Cost-Effectiveness of Screening for Celiac Disease in Children

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Abstract

Cost-effectiveness of implementing wide-scale screening and prospective preventive measures for celiac disease remain poorly known. Although these interventions may reduce the burden of disease, the testing would also incur substantial costs for the society. This study aims to estimate the cost-effectiveness of various mass screening strategies for children and the cost-effectiveness of a hypothetical enterovirus vaccination.

The progression of celiac disease in the general population is represented using a discrete-time Markov chain with seven states, each corresponding to a different stage of the disease. Each state is given an age dependent annual monetary cost and a quality-adjusted life year (QALY) score. By simulating the Markov chain from birth to death, average lifetime costs and QALY scores can be calculated for a given scenario. By comparing the results between a no-intervention scenario and a given intervention, the incremental cost-effectiveness ratio (ICER) can be calculated.

The cost-effectiveness ratio of single-time and repeated serological screening are tested at different time-points ranging from age 3 to 15 years. Additional comparisons are made between untargeted serological screening and a two-step strategy utilizing HLA genotyping that first identifies the at-risk population. The vaccination is assumed to lower the annual probability of developing celiac disease by 20% with a cost of €250.

The most cost-effective strategy for single-time mass screening is achieved using universal serological screening at age of 6 years, with an ICER of €38,528 per gained QALY. The best cost-effectiveness for repeated screening is achieved by universal serological screening at the ages of 4 and 8 years with an ICER of €47,308 per gained QALY. The ICER of the vaccine is €80,201 per gained QALY.

Universal serological screening is more cost-effective compared to the two-step approach with HLA genotyping. Given the standard threshold of €50,000 per gained QALY, screening for celiac disease in children appears to be cost-effective. The vaccine is not cost-effective in preventing the disease at the assumed price. However, lowering the cost to under €165 makes it cost-effective. The results, however, are based on multiple assumptions about the disease progression.

Keywords celiac disease, discrete-time Markov chain, health economics, incremental cost-effectiveness ratio

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Keliakian seulonta ja taudin puhkeamisen estäminen vähentäisi sairaudesta johtuvaa yhteiskunnallista taakkaa. Näiden interventioiden kustannustehokkuudet ovat kuitenkin hämärän peitossa. Tämän tutkimuksen tavoitteena on selvittää otaksutun enterovirus-rokotteen sekä moninaisten seulontastrategioiden kustannusvaikuttavuus lapsuudessa puhkeavalle keliakialle.

Keliakian etenemistä kuvataan diskreettiaikaisella Markov-ketjulla, jolla on seitsemän tilaa. Tilat kuvaavat yksinkertaistetusti taudin eri vaiheita. Jokaiselle tilalle annetaan iästä riippuva vuotuinen rahallinen kustannus sekä laatupainotettu elinvuosi. Simuloimalla Markov-ketjua väestön syntymästä kuolemaan elinaikaiset rahalliset kustannukset sekä laatupainotettujen elinvuosien määrä voidaan laskea annetulle skenaariolle. Vertailemalla eri skenaarioiden lukuja annetun intervention inkrementaalinen kustannus-vaikuttavuussuhde voidaan laskea.

Seulonnan ikää vaihdellaan ikävuosien 3-15 välillä. Toistettuja seulontoja verrataan kertaseulontaan ja kohdistamtonta seulontaa verrataan kaksivaiheiseen seulontaan, jossa geneettisesti riskiryhmässä olevat pyritään selvittämään jatkotutkimuksia varten. Rokotteen oletetaan antavan 20 % pienempi vuotuinen todennäköisyys sairastua keliakiaan ja sen hinnaksi oletetaan 250 €.

Kustannusvaikuttavimmassa seulontastrategiassa käytetään kohdistamatonta seulontaa kerran 6-vuoden iässä ja sen inkrementaalinen kustannus-vaikuttavuussuhde on 38 528 € per laatupainotettu elinvuosi. Toistettujen seulontojen kustannusvaikuttavimmassa seulontastrategiassa ikäluokka seulotaan kohdistamattomasti ensin 4- ja sitten 8-vuoden iässä. Strategian inkrementaalinen kustannus-vaikuttavuussuhde on 47 308 € per laatupainotettu elinvuosi. Rokotteen inkrementaalinen kustannus-vaikuttavuussuhde on 80 201 € per laatupainotettu elinvuosi.

Kohdistamaton seulonta on kustannusvaikuttavampi verrattuna riskiryhmän ensin tunnistavaan kaksivaiheiseen seulontaan. Yleisessä käytössä olevan 50 000 € per laatupainotettu elinvuosi kynnyksen perusteella keliakian seulominen lapsissa on yhteiskunnalle kustannusvaikuttavaa. Oletettu rokote ei ole kustannusvaikuttava tapa estää keliakian puhkeamista. Rokotteesta tulisi kustannusvaikuttava, mikäli se maksaisi alle 165 €. Tulokset pohjautuivat moniin olettamiin sairauden etenemisestä.

Avainsanat keliakia, diskreettiaikainen Markov-ketju, terveystaloustiede, inkrementaalinen kustannus-vaikuttavuussuhde

Contents

Abbreviations

HLA	Human leukocyte antigen
ICER	Incremental cost-effectiveness ratio
GFD	Gluten free diet
QALY	Quality-adjusted life year
tTg-IgA	Tissue transglutaminase immunoglobulin A
EMA	Endomysial antibody
HRQOL	Health-related quality of life
DALY	Disability-adjusted life year
ETICS	Exploring the iceberg of celiacs in sweden

1 Introduction

Undiagnosed celiac disease is associated with reduced quality of life [1, 2]. The often long diagnostic delay [3] also predisposes patients to long-term complications [4] that could be avoided with early treatment [5, 6]. The disease is heavily underdiagnosed [7, 8] and incidence rates have been rising throughout the western world during the last 70 years [9]. Notably in children, undiagnosed celiac disease can lead to nutrition malabsorption induced growth retardation, delayed puberty and dental enamel hypoplasia [4, 10]. Because the disease has no known cure and the only effective treatment is a lifelong gluten free diet (GFD) [11], the only contemporary ways to reduce the burden of disease are to lower the diagnostic delay and to prevent the disease onset.

In countries and regions with high incidence rates, mass screening could be a cost-effective way of lowering the diagnostic delay. However, decision makers responsible for designing its implementation do not currently have a way of comparing different strategies. In addition, the cost-effectiveness of mass screening is not well known, hindering the decision-making process and possibly leading to suboptimal strategies.

Previously, the cost-effectiveness of mass screening has been under investigation using Markov models [12, 13, 14, 15]. In these papers, the cost-effectiveness of different screening strategies is estimated by simulating a discrete-time Markov chain. The Markov chain acts as a simplified description of the disease progression in the general population. By giving each state an age dependent monetary cost and a quality-adjusted life year (QALY) score, the average lifetime costs and QALY scores can be calculated. Then, by comparing the results between no-screening and screening, the incremental cost-effectiveness ratio (ICER) can be calculated.

These studies have investigated the cost-effectiveness of using varying diagnostic tools [12, 14], identified factors with the highest impact on cost-effectiveness [13], and analysed the cost-effectiveness of preventing hip and vertebral fractures caused by celiac disease induced bone loss [14]. The most recent study by Norström et al. (2021) looked at the cost-effectiveness of mass screening 12-year-old children in Sweden [15]. All four studies support mass screening from a cost-effectiveness perspective. However, as the models are inevitably constructed on multiple assumptions due to a lack of data, the results can be easily disputed. In addition, none of the previous studies have thoroughly looked at how screening age and strategy might affect cost-effectiveness.

The main purpose of this study is to create a Markov model that can be used for the cost-effectiveness comparison of different mass screening strategies for children. The variables that this study focuses on are age at screening, repeated screening versus single-time screening, and at-risk screening versus universal screening. Single-time and repeated screenings are simulated between ages 3 to 15 and comparisons are made between untargeted screening and a two-step strategy utilizing genotyping to identify the at-risk population. The model design and several parameter values are influenced by the article by Norström et al. [15].

The secondary purpose of this study is to use the Markov model for assessing the cost-effectiveness of prospective measures, that could prevent the disease onset. While there have been several attempts at investigating what factors are associated with the

disease [16, 17], standardized preventive measures are unfortunately nonexistent. As gastrointestinal viral and bacterial infections can trigger the disease [17], pioneering studies have studied how effective rotavirus vaccination could be in preventing the disease. However, the results are not conclusive [18]. This study pioneers the cost-effectiveness analysis of preventive measures by investigating a hypothetical enterovirus vaccination and a generalized preventive measure. The vaccination is assumed to cost €250 per child and it lowers the annual probability of developing celiac disease by 20%. The general preventive measure is defined by the same parameters as the vaccine, its price per child and a lowered annual probability of developing the disease. To see how the cost-effectiveness behaves with regards to these variables, a price range of €25-€500 and a lowered probability range of 5-50% were used.

The structure of the thesis is as follows. In Chapter 2, fundamental concepts related to celiac disease are introduced as necessary background information for creating the Markov model. In conjunction with understanding the very basics of the disease, it is necessary to discuss how the disease is diagnosed, how it affects one's quality of life, what risk factors are associated with the disease, and what the current research says about preventive measures. Chapter 3 contains an explanation of the Markov model. First, the basic idea behind the model is introduced with the parameter values used in the simulations. Subsequently, mathematical descriptions of the simulations and cost-effectiveness calculations are presented. Chapter 4 presents the results of the simulations along with a cost-effectiveness analysis and a sensitivity analysis. Chapter 5 contains a discussion on the model - successes, failures, future development opportunities, simplifications and their impacts on the results are considered here. Finally, Chapter 6 gives a summary of the thesis.

2 Celiac disease

This chapter contains a short literature review on celiac disease related topics, that are needed in model construction and discussion. For building a Markov model of celiac disease, the range of symptoms and progression of the disease need to be discussed for deciding what states and transitions to use. This is done in Chapter 2.2, after introducing the basics in Chapter 2.1. A short look at-risk factors follows in Chapter 2.3. Genetic risks are discussed as one option in mass screening is to first check for the presence of certain genetic markers. Environmental risks are discussed as removing possible exposomes from one's environment could act as a preventive measure for the disease. Diagnosis is discussed in Chapter 2.4 to provide information on how the mass screening is implemented in the simulations. For conducting cost-effectiveness calculations, it is necessary to consider how the disease affects one's quality of life and what costs are associated with the disease. These are talked through in Chapter 2.5. Finally, a short literature review of preventive measures is presented in Chapter 2.6.

2.1 Basics

Celiac disease is a chronic disease in which the ingestion of gluten, a protein found in wheat, rye and barley, causes the body's immune system to attack healthy cells, primarily affecting the small intestine [19]. Typical disease progression starts with structural changes in the gut that give rise to gastrointestinal problems and nutrient malabsorption. However, the profile of symptoms varies heavily between cases, with some patients being asymptomatic and others developing extraintestinal symptoms [4, 20]. The disease is strongly associated with certain genetic components [21] and it can develop at any age [7]. It is also heavily underdiagnosed [7] in part due to the diverse range of symptoms that can make identification difficult, and in part due to many patients experiencing only mild adverse effects that don't require prompt attention. Currently, there are no known cures for the disease and the only treatment is for patients to follow a strict gluten free diet for the rest of their lives [11].

2.2 Symptoms and progression

When a person with celiac disease ingests gluten, the body's immune system damages the finger-like projections, called villi, that are lining the small intestine [22]. As the main purpose of villi is to increase the surface area capable of nutrient absorption, the more damaged the villi are, the harder it is to absorb nutrients. As a natural consequence, many of the symptoms associated with celiac disease are related to malnutrition and resemble common stomach problems [4]. The clinical manifestation of celiac disease presents itself with a diverse array of symptoms that can be classified as either gastrointestinal or extraintestinal.

Gastrointestinal symptoms are common but often mild in nature. These include manifestations such as diarrhea, chronic abdominal pain, vomiting, chronic constipation and distended abdomen [4]. Extraintestinal symptoms can take place

almost anywhere on the body and they cover a significant proportion of clinical manifestations [4]. To illustrate, around 10% of adults with celiac disease experience dermatitis herpetiformis, which is characterized by an intensely itchy and blistering skin [23]. Celiac disease induced nutrient malabsorption on the other hand can lead to conditions such as osteoporosis, iron-deficiency anaemia, weight loss, anorexia and dental enamel hypoplasia [4]. Also, notably in children, celiac disease can cause growth retardation and delayed puberty [10]. The disease has also been linked to many psychological and brain related conditions, such as depression, anxiety, chronic fatigue and epilepsy [24].

In addition to all of the symptomatic manifestations, celiac disease can stay hidden for long periods of time in an asymptomatic state [4]. Although, here it is very important to note, that being asymptomatic does not imply that there are no adverse effects taking place in the patient's body due to gluten ingestion. It is perfectly possible, that the patient is just used to living with mild symptoms. Indeed, there is some evidence that even asymptomatic patients can benefit from a gluten free diet [2, 6, 25, 26].

The disease often starts with mild symptoms that get progressively worse over time. This feature is important to capture in the Markov model, as the severity of the symptoms is related to patient life quality and costs induced by the disease.

