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Screening for celiac disease in the Netherlands: estimation of costs and benefits

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Summary

In the Netherlands, the incidence of recognised childhood celiac disease (gluten-sensitive enteropathy) has increased from 0.18/1,000 live births in 1975-90 (1/5,555) to 0.75/1,000 live births in 1993-98 (1/1,333). However, celiac disease is frequently unrecognised and screening studies have shown a prevalence of 1/300-1/100. A recent screening study among Dutch children 2-4 years of age showed a prevalence of unrecognised celiac disease of approximately 1/200. Therefore, many children with a gluten-sensitive enteropathy will remain unrecognised without screening programmes. These findings raise the question whether mass screening of the general population should be recommended. The aim of this study is to estimate the costs associated with a national screening programme for celiac disease in the general Dutch child population, as well as the potential health and cost benefits due to the prevention of well-known complications of celiac disease. In addition, the principles of early disease detection of Wilson and Jungner are addressed.

Selected studies were reviewed to estimate the health burden associated with various complications of celiac disease. For each complication, the population attributable fraction was calculated, representing a theoretical estimate of the percentage of cases with a health problem in the total population that can be attributed to celiac disease. Cost estimates associated with the selected complications of celiac disease were calculated, as well as the costs related to screening for celiac disease. For both purposes, the annual direct medical costs within the Dutch health care system were estimated. For the costs of screening for celiac disease, two scenarios have been assessed: serological screening (tTGA-determination at 2-4 years of age) and a combination of genetic and serological screening (HLA-determination in newborns followed by tTGA-determination in HLA-positive children at 2-4 years of age).

Given an annual birth rate in the Netherlands of approximately 200,000 infants, a national screening programme for celiac disease is estimated to identify about 1,000 children per year. The annual direct medical costs of screening are estimated on fl. 9.0 million for the serological screening scenario and fl. 14.2 million for the HLA+serological screening procedure. Thus, the estimated costs per child screened would be fl. 45 and fl. 71, respectively. The costs per child diagnosed with celiac disease would be approximately fl. 9,000 and fl. 14,000. Estimations of the health burden of complications of celiac disease indicate that each year about 300 individuals are diagnosed with osteoporosis, 65 women receive infertility treatments, 110 women experience a miscarriage, 100 women give birth to a low birthweight baby, and 22 cases are diagnosed with non-Hodgkin's lymphoma as a consequence of celiac disease. The annual direct medical costs caused by these complications are estimated on fl. 19.1 million. When the estimated costs of the described complications are discounted to present value, the annual direct medical costs would be fl. 2.4 million.

The current findings indicate that a population-based screening programme for celiac disease is unlikely to be cost-saving based on the direct medical costs of future complications alone. However, important long-term health gains can be achieved by prevention of such complications. In addition, short-term health gains appear to be considerable as well in approximately half of the children diagnosed with celiac disease after screening. That is, one-third of screening-detected children (about 330 children per year) are expected to have symptoms at diagnosis. In most cases, the parents of these

children will wish their child to be treated and the health status and quality of life of these children will improve significantly after one year of gluten restriction. Another 220 screening-detected children per year, who have no apparent symptoms at the time of diagnosis, are expected to develop symptoms soon after diagnosis when continuing a gluten-containing diet. Detection and treatment of these children may prevent health deterioration on the short term.

We conclude that celiac disease is a good candidate for disease prevention by screening because it is highly prevalent, associated with significant short- and long-term morbidity, able to be diagnosed and treatable. Serological screening of celiac disease at 2-4 years of age by a fingerprick at the Community Child Health Care Centre (CCHCC), followed by a confirmatory small bowel biopsy for test-positives, appears to be the preferrable screening method. Experience in the Netherlands, as well as several other countries, has shown this method to be feasible and acceptable. We recommend to detect all children with unrecognised celiac disease. All detected children, both symptomatic and asymptomatic cases, should be offered treatment with a gluten-free diet. When parents of asymptomatic children do not accept treatment, the patients should be followed based on clinical assessments, including bone mineral density. Treatment with a gluten-free diet should be advised again as soon as these children develop symptoms or osteopenia. Using this strategy, an unnecessary delay between the development of subtle (atypical) symptoms and treatment with a gluten-free diet could be prevented.

At the moment, there is not yet enough evidence that mass screening for celiac disease in the general child population is fully justified on a routinely basis. However, we do recommend to start a national screening programme for unrecognised childhood celiac disease as a research project. By performing a screening study in (a large representative area of) the total Dutch population, it could be possible to obtain more information about (1) the usefulness of the antitissue transglutaminase antibody (tTGA) test for population-based screening, (2) organisational aspects (datamanagement, nationwide monitoring and tracking, capacity in CCHCCs, laboratories and hospitals), (3) the actual costs of screening, (4) the willingness of parents of asymptomatic children to accept treatment, (5) the dietary compliance of both symptomatic and asymptomatic children in the first years of treatment, and (6) the development of health complaints and bone derangements in asymptomatic patients. Continuous monitoring and evaluation of such a screening programme, analogous to that of the PKU/CH/AGS screening, will enable future evidence-based decisions on installment of a national screening programme for celiac disease.

Contents

1 Introduction

Celiac disease is a chronic disorder, characterized by a permanent intolerance to gluten, leading to villous atrophy of the small bowel. The clinical features are variable, from a malabsorption syndrome to much more subtle symptoms such as chronic lassitude, or no symptoms at all. The treatment is a gluten-free diet, resulting in an important improvement of the bowel abnormalities and complaints.[1,2] Screening studies have shown that celiac disease is much more common than thought before and remains frequently undiagnosed.[3] In the Netherlands, the incidence of recognised celiac disease in Dutch children 0-14 years of age, reported by means of the Dutch Paediatric Surveillance Unit, has increased significantly from 0.18/1,000 live births in 1975-90 (1/5,555) to 0.75/1,000 live births in 1993-98 (1/1,333).[4] The Dutch pediatricians, being more and more conscious of the clinical spectrum of celiac disease, recognise a less typical clinical presentation at diagnosis. Nevertheless, a screening study among Dutch children 2-4 years of age, visiting the Community Child Health Care Centres in the province of Zuid-Holland (Praeventiefonds-ZON project 28-2229), showed a prevalence of unrecognised celiac disease of approximately 1/200.[5] Obviously, this frequency exceeds by far the prevalence rates of diseases for which screening programmes are currently applied, such as moderate to severe congenital hearing loss (1/1,000),[6] congenital hypothyroidism (CH) (1/3,400),[7] and phenylketonuria (PKU) (1/18,000).[8]

In absolute terms, one might assume that of each annual birth cohort in the Netherlands of approximately 200,000 children, about 150 children will be diagnosed with celiac disease during childhood. In addition, about 1,000 children are estimated to develop celiac disease from a very young age, but are not recognised. Some of these cases may be recognised in adolescence or adulthood, but the large majority will not be identified with current clinical practice. The estimated ratio of recognised to unrecognised celiac disease would thus be 1 to 6. Clearly, underdiagnosis and misdiagnosis of celiac disease are common in general practice,[9] even when features are suggestive of celiac disease.[10] Therefore, many children with a gluten-sensitive enteropathy will remain unrecognised without screening programmes. These findings raise the question whether mass screening of the general population should be recommended.

To decide whether mass screening for a particular disease is worthwhile, the principles for early disease detection as elaborated by Wilson and Jungner should be considered.[11] For celiac disease, an important question is the extent to which secondary complications of the disease can be prevented by early detection and treatment.[12,13] An increased risk for a range of complications has been described, such as osteoporosis, infertility, malignancy and auto-immune diseases.[1,2] However, it is not clear what the size of these risks is, and whether the risks for celiacs with few or no symptoms are as great as for those with classic symptomatic disease. Also, it is necessary to consider the costs of mass screening, which should be balanced to the costs associated with treatment of later symptoms and secondary complications.

The aim of this study is to estimate the potential health effects and costs associated with a national screening programme for celiac disease in the general Dutch child population. In addition, the extent to which the principles of Wilson and Jungner are fulfilled by celiac disease screening will be addressed in the discussion on a point-by-point basis.

