The hospital information was collected during 12 months in the year 2014. Patients attending ophthalmology appointments with VI (acuity in the better eye equal or less than 0.3logMAR) were registered in a database. For this analysis, we use only people with an acuity 0.5logMAR or worse because people with acuity better than 0.5logMAR were unlikely to be registered with ACAPO. Details of the study can be obtained from our previous publications.[70–73] At the beginning of 2015, we collected a list of people applying for VI certificates seen at the PCC and at the same time, a list of members of ACAPO for the municipality was provided by the blind association. Despite referral between these three institutions not being a standard part of eye care practice, it is likely that when people ask, for example, for social support at the hospital they are directed to ACAPO and/or to the PCC. Therefore, the dependence between lists is likely to occur.

A unique identity string was constructed for each individual in the three lists consisting of the initials of the name, date of birth and sex. Such a string identifies each individual. We matched strings from all three lists. In the next sections, we show how to estimate the number of individuals with VI in the municipality of Braga that were not present in any of the three lists using a scenario-based approach.

Scenario A: using two independent lists

In this section, we apply the Petersen estimator and the Chapman estimator. It will, for now, be assumed that all possible pairs of lists are independent and that the population is closed. After matching lists L1 and L2 we found 29 individuals that were captured in both that interception is shown in Figure 1.

Individuals that are in L1 and not in L2 have the capture history $(1, 0)$. The number of subjects with this capture history is $n_{10} = 104$. Individuals appearing in both lists have the capture history $(1, 1)$ corresponding to $n_{11} = 29$. Subjects in L2 that are absent from L1 have the capture history $(0, 1)$ and $n_{01} = 527$. Applying the Petersen estimator, we have:

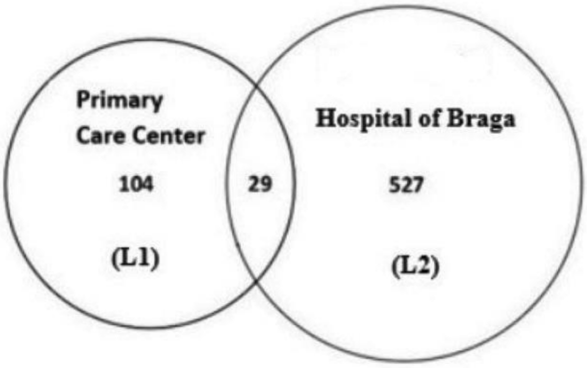

Figure 1. Venn diagram representing the matching of lists from PCC and HoB.

$$\begin{aligned}\hat{N} &= n_{10} + n_{11} + n_{01} + \frac{n_{10}n_{01}}{n_{11}} \\ &= 104 + 29 + 527 + \frac{104 \times 527}{29} \approx 2550\end{aligned}$$

The Petersen estimator can be biased for small sample sizes[74]; therefore, we are also using a slightly less biased estimator of the population size, that is, the Chapman estimator.[74]

$$\begin{aligned}\hat{N} &= \frac{(n_{10} + n_{11} + 1)(n_{01} + n_{11} + 1)}{n_{11} + 1} - 1 \\ &= \frac{(104 + 29 + 1)(527 + 29 + 1)}{29 + 1} - 1 \approx 2487\end{aligned}$$

The variance of Chapman estimator is given by:

$$\begin{aligned}var(\hat{N}) &= \frac{(n_{10} + n_{11} + 1)(n_{01} + n_{11} + 1)n_{10}n_{01}}{(n_{11} + 1)(n_{11} + 1)(n_{11} + 2)} \\ &= \frac{(104 + 29 + 1)(527 + 29 + 1)104 \times 527}{(29 + 1)(29 + 1)(29 + 2)} \\ &\approx 146622\end{aligned}$$

Chapman estimates are typically skewed, a log transformation has been used to obtain a confidence interval for the population size.[75] It is assumed that $log(\hat{N} - M)$ follows a normal distribution, with M the total number of captured individuals, that is, $M = n_{10} + n_{11} + n_{01}$. The 95% confidence interval for Chapman estimator is given by:

$$\left[M + \frac{(\hat{N} - M)}{C}, M + (\hat{N} - M) \times C\right],$$

with $C = exp\left\{1.96\sqrt{log\left[1 + \frac{var\hat{N}}{(\hat{N} - M)^2}\right]}\right\}$

Therefore, a 95% confidence interval for the population size can be computed as follows:

$$\begin{aligned}C &= exp\left\{1.96\sqrt{log\left[1 + \frac{var\hat{N}}{(\hat{N} - M)^2}\right]}\right\} \\ &= exp\left\{1.96\sqrt{log\left[1 + \frac{146622}{(2487 - 660)^2}\right]}\right\} \\ &\approx 1.5\left[M + \frac{(\hat{N} - M)}{C}, M + (\hat{N} - M) \times C\right] \\ &= \left[660 + \frac{(2487 - 660)}{1.5}, 660 + (2487 - 660) \times 1.5\right] \\ &= [1877, 3403]\end{aligned}$$

Doing the same with the list of ACAPO (L3) and the L2 the Venn diagram is shown in Figure 2.

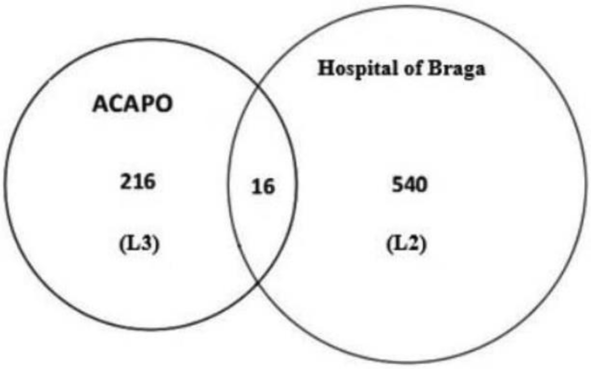

Figure 2. Venn diagram representing the matching lists from ACAPO and HoB.

Thus, $n_{10} = 216$, $n_{11} = 16$ and $n_{01} = 540$. Applying the Petersen estimator

$$\begin{aligned}\hat{N} &= n_{10} + n_{11} + n_{01} + \frac{n_{10}n_{01}}{n_{11}} \\ &= 216 + 16 + 540 + \frac{216 \times 540}{16} \approx 8062\end{aligned}$$

Applying the Chapman estimator:

$$\begin{aligned}\hat{N} &= \frac{(n_{10} + n_{11} + 1)(n_{01} + n_{11} + 1)}{n_{11} + 1} - 1 \\ &= \frac{(216 + 16 + 1)(540 + 16 + 1)}{16 + 1} - 1 \approx 7633\end{aligned}$$

The variance of this last estimator is

$$\begin{aligned}var(\hat{N}) &= \frac{(n_{10} + n_{11} + 1)(n_{01} + n_{11} + 1)n_{10}n_{01}}{(n_{11} + 1)(n_{11} + 1)(n_{11} + 2)} \\ &= \frac{(216 + 16 + 1)(540 + 16 + 1)216 \times 540}{(16 + 1)(16 + 1)(16 + 2)} \\ &= 2909968\end{aligned}$$

Therefore, a 95% confidence interval to the population size is obtained as follows:

$$\begin{aligned}C &= exp\left\{1.96\sqrt{log\left[1 + \frac{var\hat{N}}{(\hat{N} - M)^2}\right]}\right\} \\ &= exp\left\{1.96\sqrt{log\left[1 + \frac{2909968}{(7633 - 772)^2}\right]}\right\} \approx 1.62\end{aligned}$$

$$\begin{aligned}&\left[M + \frac{(\hat{N} - M)}{C}, M + (\hat{N} - M) \times C\right] \\ &= \left[772 + \frac{(7633 - 772)}{1.62}, 772 + (7633 - 722) \times 1.62\right] \\ &= [5048, 11941]\end{aligned}$$

The matching of L1 (PCC) and L3 (ACAPO) originates Figure 3.

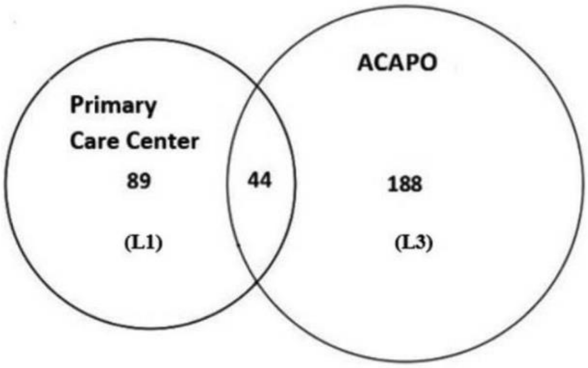

Figure 3. Venn diagram representing the matching lists from PCC and ACAPO.

The diagram shows that $n_{10} = 89$, $n_{11} = 44$ and $n_{01} = 188$. Applying the Petersen estimator:

$$\begin{aligned}\hat{N} &= n_{10} + n_{11} + n_{01} + \frac{n_{10}n_{01}}{n_{11}} \\ &= 89 + 44 + 188 + \frac{89 \times 188}{44} \approx 701\end{aligned}$$

Applying the Chapman estimator:

$$\begin{aligned}\hat{N} &= \frac{(n_{10} + n_{11} + 1)(n_{01} + n_{11} + 1)}{n_{11} + 1} - 1 \\ &= \frac{(89 + 44 + 1)(188 + 44 + 1)}{44 + 1} - 1 \approx 693\end{aligned}$$

The variance of the estimator is

$$\begin{aligned}var(\hat{N}) &= \frac{(n_{10} + n_{11} + 1)(n_{01} + n_{11} + 1)n_{10}n_{01}}{(n_{11} + 1)(n_{11} + 1)(n_{11} + 2)} \\ &= \frac{(89 + 44 + 1)(188 + 44 + 1)89 \times 188}{(44 + 1)(44 + 1)(44 + 2)} \\ &\approx 5370\end{aligned}$$

Therefore, a 95% confidence interval to the population size is obtained as follows:

$$\begin{aligned}C &= exp\left\{1.96\sqrt{log\left[1 + \frac{var\hat{N}}{(\hat{N} - M)^2}\right]}\right\} \\ &= exp\left\{1.96\sqrt{log\left[1 + \frac{5370}{(693 - 321)^2}\right]}\right\} \\ &\approx 1.47\left[M + \frac{(\hat{N} - M)}{C}, M + (\hat{N} - M) \times C\right] \\ &= \left[321 + \frac{(693 - 321)}{1.47}, 321 + (693 - 321) \times 1.47\right] \\ &= [575, 866]\end{aligned}$$

Values of N obtained with each pair of lists vary significantly and this suggests that there may be dependence between lists. Because of that, we consider Scenario B.

Scenario B: using two dependent lists

We are now going to assume that the PPC (L1) and HoB (L2) have local dependence. The population size will be estimated by the (12) log-linear model, that is expressed by:

$$\begin{aligned}\log E(n_{ij}) = u_0 + u_1 I(i = 1) + u_2 I(j = 1) \\ + u_{12} I(i = j = 1).\end{aligned}$$

Because we want to ascertain the expected value for the number of subjects with capture-history $(0, 0)$, that is, $E(n_{00})$, then $\log E(n_{00}) = u_0$, which yields $E(n_{00}) = e^{u_0}$. Then, the estimation can be done using the expression:

$$\hat{N} = n_{10} + n_{11} + n_{01} + e^{u_0}$$

To compute u_0 we can use the R package Rcapture.[54] Using Rcapture with lists L1 and L2 we get $\hat{N} = 2550$, 95%CI =$[1751, 3349]$. Assuming also other possible pairs of dependencies, we obtain with the same package for L3 (ACAPO) and L2 (HoB) $\hat{N} = 8062$, 95%CI = $[4305, 11819]$ and for L1 and L3 we get $\hat{N} = 701$, 95%CI =$[549, 854]$. Estimations obtained with pairs of lists using log-linear models are similar to the estimations obtained in *scenario A* and this is indicative that dependences between lists may not be significant. However, Rcapture retrieves a warning message informing that the three models are unreliable because the algorithm does not converge. Therefore, the next step is to consider all the 3 lists in a single model, that is, Scenario C.

Scenario C: using three independent lists

Now, the three lists are going to be used simultaneously. If we consider that the three lists are independent (the three lists among themselves and every possible combination of two), then we can estimate the population size by applying the following log-linear model:

$$\begin{aligned}\log E(n_{ijk}) = u_0 + u_1 I(i = 1) + u_2 I(j = 1) \\ + u_3 I(k = 1).\end{aligned}$$

In this model, there are no parameters to model any dependence amongst lists. We will now obtain new parameters values using the Rcapture package to this new model $\hat{N} = n_{10} + n_{11} + n_{01} + e^{u_0}$. We provide the code in a *supplementary methods file*. The final result is $\hat{N} = 2879$, 95%CI =$[2409, 3511]$. The model has a deviance of 120.5 and the AIC is 167.7. The goodness of fit test indicated that the model fit is not good because the $p - value = \Pr\left(\chi^2_{df} \geq deviance\right) = 0$, df represents the degrees of freedom of the saturated model minus the degrees of freedom of the proposed model. We have seen in *scenarios A and B* that different combinations of 2 lists were providing relatively inconsistent values and that would be caused by possible dependences between lists. In Scenario D we do a diagnostic analysis of the dependence and compute again estimates considering the dependences that we think are likely.

Scenario D: using three dependent lists

Values obtained in *scenario A* are summarized in Table 1. A brief analysis of the estimates leads us to suspect of two possible dependences. The first possible dependence is a local negative dependence between the ACAPO (L3) and HoB (L2). That is because the estimated population is too high when compared to the values reached when this same estimation is used with different pairs of lists. In addition, if this estimate of the number of people with impaired vision is used to compute prevalence, we would obtain values that are higher than expected for European countries, which is approximately 2.74%.[76] We can also suspect a positive dependence between L1 and L3 because the population size obtained by applying the Chapman estimator using these two lists is low and would lead to lower than expected prevalence.

Therefore, considering the values obtained in Scenario A, we are going to use the $(13, 23)$ log-linear model, that is:

$$\log E(n_{ijk}) = u_0 + u_1 I(i=1) + u_2 I(j=1) + u_3 I(k=1) + u_{13} I(i=k=1) + u_{23} I(j=k=1).$$

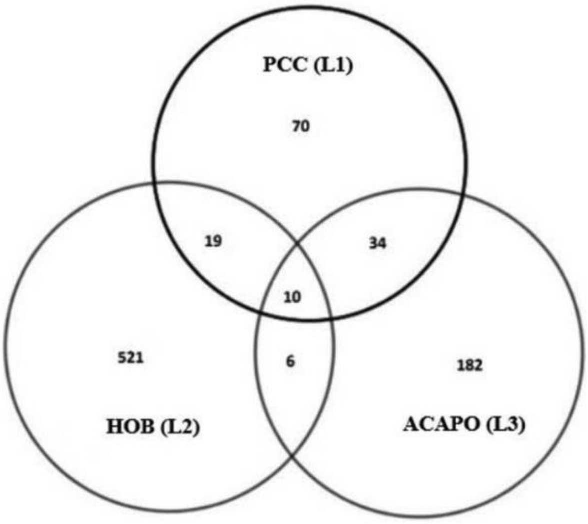

Figure 4. Venn diagram representing the matching lists from Primary Care Centre (PCC), ACAPO and Hospital of Braga (HoB).

Table 2. Number of individuals presenting each possible capture history, except the unknown capture history (0 0 0).

[L1]	[L2]	[L3]	[Freq]
1	1	1	10
1	1	0	29
1	0	1	44
1	0	0	70
0	1	1	16
0	1	0	521
0	0	1	182

To use the Rcapture package, we organize the information from Figure 4 in a matrix summarized in Table 2.In Table 2 the first three columns define the capture history and the fourth column is the number of cases with the correspondent capture history. Using the Rcapture package we obtained $\hat{N} = 2741$, 95% CI $[1997, 4110]$. This yields a crude prevalence of vision impairment of 1.51%, 95%CI =$[1.10, 2.26]$. The model has a deviance of 16.13, the AIC is 67.34 and p-value<0.001. We choose this model over the one obtained in *scenario C* (deviance equals to 120.5, AIC = 167.7 and p-value<0.001) in which we assumed that all lists were independent of each other.

We can also perform the statistical test for the independence between lists conditioned to the universe of all individuals captured at least once. It is a chi-square

Table 1. Prevalence values computed in Scenarios A, C and D.

Scenarios	Prevalence (%)	Estimate $\hat{N}$	95% CI	Residual deviance	AIC	p-value
A: L1 and L2	1.37 (1.03–1.87)	2487	1877–3403	-	-	-
A: L1 and L3	0.38 (0.32–0.48)	693	575–866	-	-	-
A: L2 and L3	4.21 (2.78–6.58)	7633	5048–11941	-	-	-
C	1.59 (1.33–1.93)	2879	2409–3511	120.5	167.7	0
D	1.51 (1.10–2.26)	2741	1997–4110	16.13	67.34	<0.001

test of independence between two categorical variables, for example, the variable first capture and the variable third capture (levels 1 and 0). Regarding L1 and L3, we obtained $\chi^2(1, N = 842) = 2.10$, $p = 0.15$. Regarding L2 and L3, we obtained $\chi^2(1, N = 842) = 495.67$, $p < 2.2 \times 10^{-16}$. These results do not reject independence between L1 and L3 and strongly reject independence between L2 and L3. However, this result should be evaluated with caution because the value in cell $(0, 0)$ of the contingency table is not, for example, the true number of uncaptured individuals in L2 or L3. The value in cell (0,0) is the number of individuals not captured in either L2 or L3 within the universe of the subjects captured at least once, the subjects detected by our system. This test is not equivalent to test whether u_{13} and u_{23} are statistically different from 0. The test for the coefficients of the Poisson regression is a z-test.

We can now compute completeness which corresponds to the proportion of cases in our three lists (L1, L2 and L3) obtained from Primary Care Centre, Hospital of Braga and ACAPO. Completeness is given by the expression:

$$\frac{n_{100} + n_{010} + n_{001} + n_{111} + n_{101} + n_{011} + n_{110}}{\hat{N}} \times 100$$
$$= \frac{70 + 182 + 521 + 10 + 19 + 6 + 34}{2741} \times 100$$
$$\approx 30.72\%$$

The results of completeness indicate that the observed data correspond to about 30% of the entire population.

In summary, in this section we have shown how to estimate the number of people with impaired vision in the municipality of Braga. Using all possible pairs of lists, assuming that lists were independent of each other, produced differing results, which suggests the existence of dependence between lists. When we used pairs of lists, assuming independence between the lists, the models were not reliable in the sense that the algorithm did not converge. When we used three lists, considering all independent of each other, we got a model with a deviance of 120.5, AIC = 167.7 and p-value<0.001. When we used the three lists with the dependences we suspect might exist, we obtained a model with a deviance of 16.13, AIC = 67.34 and p-value<0.001. We are led to believe that our dependence analysis is accurate and that the estimate of this last model is the most reliable. The best estimate was produced in, scenario D. However, the goodness of fit test of the model remains unsatisfactory and we will include more data in future estimations.

Discussion and recommendations

Capture-recapture methods are an alternative to traditional prevalence study methods such as case counting or cross-sectional studies of the population. The method allows the estimation of the number of individuals in a population that are missing from captures (registers). The method represents a fast and economical strategy to study the prevalence of diseases or conditions such as vision impairment. However, CR methods rely on assumptions that can easily be violated and researchers need to be careful when using the methodology otherwise unrealistic values will be produced.[77] Some recommendations for the presentation and evaluation of CR estimates should also be considered.[78]

One important aspect that may lead to significant estimate bias is dependence between lists. It is important to explore the dependence scenarios thoroughly because the independence assumption is unlikely to hold in an epidemiological study. CR methods may be of limited use when there is a small overlap between the lists because that can lead to unstable log-linear models.[79] Another important factor that needs to be considered is tag-loss. Poor 'tags' or unique identifiers may impact significantly the estimates as well as false-positives and false-negatives.[65,66] Also, CR methods are more likely to produce a biased estimate of the population size if one source captures very few cases.[80]

There are several CR models, applying different approaches, either classic or Bayesian. The models can vary, depending on whether the population is considered open or closed during the sampling period. Models can incorporate one or two types of dependences and they can even incorporate the tag-loss effect. Some studies advocate that the inclusion of capture-related covariates improves the accuracy of the estimate of the population size compared to estimates from simple models.[56] For example, some specific methodology can be used to identify patient characteristics related to the probability of capture by the different sources.[56] Thus, this technique can be used to identify both subsections of the population who are unlikely to be captured and population subsections who are more likely to be captured. Open population models try to produce estimates considering the population dynamics during the sampling period. The most common methodology regarding open populations use multistate CR models formulated as Hidden Markov Models.

Literature review

During the year of 2018, we searched PubMed and Web of Science to identify published articles using CR methods.

Search terms focused mainly on “capture-recapture models”, “sample independence”, “heterogeneity”, “mixed capture-recapture models”, “log-linear models”, “tag-loss”, “completeness”, “Bayesian capture-recapture models”. In addition, we searched Pubmed for publications using combination of keywords as “prevalence visual impairment capture recapture”, “prevalence causes vision loss”, “prevalence visual impairment Portugal”. We obtained 6391 results from which we selected 22 possible inclusions listed in the Supplementary Table 1, 10 of these publications used CR method for estimating the prevalence of ocular diseases and are listed with comments in Supplementary Table 2.

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ORCID

Antonio Filipe Macedo http://orcid.org/0000-0003-3436-2010

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2.3. Paper 3: Applying capture-recapture models with ascertainment probabilities depending on partial capture histories to investígate a human population size and list dependence

RESEARCH ARTICLE

Applying capture-recapture models with ascertainment probabilities depending on partial capture histories to investigate a human population size and list dependence

Pedro Lima Ramos[a,b] António Filipe Macedo[a,b] and Inês Sousa[c]

[a]Department of Medicine and Optometry Linnaeus University Kalmar, Kalmar, Sweden; [b]Department and Center of Physics, University of Minho, Braga, Portugal;[c]Department of Mathematics, School of Sciences, University of Minho, Portugal.

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ABSTRACT

Capture-recapture models can be used as an alternative technique to estimate the number of individuals with a disease or condition in a population. If applied accurately, their costs are considerably lower than the traditional cross-sectional studies. The key aspects regarding its correct application are related with list dependence and the possible heterogeneity of capture rates among subgroups of the population. In this paper, we explored the likelihood of different values for a human population size, possible list dependence scenarios and the possible existence of different capture rates between subjects. We applied capture-recapture models in which ascertainment probabilities at each list depend on partial capture histories. We investigated heterogeneity with mixtures of binomials and beta-binomial distributions. We designed a simulation with sequences of linear logistic regressions modelling ascertainment probability as a function of explanatory variables setting list dependence. Each logistic regression assumes a population size N. Our approach consists in finding the regression with maximum unconditional likelihood and consider its N the maximum likelihood estimate for the population size. It produced models with better quality of fit than the most traditional capture-recapture models. It also allowed us to assess the plausibility of all list dependence scenarios and to obtain a measure for the degree of dependence between lists. We used a real-life data set and suggest a value for the prevalence of visual impairment at the Municipality of Braga, Portugal.

KEYWORDS
Capture-recapture; prevalence; ascertainment probabilities conditioned on partial capture histories; sequences of logistic regressions with covariates setting list dependence; mixture of binomials; beta-binomial; prevalence of visual impairment.

1. Introduction

Capture-recapture models have been applied in several disciplines, as biomedical sciences, epidemiology or ecology, to estimate the size of populations [1]. In particular, they have been used to estimate the prevalence of several diseases or conditions [2–4]. Developing these inferential models is of great importance to avoid the high costs and unreasonable time spending of cross-sectional studies [5]. However, applying capture-recapture models is challenging as they are very sensitive to list dependence

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CONTACT Pedro Lima Ramos. Author. Email: pedro.limaramos@lnu.se

and possible capture rates heterogeneity among subgroups of the population. In particular, applying these models to human population samples is additionally challenging, as in most epidemiologic studies only a small number of lists are available.

In a previous paper [6] we used the combination between the Petersen Estimator and log-linear models [7] to both investigate the dependence between lists and estimate the size of a closed population. In this paper, we aim to explore other more sophisticated techniques and inferential tools to understand and model list dependence. Even more, we now aim to obtain a measure for the degree of dependence between lists. Our real-life data sets consists of a list with subjects issued with medical certificates of visual impairment from a Primary Care Centre, a list with visual impaired patients attending outpatient ophthalmology appointments at the Hospital of Braga, Portugal, and a list with subjects registered at a blind association. We will be able to suggest a value for the prevalence of visual impairment at the Municipality of Braga, Portugal.

In capture-recapture models, in the context of human populations, there is typically a small number of lists in which subjects belonging to the population of interest may be captured. A unique identity string is constructed for each individual in all lists by concatenating key characteristics such as the initials of the name, date of birth, gender, among others. By matching the lists of strings, it is possible to build a capture history to all identified individuals and to estimate the size of the hidden population. This estimation is strongly connected with the values for capture probabilities or ascertainment probabilities, as they are commonly referred to within the epidemiologic terminology. There are two main differences between human and wildlife populations. First, human population lists generally have not a well-defined time order. Second, in wildlife studies there are often more trapping samples than in human population studies. In most epidemiologic surveys only two to four lists are available [7]. This last fact tends to reduce the goodness of fit of the models. This can be problematic and is an additional difficulty when applying capture-recapture models in the context of human populations. Still, some authors, concerning human population lists, argue that the use of more than three lists does not substantially alter the results and that multiple lists should be condensed into three lists for the use of capture-recapture models [8].

Typically, there are two sources of variability that may affect the probability of capture of a unit in a list: behavioural variability, that is, the inclusion of a subject in one list has a direct causal effect on his/hers inclusion in other lists; heterogeneity due to specific characteristics of each unit, that is, observable or unobservable features of each subject may have an impact on his/hers capture probability [9].

In some capture-recapture models, capture probabilities depend on partial capture histories. The probability of a subject to be in a given list is influenced by whether the subject was captured or not in other lists [10].

In a bivariate Markov chain model both ephemeral and enduring effects are allowed [11]. The existence of enduring effects means that individuals exhibit a long lasting behavioural response to capture. Ephemeral effects mean that individuals have a short term memory and capture probability at list j depends only on the capture occurrence at list $(j-1)$ [11]. In the capture-recapture context, the Markov chain has a space state determined by the capture status (capture vs non capture) and the marking status (marked vs unmarked). We applied the bivariate Markov chain model in order to invistigate list dependence by using ephemeral and enduring effects. This approach is in Section 2 and Section 3.

The model developed by Farcomeni [12] is very flexible as capture probabilities depend on the entire partial capture history, that is, capture probabilities are conditioned on each possible partial capture history. Capture occasions do not even need to be ordered along a time horizon [13], which implies that this model can be used with epidemiologic data. However, it is commonly used within the ecology context. Therefore, another objective of this paper is to check how this model performs with human populations. There is a saturated model and constrained versions based on conditional probabilities constraints. The size of the population N is the only parameter of interest. All the other paramenters are considered nuisance parameters. The most popular approach in capture-recapture analysis to make inference on N is used. The unconditional likelihood is factorized in two factors. The first is the conditional likelihood, corresponding to the observed units. That is, the joint probability of observing the capture histories of all observed units conditionally on the fact that they are eventually observed. The second factor is the binomial likelihood, a residual term. The estimation of N follows two steps: maximizating of the conditional likelihood deriving an estimation for all nuisance parameters; maximizing the binomial likelihood as a function of N only, plugging in the estimates of all the other nuisance parameters calculated in the first step. We used this approach in Sections 4, 5 and 6.

