Early diagnosis of coeliac disease in the Preventive Youth Health Care Centres in the Netherlands: study protocol of a case finding study (GLUTENSCREEN)

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ABSTRACT

Introduction Coeliac disease (CD) occurs in 1% of the population, develops early in life and is severely underdiagnosed. Undiagnosed and untreated disease is associated with short-term and long-term complications. The current healthcare approach is unable to solve the underdiagnosis of CD and timely diagnosis and treatment is only achieved by active case finding. Aim: to perform a case finding project to detect CD children who visit the Youth Health Care Centres (YHCCs) in a well-described region in the Netherlands to evaluate whether it is feasible, cost-effective and well accepted by the population.

Methods/analysis Prospective intervention cohort study. Parents of all children aged 12 months and 4 years attending the YHCCs for a regular visit are asked whether their child has one or more CD-related symptoms from a standardised list. If so, they will be invited to participate in the case finding study. After informed consent, a point of care test (POCT) to assess CD-specific antibodies against tissue transglutaminase (TG2A) is performed onsite the YHCCs. If the POCT is positive, CD is highly suspected and the child will be referred to hospital for definitive diagnosis according to the Guideline Coeliac Disease of the European Society for Pediatric Gastroenterology, Hepatology and Nutrition guideline.

Main outcomes
1. Incidence rate of new CD diagnoses in the study region in comparison to the one in the same age diagnosed by standard of care in the rest of the Netherlands.
2. Feasibility and cost-effectiveness of active CD case finding at the YHCCs. All costs of active case finding, diagnostics and treatment of CD and the potential short-term and long-term consequences of the disease will be calculated for the setting with and without case finding.
3. Ethical acceptability: by questionnaires on parental and healthcare professionals’ satisfaction.

A statistical analysis plan was prepared and is published on the GLUTENSCREEN website (Statistical-Analysis-Plan-11-5-2021_def.pdf (glutenSCREEN.nl) and added as annex 1).

Ethics and dissemination The Medical Ethics Committee Leiden approved this study. If we prove that case finding at the YHCC is feasible, cost-effective and well accepted by the population, implementation is recommended.

Trial registration number NL63291.058.17.

INTRODUCTION

Coeliac disease (CD) is an immune-mediated systemic disorder elicited by the ingestion of gluten-containing cereals from the normal diet (among others, wheat, rye and barley) in genetically susceptible individuals. CD is characterised by a variable combination of gluten-dependent clinical manifestations, CD-specific antibodies, HLA-DQ2 or HLA-DQ8 haplotypes and enteropathy. 1 2 CD has a frequency of at least 1% in the general population, that is, 168 000 individuals and 33 600 children in the Netherlands. 3 6 It is the most common food intolerance in the Netherlands and, therefore, a significant public health problem. CD is frequently unrecognised, partially because of its variable clinical presentations and symptoms, ranging from malabsorption with chronic diarrhoea, poor growth in children and weight loss, to nonspecific...
signs and symptoms like chronic fatigue, osteoporosis/ reduced bone mineral density, iron-deficiency anaemia, anorexia, chronic abdominal pain, vomiting, flatulence, irritability, elevated liver enzymes or constipation. \(^1\) \(^7\) CD has a considerable health burden for society. In addition to the signs and symptoms, untreated disease is associated with long-term complications such as delayed puberty, neuropsychiatric disturbances, associated autoimmune disease, miscarriages, small-for-date-borns, osteoporosis and, rarely, malignancy. \(^1\) \(^8\) CD increases the overall mortality risk, reduces the quality of life and yields extensive negative economic consequences, thereby presenting a resource challenge for current and future health systems. \(^9\) \(^-\) \(^11\)