2.3 Risk factors

While the factors responsible for the geographic variation and increasing prevalence of the disease are still shrouded in mystery, there are several known risks. Genetic susceptibility seems to be a prerequisite for developing celiac disease alongside the ingestion of gluten. More specifically, the disease is found, almost exclusively, in individuals with the human leukocyte antigen (HLA)-DQ2 and/or HLA-DQ8 haplotypes [21]. In layman's terms, HLA is a system of genes that encodes several key molecules of the immune system. Out of people who possess one or more of the haplotypes only around 4% develop the disease [27] and its prevalence also varies in populations with a similar HLA background [19], giving more ground for the importance of other genetic and environmental factors. The HLA background can be broken down by the number and type of haplotypes present in a person. A 2014 study showed that children with two copies of HLA-DQ2 haplotypes were at the highest risk of developing celiac disease. The second highest risk of disease was in children with single HLA-DQ2 and HLA-DQ8 haplotypes, followed by two HLA-DQ8 haplotypes, and the group with the lowest risk had only a single HLA-DQ8 haplotype [28]. Furthermore, it is estimated that these HLA regions account for only around 25-40% of the genetic variance and that all known genetic factors only account for around 50% [29]. In a mass screening scenario where the genetically at-risk are screened, an HLA background test is used. If one or more of the HLA risk molecules are found, or if the test is inconclusive, a follow-up test is required.

There has also been much research on environmental factors, with a 2019 meta-analysis providing the most up-to-date summary on the subject. The paper lists 30 different environmental factors and assigns them a level of association (conflicting

data, no association, weak, moderate, strong) and a level of evidence found in the literature (levels 1-5, with 1 corresponding to the highest level of evidence). Most of the environmental factors had either no association or the association were weak (20/30 factors). For example, there is strong evidence that birth-related factors such as delivery mode and seasonality are only weakly associated with celiac disease. Other weakly associated factors include variables such as family size, the use of antibiotics and tobacco smoking. However, it is important to note that research on many of these factors is not yet conclusive and the results might change in the future. There were 6 factors that were either moderately or strongly associated with celiac disease. There is strong evidence, that a short duration of breastfeeding is moderately associated with the disease. The strongest association with the highest level of evidence was credited to gut microbiota and gastrointestinal infections. [17] As the environmental factors are still under research, the cost-effectiveness of removing (or adding) certain exposomes from the environment will not be looked at this study. Further research might open an avenue for researching, for example, the cost-effectiveness of preventing celiac disease with specific early life feeding practices.

2.4 Diagnosis

There are three instruments in the toolbox of a physician during the diagnostic process: genotyping, antibody tests and tissue samples. Antibody tests and tissue samples are more commonly used, while genetic tests tend to be used in special situations.

Diagnostic practices alternate between countries, but by and large, diagnosis starts with celiac disease specific antibody tests, which are then followed by a tissue sample. For example, in Finland the current recommendation for diagnosis is to measure the levels of tissue transglutaminase IgA (tTg-IgA) and endomysial antibodies (EMA). If antibody levels found in a blood sample exceed the predefined limits, a tissue sample is not required for diagnosis [30]. The European Society for Paediatric Gastroenterology, Hepatology and Nutrition published guidelines for diagnosing celiac disease in 2020 [31]. To paraphrase, the guidelines recommend that the same diagnostic criteria used in Finland can be recommended for children, provided that the family agrees.

Although the sensitivity of many widely used antibody tests are excellent (between 90-100% for EMA, for example) [32], they are not infallible. And because around 10% of people are seronegative [33], meaning that their disease cannot be detected by any of the current serological methods [34], the serological tests are often complemented by taking tissue samples and/or scrutinizing for genetic risk. Tissue samples are often necessary due to elevated antibody levels that are under the threshold needed for diagnosis. However, tissue samples are not infallible either - the most common indicator of celiac disease found in tissue samples, damage to villi, can be caused by certain medications, viral and bacterial infections and autoimmune enteropathy [34]. Furthermore, even if the villous atrophy is resulting from celiac disease, it is the end stage of gradual destruction that can take decades to develop.

Because celiac disease is almost exclusively associated with certain genetic markers, genotyping can prove beneficial in the diagnostic process. The tests have a high

negative predictive value, but low positive predictive value [35]. Therefore, genotyping is generally used for ruling out the possibility of celiac disease and not for diagnosing the disease.

Eating a gluten containing diet during diagnosis is important, as the serological tests function by detecting serum antibodies or antibody-like substances, that appear in association with the disease. In addition, irregularities in the small intestinal mucosa are more prominent during gluten containing diet, making abnormalities clearer under the microscope. Trying to get a diagnosis after a long period of gluten free diet is out of the question. The small intestine has had time to heal and the immune system doesn't produce the antibodies the tests expect.

To fully appreciate how muddy the waters of diagnosis are, consider the following - it is possible for someone to have asymptomatic celiac disease that is hidden from all current serological and histological tests for decades, only to develop severe symptoms later in life.

The simulated mass screening has two approaches for screening. One is made to follow the recommended guidelines of diagnosis in Finland - with high enough antibody levels the diagnosis is given without a tissue sample. The other strategy utilizes HLA genotyping for identifying the at-risk population. This strategy might prove especially useful for repeated screenings, as a significant part of the population does not need to participate in the second screening.

2.5 Burden of disease

Burden of disease is most often measured in terms of health (morbidity, mortality) and financial costs. Commonly used metrics include health-related quality of life (HRQOL) [36], quality-adjusted life years (QALYs), disability-adjusted life years (DALYs), and money spent on treatment [37, 38]. Assessing HRQOL is often done by creating disease specific questionnaires, that try to take a holistic view of the patient's life [36]. This allows for the comparison between the health of different patients at different stages of treatment. The results of the questionnaires can then be used to investigate how factors, such as age or gender, might affect perceived health. On the other hand, both QALY and DALY try to measure how many years of healthy life are lost due to disability by combining quantity and quality of life. These metrics are paramount when evaluating the effectiveness and impact of different intervention methods and screening strategies - something measurable is needed to distinguish options from one another. In addition, self-assessed health and patient satisfaction have also gained traction as criteria for evaluating the quality of healthcare [39].

Celiac disease has many elements that associate with health-related quality of life. These include age at diagnosis [40, 41], gender [42, 43, 44], comorbidities [40, 45] and the availability of gluten free products [46]. Furthermore, as many patients suffer from only mild adverse effects that they might be used to, compliance to gluten free diet after diagnosis is not for given. Compliance leads to better quality of life [40, 41, 44, 45, 47], but the scores still tend to stay lower when compared to control populations, with women having the tendency to suffer more from the disease [48, 49]. Symptomatic patients score lower on quality of life compared to

control populations [1, 2] and patients with severe symptoms score lower compared to patients with milder symptoms [1, 44, 45, 50]. In children, there doesn't seem to be a significant difference in quality of life when compared to healthy controls, and the children's parents tend to be more pessimistic about their child's quality of life than the children themselves, as suggested by a 2020 meta-analysis [51]. From a model building standpoint, the main takeaway is that quality of life is associated with disease progression.

The true economic cost of celiac disease is difficult to uncover. It would require estimates on the increased need of healthcare services, the cost of comorbidities, the cost of testing and diagnosis, and the cost of productivity loss due to missed days from work. In addition, this information is often country specific due to differing diagnostic practices, prevalence levels and healthcare systems. A 2019 literature review on the economic burden of celiac disease concluded that most of the available studies discussed only testing and diagnostic costs, and that the papers came chiefly from European countries [52].

2.6 Preventive measures

There have been some studies focused on the effectiveness of prospective preventive measures. Early life feeding practices and vaccinations have been under investigation.

As there is good evidence that viral and bacterial infections are strongly associated with celiac disease [17], the rotavirus vaccine has been theorized to prevent some cases. However, a 2021 review article, that summarized the effectiveness of rotavirus vaccination on preventing celiac disease, did not find evidence for the vaccination affecting the risk either way [18]. These results, however, were not conclusive.

Feeding interventions have been of interest, as there is evidence that early life feeding practices are linked to celiac disease [17]. To be exact, researchers have been interested in how the timing and dosage of gluten at weaning and the duration of breastfeeding could attribute to the risk of developing celiac disease. A 2016 meta-analysis, that aggregated the results of 17 early life feeding practice interventions, showed that there is currently no proof that breastfeeding versus no breastfeeding significantly alters the risk of celiac disease. The results, however, were not conclusive. There was some evidence for the late introduction of gluten being associated with an increased risk of celiac disease. The study didn't find that early introduction would increase the risk. [16]

The current literature does not offer a method that can be directly used for the cost-effectiveness analysis of preventive measures. Therefore, heuristics need to be used.

3 Markov model of celiac disease

This Chapter goes through the model building process and the cost-effectiveness calculations. First, the states of the model are justified in Chapter 3.1. Then, the transition probabilities and state parameters are introduced in Chapters 3.2 and 3.3 respectively. Chapter 3.4 discusses the different mass screening strategies and their costs. Chapter 3.5 gives a mathematical description on how the model is simulated in different scenarios. Finally, Chapter 3.6 discusses how the health economic evaluation is performed on the results.

3.1 States

The progression of celiac disease in the general population is described using a discrete-time Markov chain with 7 states. A simplified sketch of the model is presented in Figure 1. The simulated population starts in the healthy state at 0 years of age. During the simulation, part of the population develops celiac disease as they age and part of the diseased population gets diagnosed. The simulation uses a time-step of 1 year and stops at age 110.

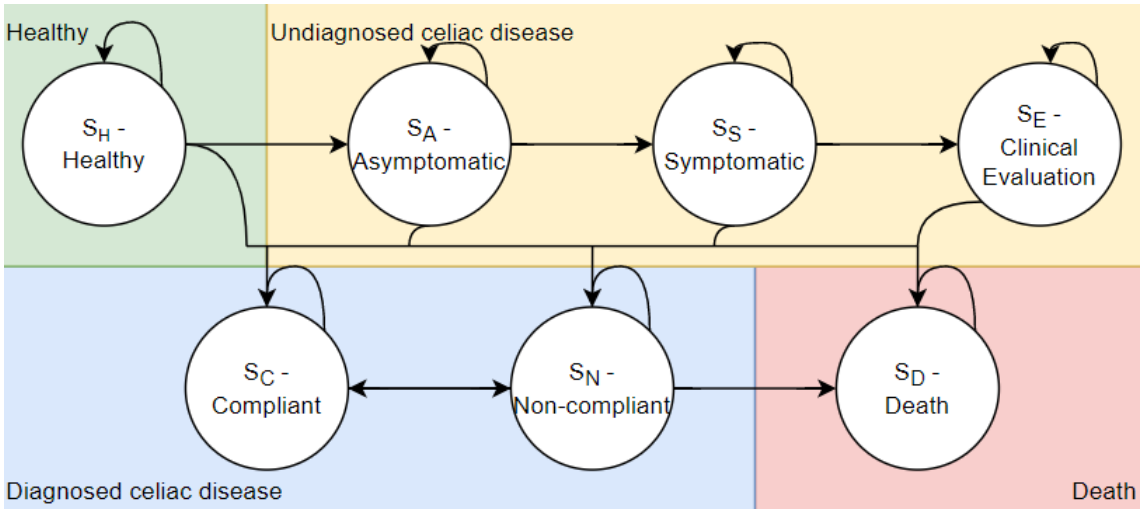

Figure 1: Sketch of the Markov model.

As was previously discussed in Chapter 2.2, celiac disease is associated with multiple symptoms of varying degrees of severity. The disease is also often in an asymptomatic state that gets progressively worse. Therefore, it is important to describe undiagnosed celiac disease using asymptomatic and symptomatic states. This allows for the use of different parameters depending on the severity of the disease. It also makes describing the disease progression possible. The clinical evaluation state is used to carry out two roles. Because diagnosing the disease can be difficult, a patient can spend an entire year in a limbo state where the diagnosis is not given even if the patient is sick. On the other hand, the clinical evaluation state is also used for

describing a more severe manifestation of the disease compared to the symptomatic state.

Because the only effective treatment is a lifelong gluten free diet that patients are not always willing to follow, two states corresponding to treatment compliance are used. Using two states is important as compliance is associated with quality of life and different age groups have different compliance rates.

To run simulations and cost-effectiveness calculations on the results, the model needs transition probabilities and state parameters. Transition probabilities describe the likelihood of moving from a given state to another within one time-step. Transition probabilities, in other words, describe how the disease progresses over time. For conducting cost-effectiveness analysis of different screening strategies and preventive measures, it is also necessary to give each state age dependent annual monetary costs and quality-adjusted life year scores. These are referred to as state parameters.

Much of the values and assumptions used in building the model overlap with the study by Norström et al. (2021) [15]. As a consequence, most of the data will be based on two studies on the Swedish population: Exploring the Iceberg of Celiacs in Sweden (ETICS) screening study [53] and a survey sent to the members of the Swedish Celiac Association [3].

3.2 Transition probabilities

The transition probability matrix of the Markov model is provided in Table 1, where abbreviations for state names found in Figure 1 have been used for compactness.

	S_H	S_A	S_S	S_E	S_C	S_N	S_D
S_H	$1-r-m$	$0.928r$	$0.038r$	$0.034r$	0	0	m
S_A	0	$0.955-1.22m$	0.027	0.009	0.009	0	$1.22m$
S_S	0	0	$0.415-1.27m$	0.135	0.450	0	$1.27m$
S_E	0	0	0	$0.478-1.27m$	0.522	0	$1.27m$
S_C	0	0	0	0	$c(1-1.22m)$	$(1-c)(1-1.22m)$	$1.22m$
S_N	0	0	0	0	$c(1-1.27m)$	$(1-c)(1-1.27m)$	$1.27m$
S_D	0	0	0	0	0	0	1

Table 1: Transition probability matrix of the Markov model.

