Widespread hyperalgesia in adolescents with symptoms of Irritable Bowel Syndrome: Results from a large population-based study

Niklas Stabell[a], Audun Stubhaug[b], Trond Flægstad[a], Emeran Mayer[c], Bruce D. Naliboff[d], Christopher S. Nielsen[e].

[a] Dept. of Pediatrics, University Hospital of North Norway and Dept. of Clinical Medicine, University of Tromsø, Tromsø, Norway.

[b] Dept. of Pain Management and Research, Oslo University Hospital and Faculty of Medicine, Oslo University, Oslo, Norway.

[c] Oppenheimer Family Center for the Neurobiology of Stress, Division of Digestive Diseases, David Geffen School of Medicine, University of California-Los Angeles, Los Angeles, California, USA

[d] Dept. of Medicine and Psychiatry and Biobehavioral Sciences, David Geffen School of Medicine at UCLA, Los Angeles, California, USA

[e] Norwegian Institute of Public Health, Division of mental Health, Oslo, Norway.

Corresponding author:

Niklas Stabell

Dept of Pediatrics, University Hospital of Northern Norway
9038 Tromsø, Norway
Telephone: 0047-7762637225
Fax: 0047-77626119
E-mail: niklas.stabell@unn.no

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Abstract

Widespread hyperalgesia is well documented among adult patients with Irritable Bowel Syndrome (IBS), but little is known about pain sensitivity among adolescents with IBS. We examined pain sensitivity in 961 adolescents from the general population (mean age 16.1 years), including pain threshold and tolerance measurements of heat (forearm) and pressure pain (fingernail and shoulder), and cold-pressor tolerance (hand). Adolescents with IBS symptoms (Rome III criteria) had lower heat pain thresholds compared to controls after adjustments for sex, co-morbid pain and psychological distress (mean difference = -0.8 ^{o}C; 95% CI = -1.6 to -0.04). Similar results were found for pressure pain threshold at the shoulder (mean difference = -46 kPa; 95% CI = -78 to -13) and fingernail (mean difference = -62 kPa; 95% CI = -109 to -15), and for an aggregate of all three threshold measures (z-score difference = -0.4; 95% CI = -0.6 to -0.2), though pressure pain threshold differences were non-significant after the final adjustments for psychological distress. No difference of pain tolerance was found between the IBS cases and controls. Our results indicate that adolescents in the general population with IBS symptoms, like adults, have widespread hyperalgesia**.**

Perspective

This is the first report of widespread hyperalgesia among adolescents with IBS symptoms in the general population, with lower pain thresholds found to be independently of sex and co-morbid pain. Our results suggest that central pain sensitization mechanisms in IBS, which may contribute to trigger and maintain chronic pain symptoms.

1.0 Introduction

Irritable Bowel Syndrome (IBS) is the most common cause of chronic or recurrent abdominal pain in the pediatric population.[19, 26, 28] IBS is more prevalent among girls than among boys and is associated with high risk of mental health problems and of co-morbid pain at other body sites.[25, 26, 51]

There is broad agreement that IBS is best conceptualized in terms of the biopsychosocial model, with multiple factors contributing to its pathophysiology.[6, 9, 16, 21, 29, 34, 49] These factors are incompletely understood, but are likely to include both peripheral gut factors,[5, 27] as well as central factors, including central pain modulation,[40] and disorders of mood and affect.[2, 24]

Visceral hyperalgesia has long been considered to be a diagnostic marker of both pediatric and adult IBS and a majority of patients show increased sensitivity to controlled rectal distension compared to healthy controls.[7, 14, 31, 33, 38, 44, 52] Though this finding could be explained by both local tissue pathology and altered processing at the primary afferent, studies have also reported increased sensitivity for different experimental pain stimuli at distal body sites (e.g. heat, cold-pressor and pressure pain).[3, 37, 39, 43] Furthermore, there is evidence of altered central endogenous pain modulation in this patient group as shown in experiments using conditioned pain modulation paradigms, which supports theories of central pain sensitization mechanisms in IBS that may contribute both to trigger and maintain chronic pain.[40, 55] Additional support for these theories is reported in a recent study using diffusion tensor imaging of the brain in adult IBS patients identified microstructural reorganization involving brain regions involved in sensory modulation and integration. [20] In large scale population based study including nearly 10,500 adults our group found increased sensitivity to cold-pressor and heat pain delivered to the arm among participants reporting IBS symptoms.[47] These results of increased widespread pain sensitivity remained robust after controlling for sex, mental health and co-morbid chronic pain.