In 1999, our research group published that childhood CD in the Netherlands was severely underdiagnosed: for every child diagnosed with CD, there were seven who have unrecognised and, therefore, untreated disease. \(^1\) \(^2\) Data from the National Dutch Paediatric Surveillance Unit (DPSU) show 1107 new cases in 2010–2013 of clinically diagnosed CD in children 0–14 years. \(^1\) \(^3\) \(^4\) The percentage of children diagnosed with CD <2 years of age was 30%, and <4 years of age was 50%. Those were also the children with the most severe clinical presentations. \(^1\) \(^3\) \(^4\)

DPSU is a unique registry of the Dutch Society of Paediatrics, comprising of all Dutch paediatric practices. Under it, Dutch paediatricians are asked to report newly diagnosed cases of certain diseases (CD in our case). DPSU respondents have a 90% mean response rate. The incidence of 1.56/1000 live births in 2010–2013 does not correspond to the prevalence in the general population. \(^1\) \(^3\) \(^5\) This illustrates that the current standard healthcare is not able to solve the problem. Once diagnosed, the patient’s health status improves after treatment with a gluten-free diet (GFD), but prevention would be more beneficial to avoid disease development by primary prevention or delayed diagnosis (or no diagnosis) by secondary prevention. \(^7\) \(^1\) \(^6\)

Results from recent prospective studies have shown that primary prevention of CD by improving the timing of gluten introduction and/or the duration or maintenance of breastfeeding is not possible. \(^1\) \(^7\) \(^-\) \(^2\) \(^1\) \(^4\) For this reason, early diagnosis and treatment of CD represent the only way to (secondary) prevention. There are two approaches to achieve this: mass screening and case finding. The Medical Ethics Committee (METC-Leiden Den Haag Delft, METC-LDD) considered the current evidence insufficient to assess the balance of benefits and harms of screening for CD in asymptomatic children (mass screening). \(^2\) \(^2\) \(^5\) Consequently, we propose an active case finding project in symptomatic children in a Youth Health Care Centre (YHCC) region in the Netherlands to achieve secondary prevention of the disease. Active case finding refers to liberal diagnostic testing of patients with CD-associated symptoms. In the general adult population, this approach has led to the early diagnosis of a large number of patients, resulting in significantly health improvement after treatment, good compliance with the GFD and good CD-related quality of life. \(^2\) \(^4\) \(^5\)

In the Netherlands, more than 95% of all children 0 months and 4 years visit the YHCCs. \(^2\) \(^6\) The goal of YHC is to promote and secure the health and safety of all children 0–18 years. \(^2\) \(^7\) YHC aims at primary and secondary prevention of diseases in order to promote healthy growth and development. Secondary prevention (early diagnosis and treatment) of CD, therefore, fits within the goals of YHC. The validated, rapid point of care test (POCT) to determine CD-specific antibodies represent a reliable, cheap and easy-to-use instrument for CD case finding in children. \(^2\) \(^8\)

Therefore, early detection of CD by case finding in the YHCCs offers a ‘window of opportunity’ to identify CD as soon as possible preventing more severe symptoms and complications of the disease.

**Aims and hypothesis**

The aim of the present study is to perform a novel case finding project to detect CD in 12 months to 4 years old children who visit the YHCCs in a well-described region in the Netherlands, to evaluate whether it is feasible, cost-effective and well accepted by the population. We hypothesise that GLUTENSCREEN is feasible, cost-effective and well acceptable by the general population. To achieve this, GLUTENSCREEN will compare the results of the case finding strategy to the outcome of current healthcare in the diagnosis of CD in children in the rest of the country.

**METHODS AND ANALYSIS**

**Study design**

The study is a prospective intervention cohort study. The project started on 4 February 2019 and will end on 1 February 2023 (with interruption of 5 months due to the COVID-19 pandemic). All parents of children aged 12 months and 4 years attending scheduled visits to the YHCCs in the region Midden and Zuid Kennemerland, to be further called ‘Kennemerland’, will be informed. At the YHCC, a standardised questionnaire on CD-related symptoms will be checked (annex 2). Symptoms are reported by the parents. Weight and growth are controlled at the YHCC. If one or more CD-associated symptoms (including growth restrictions) are present, the child is eligible for the study. The CD-related symptoms (see annex 2) are based on the recommendations of CD testing (taking into account the absence of previous laboratory or other investigations and the age of the project population) in symptomatic children and adolescents in the Guideline Coeliac Disease of the European Society for Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN). \(^1\)

**Patient and public involvement statement**

Dutch Coeliac Patients Society is involved in the design, reporting and dissemination plans of this research.
including the management of the website of the project www.glutenscreen.nl.

