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Original article

Dietary and symptom assessment in adults with self-reported non-coeliac gluten sensitivity

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SUMMARY

Background & aims: The mechanisms behind non-coeliac gluten sensitivity (NCGS) are not fully understood although clinical symptoms have shown to subside after wheat withdrawal. Self-prescription of a gluten-free diet (GFD) without medical supervision is common in NCGS subjects, resulting in dietary restrictions that can cause macro- and micronutrient deficiencies. The primary aim was to describe dietary intake, including FODMAP, in subjects with self-reported gluten sensitivity on GFD in whom coeliac disease (CD) and wheat allergy were excluded. Secondary, clinical symptoms and health-related quality of life (HR-QoL) were examined.

Methods: Baseline characteristics were obtained from 65 adults with self-reported NCGS on GFD recruited to a randomised placebo-controlled challenge trial at Oslo University Hospital. Dietary intake was obtained by a seven-day food record and symptoms recorded by questionnaires.

Results: Mean proportions of energy were 43 E% from fat, 40 E% from carbohydrate and 17 E% from protein. Intakes of vitamin D, folic acid, calcium, iodine and iron were lower than recommended, mean (SD) 7.3 (5.8) μg, 235 (105) μg, 695 (309) mg, 81 (52) μg and 9.6 (7.5) mg, respectively. Mean (SD) intake of FODMAP was 11.6 g (8.7). Gastrointestinal symptoms as scored by 100 mm visual analogue scale (VAS) were all below 15 mm of which wind and bloating were the most expressed. Tiredness, concentration difficulties, fatigue and muscle/joint pain were scored highest among extra-intestinal symptoms. Gastrointestinal symptoms as scored by gastrointestinal symptom rating scale – irritable bowel syndrome version (GSRS-IBS) were correlated with mild depression ($r = 0.43$) and inversely correlated with five sub-domains of HR-QoL ($-0.29 < r < -0.26$).

Conclusion: Subjects with self-reported NCGS on GFD had high proportion of energy from fat and sub-optimal intakes of vitamin D, folic acid, calcium, iodine and iron. Despite GFD and moderate intake of FODMAP, the subjects reported various gastro- and extra-intestinal symptoms and reduced HR-QoL. The findings highlight the importance of dietary education and nutritional follow-up of subjects on GFD.

1. Introduction

Non-coeliac gluten sensitivity (NCGS) is defined as a condition of gastrointestinal and extra-intestinal symptoms that improve as response to gluten-free diet (GFD) and where coeliac disease (CD) and wheat allergy are ruled out [1]. There are no strict, objective markers for the condition and prevalence from 0.6% to 6% have been reported [2,3]. The symptoms overlap with other

Abbreviations: BDI-II, Beck depression inventory version 2; CD, coeliac disease; FODMAP, fermentable oligo-, di-, monosaccharides and polyols; GFD, gluten-free diet; GSRS-IBS, gastrointestinal symptom rating scale irritable bowel syndrome version; HR-QoL, health-related quality of life; IBS, irritable bowel syndrome; NCGS, non-coeliac gluten sensitivity; SF-36, short form-36; VAS, visual analogue scale.

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conditions, mainly irritable bowel syndrome (IBS) and food hypersensitivities [4]. The pathogenesis of NCGS is not understood and the causal components of wheat, rye and barley, which are removed in a GFD, are not identified. Non-gluten proteins in wheat, such as amylase trypsin inhibitors and lectins, are suggested as activators of the innate immune system [5]. Further, fermentable oligo-, di-, monosaccharides and polyols (FODMAPs), in particular fructans that are found in wheat, rye and barley, may also play a role in symptom induction [6]. Despite the unclarified pathogenesis the condition is still called non-coeliac gluten or wheat sensitivity.

The diagnostic criteria of NCGS suggested in 2015 include elimination of CD and wheat allergy, symptom relief on a GFD and symptom recurrence triggered by a gluten re-challenge, preferably blinded [7]. If the condition is confirmed the subject is advised to follow a GFD. The cereals are replaced by naturally gluten-free cereals such as rice, corn, buckwheat and millet. Otherwise, subjects on GFD are recommended to follow the general dietary guidelines by the health authorities by using naturally gluten free cereals and non-processed food (meat, fish, poultry, egg, milk, legumes, vegetables and fruit) to maintain optimal health and prevent non-communicable diseases [8].