The transition probability matrix has three age dependent functions: $r = r(t)$ is the probability of developing celiac disease, $c = c(t)$ is the gluten free diet compliance rate and $m = m(t)$ is the mortality probability. Because the time-step used in this study is one year, the disease progression does not always follow the natural path from sickness to evaluation to diagnosis. The one year step is equivalent to multiple shorter steps during a year.

3.2.1 Time-invariant probabilities

Starting from the first row of the matrix, if an individual does not die or develop celiac disease, they will stay in the healthy state. Because the disease can manifest itself with a wide range of symptoms with varying degrees of severity [4], the probability of developing celiac disease was divided between the asymptomatic, symptomatic and

clinical evaluation states. The proportions were decided by the number of symptoms that children who were diagnosed with the disease disclosed in a questionnaire. The questionnaire had five categories for symptoms. Disclosing two categories was defined as being symptomatic ($9/236 \approx 3.8\%$ of respondents) and disclosing three or more was defined as being in clinical evaluation ($8/236 \approx 3.4\%$ of respondents). Most children (92.8%) therefore had an asymptomatic manifestation of the disease. [15]

The second row probabilities are based on assumptions that are tested later in Chapter 4.1. Assuming that 50% of celiac disease patients develop symptoms or get diagnosed within 15 years, the annual transition probability from the asymptomatic state to symptomatic, clinical evaluation and compliant state is,

$$1 - (1 - 0.5)^{1/15} \approx 4.5\%.$$

It is assumed that there is a 2.7% probability of developing symptoms, a 0.9% probability of going to clinical evaluation for a whole year, and a 0.9% probability of getting a diagnosis and following a gluten free diet.

For deriving the third row transition probabilities from the symptomatic state to clinical evaluation and compliance, the results of the adult celiac disease survey are being used. One of the questions the respondents were asked was, how long it took for them to get diagnosed after developing symptoms. According to the results, 73% were diagnosed within a year of first developing symptoms and 17% visited a doctor but did not get diagnosed although they had celiac disease. Among the people who did not get diagnosed during the first year after developing symptoms, 45% got diagnosed during the second year and 13.5% visited a doctor but did not get diagnosed. [3] The second year results are used for the transition probabilities from the symptomatic state to the clinical evaluation and to the compliant state. It is estimated that true symptoms began earlier than self reported symptoms, as mild symptoms can go unnoticed.

The fourth row probabilities are also based on the adult celiac disease survey results. According to the survey, 84% of the respondents were diagnosed within a year of first meeting with a doctor and 52% of those who were not diagnosed, got their diagnosis during the second year [3]. The second year probability was used for the transition probability from clinical evaluation to compliance.

Transition probabilities of rows 5 and 6 are based on time-dependent probabilities, and are therefore discussed in the next chapter. The last row corresponds to death and it is the absorbing state of the model.

Transition probabilities relating to the disease progression, starting from the asymptomatic state and ending at the compliant state, were mostly based on assumptions. These assumptions are tested against the following estimate about celiac disease diagnosis rate in Sweden. According to the National Swedish Childhood celiac disease register, using data collected on children who were born between the years 1987-1992, the expected number of diagnosed celiac disease cases during life years 12-13 was 31.2 new cases [54, 55]. For those born in the year 1993, approximately 16.1% of the age group took part in celiac disease screening at the age of 12. In this age group, a total of 149 new cases were found during life years 12-13 [56]. Assuming similar population sizes in age groups 1987-1993, approximately $149 - 31.2 \approx 127.8$

extra cases were found as a direct consequence of screening 16.1% of the age group. The number of extra cases found if the entire age group was mass screened is therefore approximately $127.8/0.161 \approx 731.68$. The annual diagnosis rate can be approximated by calculating what percentage of the diseased population would get a diagnosis without screening. This is the fraction between the expected number of diagnosed cases and the approximated number of total cases,

$$\frac{31.2}{731.68 + 31.2} \approx 4.1\%.$$

Therefore, around 4.1% of the undiagnosed population should get diagnosed annually. This result acts as a sanity check for the chosen transition probabilities. The annual diagnosis rate is examined in Chapter 4.1.

3.2.2 Time-dependent probabilities

The probability of developing celiac disease $r(t)$ gets its values from an unpublished research paper. As such, graphs and data are not shown. However, it is necessary to discuss how the data found in the paper was utilized for deriving the function $r(t)$. Among other results, the paper showed the cumulative risk of developing celiac disease in different countries as a function of age for the first 14 years of life. This study uses the cumulative risk curve of Sweden. As the data was based on a select cohort and not on the general population, the cumulative risk curve is scaled down such that the cumulative risk at the age of 12 corresponds to the true prevalence of 1.93% [57]. Furthermore, the cumulative risk does not directly tell the transition probability. To get $r(t)$ it is necessary to solve the conditional probability of being in the healthy state at age t but developing the disease at age $t+1$. The cumulative risk function is denoted with $cr(t)$ and it equals the probability of having celiac disease at a given age $cr(t) = p(CD(t))$. Being healthy at age t is denoted with $H(t)$ and having some form of celiac disease with $CD(t)$. Using Bayes' formula and assuming that $P(H(t)) = 1 - P(CD(t))$,

$$\begin{aligned} p(CD(t+1)|H(t)) &= \frac{p(H(t)|CD(t+1)) \cdot p(CD(t+1))}{p(H(t))}, \\ &= \frac{(1 - p(CD(t)|CD(t+1))) \cdot p(CD(t+1))}{1 - cr(t)}. \end{aligned}$$

Using Bayes' formula for the conditional probability inside the above expression,

$$\begin{aligned} p(CD(t)|CD(t+1)) &= \frac{p(CD(t+1)|CD(t)) \cdot p(CD(t))}{p(CD(t+1))}, \\ &= \frac{1 \cdot p(CD(t))}{p(CD(t+1))}, \end{aligned}$$

and inserting the results back into the original expression,

$$\begin{aligned} p(CD(t+1)|H(t)) &= \frac{(1-\frac{p(CD(t))}{p(CD(t+1))})\cdot p(CD(t+1))}{1-cr(t)}, \\ &= \frac{p(CD(t+1))-p(CD(t))}{1-cr(t)}, \\ &= \frac{cr(t+1))-cr(t))}{1-cr(t)}, \\ &= r(t). \end{aligned}$$

For ages $t \in [0, 14]$ raw data of the cumulative risk $cr(t)$ is available and for ages $t > 14$ a simple linear interpolation is fitted to the tail of the data.

The mortality probabilities $mr(t)$ are obtained from the Statistic Sweden open databases [58]. The data describes the mortality rates per 1000 of the mean population in age increments of 5 years for the year 2017. To transform this data to transition probabilities, the data was simply divided by 1000. These values are presented in Table 2. The standard mortality probability was used for the healthy state, however, as celiac disease has been associated with higher mortality [5, 59] the other states received hazard ratio based coefficients. In a study on the Swedish population by Ludvigsson et al. (2008), the overall hazard ratio was estimated to begin 1.39 in celiac disease patients compared to healthy controls, which was much higher than the pooled hazard ratio of 1.24 by a more recent meta-analysis by Tio et al. (2012) [5]. However, it is reasonable to assume that the severity of symptoms and treatment compliance are associated with mortality as well. Therefore, the asymptomatic and gluten free diet compliant states are given a hazard ratio of 1.22, which corresponds to the hazard ratio found in the Swedish population one to five years after diagnosis. The symptomatic, clinical evaluation and non-compliant states are given a hazard ratio of 1.27, which corresponds to the hazard ratio found in the Swedish population five years after diagnosis. [59]

Age	Probability	Age	Probability
0 years	0.241 %	45-49 years	0.138 %
1-4 years	0.010 %	50-54 years	0.221 %
5-9 years	0.006 %	55-59 years	0.366 %
10-14 years	0.009 %	60-64 years	0.647 %
15-19 years	0.024 %	65-69 years	1.045 %
20-24 years	0.043 %	70-74 years	1.721 %
25-29 years	0.055 %	75-79 years	2.995 %
30-34 years	0.055 %	80-84 years	5.659 %
35-39 years	0.064 %	85-89 years	10.963 %
40-44 years	0.090 %	90+ years	23.555 %

Table 2: Annual mortality probabilities per age group.

The compliant and non-compliant states have a function that tells the age

dependent compliance rate $c(t)$. According to a paper by Kurppa et al. (2012), gluten free diet compliance changes with age in the following way [60],

$$c(t) = \begin{cases} 0.86, & t < 13 \\ 0.72, & 13 \leq t \leq 17 \\ 0.89, & 18 \leq t \leq 64 \\ 0.91. & t > 64 \end{cases}$$

3.3 State parameters

This chapter introduces the annual monetary costs and quality-adjusted life scores that will be needed in the cost-effectiveness calculations.

3.3.1 Annual monetary costs

Annual monetary costs try to assess the costs incurred to society for living in a given state at a given age for a year. The three costs considered in this study are cost of healthcare visits and hospitalization days for the healthcare sector, and productivity loss due to sick days. The costs considered in this study focus on the societal aspect instead of the individual. That is to say, the added cost of buying premium priced gluten free products or other costs related to daily life with celiac disease are not considered.

The number of healthcare visits, hospitalization days and sick days per state and age group are provided in Table 3 and the calculated costs from Table 4. Death state is omitted as it has zero for every value.

The adult celiac disease survey is used for obtaining self-reported statistics about the number of healthcare visits, hospitalization days and sick leaves during a year [3]. This is combined with the mean healthcare visit cost (312 €) and mean hospitalization day cost (1137 €) in Sweden for the year 2017, which was obtained from the Swedish Association of Local Authorities and Regions [61]. The loss of productivity is calculated from the average monthly income (3370 €), which was reported by Statistics Sweden for the year 2017 [62], in the following way. The monthly income is divided evenly between 22 working days (3370€/22 $\approx$ 153.18 €) and a tax rate of 50% is added to convert the net income to gross income (153.18 € $\cdot 1.5 \approx$ 230 €).

The adult celiac disease survey reported an average of 5.4 healthcare visits, 2.3 hospitalization days and 7.2 sick days the year before getting diagnosed [3]. The time before diagnosis can be thought of as the worst stage in celiac disease progression, as the often severe symptoms have forced the patient to seek help. Therefore, these values are used for the most severe state of celiac disease in the model, the clinical evaluation state. The year before the questionnaire was sent, corresponding to a time when the participants were already diagnosed with the disease, the reported values were 3.7 healthcare visits, 0.7 hospitalisation days, and 2.5 sick days per year [3]. Because the participants were also mostly compliant to gluten free diet when they answered the questionnaire, these values are used for the compliant state.

Age group	0–18 years	19–65 years	66 years and older
healthcare visits (331.9 €)			
S_H – Healthy	3.7	3.7	5.1
S_A – Asymptomatic	3.7	3.7	5.1
S_S – Symptoms	3.7	3.7	5.1
S_E – Clinical evaluation	5.4	5.4	5.4
S_C – Compliant	3.7	3.7	5.1
S_N – Non-compliant	4.5	4.5	5.3
Hospitalization days (1136.9 €)			
S_H – Healthy	0.7	0.7	1.0
S_A – Asymptomatic	0.7	0.7	1.0
S_S – Symptoms	0.7	0.7	1.0
S_E – Clinical evaluation	2.3	2.3	2.9
S_C – Compliant	0.7	0.7	1.0
S_N – Non-compliant	1.5	1.5	2.0
Sick days (230 €)			
S_H – Healthy	0	2.5	0
S_A – Asymptomatic	0	2.5	0
S_S – Symptoms	0	3.7	0
S_E – Clinical evaluation	0	7.2	0
S_C – Compliant	0	2.5	0
S_N – Non-compliant	0	4.9	0

Table 3: Annual number of healthcare visits, hospitalization days and sick days per state and age group.

State	0–18 years	19–65 years	66 years and older
S_H – Healthy	€1950	€2322	€2387
S_A – Asymptomatic	€1950	€2322	€2387
S_S – Symptoms	€1950	€2516	€2387
S_C – Clinical evaluation	€4299	€5401	€4299
S_C – Compliant	€1950	€2332	€2387
S_N – Non-compliant	€3109	€3859	€3358

Table 4: State and age dependent annual costs.

Furthermore, it is assumed that these values can be used to approximate the healthy and the asymptomatic state values. The symptomatic state also uses the same values, with the exception of assuming 1.2 additional sick days. The non-compliant state is assumed to have values near the mean of the compliant and clinical evaluation states. In the questionnaire, the healthcare utilization was higher for the age group of over 65. To reflect this, the number of healthcare visits and hospitalization days is slightly increased for ages above 65. The number of sick days from work is assumed to be 0 for ages under 18 (underage) and over 65 (retired). Future productivity loss due to sick days from school or university is not in the scope of this study.

3.3.2 Quality-adjusted life year scores

The quality-adjusted life year score estimates the quality of life in a given state at a given age. A score of 0 corresponds to death and a score of 1 corresponds to theoretically perfect life. The scores used in this study are provided in Table 5, where the death state is omitted. For ages below 20 years old, the numbers are based on estimates, whereas for ages 20 and older some data was available from the adult celiac disease survey. The assumptions drawn from the data follow a very similar logic as was used in the previous chapter.