2 Methods

Estimations were based on the current evidence from studies examining the relationship between celiac disease and secondary complications. These studies were identified using a MEDLINE search from 1966 through March 2001 in English (keywords 'celiac' or 'coeliac'). In addition, the references of studies, reviews and conference reports in the same period were inspected to identify other relevant studies. We have limited the scope of the study to frequently described complications of celiac disease, including osteoporosis and bone fractures, infertility, pregnancy outcomes, and cancer.

2.1 Calculation of population attributable fractions

Selected studies were reviewed to estimate risk ratios for complications in celiac disease patients as compared to the general population. Based on these risk ratios, for each complication the population attributable fraction (*PAF*) was calculated.[14] This measure gives a theoretical estimate of the percentage of cases with a health problem in the total population that can be attributed to a particular risk factor. The *PAF* is determined by the prevalence of the risk factor (celiac disease) in the population (P_{CD}), and by the strength of the relationship between the risk factor and the health problem (complication), expressed as the relative risk (*RR*).[14] For each complication of celiac disease, the number of cases in the total population was derived from national databases, and the theoretical number of cases attributable to celiac disease was estimated using the formula:

$$\text{Population attributable fraction } (PAF) = \frac{P_{CD}\,(RR - 1)}{P_{CD}\,(RR - 1) + 1} \times 100\%$$

We assumed the prevalence of celiac disease to be 0.5% (1/200).[5] Estimation of the *RR* for complications in celiac patients were based directly on cohort studies or based indirectly on the odds ratio (*OR*) obtained from case-control studies.

2.2 Calculation of costs

Cost estimates associated with the selected complications of celiac disease were calculated, as well as the costs related to screening for celiac disease. For both purposes, the annual direct medical costs within the Dutch health care system were estimated.

The annual direct costs of diagnosis, treatment and care associated with complications of celiac disease were estimated. For each complication, the *PAF* was used to estimate the proportion of the annual health care costs in the total population that can be attributed to celiac disease. Data on costs for the total population were drawn from reports of general health care costs in the Netherlands,[15,16] and a more specific Dutch study on osteoporosis.[17] Since most of these data were based on costs in the year 1994, the cost estimates were transformed to year 2000 prices. Between 1994 and 2000 general prices have increased by a median of 2.1%, with a total increment of 13.6%.[18] In addition to nominal costs, all costs are also reported as discounted costs. It is a generally accepted economic principle that individuals and society have an 'impatience

rate', which means that the value of a future cost will be reduced compared to the same cost of today, also with a situation of no inflation.[19] In this study the social discount rate has been set to 5%, as reflecting an average of different country policies (see Appendix A). Societal and social costs associated with complications of celiac disease, including loss of leisure time, productivity, years of life or quality of life, have been omitted from the analysis due to a lack of data. These issues are addressed and partly clarified by examples in the discussion.

For the costs of screening for celiac disease, two scenarios have been assessed: serological screening and a combination of genetic and serological screening. These costs were estimated more detailed than costs of complications of celiac disease. For both scenarios, the necessary steps to be taken and the relevant cost causing elements were determined. In addition to estimation of the annual direct medical cost, we partly examined costs to society by calculating the costs of travelling and time loss of parents to visit health care providers. No attempt was made to express the social costs of screening, including quality of life consequences, in monetary values. The estimated costs are those of a running programme, thus excluding start-up problems and investments in capacity.

3 Results

3.1 Estimation of health burden and costs due to complications of celiac disease

The following paragraphs summarise the studies which have been used to obtain appropriate estimates of the health effects and costs associated with the selected complications of celiac disease. For each complication, Table 1 displays estimates for the *RR*, *PAF*, the annual number of cases presenting with the particular disease in the total Dutch population, the annual number of cases theoretically attributable to celiac disease, and the nominal and discounted costs associated with diagnosis and treatment of complications.

Table 1. Estimated health burden and associated direct medical costs of major complications of celiac disease in the Netherlands

			Annual no. of cases		Annual costs	
	RR	***PAF* (%)**	**In total Dutch population**	**Related to celiac disease**	**Nominal costs (mln.NLG)**	**Discounted costs (mln.NLG)**
Osteoporosis	6.5	2.7	11,000	300	13.4	1.2
Infertility	2.9	0.9	7,000	65	0.6	0.1
Miscarriage	2.1	0.5	22,000	110	-	-
Low birth weight	2.6	0.8	12,000	100	4.3	1.0
Non-Hodgkin's lymphoma	3.3	1.1	2,000	22	0.8	0.1
Total					19.1	2.4

3.1.1 Osteoporosis

Celiac disease predisposes to abnormalities of bone and calcium metabolism. Several studies have shown reduced bone mineral density in patients with untreated celiac disease.[20] Recently, two studies also demonstrated that patients with celiac disease have an increased prevalence of bone fractures in the peripheral skeleton.[21,22] According to WHO criteria,[23] a recent study among 86 newly-diagnosed adult celiac disease patients showed that only 34% of them had a normal bone mineral density, 40% had osteopenia, and 26% osteoporosis.[24] A study among 77 celiac disease patients also reported 26% having osteoporosis.[25] In the latter study, for each celiac patient, two age-, gender- and menopausal-status-matched control subjects were included. Only 5% of the controls was classified as having osteoporosis, yielding an *OR* of 6.5.

In the Netherlands, each year about 11,000 individuals are diagnosed with osteoporosis.[26] Given a *PAF* of 2.7%, about 300 of these cases would be related to celiac disease. The true incidence of osteoporosis is several-fold higher, however, since only those patients are diagnosed and registered who present with complaints, fractures or other specific reasons.

Based on a report of osteoporosis in the Netherlands,[17] the annual direct medical costs of osteoporosis, forearm and vertebrae fractures, and hip fractures in the total Dutch population were conservatively estimated on fl. 437.9 million (see Appendix B), being fl. 497.5 million when transformed to year 2000 prices. If we assume that 2.7% of these costs can be attributed to celiac disease, the annual nominal costs would be fl. 13.4 million. Assuming an onset of treatment for osteoporosis and/or bone fractures at a median age of 50, the present value would be fl. 1.2 million (Table 1).

3.1.2 Infertility

There is substantial evidence that celiac disease is associated with infertility in both men and women.[27] Women with celiac disease have a delayed menarche and early menopause,[28-31] and therefore the fertile period in their life is significantly reduced. Direct evidence of decreased fertility was provided by a study comparing 68 women with celiac disease to age-matched healthy controls.[30] Eleven patients (16%) and one healthy control admitted to difficulty in conceiving children at some stage. The mean number of children born to patients was 1.9 as compared to 2.5 among controls. Two screening studies among women with infertility found an increased prevalence of celiac disease. In a case-control study of 150 infertile women and 150 women undergoing sterilization as controls, 4 of 150 infertile women (2.7%) had celiac disease versus none in the control subjects.[32] All four belonged to the subgroup of 98 women with unexplained infertility. In another study, 3 of 99 infertile women (3.0%) had celiac disease,[33] as compared to 17 of 1607 (1.1%) in a control sample from the same population,[34] indicating an *OR* of 2.9.

In the Netherlands, the annual number of women receiving infertility treatments is estimated on 7,000.[35] Given a *PAF* of 0.9%, about 65 of these cases would be related to celiac disease.

A total of 13 diagnostic and treatment categories have been reported to account for nearly all of the direct medical costs of infertility management, ranging from clomiphene treatment of unexplained infertility to in-vitro fertilization of persistent infertility.[36] In the Netherlands, the annual direct medical costs of female infertility is estimated on fl. 54 million,[16] being fl. 61.3 million when transformed to year 2000 prices. If we assume that 0.9% of these costs can be attributed to celiac disease, the annual nominal costs would be fl. 0.6 million. Assuming an onset of infertility treatment at a median age of 30, the present value would be fl. 0.1 million (Table 1).

3.1.3 *Miscarriage*

Several studies have reported an increased frequency of spontaneous abortions in pregnant women with celiac disease.[28-31,37] In three studies, the prevalence of abortion in pregnancies of celiac women was 18%.[28,31,37] The largest one, comparing 265 pregnancies in 130 celiac patients with 268 pregnancies in 130 age-matched healthy controls, showed 49 abortions (18%) in celiac women versus 26 (10%) in control subjects,[31] indicating an *OR* of 2.1.