We designed another approach that consists in modeling the capture probabilty of any subject at any list with a linear logistic regression in which the independent variable is a function of their partial capture histories. Other authors have already tried to explain capture probabilities with logistic regressions[14]. We designed a simulation in which several sequences of linear logistic regressions were built, each sequence with a covariate establishing possible behavioural responses to capture. The covariates assign one number to each possible partial capture history. Within each sequence, that is, within each possible list dependence scenario, each logistic regression is associated with one possible number for the size of the population. The size of the population ranges from the number of observed units to a reasonable upper limit. Each regression has a log-likelihood value. The population size that maximizes the likelihood function is the proposed estimate to the dimension of the population of interest, within the respective list dependence scenario. The selected regressions, one for each sequence, can be compared among each other. Also, each one has a p-value to the nullity of the coefficient of the covariable, which were also compared and analysed. All this information provide an useful insight into the likelihood of different population sizes as well as the plausibility of all list dependence situations. Also very important, by applying the odds ratios of a final selected logistic regression, we were able to obtain a measure to the degree of dependence between lists. We used this approach in Sections 7 and 8.

In Section 9 we applied the traditional log-linear models to our data and compared the results with the results of the previous simulation.

Ignoring the heterogeneity of capture rates when it does exist may result in the underestimation of the size of the population [7,15]. The previous models only can be reliable if heterogeneity does not exist.

Heterogeneity can be observed in clusters if capture probabilities differ among a finite number of classes of individuals. Those classes can be males and females, juveniles and adults, among others [16]. It can also be observed individually if a different rate of capture for each individual is observed [16].

The approach consisting of modelling heterogeneity in clusters by finite mixture models has been applied by some authors[15,17,18]. The finite mixture model or latent-class model has the characteristic that the heterogeneity distribution is discrete. The mixing distribution can be interpreted as the heterogeneity distribution. To model individual heterogeneity some continuous models for the heterogeneity distribution have been proposed, as the beta-binomial [16].

We investigated the possibility of heterogeneity in clusters by using binomial mixtures to model the counting distribution [15,17]. The counting distribution is the distribution of the variable that counts the number of times a unit has been identified by the system. The estimation of parameters was done using maximum likelihood by means of the EM algorithm. Individual heterogeneity was assessed by applying beta-binomial distributions[16]. We applied this approach in Section 10.

2. Bivariate Markov chain model approach

In this section we consider a bivariate Markov chain model that includes both enduring and ephemeral behavioural effects. We aim to use these effects to investigate list dependence. Capture histories are modelled as a Markov chain with state space determined by capture status (capture/non capture) and marking status (marked/unmarked). Each individual at each list is assigned with a state vector (X_{ij}, Y_{ij}), $1 \leq j \leq t$, t the number of lists, and $1 \leq i \leq M$, M the number of individuals captured at least once, where

$$X_{ij} = I\left[\textit{the subject } i \textit{ is at list } j\right]$$

and

$$Y_{ij} = I\left[\textit{the subject } i \textit{ is marked at list } j\right],$$

with $I[.]$ the usual indicator function. If $X_{ij} = 1$, $1 \leq j \leq t$, then the subject i was captured at list j. If $Y_{ij} = 1$, then the subject i was captured at least once in lists $[1, 2, ..., j]$.

The bivariate Markov chain model assumes that (X_{ij}, Y_{ij}) is a discrete stochastic process with state space $S = \{(0,0), (0,1), (1,1)\}$. For notational convinience, $a = (0,0)$, $b = (0,1)$ and $c = (1,1)$. For all individuals $Pr\{(X_{i0}, Y_{i0}) = a\} = 1$. If s_j denote the state vector at sample j, the Markov assumption states that

$$\begin{aligned}&Pr\left\{(X_{ij}, Y_{ij}) = s_t \mid \left(X_{i(j-1)}, Y_{i(j-1)}\right) = s_{t-1}, ..., (X_{i0}, Y_{i0}) = a\right\} = \\ &Pr\left\{(X_{ij}, Y_{ij}) = s_t \mid \left(X_{i(j-1)}, Y_{i(j-1)}\right) = s_{t-1}\right\}.\end{aligned}$$

All transition probabilities are independent of the subjects, that is, homogenity in capture probabilities is assumed across individuals. Therefore, we will drop the index i and use (X_j, Y_j).

If a subject is in state a at sample $(j-1)$, then the probability of making a transition into state b at sample j is

$$P_{ab} = Pr\left\{(X_j, Y_j) = b \mid \left(X_{(j-1)}, Y_{(j-1)}\right) = a\right\}.$$

Analogously, the transitions probabilities P_{aa}, P_{ba} and P_{cc} are defined. Also, $n_{ac}(j)$ is the number of transitions from state a at sample $(j-1)$ to state c at sample j in the set of all observable capture histories. Similarly, define $n_{aa}(j)$, $n_{bb}(j)$, $n_{bc}(j)$, $n_{cb}(j)$ and $n_{cc}(j)$. When we sum over an index the subscript corresponding to that indexed is replaced by a "+" sign. For example, $n_{a+}(t) = n_{aa}(t) + n_{ac}(t)$. Also, n_{aa} will represent all transitions from state a to state a, that is, $n_{aa} = \sum_{j=1}^{t} n_{aa}(j)$. Simillarly, define n_{ac}, n_{bb}, n_{bc}, n_{cb} and n_{cc}.

The quantity $P_{bc} - P_{ac}$ measures an enduring behavioural effect because it is the difference of capture probabilty between a marked and an unmarked. If $P_{bc} \approx P_{ac}$, then there is no enduring behavioural effect. The effect of presence in a list on the transition probabilities is limited to the presence in the next list. The quantity $P_{cc} - P_{bc}$ measures an ephemeral behavioural effect as it only concerns the transition immediatly after a capture. If $P_{bc} \approx P_{ac}$, then there is no ephemeral behavioural effect and the model reduces to a classical M_b model [19].

Let $Q = (P_{aa})^t = (1 - P_{ac})^t$ be the probability that a subject is not captured, N the population size and $\mu = \{P_{ac}, P_{bc}, P_{cc}\}$ the set of transition probabilities. The likelihood function may be factorized as $L(N, \mu) = L_b(N, \mu) \times L_c(\mu)$. The binomial likelihood is

$$L_b(N, \mu) = \frac{N!}{M(N-M)!} Q^{N-M} (1-Q)^M . \tag{1}$$

The conditional likelihood is

$$L_c(\mu) = \frac{M!}{(\prod_w Z_w!)(1-Q)^M} \times \{(1-P_{ac})^{n_{aa}} (P_{ac})^{n_{ac}} \times (1-P_{bc})^{n_{bb}} (P_{bc})^{n_{bc}} \times (1-P_{cc})^{n_{cb}} (P_{cc})^{n_{cc}}\} . \tag{2}$$

The conditional maximum likelihood estimator (CMLE) of N is calculated the following way: $\hat{\mu}$ is computed by maximizing the conditional likelihood; $L_b(N, \hat{\mu})$ is maximized with respect to N. So,

$$\frac{\partial log L_c(\mu)}{\partial P_{bc}} = -\frac{n_{bb}}{1 - P_{bc}} + \frac{n_{bc}}{P_{bc}} = 0$$

and

$$\frac{\partial log L_c(\mu)}{\partial P_{cc}} = -\frac{n_{cb}}{1 - P_{cc}} + \frac{n_{cc}}{P_{cc}} = 0,$$

which yields

$$\hat{P_{bc}} = \frac{n_{bc}}{n_{b+}}, \quad \hat{P_{cc}} = \frac{n_{cc}}{n_{c+}}. \tag{3}$$

By maximizing the binomial likelihooh with respct to N, the CMLE of N is $\hat{N} = \frac{M}{(1-\hat{Q})} = \frac{M}{(1-(1-\hat{P_{ac}})^t)}$. Substituting $\frac{M}{1-Q}$ by N and Q by $\left(1 - \frac{M}{N}\right)$ in

$$\frac{\partial logL_c(\mu)}{\partial P_{ac}} = -\frac{n_{aa}}{1-P_{ac}} + \frac{n_{ac}}{P_{ac}} - \frac{M}{1-Q}\frac{Qt}{1-P_{ac}} = 0$$

originates

$$\hat{P_{ac}} = \frac{n_{ac}}{t\left(\hat{N}-M\right)+n_{a+}}. \tag{4}$$

By substituting (4) into $\hat{N} = \frac{M}{(1-(1-\hat{P_{ac}})^t)}$, it follows

$$1-\frac{M}{N} = \left(1-\frac{n_{ac}}{t(N-M)+n_{a+}}\right)^t. \tag{5}$$

By solving (5) with respect to N the CMLE $\hat{N}$ of N is obtained.
The variance of $\hat{N}$ is as follows [11,21]

$$var\left(\hat{N}\right) \approx N\left[-1+\frac{1}{Q}+\frac{t^2\left(1-P_{aa}\right)}{(1-Q)}\left(1-\frac{1}{P_{aa}}\right)\right]^{-1}.$$

A confidence interval of N is obtained by using a log transformation so that the lower bound is at least M [9].

It is important to note the possibility of occurrence of likelihood failures as (5) may not have a solution.

3. Applying the bivariate Markov chain model

Our data consists of three lists. One list with 133 subjects issued with medical certificates of visual impairment from a Primary Care Centre, PCC (L1). A second list, defined as HoB (L2), with 556 subjects, was obtained from the records of Hospital of Braga, Portugal. A third list, defined as ACAPO (L3), was obtained from a blind association. A string was constructed for each individual in the three lists consisting of the initials of his/her name, date of birth and sex. Such a string identifies each individual. We matched the strings. The list matching results are represented in the Venn diagram of Figure 1.

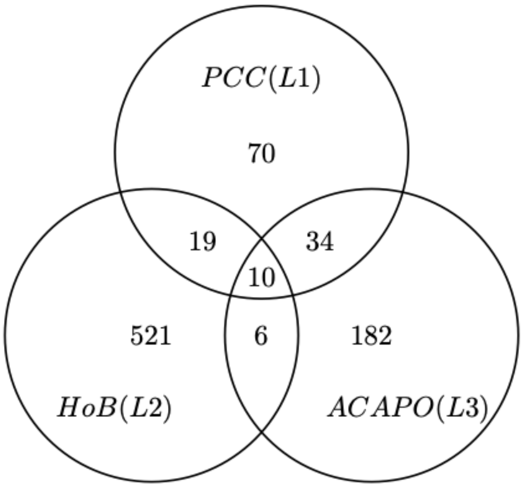


Figure 1.: Venn Diagram representing the match between the three lists.

Subsquently, the values in Table 1 were derived.

Table 1.: Number of transitions between different states at lists.

List j	$n_{ac}(j)$	$n_{bc}(j)$	$n_{cc}(j)$	$n_{aa}(j)$	$n_{bb}(j)$	$n_{cb}(j)$
1	133	0	0	709	0	0
2	527	0	29	182	0	104
3	182	34	16	0	70	540

Therefore, $n_{ac} = 842$, $n_{bc} = 34$, $n_{cc} = 45$, $n_{a+} = 1733$, $n_{b+} = 104$ and $n_{c+} = 689$. Using (5) we are led to a situation of likelihood failure.

Still, we can conclude that $\hat{P}_{bc} = \frac{n_{bc}}{n_{b+}} = \frac{34}{104} \approx 0.33$ and $\hat{P}_{cc} = \frac{n_{cc}}{n_{c+}} = \frac{45}{689} \approx 0.07$. So, $\hat{P}_{cc} - \hat{P}_{bc} = 0.07 - 0.33 = -0.26$, that is, an ephemeral effect was detected. The existence of an ephemeral effect suggests the existence of one of the three following list dependence scenarios: $L_1,\ L_2$ and $L_2,\ L_3$; $L_1,\ L_2$; $L_2,\ L_3$.

4. The Horvitz-Thompson estimator

Suppose that a system identifies a case with a probability $(1 - p_0)$. Then, the population size is $N = Np_0 + N(1 - p_0)$. Note that $N(1 - p_0)$ is the number of observed cases, n_{obsv}, or, according to the previous notation, M. So, the previous equation can be written as $N = n_{obsv} + Np_0$, which leads to the Horvitz-Thompson estimator:

$$\hat{n}_{HTE} = \frac{n_{obsv}}{(1 - \hat{p_0})}. \tag{6}$$

The Horvitz-Thompson estimator can also be derived as the maximum likelihood estimator of the number of trials in a binomial experiment when the probability of success is known and it is equal to $1 - \hat{p_0}$.

5. Models with capture probabilities conditionated on each possible partial capture history

Let us consider a discrete capture-recapture experiment in which a closed population is sampled t times. The units of such population are assumed to act independently. The units are associated with a capture history. Data can be represented as an $N \times t$ binary matrix $X = [x_{ij}]$, with $x_{ij} = 1$ if the $i-th$ unit is captured at list j and $x_{ij} = 0$ otherwise. If $\Omega = \{0,1\}$, then $\Omega^t = \{0,1\}^t$ is the set of all possible capture histories and $\Omega_*^t = \{0,1\}^t \setminus (0,...,0)$ is the set of all observable capture histories.

The simplest way to consider behavioural effects is the model M_b [19]. The individual capture probability vary only once when first capture occurs. Till first capture, the capture probabilty is p_1 to all individuals, after fist capture the capture probability is p_2 to all individuals. There is an enduring effect to capture.

Another way to deal with behavioural effects is to consider a generalized $kth-order$ Markov chain model M_{c_k}. For each unit, at each capture, capture probability only depends of what has happened in the previous k lists. Capture probability only depends on a part of the entire partial capture history. For example, for $k = 1$, M_{c_1}:

$$\begin{cases} p_{(0)} = Pr\left(x_{i1} = 1 \mid x_{i(j-1)} = 0\right) & \forall j = 1,...,t \ \forall i = 1,...,N \\ p_{(1)} = Pr\left(x_{i1} = 1 \mid x_{i(j-1)} = 1\right) & \forall j = 1,...,t \ \forall i = 1,...,N \end{cases}$$

There is also the bivariate Markov chain model explored in Section 2 that allows to handle both enduring effects, in which individuals exhibit a long lasting behavioural response to capture, and ephemeral effects, in which individuals have a short term memory and the capture probabilities depend only on the capture occurrence in the previous occasion.

Some authors [10,12,20] provided a more flexible framework. It is based on capture probabilities conditioned on each possible partial capture history as follows

$$\begin{cases} p_1() = Pr\left(x_{i1} = 1\right) \\ p_j\left(x_{i1},...,x_{i(j-1)}\right) = Pr\left(x_{ij} = 1 \mid x_{i1},...,x_{i(j-1)}\right) & \forall j > 1, \forall \left(x_{i1},...,x_{i(j-1)}\right) \in \Omega^{j-1} \end{cases} \quad (1)$$

Capture probability at each capture or list depends on the entire partial capture history. For example, $p_3(1,0)$ represents the probability of a unit to be captured at the list 3 given that was captured at list 1 and not captured at list 2. The probability of not being detected is

$$p_0 = \left[(1 - p_1()) \prod_{k=2}^{t} \left(1 - p_k(0,...,0)\right) \right]. \quad (7)$$

This is the saturated model. We reduce the number of parameters in (1) by doing a partition of the set H of all possible partial capture histories. Representing a generic partial capture history by $h = (h_1, ..., h_{l_h})$, l_h the length of the partial capture history vector, the partition $H = \{H_1, ..., H_b, ..., H_B\}$, H_b, $1 \leq b \leq B$, equivalence classes, is made in a way such that:

$$\begin{aligned}&\forall h, h^{'} \in H_b,\\&p_{(l_h+1)}(h) = p_{(l_{h^{'}}+1)}(h^{'}) = p_{H_b} \Leftrightarrow Pr\left(x_{i(l_h+1)} = 1 \mid h\right) = Pr\left(x_{i\left(l_{h^{'}}+1\right)} = 1 \mid h^{'}\right) = p_{H_b}.\end{aligned}$$

All past partial capture histories of the same equivalence class originate the same future capture probability. The likelihood function corresponding to the generic model M_H parametrized with the vector of conditional probabilities $p_H = (p_{H_1}, ..., p_{H_B})$ is:

$$L(N, p_H) \propto \left[\binom{N}{n_{obsv}} p_{H_1}^{n_{(H_1,1)}} (1 - p_{H_1})^{n_{(H_1,0)} + t(N - n_{obsv})}\right] \prod_{b=1}^{B} p_{H_b}^{n_{(H_b,1)}} (1 - p_{H_b})^{n_{(H_b,0)}} . \tag{8}$$

The number of times that the observed units which experienced partial capture history h belonging to H_b are captured at time l_{h+1} is represented by $n_{(H_b,1)}$; $n_{(H_b,o)}$ has a similar interpretation. Formally, $\forall 1 \leq b \leq B$:

$$\begin{aligned}n_{(H_b,1)} &= \sum_{i=1}^{n_{obsv}} \sum_{h \in H_b} I\left[(x_{i1}, ..., x_{il_h}) = h, x_{i(l_h+1)} = 1\right];\\n_{(H_b,0)} &= \sum_{i=1}^{n_{obsv}} \sum_{h \in H_b} I\left[(x_{i1}, ..., x_{il_h}) = h, x_{i(l_h+1)} = 0\right].\end{aligned}$$

In order to compute the conditional maximum likelihood estimator (CMLE) of N, it is appropriated to factorize (8) as follows:

$$\begin{aligned}L(N, p_H) \ &\propto \ \binom{N}{n_{obsv}} p_0^{(N - n_{obsv})} (1 - p_0)^{n_{obsv}} \times \frac{1}{(1 - p_0)^{n_{obsv}}} \prod_{b=1}^{B} p_{H_b}^{n_{(H_b,1)}} (1 - p_{H_b})^{n_{(H_b,0)}}\\&= L^b(N, p_{H_1}) \times L^c(p_H) .\end{aligned}$$

The conditional likelihood is L^c while L^b is the residual binomial likelihood.The CMLE of N is obtained in two steps. Fist, $\hat{p_H}$ is computed by maximazing $L^c(p_H)$. Then p_{H_1} is used to maximize $L^b(N, p_{H_1})$ with respect to N. This path is equivalent to the proceeding described below.

If a equivalence class H_b has r vectors such that

$$p_{k_1}\left(a_{11}, ..., a_{1(k_1-1)}\right) = ... = p_{k_r}\left(a_{r1}, ..., a_{r(k_r-1)}\right) = p_{H_b},$$

then $p_{H_b} = Pr\left(x_{ij} = 1 \mid h\right)$, $h \in H_b$, $j > 1$, $1 \leq i \leq N$, can be calculated as

$$p_{H_b}=\frac{\sum_{m=1}^{r}\sum_{i=1}^{n_{obsv}} x_{ik_m} I\left(x_{ik_m-1} = a_{m,k_m-1}, x_{ik_m-2} = a_{m,k_m-2}, \ldots, x_{i1} = a_{m1}\right)}{\sum_{m=1}^{r}(N-n_{obsv}) I\left(\cap_{h=1}^{k_m-1} a_{mh}=0\right)+\sum_{i=1}^{n_{obsv}} I\left(x_{ik_m-1}=a_{m,k_m-1}, x_{ik_m-2}=a_{m,k_m-2}, \ldots, x_{i1}=a_{m1}\right)}. \tag{9}$$

The estimates of capture probabilities computed by (9) are plugged into (7) and $\hat{p_0}$ is expressed as a function of $\hat{N}$. That expression on $\hat{N}$ is plugged into (6) yielding an equation on $\hat{N}$. By solving this last equation, an estimate to the maximum likelihood estimator of N is obtained. Solving the equation is consistent and asymptotically normal under general regularity conditions [21].

The bivariate Markov chain model described in Section 2 is a particular case of this model.

6. Defining a partition of the set H and applying the model

In this paper we study list dependence as the condition characterized by the fact that the presence of an individual on one list has a direct influence on whether or not he appears on another list. If we set that the only dependence is between L_2 and L_3, then one possible partition to the set H of all possible partial capture histories may be:

$$H = \{H_1, H_2\}\,;\; H_1 = \{(), (0), (0\,0), (1), (1\,0)\}\,;\; H_2 = \{(0\,1), (1\,1)\}\,.$$

This means, for example, that

$$Pr\left(x_{i2} = 1 \mid x_{i1} = 1\right) = Pr\left(x_{i3} = 1 \mid x_{i1} = 1, x_{i2} = 0\right).$$

In order to implement (9) a program was written importing a '.xlsx' file with the capture histories and returning the numerator and a part of the denominator. By running the program, we get *numerator* = 772 and *denominator* = 1128, which yieds:

$$p_{H_1} = \frac{772}{2(N-842)+1128};$$

$$p_0 = \left(1 - \frac{772}{2(N-842)+1128}\right)^3;$$

$$N = \frac{842}{1-\left(1-\frac{772}{2(N-842)+1128}\right)^3}.$$

By solving the last equation, we get $\hat{N} = 885$.

The program was applied to different partitions of the set H of all possible partial capture histories. Table 2 shows list dependences, the corresponding partitions of the set H and the estimate of the size population N. The model assuming only one list dependence, between L_1 and L_3, was the one that performed better.

Table 2.: List dependence scenarios, partitions of the set of all possible partial capture histories and model results.

List dependences	Partitions of the set H	$\hat{N}$	LogLik	AIC
$L_1,\ L_2$	$H_1 = \{(), (0), (0\,0), (1\,0), (0\,1), (1\,1)\}$; $H_2 = \{(1)\}$	1180	-920.09	1844.18
$L_1,\ L_3$	$H_1 = \{(), (0), (0\,0), (1), (0\,1)\}$; $H_2 = \{(1\,0), (1\,1)\}$	1227	-760.89	1525.78
$L_2,\ L_3$	$H_1 = \{(), (0), (0\,0), (1), (1\,0)\}$; $H_2 = \{(0\,1), (1\,1)\}$	885	-1186.03	2376.06
$L_1,\ L_2$ and $L_2,\ L_3$	$H_1 = \{(), (0), (0\,0), (1\,0)\}$; $H_2 = \{(1)\}$; $H_3 = \{(0\,1), (1\,1)\}$	854	-1384.7	2775.4
$L_1,\ L_2$ and $L_1,\ L_3$	$H_1 = \{(), (0), (0\,0), (0\,1)\}$; $H_2 = \{(1)\}$; $H_3 = \{(1\,0), (1\,1)\}$	1177	-782.92	1569.84
$L_1,\ L_3$ and $L_2,\ L_3$	$H_1 = \{(), (0), (0\,0), (1)\}$; $H_2 = \{(0\,1)\}$; $H_3 = \{(1\,0)\}$; $H_4 = \{(1\,1)\}$	870	-1128.34	2260.68

7. Modelling list dependence by setting an individual covariate evolving longitudinally through the capture sequence

Similarly to [14,20], we now regard each capture occurence of unit i at list j as a binary outcome whose probability of success can be modelled by a linear logistic regression with an explanatory variable $z_{ij} = q(x_{i1}, ..., x_{ij-1})$ associated to the partial capture history. That is,

$$log\left(\frac{Pr\left(x_{ij} = 1 \mid x_{i1}, ..., x_{i(j-1)}\right)}{\left(1 - Pr\left(x_{ij} = 1 \mid x_{i1}, ..., x_{i(j-1)}\right)\right)}\right) = \alpha + \beta z_{ij} \ \ \forall i, j \tag{10}$$

where z_{ij} is a suitable numeric summary of partial capture history. Contrarily to [20], we define z_{ij} not as continuous but as a factor. It assigns one value to each possible partial capture history. In this way, this covariate groups the sequences of progressive individual partial capture histories and establishes a list dependence scenario.

If $n_{obsv} + 1 \leq i \leq N$, then $z_{ij} = 0$, $\forall j$. If we set a function z and a value to N, then the unconditional likelihood function obtained from a linear logistic model fitted using $N \times t$ binary observations with the corresponding numerical covariates z_{ij} is

$$L\left(N,\alpha,\beta\right)=\binom{N}{n_{obsv}}\left[\prod_{i=1}^{N}\prod_{j=1}^{t}\left(\frac{exp\left(\alpha+\beta z_{ij}\right)}{1+exp\left(\alpha+\beta z_{ij}\right)}\right)^{x_{ij}}\left(1-\frac{exp\left(\alpha+\beta z_{ij}\right)}{1+exp\left(\alpha+\beta z_{ij}\right)}\right)^{1-x_{ij}}\right]. \tag{11}$$

For each value $N \in [n_{obsv}+1, N_{upper}]$, N_{upper} a reasonable upper limit to N, a logistic regression is performed, (11) is apllied and $\hat{L}(N) = L\left(N, \hat{\alpha}(N), \hat{\beta}(N)\right)$ is calculated. A sequence of logistic regressions is performed, which can be computationally demanding and time-consuming. The value of N that maximizes (11) is the estimate for the population size. That is, the maximum likelihood estimate for N is

$$\hat{N} = arg \max_{N\in[n_{obsv}+1,N_{upper}]} \left(\hat{L}(N)\right).$$

8. A simulation study

For the scenario in which there is only one dependence between lists, L_2 and L_3, we defined the memory-related summary z as represented in Table 3.

Table 3.: Covariate z for the scenario in which there is only one list dependence, L_2 and $L3$.

Partial capture history	z
()	0
(0)	0
(1)	0
(1 0)	0
(0 1)	1
(1 1)	1
(0 0)	0

For example, a subject is captured in list L_2. That capture will produce a value 1 in the binary variable Y. If that subject was captured in L_1, then his partial capture history is (1) and this will produce a value 0 in the variable z. The index of 1 in the binary variable Y is the same as the index of 0 in the variable z.

N took all multiple of 5 values between 850 and 4300. For example, for $N = 1500$, we will have $1500 - 842 = 658$ $(0,0,0)$ capture histories, wich adds $658 \times 3 = 1974$ values of 0 to the binary variable Y as well as 1974 values of 0 to the behavioral explanarory variable z. In fact, the first 0 of a capture history $(0,0,0)$ has associated the partial capture history () and, according to Table 3, $z\left(()\right) = 0$. The second 0 of a capture history $(0,0,0)$ has associated the partial capture history (0) and, according to Table 3, $z\left((0)\right) = 0$. The third 0 of a capture history $(0,0,0)$ has associated the partial capture history (0 0) and, according to Table 3, $z\left((0\,0)\right) = 0$. Finally, a logistic regression is apllied to Y and z. This regression models the capture probabilty of any subject at any list as a function of his/hers partial capture history assuming there is only one list dependence, L_2 and $L3$.

For each multiple of 5 value of N between 850 and 4300, a binary variable Y and a behavioural explanatory variable z, defined as in Table 4, were built and a logistic regression was applied. For each regression the log-likelihood was calculated. The population size $\hat{N}$ assigned with the regression with the highest likelihood value is the maximum likelihood population size estimate within the $L_2,\ L_3$ list dependence scenario.

We did the same for other covariates assuming other list dependences scenarios, represented in the Table 4. The covariate was considered a factor, $z = 0$ the class of reference, β_1 the coefficient of $z = 1$, β_2 the coefficient of $z = 2$, β_3 the coefficient of $z = 3$.

Table 4.: Covariates z assuming list dependences scenarios; *pch* stands for partial capture history.

