Association Between Early Adverse Life Events and Irritable Bowel Syndrome

KARA BRADFORD,[*,‡] WENDY SHIH,[§] ELIZABETH J. VIDELOCK,[*] ANGELA P. PRESSON,[‖] BRUCE D. NALIBOFF,[*,‖,¶,#] EMERAN A. MAYER,[*,‖,**,‡‡] and LIN CHANG[*,‖]

[*]Oppenheimer Family Center of Neurobiology of Stress, [§]Department of Biostatistics, [‖]Department of Medicine, [¶]Department of Psychiatry and Biobehavioral Sciences, [**]Department of Physiology, and [‡‡]Brain Research Institute, David Geffen School of Medicine at the University of California Los Angeles; and [‡]Department of Medicine and [#]Department of Psychiatry, Greater Los Angeles Veterans Administration Medical Center, Los Angeles, California

BACKGROUND & AIMS: Although childhood and adult abuse are more prevalent among patients with irritable bowel syndrome (IBS) than healthy individuals (controls), other types of early adverse life events (EALs) have not been well characterized. We investigated whether different types of EALs, before age 18 years, are more prevalent among patients with IBS, and the effects of sex and nongastrointestinal symptoms on the relationship between EALs and IBS. **METHODS:** EALs were evaluated in 294 IBS patients (79% women) and 435 controls (77% women) using the Early Trauma Inventory Self-Report Form, which delineates subcategories of general trauma and physical, emotional, and sexual abuse. Validated questionnaires assessed gastrointestinal, psychological, and somatic symptoms. **RESULTS:** Compared with controls, IBS patients reported a higher prevalence of general trauma (78.5% vs 62.3%), physical punishment (60.6% vs 49.2%), emotional abuse (54.9% vs 27.0%), and sexual events (31.2% vs 17.9%) (all $P < .001$). These significant differences were observed mainly in women. Of the EAL domains, emotional abuse was the strongest predictor of IBS ($P < .001$). Eight of the 27 EAL items were significant ($P < .001$) and increased the odds of having IBS by 108% to 305%. Although EALs and psychological variables were related, EALs had an independent association with IBS ($P = .04$). **CONCLUSIONS: Various types of EALs are associated with the development of IBS—particularly among women. Psychological distress and somatic symptoms might contribute to this relationship. When appropriate, EALs and nongastrointestinal symptoms should be assessed in IBS patients.**

Keywords: ETI-SF; Psychology; Somatization; Nervous System.

Early adverse life events (EALs) refer to traumatic experiences during childhood encompassing physical, sexual, or emotional abuse, as well as discordant relationships with a primary caretaker, or the loss of a parent.[1–5] Children with a history of EALs have an increased risk of developing a range of chronic medical disorders later in life.[6–9]

EALs also appear to be associated with an increased vulnerability toward developing functional gastrointestinal disorders (FGIDs), including irritable bowel syndrome (IBS).[1,10–12] The most common EAL assessed in IBS is childhood or adulthood abuse. In a population-based survey by Talley et al,[13] the prevalence of childhood abuse was significantly higher in individuals with vs without IBS (15.4% vs 9.5%).[13] Similarly, Drossman et al[14] found that patients with FGIDs experienced more severe forms of abuse in childhood and/or adulthood, including rape and life-threatening physical abuse, compared with patients with organic gastrointestinal (GI) diseases.[14] EALs other than abuse have not been studied extensively in IBS patients. In 1979, Hislop[15] reported that 31% of IBS patients had experienced parental death, divorce, or separation and 61% reported unsatisfactory relationships with or between their parents before the age of 15, but there was no comparison with a control group.

EALs have been associated with negative outcomes in patients with GI conditions. Among patients with upper GI and chest conditions, childhood adversity maintained an independent effect on poorer health-related quality of life in patients with noncardiac chest pain and functional dyspepsia, 2 types of FGIDs.[16] An abuse history has been associated with greater pain, disability, and psychological distress, and poorer daily functioning in GI patients independent of diagnosis.[17] In addition, sexual abuse correlated with more severe IBS symptoms, non-GI symptoms, and abdominal surgery.[18]

Although associations between an abuse history and IBS have been reported before, in the current study we aimed to assess simultaneously the association of a range of EALs, not limited to abuse, with IBS and the impact of differences in sex and psychological factors on these associations. Specifically, we aimed to address the following questions: (1) is a history of EALs before the age of 18 associated with IBS? (2) What are the types of EALs most commonly associated with IBS? (3) Is there a gender-related difference in the association of EALs and IBS? (4) What is the impact of psychological symptoms on the relationship between EALs and IBS?

