

## Original Reports

# Widespread Hyperalgesia in Adolescents With Symptoms of Irritable Bowel Syndrome: Results From a Large Population-Based Study

Niklas Stabell,<sup>\*</sup> Audun Stubhaug,<sup>†</sup> Trond Flægstad,<sup>\*</sup> Emeran Mayer,<sup>‡</sup> Bruce D. Naliboff,<sup>§</sup> and Christopher S. Nielsen<sup>¶</sup>

<sup>\*</sup>Department of Pediatrics, University Hospital of North Norway, and Department of Clinical Medicine, University of Tromsø, Tromsø, Norway.

<sup>†</sup>Department of Pain Management and Research, Oslo University Hospital and Faculty of Medicine, Oslo University, Oslo, Norway.

<sup>‡</sup>Oppenheimer Family Center for the Neurobiology of Stress, Division of Digestive Diseases, and <sup>§</sup>Department of Medicine and Psychiatry and Biobehavioral Sciences, David Geffen School of Medicine at University of California–Los Angeles, Los Angeles, California.

<sup>¶</sup>Division of Mental Health, Norwegian Institute of Public Health, Oslo, Norway.

**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, comorbid pain, and psychological distress (mean difference =  $-0.8^{\circ}\text{C}$ ; 95% confidence interval [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 3 threshold measures (z-score difference =  $-0.4$ ; 95% CI =  $-0.6$  to  $-0.2$ ), though pressure pain threshold differences were nonsignificant 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 independent of sex and comorbid pain. Our results suggest that central pain sensitization mechanisms in IBS may contribute to triggering and maintaining chronic pain symptoms.

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**Key words:** Widespread hyperalgesia, irritable bowel syndrome, comorbidity, quantitative pain sensitivity testing, adolescents.

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Address reprint requests to Niklas Stabell, MD, Department of Pediatrics, University Hospital of Northern Norway, 9038 Tromsø, Norway. E-mail: [niklas.stabell@unn.no](mailto:niklas.stabell@unn.no)

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Irritable bowel syndrome (IBS) is the most common cause of chronic or recurrent abdominal pain (RAP) in the pediatric population.<sup>19,26,28</sup> IBS is more prevalent among girls than among boys and is associated with high risk of mental health problems and of comorbid pain at other body sites.<sup>25,26,51</sup>

There is broad agreement that IBS is best conceptualized in terms of the biopsychosocial model, with multiple factors contributing to its pathophysiology.<sup>6,9,16,21,29,34,49</sup> These factors are incompletely understood but are likely

to include both peripheral gut factors<sup>5,27</sup> and central factors, including central pain modulation,<sup>40</sup> as well as disorders of mood and affect.<sup>2,24</sup>

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.<sup>7,14,31,33,38,44,52</sup> 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 (eg, heat, cold pressor, and pressure pain) at distal body sites.<sup>3,37,39,43</sup> 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 triggering and to maintaining chronic pain.<sup>40,55</sup> Additional support for these theories is reported in a recent study using diffusion tensor imaging of the brain in adult IBS patients that identified microstructural reorganization in brain regions involved in sensory modulation and integration.<sup>20</sup> In a 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.<sup>47</sup> These results of increased widespread pain sensitivity remained robust after controlling for sex, mental health, and comorbid chronic pain.

However, the above-cited studies are restricted mainly to 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 1 including pediatric IBS patients.<sup>1,17,18,56,60</sup> Results from these studies have been equivocal, possibly because of the relatively small samples sizes. Furthermore, there are no prospective studies of pain sensitivity among children with RAP and IBS, but increased somatic pain sensitivity was found in 1 study among adolescents and young adults with a history of childhood chronic abdominal pain.<sup>11</sup> However, whether 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 comorbid 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 1) compare heat, pressure, and cold pressor pain sensitivity in adolescents with IBS symptoms with the remaining adolescent participants in a population-based study and 2) test whether associations between IBS and pain sensitivity could be explained by confounding factors.

## Methods

### 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 to 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 1-day session at the Department of Research at the University Hospital of North Norway.

A total of 1,117 students from 5 high schools were invited, and among 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 to 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 2 body sites, and cold pressor pain tolerance (see the study flowchart in Fig 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.