Age	Healthy	Asymtomatic	Symptoms	Clinincal Evaluation	Compliant	Non-compliant
0-4	0.94	0.94	0.82	0.60	0.94	0.92
5-9	0.94	0.94	0.82	0.60	0.94	0.92
10-14	0.94	0.94	0.82	0.60	0.94	0.92
15-19	0.92	0.92	0.82	0.60	0.92	0.86
20-24	0.90	0.90	0.76	0.63	0.90	0.83
25-29	0.87	0.87	0.76	0.63	0.87	0.81
30-34	0.85	0.85	0.76	0.58	0.85	0.78
35-39	0.89	0.89	0.69	0.56	0.89	0.81
40-44	0.85	0.85	0.74	0.61	0.85	0.79
45-49	0.86	0.86	0.80	0.67	0.86	0.81
50-54	0.87	0.87	0.87	0.74	0.87	0.84
55-59	0.87	0.87	0.84	0.71	0.87	0.83
60-64	0.83	0.83	0.81	0.78	0.83	0.82
65-69	0.86	0.86	0.81	0.76	0.86	0.83
70-74	0.85	0.85	0.80	0.74	0.85	0.82
≥ 75	0.81	0.81	0.81	0.81	0.81	0.81

Table 5: State and age dependent quality-adjusted life year scores.

The adult celiac disease survey had data about the QALY scores for the year before diagnosis and for the day the questionnaire was filled, when all participants were diagnosed and most followed a gluten free diet. The mean QALY score of the year before diagnosis is used for the clinical evaluation state. The reasoning here is the same as was used in the previous chapter. The year before a diagnosis can be thought of as the worst in the disease progression, as often severe symptoms have forced the patient to seek help.

The QALY score of the day the questionnaire was filled is used for the compliant state, as most participants followed a gluten free diet. The study also revealed that the mean QALY was similar between diagnosed celiac disease patients and that of the general population. [3] Therefore, it is assumed that the healthy, asymptomatic and compliant states have the same QALY scores.

The QALY scores for the symptomatic state are based on assumptions due to a lack of data. As the symptomatic state is less serious than clinical evaluation but more serious than asymptomatic, the values should be somewhere in between the two. It is assumed that the QALY score of the symptomatic state is 0.13 higher

compared to the clinical evaluation state, except when the value would have been too close to the asymptomatic state value. In these cases, the average score between the asymptomatic and clinical evaluation state is used.

The QALY scores for the non-compliant state are also based on assumptions due to a lack of data. Because compliance is purely volitional, it is reasonable to assume that people who have been diagnosed with celiac disease and have severe symptoms are more likely to follow a gluten free diet. To put it another way, non-compliant patients are likely to have less severe symptoms as they do not benefit from a gluten free diet as much. Therefore, it is assumed that the QALY score is a weighted average between the clinical evaluation and compliant states scores, where the compliant state gets a weight of 3/4 and the clinical evaluation gets a weight of 1/4.

For ages below 20, the scores are based purely on estimates. A recent meta-analysis by Nikniaz et al. (2020) looked at the health related quality of life in children with celiac disease. The analysis concluded that children with diagnosed celiac disease tend to score similarly with control populations [51]. Therefore the healthy, asymptomatic and compliant states share the same values. It is assumed that healthy children and young adults have slightly better QALY scores compared to older ages and that they suffer slightly less from the disease in the symptomatic and non-compliant states. Therefore, a slightly higher QALY score was used for these states. On the other hand, spending an entire year in a state of clinical evaluation was deemed to correspond to a comparatively low QALY score of 0.60. This is because in childhood the disease can have severe symptom manifestations that are not present in adults, such as growth retardation.

3.4 Screening

In this chapter, the diagnostic procedures and related costs are discussed. This study looks at two different screening approaches. In the first approach, the entire age group is tested with an antibody test. In the second approach, an HLA genotyping test is used for identifying the genetically at-risk. For those who are deemed to be at-risk or if the test was inconclusive, a follow-up examination will take place. The follow-up examination follows the same procedure as is used in the untargeted screening approach. In addition, repeated screenings at different age points will be compared with single-time screening.

The diagnostic procedure in the untargeted serological screening first tests the entire age group with EliA Celikey, which tests for the presence and level of IgA antibodies directed to tissue transglutaminase (tTG). With high enough antibody levels the diagnosis will be given purely on the basis of the serological test. Current research suggests, that around 54% of patients with undiagnosed celiac disease belong to this group [63]. For children who have elevated antibody levels that are below the threshold (46%), a subsequent biopsy will become necessary for diagnosis. After the diagnosis, it is assumed that the patients have a subsequent visit to a physician and a dietitian.

In the two-step genotyping procedure the age group is first tested for the presence of genetic markers, that are practically always present with the disease [21]. After

screening for genetic susceptibility, those who are deemed to be genetically resistant to the disease do not need a follow-up examination. Those who are at-risk or get a false positive test result are treated to the same diagnostic procedure as was described above in the untargeted serological screening. This strategy has the added benefit of having to test fewer people in repeated screenings.

3.4.1 Costs

The prices of different diagnostic tools and follow-up procedures, that are provided in Table 6, were mostly obtained from a research paper by Norström et al. (2011) [57], with the exception of the serological tests, which were obtained by asking hospitals for the prices. Inflation of 6.5% was used to correct the 2011 prices to 2017 prices, as reported by the world bank [64]. The calculations assume that the screening would take place in a school or a comparable environment.

Item	Unit cost (€)
Blood sampling at school	7.67
Nurses' salaries	5.75
Material	1.92
Serological tests	
Antibody test	11.00
Genetic background test	17.28
Biopsy	511.20
A visit to physician	223.65
A visit to dietitian	223.65

Table 6: The estimated unit costs of items involved in the diagnostic and follow-up procedures.

Denoting the percentage of population with undiagnosed celiac disease at age t with function $ucd(t)$, the cost of biopsy and subsequent healthcare services for an average child is approximately,

$$ucd(t)(1 - 0.54) \cdot (511.20 + 223.63 + 223.65) \approx 682.43 \cdot ucd(t).$$

In untargeted screening, everyone who is not dead or already diagnosed is subject to testing. Denoting this part of the population with $te(t)$, the average cost of taking a single antibody test is the cost of blood sampling plus the cost of the antibody test itself,

$$te(t)(7.67 + 11.00) \approx 18.67 \cdot te(t).$$

The average cost of repeated untargeted antibody tests is the blood sampling cost and antibody test cost at two different age points,

$$18.67(te(t_1) + te(t_2)).$$

Thus, money spent on a child for the single-time untargeted screening is,

$$682.43 \cdot ucd(t) + 18.67 \cdot te(t),$$

and for repeated untargeted screening,

$$682.43 \cdot (ucd(t_1) + ucd(t_2)) + 18.67(te(t_1) + te(t_2)).$$

For the two-step strategy, it is assumed that the genetic background is inspected first and after processing the results a follow-up test would only concern those for who the possibility of celiac disease cannot be ruled out. According to a 2014 study by Pallav et al., celiac disease could be ruled out using an HLA test in approximately 39% of people [35]. Conversely, around 61% of the population would need a follow-up examination after the HLA test. The cost of biopsy and subsequent healthcare services for the average child are the same as in the untargeted strategy, however, the cost of serological testing differs. It is assumed that the genotyping test and the antibody test would be taken on different occasions, as processing the results of the former takes time. Therefore, the cost of doing serological tests in the single-time screening with genotyping is the price of blood sampling at school twice plus the prices of the serological tests,

$$te(t)(17.28 + 0.61 \cdot 11.00 + 2 \cdot 7.67) \approx 39.33 \cdot te(t).$$

The cost of repeated screening is cheaper the second time, as the genetically at-risk have already been identified,

$$39.33te(t_1) + te(t_2)(0.61 \cdot 11.00 + 7.67) \approx 39.33 \cdot te(t_1) + 14.38 \cdot te(t_2).$$

Thus, the total cost for a single-time screening with HLA genotyping is,

$$682.43 \cdot ucd(t) + 39.33 \cdot te(t),$$

and the cost of repeated screening is,

$$682.43 \cdot (ucd(t_1) + ucd(t_2)) + 39.33 \cdot te(t_1) + 14.38 \cdot te(t_2).$$

Values for the functions $ucd(t)$ and $te(t)$ are obtained during the simulation.

It is already possible to see that for single-time screening, the untargeted universal screening will be cheaper as,

$$682.43 \cdot ucd(t) + 18.67 \cdot te(t) < 682.43 \cdot ucd(t) + 39.33 \cdot te(t), \quad \forall t.$$

However, this cannot be said about repeated screenings.

3.5 Simulating the Markov model

This chapter introduces the mathematics behind simulating the Markov model. The three cases that are discussed are simulation without interventions (i.e. without screening or preventive measures), simulation with screening, and simulation with a preventive measure. All simulations were run using python.

3.5.1 Simulations without intervention

The simulation starts with the entire population in the healthy state at the age of 0 and stops at age 110. Therefore, the initial distribution is described by the row vector $\mu_0 = [1, 0, 0, 0, 0, 0, 0]$. Denoting the transition probability matrix at time i with $P(i)$, the population distribution at time t is a simple matrix product,

$$\mu_t = \mu_0 \prod_{i=0}^{t} P(i).$$

The results of interest in the simulation are the average lifetime costs and quality-adjusted life year scores. Denoting the age dependent cost vector (Table 4) with $c(t)$ and the QALY score vector (Table 5) with $q(t)$, these can be obtained with,

$$\sum_{t=0}^{110} c(t)\mu_t^\top,$$
$$\sum_{t=0}^{110} q(t)\mu_t^\top.$$

A 3% discount rate was assumed for both average lifetime costs and QALY scores, as recommended by the Dental and Pharmaceutical Benefits Agency for Sweden [65]. Including the discounting, the formulas become

$$C = \sum_{t=0}^{110} (1 - 0.03)^t \cdot c(t)^\top \mu_t, \tag{1}$$

$$Q = \sum_{t=0}^{110} (1 - 0.03)^t \cdot q(t)^\top \mu_t. \tag{2}$$

3.5.2 Simulations with screening

In simulations where screening is applied, much of the same logic as in the previous case applies. However, it is necessary to cut the original Markov chain into two parts, where the first part simulates the population before screening and the second part after screening. This means that when the population is screened at age point s, a new initial state vector μ_t needs to be calculated. It is assumed that everyone in the asymptomatic, symptomatic and clinical evaluation states gets placed in the compliant state during the year of screening. Therefore, the population distribution at age t during single-time screening is,

$$\begin{aligned}
\mu_t &= \mu_0 \prod_{i=0}^{t} P(i), && \text{for } t < s,\\
\mu_t &= [\mu_{t_H}, 0, 0, 0, \mu_{t_A} + \mu_{t_S} + \mu_{t_E} + \mu_{t_C}, \mu_{t_N}, \mu_{t_D}], && \text{for } t = s,\\
\mu_t &= \mu_t \prod_{i=s+1}^{t} P(i), && \text{for } t > s,
\end{aligned}$$

where $\mu_{t_H}, \mu_{t_A}, \mu_{t_S}, \mu_{t_E}, \mu_{t_C}, \mu_{t_N}, \mu_{t_D}$ are the population proportions in healthy, asymptomatic, symptomatic, clinical evaluation, compliant, non-compliant and death states at time t respectively.

For repeated screenings, the Markov chain is broken into three parts and two new initial distributions are calculated,

$$\begin{aligned}
\mu_t &= \mu_0 \prod_{i=0}^{t} P(i), && \text{for } t < s_1, \\
\mu_t &= [\mu_{t_H}, 0, 0, 0, \mu_{t_A} + \mu_{t_S} + \mu_{t_E} + \mu_{t_C}, \mu_{t_N}, \mu_{t_D}], && \text{for } t = s_1, \\
\mu_t &= \mu_t \prod_{i=s_1+1}^{t} P(i), && \text{for } s_1 < t < s_2, \\
\mu_t &= [\mu_{t_H}, 0, 0, 0, \mu_{t_A} + \mu_{t_S} + \mu_{t_E} + \mu_{t_C}, \mu_{t_N}, \mu_{t_D}], && \text{for } t = s_2, \\
\mu_t &= \mu_t \prod_{i=s_2+1}^{t} P(i), && \text{for } t > s_2,
\end{aligned}$$

where $s_1 < s_2$ are the screening ages.

For calculating the average lifetime costs and QALY scores, the equations 1 and 2 apply for both single-time and repeated screenings. However, it is also necessary to take the screening costs of the specific strategy into account as well. Screening cost calculations were explained in detail in Chapter 3.4.

3.5.3 Simulations with preventive measures

In this study, a preventive measure is defined by two parameters: its price per child and its effectiveness in preventing celiac disease. The effectiveness is defined by the percentage it lowers the annual probability of developing celiac disease. It is assumed that the effectiveness is invariant with respect to age due to a lack of better knowledge. Therefore, when simulating a preventive measure, the only difference compared to the no-intervention scenario is that the function used for calculating the probability of developing celiac disease will be scaled down by the effectiveness of the preventive measure, i.e. $r(t)^* = (1 - \text{eff}) \cdot r(t)$. Average lifetime costs and QALY scores are calculated the same as in the previous cases with the exception, that the cost of the preventive measure needs to be added to the overall costs.