Methods

Study Subjects

Male and female IBS patients who were 18 years of age and older were recruited from newspaper or internet community advertisements and from GI clinics and fulfilled Rome III diagnostic criteria.[19] Healthy control subjects (HCs) were re-

Abbreviations used in this paper: EALs, early adverse life events; ETI-SF, Early Trauma Inventory Self-Report Form; FGIDs, functional gastrointestinal disorder; GI, gastrointestinal; HAD, Hospital Anxiety and Depression scale; HC, healthy control; IBS, irritable bowel syndrome; PHQ, Personal Health Questionnaire; VSI, Visceral Sensitivity Index.

1542-3565/$36.00
doi:10.1016/j.cgh.2011.12.018

cruited by advertisement without a history of IBS or other chronic GI or pain conditions, and were not taking psychotropic medication or participating in psychotherapy. Subjects were compensated $50 for the completion of a medical history and physical examination and questionnaires.

Questionnaires

Bowel symptom questionnaire. The questionnaire included Rome III questions for IBS[20] and a 0 to 20 numeric rating scale of overall IBS symptom severity over the past week (none to most intense imaginable).[21]

Early adverse life events questionnaire. The presence of EALs (before age 18) was assessed by the Early Trauma Inventory Self-Report Form (ETI-SF).[4] It assesses EALs in the following domains (number of items): general trauma (11), physical (5), emotional (5), and sexual abuse (6). Each of the 27 items was scored as "yes" (=1) or "no" (=0) (total score range, 0–27). The ETI-SF has been validated in post-traumatic stress disorder; the best predictor of post-traumatic stress disorder symptoms was the total score.[4] General trauma includes various stressful and traumatic events. Physical punishment is defined as physical contact, constraint, or confinement with intent to hurt or injure. Emotional abuse includes events defined by verbal communication with intent to humiliate or degrade. Sexual abuse is unwanted sexual contact for the gratification of the perpetrator or for the purposes of dominating or degrading the victim.[4] The prevalence of EALs in each of the 4 domains was considered positive if any one of the items within each domain was endorsed.

Other Psychometric Instruments

The Hospital Anxiety and Depression (HAD) scale[22] measured current anxiety and depression symptoms. Trait anxiety was measured using the State-Trait Anxiety Inventory.[23] Somatic symptom severity was measured using the Personal Health Questionnaire (PHQ-15),[24] modified by removal of 3 GI symptom items (score, 0–24). The Visceral Sensitivity Index[25] (VSI) assessed GI-specific anxiety.

The study was approved by the University of California Los Angeles Institutional Review Board, and all subjects signed a written informed consent form before the start of the study.

Statistical Analysis

Logistic regression analyses controlling for age, race, education, and sex were conducted to determine the associations between individual ETI-SF items and IBS. Psychological variables were correlated highly with ETI-SF items and thus we first modeled them separately with demographic variables. To determine if ETI-SF items had an independent association with IBS not accounted for by psychological variables, we compared pseudo R^2 from these separate models with a full model containing demographics, psychological variables, and ETI-SF items.

We also modeled men and women separately relating ETI-SF items and EALs while controlling for demographics. Associations with IBS were tested by the Fisher exact test for categoric variables and the Mann–Whitney *U* test for continuous variables. Because we assessed 27 items within the ETI-SF questionnaire, the adjusted significance level was a *P* value less than .0018 for all comparisons using the Bonferroni correction.