### IBS Case Definition

The revised IBS criteria from 2006 (Rome III IBS criteria) were used to identify participants with IBS symptoms.<sup>42</sup> Adolescents were classified as IBS cases if they reported weekly abdominal pain or discomfort during the past 2 or more months and 2 or more of the following associated bowel symptoms at least 25% of the time: 1) relief with defecation, 2) change in stool frequency, and/or 3) change in stool form. Clinical examinations were not conducted to identify cases with possible gastrointestinal organic diseases. However, previous adult validation studies of the Rome criteria have shown acceptable sensitivity and specificity compared to clinical IBS diagnosis (70–90% and 70–80%, respectively).<sup>23</sup> 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 misclassification, the Rome criteria are widely used, particularly in epidemiologic studies.<sup>41</sup>

The participants who reported abdominal pain or discomfort during the past 2 months were asked to report how much abdominal pain they usually had, rated on a 0 to 10 numeric rating scale (NRS), with 0 corresponding to no pain and 10 to most intense pain imaginable. Because no one reported no pain and the NRS scores were somewhat skewed, the IBS cases were subclassified into the commonly used categories of mild (NRS score = 1–3), moderate (NRS score = 4–6), and severe (NRS score = 7–10) pain.

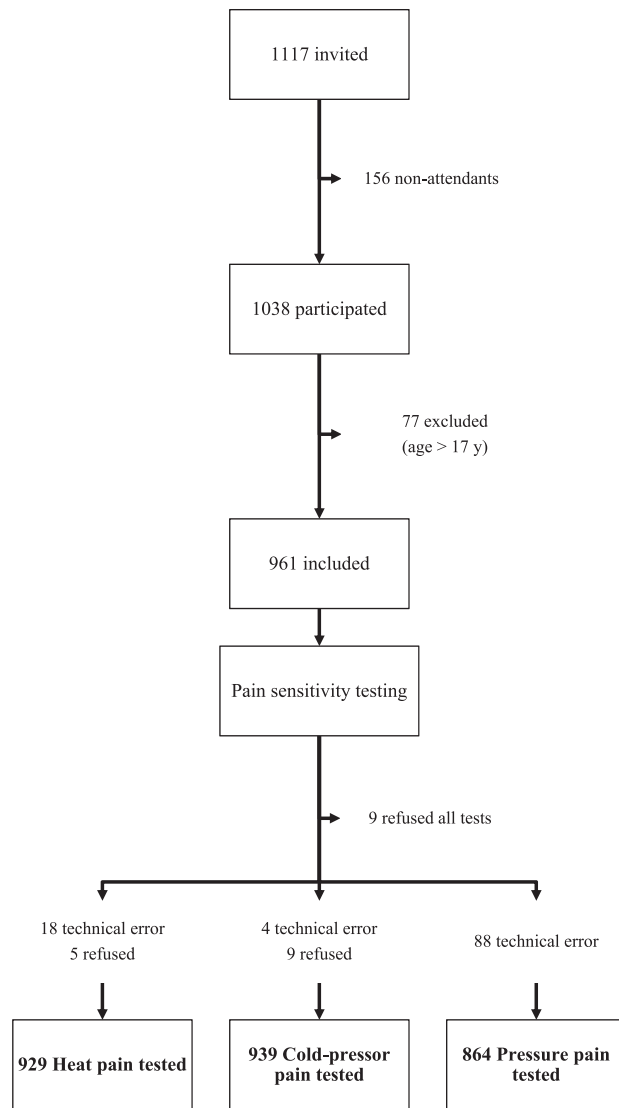


Figure 1. Study flowchart.

### Psychological Distress and Comorbid Chronic Pain Case Definition

Anxiety and depression symptoms were assessed with the Hopkins Symptom Checklist (HSCL), 10-item version. HSCL is a screening tool for detecting negative mood symptoms, is suitable for epidemiologic research among adolescents, and has been validated against clinical diagnostic depression and anxiety tools.<sup>12,13,32,45,46</sup> 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.<sup>48</sup>

Nonabdominal 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?” Because this broad question might include IBS-related pain, follow-up questions on pain location

were used to identify subjects with nonabdominal chronic pain. Thus, both IBS cases and controls reporting pain lasting 3 months or longer at any nonabdominal site (ie, head, jaw, neck, back, shoulder, arm, hand, hip, leg, foot, genitalia, or skin) were classified as having nonabdominal chronic pain.

### Pain Sensitivity Measurements

Heat pain threshold and tolerance was tested using a Medoc ATS somatosensory stimulator (Medoc Ltd, Ramat Yishai, Israel) with a 30 × 30-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. On 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 3 times; the first measurement was discarded, and the second and third measurements 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 higher temperature was used.

