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PhD in Complexity Sciences

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Resumo

Nos países desenvolvidos a retinopatia diabética é a principal causa de diminuição da acuidade visual e cegueira nas pessoas em idade ativa.

A presente investigação visa o estudo das idiossincrasias inerentes ao rastreio da retinopatia diabética da perspetiva das ciências da complexidade.

Numa primeira fase, realizamos duas revisões sistemáticas da literatura, que permitiram: i) diagnosticar as principais dificuldades, soluções possíveis, e pontos chave a serem melhorados nos rastreios de retinopatia diabética; ii) identificar os principais gaps na literatura relativa a modelos de simulação dedicados a este tipo de programas.

Seguidamente, partimos para o desenvolvimento de modelos de simulação baseados em agentes focados na problemática da adesão ao rastreio. Após o ensaio de diferentes técnicas, conseguimos desenvolver um modelo que produz resultados aproximados à realidade, com elevado grau de abstração.

Nesta fase da investigação, identificamos um outro gap na literatura: a inexistência de estudos sobre a influência da rede social na decisão de aderir ou não ao rastreio da retinopatia diabética. Prosseguimos a investigação neste sentido. O trabalho desenvolvido demonstrou que, no caso da retinopatia diabética, os contactos entre membros da população alvo têm influência na taxa de adesão aos rastreios. Foi ainda possível identificar grupos de diabéticos que apresentam menor adesão aos rastreios com base na forma como se posicionam na rede social.

Consideramos que os resultados obtidos são da maior relevância como ponto de partida para futuras investigações e como enquadramento para apoiar a tomada de decisão e planeamento de intervenções relacionadas com os rastreios de retinopatia diabética.

Palavras-chave: Retinopatia diabética; Adesão ao rastreio; Ciências da complexidade; Modelos de simulação baseados em agentes; Redes sociais;

Abstract

In developed countries, diabetic retinopathy is the main cause of decreased visual acuity and blindness in people of working age.

This research aims to study the idiosyncrasies inherent to diabetic retinopathy screening from the perspective of complexity sciences.

In a first phase, we carried out two systematic reviews of the literature, which allowed us to: i) diagnose the main difficulties, possible solutions, and key points to be improved in diabetic retinopathy screening; ii) identify the main gaps in the literature relating to simulation models dedicated to this type of programs.

We then moved on to developing agent-based simulation models focused on the issue of screening adherence. After testing different techniques, we managed to develop a model that produces results close to reality, with a high degree of abstraction.

At this stage of the investigation, we identified another gap in the literature: the lack of studies on the influence of social networks on the decision to adhere or not to the screening for diabetic retinopathy. We continue the investigation in this regard. The work carried out demonstrated that, in the case of diabetic retinopathy, contacts between members of the target population influence the rate of adherence to screenings. It was also possible to identify groups of diabetics who show lower adherence to screenings based on the way they position themselves on the social network.

We consider that the results obtained are of the greatest relevance as a starting point for future research and as a framework to support decision-making and planning of interventions related to diabetic retinopathy screening.

Key words: Diabetic retinopathy; Screening adherence; Complexity sciences; Agent based models; Social networks;

Publications

Core Publications (indexed papers)

I. Pereira, A., Laureano, R., Neto F., (2021), Five Regions, Five Retinopathy Screening Programmes: A Systematic Review of how Portugal addresses the challenge. *BMC Health Services Research (Q1),* 21(1):756, doi: 10.1186/s12913-021-06776-8.

II. Pereira, A., Laureano, R., Neto F. (2024), "Simulation Models in Diabetic Retinopathy Screening: A Systematic Review" Submitted to Journal of Simulation.

III. Pereira, A., Macedo, J., Afonso, A., Laureano, R., Neto F., (2024), "The use of social simulation modelling to understand adherence to diabetic retinopathy screening programs". *Scientific Reports (Q1),* 14(1), 4963, doi: 10.1038/s41598-024-55517-4

IV. Pereira, A., Afonso, A., Laureano, R., Neto F., (2024), "The role of the social network in the study of adherence to diabetic retinopathy screening programs" *Scientific Reports (Q1),* 14, 29389, doi: https://doi.org/10.1038/s41598-024-80996-w

Other Publications (conference proceedings)

I. Pereira, A., Laureano, R., Neto F., Macedo, J., (2020), "Adherence to the Screening of Diabetic Retinopathy: An Agent Based Simulation Model", 20th Portuguese Association for Information Systems Conference – CAPSI 2020 Proceedings, 36. https://aisel.aisnet.org/capsi2020/36.

II. Pereira, A., Laureano, R., Neto F., Macedo, J., (2021) "Computer simulation of diabetic retinopathy screening adherence: agent-based model with fuzzy logic", 16th Iberian Conference on Information Systems and Technologies – CISTI 2021 Proceedings, pp. 1-6, doi: 10.23919/CISTI52073.2021.9476265.

III. Pereira, A., Laureano, R., Neto F., (2024), "Simulation of human behaviour in adherence to preventive health programmes - A methodological proposal and an example of its application", 19th Iberian Conference on Information Systems and Technologies - CISTI 2024.

Public presentations

I. "Adherence to the Screening of Diabetic Retinopathy: An Agent Based Simulation Model", 20th Portuguese Association for Information Systems Conference – CAPSI 2020.

II. "O estudo da adesão ao rastreio da retinopatia diabética através de técnicas de simulação

computacional “, ISCTE, 4 escolas, 4 teses, 2021.

III. “Computer simulation of diabetic retinopathy screening adherence: agent-based model with fuzzy logic”, 16th Iberian Conference on Information Systems and Technologies – CISTI 2021.

IV. “Complexidade em saúde pública: até que ponto a estrutura da rede social influencia o comportamento em saúde?”, Pint of Science, 2022.

IV. “De que forma a rede social pode afetar a decisão de adesão ao rastreio da retinopatia diabética?", XXII Congresso da Associação Portuguesa de Investigação Operacional - APDIO 2022.

V. “Simulation of human behaviour in adherence to preventive health programmes - A methodological proposal and an example of its application”, 19th Iberian Conference on Information Systems and Technologies - CISTI 2024.

Contents

1. Introduction

This doctorate consists on the study of a complex public health problem, the implementation of population-based screenings for diabetic retinopathy (DR) [1], from the perspective of complexity sciences.

The choice of the theme was due to the difficulties of implementing organized population-based screenings [2] and to its' importance for the quality of life of the populations [3]. In this context, complex systems techniques, such as agent-based computer simulation models and social networks [4] [5], were applied to the enormous amount of data resulting from one of the DR screening programs implemented in Portugal. The adopted methodology allowed us to overcome some limitations of more traditional approaches and produce useful contributions for researchers and DR screening decision-makers.

1.1. Theme and problem

Diabetes Mellitus (DM) is a chronic metabolic disease and one of the most prevalent diseases worldwide. The International Diabetes Federation estimated that, in 2019, there were 463 million people with diabetes, representing 9.3% of the global adult population (20–79 years). This number is expected to increase to 578 million (10.2%) in 2030 and 700 million (10.9%) in 2045 [6]. DM can cause macro and microvascular complications, including DR, which is the most common cause of vision loss in people with diabetes, and globally is the leading cause of visual impairment and blindness among the working age population [7] [8] [9].

However, DR can be prevented or delayed by timely diagnosis and management of diabetes, and blindness can be prevented or delayed, in people with DR, by regular eye screenings and appropriate treatment [3] [8].

The 1989 St. Vincent Declaration set a benchmark for diabetes care, setting several ambitious goals that included DR, for which it was established the target of reducing the new cases of blindness by one third in five years [3]. In 2005, it was established that European Countries should reduce the risk of visual impairment due to DR by 2010 through: i) systematic screening programme, reaching at least 80% of the population with diabetes; ii) using trained professionals; and iii) assuring universal access to laser therapy [3]. The WHO's 2016 Global report on diabetes [10], and the 2019 World report on vision [11], have also highlighted the importance of DR screening, and it is one of the WHO's recommended effective interventions

for non-communicable diseases [12].

However, in 2021, the WHO conducted a situational analysis of DR screening in the 53 Member States of the European Region, and, among the main conclusions reported, it stands out the limited number of countries that provided some evidence that DR screening was carried out systematically country/region-wide (only 8). In the remaining cases, DR screening it is either not implemented or not universally available. In this report the WHO states that there is still a long way to improve the effectiveness of DR screenings and, by doing so, reduce the burden of vision impairment and blindness, even in high income level countries/regions, like most of the members of the WHO European Region (34 out of 53) [2].

Portugal is one of the countries where DR screening is not yet implemented in all regions, due to the difficulties and demands inherent to its implementation [2] [13].

Furthermore, although the complexity of implementing a screening program is widely recognized [2] [14] [15], its regional planning and organization are still often based on descriptive statistics and intuition [16], or, at most, on empirical studies focused on small fragments of the target population or on a few health services [16]. Therefore, it is of the utmost importance to promote the sharing of experiences, successes, and difficulties between countries, stakeholders and the different intervenient of such a complex public health programme. However, factors such as the existence of regional specificities, different health systems, data inexistence or inconsistencies, communication bias, and organisational barriers, make it difficult to create a solid framework that can be used as a basis for decision-making [2] [17].

Thus, the initial choice of the research domain was due to the importance of the topic for the quality of life of the populations and the pressing urgency of scientific research in this field.

During the early stages of our research, we found out that one of the main problems inherent to the population-based health screenings, not only in Portugal but around the world, is that their success largely depends on the adherence of the target population [3] [12]. In DR screenings, even countries with the more consolidated screening programs still have adherence rates below the outlined objectives (80%) [3] and this problem is worse in countries with less mature and/or less regulated programs [18]. We also found that there was a gap in literature that addresses the motives behind low adherence rates, while other aspects of screening, such as the method, ideal intervals between screenings and risk factors for DR, had already been analysed by several authors [19]. Therefore, we decided that the specific problem of the low screening adherence rate should be our focus from then on.

1.2. Research question and goals

The present research addresses the main question of "How can population-based DR screenings be planed and implemented, in order to improve their efficiency and their success in preventing the consequences of untreated DR?"

More specifically, this research aims to:

i) study the different alternative DR screenings implemented in Portugal, contextualized with the best practices and results obtained worldwide. These results will allow to define alternative scenarios (interval between screenings, use of automatic reading software, screening location, screening technicians) and can be a starting point and a comparative framework for other scientific studies in this field;

ii) determine if/how the sociodemographic characteristics of the diabetics, their past behaviour towards health institutions and towards the screening program, the interactions between members of the target population, health care providers and screening protocol features, are associated to DR screening adherence. In other words, we aim to identify which features lead to adherence to the DR screening program and which have the opposite effect;

iii) identify population groups with particularly low adherence rates, which may help to support decisions in screening planning;

iv) develop and validate a computational simulation model that provides a new set of means to analyse policies and strategies for implementing screening programs.

1.3. Methodological Approach

The first step towards achieving the proposed goals was carrying out a systematic and exhaustive review of all scientific and technical literature on screening for DR in Portugal. This step allowed the study of the different alternative DR screenings implemented in Portugal, and the definition of alternative scenarios (interval between screenings, use of automatic reading software, screening location, and screening technicians).

The second step was to carried out a second systematic review of computer simulation models applied to DR screening. This second work allowed the identification of important gaps in the literature and to establish a framework for qualitative assessment, which incorporated input parameters, modelling approach, input data sources/assumptions, sensitivity analyses, validation, and outcomes.

From the beginning, we have counted on the collaboration of the Portuguese Northern Regional Health Administration, which, in addition the knowledge and experience of experts in this field, also provided most of the data used in this research.

Therefore, our next step was conducting the preparation and statistical analysis of a data set consisting on all calls for DR screening between the years 2013 and 2018, in the Portuguese Northern Region Health Administration coverage area. The sample consists of 271,867 calls for DR screening, which corresponds to 108,620 different diabetics. This work allowed the identification of the main variables related to screening adherence.

Using the knowledge gathered so far, we developed three agent based model prototypes to simulate adherence to DR screening. In the first model, a logistic regression model was used for the agents' decision. In the second agent based model, the logistic regression was replaced by fuzzy logic, increasing the level of abstraction and the scalability of the model. Then, a hybrid model was also developed, in which the agents' decision to adhere or not to the screening used a combination of logistic regression and fuzzy components in equal proportions, to test its' scalability and accuracy. We also stage several potential interventions to illustrate the way our models can be used to support decisions in health planning.

None of our three versions of simulation models had into consideration the possible results of the interactions between members of the target population, because we did not find any literature that demonstrated its relevance for DR screening adherence behaviour. Therefore, next, we analysed the impact of the structure of the diabetics' social network and the position he occupies in this network on the DR screening adherence behaviour.

1.4. Statement of contributions

The first contribution of this research, resulted from our first systematic review [17], and was the diagnose of the main difficulties in the implementation of DR population-base screening programs, possible solutions, the key points to be improved, and the different possible screening strategies, therefore contributing to the much needed and difficult sharing of knowledge in this area [17]. This study, also, highlights the importance of adequate governmental funding, national guidelines that precise the role of the different intervenient, and of politic measures that guarantee the involvement of all parts [17].

Next, our second systematic review [19], focused on simulation models developed in the

area of DR screening, made it possible to identify two main gaps in the literature: i) despite the recognized importance of adherence to screening [18], simulation models tend to neglect this issue [19]; and ii) most of the analysed models are based on Markov processes or Discrete Event Simulation techniques [19], what led to important limitations. Agent-based models [19] [20] [21] can be an interesting alternative, however more research is needed to understand whether they can significantly contribute to the study of the complexity inherent to a population-based DR screening.

The analyses of a large set of real data relating to several years (from 2013 to 2018) of DR screening in the northern region of Portugal allowed the identification of sociodemographic and behavioural characteristics regarding health services related with adherence to the DR screening program [22]. The results are generally consistent with those found in the literature, i.e. younger and older diabetics tend to adhere less to the screening, as do those with higher incomes. Higher educational qualifications, as well as a regular habit of using primary health care services, are conducive to higher adherence rates. Diabetics who received a greater number of previous invitations for screening and who had adhered more frequently in the past, present higher adherence rates. There were, however, results not supported by the literature. Contrary to what was expected in the northern region of Portugal, men adhere more to screening than women, and diabetics with positive results in previous screenings present lower adherence rates in the next screening [22]. Regarding this last result, the literature review indicates as a possible explanation the lack of communication between different levels of health care providers resulting in the inappropriate sending of invitations to diabetics who are already being treated in a hospital environment [17].

Then, were developed three agent based simulation models aiming to capture the diabetics behaviour of adherence to DR screening programmes [22]. These models incorporated the previous results, first in a logistic regression equation, and then in several fuzzy logic components [22]. Our first model showed that the used of the agent-based model combined with the logistic regression equation was of limited usefulness, as it depended largely on known parameters from an ongoing screening. However the second model, an agent based model with fuzzy logic components, allowed to produce accurate predictions with a highest degree of abstraction. This work contributed to demonstrate that it is possible to develop models that simulate the DR adherence behaviour with a high degree of accuracy and abstraction. We also demonstrated the potential of such models to support decisions in health planning, through the staging of several potential interventions, and analyses of the predicted outcomes [22]. Therefore, the fourth contribution of this research is to put forward a framework that is robust

enough to advance the state of knowledge related to the development, calibration and validation, of simulation models concerning population-based screenings adherence behaviour. The innovative combination of agent-based models with fuzzy logic resulted in a model that provides a good alternative to the existing traditional simulation techniques that lack flexibility and capacity of generalization.

Finally, we realized that there were no studies that analysed the influence of the social network on the diabetics' decision to adhere or not to the screening [23]. The studies found were focused on oncological screenings, and the results were not consensual [23]. We decided to continue our research in this direction. This work has demonstrated that, in the case of DR, contacts between members of the target population have an influence on the rate of adherence to the screening. It was also possible to identify groups of diabetics who show lower adherence to screening, based on the way they position themselves on the social network [23]. There for, one more implication of this research is the evidence of the need to incorporate the network features in future studies concerning DR screening adherence behaviour. From the decision maker and practitioner point of view, these results provide a new set of means to influence the diabetics' decisions to adhere or not to the screening, and plan interventions aimed at particular groups of the target population.

1.5. Thesis Structure

This thesis follows the "three papers" model and it is structured in four main chapters: the present introduction, concepts and methods, the collection of papers, and the conclusions.

In the introduction, we seek to explain what motivated our research, our main objectives, as well as some of our conclusions and considerations.

Next, we have the concepts and methods chapter, in which we seek to encompass the techniques and concepts used in the papers. In this chapter, our intention is intertwine the elements and create a broader overview of them, in order to facilitate the understanding of our research.

The third chapter consists on the four main core papers we selected. For each paper is presented a short summary and contextualization, followed by the paper itself.

The first and second papers, namely "Five regions, five retinopathy screening programmes: a systematic review of how Portugal addresses the challenge" [17] and "Simulation Models in Diabetic Retinopathy Screening: A Systematic Review" [19] are focused on the assemblage of

knowledge in the field of DR screenings, and on the identification of the main gaps in the literature. The third paper "The use of social simulation modelling to understand adherence to diabetic retinopathy screening programs" [22] aims to answer the question "How to predict the rate of adherence to population-based screenings through computational simulation models with a high level of abstraction" and fulfil some of the gaps previous identified.

The last paper "The role of the social network in the study of adherence to diabetic retinopathy screening programs" [22] aims to analyse the influence of the diabetics' social network structure in the adherence to DR screening, more specifically by their contacts with other members of the target population.

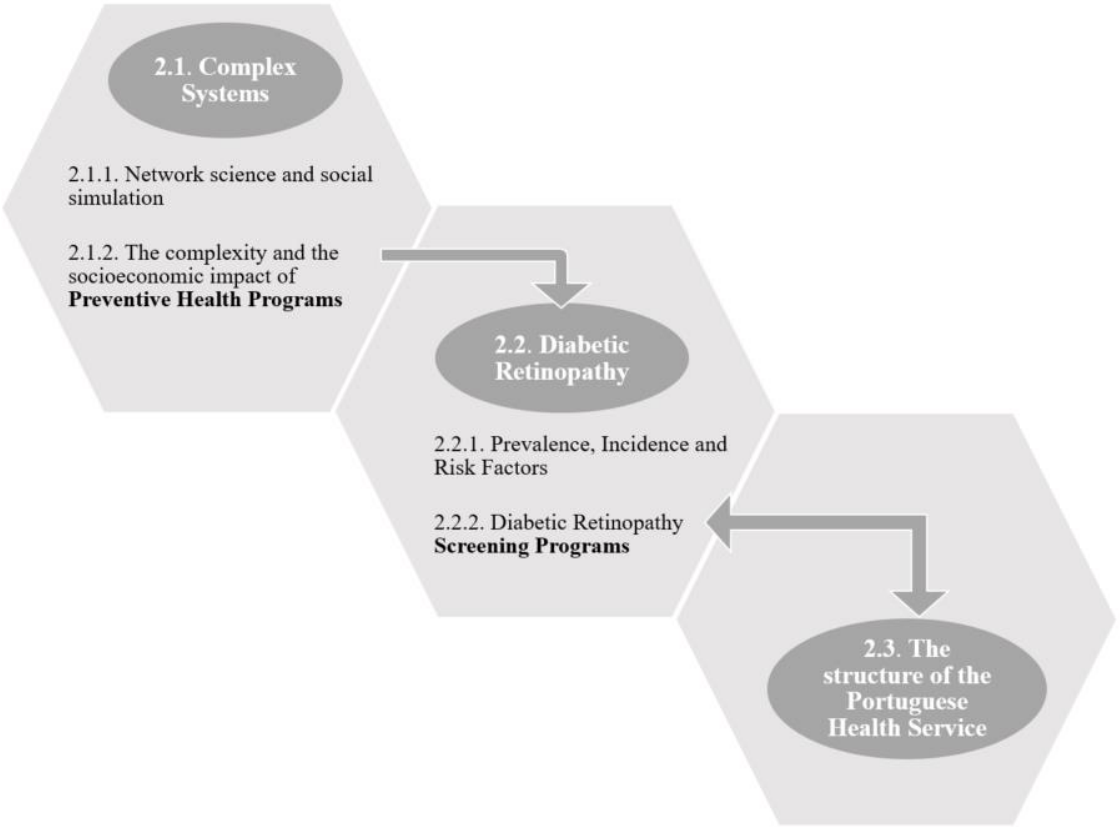
Finally, the last chapter highlights these thesis' main contributions, and discusses its practical implications, applications and limitations, as well as the gaps that still exist and the future work to be developed.

2. Concepts and methods

In this chapter, we seek to encompass the main concepts and techniques used in our research creating a background to facilitate the understanding of the following chapters.

Figure 1 presents the chapter structure and the underlying reasoning. The chapter begins with a broader section on the main characteristics of complex systems (2.1.), some of the techniques commonly used in the study of these systems (2.1.1.) and the arguments that lead several authors to consider preventive health programs as complex systems (2.1.2.). From here, we set out to clarify some important concepts about the specific health problem that is the focus of our research: DR. We began with a brief explanation about the disease and by illustrating its important impact on the quality of life of populations (2.2. and 2.2.1.) and ended with the technical aspects related to the screening (2.2.2.). Finally, we present a brief characterization of the functioning and structure of the Portuguese Health Service, as these characteristics are fundamental to understanding several of the results concerning the Portuguese DR screening discussed throughout the remaining chapters (2.3.).

Figure 1 – Chapter 2 structure



2.1. Complex Systems

Complexity is present in almost every aspect of our daily lives. From traffic queues to self-organization and collective motion in crowds, from human relationships to the way we get excited about seeing a new movie, complex behaviour is everywhere. In fact, humans, as social and empathic beings, are influenced by the behaviour of their peers, and by the environment [24]. However, these facts have not always been scientifically considered. Historically, scientists believed the possibility of predicting (and control) the future [15] [25] [26].For a long time, the only obstacle to that goal seemed to be the access to the right amount, of the right data [25] [26]. In reality, traditional science was based upon two broad philosophies: empiricism and determinism [15] [25] [27]. Empiricism claims that all knowledge comes from experience, while determinism argues that the future can be predicted from the past, based on natural laws, which are nothing more than the result of all previous scientific experience [15] [25]. Seen in this light, science is the process of converting empiricism to determinism [27]. However, there are several impediments to this process, as Chaos and Complexity [28] [29]. In the XIX century, Poincaré discovered the sensitive dependence on initial conditions in the restricted 3-body problem and in 1963 Lorenz presented the Butterfly Effect [26] [29]. It had born the Chaos theory, as a developing scientific discipline, and many of the classical convictions were called into question [28]. Chaotic systems are collections of multiple orderly subsystems, which can switch rapidly and unpredictably between different states [28]. In 1987, the Santa Fe Institute proposed the idea of the "edge of chaos" and a new research field called Complexity Science [26]. Complexity Science studies the ordered, complex systems, that sometimes spontaneously emerge out of chaotic systems [29]. This spontaneous emergence is often referred to as self-organization [29] [30]. So, complex systems are not merely complicated, static objects, they are adaptive dynamic systems [29] [30]. Complex adaptive systems can be defined as systems with a large number of independent agents that interact in a non-deterministic manner, and are able to adapt and learn [30]. In these systems, there is no centralized control, and the behaviour of the "whole" is unpredictable. In fact, in complex, adaptive dynamic systems a minimal decision, often considered insignificant, can be amplified by nonlinearity or by the large number of interactions between the components, generating an unexpected transformation someday in the future [30].

2.1.1. Complex Systems Methods: network science and social simulation

The properties inherent to complex systems can pose difficulties for traditional methods. So, a range of adaptations in traditional research methods was developed to try to improve their ability to manage complex systems [5]. In effect, optimization methods, such as mathematical programming [5], can be used to optimize some explicit and quantifiable objective, defined as a mathematical function of the decision variables, subject to a series of related constraints; Problem structuring methods [5] can be used to elicit objectives and opinions and to help develop a common understanding; Whilst system dynamics methods can be used to model the dynamics of complex systems, to gain insights into the problem structure [5]. Still, frequently, those methods prove to be limited, impractical and unintuitive, when used to address some of the major challenges of complex systems: interactions, multiple conflicting objectives and uncertainty [26].

Recently, a set of new methods for studying complex systems has been gaining interest and visibility [4] [31]. Those methods are often adaptations of methods used on other disciplines, In fact, complex systems had inspired an astonishing convergence of subjects, such as Biology, Mathematics, Social Sciences, Economy, Physical and Computer Sciences, allowing the development of a common interface, and promoting the expansion of new techniques and analogies [4] [31].

Network analysis [4] [24] is one of the methods increasingly use in the study of complex systems, and studies the interactions (edges) between parts (nodes). The mathematical study of networks arose from graph theory, which began as early as the eighteenth century with Euler's solution to the famous "Bridges of Königsberg" problem [24]. In the 1950s Erdös and Rényi did influential work on the theory of random graphs [24]. In recent years, there has been a strong upsurge in the study of networks in many disciplines, ranging from computer science and communications to sociology and epidemiology, mostly due to the huge increase in computational capacity, which make it possible to study real networks empirically [24].
Network analyses can help answer important questions, for example: how relevant are the links between people or institutions; how do the network' properties affect the dynamics of information, disease, or behaviour spreading, it resilience to noise, to component failures, or targeted attacks; how do changes in a particular node affect other connections significantly [4] [24] .

Social simulation is also a field that can provide a unique way to study complex adaptive

systems [32]. In simple terms, social simulation involves the use of computing power to replicate social behaviour in different scenarios. In the most common implementation, a model is developed to reproduce a social situation or process and then the behaviour of individuals in the simulation is observed when the program is run [32]. Simulations are typically used to produce predictive data about what might happen in a real-world situation, to test theories, and to understand the implications of human behaviour [25] [32]. Computer simulations offer a middle ground between the descriptive approach, which simply documents observations about human behaviour and social processes, and the experimental approach, which establishes a real-world representation of some situation for research purposes, with the obvious ethical implications [20].

Classical simulation generally considers the system as a whole, before going into detail about its component parts (top-down strategy). The predicted behaviour is based on various aspects of the global state of the system [21]. On the other hand, in social simulation the behaviour of the system is dictated by a bottom-up strategy: the system behaviour develops from its' basic components, theirs' individual rules and states, as well as the interactions between them [20] [32]. The bottom-up strategy makes it possible to analyse higher-level properties of living organisms such as self-organization and emergence [20] [32].

Recently, two types of social simulation models have been increasingly used in complex systems: cellular automata and agent-based models [25]. They are similar methodologies in the sense that both use agents, with broad and free drawing, that follow rules. The use of this kind of models makes it possible to simulate interactions in the system and observe the properties that emerge from those interactions. Cellular automata are most relevant to the spatial analysis study where local, physically limited interactions, are relevant to the problem at hand [25]. The agent-based models, in turn, can be modelled to be fixed or movable and can be structured such that the space is completely irrelevant [33], and can even be thought of as links in networks, thus resembling network analysis [25]. Agent-based models have three basic components: agents, interaction rules and space. As the simulation is performed, agents interact with which other and whit their environment, and change their internal states [25] [33].

The main benefits of agent-based models utilization can be divided in two main categories: their capability to deal with features as non-optimal behaviour, heterogeneity and interactions among agents; and their flexibility and the possibility of tracking the evolution of a system [31]. However, there is the risk of misusing agent-based models, due to: the lack of functional and technical specifications; the misinterpretation off the results; and lack of calibration and uncertainty analysis [33]. In fact, usually agent-based models need to incorporate assumptions,

to describe behaviours and interactions not fully known [33]. This abstraction layer, between the simulated world and the real one, is not always well described and justified, and their effects are often not fully understood. This issue is rather critical, because simulation results can be greatly affected by this kind of decisions [33]. Therefore, several authors defend an interactive research approach, were evidences of empirical literature, can be used to build bottom-up theories using agent-based models [20] [31]. A cycle of iterative research approach can be drawn, were agent-based models incorporate the behaviour knowledge from empirical studies. Then the questions raised by such models can bring new questions, leading to hypothesis, and therefore new investigation topics for empirical research [20] [31]. On the other hand, agent-based models can provide policy measures recommendations [25]. If these measures are implemented, they can and should be evaluated by empirical studies. These studies could provide new knowledge in the behaviour of the agents and process that might them be used in future agent-based models [20] [31].

2.1.2. The importance and complexity of preventive health programs

Preventive health programs comprise two distinct areas: health promotion and disease prevention [34] [35]. The WHO defines health promotion as a social and political process, which includes actions aimed at strengthening individuals' capacities, but also actions aimed at changing social, environmental and economic conditions [34] [35]. Therefore, health promotion is traditionally defined more broadly than prevention, since it refers to measures that do not address a particular disease but serve to increase the overall health and well-being [35]. In the other hand, disease prevention is understood as specific, population-based and individual-based interventions for primary and secondary (early detection) prevention, aiming to minimize the burden of diseases and associated risk factors. Primary disease prevention refers to actions that seek to avoid the manifestation of a disease. This includes, among others, quit smoking, nutritional, and oral hygiene consultations, as well as immunization and vaccination of children, adults and the elderly [35]. Differently, secondary prevention deals with the early detection and aims to improve the chances for positive health outcomes. It comprises activities such as screening programs, for early detection of diseases or for prevention of congenital malformations. Some common disease screenings include checking for hypertension (high blood pressure), hyperglycemia (high blood sugar, a risk factor for diabetes mellitus), hypercholesterolemia (high blood cholesterol), HIV, and other types of sexually transmitted

diseases, and several kinds of cancer [34] [35]. Real-life impact studies demonstrate the effectiveness of preventive health programs in the reduction of costs associated with treatments, medications, hospitalizations, outpatient visits and years of working life lost [35]. Hence, preventive health programs can contribute to the sustainability of healthcare systems by avoiding unnecessary use of financial and human resources and freeing resources for other medical interventions [34].

Therefore, in addition to the enormous impact of preventive health programs in the quality of life and social welfare of the populations, it has become a dominant economic and political issue, due to its growing importance in public finances and economy, and the need and pressure for efficiency and effectiveness in this field is more preeminent than ever [7] [20] [36].
However, this is not an easy task: preventive health care is continually changing, and is a system of multiple stakeholders, interrelations between providers and between providers and populations. Therefore, Newton's "clockwork universe," [20] in which big problems can be broken down into smaller ones, analysed, and solved by rational deduction, which has strongly influenced both health care policies and the management of organizations, is no longer sustainable. In fact, the machine metaphor is not applicable when no part of the equation is constant, independent, or predictable. However, the science of complex adaptive systems may provide new metaphors that can help to deal with these issues [20].

It is also important to notice that, broadly speaking, healthcare is in an age of transformation, where new philosophies, like distributed leadership and patient centeredness [15], are being increasingly accepted and implemented, and that there is an unprecedented convergence of multiple pressures such as growing life expectancy, increasing incidence and prevalence of chronic diseases, globalization of infectious diseases, and technological advances [15].

Complex adaptive systems are systems with no centralized control, where large number of independent agents interact in a non-deterministic manner, and are able to adapt and learn [20]. Emergence is one common characteristic of complex systems. In this context, emergence is define as the appearance of new behaviours, properties, patterns or structures at the macro level (global system), caused by interactions between the agents at the micro level, but which cannot be directly inferred from those agents individual features [20].

Healthcare has been broadly recognized as a complex system in the recent literature [1] [14] [15] [37] [38], and there are indeed strong arguments to support this hypothesis:

i) The healthcare system is hierarchical and comprises multiple (micro, meso and macro) levels that are nested or embedded within one another. Providers normally have multiple

interdependences with other providers to secure operational necessities (such as resources) and deliver services in a network of patient care; those networks exist in a broader system that sets priorities and polices, and allocates resources that dictate how patient health is managed within these multiple systems [15]. Therefore, the system is composed by a set of networks of networks of components (primary care, private clinics, patient homes, families, and patients).

ii) Health systems can be seen as the dynamic interaction of different agent's (stakeholders, providers, professionals, and individuals), where change in any one element can alter the context for all other elements, and can subsequently be influenced by them [15]. The interactions within a complex adaptive system are often more important than the discrete actions of the individual parts. A productive or generative relationship occurs when interactions among parts of a complex system produce valuable, new, and unpredictable capabilities that are not inherent in any of the parts acting alone. Although healthcare quality depends largely on productive interaction, the organization and management of its delivery surprisingly does not always reflect this insight. In several countries like Portugal and the United Kingdom, for example, having separate budgets, management, and performance targets for primary care, secondary care, and social services promotes an internal focus on the operation of each of these parts, but not necessarily the good functioning of the system as a whole [38]. As such, preventive health systems research must take account of this complexity, seeking to understand emergent patterns rather than cause-and-effect sequences; and the

iii) Healthcare systems are often characterized by high levels of uncertainty. System agents have to manage this uncertainty, taking specific behaviours, actions and roles to enable intentional adaptation. However, the multi-level and network structure of the system can lead to unanticipated outcomes from those actions and behaviours. Therefore, many times, the responses to uncertainty conduct to undesirable or at least unexpected results (un-rational decisions, lack of commitment with preventive health programs, and opportunistic screening) [15].

2.2. Diabetic Retinopathy

DM is a global epidemic, with alarming prevalence rates in highly developed countries, such as the United States, the United Kingdom, and those of the Western Europe, but also with worrying evolutions in developing, South American, African, and Asian countries [39].

In 2019, the International Diabetes Federation estimated that there were 463 million people

with diabetes, representing 9.3% of the global adult population (20–79 years). This number is expected to increase to 578 million (10.2%) in 2030 and 700 million (10.9%) in 2045 [6].
According to the Portuguese National Diabetes Observatory, in 2021, the estimated prevalence of diabetes in the Portuguese population aged between 20 and 79 years old (7.8 million individuals) was 14.1%, and there is a tendency to increase mainly driven by the aging of the Portuguese population [13].

DR is a common and specific microvascular complication from diabetes that develops over time. Without treatment, severe stages of DR, including proliferative DR (PDR) and diabetic macular edema (DME), result in visual impairment and blindness.
Although DM is a disease known since the 2nd century BC, only was associated with ophthalmological complications, namely DR, in the mid-19th century with the pioneer research of Eduard Jäger and Edward Nettleship [40] [41]. However, the first clinical application of photocoagulation in the treatment of DR, was only carried out by Paul Wetzig in 1963 [41].

In recent decades, numerous studies have been developed, contributing to a greater knowledge about risk factors, natural history, and treatment of DR. Nevertheless, DR is still the leading cause of blindness in working age populations in most of the Western countries [39].

2.2.1. Prevalence, Incidence and Risk Factors

The results of epidemiological studies dedicated to the prevalence of DR are not uniform. Although it could be argued that the features of diabetic persons may be different from country to country, and between ethnic groups, it is also true that the studies are quite heterogeneous in terms of patient selection, population characteristics, and DR method of diagnosis and classification.

A 2001 study, focused on determining the prevalence rates of DM and DR in a population of Hispanics aged 40 years or more, stated that the prevalence rate of diabetes in the Hispanic community was 22%, and the DR prevalence rate was 48%. This study was based in a random sample of the Hispanic population living in Arizona, comprising 4,774 individuals [42].
A 2005 Indian study, conducted on a representative population of a city in South India, analysed data from 26,001 individuals, aged 20 years or older, 1,529 of who were known diabetics. The subjects were first screened for diabetes, and then screened for DR. The overall prevalence of DR in the general population was 17.6% (95% confidence interval [CI]: 15.8 –19.5), and 20.8% (95% CI: 18.7–23.1) among known diabetic subjects. The authors concluded that this study

indicates that the prevalence of DR in Indians might be lower than that reported among western countries, reasoning with a lower propensity to obesity and genetic factors. However, the authors also recognize that the differences between the subjects' age group, the duration and the degree of control of DM, and the DR screening method and grading, limited the capability to compare results and extract valid conclusions [43].

A 2004 U.S. study, which consists on a meta-analysis based on data from eight population-based eye surveys conducted between the years 1982 and 2000, corresponding to 4,440 diabetic persons, estimate a prevalence rate of DR of 40%, among persons with diabetes mellitus (DM). However, this study, was limited to individuals with type 2 diabetes aged 40 years and older, the data were mostly derived from Caucasian individuals, and did not include Asian persons. Another limitation, recognized by the authors themselves, is the oldness of some of the surveys used in the analysis. The increased screening and the improvements in the management of DM, may have led to lower DR incidence and prevalence over time since the early 1980s, when some of those surveys were conducted, and the results obtained may not be directly applicable to the 2000s U.S. population [44].

In fact, some studies support the hypothesis that the change in DM diagnostic and management had an important impact on the prevalence of DR. A study was carried out with a population of patients with type 2 DM, with the data obtained in 2005 being compared with a study carried out in 1993, by the same author and under the same conditions. The results obtained left no doubt, with the prevalence of DR in the 1993 study being 39.41% and in the 2005 study of 27.55% [45].

In 2012, the Meta-Analysis for Eye Disease (META-EYE) Study Group, published a very rigorously conducted study that provides a global estimate of the prevalence of DR and the severe stages of DR (PDR, DME) using individual-level data from population-based studies worldwide. The authors collected data from 35 studies conducted between 1980 and 2008, in the U.S., Australia, Europe, and Asia. The collected data corresponded to 22,896 individuals with diabetes, aged between 20 and 79 years. This study determined an overall prevalence of 34.6% (95% CI 34.5–34.8) for any DR, 6.96% (6.87–7.04) for proliferative DR, 6.81% (6.74–6.89) for diabetic macular edema, and 10.2% (10.1–10.3) for VTDR. The estimated prevalence of DR was highest in African Americans and lowest in Asians. However, as in other studies already mentioned, some of the surveys were quite old, which may have contributed to inflating the general prevalence value of DR.

In 2010, a study addressing the epidemiology of DR in the Paris metropolitan region, found a global prevalence of DR of around of 24% [46].

Several UK screening programs have evaluated the prevalence of DR for type 2 diabetes. In the Scottish programme, the estimated prevalence of DR, in 47,090 patients newly diagnosed with type 2 diabetes, was of 19.3% [47]. In Wales, an analysis cross-sectional study of 86,390 patients with type 2 diabetes, documented an overall prevalence of DR 30.3% [48].

More recently, a study, estimated that, in 2020, the global prevalence of DR among individuals with diabetes was 22.3% (95% confidence interval, 19.7%–25.0%), that is, the number of adults worldwide with DR was estimated to be 103.12 million. The same study, projects an increase to 160.50 million of the number of DR cases by 2045 [49].

In Portugal, a study (RETINODIAB) used data from 52,739 people with diabetes who participated in the DR screening program in the Lisbon and Tagus Valley Health Region, implemented between July 2009 and December 2014, to assess the prevalence in this target population. DR was detected in 8,584 patients, 16.3%. This prevalence of DR identified in the Portuguese population is slightly lower than that described in epidemiological studies from other European countries. However, as previously mentioned, these studies are not uniform in terms of patient selection and inclusion criteria (age, gender, duration of DM, type of DM, comorbidities and classification of DR), making comparisons difficult [50].

The RETINODIAB study also evaluated the incidence of DR in type 2 diabetic patients, in the Lisbon and Tagus Valley Health Region, analysing 109,543 retinography scans of 56,903 patients. An incidence of DR of 4.60% in the first year and 3.87% in the fifth year of screening was identified, with a cumulative incidence at 5 years of 14.47%. Once again, this analysis verifies that the risk of any degree of DR was strongly associated with an increase in the duration of DM and an earlier age at diagnosis [50].

The Liverpool Diabetic Eye Study included 20,570 screenings carried out between 1991 and 1999. An annual incidence of referable diabetic retinopathy (RDR) was measured at 0.2% in the first year, and an incidence cumulative 1.7% at 4 years [51].

Another study in Wales assessed the relative incidence of DR to a population-based screening that included 57,199 people with type 2 diabetes over a 4-year period. An overall cumulative incidence of DR and RDR at 4 years was 36.0% and 1.2%, respectively [48].

Comparing these European results, we see some discrepancy in incidence rates. However, there is, again, great variability between different studies due to population differences and different ways of classifying DR, making comparison limited.