Table 1. Clinical Characteristics

Variable (±SEM)	IBS patients (n = 294)	Controls (n = 435)	*P* value
Age, *y*	36.17 ± 0.72	29.45 ± 0.50	<.001
Sex, % female	79	76.7	.468
Racial/ethnic category, %			<.001
Hispanic	13.61	18.39	
Asian	8.84	26.21	
Black or African American	11.22	11.26	
White	55.44	35.40	
Decline to answer/ other/multiracial	10.88	8.74	
Education, %			<.001
At least some high school but no college	7.61	5.37	
Some college	28.02	43.22	
College graduate	38.41	32.71	
Any postgraduate work	25.95	18.69	
Bowel habit type			
IBS-C	29.3	NA	
IBS-D	29.9	NA	
IBS-M	27.2	NA	
IBS-U	13.6	NA	
GI symptom severity score (0–20)	10.64 ± 0.25	NA	NA
HAD anxiety score (0–21)	7.42 ± 0.25	3.86 ± 0.14	<.001
HAD depression score (0–21)	3.90 ± 0.20	1.52 ± 0.10	<.001
STAI trait anxiety (34–112)	54.45 ± 0.80	45.02 ± 0.47	<.001
VSI score (0–75)	35.50 ± 0.94	3.47 ± 0.41	<.001
PHQ-12 score (0–24)	10.68 ± 0.30	2.43 ± 0.11	<.001

IBS-C, IBS with constipation; IBS-D, IBS with diarrhea; IBS-M, IBS with mixed pattern; IBS-U, IBS unsubtyped; NA, not applicable; SEM, standard error of the mean; STAI, State-Trait Anxiety Inventory.

Results

Subject Characteristics

Subjects were recruited primarily from community advertisements in the greater Los Angeles area and included 294 IBS patients and 435 HCs (79% and 77% women, respectively) (Table 1). Ninety-four percent of the IBS patients were recruited from an advertisement. There were no significant differences in demographic or clinical symptoms between those recruited by advertisement and from the GI clinic. Forty-two percent of the subjects recruited from advertisements had seen a physician in the past year for their abdominal symptoms and 58% had not. Compared with IBS nonconsulters in the past year, IBS consulters had higher GI symptom severity ratings (11.25 ± 0.4 vs 10.16 ± 0.36; $P = .06$), and significantly greater current anxiety symptom scores (8.03 ± 0.44 vs 6.73 ± 0.37; $P = .04$), GI symptom anxiety scores (40.48 ± 1.48 vs 31.99 ± 1.37; $P < .001$), and somatic symptom severity ratings (6.76 ± 0.50 vs 5.22 ± 0.33; $P = .02$). However, there were no differences in EAL scores. Compared with HCs, IBS patients were older, had achieved a higher education level, and had higher scores for anxiety and depression, trait and symptom-specific anxiety, and somatic symptom severity. Ninety percent of the HCs had no (0) or mild somatic symptoms (score, 1–4).

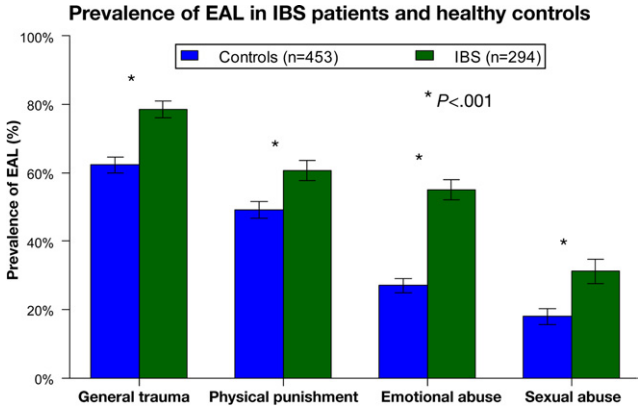

Figure 1. The prevalence of the 4 subcategories of EALs based on the ETI-SF questionnaire in IBS patients and controls is shown. The prevalence of the 4 subcategories was significantly higher in IBS patients vs controls. *$P < .001$.