In NCGS, an important role of the dietitian is to complete a nutritional assessment, educate on GFD, and evaluate diet adherence. Balanced meal planning, hidden gluten sources, label-reading and additional food allergies or intolerances are addressed [9]. However, most individuals with suspected NCGS have already started on a GFD without seeing a dietitian [10]. Cereals, especially wheat, are an important source of energy, fibre and nutrients in the Nordic diet [11]. Hence, excluding cereals increases the risk of an unbalanced diet. The GFD of CD patients has a high content of fat and low content of protein and fibre [12]. GFD in NCGS subjects is less studied. Unbalanced diet and low dietary calcium intake have been described as well as weight loss, anemia and reduced bone mineral density [13,14]. Whether the nutrient deficiency is a consequence of malabsorption or an unbalanced diet is unclear. Certainly, the vast majority does not see a dietitian before they exclude dietary gluten [10]. The prevalence of micronutrient deficiencies in NCGS is unknown. Previous studies have been conducted with non-standardised methods in small, highly selected patient groups [15] and with study samples consisting of subjects with inadequate exclusion of CD [15] or subjects on a gluten-containing diet [16,17].

Baseline data collected in a randomised controlled trial (RCT) provided us with the unique opportunity to describe dietary intake, including FODMAP, in subjects with self-reported NCGS, adequately excluded CD and at least six months adherence to a GFD [18]. In addition, prior to commencing the challenge study, the clinical symptoms and health-related quality of life (HR-QoL) were examined [18].

2. Material and methods

This is a cross-sectional analysis of baseline data collected in a randomised, double-blind placebo-controlled crossover trial at Oslo University Hospital, Rikshospitalet from October 2014 to March 2016. The trial has been described in detail [18]. Subjects were mainly recruited by advertisements on the hospital's web page, at the University of Oslo, at the web page of the Norwegian Coeliac Association and their social media. Subjects were to a lesser extent recruited by referrals from general practitioners and other hospitals in the area. The advertisement sought adults who believed they were gluten sensitive and willing to participate in a clinical trial that involved gastroscopy, blood withdrawal, faecal sampling and gluten re-challenge.

2.1. Study sample

Eligible subjects were adults aged 18–80 years who self-instituted a GFD. They were required strict adherence for at least six months. They were asked on a re-call basis for relief of gastrointestinal and extra intestinal symptoms. CD was considered adequately excluded if the duodenal biopsy was normal while on gluten-containing diet or if the individual was negative for both human leukocyte antigen HLA-DQ2 and HLA-DQ8 (human leukocyte antigen). Wheat allergy was considered excluded if serology showed negative wheat specific IgE levels. Exclusion criteria were pregnancy or lactation, use of immunosuppressive agents, inflammatory bowel disease or other comorbidity, substantial infection, severe reactions to nuts or sesame seeds and people living more than a two hours' drive from the recruitment center. In the RCT, three of the 68 randomised subjects were excluded due to protocol violation [18]. The rest (n = 65) were included in the current study. They consisted of 59 subjects that had participated in the RCT and six that were drop outs (Supplemental Fig. 1).

2.2. Data collection

The baseline screening visit included blood tests, anthropometrics and a structural interview. Instructions were given for the food and symptom records.

Body mass index (BMI) was categorised as normal (18.5–24.9 kg/m^2), overweight (25–29.9 kg/m^2) and obese (>30 kg/m^2) [19]. Blood test included standard biochemical, nutritional and hormonal parameters. Hospital laboratory standards were used as reference. Information on CD investigation and co-morbidities has been described elsewhere [18].

GFD adherence was self-reported and assessed by trained dietitians, evaluated by a standardised locally-developed questionnaire based on the Coeliac Diet Adherence Test and finally confirmed by the seven-day food record [20].

A seven-day food record was used to obtain nutritional intake (supplements were not included). Nutritional intake was compared to Nordic Nutrition Recommendations [8]. A picture book containing photographs of food items was used for defining portion sizes [24]. FODMAP intake was compared to a sample of Australian subjects (n = 37) with self-reported gluten sensitivity on GFD and on low FODMAP diet, to our knowledge the most comparable sample that is published [21].

