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ORIGINAL ARTICLE

Validation of red flags in the workup of children with long-term abdominal pain – A retrospective study

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Abstract

Aim: To evaluate red flags as an instrument to distinguish other medical conditions from Functional Gastrointestinal Disorders (FGID) in children with long-term abdominal pain.

Methods: In a retrospective follow-up, data were collected from 317 children who were referred for medical assessment due to long-term abdominal pain between the years 2011 and 2012 at three Swedish paediatric open clinic units in Sweden. Throughout the review of medical records, any documented red flags at the *primary consultation* and finally set diagnosis after 1 year were noted for all cases.

Results: A non-FGID disease was diagnosed in 32 cases (10.1%). The sensitivity of red flags to predict inflammatory bowel disease (IBD) was 100% and the specificity 64.1%. The sensitivity of red flags to predict celiac disease was 45.5% and the specificity 63.7%. The sensitivity of red flags to predict any non-FGID disease was 59.4%, and the specificity was 65.6%.

Conclusion: The use of red flags is a sensitive instrument to identify patients with IBD but less applicable when identifying celiac disease and other organic diseases. Specificity is generally low and future biomarkers for assessing children with long-term abdominal pain is needed.

KEYWORDS
children, functional gastrointestinal disorders, long term abdominal pain, red flags, Rome IV

1 | INTRODUCTION

Functional Gastrointestinal Disorders (FGID's) include several chronic conditions characterised by recurrent gastrointestinal symptoms, with a prevalence of 21%–25% in children aged 4–18 years,[1–4] and significant related costs and negative effects on quality of life.[3,5,6] The subgroup of FGID's related to long-term abdominal pain is referred to as functional abdominal pain disorders (FAPD), with the subgroups irritable bowel syndrome (IBS), functional dyspepsia (FD), abdominal migraine (AM), and functional abdominal pain – not otherwise specified (FAP-NOS).[7] The internationally acknowledged Rome criteria for FGID's are a diagnostic instrument for both children and adults, with the latest version, the Rome IV-criteria, published in 2016.[7–9]

Due to the lack of pathognomonic symptoms and sensitive biomarkers, FGIDs and the different subgroups are generally defined based on characteristics identified in the medical history, together with the exclusions of other diagnoses, mostly referred to as organic.

Abbreviations: FAPD, functional abdominal pain; IBD, inflammatory bowel disease; p-FAPD, probable functional abdominal pain.

Questionnaires in multiple languages have been created to simplify the clinic workup for clinicians and researchers. A central part of the procedure is to identify so-called red flags in the anamnestic work-up, that is, symptoms that could indicate an underlying organic disease (Table 1). For children aged 4–10 years, the Rome foundation offers a parent report form and for children 10 years of age and older, there is another report form aimed to be filled in by the child/adolescent themselves.[7,8] Validation of the paediatric questionnaires is still ongoing, and the Rome committee's recommendations are mostly based on expert opinion, including a consensus to limit the number of tests if red flags are lacking.[8–12] However, the validation of red flags is scarce, and there are few studies specifically evaluating the significance of the Rome IV alarm features alone or grouped.[13,14]

The paediatric Rome IV criteria underscore that diagnostic procedures assessing possible organic disease should be kept to a minimum, and the dictum 'no evidence for organic disease' has been replaced by 'after appropriate medical evaluation the symptoms cannot be attributed to another medical condition'.[7,11] However, there is still a lack of knowledge and validated international guidelines regarding the exact choice of workup. Furthermore, the positive predictive value for laboratory workup is low.[3,15–17] Therefore, in Sweden, the recommended basic laboratory workup for all children with long-term abdominal pain is based on expert opinions and includes growth chart assessment, IgA-transglutaminase, blood count, c-reactive protein/erythrocyte sedation rate and dipstick urine analysis. If the patient has extensive diarrhoeas, it is also recommended to analyse faecal calprotectin (Swedish guidelines downloaded from www.gastro.barnlakarforeningen.se).

In this retrospective study, the primary objective was to evaluate the applicability of red flags as an instrument to distinguish FGID from other medical conditions in children with long-term abdominal pain. Secondary, we assessed the clinical work-up used for this group of patients at the same Swedish tertiary centra.