As with heat pain, the pressure pain threshold and tolerance were recorded by pressing a button when the sensation changed from nonpainful 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 handheld algometer (Somedic, AB, Hörby, Sweden) with a circular probe of 1 cm<sup>2</sup>. Starting at 0 kPa, pressure was increased by 30 kPa/s up to a maximum of 1,000 kPa. Threshold measurement was repeated 3 times, followed by tolerance measurements, repeated twice. For each site, the second and third threshold measures were averaged and the higher tolerance measurements were used.

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

### Statistical Analysis

SPSS version 20 (SPSS Inc, Chicago, IL) 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 because of 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 was carried out adjusting for sex, nonabdominal chronic pain, and psychological distress. Where significant group differences were observed, post hoc analysis of covariance was performed to compare IBS pain subgroups (ie, 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 [forearm] and pressure [fingernail and shoulder]), averaging the 3 variables and finally z-transforming the average. A similar procedure has been used by other research groups previously.<sup>15</sup>

Because of right censoring of the heat, pressure, and cold pressor pain tolerance data, Cox proportional hazard regression was used to analyze the outcomes. Heat pain tolerance below 50°C, pressure pain tolerance below 1,000 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, nonabdominal chronic pain, and psychological distress. Further analyses including the IBS pain subgroup or total pain tolerance scores were not performed because of missing significant associations of IBS and pain tolerances in the analyses above.

Some participants failed to undergo all pain sensitivity measurements as shown in Fig 1. Technical failures were the most common cause. However, as missing data were 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.

## Results

### Demographics, Prevalence, and Comorbidity

Mean age was 16.1 years (standard deviation [SD] = .4), and without significant differences between IBS cases and controls (*P* > .05). Overall, 8.2% of the participants met the case definition of IBS. All of the IBS cases reported chronic abdominal pain (NRS scores >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* < .05) (Table 1).

The median HSCL score for the whole sample was 1.3 (interquartile range = .6). Psychological distress (HSCL score ≥ 1.85) was reported nearly 3 times as often by girls than by boys (*P* < .01). Psychological distress was reported by approximately half the IBS cases and by 16% of controls (*P* < .01). Conversely, of the participants reporting psychological distress, 21.7% met the IBS case definition, versus 5.1% in the remaining sample (*P* < .01).

Overall, 17.6% of the participants reported nonabdominal chronic pain. Nonabdominal chronic pain was also more common in girls than in boys (22.6% vs 13.5%, respectively, *P* < .01). Nearly one third of the IBS cases reported nonabdominal chronic pain, compared to 16.4% in the control group (*P* < .01).

### Pain Thresholds

Heat pain thresholds were significantly lower among IBS cases than among controls (mean difference = −.8°C with 95% confidence interval [CI] = −1.5 to −.04). This difference remained significant and unchanged after adjustment for all covariates (mean difference = −.8°C with 95% CI = −1.6 to −.04, as seen in Table 2). Furthermore, the differences between cases and controls were dependent on abdominal pain severity, as shown in Fig 2. As seen, mild abdominal pain symptoms were not significantly associated with reduced heat pain thresholds (mean differences = +.3°C and 95% CI = −1.2 to

**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	—	—
Nonabdominal 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, °C	44.2 (3.1)*	44.6 (3.3)	44.6 (3.1)	43.8 (3.4)*
Pressure (fingernail), kPa	384 (155)**	499 (211)	447 (193)	385 (165)*
Pressure (shoulder), kPa	256 (116)**	312 (142)	290 (136)	245 (91)**
Sum score (z values)	−.2 (.9)**	.2 (1.1)	.04 (1.0)	−.4 (.9)**
Pain tolerance (median, IQR)				
Heat, °C	48.4 (3.3)**	50.0 (1.1)	49.4 (2.2)	49.0 (2.4)
Pressure (fingernail), kPa	770 (402)**	1,000 (196)	914 (338)	966 (402)
Pressure (shoulder), kPa	529 (426)**	816 (482)	635 (564)	680 (573)
Cold pressor endurance, s	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

Abbreviation: IQR, interquartile range.

NOTE. Values are % unless otherwise indicated.

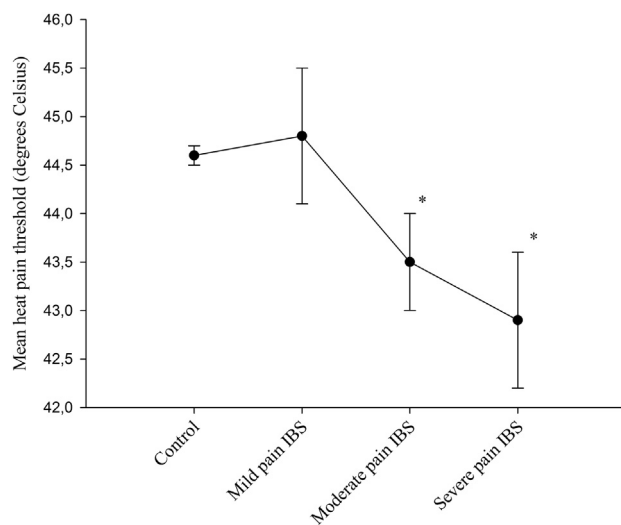
\**P* < .05 and \*\**P* < .01 in analyses of girls vs boys, control vs IBS ( $\chi^2$  tests, t-tests, and Mann-Whitney U tests).