Regarding the main risk factors for DR, epidemiological studies indicate, in addition to genetic factors, the duration of diabetes, age, HbA1c, high blood pressure and cholesterol. The Portuguese RETINODIAB study, showed a strong association between the presence of DR and

the duration of DM, as well as with the age of the patients [41]. The Meta-Analysis for Eye Disease (META-EYE) Study Group, found out that the prevalence rates were substantially higher in diabetic persons with type 1 diabetes and increased with the duration of diabetes, values for HbA1c, blood pressure, and cholesterol [52]. The "United Kingdom Prospective Diabetes Study" (UKPDS) and the "Wisconsin Epidemiologic Study of Diabetic Retinopathy" (WESDR), showed results similar to the 2 previous studies based, respectively, on 4,209 patients with type 2 DM newly diagnosed, and 2,366 patients, with Type 1 and type 2 DM, observed over a period of between 4 and 10 years [53]. Several studies have tried to prove the relation between smoking, obesity, alcohol consumption and RD, however, although it is undeniable that these factors indirectly aggravate the risk of developing DR (for example, smoking and obesity can lead to high blood pressure), there is no scientific prove that they constitute direct risk factors [53] [54].

2.2.2. Diabetic Retinopathy Screening Programs

According to the WHO, the screening process is the presumed identification of unrecognized disease in an apparently healthy, asymptomatic population by means of tests, examinations or other procedures that can be applied rapidly and easily to the target population [55]. According to the same organization, screening programmes can reduce the number of deaths and also the risk of developing diseases, provided appropriate counteractions are effectively planned, funded and dully implemented [56].

In the European Union, screening has led to reductions in mortality of 25% for breast and colorectal cancer, and up to 75% for cervical cancer [57]. Furthermore, disease prevention, when feasible, is usually much more cost effective than treatment.

The WHO published a list of generally accepted criteria for the assessment of evidence on benefits, risks, and costs of screening [55]. That list includes:

i) the recognition that the condition is an important health problem;
ii) the existence of a recognizable latent or early stage;
iii) knowledge about the natural history of the condition;
iv) the existence of an effective treatment for positive cases;
v) the existence of a suitable diagnostic test or examination;
vi) the evidence that the cost of the screening is economically balanced in relation to possible expenditure on medical care as a whole; and

vii) the guarantee that the screening is a continuing process.

The decision of recommending a population based screening is influenced by the relative strength of the available scientific evidence in relation to those criteria. Most importantly, there should be sufficient direct evidence from well-conducted studies that early detection improves health outcomes, and that the benefits of screening outweigh any potential harms [35].

Since the Saint Vincent Declaration in 1989, it has been globally recognized that DR is one of the diseases whose effects can be largely reduced through periodic screening of the population [11]. However, in 2021, the WHO conducted a situational analysis of DR screening in the European Region and the results were below the expectations set in the early 2000's WHO's recommendations [2].

Before analysing the results of the aforementioned report, it is important to remember the minimum requirements for organized screening relevant for DR in accordance with the WHO [56]:

i) the screening test is offered to an identified cohort of people with diabetes based on a register or list, rather than ad hoc offers being made or relying on individuals to request a test;

ii) a complete screening pathway, governed by protocols and guidelines, is in place, from the call/ recall of the target population, to the screening test to the treatment of positive cases.

iii) there are quality standards based on evidence; and

iv) the screening is supported by an information system that can monitor performance.

For the purposes of the 2021 situational report, is considered that a systematic or organized DR screening is in place if it has at least three of these components. The main conclusions of this report include the following [2]:

i) Although, there is evidence of some screening taking place in most countries/regions, there are very different degrees of organization. Only eight of the forty-eight respondent countries provided evidences of a systematic, country-/region-wide, DR screening. Five only conduct systematic screening either in a region or a part of their health system, but systematic screening was not available for all diabetic persons. Two countries stated that they are in the process of implementing a systematic screening;

ii) There seems to exist a wide variability in the way screening is carried out across the countries, what in part may be due to lack of direction from policy-makers. Although respondents from most (twenty-eight) countries/regions reported some kind of clinical guidelines that covered DR screening, many were unable to point to national/regional policy documents;

iii) The few countries/regions with systematic screening in place reported the involvement of

different professionals in the screening (technicians, nurses, optometrists). However, sixteen of the other respondents stated that the partial screening conducted in their countries/regions where carried out exclusively by ophthalmologists which will never be feasible in population-based screening;

iv) The countries/regions with systematic screening in place predominantly reported that the screening method was retinal photography;

v) Only six of the respondents indicated that they had a complete list of all people with diabetes in their country they can use for invitations, call–recall and monitoring of screening coverage. Seventeen of the respondents could not provide any information on DR screening coverage or uptake. Without this basic information, it will be difficult for policy-makers to design, implement and monitor the effectiveness of future DR screening programmes. It is urgent the implementation of an information system that can monitor screening indicators;

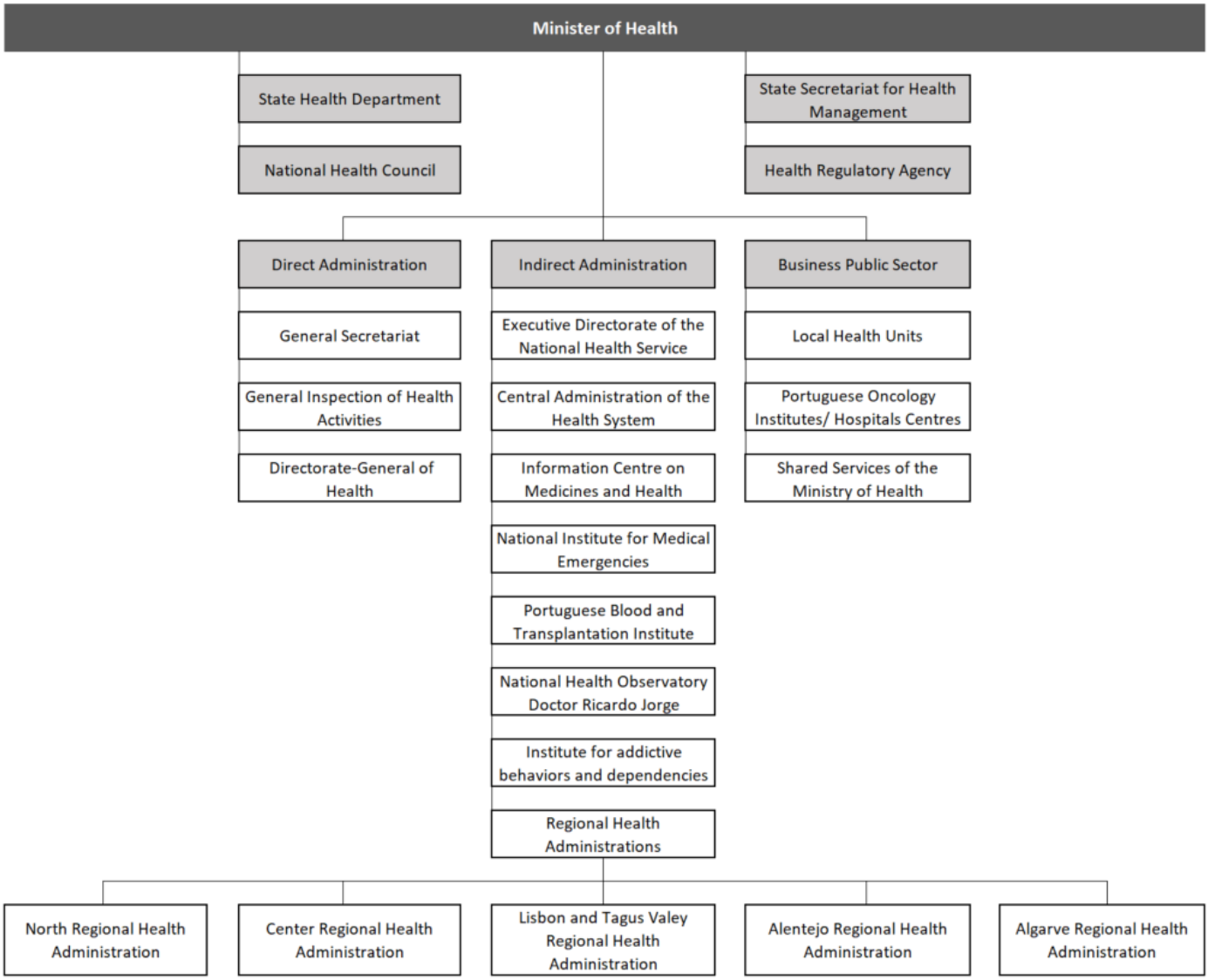
vi) Collecting rigorous and comparable information on how different countries conduct screening is very difficult, due to the complexity inherent to these programs, different health systems and organizations, and linguistic barriers that condition the interpretation of the questions asked. The authors acknowledge that the report has limitations on what can be inferred from some of the data because of inconsistencies in the way the survey was answered, and that further research is needed.

Our first paper, "Five regions, five retinopathy screening programmes: a systematic review of how Portugal addresses the challenge", aims to contribute to fulfil these need, providing an exhaustive systematic scientific and technical literature review of DR screening in Portugal. However, first there is a subsection with a short characterization of the Portuguese Health Service, which aims to facilitate the reading and understanding of the work presented later.

2.3. The structure of the Portuguese Health Service

The public healthcare system in Portugal is delivered through the Portuguese National Health Service (SNS), which was founded in 1979. In Portugal, SNS is practically free of cost (users only pay a small fee) and is available to all residents [36] [58] [59] . SNS covers all Portugal mainland (the regions of Azores and Madeira have their own healthcare systems), and comprehends institutions within the government direct and indirect administration. Figure 1 illustrates the SNS hierarchical organization [60].

Figure 2 - Portuguese SNS Organization (adapted from *[60]*)



SNS is managed by the Central Administration of the Health System (ACSS), and delivered by five Regional Health Administrations (ARS North, Central, Lisbon and Tagus Valley, Alentejo and Algarve). Recently, the Executive Directorate of the National Health Service (DE-SNS), was created, whose mission is to coordinate and manage the SNS assistance response, ensuring its network functioning, continuous improvement of access to healthcare, the participation of users and the alignment of clinical and health governance.

SNS covers Primary Health Care (Primary Health Centres) and Secondary Care (Hospitals and Specialized Units) [59] [61].

Primary Health Centres are associated in Health Centre Clusters (ACES). There are 55 ACES distributed nationwide. According to the supporting legislation, ACES are public health services with administrative autonomy, decentralized from ARS but subjected to their directive

power. They aim to ensure the provision of customized healthcare to the population of the geographical area within their administrative boundaries [60]. Each ACES includes several functional units:

i) Family Primary Health Care Units (USF): established on a voluntary application of a multidisciplinary set of professionals (family doctors, nurses, and clinical secretaries) for the creation of self-organized healthcare teams with technical and functional autonomy. USF autonomy is regulated by a contract letter of commitment with the ARS, and they are evaluated and held accountable for their performance. USF family doctors have a mixed remuneration system with adjusted capitation, payments per service performed, which awards quality and efficiency. On the other hand, nurses and clinical secretaries can access financial incentives, and their attribution depends on the achievement of the contracted goals related to key performance indicators (KPI) [60];

ii) Personalized Primary Health Care Units (UCSP): Although a great number of USF had been implemented across the Portuguese territory in the last years, the previous model of organization (before a 2005 structural reform), non USF (also called UCSP) still exists, in cases where professionals are not willing or cannot be organized in USF. These units are structured in the more vertically hierarchized and less autonomous model [60];

iii) one Public Health Unit – USP, created to operate as health observatory within the geodemographic area of the ACES [60];

iv) one unit to provide advisory services to all other functional units that includes resources like social workers, physiotherapists and psychologists – URAPs (31); and

v) a community care unit, which provides healthcare, psychological and social support at home and community level - UCC [60].

With regard to hospital institutions, the articulation with guardianship (Regional / central Administration) is currently materialized through a negotiation process based on the link between the allocated funding and the results expected [61]. The management contract consists of duties and obligations translated in to physical and quality goals and is an important tool because it allows to monitor the performance of the hospital service, so that necessary interventions can be performed [61].

The contract with the hospitals is supervised by ACSS, which has the strategic responsibility to make the contracting process compatible with the health policy objectives [59] [61]. ARS have the responsibility to operationalize the whole process, from the elaboration of contracts, to the monitoring, evaluation, and negotiation of the incentive system [59] [60].

The General Health Department (Direção Geral de Saúde - DGS) is a government institution, with a vital role on the organization and monitoring of population-based screenings. DGS has the mission of regulate, guide and coordinate activities of health promotion and disease prevention, define the technical conditions for adequate health care, as well as ensuring the elaboration and execution of the National Health Plan [62].

The National Health Observatory Doctor Ricardo Jorge is a public body integrated in the indirect administration of the State, endowed with scientific, technical, administrative, financial and proprietary autonomy. It develops a triple mission as state laboratory in the health sector, national reference laboratory and national health observatory [60].

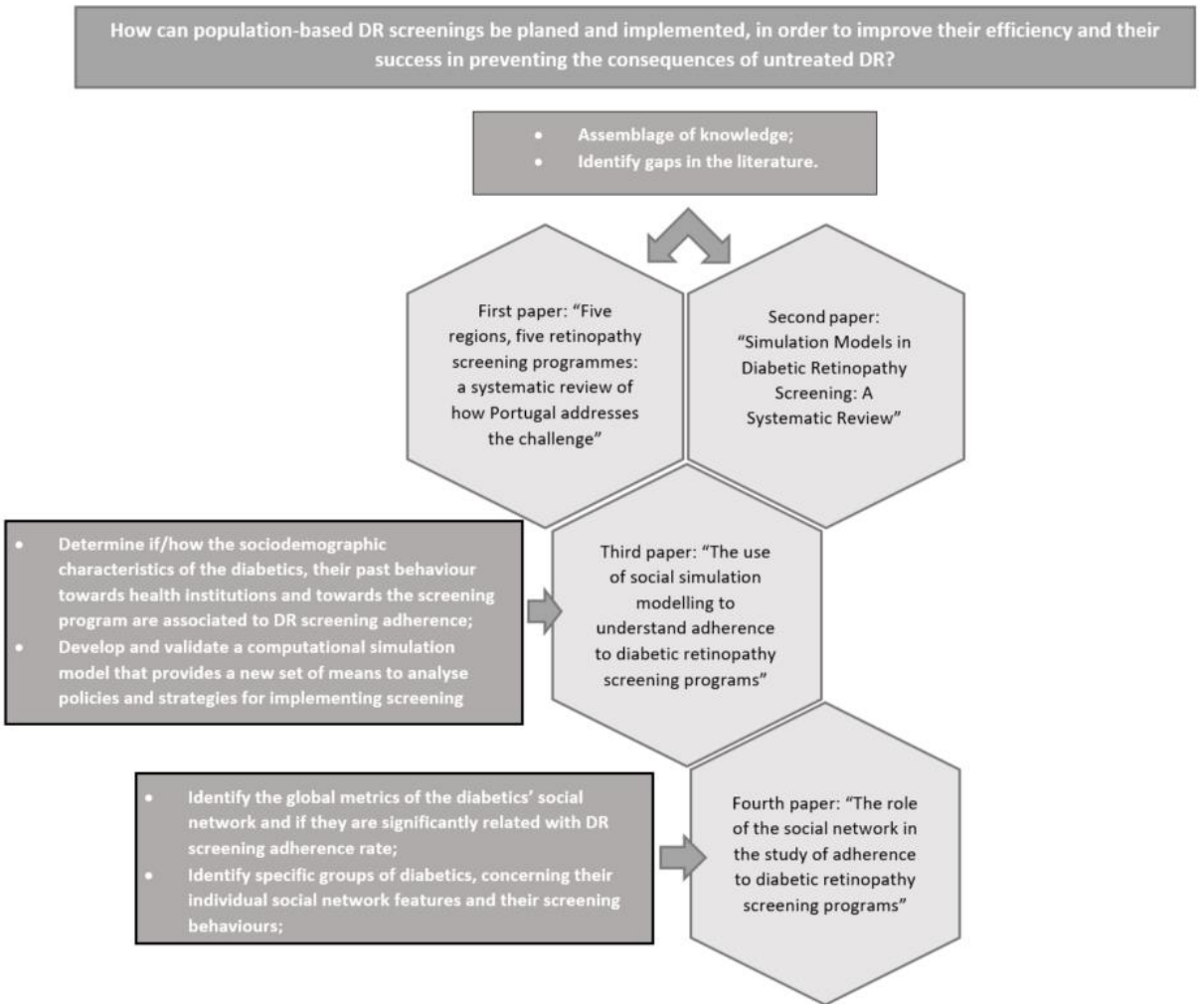
3. Core papers

This chapter consists on the four core papers selected. For each paper is presented a short summary and contextualization, followed by the paper itself.

The first paper "Five regions, five retinopathy screening programmes: a systematic review of how Portugal addresses the challenge" [17] is focused on the assemblage of knowledge in the field of DR screenings, providing the first systematic review of the Portuguese experience. After an extensive systematic literature review, it was possible to identify the main DR screening implementation problems, the possible solutions for operational planning of future screenings, the improvements possible for the existing ones, and to put forward a framework to comparative analyses. The second document "Simulation Models in Diabetic Retinopathy Screening: A Systematic Review" [19], promotes the assemblage of knowledge about simulation models for DR screening of the general population until 2023. The third paper "The use of social simulation modelling to understand adherence to diabetic retinopathy screening programs" [22] uses the results of the two previous literature reviews and aims to answer the following question: How to predict the rate of adherence to population-based screenings through computational simulation models with a high level of abstraction. More specifically, this paper aims to i) demonstrate that it is possible to develop a computational simulation model that faithfully portrays the individual decision to adhere or not to screening, using the intrinsic features of the diabetic patients and of the screening programmes. ii) demonstrate that a simulation model with the aforementioned characteristics can be used in contexts other than the one where the data for its development were collected. iii) demonstrate the utility of combining agent-based models and fuzzy logic in models that intend to simulate human behavior. To fulfil those purposes, we developed three versions of an agent-based simulation model: the first one uses a logistic regression model to determine the individual decision to adhere or not to the screening; in the second one, the logistic regression is replaced by three fuzzy logic components; and the last one is a combination of the first two methods. The results obtained are very close to the real ones. Moreover, the simulations have a high degree of abstraction from the real data, which attests to the validity of the approach and its usefulness as a predictive tool for public health action planning [22]. The last paper "The role of the social network in the study of adherence to diabetic retinopathy screening programs" [22] arouse from a gap in the literature identified during the development of the previous models concerning the influence of the diabetics' social network structure in the adherence to DR screening. To fulfill this gap this paper aims to identify: (i) the global metrics of the diabetics' social network and if they are

significantly related with DR screening adherence rate, and (ii) specific groups of diabetics, concerning their individual social network features and their screening behaviors. The results allowed us to conclude that the structure of the social network and the position occupied by the diabetic in this network influence the behavior of adherence to DR screening.

Figure 3 – Core papers organization and main goals



3.1. Five regions, five retinopathy screening programmes: a systematic review of how Portugal addresses the challenge

3.1.1. Context and summary

"Five Regions, Five Retinopathy Screening Programmes: A Systematic Review of how Portugal addresses the challenge" [17], is a study that promotes the systematic assemblage of knowledge about the implemented, organizational and management, practices in DR screening programmes, providing the first systematic review of the Portuguese experience. In fact, the implementation of a population-based DR screenings requires the intervention of many stakeholders (government, hospitals, primary health units) and involves numerous challenges, which often lead to unexpected setbacks at high human and material costs. Thus, the sharing of knowledge and experiences among countries is of recognized utility, and there is a permeant need for a solid framework, which can be used as a basis for future projects. However, the desirable interchange is not easy to accomplish. In fact, different countries often have different health systems, which makes it i) difficult to understand and categorize procedures, ii) screening programmes may be implemented at a national, regional, or local level, all that resulting in sparse information at a various granularity, and there are organizational and even linguistic barriers that complicates the process even more. This study provides a systematic scientific and technical literature review of the Portuguese experience, which can be used to plan future programmes or implement improvements in the existing ones. This not only in Portugal but also in the rest of the world, putting forward a framework of comparative analyses and optimization tools for simulation of strategic scenarios. The highlights of this work are the identification of effective and ineffective organizational practices, as well as the main DR screening implementation problems and possible solutions. A high scientific and rigorousness methodology, using Preferred Reporting Items for Systematic Reviews (PRISMA) [63] was applied. This when selecting and reviewing PubMed, Science Citation Index scientific papers and technical documents in existence on all Portuguese governmental and non-governmental organizations with a relevant role on DR screening programmes. The obtained findings reveal that this work has the potential to support the planning of future DR screening programmes and improvements in the existing ones.

3.1.2. Paper verbatim copy

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BMC Health Services Research

Five regions, five retinopathy screening programmes: a systematic review of how Portugal addresses the challenge

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Abstract

Background: The implementation of a population-based screening programme for diabetic retinopathy involves several challenges, often leading to postponements and setbacks at high human and material costs. Thus, it is of the utmost importance to promote the sharing of experiences, successes, and difficulties. However, factors such as the existence of regional programmes, specificities of each country's health systems, organisational and even linguistic barriers, make it difficult to create a solid framework that can be used as a basis for future projects.

Methods: Web of Science and PubMed platforms were searched using appropriate key words. The review process resulted in 423 articles adherent to the search criteria, 28 of which were accepted and analysed. Web sites of all Portuguese governmental and non-governmental organisations, with a relevant role on the research topic, were inspected and 75 official documents were retrieved and analysed.

Results: Since 2001, five regional screening programmes were gradually implemented under the guidelines of Portuguese General Health Department. However, complete population coverage was still not achieved. Among the main difficulties reported are the complex articulation between different levels of care providers, the low number of orthoptic technician in the national health system, the high burden that images grading, and treatment of positive cases represents for hospitals ophthalmology services, and low adherence rates. Yet, the comparison between strategies adopted in the different regions allowed the identification of potential solutions: hire orthoptic technician for primary health care units, eliminating the dependence of hospital professionals; use artificial intelligence algorithms for automatic retinographies grading, avoiding ophthalmologists overload; adoption of proximity strategies, as the use of portable retinographers, to promote adherence to screening.

Conclusion: Access to diabetic retinopathy screening remains remarkably variable in Portugal and needs urgent attention. However, several characteristics of effective screening programmes were found in Portuguese screening programmes, what seems to point toward promising outcomes, especially if each other highlights are considered. The findings of this research could be very useful for the other countries with similar socio-political characteristics.

Trial registration: PROSPERO registration ID CRD42020200115.

Keywords: Diabetic retinopathy, Population-based screening, Systematic review, Portuguese screenings

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Contributions

- This study contributes to the assemblage of knowledge in the field of diabetic retinopathy screenings, providing the first systematic review of the Portuguese experience.
- The study also details the main diabetic retinopathy screening implementation problems. It points out the possible solutions for operational planning of future screenings, the improvement possible for the existing ones, and put forward a framework to comparative analyses.
- This study highlights the importance of adequate governmental funding, national guidelines that precise the role of the different intervenient, and of politic measures that guarantee the involvement of all parts.

Background

Diabetes Mellitus (DM) is a chronic metabolic disease and one of the most prevalent diseases worldwide [1–4]. DM can cause macro and microvascular complications, including diabetic retinopathy (DR) [5–7]. DR occurs when blood vessels in the light-sensitive region of the eye, the retina, leak or become blocked, due to pro- longed high blood glucose levels [8, 9]. DR is the most common cause of vision loss in people with diabetes [7, 10] and globally is the leading cause of visual impairment and blindness among working age population [11– 13]. However, DR can be prevented or delayed by timely diagnosis and management of diabetes [14, 15], and blindness can also be prevented or delayed by regular eye screening and appropriate treatment [16, 17].

Nonetheless, although extremely important, the implementation of a population-based DR screening, requires the intervention of many stakeholders (government, hospitals, primary health care units) and involves numerous challenges, which often lead to unexpected setbacks at high human and material costs [18, 19]. Thus, the share of knowledge and experiences between countries is of recognised utility, and there is a permeant need for a solid framework, that can be used as a basis for future projects [5, 18, 20]. However, the desirable interchange is not easy to accomplish. In fact, different countries often have different health systems, which makes it difficult to understand and categorise procedures [5, 21], screening programmes may be implemented at a national, regional, or local level, resulting in sparse information at a national level, and there are organisational and even linguistic barriers, that complicate the process [18, 20].

In this context, this study intends to answer the following research question: How is the population-based DR screening programme conducted in Portugal? And, consequently, to contribute to the assemblage of knowledge in the field of DR screening, providing a systematic scientific and technical literature review of the Portuguese experience, which can be used to plan future programmes or implement improvements in the existing ones.

The strategic planning of a DR screening requires a deep knowledge to be successful [20]. So, in this paper five key questions are addressed, namely: i) What are the general guidelines of the screening programmes in Portugal? ii) How did each region implement the screening? iii) What are the main metrics used to measure the results of each screening programme and how did DR Screening results evolved through time? iv) What are the main problems reported when implementing DR screening programmes and how can eventual risks be mitigated?

By analysing the accepted 28 scientific peer-reviewed articles and 75 technical documents from government (e.g., [22, 23]) and non-governmental organisations (e.g., [24, 25]), five Portuguese regional DR screening programmes, within the context of the National Health System (SNS), allowed the identification of the advantages and weaknesses of each regional strategy and are discussed in the light of documented international experiences. Most of the available studies about DR screening are cost-effectiveness analyses (e.g., [26, 27]), or are focused on very specific aspects of the process (for example automatic reading grading [19, 28]). However, the overall screening strategy is rarely well described [16] and normally only the unilateral point of view of one type of stakeholder is explored, e.g., diabetics [29], health professionals [30], primary health care units [30], hospitals [31] and government [27]. As opposed to that, in this review we specifically tried to identify alternative screening strategies and assess the challenges faced by the different levels of health care providers, producing a synthesis of the evidence available in the literature.

This work is organised as follows. The first section concerns the adopted methodology and literature selection. Then, the general guidelines of the screening programme in Portugal, the differences between regional protocols, the indicators used to measure screening results, the quality evaluation, and the main problems reported in implementing DR screening programmes, are analysed. Finally, the implications of the different scenarios are examined considering the best national and international practices.

Methods

Search for studies

We performed a systematic review according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) checklist [32] (see Additional file 1).

For the scientific review, Web of Sciences (www.webofknowledge.com) and PubMed (https://www.ncbi.nlm.nih.gov/pubmed/) databases were searched. The selection of scientific databases was based on their scope and their wide range of publications in the field of interest [33, 34]. Moreover, these databases are frequently used in other researches [33].

The search was performed according to the following query: ((“Diabetic retinopathy” or “DR” or “diabetic vision lost” or “diabetic complication*”) and (“screening” or “preventive public policy*” or “preventive eye exam” or “early diagnosis” or “retinography”) and (“population based” or “mass”)).

The query was applied to the topic (title, abstract and keywords) field, for the period 2009–2020 and only considering articles written in English or Portuguese languages. The time constraint was imposed because, in Portugal, there is no truly population-based DR screening, prior to the year 2009. The linguistic restriction is due to the very purpose of this systematic review – to analyse the screening of DR in Portugal – and, to the fact, that English is nowadays the universal language in the scientific world.

Technical documents were retrieved from the web sites of all Portuguese governmental and non-governmental organisations, with a relevant role on DR Screening (see Additional file 2). Governmental organisations were selected based on their mission and in the organisational chart of the National Health System. Non-governmental organisations were identified through references of papers and official documents.

Inclusion and exclusion criteria

Inclusion and exclusion criteria were applied to select the relevant set of articles to be reviewed.

For the scientific review, were included studies published in pear review journals, referring to the DR screening programme in Portugal. Articles that were focused on interventions, clinical rehearsals, research with methodological deficiencies, and duplicate work were excluded. Four hundred and twenty-three articles were retrieved from Web of Sciences and PubMed databases. A preliminary review process was applied according to the following steps: 1) exclusion duplicate articles; 2) evaluation of scientific articles according to abstracts excluding those focused-on interventions, clinical rehearsals, research with methodological deficiencies. This preliminary evaluation resulted on the exclusion of 64 articles.

For the technical review were included only official documents, available on the institution web site, and referring to DR screening programme. Excluded documents were those that are not dully substantiated and duplicate work. Regarding technical documents, 1 hundred and 75 were retrieved from the web sites of all Portuguese governmental and non-governmental organisations (listed in Additional file 2), with a relevant role on DR Screening. After the preliminary evaluation, 97 official documents were selected and analysed.

Finally, all the selected documents were submitted to a critical full document evaluation, what allowed to exclude articles that did not mentioned the Portuguese DR screening programmes, scientific or technical documents with methodological deficiencies and the ones not dully substantiated. Two experts of the Portuguese North Region Health Administration validated both selection procedures. After the selection process, 28 articles and 25 official documents remained. Figure 1 illustrates the selection process.

Articles and documents analyses procedure

To facilitate the documents analysis, they were organised in different categories. The documents classification was carried out by two of the three authors of this systematic review. The third researcher was called to break the tie, whenever there was no agreement between the first two. Scientific documents were divided in three categories:
i) DR Incidence / prevalence studies or studies focus on DR characteristics, such as risk factors, natural history and, progression (10 papers); ii) Machine learning algorithms for images grading (10 papers); and iii) Screening strategies (five papers). Three papers were classified in both 1 and 2 categories. Additionally, to access the quality of the scientific articles eight quality items were considered (Table 1) and graded according with the following rule: Yes(Y) = 1; No(N) = 0; Partially(P) = 0.5. The marking of the selected papers in each of the quality criteria is available in Additional file 3.

Official technical documents were classified as documents of national scope (24) or documents of regional scope (51). Regional documents were distributed by North (11), Central (10), Lisbon and Tagus Valley (10), Alentejo (10) and Algarve (10) regions.

Results

General guidelines of the Portuguese screening programme

In 1998, the Portuguese General Health Department (DGS) has established the first guidelines for DR population-based screening programmes. Non-mydriatic Chamber Fundus Photography (colour retinography) was the recommended screening method, due to its high sensitivity and specificity (92 and 90% respectively), and because this method can be performed by trained para- medical personnel and later sent for ophthalmologist analyses. Annual screenings were recommended for diabetics after puberty [22]. The costs of the screening and treatment for DR are completely covered by the government. Only indirect costs, as transportation to the

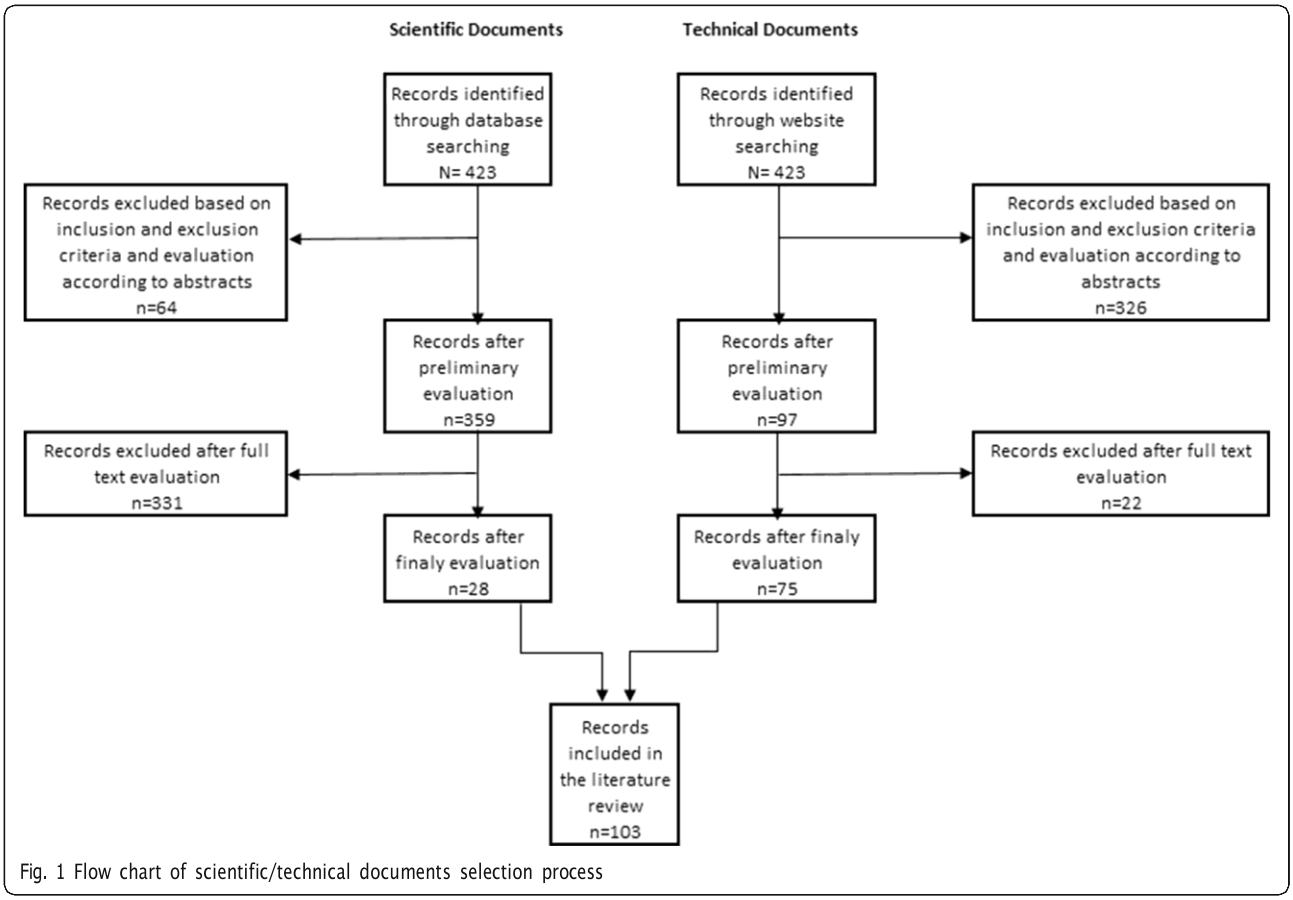

Fig. 1 Flow chart of scientific/technical documents selection process

screening or treatment facility, are supported by the diabetics [22]. Regional Health Administrations (ARS) have the responsibility of operationalise population-based screening programmes. In Portugal there are five ARS (ARS North, Central, Lisbon and Tagus Valley, Alentejo and Algarve). So, since 2001, the ARS began the implementation of screening strategies under DGS guidelines [35–39]. None the less, the guidelines were vague in what concerns to major operationalisation aspects as what services and health staff should be involved and which are their responsibilities, where the screening test should take place, who identifies and convokes the diabetic populations, etc. Therefore, the strategies adopted by each ARS are significantly different [35–39]. Regarding positive cases, all the ARS mention referral for a hospital ophthalmology consultation, where a diagnosis is made and a treatment plan appropriate to the stage of the disease is established. However, despite the treatment being guaranteed, there were no guidelines for its standardisation at national level. The definition of a

Table 1 Quality Criteria Items

ID	Quality Criteria
PQ02	Are the details of the screening protocol well described?
PQ03	Are the sources reliable?
PQ04	Is the methodology used rigorous and replicable?
PQ03	The geographical area covered and the institution responsible for the screening are well identified?
PQ04	Are the indicators used to measure screening results well described?
PQ05	Does it identify the problems that affect the implementation of population-based screening programs?
PQ06	Does it identify the constraints that affect the implementation of population-based screening programs?
PQ07	Does it identify solutions and best practices from national or international experiences concerning population-based DR screening?
PQ08	Does it objectively describe the evolution of DR screening over a considerably large period?

positive case itself, that is, requiring referral for ophthalmology consultation, was not uniform in all regions [35–39].

In 2018, DGS issued new and more detailed, guidelines for the organisation of regional screening programmes [40], proposing a flow chart for the screening process (Fig. 2).

DR Grading and the definition of Positive and Negative, were also clarified and normalised, trough the referral guidelines summarised in Table 2 [40].

Table 3 summarises the DGS recommended procedures and treatments for the different stages of DR [40].

Regional DR screening protocols

At the North Regional Health Administration (ARSN), the DR Screening Programme began in 2009, and has been gradually implemented in the following years. In 2009, ARSN, developed exhaustive proceedings, documentation, and protocols, which have been subsequently expanded and adjusted [39]. In this region, retinographies are performed in Primary Health Centres. However, there are no fixed retinographers in health facilities. The equipment remains in mobile units, moving from health centre to health centre, according to prior established schedule [39]. Primary Health Centres are responsible for identifying and convening the diabetic population and retinographies are performed by orthoptics technicians. However, there are no orthoptics technicians dedicated solely to the screening programme. Those professionals are provided by local hospitals, and usually accumulate the functions inherent to the screening programme, with the functions they perform regularly in the hospitals. After the retinographies are performed they are analysed and graded by ophthalmologists [39]. ARSN is conducting a research aiming the introduction of automatic image reading software in DR screening programme, however, this technology is still experimental [42]. After the grading, positive cases are referred to the hospital for treatment. Since the beginning of the screening programme, ARSN uses the International Clinical Classification System, which categorises DR severity in 5 levels, including 3 stages of low risk: none, mild, and moderate NPDR, a fourth stage of severe NPDR, and a fifth stage of PDR, in the presence or absence of DME, which is graded separately (as recommended by the 2018 DGS guidelines – Table 1) [39, 40]. The ARSN uses a specific software to support the screening programme (SIIMAScreenings) [23].

At the Portuguese Central Region Health Administration (ARSC), the DR Screening Programme is running since 2001 [37]. As in the North Region, the screening method and the target population follow the 1998 DGS guidelines [37]. Until 2011, the screening protocol was similar to the one implemented at ARSN. However, in that year, was introduced the use of an automatic image reading software (RetmarkerSR) in conjunction with the traditional human analysis and grading. This software allows the detection of RD lesions such as DME and small haemorrhages in retinal photographs, through a method based on image processing algorithms [37]. Two of the selected papers focus on the performance of this particular software revealing a sensitivity of 99.76% and a specificity of 99.49% [43, 44]. The grading scale used in ARS Centro, is different from the 2018 DGS guidelines. The scale includes 5 different classification levels: NC – not classifiable; R0 – no DR lesions; RL - NPDR without maculopathy; M - maculopathy; and RP - PDR. In ARS Centro, referable diabetic retinopathy, was defined for all patients graded as NPDR, PDR, or M [43]. Another particularity of ARSC Screening is that there is no software application to support the screening programme. The data are requested by the ARSC to each of the Primary Health Centre Clusters (ACES) and compiled into Excel sheets [37].

Lisbon and Tagus Valley Regional Health Administration (ARSLVT) and the Association for the Protection of Diabetics of Portugal (APDP) signed a cooperation protocol in 2009, for DR screening [38]. It was the beginning of Diabetic Retinopathy Screening Service for Lisbon and Tagus Valley (RETINODIAB), commissioned and driven by APDP and supported by ARSLVT. The RETINODIAB follows the 1998 DGS norms in terms of screening test and target population [45]. In 2016, the ARSLVT implemented their own pilot screening in four ACES. Accordingly, with this established protocol, the retinographies are performed by orthoptists, in the ACES, and automatically analysed and graded by a software - “Retmarker”. When classified by the software as “necessary human reading”, they are sent for ophthalmologists’ analysis. The results of these readings are made available to the family doctor by means of a computerised screening platform. As in ARSN, the DR grading scale used is according to the 2018 DGS guidelines [45]. Positive (except Mild NPDR) and inconclusive cases are referenced to hospital ophthalmology services [38]. Nowadays, ARSLVT, extended this new screening programme, and APDP, RETINODIAB, is still a complementary response, continuing to cover 7 of the 15 ACES [38]. In ARSLVT, the screening programme is computer-supported by SIIMAScreenings in 4 ACES and by the APDP system in 7 [38]. An internal recruitment process for orthoptists for Primary Health Care has begun in 2017 [38].