Key notes

- Red flags in the workup of children with long-term abdominal pain are sensitive for identifying inflammatory bowel disease (IBD).
- Using the concept of red flags is not enough to identify patients with celiac disease and other organic diseases.
- Specific biomarkers for assessing children with long-term abdominal pain are needed.

2 | METHOD

2.1 | Study design and participants

This was a retrospective follow-up study assessing children/adolescents who were, between the years 2011 and 2012, referred to a paediatric clinic due to long-term abdominal pain.

The study was conducted at three paediatric open clinic units in Västerbotten county, Sweden. These three units (Umeå, Lycksele and Skellefteå) are all a part of the Department of Paediatrics at Umeå University Hospital. The children with long-term abdominal pain were initially identified based on the ICD-10 diagnosis they received at their primary consultation at the paediatric outpatient clinic. Patients with the following ICD codes (x representing any number) were considered eligible and their charts were assessed: Kxx.x (gastrointestinal diseases), R10.x (symptom-based diagnoses related to pain in the abdomen), R11.x (symptom-based diagnoses related to nausea and vomiting) and Z038E (observation for a susceptible gastrointestinal disease). From this selection, the patients that hereafter met the following inclusion criteria were included: First visit during 2011 or 2012, at least 2 months of discomfort or pain in the abdomen (not just constipation), age 4–17 years, no congenital or neuromuscular disease, no confirmed organic gastrointestinal disease at the primary consultation.

2.2 | Retrospective analysis and definitions

The medical records from the visits and workups performed during the first 12 months were assessed retrospectively to identify the final diagnosis set by the investigating clinician. We primary used the diagnosis given in the final assessment (written text in medical record) rather than the ICD10 code chosen since Swedish tradition in using specific ICD code is scarce. Cases where the clinician diagnosed the patient with a FAPD-condition without specifying any of the subgroups IBS, FD, or AM were categorised as FAP-NOS. If the clinician did not conclude a clear diagnosis (functional or organic) in written text, the ICD code used was assessed. For cases diagnosed only with symptomatic vocabularies and any of the ICD codes R10.xx, R11.xx or Z038E, functional abdominal pain was assumed, and they were defined as probable FAPD (p-FAPD). For cases where clinician used the term 'gastritis' in written text or ICD code (K29.x), only those with a confirming histological finding were kept as final diagnosis and the others included in the p-FAPD group.

Throughout the review of medical records, any documented occurrence of red flags at the *primary consultation* was noted for all included cases. Furthermore, for each case, the included workup performed, both at the referring primary healthcare centre and the present tertiary centre was also registered and categorised.

2.3 | Statistics

Descriptive statistics was used to assess collected data. To assess the validity and reliability of red flags, calculations of sensitivity, specificity, positive predictive value and negative predictive value were performed separately for inflammatory bowel disease (IBD), celiac disease and finally for the combined group of all non-FGID diagnoses. For each calculation, all other cases were set as controls.

TABLE 1 Alarm features for potential organic disease in chronic abdominal pain (ref. 2).

Dysphagia
Odynophagia
Persistent vomiting
Gastrointestinal bleeding
Persistent right upper or right lower quadrant pain
Nocturnal diarrhoea
Perirectal disease
Involuntary weight loss
Deceleration of linear growth
Delayed puberty
Unexplained fever
Arthritis
Family history of inflammatory bowel disease, celiac disease or peptic ulcer disease

In secondary analyses, chi-square tests were used to compare the investigational tests performed on the group *with* red flags and those *without* red flags. Tests with a *p*-value below 0.05 were considered statistically significant. A relative risk (RR) was calculated for all results that were statistically significant.

3 | RESULTS

3.1 | Sample characteristics, workups and final diagnoses

A total number of 317 patients were included in the study whereof a majority were girls (58%) and above 10 years of age (62%). Red flags were documented in 117 children. Frequencies of diagnostic workups performed during the first year were compared between patients with or without red flags (Table 2). The presence of red flags significantly increased the frequency of assessing iron status ($p = 0.018$ and relative risk [RR] = 1.66), faecal Hb ($p = 0.001$ and RR = 1.79), faecal cyst-and worm eggs ($p = 0.013$ and RR = 1.77), elimination attempt gluten ($p = 0.006$ and RR = 3.76) and other microbiological tests ($p = 0.006$ and RR = 3.43). In contrast, the occurrence of red flags was associated with a decreased frequency of helicobacter serology analyses ($p = 0.034$ and RR = 0.45). For all other parameters, there was no significant difference (Table 2).