Control population
A national control group is based on the data reported by DPSU. Dutch paediatricians are asked by the DPSU to report newly diagnosed cases of certain diseases (CD in our case) monthly during the time of this case finding project. The CD cases are clinically diagnosed by the paediatricians to the current standard of care. DPSU respondents have a 90% mean response rate. The cases of clinically diagnosed CD in the study region will be identified by the data of the YHCC.

Inclusion and exclusion criteria
Inclusion criteria are (1) 12 months to 4 years of age, (2) following a gluten-containing diet, (3) one or more CD-associated symptoms (annex 2), (4) parents have a sufficient knowledge of Dutch language, (5) informed consent.

Exclusion criteria: (1) diagnosed with CD.

Recruitment and procedure
Eligible children will be identified by the YHCC administration. During 2.5 years, the parents/legal guardians (from this point on called ‘parents’) will receive an advance invitation from the YHCC Kennemerland with information about the study. During the regularly scheduled visit at the YHCC, the nurse or the doctor will check the symptom list (annex 2); if one or more CD-associated symptoms are present, the nurse/doctor will give the parents the information letter and informed consent form and, after informed consent is given, she/he will make a new appointment to perform the POCT. The POCT for TG2A will be performed. The symptom list and informed consent form will be stored in a separate file in the child’s electronic record.

Intervention
After informed consent, a validated POCT to determine CD-specific antibodies (TG2A, Celiac Quick Test; BioHit Oyj, Finland), which is also suitable for IgA-deficient patients, will be performed. It requires one drop of fresh blood, obtained by finger prick. The result (positive/negative) should be interpreted after 10 min. If the result is negative (no tissue transglutaminase (TG2A)), the child is considered not to have CD and the procedure is finished for this child. If the POCT is positive, the child will be referred to the paediatric gastroenterologist for further investigation for CD diagnosis at the Outpatient Clinic of the Department of Paediatric Gastroenterology of the Leiden University Medical Center (LUMC) in the following 3 weeks. In the LUMC, CD will be diagnosed according to the ESPGHAN guidelines.2 A second visit (face-to-face or by telephone, depending on parental preference) will be scheduled 14 days later to discuss results. There are three possible outcomes: 1. CD ruled out: No further follow-up is needed.

2. CD likely, but unproven; diagnostic duodenal biopsies are advised.
3. CD is diagnosed. The patient/parents will be counselled on treatment and follow-up.

If an endoscopy to obtain duodenal biopsies under general anaesthesia is advised, the parents will receive written information on the procedure, as all other parents do in the outpatient clinic when this procedure is advised. Parents have to give oral informed consent for this procedure, and this will be noted in the patient’s medical record. The procedure will be carried out per usual LUMC regulations. Biopsies will only be performed when medically indicated for the child and not just for purpose of scientific research.

Training and protocol adherence
To perform the POCT, the YHCC healthcare professionals followed a training provided by the employees of BioHit and according to the manufacturer’s instructions. To prevent protocol drifting, they receive monthly supervision by a senior clinical physician. All POCT results are photographed and stored in the electronic patient’s file. Monthly, the researchers and the senior clinical physician of the YHCC evaluate the organisation, procedure and results.

Outcome measures
The main study outcomes are:

1. The incidence rate of new CD diagnoses in the study region of Kennemerland in comparison to the one in the same age category diagnosed according to the standard of care in the rest of the Netherlands as reported to the DPSU.
2. Cost-effectiveness of active case finding of CD in the YHCCs compared with standard care.
3. Ethical acceptability: by questionnaires on parental satisfaction and healthcare professionals.