List dependences Scenarios	**Covariate** z
$L_1,\ L_2$	$z = \begin{cases} 1 & if\ pch = (1) \\ 0 & otherwise \end{cases}$
$L_1,\ L_3$	$z = \begin{cases} 1 & ifpch = (10)\ or\ pch = (1\ 1) \\ 0 & otherwise \end{cases}$
$L_2,\ L_3$	$z = \begin{cases} 1 & if\ pch = (0\ 1)\ or\ pch = (1\ 1) \\ 0 & otherwise \end{cases}$
$L_1,\ L_2$ and $L_2,\ L_3$	$z = \begin{cases} 2 & if\ pch = (0\ 1)\ or\ pch = (1\ 1) \\ 1 & if\ pch = (1) \\ 0 & otherwise \end{cases}$
$L_1,\ L_2$ and $L_1,\ L_3$	$z = \begin{cases} 2 & if\ pch = (1\ 0)\ or\ pch = (1\ 1) \\ 1 & if\ pch = (1) \\ 0 & otherwise \end{cases}$
$L_1,\ L_3$ and $L_2,\ L_3$	$z = \begin{cases} 3 & if\ pch = (1\ 1) \\ 2 & if\ pch = (0\ 1) \\ 1 & if\ pch = (1\ 0) \\ 0 & otherwise \end{cases}$

Our simulation performed 4146 logistic regressions, 691 regressions for each covariate establishing a list dependence scenario. The results are represented in Figure 2.

Regardless of the value of N, the unconditional log-likelihood of the list dependence scenario $L_1,\ L_3$ and $L_2,\ L_3$ is always greater than the unconditional log-likelihood of all other scenarios. It reaches the peak at $\hat{N} = 1780$. The scenario $L_1,\ L_2$ and $L_2,\ L_3$ reaches its maximum at $\hat{N} = 2090$, $L_2,\ L_3$ at $\hat{N} = 1930$, $L_1,\ L_2$ at $\hat{N} = 3760$. The scenario $L_1,\ L_3$ as well as the scenario $L_1,\ L_2$ and $L_1,\ L_3$ either diverge or reach the peak for values of N greater than 4300, wich is an unrealistic situation.

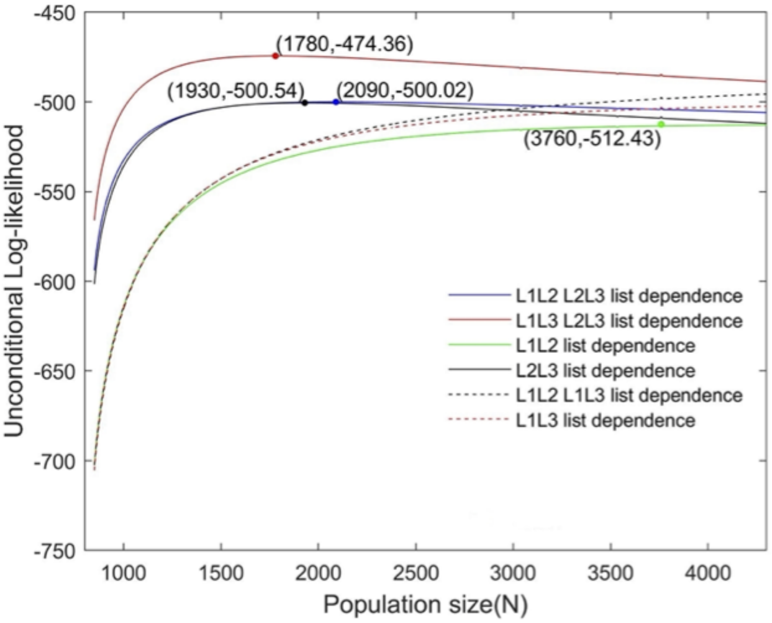


Figure 2.: Unconditional log-likelihood varying with the population size to several list dependence scenarios.

The logistic regressions associated with the four highlighted peak points were analysed with detail and the results are in Table 5.

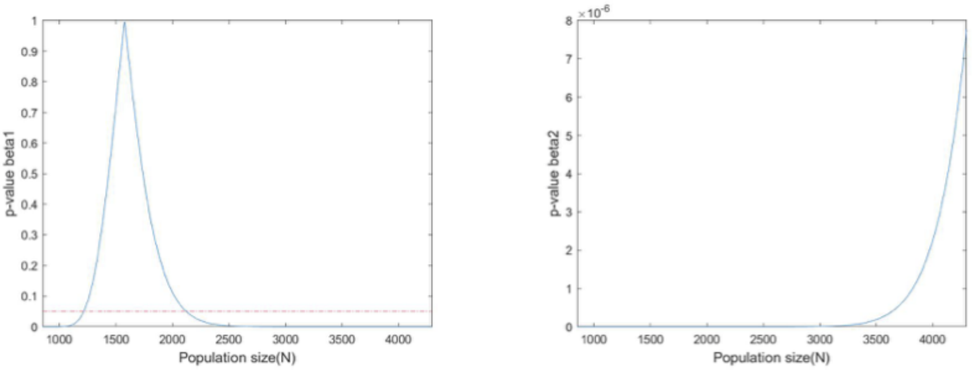
Table 5.: Logistic regressions associated with the four maximum likelihood estimates of N

Scenarios	LogLiK	AIC	α	p-value α	β	p-value β
$L_1,\ L_3$ and $L_2,\ L_3$	-474.36	4647	-1.44	$< 2e$-16	β_1 =-17.13 β_2 =-17.13 β_3 = 20.00	0.98 0.95 0.90
$L_1,\ L_2$ and $L_2,\ L_3$	-500.02	5118.6	-1.67	$< 2e$-16	β_1 = 0.40 β_2 =-2.31	0.0625 5.74e-13
$L_2,\ L_3$	-500.54	4945.2	-1.56	$< 2e$-16	-2.43	3.81e-14
$L_1,\ L_2$	-512.43	6359.6	-2.44	$< 2e$-16	1.16	4.44e-08

The scenario $L_1,\ L_3$ and $L_2,\ L_3$ has the best Log-likelihood curve. However, its logistic regression with maximum likelihood only has the intercept as statistically significant. The logistic regression with maximum likelihood of the scenario $L_1,\ L_2$ and $L_2,\ L_3$ has the coefficient of the class $z = 2$ as statistically significant while the level $z = 1$ almost reaches such status. This information suggests that the levels $z = 0$ and $z = 1$ should be merged, which would lead to the covariate of the $L_2,\ L_3$ scenario. Both the $L_2,\ L_3$ scenario and the $L_1,\ L_2$ scenario have statistically significant covariate coefficients. In the $L_2,\ L_3$ scenario though, such p-value is lower as well as the AIC. The goodness of fit test indicates that this model fits the data well, $p = Pr\left(\chi^2_{5788} \geq 4941.2\right) \approx 1$.

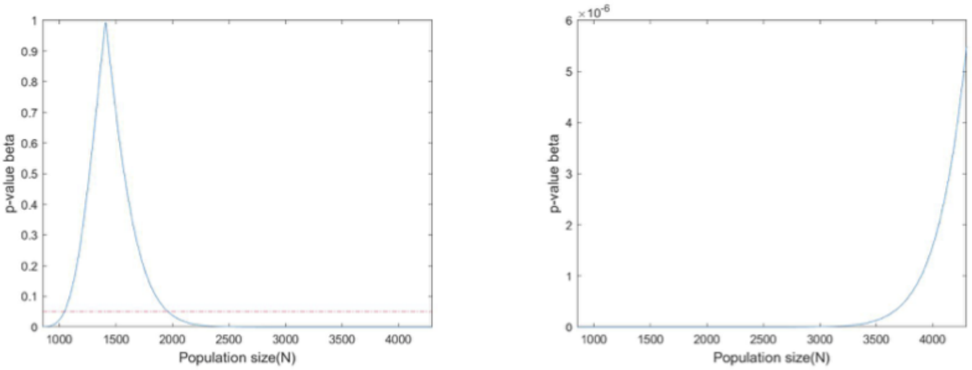
Figure 3 represents the p-value for the nullity of the coefficient of z varying with the population size within the last three scenarios.

As it can be observed, regarding the list dependence scenario $L_1,\ L_2$ and $L_2,\ L_3$, the p-value for the nullity of the coefficient of $z = 1$ is above 0.05 to values of N approximately between 1200 and 2100. Regarding the scenario $L_1,\ L_2$, the p-value also is not always significant. On the contrary, within the scenario $L_2,\ L_3$, the p-value is always significant no matter the value of N and always with extremely low values. The variable establishing this list dependence scenario is always statistically significant predicting capture probabilities regardless of the value of N.



(a) List dependence $L_1L_2\ L_2L3$.

(b) List dependence $L_1L_2\ L_2L3$.



(c) List dependence L_1L_2.

(d) List dependence L_2L_3.

Figure 3.: The p-value for the nullity of the coefficient of z varying with the population size.

All considered, the $L_2,\ L_3$ list dependence scenario is perhaps the most likely. By choosing the logistic regression with maximum likelihood assuming this scenario, we consequently are led to two conclusions. First, a prevalence of 1.06%, 95% CI [0.78% 1.71%], for visual impairment to the Municipality of Braga, Portugal, is obtained. Second, the odds ratios related to this regression produced interesting information. The odds of being captured if your partial capture history is (0 1) or (1 1) are $exp(2.43) = 11.36$ lower than the odds of being captured if your partial capture history is (1 0) or (0 0). In other words, the odds of being captured in L_3 are 11.36 lower if you are also in L_2.

9. Log-linear models

Capture-recapture models can avoid the high monetary costs of other methods of screening the population, such as cross-sectional studies or population surveys. The most traditional capture-recapture models to compute prevalence are log-linear models. We will now apply log-linear models to our data and compare the results with the results of the simulation described in Section 7 and Section 8.

Log-linear models result from applying Poisson models to a table such as Table 6, with the number of cases of each possible capture history.

Table 6.: Number of individuals presenting each possible capture history

Capture history	Count
(111)	10
(110)	19
(011)	6
(101)	34
(100)	70
(010)	521
(001)	182
(000)	n_{000}

The logarithm of the count in each cell of Table 6 is modelled as a linear function with terms indicating the presence or absence in the lists and terms modelling possible pair-wise dependences between lists. For example, if the list dependence scenario L_1L_2 L_2L3 is established, then the expected value to n_{ijk}, that is, the number of cases with capture history (ijk) is

$$log[E\left(n_{ijk}\right)]=u_0+u_1I\left(i=1\right)+u_2I\left(j=1\right)+u_3I\left(k=1\right)+u_{12}I\left(i=j=1\right)+u_{23}I\left(j=k=1\right), \tag{12}$$

with I the identity function. In this way, an estimate to the size of the hidden population is obtained, that is, $E\left(n_{000}\right)$. We applied log-linear models to our data and the results are in Table 7.

Table 7.: All possible log-linear models and model results

List dependences	$\hat{N}$	p(goodness of fit test)
$L_1,\ L_2$	3054	0
$L_1,\ L_3$	5087	6.29e-07
$L_2,\ L_3$	1623	2.43e-14
$L_1,\ L_2$ and $L_2,\ L_3$	1210	8.77e-11
$L_1,\ L_2$ and $L_1,\ L_3$	6576	5.79e-12
$L_1,\ L_3$ and $L_2,\ L_3$	2741	5.89e-05

The goodness of fit test tests the null hypothesis ”the model fits the data well”. Note that the traditional log-linear models present p-values close to 0. Therefore, they fit the data poorly whereas the selected logistic regression model of the simulation we designed has a goodness of fit test p-value close to 1, which means it fits the data very well, which suggests the prevalence value it produces is trustworthy.

Log-linear models are fundamentally different from our simulation. The first are Poisson regression models applied to the counts of capture histories. The second are sequences of logistic regressions. Each logistic regression has the binary variable being or not being captured and an explanatory variable establishing list dependence. Each also assumes a population size N. In short, our approach consists in finding the regression with maximum unconditional likelihood and consider its N the maximum likelihood estimate for the population size.

10. Investigating heterogeneity

The previous models assumed that the heterogenity between individuals, regarding capture probabilities, is not significant. To investigate the possibility of existence of heterogeneity through clusters, we applied binomial mixtures to model the counting distribution [15,17], that is, the distribution of the variable that counts how many times a case has been identified by the registration system.

By counting the number of times every case is captured several parameters can be calculated. The number of cases that were captured exactly 1 time is n_1, the number of cases captured exactly 2 times is n_2 and so on till the number of cases captured exactly t times n_t, with t the number of lists. Modelling the counting distribution with a mixture of binomials, yields

$$f\left(y, Q, \Theta\right) = \sum_{j=1}^{k} q_j \binom{t}{y} \theta_j^y \left(1-\theta_j\right)^{t-y}, \tag{13}$$

with k the number of clusters, $y = 0, 1, ..., t$, $\Theta = \{\theta_1, ..., \theta_k\}$ and $Q = \{q_1, ..., q_k\}$, Q the mixing distribution.

Supposing that $f\left(y, Q, \Theta\right)$ is a suitable distributional model for the counting distribution of the number of times Y a case was captured, the Horvitz-Thompson estimator becomes

$$\hat{n}_{HTE} = \frac{n_{obsv}}{1 - f\left(0, Q, \Theta\right)}. \tag{14}$$

In order to calculate the maximum likelihood estimation of Q and Θ we applied the EM algorithm. We used the popular algorithmic framework for mixtures of distributions [17], described below.

Step 0 Choose some initial value for $Q^{(0)}$; $j = 0$.

Step 1 Choose some initial value for $\Theta^{(0)}$;

Step 2 Compute $\hat{n}^{(j+1)} = \frac{n_{obsv}}{1-f(0,Q^j,\Theta^j)}$ and $\hat{n_0}^{(j+1)} = \hat{n}^{(j+1)} - n_{obsv}$;

Step 3 Use the complete frequency table $\hat{n_0}^{(j+1)}, n_1, ..., n_t$ to compute a new maximum likelihood estimator $Q^{(j+1)}$;

Step 4 $j = j + 1$; go back to Step 2.

In Step 3 the non-parametric maximum likelihood estimation of the mixing distribution Q needs itself to be algorithmically calculated. The EM steps for mixtures are well known. First, define $e_{il}^{j} = \frac{f\left(i,\theta_l^j\right)q_l^j}{f(i,Q^j)}$ and let $n_0 = \hat{n_0}^{(j+1)}$. Then:

Step 3.1 $q_l^{(j+1)} = \frac{1}{\hat{n}^{(j+1)}} \sum_{i=0}^{t} n_i e_{il}^{(j)}$;

Step 3.2 Find solution $\theta_l^{(j+1)}$ for the $l - th$ component scoring equation in θ_l

$$\sum_{i=0}^{t} n_i e_{il}^{(j)} \frac{\partial}{\partial \theta_l} f\left(i, \theta_l\right)$$

for $l = 1, ..., k$. The solution of the previous equation for the binomial density is

$$\theta_l^{(j+1)} = \frac{\sum_{i=0}^{t} i\, n_i e_{il}^{(j)}}{\sum_{i=0}^{t} n_i t\, e_{il}^{(j)}}.$$

We applied the algorithm to our data. The results are in Table 8.

Table 8.: Model parameters and results.

k	$\hat{q}_j$	$\hat{\theta}_j$	$\hat{N}$	LogLik
1	1	0.0884	3474	-944.01
2	0.9871	0.0241	10526	-1121.12
	0.0129	0.4169		
3	0.2042	0.0242	10482	-1144.42
	0.7828	0.0242		
	0.0129	0.4174		
4	0.3416	0.0244	10424	-1139.01
	0.4949	0.0244		
	0.1506	0.0244		
	0.0129	0.4181		

The situation with only one cluster $k = 1$ has produced the best log-likelihood value and the only credible value for $\hat{N}$. This suggests that heterogeneity through clusters is unlikely.

We investigated the possibility of individual heterogeneity with another type of model that considers the individual capture probability θ as being drawn from a continuous probability distribution on the interval (0, 1). If the distribution of θ has probability density function (pdf) $g\left(\theta\right)$, then the probability of an individual being captured y times becomes

$$\pi_y = \int_0^1 \binom{t}{y} \theta_j^y \left(1 - \theta_j\right)^{t-y} g\left(\theta\right) d\theta, \qquad y = 0, 1, ..., t. \tag{15}$$

We considered $g(\theta)$ to be the pdf of a beta distribution $Beta(\alpha, \beta)$, $\alpha, \beta > 0$. It follows that

$$\pi_y = f(y \mid t, \alpha, \beta) = \frac{\Gamma(\alpha\beta)}{\Gamma(\alpha)\Gamma(\beta)} \frac{\Gamma(\alpha + y)\Gamma(t - y + \beta)}{\Gamma(t + \alpha + \beta)}, \qquad y = 0, 1, ..., t. \qquad (16)$$

This is the so-called beta-binomial distribution. The multinomial likelihood function as well as the estimation of N, α and β, through maximum likelihood calculations can be seen in [16]. In order to perform these calcultions, we used the programs, written in R, in [22]. We specified several initial parameter values and obtained values for the population size with magnitudes of millions. So, when we estimate the population size on the assumption that individual heterogeneity exists, we obtain values even more unrealistic than when we consider heterogeneity through the existence of clusters. We conclude that individual heterogeneity is also unlikely. The capture probability of a subject at a given list is only a function of whether or not he/she is present on the other lists.

11. Discussion

There are several models and techniques to investigate list dependences and to estimate the size of closed populations. However, such tools are not always in agreement. The sequences of logistic regressions we designed, modelling capture probability as a function of covariates establishing list dependence, allowed us to investigate both the likelihood of different population sizes and the plausibility of different list dependence scenarios. Which is more, by applying the odds ratios of a selected logistic regression, we were able to obtain a measure for the degree of dependence between lists. Our approach produced the models with best performances, with goodness of fit tests with p-values close to 1, despite the small number of lists. It is our opinion that this approach is suitable to epidemiologic data. The fact that it is computationally time-consuming is its weakness. The models that calculate capture probabilities conditionated on each possible partial capture history are very flexible and provided useful insight about list dependence. The bivariate Markov chain model was also useful by detecting an ephemeral effect. However, these last two types of models did not perform as well as we were expecting, probably because epidemiologic data tends to have a low number of lists. The sequences of logistic regressions led us to conclude that the most likely scenario is the existence of one list dependence, L_2 L_3. This is in agreement with the information provided by the bivariate Markov chain model in which an ephemeral effect was detected. It produced a prevalence value of 1.06%, 95% CI [0.78% 1.71%] for visual impairment to the Municipality of Braga, Portugal. This value is in line with the prevalence values of visual impairment in European countries [23,24].

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2.4. Paper 4: Prevalence and causes of vision impairment in Portugal: a capture and recapture study

Prevalence and causes of vision impairment in Norwest Portugal: a capture and recapture study

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Complete List of Authors:	Ramos, Pedro Lima; Linnaeus University, Department of Medicine and Optometry; University of Minho, Low Vision and Visual Rehabilitation Lab, Department and Center of Physics - Optometry and Vision Science Santana, Rui; Universidade Nova de Lisboa Comprehensive Health Research Centre Escola Nacional Saude Publica Marques, Ana Patricia; London School of Hygiene and Tropical Medicine International Centre for Eye Health; Universidade Nova de Lisboa Comprehensive Health Research Centre Escola Nacional Saude Publica Sousa, Ines; University of Minho, Department of Mathematics and Applications and Center of Molecular and Environmental Biology, School of Sciences Rocha-Sousa, Amandio; University of Porto, Department of Surgery and Physiology, Faculty of Medicine Macedo, Antonio Filipe; Linnaeus University, Department of Medicine and Optometry; University of Minho, Low Vision and Visual Rehabilitation Lab, Department and Center of Physics - Optometry and Vision Science
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Title

Prevalence and causes of vision impairment in Norwest Portugal: a capture and recapture study

Authors

Pedro Lima Ramos (1,2); pedro.limaramos@lnu.se
Rui Santana (3); ruisantana@ensp.unl.pt
Ana Patrícia Marques (3, 4); patricia.marques@lshtm.ac.uk
Inês Sousa (5); isousa@math.uminho.pt
Amândio Rocha-Sousa (6); arsousa@med.up.pt
Antonio Filipe Macedo (1,2)**; antonio.macedo@lnu.se; a.macedo@ucl.ac.uk

(1) Department of Medicine and Optometry Linnaeus University, Kalmar, Sweden;

(2) Low Vision and Visual Rehabilitation Lab, Department and Center of Physics – Optometry and Vision Science, University of Minho, Braga, Portugal;

(3) Escola Nacional de Saúde Pública, Comprehensive Health Research Centre, NOVA University of Lisbon, Lisboa, Portugal;

(4) International Centre for Eye Health, London School of Hygiene & Tropical Medicine, London, UK;

(5) Department of Mathematics and Applications and Center of Molecular and Environmental Biology, School of Sciences, University of Minho.

(6) Department of Surgery and Physiology, Faculty of Medicine, University of Porto, Porto, Portugal;

**** Corresponding author**
Name: Antonio Filipe Macedo
Address: Linnaeus University, Department of Medicine and Optometry, SE 39182,
Kalmar, Sweden: a.macedo@ucl.ac.uk

Abstract

Purpose

The aim of this study was to estimate the prevalence and causes of vision impairment (VI) in the Norwest of Portugal.

Methods

Information about people with VI was obtained from different sources in the Norwest of Portugal during a period spanning years 2014-2015. Log-linear models were applied to estimate the number of individuals missing from lists of cases obtained from Primary Care Centres, blind association (ACAPO) and from hospitals (the PCVIP-study). Log-linear models were used to estimate the crude prevalence and the category specific prevalence of VI. Causes of VI were obtained from the PCVIP-study.

Results

Crude prevalence of VI was 1.97% (95%CI=1.56-2.54), and normalized prevalence was 1% (95%CI=0.78-1.27). The age-specific prevalence was 3.27% (95% CI,=2.36-4.90), older than 64 years, 0.64% (95%CI=0.49-0.88), aged 25-64 years, and 0.07% (95%CI=0.045-0.13), aged less than 25 years. Prevalence amongst females was 1.3 times higher than amongst males. The five leading causes of VI were Diabetic Retinopathy, Cataract, Age-related Macular Degeneration, Glaucoma and Disorders of the Globe.

Conclusion

The prevalence of VI in Portugal was within the expected range and in line with other European countries. A significant number of cases of VI might be due to preventable cases and, therefore, a reduction of the prevalence of VI in Portugal seems possible. Women and old people were more likely to have VI and, therefore, these groups require extra attention. Future studies are necessary to characterize temporal changes in prevalence of VI in Portugal.

Keywords

Prevalence, vision impairment, low vision, blindness, capture-recapture, cataract, diabetic retinopathy, age-related macular degeneration

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Pedro Lima Ramos (1,2); pedro.limaramos@lnu.se
Rui Santana (3); ruisantana@ensp.unl.pt
Ana Patrícia Marques (3, 4); patricia.marques@lshtm.ac.uk
Inês Sousa (5); isousa@math.uminho.pt
Amândio Rocha-Sousa (6); arsousa@med.up.pt
Antonio Filipe Macedo (1,2)**; antonio.macedo@lnu.se; a.macedo@ucl.ac.uk

(1) Department of Medicine and Optometry Linnaeus University, Kalmar, Sweden;

(2) Low Vision and Visual Rehabilitation Lab, Department and Center of Physics – Optometry and Vision Science, University of Minho, Braga, Portugal;

(3) Escola Nacional de Saúde Pública, Comprehensive Health Research Centre, NOVA University of Lisbon, Lisboa, Portugal;

(4) International Centre for Eye Health, London School of Hygiene & Tropical Medicine, London, UK;

(5) Department of Mathematics and Applications and Center of Molecular and Environmental Biology, School of Sciences, University of Minho.

(6) Department of Surgery and Physiology, Faculty of Medicine, University of Porto, Porto, Portugal;

**** Corresponding author**
Name: Antonio Filipe Macedo
Address: Linnaeus University, Department of Medicine and Optometry, SE 39182, Kalmar, Sweden: a.macedo@ucl.ac.uk

Introduction

Vision impairment (VI) leads to a significant loss of quality of life mostly due to activity limitations, loss of independence and difficulties to find jobs [1-6]. Because VI leads to a significant burden it is important to have regular vigilance (estimates) of cases of VI so that the quality of eye care and events such as diseases that may be leading to more cases of VI can be detected, evaluated, monitored and, eventually, vision loss can be prevented [7, 8]. One example of initiatives based on prevalence is VISION 2020 - an action of World Health Organization and the International Agency for the Prevention of Blindness, aiming to prevent and monitor VI and promote vision rehabilitation worldwide [9]. Recent estimates indicate that VI remains a significant health problem in Europe; although, in some countries reliable and updated information is lacking [9].

In 2020, in Western Europe, it has been estimated that there were 15 400 000 (95% CI, 13 900 000–16 900 000) people with moderate or severe VI [9]. However, the prevalence of VI and the methodology for the estimation varies significantly from country to country. For example, a population-based study conducted in Denmark in 2016 defined VI as best corrected visual acuity worse than 20/40 in the better-seeing eye. The study involved people aged 20 to 94 years and found a prevalence of 0.4% (95% CI, 0.2–0.7) [10]. A very different estimation with significantly different values was performed France in 2005 [11], in this study VI was self-reported and the prevalence was 1.95%. In 2007 and for the population aged 50 years or older, a study from Hungary reported a prevalence of 0.5% (95% CI, 0.2–0.7) for severe VI and 5.1% (95% CI, 4.3–5.9) for moderate VI [12]. These numbers are often hard to compare due to different age categories included and recruitment methods used; although, they point to differences among European nations.

Differences in prevalence of VI in Europe, as summarized in **Table 1**, may be due to not only study design but also, for example, due to differences in disease prevalence. VI and blindness in Western Europe is mostly linked to age-related eye diseases, in Germany, for example, that corresponds to 70% of all cases of blindness [13]. In Scotland, the leading causes of VI are Age-related Macular Degeneration (AMD), Glaucoma, Diabetic Retinopathy (DR), Myopic Degeneration, and Optic Atrophy [14]. Differences in disease prevalence and disease severity are associated with factors such as prevention and access to treatments [8]. Inequalities in accessing treatments can be seen even within a single country such as Portugal where unequal access to anti-VGEF injections was detected [15]. This makes it important to investigate prevalence and causes of VI as detailed as possible at national and regional levels. One method to study prevalence when cross-sectional studies of the population are unavailable is called capture-recapture (CR).

CR methods have been used to estimate the prevalence of several eye conditions [16-24]. CR methods is a methodology that can overcome the problem of cases that are never captured by, for example, registers for the visual impaired [25-27]. For a detailed description on how to use CR methods we recommend reading our review about the method [28]. Due the lack of information about the prevalence of VI in Portugal, we conducted a study with CR methods using data from different sources. The aim of this study was to estimate the prevalence and the main causes of VI in Portugal using CR methods.

== Table 1: Prevalence of vision impairment in European countries ==

Methods

Information about people with VI was obtained from different sources in the Norwest of Portugal during a period spanning years 2014-2015. The geographical coverage included 42 municipalities from two provinces: Minho, population density = 241.1 inhabitants/km^2 and Douro Litoral, population density = 742.4 inhabitants/km^2, national CENSUS 2011 [29]. The study was conducted in accordance with the tenets of the Declaration of Helsinki, approved by the local ethics committees of the participating hospitals and by the ethical committee for Life Sciences and Health of the University of Minho, Ref. SECVS-084/2013; data protection process numbers 9936/2013 and 9793/ 2017.