At the end of clinical workup, a non-FGID diagnosis was set in 32 cases (10.1%) and a FGID diagnosis (including p-FAPD) in 285 cases (89.9%; Figure 1).

3.2 | The red flag prediction of inflammatory bowel disease (IBD)

Four of the included 317 patients were diagnosed with IBD, all verified with gastroscopy, coloscopy, histology and diagnostic criteria (gold standard). For all four cases, one or multiple red flags were identified at the primary consultation (Tables 3 and 4). Of the remaining 313 children with long-term abdominal pain, 112 patients had red flags identified at the primary consultation (Table 3). The sensitivity was calculated at 100% and the specificity at 64.1%, hence giving an accuracy of 1.64. The positive predictive value was calculated at 3.4%, and the negative predictive value was 100% (Table 5).

3.3 | The red flag prediction of celiac disease

Twenty-two out of the included 317 patients were diagnosed with celiac disease, all histologically verified (gold standard). Ten of the 22 patients with celiac disease had one or multiple red flags identified at the primary consultation (Tables 3 and 4). The sensitivity was calculated to be 45.5% and the specificity to be 63.7%, hence giving an accuracy of 1.09. The positive predictive value was calculated to be 8.5% and the negative predictive value was 94.0% (Table 5).

3.4 | The red flag prediction of all non-FGID

Thirty-two out of the included 317 patients were diagnosed with a non-FGID disease (Figure 1). Nineteen out of 32 patients with a non-FGID had one or multiple red flags identified at the primary consultation (Tables 4 and 5). The sensitivity was calculated to be 59.4%, and the specificity 65.6% hence giving an accuracy of 1.25. The positive predictive value was calculated to be 16.2%, and the negative predictive value was 93.5% (Table 5).

4 | DISCUSSION

In this novel retrospective study, the primary objective was to evaluate the applicability of red flags as an instrument to distinguish other medical conditions from functional abdominal pain disorders (FAPD) in children with long-term abdominal pain. We found that the concept of red flags is a useful instrument to identify patients with IBD but for celiac disease and non-FGID in general, the concept is less applicable and complementary investigational methods are required.

The high prevalence of FAPD's among children and adolescents and the high annual cost of care for this group of patients underscore the need for an effective and validated diagnostic instrument and clear validated guidelines.[1–4] In a review, Friesen et al.[13] recently concluded that red flags are highly utilised in practice, but there is little evidence supporting their validity, supporting the clinical applicability of our study.

As expected, the present cohort of children with long-term abdominal pain had a high number of patients diagnosed with probable or definite FGID (89.9%). The number of non-FGID patients (10.1%) is in line with several previous studies suggesting that even in a tertiary centre, a vast majority of patients suffer from FGID's. In a study on

TABLE 2 Diagnostic measures performed in patients with long term abdominal pain.