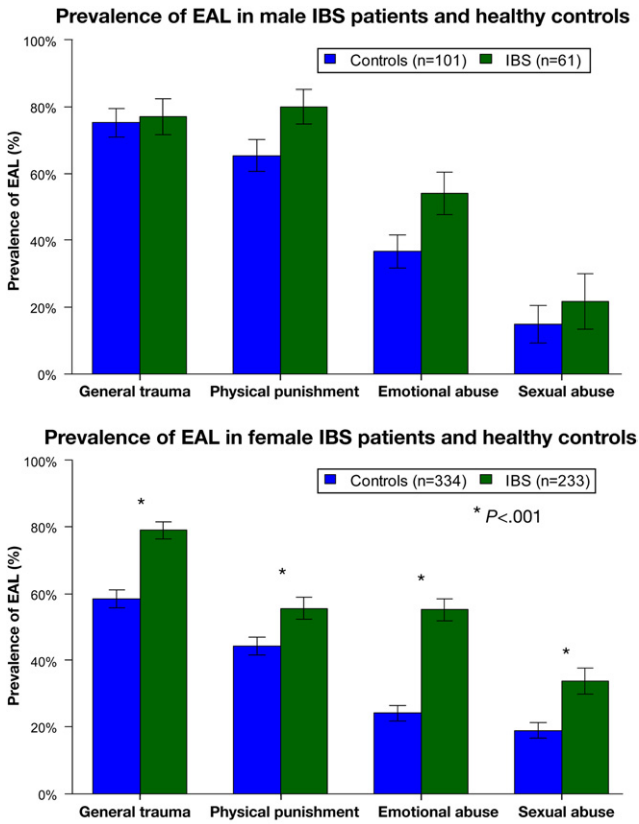

Figure 2. The prevalence of the 4 subcategories of EALs based on the ETI-SF questionnaire in the (*top*) male and (*bottom*) female IBS patients and controls is shown. (*Top*) In the male subjects, EALs were not different between IBS patients and controls after controlling for multiple comparisons. (*Bottom*) In the female subjects, all 4 types of EALs were significantly more prevalent in IBS patients vs controls. *$P < .001$.

Prevalence of Early Adverse Life Events in Irritable Bowel Syndrome and Control Subjects

Compared with HCs, IBS patients had a significantly higher prevalence of the 4 EAL domains even after adjusting for demographic variables (Figure 1, Supplementary Table 1) ($P < .001$). IBS patients also had significantly higher scores for the total number of ETI-SF items and for the domains of general trauma, physical punishment, emotional abuse, and sexual abuse (all $P < .001$, Supplementary Table 2). Emotional abuse was the strongest predictor of IBS status ($P < .001$). Eight of the 27 ETI-SF items were associated significantly with the odds of having IBS after adjusting for multiple comparisons (Table 2). Sexual abuse and feeling ignored or made to feel not counted conferred the highest odds of having IBS (odds ratios of up to 4.05).

Impact of sex. Among men, the prevalence of an EAL within the 4 domains (Figure 2*A*, Supplementary Table 3) and ETI-SF total and domain scores (Supplementary Table 2) were not significantly different between IBS and HCs after correcting for multiple comparisons. Only 1 of the 27 items ("Were you often ignored or made to feel that you did not count?") was reported by significantly more men with IBS than healthy men (39.3% vs 15.8%; $P < .001$).

In women, the prevalence of general trauma (78.9% vs 58.5%; $P < .001$), physical punishment (55.6% vs 44.3%; $P = .01$), emotional abuse (55.2% vs 24%; $P < .001$), and sexual abuse (33.6% vs 18.9%; $P < .001$) was significantly higher in IBS

Table 2. Individual Items Associated With IBS

Question	Coefficient (standard error)	Odds ratio	Interpretation
Did you ever witness violence toward others, including family members?	0.73 (0.19)	2.08	If yes, the odds of having IBS is 108% higher
Did anyone in your family ever suffer from mental or psychiatric illness or have a "breakdown?"	0.82 (0.21)	2.27	If yes, the odds of having IBS is 127% higher
Were you often put down or ridiculed?	0.82 (0.18)	2.26	If yes, the odds of having IBS is 126% higher
Were you often ignored or made to feel that you did not count?	1.13 (0.21)	3.08	If yes, the odds of having IBS is 208% higher
Most of the time were you treated in a cold, uncaring way or made to feel like you were not loved?	0.97 (0.29)	2.64	If yes, the odds of having IBS is 164% higher
Did your parents or caretakers often fail to understand you or your needs?	0.92 (0.2)	2.51	If yes, the odds of having IBS is 151% higher
Were you ever forced or coerced to touch another person in an intimate or private part of their body?	1.07 (0.31)	2.92	If yes, the odds of having IBS is 192% higher
Did anyone ever have genital sex with you against your will?	1.4 (0.41)	4.05	If yes, the odds of having IBS is 305% higher

NOTE. Each odds ratio was statistically significant ($P < .001$) and was adjusted for age, sex, education, and race using logistic regression.

patients vs HCs even after adjusting for demographic variables (Figure 2*B*, Supplemental Table 4). Similar results were obtained with respect to ETI-SF scores (Supplementary Table 2). Women with IBS reported 16 EAL items significantly more often than healthy women ($P < .001$).