At Alentejo Regional Health Administration (ARS Alentejo), there is no standardised screening strategy. In fact, there are three different screenings. The DR screening managed by ARS Alentejo, which began in 2011 and follows the 1998 DGS guidelines in terms of method and

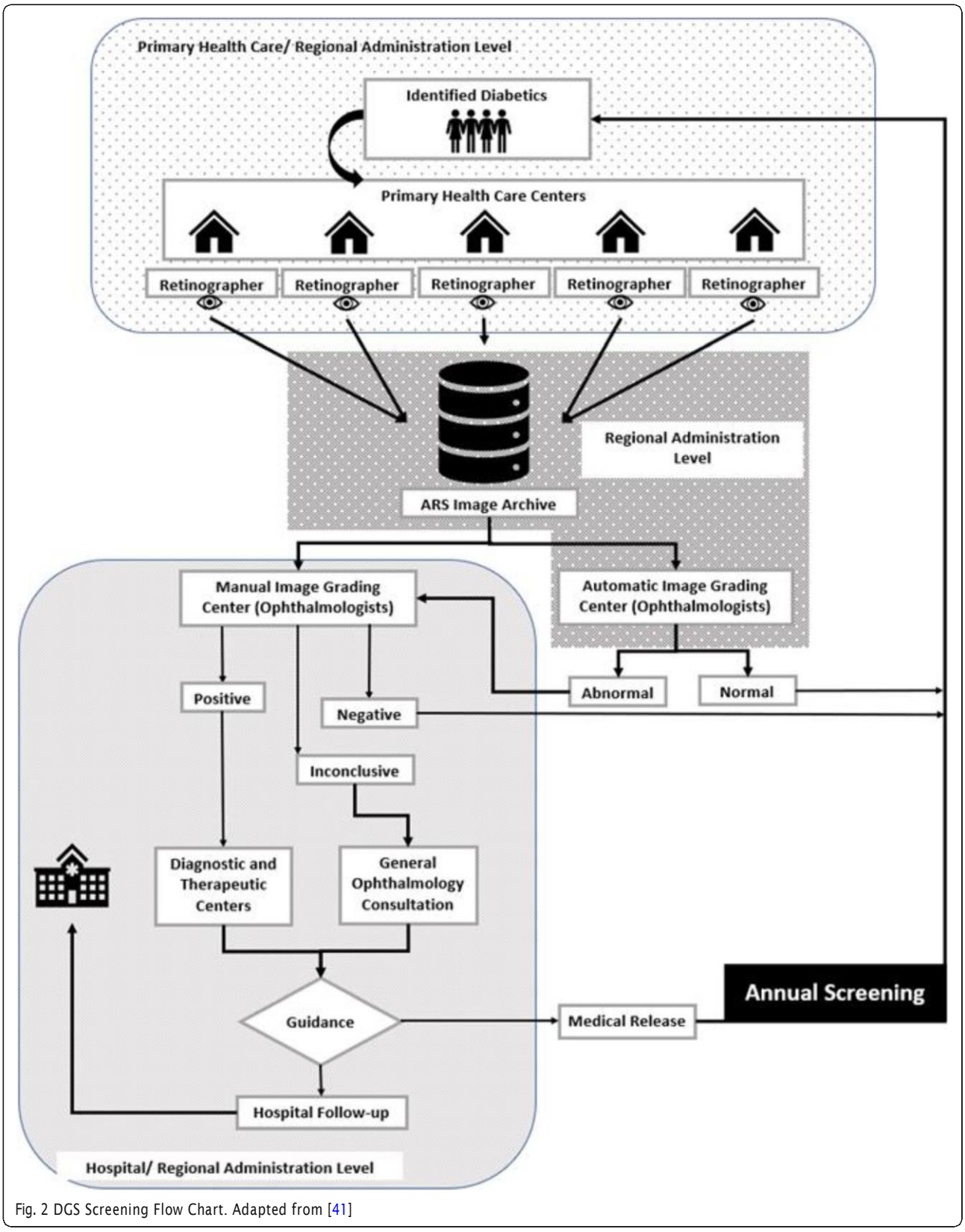

Fig. 2 DGS Screening Flow Chart. Adapted from [41]

Table 2 DGS 2018 referral guidelines. Adapted from [40]

Diabetic retinopathy screening result		Referral
R0	No disease visible	Repeats screening after a year
R1	Mild No Proliferative DR (NPDR)	Repeats screening after a year
R2	Moderate NPDR	CDTI 1, 2, 3 RD ophthalmologic consultation in a two-month period
R3	Severe NPDR	CDTI 2, 3 RD ophthalmologic consultation in 1 month period
	Proliferative DR (PDR)	
M1	Diabetic Macular Edema (DME)	
V1	Hight risk PDR, vitreous haemorrhage, or tractional retinal detachment	CDTI 3 RD ophthalmologic consultation in a 15-day period
ICN	Inconclusive or comorbidities	General ophthalmology consultation
Treatment follow-uo		
P0	Stable LASER	Repeats after a year
P1	Insufficient LASER	CDTI 1 (Thermic LASER)

target population, is implemented in one ACES. The retinographies are performed by orthoptic technicians provided by hospitals and uses SIIMAScreenings as screening computer-system [35]. In a second ACES, family doctors refer patients with diabetes to perform the retinography in the hospital, so the data related to this ACES are not introduced in the screening platform. And, in a third area the screening is carried out in partnership with APDP [35].

In March 2013, the Algarve Regional Health Administration (ARS Algarve) began the implementation of a population-based screening for all diabetics in the region [36].

The screening test is performed by the two Hospitals in Algarve, in the ophthalmology departments. The articulation between ARS Algarve and the hospitals is performed through protocols and annual contracting. Screening monitoring is computer-supported [36].

During the year 2014, hospitals were reticent about the renewal of the screening protocol due to the reduce installed capacity. So, ARS Algarve proposed to limit the screening, in this period, to the "new cases" diagnosed during 2013 and 2014 what was accomplished by the end of the year [36]. In 2015 and 2016, the screening was resumed in a normal way. However, in 2017 and 2018, the screening did not take place. In that year's activities report, ARS Algarve claims that, although the normal procedures for the renewal of the programme were carried out, there was any hospital response and that, despite having taken countless efforts to develop a screening programme less dependent on hospital capacity (similar to those existing in the North, Centre and part of Lisbon and Vale do Tejo), this was not possible due to numerous procedural constraints [36].

The analysis of the technical documentation of the five ARS, showed that there are considerable differences between the implemented screening programmes (Table 4) [35–39]:

- The screening location varies according to the region: in ARSN and ARSC there are portable retinographers which, in turn, are allocated to the Primary Health Centres of the region [37, 39]; at ARSLVT there are fixed retinographers in Primary Health Care units [38], and in ARS Algarve all screening phases are performed by hospital ophthalmology services.

Table 3 DGS 2018 treatment guidelines. Adapted from [40]

Diabetic retinopathy stage	Procedure and treatment
No disease visible or Mild NPDR	DR screening
NPDR moderate or severe	DR ophthalmologic consultation Optical coherence tomography (OCT)
NPDR with DME focal or multifocal or PDR without DME	Fluorescein angiography (FA) and OCT Laser therapy
PDR with MDE Diffuse DME	FA + OCT Combined DR therapy: Laser + Intravitreal injection of anti-vascular endothelial growth and/or long-acting corticosteroids
Advanced PDR with: - Vitreous or sub hyaloid haemorrhage - Retinal detachment - Neovascular glaucoma - Chronic DME with no response to treatment or refractory	DR chirurgic therapy: vitrectomy Combined DR therapy: FA + OCT + Laser + Intravitreal injection of anti-vascular endothelial growth and/or long-acting corticosteroids Corticosteroids extended-release injectable devices

Table 4 Screening Protocol

	North	Central	LVT	Alentejo	Algarve
Screening method - colour fundus photography	Yes	Yes	Yes	Yes	Yes
Electronic transfer of images	Yes	Yes	Yes	Yes	Yes
Retinografers location	Portable	Portable s	Non-portable - ACES	U	Hospital
Pupil dilatation	No	No	No	No	No
Calls to the target population through postal invitations	Yes	Yes	Yes	Yes	Yes
Who performs the photography	Orthoptic technicians provided by hospitals	Orthoptic technicians provided by hospitals	Primary Health Centres orthoptists	U	Hospital Orthoptic technicians
Software for automatic readings	No	Yes	Yes	No	No
Camara Device	Non-mydriatic camera, CR-2 Digital Retinal Camera (Canon)	Nonmydriatic cameras – Canon CR6-45NM with a Sony DXC-950P 3CCD colour video camera	Non-mydriatic camera, CR-2 Digital Retinal Camera (Canon)	U	U
Screening test procedure	Retinography of both retinal fields, both with 45° field, one focusing on the macula and the other on the optic nerve	Retinography of both retinal fields, both with 45° field, one focusing on the macula and the other on the optic nerve. When impossible to obtain an image with minimum quality is performed an iatrogenic pupil dilation with a topical mydriatic.	Retinography of both retinal fields, both with 45° field, one focusing on the macula and the other on the optic nerve	U	U

U Unavailable

- If, in some ARS, retinographies are performed by hospital orthoptic technicians, which accumulate the functions in the hospital with the DR screening [39], other (ARSLVT) are hiring optometrists for primary health care units [38]. Although this solution seems simple and effective on eliminating the dependence of available hospital technicians, it is not easy to implement, mostly due to the lack of consensus on the competence of optometrists to perform retinographies. In fact, there are substantial differences in the training of the two types of professionals: orthoptic technicians are qualified to detect vision abnormalities and ocular motility disorders. Therefore, the orthoptic technician is active in diagnosis, therapy, and rehabilitation; on the other hand, optometrists are the professionals that, through examination of the eye, diagnoses refractive errors and prescribes appropriate lenses and/or exercises, without the need for drug or surgical treatments [40, 46]. However, there are several countries in which the retinographies are carried out by professionals other than orthotics technicians or optometrists, for example, primary care physicians or nurses [17, 47], but in Portugal those options were never considered.
- In the ARSC and in part of the ARLVT region, artificial intelligence software is implemented for automatic retinographies grading [43–45]. Several studies state its acceptable sensitivity and specificity levels and its effectiveness to reduce ophthalmology services burden [48–50].

The new DGS directives substantiate an important attempt to guarantee quality, equity of access and standardisation of screening at national level [40]. However, the analysis of the latest activity reports of the ARS (2018), clearly shows that, so far, the new guidelines have not produced many effects at the regional level. Thus, while some ARS established procedures perfectly framed with the guidelines now issued, there are others, in which the so-called population-based screening programmes fall far short of the requirements that the denomination, and the current national guidelines, require [35–39].

Main indicators and screening results

The analysis of the official reports of the Portuguese institutions directly involved in the implementation of the DR screenings allowed to determine a set of common

indicators, used to monitor the process and the results of the screening programmes.

However, the number of available indicators is very small, reflecting only the concern with the coverage of the screening [35–39]. No indicators inherent to the quality of the process were found in any of the five ARS. In rare cases, references to the evolution of the number of positive DR cases were found, which, however, were discarded due to important inconsistencies in the concept of "positive case" itself. Still, it was found that most ARS collect and report the following indicators [35–39]:

$$\text{Geographic coverage} = \frac{\text{Number of ACES on the programme}}{\text{Total ACES of the Region}}$$

$$\text{Adherence rate} = \frac{\text{Number of retinographies}}{\text{Number of invitations}}$$

$$\text{Population coverge} = \frac{\text{Number of invitations}}{\text{Number of identified diabetics}}$$

$$\text{Screened population} = \frac{\text{Number of retinographies}}{\text{Number of identified diabetics}}$$

As previously mentioned, generally, the indicators are calculated by the ARS, although the data are obtained directly through an operating system dedicated to screening, or indirectly, through requests to the primary health units, or associations involved (APDP, hospitals) Of course, when the second case occurs, less reliability of the data is expected, since it is common for different entities to follow different criteria for extracting and pre-processing the information.

But, in addition to this issue, there are other inconsistencies in the calculation of the indicators [35–39]:

1- First, as we have seen, there are several ARSs (part of ARS LVT, ARS Alentejo and ARS Algarve) where screening is still conducted, in whole or in part, by other institutions, leaving the question of whether it is truly a population-based screening. Normally, the ACES where this happens are counted as being covered by a screening programme, but, at the risk of, in some cases, pro- viding only an opportunistic screening to registered diabetics. This inconsistence will affect the "Geo- graphic Coverage" indicator.

2- The variable "number of identified diabetics" is also likely to introduce some bias in the analysis of the results. In reality, not all identified diabetics are convolved into screening. According to the DGS guidelines, family doctors should remove from the list the subjects who are unable to remain seated, those who underwent a retinography less than a year ago and those who are blind. Thus, it is important to distinguish whether the ARS account for the initial number of identified diabetics, or that obtained after the purging of the initial listings. The "Population coverage" and "Screened population" indicators could be affected by these decisions.

3- The variable "Number of invitations" is also not easy to measure. In fact, so far, none of the ARS has managed to strictly comply with the 12-month interval between screenings. Therefore, at the time of the change of civil year, there are several locations with the annual screening still in progress.
Thus, these questions arise: is it effective only to consider invitation letters in places where the screening has already been completed? All invitation letters sent should be considered, even if, in some cases diabetics have not yet had the opportunity to adhere to the screening, simply because, the screening was scheduled for a date later than the present moment? The assumptions in each case are not clear and may condition the comparison of adherence rates between ARS. The "Population coverage" and the "Adherence rate" are affected by this bias.

Despite the constraints mentioned previously, the following Tables 5, 6, and 7 show the available indicators, in each of the five ARS. Due to the scarcity of information in some of the ARS, it was decided to present the results only for 2015 and 2017 (years in which more comprehensive information was obtained) [39]. The variable "Number of retinographs performed" was the only one that allowed an evolutionary analysis, which is presented in Table 7 [35–39].

Despite several setbacks in all regions, the number of screenings has been increasing since 2009. In 2015, a total of 113,443 retinographies were taken, 19% more than in the same period of 2014 (Table 7). However, access to diabetic retinopathy screening is still remarkably variable in Portugal and needs urgent attention. Population coverage, in 2017 varies from 0% in ARS Algarve to 100% in ARSLVT (Table 6) [35–39].

Discussion

Retinopathy screening involves several interfaces where communication can be problematic (family doctor, patients, optometrists, regional screening teams, hospitals, ophthalmologists) [20, 21, 51, 52]. A major effort is necessary to understand and coordinate this complex system with dynamic interactions of different agents (stakeholders, providers, professionals, and individuals), and where change in any one element can alter the con- text for all other elements [20]. So, national guidelines should precise the role of the different intervenient, and politic measures should be created to guarantee the involvement of all parts.

Table 5 2015 Results

	North	Central	LVT	Alentejo	Algarve	Total
ACES on the programme (a)	17	8	11	4	2	42
Total ACES (b)	24	8	15	4	3	54
Geographic coverage (a)/(b)	70.8%	100.0%	73.3%	100.0%	66.7%	77.8%
Identified diabetics (c)	277,706	142,008	183,958	47,221	U	674,537
Number of invitations (d)	75,767	U	57,049	3501	23,404	159,721
Number of retinographies (e)	45,119	19,792	35,602	3477	16,491	120,481
Percentage of ungradable images	3,2%	3,5%	3,7%	U	U	U
Adherence rate = (e)/(d)	59.5%	U	62.4%	99.3%	70.5%	75.4%
Population coverage = (d)/ (c)	27.3%	U	31,0%	7,4%	U	23.7%
Screened population = (e)/ (c)	16.2%	13.9%	19.4%	7.4%	U	17.9%

U Unavailable

According to official documents, another of the major problems for the sustainability of Portuguese screening programmes is the lack of orthoptic technicians in the SNS. ARS where retinographies are performed by hospital orthoptic technicians, which accumulate the functions in the hospital with the DR screening, are dealing with permanent difficulties to ensure the full coverage of the programme [37, 39]. In fact, this situation led to interruption of screenings in sites that had already started and can represent a major sustainability problem [39]. In addition, some ARS reported difficulties in ensuring the first hospital visit within 30 days of the diagnosis of DR [39].

To truly understand these problems is important to know the hospitals point of view. Opportunely, one of the selected studies took place at the Hospital Centre of Oporto (CHP), and provides the perspective of this hospital ophthalmology services [31]. The CHP is the reference hospital for 2 ARSN's ACES, which together represent about 293,900 inhabitants and 24,902 diabetics (data for 2016) [31]. An important finding that emerges from this research is that the screening programme is referencing to ophthalmologic consultation, patients who are already being followed in hospital services. ARSN screening protocol recommends the exclusion of these cases from the call lists [23], however, hospitals and primary health care computer systems are not fully integrated, and family physicians do not always have access to information to identify those situations. During the period under review, 56% of referrals were cancelled due to this reason [31]. The same study also refers to the overloading of ophthalmology services with the dispensing of orthoptic technicians for screening. The authors conclude that, the screening programme relevance and advantage to public health is evident. However, they highlight that at a time when involvement in the programme represents an increased effort for ophthalmology services, it is important to optimise all steps of the process [31].

Hire orthoptic technicians exclusively for the screening programme could lighten the effort of hospital services, however, for that to happened, it is necessary to ensure an increased number of university positions in courses for orthoptic technicians [38]. On the other hand, optometrists claim for a more relevant role in DR screening planning and implementation [46]. In this context, ARS LTV is already hiring optometrists for primary health care units [38]. In England, this solution is implemented in a broader way. There are some regions where retinographies are carried out at high-street optometrists with cooperation protocols [17, 30, 47]. However, studies show that, in some of those areas, there are problems with access due to long waiting lists. So, uptake rates have not been found to be higher for those accessing screening services via high-street optometrists, despite this modality of screening being thought to offer in- creased proximity to the patients and appointment flexibility [18, 19, 29]. In Spain and in Mexico,

Table 6 2017 Results

	North	Central	LVT	Alentejo	Algarve
Geographic coverage 2017	75%	63%	100%	50%	0%
Adherence rate 2017	60%	U	52%	91%	NA
Screened population 2017	35%	9%	29%	6%	0

U Unavailable, *NA* Not Applied

Table 7 Evolution of the number of retinographies

ARS	2009	2010	2011	2012	2013	2014	2015	2016	2017
North	791	8839	39,006	49,354	57,385	47,454	45,121	68,309	105,462
Central	14,760	15,271	15,258	18,496	11,856	13,235	19,792	U	U
LTV	3131	13,867	23,221	24,819	28,272	25,853	28,562	35,602	74,744
Alentejo	U	2761	2872	2512	1668	7573	3477	7144	2799
Algarve	10,907	9395	13,580	7937	16,103	1420	14,491	U	0

U Unavailable

retinographies and the first interpretation of the test are performed by family nurses or physicians. Then, there is a second valuation by the ophthalmologist, who knows the previous diagnosis and sends his opinion to primary care [17].

Computer systems are also important in the screening process: maintaining and sharing disease registers across different agents, management of patient records; automatic call/recall routines, electronic image transfer, and programme monitoring, are some aspects where new technologies have a critic role [16, 47].

The other major problem reported by CHP is the high burden that image grading and treatment of positive cases represents for hospitals ophthalmology services [31, 51]. Portugal may have about 1 million people with diabetes, of whom 700,000 diagnosed and on medical treatment and who should be consulted annually according to the DGS criteria. According to the Portuguese Ophthalmology Society, each of the 988 Portuguese ophthalmologists (2014 data) would have to observe about 708/each year, an infeasible number in terms of logistics specialty requirements. Moreover, only 422 of the 988 Portuguese ophthalmologists works in the SNS [53]. Automated grading software can decrease the cost of screening and reduce the amount of work for retinal grading ophthalmologists [8, 19, 28, 52]. Studies suggest it has an acceptable level of accuracy [19, 43, 44, 48, 49], and, besides the two Portuguese regions (ARSC and ARSLVT), it is already implemented throughout Scotland, in parts of Spain, Denmark and Hungary [16, 47, 50].

Mobile units using non-mydriatic cameras, may have an important role in increasing rates of screening attendance [47], another of the constrains mentioned by ARS.

In most ARS it has not been possible to have an annual frequency of generalised screening [51]. The implementation of screening programmes with extended intervals (more than 12 months between tests) may, in fact, be an option to free up resources and provide better care, but there are some concerns around this subject [20]. Actually, there are three determining factors when considering the use of extended screening intervals: the control of the diabetes, the sensitivity of the screening test and the adherence rate [20]. If the first two are objective and easy to quantify, the third factor may have more complex implications. Even if the rate of adherence of a certain population is high, it is possible that by increasing the interval between screenings, the message that the test is not important is being involuntarily transmitted, which can in the medium-term lead to a decrease of population adherence and consequently making the use of extended intervals a risky option [20]. Currently in Europe, the implementation of screening programmes with intervals of more than 1 year between calls is already quite frequent. However, some countries have adopted this measure in conjunction with the in- creased frequency of screening for diabetics identified as high risk (usually with calls every 6 months) [11, 47, 50]. On the other hand, the results of these options are not completely consistent. In Denmark and Finland there are no reports of problems associated with the increase of screening intervals, while in Sweden, the adherence rate has dropped significantly after the adoption of this measure (although the cause-and-effect relationship has not been fully proven) [47].

The actual practice in other countries shows that the medium and long-term effect of rigorous screening implementation is effective [21, 47]. The United Kingdom began in the 1960s to screen diabetic retinopathy nationally and transversally [24]. It is concluded that in the 2009–10 biennium, for the first time, diabetic retinopathy was not the first cause for the attestation of incapacity for visual blindness of working age in England and Wales, 40 years after the implementation of the screening [24, 47]. Therefore, it is not expected that the implementation of public policies on diabetes and diabetic retinopathy lead to visible results in 3 or 4 years, but those results should appear in the medium and long term [21].

Conclusions

This study allowed the analysis of the diabetic retinopathy screenings implemented in mainland Portugal. There was some difficulty in collecting uniform data since there are different degrees of implementation, methodologies, and monitoring in the five ARS. However, this analysis allows to assess the differences, detect constraints, and identify possible solutions and improvements.

The main conclusion is that access to diabetic retinopathy screening remains remarkably variable in Portugal and needs urgent attention. Due to its importance DR screening should be a public health priority, and governments should ensure adequate funding to population- based programmes. National guidelines should also precise the role of the different intervenient, and politic measures should be created to guarantee the involvement of all parts.

Even though characteristics of effective screening programmes (adequate sensitivity and specificity, a convenient method for the patient, proximity strategies) were found in Portuguese screening programmes, which could be pointing towards promising outcomes, we notice lots of room for improvement. With a continued effort, hopefully, in a few years there will be a national, standardised, population-based, DR screening programme.

The findings of this research could be very useful for other Countries with similar socio-political characteristics.

Abbreviations
ACES: Primary Health Centre Clusters; APDP: Association for the Protection of Diabetics of Portugal; ARS: Regional Health Administrations; ARS Alentejo: Alentejo Regional Health Administration; ARS Algarve: Algarve Regional Health Administration; ARSC: Central Region Health Administration; ARSLVT: Lisbon and Tagus Valley Regional Health Administration; ARSN: North Regional Health Administration; CHP: Hospital Centre of Oporto; DGS: Portuguese General Health Department; DM: Diabetes Mellitus; DR: Diabetic Retinopathy; PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analysis; SNS: National Health System; RETINODIAB: Diabetic Retinopathy Screening Service for Lisbon and Tagus Valley

Supplementary Information

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Additional file 1. PRISMA 2009 Checklist.

Additional file 2. Overview of the Portuguese governmental and non-governmental health organizations, with a relevant role on DR Screening.

Additional file 3. Quality assessment of the selected scientific papers.

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Authors' contributions
AP, RL and FN author conceived the design of the study. AP and RL led the review of abstracts, titles, and full texts, with support from FN for data abstraction. AP led the drafting of the manuscript, with all authors contributing to review, feedback, and collective decision-making. The author(s) read and approved the final manuscript.

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Availability of data and materials
Abstracted data collected and analysed during this study and described in this systematic review will be available from the corresponding author upon request.

Declarations

Ethics approval and consent to participate
This systematic review was conducted using published data, and study authors were contacted for additional contextual information, thus, the need for written ethics approval and consent to participate is not applicable.

Consent for publication
Not applicable.

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

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Publisher's Note

3.2. Simulation Models in Diabetic Retinopathy Screening: A Systematic Review

3.2.1. Context and summary

The present study [19] promotes the systematic assemblage of knowledge about simulation models for DR screening of the general population until 2023.

In total, 326 papers were retrieved from Web of Sciences and PubMed databases and, after exclusions, 21 papers were accepted and fully reviewed. A framework for qualitative assessment, which incorporated input parameters; modelling approach, transparency of input data sources/assumptions, sensitivity analyses, validation, and outcomes was developed. This, and the conclusions put forward are deemed to be valuable for providing insights and directions for future modelling problems that need not only quantitative assessment.

A high scientific and rigorousness methodology, using PRISMA [63] was applied.

This systematic review allowed the identification of two important gaps in the literature: the lack of simulation models focused on screening adherence; the lack of simulation models that relay on techniques suitable to the study of the complexity inherent to population-based DR screening.

The obtained findings have the potential to support the development of future DR screening computational simulations.

3.2.2. Paper author's copy

Simulation Models in Diabetic Retinopathy Screening: A Systematic Review

Andreia Marisa Penso Pereira, Raul Manuel da Silva Laureano and Fernando Buarque de Lima Neto

Abstract

Main objectives: The present article is a systematic review of all published simulation models for diabetic retinopathy screening of the general population until 2023. This study intends to answer the following research question: How computational simulation techniques tackle population-based retinopathy screenings? More specifically in this paper seven key questions are addressed, namely: (i) Do the studies describe how computational simulation techniques are useful to support the retinopathy population-based screenings? (ii) What modelling techniques should be considered? (iii) What are the strengths of each modelling technique? (iv) What are their weaknesses? (v) What are the threats that can negatively affect the outcomes using the different modelling techniques? (vi) What are the opportunities of each modelling technique? (vii) How are the simulation outputs evaluated?

Methods: The present systematic review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) Checklist. The search was conducted in September 2023 aiming all publications, in PubMed and Web of Science. In total, 326 articles were retrieved, and after exclusions 21 articles were accepted and fully reviewed. A framework for qualitative assessment, which incorporated input parameters; modelling approach, transparency of input data sources/assumptions, sensitivity analyses, validation, and outcomes was developed.

Results: This systematic review allowed the identification of two important gaps in the literature: despite the recognized importance of adherence to screening, simulation models tend to neglect this issue; most of the analyzed models are based on Markov processes or Discrete Event Simulation techniques, what led to important limitations. Agent-based models can be an interesting alternative, however more research is needed to understand whether they can significantly contribute to the study of the complexity inherent in a population-based diabetic retinopathy screening.

Conclusions: The framework for qualitative assessment and the conclusions put forward are deemed to be valuable for providing insights and directions for future modelling problems that need not only quantitative assessment.

Keywords: population-based screenings; diabetic retinopathy; computational simulations.

Introduction

Diabetic eye disease is one of the major causes of blindness around the world and remains one of the most serious complications of diabetes mellitus [1]. Retinopathy is the ocular complication of diabetes that most often leads to impaired vision [1]. In recent years, laser treatment has been introduced and it has been proved its ability to significantly decrease the likelihood of blindness in diabetic patients, if applied at the appropriate stage of the disease [2] [3]. So, it remains a public health problem to decide if and how screening programs should be implemented [4].

In general, randomized control trials (RCTs) are the most valuable method for evaluating health interventions, including screening programs, prior to their broad population-based implementation [5]. However, evaluating the effect of a screening program on the population health demands a long follow-up time and large groups of participants; thus, it is considerably difficult to make an evaluation in terms of such categories as sex, age, and risk factors [5]. On the other hand, several authors argue that it would be unethical to conduct RCTs to evaluate some of the aspects of this public health problem (for example screening vs no screening) [6]. Accordingly, simulation models are often applied along with RCTs to ensure proper and ethical evaluation of the effects of screening [7]. Simulation models provide the opportunity to evaluate health interventions and compare scenarios to find the best policy without having to trial each variant [3] [4]. Simulation can extrapolate the results of RCTs to different population sub-groups and provide health technology assessment of screening interventions [4] [7].

In this context, this study intends to answer the following research question: How computational simulation techniques tackle population-based retinopathy screenings? More specifically in this paper seven key questions are addressed, namely: (i) Do the studies describe how computational simulation techniques are useful to support the retinopathy population-based screenings? (ii) What modelling techniques should be considered? (iii) What are the strengths of each modelling technique? (iv) What are their weaknesses? (v) What are the threats that can negatively affect the outcomes using the different modelling techniques? (vi) What are the opportunities of each modelling technique? (vii) How are the simulation outputs evaluated?

For the presented study, 21 scientific peer-reviewed articles were accepted and carefully analyzed, remaining after the exclusions of the 326 initially selected ones.

This work is organized as follows. The first section describes the adopted methodology and literature selection procedure. Then, in the second section, for each one of the accepted papers, a critical analysis is presented that delves in the input parameters, modelling approach,

transparency of input data sources/assumptions, sensitivity analyses, validation, and outcomes. Finally, a discussion if offered on the weakness and strengths of each simulation technique identified, the gaps on the studies of diabetic retinopathy (DR) screenings, and eventual future direction of simulation models applied to this theme.

Methodology

The present systematic review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) Checklist [8].

Information sources and search strategy

The search was conducted in September 2023 aiming all publications, in PubMed and Web of Science adhering to the keywords. The search query was *(Health screening or Medical screening or Health control or Mass screening or Population-based screening or Preventive test or Secondary prevention or Health care policy)* ***and*** *("Diabetic retinopathy" or "diabetic vision lost" or "diabetic complications")* ***and*** *(Health care modelling or Social simulation or Group behavior simulation or Group behavior simulation or Individual learning or Evolutionary learning or Social learning or Hypothetical scenarios or Computational simulation or Self-organization or Emergent behavior or Emergent behavior or Approximate Bayesian computation or Bayesian simulation or Microsimulation or Discrete Event or Differential Equations or ABM or Agent Based Model or ABSS or Multi-agent simulation or Continuous Time Model or Discrete Time Model or Deterministic Models or Probabilistic Models or Dynamic Models or Trace-Driven Simulation or Event-Set Algorithms).*
These keywords were taken from other reviews in DR screening and simulation and were refined to be more focused to the field of interest.

Eligibility criteria

Were included studies published in pear review journals, referring to simulation models applied to diabetic retinopathy screening programs. Were exclude conference papers, papers focused on interventions, clinical rehearsals, studies that were not simulation studies, statistical studies, works that are not fully available, duplicate work and research with methodological deficiencies.

Three hundred and twenty-six articles were retrieved from Web of Sciences and PubMed databases. A preliminary review process was applied according to the following steps: (1) exclusion of articles that are not fully available and duplicate work (102); (2) evaluation of scientific articles according to abstracts excluding those that didn't addressed DR screening (76), didn't used simulation techniques (116), focused-on interventions, clinical rehearsals and research with methodological deficiencies (13). This preliminary evaluation resulted on the exclusion of two hundred and five articles. Finally, two papers were added based on references, and the twenty-one selected papers were submitted to a critical full document evaluation. Figure 1 illustrates the selection process.

Articles and Documents analyses procedure

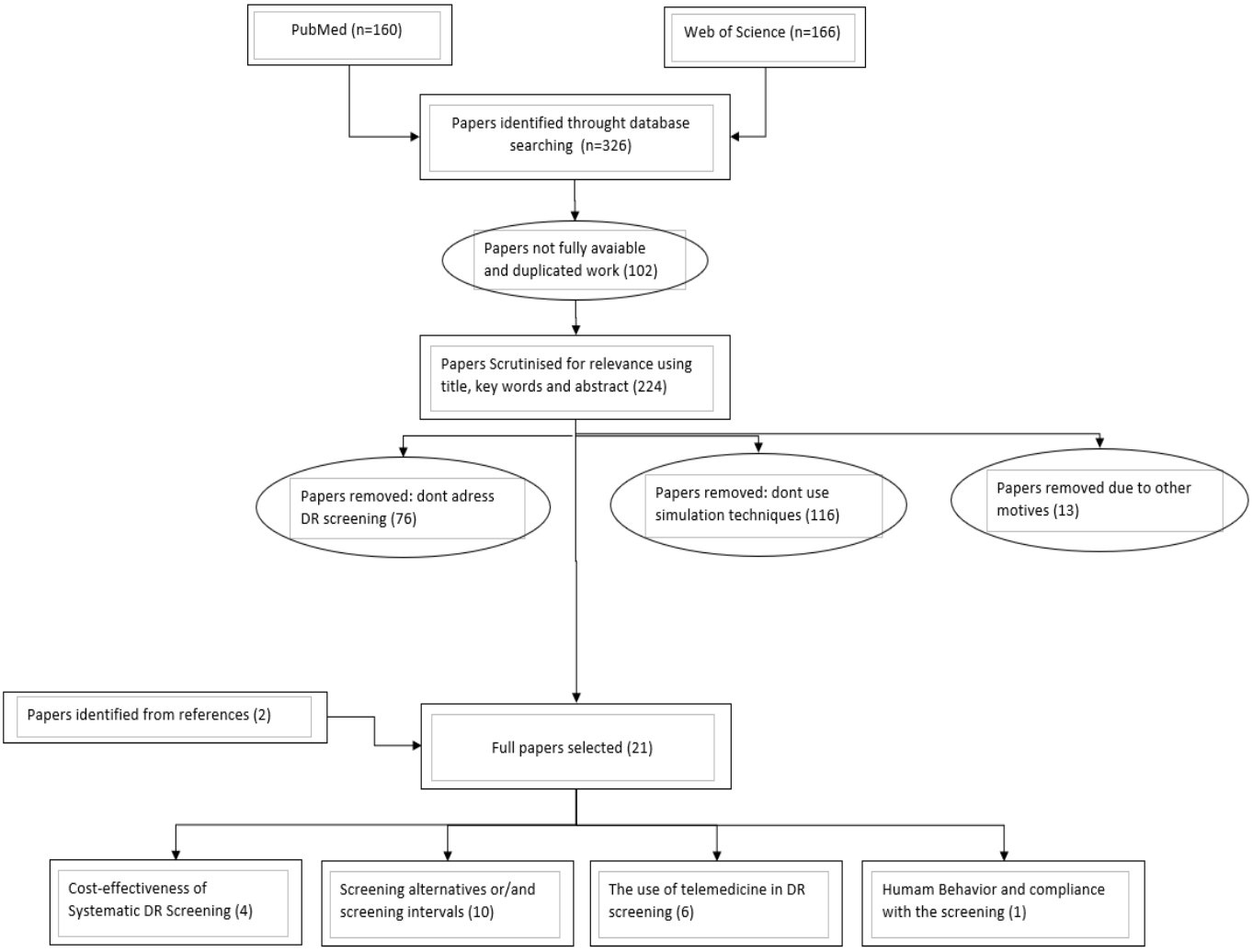
To facilitate the analysis, papers were classified in one of four categories according to their main objective: (i) cost-effectiveness of systematic DR screening, (ii) screening alternatives or/and screening intervals, (iii) the use of telemedicine in DR screening, and (iv) human behavior and compliance with the screening. The papers classification was carried by at least two of the three authors of this systematic review. A third qualified researcher was called to break the tie, whenever there was no agreement between the first two.

Additionally, to access the quality of the scientific articles eight quality items were considered (Table 1) and graded according with the following rule: YES(Y)=1; NO(N)=0; PARTIALLY(P)=0.5. The marking of the selected papers in each of the quality criteria is available in Appendix 1.

ID	QUALITY CRITERIA
PQ01	In what aspects of the screening are the simulation models useful?
PQ02	What modelling techniques are used?
PQ03	How is the modelling achieve?
PQ04	How is the simulation performed?
PQ05	Are the advantages of the modelling technique well described?
PQ06	Are the weaknesses of the modelling technique well described?
PQ07	Does it identify problems or threats in the development and implementation of such models?
PQ08	Does it explore new research opportunities and discusses the effects of their application?
PQ09	Is the model properly calibrated with real data?
PQ10	Is the model properly validated?
PQ11	Are the indicators used to evaluate the simulation results, well described?

Table 1 – Quality Criteria Items

Figure 1– Flow chart of scientific/technical documents selection process



Results

Of the twenty-one selected articles, four correspond to population-based screening cost-efficiency studies, compared to the lack of screening and /or opportunistic screening, ten compared the outcomes of the implementation of different screening strategies or intervals, six focus on the evaluation of the use of telemedicine and one tackle the incorporation of human behavior models into DR screening simulations.

Cost-effectiveness of Systematic DR Screening

Javitt et al. were the precursors of the simulation of DR screenings and are still cited today by most of the research works that involve this theme. In the early 1990s, the authors developed a computational model that simulates a cohort of individuals and their evolution over a set of state transitions based on some underlying risk factors, such as age, duration of diabetes, level

of retinopathy and the existence or not of previous treatment of the disease. (PROPHET-Prospective Population Health Event Tabulation) [1]. The program incorporates data from population-based epidemiological studies and clinical trials. The authors recognize the need to model each diabetic individually, using Monte Carlo's simulation for the effect, which allows the incorporation of risk factors that evolve over time. The progression of the disease is simulated using a combination of Markov processes and decision trees [1]. A sensitivity analysis was performed to assess the effect of the variation on screening costs and the sensitivity of the screening test. The simulation allowed to conclude that screening for DR and the appropriate treatment can significantly reduce blindness related to diabetes. Screening and treatment are effective and cost-effective [1]. However, this research presents some limitations: the transition between states does not occur independently of the screening; the model includes only a very limited set of risk factors, neglecting important aspects as glycemic control (HbA1c), adherence rate and social demographic factors.

Craig et al. [9] also propose a Markov model to access the costs and benefits of DR screening. The natural history of the disease is described by transitions among five severity states, assuming that DR is a semi-progressive disease, with regression possible between the first three states. In this model transitions probabilities from state to state can vary across time and subject, through a set of logistic curves that established a relationship between the transition probability and the duration of the diabetes. Although the model only incorporates the duration of the diabetes as a risk factor that affects the disease progression, the authors claim that other variables, like glycosylated hemoglobin level could be easily included. Factors as adherence rate and social-demographic factors were not addressed [9].The model allows an assessment of the sensitivity of the results to each specific parameter, as well as the estimation of joint uncertainty, considering all model parameters [9].

Palmer et al. [3] developed a computer simulation model, based on Markov techniques, to compare the cost-effectiveness of different treatment strategies for seven complications of diabetes (including diabetic retinopathy). The sub-model regarding DR presents 5 Markov states, corresponding to 4 stages of disease progression and 1 corresponding to mortality from non-specific causes. The model does not predict the possibility of the disease reverting to less severe stages. The rate of progression of the disease, in some states, depends on the duration of diabetes and the blood glucose values (HbA1c) and whether intensive insulin therapy is administered [3]. This study has the merit of highlighting the important role that glycemic control plays in the progression of diabetic retinopathy. The model predicted that, without intervention, blindness would occur in 42% of patients up to 50 years of age. By adding

intensive insulin therapy, the incidence was reduced to 7% and with the combination of intensive insulin therapy, screening and laser treatment of diabetic retinopathy, the model predicted that the incidence of blindness at age 50 would be only 2 %. The authors concluded that screening for diabetic retinopathy when combined with adequate control of diabetes is more cost-effective than just the latter [3]. However, once again, many important risk factors were neglected, the possibility of non-compliance was not considered, and the progression of the disease is not independent of the screening process. Another limitation is the lack calculation of measures of dispersion for the results. The authors recognize this limitation and present the main underlying reasons. First, the authors refer to the difficulty of defining costs and probabilities distributions based on real data and consider the use of artificial distributions with little guarantee of adherence to reality, and therefore of little use. Secondly, the authors, recognize that, even if such distributions were available, their incorporation into the model, through traditional techniques such as Monte Carlo simulations, would lead to completely impractical processing times (it may take up to two years of processing to obtain the first results) [3].