Baseline recordings also included gastrointestinal symptoms assessed by gastrointestinal symptom rating scale – irritable bowel syndrome version (GSRS-IBS, scores 13–91) and a 100 mm visual analogue scale (VAS) used for seven day recording of pain, bloating, passage of wind, nausea, stool dissatisfaction and overall gastrointestinal symptoms [22]. Symptoms of depression were assessed by the Beck Depression Inventory, version 2 (BDI-II), graded according to Siqveland et al. as mild (scores 14–19), moderate (scores 20–28) and severe (scores 29–63) and compared to the general Norwegian population [23,24]. Fatigue was measured using VAS for the six complaints within the exhaustion subscale of the questionnaire Giessen Subjective Complaint List questionnaire; weakness, sleepiness, exhaustion, tiredness, dizziness and fatigue [25]. VAS was also used to record muscle and joint pain, concentration difficulties, numbness and tingling in hands and feet. HR-QoL was assessed by the Short Form-36 (SF-36), a 36-item questionnaire organised in eight subdimensions; physical functioning, role physical, bodily pain, general health, vitality, social functioning, role emotional and mental health (each scored 0–100, higher score denotes better quality of life) [26]. Jacobsen et al. was used for reference values for the Norwegian population [27]. All recordings were done

retrospectively, except the seven-day VAS recording of gastrointestinal symptoms and the seven-day food record.

Forty of the subjects voluntarily underwent a three-day open wheat challenge in the clinical routine after the RCT where symptoms were assessed by GSRS-IBS. The challenge is described in details elsewhere [43].

2.3. Statistical analysis

Estimation of sample size has been described previously [18]. Data are presented as means (standard deviations, SDs) or medians (inter quartile ranges, IQRs). Associations between GSRS-IBS and depression and HR-QoL were estimated by Spearman correlation coefficient (r). The analyses were carried out using IBM SPSS, version 23.0 (SPSS Inc, Chicago IL) and a p-value of <0.05 was considered statistically significant.

2.4. Ethics

The study was approved by the Norwegian Regional Committee of Medical and Health Research Ethics on the 16th September 2014 with the identification 2013/1237 REC South East A. The study is registered in ClinicalTrials.gov no: NCT02464150. Written informed consent was obtained from all subjects.

3. Results

Subject characteristics are given in Table 1. The 65 subjects (11 referrals, 54 advertisement responders) had a mean age of 44 (range 21–72) years and 57 (88%) were female. Mean body mass index was 24.7 (range 17.8–34.5) kg/m^2, and 31 (48%) were classified as normal (Table 1).

Table 1
Subject characteristics (n = 65).

Female/male, n	57/8
Age (years), mean (SD)	44 (12)
BMI (kg/m^2), mean (SD)	24.7 (4.2)
Underweight, n (%)	3 (5)
Normal, n (%)	31 (48)
Overweight, n (%)	23 (35)
Obese, n (%)	8 (12)
Months on GFD[b], median (IQR)	20 (11, 51)
GFD information	
Advised by a medical doctor, n (%)	22 (34)
Advised by a dietitian, n (%)	2 (3)
Self-educated, n (%)[a]	40 (63)
Gluten adherence past six months, n (%)	
All the time, n (%)	52 (81)
Most of the time, n (%)	12 (19)
Consumption of gluten containing foods (n = 64), n (%)	
Regular bread	
Yes, n (%)	0 (0)
Occasionally, n (%)	1 (2)
No, n (%)	63 (98)
Ordinary oats	
Yes, n (%)	3 (5)
Occasionally, n (%)	8 (13)
No, n (%)	53 (83)
Spelt flour	
Yes, n (%)	0 (0)
Occasionally, n (%)	2 (3)
No, n (%)	62 (97)
Registered gluten intake in seven-day food record, n (%)	
Gluten-containing foods, n (%)	2 (3)
Ordinary oats, n (%)	4 (6)

SD, standard deviation, BMI, body mass index, GFD, gluten-free diet, IQR, interquartile range.
[a] Included information obtained from family (n = 9), friends (n = 6), internet (n = 11) and other sources (n = 14).
[b] n = 64.

Adherence to a GFD "all the time" for the past six months was reported by 81%. Three subjects included ordinary oats in their habitual GFD, eight subjects had occasional intake of oats and two had occasional intake of spelt flour. The seven-day food records revealed one subject with accidental transgression by intake of rye crisp bread and one subject that ate barley porridge on two occasions. They were otherwise diet adherent.

Table 2 shows energy and nutrient intake. Three subjects had more than 60% energy from fat, 39 had >40% and none had <25% from fat. Intakes of vitamin D, calcium, iodine and iron were lower than recommended (Table 2).