Possible sources of patients with visual acuity in the better eye of 0.5 decimal (0.30logMAR) or worse and/or visual field less than 20 degrees were investigated [30]. The first source were Primary Care Centres that were used for list L1. This list contained subjects that applied, for example, for medical certificates of VI. According to the Portuguese law people with a level of impairment of 60% or more are entitled to, amongst other, tax exemption, completely free health care or early retirement [31]. As an example, to get a degree of 60% or more from vision only, one eye must have no measurable acuity and the other can have acuity up 0.2 decimal [32] Although, for this certificate all types of impairments can be combined, e.g. vision and motor impairments, to reach the final score. Because of that, cases mapped as having VI were analysed and only those with field or acuity matching the inclusion criteria were included in this study. The second source used was an association for the visually impaired named ACAPO and their records were used in the second list L2. To be member of ACAPOI people must be visually impaired (low vision or blind).

The third list L3 was obtained from the PCVIP-study, a hospital-based study whose aim was to determine prevalence, causes and costs of VI in Portugal [33-35].The study gathered demographic, clinical, and socioeconomic information of people with VI. Participants were selected among patients attending ophthalmologists' appointments at four Portuguese public hospitals: Hospital de Braga, Hospital Senhora da Oliveira-Guimarães, Hospital de Santa Maria Maior-Barcelos and Centro Hospitalar e Universitário de São João - Porto. The initial database included people with acuity 0.5 decimal (0.30logMAR) or worse, to make compatible with the definition of VI in the ICD9 [30] and with the acuity in the other lists only cases with visual acuity below 0.3 decimal in the better-seeing eye were used for the estimation of prevalence.

All lists had variables that allowed assessment of repeated cases by using a string or combination of strings that form identifiers or "tags". Information available included: initials, date of birth, sex and municipality. The list from the hospitals also included information about the cause of VI. An example of a tag could be JS130519802 where JS are the initials (first and last name), 13051980 is the date of birth (13-05-1980) and the last digit (2) defines sex – 2 is a female in the example given. By matching the identity strings (tags) of the three lists, it was possible to ascertain the number of individuals present in all three lists and the number of individuals present at any combination of two lists.

To be used in CR lists need to be obtained at approximately the same time, or based on different sources that represent approximately the same population [36]. In addition, to obtain reliable results with CR certain assumptions need to be meet: 1) the sources of lists are independent - this implies that the probability of a subject being in both list A and list B equals the product between the probability of being in A alone and the probability of being in B alone [37], 2) the probability of association within each source (catchability) is equal for all individuals - the probability may vary from one list to another, or be constant overall [37, 38], 3) the population is closed (no births, deaths or migrants). These assumptions are restrictive and, when applied to medical conditions, are unlikely to be strictly followed. Log-linear models are one way of handling, for example, lists that are not completely independent [37].

Log-linear models were applied to estimate the number of individuals missing from all three lists [38]. Log-linear models result from the application of Poisson regression models to **Table 2,** the table summarizes all possible capture history for any case listed. The capture history is illustrated in **Figure 1**. The logarithm of the count in each cell of the table is modelled as a linear function with terms indicating the presence or absence in the lists and terms modelling possible pairwise dependences between lists. After choosing the best possible model we obtained an estimate of the dimension of the hidden population and consequently an estimate of the number of individuals with VI. The same procedure was used to compute category specific prevalence according to age and sex. Within each category several models were applied to sub-lists obtained from the main lists.

Results

The total number of inhabitants in the geographical area covered by the current study was 3 010 964. The list from Primary Care Centres (L1) had 208 cases (52% females) with a mean age of 60 years (SD=18.93). The list with the cases from ACAPO (L2) had 878 cases (43% females) with a mean age of 54 years (SD=18.0). The list from the Hospitals (L3) had 4272 cases (58% females) with a mean age of 74 years (SD=18.0). The Venn diagram in **Figure 1** shows the intersection between lists obtained from comparisons between identity strings. **Figure 1** shows that, for example, 39 individuals were in L3 and L1 and were not in L2; 13 individuals were in all three lists; 4161 individuals were only in L3. Table 2 provides the possible capture histories and the number of individuals with that history. For example, a subject has a capture history (1 1 0) when she or he was in L1 and L2 but not in L3.

== Figure 1: Venn diagram representing the intersection between the three lists ==

== Table 2: Number of individuals presenting each possible capture history ==

Log-linear models admitting possible list dependence scenarios were applied to model the counts in **Table 2**. The model is expected to estimate the value of *x* (**see also Table 2**) that corresponds the number of individuals with capture history (0 0 0). That is, the size of the hidden population or the number of individuals not captured by any of the three lists. The estimate of total number of people with VI (N) was given by the expression: N= x+13+38+39+59+118+768+4162, the value of N changes from model to model because the estimates obtained to the unknown *x* value. All possible list dependence scenarios were considered resulting in seven models summarized in **Table 3**. Code used to implement these models in R Statistics (v3.6.1), package Rcapture [39, 40] is provided in Appendix A.

== Table 3: All possible log-linear models and resulting prevalence estimates ==

The list dependence scenario L1L2 and L1L3 generated a model fitting the data well, goodness of fit test $p = Pr(\chi_1^2 \geq 0.009) = 0.92$. It is also the model with the lower value of AIC. According to the model the crude prevalence of VI as estimated in this study was 1.97% (95% CI, 1.56-2.54). The normalized prevalence was 1% (95% CI, 0.78-1.27).

Completeness, that is, the proportion of the population with VI that has been captured by our three lists, assuming that the size N of the population with VI was 59 316, was 9%. Completeness was computed using the formula below, in the formula, n_{100} is the number of cases with capture history (1 0 0) and the meaning is the same for all other parcels such as n_{010} in the denominator of the fraction.

$$\frac{n_{100} + n_{010} + n_{001} + n_{111} + n_{101} + n_{011} + n_{110}}{\hat{N}} \times 100$$

$$= \frac{118 + 768 + 4161 + 13 + 39 + 59 + 38}{59316} \times 100 \approx 9\%.$$

Table 4 shows category specific prevalence according to age and **Table 5** category specific prevalence according to sex. To run new log-liner models for each category we divided the initial lists according to the desired categories. Subsamples for each category were used to generating new Venn diagrams. Log-linear models for each subsample were set as given in **Table 3**, that means seven different dependency scenarios for each, for example, age category. The best model was chosen using criteria of AIC and p-values.

== Table 4: Age-specific prevalence ==

== Table 5: Sex-specific prevalence ==

Figure 2 illustrates the distribution of causes of VI. This information was available from L3 (from the hospitals), causes were classified according to the ICD9. DR was the most common cause of VI with 31% (95% CI, 29 - 32) of the cases in L3, followed by Cataract 15% (95% CI, 14 - 17), AMD 14% (95% CI, 13 - 15), Glaucoma 10% (95% CI, 9 - 11) and Disorders of the globe (DG) 5% (95% CI, 4 - 6). Figure 2 also shows the causes per age group and confidence interval for each cause are given in the figure legend.

== Figure 2: Distribution of causes of visual impairment ==

Discussion

The current study investigated the prevalence and causes of VI in the Norwest of Portugal. Crude estimates of prevalence point that 2 out of 100 inhabitants of the Portuguese north-western population suffer from VI. Category-specific prevalence by age and by sex revealed higher prevalence among older people and among women. The top causes of VI included DR and Cataract, information about causes of VI was available only from cases detected at hospitals.

Prevalence of VI for the general population was within the expected values. Our results are in line with those reported in neighbour countries such as Spain [41]. This was an expected result because both countries have similar populations. Our results were also in line with a French study reporting a prevalence of VI of 1.95% [11]. A study from Iceland reported a prevalence of 0.96% (95% CI, 0.37–1.55) [1] that is similar to our study if we consider the normalized prevalence instead of the crude prevalence. Another study conducted in 2000 in Copenhagen, urban Denmark, also found a value for prevalence close to 1% [42]. In contrast, a study from 2016 in rural Denmark found a prevalence of 0.4% (95% CI, 0.2–0.7) [10] which is similar to what has been reported in Germany 0.37% (95% CI, 0.28–0.49) [7]. Recent studies show that the incidence of VI in countries like Germany has been reducing and, therefore, more recent studies are likely to report lower prevalence of VI than older studies [43]. One possible explanation for slightly higher values of prevalence of VI in our study in Portugal can be the prevalence and incidence of, for example, diabetes and DR [44, 45]. In other words, some European countries seem better at preventing vision loss from common eye diseases such has DR and removing it from top cause of VI, while in Portugal at the time of our study DR was still the top cause of VI [46]. In other parts of Europe such as Hungary prevalence of VI was higher than our study, here VI is expected affect more than 5% of the population [12]. In short, prevalence of VI in Portugal was similar to neighbour countries, but slightly higher than in countries with, possibly, better preventive mechanisms of vision loss. Our results point that is possible to reduce the prevalence of VI in Portugal, the exact strategies can be inspired from European countries reporting lower prevalence of VI.

VI was more common among elderly people, it increased from about 7 out of 10,000 in the population under 25 years to 60 out of 10,000 in the age range 25-64 years and about

300 out of 10,000 in the population with 64 or more years, these findings are in line with other studies [7]. A study in Denmark found that VI was 9 times more prevalent amongst people with more than 64 years than amongst people in the age range 20-64 years [42]. Our results for the older population are also in line with the estimates from a recent meta-analysis estimating the prevalence of VI in people 55 years or older in European countries. The study that included data from Portugal, estimated an overall prevalence of VI for those above 55 years close to 2.75% [47, 48]. For age under 25 years, prevalence of VI in our study was low and in line with several other studies [49-51]. For example, our results were similar to data available from Sweden, in 1997 the age-specific prevalence of VI as 10.9/10,000 amongst people under the age of 19 years [51]. A more recent study from China that investigated VI amongst pre-school children also found a similar prevalence [52]. There was a good agreement between our results and similar studies, small differences might be due, among other factors, to temporal changes in prevalence of VI and the age-range criteria.

Prevalence of VI among females was 1.3 times higher than the prevalence among males, this result is in line with the trend reported in a recent meta-analysis covering European countries [47]. These results are also consistent with studies from Germany [7], VI among females was 1.4 times higher than among males, and from Spain [41], prevalence amongst females was 1.7 times higher than amongst males. The female-to-male ratio is expected to vary from 1.1 is Sub-Saharan Africa to 1.25 in Europe [53]. Causes for this female-to-male ratio above 1 are likely to include factors such as gender inequalities in access to health care [54].

The top two causes of VI in our study were DR and Cataract. Information about causes of VI in our study was available from hospitals and that might increase the frequency of cases with treatable diseases such as the top two causes. The main causes of VI in Europe are diverse [55] and we provide a summary of some studies in Table 6 [7, 14, 42, 56, 57]. Studies compiled in Table 6 show that, for example, DR was the top cause of VI only in our study. We can speculate that the main reason was that when our study was conducted the preventive effects of DR screening were not yet visible in Portugal and, therefore, the number of cases of VI caused by DR was high [44]. This contrasts with other countries such as Germany or Denmark where DR appears down in the list of main causes of VI. Probably preventive DR measures were implemented earlier than in Portugal [44]. While in some studies DR remains in second place as cause of VI [58] it seem that the trend is to go further down in the list [59, 60]. Our second cause of VI, Cataract, has also been reported as important cause of VI in Denmark, Canada and the UK [10, 61, 62]. We believe that, for example, in Denmark, the high number of cases of Cataract causing VI was due to the inclusion criteria with acuity 20/40. In many countries this is also the criteria to undergo cataract surgery. In our study we believe that a considerable percentage of cases of VI caused by Cataract was due to long queues for surgery at the time of our study [63].

==Table 6: Causes of visual impairment in 6 European countries, including Portugal ==

In this study we used capture-recapture models to investigate prevalence of VI. Some models showed high quality of fit which gives credibility to the prevalence values that we obtained. The best models were the ones with the list dependences Primary Care Centres/Hospitals and Primary Care Centres/Blind Association, it is important to recapitulate that CR methods give the estimates for the non-captured cases or hidden population unavailable from our data sources. The Primary Care Centres/Hospitals dependence is understandable because medical certificates of VI require a report from an ophthalmologist that, most likely, is the assistant physician at the hospital. The Primary Care Centers/Blind Association dependence is explained by the fact that the Blind Association recommends their members to get a medical certificate of VI. The fact that completeness was about 9% is a limitation of our study, to solve this we needed more information from Primary Care Centres. This limitation may be addressed in future studies with better standardized digital records that allow more efficient anonymous data sharing.

In conclusion, the results of the current study showed that prevalence of VI in Portugal was within the expected range and in line with other neighbour countries. A significant number of cases of VI detected was due to preventable causes, in other words, a reduction of cases of VI in Portugal is possible with improved access to eye care and effective diseases monitorization. In addition, basic and comprehensive vision rehabilitation is necessary to support people with VI [64]. Future studies are necessary to characterize temporal changes and the efficacy of public health measures such as DR screening at reducing prevalence of VI.

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Appendix A

Code used to implement the models according to Table 3

```
library(Rcapture)
X=matrix(c(1,0,0,118,1,1,0,38,1,0,1,39,0,1,1,59,1,1,1,13,0,1,0,768,0,0,1,4161),nrow=
7,ncol=4,byrow=TRUE)
Model1=closedpCI.t(X,dfreq=TRUE,mX=~.+c1:c2+c2:c3)
Model2=closedpCI.t(X,dfreq=TRUE,mX=~.+c2:c3)
Model3=closedpCI.t(X,dfreq=TRUE,mX=~.+c1:c3+c2:c3)
Model4=closedpCI.t(X,dfreq=TRUE,mX=~.+c1:c2+c1:c3)
Model5=closedpCI.t(X,dfreq=TRUE,mX=~.+c1:c2)
Model6=closedpCI.t(X,dfreq=TRUE,mX=~.+c1:c3)
Model7=closedpCI.t(X,dfreq=TRUE,mX=~.)
```

Legends of Figures

Figure 1: Venn diagram representing the overlap between the three lists.

Figure 2: Distribution of causes of visual impairment. ORD = Other retinal disorders; OND = Optic nerve disorders DG = Disorders of the globe DR = Diabetic Retinopathy AMD = Age-related Macular Degeneration RDD= Retinal detachments and defects. The top 5 causes were: - for age less than 25 years, OND 8% (95%CI, 4 - 13), OND 7% (95%CI, 4 - 12), RDD 4% (95%CI, 2 - 9), DG 3% (95%CI, 1 - 8), ORD 3% (95%CI, 1 - 8); for age 25-64 years, DR 25% (95%CI, 22 - 28), DG 10% (95%CI, 8 - 12), Glaucoma 8% (95%CI, 7 - 11), Cataract 7% (95%CI, 6 - 9), Cornea 7% (95%CI, 6 - 9) and for age more than 64 years, DR 33% (95%CI, 32 - 35), Cataract 18% (95%CI, 17 - 19), AMD 17% (95%CI, 15 - 18), Glaucoma 11% (95%CI, 10 - 12), DG 4% (95%CI, 3 - 5).

Tables and legends

Table 1: Prevalence of visual impairment in European countries. SVI= severe visual impairment; MVI=moderate visual impaiment; VA= visual acuity.

Country	Year	Sample	VI definition	Prevalence
Denmark	2016	3826 participants aged 20-94 years old from the Danish General Suburban Population Study	The best corrected visual acuity worse than 20/40 in the better-seeing eye	0.4% (95% CI, 0.2–0.7)
Hungary	2017	105 clusters of 35 people 50 years of age or older	SVI-VA < 6/60–3/60 MVI- VA < 6/18–6/60	SVI, 0.5% (95% CI, 0.2–0.7) MVI, 5.1% (95% CI, 4.3–5.9)
France	2005	Random stratified sample of 359 010 French citizens	Self-reported visual impairment	1.95%
Spain	2014	213 626 participants aged ≥15 years from a 2008 Spanish Survey	Distance and near visual impairment distinguished by applying a questionnaire	Near visual impairment - 1.89% Distance visual impairment - 1.89%
Germany	2019	Population-based cohort study in Germany concerning 14687 adults aged 35 to 74	Acuity below 0.3 in the better-seeing eye	0.37% (95% CI, 0.28–0.49)
Iceland	2008	Random sample of 1045 citizens of Reikjavik aged 50 or more years	Bilateral VI - best corrected visual acuity VA < 6/18 or visual field of > or = 5 degrees and < 10 degrees around the fixation point in the better eye	0.96% (95% CI, 0.37–1.55)
UK	2002	14600 participants aged 75 years and older	Binocular visual acuity <6/18	12.4% (95% CI, 10.8–13.9)

Table 2: Number of individuals presenting each possible capture history.

L1	L2	L3	Freq
1	1	1	13
1	1	0	38
1	0	1	39
0	1	1	59
1	0	0	118
0	1	0	768
0	0	1	4161
0	0	0	*x*

Table 3: All possible log-linear models and resulting prevalence estimates. When we write, for example, L1L2 we are indicating that the model assumed dependence between L1 and L2. N- and N+ represent lower and upper estimates of N according to a 95% confidence interval. P-values test the hypothesis of the model fitting well (a value above 0.05 is indicative that the difference between the model predictions and the data is not statistically significant) the data and the Akaike's Information Criteria (AIC) is a criterion to choose between models by considering a balance between the number of fitted parameters and the maximum likelihood. Lower AIC values indicate better fitting of the data by the model.

List Dependence	N	N-	N+	Prevalence	AIC	P-value (goodness of fit test)
L1L2 L2L3	17754	14017	23467	0.60% (95% CI, 0.47 - 0.79)	74.28	<0.001
L2L3	11781	10200	13888	0.40%(95% CI , 0.34 - 0.47)	142.10	<0.001
L1L3 L2L3	7682	6931	8835	0.26%(95% CI , 0.23-0.30)	109.86	<0.001
L1L2 L1L3	59316	47038	76590	1.97% (95% CI, 1.56-2.54)	58.59	0.92
L1L2	41042	34713	49157	1.38%(95% CI ,1.17-1.65)	105.25	<0.001
L1L3	36608	30991	43820	1.23%(95% CI, 1.04-1.47)	234.08	<0.001
All independent	29587	25833	34201	0.98%(95% CI, 0.86-1.14)	252.58	<0.001

Table 4: Age-specific prevalence. P-values test the hypothesis of the model fitting well (a value above 0.05 is indicative that the difference between the model predictions and the data is not statistically significant) the data and the Akaike's Information Criteria (AIC) is a criterion to choose between models by considering a balance between the number of fitted parameters and the maximum likelihood. Lower AIC values indicate better fitting of the data by the model.

Age	Prevalence	AIC	P-value (goodness of fit test)
<25	0.07% (95% CI, 0.045-0.13)	22.37	0.94
25-64	0.64% (95% CI, 0.49-0.88)	53.94	0.77
>64	3.27% (95% CI, 2.36-4.90)	50.43	0.82

Table 5: Sex-specific prevalence. P-values test the hypothesis of the model fitting well (a value above 0.05 is indicative that the difference between the model predictions and the data is not statistically significant) the data and the Akaike's Information Criteria (AIC) is a criterion to choose between models by considering a balance between the number of fitted parameters and the maximum likelihood. Lower AIC values indicate better fitting of the data by the model.

Sex	Prevalence	AIC	P-value (goodness of fit test)
Male	1.67%(95% CI , 1.32-2.19)	28.85	1
Female	2.20% (95% CI, 1.65-3.08)	28.58	1

Table 6: Causes of visual impairment in 6 European countries, including Portugal.

Our study	**Denmark[42]**	**Scotland[14]**	**Italy[56]**	**Poland[57]**	**Germany[7]**
Diabetic retinopathy	Cataract	Age related macular degeneration	Cataract	Age related macular degeneration	Age related macular degeneration
Cataract	Age related macular degeneration	Glaucoma	Myopia	Cataract	Glaucoma
Age related macular degeneration	Diabetic retinopathy	Cataract	Age related macular degeneration	Amblyopia	Diabetic retinopathy
Glaucoma	Myopic degeneration	Diabetic retinopathy	Diabetic retinopathy	Diabetic retinopathy	Corneal Disease
Cornea	Other retinal causes	Myopia	**not available**	Cornea	Genetic illness

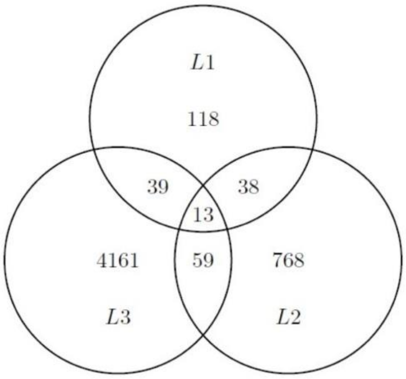
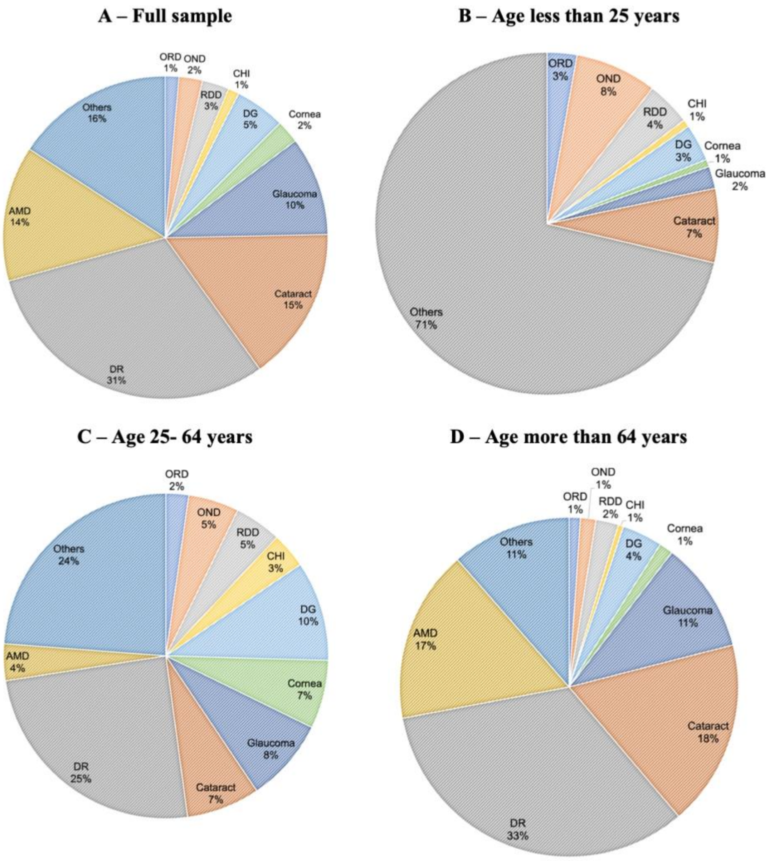


Figure1: Venn diagram representing the overlap between the three lists

337x190mm (154 x 154 DPI)



A – Full sample

B – Age less than 25 years

C – Age 25- 64 years

D – Age more than 64 years

Figure 2: Distribution of causes of visual impairment. ORD = Other retinal disorders; OND = Optic nerve disorders DG = Disorders of the globe DR = Diabetic Retinopathy AMD = Age-related Macular Degeneration RDD= Retinal detachments and defects. The top 5 causes were: - for age less than 25 years, OND 8% (95%CI, 4 - 13), OND 7% (95%CI, 4 - 12), RDD 4% (95%CI, 2 - 9), DG 3% (95%CI, 1 - 8), ORD 3% (95%CI, 1 - 8); for age 25-64 years, DR 25% (95%CI, 22 - 28), DG 10% (95%CI, 8 - 12), Glaucoma 8% (95%CI, 7 - 11), Cataract 7% (95%CI, 6 - 9), Cornea 7% (95%CI, 6 - 9) and for age more than 64 years, DR 33% (95%CI, 32 - 35), Cataract 18% (95%CI, 17 - 19), AMD 17% (95%CI, 15 - 18), Glaucoma 11% (95%CI, 10 - 12), DG 4% (95%CI, 3 - 5).

190x274mm (208 x 208 DPI)

CHAPTER III CONCLUSION

The aim of this thesis was to estimate the prevalence of VI in Portugal using the capture-recapture (CR) methods. The aim of this thesis has been accomplished and the results have now been submitted to publication. The methodology of capture and recapture was the best possible solution to determine the prevalence of VI in Portugal with the data sources available for this thesis. That is, when computing prevalence of visual impairment CR methods are better than case counting but eventually less ideal that cross-sectional studies [101]. As a cross-sectional study of the population was impossible in our case, we can say the CR was the best methodology to reach our aim.

The concept behind the methodology of CR methodology given in 1.5.3 is intuitive but the correct use of CR can be complex [75]. Typical missteps such as poor control of the dependence between sources or lists and the possible capture rates heterogeneity among subgroups of the population can lead to substantial errors in computation of the prevalence [5, 102]. In particular, applying these models to human population samples is additionally challenging, as in most epidemiologic studies only a small number of lists are available [75]. Because of that, for this thesis it was necessary to define specific goals to develop the knowledge and sensitivity to work with the data from people with impaired vision. The three goals are discussed below each one in his own section to keep the ideas organized.

3.1. First goal: theoretical basis of CR methods

The first goal of this thesis was to explore the theoretical basis of CR methods to face our experimental data with superior knowledge of the mathematical concepts behind the estimators. This goal was achieved by writing the literature review given in Paper 2 and by developing the simulation given in Paper 3.

The comprehensive literature review given in Paper 2 was an important contribution for this thesis because it gave the knowledge and allowed the development of the concepts of the methodology of CR when applied to human populations. This was a key development of this thesis because animal count (the initial purpose of CR methods) and people count have different specificities [101]. The review can be considered a substantial contribution to the field because is the first time that has been written in accurate but simple language with the purpose of being used in ophthalmic data. In this paper we explored what can be the problems with human samples when using CR, such as list dependence and open vs closed populations. In the paper we explain, for example, that the assumption of closed population in the case of humans is very unlikely to hold, but several authors have now shown that it represents a minor threat to the validity of the values of prevalence [75]. One initial question that we had at the beginning of this thesis was about list dependence because we knew from the lists available for this thesis that some dependence was expected.

The literature review was fundamental to describe and to learn how to deal with dependence between lists from a mathematical point of view. For example, when writing this paper, I learned that the one possible analytical approach to deal with list dependence was to apply the Petersen Estimator several times, analyse the resulting values and finally applying the log-linear models described in the section 1.5.3. This debate inspired the deep investigations about assessing list dependences.

In Paper 3, I explored more sophisticated techniques and inferential tools to understand and model list dependence. Even more, I tried to obtain a measure to the degree of dependence between lists. In addition, I also investigated the possible heterogeneity of our data. I applied recent models with ascertainment probabilities conditioned on partial capture histories. I used a bivariate Markov Chain model in order to investigate list dependence by using ephemeral and enduring effects. A simulation was designed with several sequences of logistic regressions, each modelling capture probability with variables setting list dependence. I believe this simulation was original and allowed us to assess the plausibility of all list dependence scenarios and to estimate the size of the hidden population. The final logistic regression selected after the simulation had a very high quality of fit, despite the small number of lists. Log-linear models are fundamentally different from our simulation. The first are Poisson regression models applied to the counts of capture histories. The second are sequences of logistic regressions. Each logistic regression has the binary variable being or not being captured and an explanatory variable establishing list dependence. Each also assumes a population size. In short, our approach consisted in finding the regression with maximum unconditional likelihood and consider its population size value the maximum likelihood estimate for population size. Finally, I also used mixtures of binomials and beta-binomial distributions to investigate heterogeneity.