More recently (2018), Vetrini et al. [10] developed a Markov model to determine the cost-effectiveness of screening and treating DR, in a low-income country with no screening implemented. A virtual cut of 1000 diabetics was distributed across six Markov states (which reflect different stages of the disease) according to epidemiological data [10]. This model predicts the possibility of the disease reverting to previous stages. Unlike Palmer and Javitt, no effort was made to model individual factors for each diabetic and how they affect the progression of the disease. Thus, variables such as age, disease duration, control of glucose levels, etc. are not considered in the calculus of transition probabilities. The main conclusions of the study are that screening is cost-efficient in terms of QALYs gained, but that this cost-effectiveness may depend on factors such as the adherence rate and the age of diabetics [10]. In fact, the authors performed the simulation of three what if scenarios, and, for each one of them a probabilistic sensitivity analysis was carried out. The variable parameters in each scenario are the age of diabetics, the income level of the personnel assigned to the screening and the utilization rate. This analysis revealed that the utilization rate has a marked impact on the cost-effectiveness of the screening because the highest costs are the fixed, remaining the same even when less screening tests and treatments are performed.

Screening alternatives or/ and Screening intervals

Marbeley et al. [11] used Monte Carlo modelling techniques to perform a comparative analysis of alternative strategies for diabetic retinopathy screening in rural and isolated areas. Thus, the authors compared the cost-utility of using retinal photographs, using portable cameras, with the alternative of regular travels of retinal specialists to remote screening sites. The effectiveness of each strategy was measured in terms of QALYs and sight years gained. Utilities for individuals with diabetes and for those with severe vision loss related with diabetic retinopathy were estimated from the literature. This research concludes that the use of retinal photographs is the most cost-effective screening strategy in rural and isolated areas, even with coverage as low as 65% [11].

Davies and its colleges used data from the UK National Health System. The four articles published by the authors are based on discrete event simulations and aim at identifying the best screening alternatives and issuing recommendations to the government. Davies' models contribute with an improvement over the previous works [1], since they allow independence between screening and the evolution of the disease. In fact, discrete event simulation is based on the concepts of entities progressing through a network of queues and activities and assume that each entity can only be in one place at the time. However, this can be a limitation in the simulation of a disease progression and screening, where the screening and treatment affects the transition between the different states of the disease. However Davies and it's colleges work around this problem by associating a list of activities and queues to each entity, thus creating the possibility that each entity is linked to an unlimited number of processes in simultaneous [12] [13]. The first model published only simulates the screening of insulin dependent diabetic patients – type 1 diabetics, using a sample of 1460 patients between ages 0 and 35 years [12] [13]. However, the model was later expanded to type two type 2 diabetics and run for a population of 500 000 [14] [15]. The authors recommended annual screenings for diabetics without DR and 6-monthy screenings for diabetics with background DR. Another important finding of these works was the important role of the population's compliance to the screening. In fact, the authors report that the probability of a diabetic complies to the screening, when convoked, significantly affects the screening results, conditioning decisions such as the screening method, the professionals responsible for the initial test (in terms of sensitivity) and the intervals between screenings. However, despite the authors recognizing the importance of this variable, their models adopt a fixed probability of adherence, and no attempt was made to

model the individual behavior of the diabetics. Diabetics individual features and state of health are not considered in these models [15].

Davies model was the base of the simulation model presented by Chalk et al. [16]. This new model builds upon Davies model [14] [15], by implementing a framework that explicitly models each patient separately, allowing a more flexible abstraction of the disease progression and screening process. The study aimed to predict the impact of screening patients with type II diabetes, who have not been diagnosed with DR, every two years rather than annually [16]. The study used data from 3,537 unique patients, and 33,810 unique screening appointments from a UK National Health Service Foundation Trust. Patient records included patient sex, type and duration of the diabetes, screening dates and last screening result. The proposed model provides the possibility of non-attendance. In these situations, the screening is rescheduled, and if the diabetic fails to appear more than 3 times, it is removed from the model [16]. The simulation predicts that screening people with type 2 diabetes, who have not yet developed DR, every two years does not increase the risk of vision loss and is cost-effective. However, the authors didn't explore the impact of nonattendance on the costs and benefits of 2-year screening intervals [16]. Vijan et al. [17] reported a cost–utility analysis of screening intervals for DR in patients with type 2 diabetes in an American population. The authors employed a Markov model using quality-adjusted life-years (QALYs) as the main outcome measure, with costs being assessed from a third-party payer perspective. An ordinal logistic regression was used to smooth the predictions of levels of eye disease based on age and glycemic control. The possibility of disease regression was not considered. One-way sensitive analyses were conducted on individual parameters to access their impact on the costs and effectiveness of the screening. The authors reported that annual retinal screening for all type 2 diabetic patients was not cost-effectiveness and concluded that tailoring recommendations to individual circumstances may be preferable [17].

A UK study by Brailsford et al. [18] also found similar results to that of Vijan et al. [17]. The study, focused on accessing the cost-effectiveness of screening intervals in diabetic patients (both types 1 and 2), concluded that a 30-month screening interval was the most cost-effective option [18]. In terms of simulation techniques, the authors propose a combined discrete event simulation and ant colony optimization model. The effects of different screening strategies are simulated and then compared in terms of two objective functions: minimum incremental cost per year of sight saved, compared with no-screening, and maximum years of sight saved [18]. Day et al. [19] propose a new approach to model a cohort of patents with DR representative of a real-world population, in which experimentation of what if scenarios can be conducted. The

authors present an Agent Based Model (ABM) supported by medical data abstracted from 535 patients' records. Each agent is imbued with a data structure describing the demography and health status of the agent. The data abstraction was accomplished through probability density functions incorporated into de model. Agents' features are updated in each simulation period. The variables included in the data structure them are used as predictors for the DR progression, through a multivariate logistic regression model that provides the probability of transition from one state of the disease to another, individually for each agent [19]. The simulations results were validated against real-world data, and there were no significative deviations in the proportion of patients in each DR stage, duration of DM, or other abstracted predictors [19]. In the continuation of this research the authors published another paper in which the described model is extended and used to simulate the effect of changes to screening interval on the incidence of vision loss [20]. The computational model integrates the previous developed ABM with a discrete event simulation model that allows the simulation of the path of a virtual cohort of diabetics in a screening and treatment clinic for diabetic retinopathy. So, the discrete event model has two fundamental aspects: eye screenings to determine the state of DR and chirurgical laser treatment of the positive cases. The two models (ABM and DES) were integrated by the creation of a rule which determines that each agent visits the DES clinic according to an exponentially distributed random variable. The results suggest that increasing the interval for diabetic patients who have not yet developed DR from 1 to 2 years is safe, while increasing the interval to 3 years increases the risk of vision loss [20].

There is, however, an important limitation with Chalk, Brailsford, Vijay and Day studies: unlike Davies that searched for solutions robust to fluctuations in the adherence to the screening, the authors did not consider the rate of population compliance. This fact may be the explanation for the different recommendations proposed by these papers [15] [16] [17] [18].

There is also other criticism that could be address to Davies [12] [13] [15], Chalk [16], Brailsford [18] and Day's [20] work. Both of the UK and USA studies used sight years saved as their main outcome measure rather than a more generalizable health outcome, such as QALYs, that can be readily compared across interventions and disease areas, aiding the decision process. In addition, the use of QALYs captures the full impact of the disease, in this case sight loss or blindness, on patients' lives.

The use of telemedicine in DR screening

Other recurrent topic of the selected articles is the used of telemedicine in DR screening. Telemedicine uses digital retinal photography to enable screening in non-ophthalmologic settings. Images are then electronically transferred to a grading center for evaluation, and, when the result is positive, patients are referred to an eye-care professional for a full evaluation. Six of the selected papers address this subject, developing simulation models to access the cost-effectiveness and economic impact of the use of this alternative screening strategy.

Aoki et al. [21] published a cost–utility analysis of diabetic retinopathy screening using teleophthalmology in a prison population using a hypothetical telemedicine system and a Markov decision model. Cost data were derived from US Medicare reimbursement fees and outcome measures for the study were cost and QALYs gained. This study recognizes telemedicine as a valuable tool for providing health care to the prison population, although 'the clinical effectiveness and economic value of telemedicine has not been clearly established' [21]. The study uses a reference case patient, a 40-year-old African American with Type 2 diabetes. The main findings of the simulation were that the teleophthalmology system is dominant, i.e. more effective and less costly, than the non-tele-ophthalmology system in the cost-effectiveness analysis for the reference case. The authors conclude that, if the number of diabetic inmates in the prison population is over 500, teleophthalmology could be a more cost-effective way of delivering diabetic retinopathy screening [21].

Another US study by Whited et al. [22] used decision analysis techniques, including Monte Carlo simulation, to model the use of a non-mydriatic digital teleophthalmology system compared with conventional clinic-based ophthalmology in the diabetic populations served by three different US federal agencies. The economic perspective of the study was that of each federal agency. Cost data for the model were taken from the published literature, administrative data, expert opinion and market prices. The outcome measure was the number of true positive cases of proliferative diabetic retinopathy detected. The findings showed the tele-ophthalmology was the dominant strategy in most of the modelled scenarios. The authors note the future potential of the tele-ophthalmology system to be more effective and less costly than clinic-based ophthalmology in detecting proliferative diabetic retinopathy [22].

In a very well conducted cost-effectiveness analyses, Rein et all [23] compare DR screening alternatives for diabetics with no or early DR accounting for imperfect compliance with screening recommendations and the ability of eye evaluation to detect other common visual disorders in people with diabetes (glaucoma, aged-related macular degeneration, etc). The

authors estimated the cost-effectiveness of four possible screening strategies: patient self-referral following visual symptoms, annual eye evaluation, biennial eye evaluation, and annual telemedicine screening in primary care settings. The disease progression was modelled through a combination of Markov and Monte Carlo simulation techniques. The model provides the possibility of the disease reverting to less severe stages, and the rate of progression depends on the duration of diabetes and the blood glucose values (HbA1c). The authors present the model validation process and a sensitivity analysis [23]. This study concludes that biennial eye evaluation was the most cost-effective treatment option when the ability to detect other eye conditions was included in the model. Telemedicine was most cost-effective when other eye conditions were not considered [23].

Kirizlar et al. [24] also explore the cost-effectiveness of telemedicine for the screening of DR. One important contribution of this study is the diversity in the population and geography compared with earlier studies. The authors use a finite horizon, time discrete, Markov model populated by parameters obtain from real patient's records. The outcome measures are QALYs and costs. The results concluded that telemedicine is cost-effective under most conditions and may increase screening rates [24].

A similar study was conducted by Nguyen et al. [25] using data from a DR screening program in Singapore. The authors developed a hybrid decision tree/ Markov model to simulate costs, effectiveness (in terms of QALYs) and incremental cost-effectiveness ratio of telemedicine based relative to family physician-based DR screening. Like in the previous studies simulation results indicate that telemedicine-based DR screening saves costs and generates similar health outcomes [25].

A very recent Brazilian Study, conducted by Ben and colleges, lead to similar conclusions [26]. The authors also used Markov states to model the progression of the disease, and model parameters were based literature and country databases. Three DR screening strategies were compared: the opportunistic ophthalmology referral-based screening; the systematic ophthalmology referral-based screening; and the systematic teleophthalmology-based screening. Individual features were not considered for the calculation of Markov transition probabilities, so all individuals in a given health state present a similar disease progression [26]. The probability sensitivity analyses show a considerable amount of uncertainty in the model's parameters [26].

Although all the selected studies main conclusions are similar [4] [21] [23] [24] [25] [26], only Rein et al. [23] considered telemedicine lowest ability to detect other common visual disorders in people with diabetes, which may be an important factor for decision makers.

Human behavior and compliance with the screening

An attempt to include human behavior in DR screening simulation models was made by Brailsford and Schmidt [27], when incorporating the HBM-Health Belief Model in a theoretical architecture that makes it possible to obtain a result (behavior - output) through the combination of several factors (inputs) that influence adherence to screening. Subsequently, the authors developed a DES, in which a population of diabetic patients is tracked over time. Each patient is an individual entity in the model, with its own characteristics. This approach was implemented through numerical attributes, to represent various characteristics of the diabetic (number of times that adhered to previous screenings, perception of their general health status, current stage of the DR, information and anxiety about the DR and educational qualifications). The probability of participation in the screening was calculated simply as a binary variable and the model uses only artificial data, defined in a plausible way, but quite arbitrary, leading to the results of this model being theoretical artefacts, which need validation with real data (Schmidt and Brailsford (2003)). Finally, this investigation also showed the difficulty of incorporating qualitative variables, such as those used by HBM, in models based on DES, thus arising the need to apply another type of simulation models [27].

Discussion

Since the early nineties, several authors have demonstrated the importance of using simulation models to support the decision regarding screening programs for diabetic retinopathy [1] [3] [9]. The cost-effectiveness of population-based screening and subsequent treatment of positive cases has been demonstrated [1] [3], however, some aspects of screening are still controversial, such as the optimal interval between screenings [13] [17] [20]. Although many authors refer to the vital importance of adherence to screening [13] [18] [20] in the programs cost-effectiveness and in the definition of screening strategies, studies that address this issue are very rare and don’t use real data [27].

One of the most important aspects in these researches are the technics used to model disease progression and the effects of the screening. Eleven of the selected papers propose the use of Markov processes, sometimes combined with other simulation techniques such as decision trees or Monte Carlo simulation [1]. Seven papers use DES [13] [18] [27] and only two of the papers tackles this problem with a different simulation technic – Agent based models [19] [20].

Markov modelling is a decision-analytic technique that allows to model a disease progression by assigning patients to a fixed number of health states and then establishing transition probabilities among health states [1]. Typically, the transition probabilities are assumed to be constant over time [1] [9]. However, it is possible to bypass this strict assumption by modelling non-homogeneous (i.e. time-dependent) Markovian stochastic processes [9]. However, Markov models are not the most suitable technique to take into consideration patient-specific sociodemographic characteristic. Some authors tried to do it by defining multiple health states, but this strategy may lead to too complex analysis [3]. So, the efficiency of such a method in complicated scenarios is questionable. For example, consider important factors like patients' attitude towards the disease, patients' income, age, qualifications, general health condition, etc, would require further splitting each state into several more states. With every additional factor, the model becomes increasingly more difficult to handle, too complex and prone to bias. As demonstrated Markov models have previously been used to model the cost-effectiveness of DR screening [1] [25]. However, we were unable to find any Markov model that simultaneously took into consideration the main predictive factors mentioned in the literature [27].These factors are of great interest to researchers and decision makers a like and, naturally, may merit a more flexible simulation method.

An alternative approach is provided by – discrete event simulation (DES). This technique was developed in operations research to model systems where entities compete for limited resources, forming queues. DES has been adapted for modelling health interventions, by redefining the events as clinically relevant occurrences and entities as patients, with individual attributes that reflect characteristics that determine their course [12] [18]. A DES can address a wide variety of problems because the event basis is much more flexible and natural than using states. However, the event representation does not require abandoning states. Entity attributes can be used to reflect the states the entity is in, allowing these to change over time [13]. The largest disadvantage of using DES for health interventions modelling is that the technique was not intended for this purpose. It was designed to model industrial systems, typically with actual physical structures, and the concepts have been developed accordingly. Its use for disease and health intervention modelling involves make the most of these tools by adapting them to different purposes, so many of its elements are superfluous (e.g. explicit resources, queues, even entities) and others are heavily modified (e.g. events are clinical occurrences rather than places where the system variables change) [68] Although the technique permits framing the model to the depth required to adequately address the health intervention problems, this may lead to a more complex structure and the need for additional controlling equations. The

increased complexity and level of detail, even if appropriate to the problem, may appear to reduce transparency and make it more difficult for reviewers to grasp the model and verify that it is a reasonable representation and correctly implemented [68]. DES has been found to be difficult to implement in some situations, especially when involving human behavior, because entities in DES are not autonomous and capable of making independent decisions. So, this technique is not the most adequate to represent complex human behavior such as proactive behavior [68].

Agent Based Models (ABM), have the advantage of allowing to incorporate a massive range of individual level features and the implementation of arbitrarily complex probability distributions for disease progression [19] [20]. The ability to capture such heterogeneity can aid in not only capturing behavioral variability in underlying processes but also evaluating targeted interventions in specific populations [19] [20]. The major problem with the use of ABM is that the lower-level description involves describing the individual behavior of potentially many constituent units (even if the aggregate level could be described with just a few equations). So, simulating the behavior of all the units can be extremely computation intensive and therefore time consuming [68]. Because of that new less computer intensive Machine Learning technique may be a good avenue for future modelling [68].

Conclusion

There are numerous examples of simulation models applied to the study of screening for diabetic retinopathy, however, this systematic review allowed us to identify two important gaps in the literature. First, it became evident that, despite many authors recognizing the undeniable importance of adherence to screening, simulation models focused on this issue were not developed (except for one model that does not use real data, and therefore was not truly validated). The second problem is related to the simulation techniques used. Most of the analyzed models are based on Markov processes or Discrete Event Simulation techniques. However, the authors themselves often recognize that these techniques have serious limitations, making it impracticable to combine the large number of variables necessary for study this problem. Agent-based models can be an interesting alternative; however more research is needed to understand whether they can significantly contribute to the study of the complexity inherent in a population-based diabetic retinopathy screening.

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Declaration of interest statement

The authors declare that they have no competing interests.

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3.3. The use of social simulation modelling to understand adherence to diabetic retinopathy screening programs

3.3.1. Context and summary

The paper "The use of social simulation modelling to understand adherence to diabetic retinopathy screening programs" [22] demonstrates that it is possible to simulate the behaviour of adherence to DR screening using computer social simulation models. In fact, although there are several studies that show the importance of the screening adherence rate to the success of DR screening programmes, as far as we know, only one has tried to simulate the individual adherence behaviour, albeit based on theoretical data [19]. To contribute to fulfil this gap, the present research answers the following question: How to predict the rate of adherence to population-based screenings through computational simulation models with a high level of abstraction? More specifically, this paper aims to i) demonstrate that it is possible to develop a computational simulation model that faithfully portrays the individual decision to adhere or not to screening, using the intrinsic features of the diabetic patients and of the screening programmes; ii) demonstrate that a simulation model with the aforementioned characteristics can be used in contexts other than the one where the data for its development were collected; and iii) demonstrate the utility of combining agent-based models and fuzzy logic in models that intend to simulate human behaviour. To accomplish those purposes, we developed three versions of an agent-based simulation model: the first one uses a logistic regression model to determine the individual decision to adhere or not to the screening; in the second on, the logistic regression is replaced by three fuzzy logic components [22]; and the last one is a combination of the first two methods. All three versions were calibrated and validated using real data from 271,867 calls for screening in the North Region Health Administration of Portugal. The results obtained are very close to the real ones. Moreover, the simulations have a high degree of abstraction from the real data, which attests to the validity of the approach and its usefulness as a predictive tool for public health action planning.

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The use of social simulation modelling to understand adherence to diabetic retinopathy screening programs

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The success of screening programs depends to a large extent on the adherence of the target population, so it is therefore of fundamental importance to develop computer simulation models that make it possible to understand the factors that correlate with this adherence, as well as to identify population groups with low adherence to define public health strategies that promote behavioral change. Our aim is to demonstrate that it is possible to simulate screening adherence behavior using computer simulations. Three versions of an agent-based model are presented using different methods to determine the agent's individual decision to adhere to screening: (a) logistic regression; (b) fuzzy logic components and (c) a combination of the previous. All versions were based on real data from 271,867 calls for diabetic retinopathy screening. The results obtained are statistically very close to the real ones, which allows us to conclude that despite having a high degree of abstraction from the real data, the simulations are very valid and useful as a tool to support decisions in health planning, while evaluating multiple scenarios and accounting for emergent behavior.

Keywords Computational simulation, Agent-based models, Logistic regression, Fuzzy logic, Diabetic retinopathy, Screening adherence rate

Diabetic retinopathy (DR), ICD-9 code 362.0, is a complication of diabetes that causes structural changes in the blood vessels of the retina. It is currently one of the main causes of blindness in developed countries[1]. As DR is asymptomatic until the later stages, patients with diabetes should have regular eye tests[1,2]. Several countries have therefore implemented population-based DR screenings[3].

The literature demonstrates that the success of screening programs depends to a large extent on the adherence of the target population, but as far as we know there is a gap in the study of the behavioral mechanisms behind the phenomenon (as demonstrated in "Literature review").

In order to bridge this gap, our research focuses on the development of computer simulation models that make it possible to understand the factors that correlate with adherence rates, identify population groups with particularly low adherence and may help to support decisions in health planning, while evaluating multiple scenarios and accounting for emergent behavior.

In this article we are mostly focused on the first step of the process: how to predict the rate of adherence to population-based screenings through computational simulation models with a high level of abstraction. More specifically, this article aims to (i) demonstrate that it is possible to develop a computational simulation model that faithfully portrays the individual decision to adhere to screening or not, using the intrinsic features of the diabetic patients and of the screening programs, (ii) demonstrate that a simulation model with the aforementioned

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characteristics can be used in contexts other than the one in which the data for its development was collected, (iii) hopefully, demonstrate the utility of combining ABM and fuzzy logic in models that intend to simulate human behavior. To this end, we developed three versions of an agent-based simulation model (ABM), using a logistic regression equation and fuzzy logic components to predict the individual decision concerning whether to adhere to the screening or not. By integrating the fuzzy components with the result of the logistic linear regression, with parametrizable weights, the proposed model can be used to compare the two methods, and a combination of both techniques. The first set of simulations, in which the individual decision on whether to adhere to the screening or not was based on logistic regression, proved to be good at replicating reality and useful in staging scenarios in a specific geographic context, but we recognize that its scalability and level of abstraction is limited, as it is mainly based on behaviors previously observed in a concrete screening program[27]. The second set of simulations allows us to overcome the aforementioned limitations, despite some decline in the accuracy of the previsions, by replacing the logistic regression equation with three fuzzy logic components to simulate individual decision-making. Finally, a third set of simulations was performed, combining the logistic regression and fuzzy components in equal proportions.

Literature review

The first computer simulations of DR screenings date back to the 1990s and mainly used Markov chains to demonstrate the cost-effectiveness of implementing population-based screening programs[4–7]. In subsequent years, and with a broad consensus on the cost-effectiveness of population-based DR screenings, researchers started to focus on the analysis of different screening alternatives. Several simulation models were developed to compare screening methods[8–12], the results of adopting different screening intervals[9–17], and to analyze the cost-effectiveness of telemedicine[18–23]. We highlight the works of Davies and his colleagues, who developed a simulation model based on discrete events (DES) to stage different screening intervals[9–12] and found that the population's adherence to the screening plays a decisive role in its success. However, in subsequent models the authors continued to adopt a fixed probability of adherence and no attempt was made to model the subjects' individual behavior[9–12]. An attempt to include human behavior was made by Schmidt and Brailsford[24], by incorporating the Health Belief Model (HBM) into a DES model that produces a result (behavior—output) through a combination of several factors (inputs) that influence screening adherence. In this model each patient is an individual entity, with their own features. This approach was implemented using numerical attributes to represent the various features of the diabetics (number of times they adhered to previous screenings, perception of general health status, current DR status, information and anxiety regarding DR, and educational qualifications). The probability of participating in the screening was calculated as a binary variable and the model uses only artificial data, leading to results that are theoretical artifacts which lack validation with real data. This research also stresses the difficulty of incorporating qualitative variables, such as those used by the HBM, in DES models, emphasizing the need for the use of another type of technique[24]. Supplementary Table S1 provides further details on the strengths and limitations of each of these studies.

The literature suggests that ABM are a good alternative for the study of systems in which individual behavior has a relevant impact, since they are composed of networks and processes formed by interactive and adaptive agents[26]. In fact, in an ABM the social system is represented as a set of autonomous agents capable of taking decisions. In each iteration, each agent individually assesses their situation and makes decisions based on a set of rules, then takes a certain action. Even a simple ABM can exhibit complex behavior patterns and provide valuable information on the dynamics of the real-world system it simulates[25,26]. Among the main advantages of using such an approach, we highlight its ability to simulate different scenarios and emergent behavior that is not explained by classic theories, such as the adoption of behaviors that repeatedly do not result in the best outcome; heterogeneity and interactions between agents; flexibility and the possibility of following the evolution of a system[26].

The concept of fuzzy logic, introduced by Lotfi Zadeh in 1965, is based on the observation that human beings make decisions based on imprecise, subjective and non-numerical information[28,29]. Thus, fuzzy sets are mathematical entities that aim to represent imprecise information and give models the ability to recognize, represent, manipulate, interpret, and use vague and/or subjective information, allowing for a high level of abstraction in relation to the original data[29]. Techniques based on fuzzy logic are therefore especially suitable for simulating human behavior, having already been used quite successfully for this purpose[30], and fuzzy rules can be embedded in within the intelligent agents of the ABM[31].

Methods

This research focuses on the concept of model development driven by real data[32]. Thus, the research process began with the important steps of identifying sources and collecting, integrating, and processing data. After this, the modelling process itself began. The following flowchart (Fig. 1) illustrates the main steps performed, which will be described in greater detail in the following subsections.

Sample and data gathering

This research used data on all calls for DR screening between the years 2013 and 2018, provided by the Portuguese Northern Region Health Administration (ARSN). Figure 2 illustrates the geographic area covered by ARSN.

The sample consists of 271,867 calls for DR screening, which corresponds to 108,620 different diabetics. The following variables were used: age; gender; professional status; existence of telephone contact for sending reminders; Health Centre Cluster (ACES); Primary Health Care Unit; type of Primary Health Unit; existence of a family doctor; reason for exemption from payment of charges for services, when applicable; number of consultations at the Primary Care Unit in the last 12 months; type of diabetes (I or II); Body Mass Index (BMI);

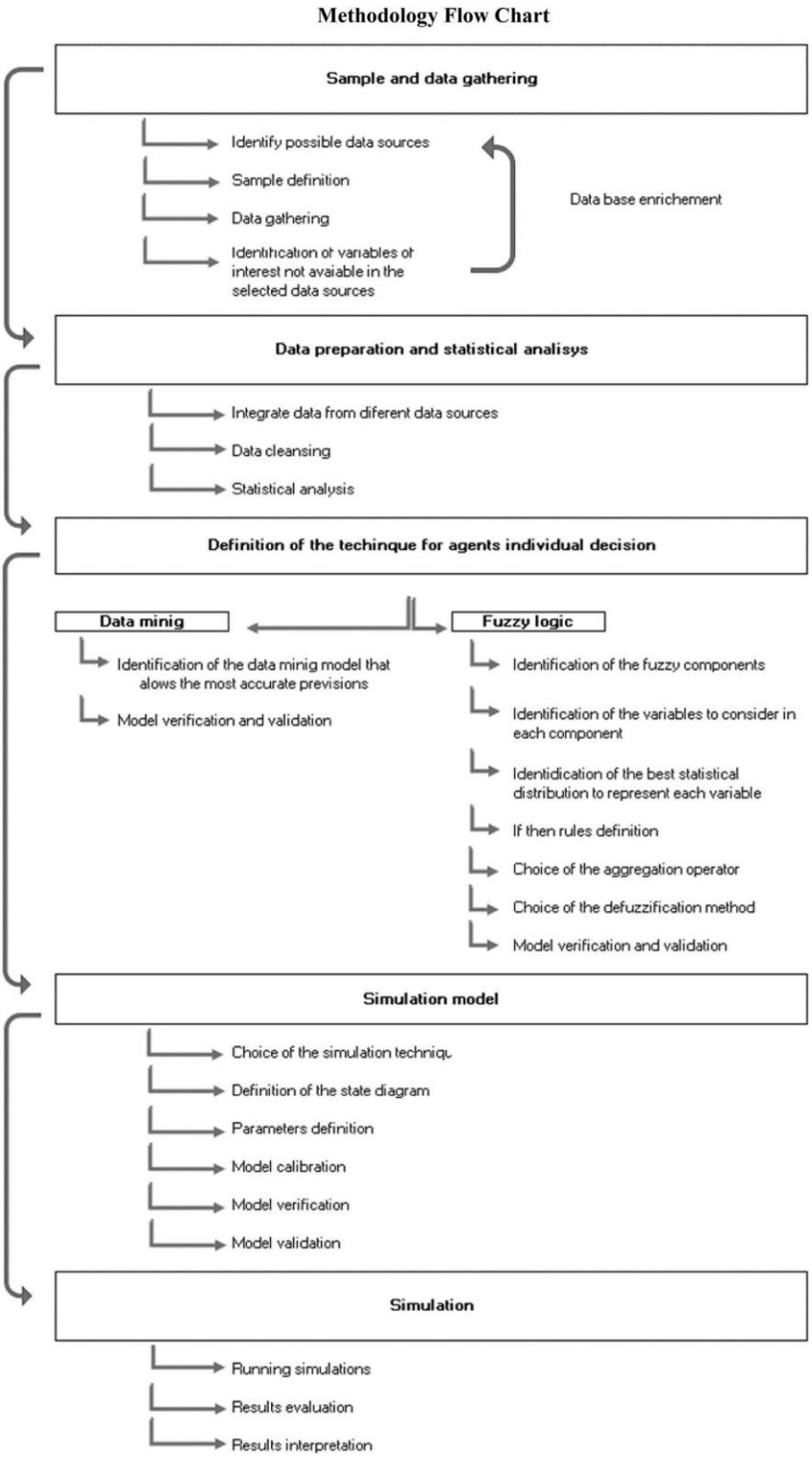

Figure 1. Methodology flow chart.

blood glucose levels (HBA1C); month of call for screening; days elapsed between calls; number of times the diabetic was called; last screening result; percentage of times the diabetic adhered to previous screenings. Subsequently, data from the National Institute of Statistics (INE) was used to obtain the variables "income (median)" and "educational qualifications (distribution by postal code with 7 digits)"[33], as these variables are identified in the literature as closely related to the adherence rate[24]. For the classification of geographical areas according to the degree of urbanization, data from the Typology of Urban Areas 2014 (TIPAU, 2014), available on the INE website[33], was used.

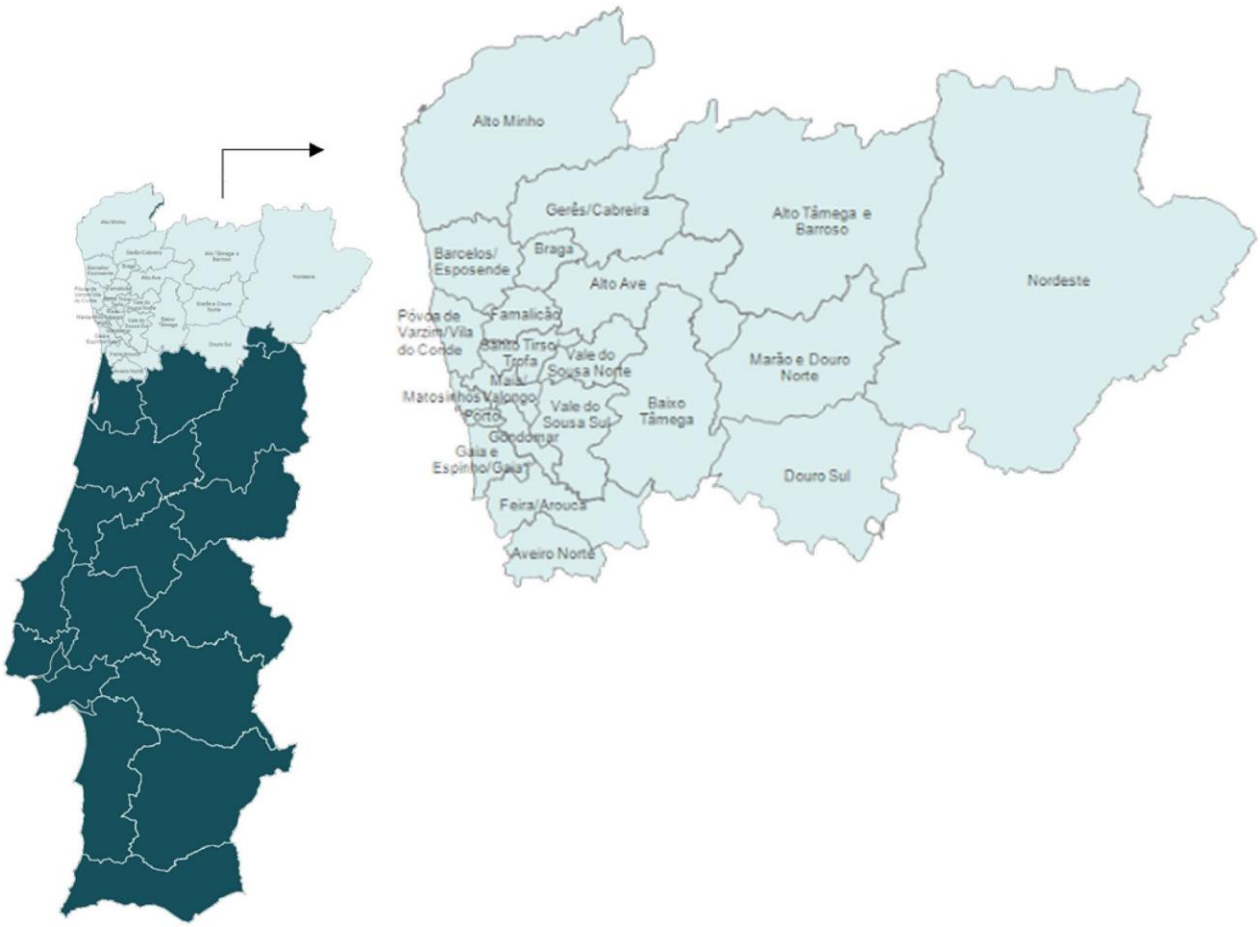

Figure 2. ARSN location and geographical coverage.

All methods of data gathering were carried out in accordance with relevant guidelines and regulations.

The authors did not have any direct contact with the subjects participating in the study.

The data obtained from INE are publicly available and of a general nature, not allowing the identification of the subjects involved[33].

The data provided by ARSN were collected by the institution, in accordance with the legislation applicable in the Portuguese Public Administration, including informed consent from all subjects and/or their legal guardian(s).

Moreover, the data provided by ARSN for this research went through a set of mechanisms that guarantee the protection of privacy (for example encryption and anonymization), and all the procedures were duly endorsed by the ARSN ethics committee, in strict compliance with all issues related to access to Public Administration data, and the data protection regime.

The present research does not include the use of experimental protocols.

Data preparation and Statistical analysis

A large percentage of the work in data analysis involves preparing the data[32]. Hence, in this phase it was necessary to integrate data from different data sources and perform data cleansing: identifying impossible or incorrect values for specific variables, cases that should not be in the study (because they do not meet the inclusion criteria), duplicate cases, missing data, and outliers, while also ensuring that the same value for string variables is always written in a coherent manner throughout the data set. The SPSS Modeler 18.2 software[34] was used to carry out this step.

In a second phase, a descriptive statistical analysis was carried out, aiming to identify the variables that best explain adherence to screening. The results of the statistical analysis are presented in "Sample and data gathering".

The diabetic's individual decision

In order to select the data mining model, eight models were tested using SPSS Modeler 18.2 software[34]: decision trees (C5, Tree-AS, CHAID, Quest, C&R Tree), neural network, Bayesian network and logistic regression. For this study, the adherence to screening variable was used as a dichotomous dependent variable. A set X of 21 independent variables was considered. The logistic regression model (Fig. 3) revealed the most accurate results

$$P(x) = \frac{1}{1 + e^{-(0.49*\text{previous screening adherence} + 0.27*\text{last scrennig result} + 0.05*\text{number of previous invitations})}}$$

Figure 3. Logistic regression equation.

(62.23% correct in the training set, AUC = 0.68 and 63.62% in the testing set, AUC 0.681). Only 3 independent variables were included in the regression model that was generated, since the others were discarded (using the stepwise method) due to their low significance in the model. The predictors of the behavior of adherence to the screening are the percentage of times the diabetic had previously adhered to the screening, the last screening result, and the number of times the diabetic was called for DR screening, which is in line with the literature[24].

As an alternative to the data mining model, a set of fuzzy components was developed to measure the result of the individual decision on whether to adhere to the screening or not.

The fuzzy components, as well as the variables that constitute each component, were established on the basis of the statistical analysis results, those in the literature that focus on explaining the rate of adherence to health programs, and the HBM[23,24]. This analysis resulted in three common-sense fuzzy components: “access barriers”, “knowledge of the disease”, “quality/strategy of the screening program”. The selection of the representative function for the variables that comprise each component was based on an analysis of the distribution of real data. The “access barriers” component comprises variables B1, B2, B3 and B4. B1 concerns the perception of access barriers due to age. “Difficult access due to age” is defined by the linear function that passes through the points [0, 1], [100, 0]. “Easy access” is defined by the linear function that passes through the points [0, 0] and [100, 1]. Variable B2 corresponds to the perception of access barriers as a function of income. "Difficult access due to income" is defined by the normal distribution of the mean 50,000 euros/year and standard deviation 17,000 euros/year. The classification "easy access due to income" corresponds to the maximum of two normal distributions with averages of 0 and 100,000 euros/ year respectively and standard deviations of 17,000 euros/year. B3 corresponds to the perception of access barriers depending on the location of the screening. “Difficult to access due to screening location” is defined by the linear function that passes through the points [0, 0], [100, 1]. “Easy access due to screening location” is defined by the linear function that passes through the points [0, 1] and [100, 0]. B4 corresponds to the perception of access barriers depending on the degree of urbanization of the place of residence. The “difficult access due to the degree of urbanization” is defined by the normal distribution of mean 0.3 and standard deviation 0.1. The classification “easy access due to the degree of urbanization” corresponds to the maximum of two normal distributions with means 0 and 0.5 respectively and standard deviations 0.1. The component relating to knowledge about the disease comprises variables C1, C2 and C3. Variable C1 assesses knowledge of the disease as a function of age. "High knowledge level due to age" is defined by a normal distribution of the mean 65 years and standard deviation 30. "Low knowledge level due to age" corresponds to the maximum of two normal distributions with means 18 and 100 years respectively and deviation pattern 30. Variable C2 corresponds to knowledge of the disease as a function of educational qualifications. “High knowledge level due to educational qualifications” is defined by a linear function that passes through the points [0, 0] and [100, 1]. “Low knowledge level due to educational qualifications” is defined by a linear function that passes through the points [0, 1] and [100, 0]. Variable C3 corresponds to knowledge of the disease as a function of the percentage of times the agent previously adhered to screening. “High knowledge level due to prior adhesion” is defined by a linear function that passes through the points [0, 0] and [100, 1]. “Low knowledge level due to prior adhesion” is defined by a linear function that passes through the points [0, 1] and [100, 0]. The component relating to the quality of the screening strategy comprises variables E1, E2 and E3. Variable E1 corresponds to the quality of the strategy in terms of the sending of reminders. “High quality, considering sending reminders” is defined by a linear function that passes through the points [0, 0] and [100, 1]. “Low quality, considering sending reminders” is defined by a linear function that passes through the points [0, 1] and [100, 0]. Variable E2 corresponds to the quality of the strategy considering the waiting time at the time of screening (in minutes). “High quality, considering the waiting time” is defined by a linear function that passes through the points [0, 1] and [500, 0]. “Low quality, considering the waiting time” is defined by a linear function that passes through the points [0, 0] and [500, 1]. Variable E3 corresponds to the time (in weeks) between sending the call notice and the date of the screening. "High quality, considering advance notification of the call" is defined by a normal distribution of mean 4 and standard deviation 2. "Low quality, considering advance notification of the call" corresponds to the maximum of two normal distributions with means 0 and 8 respectively and standard deviations 2. Finally, a random noise was added, whose magnitude is controlled by the “variability” parameter. In each component, rules of the IF–Then type were defined, so that if the easy/high/high value is obtained in at least half of the variables that comprise it, there is a strong probability that the agent will adhere to the tracking. Therefore, for the “barriers of access” component, 16 rules were defined, 8 for the “knowledge of the disease” component and 8 for the “quality/strategy of the screening program” component, resulting in a total of 32 IF–then rules (listed in Supplementary Information S2). The maximum as aggregation operator and the Mamdani Fuzzy Inference Method were used, and the defuzzification of each component was performed by the Centre of Gravity (COG) method[28,29]. The final result corresponds to the average of the results of the three components.