Impact of psychological and nongastrointestinal symptoms. Each individual psychological variable was evaluated for its relationship with IBS while controlling for demographics. As expected, HAD scores for symptoms of anxiety and depression, PHQ-12 score, trait anxiety, and the VSI score had significantly positive associations with IBS (all $P < .001$; Supplementary Table 5), with the strongest association for PHQ-12 (odds ratio, 1.73). Psychological variables and ETI-SF scores were highly correlated but we wanted to measure the independent contribution of each to the presence of IBS. We modeled the relationship between the psychological variables and EALs with IBS controlling for demographic variables. The variance explained by demographics alone was increased from 0.109 to 0.298 when psychological variables (HAD anxiety, HAD depression, trait anxiety) were added. When ETI-SF scores were added to the model, the variance increased further to 0.304 ($P = .04$). Similarly, the variance explained by demographics alone increased from 0.109 to 0.149 when ETI-SF scores were added, and increased further when the psychological variables were included ($P < .01$). Thus, although EALs and psychological variables are interrelated, they have some independent association with IBS.

Discussion

The main findings of the current study were as follows: (1) IBS patients had a significantly greater prevalence of EALs, including general trauma, and physical, emotional, and sexual abuse compared with HCs; (2) these differences were seen mainly in women; (3) of the EAL domains measured, emotional abuse was the strongest predictor of having IBS; and (4) the strength of the relationship between EALs and IBS was reduced after controlling for the presence of psychological and other non-GI symptoms.

Association of Early Adverse Life Events and Irritable Bowel Syndrome

General trauma and emotional, physical, and sexual abuse were reported significantly more often by patients than HCs. With respect to individual items, these events included witnessing violence, mental illness in the family, emotional abuse, and being forced to touch intimate parts of a person's body or have genital sex. The prevalence of specific types of abuse was similar to previously reported prevalence numbers in IBS patients, including the prevalence of a history of sexual abuse[14] and the prevalence of disturbances in the child-caregiver relationship.[15] Our study found that 47% of IBS patients experienced divorce, separation, or death of parents (vs 36% in HCs; $P = .004$) and 18% had parents or primary caregivers with alcoholism or drug abuse (vs 13% in HCs; $P = .06$). In addition, 35% of patients in our study stated that their parents or caretakers often failed to understand them or their needs compared with 14% of HCs ($P < .001$).

Possible neurobiological mechanisms underlying the observed association between EALs and IBS have been identified in animal models and in human beings linking early life psychosocial exposures with long-lasting changes in gene expression.[6,26] For example, exposure to perinatal stress (ie, maternal separation) predisposes adult rats to develop stress-induced visceral hypersensitivity, enhanced defecation, intestinal mucosal dysfunction, increased hypothalamic-pituitary-adrenal axis responses, and anxiety-like behavior.[27–30] Studies in adult IBS patients have shown stress-induced alterations in gastrointestinal motility, visceral sensitivity, autonomic tone, and hypothalamic-pituitary-adrenal axis responses.[31] Previous studies on the role of mother–offspring interactions on adult stress responsiveness have shown a link between specific maternal behaviors (licking and grooming) and epigenetic alterations at the glucocorticoid-receptor gene locus in the adult offspring.[32] Homologous findings of glucocorticoid receptor methylation have been shown in human beings by analyzing autopsy specimens from suicide victims with a history of childhood abuse.[33] Consistent with alterations in the hypothalamic-pituitary-adrenal axis regulation, we recently showed that EALs were associated with increased cortisol response to a visceral stressor in both IBS and control subjects and the return to basal levels correlated with IBS symptom severity.[34]

Impact of Sex on Early Adverse Life Events in Irritable Bowel Syndrome

Group differences in EALs were observed primarily in women. The lack of differences within men may be owing to the smaller sample size relative to the women and/or the variations in the prevalence of the EAL domains in the overall population. Although abuse has been studied predominantly in women,[6,13,17] a survey conducted in equal numbers of men and women also found that abuse was reported more often by women (41%) than men (11%).[13] These differences may be because our subjects were recruited mainly from advertisements and not randomly sampled from the community and were more diverse in race and ethnicity. Our study suggests that a history of EALs increases the vulnerability to develop IBS in women, but larger studies with more men are needed to evaluate the relationship in men. Interestingly, the association of EALs and increased cortisol response to a visceral stressor was seen mainly in men and not in women.[34]

Impact of Psychological and Somatic Symptoms on Early Adverse Life Events and Irritable Bowel Syndrome

Controlling for psychological and somatic symptoms weakened the association of ETI-SF scores with IBS, although EAL still had some independent association with IBS. These findings suggest that factors associated with the presence of non-GI symptoms mediate the relationship between EALs and IBS. Previous studies, which measured EALs in a managed-care patient population, found a graded response to early adversity with higher scores related to increased somatic and psychiatric comorbidity, as well as organic diseases such as chronic obstructive pulmonary disease.[6,7] Other investigators[9,35–39] have speculated that individuals with a history of EALs have a heightened awareness of bodily sensations, and a tendency to amplify these perceptions.