**Table 2. Multivariate Analyses of Pain Thresholds in IBS**

	<i>F</i> ( <i>DF</i> = 1)	MEAN DIFFERENCE (95% CI)
Heat pain		
IBS	4.6*	-.8 (-1.6, -.04)°C
Girls	5.5*	
Nonabdominal chronic pain	.05	
Psychological distress (HSCL ≥ 1.85)	1.7	
Pressure pain: fingernail		
IBS	2.8	-40 (-87, 7) kPa
Girls	21.8**	
Nonabdominal chronic pain	.35	
Psychological distress (HSCL ≥ 1.85)	1.9	
Pressure pain: shoulder		
IBS	3.8	-33 (-65, 2) kPa
Girls	29.3**	
Nonabdominal chronic pain	1.5	
Psychological distress (HSCL ≥ 1.85)	1.7	
Sum score (z values)		
IBS	7.4**	-.3 (-.6, -.1)
Girls	40.0**	
Nonabdominal chronic pain	.5	
Psychological distress (HSCL ≥ 1.85)	.1	

\**P* < .05, \*\**P* < .01 in analysis of covariance: IBS vs control, adjusting for sex, nonabdominal chronic pain, and psychological distress. Mean differences: pairwise comparisons of IBS vs control.

+1.7°C), whereas moderate and severe pain groups had mean heat pain thresholds of -1.0°C (*P* < .05 and 95% CI = -2.0 to -.1°C) and -1.6°C (*P* < .05 and 95% CI = -3.2 to -.1°C) below controls in the multivariate analysis, suggesting a dose-response relationship between abdominal pain severity and heat pain threshold.



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

**Figure 2.** Heat pain thresholds in IBS pain subgroups and controls.

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; 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 comorbid chronic pain in the multivariate analyses (fingernail: *F* = 4.1; shoulder: *F* = 5.4; *P* < .05 for both). However, the differences were nonsignificant after further adjustment for psychological distress, as seen in Table 2, though a statistical trend remained at the shoulder site (*P* = .05). Because of a lack of significant results in the multivariate analysis, post hoc analysis of pain severity was not performed for pressure pain thresholds.

Total threshold score was lower for IBS than for controls (mean difference = -.4 with 95% CI = -.6 to -.17), and this difference remained significant after adjustment for all covariates (mean difference = -.3 with 95% CI = -.6 to -.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 -.26 (95% CI = -.7 to .2 SD), -.33 (*P* < .05 and 95% CI = -.7 to -.02 SD), and -.37 (95% CI = -.9 to .1), respectively, after adjustments for sex, nonabdominal 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 (fingernail: -117 kPa with 95% CI = -193 to -41 kPa; shoulder: -72 kPa with 95% CI = -113 to -31 kPa; both *P* < .01), but the heat pain thresholds differences were not significantly lower (-.5°C with 95% CI = -2.1 to 1.1 and *P* > .05). Among participants without IBS symptoms, pain thresholds for heat and pressure were lower among female compared to male participants (heat pain: -.4°C with 95% CI = -.9 to -.1 and *P* < .05; pressure pain shoulder: -53 kPa with 95% CI = -72 to -34 kPa; pressure pain fingernail: -113 kPa with 95% CI = -139 to -87 kPa; both *P* < .01).

In contrast to female sex, neither nonabdominal chronic pain nor psychological distress emerged as a significant covariate in any of the pain threshold analyses (Table 2).

### Pain Tolerance

In contrast to the pain thresholds, there were no significant differences in pain tolerance between cases and controls for the heat, pressure, or cold pressor tests, as shown in Table 1. Because large sex differences in pain tolerance were found for all measures (*P* < .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, whereas nonabdominal chronic pain emerged as nonsignificant (Table 3).