In the Netherlands, an estimated 10% of pregnancies result in (recognized) miscarriages,[35] representing about 22,000 cases a year. Given a *PAF* of 0.5%, about 110 miscarriages would be related to celiac disease.

Treatment options for miscarriage include expectant management, dilatation and curettage in an outpatient setting, and medical management with misoprostol.[38] The direct medical costs of the management of early pregnancy failure are negligible in view of the costs of other complications.

3.1.4 *Low birthweight*

Two studies have examined the risk of low birthweight (< 2,500 g) in infants born to celiac women.[37,39] In one study, 27 of 212 pregnancies (13%) in patients with untreated celiac disease resulted in low birthweight babies versus 1 of 41 (2%) in patients on a gluten-free diet.[37] In a well-controlled population-based study including 211 newborns to 127 mothers with celiac disease and 1,260 control deliveries, low birthweight (< 2,500 g) occurred in 19 of 155 babies (12%) of patients with untreated disease, in 3 of 50 newborn (6%) of those on a gluten-free diet, and in 60 of 1,253 cases (5%) of control women.[39] Comparison of untreated celiac disease patients to control subjects yielded an adjusted *OR* of 2.6.

In the Netherlands, each year about 12,000 newborns with low birthweight are registered.[40] Given a *PAF* of 0.8%, about 100 of these cases would be related to celiac disease.

Medical and technological advances in the care of infants with low birth weight (< 2,500 g) and very low birth weight (< 1,500 g) have significantly improved their survival prospects, but at a high cost.[41,42] Low birth weight has been estimated to account for 10% of all health care costs for children 0 to 15 years of age.[41] In the Netherlands, the annual costs of health care for children (ages 0-14) is estimated on fl. 4,703 million.[15] If low birth weight accounts for 10% of these costs, the annual costs of low birth weight in the total Dutch population would be fl. 470.3 million, being fl. 534.3 million when transformed to year 2000 prices. If we assume that 0.8% of these costs can be attributed to celiac disease, the annual nominal costs would be fl. 4.3 million. Assuming a median age of delivery of 30, the present value would be fl. 1.0 million (Table 1).

3.1.5 Non-Hodgkin's lymphoma

Patients with recognized celiac disease are at greater risk than the general population for the development of malignancies, in particular lymphomas, small-intestinal adenocarcinomas, and esophageal and pharyngeal squamous carcinomas.[43,44] A pooled analysis of five reports on causes of death in celiac disease showed that 43% of deaths were due to malignancy.[45] Of all cancer deaths, 42% were due to lymphomas. As a comparison, in the total population of the Netherlands about 25% of deaths are due to malignancy,[46] of which only 3% are caused by lymphomas.[47] In a frequently cited study,[48] a two-fold *RR* of cancer was found, and a highly significant excess of non-Hodgkin's lymphoma (*RR* = 42.7). However, the celiac disease patients in the above mentioned studies, reported mostly from centres with a special interest in celiac disease to which the most seriously ill patients are referred, may not be representative of other less ill patients. Currently, a cross-European case-control study is carried out to determine the frequency of celiac disease in patients with non-Hodgkin's lymphoma as compared to the general population.[49] Preliminary analysis of the data shows 14 out of 959 patients with non-Hodgkin's lymphoma to have celiac disease, as compared to 27 of 5999 controls, suggesting an *OR* of 3.3. For other malignancies which may be associated with celiac disease, no appropriate risk estimates are available, so that we refrain from making further inferences for other types of cancer.

In the Netherlands, each year about 2,000 individuals are diagnosed with non-Hodgkin's lymphoma.[47] Given a *PAF* of 1.1%, 22 of these would be related to celiac disease.

The annual direct medical costs of non-Hodgkin's lymphoma in the total Dutch population is estimated on fl. 61 million,[15] being fl. 69.3 million when transformed to year 2000 prices. If we assume that 1.1% of these costs can be attributed to celiac disease, the annual nominal costs would be fl. 0.8 million. Assuming an onset of treatment for non-Hodgkin's lymphoma at a median age of 50, the present value would be fl. 0.1 million (Table 1).

3.2 Estimation of costs of screening

To assess the costs of celiac disease screening, different screening strategies could be considered. One possible approach could be to screen high risk populations, including individuals having symptoms, complications or diseases associated with celiac disease, and/or first degree relatives of celiac disease patients. While several initiatives employing this case-finding approach are ongoing, a clear disadvantage of this strategy is that only a part of all celiac disease cases will be recognized. That is, individuals with mild or atypical symptoms or currently unknown complications, as well as the relatively large group of individuals with asymptomatic celiac disease will remain undiagnosed. The other strategy could be to screen the general population at a young age, thereby enabling early prevention of symptoms and complications. For the latter screening approach, the costs of two scenarios have been assessed: serological screening and a combination of genetic and serological screening. For both scenarios, the following paragraphs describe the various steps to be taken and the relevant cost causing elements (or cost units) to be distinguished.

3.2.1 *Serological screening*

The serological screening scenario is similar to that employed in the screening study in the Dutch province of Zuid-Holland,[5] except for the type of serological test. Following recent developments, the IgA antitissue transglutaminase antibody test will be used instead of the IgA antiendomysium antibody test (see chapter 5, criterion 5). In this scenario, we take advantage of the Community Child Health Care Centres (CCHCC) infrastructure in the Netherlands. All parents of children visiting the CCHCC 1-2 years after gluten introduction (age 2-4 years) will be sent an information leaflet about celiac disease screening. During a routine health check at the CCHCC, all children are screened for celiac disease by determination of IgA antitissue transglutaminase antibodies (tTGA) in serum. The blood sample will be taken by a district nurse and will be analysed in a laboratory. Parents of tTGA-positive children are notified of the result and referred to a pediatrician. After a consultation with this doctor, these children are offered a small bowel biopsy at an academic or other large hospital. The procedure of a biopsy intervention consists mostly of anaesthesiological consultation and an upper gastrointestinal endoscopy at the day-care department. All parents are notified of the result. Parents of biopsy-positive children are referred to their general practitioner to be advised a gluten-free diet.

The following steps are distinguished:

1. *Sending an information leaflet about celiac disease screening*

Parents visiting the CCHCC will be sent an information leaflet about celiac disease screening. The post costs and printing costs together are assumed to be fl. 1.- a piece.

2. *Staff costs to take blood sample*

It is assumed that it will take a district nurse at the CCHCC an extra 20 minutes to take a blood sample. The district nurse has an average gross hourly wage of fl. 28.40.[50]

3. *Time loss to take blood sample*

The 20 minutes for taking the blood sample are valued at the average net hourly wage of a working individual, which is fl. 20.63.[51]

4. *Lab costs of tTGA-determination*

The laboratory costs for tTGA-determination is estimated at fl. 21.-. This is the price at wich great numbers of panel sera in laboratories are accounted for.[52]

5. *Consultation with pediatrician*

The parents of the tTGA-positive children are referred to a pediatrician. The consultation with the pediatrician is valued at the guideline for medical consultations, which is fl. 46.-.[53]

6. *Time loss and travel costs to visit pediatrician*

The parents of the tTGA-positive children have to go to the hospital to meet the pediatrician. With an average distance of 7 kilometres to the hospital,[53] it is estimated that it will take 50 minutes to drive back and forth. The time of the consultation is assumed to be half an hour. Travel and consultation time is valued again at fl. 20.63 per hour. The travel costs are valued at a kilometre price of fl. 0.25 and parking money at fl. 2.50.[53]

7. *Costs of biopsy*

The price of the biopsy intervention is estimated on fl. 1410.50.[54] This includes anaesthesiological instruction, day-care during the day of the biopsy intervention, narcosis, duodenal scopy and biopt, and the assessment of the biopt by the pathologist. The tariff is a high estimation of the unit price, because it includes non-marginal costs like overhead.