An association between abuse and somatic symptoms has been reported in FGID patients. Van Oudenhove et al[40] found that somatization (eg, the presence of several somatic symptoms) mediated the effect of sexual and physical abuse on

health-related quality of life in functional dyspepsia. Creed et al[9] showed that the level of somatization in IBS patients was associated with symptom severity, health-related quality of life, and history of sexual abuse. These findings suggest that trauma and abuse is associated with an increased vulnerability for multiple somatic symptoms and syndromes, and that the association is not unique to the symptom complex of IBS.

Studies have shown that patients with an abuse history tend to use health care and have greater symptom reporting compared with those without this history.[13,14] However, treating providers infrequently inquire about EALs. In a study by Drossman et al,[14] only 17% of providers knew of their patients' abuse history. This information is an integral part of a patient's presentation and should be asked by the health care provider when appropriate.[13,14] Treatment addressing EALs and psychological symptoms potentially can improve symptoms and reduce health care use. Although studies have not evaluated the impact of EALs on treatment response in IBS directly, they have been conducted in other conditions. For example, depressed patients with EALs experienced greater efficacy with psychotherapy with or without an antidepressant when compared with the antidepressant alone.[41] However, in patients with depression without a history of childhood abuse, a combination of an antidepressant and psychotherapy was superior to either one alone.[41]

Limitations of the present study included the possibility of recall bias given our focus on childhood traumatic events. In addition, the ETI-SF questionnaire includes events of abuse, major losses, and other types of trauma but does not allow distinction between the types of trauma. It also has been validated in post-traumatic stress disorder, but not in IBS.

In summary, various types of EALs are more prevalent in IBS patients compared with HCs, particularly among women with IBS, and are associated with a greater prevalence of psychological and somatic symptoms. Addressing EALs and associated psychological symptoms in IBS patients is important and may help guide management approaches in an effort to reduce symptoms and health care use and improve overall well-being.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Clinical Gastroenterology and Hepatology* at www.cghjournal.org, and at doi:10.1016/j.cgh.2011.12.018.