However, the above cited studies are restricted to mainly adult IBS patients and are not necessarily valid for pediatric populations. Few studies have examined somatic pain sensitivity among children with chronically recurring abdominal pain, and only one including pediatric IBS patients.[1, 17, 18, 56, 60] Results from these studies have been equivocal, possibly due to the relatively small samples sizes. Furthermore, there are no prospective studies of pain sensitivity among children with recurrent abdominal pain and IBS, but increased somatic pain sensitivity was found in one study among adolescents and young adults with a history of

childhood chronic abdominal pain.[11] But, if increased pain sensitivity in childhood is a risk-factor for or a consequence of chronic pain remains an unanswered question. Therefore, to better understand possible age-related differences, more knowledge on pediatric IBS pain sensitivity is required. Finally, little is known about the importance of co-morbid pain, anxiety and depression in the association between pediatric IBS and pain sensitivity.

In the current population based study performed in a large number of adolescents with and without self reported IBS symptoms, we aimed to a) compare heat, pressure and cold-pressor pain sensitivity in adolescents with IBS symptoms with the remaining adolescent participants in a population based study, and b) test whether associations between IBS and pain sensitivity could be explained by confounding factors.

2.0 Methods

2.1 Sample

This study was conducted as part of the Tromsø Study, a longitudinal population based study, previously only including adults from the municipality of Tromsø in Northern Norway. In 2010-2011 the study was expanded to include adolescents, including all pupils in first-year high school (11th school year) in both academic and vocational educational programs from all high schools in the study area. Each participant completed a health questionnaire, and participated in physical measurements and medical examinations during a one-day session at the Department of Research at the University Hospital of North Norway.

A total of 1,117 students from five high-schools were invited and of these 1,038 students participated (participation rate = 92.9%). Participants 18 years or older were excluded from the analysis (n= 77), leaving a final sample of 961 (469 girls and 492 boys), aged 15-17 years (mean=16.1). As part of the physical examination, participants were asked to complete tests of pain sensitivity, which included in order of testing: heat pain threshold and tolerance, pressure pain threshold and tolerance in two body-sites and cold-pressor pain tolerance (see the study flowchart in figure 1 for further details).

The study was approved by the Regional Committee for Medical and Health Research Ethics, Health Region North. All participants gave written informed consent before inclusion in the study. For participants younger than 16 years, additional consent was given by a parent.

[Place Figure 1 about here]

2.2 IBS case definition

The revised Irritable Bowel Syndrome criteria from 2006 (Rome III IBS criteria) were used to identify participants with IBS symptoms.[42] Adolescents were classified as IBS cases if they reported weekly abdominal pain or discomfort during the past two or more months and two or more of the following associated bowel symptoms at least 25% of the time: (1) relief with defecation (2), change in stool frequency (3) and /or change in stool form. Clinical examinations were not conducted to identify cases with possible gastro-intestinal organic diseases. However, previous adult validations studies of the Rome criteria have shown acceptable sensitivity and specificity compared to clinical IBS diagnosis (70 - 90 % and 70 - 80 % respectively).[23] Nevertheless, there is some uncertainty with respect to how the criteria perform in a population based setting. Previous studies are limited to clinical cases and very few include pediatric patients. Despite the risk of mis-classification, the Rome criteria are widely used, particularly in epidemiological studies.[41]

The participants that reported abdominal pain or discomfort during the past two months were asked to report how much abdominal pain they usually had, rated on a 0-10 numeric rating scale (NRS), with zero corresponding to no-pain and ten to most intense pain imaginable. Since-no-one reported no pain, and the NRS scores were somewhat skewed the IBS cases were sub-classified into the commonly used categories of mild (NRS = 1-3), moderate (NRS = 4-6) and severe (NRS = 7-10) pain.

2.3 Psychological distress and co-morbid chronic pain case definition

Anxiety and depression symptoms were assessed with the Hopkins Symptom Check List, 10-item version (HSCL). HSCL is a screening tool for detecting negative mood symptoms, suited for epidemiological research, also among adolescents, and has been validated against clinical diagnostic depression and anxiety tools.[12, 13, 32, 45, 46] Subjects with a mean score of 1.85 or higher were classified as having psychological distress. This cut-off has previously been

shown to have a sensitivity of 89 % and specificity of 98 % with respect to detecting anxiety or depression compared to the more extensive 25-item HSCL version.[48]

Non-abdominal chronic pain was assessed in a separate section of the questionnaire, independent of the IBS-module. Participants were classified as having chronic pain if they responded 'yes' to the question "Do you have persistent pain that has lasted for three months or longer?" Since this broad question might include IBS related pain, follow-up questions on pain location were used to identify subjects with non-abdominal chronic pain. Thus both IBS cases and controls reporting pain lasting 3 months or longer at any non-abdominal site (i.e. head, yaw, neck, back, shoulder, arm, hand, hip, leg, foot, genitalia, or skin), were classified as having non-abdominal chronic pain.