8. *Time loss and travel costs to visit academic or large hospital to make biopsy*
Time loss of the biopsy intervention procedure is estimated on 6 hours. Assuming a travel time back and forth to an academic hospital of 1.5 hours, the total time investment adds up to 7.5 hours, which is valued again at fl. 20.63 per hour. The travel costs are valued again at a kilometre price fl. 0.25 and parking money at fl. 2.50. The average distance to an academic hospital is estimated on 24.5 kilometres.[55]
9. *Consultation with general practitioner*
The parents of the biopsy-positive children are referred to a general practitioner to be advised a gluten-free diet. The consultation with the general practitioner is valued at fl. 36.57.[53]
10. *Time loss and travel costs to visit general practitioner*
The time loss of the visit to the general practitioner is estimated at 1 hour, including travel time and the consultation. This time is valued again at fl. 20.63 per hour. Travel costs of parents to visit a general practitioner are based on the average distance of a household to a general practitioner of 1.8 kilometre,[53] and a kilometre price of fl. 0.25.

3.2.2 *HLA + serological screening*

In this scenario, individuals with a genetic predisposition for celiac disease will be selected first by determination of the HLA-DQ heterodimers being present in 99% of celiac disease patients, in 30% of the Caucasian population, and to our knowledge not associated with other diseases.[56] The advantage of this method is that only 30% of the general population, who have the genetic predisposition for celiac disease, has to be further screened serologically for celiac disease. The genetic screening in the general child population could take place simultaneously with the newborn national screening programme for congenital metabole defects (PKU, CH, AGS), using the same blood sample. The blood sample will be analysed in a laboratory. Based on the HLA-DQ typing, all cases with potential celiac disease are detected. The parents of the HLA-DQ-negative newborns are not notified. The parents of the HLA-DQ-positive newborns (roughly 30%) are notified by mail and referred to a consultation with their general practitioner for more information. At the age of 2-4 years, the HLA-DQ-positive children are sent a screening invitation during a routine health check at the CCHCC. The next steps are the same as described for the serological screening.

The following steps are distinguished:
1. *Staff costs to prepare the HLA-blood sample*
It is assumed that it will take a district nurse 15 minutes extra time to prepare the HLA-blood sample during the neonatal heel puncture for PKU/CH/AGS screening. This time is valued at the average gross hourly wage of a district nurse of fl. 28.40.[50]
2. *Lab costs of HLA-determination*
The laboratory costs for an HLA-determination is assumed to be fl. 30.-,[57] using DNA extraction and purification, subsequent DNA amplification in PCR and detection of amplifies on agarose gel.
3. *Referral letter*
The parents of the HLA-DQ-positive newborns are notified by mail and referred to a consultation with their general practitioner for more information. The post costs and printing costs together are assumed to be fl. 1.- a piece.
4. *Consultation with general practitioner*
Parents of HLA-positive children are informed about celiac disease and their children's risk of the disease. The consultation is valued at fl. 36.57.[53]

5. *Time loss and travel costs to visit general practitioner*
The time loss of the visit to the general practitioner is estimated at 1 hour, including travel time and the consultation. This time is valued at the average net hourly wage of working individuals, which is fl. 20.63.[51] Travel costs of parents to visit a general practitioner are based on the average distance of a household to a general practitioner of 1.8 kilometre,[53] and a kilometre price of fl. 0.25.
For the next steps, see steps 1 to 10 of the serological screening scenario.

3.2.3 Cost estimates

The described cost units are used to estimate the costs of the two screening strategies. In addition, assumptions need to be made about the frequency of several events. The number of infants born each year in the Netherlands is assumed to be 200,000.[51] For the serological screening scenario, all assumptions are based on the results of the screening study in Zuid-Holland.[5] According to this study, the frequency of positive tTGA-tests is expected to be 1.2% (2,400 children). With a 25% refusal rate to undergo a biopsy, the frequency of children undergoing small bowel biopsy is estimated on 0.9% (1,800 children). The frequency of biopsies with flat mucosa (i.e., children with celiac disease) is expected to be 0.5% (1,000 children). In the HLA+serological screening scenario, the percentage of HLA-DQ-positive children is assumed to be 30% (60,000 children).[58] The numbers of children who have a positive tTGA-test, are willing to undergo a biopsy, and have a flat small bowel mucosa are assumed to be the same as for serological screening.

Table 2 gives the estimated costs for the two screening alternatives. The annual direct medical costs of screening are estimated on fl. 9.0 million for the serological screening scenario and fl. 14.2 million for the HLA+serological screening procedure. Thus, the estimated costs per child screened would be fl. 45 and fl. 71, respectively. The costs per child diagnosed with celiac disease would be approximately fl. 9,000 and fl. 14,000. When time loss and travel costs of parents to visit health care providers are included, the total annual costs are estimated on fl. 10.8 million and fl. 16.4 million for the serological screening and the HLA+serological screening scenario, respectively.

Table 2. Estimated annual costs of two scenarios of screening for celiac disease in the Netherlands

Cost component	Unit price	Serological		HLA+serological	
	(NLG)	n	(NLG)	n	(NLG)
HLA-determination				200,000	
Staff	7.10				1,420,000
Lab costs	30.00				6,000,000
Referral to GP				60,000	
Referral letter	1.00				60,000
Consultation	36.57				2,194,200
Time loss parents	20.63				1,237,800
Travel cost parents	0.90				54,000
tTGA-determination		200,000		60,000	
Information leaflet	1.00		200,000		60,000
Staff	9.47		1,894,000		568,200
Time loss parents	6.88		1,376,000		412,800
Lab costs	21.00		4,200,000		1,260,000
Referral to pediatrician		2,400		2,400	
Consultation	46.00		110,400		110,400
Time loss parents	27.50		66,000		66,000
Travel costs parents	6.00		14,400		14,400
Biopsy		1,800		1,800	
Biopsy	1410.50		2,538,900		2,538,900
Time loss parents	154.75		278,550		278,550
Travel costs parents	14.75		26,550		26,550
Referral to GP		1,000		1,000	
Consultation	36.57		36,570		36,570
Time loss parents	20.63		20,630		20,630
Travel costs parents	0.90		900		900
Total direct medical costs			8,979,870		14,248,270
Total time loss/travel costs			1,783,030		2,111,630
Total costs			10,762,900		16,359,900

4 Interpretation of findings

This study aimed to address the costs associated with a national screening programme for celiac disease in the general Dutch child population, as well as the potential health and cost benefits due to the prevention of well-known complications of celiac disease. All estimates are based on the assumption that the prevalence rate of unrecognised celiac disease in the total population is similar to that observed in the screening study in Zuid-Holland,[5] that is 1/200 children (0.5%). This assumption seems reasonable in view of the observed prevalence rates in several other screening studies, which varied between approximately 1/300 – 1/100.[3,34,59-65] Given an annual birth rate in the Netherlands of approximately 200,000 infants, a national screening programme for celiac disease is estimated to identify about 1,000 children per year.

4.1 Costs of screening for celiac disease

Based on a similar screening procedure as employed in the screening study in Zuid-Holland, i.e. serological screening at age 2-4 years, the direct medical costs of screening are estimated on fl. 9.0 million. Thus, the estimated costs per child screened would be fl. 45, and per child diagnosed with celiac disease fl. 9,000. These estimates are based on the unlikely assumption that all 200,000 children of a particular birth cohort will be serologically screened. Since about 10% of the children may not attend the CCHCC, and not all parents will consent to participate, a more realistic assumption might be that 85% of the children are screened. This would yield a reduction in the screening costs of fl. 1.4 million. In this scenario, all children visiting the CCHCC are screened for celiac disease by determination of IgA antitissue transglutaminase antibodies (tTGA) in serum. This is reflected in the high direct medical costs for tTGA-determination (fl. 6.3 million), for a large part due to laboratory costs (fl. 4.2 million). This means that reduction of the lab costs for a tTGA-determination would substantially decrease the costs of screening. For example, when the same unit price would be employed as in the screening study in Zuid-Holland (fl. 15, instead of the assumed fl. 21), this would decrease the costs of screening by fl. 1.2 million. Given the time-saving and the quantitative character of the assay, costs for large scale tTGA testing can probably be reduced (see chapter 5, criterion 5). When possible, future developments should also aim at further improvement of the predictive value of a positive test (i.e., 55% in the Zuid-Holland study), so that less children need to be referred for a small bowel biopsy. Since the costs for biopsies form a relatively large part of the total screening procedure (fl. 2.5 million), this could yield further cost reductions. As shown in Appendix C, changing assumptions as described above (i.e., 85% attendance/participation rate, unit price of fl. 15,- for tTGA-determination, 70% predictive value of a positive tTGA-test) would decrease the direct medical costs of screening to an estimate of fl. 6.1 million. Since 850 (instead of 1000) children would be identified to have celiac disease, the estimated costs per child diagnosed with celiac disease would be about fl. 7,200.