Simulation model

The ABM was developed using NetLogo 6.1.1 software[35], a simulator written in Scala language. The status diagram that was implemented (Fig. 4) contemplates four possible states: (i) not called; (ii) called; (iii) attended screening; (iv) did not attend screening. Initially, all diabetics assume the “not called” status. At the beginning

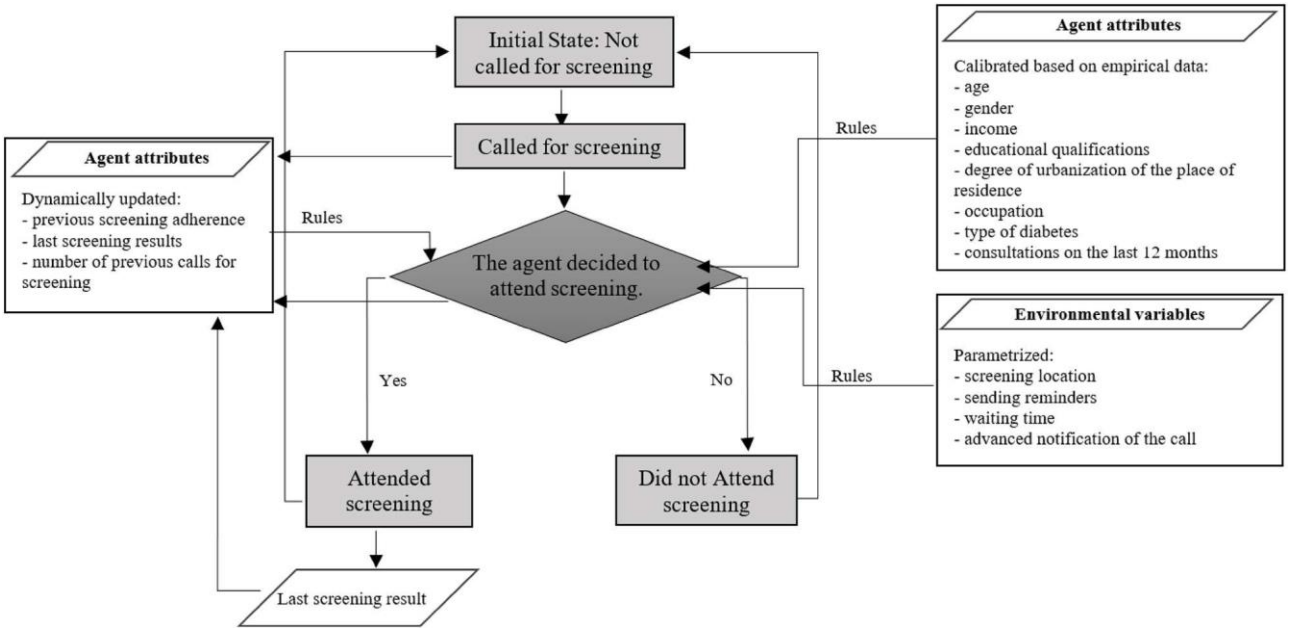

Figure 4. ABM Conceptual Model: Status Diagram and Decision Process.

of the simulation, each diabetic is called for screening by means of an invitation letter. At that moment, the diabetic assumes the status "Called for screening" (until the date of the screening). On the date of the screening, it is verified whether the diabetic has attended the screening or not. According to the diabetic's action, he can assume the status "attended screening" or "did not attend screening", as the case may be. After this phase, a new cycle begins in which the diabetic returns to the "Not called" state until the stipulated interval between screenings elapses. At that moment, a new invitation letter is issued, and the diabetic again assumes "Called for screening" status, repeating the entire process.

By integrating the fuzzy components with the result of the logistic linear regression, the current model allows the two methods to be compared, as well as the results obtained with the use of different weights selected by the user. The information regarding the screening strategy was based on the opinion of ARSN experts and on an analysis of official documents provided by the institution[36]. Hence, the following parameters were used: Screening location = Primary Health Care Unit; Screening test sensitivity = 96%; Screening test specificity = 94%; Probability of a positive screening test = 4%; Probability of a negative screening test = 93%; Probability of an inconclusive screening test = 3%; Screening intervals = 52 weeks.

Simulations

A virtual population of 10,000 diabetics was generated and the call for screening was simulated over a period of ten screening cycles. A 52-week interval was defined between screenings. The initial population of agents was designed according to the characteristics of the ARSN diabetic population, and the model was initialized with the parameters measured from the available data. Five simulations were performed for each version of the model. In order to test the model's ability to capture geographic specificities, the simulation results obtained for each subregion were compared with the real adherence rates.

For the version that bases the individual decision of whether or not to adhere to the screening exclusively on fuzzy components, the data set was divided into two groups: training and testing. Data relating to the geographical areas of Tâmega e Sousa, Cávado, Douro, Trás-os-Montes and the Metropolitan Area of Porto, which corresponds to 66.41% of the total diabetic population covered by the ARSN, was used for training. Data relating to the geographical areas of Alto Minho, Ave and Entre Douro e Vouga, which correspond to 33.59% of the ARSN diabetic population, was reserved for testing. It was not possible to conduct a similar procedure for the version that only uses the logistic regression model because the model needs previous regional screening information to run.

For the version that uses fuzzy components, we also compared the results obtained for the entire population, with the ones obtained defining sets based on specific subgroups determined by a previous cluster analysis. To this end, we performed a cluster analysis using SPSS Modeler 18.2 software[34]. The initial data set of 271,867 calls for DR screening, corresponding to 108,620 different diabetics, was divided in two clusters, using the TwoStep Cluster Analysis procedure's algorithm. The model summary table indicates that two clusters were found based on seven input features. The cluster quality chart indicates that the overall model quality is "Fair". 50.9% (138,258) of the records were assigned to the first cluster and 49.1% (133,609) to the second. The cluster means suggest that the clusters are well separated for some of the variables, but to better evaluate the quality of the model, chi-squares and Cramér's V tests were performed for each variable. Although the chi-square tests point to the significance of the relation between clusters and all the input variables, this is mostly due to the large dimension of the data set. In this conditions, Cramér's V tests are better suitable to understand the correlations between input variables

and clusters. The Cramer's V tests revealed that only two of the seven variables have strong correlations with the cluster variable: age groups and occupation.

So, tendentially Cluster 1 is comprised by younger diabetics, mostly active, and Cluster 2 by older diabetics, mostly retired. The main aspects of the cluster analysis were included in the manuscript and the details are available in Supplementary Information—Tables S3 and S4.

Results

Statistical analysis results

The statistical analysis results (Supplementary Information Table S5) are, in general, consistent with those found in the literature on population-based screening. Younger and older diabetics tend to adhere less to screening, as well as those earning higher incomes[37]. Higher educational qualifications, as well as a regular habit of using primary health care—visits to the health unit in the last 12 months—are conducive to higher rates of adherence[37–39]. Diabetics who received a higher number of invitations for previous screening and who had adhered more frequently in the past had higher rates of adherence[24,39]. There are, however, results that are not supported by the literature. Contrary to expectations[37–39], men in the ARSN adhere more to screening, and diabetics with previous positive results have lower adherence rates in the next screening. Regarding this second result, a scientific article focusing on the perspective of one of the main hospitals in the northern region which is an integral part of the ARSN screening program may indicate a possible explanation[40]. In fact, the lack of communication between hospital services and primary health care often results in calls for screening being sent to diabetics who are already being followed up and undergoing treatment in a hospital environment.

Simulation results using logistic regression only

The objective of this first set of simulations was to compare the simulated adherence rate with the real ARSN adherence rate, using logistic regression only in the agent decision process. In order to test the model's ability to capture geographic specificities, the simulation results obtained for each subregion were compared with the real adherence rates. The model was run for 520 simulated weeks to ensure convergence of results. In all cases, there was a significant initial increase in the global adherence rate, after which the model converges to an average adherence rate of 67.6%, with a standard deviation of 0.16%. The real adherence rate is slightly lower (66.6%). Figure 5 illustrates the simulation results obtained after 52, 260, 312 and 520 weeks.

When the model stabilizes, the simulated values approach the real ones. Only in one subregion (Douro) does the actual value of the adherence rate fall outside the 99% confidence interval. The simulation results also reflect the geographical asymmetries well (Table 1, Fig. 7).

Simulation results using fuzzy components only

In this second phase, the simulations were obtained using fuzzy components only to establish the agent decision rules. The initial population of agents was designed according to the characteristics of the diabetic population in each of the geographic areas that belong to the ARSN. Since all the real data belongs to the same Regional Health Administration, the screening strategy is similar in all sub-regions (both for training and testing). Hence, sending

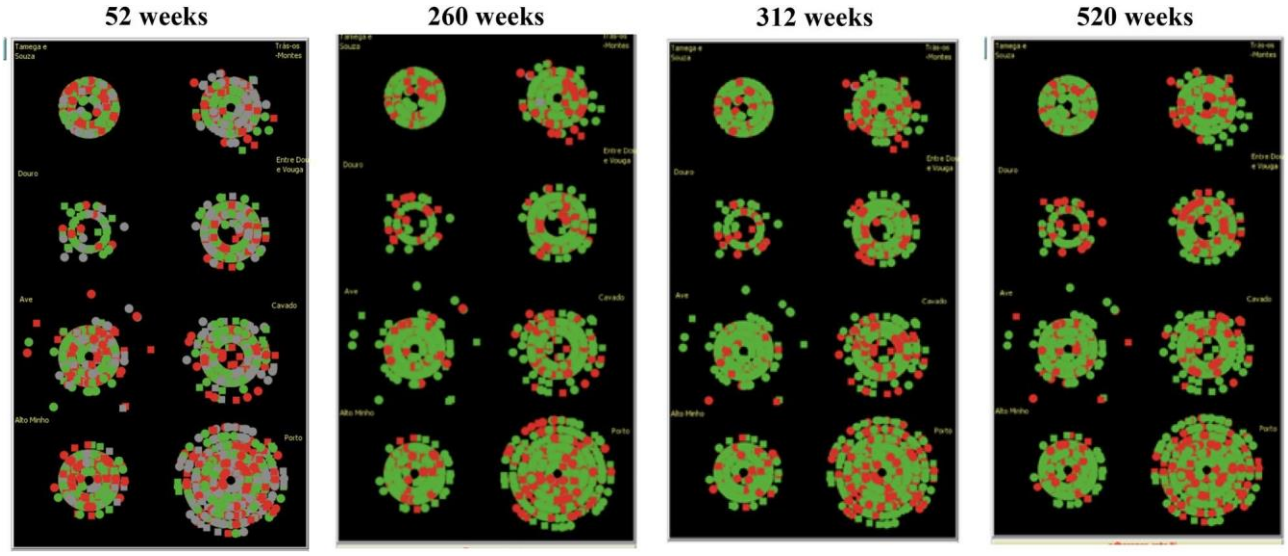

Figure 5. Evolution of the adherence rate in the different geographic areas throughout the simulation (output Netlogo). Each point on the diagram corresponds to a diabetic. The points cluster in concentric shapes which represent the different subregions (8) and whose size reflects the number of people with diabetes. The approximation of each point to the centre is determined by the income bracket of the diabetic represented. The colour assigned to each point corresponds to the status of the diabetic: grey indicates not called or called for nscreening; green indicates attended screening; red indicates did not attend.

	NUTS II	Simulation results		Real results (%)	Differences (%)	Confidence interval 95%	Confidence interval 99%
		Mean (%)	Standard deviation (%)				
	Agent decision based on logistic regression						
	Alto Minho	74.30	0.81	74.10	0.20	]72.99; 75.01[	]72.33; 75.67[
	Ave	72.44	0.67	72.09	0.35	**]71.17; 72.83[**	]70.62; 73.38[
	Cávado	66.75	0.83	67.02	−0.27	]64.97; 67.03[	]64.29; 67.71[
	Douro	68.13	0.29	66.86	1.27	**]67.64; 68.36[**	**]67.40; 68.60[**
	Entre Douro e Vouga	66.95	0.63	66.25	0.70	]65.22; 66.78[	]64.70; 67.30[
	Metrop. Area of Porto	65.35	1.01	63.38	1.97	**]63.75; 66.25[**	]62.92; 67.08[
	Tâmega e Sousa	69.50	0.76	67.59	1.91	**]68.06; 69.94[**	]67.44; 70.56[
	Trás-os-Montes	66.83	0.65	65.69	1.14	]63.58; 66.42[	]62.65; 67.35[
	Agent decision based on fuzzy components						
Training	Cávado	65.58	1.42	67.02	−1.44	]63.82; 67.34[	]62.66; 68.50[
	Douro	65.44	0.66	66.86	−1.42	**]64.18; 65.82[**	**]63.64; 66.36[**
	Metrop. Area of Porto	62.00	1.00	63.38	−1.38	**]60.76; 63.24[**	]59.94; 64.06[
	Tâmega e Sousa	67.03	1.13	67.59	−0.56	]65.60; 68.40[	]64.67; 69.33[
	Trás-os-Montes	62.79	0.90	65.69	−2.90	**]60.88; 63.12[**	**]60.15; 63.85[**
Test	Alto Minho	70.92	0.81	74.10	−3.18	**]68.99; 71.01[**	**]68.33; 71.67[**
	Ave	70.78	0.87	72.09	−1.31	**]68.92; 71.08[**	**]68.21; 71.79[**
	Entre Douro e Vouga	65.40	0.93	66.25	−0.85	**]63.85; 66.15[**	]63.09; 66.91[
	Agent decision based on fuzzy components—Cluster 1						
Training	Cávado	64.62	1.48	65.46	−0.84	]63.32; 65.91[	]62.92; 66.32[
	Douro	66.25	0.84	68.72	−2.47	**]65.51; 66.98[**	**]65.28; 67.21[**
	Metrop. Area of Porto	61.70	1.30	62.34	−0.64	]60.56; 62.84[	]60.20; 63.20[
	Tâmega e Sousa	66.48	1.09	67.41	−0.93	]65.52; 67.43[	]65.22; 67.73[
	Trás-os-Montes	61.42	1.50	65.22	−3.80	**]60.11; 62.73[**	**]59.70; 63.15[**
Test	Alto Minho	70.80	0.78	72.34	−1.54	**]70.12; 71.49[**	**]69.90; 71.7[**
	Ave	69.65	0.78	70.28	−0.63	]68.96; 70.33[	]68.75; 70.55[
	Entre Douro e Vouga	64.33	1.59	65.10	−0.77	]62.93; 65.73[	]62.49; 66.17[
	Agent decision based on fuzzy components—Cluster 2						
Training	Cávado	67.93	0.70	68.83	−0.90	**]67.31; 68.54[**	**]67.12; 68.73[**
	Douro	66.61	0.61	64.66	1.95	**]66.07; 67.14[**	**]65.90; 67.31[**
	Metrop. Area of Porto	64.27	0.74	64.33	−0.06	]63.62; 64.92[	]63.41; 65.13[
	Tâmega e Sousa	67.89	0.59	67.76	0.13	]67.37; 68.40[	]67.21; 68.57[
	Trás-os-Montes	64.65	0.56	66.37	−1.72	**]64.16; 65.15[**	**]64.01; 65.30[**
Test	Alto Minho	71.47	0.44	76.04	−4.57	**]71.08; 71.85[**	**]70.96; 71.97[**
	Ave	71.91	0.50	73.74	−1.83	**]71.47; 72.36[**	**]71.33; 72.49[**
	Entre Douro e Vouga	66.90	0.38	67.32	−0.42	**]66.57; 67.24[**	]66.46; 67.34[
	Agent decision based on a combination of logistic regression and fuzzy components						
Training	Cávado	65.76	1.23	67.02	−1.26	**]63.47; 66.53[**	]62.47; 67.53[
	Douro	67.13	0.56	66.86	0.27	]66.30; 67.70[	]65.85; 68.15[
	Metrop. Area of Porto	61.44	1.13	63.38	−1.94	**]59.60; 62.40[**	**]58.67; 63.33[**
	Tâmega e Sousa	64.67	0.98	67.59	−2.92	**]62.78; 65.22[**	**]61.98; 66.02[**
	Trás-os-Montes	61.56	0.87	65.69	−4.13	**]59.92; 62.08[**	**]59.21; 62.79[**
Test	Alto Minho	71.42	0.79	74.10	−2.68	**]70.02; 71.98[**	**]69.37; 72.63[**
	Ave	71.30	0.86	72.09	−0.79	**]69.93; 72.07[**	]69.23; 72.77[
	Entre Douro e Vouga	68.21	0.83	66.25	1.96	**]66.97; 69.03[**	**]66.29; 69.71[**

Table 1. Simulation results versus real data. Bold cells signal cases where the actual value of the adherence rate falls outside the confidence interval.

reminders is still a very incipient practice and the screening is carried out in primary care units in all the eight subregions under analysis. It has not yet been possible to obtain information on the other variables that comprise the "quality/screening strategy" component. Therefore, it was assumed that the call is sent 4 weeks in advance in all locations and that the waiting time on the screening day is always 10 min. Five simulations were performed. Figure 6 corresponds to Netlogo's graphic output obtained with the first simulation performed.

Table 1 and Fig. 7 summarize the results obtained in comparison to the real data.

The overall ARSN adherence rate obtained using the simulation model is 1.55% below the region's real adherence rate (65.05% versus 66.6%). In fact, the results obtained with the simulations are slightly below the actual adhesion rate in all geographic subregions, with the smallest difference being registered in Tâmega and Sousa (0.56%) and the largest in Alto Minho (3.18%). In four subregions the actual value of the adherence rate does not belong to the 99% confidence interval. However, the model is able to effectively capture the nuances between different regions in terms of adherence to screening.

The results obtained using the previous defined clusters are very satisfactory, and, particularly for cluster 1, the simulation results are in fact a better representation of reality, when compared with the results obtain using the entire population (Table1).

It should also be noted that the adjustment to reality in the test set and the model's ability to predict higher adherence rates supports the belief that the model has a predictive capacity in new contexts.

Simulation results using a combination of logistic regression and fuzzy components

In this last set of simulations, the agent decision results from a combination of the results obtained with logistic regression and with fuzzy components, in a ratio of 50/50. The simulations were performed as described in the two previous sections. Table 1 and Fig. 7 illustrate the results obtained.

The overall ARSN adherence rate obtained was 1.52% below the region's real adherence rate (65.08% versus 66.6%). The biggest difference (absolute value) was registered in Trás-os-Montes (4.13%) and the smallest in Douro (-0.27%). In five subregions the actual value of the adherence rate does not belong to the 99% confidence interval.

Comparation of the results obtain with the three versions of the ABM

The results obtained are close to the real ones, even though four of the eight subregions in the version that uses fuzzy components present real values that fall outside the 99% confidence interval for the mean of the simulation results. Therefore, the model captures the geographic asymmetries very well. The use of the fuzzy components leads to a high level of abstraction from the real data and shows predictive capability in new contexts (the test set), which attests to the validity of the model for the study of this problem and its usefulness as a predictive tool for public health planning. In fact, the use of logistic regression (version 1) led to the best global result: a predicted adherence rate of 67.6%, a difference of only 1% in relation to the real value (66.6%). However, the logistic regression technique is of limited use in geographic areas aiming to begin a screening program, since the main predictors included in its equation are the percentage of times the diabetic had previously adhered and the

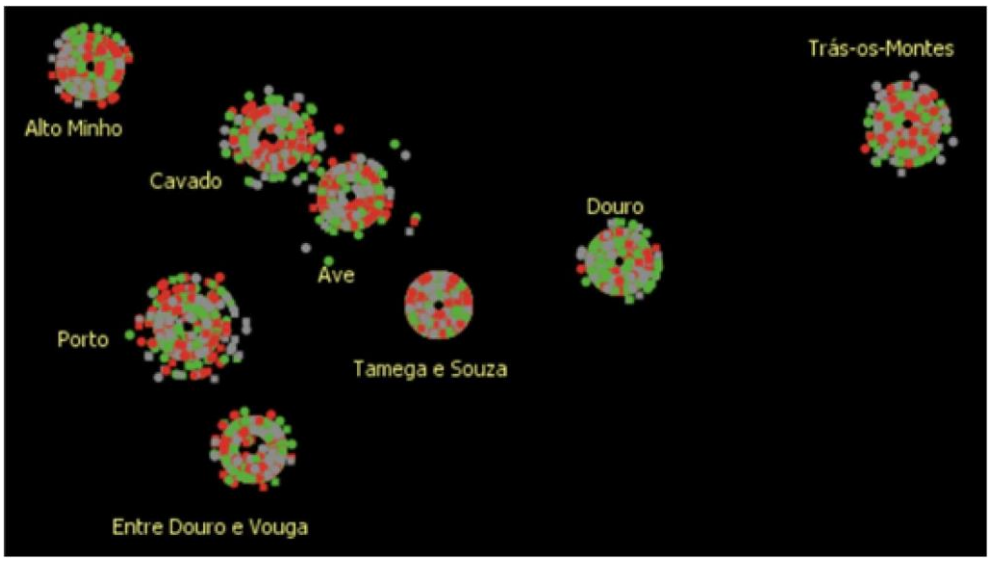

Figure 6. Adherence rate by geographic area (output Netlogo). Each point in the diagram corresponds to a diabetic residing in a certain health subregion at a certain moment in the simulation. The points cluster in concentric shapes which represent the different subregions (8) and whose size reflects the number of people with diabetes. The approximation of each point to the centre is determined by the income bracket of the diabetic represented. The colour assigned to each point corresponds to the status of the diabetic: grey indicates not called or called for screening; green indicates attended screening; red indicates did not attend.

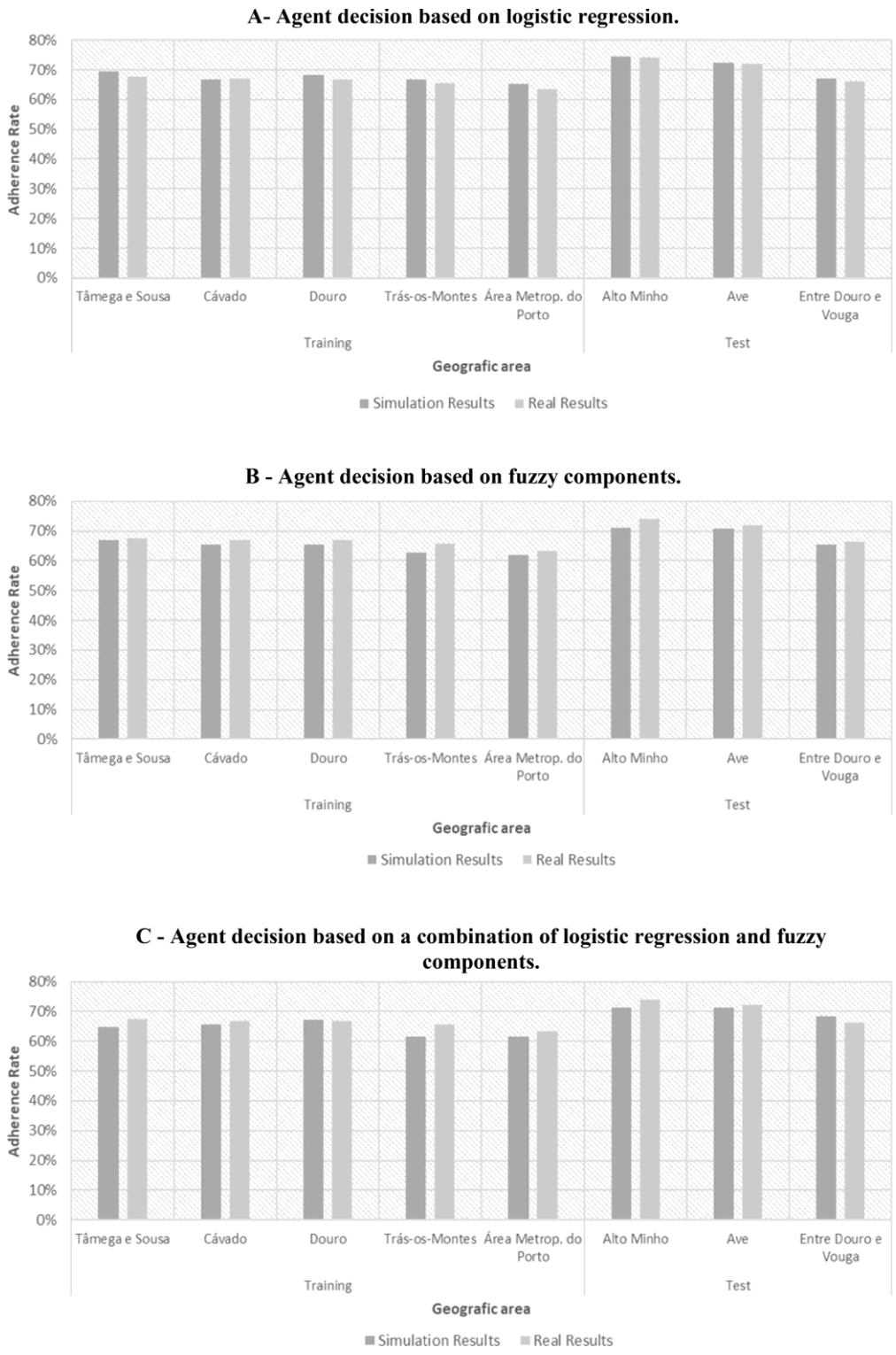

Figure 7. Simulation results versus real data.

result of the last screening. Nevertheless, this technique can be very useful and effective if the necessary data is available. The combined version 3 showed no overall improvement in comparison to version 2.

Figure 8 allows for direct comparation of the differences between the results obtained with each of the ABM versions and the real results, in all the geographic areas. As can be seen, most subregions follow the general trend, producing better results when using logistic regression only. However, in subregions where screening was started more recently (and therefore has fewer years of history), such as Douro and Tâmega e Sousa, the version that relies on fuzzy components or the combined version tend to have better results.

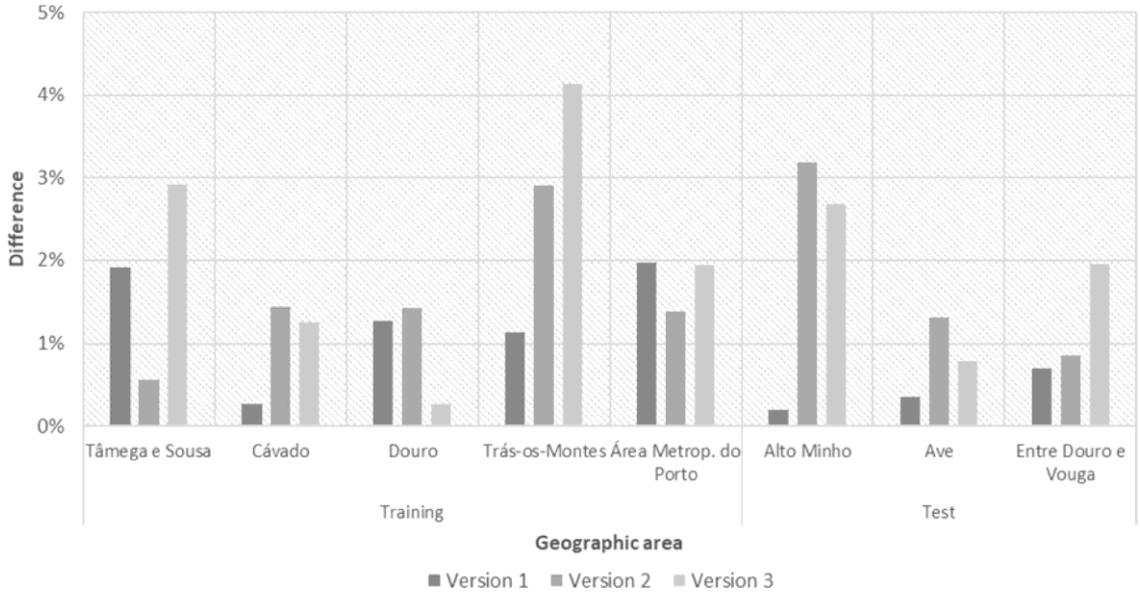

Figure 8. Simulation results versus real results in each of the ABM versions.

Effect of different interventions on adherence rate

Since the region's adherence rate is lower than desired (80%), it will be necessary to develop public health interventions in this area. Therefore, in order to predict and compare the results of several possible interventions, simulations were carried out for different hypothetical scenarios. These are only first examples of the applications of our research (a prove of concept), and we plan to continue to improve our model so that it can be used to analyze a wider range of scenarios. All the simulations on this section were carried out using the ABM version with the logistic regression (version 1).

Scenario 1—intervention that allows increasing adherence of diabetics who tested positive in the previous screening to 95%

According to ARSN experts, it makes no sense for this group of diabetics to have lower adherence rates than those who had a negative result. Therefore, and based on the literature referred to previously[40], the hypothesis was formulated that the existing data are biased due to a weak articulation between hospital services and primary health care, which leads to the sending of calls to diabetics followed in a hospital environment. In this way, this intervention would not actually consist of an increase in the real adherence rate, but rather an increase in the quality of data and the screening process.

Since only 4% of screening results are positive, a very significant impact on the overall adherence rate was not expected. In fact, the results of this simulation (in which the adherence rate of diabetics with a previous positive result was parameterized to 95% in all sub-regions) are in line with empirical knowledge, revealing that only the sub-regions with greater differences between the adherence of diabetics with previous negative and positive results show increases in the adherence rate (Table 2). Overall, the region's adherence rate would increase from 67.6 to 68.23%.

Scenario 2—Intervention that increases adherence by 5% of all diabetics who have already taken part in screening at least once.

According to experts, this increase could be viable, taking advantage of the presence of diabetics at screening to provide them with a small training session on the disease and the importance of annual screenings.

Therefore, in this simulation, the adherence rate of all diabetics who have already taken part in screening was programed to be increased by 5%.

According to the results obtained, this intervention would lead to substantial increases in all sub-regions (Table 2) and an increase in the global adherence rate from 67.6 to 70.28%.

Scenario 3—Intervention that allows the adherence rate of younger diabetics, particularly students, to increase by 20%.

Although 20% is an ambitious increase, experts consider that it could be possible through information sessions in schools and with the collaboration of teachers. Therefore, in this simulation the adherence of diabetics under 25 years of age and students was programed to be increased by 20%.

Since the percentage of diabetics of school age is very small (only 5.2% of the total number of diabetics in the region) the impact of this measure is minimal in terms of increasing the overall adherence rate—from 67.6

	Simulated adherence rate (%)		
	Without intervention	Scenario (1)	Difference
Scenario 1			
Alto Minho	74.30	74.94	0.64
Área Metropolitana do Porto	65.35	65.76	0.41
Ave	72.44	73.71	1.27
Cavado	66.75	67.27	0.52
Douro	68.13	68.19	0.06
Entre Douro e Vouga	66.95	66.98	0.03
Tâmega e Sousa	69.50	70.07	0.57
Trás-os-Montes	66.83	67.94	1.11
Scenario 2			
Alto Minho	74.30	77.14	2.84
Área Metropolitana do Porto	65.35	67.61	2.26
Ave	72.44	74.60	2.16
Cavado	66.75	69.06	2.31
Douro	68.13	70.53	2.40
Entre Douro e Vouga	66.95	68.75	1.80
Tâmega e Sousa	69.50	73.57	4.07
Trás-os-Montes	66.83	70.31	3.48
Scenario 3			
Alto Minho	74.30	74.32	0.01
Área Metropolitana do Porto	65.35	65.71	0.36
Ave	72.44	72.43	-0.01
Cavado	66.75	67.05	0.30
Douro	68.13	69.62	1.49
Entre Douro e Vouga	66.95	66.92	-0.03
Tâmega e Sousa	69.50	70.23	0.73
Trás-os-Montes	66.83	66.92	0.09

Table 2. Scenarios results.

to 67. 9%. The measure is a little more interesting in regions where the adherence rate of this group is extremely low, and/or where this age group is more significant (Table 2).

Conclusions

This research aimed to demonstrate that it is possible to predict the rate of adherence to population-based screenings with a high level of abstraction using ABMs. More specifically, it intended: (i) to demonstrate that it is possible to develop an ABM that faithfully portrays the decision on whether to adhere to screening or not, using the intrinsic features of the agent and the screening program; (ii) to demonstrate that an ABM with the aforementioned characteristics can be used in contexts other than the one for which the data for its development were collected; (iii) to demonstrate the utility of combining ABM and fuzzy logic in models intended to simulate human behavior. To this end, three versions of an agent-based model were presented, differing in terms of the method used to infer the individual decision on whether to adhere to screening or not. For the first, we used a logistic regression equation, in the second logistic regression was replaced by three fuzzy logic components, and in the third a combination of the two methods was used. All three versions were calibrated and validated using real data from 271,867 calls for screening in the Northern Region Health Administration. The results obtained indicate that it is possible to predict the rate of adherence to screening for diabetic retinopathy using demographic and socioeconomic data for the target population, and information regarding the screening strategy. The use of the fuzzy components leads to a high level of abstraction from the real data and shows predictive capability in new contexts (the test set), which attests to the validity of the model for the study of this problem and its usefulness as a predictive tool for public health planning. In fact, the use of logistic regression (version 1) led to the best global result: a predicted adherence rate of 67.6%, a difference of only 1% in relation to the real value (66.6%). However, the logistic regression technique is of limited use in geographic areas aiming to begin a screening program, since the main predictors included in its equation are the percentage of times the diabetic had previously adhered and the result of the last screening. Nevertheless, this technique can be very useful and effective if the necessary data is available. The combined version 3 showed no overall improvement in comparison to version 2.

Discussion

Since the 1990s, several simulation models focused on screening for diabetic retinopathy have been developed. However, despite the recognized importance of adherence to screening success, we only found one attempt to model the subjects' individual behavior[24]. This model incorporated the Health Belief Model (HBM) into a DES model through a combination of several factors (inputs) that influence screening adherence. The model used only artificial data, leading to theoretical results, which lack validation with real data. That research also stresses the difficulty of incorporating qualitative variables, such as those used by the HBM, in DES models, emphasizing the need for the use of another type of technique. The objective of our research was to overcome those limitations, proving that is possible to simulate screening adherence behavior using computer simulations, in particular agent-based models embedded with logistic regression or/and fuzzy logic components. Regarding the logistic regression, we found that only three independent variables had predictive value: percentage of times the diabetic had previously adhered to the screening, the last screening result, and the number of times the diabetic was called for DR screening, which is in line with the literature[24]. Has far as we know, our research is the first that aims to simulate adherence to RD screening using an ABM. However, ABM have been used quite successfully to model health behaviors, like alcohol use, diet, smoking.[25,26]. Techniques based on fuzzy logic have also been used for simulating human behavior with good results[30]. So, our results are in line with the literature, reinforcing the idea that these computational modeling techniques are very effective when it comes to human behavior, and are the first application on DR screenings. Moreover, we think we demonstrate the utility of the use of fuzzy logic embedded in an ABM that intend to simulate human behavior. As we did not find any research, in the health area, that combinates the two techniques we believe our results could be an important contribution to future research. Despite the main focus of this article was proving that is possible to simulate adherence to population-based screenings through computational simulation models with a high level of abstraction, we also did some experiments to illustrate as such model can be used to support decisions in health planning, while analyzing the effectiveness of various interventions. For example, we studied the impact of promoting continuity in adherence to screening by providing the diabetic with a short training session on the day of the test, and of promoting adherence among younger diabetics through information sessions in schools. We are improving the model so that it can analyze a wider range of scenarios, the results of which we intend to present in our future research. We believe that the models developed can be of great importance when staging hypothetical interventions, enhancing the discovery of knowledge and when proposing measures to the public and private entities responsible for laws and decision-making. They can also facilitate the identification of groups/geographical locations where the problem of adherence to screening is particularly relevant and which factors have the greatest impact on the decision to adhere to the screening.

One limitation of this research is the fact that we did not have access to data from other locations with different screening strategies. In future, with the intention of improving the validation of our model, we intent to test our model with data from other geographic locations where both population characteristics and screening strategies differ substantially from those found in this training group. We also acknowledge that our approach relies on specific assumptions and data. To address data biases, we plan to test the model with data from other population-based screenings and gauge its ability to replicate the real-life adherence rates.

Data availability

The data that support the findings of this study are available from Portuguese North Region Health Administration, but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request, addressed to the corresponding author, and with permission of the Portuguese North Region Health Administration.

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Author contributions

A.P.: Conceptualization, Methodology, Data preparation, Software development, Calibration, Validation. Writing original draft. J.M.: Software development, Writing-Reviewing and Editing. A.A.: Conceptualization, Methodology, Expert advice, Writing-Reviewing and Editing. R.L. and F.N.: Conceptualization, Methodology, Supervision, Writing-Reviewing and Editing.

Competing interests

The authors declare no competing interests.

Additional information

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3.4. The role of the social network in the study of adherence to diabetic retinopathy screening programs

3.4.1. Context and summary

In our previous paper "The use of social simulation modelling to understand adherence to diabetic retinopathy screening programs" [22] we demonstrated that is possible to simulate adherence to DR population-based screenings through computational simulation models with a high level of abstraction, and that the combination of Agent Based Models and Fuzzy Logic can be a viable path to accomplish that goal. However, no social network was considered in our ABM model, because we did not find any literature that demonstrated that such networks are relevant for the diabetics screening adherence behaviour.

Once we identified this gap in the literature, we decided to continue our research in this direction. So, the present paper "The role of the social network in the study of adherence to diabetic retinopathy screening programs" [23] aims to analyse the influence of the diabetics' social network structure in the adherence to DR screening, more specifically by their contacts with other members of the target population. We aim to identify: (i) the global metrics of the diabetics' social network and if they are significantly related with diabetic retinopathy screening adherence rate, and (ii) specific groups of diabetics, concerning their individual social network features and their screening behaviours.

Global and node level network metrics were calculated and its relationship with the adherence to screening was analysed using two different perspectives: correlation between global level network metrics and the ACES adherence rate; cluster analyses based on node level network metrics. Due to the main goals of this second research, the evolution of the adherence rate was not relevant, and that we opted by restringing the initial data set to the cohort convened in the last year available, 2018. Social and demographic variables, as well as does concerning the previous health care services utilization, which were only used as additional information to better characterize the diabetic clusters formed through the social network node level metrics.

The present paper allowed to conclude that the structure of the social network and the position occupied by the diabetic in this network influence the behaviour of adherence to diabetic retinopathy screening. Our research showed that less connected networks (where the average number of steps along the shortest path between two nodes is higher), strongly divided into communities and with a great number of connected components present the highest adherence rates. Node level metrics allowed the identification of groups where the problem of

non-adherence is especially high. In our research, the non-adherence phenomenon is especially evident in a small group of highly connected individuals, which is contrary to the findings in the literature concerning oncologic screenings.

We think that these results are of utmost relevance as a starting point for future research and as a framework to support decision-making and planning of interventions related with adherence to DR screenings.

3.4.2. Paper verbatim copy

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The role of the social network in the study of adherence to diabetic retinopathy screening programs

Andreia Penso Pereira[1], Ana Afonso[2,5], Raul M. S. Laureano[3] & Fernando Buarque de Lima Neto[4]

Diabetic retinopathy screenings are a vital strategy to avoid the severe consequences of this disease. However, their success depends on the adherence of the target population. The present work aims to review the adherence to diabetic retinopathy screening, more specifically the influence of the persons with diabetes' social network (contacts between persons with diabetes) on their screening behaviour. The used data set comprises information of 75,921 persons with diabetes, distributed by 20 Primary Health Centre Groups of the Portuguese North Region. Persons with diabetes of the same Group were organized in an N-by-N matrix, resulting in 20 social networks. Network metrics were calculated and its relationship with the adherence to screening was analysed using two perspectives: correlation between global network metrics and adherence rate; cluster analyses based on node level metrics. The results obtained show that: (1) Less connected networks, strongly divided into communities and with a great number of connected components, present the highest adherence rates. (2) The node level metrics allow the identification of groups where the problem of non-adherence is especially high. (3) The non-adherence phenomenon is especially evident in a small group of highly connected individuals. We believe that these results are of utmost relevance as a starting point for future research and as support to the planning of interventions related to diabetic retinopathy screening adherence.