2.4 Pain sensitivity measurements

Heat-pain threshold and tolerance was tested using a MEDOC ATS somatosensory stimulator (MEDOC Ltd, Israel) with a 30x30 mm thermode. Stimuli were applied to the volar surface of the right forearm. Stimulation started from a baseline temperature of 32.0 °C and increased by 1 °C/s, with an upper safety limit of 50.0 °C. For pain threshold measurements, subjects were instructed to press a button when the sensation changed from warmth to pain. Upon pressing the button, the temperature was registered and the thermode temperature returned to baseline at a rate of 8 °C/s. This procedure was repeated three times, the first measurement was discarded and second and third measures were averaged. Thereafter the participants were asked to press the button at a maximum tolerable pain level, informed about the preset safety-limit at 50.0 °C. Heat pain tolerance was measured twice and the highest temperature was used.

As for heat-pain, pressure-pain threshold and tolerance was recorded by pressing a button when the sensation changed from non-painful pressure to pain and at a maximum tolerable pain level respectively. Pressure was applied to the cuticle of the ring finger nail of the right hand and on the midline of the right trapezius muscle and in shoulder-height with a hand held algometer (Somedic, AB, Sweden) with a circular probe of 1 cm^2. Starting at 0 kPa, pressure was increased by 30 kPa/s up to a maximum of 1000 kPa. Threshold measurement was repeated three times, followed by tolerance measurements, repeated twice. For each site the

second and third threshold measures were averaged and the highest tolerance measurements were used.

Cold-pressor pain was induced using a 3°C water bath (Julabo PF40-HE, JULABO Labortechnik GmbH, Germany), connected to a 13 L external plexi-glass container with a flow rate of 22 L/Min. The participants submerged their left hand and wrist in the cold water of the plexi-glass container as long as they were able to, up to maximum 105 seconds. Time to withdrawal of the hand was recorded.

2.5 Statistical analysis

SPSS version 20 was used for statistical analysis. Pearson's chi-square test and t-tests were used in univariate comparisons of categorical and continuous variables respectively. Mann-Whitney U tests were used for univariate comparisons of non-normally distributed continuous data. Mean heat and pressure pain thresholds are reported for cases and controls. Median pain tolerance for heat, pressure and cold-pressor pain are reported for cases and controls due to the skewed and right censored distribution of the tolerance data.

For pain threshold measures, where univariate analysis revealed significant differences between IBS cases and controls, Analysis of Covariance (ANCOVA) was carried out adjusting for sex, non-abdominal chronic pain and psychological distress. Where significant group differences were observed, post-hoc ANCOVA was performed to compare IBS pain subgroups (i.e. mild, moderate and severe abdominal pain) with controls, including the same covariates. Recognizing that individual experimental pain modalities may imperfectly reflect the underlying trait of central sensitization, we also carried out these analyses on a total threshold score, constructed by z-transforming each measure (heat, pressure arm and shoulder), averaging the three variables, and finally z-transforming the average. A similar procedure has been used by other research groups previously. [15]

Due to right censoring of the heat, pressure and cold-pressor pain tolerance data, Cox proportional hazard regression was used to analyze these outcomes. Heat pain tolerance below 50 degrees Celsius, pressure pain tolerance below 1000 kPa and cold-pressor endurance time below 105 seconds were considered an event in each test respectively and individuals reaching the preset test-limits were treated as censored in the Cox regression analyses. Group comparisons of IBS and controls were done including adjustments for sex, non-abdominal

chronic pain and psychological distress. Further analyses including the IBS pain subgroup or total pain tolerance scores were not performed due to missing significant associations of IBS and pain tolerances in the analyses above.

Some participants failed to conduct all pain sensitivity measurements as shown in Figure 1 (Study flowchart). Technical failures were the most common cause. However, as missing data was equally distributed among the IBS cases and controls, this is unlikely to affect the overall case control differences.

Interaction-effects in the multivariate analysis are reported when statistically significant. Results were considered significant if p-values were less than .05.

3.0 Results

3.1 Demographics, prevalence and co-morbidity

Mean age was 16.1 years (SD = 0.4), and without significant differences between IBS cases and controls ($p > 0.05$). Overall, 8.2% of the participants met the case definition of IBS. All of the IBS cases reported chronic abdominal pain (NRS > 0). Mild pain was reported by 26.0 % (n = 20), moderate by 51.9 % (n = 40) and severe by 22.1 % (n= 17) of the IBS cases. Symptoms of IBS were more common among girls ($p < 0.05$) (Table 1).

The median HSCL score for the whole sample was 1.3 (IQR = 0.6). Psychological distress (HSCL $\geq$ 1.85) was reported nearly three times as often by girls than by boys ($p < 0.01$). Psychological distress was reported by approximately half the IBS cases and by 16 % of controls ($p < 0.01$). Conversely, of the participants reporting psychological distress, 21.7 % met the IBS case definition, versus 5.1% in the remaining sample ($p < 0.01$).