Diagnostic measure	All *N* = 317 (%)	No red flags *N* = 200 (%)	Red flag(s) *N* = 117 (%)	*p*-value
Blood samples				
Inflammatory markers[a]	199 (62.8)	126 (62.7)	73 (62.9)	0.965
Blood count	237 (74.8)	143 (71.1)	93 (81.0)	0.051
Transaminases	182 (57.4)	109 (54.2)	72 (62.9)	0.131
Creatinine and/or electrolytes	49 (15.5)	26 (12.9)	23 (19.8)	0.102
Glucose	29 (9.1)	18 (9.0)	11 (9.5)	0.875
Iron status (any)	65 (20.5)	33 (16.4)	32 (27.86)	0.018
Thyroid status	99 (31.2)	59 (29.4)	40 (34.5)	0.342
Faecal helicobacter antigen	58 (18.3)	37 (18.5)	21 (18.1)	0.946
Helicobacter serology	38 (12.0)	30 (14.9)	8 (6.9)	0.034
Transglutaminase/celiac test	266 (83.9)	168 (83.6)	98 (84.5)	0.833
Other tests				
Dipstick urine analysis	75 (23.7)	50 (24.9)	25 (21.6)	0.502
Faecal calprotectin	215 (67.8)	132 (65.7)	83 (71.6)	0.280
Faecal haemoglobin	92 (29.0)	45 (22.4)	47 (40.5)	0.001
Faecal culture, general	57 (17.0)	30 (14.9)	24 (20.7)	0.189
Faecal test, cyst and worm eggs	53 (18.0)	28 (13.9)	29 (25.0)	0.013
Lactose intolerance genotype	46 (14.5)	25 (12.4)	21 (18.1)	0.168
Abdominal ultrasound	78 (24.6)	52 (25.9)	26 (22.4)	0.491
Other radiology	41 (12.9)	27 (11.9)	14 (12.1)	0.727
Gastroscopy	58 (18.3)	31 (15.4)	27 (23.3)	0.082
Test treatment PPI/antiacids	140 (44.2)	89 (44.3)	51 (44.0)	0.957
Test treatment constipation	85 (26.8)	55 (27.4)	30 (25.9)	0.771
RAST nutrients panel	83 (26.2)	49 (24.4)	34 (29.3)	0.336
Elimination attempt milk protein	112 (35.3)	71 (35.3)	41 (35.3)	0.997
Elimination attempt lactose	84 (26.5)	52 (25.9)	32 (27.9)	0.739
Elimination attempt gluten	16 (5.0)	5 (2.5)	11 (9.5)	0.006
Oesophageal pH monitoring	7 (2.2)	6 (3.0)	1 (0.9)	0.215
Helicobacter pylori eradication	9 (2.8)	6 (3.0)	3 (2.6)	0.837
Test treatment antibiotics	5 (1.6)	2 (1.0)	3 (2.6)	0.273
Test treatment tricyclic antidepressants	12 (3.8)	8 (4.0)	4 (3.5)	0.822
Test treatment cyproheptadine	3 (0,9)	2 (1.0)	1 (0.9)	0.906
HLA genotype test	6 (1.9)	4 (2.0)	2 (1.7)	0.867
Other microbiological diagnostic tests	18 (5.7)	6 (3.0)	12 (10.3)	0.006

[a]Erythrocyte sedation rate (ESR) and/or C-reactive protein (CRP).

adults carried out by Yang et al.[18] in 2022, the prevalence of organic disease was 10.41% in suspected IBS-patients. In another study by Helgeland et al.[17] in 2009, 93% of patients referred to 4 general paediatric outpatient clinics for evaluation of recurrent abdominal pain had functional abdominal pain. In a Swedish study by Usijärvi et al.,[14] exploring children aged 4–17 years who consulted a paediatrician in secondary or tertiary care due to gastrointestinal complaints, 16% of the children were diagnosed with organic disease.

Regarding specificity and sensitivity of organic disease, we found the highest sensitivity (100%) for IBD. This is in line with a previous study conducted by Ël-Chammas et al.[19] showing that alarm symptoms of haematochezia and weight loss could be a useful instrument to differentiate between chronic abdominal pain and Crohn's disease. The above-mentioned multicentre cross-sectional study by Yang et al.[18] also showed that anaemia, faecal occult blood and unintended weight loss have high predictive