In short, the work developed in the first goal was pivotal to develop the second goal. That is, the theoretical knowledge and the development of a systematic analytic approach to the use of CR methods was fundamental to deal with the experimental data available.

3.2. Second goal: quality of the experimental lists

The second goal of this thesis was to investigate the quality of the experimental lists available to compute prevalence of visual impairment. In this part of the thesis was dedicated data collection, quality assessment and exploratory analysis of the experimental lists.

At the beginning of this thesis there was already some data collected from the PCVIP-study. The large database (roughly 7000 records) contained information about patients attending appointments for eye checks or treatments at four hospitals: Hospital de Braga, Hospital Senhora da Oliveira-Guimarães, Hospital de Santa Maria Maior-Barcelos and Centro Hospitalar e Universitário de São João -Porto. The process of data collection for this study is given in detail in Paper 1, in the paper we describe the process of data collection and also the process of recruiting participants for interviews to other steps of the PCVIP-study. Some of the data collected during interviews has been used in the papers in which I was involved and are given in Appendix papers 5-6-7. These papers are not discussed here because they are outside the core objective of this thesis, but the results of this thesis are important to, for example, compute costs of illness or conditions such as vision impairment [103]. In other words, to estimate costs the prevalence should also be known. The information from medical records recorded during the PCVIP-study was fundamental to be able to perform this thesis, but it was not enough, and, therefore, it was necessary to identify more sources that could be used in our calculations. After some refection and debate with the supervisors and other experts we concluded that Primary Care Centres where people register to receive certification of impairment and the visually impaired association ACAPO were the best sources.

The heterogeneity of the lists and the lack of standardization of the information contained in each database was a challenge to deal with and in several occasions we needed to contact the sources to obtain complementary information. After obtaining information about the lists was possible to make them suitable for this thesis. For example, a requirement that has been explored in the first goal was the “equal catchability“ in all lists [104] for all individuals. Early in this second goal it was important to filter from the PCVIP-list (hospitals) cases with acuity better than 0.3 decimal units. That was because the other sources were unlikely to have this kind of records. During this second goal it was also necessary to make other correct and informed methodological decisions such as what was the best way to combine lists (the initial amount was high, for example, 1 list per hospital) and which municipalities to include in the calculations of prevalence (the denominator for prevalence calculations). According to the research performed during the first goal we considered that it would be correct to merge several lists (from the 4 hospitals) in one big list before starting with computations of prevalence [96]. The decision to merge the four lists from the four hospitals can be considered correct; although, it was necessary to find possible repeated records in the list of the hospitals because patients can be seen in different hospital at around the same time due to referrals between hospitals. During the process of making decisions about the most accurate methodology to prepare the information for the third goal, we performed several simulations and performed sensitivity analysis to understand the possible impact of methodological options.

In brief, the second goal as very important to the aim of this thesis and we succeed at handling and obtaining the necessary information to move to the third goal of the thesis. Handling the data and the simulations performed during this part of the thesis were fundamental to be confident about the main results in goal 3. This work is an original contribution to the field because if the first time that this type of data is used to compute prevalence of VI using CR. Other researchers in the field have now access to information how to use similar information to compute prevalence of VI.

3.3. Third goal: prevalence of VI in Portugal

Finally, we could advance to fulfil the third goal. The goal of applying several models to a dataset connected to an area as broader as possible, from which the final proposed value for prevalence of VI in Portugal would arise. Reaching that value was the most relevant aspect of this thesis. In Paper 2 and Paper 3**,** the real-life dataset consisted of lists associated to the Municipality of Braga. Such dataset was expanded with data from more Hospitals, Primary Care Centres and ACAPO registers. That enabled us to estimate the prevalence of VI to a broader region, specifically the Northwest region of the country. Such final results were reported in Paper 4.

The relevance of fulfilling this goal is considerable as there was no estimate available to the prevalence of VI in Portugal. It is the first time it has been estimated and it is important to do so regularly so that the health of the population can be monitored and policies can be designed to lower the number of cases as much as possible.

Regarding the last values presented in Paper 4, I used several lists and several models. For example, I used a total of seven lists, the all Hospitals separated, the Primary Care Centres of Braga and Barcelos also separated and the ACAPO list. However, that approach led to a situation in which some lists intersection was the empty set. In the context of capture-recapture models that usually means the models will perform badly, which was exactly what happened. Then, I used another approach. The hospitals of Braga and Porto normally receive patients from other Hospitals. When small Hospitals cannot solve serious health problems they refer to these two Hospitals. Because of that I constructed five lists. Hospital of Porto, Hospital of Braga, Hospital of Guimarães and Barcelos combined in one list, Primary Care Centres combined in one list and finally the list of ACAPO. I have applied several models, log-linear models, Chapman Estimator, all the models described in Paper 3 and models with covariates. Some fitted the data well, according to the goodness of fit test. At last, I used only three lists, all the Hospitals, all the Primary Care Centres and ACAPO. Once again, I applied several models and some fitted the data well. One particular log-linear model performed better than all the others concerning both the three lists scenario and the five lists scenario. This is not very usual as capture-recapture models tend to perform better with a higher number of lists. Because the best model was within the three lists scenario, I have chosen the three lists approach. Subsequently, I have estimated the values for categoric-specific prevalence.

The final global prevalence of VI in our study was similar to South European countries, higher than Northern European counties and lower than Eastern European countries. The main reason behind these differences is probably related with different mechanisms of eye care in different countries. Our prevalence was higher than in countries with better preventive mechanisms and lower than other with likely worse access to eye care and or preventive mechanisms of vision loss.

As expected, the prevalence of VI varies with age and it is more common among elderly people. The prevalence from age 65 onwards was about 5 times higher than in younger age groups. In a study from Germany [38] it was about 3 times higher. A study in Denmark found that VI was 9 times more prevalent amongst people with more than 64 years than amongst people in the age range 20-64 [105]. Our results for the older population are also in line with the estimates from a recent meta-analysis estimating the prevalence of VI in people 55 years or older in European countries. The study that included data from Portugal, estimated an overall prevalence of VI for those above 55 years would be close to 2.75% [106, 107].For age under 25 years, prevalence of VI was low and in line with several other studies [108-110]. For example, our results were similar to data available from Sweden, in 1997 the age-specific prevalence of VI as 10.9/10,000 amongst people under the age of 19 years [109]. There was a good agreement between our results and similar studies, small differences might be due, among other factors, to temporal changes in prevalence of VI and the age-range criteria.

Also as expected, females suffer from this condition more than males, as the prevalence of VI among females was 1.3 times higher than the prevalence among males. In a study from Germany [38] the prevalence of VI among females was 1.4 times higher than among males. In a study from Spain [43] the prevalence of VI among females was 1.7 times higher than among males. The female-to-male ration is expected to vary from 1.1 is Sub-Saharan Africa to 1.25 in Europe Possible causes for this female-to-male ratio above 1 are likely to include factors such as gender inequalities in access to health care [111].

The information concerning the cause of VI was available from the Hospitals lists. The causes were classified according to ICD9 [114]. Diabetic Retinopathy was the main cause, followed by Cataract, Age-related Macular Degeneration and Glaucoma. The main difference between our distribution of causes of VI and the distribution of other studies in other countries is that our first cause is Diabetic Retinopathy. That can be explained by the fact that the Diabetic Retinopathy Screening in Portugal was at an incipient phase when we collected data for this study [112]. We also have a considerable percentage of cataract due to long Hospital waiting lists to surgery [113].

3.4. Limitations of this thesis and future research

The fact that the completeness is about 9% is a limitation of our study. In order to increase this value more data from the Primary Care Centers would be needed. During this study, we have tried to get access to several other Primary Care Centres. However, when we were close to achieve this objective, the Covid-19 pandemic started and the Health authorities were no longer available to collaborate with us.

Other limitation was the missing data in our lists. There was a lack of information about causes from ACAPO and Primary Care Centres. Thus, our study concerning the causes of VI only used the lists from the Hospitals. Conversely, the fact that the causes from the PCVIP-study were classified according to ICD9 was a positive factor. The lack of visual acuity from ACAPO also was a limitation as we could have explored deeply models with covariates.

Future studies are necessary to characterize temporal changes and the efficacy of public health measures such as Diabetic Retinopathy screening at reducing prevalence of VI.

3.5. Final remarks

Capture-recapture models have been applied in several disciplines, as biomedical sciences, epidemiology or ecology, to estimate the size of populations. In particular, they have been used to estimate the prevalence of several diseases or conditions [12, 105, 106]. Developing these inferential models is of great importance to avoid the high costs and unreasonable time spending of cross-sectional studies. However, applying capture-recapture models is challenging, as they are very sensitive to list dependence and possible capture rates heterogeneity among subgroups of the population. In particular, applying these models to human population samples is additionally challenging, as in most epidemiologic studies only a small number of lists are available. In this study, we used several types of capture-recapture models to investigate the prevalence of VI. Some models showed high quality of fit, which gives credibility to the prevalence values that we obtained. Other, did not perform well. The capture probability or ascertainment probability, as it is commonly referred to within the human populations' terminology, in our study only varied according to the fact of the subject being or not present in other lists. The group each subject could belong to, male, female, young, old, among others, did not influence ascertainment probabilities.

In conclusion, the results of the current study showed that prevalence of VI in Portugal was within the expected range and in line with other neighbour countries. A significant number of cases of VI detected was due to preventable causes. In other words, a reduction of cases of VI in Portugal is possible with improved access to eye care and effective diseases monitorization.

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APPENDIXES

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

The AI includes 46 goals split between three objectives: social functioning, recreation and daily living, and 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. We explained AI and EQ-5D using predictors as sex, age, level of VI in the better eye and in the worse eye and number of comorbidities.

My participation in this paper was to perform the statistics analysis. Variables were tested for normality using Kolmogorov-Smirnov test. ANOVA was used for multiple comparisons and t-test to compare two normally distributed variables. Kruskal-Wallis or Man-Whitney U tests were used for comparisons when variables failed normality tests. When necessary, Bonferroni correction was applied. Associations between variables were tested with Pearson correlations when both variables were continuous and Spearman`s rank-order correlation when any of the variables were ordinal. Multiple 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. Multiple regression analysis also showed that gender, age, level of VI in the better eye and number of comorbidities are significant independent predictors of EQ-5D-3L index.

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

Antonio Filipe Macedo,[1,2] Pedro Lima Ramos,[2] Laura Hernandez-Moreno,[2] Joana Cima,[3] António M. G. Baptista,[2] Ana Patricia Marques,[3] Robert Massof[4] and Rui Santana[3]

[1]Department of Medicine and Optometry, Linnaeus University, Kalmar, Sweden
[2]Vision Rehabilitation Lab, Centre/Department of Physics and Optometry, University of Minho, Braga, Portugal
[3]Centro de Investigação em Saúde Pública, Escola Nacional de Saúde Pública, Universidade NOVA de Lisboa, Lisbon, Portugal
[4]Johns Hopkins Wilmer Eye Institute, Baltimore, Maryland, USA

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, and 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 ($p < 0.001$), and their results were strongly correlated $r(134) = 0.825$, ($p < 0.001$). Explanatory factors for visual ability were level of VI in better eye, age and gender, $R^2 = 0.43$, ($p < 0.001$). Explanatory factors for the EQ-5D-3L were level of VI in the better eye, comorbidities and gender, $R^2 = 0.36$, ($p < 0.001$).**
Conclusion: **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, it 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.**

Key words: patient reported measures – utilities – visual ability – visual impairment

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Introduction

Patient-reported outcome measures are fundamental for evaluation of health technologies or interventions (Brazier 2007). 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 (Fitzpatrick et al. 1998). 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 (Brooks 1996; Langelaan et al. 2007; van Hout et al. 2012; Butt et al. 2013), the SF-6D (Espallargues et al. 2005; Butt et al. 2013), the Geriatric Depression Scale (Lyness et al. 1997) and other rating scale questionnaires. Health utilities typically are estimated from time trade-off (Weinstein et al. 2009) or standard gamble methods (Drummond et al. 1987), or from one of several stated-preference methods (e.g. discrete choice (Kessels et al. 2011), pairwise comparison (Bradley & Terry 1952), best-worst scaling

(Flynn et al. 2007) or iterative bidding games (Brookshire & Crocker 1981)). 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 (Ferreira et al. 2014). 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 five 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; Rein et al. 2007). However, it often has been suggested that the EQ-5D-3L can have unreliable and unresponsive outcomes in the case of visual disorders (Tosh et al. 2012; Malkin et al. 2013).

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 (Brown et al. 2003), but that approach has been criticized because it overestimates the utility of vision relative to that of overall health (Kymes 2008; Frick & Massof 2009).

Condition-specific (individualized) 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 (Fitzpatrick et al. 1998). Self-report instruments used to assess visual functioning include the National Eye Institute Visual Functioning Questionnaire (NEI-VFQ; Mangione et al. 2001), the Impact of Vision Impairment Questionnaire (IVI; Weih et al. 2002) and the Activity Inventory (AI; Massof et al. 2005a,b, 2007). 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 (Massof et al. 2005 a,b; Goldstein et al. 2014). 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 individualized 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 VI 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 VI to develop effective and inclusive public health strategies (Binns et al. 2012). 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 to understand the effectiveness of current low-vision rehabilitation practices (Binns et al. 2012). Without evidence of cost-effectiveness of interventions intended to tackle the burden of VI, 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 VI 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 VI and the impact of low-vision rehabilitation (Malkin et al. 2013). 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 (DR) (Tosh et al. 2012; Malkin et al. 2013). 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 (VA) can influence health utilities in visually impaired people.

The purpose of our study was to investigate whether the EQ-5D-3L and the AI have equivalent ability to discriminate between VI 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 VI and that each instrument is influenced by a different set of visual and non-visual factors.

Patients and Methods

Participant recruitment and data collection

Participants were recruited in three public hospitals as a part of a study of prevalence and costs of VI in Portugal (PCVIP-study). Outpatients at these hospitals with VA, 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 (VA) was assessed using an internally illuminated ETDRS chart (Lighthouse International, New York, NY, USA) at 4, 2 or 1 m 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 (Ferris et al. 1982).

During interviews, participants were asked about 16 systemic health problems detailed in Table A1 in Appendix that are consistent with those assessed in other studies (van Nispen et al.

2009; Morales et al. 2010; Whitson et al. 2011). Demographic information and other descriptive information for our sample of 134 participants are summarized in Table 2. 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 (AI)

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. 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 (van Leeuwen et al. 2015). Difficulties achieving a goal are said to depend on the difficulty experienced in the tasks that underlie each goal (Massof et al. 2005). The investigators translated the AI into Portuguese (Hernández-Moreno et al. 2015). 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; Winsteps.com). 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 VI such are chronic pain, fatigue or depression (Tabrett & Latham 2011).

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 (Brooks 1996; Dolan 1997). 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 three-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 five 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 (Ferreira et al. 2014). During the questionnaire administration, clear instructions were given to consider difficulties associated with VI.

Categories of visual impairment (VI)

Visual impairment (VI) was categorized according to the guidelines of the International Council of Ophthalmology using VA intervals on a logMAR scale (International-Council-of-Ophthalmology 2002). 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 4 m, 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 1).

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 α values <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 (Swinscow 1997). Vision-specific tools for quantifying visual ability and generic utility measures need to be compared with caution.

Table 1. 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	

But comparisons have been tried in the past because they are necessary to gather information about the overall impact of vision loss in health (Espallargues et al. 2005; Crewe et al. 2011). 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, VI level in the better and in the worse eye and number of comorbidities. We included the level of VI 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 (Finger et al. 2013).

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 <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 2.

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 2 provides a summary of these results, and the distribution of visual ability person measures for different age groups is shown in Fig. 1. A three-dimensional scatter plot of visual ability person measures as a function of logMAR acuity in the better eye and in the worse eye is shown in Fig. 2. The difference between visual ability person measures for different groups, defined by the VA 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 2. For VI 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 VI given by acuity were associated with lower visual ability person measures.

Table 2. Demographic characteristics of the participants and descriptive statistics.

Variable	*N*	EQ-5D index 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

DR = diabetic retinopathy; RD = Retinal disease; ON = optic nerve; AMD = Age-related macular degeneration.

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 Table A2 in Appendix. The mean EQ-5D-3L index for the entire sample was 0.442 (SD = 0.311), comparisons between groups are given in Table 2. A 3-D scatter plot of the EQ-5D-3L index as a function of logMAR VA in the better eye and the number of comorbidities is shown in Fig. 3. The differences between EQ-5D-3L index for different VI groups, based on the acuity of the better eye, tested with ANOVA, were statistically significant, *F*(2,131) = 24.05 ($p < 0.001$). *Post hoc* tests revealed that for VI 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

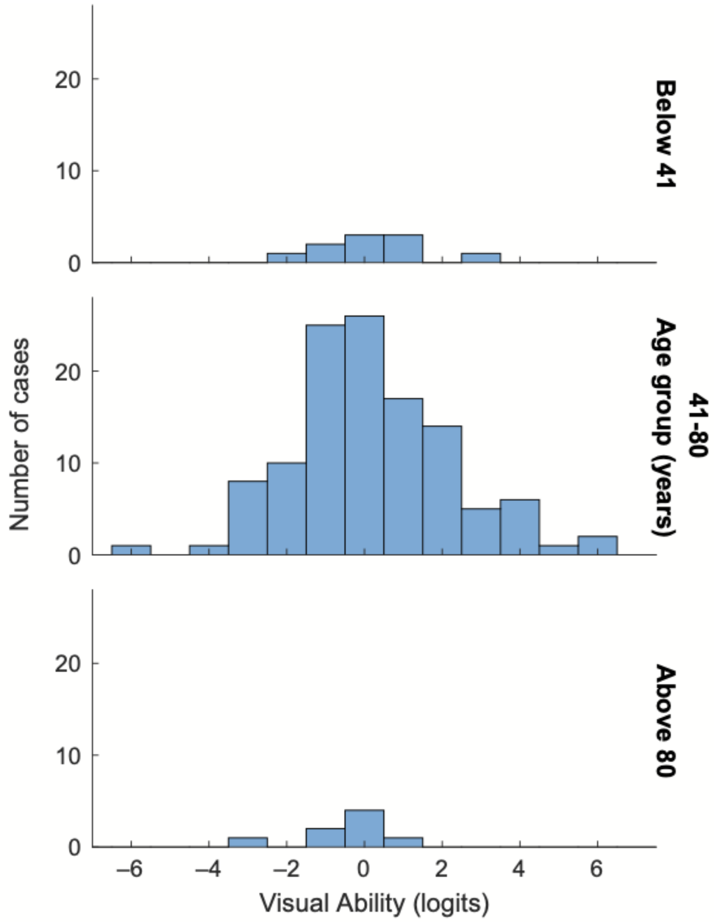

Fig. 1. Histogram showing the distribution of visual ability person measure per age group in the all sample.

(p = 0.035). The negative correlation indicates that the index tends to reduce with age.

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 3; the four predictors account for 45% of the variance in visual ability person measures. Those with higher VA in the better eye have higher visual ability. The typical difference between VI groups (stratified by acuity in the better eye) was approximately 1.4 logits (unstandardized beta coefficients in Table 3). Level of VI in the worse eye does not achieve statistical significance in our model (p = 0.053).

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 4; the three 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 four or more comorbidities have lower EQ-5D-3L scores.

Figure 4 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).

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 AI. Both measures were related positively to VI in the better eye. Regression analysis suggests that EQ-5D-3L utility index is associated with both, VI level in the better eye and the number of reported comorbidities. Visual ability measures are associated with age and VI 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 VI 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 (Langelaan et al. 2007; van Nispen et al. 2009) and other health utilities instruments (Crewe et al. 2011; Briesen et al. 2014). In contrast to our results, a study by Lloyd and colleagues found inconsistent associations of utilities with VA in patients with DR (Lloyd et al. 2008). 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. (2012), the association of EQ-5D-3L utility indices with visual impairments might depend on the visual disorder studied. However, our study included a range of disorder diagnoses and we found no evidence of disorder

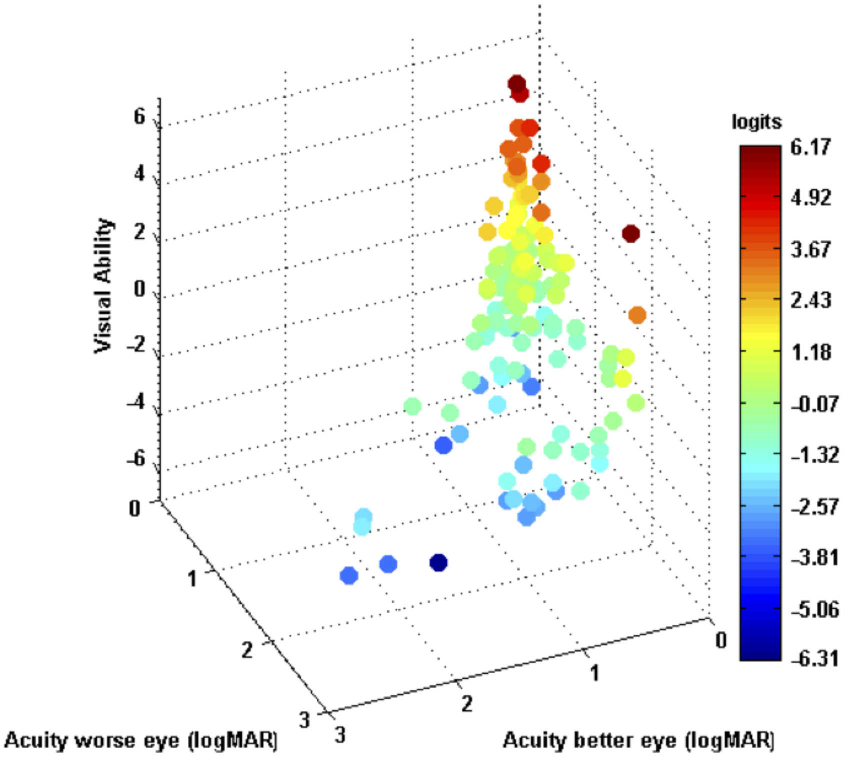

Fig. 2. Scatter plot showing the distribution of visual ability according with acuity in the better and worse eye.

diagnosis dependence. van Nispen et al. (2009) have found index results slightly higher than ours in an observational study applying the EQ-5D-3L in mixed causes of VI. 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 DR. 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 versus 78 years for their study). As reported by others, younger subjects with VI might feel, for example, more often anxious or depressed (Langelaan et al. 2007; van Nispen et al. 2016). As shown in Table A2 in Appendix, 19 of our participants reported 'severe depression or anxiety' 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 (Ferreira et al. 2014).

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. (2007) did report significance of gender and that is in line with what has been found in the general population in some countries (Burström et al. 2001). Comorbidities also had an effect in the EQ-5D-3L; however, 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 (Langelaan et al. 2007). In our case, sometimes these two conditions (VI and stroke) were present in the same participant. As shown in Fig. 4, there are noticeable changes in response patterns when comparing people with four or more comorbidities with people with three 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 four of the five 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 comorbidities combine with VI effects to produce the final response.

In agreement with previous studies, utility results were independent of the cause of VI and age (van Nispen et al. 2009; Crewe et al. 2011; Briesen et al. 2014). 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 <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 (Langelaan et al. 2007). 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 (Senra et al. 2011, 2015). 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 VI can affect domains that are not currently included in the questionnaire such as sleep quality or concentration (Flynn-Evans et al. 2014; Jelsma & Maart 2015).

Results of the AI 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 (Pearce et al. 2011; Goldstein et al. 2014) or VI caused by specific eye diseases such as DR (Dunbar et al. 2012). 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 (Goldstein et al.

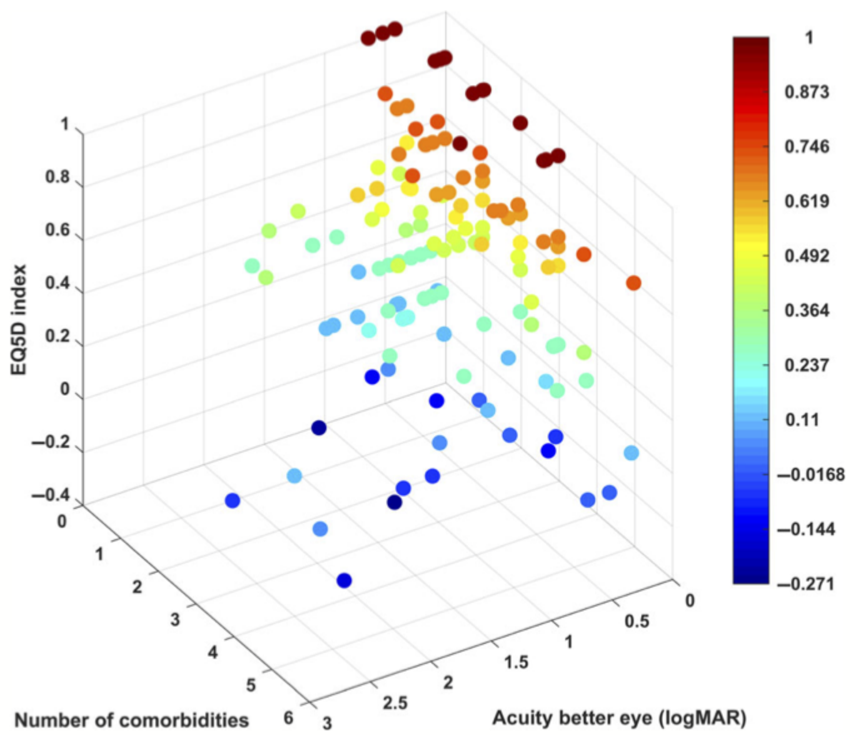

Fig. 3. Scatter plot showing the distribution of the EQ-5D index according with acuity in the better eye and number of comorbidities.

Table 4. Factors associated with EQ-5D index in a multivariate regression model with forward selection of variables.

Predictor	Un-standardized beta coefficients	p Value	Standard error
Intercept	0.726	<0.001	0.042
Gender			
Male*	–		
Female	−0.140	0.001	0.043
VI better eye			
1*	–		
2	−0.242	<0.001	0.048
3	−0.439	<0.001	0.060
Comorbidity			
0–3*	–		
3–6	−0.175	<0.001	0.050

* 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.

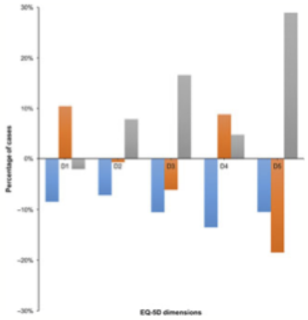

Fig. 4. Change in the percentage of participants reporting no problems (blue bars), some problems (orange bars) or extreme problems (grey bars) when comparing the group with 0–3 comorbidities with the group 4–6 comorbidities in each of the five domains of the EQ-5D. D1 (mobility); D2 (self-care); D3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

Table 3. Factors associated with visual ability scores (person measure) 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*	–		
Female	−0.691	0.009	0.264
Age			
Below 80*	–		
Above 80	−1.495	0.010	0.576
VI better eye			
1*	–		
2	−1.397	<0.001	0.307
3	−2.940	<0.001	0.442
VI worse eye			
1*	–		
2[†]	–		
3	−0.622	0.053	0.318

* Reference category.