Overall, 17.6 % of the participants reported non-abdominal chronic pain. Non-abdominal chronic pain was also more common in girls than among boys (22.6 % vs. 13.5 % respectively, $p < 0.01$). Nearly one third of the IBS cases reported non-abdominal chronic pain, compared to 16.4 % in the control group ($p < 0.01$).

3.2 Pain thresholds

Heat pain thresholds were significantly lower among IBS cases than among controls (mean difference = - 0.8 ^{o}C with 95 % CI = -1.5 to - 0.04). This difference remained significant and unchanged after adjustment for all covariates (mean difference = - 0.8 ^{o} C with 95 % CI = - 1.6 to - 0.04, as seen in Table 2). Furthermore, the differences between cases and controls were dependent on abdominal pain severity as shown in Figure 2. As seen, mild abdominal pain symptoms were not significantly associated with reduced heat pain thresholds (mean differences = + 0.3 ^{o}C and 95 % CI = -1.2 to + 1.7 ^{o}C), while moderate and severe pain groups had mean heat pain thresholds of - 1.0 degree Celsius ($p < 0.05$ and 95 % CI = -2.0 to - 0.1 ^{o}C) and - 1.6 degree Celsius ($p < 0.05$ and 95 % CI = -3.2 to - 0.1 ^{o}C) below controls in the multivariate analysis, suggesting a dose-response relationship between abdominal pain severity and heat pain threshold.

[Place Table 1 about here]

Participants with IBS symptoms had lower pressure pain thresholds at both body-sites compared to controls, as shown in Table 1 (mean difference fingernail = - 62 kPa with 95 % CI = -109 to -15 and shoulder = - 46 kPa with 95 % CI = -78 to - 13). The pressure pain threshold differences between IBS and controls remained significant after adjustment for sex and co-morbid chronic pain in the multivariate analyses (Finger test: F = 4.1; Shoulder test: F = 5.4; $p < 0.05$ both). However, the differences were non-significant after further adjustment for psychological distress, as seen in Table 2, though a statistical trend remained at the shoulder site ($p = 0.05$). Due to lack of significant results in the multivariate analysis, post-hoc analysis of pain severity was not performed for pressure pain thresholds.

[Place Table 2 about here]

Total threshold score was lower for IBS than for controls (mean difference = - 0.4 with 95 % CI = - 0.6 to - 0.17) and this difference remained significant after adjustment for all covariates (mean difference = - 0.3 with 95 % CI = - 0.6 to - 0.1). In the post-hoc analysis, total threshold score decreased with increasing IBS pain severity. Compared to controls, IBS cases with mild, moderate and severe pain had z-scores - 0.26 (95% CI = - 0.7 to 0.2 SD), - 0.33 ($p < 0.05$ and 95% CI = - 0.7 to - 0.02 SD) and - 0.37 (95% CI = - 0.9 to 0.1) respectively after adjustments for sex, non-abdominal chronic pain and psychological distress symptoms.

Female sex was a significant covariate in all the pain threshold analyses comparing IBS with controls (Table 2). Female participants with IBS symptoms had lower pressure pain thresholds compared to the male IBS participants (shoulder: - 72 kPa with 95 % CI = -113 to -31 kPa and Finger: -117 kPa and 95 % CI = - 193 to -41 kPa, both $p < 0.01$), but the heat pain thresholds differences were not significantly lower (- 0.5 degrees Celsius with 95 % CI = - 2.1 to 1.1 and $p > 0.05$). Among participants without IBS symptoms, pain thresholds for heat and pressure were lower among female compared to male participants (heat pain: -0.4 degrees Celsius with 95 % CI = -0.9 to -0.1 and $p < 0.05$, pressure pain shoulder: -53 kPa with 95 % CI = -72 to -34 kPa and pressure pain finger: -113 kPa with 95 % CI = -139 to -87 kPa, both $p < 0.01$).

In contrast to female sex, neither non-abdominal chronic pain nor psychological distress emerged as significant covariates in any of the pain threshold analyses (Table 2).

[Place Figure 2 about here]

3.3 Pain tolerance

In contrast to the pain thresholds were there no significant differences in pain tolerance between cases and controls, for either the heat-, pressure- or cold-pressor tests, as shown in Table 1. Since large sex-differences in pain tolerance were found for all measures ($p < 0.01$), differences between cases and controls were tested within each sex, but no results approached significance in this stratified analysis (data not shown).

In the multivariate Cox regression analyses IBS was not associated with altered pain tolerance for any of the tests. Both female sex and psychological distress were significant predictors in these analyses, while non-abdominal chronic pain emerged as non-significant (Table 3).