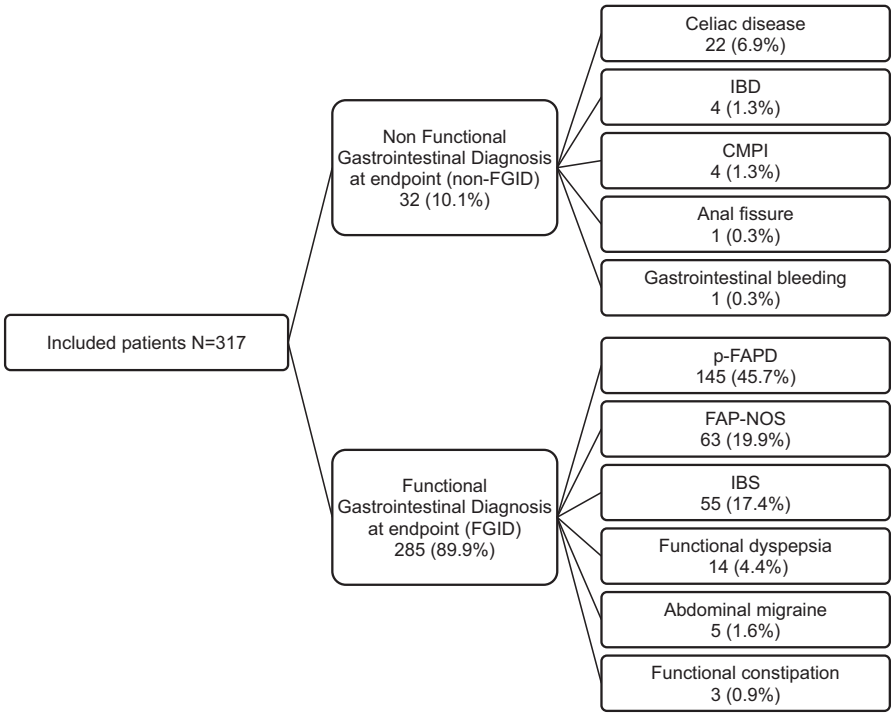

FIGURE 1 Diagnosis set by clinician at endpoint for 317 children assessed for recurrent abdominal pain. pFAPD represents cases where clinician was unclear in describing diagnosis and used symptomatic ICD10-codes (R10.x or R11.x) or incorrectly used the diagnosis 'Gastritis' without histological confirmation.

TABLE 3 Presence of red flags in 317 patients with long-term abdominal pain, categorised by final diagnosis.

	Red flags		
Diagnosis	**No**	**Yes**	**Total**
Organic diagnoses			
Inflammatory bowel disease (IBD)	0	4	4
Celiac disease	12	10	22
Cow milk protein allergy	1	3	4
Anal fissure	0	1	1
Gastrointestinal bleeding	0	1	1
Functional diagnoses			
Functional constipation	2	1	3
Functional dyspepsia	11	3	14
Irritable bowel disease (IBS)	39	16	55
Functional abdominal pain – not otherwise specified (FAP-NOS)	45	18	63
Abdominal migraine	2	3	5
Probable functional abdominal pain disease (p-FAPD)	88	57	145
Total	200	117	317

value for organic disease in suspected IBS patients. In our study, haematochezia and/or weight loss were also identified as predominant red flags for IBD.

In the present study, the sensitivity for celiac disease and other non-FIGD's was lower (45.5% and 59.4% respectively), indicating that complementary workup is needed to identify these group of patients. The standardisation of IgA-transglutaminase testing is already acknowledged by the Rome IV committee, who recommends serologic screening for celiac disease in children with a presumed IBS considering the inconsistency of data and the risk of missing potential cases.[7,13,20] Our result emphasises this conclusion.

Regarding specificity, it was low for detecting any of the non-FGID diseases (<66%). It could therefore be argued that it is pedagogically important for clinicians using the red flags concept to know that they are going to over-identify patients that need further workup, and further guidelines on how to proceed with positive red flags are needed to avoid unnecessary referrals and invasive tests.

Few comparable previous studies have explored the specificity and sensitivity of using red flags to identify organic disease, making the present study a novel contribution. In the study mentioned above by Uusijärvi et al.,[14] a similar approach was used. Combining the absence of red flags with the Rome III criteria, they found high specificity but low sensitivity for diagnosing FAPD in a comparable cohort.

As a secondary aim, the present study also assessed the workups performed in children with long-term abdominal pain at the Swedish centre. We observed that children, both with and without red flags, underwent extensive workup. This is not in line with the Rome committee's recommendations, which suggest limiting the number of tests if red flags are lacking.[8–12] As for the analyses recommended as a basic workup (IgA-transglutaminase, blood count, c-reactive protein/erythrocyte sedation and dipstick urine analysis), the frequency of carrying out these tests was high with no significant difference if the patient in the workup had a red flag or not. This is in line with the Swedish guidelines that all patients with long-term abdominal pain should undergo routine testing, despite red flags or not.[3,15,17]

TABLE 4 Type of red flag according to diagnosis and frequency of every specific red flag.