Gluten-free bread and cereals counted for 19% of total energy intake and 34% of the carbohydrates (Table 3). The second highest contributor of energy was meat (14%) which counted for 34% of the protein intake. Sugar, cakes and snacks counted for 11% of total energy, 16% of total carbohydrate and 59% of the sugar intake, while dairy food counted for 9% of total energy and 13% of the fat intake.

Micronutrient deficiencies by blood values were not found according to the Oslo University Hospital reference values (Table 4).

Fig. 1 shows mean intake of total and subgroups of FODMAPs in the current sample as compared to mean FODMAP intake of Australian subjects with self-reported NCGS on GFD (Australian NCGS) (n = 37) [21]. Mean total intake of FODMAPs was 12 g and mean lactose intake 7 g in our study, and lower compared to 19 g and 14 g, respectively, in the Australian NCGS subjects on GFD (Fig. 1). Mean total FODMAP intake was similar in our study and in Australian NCGS subjects on a low FODMAP diet (n = 37).

Mean (SD) gastrointestinal symptoms score assessed by GSRS-IBS was 29.6 (11.5). Median VAS scores were <15 mm for all gastrointestinal symptoms (Fig. 2A). Wind had highest median value followed by bloating and stool dissatisfaction (Fig. 2A). Tiredness was the most expressed extra-intestinal symptom with median VAS score of 43 mm (Fig. 2B).

The prevalence of mild depressive symptoms measured by BDI-II was 19% in our sample as compared to 11% of the general Norwegian population (Fig. 3A). Mean scores of all sub-dimensions of SF-36 were lower in NCGS subjects as compared to estimates in normative data from the general Norwegian population except for social functioning (Fig. 3B). Largest differences were found for role physical (60 vs 80), bodily pain (61 vs 69), general health (61 vs 72), vitality (48 vs 56) and role emotional (74 vs 87) (Fig. 3B).

We found significant positive correlation between gastrointestinal symptoms as scored by GSRS-IBS and depression scored by BDI-II ($r = 0.43$, $p = 0.003$). GSRS-IBS was weakly negatively correlated with all SF-36 sub-dimensions ($-0.29 \leq r \leq -0.10$), significantly for role physical, bodily pain, vitality and social functioning ($-0.29 \leq r \leq -0.26$, $p \leq 0.04$).

The results of the three-day open wheat challenge in the clinical routine after the RCT showed that mean (SD) overall GSRS-IBS before challenge was 18.6 (5.1) and 38.3 (12.0) after challenge. 35 of 40 had a change in symptoms >30% (n = 40).

4. Discussion

In this cross-sectional study of subjects with self-reported NCGS on GFD participating in an RCT, BMI was mainly within the normal and obese category. The subjects had higher total and saturated fat intake and lower carbohydrate and dietary fiber intake than recommended by the Norwegian health authorities [28]. Intakes of micronutrients were lower than recommended for vitamin D, folic acid, calcium, iodine and iron, but blood values did not show nutrient deficiencies. Persistent symptoms were reported despite GFD adherence and moderate to low intake of

Table 2
Nutrient intake in individuals with self-reported gluten sensitivity (n = 65).