[†] 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.

2014). 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 (Finger et al. 2013). 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 VI. Given the coarseness of the response scale of the EQ-5D-3L, the limited spectrum of domains assessed (Jelsma & Maart 2015) and the influence of comorbidities, it might be of limited use in vision rehabilitation (Malkin et al. 2013). Further studies are necessary to investigate whether the new versions of the instrument are able to improve these limitations.

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Appendix

Table A1. List of comorbidities used for the interview.

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

Table A2. Most frequently reported health states.

Health state	EQ-5D index	No. 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

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Correspondence:
Antonio Filipe Macedo
Department of Medicine and Optometry
Linnaeus University
SE 39182, Kalmar
Sweden
Tel./Fax: +46 480 446 036
Email: a.macedo@ucl.ac.uk

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Appendix paper 6: The use of informal care by people with vision impairment

In this paper, we wanted to estimate and characterize the use of informal care by people with vision impairment in Portugal. A total of 546 visually impaired individuals were recruited from Portuguese hospitals. Clinical information was obtained from medical records, socio-demographic details and informal care use were collected during face-to-face interviews. In addition, participants responded to a functional vision questionnaire (activity inventory) to assess their visual ability. I applied Logistic regressions to determine independent factors associated with informal care use and linear regressions to determine independent predictors of the amount of informal care needed. 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.

RESEARCH ARTICLE

The use of informal care by people with vision impairment

Ana Patricia Marques[1,2☯]*, **Antonio Filipe Macedo**[3,4☯], **Laura Hernandez-Moreno**[4], **Pedro Lima Ramos**[3], **Thomas Butt**[5,6], **Gary Rubin**[5], **Rui Santana**[1,2], **for the Portuguese visual impairment study group (PORVIS-group)**[¶]

1 National School of Public Health, NOVA University of Lisbon, Lisbon, Portugal, **2** Public Health Research Center, National School of Public Health, NOVA University of Lisbon, Lisbon, Portugal, **3** Department of Medicine and Optometry Linnaeus University Kalmar, Kalmar, Sweden, **4** Low Vision and Visual Rehabilitation Lab, Department and Center of Physics—Optometry and Vision Science, University of Minho Braga, Braga, Portugal, **5** University College London, Institute of Ophthalmology, London, United Kingdom, **6** National School of Development, Peking University, Beijing, China

☯ These authors contributed equally to this work.
¶ Membership of the Portuguese visual impairment study group (PORVIS-group) is provided in the Acknowledgments.
* ap.marques@ensp.unl.pt

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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 medical records, socio-demographic details and informal care use were 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 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

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of visual loss at personal and societal level. This could 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 [1–4]. 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" [5, 6]. Some factors such as age, type of activities, type of disability and severity level can influence the demand for informal care [5, 7]. In addition, it can be influenced by socio-cultural aspects such as family structures, levels of income per capita and availability of formal long-term care systems [5]. 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, 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 [8]. 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 [9–11] considering, in a few instances, self-reported difficulties [9, 10]. However, one study relied in presumed visual acuity [9] and another failed to investigate the effect of self-reported difficulties in informal care [10]. 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 [12, 13]. In general, self-reported difficulties have been overlooked in past studies so 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 went 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 that at least 3000 reached 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 MC (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 [14]. 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 [15].

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 [16–19]. 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) [18, 20]. We use the term 'visual ability' to define the overall ability to perform activities that depend on vision [21].

Participants also reported comorbidities based on a list of 16 categories as described in S1 Appendix. 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 the final measured acuity [15].

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 [22, 23]. The questionnaire was drawn from previously validated instruments [23, 24], 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 1.

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 [5, 10, 25, 26]. The number of reported hours

Table 1. 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).

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 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?	a) Yes (ask question 3.1) b) 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)

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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. [27].

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 2). 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 were 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 S2 Appendix. 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 older individuals, 50% (n = 275) were older than 65 years. The most common causes of vision impairment were: diabetic retinopathy, age-related macular degeneration (AMD), glaucoma and other retinal disorders and

Table 2. 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 older	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%	

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detachments. Participants were divided in 2 groups: "users" and "non-users" to identify socio-demographic and clinical independent predictors of the use of informal care. We compared the distribution of cases, between groups, according to several categories. These results are summarized in Table 2. 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 3 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 worse in the users group.

Table 4 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 4 is less

Table 3. 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)[a]						
	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; **$p<0.001$**

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

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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.

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 vision impairment, presence of comorbidities, marital status and living arrangement were not statistically significant.

Table 4. Explanatory variables of informal care usage. In the first column, brackets show dummy variables categories (category = 1 versus reference category = 0).

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

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Table 5. 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

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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 5 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 a 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 vision impairment (2 categories) that were not statistically significant. The R-squared of the model was 0.157.

Discussion

In this study, we quantified and characterized the use of informal care in a sample of 546 individuals with impaired vision. Informal care was reported by 39.6% of the participants requiring, each requiring a median of 390 hours of informal care 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 [9, 12]. One study 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 [12]. Others found that 36% of AMD patients use paid or unpaid assistance [9]. 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 [9, 11].

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 care may be because, although they rely on 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 [12, 13]. It is know that informal care can be influenced by many factors and, in particular, by the organization of the society [5]. Therefore, our results need to be interpreted in the Portuguese context and may also be applicable to similar societies [28].

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 [10, 13, 29, 30]. 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. [12] found an increase in intensity with increased self-reported walking difficulties. Keefe et al. [26] 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 [5, 25]. 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 [22, 31]. 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 [31].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 care [22]. Keeping a diary would minimize this limitation but would be significantly more expensive and time consuming [5, 32]. In addition, the amount of missing data and the complexity of the information available may increase substantially with a diary [33, 34]. Thus, the method adopted could have led 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 [5, 10, 25, 26] and is within the interval used in studies using the opportunity cost method [5, 27]. Therefore, it seems appropriate and ensures comparability with others studies [10, 26].

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 [5, 7], 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.

Supporting information

S1 Appendix. List of comorbidities.
(DOCX)

S2 Appendix. Regression models description.
(DOCX)

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Authors report on behalf of the Portuguese visual impairment study group (PORVIS-group): António Filipe Macedo, PhD, Research Project Principal Coordinator; Department of Medicine and Optometry Linnaeus University Kalmar, Sweden and Vision Rehabilitation Lab Centre/Department of Physics and Optometry University of Minho Braga, Portugal.Amandio Rocha-Sousa, MD, PhD, FEBO; Marta Silva, MD, ophthalmology resident; Sara Perestrelo, MD, ophthalmology resident; João Tavares-Ferreira, MD, Ophthalmologist; Ana Marta Oliveira, research coordinator; Department of Surgery and Physiology, Faculty of Medicine University of Porto and/or Ophthalmology Department: Centro Hospitalar de São João. Cristina Freitas, MD Ophthalmologist; Keissy Sousa, MD Ophthalmologist; Ricardo Leite, MD, ophthalmology resident; José Carlos Mendes, MD, ophthalmology resident; Andreia Braga Soares, MD, ophthalmology resident; Rui Carneiro Freitas, MD, ophthalmology resident; Department of Ophthalmology, Hospital de Braga. Pedro Reimão, MD, Ophthalmologist; Marco Vieira, MD, Ophthalmologist; Joel Monteiro, MD, cardiology resident; Department of Ophthalmology, Centro Hospitalar de Alto Ave, Guimarães. Natacha Moreno, MD, Ophthalmologist; Department of Ophthalmology, Hospital Sta Maria Maior, Barcelos. Gary Rubin, PhD (project adviser); UCL-Institute of Ophthalmology, London, UK. Ana Patricia Marques, PhD candidate; Rui Santana, PhD; Research Project Coordinator; National School of Public Health, NOVA University of Lisbon, Portugal. Laura Hernandez-Moreno, PhD candidate; Pedro Lima, PhD candidate; Low Vision and Visual Rehabilitation Lab, Department and Center of Physics–Optometry and Vision Science, University of Minho, Braga, Portugal.

The lead author of this group is: António Filipe Macedo: antonio.macedo@lnu.se

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Author Contributions

Conceptualization: Ana Patricia Marques, Antonio Filipe Macedo, Thomas Butt, Gary Rubin, Rui Santana.

Data curation: Ana Patricia Marques, Laura Hernandez-Moreno, Pedro Lima Ramos.

Formal analysis: Ana Patricia Marques, Antonio Filipe Macedo, Pedro Lima Ramos.

Funding acquisition: Antonio Filipe Macedo, Rui Santana.

Investigation: Ana Patricia Marques, Antonio Filipe Macedo, Laura Hernandez-Moreno.

Methodology: Ana Patricia Marques, Antonio Filipe Macedo, Thomas Butt, Gary Rubin, Rui Santana.

Project administration: Antonio Filipe Macedo, Rui Santana.

Resources: Antonio Filipe Macedo, Rui Santana.

Software: Ana Patricia Marques, Pedro Lima Ramos.

Supervision: Antonio Filipe Macedo, Thomas Butt, Gary Rubin, Rui Santana.

Validation: Ana Patricia Marques, Antonio Filipe Macedo, Laura Hernandez-Moreno, Pedro Lima Ramos, Thomas Butt, Gary Rubin, Rui Santana.

Visualization: Ana Patricia Marques, Laura Hernandez-Moreno.

Writing – original draft: Ana Patricia Marques, Antonio Filipe Macedo.

Writing – review & editing: Ana Patricia Marques, Antonio Filipe Macedo, Laura Hernandez-Moreno, Pedro Lima Ramos, Thomas Butt, Gary Rubin, Rui Santana.

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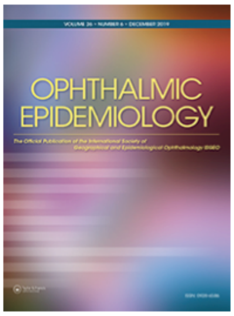
Appendix paper 7: Productivity Losses and Their Explanatory Factors Amongst People with Impaired Vision

People with visual impairment may have reduced chances in finding and maintaining jobs. In this paper, we wanted to estimate productivity losses amongst people with impaired vision in Portugal and to investigate explanatory factors associated with non-participation in the labour market. A total of 546 visually impaired individuals participated in face-to-face interviews. Participants were asked about their workforce participation to determine productivity (employment status questionnaire), their health-related quality of life - HRQoL (EQ-5D) and their visual acuity and visual ability (Activity Inventory). My participation in this paper was to perform the statistics analysis. Logistic regression was used to determine independent factors associated with participation in the labour market. After controlling for visual acuity and ability, younger individuals, with more years of education, without comorbidities and high HRQoL had a higher probability of being employed. The probability of being employed was associated with education, HRQoL and comorbidities.



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Productivity Losses and Their Explanatory Factors Amongst People with Impaired Vision

Ana Patricia Marques[a,b], Antonio Filipe Macedo[c,d], Pedro Lima Ramos[c,d], Laura Hernandez Moreno[d], Thomas Butt[e,f], Gary Rubin[f], and Rui Santana on behalf of the Portuguese visual impairment study group (PORVIS-group)[a,b]

[a]National School of Public Health, NOVA University of Lisbon, Lisbon, Portugal; [b]Public Health Research Center, National School of Public Health, NOVA University of Lisbon, Lisbon, Portugal; [c]Department of Medicine, Optometry Linnaeus University Kalmar, Kalmar, Sweden; [d]Low Vision and Visual Rehabilitation Lab, Department and Center of Physics—Optometry and Vision Science, University of Minho Braga, Braga, Portugal; [e]National School of Development, Peking University, Beijing, China; [f]Institute of Ophthalmology, University College London, London, UK

ABSTRACT

Purpose: To estimate productivity losses amongst people with impaired vision in Portugal and to investigate explanatory factors associated with non-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 to determine productivity (employment status questionnaire), their health-related quality of life – HRQoL (EQ-5D) and their visual acuity and visual ability (Activity Inventory). Productivity losses included absenteeism and reduction in workforce participation. Logistic regression was used to determine independent factors associated with participation in the labour market.

Results: From the 546 participants, 50% were retired, 47% were of working age and 3% were students. The employment rate was 28%, and the unemployment rate was 21% for the working age sample. For those of working age, productivity losses were estimated at €1.51 million per year, mean of €5496 per participant. The largest contributor to productivity 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 a higher probability of being employed.

Conclusions: Our findings show a high unemployment rate and high productivity losses amongst people with impaired vision. 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 help to increase participation in the labour market. These findings can inform decisions to intervene to reduce the burden of vision loss.

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Introduction

People with impaired vision face barriers to the acquisition and development of skills and abilities, which leads to disability.[1–6] They are limited in their ability to perform valued activities of daily living and self-care such as driving or reading documents without the help of special devices or software.[7,8] In addition to the direct impact on their ability to perform activities of daily living and self-care, difficulties to perform vision-related tasks can also cause stress and anxiety in persons with impaired vision.[9] These challenges may not only impact on health, but also on productivity. People with impaired vision may face reduced chances of finding and retaining employment, a reduced range of jobs open to them[9-12], or increased chance that they never look for a job in the first place.[12] The opportunity to have a paid job is important to most individuals living in society since provides opportunities for maintaining or increasing one's financial independence, enables relationships and social

CONTACT Ana Patricia Marques ap.marques@ensp.unl.pt National School of Public Health, NOVA University of Lisbon Escola Nacional de Saúde Pública, Avenida Padre Cruz, Lisboa 1600-560, Portugal

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inclusion and increases quality of life.[13,14] It is therefore important to understand the causes of reduced employment amongst people with impaired vision and the financial and the health burden for the individual and for the society.

From the economic perspective, the burden for society is captured by productivity costs. Productivity costs may be defined as "costs associated with production loss and replacement costs due to illness, disability and death of productive persons, both paid and unpaid".[15] 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.[16] Working with limitations due to illness, or presenteeism, is another component of reduced productivity. However, there is no consensus on the measurement of presenteeism meaning that it is rarely included in economic calculations of productivity costs.[17]

For those in the labour market, absenteeism may be defined as the number of workdays lost due to health-related issues.[18] For those of working age, but out of the labour market, reduced workforce participation can be defined as production missed due to the premature exit from the labour market.[19] Some studies found high productivity costs and high rates of unemployment, job loss and early retirement amongst persons with vision impairment.[16,20–24]

From our perspective, the information available from studies published in the past decade is limited in two aspects: 1) the samples studied had too restrictive inclusion criteria and 2) the explanatory factors used lacked accuracy. For example, one study used self-reported vision impairment,[20] another used exclusively blind individuals[22] and another used an unclear definition of vision impairment.[21] 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 on quality of life.[20–23] 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. HRQoL is likely to influence the ability to look for jobs and to retain them, therefore we chose to include measures of patient-reported HRQoL when investigating 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 variables, patient-reported and clinical measures that may be explanatory factors for employment.

Methods

Study design, setting and participant selection

Participants were recruited from four public hospitals with an area of influence of nearly 2 million inhabitants in three regions of Portugal: Porto, Braga and Viana do Castelo. Patients attending medical appointments at the department of ophthalmology in these hospitals with last recorded visual acuity of 0.30 logMAR or worse were invited to take part in face-to-face interviews with trained researchers. Principal diagnosis, designated here as 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 also collected information about gender, date of birth and systemic diseases. The information was registered in a secure online platform (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 participating 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.[25–27]

Clinical and quality of life measurements

During face-to-face interviews, patients were asked to respond to the EuroQol EQ-5D (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 dimensions: mobility, self-care, usual activities, pain or discomfort, anxiety and depression. Each dimension is rated on a 3-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.[28]

In addition, participants 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. Participants are asked to rate goals which depend on the difficulty experienced in the tasks that underlie each goal.[29–32] 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.[33]

During the interview, visual acuity was (re)measured using an internally illuminated ETDRS chart (Lighthouse International, NY, USA) at 4, 2 or 1 m according with the severity of the (expected) vision loss. Letter by letter scoring was employed to specify the final measured acuity.[25]

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

Employment status questionnaire

We used a questionnaire to collect information about absenteeism and workforce participation. The questionnaire was drawn from previously validated instruments.[34,35] 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 1 summarizes a translated version of the questionnaire.

Productivity costs were estimated from the societal perspective. Productivity costs encompass absenteeism and reduced workforce participation.

Absenteeism was measured by the number of absent workdays due to health problems. Absenteeism was divided into short-term absenteeism and long-term absenteeism. Long-term absenteeism includes individuals reporting absent for more than three consecutive months. Other cases were considered short-term absenteeism. 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 mean hourly pay rate according with the category of income level reported by the participant (see Table 1). We extrapolated the 2-week recall period to an annual rate multiplying by 24 working weeks adjusting for annual leave and public holidays.

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 (65 or more).[36,37] 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 given in Appendix B. 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 may be an active choice of the individual to not participate in the labour market and therefore cannot be attributable to vision impairment.

Statistical analysis

Descriptive statistics regarding sociodemographic and clinical participant characteristics were analysed. Participants were divided into 3 age categories: (1) 17–39 years, (2) 40–64 years and (3) 65 years or older. Working-age participants are within age categories 1 and 2. Working-age participants were divided into these two categories because some studies report that older individuals are more likely to lose their jobs, to stay longer as unemployed or to be early retired.[38] In addition, younger participants face difficulties to develop certain skills and abilities and to enter the labour market.[9] Causes of vision impairment were divided into eight categories.

Chi-square tests were used to test differences between participants working and not working. Categorical binary variables included gender, marital status, living arrangement, secondary diagnosis and comorbidities. Visual acuity was used either as a continuous variable or categorical variable whichever was deemed more appropriate. Visual acuity categories were defined accordingly to the World Health Organization.[39] 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 than 12 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). Independent

Table 1. Questions used to collect information about sociodemographic information, employment status and absenteeism. Absenteeism questions were applicable to participants in the working age range (17–64 years) who reported being employed. In all questions, there was one 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 third cycle (PhD) b. Up to university second cycle (Master) c. Up to university first 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 years 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) [#]including self-employment
	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

predictors were determined following a two steps procedure. First, we looked in the literature for variables that may influence the chances of persons with impaired vision to be in the labour market. Second, we incorporated variables with statistically significant differences between groups in independent t-tests, z-tests or chi-square tests. 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 of working age 28% (n = 71) were working full time or part time and 72% were not working because: i) 105 required early retirement due to impaired vision, ii) 54 were unemployed, iii) 14 were homemakers, iv) 4 were students and v) 6 for unspecified reasons. The employment rate was 28% and the unemployment rate was 21% for those within the working age and 13% and 10%, respectively, for the whole sample. Diabetic retinopathy, high myopia and diseases of the cornea were the major causes of vision impairment amongst participants of working age. We divided the group of working age into two subgroups: "working" and "non-working" and compared the characteristics of the groups. These results are summarized in Table 2.

The working group had a higher proportion of individuals within the age range 17–39 years (p = .023), a higher proportion of participants with up to 9 years of education or more (p = .007), a higher proportion of participants reporting higher income level (p < .001) and a lower proportion of participants with other comorbidities (p = .037) when compared with the non-working group. There were differences in causes of vision impairment between groups (p = .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 3 provides details about participants' distance visual acuity, near visual acuity and category of vision impairment. The median logMAR distance acuity in the better eye (z-test = − 2.03; p = .042) and binocular near vision acuity (z-test = − 2.59; p = .010) was higher in the non-working group meaning higher severity of vision impairment. The working group had a smaller proportion of individuals categorized as severe VI or profound VI/ blindness. These categories corresponded to 8% of the working group and 22% in the non-working group; although, the difference in proportion was not statistically significant (p = .110).

An analysis of income by category of VI revealed that participants with profound VI/blindness reported lower income. Fifty-four per cent of those with profound VI/blindness reported an income level of less than €485 per month. Conversely, participants with mild or no VI corresponded to 69% of those reporting income levels above €1000 per month. Differences between proportions were statistical significant (chi-square = 19.08; p = .014). An analysis of income by age categories showed that there were no differences between the distribution of income by age categories (chi-square = 3.461; p = .177). Nevertheless, we tested the impact of VI on reported income controlling for age categories (results are shown in Appendix C1) and concluded that VI may be associated with the probability of having a higher income whilst age categories were not.

Table 4 summarizes visual ability and HRQoL in both groups, working and non-working. The non-working group reported lower health-related quality of life (z-test = −4.17; p < .001) and lower visual ability (t-test = −45.04; p < .001) compared to the working group.

Absenteeism was reported by 28 individuals out of 71 (39%). In total 22,296 hours of work were lost over 1 year, which represents productivity costs of 102 thousand euros based on the average hourly pay rate calculated according to the income level reported by participants. Long-term absenteeism (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 due to impaired vision, and represented an annual cost of 1.4 million euros 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 summarized in Table 5. 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 the EQ-5D utility score is associated with odds of being in the labour market of 162. Since the EQ-5D score maximum value is 1, our results show that a change of 0.1 unit of health utility increase corresponds to odds of being in the labour market of 16. 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 2.8 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).

Figure 1 shows the probability of participation in the labour market as a function of HRQoL (EQ-5D utility score) for two scenarios: best-case and worst-case, details of the computations are given in Appendix C2. 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 and equal to the mean value for the group. Five curves were computed according to five 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 and equal to the mean value for the group.

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

Table 2. The socio-demographic and clinical characteristics of study participants within working age (n = 254).

	Working age participants				
	Working n = 71		Non-working n = 183		
	n	(%)	n	(%)	Group comparison
Gender					Chi-Square = 3.9; $p = .052$
– Female	28	39%	97	53%	
– Male	43	61%	86	47%	
Age categories (years)					Chi-Square = 5.2; $p = .023$
– 17 to 39	14	20%	17	9%	
– 40 to 64	57	80%	166	91%	
Education level					Chi-Square = 14.1; $p = .007$
– Do not Know/Do not answer	0	0%	12	7%	
– Up to university first 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%	
Monthly household income level*					Chi-Square = 23.1; $p < .001$
– less than €485	16	23%	98	55%	
– between € 485 and €1000	37	53%	62	35%	
– above €1000	17	24%	18	10%	
Marital status					Chi-Square = 1.1; $p = .301$
– Not Married	20	28%	64	35%	
– Married	51	72%	119	65%	
Living arrangement					Chi-Square = 1.5; $p = .219$
– Live alone	3	4%	16	9%	
– Live with others	68	96%	167	91%	
Cause of visual impairment (principal diagnosis)					Chi-Square = 21.6; $p = .003$
– 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; $p = .214$
– Yes	28	39%	88	48%	
– No	43	61%	95	52%	
Other comorbidities					Chi-Square = 4.4; $p = .037$
– Yes	39	55%	126	69%	
– No	32	45%	57	31%	

* 6 participants did not answer income level question and therefore were not considered in this group comparison.

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 of 0.07.

Discussion

In this study, we quantified and characterized productivity losses in a sample of 546 persons with impaired vision, 254 were of working age and from those 28% were

Table 3. Distance visual acuity in better and worse eye, near vision and severity of vision impairment by categories of participants within working age.

	Working age (17–64 years old)					
	Working n = 71		Non-working n = 183		Group Comparison	
Visual acuity (logMAR) [a]						
Distance vision	**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	z-test = −1.83
Median (IQR)	0.42 (0.40)	0.82 (0.80)	0.52 (0.60)	1 (1.10)	*p* = .042	*p* = .067
Near Vision	**Binocular vision acuity**		**Binocular vision acuity**			
Mean (SD)	0.47 (0.43)		0.61 (0.44)		z-test = −2.59	
Median (IQR)	0.4 (0.42)		0.52 (0.5)		*p* = .010	
Severity of vision impairment [b]	**N**	**%**	**N**	**%**		
No VI	21	30%	43	25%	Chi.Square = 7.5;	
Minor VI	19	27%	47	26%	*p* = .110	
Moderate VI	25	35%	52	28%		
Severe VI	4	5%	18	10%		
Profound VI & Blindness	2	3%	23	12%		

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

[b] No VI: from −0.3 to 0.3 logMar; Minor VI: from 0.32 to 0.5 logMar; Moderate VI: from 0.5 to 1.0 logMar; Severe VI: from 1.02 to 1.3; Profound VI or blind: from 1.32 to 3.0.

Table 4. Visual ability and health-related quality of life characteristics of participants within working age.

	Working age (17–64 years old)		
	Working n = 71	Non-working n = 183	Group Comparison
Visual ability (Activity Inventory)			
Mean (SD)	1.78 (1.8)	0.55 (2.0)	t-test = −45.04;
Median (IQR)	1.91 (2.89)	0.30 (2.43)	*p* < .001
Health-Related Quality of Life (EQ-5D Utility Score)			
Mean (SD)	0.65 (0.29)	0.48 (0.28)	z-test = −4.17;
Median (IQR)	0.66 (0.55)	0.45 (0.38)	*p* < .001

Table 5. Explanatory variables of participation in the labour market.

			95% C.I. for OR		
Variable	Interval	Working Vs Not Working Odds Ratio (OR)[a]	Lower	Upper	Sig.
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

[a] higher odds means greater chances of participation in the labour market.

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 was due to RWP estimated from 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 employment rate of 28% was lower than expected when compared with the 38% employment rate for people in Europe with disabilities reported by Eurostat in 2015 and even smaller when compared with the 68% employment rate for people without disabilities (64% in Portugal).[40,41] However, the Eurostat report does not specify 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.[42] 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.[19] 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.[19,43] 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 substantially lower than RWP costs.[44]

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.[38,45] In our sample

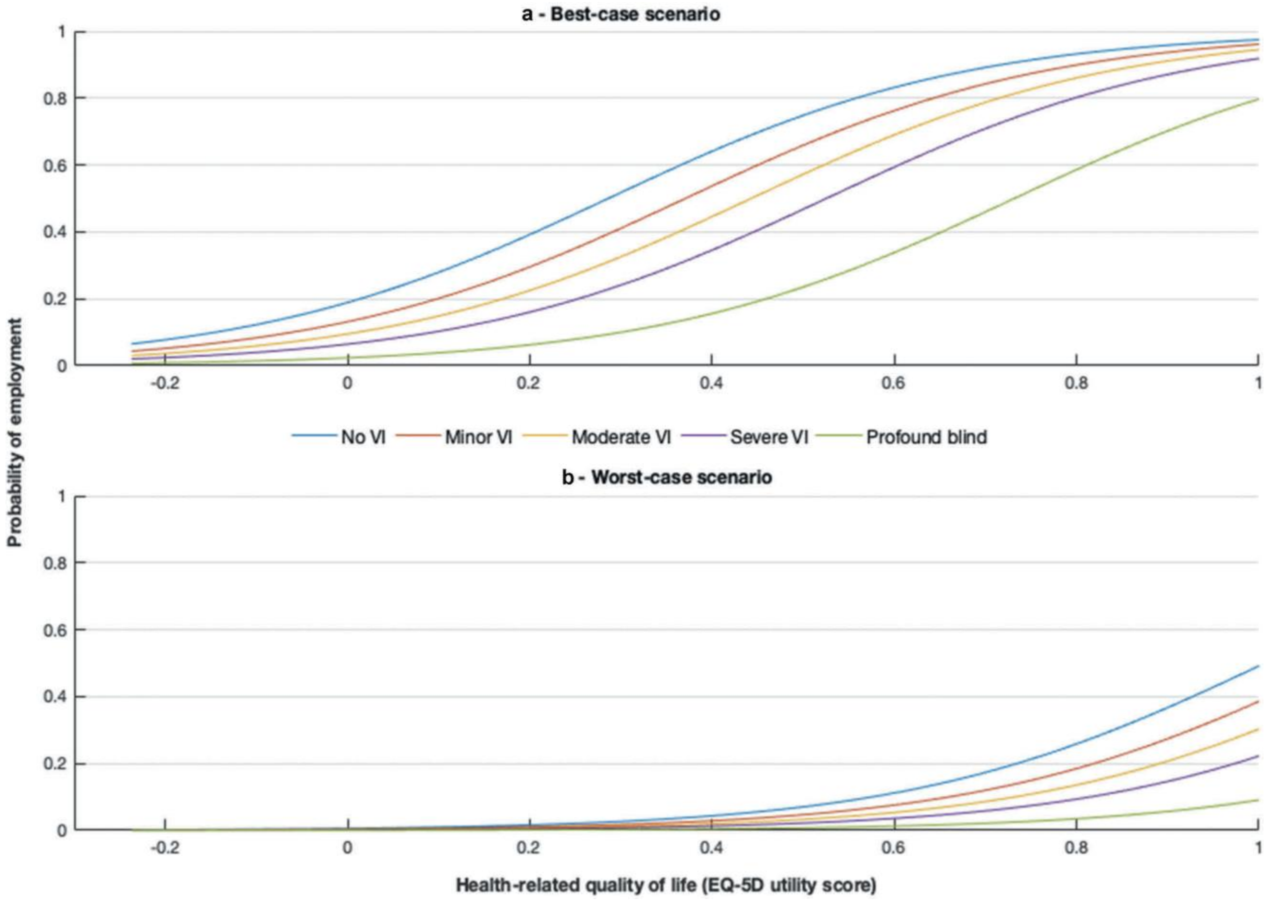

Figure 1. Probability of employment as a function of health-related quality of life for five categories of vision impairment and for A) best-case scenario and B) worst-case scenario. Best-case scenario includes: participants within the age 17–39 years, 12 years of education or more, no comorbidities 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-case scenario.

individuals with 12 or more years of education had higher odds of being employed compared with less educated individuals, these findings are consistent with other studies.[21,46] 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.