The advantage of the HLA+serological screening scenario is that only 30% of the general population, who have the genetic predisposition for celiac disease, has to be further screened serologically for celiac disease. tTGA-determination for the assumed 60,000 children (as compared to 200,000 children) would yield a cost saving of fl. 4.4 million. Instead, HLA-determination needs to be done for the total population, the costs of which are estimated on fl. 7.4 million. In addition, the parents of HLA-positive

children need to be informed about the consequences of the HLA-positive screening result. If the information is given by general practitioners, additional direct medical costs are estimated on fl. 2.3 million.

The cost estimates discussed above represent the direct costs for the Dutch health care system. These estimates are not absolute, but are the result of various choices, assumptions and estimations, which means that all outcomes should be interpreted with caution. Several additional cost components have not been addressed, including initial costs for start-up of the screening programme, and costs for datamanagement, nationwide monitoring and tracking. Cost estimates are restricted to the screening process itself. That is, all costs following a diagnosis of celiac disease have not been considered, such as costs of the gluten-free diet (in the Netherlands to be paid by the parents themselves) and costs of follow-up visits for evaluation of the disease.

In addition to direct medical cost, we partly addressed costs to society by calculating the costs of travelling and time loss of parents to visit health care providers. These costs were estimated on approximately fl. 2 million. However, this was mainly due to time loss during bloodsampling. Although the time loss for bloodsampling is substantial for a total annual birth cohort, the time investment is minimal for individual parents. Time investment is more considerable only for parents whose child is eventually diagnosed with celiac disease, amounting to about 11 hours. No attempt has been made to value others costs to individual parents and children, such as the necessity to undergo a small bowel biopsy following a positive serological test, anxiety in case of false-positive screening results, and (in the HLA+serological screening scenario) possible anxiety of inheriting a gene which may have adverse effects. More importantly, children identified with celiac disease and their parents are confronted with the stigma of a life-long disease and the burden of a gluten-free diet.

4.2 Benefits of avoiding complications of celiac disease

The current study also aimed to address long-term adverse events of untreated celiac disease. Estimations have been limited to well-known complications. The findings indicate that the health burden and costs of celiac disease in terms of complications, including osteoporosis, bone fractures, infertility, birth outcomes and cancer, are considerable. In the Netherlands, our estimates indicate that each year about 300 individuals are diagnosed with osteoporosis, 65 women receive infertility treatments, 110 women experience a miscarriage, 100 women give birth to a low birthweight baby, and 22 cases are diagnosed with non-Hodgkin's lymphoma as a consequence of celiac disease. The annual direct medical costs caused by these complications are estimated on fl. 19.1 million, for a large part due to osteoporosis and associated bone fractures (fl. 13.4 million) and low birthweight children (fl. 4.3 million). However, while the costs of screening are incurred in the present, costs of complications appear well into the future. When the estimated costs of the described complications are discounted to present value, the annual direct medical costs would be fl. 2.4 million.

Clearly, these outcomes should be interpreted with caution. The epidemiological estimates depend on the appropriateness and the quality of the studies and national data sources employed to determine risk ratios for patients with celiac disease and incidence rates in the total Dutch population. For example, the estimated risks of two important complications, osteoporosis and low birthweight children, have been based on studies

among patients diagnosed in normal clinical practice. It is not clear whether the risks for unrecognised patients, either with health complaints or asymptomatic, are similar. In unrecognised individuals, the histological features of celiac disease in the proximal small intestine are the same as in recognised patients. Therefore, it seems prudent to assume that they have the same long-term risks. With regard to osteoporosis, a number of studies indicate that osteoporosis is also significantly associated with unrecognised celiac disease, but the extent of bone and mineral metabolism derangements may be lower than in classical celiac disease.[66-70] The cost estimates have been based on annual health care costs in the total population. Although informative, such prevalence-based estimates do not provide a framework for assessing costs of future complications of celiac disease or projecting benefits from avoided complications in cohorts of individuals. A more extensive investigation to model the economic impact of future complications was beyond the scope of this study.

It is important to realise that the estimations of the health burden and costs of complications of celiac disease offer a theoretical picture, showing the benefits which could be achieved under optimal circumstances. In practice, the achievable benefits depend on several factors, including attendance rates and acceptability of the screening procedure and compliance to dietary treatment. As mentioned earlier, it is unlikely that all 200,000 children of a particular birth cohort will be serologically screened. A more realistic assumption might be that for 85% of the children the parents attend the CCHCC and are willing to participate in the initial blood testing. Confirmatory investigation by a small bowel biopsy will not always be acceptable, therefore the presented calculations already account for a refusal rate of 25%. The most important factor affecting the effectiveness of screening, however, will be acceptability of and compliance to a strict gluten-free diet (see chapter 5, criterion 2). When assuming an 85% attendance and participation rate in initial blood testing, and a 60% acceptance and compliance rate with a gluten-free diet, the health benefits of screening would be halved. Similarly, the direct medical cost benefits due to prevention of complications of celiac disease would be halved to an estimated fl. 9.6 million, with a present value of 1.2 million. Another factor affecting the effectiveness of screening is the strength of the causal relationship between unrecognised celiac disease and the described complications. Although we limited our estimations to complications of which the underlying mechanisms are fairly well understood, it is uncertain if removal of gluten from the diet will prevent these complications in all cases.

On the other hand, the health burden and costs of celiac disease as described in the current study do not give a full picture of the possible health consequences and costs, and thus of possible benefits of screening. Importantly, the burden and costs associated with the many possible symptoms of celiac disease (e.g., lassitude, abdominal pain, chronic diarrhoea), which frequently occur from an early age, have not been included. The short-term health gains of screening and treatment of celiac disease appear to be considerable.[71] Also, additional complications of celiac disease have been described, such as iron-deficiency anaemia,[72] autoimmune disorders[73] and neurological disorders.[74] Moreover, we limited ourselves to the narrow perspective of direct medical costs. A great part of the health care is devoted, however, to saving lives, years of life and quality of life. For example, one might assume that each year 12 patients die of non-Hodgkin's lymphoma and 2 very low birthweight babies do not survive. The social cost of avoiding loss of life from illness could be compared with attempts to value loss of life in traffic accidents. In such calculations, the loss of one statistical life has been valued to a social cost of £1 million (fl. 5 million, year 2000 prices).[75] The present value

of avoiding 12 deaths from non-Hodgkin's lymphoma and 2 deaths from very low birthweight can be estimated on fl. 4.6 million (see Appendix D). Furthermore, complications of celiac disease may seriously compromise patients' quality of life. For example, the direct medical costs of infertility may be limited, but the value of avoiding this complication is considerable.[76] Also, costs to society (e.g., costs of time and productivity loss due to sickness and disability) have not been included. Finally, the current cost estimates have been based on a conservative discount rate of 5%. Dutch pharmaco-economic guidelines, however, tend to employ a discount rate of 4%,[53] and others even recommend a discount rate of 3%.[77] When using the latter discount rates, the present value of the described complications of celiac disease would be fl. 3.5 million and fl. 5.3 million, respectively.