This study examines the cost-effectiveness of a potential enterovirus vaccination with a cost of €250 and preventive effectiveness of 20%. The vaccination would be given before the first birthday in the national vaccination program. Therefore, there are no additional costs for administering the vaccination and the lowered probability is assumed for all life years. The cost-effectiveness behavior of a general preventive measure that would be given before the first birthday is also examined. The price is altered between €25-€500 and a lowered probability range of 5-50% is used.

3.6 Health economic evaluation

The cost-effectiveness of different screening strategies and preventive measures is calculated using the incremental cost-effectiveness ratio (ICER). The ICER tells

the cost-effectiveness of a given healthcare intervention by comparing the costs and number of quality-adjusted life years in a no-intervention scenario with an intervention. It is defined by the formula,

$$ICER = \frac{C_1 - C_2}{Q_1 - Q_2} = \frac{\Delta C}{\Delta Q}, \tag{3}$$

where C_1, C_2 are the total costs and Q_1, Q_2 are the total QALY scores of different scenarios. In this study, the scenario where no screening or preventive measure is applied is the no-intervention scenario, and it corresponds to the values C_2 and Q_2.

Because the differences in both costs and QALY scores can be either positive or negative, there are four possible scenarios that need to be considered when interpreting an ICER value. These are presented in Table 7. On the first row, the healthcare intervention leads to both lower costs and a better QALY score. This corresponds to a situation where the intervention wins over the no-intervention scenario and it should be implemented. On the second row, the intervention leads to higher costs and worse QALY scores. This is the reverse of the previous scenario, the intervention should not be implemented. On the third row, the intervention leads to lower costs but a worse QALY score. In other words, implementing the intervention would exchange quality and quantity of life for monetary gain. The last case is the opposite of this - a higher QALY score and higher costs mean that by implementing the intervention it is possible to can gain in terms of quality and quantity of life by spending money.

In the last row scenario, the lower the ICER value is the cheaper it is, in a manner of speaking, to buy health. A typical threshold for accepting an intervention has been \$50,000 per gained QALY [66]. This is the threshold used in this study, however, the monetary unit is changed from dollars to euros.

Incremental cost (ΔC)	Incremental health effect (ΔQ)	Preference
$\Delta C < 0$	$\Delta Q > 0$	Intervention
$\Delta C > 0$	$\Delta Q < 0$	No-intervention
$\Delta C < 0$	$\Delta Q < 0$	Trade-off
$\Delta C > 0$	$\Delta Q > 0$	Trade-off

Table 7: Preference of a healthcare intervention based on the differences in costs and QALY scores.

Because the ICER calculates changes in both costs and QALY scores, there are special situations where it is possible to show that certain model parameters do not affect the final results. This is the case, for example, when an intervention does not affect the life course of given individuals. For the Markov model of this study, it is possible to show that the state costs and QALY scores assigned to the healthy state (found in Tables 5, 4) do not affect the ICER results. Proof of this follows.

The total costs of a screening scenario consist of the screening cost of the specific strategy (expressed by SC) and of the two Markov chains, whereas the no-screening scenario gets its cost from only a single Markov chain. Therefore, the difference in costs is expressed by,

$$C_1 - C_2 = CS + \sum_{t=0}^{s} c(t)^\top \mu_t^1 + \sum_{t=s}^{110} c(t)^\top \mu_t^1 - \sum_{t=0}^{110} c(t)^\top \mu_t^2,$$

where μ_t^1 and μ_t^2 refer to the population distributions at different age points between the two scenarios. Because healthy people are left in the healthy state after screening, the proportion of the population in the healthy state is the same between both scenarios for all age points, i.e. $\mu_t^1(A) = \mu_t^2(A), \forall t$. Expressing the vector product as a sum, the following applies,

$$\begin{aligned}
&CS + \sum_{t=0}^{s} \sum_{i} c(t,i)\mu_t^1(i) + \sum_{t=s}^{110} \sum_{i} c(t,i)\mu_t^1(i) - \sum_{t=0}^{110} \sum_{i} c(t,i)\mu_t^2(i), \\
=&CS + \sum_{t=0}^{s} \sum_{i \neq A} c(t,i)\mu_t^1(i) + \sum_{t=s}^{110} \sum_{i \neq A} c(t,i)\mu_t^1(i) - \sum_{t=0}^{110} \sum_{i \neq A} c(t,i)\mu_t^2(i) \\
&+ \left(\sum_{t=0}^{110} c(t,A)\mu_t^1(A) - c(t,A)\mu_t^2(A) \right), \\
=&CS + \sum_{t=0}^{s} \sum_{i \neq A} c(t,i)\mu_t^1(i) + \sum_{t=s}^{110} \sum_{i \neq A} c(t,i)\mu_t^1(i) - \sum_{t=0}^{110} \sum_{i \neq A} c(t,i)\mu_t^2(i).
\end{aligned}$$

In a similar fashion, the difference in average lifetime QALY scores is invariant with regard to the healthy state values, when comparing a screening scenario with the no-screening scenario. Therefore, the ICER of a screening strategy is not affected by the healthy state values. The same logic does not apply for a preventive measure. As the two scenarios have different annual probabilities for developing celiac disease, the proportion of the population in the healthy state changes between the scenarios.

4 Intervention cost-effectiveness analysis

This chapter discusses the results of the simulations, cost-effectiveness calculations and the sensitivity analysis.

4.1 Simulated population distribution

In Figure 4, the population distribution between ages $t \in [0, 110]$ is shown. The left plot shows the entire population and the right plot shows how the population with some manifestation of celiac disease behaves. From the left plot, it can be seen that most people never develop celiac disease as they move from the healthy state straight to the dead state. On the other hand, from the right plot, it can be seen that the number of people with asymptomatic celiac disease rises sharply for the first 10 years, after which it plateaus. In other words, the number of asymptomatic people developing symptoms and getting a diagnosis balances out with new cases. The number of diagnosed people (states compliant, non-compliant) rises steadily until around the age of 70, after which the mortality rate increases significantly. The right plot also shows lower compliance to GFD during teenage years ($t \in [13, 17]$) and higher compliance in the elderly ($t > 64$).

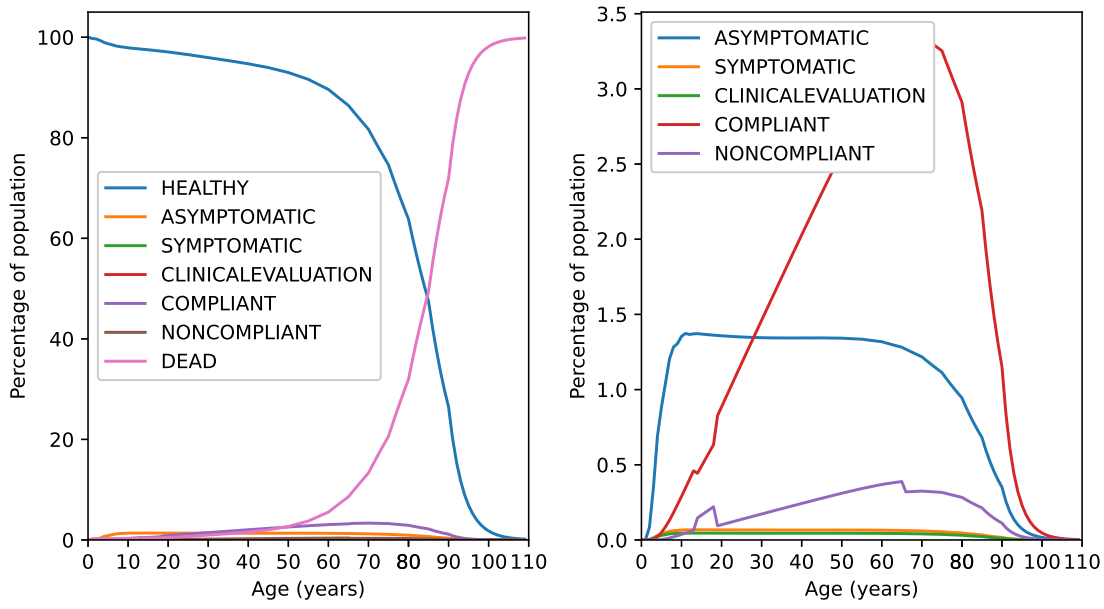

Figure 2: Simulated Markov chain without screening. The entire population is on the left plot and the subset with some form of celiac disease is on the right plot.

In Chapter 3.2, it was discussed that the transition probabilities from undiagnosed to diagnosed states should be chosen such, that annually around 4.1% of undiagnosed cases get diagnosed. This percentage can be calculated from the population distribution by seeing how much the diagnosed population increases between subsequent

time steps, and dividing the result with the proportion of people in the undiagnosed states,

$$\text{Annual diagnosis rate} = \frac{\sum_{\text{diagnosed}} \mu_{t+1} - \sum_{\text{diagnosed}} \mu_t}{\sum_{\text{undiagnosed}} \mu_t}.$$

The annual diagnosis rate is presented in Figure 3 as a function of age. For the first 50 years or so, the diagnosis rate stays close to the sanity check of 4.1%. After 50 years it starts to drop sharply - as the probability to die grows with age, the number of diagnosed people between subsequent time steps starts to get smaller and smaller until it turns negative.

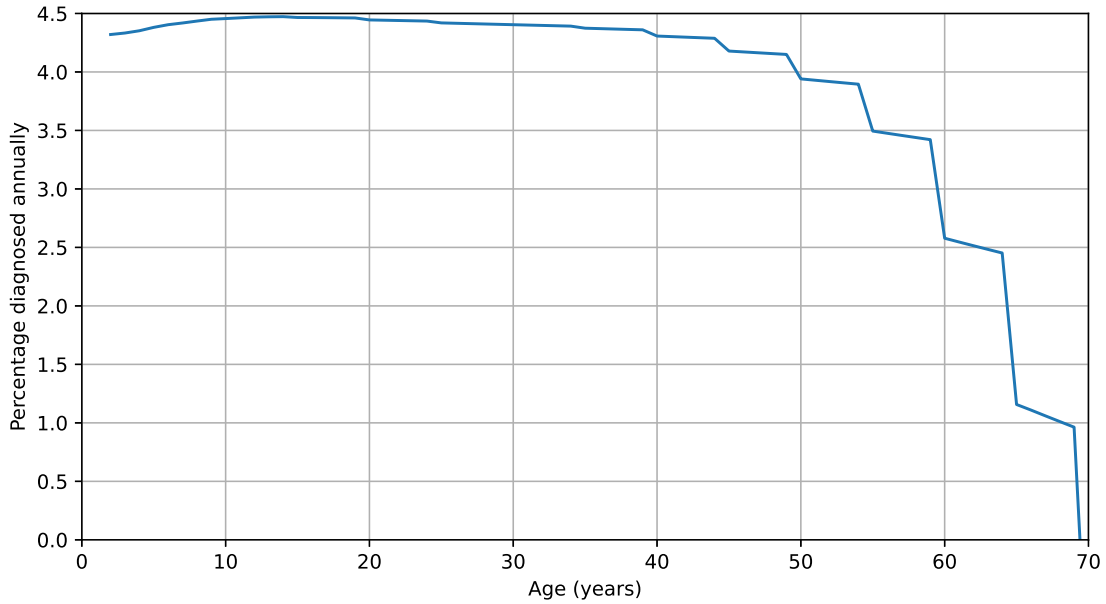

Figure 3: Percentage of undiagnosed celiac disease getting diagnosed on an annual basis.

To show an example of how screening affects the population distribution, both single-time and repeated screenings are presented in Figure 4, where the celiac disease population behavior is shown between ages $t \in [0, 30]$. In the left plot, the population was screened once at the age of 10. In the right plot, the population was screened twice at the ages of 5 and 15. The graph shows that during the year of screening, the proportion of people in asymptomatic, symptomatic and clinical evaluation states goes to zero and the proportion of people in the compliant state rises very sharply. As compliance after diagnosis is assumed, the percentage of the compliant population drops noticeably one year after diagnosis - part of the population becomes non-compliant. The percentage of the population in the non-compliant state rises as a consequence. Figure 4 also displays the lower compliance rate in teenagers more clearly.

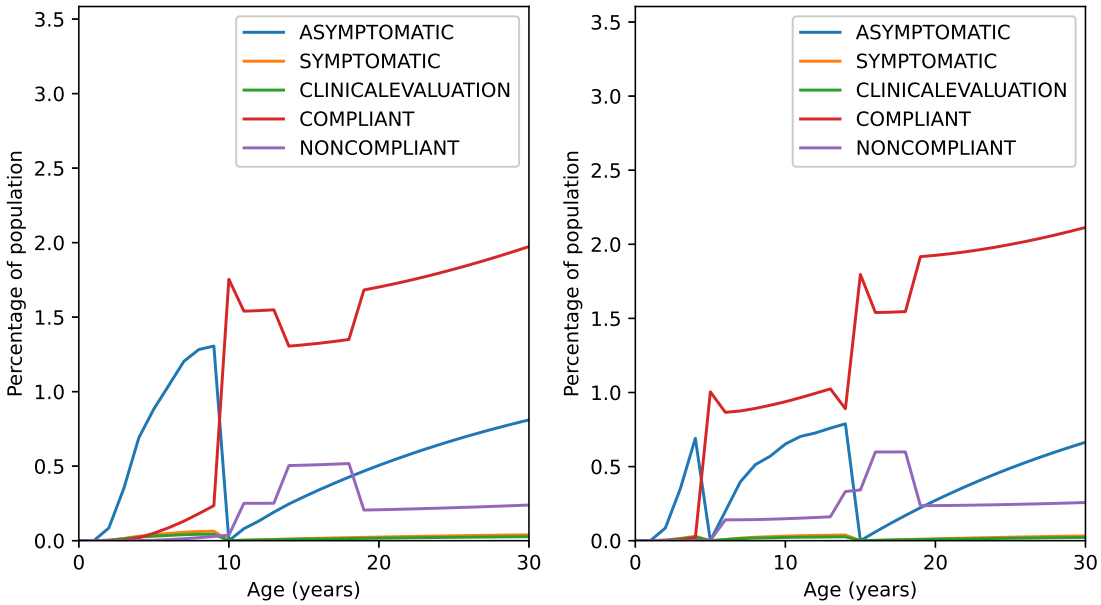

Figure 4: Simulated Markov chain with screening. On the left screening at age 10 and on the right screening at ages 5 and 15.