	Mean (SD)			NNR 2012[a]
	Total	Women (n = 57)	Men (n = 8)	
Energy (MJ)	7.7 (2.0)	7.4 (1.5)	10 (3)	
Protein (E%)	17 (4)	178 (4)	16 (2)	10–20
Fat (E%)	43 (9)	43 (9)	45 (11)	25–40
Saturated fat (E%)	16 (7)	15 (5)	20 (14)	<10
Mono unsaturated fat (E%)	15 (5)	15 (5)	14 (5)	10–20
Poly unsaturated fat (E%)	6.6 (2.7)	6.6 (2.8)	6.0 (2.6)	5–10
Carbohydrates (E%)	40 (10)	40 (10)	39 (11)	45–50
Added sugar (E%)	5.8 (4.1)	5.7 (4.1)	6.3 (4.8)	<10
Dietary fibre (g)	21 (9)	21 (8)	20 (11)	25–35
Alcohol (E%)	3.2 (3.0)	2.2 (3.0)	2.1 (3.0)	<10
Vitamin A (RE)	717 (513)	724 (542)	669 (231)	700/900
Vitamin D (μg)	7.3 (5.8)	7.1 (5.4)	8.2 (8.5)	10
Vitamin E (α-TE/d)	14 (7)	14 (7)	16 (7)	8/10
Thiamine (mg)	1.3 (0.5)	1.2 (0.3)	1.8 (1.0)	1.1/1.3
Riboflavin (mg)	1.6 (0.5)	1.6 (0.5)	1.6 (0.3)	1.2/1.5
Vitamin B6 (mg)	1.7 (0.7)	1.7 (0.5)	2.3 (1.3)	1.3/1.5
Vitamin B12 (μg)	5.4 (2.5)	5.2 (1.9)	6.9 (5.2)	2
Folic acid (μg)	235 (105)	227 (73)	291 (234)	400
Vitamin C (mg)	100 (62)	96 (62)	12 (126)	75
Calcium (mg)	695 (311)	695 (309)	698 (348)	800
Iodine (μg)	81 (52)	77 (49)	106 (68)	150
Iron (mg)	9.6 (7.5)	8.7 (2.7)	16.0 (20.2)	15/9
Magnesium (mg)	308 (167)	289 (101)	438 (389)	280/350
Sodium (g)	2.1 (0.8)	2.1 (0.8)	2.2 (0.8)	2.3
Potassium (g)	3.2 (1.1)	3.1 (0.9)	3.6 (2.1)	3.1/3.3

SD, standard deviation, RE, retinol equivalents, TE, tocopherol equivalents.
[a] Nordic Nutrition Recommendations 2012, women/men 31–60 years.

Table 3
Dietary sources of macronutrients as percentage of total intake per person per day (n = 65).

	Total intake (g)	Energy	Protein	Fat	Carbohydrate	Fiber	Sugar
	Mean (SD)	%					
Bread and cereals (GF)	145 (104)	19	10	7	34	31	11
Potatoes	40 (44)	2	1	0	4	4	1
Vegetables and fruit	360 (206)	10	6	5	15	41	4
Juice	87 (135)	2	1	0	4	1	0
Meat	130 (137)	14	34	17	1	0	0
Fish	48 (39)	5	12	6	0	1	2
Egg	41 (41)	3	6	6	0	0	0
Dairy	220 (234)	9	9	13	6	4	6
Cheese	36 (37)	5	9	9	1	0	0
Fat, butter and oils	23 (21)	8	1	18	0	0	2
Sugar, cakes and snacks	73 (57)	11	4	11	16	8	59
Nuts and seeds	17 (21)	5	4	9	1	9	0
Sodas, sugar	49 (120)	1	0	0	2	0	11
Other[a]	47 (64)	2	3	1	2	3	52

GF, gluten-free.
[a] Instant tomato and cauliflower soup, dressing, ketchup, mustard, soy sauce, stew.

Table 4
Micronutrient blood values and laboratory reference values (n = 65).

	Mean (SD)			References[a]	
	Total	Women (n = 57)	Men (n = 8)		
Haemoglobin	14.0 (1.0)	13.8 (0.9)	15.2 (1.2)	12/13.5	g/100 ml[b]
Ferritin	89 (60)	78.8 (2.9)	164 (87)	10–170/30–400	μg/L[b]
Iron	17.6 (5.8)	17.5 (6.0)	18.1 (4.1)	9–34	μmol/L
Transferrin	2.6 (0.4)	2.6 (0.3)	2.5 (0.4)	2.0–3.3	g/L
Vitamin B_{12}[c]	455 (222)	467 (214)	374 (268)	150–650	pmol/L
Folic acid	26 (9)	25 (9)	30 (13)	≥10	nmol
25-OH vitamin D	68 (19)	69 (19)	56 (12)	37–131	nmol/L

[a] Oslo University Hospital reference values.
[b] Women/men.
[c] n = 63.

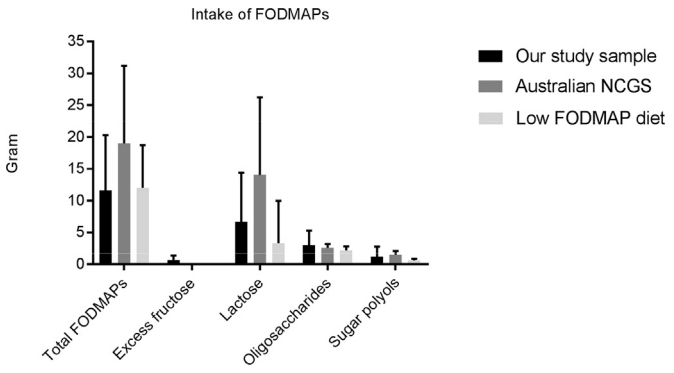

Fig. 1. Mean daily intake (g) of FODMAPs in our study sample (n = 64) as compared to FODMAP intake of Australian subjects with self-reported non-coeliac gluten sensitivity (NCGS) on gluten-free diet and on low FODMAP diet (n = 37) [21].