Keywords Health screenings, Diabetic retinopathy screening, Social networks, Screening adherence, Patient-level factors influence in adherence to screening

Nowadays it is consensual that social networks influence health behaviours[1]. Since the early works on the influence of social network characteristics on suicidal behaviour[2–4], there has been a growing interest in this field of research. Several studies proved the influence of the social network structure in disease spreading[5,6], the habit of smoking cigarettes[7,8], physical activity and eating habits[9–12]and risk behaviours[13]. Concerning screenings adherence, the research is much sparser, and the conclusions are not consistent. A first study concluded that social networks have an important influence on cancer-screening behaviour among low-income, older Mexican American women[14], however, in the continuation of the research, the authors found out that the effect is not universal across Hispanic groups[15]. Other researchers, aimed to identifying the main characteristics of successful interventions to promote cancer screening adherence and concluded that effective interventions need to use a variety of strategies, including the structure of the social network[16]. A study focused on the relationship between social network characteristics and breast cancer screening practices among employed women, found statistically significant relationships between network characteristics and screening behaviour, after removing the effects of previous mammography screening adherence[17]. A study that examines the influence of social networks in colorectal cancer screening adherence found that individuals who are socially isolated are less likely to adhere to the screening[18]. Another study regarding the influence of the social network in cancer screening adherence concluded that the screening behaviour of siblings, friends, or co-workers does not have significant influence

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on cancer screening behaviours[19]. Table 1 presents more details about the strengths and main outcomes of these research.

The literature focused on identifying the factors that induce the adherence to diabetic retinopathy (DR) screenings, highlights the importance of some sociodemographic variables, health status, knowledge about the disease, and previous health related behaviour[20–23]. Despite de interesting conclusions of these studies, we could not find any research related with the influence of the persons with diabetes' social network on the adherence to DR screening. The present work aims to contribute to fulfil this gap, reviewing adherence to DR screening, more specifically the influence of the persons with diabetes' social network structure (contacts with other persons with diabetes) in the adherence to DR screening. We aim to identify: 1—the global metrics of the persons with diabetes' social network and if they are significantly related with DR screening adherence rate, and 2— specific groups of persons with diabetes, concerning their individual social network features and their screening behaviours.

We believe that the results obtain could be particularly relevant as a starting point for future research and also as a framework to support the planning of interventions related with adherence to DR screenings.

	Refs	Authors	Year	Strengths and main outcomes
The influence of social network characteristics on health-related behaviour	2	E. Durkheim	1897	Durkheim studied the connections between individuals and society, demonstrating the usefulness of sociology as a science. Abnormally low or high levels of social integration can result in increased suicide rates
	3	B. A. Pescosolido e S. Georgianna	1989	This article analyses the characteristics of individuals' social networks to deepen the study of Durkheim's general proposition regarding the protective power of religion, with regard to suicide
	4	P. S. Bearman e J. Moody	2004	The authors concluded that friendship environment affects suicidality and that female adolescents' suicidal thoughts are significantly increased by social isolation
	5	A. S. Klovdahl, E. A. Graviss, A. Yaganehdoost, M. W. Ross, A. Wanger, G. J. Adams e J. M. Musser	2001	The authors use social network methods to reconstruct a tuberculosis outbreak network and to quantify the relative importance o persons and places in that outbreak (betweenness' centrality). This work provides the basis for a new approach to outbreak investigation and disease control
	6	L. A. Meyers, B. Pourbohloul, M. E. Newman, D. M. Skowronski e R. C. Brunham	2005	Traditionally epidemiology assumed that each individual has an equal chance of spreading the disease to everyone else, this study questions this assumption. The authors apply epidemiology methods to the contact network to illustrate that, for a single value of R0, any two outbreaks, even in the same environment, can have very different epidemiological outcomes
	7	S. T. Ennett e K. E. Bauman	1993	Social network theory and analysis were applied to examine the relation between adolescents' social positions and current smoking prevalence. The authors conclude that the chances of being a smoker are significantly higher for isolated adolescents. The relationship was not explained by demographic variables or the number of friends who smoked
	8	N. A. Christakis e J. H. Fowler	2008	The authors used network analytic methods and longitudinal statistical models to determine the extent of the person-to-person spread of smoking and quitting behaviour. The authors concluded that the social network is relevant to these behaviours
	9	J. Zhang, D. Brackbill, S. Yang, J. Becker, N. Herbert e D. Centola	2016	The authors demonstrate that social networks can play an important role in the design of more effective interventions for increasing children's physical activity
	10	J. Zhang, D. Brackbill, S. Yang e D. Centola	2015	
	11	J. Zhang, D. A. Shoham, E. Tesdahl e S. Gesell	2015	
	12	N. A. Christakis e J. . H. Fowler	2007	The authors concluded that the social network is relevant to the behavioural trait of obesity, and obesity appears to spread through social ties
	13	T. W. Valente, S. C. Watkins, M. N. Jato, A. Van Der Straten e L. P. M. Tsitsol	1997	The authors studied the association between social networks and contraceptive use. They concluded that the personal network is associated with contraceptive use. This association is even more significative than the individual characteristics usually considered relevant
The influence of social network characteristics on screening behaviour	14	L. Suarez, L. Lloyd, N. Weiss, T. Rainbolt e L. Pulley	1994	This research aims to determine the extent to which differences in social networks are relevant for adherence to breast and cervical cancer-screening, among low-income Mexican American women. The authors concluded that social networks seem to be a relevant factor for cancer-screening behavior in this group of women
	15	L. Suarez, A. G. Ramirez, R. Villarreal, J. Marti, A. McAlister, G. A. Talavera, E. Trapido e E. J. Perez-Stable	2000	The focus of this research is the influence of social integration on cancer screening participation of Hispanic women. The authors concluded that social networks have the potential to change screening behaviour. However, they also highlight that the influence of the social network was not universal across Hispanic groups and was stronger for Pap smear than for mammography screening behaviour
	16	B. Curbow, J. Bowie, M. A. Garza, K. McDonnell, L. B. Scott, C. A. Coyne e T. Chiappelli	2004	The authors preformed a comprehensive literature review of community-based breast, cervical and colorectal cancer screening interventions, aiming to Identify characteristics of the most successful ones. Their results show that effective interventions combined a variety of strategies, including the use of social networks
	17	J. D. Allen, A. M. Stoddard e G. Sorensen	2008	The authors examined the relationship between social network characteristics and adherence to breast cancer screening. The results obtained indicate that social network characteristics have a modest impact on screening, and that previous adherence is the main predictive factor of future behaviour
	18	J. Ye, S. D. Williams e Z. Xu	2009	The aim of this research was to analyse the relationship between social networks and colorectal cancer screening adherence. The authors concluded that individuals who were socially isolated were less likely to adhere to colorectal cancer screening
	19	N. L. Keating, A. J. O'Malley, J. M. Murabito, K. P. Smith e N. A. Christakis	2011	The aim of this research was to assess if adherence to screening for breast, prostate, or colorectal cancer is influenced by the screening behaviours of friends, coworkers, and close family members. The authors concluded that the screening behaviours of the network contacts had minimal influence on screening behaviours

Table 1. State of the art.

Methods

Data

This original research is based on data of the Portuguese North Regional Health Administration (ARSN) concerning persons with diabetes convened for DR population-based screening.

Were selected the subjects that met cumulatively the following inclusion criteria:

– Persons with diabetes registered in the ARSN's primary health care units;
– Persons with diabetes convened for DR screening during the year 2018.

The subjects correspond to 75,921 persons with diabetes invited for DR screening, distributed by twenty ACES, as illustrated in Table 2. Figure 1 illustrates the geographic area covered by each ACES.

The initial data set includes the following variables: age; gender; 7-digit home address postal code; professional status; ACES; Primary Health Care Unit; type of Primary Health Care Unit; family file number in Primary Health Care Unit (encrypted); existence or not of a family physician, number of consultations at the Primary Health Care Unit in the last 12 months, and type of diabetes. Subsequently, data from the National Institute of Statistics (INE)[25]were used to obtain the variables "income (median)" and "educational qualifications (distribution)", by postal code with 7 digits, as these variables are identified in the literature as strongly related to the adherence rate[22].

All methods of data gathering were carried out in accordance with relevant guidelines and regulations. The experimental protocol was approved by ARSN.

The authors did not have any direct contact with the subjects participating in the study.

The data obtained from INE are publicly available and of a general nature, not allowing the identification of the subjects involved. The data provided by ARSN were collected by the institution, in accordance with the legislation applicable in the Portuguese Public Administration, including informed consent from all subjects and/or their legal guardian(s)[26,27].. Moreover, the data provided by ARSN for this research went through a set of mechanisms that guarantee the protection of privacy (for example encryption and anonymization), and all the procedures were duly endorsed by the ARSN ethics committee, in strict compliance with all issues related to access to Public Administration data, and the data protection regime.

Network construction

We consider three types of relationships obtained through the variables provided by ARSN. The first relationship (probability equal to 1) was based exclusively on the existence of a close family relationship, obtained through the family file number registered in the primary health care unit. The second type of connection is based on

ACES	Resident population	Persons with diabetes	Persons with diabetes invited for DR screening
Alto Ave	256,696	22,028	5561
Alto Tâmega e Barroso	94,143	9062	0
Aveiro Norte	113,188	9603	1653
Baixo Tâmega	182,125	14,766	2514
Barcelos/ Esposende	154,645	13,312	4140
Braga	181,494	13,140	2691
Douro Sul	74,095	7316	0
Espinho/ Gaia	183,524	16,365	919
Famalicão	133,832	10,176	3279
Feira/ Arouca	161,671	12,137	3307
Gaia	152,062	12,660	1840
Gerês/ Cabreira	108,913	9052	3040
Gondomar	166,522	15,148	2984
Maia/ Valongo	229,164	17,564	4516
Marão e Douro Norte	105,025	10,030	0
Porto Ocidental	136,369	12,038	174
Porto Oriental	101,222	9743	2857
Póvoa de Varzim/ Vila do Conde	142,941	12,575	3226
Santo Tirso/ Trofa	110,529	10,698	2674
ULS Alto Minho	244,836	22,253	7802
ULS Matosinhos	175,478	15,129	3660
ULS Nordeste	136,252	13,511	4180
Vale Sousa Norte	161,792	13,465	2008
Vale Sousa Sul	175,852	13,724	0

Table 2. Distribution of the persons with diabetes invited for DR Screening, number of persons with diabetes and resident population by ACES.

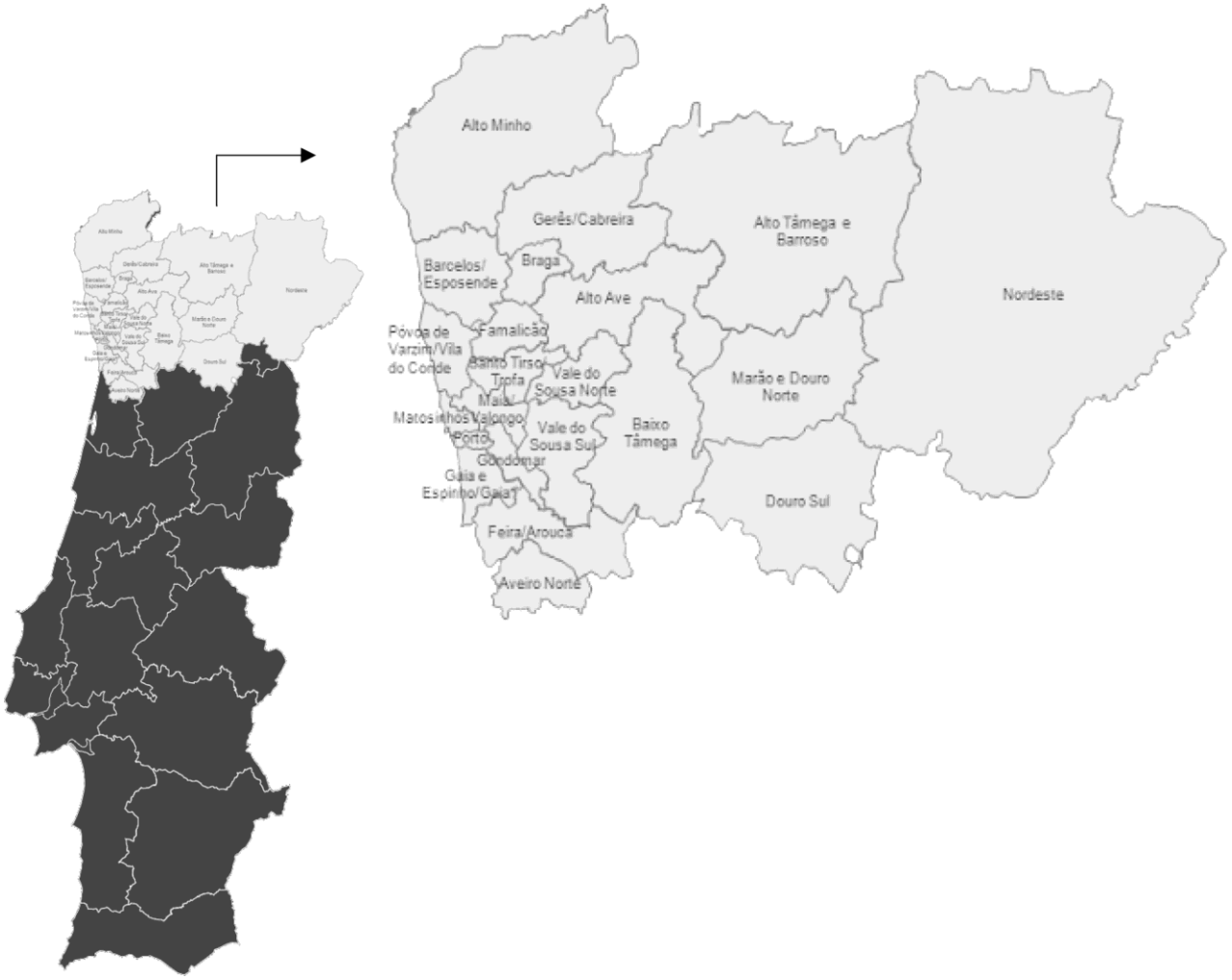

Fig. 1. ARSN's ACES geographical coverage. (Adapted from[24]).

the variables age and postal code with seven digits of the area of residence, namely the possible existence of a relationship was considered when the persons with diabetes live in the same postal code and the age difference is less than 5 years. The third type of relationship is based on the primary care unit where the person with diabetes is registered and the number of times he/she has had an appointment in the last 12 months. We considered the possibility of the existence of a relationship when the persons with diabetes are enrolled in the same health unit and had at least 5 consultations in the last 12 months. As it was not possible to accurately determine the probabilities in the last two types of relationships, it was decided to consider the value of 0.25 in both cases. The literature focused on the study of human interactions in near geographic spaces[28,29] provided some support for the reasonableness of the assumption in the case of geographic proximity to the residence (second type of relationship). As for the third type of relationship, based on diabetes consultations in the same health unit, we were advised by ARSN experts. According to them, it is common practice to schedule these appointments for the same day and at the same hour, for reasons of logistical ease of services. Therefore, it is not uncommon for the time spent in the waiting room to be prolonged and for persons with diabetes to end up establishing some complicit relationships.

After defining the probability of a social relation, persons with diabetes (nodes) of the same ACES were organized in an N-by-N square matrix using SPSS Modeler 18.2 software. The data entries represent a relationship between a pair of nodes (edges). Twenty social networks were built, one for each ACES, which reflect the way the diabetic population relates to each other. Figure 2presents the graphic representation of each of the 20 social networks (one for each ACES) built on Gephi software, using the force Atlas algorithm for network spatialization and to help its interpretation[30]. Visually the networks are made up of dots, which correspond to the persons with diabetes, and edges that represent the existence of a relationship between two persons with diabetes in the network. The edges are thicker the greater the probability of the relationship existing. Different colours were assigned to correspond to different communities. For example, in the case of ACES Espinho/Gaia, made up of health centres in the area covered by two main cities (Espinho and Gaia), we can observe the existence of two main communities (blue and green dots) strongly connected. There are also numerous less connected persons with diabetes (red dots).

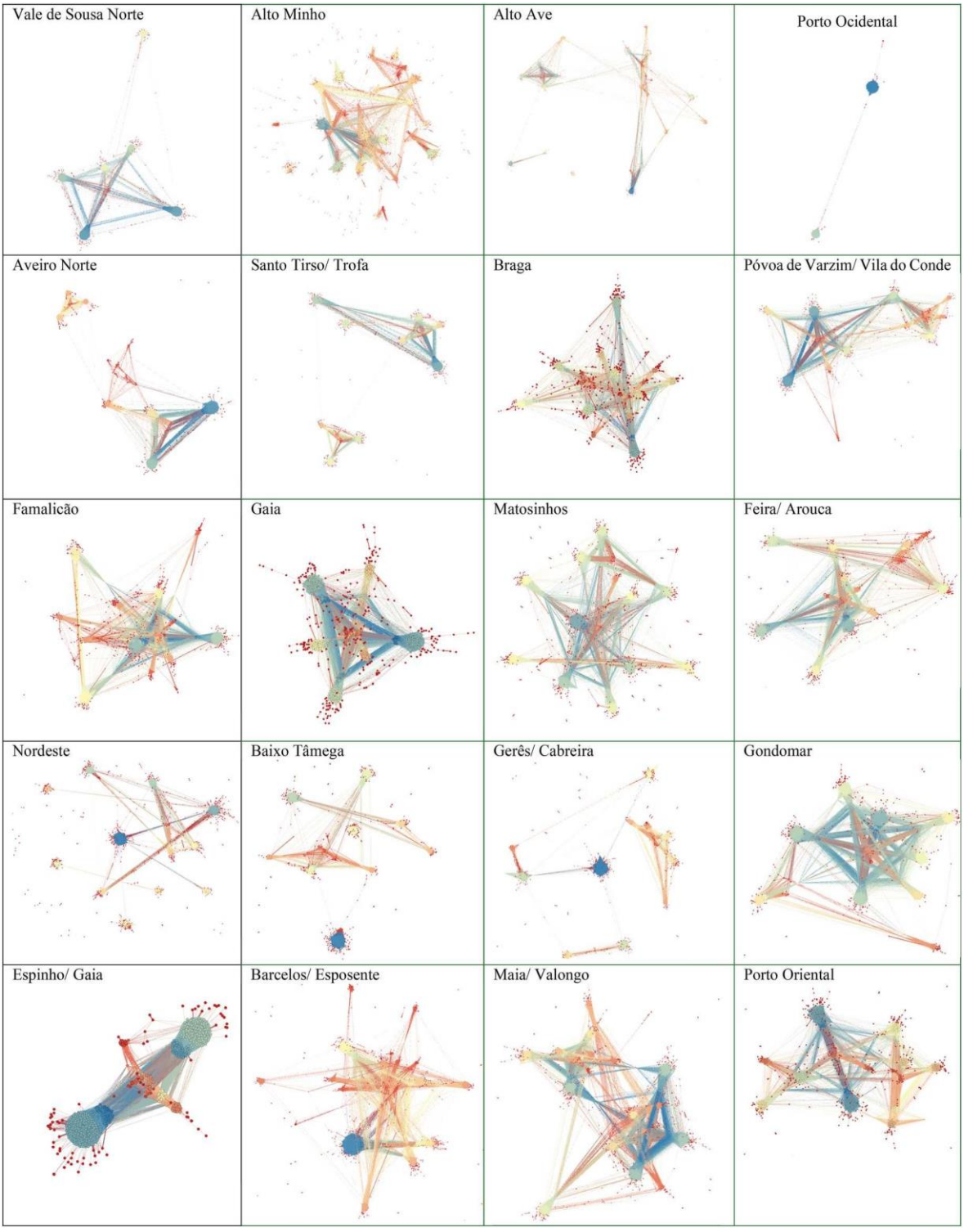

Fig. 2. Network's graphic representation.

Social networks evaluation metrics

After obtaining the 20 social networks, the Gephi software was also used to calculate two different sets of metrics, differentiated by the level of analysis: metrics at the level of the whole network; and node level metrics. The first set of metrics provides more compact information and allows the assessment of the overall structure of the network, giving insights about important properties of the underlying social phenomena. The second explores individual metrics to understand how the position of a node (individual) within the overall structure of the graph, helps to understand behavioural patterns. Tables 3 and 4present, respectively, the list of global and individual metrics calculated for this research[31]. Modularity, Connected Components, Average Degree, and

Network Metrics	Description
Number of Nodes	Number of individuals composing the network
Number of Edges	Number of relations (interactions) between individuals
Average Degree	The average degree is the mean of the degrees of all nodes in a network
Avg. Weighted Degree	Average sum of weights of the edges of nodes
Network Diameter	The diameter is given by the maximum eccentricity of the set of vertices in the network. Sparser networks have generally greater diameter than full matrices, due to the existence of fewer paths between pairs of nodes. This metric gives an idea about the proximity of pairs of nodes in the network, indicating how far two nodes are, in the worst of cases
Graph Density	Density can explain the general level of connectedness in a network. It is given by the proportion of edges in the network relative to the maximum possible number of edges. It goes from a minimum of 0, when a network has no edges at all, to a maximum of 1, when the network is perfectly connected (also called complete graph or clique)
Modularity	Modularity metrics strength of division of a network into communities (modules, clusters). Metrics takes values from range $< -1, 1 >$. Value close to 1 indicates strong community structure. When Q = 0 then the community division is not better than random
Connected Components	Connected components refer to a set of vertices that are connected to each other by direct or indirect paths. In other words, a set of vertices in a graph is a connected component if every node in the graph can be reached from every other node in the graph
Avg. Cluster Coefficient	The local clustering of each node is the fraction of triangles that actually exist over all possible triangles in its neighbourhood. Roughly speaking it tells how well connected the neighbourhood of the node is. If the neighbourhood is fully connected, the clustering coefficient is 1 and a value close to 0 means that there are hardly any connections in the neighbourhood. The average clustering coefficient of a graph is the mean of local clustering
Avg. Path Length	Average path length is a concept in network topology that is defined as the average number of steps along the shortest paths for all possible pairs of network nodes. It is a measure of the efficiency of information or mass transport on a network

Table 3. Description of network level metrics.

Node Level Metrics	Description
Eccentricity	The eccentricity measure captures the distance between a node and the node that is furthest from it
Closeness Centrality	Closeness centrality is a measure that indicates how close a node is to all the other nodes in a network. A high closeness centrality means that there is a large average distance to other nodes in the network
Harmonic Closeness centrality	Harmonic Centrality is a variant of Closeness Centrality, that reverses the sum and reciprocal operations in graphs with unconnected clusters, the harmonic centrality could be a better indicator of centrality than closeness centrality
Betweenness Centrality	Betweenness centrality is a measure based on the number of shortest paths between any two nodes that pass through a particular node. Nodes around the edge of the network would typically have a low betweenness centrality. A high betweenness centrality might suggest that the individual is connecting various parts of the network together
Degree	The degree of a node is the number of relation (edge) it has. It is the sum of edges for a node
Weighted Degree	The weighted degree is based on the number of edges for a node but pondered by the weight of each edge. It is the sum of the weight of the edges
Authority	The authority indicates the value of the information that the node holds. The relevance of an authority is "measured" by the number of inward links (or simply by the number of links in undirected graphs)
Modularity Class	Modularity class identifies nodes that are more densely connected than to the rest of the network. Those nodes have the same modularity class
Component Number	A connected component of an undirected graph is a maximal set of nodes such that a path connects each pair of nodes. The component number identifies a group of nodes that belong to the same components
Clustering	Clustering is the fraction of triangles that do exist over all possible triangles in its neighbourhood. Roughly speaking it tells how well connected the neighbourhood of the node is. If the neighbourhood is fully connected, the clustering coefficient is 1 and a value close to 0 means that there are hardly any connections in the neighbourhood
Triangles	Counts the number of triangles for each node in the graph. A triangle is a set of three nodes where each node has a relationship to the other two. In graph theory terminology, this is sometimes referred to as a 3-clique Triangle counting is used to detect communities and measure the cohesiveness of those communities. It is also used to determine clustering coefficients
Eigen centrality	Eigenvector centrality is a centrality index that calculates the centrality of a node based not only on their connections, but also based on the centrality of that node's connections

Table 4. Description of node level metrics.

Average Path Length are the most relevant global metrics for our research. Degree and Weight Degree are the most relevant individual metrics.

Global and node level network metrics relationship with the adherence to screening was analysed using two different perspectives: correlation between global level network metrics and ACES adherence rate and cluster analyses based on node level network metrics. For the first analysis, Pearson and Spearman correlations[32] between global level network metrics and the ACES adherence rate were calculated, based on the results obtain from each ACES network (Table 3). The clusters analysis using the k-means algorithm was conducted with IBM SPSS Modeler 18.2[33],, being the inputs, the node level metrics described in Table 4, and the "Adherence", that assumes the value 1 when the diabetic adhered to the screening and 0 otherwise.

Statistical analysis

This research aims to analyse the influence of the persons with diabetes' social network structure in the adherence to DR screening, by prosecuting to specific objectives: 1 – identify the correlation of the networks global metrics and the ACSE screening adherence rate. 2 – identify specific groups of persons with diabetes, concerning their individual social network features and their screening behaviours. To achieve the first goal, global network

ACES	Nodes	Edges	Average Degree	Avg. Weighted Degree	Network Diameter	Graph Density	Modularity	Connected Components	Avg. Cluster Coefficient	Avg. Path Length	Adherence rate
Vale do Sousa Norte	2008	197,154	196.369	4933.765	9	0.098	0.801	32	0.943	3.123	75.94%
ULS Alto Minho	7802	846,604	217.022	5480.531	14	0.028		103	0.933	5.302	73.36%
Alto Ave	5561	467,894	168.277	4235.794	14	0.03	0.907	124	0.942	4.567	72.49%
Aveiro Norte	1653	121,016	146.42	3691.349	10	0.089	0.753	25	0.935	3.628	70.68%
Santo Tirso/ Trofa	2674	240,044	179.539	4518.811	11	0.067	0.85	49	0.943	4.104	70.05%
Braga	2691	137,013	101.831	2559.922	10	0.038	0.864	72	0.915	3.207	67.61%
Famalicão	3279	272,923	166.467	4195.669	10	0.051	0.806	94	0.91	3.098	66.95%
Gaia	1840	155,317	168.823	4250.951	11	0.092	0.751	49	0.907	2.727	65.71%
UlS Matosinhos	3660	329,296	179.943	4520.082	10	0.049	0.881	96	0.942	3.221	65.40%
ULS Nordeste	4180	299,093	143.107	3608.026	15	0.034	0.892	134	0.928	5.105	64.67%
Baixo Tâmega	2514	205,256	163.29	4108.055	14	0.065	0.825	47	0.958	4.414	64.60%
Gerês/ Cabreira	3040	290,352	191.021	4810.411	13	0.063	0.832	52	0.946	4.697	63.63%
Espinho/ Gaia	919	105,076	228.675	5827.258	7	0.249	0.514	16	0.922	2.168	63.06%
Barcelos/ Esposende	4140	488,785	236.128	5957.391	10	0.057	0.779	52	0.939	3.423	62.37%
Maia/ Valongo	4516	477,864	211.632	5343.08	13	0.047	0.847	65	0.913	3.806	60.66%
Porto Oriental	2857	305,344	213.751	5380.942	9	0.075	0.813	45	0.937	2.901	57.38%
Gondomar	2984	356,444	238.903	6007.976	11	0.08	0.831	49	0.943	2.938	56.70%
Feira/ Arouca	3307	335,054	202.633	5106.033	11	0.061	0.848	32	0.916	3.3	54.07%
Póvoa Varzim/ Vila do Conde	3226	310,813	192.692	4844.529	10	0.06	0.83	49	0.929	3.177	52.37%
Porto Ocidental	174	5397	62.034	1561.207	7	0.359	0.452	4	0.984	2.232	44.36%

Table 5. Network level metrics. As showed, the adherence rate varies between 44.36% in ACES Porto Ocidental, and 75.94% in ACES Vale do Sousa Norte.

Network Measure	Correlation with Adherence Rate
Nodes	0.371
Edges	0.260
Average Degree	0.137
Avg. Weighted Degree	0.136
Network Diameter	0.363
Graph Density	−0.513**
Modularity	0.435*
Connected Components	0.440*
Avg. Cluster Coefficient	−0.261
Avg. Path Length	0.481**

Table 6. Pearson linear correlation coefficients. Notes: * p-value < = 0.1; ** p-value < = 0.05.

metrics were calculated, and Pearson and Spearman correlation coefficients were determined to assess a possible linear or ordinal association between each of the network metrics and the adherence rate[32]. To accomplish the second goal, was performed a node level cluster analyses based on diabetic (node) level network metrics, and his screening behaviour. Chi-square tests were performed to access the underline interference of socio-economic, health related and previous DR screening behaviour in the cluster's formation.

Results

Networks metrics and screening adherence

For each one of the 20 social networks were calculated 10 global metrics. Table 5 presents the values obtained and Table 6 presents the Pearson linear correlation coefficients between each measure and the adherence rate.

Modularity, Connected Components, and the Average Path Length present significant positive and moderate linear correlations (values between 0.4 and 0.5), showing that when these metrics increase the adherence rate also tends to increase. Graph Density is negatively and moderate correlated with the adherence rate, presenting a Pearson coefficient of −0.513, showing that when this metric increases the adherence rate tends to decrease.

Metrics for individual nodes and clusters analysis

The quality of the clusters analysis is classified as "fair" (Silhouette measure of cohesion and separation of 0.4. The centroids (average of the input variables) of each one of the five clusters obtained is presented in Table 7. Moreover, we perform the parametric test analysis of variance (one-way ANOVA) to determine whether

		Cluster—1	Cluster—2	Cluster—3	Cluster – 4	Cluster – 5	Total	ANOVA F test	η	η^2
Inputs	Adherence	Yes	Yes	Yes	Yes	No	Yes	18,106.51 **	0.697	0.486
		(52.20%)	(100.00%)	(65.90%)	(74.50%)	(100.00%)	(65,0%)			
	Authority	0	0.05	0	0	0.03	0.01	43,952.45 **	0.890	0.792
	Closeness centrality	0.26	0.34	0.97	0.31	0.35	0.33	41,541.57 **	0.884	0.782
	Clustering	0.68	0.96	0.19	0.96	0.94	0.84	6658.12 **	0.604	0.365
	Degree	45.22	380.38	16.13	223.52	363.74	186.63	39,608.48 **	0.880	0.774
	Eccentricity	8.35	7.22	1.26	7.78	7.07	7.55	9438.939 **	0.670	0.449
	Eigen centrality	0.02	0.91	0	0.16	0.78	0.22	64,359.98 **	0.921	0.848
	Harmonic closeness centrality	0.29	0.42	0.98	0.36	0.43	0.38	38,785.89 **	0.878	0.770
	Triangles	2280.07	73,573.81	1284.42	25,137.59	64,469.60	24,519.94	18,497.75 **	0.784	0.615
	Weighted Degree	1141.34	9592.14	422.17	5621.78	9188.08	4700.93	38,687.49 **	0.877	0.770
	Betweenness centrality	1455.51	4203.59	2.48	5621.60	5280.26	4144.13	42.25 **	0.060	0.004
Size		28.66%	9.29%	4.55%	50.71%	6.80%	100.00%	100.00%	100.00%	100.00%
		(13,272)	(4,300)	(2,105)	(23,484)	(3,150)	(46,311)	(46,311)	(46,311)	(46,311)

Table 7. Clusters' centroids, ANOVA F test, eta (η) measure of association and effect size (η2). Notes * p_value < = 0.1; ** p_value < = 0.05.

there are any statistically significant differences between the means of the input variables in the five clusters (independent groups) and we assess the effect size using the eta squared ratio (η^2). The results show significant differences between the means of all the input variables in the five clusters (all $p < 0.001$) and for all the input variables the effect size is considered large, except for Betweenness Centrality ($\eta^2 = 0.004$) where it is considered negligible Thus, these results reinforce the quality of the clusters and the differences between the five clusters[34].

The observation of each cluster characteristics leaded to the following analysis:

Cluster 1 – Poorly connected with low adherence: subjects with few connections to other elements of the diabetic community (Degree = 45.22; Weighted Degree = 1141.34), with an adherence below average, although most of the members adhere to the screening program (adherence rate = 52.2%).

Cluster 2 –Very connected, adherents: subjects very connected with other members of the diabetic population (Degree = 380.38; Weighted Degree = 9592.14), who adhered to screening (adherence rate = 100%).

Cluster 3 – Isolates, with average adherence: have few or no links to other persons with diabetes in the network (Degree = 16.13; Weighted Degree = 422.17). This group adherence is close to average.

Cluster 4 – Reasonably connected, with high adherence: subjects with a reasonable number of connections (Degree = 223.52; Weighted Degree = 5621.78) and an adherence above average.

Cluster 5 –Very connected, non-adherent: subjects very connected with other members of the diabetic population (Degree = 363.74; Weighted Degree = 9188.08), who did not adhere to screening.

Contrary to the conclusions of the previous studies, that state that individuals who are socially isolated are less likely to adhere to the colorectal cancer screening[18], the results obtained in this research revealed that, in DR screening, the group of "isolated" persons with diabetes is not the most problematic regarding adherence (adherence rate of 65.9%, slightly higher than the global adherence rate of 65.0%). In fact, the non-adherence phenomenon is especially evident in cluster 5, a group of highly connected individuals with 100% of non-adherence, which represents 6.7% of the target population. The second cluster with the lower adherence rate (52.2%) is cluster 1, a group of individuals with few connections with other persons with diabetes, but higher connected than the "Isolates" group, with corresponds to 28.8% of the target population.

Regarding a more general characterization of the persons with diabetes of each cluster, Table 8 presents Chi-squared test of independence and Cramer's V, between the five clusters, socio-demographic, health status, and health services utilization variables.

As we can see there is a significant relationship between the cluster and most of the variables analysed ($p < 0.001$). However, Cramer's V show that generally those variables have a low effect, except for the Number of primary health care consultations in the last 12 months (Cramer's V = 0.31). Indeed, the persons with diabetes of clusters 1 e 3 tend to have fewer consultations in the past 12 months. There is also a slight tendency for users of UCSP (health units dedicated to users without a family doctor) and/or USF model A (transition model for model B health units) to be more prevalent in clusters 1 and 3 (Cramer's V = 0.17).

Discussion

The present work aims to analyse the influence of the persons with diabetes' social network, more specifically their contacts with other members of the target population, in the individual decision of adhere or not to the screening. More specifically, it is intended to: analyse the influence of the characteristics of social networks in different regions on the adherence rates; categorize the persons with diabetes based on their social network and screening behaviour.

To conduct this research, global and node level network metrics were calculated and its relationship with the adherence to screening was studied using two different perspectives: correlation between global level network metrics and the Primary Health Centre Group adherence rate; cluster analyses based on node level network metrics.

Type	Variable	Cluster						
		1 - Poorly connected, low adherence	2 - Very connected, adherents	3 - Isolates, average adherence	4 - Reasonably connected, high adherence	5 - Very connected, non-adherent	Total	Chi-squared test Cramer's V
Size		28.7% (13,272)	9.3% (4,300)	4.6% (2,105)	50.7% (23,484)	6.8% (3,150)	100.0% (46,311)	
Sociodemographic	Age (years)							
	[18;39]	0.6%	0.6%	1.1%	1.0%	1.6%	0.9%	X2=469.45** Cramer's V=0.05
	[39;54]	6.9%	6.8%	10.9%	8.1%	8.4%	7.8%	
	[54;64]	22.5%	22.0%	28.9%	21.9%	16.3%	22.0%	
	[64;74]	33.9%	35.5%	35.0%	33.2%	25.7%	33.2%	
	≥74	36.1%	35.0%	23.8%	35.8%	48.0%	36.1%	
	Gender							
	Masculine	49.2%	52.0%	46.1%	53.1%	57.3%	51.8%	X2=117.59** Cramer's V=0.05
	Feminine	50.8%	48.0%	53.9%	46.9%	42.7%	48.2%	
	Degree of urbanization f the area of residence							
	0	10.0%	10.6%	7.2%	8.7%	6.5%	9.0%	X2=1378.51** Cramer's V=0.10
	1	20.4%	14.6%	12.8%	13.5%	7.5%	15.1%	
	2	27.3%	19.8%	36.1%	26.5%	13.0%	25.6%	
	5	42.3%	55.0%	43.9%	51.3%	73.0%	50.2%	
	Professional status							
	Active	42.7%	38.8%	53.1%	37.4%	32.9%	39.5%	X2=404.74** Cramer's V=0.05
	Student	0.2%	0.1%	0.7%	0.3%	0.5%	0.3%	
	Not active	11.5%	13.5%	11.0%	13.4%	12.6%	12.7%	
	Retired	45.1%	47.3%	34.6%	48.5%	53.7%	47.1%	
	Unknown	0.5%	0.3%	0.6%	0.4%	0.3%	0.4%	
	Income (median)							
	Unknown	2.2%	3.6%	3.2%	3.9%	3.8%	3.3%	X2=689.13** Cramer's V=0.06
	≤ 8,511	8.6%	8.3%	13.4%	10.2%	9.0%	9.6%	
	[8,511;9,811]	19.0%	16.6%	17.2%	20.6%	16.5%	19.3%	
	[9,811;11,167]	20.7%	18.9%	18.3%	19.3%	14.8%	19.3%	
	[11,167;12,649]	22.1%	26.5%	21.1%	16.0%	21.0%	19.3%	
	[12,649;17,400]	19.3%	18.6%	18.7%	19.3%	21.5%	19.4%	
	≥17,400	8.1%	7.5%	8.0%	10.6%	13.4%	9.7%	
	Education							
	Less than elementary school	2.2%	3.6%	3.2%	3.9%	3.8%	3.3%	X2=394.88** Cramer's V=0.06
	Less than middle school	20.3%	16.8%	21.3%	21.4%	17.3%	20.4%	
	Less than high school	55.3%	56.7%	55.6%	50.6%	47.3%	52.5%	
	High school	12.5%	14.4%	10.3%	11.8%	16.2%	12.5%	
	College degree	9.6%	8.6%	9.6%	12.2%	15.4%	11.2%	
Relationship with health services	Type of Health Unit							
	UCSP	24.0%	22.2%	17.6%	12.7%	19.9%	17.5%	X2=2686.02** Cramer's V=0.17
	USF A	25.7%	0.3%	28.9%	24.9%	7.6%	21.9%	
	USF B	50.3%	77.5%	53.5%	62.4%	72.5%	60.6%	
	Followed by family physician							
	No	13.8%	8.5%	15.9%	9.2%	16.3%	11.2%	X2=114.38** Cramer's V=0.04
	Yes	86.2%	91.5%	84.1%	90.8%	83.7%	88.8%	
	Number of consultations at the Primary Care Unit in the last 12 months							
	0	3.1%	0.0%	5.7%	0.0%	0.0%	1.1%	X2=17972.36** Cramer's V=0.31
	1	2.8%	0.0%	4.3%	0.0%	0.0%	1.0%	
	2–3	35.1%	0.0%	51.5%	0.3%	0.0%	12.6%	
	4–6	36.2%	33.6%	32.4%	35.3%	31.7%	35.0%	
	≥ 6	22.8%	66.4%	6.2%	49.1%	33.9%	41.6%	

Continued

Type	Variable	Cluster					Total	Chi-squared test Cramer's V
		1 - Poorly connected, low adherence	2 - Very connected, adherents	3 - Isolates, average adherence	4 - Reasonably connected, high adherence	5 - Very connected, non-adherent		
Health Status	Type of diabetes (I or II)							
	Type I	7.2%	7.4%	5.7%	8.0%	11.4%	7.8%	X2=78.68** Cramer's V=0.04
	Type II	92.8%	92.6%	94.3%	92.0%	88.6%	92.2%	
	Body Mass Index (BMI)							
	NA	67.50%	65.20%	64.70%	61.70%	75.70%	64.8%	X2=335.10** Cramer's V=0.04
	≤18.5	0.10%	0.10%	0.00%	0.10%	0.10%	0.1%	
	[18.5;24.9]	5.00%	5.10%	5.20%	5.70%	4.80%	5.4%	
	[25;30]	14.30%	15.70%	16.20%	15.90%	10.50%	15.1%	
	≥30	13.10%	13.90%	14.00%	16.50%	8.80%	14.6%	
	Blood Glucose Leves (HBA1C)							
	NA	67.50%	65.40%	64.90%	61.90%	75.80%	64.9%	X2=338.77** Cramer's V=0.06
	<8	28.70%	29.30%	31.10%	32.80%	19.30%	30.3%	
	≥8	3.80%	5.30%	4.00%	5.30%	4.80%	4.8%	
DR Screening	Days elapsed between calls							
	NA	16.80%	16.10%	16.20%	13.20%	13.70%	14.7%	X2=522.65** Cramer's V=0.05
	<365	21.00%	16.10%	20.50%	22.20%	13.80%	20.6%	
	[365;455]	25.60%	26.10%	31.10%	29.20%	27.00%	27.8%	
	[455;545]	15.30%	17.70%	13.40%	15.80%	15.00%	15.7%	
	[545;635]	6.70%	7.80%	6.80%	5.20%	8.50%	6.2%	
	≥635	14.60%	16.10%	12.10%	14.30%	22.00%	15.0%	
	Number of times the diabetic was convened							
	1	17.10%	16.10%	16.30%	13.50%	13.70%	14.9%	X2=643.42** Cramer's V=0.06
	2	23.90%	20.90%	22.40%	24.20%	24.10%	23.7%	
	3	41.40%	48.80%	36.70%	38.30%	48.00%	40.8%	
	4	15.60%	12.00%	20.70%	20.30%	13.00%	17.7%	
	5	2.00%	2.20%	3.90%	3.70%	1.20%	2.9%	

Table 8. Distribution of the diabetic population variables by cluster, Chi-squared independence test and Cramer's V. Notes: * p_value < = 0.1; ** p_value < = 0.05.