4.2 Mass screening

Mass screening is simulated between ages 3-15. Repeated screenings are compared with single-time screening. Universal serological screening is compared with a two-step approach, where the genetically at-risk population is identified for a follow-up examination using HLA genotyping. This resulted in a total of 182 plausible strategies. All strategies had a positive cost difference compared to the no-intervention scenario ($\Delta C > 0$) and a positive QALY score difference ($\Delta Q > 0$). This corresponds to the trade-off whereby spending money quality and quantity of life can be gained. The ICER of the strategies can be seen in Figure 5, where the top plot displays the cost-effectiveness of all strategies and the bottom plot displays the 20 best-performing strategies. The smaller the ICER is the more cost-effective the screening strategy is.

The best 6 strategies use the same procedure of untargeted serological screening at a single age point. The best cost-effectiveness is achieved by screening at the age of 6 (38,528 €/QALY), with ages 7 and 5 following closely. The best repeated screening strategy is also achieved by the untargeted serological screening, with screenings occurring at the ages of 4 and 8 (47,308 €/QALY). However, the differences between the most cost-effective repeated screening strategies were relatively small, implying that the first screening could take place between the ages of 4-5 years old and the second screening between the ages of 7-9 years old. The two-step genotyping approach performs much worse in both single and repeated screenings. Assuming a commonly used cost-effectiveness threshold of €50,000 per gained QALY, screening for celiac disease in children is cost-effective according to this model.

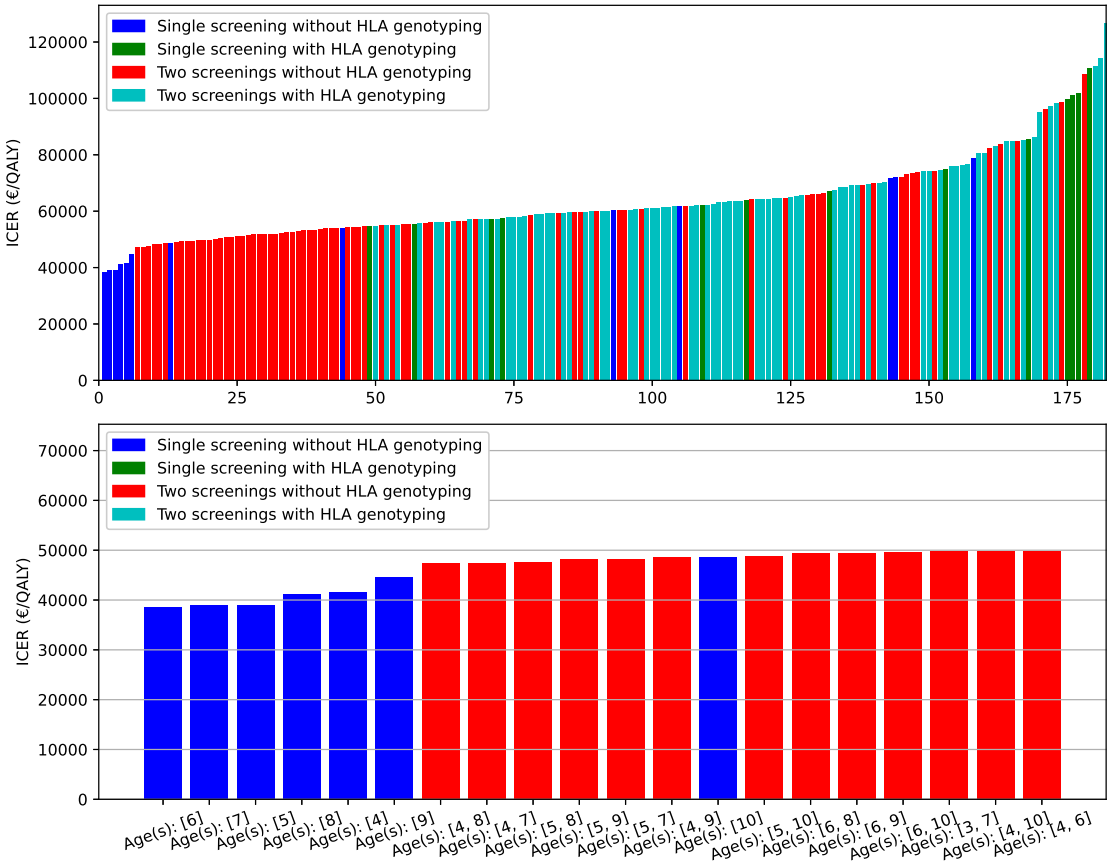

Figure 5: Incremental cost-effectiveness of all screening strategies and the best 20 strategies.

To see how the cost-effectiveness of the leading strategy behaves as a function of screening age, Figure 6 displays the ICER of untargeted universal single-time screening as a function of screening age. The cost-effectiveness of screening gets better between ages 3-6, worse between ages 6-14 and better again between ages 14-15.

The worse cost-effectiveness in very early life years can most likely be attributed to the fact that developing celiac disease by the age of 3-4 is relatively rare. Many people who will develop the disease during childhood would be missed by the screening. Screening at an older age point would result in more diagnosed cases. However, it would be at the expense of some people having a longer delay to diagnosis. Looking at Figure 2, it can be seen that the number of people with undiagnosed celiac disease peaks around the ages 10-13. Therefore, mass screening after these ages will likely result in suboptimal cost-effectiveness. A likely explanation for the best cost-effectiveness being at ages 5-7 is that it strikes a balance between finding the maximum number of patients and having the lowest delay to diagnosis.

The drop in ICER between ages 14-15 could be due to two abrupt assumption

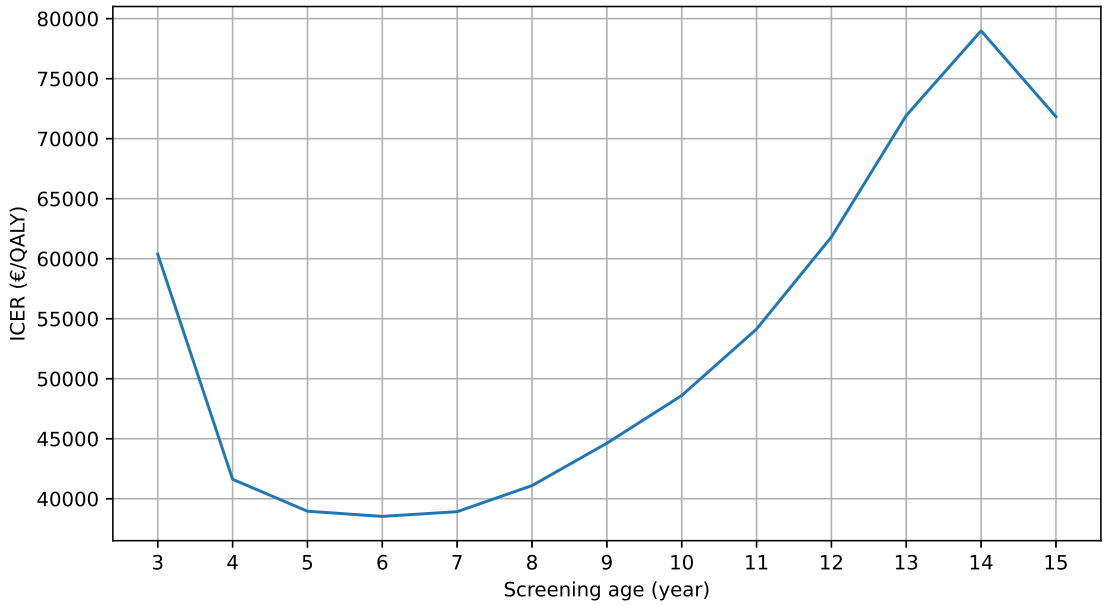

Figure 6: Incremental cost-effectiveness ratio as a function of screening age for the single-time untargeted serological screening strategy.

changes at ages 18 and 19. At age 18, a significantly higher compliance rate (72% → 89%) is assumed, and at age 19 higher costs to society due to sick days (€0 → €230 per sick day) are assumed. This means that undiagnosed celiac disease will cause more costs and diagnosed disease would lead to better average QALY score due to the higher compliance rate when compared to the teenage years. In other words, living with undiagnosed celiac disease in early adulthood is more detrimental compared to teenage years. Thus, the model might prefer later diagnosis.

4.3 Enterovirus vaccination

The hypothetical enterovirus vaccination is assumed to lower the annual probability of developing celiac disease by 20%, it would cost €250 per child and it would be given before the first birthday. The lower probability is assumed to hold true for all life years. The effect of the vaccination on the celiac disease population is presented in Figure 7, where the celiac disease population without vaccination is on the left and the population with the vaccination on the right. It can be seen, that the number of celiac disease cases between the two scenarios is different, as the vaccination is able to prevent some of the cases.

The vaccination leads to a better average lifetime QALY score but higher costs. Therefore, it also belongs to the trade-off scenario, whereby spending money quality and quantity of life can be increased. The cost-effectiveness of the vaccination was,

$$ICER = \frac{€65398.315 - €65163.285}{27.308\ \text{QALY} - 27.305\ \text{QALY}} \approx 80201.16\,\frac{€}{\text{QALY}},$$

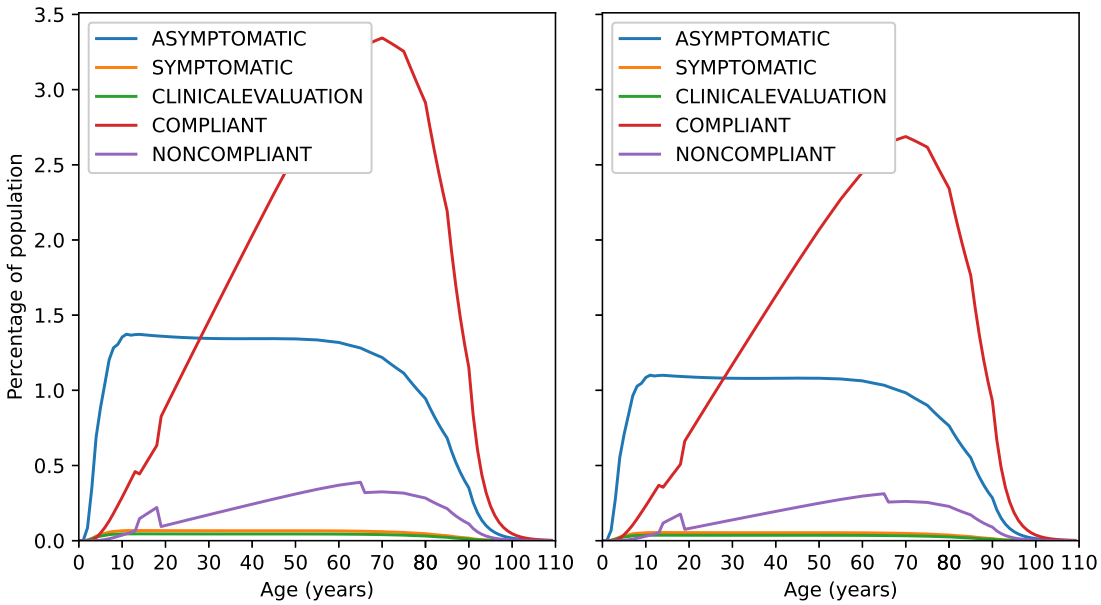

Figure 7: Celiac disease population without vaccination on the left and with vaccination on the right. With vaccination the incidence of the disease is lower.

meaning that by using the threshold of €50,000 per gained QALY, the vaccination is not cost-effective. By changing the price of the vaccination, the only variable that changes in the ICER calculation is the total cost in the intervention scenario. Therefore, the following linear function describes the cost-effectiveness of the vaccination as a function of its price,

$$f(vc) = \frac{€65398.315 - €250 + vc - €65163.285}{27.308 \text{ QALY} - 27.305 \text{ QALY}},$$

where vc is the cost of the vaccination. The cost-effectiveness of the vaccination as a function of its price is presented in Figure 8. We can solve the price point below which the vaccination would be cost-effective from the equation as follows,

$$f(vc) = \frac{€65398.315 - €250 + vc - €65163.285}{27.308 \text{ QALY} - 27.305 \text{ QALY}} < 50000 \frac{€}{\text{QALY}},$$
$$vc < €164.97,$$

therefore, if the price of the vaccination would be lower than €164.97, it would be a cost-effective way to prevent the disease.