FODMAP. Extra-intestinal symptoms, in particular tiredness and mild depression, were observed. HR-QoL was also lower than recent estimates from the general Norwegian population. Gastrointestinal symptoms as scored by GSRS-IBS were significantly positively correlated with mild depression and weakly inversely correlated with HR-QoL.

BMI was within the normal range in 48% of the subjects, and except for three subjects that were underweight, the rest was classified as overweight or obese, which is in accordance with a Norwegian health survey in adults [29]. There was an imbalance in intake of macronutrients shown by the high proportion of energy from fat and lower intake of dietary fibre as compared to the national recommendations. Gluten-free replacement products tend to be high in fat and sugar and might partly explain the finding [12]. The finding is in accordance with earlier studies in patients with CD on GFD [30,31], but in contrast to Zingone et al. who reported on a lower fat intake among NCGS subjects on GFD as compared to controls [13]. Their subjects had also adhered to a GFD for at least six months, but different tools were used for assessing dietary intake. Further, Zingone et al. [13] reported a mean energy intake of 1030 kcal/day which indicates substantial under-reporting of food intake according to energy intakes of 1911 kcal/day in women and 2603 kcal/day in men in the last national dietary survey in Norway [24].

We found sub-optimal intakes of vitamin D, folic acid, calcium, iodine and iron, which may put patients at risk of nutrient deficiencies. This finding emphasizes the need for proper dietetic guidance before starting GFD. The restricted intake of milk and other dairy products is reflected by the low intake of calcium and iodine. Exclusion of dairy products is consistent with other findings [15] and other food avoidances and intolerances are commonly reported in this group [13,15,16]. A low intake of calcium was also found by Carroccio et al. [14]. Self-education of the GFD, other food avoidances and macronutrient imbalance might put subjects with self-reported NCGS on GFD at risk of unfavourable health consequence. However, gluten-free products in the nutrition software database often lack information on micronutrient content. Thus, intake of micronutrients might be falsely low.

Despite low intake of certain micronutrients in our subjects, blood analysis did not show micronutrient deficiencies. However, if iron intake (8.7 g/day in women) is low over extended period of time, anemia might develop. Carroccio et al. reported on weight loss and anemia in a similar study sample [14,32]. However, their subjects were newly diagnosed, while our sample had followed a GFD for at least 6 months [14]. The differences may also be explained by selection of subjects with nutritional disorders in previous studies. In a prospective multicenter study of subjects