The results revealed that Modularity, Connected Components and the Average Path Length present significant positive Pearson linear correlations and that Graph Density is negatively correlated with the adherence rate.

The second perspective of analysis showed that node level metrics, associated with each diabetic position on the social network, allows the identification of groups where the problem of non-adherence is especially high. The analysis led to the identification of five different clusters:

Cluster 1 – Poorly connected: subjects with few connections to other elements of the diabetic community.

Cluster 2 – Adherents, very connected: subjects very connected with other members of the diabetic population, who adhere to screening.

Cluster 3 – Isolates: have few or no links to other persons with diabetes in the network.

Cluster 4 – Reasonably connected.

Cluster 5 – Non-Adherent, very connected: subjects very connected with other members of the diabetic population, who did not adhere to screening.

Contrary to the conclusions of previous studies, that individuals who are socially isolated are less likely to adhere to the colorectal cancer screening[18], the results obtained in this research demonstrate that, in DR screening, the group of "isolated" persons with diabetes is not the most problematic regarding adherence (adherence rate of 65.9%, slightly higher than the global adherence rate of 65.0%). The non-adherence phenomena is especially evident in cluster 5, a group of highly connected individuals with 100% of non-adherence, which represents 6.7% of the target population. In Portugal, there is a coexistence of a National Health Service, which tends to be free, and Private Health Care Providers where the user bears the costs. In this context, in meetings with ARSN experts, a hypothesis was put forward to explain a small percentage of non-adherence. They believed in the existence of a group of persons with diabetes (although not very significant) who do not adhere to screening because they are being monitored in the private sector. Theoretically, this group would be characterized by higher incomes, residence in urban areas (where most private institutions are located) and higher levels of education. E.g., Cluster 5 seems to bring together these characteristics, however more research will be needed to verify the validity of this hypothesis. The second cluster with the lower adherence rate (52.2%) is cluster 1, a group of individuals with few connections with other persons with diabetes, but higher connected than the "Isolates" group, representing28.8% of the target population. The persons with diabetes in this cluster, in general, received fewer previous calls for DR screening (what could indicate that the diabetes is more recent), and have more controlled HBA1C levels (lower risk of DR), which could be part of the explanation to the low screening

adherence rate.

Among the strengths of this research, we highlight the used of real data and the large dimension of the data set (75.921 persons with diabetes distributed by 20 Primary Health Centre Groups of the Portuguese North Region Health Administration, invited for screening in 2018), in addition to sound techniques of Statistics and Network Science.

This research presents some limitations, namely, the social networks only comprise ties between members of the target population, neglecting other possible subjects that could influence the persons with diabetes decision of adhere or not to the screening; the links between persons with diabetes (edges) result of plausible, but not factual relations, except for the family relationship. However, even with the assumption of a 0.25 probability for type 2 and 3 relationships, the obtained very different networks that allowed to draw significant conclusions for the problem being studied. The former is next to be investigated in our research as well as with a robust sensitivity analysis to the probabilities here assumed.

Finally, more research is needed to better understand this phenomenon. The influence of the social network in DR screening could be studied considering different groups with different social and demographic features, like in the studies of Suarez et al., concerning cancer screening behaviour[14,15]. Would be important to assess the effectiveness of interventions that take into a count the structure of the social network, aiming to promote adherence to DR screening, and the influence of a broader social network, including members outside the diabetic community, should also be analysed. Some research was done in these areas focusing on cancer screenings[16,17], but not in DR screenings. In future work we intend to focus on some of these topics and test the predictive value of the persons with diabetes' social network features to their DR screening behaviour.

Conclusions

The results obtained allowed us to conclude that the structure of the social network and the position occupied by the diabetic in this network influence the behaviour of adherence to DR screening. Our research showed that less connected networks (where the average number of steps along the shortest path between two nodes is higher), strongly divided into communities and with a great number of connected components present the highest adherence rates. Node level metrics allowed the identification of groups where the problem of non-adherence is especially high. In our research, the non-adherence phenomenon is especially evident in a small group of highly connected individuals, which is contrary to the findings in the literature concerning oncologic screenings. We think that these results are of utmost relevance as a starting point for future research and as a framework to support decision-making and planning of interventions related with adherence to DR screenings.

Data availability

The data obtained from INE are publicly available [25]. The data from the Portuguese North Region Health Administration, were used under license for the current study, and so are not publicly available. However, data are available from the authors upon reasonable request, addressed to the corresponding author, and with permission of the Portuguese North Region Health Administration.

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Author contributions
AP: Conceptualization, Methodology, Data preparation, Network construction, Data analyses. Writing original draft. AA: Conceptualization, Methodology, Expert advice, Writing- Reviewing and Editing. RL and FN: Conceptualization, Methodology, Supervision, Writing- Reviewing and Editing.

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Declarations Competing interests
The authors declare no competing interests.

Ethics approval
All methods of data gathering were carried out in accordance with relevant guidelines and regulations. The authors did not have any direct contact with the subjects participating in the study. The data obtained from INE are publicly available and of a general nature, not allowing the identification of the subjects involved[25]. The data provided by ARSN were collected by the institution, in accordance with the legislation applicable in the Portuguese Public Administration, including informed consent from all subjects and/or their legal guardian(s)[26,27]. Moreover, the data provided by ARSN for this research went through a set of mechanisms that guarantee the protection of privacy (for example encryption and anonymization), and all the procedures were duly endorsed by the ARSN ethics committee, in strict compliance with all issues related to access to Public Administration data, and the data protection regime. The present research does not include the use of experimental protocols.

Additional information

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4. Conclusion

The main objective of the present research was the study of population-based DR screenings, from the perspective of complexity sciences.

The enormous social, economic and personal impact of DR [45], when left untreated, its' proven trend of increasing prevalence [6], along with the complexity inherent to a population-based screening program [15], guided our initial motivation for choosing this topic.

However, the research process was not linear, undergoing adjustments as knowledge about the problem and the state of the art increased.

4.1. Summary and integration of contributions from published works

Initially, we dedicated our efforts to increasing our knowledge on the topic. Here we got a real sense of the difficulties that exist in collecting rigorous and comparable information about the different DR screenings implemented in different parts of the world. As the WHO recognizes [2], the existence of different perceptions of what could appear to be objective concepts, multiple screening strategies (method, screening intervals, location, professionals involved, new technologies, etc.), different health systems and services, different stakeholders and organizations involved, and even language barriers, make the sharing of knowledge a very difficult task. Therefore, we decided to contribute to fulfil this gap, developing a systematic and exhaustive review of all scientific and technical literature on screening (or screenings) for DR in Portugal. This work resulted in our first paper: "Five Regions, Five Retinopathy Screening Programmes: A Systematic Review of how Portugal addresses the challenge" [17]. The main contributions of this paper are: i) the assemblage of knowledge in the field of DR screenings, providing the first systematic review of the Portuguese experience; ii) the identification of the main diabetic retinopathy screening implementation problems, the possible solutions for operational planning of future screenings and the possible improvements for the existing ones; iii) evidence of the importance of adequate governmental funding, national guidelines that precise the role of the different intervenient, and of politic measures that guarantee the involvement of all parts.

The conclusions obtained are in line with the results presented by the WHO, in its' 2001 situational analysis [2], both in terms of general conclusions and on the Portuguese situation. In fact, by providing a high level of detail, our study indicates potential explanations for some of the facts observed by the WHO.

Next, and since we were considering approaching the study of DR screening through

computer simulation techniques, we carried out a systematic review of computer simulation models applied to DR screening. This work gave rise to our second paper: "Simulation Models in Diabetic Retinopathy Screening: A Systematic Review" [19]. This systematic review allowed the identification of two important gaps in the literature: the lack of simulation models focused on screening adherence; and, the lack of simulation models that relay on techniques suitable for the study of the complexity inherent to population-based DR screening. Moreover, a framework for qualitative assessment, which incorporated input parameters; modelling approach, transparency of input data sources/assumptions, sensitivity analyses, validation, and outcomes was developed.

The Portuguese Northern Region Health Administration made available for this research data of all calls for DR screening, in its geographic coverage area, sent between the years 2013 and 2018. The sample consists of 271,867 calls for DR screening, which corresponds to 108,620 different diabetics. Since the Northern Region Health Administration manages the north region entire screening process, the database allowed a 360-degree view, starting from the individual characteristics of each diabetic, to the sending of the call, personal decision to adhere or not to the screening, result of the retinography, when applicable, and subsequent treatment in a hospital environment of the positive cases. The following variables were collected: age; gender; professional status; existence of telephone contact for sending reminders; Health Centre Cluster; Primary Health Care Unit; type of Primary Health Unit; existence of a family doctor; reason for exemption from payment of charges for services, when applicable; number of consultations at the Primary Care Unit in the last 12 months; type of diabetes (I or II); Body Mass Index (BMI); Blood Glucose Levels (HBA1C); month of call for screening; days elapsed between calls; number of times the diabetic was called; last screening result; percentage of times the diabetic adhered to previous screenings, and, indication of whether the patient is receiving hospital treatment. Subsequently, data from the National Institute of Statistics was used to obtain the variables income (median), educational qualifications (distribution by postal code with 7 digits), and degree of urbanization of the geographical areas. The statistical analyses of the data set allowed the identification of sociodemographic and behavioral characteristics regarding health services, related with adherence to the DR screening program. The results are generally consistent with those found in the literature, i.e. younger and older diabetics tend to adhere less to the screening, as do those with higher incomes. Higher educational qualifications, as well as a regular habit of using primary health care services, are conducive to higher adherence rates. Diabetics who received a greater number of previous invitations for screening and who had adhered more frequently in the past, present higher adherence rates. There were,

however, results not supported by the literature. Contrary to what was expected in the northern region of Portugal, men adhere more to screening than women, and diabetics with positive results in previous screenings present lower adherence rates in the next screening. Regarding this last result, a more in-depth analysis indicates as a possible explanation the lack of communication between different levels of health care providers resulting in the inappropriate sending of invitations to diabetics who are already being treated in a hospital environment.
The main contributions of this step of the research were the identification of sociodemographic and behavioral features that influence DR screening adherence, and the detection of internal failures in the screening process.

Armed with the knowledge obtained through the two systematic reviews of the literature, the results of the statistical analyses, and counting on the guidance of the experts from North Regional Health Administration, we developed our first agent based model prototype, to simulate adherence to DR screening. In this first model, we used a logistic regression model for the agents' decision. The results from our previous work were used for calibration and validation of the results obtained. Agent based modelling gave the model flexibility in the implementation of the predictive variables. The model showed a good ability to replicate reality and usefulness in staging scenarios in a specific geographic context. However, the model scalability and abstraction level were reduced since the main predictor, in the logistic regression, was the previously observed behavior in a specific screening program. This work resulted in a paper entitled "Adherence to the Screening of Diabetic Retinopathy: An Agent Based Simulation Model", published and presented in the 20th Portuguese Association for Information Systems Conference (CAPSI 2020) [64].

Given the limitations of our first model, we decided to develop a second prototype. This model was an agent-based model, which uses fuzzy logic for the agents' decision-making. The fuzzy logic components, as well as the variables that constitute each component, were established on the basis of the previous statistical analysis results and on the structure proposed by the Health Believe Model. Therefore, three fuzzy components were implemented: "access barriers", "knowledge of the disease", "quality/strategy of the screening program". The selection of the representative function for the variables that comprise each component was based on a statistical analysis of the distribution of the real data. The use of fuzzy logic components, allowed to increase the level of abstraction and the scalability of the model. The results obtained show close resemblance to the real world values, both in the training and in the test sets, which attests to the validity of the model for the study of DR screening adherence and its usefulness as a predictive tool for public health planning. This work resulted in the paper

“Computer simulation of diabetic retinopathy screening adherence: agent-based model with fuzzy logic”, published and presented in the 16th Iberian Conference on Information Systems and Technologies (CISTI 2021) [65].

We then developed a hybrid model, in which the agents' decision to adhere or not to the screening used a combination of logistic regression and fuzzy logic components in equal proportions. The exhaustive explanation of the development methodology, the results obtained and the critical comparison of the three models, resulted in one of our core publications: “The use of social simulation modeling to understand adherence to diabetic retinopathy screening programs” [22]. The results obtained indicate that it is possible to predict the rate of adherence to screening for DR using demographic and socioeconomic data for the target population, and information regarding the screening strategy. The use of the fuzzy components led to a high level of abstraction from the real data and showed predictive capability in new contexts. In fact, the model that used the logistic regression presented the best global result: a predicted adherence rate of 67.6%, a difference of only 1% in relation to the real value (66.6%). However, the logistic regression technique is of limited use in geographic areas aiming to begin a screening program, since the main predictors included in its equation are the percentage of times the diabetic had previously adhered and the result of the last screening. Nevertheless, this technique can be very useful and effective if the necessary data is available. The combined version showed no overall improvement in comparison to the fuzzy logic version. One important contribution of this research was to put forward a framework that is robust enough to advance the state of knowledge related to the development, calibration and validation of simulation models focused on the study of the adherence to population based screenings. The innovative combination of agent-based models with fuzzy logic resulted in a model that provides a good alternative to the existing traditional simulation techniques that lack flexibility and capacity of generalization.

We also conducted a set of experiments to illustrate as our models can be used to support decisions in health planning, while analyzing the effectiveness of various interventions.
We believe that the models developed can be of great help to the entities responsible for laws and decision-making by allowing the identification of groups/geographical locations where the problem of adherence to screening is particularly relevant, which factors have the greatest impact on the decision to adhere or not to the screening, and also when staging hypothetical interventions. Moreover, our model can easily be adapted to the study of adherence to other types of population-based screenings.

Throughout our research, we encountered numerous difficulties inherent to health

simulation with the incorporation of human behavior. We believe that sharing these difficulties and proposing a methodological approach to mitigate them would be useful. So, the paper "Simulation of human behavior in adherence to preventive health programmes - A methodological proposal and an example of its application", published and presented in the 19th Iberian Conference on Information Systems and Technologies (CISTI 2024) [66], presents a methodological proposal to the development of simulation models that consider heath related individual behavior and the relations and patterns that explain it.

None of our three versions of simulation models had into consideration the possible results of the interactions between members of the target population. This was because we did not find any literature that demonstrated that the social network could be relevant for the diabetics adherence behavior to screening.

Once we identified this gap in the literature, we decided to continue our research in this direction. So, our last paper "The role of the social network in the study of adherence to diabetic retinopathy screening programs" [23] aims to analyze the influence of the diabetics' social network structure in the adherence to DR screening, more specifically by their contacts with other members of the target population. This paper allowed to conclude that the structure of the social network and the position occupied by the diabetic in this network influence the behavior of adherence to DR screening. Our research showed that less connected networks (where the average number of steps along the shortest path between two nodes is higher), strongly divided into communities and with a great number of connected components present the highest adherence rates. Node level metrics allowed the identification of groups where the problem of non-adherence is especially high. In our research, the non-adherence phenomenon is especially evident in a small group of highly connected individuals, which is contrary to the findings in the literature concerning oncologic screenings. We think that these results are of utmost relevance as a starting point for future research and as a framework to support decision-making and planning of interventions related with adherence to DR screenings.

Figure 4 and Table 1 resume the main contributions of our research and their potential beneficiaries.

Figure 4 – Main Contributions

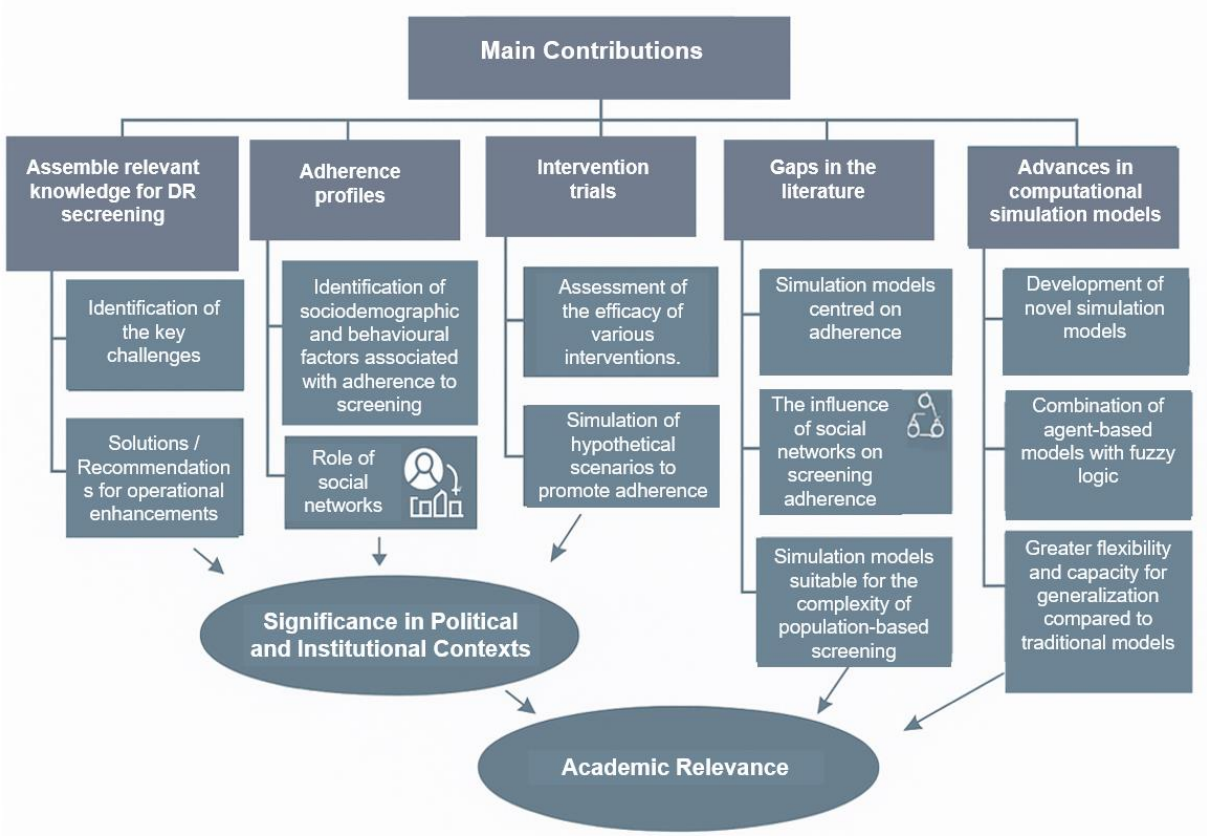

Table 1 – Main Contributions and Potential interested parties

	Contributions	Papers	Potential interested parties
Literature Reviews	Assemblage of knowledge in the field of DR screenings, providing the first systematic review of the Portuguese experience;	Pereira, A., Laureano, R., Neto F., (2021), Five Regions, Five Retinopathy Screening Programmes: A Systematic Review of how Portugal addresses the challenge. BMC Health Services Research (Q1), 21(1):756 (Core Publication) Pereira, A., Laureano, R., Neto F. (2024), "Simulation Models in Diabetic Retinopathy Screening: A Systematic Review" Submitted to Journal of Simulation (Core Publication)	National and international institutions with a role in issuing guidelines related to screening; Governments and policy makers; Institutions responsible for planning and implementing of DR screening; practitioners, academic researchers and general population.
	Identification of the main DR screening implementation problems, internal failures, possible solutions for operational planning of future screenings, and possible improvements for the existing ones;		National and international institutions with a role in issuing guidelines related to screening; Governments and policy makers; Institutions responsible for planning and implementing of DR screening; practitioners, academic researchers and general population.
	Evidence of the importance of adequate governmental funding, national guidelines that precise the role of the different intervenient, and of politic measures that guarantee the involvement of all parts;		National and international institutions with a role in issuing guidelines related to screening; Governments and policy makers; academic researchers.
	Identification of important gaps in the literature: the lack of simulation models focused on screening adherence; the lack of simulation models that relay on techniques suitable for the study of the complexity inherent to population-based DR screening; studies concerning the influence of the diabetics' social network in the adherence behaviour; studies concerning the influence of a parallel private health sector in population-based screening adherence;		Academic researchers
	Development of a framework for simulation models concerning population-based DR screenings that includes qualitative assessment, input parameters; modelling approach, transparency of input data sources/assumptions, sensitivity analyses, validation, and outcomes;		Academic researchers

	Contributions	Papers	Potential interested parties
Social Simulation Models	Identification of sociodemographic and behavioural features that influence DR screening adherence.	Pereira, A., Macedo, J., Afonso, A., Laureano, R., Neto F., (2024), "The use of social simulation modelling to understand adherence to diabetic retinopathy screening programs". Scientific Reports (Q1), 14(1), 4963 (Core Publication). Pereira, A., Laureano, R., Neto F., Macedo, J., (2020), "Adherence to the Screening of Diabetic Retinopathy: An Agent Based Simulation Model", 20th Portuguese Association for Information Systems Conference – CAPSI 2020 Proceedings, 36. Pereira, A., Laureano, R., Neto F., Macedo, J., (2021) "Computer simulation of diabetic retinopathy screening adherence: agent-based model with fuzzy logic", 16th Iberian Conference on Information Systems and Technologies – CISTI 2021 Proceedings, pp. 1-6. Pereira, A., Laureano, R., Neto F., (2024), "Simulation of human behaviour in adherence to preventive health programmes - A methodological proposal and an example of its application", 19th Iberian Conference on Information Systems and Technologies - CISTI 2024.	National and international institutions with a role in issuing guidelines related to screening; Governments and policy makers; Institutions responsible for planning and implementation of DR screening; practitioners, academic researchers and general population.
	Development of a framework to advance the state of knowledge related to the development, calibration and validation of simulation models focused on the study of the adherence to population-based screenings. The innovative combination of agent-based models with fuzzy logic resulted in a model that provides a good alternative to the traditional simulation techniques that lack flexibility and capacity of generalization.		Academic researchers
	Analysis of the effectiveness of various interventions to improve DR screening adherence, by staging hypothetical scenarios.		Institutions responsible for planning and implementing of DR screening; practitioners, academic researchers
Network Analysis	Results indicating that/how the structure of the social network and the position occupied by the diabetic in this network influence the behaviour of adherence to DR screening.	Pereira, A., Macedo, J., Afonso, A., Laureano, R., Neto F., (2024), "The role of the social network in the study of adherence to diabetic retinopathy screening programs" Scientific Reports (Q1), 14, 29389 (Core Publication).	National and international institutions with a role in issuing guidelines related to screening; Governments and policy makers; Institutions responsible for planning and implementing of DR screening; practitioners, academic researchers and general population.
	Identification of groups/geographical locations where the problem of adherence to screening is particularly relevant.		National and international institutions with a role in issuing guidelines related to screening; Governments and policy makers; Institutions responsible for planning and implementing of DR screening; practitioners, academic researchers and general population.

4.2. Discussion

Among the strengths of this research, we highlight: i) the used of real data and the large dimension of the data set used (271,867 calls for DR screening, which corresponds to 108,620 different persons with diabetes); ii) the 360-degree view provided by the data set, starting on the individual features of each diabetic, to the sending of the calls, personal decision to adhere or not to the screening, screening result, and treatment of the positive cases in hospital environment; iii) the use of a innovative combination of sound techniques of Statistics, Simulation and Network Science.

Nonetheless, our research has some limitations: i) in our first literature review [17] we had some difficulty in collecting uniform data since there are different concepts, methodologies, degrees of implementation, documentation and monitoring in the five Portuguese Regional Health Administrations responsible for the implementation of DR screening programs; ii) we identified some aspects that can affect the screening, like the use of the private health sector, that are not currently studied or taken into account by decision makers in the planning and implementation of DR screening. Additional data will be needed to study the extent to which these phenomena affect screening adherence; iii) our approach to the development of simulation models [64] [65] [22] [66] relied on specific assumptions and data, and we did not have access to data from other locations with different screening strategies. It would have been desirable to test our models with data from other population-based screenings where both population features and screening strategies differ substantially from those used for the models development, and gauge their ability to replicate the real-life adherence rates; iv). in our research concerning the impact of the social networks [23], we only considered ties between members of the target population, neglecting other possible subjects that could influence the persons with diabetes decision of adhere or not to the screening. On the other hand, the links between persons with diabetes result of plausible, but not factual relations, except for the family relationship.

Therefore, we recognize that our research would have benefited from an earlier acknowledgment of the need to obtain additional data to enrich our data set and of the establishment of protocols to access data from other screening programs of different geographical areas for broader validation of the models. However, we consider that the results obtained can be of great use for further researches in this field, and to support decisions related to the planning and implementation of DR screenings.

4.3. Future works

We intend to continue our research by collecting new data, improving our models, and strengthening and broadening our conclusions. To this end, we are already:

i) Conducting a survey of a sample of the diabetic population to collect additional data concerning the role of the private health sector in DR diagnosis and treatment, and the role of social networks in adherence to DR screening;

ii) Developing a fourth ABM that incorporates the diabetics' social networks and their influence on screening adherence.

In the future, we also intend to:

iii) Incorporate other types of agents, with relevant roles in screening, into the ABM, such as healthcare professionals and institutions including primary care services, hospitals, and local authorities;

iv) Develop an alternative version of the ABM that uses Monte Carlo simulation for the agents' decision-making process regarding adherence to screening, and compare its results with those obtained using logistic regression and fuzzy logic;

v) Enhance our ABM to analyse a wider range of scenarios, including alternative screening strategies, intervals, and methods;

vi) Improve the validation of our ABM by testing them with data from DR screenings in other geographic locations, where population characteristics and screening strategies differ substantially from the current context, as well as with data from other population-based screening programmes;

vii) Examine the influence of social networks on DR screening in different groups with varying social and demographic characteristics, including the influence of broader social networks beyond the diabetic community;

viii) Continue studying the influence of the social network using techniques such as preferential attachment and population normalisation;

ix) Assess the effectiveness of interventions designed to promote adherence to DR screening that take into account the structure of social networks.

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APPENDICES

Paper 1 - Five regions, five retinopathy screening programmes: a systematic review of how Portugal addresses the challenge

Supplementary Information

Additional file 1 - PRISMA 2009 Checklist

1Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	1
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	2,3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	2,3
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	3,4,5,6
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	4,5
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	3,4
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	4
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	4,5,6
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	5,6
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	10,11,12,13
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	10,11,12,13
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	10,11,12,13
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	5,10,11,12,13

Additional file 1 - PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	3,4,5,6
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	n.a.
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	3,4,5,6
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	6
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	10, 11, 12, 13
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	n.a.
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	n.a.
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	10, 11, 12, 13
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	n.a.
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	13,14,15,16
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	13,14,15,16
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	13,14,15,16
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	16,17

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit: **www.prisma-statement.org**.

Additional file 2. Overview of the Portuguese governmental and non-governmental health organizations, with a relevant role on DR Screening

Briefly, the public healthcare system in Portugal is delivered through the Portuguese National Health Service (SNS). The Portuguese SNS comprehends institutions within the government direct and indirect administration. Among those institutions, we will focus only in the ones with a relevant role in DR screening (Figure 1 illustrates their hierarchical organization) (1).

SNS is managed by the Central Administration of the Health System (ACSS), and delivered by five Regional Health Administrations (ARS North, Central, Lisbon and Tagus Valley, Alentejo and Algarve). SNS covers Primary Health Care (Primary Health Centers), and Secondary Care (hospitals and specialist units) (1) (3).

Primary Health Centers are associated in Health Center Clusters (Agrupamentos de Centros de Saúde - ACES) with administrative autonomy, decentralized from ARS but subjected to their directive power (1) (2) (3) .

With regard to hospital institutions, the articulation with guardianship (Regional / central Administration) is currently materialized through a negotiation process based on the link between the allocated funding and the results expected (3).

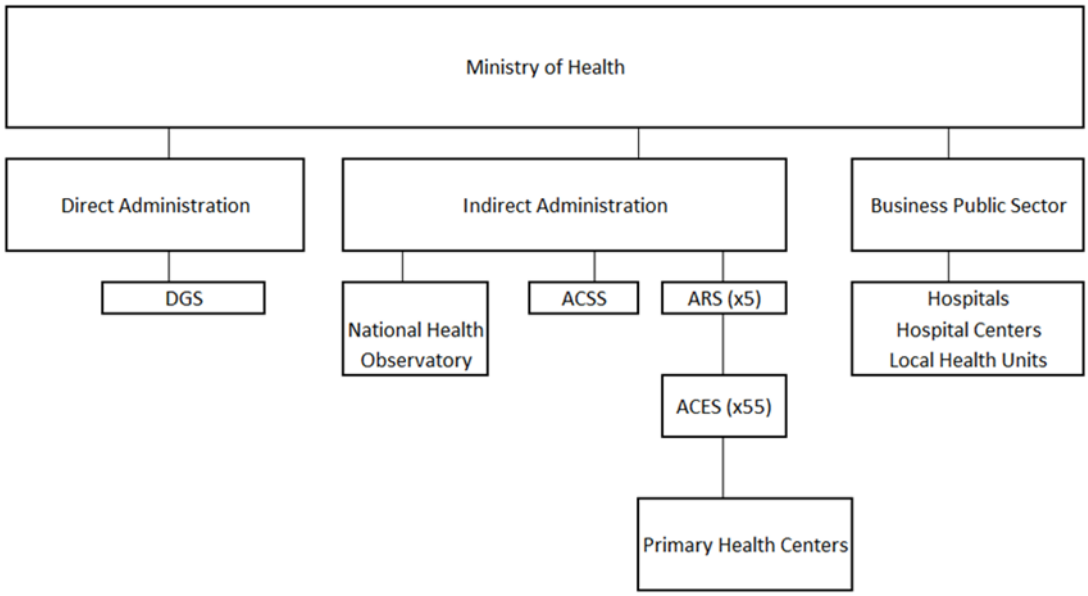
The management contract consists of duties and obligations translated in to physical and quality goals and is an important tool because it allows to monitor the performance of the hospital service, so that necessary interventions can be performed (3).

The contract with the hospitals is supervised by ACSS, which has the strategic responsibility to make the contracting process compatible with the health policy objectives (1) (3). ARS have the responsibility to operationalize the whole process, from the elaboration of contracts, to the monitoring, evaluation, and negotiation of the incentive system (1) (2) (4).

The General Health Department (Direção Geral de Saúde - DGS) is a government institution, with a vital role on the organization and monitoring of population-based screenings. DGS has the mission of regulate, guide and coordinate activities of health promotion and disease prevention, define the technical conditions for adequate health care, as well as ensuring the elaboration and execution of the National Health Plan (4).

Additional file 2. Overview of the Portuguese governmental and non-governmental health organizations, with a relevant role on DR Screening

Figure 1 – Portuguese SNS Organization



The National Institute of Health Doctor Ricardo Jorge (ONS) also has an important role on RD Screening. ONS is a public body integrated in the indirect administration of the State, endowed with scientific, technical, administrative, financial and proprietary autonomy. It develops a triple mission as state laboratory in the health sector, national reference laboratory and national health observatory (5).

Aside from the governmental organizations involved in DR screening programmes, there are also two non-governmental organizations with very important roles: The National Diabetes Observatory (Observatório Nacional da Diabetes - OND) and the Portuguese Diabetes Association (Associação Protetora dos Diabéticos de Portugal -APDP). OND is responsible for collecting, validating, generating and disseminating reliable and scientifically credible information on Diabetes in Portugal. APDP is the world's oldest diabetes association and a senior member of the International Diabetes Federation. It is a non-governmental institution, which aims to improve the quality of life of people with diabetes (6).

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Additional file 2. Overview of the Portuguese governmental and non-governmental health organizations, with a relevant role on DR Screening

3. Central Administration of the Health System - ACSS. Rede nacional de especialidade hospitalar e de referenciação: oftalmologia. ; 2017.

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6. Portuguese Society of Diabetology. [Online]. [cited 2019 10 25. Available from: https://www.spd.pt/index.php/observatrio-mainmenu-330.

Additional file 3. Quality assessment of the selected scientific papers

Paper	Ref	Year	Journal	PQ01	PQ02	PQ03	PQ04	PQ05	PQ06	PQ07	PQ08	PQ09	Total
Epidemiology of diabetic retinopathy and macular edema: a systematic review.	1	2004	Eye	0	1	1	0	0	0	0	0	0	2
Global Prevalence of Diabetes: Estimates for the year 2000 and projections for 2030.	2	2004	Diabetes Care	0	1	1	0	0	0	0	0	0	2
Global estimates of undiagnosed diabetes in adults.	3	2014	Diabetes Research and Clinical Practice	0	1	1	0	0	0	0	0	0	2
Diabetes in Europe: An update.	5	2014	Diabetes Research and Clinical Practice	0	1	1	0	0	0,5	0	0	0	2,5
Burden of illness of diabetic macular edema: literature review.	6	2010	Current Medical Research & Opinion	0,5	1	1	0,5	0,5	0	0	0,5	0	4
Major automatic diabetic retinopathy screening systems and related supporting algorithms: a review.	7	2019	Machine Vision and Applications	0,5	1	1	0,5	0,5	0,5	0,5	0,5	0	5
Prevalence of diabetic retinopathy in India: The All India Ophthalmological Society Diabetic Retinopathy Eye Screening Study 2014	8	2015	Indian Journal of Ophthalmology	0,5	1	1	1	0	0,5	0,5	0,5	0	5
Retinal Imaging Techniques for Diabetic Retinopathy Screening.	9	2016	Journal of Diabetes Science and Technology	0,5	1	1	0,5	0,5	0,5	0,5	0,5	0	5
Epidemiology of diabetes and complications among adults in the Republic of Ireland 1998-2015: a systematic review and meta-analysis	10	2016	BMC Public Health	0	1	1	0	0	0	0	0	0	2
Epidemiology of diabetic retinopathy, diabetic macular edema and related vision loss.	11	2015	Eye and Vision	0	1	1	0,5	0,5	0	0	0	0	3
Screening intervals for diabetic retinopathy and incidence of visual loss: a systematic review.	12	2013	DIABETIC Medicine	0,5	1	1	0,5	0,5	0,5	0,5	0,5	0	5
Evidence-Based Medicine of Screening of Diabetic Retinopathy among Type 2 Diabetes: A Clinical Overview.	13	2015	Health	0,5	1	1	0,5	0,5	1	1	1	0	6,5
Prevalence of Diabetic Retinopathy in Various Ethnic Groups: A Worldwide Perspective.	14	2012	Survey of ophthalmology	0	1	1	0,5	0	0,5	0	0	0	3
Frequency of diabetic retinopathy and associated risk factors in Khartoum, Sudan: population-based study.	15	2017	International Journal of Ophthalmology	1	1	1	1	0	0	0	0	0	4

Additional file 3. Quality assessment of the selected scientific papers.