Data collection
The result of the POCT will be noticed in the medical file as well as the diagnosis after further investigation. Diagnostic tools and consultations after a positive POCT will be noticed in a database and in the medical file of the child.

Parents of children who visit the YHCC and/or participate in GLUTENSCREEN will be asked to fill in standardised questionnaires on their opinion regarding the actual case finding and on mass screening for CD. We will ask the opinion of (1) parents of asymptomatic children (by definition excluded for participation in case finding), (2) parents who decline participation in the study, (3) parents participating in the case finding and (4) parents of children with suspected CD by the case finding procedure who will be referred to the hospital for definitive CD diagnosis.

Also the healthcare professionals in the YHCCs with various tasks within GLUTENSCREEN will also be asked to give their opinion about the case-finding.
Costs of active case finding, diagnostic and treatment of CD will be compared with the costs of diagnostics and treatment by standard of care. The costs of active case finding are the costs of discussing the symptom list, measurement of TG2A by POCT and the diagnostic costs after a positive test (repeated TG2A measurement, endomysium antibodies, human leucocyte antigen (HLA)-tying, biopsy, paediatric consultation etc). These costs will be measured in the prospective intervention cohort study. Cost of measurement of TG2A levels includes time needed from YHC professionals and cost of test equipment and materials. Resource use after a positive test will be measured by means of a case record form. Information on diagnostic procedures of clinically diagnosed CD will be collected by the DPSU and the Dutch Coeliac Society (Nederlandse Coeliakie Vereniging (NCV)), supplemented with parent questionnaires on healthcare use outside the hospital. Healthcare use will be valued according to the Dutch guideline for costing research.

In addition, an estimate for the costs of long-term consequences of undiagnosed CD as delayed puberty, neuropsychiatric disturbances, dental enamel hypoplasia, associated autoimmune diseases, miscarriages, small for date-births, osteoporosis and (rarely) malignancy will be made based on the literature. The probability of long-term consequences in a situation with and without case finding will be based on the literature and expert opinion. Together, this will enable a comparison between lifetime cost in a situation with and without case finding.

Furthermore, by means of a questionnaire to recently diagnosed patients, the quality of life before and after the start of GFD will be assessed. Quality of life for long-term consequences of undiagnosed CD will be based on the literature. In a cost-effectiveness analysis, the lifetime differences in quality of life in a situation with and without case finding will be compared with the difference in cost.

Withdrawal

Subjects can leave the study at any time for any reason if they wish to do so without any consequences. The investigator can decide to withdraw a subject from the study for urgent medical reasons. The parents of children who withdraw are asked to fill in the questionnaire on acceptability.

Sample size

We assume that in the Dutch population outside the case finding project, the incidence of children 1–4 years old with a diagnosis of CD equals 0.62/1000 children years. With 2.5 years inclusion period, we expected 5434 children taking the POCT would give high power (about 95%) to detect an at least two times higher incidence rate in the study region (alpha 5%). We expected 60% of the children to be symptomatic, and 60% participation of those symptomatic children in the POCT-ing, so 15 100 children would need to be requested for participation, in order to obtain 5434 children available for case finding using a rapid POCT. Since the population in the YHCCs in the Kennemerland region is approximately 12 000 children/year with additional 4000 added per year, and 2.5 years of study duration was considered sufficient to achieve sufficient sample size. When in March 2020, the study had to be interrupted for 5 months due to the COVID-19 pandemic, the sample size calculation was re-evaluated based on the results up to that moment, including the number of cases found in the study region in the first year of the study. Based on this evaluation, it was decided that the original inclusion period of 2.5 years could be retained.