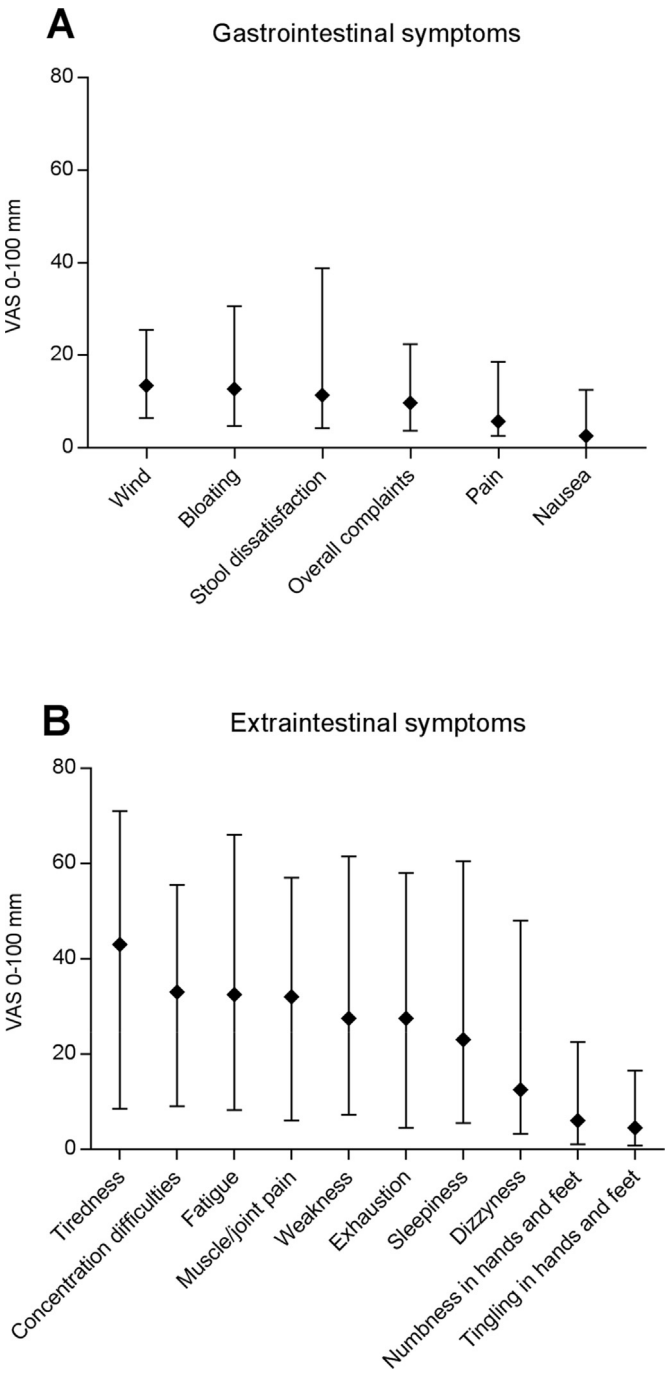

Fig. 2. Median and interquartile range of **A** gastrointestinal and **B** extra-intestinal symptoms as measured by 100 mm visual analogue scale (VAS) (n = 65).

with suspected NCGS, Volta et al. reported low blood levels of ferritin, folic acid and vitamin D in 23%, 5% and 11% of the study subjects, respectively [33]. However, their study subjects were patients recruited from referral centers, while our study sample was mainly recruited from the general community. Low vitamin D levels are reported evident throughout European populations [34]. In the present study, nutritional supplements were consumed by the study subjects in some extent, but not recorded, and might explain why there were no micronutrient deficiencies revealed by blood tests.

Gastrointestinal and extra-intestinal symptoms were present despite being on a GFD. Compared to what is considered a low