5 General considerations

To decide whether a nationwide screening programme for celiac disease is worthwhile, a number of questions need to be considered. In this paragraph, the principles for early disease detection as elaborated by Wilson and Jungner are addressed.[11]

1. *The condition should be an important health problem*
Diseases are considered important health problems when they have a high prevalence and/or have serious consequences both for the individual and for the community. Screening studies in different countries, including the Netherlands, have shown that unrecognised celiac disease is a frequent disorder in the general population, with a prevalence of approximately 0.5%.[3,5,34,59-65] As argued in the introduction, one might assume that of each annual Dutch birth cohort of 200,000 children, about 150 children will be diagnosed with celiac disease during childhood. In addition, about 1000 children will develop celiac disease from a very young age, most of whom will not be recognised.
In the screening study in Zuid-Holland, one-third of the children detected with unrecognised celiac disease (10 out of 31 children) had symptoms such as lassitude, abdominal pain and/or distension, constipation, chronic diarrhoea, and anaemia.[5] That is, of the 1000 screening-detected celiac disease patients per year, about 330 can be expected to have one or more symptoms. The current study provides an estimation of the health burden associated with complications of celiac disease in the Dutch population: per year about 300 individuals with osteoporosis, 65 women receiving infertility treatments, 110 women experiencing a miscarriage, 100 women giving birth to a low birthweight baby, and 22 cases with non-Hodgkin's lymphoma.
On the basis of these considerations, celiac disease can be classified as an important health problem. It concerns a disease with a high prevalence, associated with non-specific low-grade morbidity and long-term complications.

2. *There should be an accepted treatment for the disease*
Since the meticulous dietary studies performed from 1936 by the Dutch pediatrician, Karel Dicke, a medical accepted treatment of celiac disease is available. It consists of a life-long strict gluten-free diet.[78] This treatment usually suffices to restore the histological alterations of the small bowel and to prevent the clinical symptoms.[79]
While there is an accepted treatment of celiac disease from the medical point of view, a strict gluten-free diet may be less acceptable for children with celiac disease themselves or their parents. Especially when children are diagnosed with celiac disease by mass screening but have no symptoms, parents may not always accept a strict gluten-free diet. For example, in the Zuid-Holland study the parents of 6 out of 21 children without symptoms (29%) did not accept a gluten-free diet.[71] When they do accept treatment, compliance may sometimes be difficult in the long run. The percentage of patients with celiac disease who do not strictly adhere to a gluten-free diet has been reported to range from 7% to 55%.[80] Studies on compliance in screening-detected celiac disease, however, are scarce. In a group of Italian adolescents, who had been diagnosed with celiac disease by mass screening at a mean age of 13 years, 17 out of 22 children (77%) did not strictly adhere to the diet after 5 years of follow-up.[81] However, compliance may be better when children are screened for celiac disease and treatment is started at 2-4 years of age. In this situation, the parents and children can get used to their situation and eating habits from a very young age. In a cohort of Italian adolescents with celiac disease, diagnosed in the first three years of life, 65% were adhering to a strict gluten-

free diet.[82] In Dutch adolescents diagnosed in early childhood, the compliance may be higher. That is, a recent study among members of the Dutch Celiac Patients Society reported compliance with a strict gluten-free diet in 81% of the adolescents.[83]
One might speculate that the social burden of a life-long strict gluten-free diet could result in decreased levels of quality of life. On the short term, however, treatment with a gluten-free diet has been shown to improve the health related quality of life of symptomatic children with unrecognised celiac disease.[71] In addition, no health related quality of life deterioration was observed after one year follow-up in asymptomatic children treated with a gluten-free diet. Yet, the levels of emotional, physical and home functioning of adolescents with celiac disease have been found to be lower than those of children in the general population.[84] Similar results have been noted in quality of life studies in adult celiac disease patients.[85,86] In the initial phase of treatment, complaints diminish markedly and quality of life scores increase significantly. In the long run, patients may fail to attain the same degree of quality of life as the general population.[85]
Another important problem of the life-long treatment are the high costs of the gluten-free diet, which have been estimated to range between fl. 1,500-2,000 per year when the patient maintains a strict diet regimen.[87] However, the costs of the diet can be covered partly by savings from usual consumption expenses. Moreover, if screening programmes identify 0.5% of populations as potential consumers of gluten-free products, it is reasonable to expect that the prices of such products decrease, together with an increase in their quality and availability.

3. *Facilities for diagnosis and treatment should be available*
To establish the diagnosis a small bowel biopsy has to be performed. Histological identification of gluten sensitive enteropathy is still the only accepted basis for diagnosing celiac disease.[88] Since the biopsies are taken with an endoscopic forceps instead of the use of the Crosby capsule,[89] and accurate anaesthetic methods are available, the diagnostic procedure has become more and more acceptable for the patients.
If each year 1,800 children would be offered a small bowel biopsy, the current availability of facilities to establish the diagnosis of celiac disease may not be sufficient. If we assume that the biopsies can be performed in 10 hospitals in the Netherlands, about 15 biopsies should be performed per month in each hospital. This is more than the number of biopsies performed at the moment (e.g., 5-6 per month in Leiden). However, when future developments enable further improvement of the predictive value of serological tests, less children need to be referred for a small bowel biopsy. In addition, the technique to perform small bowel biopsies will probably change in the future, taking advantage of the wireless capsule endoscopy (already in use for adults). Thus, the burden and discomfort of internal gastrointestinal examination will be a thing of the past.[90] Similarly, laboratory facilities and staff for serological testing may need to be expanded, as well as staff for guiding the dietary treatment of children diagnosed with celiac disease.

4. *There should be a recognisable latent or early symptomatic stage*
Celiac disease is no longer restricted to the classical presentation, but frequently presents with mild or less typical symptoms, or no symptoms at all. Thus, in unrecognised celiac disease there is a clearly detectable stage in which children have a gluten-sensitive enteropathy, but no or mild symptoms. Due to this asymptomatic or mildly symptomatic stage, celiac disease may remain unrecognised without screening.

5. *There should be a suitable test for disease detection*

Several serological tests have become available to screen for celiac disease. Until recently, the most suitable screening test was the determination of IgA antiendomysium antibodies, detected by immunofluorescence on sections of monkey oesophageal or human umbilical cord smooth muscle on exposure to sera. Although the test relies on subjective operator assessment of fluoresescence, its sensitivity and specificity in detecting untreated celiac patients are high, between 92-100 and 97-100, respectively.[91,92] The positive predictive value of a positive test has been shown in the Zuid-Holland study to be 55%.[5] Thus, the properties are considered suitable for a screening programme.

In 1998, Dieterich et al. identified the tissue transglutaminase as being the autoantigen recognised in endomysium.[93] The measurement of IgA antitissue transglutaminase antibodies in an enzyme linked immunosorbent assay system is likely to be the first choice screening test of the future, when considering the time-saving and the quantitative character of the assay and its lower price. The sensitivity and specificity rates of the IgA antitissue transglutaminase antibody test seem to be as high as those of the IgA antiendomysium antibody test, particularly when using human recombinant enzyme as substrate.[93-96] Current research efforts aim at further investigation of the sensitivity, the predictive value and the usefulness of the IgA antitissue transglutaminase antibody test for population-based screening of celiac disease. Increasing the predictive value of a positive test, so that less children need to be referred for a small bowel biopsy, would further enhance the suitability of the test. The relative large number of 'false positives' in the Zuid-Holland study is largely due to fluctuations of autoantibody levels in young children with genetic susceptibility for the disease, and can be decreased by using the IgA antitissue transglutaminase antibody test and by performing the biopsy as close as possible to the moment of antibody determination.[97]

6. *The test should be acceptable for the population*

In recent years, large-scale screening studies on celiac disease have been performed in the general population, using serological tests.[3,5,34,59-65] The blood samples were obtained by a finger prick or a bloodpuncture, which seems to have been well accepted by the different populations. In the screening study in Zuid-Holland, a blood sample was taken once from a finger prick or a venapuncture (choice by parents).[5] Of the invited parents, 50% agreed to their child's participation in the study. We did not evaluate afterwards how acceptable the parents found this screening method. However, since the participation rate in the newborn screening programme for congenital defects (PKU, CH, AGS) has been over 99% for the last decades, Dutch parents apparently accept bloodsampling for screening purposes.