[Place Table 3 about here]

4.0 Discussion

This is to our knowledge the first population based study of pain sensitivity among adolescents reporting IBS symptoms. The prevalence of IBS was somewhat higher than in our previous adult study (8.2 % vs. 5.3 %),[47] but comparable to other adult IBS prevalence

reports. [41] Little is known about IBS prevalence among adolescents and direct comparisons with previous studies is difficult due to differences in the IBS definitions and ages of the participants. [28, 57]

Our principal finding was that IBS cases had lower pain thresholds compared to controls, while there were no significant group differences in pain tolerance measures. Differences in heat and total threshold score remained significant after adjusting for sex, co-morbid chronic pain and psychological distress. Results also suggested a dose dependent relationship between pain thresholds and degree abdominal pain, with lowest pain thresholds occurring in severe abdominal pain IBS cases. The magnitude of the differences may seem small, but is probably related to the heterogeneity of the study sample with participants from the general population. The heat pain threshold results are comparable to our previous report of increased pain sensitivity among almost six hundred adults reporting IBS symptoms in the general population.[47] Furthermore, the level of increased heat pain sensitivity among the severe pain IBS cases is in accordance to what is reported in independent studies of adult IBS patients. [37, 58, 59] Though increased somatic pain sensitivity in general cannot be considered a diagnostic marker of the clinical condition, our findings support theories of central pain sensitization mechanisms in IBS.[40]

Pressure pain threshold at both trapezius and finger nail sites were lower in IBS compared to controls and remained so after correction for sex and co-morbid pain, but not after further adjustment for psychological distress, though differences at the shoulder site bordered on significance. Even if we cannot rule out the possibility that the relationship between pressure pain thresholds and IBS is indeed an effect of confounding with mental health, it is more likely that this represents a false negative result due to over-parameterization of the model in a sample including a modest number of IBS cases with varying degrees of symptom severity. By comparison, Caldarella et al. reported lower pressure pain thresholds in adult IBS patients with and without Fibromyalgia, while no differences were reported in two other adult studies.[4, 8, 58] In addition, we found lower pressure pain thresholds among adults reporting IBS symptoms in a previous population based study.[47] Unlike adolescents, this result emerged non- significant after adjusting for sex and non-abdominal chronic pain. A possible explanation for this inconsistency between the two age- cohorts is that pressure pain measurements were not directly comparable (threshold vs. supra-threshold). Thus, though the association between pressure pain thresholds and IBS is reasonably consistent across studies and age cohorts, there is some inconsistency with respect to the contribution of confounding

factors. Specifically, the importance of co-morbid anxiety and depression in this association remains uncertain.

Unlike pain thresholds, pain tolerance measures were not significantly related to case status. It is unlikely that this is due to lack of statistical power, as pain tolerance was marginally higher among IBS cases for three out of four stimuli. Comparable data from other pediatric studies is limited. In a small sample of pre-menarchal girls, Williams, et al. found no difference in heat pain threshold or in supra-threshold cold-pressor pain intensity, but evidence of impaired endogenous pain inhibition in IBS patients compared to healthy controls.[56] However, the latter result was not significant after controlling for psychological distress symptoms. As the authors note, this may be due to lack of statistical power. To our knowledge, no other studies of somatic pain sensitivity in pediatric IBS have been published though four studies of recurrent abdominal pain (RAP) are available. RAP is a symptom based pediatric classification, with at least three attacks of abdominal pain during three consecutive months that interferes with daily activity, which includes a higher percentage of patients who also meet IBS diagnostic criteria.[19, 53] In a sample of 21 RAP cases, Dufton, et al. [18] found no differences in cold-pressor tolerance or pain intensity, which is consistent with our findings and those of Williams et al. cited above. In a small sample including 20 RAP cases, Zohsel, et al. found no difference in heat pain threshold or pressure pain threshold between cases and controls.[60] Finally, Alfven [1] and Duarte et al. [17] found lower pressure pain thresholds in children with RAP compared to healthy children. Taken together these latter two studies included 149 RAP cases, giving grounds for confidence in the findings, though neither study controlled for co-morbid chronic pain and only Alfven included measurements of psychological factors (behavioral traits) in his study. In summary, the results of the current study are consistent with results from previous, smaller studies in children with chronically recurrent abdominal pain in failing to show an association between pain tolerance and case status, while a majority cases are found to have lower pain thresholds compared to controls.