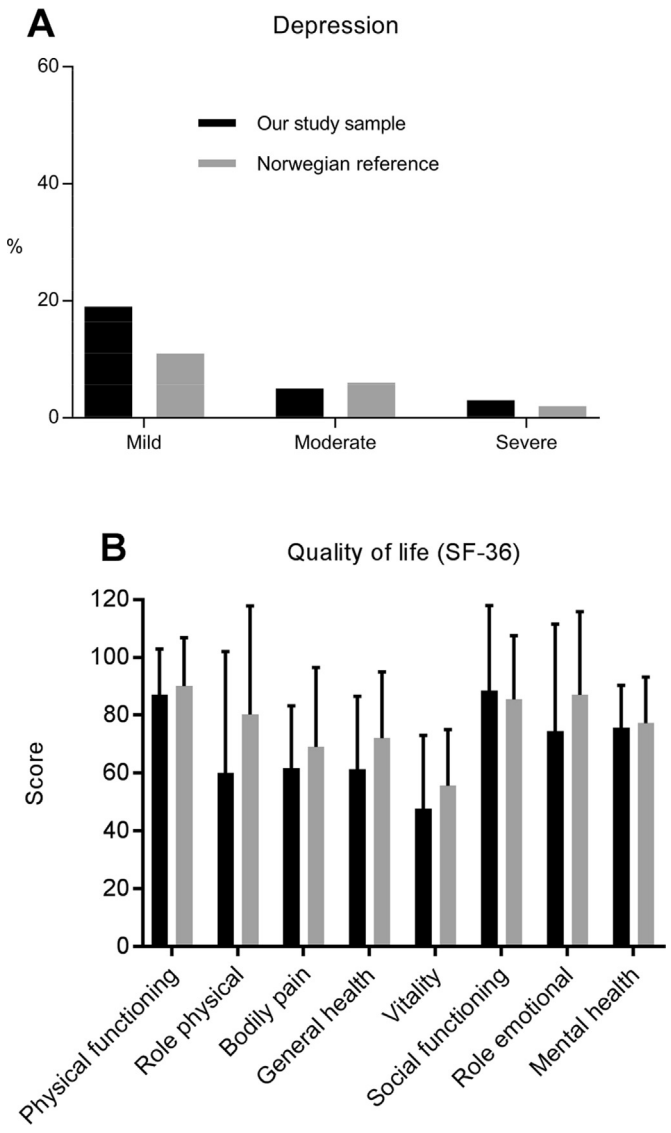

Fig. 3. A Prevalence of depression assessed by Beck Depression Inventory –version 2 compared to Norwegian reference values from Siqveland et al. [23]. **B** Mean scores and standard deviation of health-related quality of life as measured by Short Form –36 (SF-36) compared to the Norwegian reference values from Jacobsen et al. (Our study sample n = 65) [27].

FODMAP diet (2.0–2.5 g per day, excluding lactose) the current intake of total FODMAP of 11.6 g per day might explain the persistence of gastrointestinal symptoms [35]. However, recently 10 g of total FODMAP was used as low FODMAP diet compared to a sham diet of 17 g [36] which is similar to the total FODMAP of 19 g on GFD and 12 g on GFD combined with low FODMAP in the sample of self-reported NCGS in the study of Biesiekierski e al [21]. Compared to this, our sample had a quite low intake of total FODMAP on their habitual GFD. Further, a seven-day challenge of 2.1 g of fructans per day significantly increased bloating and overall gastrointestinal symptoms in a randomised double-blind placebo-controlled challenge [18].

One fifth of our NCGS sample was classified as having mild depression; almost twice as many as in a sample from the general Norwegian population [23]. The results are in accordance with a large cohort of subjects with suspected NCGS in Italy [33]. However, while higher prevalence of mild depression was found in our study sample as compared to the general population, Brottveit et al. reported no depression in both NCGS subjects and CD patients and no difference as compared to healthy controls [37]. The contradictory findings might be related to different recruitment methods.

Symptoms of depression are described in treated CD patients, but it is not known whether depression is a cause or a consequence of the gluten intolerance [38]. Limitations in daily life and social activities due to the GFD, accompanied by sleep disturbances are possible explanations, which might also apply to NCGS subjects [38,39]. Many studies have described that gastrointestinal symptoms negatively impact HR-QoL [40,41] and that patients with IBS have significantly higher anxiety and depression scores than controls [42]. Interestingly, we observed the same in our NCGS subjects.

Another important characteristic of this self-reported NCGS sample is the result of the three-day open wheat challenge that showed a clinically significant increase of gastrointestinal symptoms. The results confirmed the findings of the RCT; that the subjects were more likely to be sensitive to fructans than to gluten. Thus, the GFD had effect in these subjects not because of the absence of gluten, but rather because of the reduction of fructans. However, fructans in other food sources than wheat and cereals are not excluded in a GFD. This may explain why there were some persistence of symptoms despite the GFD.

A weakness of the study is the recruitment process by web and social media that might have resulted in selection bias. On the other hand, this recruitment method is also a strength. It has been observed that subjects with suspected NCGS self-institute a GFD before they seek the health care system. To represent the group of self-reported gluten sensitivity in the general population the study subjects were invited “off the street” and only few from referral centers.

There are no patient reported outcome measures validated for individuals with self-reported NCGS. However, the psychometric outcome measures were validated for the general Norwegian population, and GSRS-IBS for the IBS population, which is comparable to NCGS subjects.

Seven-day food record is considered the best practise of measuring dietary history of adults when the aim is to measure intake of energy and nutrients. Further, the FODMAP intake was calculated in detail at the carbohydrate level, which enabled information on intake of the subtypes of FODMAP. To our knowledge this is the first study to estimate the intake of FODMAP in a group of self-reported non-coeliac gluten sensitive subjects.

In conclusion, in this cross-sectional study, subjects with self-reported NCGS on GFD had BMI within the normal range or above, comparable to Norwegian population estimates. The high proportion of energy from fat and the sub-optimal intakes of vitamin D, folic acid, calcium, iodine and iron may put patients at risk of nutrient imbalance and deficiencies. Despite good adherence to the GFD and a moderate to low intake of FODMAP, gastrointestinal symptoms were still present and HR-QoL was lower than in the general population. Our findings highlight the importance of adequate diagnosis, dietary education and nutritional follow-up in this patient group.

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Conflict of interest

All authors declare no conflict of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clnesp.2019.02.012.

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