	N	Dysphagia	Odynphagia	Persistent vomiting	Gastrointestinal bleeding	Nocturnal diarrhoea and/or pain	Persistent upper or right lower quadrant pain	Perirectal disease	Involuntary weight loss	Deceleration of linear growth	Delayed puberty	Unexplained fever	Arthritis	Family history IBD	Family history celiac disease	Family history peptic ulcer	No red flag
	N	*n* = 0	*n* = 0	*n* = 4	*n* = 23	0	22	5	23	0	0	3	0	18	25	5	200
IBD	4	0	0	0	4	0	2	0	1	0	0	0	0	1	0	0	0
Celiac disease	22	0	0	1	0	0	0	0	2	0	0	0	0	1	7	0	12
CMPI	4	0	0	0	2	0	0	0	0	0	0	0	0	0	1	0	1
Anal fissure	1	0	0	0	1	0	0	0	0	0	0	0	0	1	0	0	0
Gastrointestinal bleeding	1	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0
Functional constipation	3	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	2
Functional dyspepsia	14	0	0	0	1	0	2	0	0	0	0	0	0	0	0	0	11
Irritable bowel disease	55	0	0	0	1	2	5	0	2	0	0	0	0	4	2	2	39
FAP-NOS	63	0	0	1	0	0	2	5	5	0	0	1	0	1	4	1	45
Abdominal migraine	5	0	0	1	1	0	0	0	0	0	0	0	0	1	0	0	2
Probable functional abdominal pain disease	145	0	0	1	11	0	11	0	13	0	0	2	0	9	11	2	88

Note: Twelve patients had more than one red flag.

Abbreviations: CMPI, cow milk protein intolerance; FAP-NOS, functional abdominal pain-not other specified; IBD, inflammatory bowel disease.

TABLE 5 Validity of red flags for diagnosis of inflammatory bowel disease, celiac disease or any organic disease.

Diagnosis	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)
Inflammatory bowel disease	100	64.1	3.4	100
Celiac disease	45.5	63.7	8.5	94.0
Any organic disease	59.4	65.6	16.2	93.5

5 | STRENGTHS AND LIMITATIONS

The present study is novel with a relatively large sample size representing a typical paediatric open clinic. The results are valid and clinically applicable. However, there are identifiable limitations. When retrospectively reviewing the records, it was difficult to extract the frequency of symptoms at baseline. Therefore, one could argue that the use of the term p-FAPD is not appropriate for the Rome criteria since we lack the exact data on symptom frequency. Another limitation is that the diagnoses were set by the individual clinician, and therefore we cannot be sure that all diagnostic criteria were taken into consideration and were fully fulfilled, neither for functional diagnoses nor organic diagnoses. Also, a large proportion of cases had no final set diagnosis but remained on symptom-base descriptions and ICD-codes R10.x and R11.x. Our assumption that those represent probable FAPD could be questioned. Furthermore, it should be mentioned that there are some differences between the Rome III criteria and Rome IV criteria for all included functional pain disorders, which could affect the applicability of the result. However, the aim of the study was mainly to separate organic disease from functional disease and we argue that the approach used is valid for that purpose. Another limitation of this study is the low prevalence of organic disease, particularly IBD, which limits the validity of calculated sensitivity and specificity. Furthermore, the review of medical records opens for observer bias. Finally, the patients have not been structurally asked about red flags, and the documentation of red flags in the journal was not standardised.

6 | CONCLUSIONS

We found that the concept of red flags is a good instrument to identify patients with IBD in a cohort of children with long-term abdominal pain. The red flag concept is less applicable to identify celiac patients and other organic diseases in the same group. This could motivate the standardisation of IgA-transglutaminase testing in all patients seeking medical attention for long term abdominal pain. Overall, the validity of red flags in general was scarce and the need of future biomarkers or other investigational assessments is warranted.

AUTHOR CONTRIBUTIONS

Malin Delin: Data curation; investigation; project administration; visualization; writing – original draft. **Staffan K. Berglund:** Conceptualization; data curation; formal analysis; funding acquisition; investigation; methodology; project administration; resources; software; supervision; writing – review and editing.

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CONFLICT OF INTEREST STATEMENT

The authors have no conflicts of interest to declare.

ETHICS STATEMENT

The study was approved by the Regional Ethical Review Board in Umeå (ref 2016/07-31Ö) and registered at clinicaltrials.gov (NCT02689648).

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