Lower pain tolerance has been reported among adult IBS patients compared to controls[3, 59], in contrast to what found in the current study adolescent and in previous adolescent studies of RAP. Unlike adolescents, we have previously found that adults IBS cases have lower cold-pressor tolerance.[47] The stimulus paradigm was in this case identical, even including the same apparatus, so procedural differences are unlikely to be the cause of this inconsistency. Nor, as argued above, is it not plausible that this is a power issue. The lack of pain tolerance differences in pediatric IBS and RAP compared to controls could be related to psychological

mechanisms, possibly differing in children and adults. However, as the association between pain tolerance and IBS did not even approach significance in the univariate analysis, this seems unlikely. Rather, the results indicate that this is either a cohort effect, age effect, or that pain tolerance in IBS is altered only when the symptoms persist over a substantial time span. As far as we know, no prospective studies of chronic pain have so far investigated whether pain tolerance is related to the duration of pain symptoms. Still, there is some support for this interpretation in the study by Walker et al., reporting evidence of enhanced central pain sensitization among female adolescents and young female adults with a history of recurrent abdominal pain in childhood, with greatest sensitivity for heat pain among the participants with persistent abdominal pain.[11] One could speculate that persistence of chronic visceral pain results in neuroplastic remodeling of the brain,[20] and that such remodeling is associated with reduced pain tolerance.

Although the prior studies of RAP included both boys and girls none examined their data for sex differences. Sex differences in pain sensitivity to pressure and heat have been frequently reported for healthy adults and when present, females are consistently more sensitive than males.[22, 35] A female bias in the prevalence of many but not all chronic pain conditions (including IBS) has also been found and some data indicates these sex differences emerge or become larger with puberty.[22] Thus the current findings of somewhat greater pressure and heat sensitivity among female compared to male adolescents is consistent with the adult literature. Importantly, controlling for sex differences did not alter the results of increased pain sensitivity in IBS, supporting the general hypothesis of a sex-independent pain sensitization in this group.

A strength of this study, is the population based sampling with very high response rate. This ensures that the participants are representative of the population and that the findings are generalizable. However, this strength is also a weakness; since the participants defined as having IBS symptoms may include both clinical and subclinical cases. It is important to emphasize that the IBS cases were identified solely through self-reported symptoms, without supplementary clinical diagnostics. Thus there is a risk of misclassifying organic diseases as IBS. Still, with the knowledge that most pediatric patients with abdominal pain have functional gastroenterological disorders,[10, 30, 53] and that IBS is the most common cause,[19] the risk of misclassification is most likely acceptably low if typical symptoms of IBS are present.

In contrast to previous pediatric IBS and RAP pain sensitivity studies we controlled for both co-morbid chronic pain, in addition to anxiety and depression. There is still a risk of residual confounding, including other psychological mechanism that are shown to be related to increased pain sensitivity among children and adolescents. [36, 50] To what degree the same factors explain a possible age-related difference of pain sensitivity in IBS remains unanswered.

Summary and Conclusions

Adolescents with IBS symptoms have lower heat pain and pressure pain thresholds compared to individuals without IBS symptoms, which indicate the presence of widespread hyperalgesia among adolescents with IBS, and supports theories of central pain sensitization in this patient group.[40, 54]. These central mechanisms may contribute to maintaining and reinforcing abdominal pain in IBS, and possibly contribute to the high prevalence of co-morbid non-abdominal pain. As changes in pain tolerance were not evident in the current study, but have previously been reported in adult IBS patients, it is possible that tolerance differences emerge as IBS-symptoms persist over longer periods of time.

Disclosures:

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Figure 1 Study flowchart

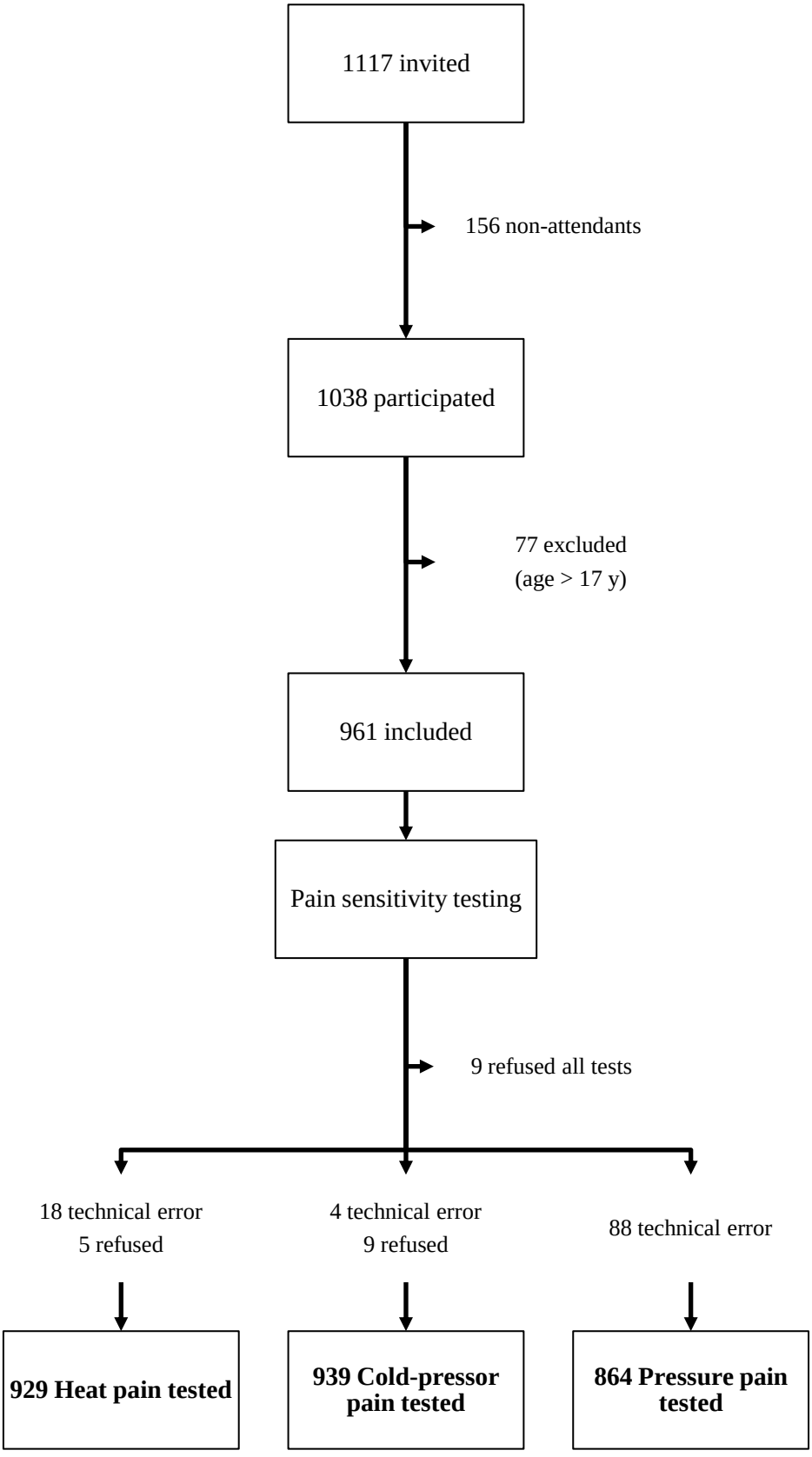


Table 1 Descriptive statistics

	Girls (N =469)	Boys (N =492)	Control (N=861)	IBS (N= 77)
Girls	-	-	47.7 %	61.0 % *
IBS	10.3 % *	6.2 %	-	-
Non-abdominal chronic pain	22.6 % **	13.5 %	16.4 %	32.5 % **
Psychological distress (HSCL ≥ 1.85)	27.2 % **	10.8 %	16.0%	49.4 % **
Pain Threshold (mean, SD)				
Heat, degrees Celsius	44.2 (3.1) *	44.6 (3.3)	44.6 (3.1)	43.8 (3.4) *
Pressure (finger), kPa	384 (155) **	499 (211)	447 (193)	385 (165) *
Pressure (shoulder), kPa	256 (116) **	312 (142)	290 (136)	245 (91) **
Sum score (z-values)	- 0.2 (0.9) **	0.2 (1.1)	0.04 (1.0)	- 0.4 (0.9) **
Pain Tolerance (median, IQR)				
Heat, degrees Celsius	48.4 (3.3) **	50.0 (1.1)	49.4 (2.2)	49.0 (2.4)
Pressure (finger), kPa	770 (402) **	1000 (196)	914 (338)	966 (402)
Pressure (shoulder), kPa	529 (426) **	816 (482)	635 (564)	680 (573)
Cold-pressor endurance, seconds	80.6 (61.4)**	105.0 (54.5)	105 (56.6)	105.0 (55.3)
Cold-pressor endurance < 105 s	54.4 %**	45.6 %	48.1 %	45.5 %