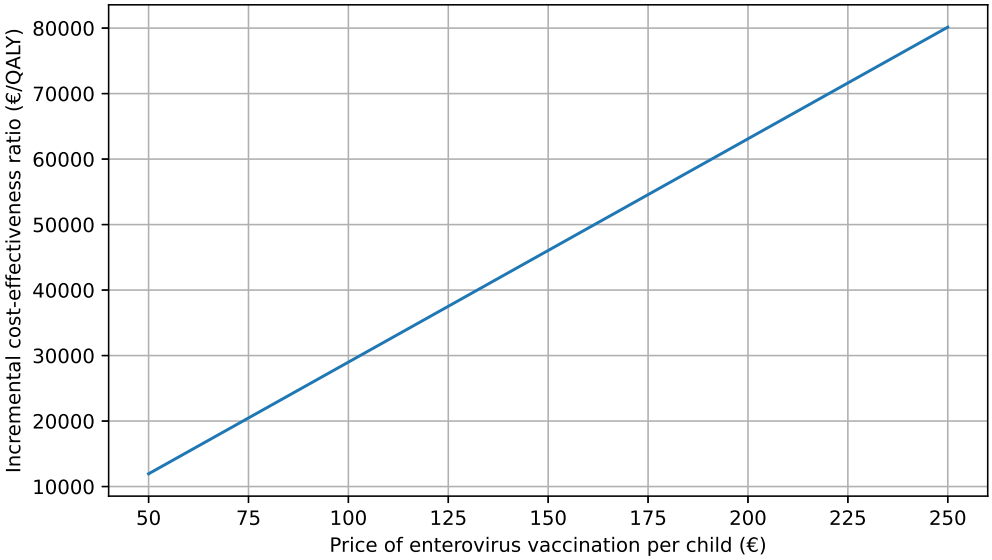

Figure 8: Incremental cost-effectiveness ratio of enterovirus vaccination as a function of price.

The combined effect of first vaccinating and then mass screening is provided in Figure 9. The ICER of all screening strategies is plotted in a scenario, where the hypothetical enterovirus vaccination is administered to the whole age group before the age of 1. The cost-effectiveness of the best screening strategy is somewhere between the mass screening and vaccination scenarios. As the number of cases drops with the vaccination, mass screening finds fewer people suffering from undiagnosed celiac disease. This makes mass screening less cost-effective. In addition, the vaccination adds €250 to the total costs of every mass screening scenario, creating a larger cost difference compared to the no-intervention scenario.

The best 20 strategies are mostly the same as in the no-vaccination scenario. However, the order of some strategies has changed and some strategies have also been replaced. The most cost-effective screening age changed from 6 to 7 years of age. Also, in the no-vaccination scenario, screening once at the age of 4 without HLA genotyping was the 5th most cost-effective strategy, but this strategy is now the 20th most cost-effective. The top 20 also no longer contains a strategy of repeated screenings at ages 4 and 6, but now contains strategies for screening at ages 5-6 and 11. These differences strengthen the argument that screening too early when many children have not developed celiac disease, can lead to suboptimal cost-effectiveness. The previously discussed trade-off between early detection and diagnosing the maximum number of cases applies here as well.

Combining the hypothetical vaccination with mass screening does not seem to be a cost-effective way to reduce the burden of celiac disease. The ICER of the most cost-effective strategy is €71,562 per gained QALY.

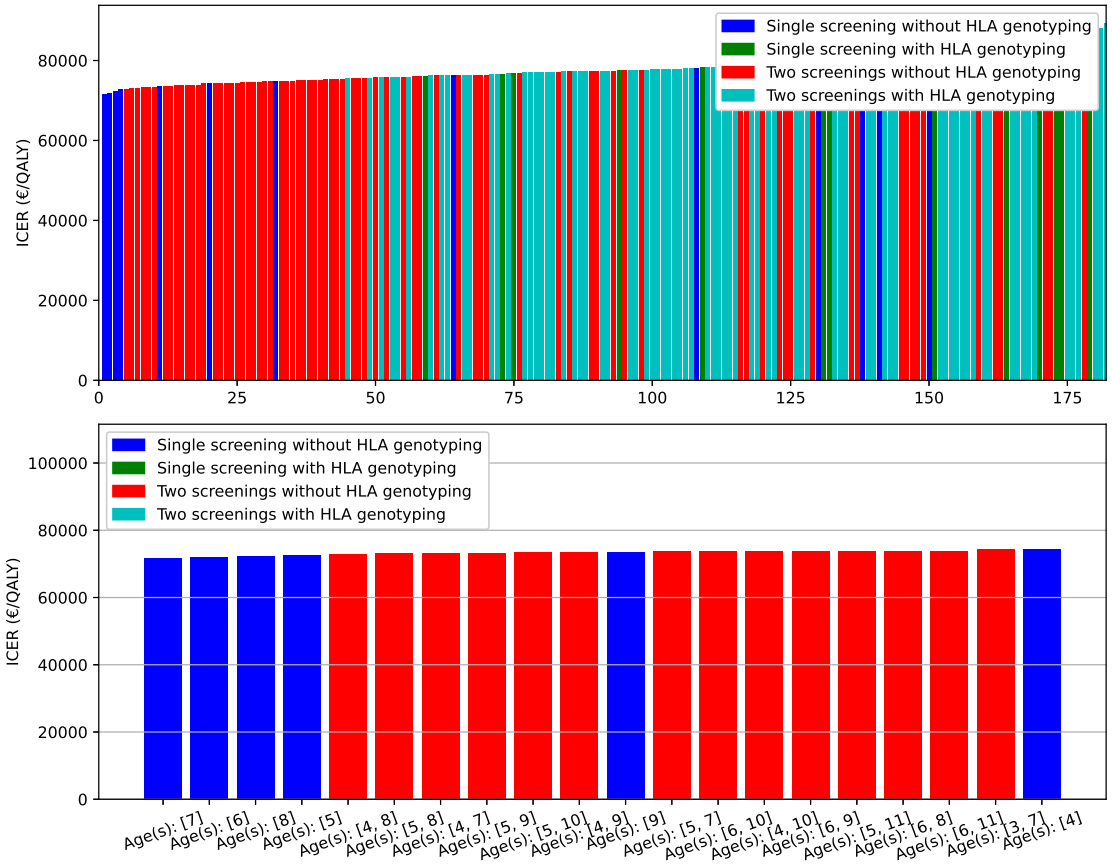

Figure 9: Incremental cost-effectiveness of all screening strategies and the best 20 strategies with enterovirus vaccination.

4.4 General preventive measure

The general preventive measure is defined by the same parameters as the vaccination, price per child and an age invariant percentage of reduced probability of developing celiac disease. The lower probability is assumed for all life years.

In Figures 10 and 11, the cost-effectiveness of a general intervention is plotted as a function of its price and effectiveness. All ICER values belonged to the higher cost ($\Delta C > 0$) but better health outcome scenario ($\Delta Q < 0$). The price varied between €25-500 and the effectiveness between 5-50% reduced annual probability of developing the disease. Figure 11 displays where the threshold of €50,000 per gained QALY lies, with the blue areas belonging to the acceptable region. It also shows the hypothetical enterovirus vaccination. From Figure 11, it can be seen that the cost-effectiveness of a general intervention is highly dependent on both variables. That is to say, a highly effective but expensive preventive measure should become cost-effective if its price can be reduced. Conversely, a cheap but less effective preventive measure should become cost-effective if its effectiveness can be improved.

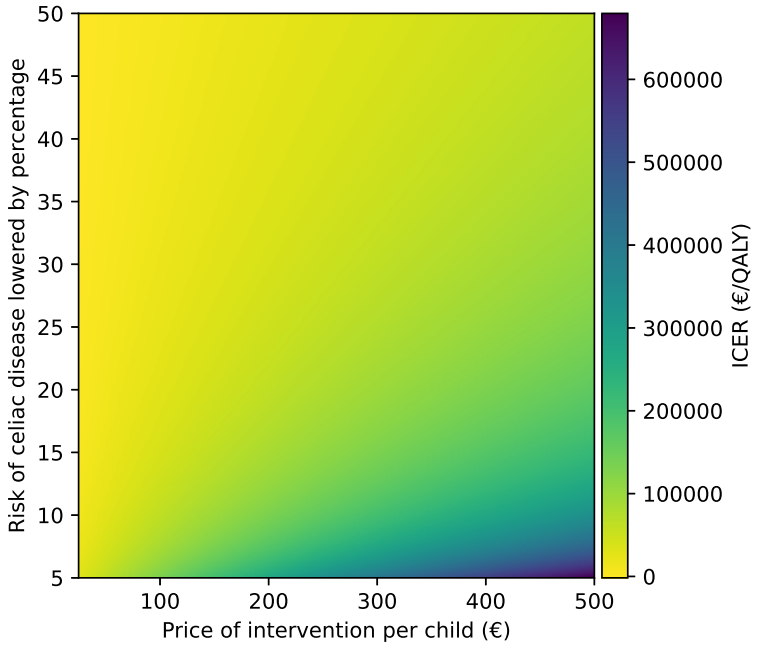

Figure 10: Incremental cost-effectiveness ratio of a general intervention as a function of price and effectiveness.

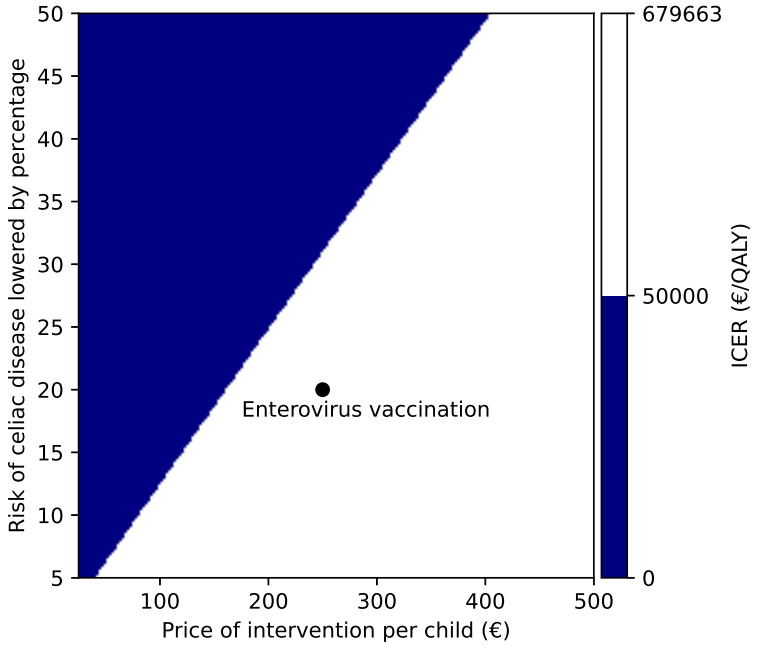

Figure 11: Incremental cost-effectiveness ratio of a general intervention as a function of price and effectiveness using a threshold of €50,000 per QALY.

4.5 Sensitivity analysis

In this chapter, one-way deterministic sensitivity analysis is performed on some uncertain key variables. Because the main purpose of this study is to find the most cost-effective screening strategy, the sensitivity analysis only focuses on how the best screening strategy and its ICER change with alternative parameter values.

Table 8 shows the differences in average lifetime costs and QALY scores, as well as the most cost-effective screening strategy and its ICER. The first two rows represent the base scenario, i.e. the model with the default parameter values with and without the annual 3% discounting. For all other scenarios, a discount of 3% was assumed. All scenarios have positive differences in both costs and QALY scores, meaning that by spending money quality and quantity of life can be gained.

In the scenario where discounting is removed the ICER gets significantly better. As discounting effectively gives less weight to future changes, the overall changes also decrease. The same reasoning can be used for explaining why screening at a slightly older age of 7 becomes more cost-effective. The differences in both costs and QALY scores matter more at older ages compared to the 3% discount scenario.

Doubling the screening cost significantly increases the ICER of the best strategy. However, the best strategy is the same as in the base scenario with no discounting. In other words, the overall price of mass screening does not seem to greatly affect the best strategy, but it does affect the overall cost-effectiveness of screening to a great degree.

In the imperfect screening scenario, it is assumed that during the year of screening some people with celiac disease do not get a diagnosis. Around 1/500 in the general population are estimated to be IgA deficient [67], meaning that they would not be detected by the serological test, and the test is estimated to have a specificity of around 96% [68]. The probability of a positive serological test for someone with celiac disease can be calculated using the law of total probability. Denoting a positive serological test with PS, celiac disease with CD, IgA deficiency with DF and normal IgA presence with NDF, the probability is,

$$\begin{aligned} p(PS|CD) &= p(PS|CD, DF) \cdot p(DF) + p(PS|CD, NDF) \cdot p(NDF), \\ &= 0 \cdot 1/500 + 0.96 \cdot 499/500, \\ &\approx 95.808\%. \end{aligned}$$

Therefore, it is assumed that 95.808% of people in asymptomatic, symptomatic and clinical evaluation states get diagnosed to the compliant state. As can be seen from Table 8, assuming a lower diagnostic rate makes the ICER only slightly higher, with a difference of around €781 per gained QALY compared to the base scenario. The optimal screening strategy stays the same.

In the identical mortality scenario, the hazard ratios of all mortalities are changed to 1. This corresponds to a situation where celiac disease does not affect mortality regardless of its state. While the optimal strategy stays the same, the cost-effectiveness of mass screening gets a slightly better value. The probable reason is that as screening in the base scenario moves people from states with higher mortality to lower mortality,

the population on average lives to a higher age. This in turn makes the total healthcare costs and QALY scores higher.