Severity of vision loss, measured with visual acuity as a continuous variable, 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.[21,46,47] However, in our study, in the logistic regression analysis, only the presence of comorbidities had a statistically significant effect on employment status. Severity of vision loss, expressed by visual acuity had an odds ratio of 0.35 (p-value = 0.163), which points to a tendency for individuals with worse visual acuity (higher values in LogMar) having lower chances of participation in the labour market. While this effect was not significant, the trend is similar to previous findings and we speculate that if we included participants with a full range of acuities, visual acuity would emerge as a determinant of participation in the labour market.

We included patient-reported measures in our regression analysis to explain employment status. The EQ-5D used to assess HRQoL includes questions about anxiety and depression and pain and discomfort which are known factors associated with the ability to work.[48–50] Visual ability measured by the AI allowed us also to incorporate difficulties performing vision-related tasks.[32] Whilst the effect of visual ability was not statistically significant, we found that EQ-5D utility score was a strong predictor of employment and therefore of RWP. This possibility was also raised in other studies which tried to predict absenteeism and presenteeism using EQ-5D.[51] Given this strong effect of the EQ-5D utility score, we performed the simulation with the equations given in Appendix C2 and obtained the scenarios shown in Figure 1. The results of the scenarios show that at increased levels of self-reported HRQoL the levels of participation in the labour market 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 into consideration when planning initiatives to promote inclusion of people with impaired vision in the labour market. This also shows the importance of maintaining other aspects of health of people with impaired vision.

We highlight that the relationship between HRQoL and productivity losses is a controversial topic in economic evaluation.[46,52] Some authors consider that taking productivity loss as costs and quality of life as an outcome to be double counting because these two measures may capture the same reality.[53,54] Whilst this issue is important when interpreting estimates of productivity losses incorporated in cost-effectiveness studies, our study was not designed to contribute to this discussion, and it is addressed in detail elsewhere.[55–57]

A possible limitation of our study is the lack of measures of presenteeism, which is defined as reduced productivity at work. A recent systematic review of the economic burden of visual impairment found that in five studies that estimated indirect costs and productivity losses only one included presenteeism.[16] 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.[18,58] Accordingly to the references used by Cruess[44] 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 by less than 8%, so the impact of presenteeism in our sample may not be substantial. Productivity losses incurred by informal caregivers for participants in our study were reported in a previous publication. In brief, based on opportunity costs, using the same participants as in this study, we estimated 92,144 hours of informal care per year, which was equivalent to an annual cost of €610,915.[26]

In addition, our estimates of productivity losses might have been affected by at least two factors. The first is the study setting: our participants were recruited at public hospitals and that means that they may be reporting, for example, lower income when compared to those attending private clinics and hospitals leading to underestimation of productivity losses. Furthermore, people attending private clinics and hospitals may differ in other sociodemographic characteristics such as education level and unemployment rate. Although before conducting the study we were advised by clinicians that people with impaired vision that use private care also attend public hospitals. The second factor is our assumption of 0% productivity losses amongst people aged 65 or older. In Portugal nearly 11% of the general population remains in the labour market after the age of 65[59]; therefore, the assumption may lead to a conservative estimation of productivity losses. However, it should be noted that none of our participants aged 65 or older reported being in the labour market.

In conclusion, in our sample, we found a low frequency of employment amongst people with impaired vision, lower income for non-working participants, lower income for working participants with VI/ Blindness and large productivity losses. 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.

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Ave, Guimarães. Natacha Moreno, MD, Ophthalmologist; Department of Ophthalmology, Hospital Sta Maria Maior, Barcelos. Gary Rubin, PhD (project adviser); UCL-Institute of Ophthalmology, London, UK. Ana Patricia Marques, PhD candidate; Rui Santana, PhD; Research Project Coordinator; National School of Public Health, NOVA University of Lisbon, Portugal. Laura Hernandez-Moreno, PhD candidate; Pedro Lima, PhD candidate; Low Vision and Visual Rehabilitation Lab, Department and Center of Physics – Optometry and Vision Science, University of Minho, Braga, Portugal .

The lead author of this group is: António Filipe Macedo: antonio.macedo@lnu.se

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ORCID

Ana Patricia Marques http://orcid.org/0000-0001-8242-7021
Antonio Filipe Macedo http://orcid.org/0000-0003-3436-2010

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Appendix A
List of comorbidities

1. Cancer
2. Diabetes
3. Heart condition
4. Hypertension
5. Musculoskeletal disorder
6. Pulmonary disease
7. Stroke or brain hemorrhage
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 B

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 C1

Ordinal logistic regression is a type of regression analysis used for predicting an ordinal variable, i.e. a categorical variable for which the possible values are ordered. Here, ordinal logistic regression was used to determine the impact of vision on reported income categories controlling for age.

The dependent variable was income level categories (income level less than €485 = 1; income level between €485 and €1000 = 2; income level above €1000 = 3). Independent predictors were: age (categories: 40–64 years = 0; 17–39 years = 1); Visual Impairment

(No VI (from −0.3 to 0.3 logMar) = 0; Minor VI (from 0.32 to 0.5 logMar) = 1; Moderate VI (from 0.5 to 1.0 logMar) = 2; Severe VI (from 1.02 to 1.3) = 3; Profound VI or blind (from 1.32 to 3.0) = 4). Six participants did not answer the income level question and therefore were not considered in this analysis.

Table A1. Parameter estimates for ordinal logistic regression model.

							95% Confidence Interval	
		Estimate	Std. Error	Wald	df	Sig.	Lower Bound	Upper Bound
Threshold	Income level less than €485 = 1	0.710	0.432	2.709	1	0.100	−0.136	1.556
	Income level between € 485 and €1000 = 2	2.766	0.465	35.326	1	0.000	1.854	3.679
Location	No VI = 0	1.493	0.490	9.287	1	0.002	0.533	2.452
	Minor VI = 1	0.684	0.489	1.955	1	0.162	−0.275	1.643
	Moderate VI = 2	0.838	0.479	3.065	1	0.080	−0.100	1.777
	Severe VI = 3	0.401	0.598	0.450	1	0.502	−0.771	1.573
	Profound VI or blind = 4	0^a			0			
	Age categories = 17 to 39	0.428	0.367	1.360	1	0.244	−0.291	1.146
	Age categories = 40 to 64	0^a			0			

[a] This parameter is set to zero because it is redundant.

We started to analyse how the model fits the data. The likelihood ratio test shows that at least one of the independent variables is associated with income level categories (chi-square = 14.488; *p*-value = 0.013). To determine the impact of severity of vision impairment and age on reported income, we looked for parameter estimates of our ordinal logistic regression model. As shown in Table A1 age categories are not statistically significant (*p*-value = 0.244) like vision impairment severity levels Severe VI = 3 (*p*-value = 0.502) and Minor VI (*p*-value = 0.162). The remaining vision impairment severity levels are statistically significant at $\alpha < 0.05$ (category No VI) or $\alpha < 0.10$ (Moderate VI). The ordered log odds for vision impairment severity level No VI in a higher income level is 1.493 higher than Profound VI or blind when the other variables in the model are held constant.

Appendix C2

Logistic regression estimates the probability of the outcome occurring **given that the predictor assumes certain values**. Here, 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:

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

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 into two categories: 40–64 years = 0; 17–39 years = 1;
- Comorbidities are divided into two categories: No = 0; Yes = 1;
- Education is divided into 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:

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

Probability is the ratio between the number of events favourable to some outcome and the total number of events. It is constrained between 0 and 1.

To illustrate our logistic regression model we have built to two scenarios: best-case and worst-case. For both scenarios, five curves were computed according to five 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 A2 shows categorical variables and linear predictor equations computed for the five categories of visual acuity in the better eye for best-case scenario:

Table A2. Best-case scenario computed for five 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 = .96 Age categories = 17–39 years = 1 Comorbidities = No = 0 Education = 12 years or more = 1	$linearpredictor = \varepsilon = -3.838 - 0.039\ Visualability$	No VI: from −0.3 to 0.3 logMar Mid point **ACUITY = 0**	$\varepsilon = -3.838 - 0.039 \times (0.96) + 1.369 + 1.05 + 5.091HRQL$
		Minor VI: from 0.32 to 0.5 logMar Mid point **ACUITY = 0.41**	$\varepsilon = -3.838 - 0.039 \times (0.96) - 1.05 \times (0.41) + 1.369 + 1.05 + 5.091HRQL$
		Moderate VI: from 0.5 to 1.0 logMar Mid point **ACUITY = 0.76**	$\varepsilon = -3.838 - 0.039 \times (0.96) - 1.05 \times (0.76) + 1.369 + 1.05 + 5.091HRQL$
		Severe VI: from 1.02 to 1.3 Mid point **ACUITY = 1.16**	$\varepsilon = -3.838 - 0.039 \times (0.96) - 1.05 \times (1.16) + 1.369 + 1.05 + 5.091HRQL$
		Profound VI or blind: from 1.32 to 3.0 Mid point **ACUITY = 2.16**	$\varepsilon = -3.838 - 0.039 \times (0.96) - 1.05 \times (2.16) + 1.369 + 1.05 + 5.091HRQL$

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

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

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

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 A3 shows categorical variables and linear predictor equations computed for the five categories of visual acuity in the better eye for Worst-case scenario:

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

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

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

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.

Table A3. Worst-case scenario computed for five 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 = .96 Age categories = 40 − 64 years = 0 Comorbidities = Yes = 1 Education = less than 12 years = 0	$linear\ predictor = \varepsilon = -3.838 - 0.039\ Visual\ ability - 1.05\ Visual\ acuity + 1.369\ (Age\ categories = 1) + 1.05(Education\ categories = 1) + 5.091\ HRQL$	No VI: from −0.3 to 0.3 logMar Mid point **ViLogmar = 0**	$\varepsilon = -3.838 - 0.039\times - 1.25 + 5.091HRQL$
		Minor VI: from 0.32 to 0.5 logMar Mid point **ViLogmar = 0.41**	$\varepsilon = -3.838 - 0.039 \times (0.96) - 1.05 \times (0.41) - 1.25 + 5.091HRQL$
		Moderate VI: from 0.5 to 1.0 logMar Mid point **ViLogmar = 0.76**	$\varepsilon = -3.838 - 0.039 \times (0.96) - 1.05 \times (0.76) - 1.25 + 5.091HRQL$
		Severe VI: from 1.02 to 1.3 Mid point **ViLogmar = 1.16**	$\varepsilon = -3.838 - 0.039 \times (0.96) - 1.05 \times (1.16) - 1.25 + 5.091HRQL$
		Profound VI or blind: from 1.32 to 3.0 Mid point **ViLogmar = 2.16**	$\varepsilon = -3.838 - 0.039 \times (0.96) - 1.05 \times (2.16) - 1.25 + 5.091HRQL$

Appendix paper 8: Cost-effectiveness of basic vision rehabilitation (The basic VRS-effect study): study protocol for a randomised controlled trial

We investigated the cost-effectiveness of a basic vision rehabilitation service in Portugal. We designed a parallel group, randomized controlled trial whose aim is to compare the effects and costs of 'usual low vision care' with a 'basic-VRS intervention' on self-reported visual ability and other psychosocial and health-related quality-of-life outcomes.

My participation in this paper was to perform the statistics analysis and to compute the sample size. Concerning sample size, in order to compute the minimum number of participants required to detect a significant difference in the activity inventory score (main outcome measure) at 12 weeks, I used information from previous studies and some preliminary data from our study. From our pilot data I set a change in AI scores from −0.13 logits in week 1 to 0.93 logits in week 12 in the IMI. With type I error rate (alpha) set at 0.05 (two-tailed) and aiming to a power of 0.90, a minimum of 22 participants per arm is required. Sample size calculations were performed with SAS analytics software. Based on the number of dropouts in the first 20 participants recruited, we expect a dropout ratio of 15% and because of that a total of 52 patients will be recruited.

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Cost-effectiveness of basic vision rehabilitation (The basic VRS-effect study): study protocol for a randomised controlled trial

Laura Hernández-Moreno[1], Hugo Senra[2,3], Peter Lewis[4], Natacha Moreno[5], João Linhares[1], Rui Santana[6], Pedro Lima Ramos[1,4], Ana Patrícia Marques[6] and Antonio Filipe Macedo[1,4]

[1]Department and Center of Physics—Optometry and Vision Science, University of Minho, Braga, Portugal, [2]School of Health and Social Care, University of Essex, Colchester, UK, [3]Centre for Research in Neuropsychology and Cognitive Behavioural Intervention (CINEICC), Faculty of Psychology and Educational Sciences, University of Coimbra, Coimbra, Portugal, [4]Department of Medicine and Optometry, Linnaeus University, Kalmar, Sweden, [5]Hospital Santa Maria Maior E.P.E, Barcelos, Portugal, and [6]Public Health Research Centre, National School of Public Health, University NOVA, Lisbon, Portugal

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Correspondence: Antonio Filipe Macedo
E-mail address: antonio.macedo@lnu.se; a.macedo@ucl.ac.uk

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Abstract

Purpose: To investigate the cost-effectiveness of a basic vision rehabilitation service (basic-VRS) in Portugal. We designed a parallel group, randomised controlled trial whose aim is to compare the effects and costs of 'usual low vision care' with a 'basic-VRS intervention' on self-reported visual ability and other psychosocial and health-related quality-of-life outcomes.
Methods: The trial will recruit participants that meet the following inclusion criteria: (1) visual acuity between 0.4–1.0 logMAR in the better-seeing eye, (2) cause of vision loss is diabetic retinopathy or age-related macular degeneration, (3) 18 years or older and iv) live in the community (not in nursing homes or other type of institution). Participants will be randomised to one of the study arms consisting of immediate intervention and delayed intervention. The delayed intervention group will receive 'usual care' or no intervention in the first 12 weeks. Visual acuity, contrast sensitivity and retinal structure will be assessed during the study.
Results: The primary outcome measure is visual ability, which will be evaluated with the Massof Activity Inventory, we expect that the intervention will raise the overall person measure or visual ability. Reading, health-related quality-of-life, anxiety and depression and social support will be also assessed. The analysis will be undertaken on an intention-to-treat basis. A cost-effectiveness analysis will be performed to provide information about the cost per unit of utility. To evaluate the cost-effectiveness of the intervention we will adopt the perspective of the healthcare system.
Conclusion: This study will provide additional evidence about the effects of basic-VRS on self-reported visual ability. Findings from this study should also contribute to better planning of low vision provision and, consequently, may contribute to reduce barriers to basic-VRS.

Introduction

Vision loss is an important cause of disability due to direct implications on physical, psychological and social aspects.[1] The World Health Organization International Statistical Classification of Diseases and Related Health Problems, 10th Revision (ICD-10) designates visual (or vision) impairment (VI), which includes blindness and low vision, based on presenting distance visual acuity. In the ICD-10, Chapter VII, H54, low vision is defined as visual acuity of less than 0.3 decimal Snellen (6/18, 0.5 logMAR) but equal to or better than 0.05 decimal Snellen (3/60, 1.3 logMAR), or a corresponding visual field loss to less than 20 degrees. Blindness is defined as visual acuity of less than 0.05 decimal Snellen (3/60, 1.3 logMAR), or a corresponding visual field loss to less than 10 degrees in the better eye.[2] Vision impairment can lead to reduction of mobility,[3] well-being and an increased risk of depression and anxiety.[4–6] It can also lead to increased risk of family distress, social isolation, and reduced social participation.[4,7,8]

Vision rehabilitation (VR) can be defined as a mixture of health, educational and social interventions whose ultimate goal is to reduce the negative impact of VI. Visual ability, defined as the overall ability to perform activities that depends on vision, is normally reduced in people with VI.[9,10] The main goal of VR is to maximise an individual's visual function. Enhancing visual function in people with low vision includes, for example, the use of assistive devices or improving lighting. VR often requires also the acquisition of new skills such as handling assistive devices (e.g. haptic devices such as BrainPort[11]), adaptive mobility strategies, modifying the environment, or some other activity-specific intervention.[12–14] For instance, reading is a highly-valued activity in society and individuals who are unable to read face barriers in their daily activities.[15,16] In many cases the ability to read can be restored through the use of magnifiers and little training with the devices prescribed.[15,17] There is evidence that VR can improve the quality-of-life and independence to perform activities of daily living in people with VI.[5,18–20]

It is known that VI can increase expenditure at personal and societal levels, but information about the 'value for money' (benefits vs costs) of VR is still limited. VI leads to a significant economic burden due to direct costs such as inpatient and outpatient care and indirect costs such as informal care or productivity losses.[21–25] Informal care and productivity losses are likely to be consequences of vision disability (barriers faced by people with VI to live and develop skills) caused by reduced independence to perform activities of daily living and less job opportunities due to reduced ability to work.[26–28] These are the type of problems that can be tackled with effective VR. However, there is still a lack of knowledge regarding what impact VR can have on those economic issues.[14,19,29–31] Cost-effectiveness analysis (CEA) and health economic analysis will reveal the impact of VR.

Cost-effectiveness analysis consist of an economic analysis that compares the cost and effects of health interventions in order to evaluate which alternative presents the most favourable cost/benefit ratio. The results can be expressed in terms of incremental cost per unit of effect or in terms of the effect per unit cost.[32,33] The current lack of CEA addressing the economic impact of VR services is contributing to the poor development of integrated vision care that people with VI receive in several countries.[34,35] Additionally, the lack of CEA in this field is also contributing to the limited knowledge on the benefits of VR amongst patients, families and professionals, as well as to sub-standards of the services provided.[36–38] Eventually, CEA will also characterise the value for money of VR in terms of an optimisation of resources and reduction of the burden entailed by VI.

In this manuscript we present the study protocol for a parallel group, randomised controlled trial (RCT) addressing the cost-effectiveness of a basic vision rehabilitation service (basic-VRS) in Portugal ('The basic VRS-effect Study'). We define basic-VRS as: dispensing new glasses and magnifiers with little training and instructions to use the devices and help with activities of daily living. All provided in clinical settings with emphasis on reading tasks.

Methods/Design

Study design

To investigate the CEA of basic-VRS we designed a parallel group RCT whose aim is to compare the effects and costs of 'usual low vision care', which is currently 'no intervention' in Portugal, with a 'basic-VRS intervention' on self-reported visual ability. Participants' flow during the study is shown in *Figure* 1, the information included in this protocol is summarised in *Appendix* S2, *Consolidated Standards of Reporting Trials (CONSORT) Checklist*. Participants will be allocated to an immediate intervention group (IMI), or to a delayed intervention group (DEI). The schedule for the intervention as well as the procedures and instruments for this trial are summarised in *Table* 1. The delayed intervention group was included despite previous evidence that the intervention is likely to be superior to 'usual care' (or no intervention), to control for a possible effect of 'attention to the problem'. In other words, we suspected that people with low vision may feel more optimistic and give more positive responses during interviews only because they start a process of 'solving their vision problems'. Therefore, the delayed intervention group is tested and receives attention from the research optometrist also at baseline, but only a real intervention at week 12. If attention is to have an effect on the main outcome measure without a real intervention, the effects are captured during the first 12 weeks in the delayed intervention group and can then be taken into consideration when assessing and discussing the impact of the intervention.

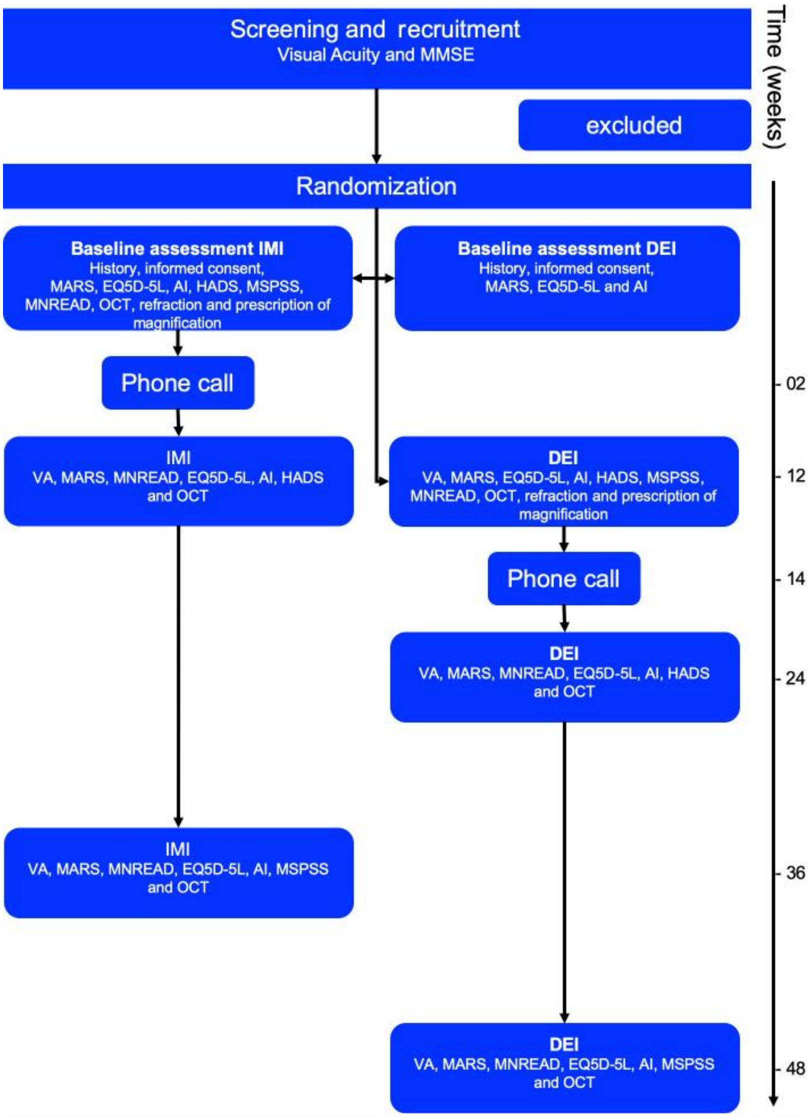

Figure 1. Diagram showing planned participant flow. Note: DEI, delayed intervention group; IMI, immediate intervention group; MMSE, mini-mental state examination. EQ5D and AI are defined in section 'Measures'.

Inclusion and exclusion criteria

Participants (IMI and DEI) need to meet the following inclusion criteria: (1) visual acuity between 0.4–1.0 logMAR in the better-seeing eye; (2) primary diagnosis and cause of vision loss diabetic retinopathy or age-related macular degeneration; (3) 18 years or older and (4) live in the community (not in nursing homes or any type of institution). Recruited people that meet one or more of the following criteria will be excluded: (1) cognitive impairment based on scores on mini-mental state examination, (2) communication problems due to, for example, hearing impairment, or inability to speak Portuguese; (3) unable to read due to low level of education; (4) unable to attend the requested appointments at the study setting.

The spectrum of acuities for the inclusion criteria corresponds to moderate vision impairment and they have been chosen because reading ability is expected to improve with strong reading glasses and moderate power magnifiers.[2,39] The rationale to include patients diagnosed with diabetic retinopathy and age-related macular degeneration is that these diagnoses represent the leading causes of low vision in the adult population in developed countries. These diseases typically affect people within different age groups which might be challenging when computing, for example, productivity losses or gains due to the intervention.

Table 1. Summary of the measurements and schedule of the measurements that will be performed during the study

		Study phase				
Procedures	**Instruments**	**Base**	**12 weeks**	**24 weeks**	**36 weeks**	**48 weeks**
Demographic information	Electronic form	IMI,DEI	–	–	–	–
Visual acuity at far and near	ETDRS charts	IMI,DEI	IMI,DEI	DEI	IMI	DEI
Contrast sensitivity	MARS test	IMI,DEI	IMI,DEI	DEI	IMI	DEI
Refraction	Objective and subjective refraction at distance and near	IMI	DEI	–	–	–
Best magnifier for reading and near tasks	Magnifier or spectacles that will enable reading font N8 (0.4 logMAR)	IMI	DEI	–	–	–
Training with the magnifier	See *Table* 2 for a complete list	IMI	DEI	–	–	–
Reading assessment	MNread test	IMI	IMI,DEI	DEI	IMI	DEI
Cognitive status	Mini Mental State Examination (MMSE)	IMI,DEI	–	–	–	
Health utilities	EQ-5D	IMI,DEI	IMI,DEI	DEI	IMI	DEI
Visual ability	Massof Activity Inventory (MAI)	IMI,DEI	IMI,DEI	DEI	IMI	DEI
Depression and anxiety	Hospital Anxiety and Depression Scale (HADS)	IMI	IMI,DEI	DEI		
Social support	Multidimensional Scale of Perceived Social Support (MSPSS)	IMI	DEI	–	IMI	DEI
Analysis of structural stability of the macula	Optical coherence tomography (OCT)	IMI	IMI,DEI	DEI	IMI	DEI
General instructions	See *Appendix* S4 *Table* with Instructions	IMI	DEI	–	–	

'Study phase' define the measurements that will be performed in each group at the given timepoint. Base, baseline visit; DEI, delayed intervention group; IMI, immediate intervention group; W, weeks.

Nevertheless, productivity will be excluded from our CEA because we will adopt the perspective of the healthcare system, productivity needs to be considered when adopting the societal perspective.