In addition, the diagnostic test should be acceptable. In the Zuid-Holland study, 25% of parents refused the biopsy offer for their child, presumably because the child had no symptoms. In these cases, awareness of the positive serological screening test may prompt future biopsy if symptoms should occur. Moreover, acceptability of the small bowel biopsy may further increase when future, less burdensome techniques are adopted (see criterion 3).

7. *The natural history of the condition, including development from latent to declared disease should be understood*

The natural history of unrecognised celiac disease is not fully known. In the screening study in Zuid-Holland,[5] one-third of the children diagnosed with celiac disease (10 out of 31 children) already had symptoms at diagnosis. The remaining asymptomatic children were either treated with a gluten-free diet or a normal gluten-containing diet

during one year. One-third of the asymptomatic children receiving a gluten-containing diet (4 out of 12 children) developed symptoms in few weeks or months following their diagnosis.[71] However, this study does not provide information on the long term.
As described in the current study, celiac disease is associated with an increased risk on a number of complications, both in recognised and unrecognised celiac disease. Some of these complications (such as osteopenia and bone fractures) may occur from an early age, some (such as infertility, miscarriage and low birthweight) by definition present at young adulthood, and some (such as non-Hodgkin's lymphoma, other malignancies and hip fractures) more likely present in middle or older age. However, it is not known how many individuals with celiac disease develop one or more of these complications. Some individuals may go through life without symptoms or major sequelae despite having significant mucosal changes.
Nevertheless, the current evidence suggests that the health burden of unrecognised celiac disease in terms of symptoms and complications is considerable. We know that a range of complications more often develop in individuals with celiac disease than in controls. Conversely, we know that celiac disease is more often observed in patients having such complications than in the general population. Full knowledge of the natural history of unrecognised celiac disease will be hard to obtain. A theoretical way to study this aspect is to screen large samples of the population, to randomise identified patients for gluten-free versus normal gluten-containing diet, and to follow them for 50 years. Obviously, this approach is not practical. Moreover, given the current evidence of the increased risk on symptoms and complications, one might argue that it is unethical not to offer patients identified to have celiac disease a gluten-free diet. Thus, the natural history of unrecognised celiac disease can only be examined by follow-up of (selected) patients who do not accept a gluten-free diet or who have a poor dietary compliance.

8. *There should be an agreed policy of whom to treat as patient*
For symptomatic celiac disease patients, including the cases with the classical clinical presentation as well as those presenting with atypical symptoms, there is no doubt that such cases will benefit from a gluten-free diet. This treatment usually causes an improvement of the clinical symptoms and suffices to restore the architecture of the small bowel mucosa.[78,79] Furthermore, the screening study in Zuid-Holland showed that parents of symptomatic children wished their child to be treated and that the quality of life of all symptomatic children (as reported by the parents) had improved significantly after one year of food intervention.[71] Also, several studies have shown that a gluten-free diet initiated during childhood or adolescence enables to achieve normal bone density and bone metabolism.[98-103]
For asymptomatic celiac disease patients, the benefits of treatment may be more doubtful. When children have no apparent symptoms, parents may not always accept a strict gluten-free diet. When they do accept treatment, compliance may sometimes be difficult (see criterion 2). On the other hand, the screening study in Zuid-Holland demonstrated that the serological and the small bowel alterations disappeared or significantly improved in all treated children, which was not the case in the children who went on consuming gluten.[71] In addition, none of the treated children developed symptoms in the first year after diagnosis as compared to one-third of the children on a normal diet. Finally, no adverse effect on the quality of life was observed in treated children due to the potential burden of the gluten-free diet. For asymptomatic cases it is also important to obtain an adequate peak bone mass at the end of puberty. That is, several studies have shown that the effect of a gluten-free diet initiated in adulthood on the degree of bone improvement varies considerably from patient to patient, and that the diet alone is unable to normalize the bone mineral density in all patients.[104-108]

Thus, we recommend to advise treatment with a gluten-free diet to both symptomatic and asymptomatic celiac disease patients. When parents of asymptomatic children do not accept treatment, the patients should be followed based on clinical assessments, including bone mineral density. Treatment with a gluten-free diet should be advised again as soon as these children develop symptoms or osteopenia.

9. *The costs of case-finding should be economically balanced in relation to possible expenditure on medical care as a whole*

The costs of a serological screening programme at 2-4 years of age are estimated on fl. 9.0 million per year (fl. 45 per child screened, fl. 9,000 per child diagnosed with celiac disease). Combination with HLA-DQ typing is more expensive and more complicated from a logistical and ethical point of view. Future cost savings due to prevention of complications of celiac disease are considerable (direct medical costs estimated on fl. 19.1 million). The present value of the cost savings for children screened in a particular year is estimated on fl. 2.4 million per year, which suggests that a nationwide screening programme for celiac disease is unlikely to be cost-saving based on the direct medical costs of future complications alone.

While direct comparisons with other screening programmes are difficult to make, it is interesting to look at the cost estimates of some other Dutch screening programmes. The costs of universal neonatal hearing screening have been estimated on fl. 46 per child screened and fl. 63,800 per child detected with a hearing loss.[109] The costs of newborn screening for congenital adrenal hyperplasia (CAH) have been estimated on fl. 99,000 per CAH patient detected.[110] Rough estimates of the annual costs of the newborn screening programmes for phenylketonuria (PKU) and congenital hypothyroidism (CH) date from almost two decades ago,[111,112] being fl. 2.5 million and fl. 2.7 million for PKU and CH screening, respectively. Based on approximately 10 PKU and 60 CH patients diagnosed per year, the costs per child detected would be fl. 250,000 and fl. 45,000 for PKU and CH, respectively.

As a more general frame of reference, in 1994 about fl. 60 billion has been spent on health care in the Netherlands, of which fl. 4.7 billion for children aged 0-14 years.[15] Of the total annual health care budget, 5% (about fl. 3 billion) is spent on preventive health care (all activities). In 1990, costs of the Dutch child health care system for children 0-4 years of age have been estimated on fl. 193.4 million, mainly due to the CCHCC infrastructure (fl. 146.1 million) and the vaccination programme (fl. 21.7 million).[113]

10. *Case-finding should be a continuous process*

Through the national screening programme of infants for congenital PKU, CH and AGS and the infrastructure of the Community Child Health Care Centres, which are attended regularly by around 90% of the children until the age of 4 years, screening for celiac disease could be a continuous process in the Netherlands.

6 Conclusions and recommendations

Celiac disease is a good candidate for disease prevention by screening because it is highly prevalent, associated with significant morbidity, able to be diagnosed and treatable. A national screening programme for celiac disease is estimated to identify about 1,000 children per year. One-third of these children are expected to have symptoms. In most cases, the parents of these children will wish their child to be treated and the health status and quality of life of these children will improve significantly after one year of gluten restriction. Also, the gluten-free diet enables to achieve normal bone density and bone metabolism, so that osteoporosis and bone fractures are prevented. On the longer term, several other complications, such as infertility, miscarriage, low birthweight and malignancies, can be prevented as well. Thus, short- and long-term health gains are realised for approximately 330 children per year.

For the remaining two-third of screening-detected patients, who have no apparent symptoms, the benefits of screening may be more doubtful. These children and their parents are confronted with the stigma of a life-long disease and the burden of a gluten-free diet. However, the children are seemingly healthy, so that both the short- and long-term benefits of treatment may be difficult to comprehend. Consequently, parents may not always accept a strict gluten-free diet, and compliance may be more difficult. Yet, detection and treatment of these children may prevent health deterioration on the short term in one-third of the cases. Thus, in another 220 children health gains are realised as well in the years following screening. In addition, as for children with symptoms, treatment of the small bowel alterations may prevent bone derangements and other long-term complications.

We recommend to detect all children with unrecognised celiac disease. All detected children with celiac disease, both symptomatic and asymptomatic cases, should be offered treatment with a gluten-free diet. When parents of asymptomatic children do not accept treatment, the patients should be followed based on clinical assessments, including bone mineral density. Treatment with a gluten-free diet should be advised again as soon as these children develop symptoms or osteopenia. Using this strategy, an unnecessary delay between the development of subtle (atypical) symptoms and treatment with a gluten-free diet could be prevented.