	ΔC	ΔQ	ICER	Screening strategy Genotyping	Age(s)
Base scenarios					
3% Discount	40.11	10.4×10^{-4}	38,528	No	6
No Discount	56.95	18.4×10^{-4}	31,037	No	7
Sensitivity analyses					
Double screening costs	70.66	11.1×10^{-4}	63,660	No	7
Imperfect screening	39.22	10.0×10^{-4}	39,309	No	6
Identical mortality	40.14	10.5×10^{-4}	38,423	No	6
Accurate genotyping	40.11	10.4×10^{-4}	38,528	No	6
Accurate & cheap genotyping	31.89	95.0×10^{-5}	33,565	Yes	5
Higher prevalence	55.23	18.9×10^{-4}	29,199	No	5
Lower prevalence	30.95	55.7×10^{-5}	55,585	No	7
Faster disease progression	30.58	20.3×10^{-4}	15,057	No	7
Slower disease progression	40.76	19.4×10^{-6}	210,289	No	4
Higher compliance	34.21	14.2×10^{-4}	24,099	No	7
Lower compliance	43.93	72.7×10^{-5}	60,390	No	5

Table 8: Cost-effectiveness analysis of one-way deterministic sensitivity analyses.

In the accurate genotyping scenario, the HLA background test is assumed to have a sensitivity and specificity of 100%. According to an unpublished research result, around 41.6% of the Swedish population is genetically susceptible to the disease, and would therefore need a follow-up antibody test in this scenario. Recall that in the base scenario 61% needed a follow-up test. In this scenario, the optimal screening strategy does not change. Even if genotyping would always produce accurate results, it would be significantly more expensive as an additional step would be required in the screening process.

In the accurate and cheap genotyping the previous assumption of perfect sensitivity and specificity is combined with a lower cost. It is assumed that the genotyping test would cost one-third of its original price and that the genotyping and the follow-up antibody test could take place during the same examination. With these assumptions, genotyping becomes the more cost-effective option.

In the higher and lower prevalence scenarios, the transition probability from the healthy state to a state with celiac disease was doubled and halved respectively. The ICER changes significantly in both scenarios. Screening in the high prevalence population becomes significantly more cost-effective and conversely screening in the low prevalence population would not be cost-effective, assuming the previously used threshold of €50,000 per gained QALY. The optimal screening age also changes. The higher the prevalence the more cost-effective it is to screen at a younger age, and vice versa.

In the faster and slower disease progression scenarios the transition probabilities

from asymptomatic to symptomatic, clinical evaluation and compliant states were doubled and halved respectively. When celiac disease stays in an asymptomatic form for a longer time, the ICER of mass screening gets an appalling value of €210,289 per gained QALY. Because the model assumes that asymptomatic celiac disease does not cause deteriorated quality of life or higher costs compared to the healthy state, the slower disease progression leads to less harm from celiac disease. Less harm on the other hand makes the cost-effectiveness of mass screening worse. The converse is true as well - faster disease progression to more severe states of celiac disease causes more harm, making the cost-effectiveness of screening better.

In the higher and lower compliance scenarios the compliance to gluten free diet was increased and reduced by 5% for all ages. The sensitivity analysis reveals, that even relatively small changes in compliance affect the cost-effectiveness of mass screening significantly. Mass screening has good cost-effectiveness in the higher compliance scenario, and it is not cost-effective in the lower compliance scenario.

Overall the parameters that seem to have the biggest impact on the cost-effectiveness of mass screening are related to the pace of the disease progression, price of screening and treatment compliance. These results are in line with previous studies that have performed sensitivity analyses on similar Markov models [13, 15]. While the cost-effectiveness changed considerably between different scenarios, the optimal screening strategy stayed mostly the same. Excluding two exceptions, the best cost-effectiveness was achieved with single-time untargeted universal serological screening between ages 5-7 years old. Screening at two age points was never the best strategy and genotyping only became the best when a sensitivity and specificity of 100% was assumed with a cheap testing price.

According to the sensitivity analysis, the overall cost-effectiveness of mass screening is still up for debate. However, the optimal screening strategy changed relatively little between different scenarios. Therefore, it seems that if mass screening would be implemented, the most cost-effective strategy would be to use untargeted serological screening once between ages 5-7.

5 Discussion

This study presents the most thorough look at the cost-effectiveness of different mass screening strategies and intervention methods against celiac disease for children. The results suggest that mass screening is most cost-effective when it is done at 6 years of age using untargeted serological screening. The supposed enterovirus vaccination would become cost-effective in preventing the disease if its price was lowered to under €164 per child.

The biggest strength of this study is that it managed to expand on the model of the most up-to-date study on the subject by Norström et al. (2021) [15]. By incorporating data on the cumulative risk of celiac disease in Swedish children, it became possible to include age dependent prevalence in the model. This opened the avenue for examining different age points for mass screening. In addition, by including HLA background information of the Swedish population, it was possible to compare at-risk screening against untargeted screening. Implementing the model in python allowed automated generation of feasible screening strategies and their comparison.

Integrating the cumulative risk of celiac disease in the model also allowed for the cost-effectiveness assessment of prospective intervention methods against the disease onset. A topic pioneered by this study. By estimating the monetary cost and effectiveness of preventing disease onset, the cumulative risk and average lifetime costs were altered accordingly. While there are no known effective preventive measures, the topic is under research [16, 18]. As novel preventive measures are found, decision makers face the same problem as with mass screening - someone needs to decide what measures should be implemented. To support the decision-making process, some quantifiable way of discerning the best prevention strategy needs to exist. This model could serve as such support in the future.

This study suffers much from the same limitations as its predecessors. While there was ample data for parameters such as the cumulative risk of celiac disease in childhood, several parameters are the result of heuristics and simplifications. Due to the lifetime horizon of the model, especially the long-term health effects of celiac disease, gluten free diet and disease progression are significant sources of uncertainty. Future costs caused by the disease for society and the cumulative risk for ages above 14 years of age are also uncertain. For conducting a more reliable cost-effectiveness analysis, additional longitudinal studies on the disease would be required.

Furthermore, due to the regional variability in factors such as genetic background [21], prevalence [9], costs and healthcare systems, the results obtained in this study do not apply globally. The results are, however, indicative of the Swedish context and to some extent of other Nordic countries due to the similar population and social makeup. If data on specific risk groups or populations was available, the model could be tuned for examining cost-effectiveness in other contexts as well.

Many limitations arise from the focus on the general population and society instead of the individual. As celiac disease has a strong genetic component, it would be beneficial to assess the cost-effectiveness of screening certain risk groups. These include, for example, first- and second-degree relatives of celiac disease patients

and people with certain other autoimmune diseases. If wide-scale screening is not cost-effective, it becomes important to solve if certain risk groups should be screened. As the disease is more prevalent in women, who also tend to suffer more from the disease [48, 49], using gender-specific data would make sure that the results are not biased towards one gender. It is also difficult to take into account rare but serious complications, such as growth retardation and delayed puberty, and their long-term effects. With large datasets, even such rare occurrences tend to be represented, but it is difficult to assess if this is actualized in the data used for this study. The costs considered in this study do not take into account the premium price of buying gluten free products and other daily expenses related to living with the disease. Mass screening would also increase the number of people with a false positive diagnosis, which could lead to reduced quality of life and increased costs for society and the individual. The difficulty in evaluating the aforementioned simplifications is the lack of data. Even with using the general population - which is the target group with the most data - as the subject of this study, several key parameters remain uncertain.

Sensitivity analysis revealed that although the overall cost-effectiveness is uncertain, the optimal screening strategy remained largely the same. The results suggest that mass screening against a disease that can develop at any age is a balancing game between delaying the screening to capture as many diseased as possible and making the diagnostic delay as short as possible by screening earlier. Hence, the shape of the cumulative risk function can largely determine the optimal screening age, if other age dependent properties are not taken into account. While almost all state parameters and transition probabilities had an age dependent component to them, the transition probabilities from an asymptomatic state to more severe manifestations were static. Therefore, the model could be made more accurate if additional longitudinal studies focusing on disease progression were available.

The previous studies have reached similar conclusions to this paper - screening for celiac disease seems to be cost-effective, however, the results are based on unconfirmed parameter values. Much of the focus has also been on figuring out the factors with the biggest impact on cost-effectiveness. If these factors can be identified, even if mass screening was not a viable option, decision makers become aware of where to focus for alleviating the burden of celiac disease. A paper by Hershcovici et al. (2010) argued that the factors with the biggest impact on cost-effectiveness were the time delay from symptom onset to diagnosis and adherence to gluten free diet [13]. While the delay was not specifically tested in the sensitivity analysis, the disease progression rate and compliance to gluten free diet were significant factors. The authors suggested that if celiac disease could be detected in an early stage, mass screening would not be required. Shamir et al. (2006) concluded that prevalence and mortality of celiac disease patients were the two key factors in determining cost-effectiveness [12]. In this study, changing the mortality ratio did not significantly alter the results. Prevalence, on the other hand, was significant. Park et al. (2014) focused on the cost-effectiveness of preventing hip and vertebral fractures by screening for celiac disease [14]. If quality data on complications and extraintestinal symptoms become more accessible, changing the model structure to include additional states could make the results more reliable. This, however, was not considered as the purpose of this

study was to expand on the model of the most recent study. Due to the similarity of model structure and parameter values, the results of this study are in line with the study by Norström et al. (2021) [15]. The biggest factors affecting cost-effectiveness seem to be compliance to gluten free diet and the disease progression rate from mild to serious symptoms. Therefore, this study suggests that focusing on treatment compliance and slowing the disease progression are the two most important factors for alleviating the burden of disease.

Screening at 6 years of age could be beneficial for several reasons. It might be possible to orchestrate screening with kindergartens, making participation effortless and keeping costs low. In addition, younger patients (ages 0-12) are more willing to follow a gluten free diet compared to teenagers (13-17) [60]. Starting a gluten free diet in childhood could result in better adherence to the diet during later life, reducing the number of complications caused by the disease. A 2011 study by Rosén et al. also revealed that most parents (92%) are in favor of their children participating in screening [69].

Screening would, however, increase the number of false positives, possibly reducing their quality of life and causing more costs for both the individual and society. Also, as celiac disease often manifests itself in an asymptomatic state, imposing gluten free diet on some patients might not be beneficial. In such cases, delaying the treatment might be of value, as suggested by van Koppen et al. (2009) [70]. Choosing the treatment based on symptoms could also make sure that fewer patients with a false positive diagnosis would suffer from the diagnosis. Later in life, if symptoms become prominent, the patients could have an initial guess as to what might be the origin and seek professional help more actively. If mass screening is implemented, it is important to assess if treatment should be imposed based on individual symptoms.

Mass screening is not the only option for reducing the burden of celiac disease. If the general public is made more aware of the disease through, for example, information campaigns, patients suffering from the disease might become more proactive in contacting a doctor. Furthermore, if it is possible to recognize the disease more accurately, the delay to diagnosis could be dropped further. The quality of life of celiac disease patients could also be made better by making gluten free products more accessible and cheaper.

6 Summary

Celiac disease is heavily underdiagnosed [7, 8], causing deteriorated quality of life for the patients [1, 2] and increased costs for society [3]. Mass screening and measures that prevent disease onset could alleviate the problem, but decision makers need support for discerning what strategies should be implemented. The aim of this study was to shed light on what the most cost-effective strategy for mass screening celiac disease in children is. The secondary aim was to create a model, that could be used for assessing the cost-effectiveness of prospective methods that lower the probability of developing the disease. A hypothetical enterovirus vaccination was used as an example.

The cost-effectiveness was acquired by simulating a discrete-time Markov chain with a lifetime horizon. By simulating how the disease manifests itself in the general population from birth to death, estimates could be made for costs and quality of life loss due to the lack of an intervention. These results were used to calculate the incremental cost-effectiveness ratio of the given intervention. The data and model structure were mostly based on the most up-to-date study on the subject by Norström et al. (2021) [15]. This study expanded on the study by incorporating an age dependent risk of developing the disease and the percentage of the population susceptible to the disease. This allowed for the comparison of screening at different age points, comparing at-risk screening with universal screening, and seeing how cost-effective disease prevention might be. Simulating the Markov chains using python allowed for the effortless generation and comparison of numerous strategies.

According to the results, it is more cost-effective to screen without genotyping the at-risk population and screening once is more cost-effective compared to repeated screenings. The optimal screening age is 6 years old with an ICER of €38,528 per QALY. Therefore, mass screening is cost-effective, assuming the threshold of €50,000 per gained QALY. However, the cost-effectiveness changed significantly in the sensitivity analysis, leaving it ultimately up for debate. The optimal screening strategy was not very sensitive to changes. The optimal screening age varied between 4-7 years old and single-time screening without genotyping was always the optimal strategy bar one scenario. The hypothetical enterovirus vaccination was not cost-effective in preventing the disease with an assumed price of €250 per child and a 20% lower annual probability of developing celiac disease. However, it would become cost-effective would its price be lowered to under €165.

Due to the lifetime horizon of the model, many parameter values were uncertain. Especially, more longitudinal studies on the disease progression would be required for more accurate results. The factors with the biggest impact on cost-effectiveness were the disease progression rate from mild to severe symptoms and the compliance rate. Therefore, if mass screening is not implemented, the focus should be put on treatment compliance and slowing the disease progression. For prospective preventive measures, the research should aim to produce its price per child and its effectiveness in preventing the disease. If more data was available, it would be beneficial to examine the cost-effectiveness of screening certain risk groups instead of the general public.

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