**Table 3. Multivariate Analyses of Pain Tolerance in IBS**

	PAIN MODALITY HAZARD RATIO (95% CI)			
	PRESSURE			
	HEAT	FINGERNAIL	SHOULDER	COLD PRESSOR
IBS	1.0 (.7, 1.4)	.8 (.6, 1.1)	.8 (.6, 1.0)	.7 (.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)**
Nonabdominal chronic pain	1.0 (.8, 1.3)	1.0 (.8, 1.3)	1.1 (.9, 1.4)	1.0 (.8, 1.3)
Psychological distress (HSCL $\geq$ 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)**

\* $P < .05$ , \*\* $P < .01$  in multiple Cox regression analyses of pain tolerance in IBS vs control, adjusted for sex, nonabdominal chronic pain, and psychological distress.

## 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%)<sup>47</sup> but comparable to other adult IBS prevalence reports.<sup>41</sup> Little is known about IBS prevalence among adolescents, and direct comparison with previous studies is difficult because of differences in the IBS definitions and ages of the participants.<sup>28,57</sup>

Our principal finding was that IBS cases had lower pain thresholds compared to controls, whereas there were no significant group differences in pain tolerance measures. Differences in heat and total threshold score remained significant after adjusting for sex, comorbid chronic pain, and psychological distress. Results also suggested a dose-dependent relationship between pain thresholds and degree of abdominal pain, with lowest pain thresholds occurring in IBS cases with severe abdominal pain. 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 600 adults reporting IBS symptoms in the general population.<sup>47</sup> Furthermore, the level of increased heat pain sensitivity among the severe pain IBS cases is in accordance with what is reported in independent studies of adult IBS patients.<sup>37,58,59</sup> 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.<sup>40</sup>

Pressure pain threshold at both trapezius and fingernail sites were lower in IBS compared to controls and remained so after correction for sex and comorbid 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 overparameterization 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,

whereas no differences were reported in 2 other adult studies.<sup>4,8,58</sup> In addition, we found lower pressure pain thresholds among adults reporting IBS symptoms in a previous population-based study.<sup>47</sup> Unlike that for adolescents, this result emerged nonsignificant after adjusting for sex and nonabdominal chronic pain. A possible explanation for this inconsistency between the 2 age cohorts is that pressure pain measurements were not directly comparable (threshold vs suprathreshold). 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 comorbid 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 3 out of 4 stimuli. Comparable data from other pediatric studies is limited. In a small sample of premenarchal girls, Williams et al found no difference in heat pain threshold or in suprathreshold cold pressor pain intensity but noted evidence of impaired endogenous pain inhibition in IBS patients compared to healthy controls.<sup>56</sup> 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 4 studies of RAP are available. RAP is a symptom-based pediatric classification, with at least 3 attacks of abdominal pain during 3 consecutive months that interferes with daily activity, which includes a higher percentage of patients who also meet IBS diagnostic criteria.<sup>19,53</sup> In a sample of 21 RAP cases, Dufton et al<sup>18</sup> 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.<sup>60</sup> Finally, Alfvén<sup>1</sup> and Duarte et al<sup>17</sup> found lower pressure pain thresholds in children with RAP compared to healthy children. Taken together, these latter 2 studies included 149 RAP cases, giving grounds for confidence in the findings, though neither study controlled for comorbid

chronic pain and only Alfvén 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 chronic RAP in failing to show an association between pain tolerance and case status, whereas a majority of cases are found to have lower pain thresholds compared to controls.

Lower pain tolerance has been reported among adult IBS patients compared to controls,<sup>3,59</sup> in contrast to what was found in the current study on adolescents and in previous adolescent studies of RAP. Unlike that seen in adolescent cases, we have previously found that adult IBS cases have lower cold pressor tolerance.<sup>47</sup> 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 or 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 RAP in childhood, with greatest sensitivity for heat pain among the participants with persistent abdominal pain.<sup>11</sup> One could speculate that persistence of chronic visceral pain results in neuroplastic remodeling of the brain<sup>20</sup> 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.<sup>22,35</sup> A female bias in the prevalence of many but not all chronic pain conditions (including IBS) has also been found, and some data indicate that these sex differences emerge or become larger with

puberty.<sup>22</sup> 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 a 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, because 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,<sup>10,30,53</sup> and that IBS is the most common cause,<sup>19</sup> 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 comorbid chronic pain in addition to anxiety and depression. There is still a risk of residual confounding, including other psychological mechanisms that are shown to be related to increased pain sensitivity among children and adolescents.<sup>36,50</sup> To what degree the same factors explain a possible age-related difference of pain sensitivity in IBS remains unanswered.

## 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.<sup>40,54</sup> These central mechanisms may contribute to maintaining and reinforcing abdominal pain in IBS and possibly contribute to the high prevalence of comorbid nonabdominal 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.

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