Cognitive status will be assessed using the Portuguese version of The Mini-Mental State Examination (MMSE).[40,41] MMSE scores 25–30 suggest a questionably significant degree of cognitive impairment, scores 21–24 mild cognitive impairment, 10–20 moderate cognitive impairment; and below 10 severe impairment.[42] We adjusted some vision-related tasks to make them suitable for people with VI: (1) for the task 'reading a sentence' we provide large print, and for (2) 'identifying a pen and a watch' we allow adjustment of the seeing distance to compensate for poor acuity. We exclude the last tasks, one consisting in 'writing a sentence' and the other asking to copy a pair of intersecting pentagons. Final scores will, therefore, be adjusted from 0 (minimum) to 28 (maximum).[43,44] These measures should be enough to use the instrument as a screening tool because previous studies have shown that a 6-item subset derived from the MMSE can be used to screen for cognitive impairment. [45]

Recruitment and randomisation

Potential participants will be identified on a consecutive basis from the outpatient bookings at the department of ophthalmology, Hospital Santa Maria Maior E.P.E, Barcelos, Portugal. After selection, the first author will invite candidates by telephone to participate in this study. Candidates willing to participate will receive, by post or at the hospital, a 'participant information booklet' with complete information about the study. After agreeing with the terms of participation, participants are screened and, if they pass the screening, they will sign the consent form. Recruited participants will be included in the trial if they fulfil conditions imposed by the inclusion/ exclusion criteria. Participants will be allocated to the IMI or DEI to create the best possible match between the groups according to age and visual acuity. A blocked randomisation list with four participants per block was generated online using the platform Sealed Envelope Ltd. (https://www.sealedenvelope.com/simple-randomiser/v1/lists) by the last author (AFM). Blocks were stratified by age (64-or-less vs 65-or-more) and acuity (0.4–0.68 vs 0.70–1.00) categories leading to a total of 4 strata. The platform also generated a unique randomisation code. For each block, randomisation codes were placed in envelopes and divided according to strata, each participant takes the randomisation code from a sealed envelope. The randomisation code is sent by the accessor to the last author (AFM) that decodifies de code using the block randomisation list and gives information about the participant's group. In the clinical setting the first (LHM, Optometrist) and the fourth author (NM, Ophthalmologist) have training in low vision assessment and rehabilitation at clinical and research levels.

Experimental intervention and usual care

Usual care

Patients with low vision who receive medical eye care at the hospital where this study will be conducted do not receive any low vision magnifiers or special attention regarding strategies to deal with low vision. There are general guidelines from the Portuguese government to help people with impairments, but none specifies interventions to be delivered to people with low vision.[46,47] Therefore, 'usual care' in Portugal is commonly defined as treatment of eye diseases and standard refraction.

Intervention: 3 components

Best refractive correction for far and near. New glasses will be prescribed when the difference between refractions (the current glasses and the new refraction) is 2D or more, or if visual acuity improves at least five letters with the new refraction.[48] These are reference values and the patient will be involved in the decision, all prescribed glasses and the changes in acuity will be recorded. All further visual tests will be performed based on the 'normal' near addition with a starting add of 2.5 D. After that and according to the participant's preference, the near add for reading glasses will be adjusted to its maximum possible value (shortest working distance defined subjectively). For more details see *Appendix* S3, *Detailed Procedures.*

Prescription of magnification for reading. To find the required magnification we will use a method based on equivalent viewing distance (EVD).[49] The formula that will be used to determine the EVD and the power of the magnifier has been suggested by others[49] and is given by the expression below in which TPS stands for 'threshold print size':

$$\begin{aligned}\text{Required EVD} = {} & (\text{Required TPS}/\text{Current TPS}) \\ & \times (\text{Current viewing distance}).\end{aligned}$$

We want our participants to be able to read N8 (0.4 logMAR). We will assume that an acuity reserve of 2:1 (0.3 log units) is necessary for fluent reading (approximately 80 words-per-minute);[49] therefore, the required TPS is set at N4. The final power of the magnifier will be discussed with each participant to take into consideration individual preferences. For example, some people will choose to have lower magnification if it provides a wider field of view, while others might like the higher magnification. In some cases, only spectacles with high addition lenses including prisms to support convergence may be sufficient, lenses are supplied by Essilor (https://www.essilor.pt/). Other magnifiers are selected from a Schweizer catalogue (https://www.schweizer-optik.de/unternehmensbereich/improvision/). LED illuminated hand magnifiers are the first choice of prescribing devices and are available in powers ranging from 6 D to 56 D. LED illuminated stand magnifiers and special magnifiers (reading bars or bright field magnifiers) are also available. These will be prescribed if participants show difficulties using LED Illuminated magnifiers (for example if they have a hand tremor) or when this type of device is considered inadequate for the participant's preferred near or reading task(s).

Instructions and training. We will provide a list of instructions on how to minimise the effect of reduced vision during activities of daily living, see *Appendix* S4, *Table* with instructions.[50–54] During the in-office training, participants will receive a supervised training session with their devices as given in *Table* 2, a large print version of the list is provided to take home.[48,55,56]

The intervention will be followed by a telephone call to ensure that participants are using their devices. If participants stop using the devices, the reasons for abandonment will be documented and the use will be encouraged. The phone call should take place within 2–3 weeks after participants have received their devices.

Measures

We included different types of measures because VR is likely to influence and be influenced by many factors. The key measurement is given by the Massof Activity Inventory (AI). AI gives a comprehensive summary of the ability to perform vision related activities and is expected to capture improvements in self-efficacy given by or developed during rehabilitation. The EQ-5D will be used to compute QALYs (defined in section Health-Related Quality of Life) and forms the basis of the CEA. Emotional status and social support are variables that can influence the effects of rehabilitation, or the attitude towards it.[57,58] Therefore, the inclusion of such metrics will provide key information to understand whether our intervention has been influenced by changes in these aspects.

Visual measures such as reading speed provide information about a very demanding visual task. Improvements in reading speed are also expected to reflect improvements in other vision related tasks. This information can therefore be interpreted in combination with patient-reported measures to characterise the impact of the intervention. Because we rely on patient-reported measures, it is important to ensure that participants have good judgement of their abilities/difficulties. We included the MMSE as a screening test for cognitive

Table 2. Instructions about using and practice with low vision aids

Aid	Description
Spectacles	• To find the correct working distance slowly bring the print closer to your eyes until the print comes into focus; using strong lenses may require a closer than usual working distance; • Move the print from right to left in front of your eye or move your head, be aware that moving your head may result in losing the focus; • Use good illumination during reading or other visually demanding tasks; • Use a reading stand if you find it difficult to maintain the correct distance or you feel fatigue due to postural demands imposed by your glasses;
Magnifiers	• Place the magnifier flat on the page and raise slowly away from the page until you get the clearest image. This procedure requires practice but after a while finding the lens-to-object distance should be almost automatic; • Be aware of the lens-to-eye distance, that changes the amount of information that you can see (field-of-view), shorter distances give a wider view; • To read move the page or move the magnifier and eye, depending on the task and the type of material;

- Use the aid every day starting with short training periods of 5–10 min each;
- Be aware that initially reading may be slow because concentration is on the use of the device rather than the reading but that will get better with practice;
- You may experience of headache and eyestrain, but this is harmless to your eyes and vision, take a break if you feel this way;

impairment to perform self-reported measures and, consequently, to participate in the study.

Baseline and control measures

Clinical and demographic information. Demographic information will include date of birth, marital status, occupation and years of education. Clinical information will include the disease that is the primary cause of VI, associated eye diseases, number of years with VI and comorbidities.

Visual acuity. Visual acuity (VA) is going to be used as reference for prescribing new glasses. Distance VA will be assessed in a dim light room using an internally illuminated high contrast ETDRS chart, model 2425E, luminance 180 cd × square-meter^{-1} (https://www.precision-vision.com/) at 4 m or 2 m or 1 m, according with the severity of vision loss. The chart distance will be reduced to ensure that the participant can read at least 10 letters. A reduction of the distance to half of the calibrated chart size requires the addition of 0.3 logMAR units to the final acuity score.[59] Near VA will also be assessed with Early Treatment Diabetic Retinopathy Study (ETDRS) charts (https://www.precision-vision.com/) at 40 cm or at 20 cm or 10 cm. In both procedures, a letter by letter scoring will be employed.[60] VA will be measured monocularly at distance and binocularly at near.

Monitoring retinal changes. Retinal thickness in the macula will be monitored with Topcon 3D OCT-2000 optical coherence tomography (OCT) (https://www.topcon.co.jp/en/eyecare/products/product/diagnostic/oct/3DOCT-2000_E.html) during the duration of study (48 weeks). The programme selected for the capture is the 'Macula Radial' which measures a diameter of 6 mm centred at the fovea. This will allow us to determine if changes in VA are associated with changes in retinal structure and ultimately will be used to exclude participants, whose retinal structure deteriorates, from the study or from analysis.

Main outcome measures

Visual ability. Visual ability, as previously defined, will be measured before and after the intervention to quantify the effect of rehabilitation. We will use the Massof Activity Inventory (AI)[61,62] which is an adaptive instrument designed to provide an individualised assessment of difficulties caused by vision impairment. The AI consists of a hierarchal structure in which specific cognitive and motor visual tasks (e.g., pouring or mixing without spilling) underlie more global goals (e.g., preparing meals). Disabilities occur when an individual reports difficulty in achieving important goals. Difficulties achieving a goal are said to depend on the difficulty experienced in the tasks that underlie each goal. Goals are split between three objectives: social functioning, recreation and daily living. Respondents first rate the importance of each goal with four possible responses ranging from 'not important' to 'very important'. Goals rated 'not important' are skipped, and as such are not considered in the final visual ability score as these are not relevant to the person's daily life. For goals rated consequences. Consequences in economic evaluation can be measure through changes in physical, social or functioning (effects) or through changes in quality of life of patients (utility).[76] To evaluate the cost-effectiveness of the intervention in our RCT we will adopt the perspective of the healthcare system.

Health-related quality of life

Health-Related Quality of Life (QoL) and well-being are two separate concepts; although, QoL is often used as a proxy for well-being in health-related interventions. The Centre for Disease Control and Prevention states in its website that 'there is general agreement that, at minimum, well-being includes the presence of positive emotions and moods (e.g., contentment, happiness), the absence of negative emotions (e.g., depression, anxiety), satisfaction with life, fulfilment and positive functioning. In simple terms, well-being can be described as judging life positively and feeling good. For public health purposes, physical well-being (e.g., feeling very healthy and full of energy) is also viewed as critical to overall well-being. QoL is more linked to patient outcomes and has generally focused on deficits in functioning (e.g., pain, negative affect). In contrast, well-being focuses on assets in functioning, including positive emotions and psychological resources (e.g., positive affect, autonomy, mastery) as key components'.[77]A possible interpretation of these definitions is that the boundaries between well-being and QoL are often fuzzy, and some patient outcomes may be capturing both. In this trial we use a generic instrument to assess QoL but it is possible that we also capture aspects of well-being. Measuring QoL before and after the intervention will allow us to determine the impact of vision rehabilitation on this variable and the results will be expressed in quality-adjusted life-year. The quality-adjusted life year or quality-adjusted life-year (QALY) is a generic measure of disease burden, including both the quality and the quantity of life lived. One QALY equates to one year lived in perfect health and it assumes that health is a function of length of life and quality of life and combines these values into a single index number.[78] To determine QALYs, one multiplies the utility value associated with a given state of health by the years lived in that state. A year of life lived in perfect health is worth 1 QALY (1 year of life × 1 utility value). The gains (or losses) are determined by the differences between QALYs,[79,80] in our case, the difference between the QALYs obtained before and after the intervention.

We selected the EQ-5D-5L, which is a standardised instrument developed by the EuroQol Group (www.euroqol.org), to measure of health-related quality of life. The descriptive questionnaire compromises five dimensions, where three are related to function (Mobility, Self-Care and Usual Activities) and the other two describe feelings (Pain/Discomfort and Anxiety/Depression). All dimensions have five possible levels of response, these define a total of 55 possible combinations of items that correspond to 3125 unique health states.[81,82]

Costs of the intervention—estimates

A provisional and theoretical estimate of the costs of the intervention based on the healthcare perspective is given in *Table* 3. Costs are estimated considering the material and equipment (e.g., visual tests and visual aids set) needed to provide a basic rehabilitation service in a hospital. Allowing for an initial investment for the material and equipment of 3870€ and an equipment lifetime of 8 years, the value of annual depreciation is 483.75€, which means that per year, the material and equipment have a cost of 483.75€ for the hospital. Furthermore, we estimate the total time spent by the rehabilitation professional with each patient is one and a half hours. Overhead hospital costs include administrative and clerical support and were estimated using hospital annual reporting costs for the ophthalmology department. We calculated overhead costs per medical appointment dividing overhead annuals costs for the ophthalmology department by the number of appointments in that year.

Magnifiers and/or lenses for glasses will be also considered for the estimation. The actual costs will be calculated with the data collected from each participant in the trial. For cost-effectiveness analyses the incremental cost-effectiveness ratio (ICER) needs to be computed using the expression:

$$\begin{aligned}\text{ICER} = {} & (\text{Cost intervention} \\ & - \text{Cost alternative})/(\text{Effect intervention} \\ & - \text{Effect alternative})\end{aligned}$$

In our case the Cost-alternative will be zero, the Effect-intervention will be measured in both groups (IMI and DEI). Costs will be expressed in euro and effects in QALY. The effects (benefits) of a basic-VRS are expected to have limited duration as a result of factors such as changes in visual acuity or refraction. Therefore, in our analysis we will estimate the number of years during which participants are expected to benefit from the intervention, using recommendations from the literature.[83] A 3% discount rate will be applied for each year passed since the intervention.[84–86] For example, if the benefit in the first year is 1 QALY we assume that will be 0.97 in the second year after intervention. In CEA some decisions are based on limited number of patients and for that reason various assumptions are made. However, these assumptions may be inaccurate, which introduces uncertainty.[87] In order to measure and evaluate uncertainty a sensitivity analysis will be also performed.

'slightly important' or above, participants are asked to rate difficulty on a five-point scale ranging from 'not difficult' to 'impossible to do'.[61,62] As in previous studies we establish visual ability as the main outcome measure, to compute the sample size, we are assuming a change of 0.7 logit on visual ability measured 12 weeks after the intervention (details in section sample size).

Reading. Reading will be tested to determine vision related reading difficulties before and after the intervention. Reading parameters will also be used to estimate the magnification required for reading. Specifically, we will determine: (1) reading acuity (RA)—which is the smallest size of the font that the patient can read without making significant errors; (2) maximum reading speed (MRS)—which is the patient's reading speed when it is not limited by the font size; and (3) critical print size (CPS)—which is the smallest size that the patient can read with the maximum read speed. After the intervention, reading will be assessed with the prescribed magnification. For measuring reading parameters we will use the Portuguese version of the Minnesota Low-Vision Reading Test (MNread test)[63–65] (https://www.precision-vision.com/). This instrument uses 28 sentences, each sentence fits into 3-line paragraphs without use of hyphenation or extra blank spaces. No punctuation is shown and uppercase letters are used only for initial capitalisation of sentences and proper names. Reading speed will be measured binocularly at a distance of 40 cm or adjusted, according with the needs, to 20 or 10 cm.

Secondary outcome measures

Contrast sensitivity. Contrast sensitivity is a good predictor of print size for reading and helps to predict reading fluency.[43] For example, a patient with near VA between 0.85 and 1.00 logMAR is likely to achieve fluent reading only if contrast sensitivity is better than 1.05 logCS.[43] Contrast sensitivity will be assessed binocularly at 40 cm with near correction of 2.5 D using the Mars Contrast Sensitivity Test (https://www.marsperceptrix.com/), which has a gradual letter-by-letter contrast, illuminance on the surface of the test is approximately 330 lux. The patient will be encouraged to respond until two consecutive letters are read incorrectly. The log contrast sensitivity is given by the final correctly read letter, which is the letter prior to the two consecutive errors, minus the number of errors prior to the final correct letter.

Anxiety and depression. Anxiety and depression will be assessed with the Portuguese version of the Hospital Anxiety and Depression Scale (HADS).[66] HADS is a 14-item self-report scale, comprising 2 subscales evaluating levels of depression (HADS-Depression) and levels of anxiety (HADS-Anxiety). The HADS has been used extensively in the hospital setting as a standardised psychological screening tool for emotional disorders,[67] and has also been used in studies addressing vision loss.[44,68] Each subscale includes seven items, generating scores between 0 and 21, for anxiety (Cronbach's alpha of 0.89) and depression (Cronbach's alpha of 0.91). A score of 8 and above is widely used to indicate the presence of clinical levels of anxiety or depression that may warrant further psychological investigation.[44,67,69,70]

Social support. Previous research has suggested that people with vision impairment have increased risk of suffering from social isolation and reduced social support.[6,71] In our study we will measure patients' perceived social support using the Portuguese version of Multidimensional Scale of Perceived Social Support (MSPSS).[72] This scale has 12 questions that are divided into 3 subcategories (family, friends and significant others) of 4 questions each. The score for each question ranges 1–7, where 1 is 'strongly disagrees' and 7 is 'completely agree'. To assess individual sub-categories, the score for the questions of the category need to be summed and then divided by 4. To assess to the whole scale the sum of rating for all questions is added up and then the total score is divided by 12. The lower the score the lower the perceived social support.

Sample size

To compute the minimum number of participants required to detect a significant difference in the activity inventory score (main outcome measure) at 12 weeks, we used information from previous studies and some preliminary data from our study.[73–75] From our pilot data we set a change in AI scores from −0.13 logits in week 1 to 0.93 logits in week 12 in the IMI. With type I error rate (alpha) set at 0.05 (two-tailed) and aiming to a power of 0.90, a minimum of 22 participants per arm is required. Sample size calculations were performed with SAS analytics software, Studio Release: 3.7 (www.sas.com), the code and the results of the simulation are given in *Appendix* S1, *Sample Size.* Based on the number of dropouts in the first 20 participants recruited, we expect a dropout ratio of 15% and because of that a total of 52 patients will be recruited.

Health economic evaluation

Economic evaluation is important to help decision makers with resource allocation issues and setting priorities.[33] It requires a comparative analysis in terms of cost and

Table 3. Estimates of costs (healthcare system perspective) for a basic vision rehabilitation service (basic-VRS) per patient

	Resource use (units = hours)	Costs (units = euro)
Material and equipment	NA	4.84
Optometrist's preparation	0.25	2.09
Optometrist's examination	1	8.35
Device dispensing and training	0.5	4.175
Overhead hospital costs	NA	11.81
Magnifiers and lenses for the glasses	NA	100
Total	1.75	131.26

Plan for data analysis

Data analysis will be performed with SPSS statistics software (https://www.ibm.com/SPSS/Modeler) and R (lme4 package) (https://cran.r-project.org/). For descriptive statistics means, median, standard deviation, interquartile range and frequency distribution will be calculated according to the type of variable (continuous/ discrete) and its distribution (normal or skewed). Kolmogorov-Smirnov tests or equivalent will be performed to assess normality. To detect changes in repeated (longitudinal) measurements we will consider the effect of group (IMI vs DEI) and time. Linear mixed models will be used to analyse repeated measurements. Longitudinal data analysis will be performed by fitting random coefficient models which will allow the regression coefficients (intercepts and slopes) to be unique to each subject, i.e., the individual time trajectories can vary randomly.[88–92] For this analysis, individual outcome measures will be defined as 'dependent variable' or 'response variable of interest' (e.g., 'visual ability'). Participants will be defined as 'random factors' or 'group specific effects'. Explanatory factors or 'fixed factors' are 'group' and 'timepoint'.

Rasch analysis will be used to analyse results of the AI. The analysis will be conducted using the Andrich rate scale model[93] for polytomous data with Winsteps software,version 4.4.0, (https://www.winsteps.com/winsteps.htm) to estimate person measures, item difficulties and threshold for each response category.[94] The unit of measure used by Rasch for calibrating items and measuring persons is logits (log-odd units). Items with positive scores are harder to perform than the mean of the items; the higher the score the higher level of vision required. The opposite is expected for item with negative scores. Positive person measures indicate visual ability above the mean ability required for the items, while a negative person measure score indicates the opposite.[95]

Ethics approval and trial registration

The trial started in 02/09/2016 with ethics application, the first participant has been assessed in March 2017. The study has been reviewed by the Ethics Committee for Life Sciences and Health of the University of Minho received approval number SECVS 147/2016 and also by the ethics committee at the hospital. The study was registered with the Portuguese data protection authority with the approval number 7012/ 2017. The basic VRS-effect study is registered in the ISRCTN at http://www.isrctn.com (Identifier: ISRCTN10894889), adheres to the CONSORT guidelines (http://www.consort-statement.org), and conforms to the tenets of the Declaration of Helsinki. The provisional date to stop the trial is 30/09/2020.

Data input, storage and quality control

Data from each of the study visits will be recorded manually by the researcher and stored on a secure server for subsequent data analysis. Members of the research team not involved in data collection will perform random checks to assess the quality of the recorded data. This step will require manually cross checking the entries in the spreadsheets with the original data collection forms.

Discussion

This study has been motivated by the lack of evidence about the 'value for money' of basic vision rehabilitation services (basic-VRS) in Portugal. Previous research has shown that vision impairment in Portugal is a common condition that leads to significant costs at personal and societal levels.[24,25,96] The general lack of cost-effectiveness analysis (CEA)[97] may delay decisions to implement more and better basic-VRS and creates barriers to the development of vision rehabilitation.[31,98–100] But, why do we need to perform a CEA now if magnifiers have been dispensed in many hospitals regularly since, at least, 1970?[101] Recent systematic reviews showed that better evidence on the cost-effectiveness of using magnifiers is necessary.[14] In addition, despite the widespread prescription of magnifiers, there still is insufficient evidence on the effect of different types of low-vision aids on reading performance.[17,102] In summary, there is sufficient evidence that more studies, in particular trials, are necessary to increase the knowledge about the 'value for money' of basic-VRS.

The expected impact of this study

Previous studies have shown that vision rehabilitation increases quality of life.[5,19,20] These studies presented a few limitations such as participants receiving more than one type of intervention simultaneously and the absence of control group.[12,19] The charcaterisation of cost-effectiveness of a basic-VRS will provide information about resource utilisation and their effects, such information can be used to improve service delivery and access. Research has identified three types of barriers when developing and referring patients to low vision services: (1) ophthalmologists often forget to refer their patients; (2) patients are not familiar with the concept of rehabilitation; and (3) patients think that rehabilitation is only for blind individuals.[36,99,103] We hope that our trial will help to reduce these barriers at a local level (Portugal) and at global level where the mentioned issues exist.

In the current manuscript we refer, at least, three published study protocols that, at first glance, seem to be similar to our work. Therefore, we briefly discuss what is different in the current design and motivation. The Low Vision Intervention Trial (LOVIT II) and the Portable Electronic Vision Enhancement System (p-EVES) are different from our study because they were designed to answer a different question, that is, these studies compared two different types of low vision interventions. The LOVIT II compared impact of basic low vision intervention with low vision rehabilitation,[73,98] whereas the p-EVES compared the impact of electronic vision enhancement system devices with conventional optical low vision aids.[104] Both protocols include an economic evaluation comparing the two types of interventions, the LOVIT II uses a parallel arms design and the p-EVES uses a cross-over design. These two studies have also adopted different primary and secondary outcome measures. Cross-over designs have some advantages when compared with parallel arms (LOVIT II), for instance, a smaller sample is typically required when using cross-over.[105] All participants in our study will have access to the benefits of the intervention which increases the benefits of participating. A study conducted by Dunbar *et al.* (2012) was designed to find benefits of vision rehabilitation according to the level of visual acuity (participants' interquartile range for acuity was 0.06–0.30 logMAR).[73] Dunbar's study was expected to answer a different research question and also differs from ours in several of the secondary outcome measures. Although we learned some lessons from Dunbar's study, according to the author, Chapter 6 of the thesis,[58] it is important to address outcomes of emotional status and social support in order to explain the variability of the rehabilitation effects. Therefore, we decided to include some of these measures in our protocol.

Strengths of this trial

According to the available literature, our clinical trial is the first designed to perform a CEA of a basic-VRS despite other trials have been conducted in recent years to assess the effects of vision rehabilitation.[73,104,106] We are using state-of-the-art instruments to perform a comprehensive characterisation of the outcomes of the intervention and the factors that can interfere with it, including instruments for characterisation of well-being (anxiety and depression scale and perception of social support) and QoL (EQ5D).

The AI is an adaptive visual function questionnaire designed to provide an individualised assessment of difficulties of a visually impaired respondent when performing valued activities. Because our intervention is likely to affect only 'near vision' or 'reading' tasks one can ask if it is sensitive enough to detect changes in visual ability after our intervention. To deal with this we plan to perform an analysis of the AI scores using all items (46 in the Portuguese version) and also using those only related to reading and/or near vision. However, we consider that the intervention is likely to bring extra levels of confidence to our participants to attend social events and to participate in activities in which reading is important but note the only requirement. In other words, the intervention is likely to affect several aspects beyond reading and the overall person measure obtained from the AI is likely to capture that. The preliminary results used to compute the sample size are already indicative of that (see *Appendix* S1, *Sample Size*). Previous studies have shown that there is a crosstalk between improving visual performance, being able to perform visual tasks, emotional and social factors.[107] Because of that we believe that assessing depression, anxiety and perceived social support before and after the intervention will help to understand if these aspects also influenced our intervention.

Other studies provided information about costs and effects of rehabilitation interventions in people with impaired vision. However, most studies involved other domains such as preventing depression.[108,109] Our study investigates the effect of a basic-VRS delivered in a public hospital focused on a single interaction with an optometrist that will provide a reading aid, basic training with the aid and instructions to reduce the effect of low vision in activities of daily living. This study is expected to provide for the first time the costs and consequences of a basic-VRS. In addition, our study design can be easily replicated in other countries to assess basic-VRS.

Challenges and limitations of the current study protocol

We have a few threats to our protocol and the first is the risk of being unable to capture the effects of basic-VRS with the EQ5D-5L. That is, it may be impossible to observe a significant change in QALY. Others have shown that this is a possibility, but meanwhile the instrument has been updated.[110] According to recent literature, condition-specific questionnaire scores (NEI VFQ-25) can be converted to EQ5D-based utility scores but the results are often inadequate.[111] An alternative to the EQ5D in future studies can be The Health Utilities Index.[112] The main difference between the current and the previous version of the EQ5D is that it incorporates a 5-point scale, in contrast with a previous 3-point scale, which may produce 3125 unique health states. This allows better measurement properties in terms of distribution, ceiling, informativity, discriminatory power and patient preferences.[113,114] We have conducted a pilot analysis with 17 participants and the results were encouraging. The 5-point scales reduced significantly the ceiling effects when compared with the previous 3-points scale.[59,115]

A second limitation of our protocol is the follow-up period that cannot be more than 36 weeks due to funding constraints. We consider that this is not a major limitation because most of the previous studies have shown that the effects of rehabilitation should be perceived within 12 weeks (~3 months); although, that may depend on nature of the intervention (e.g. psychosocial vs provision of training with devices).[48,73,75,83]

Another possible problem for the final conclusions lies in the recruitment process. The number of patients attending the hospital where the study is conducted is limited; thus, preventing us from recruiting all participants at a single time point. Our researcher will not be blinded for the group allocation and we recognise that increases the risk of bias. We specifically discuss this in work meetings and the researcher is alerted to this fact.

Trial status

At the time of submission of this protocol this trial is recruiting.

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Conflict of interest

The authors report no conflicts of interest and have no proprietary interest in any of the materials mentioned in this article.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Appendix S1. Sample size.

Appendix S2. CONSORT checklist.

Appendix S3. Detailed procedures.

Appendix S4. Table with instructions.