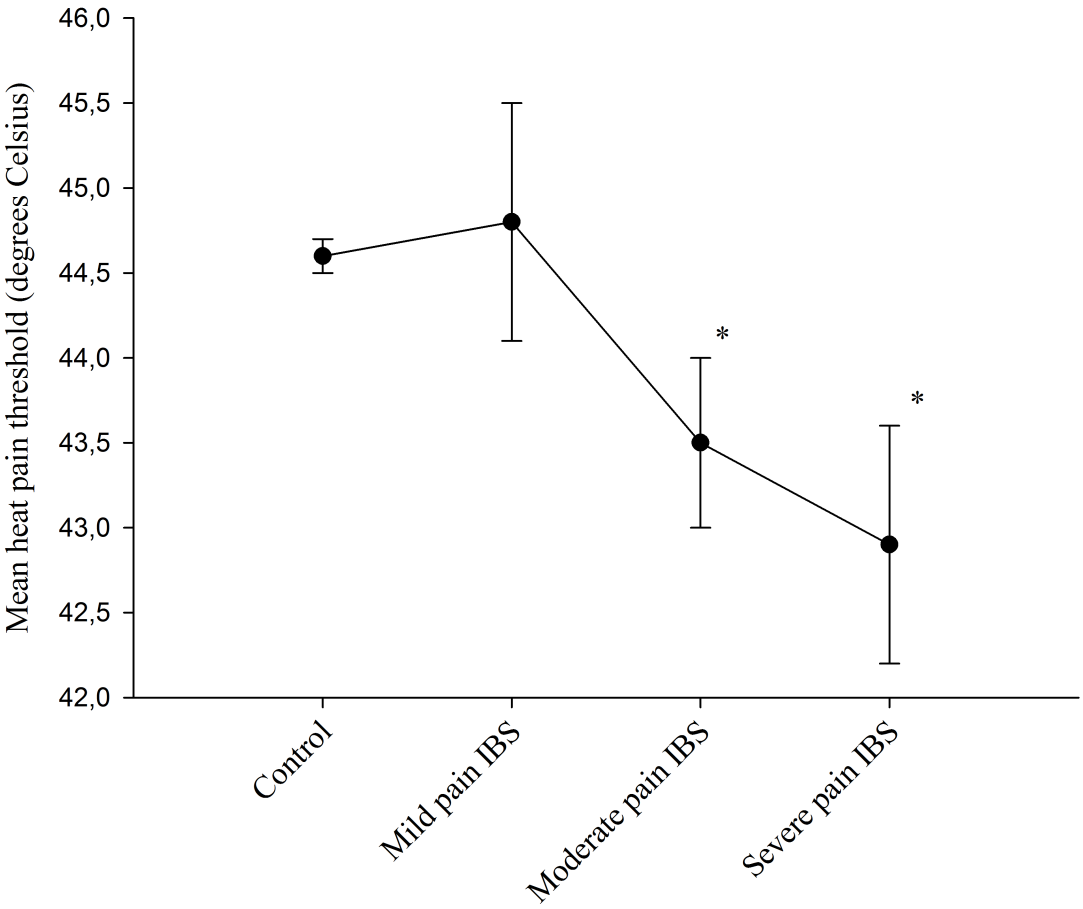
*$p < 0.05$ and **$p < 0.01$ in analyses of girls vs. boys, control vs. IBS (Chi-square tests, t-tests and Mann-Whitney U-tests).

Table 2 Multivariate analyses of pain thresholds in IBS

		F (df = 1)	Mean difference (95 % CI)
Heat pain			
	IBS	4.6 *	- 0.8 (- 1.6 to - 0.04) ^{o}C
	Girls	5.5*	
	Non-abdominal chronic pain	0.05	
	Psychological distress (HSCL ≥1.85)	1.7	
Pressure pain Finger			
	IBS	2.8	- 40 (- 87 to 7) kPa
	Girls	21.8**	
	Non-abdominal chronic pain	0.35	
	Psychological distress (HSCL ≥1.85)	1.9	
Pressure pain Shoulder			
	IBS	3.8	- 33 (- 65 to 2) kPa
	Girls	29.3 **	
	Non-abdominal chronic pain	1.5	
	Psychological distress (HSCL ≥1.85)	1.7	
Sum score (z-values)			
	IBS	7.4 **	- 0.3 (- 0.6 to - 0.1)
	Girls	40.0**	
	Non-abdominal chronic pain	0.5	
	Psychological distress (HSCL ≥1.85)	0.1	

*p < 0.05, **p < 0.01 in ANCOVA: IBS vs. control, adjusting for sex, non-abdominal chronic pain and psychological distress. Mean differences: Pair-wise comparisons of IBS vs. control.

Figure 2 Heat pain thresholds in IBS pain subgroups and controls



* $p < 0.05$ in pairwise comparisons of IBS pain subgroups vs. control, adjudted for sex, non-abdominal chronic pain and psychological distress.

Table 3 Multivariate analyses of pain tolerance in IBS

	Pain modality Hazard ratio (95 % CI)			
	Heat	**Pressure**		**Cold-pressor**
		Finger	Shoulder	
IBS	1.0 (0.7-1.4)	0.8 (0.6-1.1)	0.8 (0.6-1.0)	0.7 (0.5-1.1)
Girls	2.6 (2.2-3.1) **	2.4 (2.0-2.9) **	1.9 (1.6-2.3) **	1.3 (1.1-1.6) **
Non-abdominal chronic pain	1.0 (0.8-1.3)	1.0 (0.8-1.3)	1.1 (0.9-1.4)	1.0 (0.8-1.3)
Psychological distress (HSCL ≥1.85)	1.3 (1.0-1.6) *	1.3 (1.0-1.6) *	1.4 (1.2-1.8) **	1.8 (1.4-2.3) **

*$p < 0.05$, **$p < 0.01$ in multiple Cox regression analyses of pain tolerance in IBS vs. control, adjusted for sex, non-abdominal chronic pain and psychological distress.