Statistical analyses

For the primary analysis, the incidence rate in the case finding population will be calculated along with a 95% CI and will be compared with the incidence rate in the Netherlands, obtained from the DPSU, in the same period, assuming the latter has no sampling variability (so using the incidence rate in the rest of the Netherlands as a fixed reference value). All costs of active case finding, diagnostics and treatment of CD and the potential short-term consequences of the disease will be calculated for the setting with and for the cost-effectiveness without active case finding. Healthcare use will be valued according to the Dutch guideline for costing research. For the acceptability descriptive and univariate logistic regression, analyses will be performed comparing the answers from the different groups. Also, univariable logistic regression analysis of negative feelings and POCT-result in relation to acceptability will also be done.

Ethics approval

The study is approved by the METC of the LUMC. All study data will be handled confidentially and coded with a unique study number. Only the research team will have access to the data. A data management plan is available.

DISCUSSION

Several studies have shown that an active case finding strategy in the primary care setting is an effective means to improve the (early) diagnostic rate of CD and to achieve secondary prevention.

National guidelines on the diagnosis and treatment of CD published in 2008 recommend testing for CD in patients with a wide spectrum of intestinal and extra intestinal manifestations, in asymptomatic family members of CD cases and in groups with related conditions. This approach, together with the availability of reliable CD antibody tests, has led to a rise in the incidence of diagnosed CD in Dutch children from 1.21/1000 live births in 2000 to 1.56/1000 live births in 2010–2013. Nevertheless, the increased incidence rate does not closely correspond to its frequency in the general population. In the Generation-R project, a population-based prospective cohort study, the prevalence of CD at 6 years of age
was 1.5%. Due to the shift in CD presenting symptoms towards a milder form, the delay from first symptoms to CD diagnosis has been reported to be unacceptably long, at between 5 and 10 years for many persons, and so the need for earlier diagnosis has been advocated. Early diagnosis is expected to reduce serious clinical CD. Data from the DPSU show that 50% of the 1107 new cases of clinically diagnosed CD in children aged 0–14 years between January 2010 and December 2013 were <4 years. These young children had the most severe symptoms of CD, including chronic diarrhoea and weight loss (71.0%) or wasting/failure to thrive (65.9%). Therefore, with active case finding, we aim to prevent the most serious manifestations of childhood CD.

Our study has several strengths: first, we propose an innovative strategy for secondary prevention by early detection of CD in the general population in the Netherlands. Since the majority of the children aged 1–4 years visit the YHCC, the study will provide insight into the incidence of childhood CD in symptomatic children in the Netherlands. Second, the actual health costs of the diagnosis of childhood CD and the cost-effectiveness of active case finding in the Netherlands have never been prospectively investigated. Third, this study will provide important information about the acceptability of the general Dutch population concerning active case finding and in addition about the willingness of parents of asymptomatic children to participate in a mass screening project on CD.

It would also have been interesting to explore the possibility of HLA determination at the YHCCs. Since more than 95% of patients with CD carry these HLA haplotypes, their presence is valuable in identifying the population that may develop CD. In the Netherlands, about 40% of the general population is HLA-DQ2 or DQ8 positive, and the presence of these haplotypes is, thus, not discriminative for the disease. On the other hand, repeated CD testing will be unnecessary in HLA-DQ2/DQ8-negative individuals. However, HLA-DQ typing currently present important drawbacks for it to be used outside the hospital. HLA typing requires DNA preparation, which takes (some) time. Material for DNA extraction can be obtained from whole blood (minimum quantity 4–5 mL) or from other cells, such as cheek mucosa. Venepunctures are not feasible at YHCCs. Obtaining cheek cells by smoothly brushing the buccal mucosa is a possibility, but the necessary mechanisms to store and transport the material pose logistical and economic challenges. The costs of transport, DNA extraction, HLA typing and distribution of test results are likely to increase the costs of the active case-finding.

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Contributors MLM designed and supervised the trial. MLM wrote the grant proposals and helped in designing the trial. CM-B drafted this paper, which was edited and modified by MLM. LS is responsible for supervision of the healthcare professionals at the YHCCs. The healthcare professionals were trained according to the manufacturer’s protocol by employees of Biohit. All authors read and approved the final manuscript.

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