Paper	Ref	Year	Journal	PQ01	PQ02	PQ03	PQ04	PQ05	PQ06	PQ07	PQ08	PQ09	Total
Review of diabetic retinopathy screening methods programmes adopted in different parts of the world.	17	2016	European Ophthalmic Review	1	1	1	1	0	0,5	0,5	0,5	0	5,5
Automated diabetic retinopathy imaging in Indian eyes: A pilot study.	19	2014	Indian Journal of Ophthalmology	0,5	1	1	0,5	0,5	0,5	0,5	0,5	0	5
Diabetic retinopathy: global prevalence, major risk factors, screening practices and public health challenges: a review.	20	2016	Clinical and Experimental Ophthalmology	0,5	1	1	1	0,5	1	1	1	0	7
Diabetic Retinopathy Screening: Progress or Lack of Progress.	21	2012	Ophthalmology Research	0,5	1	1	0,5	0	0,5	0,5	0,5	0	4,5
Automated detection of Diabetic Retinopathy in Three European Populations.	28	2016	Journal of Clinical & Experimental Ophthalmology	0,5	1	1	0,5	0,5	0,5	0,5	0,5	0	5
First 5 years of Implementation of Diabetic Screening Program in Centro Hospitalar do Porto.	31	2017	Revista Brasileira Oftalmologia,	1	1	1	1	0,5	1	1	1	1	8,5
SCREEN-DR: Collaborative platform for diabetic retinopathy.	42	2018	International journal of medical informatics	1	1	1	1	0,5	0,5	0,5	0,5	0,5	6,5
Screening for Diabetic Retinopathy in the Central Region of Portugal. Added Value of Automated 'Disease/No Disease' Grading	43	2014	Ophthalmologica	1	1	1	1	0,5	0,5	0,5	0,5	0,5	6,5
Improved automated screening of diabetic retinopathy.	44	2011	Ophthalmologica	1	1	1	1	0,5	0,5	0,5	0,5	0,5	6,5
First Diabetic Retinopathy Prevalence Study in Portugal, the RETINODIAB Study - Evaluation of the Screening Programme for Lisbon and Tagus Valley Region	45	2015	American Academy of Ophthalmology	1	1	1	1	0	0	0	0,5	1	5,5
Automated Screening for Diabetic Retinopathy – A Systematic Review.	49	2017	Ophthalmic Research	0,5	1	1	0,5	0,5	0,5	0,5	0,5	0	5
Automated Retinal Image Analysis for Diabetic Retinopathy in Telemedicine.	51	2015	Current Diabetes Reports	0,5	1	1	1	0,5	0,5	0,5	0,5	0,5	6
Automated detection of diabetic retinopathy in retinal images.	52	2016	Indian Journal of Ophthalmology	0,5	1	1	0,5	0,5	0,5	0,5	0,5	0	5
Glycaemic threshold for diabetes-specific retinopathy among individuals from Saudi Arabia, Algeria and Portugal.	54	2013	Diabetes Research and Clinical Practice	1	1	1	1	0,5	0	0	0	0	4,5

Paper 2 - Simulation Models in Diabetic Retinopathy Screening: A Systematic Review

Supplementary Information

Appendix 1 - Ranking of the selected papers in each of the quality criteria

Ref. Number	Paper Identification	PQ01	PQ02	PQ03	PQ04	PQ05	PQ06	PQ07	PQ08	PQ09	PQ10	PQ11	Total
1	J. C. Javitt, L. P. Aiello, Y. Chiang, F. L. Ferris, J. K. Canner and S. Greenfield, "Preventive eye care in people with diabetes is cost-saving to the federal government," Diabetes care, vol. 17, pp. 909-917, 1994	1	1	1	1	1	0.5	0.5	1	1	1	0.5	9.5
3	A. J. Palmer, C. Weiss, P. P. Sendi, K. Neeser, A. Brandt, G. Singh, H. Wenzel and G. A. Spinas, "The cost-effectiveness of different management strategies for Type I diabetes: a Swiss perspective," Diabetologia, no. 43, pp. 13-26, 2000.	1	1	1	1	0.5	1	1	0.5	0.5	0.5	0.5	8.5
9	B. A. Craig, D. G. Fryback, R. Klein and B. E. K. Klein, "A bayesian approach to modelling the natural history of a chronic condition from observations with intervention," Statistics in Medicine, vol. 18, pp. 1355-1371, 1999.	1	1	1	1	1	0.5	0.5	1	1	0.5	0.5	9
10	D. Vetrini, C. A. Kiire, I. P. Burgess, S. P. Harding, P. C. Kayange, K. Kalua, G. Msukwa, N. A. Beare and J. Madan, "Incremental cost-efectiveness of screening and laser teatment for diabetic retinopathy and macular edema in Malawi," PLoS ONE, p. 1:14, 2018.	1	1	1	1	0.5	0.5	0.5	0.5	1	0.5	0.5	8
11	D. Maberley, H. Walker, A. Koushik and A. Cruess, "screening for diabetic retinopathy in -james Bay Ontario: a cost-effectiveness analysis.," CMAJ, vol. 168, pp. 160-164, 2003.	1	1	1	1	1	0.5	0.5	0.5	0.5	0.5	0.5	8
12	R. Davies and C. Canning, "Discrete Event Simulation to evaluate screening for diabetic eye disease," Simulation, pp. 209-216, 1996.	1	1	1	1	1	1	1	0.5	0.5	1	0.5	9.5
13	R. Davies, P. Sullivan and C. Canning, "Simulation of diabetic eye disease to compare screening policies," British Journal of Ophthalmology, vol. 80, pp. 945-950, 1996.	1	1	1	1	1	1	1	0.5	0.5	1	0.5	9.5
14	R. Davies, S. Brailsford, P. Roderick, C. Canning and D. Crabbe, "Using simulation modelling for evaluating screening services for diabetic retinopathy," Journal of the operational research society, vol. 51:4, pp. 476-484.	1	1	1	1	1	0.5	0.5	0.5	1	0.5	0.5	8.5

Appendix 1 - Ranking of the selected papers in each of the quality criteria

Ref. Number	Paper Identification	PQ01	PQ02	PQ03	PQ04	PQ05	PQ06	PQ07	PQ08	PQ09	PQ10	PQ11	Total
15	R. Davies, P. Roderick, C. Canningt and S. Brailsford, "The evaluation of screening policies for diabetic retinopathy using simulation," Diabetes Medicine, vol. 19, pp. 762-770, 2002.	1	1	1	1	1	0.5	0.5	0.5	1	0.5	0.5	8.5
16	D. Chalk, M. Pitt, B. Vaidya and K. Stein, "Can the retinal screening interval be safely increased to 2 years for type 2 diabetic patients without retinopathy?," Diabetes care, vol. 35, pp. 1663-1668, 2012.	1	1	1	1	1	0.5	0.5	0.5	1	0.5	0.5	8.5
17	S. Vijan, T. P. Hofer and R. A. Hayward, "Cost-utility analysis of screening intervals for diabetic retinopathy in patients with type 2 diabetes mellitus," Journal of the American Medical Association, vol. 283, no. 7, pp. 889-896, 2000.	1	1	1	1	1	0.5	0.5	0.5	0.5	0.5	0.5	8
18	S. C. Brailsford, W. J. Gutjahr, M. S. Rauner and W. Zeppelzauer, "Combined discret-event simulation and ant colony optimization approach for selecting optimal screening policies for diabetic retinopathy," CMS, vol. 4, pp. 59-83, 2007.	1	1	1	1	1	0.5	0.5	1	1	1	0.5	9.5
19	E. T. Day, N. Ravi, H. Xian and A. Brugh, "Sensitivity of diabetic retinopathy associated vission loss to screening interval in an agent-based/ discret event simulation model".	1	1	1	1	1	0.5	0.5	1	1	1	0.5	9.5
20	N. Aoki, K. Dunn, T. Fukui, J. R. Beck, W. J. Schull and H. K. Li, "Cost-effectiveness analysis of telemedicione to evaluate diabetic retinopathy in a prision population," Diabetes care, vol. 27, pp. 1095-1101, 2004.	1	1	1	1	1	0.5	0.5	0.5	0.5	1	0.5	8.5
21	J. D. Whited, S. K. Datta, L. M. Aiello, L. P. Aiello, J. D. Cavallerano, P. R. Conlin, M. B. Horton, R. A. Vigersky, R. K. Poropatich, P. Challa, A. Darkins and S.-E. Bursell, "A modeled economic analysis of a digital teleophtalmology system as used by three Federal Healthcare Agencies for detecting proliferative diabetic retinopathy," Telemedicine and e-health, vol. 11, no. 6, pp. 641-651, 2005.	1	1	1	1	1	0.5	0.5	0.5	1	1	0.5	9

Appendix 1 - Ranking of the selected papers in each of the quality criteria

Ref. Number	Paper Identification	PQ01	PQ02	PQ03	PQ04	PQ05	PQ06	PQ07	PQ08	PQ09	PQ10	PQ11	Total
22	D. B. Rein, J. S. Wittenborn, X. Zhang, B. A. Allaire, M. S. Song, R. Klein and J. B. Saaddine, "The cost-effectiveness of three screening alternatives for people with no or early diabetic retinopathy," Health services research, pp. 1534-1561, 2011.	1	1	1	1	1	0.5	0.5	0.5	1	1	0.5	9
23	E. Kirkizlar, N. Serban, J. A. Sisson, J. L. Swann, C. S. Barnes and M. D. Williams, "Evaluation of telemedicine for screening of diabetic retinopathy in the Veterans Health Administration," American academy of ophthalmology, pp. 2604-2610, 2013.	1	1	1	1	0.5	0.5	0.5	0.5	1	1	1	9
24	H. V. Nguyen, G. S. W. Tan, R. J. Tapp, S. Mital, D. S. W. Ting, H. T. Wong, C. S. Tan, A. Laude, E. S. Tai, N. C. Tan, E. A. Finkelstein, T. Y. Wong and E. L. Lamoureux, "Cost-effectiveness of a national telemedicione diabetic retinopathy screening program in Singapore," American academy of ophthalmology, vol. 123, no. 12, pp. 2571-2580, 2016.	1	1	1	1	0.5	0.5	0.5	0.5	0.5	1	0.5	8
25	A. J. Ben, J. L. Neyeloff, C. F. Souza, A. P. O. Rosses, A. L. Araujo, A. Szortika, F. Locatelli, G. Carvalho and C. R. Neumann, "Cost-utility analysis of opportunistic and systematic diabetic retinopathy screening strategies from the perspective of the Brazilian public healthcare system," Applied health economics and health policy, vol. 18, pp. 57-68, 2020	1	1	1	1	0.5	0.5	0.5	0.5	0.5	1	0.5	8
26	S. Brailsford and B. Schmidt, "Towards incorporating human behaviour in models of health care systems: an approach using discrete event simulation," European journal of operational research, vol. 150, pp. 19-31, 2003	1	1	1	1	0.5	0.5	0.5	0.5	0.5	0.5	0.5	7.5
27	T. E. Day, N. Ravi, H. Xian and A. Brugh, "An agent-based modelling template for a cohort of veterans with diabetic retinopathy," PLoS ONE, vol. 8, 2013.	1	1	1	1	1	0.5	0.5	1	1	1	0.5	9.5

Paper 3 - The use of social simulation modelling to understand adherence to diabetic retinopathy screening programs

Supplementary Information

Supplementary Table S1 – State of the art of simulation models of DR screening

	Ref.	Authors	Year	Strengths and main outcomes	Limitations
Cost-effectiveness of systematic DR screenings	3	J. C. Javitt, L. P. Aiello, Y. Chiang, F. L. Ferris, J. K. Canner and S. Greenfield	1994	Each diabetic is modelled individually, and the importance of DR population-based screening is highlighted.	The models include only a very limited set of risk factors, neglecting important aspects as adherence rate and sociodemographic factors; as some of the authors recognized, Monte Carlo simulation and Markov processes are not the most suitable techniques for modelling multiple individual characteristics.
	4	A. J. Palmer, C. Weiss, P. P. Sendi, K. Neeser, A. Brandt, G. Singh, H. Wenzel and G. A. Spinas	2000	The rate of DR progression takes into consideration the duration of the diabetes, the blood glucose values, and insulin therapy, highlighting the importance of combining screening with proper control of diabetes.	
	5	B. A. Craig, D. G. Fryback, R. Klein and B. E. K. Klein	1999	The model allows for an assessment of the sensitivity of the results to each specific parameter and an estimation of joint uncertainty considering all model parameters. The model highlights the importance of DR population-based screening.	
	6	D. Vetrini, C. A. Kiire, I. P. Burgess, S. P. Harding, P. C. Kayange, K. Kalua, G. Msukwa, N. A. Beare and J. Madan	2018	The authors performed three "What If" scenarios with different adherence rates, revealing that the adherence rate has an important impact on the cost-effectiveness of the screening, since the highest costs are fixed and remain the same even when fewer screenings are performed.	No effort was made to model individual features; the underlying factors behind adherence rates were not considered, not even the impact of each of the proposed strategies (a fixed probability of adherence was parametrized for each set of simulations).
Screening alternatives and screening intervals	7	D. Maberley, H. Walker, A. Koushik and A. Cruess	2003	The authors modelled the cost-effectiveness of retinopathy screening by travelling retina specialists versus retinal photography with a portable digital camera, presenting a sensitivity analysis of different adherence rates or population coverage. It was demonstrated that highest percentages of adherence rates/ population coverage led to more cost-effective programs.	
	8	R. Davies and C. Canning	1996	The authors recommended annual screenings for diabetics without DR and 6-monthy screenings for diabetics with background DR. Another important finding in these studies was the important role of the population's compliance with screening. In fact, the authors report that the probability of a diabetic attending a screening when called significantly affects the screening results, influencing decisions such as the screening method, the professionals responsible for the initial test (in terms of sensitivity) and the intervals between screenings.	The individual features and state of health of diabetics are not considered in these models; the underlying factors behind adherence rates were not considered, (a fixed probability of adherence was parametrized for each set of simulations). DES has been found to be difficult to implement in situations involving human behavior, because entities in DES are not autonomous and capable of making independent decisions. Therefore, this is not the most suitable technique for representing complex proactive human
	9	R. Davies, P. Sullivan and C. Canning	1996		
	10	R. Davies, S. Brailsford, P. Roderick, C. Canning and D. Crabbe	2000		
	11	R. Davies, P. Roderick, C. Canningt and S. Brailsford	2002		
	12	D. Chalk, M. Pitt, B. Vaidya and K. Stein	2012	The framework explicitly models each patient separately. Patient records included patient sex, type and duration of the diabetes, screening dates and last screening result. The proposed model allows for the possibility of non-attendance. The simulation predicts that screening people with type 2 diabetes, who have not yet developed DR, every two years does not increase the risk of vision loss and is cost-effective.	The model includes only a very limited set of risk and sociodemographic factors. The authors did not explore the impact of non-attendance on the costs and benefits of 2-year screening intervals. The underlying factors behind adherence rates were not considered. DES is not the most suitable technique to represent complex proactive human behavior.
	13	S. Vijan, T. P. Hofer and R. A. Hayward	2000	One-way sensitive analyses were conducted on individual parameters to access their impact on the costs and effectiveness of the screening. The authors reported that annual retinal screening for all type 2 diabetic patients was not cost-effective and concluded that tailoring recommendations to individual circumstances may be preferable.	The individual features, state of health and adherence rate of diabetics were not considered in this model. Markov processes are not the most suitable technique for modelling multiple individual characteristics.

Supplementary Table S1 – State of the art of simulation models of DR screening

	Ref.	Authors	Year	Strengths and main outcomes	Limitations
	14	S. C. Brailsford, W. J. Gutjahr, M. S. Rauner and W. Zeppelzauer	2007	The study concluded that a 30-month screening interval was the most cost-effective option. In terms of simulation techniques, the authors propose a combined DES and ant colony optimization model. The effects of different screening strategies are simulated and then compared in terms of two objective functions: minimum incremental cost per year of sight saved, compared with no-screening, and maximum years of sight saved.	The individual features, state of health and adherence rate of diabetics were not considered in this model. The authors did not explore the impact of non-attendance. The underlying factors behind adherence rates were not addressed.
	15	T. E. Day, N. Ravi, H. Xian and A. Brugh	2013	The authors present an Agent Based Model (ABM) supported by medical data abstracted from 535 patients' records. Each agent is imbued with a data structure describing the demography and health status of the agent. The data abstraction was accomplished through probability density functions incorporated into the model. The variables included in the data structure are used as predictors for the DR progression, through a multivariate logistic regression model that provides the probability of transition from one state of the disease to another, individually, for each agent. The simulation results were validated against real-world data. In the continuation of this research the authors extended the model, integrating the previously developed ABM with a DES model that allows for the simulation of the path of a virtual cohort of diabetics in a screening and treatment clinic for DR. The results suggest that increasing the interval from 1 to 2 years for diabetic patients who have not yet developed DR is safe, while increasing the interval to 3 years increases the risk of vision loss.	The authors did not explore the impact of non-attendance. The underlying factors behind adherence rates were not considered.
	16	T. E. Day, N. Ravi, H. Xian and A. Brugh	2013		
The use of telemedicine in DR screening	17	N. Aoki, K. Dunn, T. Fukui, J. R. Beck, W. J. Schull and H. K. Li	2004	The main findings of the simulation were that the teleophthalmology system is more effective and less costly than the non-teleophthalmology system in the cost-effectiveness analysis for the reference case.	The individual features and adherence rate of diabetics were not considered in this model. Markov processes are not the most suitable technique for modelling multiple individual characteristics. The clinical effectiveness and economic value of telemedicine has not been clearly established.
	18	J. D. Whited, S. K. Datta, L. M. Aiello, L. P. Aiello, J. D. Cavallerano, P. R. Conlin, M. B. Horton, R. A. Vigersky, R. K. Poropatich, P. Challa, A. Darkins and S.-E. Bursell	2005	The main findings of the simulation were that the teleophthalmology system is more effective and less costly than the non-teleophthalmology system.	The individual features and adherence rates of diabetics were not considered in this model. Monte Carlo simulation is not the most suitable technique for modelling multiple individual characteristics.
	19	D. B. Rein, J. S. Wittenborn, X. Zhang, B. A. Allaire, M. S. Song, R. Klein and J. B. Saaddine	2011	The authors compare DR screening alternatives for diabetics with no or early DR, accounting for imperfect compliance with screening recommendations and the ability of eye tests to detect other common visual disorders in people with diabetes (glaucoma, aged-related macular degeneration, etc). There is a model validation process and a sensitivity analysis. This study concludes that biennial eye evaluation was the most cost-effective treatment option when the ability to detect other eye conditions was included in the model. Telemedicine was most cost-effective when other eye conditions were not considered.	The models include only a very limited set of risk and sociodemographic factors; Monte Carlo simulation and Markov processes are not the most suitable technique for modelling multiple individual characteristics.
	20	E. Kirkizlar, N. Serban, J. A. Sisson, J. L. Swann, C. S. Barnes and M. D. Williams	2013	One important contribution of this study is the diversity of the population and geography, compared with earlier studies. The results concluded that telemedicine is cost-effective under most conditions and may increase screening rates.	Markov processes are not the most suitable technique for modelling multiple individual characteristics.
	21	H. V. Nguyen, G. S. W. Tan, R. J. Tapp, S. Mital, D. S. W. Ting, H. T. Wong, C. S. Tan, A. Laude, E. S. Tai, N. C. Tan, E. A. Finkelstein, T. Y. Wong and E. L. Lamoureux	2016	Simulation results indicate that telemedicine-based DR screening saves costs and generates similar health outcomes	The individual features and adherence rates of diabetics were not considered in this model; Markov processes are not the most suitable technique for modelling multiple individual characteristics.

Supplementary Table S1 – State of the art of simulation models of DR screening

	Ref.	Authors	Year	Strengths and main outcomes	Limitations
	22	A. J. Ben, J. L. Neyeloff, C. F. Souza, A. P. O. Rosses, A. L. Araujo, A. Szortika, F. Locatelli, G. Carvalho and C. R. Neumann	2020		The individual features and adherence rate of diabetics were not considered in this model; Markov processes are not the most suitable technique for modelling multiple individual characteristics. The probability sensitivity analyses show a considerable amount of uncertainty in the model's parameters
Human Behaviour and compliance with the screening	23	S. Brailsford and B. Schmidt	2003	This model uses a combination of several factors to study adherence to screening (number of times the patient has adhered to previous screenings, perception of their general health status, current stage of the DR, information and anxiety about the DR, and educational qualifications). Each patient is an individual entity in the model, with their own characteristics.	The probability of participation in the screening was calculated simply as a binary variable and the model uses only artificial data, meaning that the results of this model are theoretical artefacts which need to be validated with real data. Qualitative variables are difficult to incorporate into DES models.

Supplementary Information S2- Fuzzy IF-THEN rules

1- Access barriers

Variables:
B1 - age.
“Difficult access due to age” is defined by the linear function that passes through the points [0, 1], [100, 0]. “Easy access” is defined by the linear function that passes through the points [0, 0] and [100, 1].
B2 - income.
"Difficult access due to income" is defined by the normal distribution of the mean 50,000 euros/year and standard deviation 17,000 euros/year. The classification "easy access due to income" corresponds to the maximum of two normal distributions with averages of 0 and 100,000 euros/ year respectively and standard deviations of 17,000 euros/year.
B3 - screening location
“Difficult to access due to screening location” is defined by the linear function that passes through the points [0, 0], [100, 1]. “Easy access due to screening location” is defined by the linear function that passes through the points [0, 1] and [100, 0].
B4 - degree of urbanization of the place of residence.
The “difficult access due to the degree of urbanization” is defined by the normal distribution of mean 0.3 and standard deviation 0.1. The classification “easy access due to the degree of urbanization” corresponds to the maximum of two normal distributions with means 0 and 0.5 respectively and standard deviations 0.1.
Rules:
R1: IF (B1 is high_B1 AND B2 is high_B2 AND B3 is high_B3 And B4 is high_B4), THEN it is likely that I will attend_screening.
R2: IF (B1 is high_B1 AND B2 is low_B2 AND B3 is high_B3 And B4 is high_B4), THEN it is likely that I will attend_screening.
R3: IF (B1 is high_B1 AND B2 is high _B2 AND B3 is low_B3 And B4 is high_B4), THEN it is likely that I will attend_screening.
R4: IF (B1 is high_B1 AND B2 is high _B2 AND B3 is low_B3 And B4 is high_B4), THEN it is likely that I will attend_screening.
R5: IF (B1 is high_B1 AND B2 is high _B2 AND B3 is high_B3 And B4 is low _B4), THEN it is likely that I will attend_screening.
R6: IF (B1 is low_B1 AND B2 is low_B2 AND B3 is high_B3 And B4 is high_B4), THEN it is likely that I will attend_screening.
R7: IF (B1 is low_B1 AND B2 is high_B2 AND B3 is low_B3 And B4 is high_B4), THEN it is likely that I will attend_screening.
R8: IF (B1 is low_B1 AND B2 is high_B2 AND B3 is high_B3 And B4 is low_B4), THEN it is likely that I will attend_screening.
R9: IF (B1 is high_B1 AND B2 is low_B2 AND B3 is low_B3 And B4 is high_B4), THEN it is likely that I will attend_screening.
R10: IF (B1 is high_B1 AND B2 is low_B2 AND B3 is high_B3 And B4 is low _B4), THEN it is likely that I will attend_screening.
R11: IF (B1 is high_B1 AND B2 is high_B2 AND B3 is low_B3 And B4 is low_B4), THEN it is likely that I will attend_screening.
R12: IF (B1 is high_B1 AND B2 is low_B2 AND B3 is low_B3 And B4 is low_B4), THEN it is unlikely that I will attend_screening.
R13: IF (B1 is low_B1 AND B2 is high_B2 AND B3 is low_B3 And B4 is low_B4), THEN it is unlikely that I will attend_screening.
R14: IF (B1 is low_B1 AND B2 is low_B2 AND B3 is high_B3 And B4 is low_B4), THEN it is unlikely that I will attend_screening.
R15: IF (B1 is low_B1 AND B2 is low_B2 AND B3 is low_B3 And B4 is high_B4), THEN it is unlikely that I will attend_screening.
R16: IF (B1 is low_B1 AND B2 is low_B2 AND B3 is low_B3 And B4 is low_B4), THEN it is unlikely that I will attend_screening.

Supplementary Information S2- Fuzzy IF-THEN rules

2- Knowledge of the disease component

Variables:

C1 - age.

"High knowledge level due to age" is defined by a normal distribution of the mean 65 years and standard deviation 30. "Low knowledge level due to age" corresponds to the maximum of two normal distributions with means 18 and 100 years respectively and deviation pattern 30.

C2 - educational qualifications.

“High knowledge level due to educational qualifications” is defined by a linear function that passes through the points [0, 0] and [100, 1]. “Low knowledge level due to educational qualifications” is defined by a linear function that passes through the points [0, 1] and [100, 0].

C3 - percentage of times the agent previously adhered to screening.

“High knowledge level due to prior adhesion” is defined by a linear function that passes through the points [0, 0] and [100, 1]. “Low knowledge level due to prior adhesion” is defined by a linear function that passes through the points [0, 1] and [100, 0].

Rules:

R1: IF (C1 is high_C1 AND C2 is high_C2 AND C3 is high_C3), THEN it is likely that I will attend_screening.
R2: IF (C1 is high_C1 AND C2 is low_C2 AND C3 is high_C3), THEN it is likely that I will attend_screening.
R3: IF (C1 is high_C1 AND C2 is high_C2 AND C3 is low_C3), THEN it is likely that I will attend_screening.
R4: IF (C1 is low_C1 AND C2 is high_C2 AND C3 is high_C3), THEN it is likely that I will attend_screening.
R5: IF (C1 is high_C1 AND C2 is low_C2 AND C3 is low_C3), THEN it is unlikely that I will attend_screening.
R6: IF (C1 is low_C1 AND C2 is high_C2 AND C3 is low_C3), THEN it is unlikely that I will attend_screening.
R7: IF (C1 is low_C1 AND C2 is low_C2 AND C3 is high_C3), THEN it is unlikely that I will attend_screening.
R8: IF (C1 is low_C1 AND C2 is low_C2 AND C3 is low_C3), THEN it is unlikely that I will attend_screening.

3- Quality/strategy of the screening program

Variables:

E1 - sending reminders.

“High quality, considering sending reminders” is defined by a linear function that passes through the points [0, 0] and [100, 1]. “Low quality, considering sending reminders” is defined by a linear function that passes through the points [0, 1] and [100, 0].

E2 - waiting time at the time of screening (in minutes).

“High quality, considering the waiting time” is defined by a linear function that passes through the points [0, 1] and [500, 0]. “Low quality, considering the waiting time” is defined by a linear function that passes through the points [0, 0] and [500, 1].

E3 - time (in weeks) between sending the call notice and the date of the screening.

. "High quality, considering advance notification of the call" is defined by a normal distribution of mean 4 and standard deviation 2. "Low quality, considering advance notification of the call" corresponds to the maximum of two normal distributions with means 0 and 8 respectively and standard deviations 2.

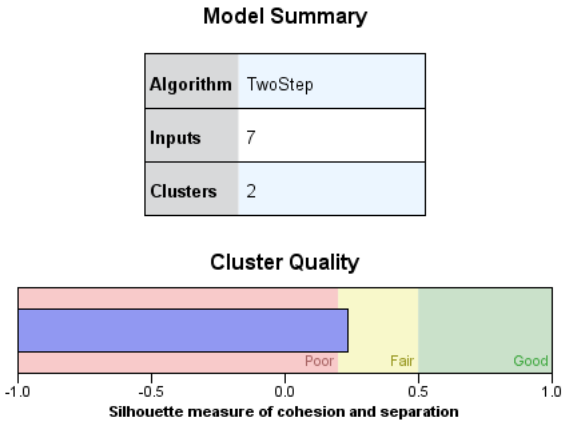
Rules:

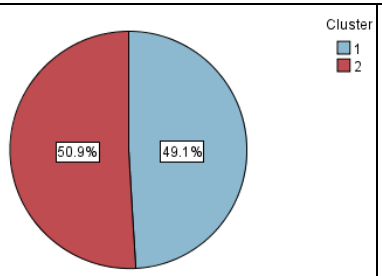
Supplementary Information S2- Fuzzy IF-THEN rules

R1: IF (E1 is high_E1 AND E2 is high_E2 AND E3 is high_E3), THEN it is likely that I will attend_screening.
R2: IF (E1 is high_E1 AND E2 is low_E2 AND E3 is high_E3), THEN it is likely that I will attend_screening.
R3: IF (E1 is high_E1 AND E2 is high_E2 AND E3 is low_E3), THEN it is likely that I will attend_screening.
R4: IF (E1 is low_E1 AND E2 is high_E2 AND E3 is high_E3), THEN it is likely that I will attend_screening.
R5: IF (E1 is high_E1 AND E2 is low_E2 AND E3 is low_E3), THEN it is unlikely that I will attend_screening.
R6: IF (E1 is low_E1 AND E2 is high_E2 AND E3 is low_E3), THEN it is unlikely that I will attend_screening.
R7: IF (E1 is low_E1 AND E2 is low_E2 AND E3 is high_E3), THEN it is unlikely that I will attend_screening.
R8: IF (E1 is low_E1 AND E2 is low_E2 AND E3 is low_E3), THEN it is unlikely that I will attend_screening.

Supplementary Table S3 – TwoStep Cluster Analysis

Model Summary

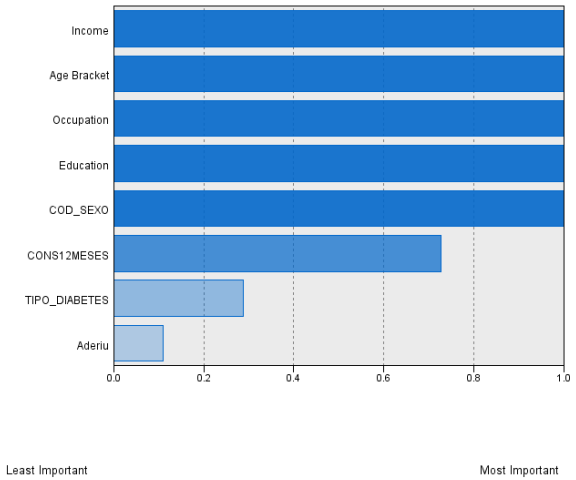




Size of Smallest Cluster	133609 (49.1%)
Size of Largest Cluster	138258 (50.9%)
Ratio of Sizes: Largest Cluster to Smallest Cluster	1.03

Cluster Sizes

Predictor importance



Supplementary Table S4 –Cluster Analysis – Crosstabulation, Chi-saquare and V'Cramer tests

Crosstabulation

Age Bracket

		TwoStep Cluster Number 1	2	Total
18-54	Count	0	1796	1796
	Expected Count	882.6	913.4	1796.0
	% within Age Bracket	0.0%	100.0%	100.0%
54-64	Count	0	14463	14463
	Expected Count	7107.8	7355.2	14463.0
	% within Age Bracket	0.0%	100.0%	100.0%
64-74	Count	54	89494	89548
	Expected Count	44008.4	45539.6	89548.0
	% within Age Bracket	0.1%	99.9%	100.0%
>74	Count	133555	32505	166060
	Expected Count	81610.2	84449.8	166060.0
	% within Age Bracket	80.4%	19.6%	100.0%
Total	Count	133609	138258	271867
	Expected Count	133609.0	138258.0	271867.0
	% within Age Bracket	49.1%	50.9%	100.0%

Chi-saquare

	Value	df	Asymptotic Significance (2-sided)
Pearson Chi-Square	167050.92[a]	3	.000
Likelihood Ratio	211685.04	3	.000
N of Valid Cases	271867		

V'Cramer

	Value	Approximate Significance
Cramer's V	.784	.000
N of Valid Cases	271867	

Supplementary Table S4 –Cluster Analysis – Crosstabulation, Chi-saquare and V'Cramer tests

Gender

		TwoStep Cluster Number		
		1	2	Total
M	Count	54535	80139	134674
	Expected Count	66185.5	68488.5	134674.0
	% within COD_SEXO	40.5%	59.5%	100.0%
W	Count	79074	58119	137193
	Expected Count	67423.5	69769.5	137193.0
	% within COD_SEXO	57.6%	42.4%	100.0%
Total	Count	133609	138258	271867
	Expected Count	133609.0	138258.0	271867.0
	% within COD_SEXO	49.1%	50.9%	100.0%

	Value	df	Asymptotic Significance (2-sided)
Pearson Chi-Square	7991.32[a]	1	.000
Likelihood Ratio	8031.30	1	.000
N of Valid Cases	271867		

	Value	Approximate Significance
Cramer's V	.171	.000
N of Valid Cases	271867	

Supplementary Table S4 –Cluster Analysis – Crosstabulation, Chi-saquare and V'Cramer tests

Education

		TwoStep Cluster Number		
		1	2	Total
KS2	Count	32085	17290	49375
	Expected Count	24265.3	25109.7	49375.0
	% within Education	65.0%	35.0%	100.0%
KS3	Count	68722	89917	158639
	Expected Count	77963.1	80675.9	158639.0
	% within Education	43.3%	56.7%	100.0%
KS4	Count	17312	16410	33722
	Expected Count	16572.7	17149.3	33722.0
	% within Education	51.3%	48.7%	100.0%
KS5 or more	Count	15490	14641	30131
	Expected Count	14807.9	15323.1	30131.0
	% within Education	51.4%	48.6%	100.0%
Total	Count	133609	138258	271867
	Expected Count	133609.0	138258.0	271867.0
	% within Education	49.1%	50.9%	100.0%

	Value	df	Asymptotic Significance (2-sided)
Pearson Chi-Square	7235.685[a]	3	.000
Likelihood Ratio	7310.902	3	.000
N of Valid Cases	271867		

	Value	Approximate Significance
Cramer's V	.163	.000
N of Valid Cases	271867	

Supplementary Table S4 –Cluster Analysis – Crosstabulation, Chi-saquare and V'Cramer tests

Income (euros)

		TwoStep Cluster Number 1	2	Total
<8511	Count	1898	1657	3555
	Expected Count	1747.1	1807.9	3555.0
	% within Income	53.4%	46.6%	100.0%
8511-9811	Count	54844	41870	96714
	Expected Count	47530.1	49183.9	96714.0
	% within Income	56.7%	43.3%	100.0%
911-11167	Count	68924	86862	155786
	Expected Count	76561.0	79225.0	155786.0
	% within Income	44.2%	55.8%	100.0%
11167-12649	Count	3960	4626	8586
	Expected Count	4219.6	4366.4	8586.0
	% within Income	46.1%	53.9%	100.0%
12649-17400	Count	3178	2437	5615
	Expected Count	2759.5	2855.5	5615.0
	% within Income	56.6%	43.4%	100.0%
>17400	Count	805	806	1604
	Expected Count	788.3	815.7	1604.0
	% within Income	50.2%	49.8%	100.0%
Total	Count	133609	138258	271867
	Expected Count	133609.0	138258.0	271867.0
	% within Income	49.1%	50.9%	100.0%

	Value	df	Asymptotic Significance (2-sided)
Pearson Chi-Square	3900.36[a]	6	.000
Likelihood Ratio	3912.12	6	.000
N of Valid Cases	271867		

	Value	Approximate Significance
Cramer's V	.120	.000
N of Valid Cases	271867	

Supplementary Table S4 –Cluster Analysis – Crosstabulation, Chi-saquare and V'Cramer tests

Occupation

		TwoStep Cluster Number		
		1	2	Total
Active	Count	16865	94623	111488
	Expected Count	54790.8	56697.2	111488.0
	% within Occupation	15.1%	84.9%	100.0%
Inactive	Count	4064	28414	32478
	Expected Count	15961.3	16516.7	32478.0
	% within Occupation	12.5%	87.5%	100.0%
Retired	Count	112390	13286	125676
	Expected Count	61763.5	63912.5	125676.0
	% within Occupation	89.4%	10.6%	100.0%
Student	Count	2	1008	1010
	Expected Count	496.4	513.6	1010.0
	% within Occupation	0.2%	99.8%	100.0%
Unknow	Count	288	927	1215
	Expected Count	597.1	617.9	1215.0
	% within Occupation	23.7%	76.3%	100.0%
Total	Count	133609	138258	271867
	Expected Count	133609.0	138258.0	271867.0
	% within Occupation	49.1%	50.9%	100.0%

	Value	df	Asymptotic Significance (2-sided)
Pearson Chi-Square	151942.13[a]	4	.000
Likelihood Ratio	171391.65	4	.000
N of Valid Cases	271867		

	Value	Approximate Significance
Cramer's V	.748	.000
N of Valid Cases	271867	

Supplementary Table S4 –Cluster Analysis – Crosstabulation, Chi-saquare and V'Cramer tests

Consultation in the last 12 months

		TwoStep Cluster Number 1	2	Total
No	Count	1695	4233	5928
	Expected Count	2913.3	3014.7	5928.0
	% within CONS12MESES	28.6%	71.4%	100.0%
Yes	Count	131914	134025	265939
	Expected Count	130695.7	135243.3	265939.0
	% within CONS12MESES	49.6%	50.4%	100.0%
Total	Count	133609	138258	271867
	Expected Count	133609.0	138258.0	271867.0
	% within CONS12MESES	49.1%	50.9%	100.0%

	Value	df	Asymptotic Significance (2-sided)
Pearson Chi-Square	1024.171[a]	1	.000
Likelihood Ratio	1059.768	1	.000
N of Valid Cases	271867		

	Value	Approximate Significance
Cramer's V	.061	.000
N of Valid Cases	271867	

Type of diabetes

		TwoStep Cluster Number 1	2	Total
Tipo I	Count	10721	14163	24884
	Expected Count	12229.2	12654.8	24884.0
	% within TIPO_DIABETES	43.1%	56.9%	100.0%
Tipo II	Count	122888	124095	246983
	Expected Count	121379.8	125603.2	246983.0
	% within TIPO_DIABETES	49.8%	50.2%	100.0%
Total	Count	133609	138258	271867
	Expected Count	133609.0	138258.0	271867.0
	% within TIPO_DIABETES	49.1%	50.9%	100.0%

	Value	df	Asymptotic Significance (2-sided)
Pearson Chi-Square	402.621[a]	1	.000
Likelihood Ratio	404.029	1	.000
N of Valid Cases	271867		

	Value	Approximate Significance
Cramer's V	.038	.000
N of Valid Cases	271867	

Supplementary Table S5 - Distribution of sociodemographic, health service utilization, health status and screening features by screening adherence

Category	Variable	Screening adherence		Test results
		No	Yes	
Sociodemographic	**Age**			
	18-39	53.60%	46.40%	X2=861.,57 (p_value=0.00) Cramer's V=0.14
	39-54	37.25%	62.75%	
	54-64	29.79%	70.21%	
	64-74	28.71%	71.29%	
	>74	42.54%	57.46%	
	Gender			
	M	32.87%	67.13%	X2=83.41
	W	36.92%	63.08%	(p_value=0.00)
	Degree of urbanization of the area of residence			
	0	34.33%	65.67%	X2=74.94 (p_value=0.00) Cramer's V=0.06
	1	39.07%	60.93%	
	2	34.08%	65.92%	
	5	34.27%	65.73%	
	Professional status			
	Active	32.03%	67.97%	X2=181.23 (p_value=0.00) Cramer's V=0.06
	Unknown	41.09%	58.91%	
	Student	55.83%	44.17%	
	Not active	33.03%	66.97%	
	Retired	37.78%	62.22%	
	Existence of telephone contact for sending reminders			
	N	45.18%	54.82%	X2=383.60
	Y	33.12%	66.88%	(p_value=0.00)
	Income (median)			
	Unknown	38.57%	61.43%	X2=97.67 (p_value=0.00) Cramer's V=0.05
	<8511	36.12%	63.88%	
	8511-9811	33.98%	66.02%	
	9811-11167	31.76%	68.24%	
	11167-12649	34.16%	65.84%	
	12649-17400	37.16%	62.84%	
	>17400	38.18%	61.82%	
	Education			
	KS2	38.57%	61.43%	X2=60.02 (p_value=0.00) Cramer's V=0.04
	KS3	35.45%	64.55%	
	KS4	33.54%	66.46%	
	KS5	36.33%	61.82%	
	College degree	38.18%	63.67%	
Relationship with health services	**Type of Health Unit**			
	UCSP	38.29%	61.71%	X2=114.38 (p_value=0.00) Cramer's V=0.04
	USF A	37.57%	62.43%	
	USF B	33.06%	66.94%	
	Family doctor			
	N	45.26%	54.74%	X2=114.38
	Y	34.93%	65.07%	(p_value=0.00)
	Exemption from charges for services			
	Not exempt	33.57%	66.43%	X2=35.42
	Insufficient income	35.59%	64.41%	(p_value=0.00)
	Exempt for another reason	38.70%	61.30%	Cramer's V=0.03
	Number of consultations at the Primary Care Unit in the last 12 months			
	0	71.59%	28.41%	X2=501.62 (p_value=0.00) Cramer's V=0.10
	1	60.30%	39.70%	
	2-3	34.83%	65.17%	
	4-6	33.69%	66.32%	
	7-9	32.47%	67.53%	
	>=10	36.55%	63.45%	
	Type of diabetes (I or II)			

Supplementary Table S5 - Distribution of sociodemographic, health service utilization, health status and screening features by screening adherence

Category	Variable	Screening adherence		Test results
		No	Yes	
Health status	Type I	44.34%	55.66%	X2=8.89
	Type II	34.12%	65.83%	(p_value=0.00)
	Body Mass Index (BMI)			
	NA	37.99%	62.01%	
	<18.5	38.46%	61.54%	X2=362.91
	18.5-24.9	33.05%	66.95%	(p_value=0.00)
	25-30	28.19%	71.81%	Cramer's V=0.09
	>=30	29.26%	70.74%	
	Blood glucose levels (HBA1C)			
	NA	37.97%	62.03%	X2=373.87
	<8	28.54%	71.46%	(p_value=0.00)
	>=8	34.90%	65.10%	Cramer's V=0.09
DR Screening	**Days elapsed between calls**			
	NA	32.08%	67.92%	
	<365	36.94%	63.06%	X2=64.41
	365-455	34.92%	65.08%	(p_value=0.00)
	455-545	33.51%	66.49%	Cramer's V=0.04
	545-635	33.82%	66.18%	
	>=635	37.16%	62.84%	
	Month of call for screening			
	01	34.84%	65.16%	
	02	34.73%	65.27%	
	03	31.34%	68.66%	
	04	31.98%	68.02%	
	05	34.45%	65.55%	X2=277.22
	06	43.18%	56.82%	(p_value=0.00)
	07	33.67%	66.33%	Cramer's V=0.08
	08	36.23%	63.77%	
	09	31.17%	68.83%	
	10	33.46%	66.54%	
	11	36.36%	63.64%	
	12	47.20%	52.80%	
	Number of times the diabetic was called			
	1	32.49%	67.51%	
	2	37.63%	62.37%	X2=184.80
	3	36.46%	63.54%	(p_value=0.00)
	4	31.94%	68.06%	Cramer's V=0.06
	5	23.32%	76.68%	
	6	21.43%	78.57%	
	Last screening result			
	NA	31.09%	68.91%	
	Did not attend	60.71%	39.29%	X2=6318.43
	Negative	20.62%	79.38%	(p_value=0.00)
	Inconclusive	33.08%	66.92%	Cramer's V=0.37
	Positive	38.80%	61.20%	
	Percentage of times the diabetic attended previous screenings			
	NA	32.08%	67.92%	
	0%	68.11%	31.90%	X2=7095.41
	25%-50%	56.80%	43.20%	(p_value=0.00)
	50%-75%	36.67%	63.33%	Cramer's V=0.39
	>=75%	19.17%	80.83%	