Serological screening of celiac disease at 2-4 years of age by a fingerprick at the CCHCC, followed by a confirmatory small bowel biopsy for test-positives, appears to be the preferrable screening method. Experience in the Netherlands, as well as several other countries, has shown this method to be feasible and acceptable. The costs of this screening method are estimated on fl. 9.0 million per year (fl. 45 per child screened, fl. 9,000 per child diagnosed with celiac disease). Combination with HLA-DQ typing is, at the moment, more expensive and more complicated from a logistical and ethical point of view. Yet, the possibility to select 30% of the children who have the genetic predisposition for celiac disease may enable the development of strategies to prevent celiac disease (e.g., inducing tolerance to gluten in predisposed children by early introduction of (minor amounts of) gluten during breastfeeding).

Future cost savings due to prevention of complications of celiac disease are considerable (direct medical costs estimated on fl. 19.1 million). The present value of the cost savings for children screened in a particular year is estimated on fl. 2.4 million per year, which suggests that a population-based screening programme for celiac disease is unlikely to be cost-saving based on the direct medical costs of future complications alone. However, short-term health gains appear to be considerable in approximately half of the children diagnosed with celiac disease after screening, yielding screening costs of fl. 18,000 per child that directly benefits from the screening and subsequent treatment.

At the moment, there is not yet enough evidence that mass screening for celiac disease in the general child population is fully justified on a routinely basis. However, we do recommend to start a national screening programme for unrecognised childhood celiac disease as a research project. By performing a screening study in (a large representative area of) the total Dutch population, it could be possible to obtain more information about (1) the usefulness of the IgA human recombinant antitissue transglutaminase antibody test for population-based screening, (2) organisational aspects (e.g., datamanagement, nationwide monitoring and tracking, capacity in CCHCCs, laboratories and hospitals), (3) the actual costs of screening, (4) the willingness of parents of asymptomatic children to accept treatment, (5) the dietary compliance of both symptomatic and asymptomatic children in the first years of treatment, and (6) the development of health complaints and bone derangements in asymptomatic patients. Continuous monitoring and evaluation of such a screening programme, analogous to that of the PKU/CH/AGS screening, will enable future evidence-based decisions on installment of a national screening programme for celiac disease.

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Appendices

Appendix A. Discounting

The procedure of discounting makes costs and effects comparable if they occur at different points in time. Costs that can be postponed to the future are valued less than those that have to be payed today. Likewise, if a treatment effect is gained today it is more valued than the same effect years ahead. It can be shown that the value (social or individual) of a treatment can been calculated using the formula:

$$P = \frac{A}{(1+i)^t}$$

where P is the discounted present value, A is the nominal future value, i is the discount rate and t is the time period to the year this cost appears.

The discounting reflects a general notion among individuals, and thus also in public policy and economic research has found the discount rate to be around 5 %, with wide variations. The choice of discount rate will often have important consequences for the cost results.

The table shows a selection of factors transforming the future value A to the present value P according to the formula above. In the case of a cost appearing repeatedly several years the formula gets more complex but follows the same pattern. For a comprehensive discussion of discounting see Drummond et al. Pp. 68-74.[19]

Table. Selected discounting factors

age (years)	3%	4%	5%
30	0.4120	0.3083	0.2314
50	0.2281	0.1407	0.0872
70	0.1263	0.0642	0.0329

An example: A fl. 1 million cost appears 50 years ahead. This cost has a present value of 0.0872 x 1,000,000 = fl. 87,200 with a discount rate of 5%, fl. 140,700 with 4% and fl. 228,100 with 6%.

Appendix B. Costs of osteoporosis and fractures

The direct medical costs of osteoporosis and associated fractures have been estimated in a specific report of osteoporosis in the Netherlands.[17] The authors used two approaches to come to a yearly cost of osteoporosis and fractures in the population aged 50 years and over. The results of both the global and detailed approach were comparable, and indicated a yearly cost between fl. 390 million and fl. 470 million. Based on the detailed approach, the table shows an overview of costs for osteoporosis and associated fractures. The overview includes cost estimates for the use of drugs in the treatment or prevention of osteoporosis (pharmacotherapy), and for the different types of care following fractures (hospitalisations, full care and day care in nursing homes, outpatient care, and home health care). For hospitalisations of non-hip fractures and home health care only maximum estimates could be provided. Excluding the latter estimates, we employed fl. 437.85 million as a conservative estimate of the annual direct medical costs of osteoporosis and associated fractures in the Netherlands.

Table. Detailed overview of costs for osteoporosis in the Netherlands in 1993 (fl. million)

	Estimated yearly cost
Pharmacotherapy	15.63
Hospitalisations hip fractures	294.80
Non-hospital inpatient care (full care)	81.10
Day care	3.66
Outpatient care	42.66
Total (excluding maximum estimates)	**437.85**
Hospitalisations non-hip fractures (max. estimate)	16.96
Home health care (max. estimate)	12.71
Total **(including maximum estimates)**	**467.52**

Source: Osteoporosis in the Netherands, de Laet et al. 1996[17]

Appendix C. Costs of screening with different assumptions

The table shows the costs of the serological screening scenario based on the basic assumptions used in this report (first column), as well as those based on changing three assumptions (second column):
- 85% (instead of 100%) of the children are screened, since about 10% of the children may not attend the CCHCC, and not all parents will consent to participate.
- unit price of fl. 15,- for tTGA-determination (instead of fl 21,-).
- 70% predictive value of a positive tTGA-test (instead of 55%).

Table. Estimated annual costs of serological screening with different assumptions

Cost component	**Basic assumptions**		**Changed assumptions**	
	n	**(NLG)**	**n**	**(NLG)**
tTGA-determination	200,000		170,000	
Information leaflet		200,000		170,000
Staff		1,894,000		1,609,900
Time loss parents		1,376,000		1,169,600
Lab costs		4,200,000		2,550,000
Referral to pediatrician	2,400		1,600	
Consultation		110,400		73,600
Time loss parents		66,000		44,000
Travel costs parents		14,400		9,600
Biopsy	1,800		1,200	
Biopsy		2,538,900		1,692,600
Time loss parents		278,550		185,700
Travel costs parents		26,550		17,750
Referral to GP	1,000		850	
Consultation		36,570		31,085
Time loss parents		20,630		17,535
Travel costs parents		900		765
Total direct medical costs		8,979,870		6,127,185
Total time loss/travel costs		1,783,030		1,444,901
Total costs		10,762,900		7,572,085

Appendix D. Value of loss of life (years)

The social cost of avoiding loss of life from illness could be compared with attempts to value loss of life in traffic accidents. In such calculations, the loss of one statistical life has been valued to a social cost of £1 million (about fl. 5 million, year 2000 prices).[75]

In many cases, a value is needed to estimate premature death (i.e., lost life years). For example, if a person dies of non-Hodgkin's lymphoma at the age of 60 instead of 80, we would say that the loss is 20 years. The value of lost-life years is also subject to the general economic principle of discounting (see Appendix A). This means that the value of losing 40 years is far more than double the loss of 20 years. The nominal value of lost life years, assuming a length of life of 80 years, can be calculated using the formula:

$$L = \sum_{y=1}^{80} \frac{C_y}{(1+i)^y}$$

where C_y is an annual value that in a consecutive discounted series of 80 years and a discount rate i=5.00% will sum to a value of L= fl. 5 million. Under these assumptions, the nominal value for one year (C_y) is about fl. 255,000. Each of the 20 lost life years (from 60 to 80 years of age) are then discounted to present value and then summed to a total value of all lost life years, yielding a present value of fl. 184,000. Thus, when assuming 20 lost life years for patients dying of non-Hodgkin's lymphoma, the present value would be fl. 184,000 for one person.

The value of very low birthweight babies who do not survive can be estimated by the value of a lost life (fl. 5 million). However, when assuming that a woman with celiac disease delivers a baby at a median age of 30 years, the present value would be fl. 1.2 million.

In sum, the present value of avoiding 12 deaths from non-Hodgkin's lymphoma and 2 deaths from very low birthweight would be fl. 4.6 million.