References

1. Chitkara DK, van Tilburg MA, Blois-Martin N, et al. Early life risk factors that contribute to irritable bowel syndrome in adults: a systematic review. Am J Gastroenterol 2008;103:765–774; quiz, 775.
2. Heim C, Newport DJ, Heit S, et al. Pituitary-adrenal and autonomic responses to stress in women after sexual and physical abuse in childhood. JAMA 2000;284:592–597.
3. Heim C, Nemeroff CB. The role of childhood trauma in the neurobiology of mood and anxiety disorders: preclinical and clinical studies. Biol Psychiatry 2001;49:1023–1039.
4. Bremner JD, Bolus R, Mayer EA. Psychometric properties of the Early Trauma Inventory Self Report. J Nerv Ment Dis 2007;195:211–218.
5. Anda RF, Croft JB, Felitti VJ, et al. Adverse childhood experiences and smoking during adolescence and adulthood. JAMA 1999;282:1652–1658.
6. Anda RF, Felitti VJ, Bremner JD, et al. The enduring effects of abuse and related adverse experiences in childhood. A convergence of evidence from neurobiology and epidemiology. Eur Arch Psychiatry Clin Neurosci 2006;256:174–186.
7. Anda RF, Brown DW, Dube SR, et al. Adverse childhood experiences and chronic obstructive pulmonary disease in adults. Am J Prev Med 2008;34:396–403.
8. Anda RF, Brown DW, Felitti VJ, et al. Adverse childhood experiences and prescription drug use in a cohort study of adult HMO patients. BMC Public Health 2008;8:198.
9. Creed F, Tomenson B, Guthrie E, et al. The relationship between somatisation and outcome in patients with severe irritable bowel syndrome. J Psychosom Res 2008;64:613–620.
10. Mayer EA, Naliboff BD, Chang L, et al. V. Stress and irritable bowel syndrome. Am J Physiol Gastrointest Liver Physiol 2001;280:G519–G524.
11. Anand KJ, Runeson B, Jacobson B. Gastric suction at birth associated with long-term risk for functional intestinal disorders in later life. J Pediatr 2004;144:449–454.
12. Bengtson MB, Rønning T, Vatn MH, et al. Irritable bowel syndrome in twins: genes and environment. Gut 2006;55:1754–1759.
13. Talley NJ, Fett SL, Zinsmeister AR, et al. Gastrointestinal tract symptoms and self-reported abuse: a population-based study. Gastroenterology 1994;107:1040–1049.
14. Drossman DA, Leserman J, Nachman G, et al. Sexual and physical abuse in women with functional or organic gastrointestinal disorders. Ann Intern Med 1990;113:828–833.
15. Hislop IG. Childhood deprivation: an antecedent of the irritable bowel syndrome. Med J Aust 1979;1:372–374.
16. Biggs AM, Aziz Q, Tomenson B, et al. Effect of childhood adversity on health related quality of life in patients with upper abdominal or chest pain. Gut 2004;53:180–186.
17. Drossman DA, Li Z, Leserman J, et al. Health status by gastrointestinal diagnosis and abuse history. Gastroenterology 1996;110:999–1007.
18. Longstreth GF, Wolde-Tsadik G. Irritable bowel-type symptoms in HMO examinees. Prevalence, demographics, and clinical correlates. Dig Dis Sci 1993;38:1581–1589.
19. Thompson WG, Longstreth GF, Drossman DA, et al. Functional bowel disorders and functional abdominal pain. Gut 1999;45(Suppl 2):II43–II47.
20. Brun R, Kuo B. Functional dyspepsia. Ther Adv Gastroenterol 2010;3:145–164.
21. Spiegel BM, Harris LA, Lucak SL, et al. Measuring IBS patient reported outcomes with a single item numeric rating scale: results from the PROOF cohort. Gastroenterology 2008;134(Suppl 1):A-467.
22. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. Acta Psychiatr Scand 1983;67:361–370.
23. Kvaal K, Ulstein I, Nordhus IH, et al. The Spielberger State-trait anxiety inventory (STAI): the state scale in detecting mental disorders in geriatric patients. Int J Geriatr Psychiatry 2005;20:629–634.
24. Kroenke K, Spitzer RL, Williams JB. The PHQ-15: validity of a new measure for evaluating the severity of somatic symptoms. Psychosom Med 2002;64:258–266.
25. Labus JS, Bolus R, Chang L, et al. The Visceral Sensitivity Index: development and validation of a gastrointestinal symptom-specific anxiety scale. Aliment Pharmacol Ther 2004;20:89–97.
26. Felitti VJ, Anda RF, Nordenberg D, et al. Relationship of childhood abuse and household dysfunction to many of the leading causes of death in adults. The adverse childhood experiences (ACE) study. Am J Prev Med 1998;14:245–258.
27. Coutinho SV, Plotsky PM, Sablad M, et al. Neonatal maternal separation alters stress-induced responses to viscerosomatic

nociceptive stimuli in rat. Am J Physiol Gastrointest Liver Physiol 2002;282:G307–G316.
28. Gareau MG, Jury J, Yang PC, et al. Neonatal maternal separation causes colonic dysfunction in rat pups including impaired host resistance. Pediatr Res 2006;59:83–88.
29. Gareau MG, Jury J, Perdue MH. Neonatal maternal separation of rat pups results in abnormal cholinergic regulation of epithelial permeability. Am J Physiol Gastrointest Liver Physiol 2007;293: G198–G203.
30. Ladd CO, Owens MJ, Nemeroff CB. Persistent changes in corticotropin-releasing factor neuronal systems induced by maternal deprivation. Endocrinology 1996;137:1212–1218.
31. Chang L, Sundaresh S, Elliott J, et al. Dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis in irritable bowel syndrome. Neurogastroenterol Motil 2009;21:149–159.
32. McGowan PO, Meaney MJ, Szyf M. Diet and the epigenetic (re)programming of phenotypic differences in behavior. Brain Res 2008;1237:12–24.
33. McGowan PO, Sasaki A, D'Alessio AC, et al. Epigenetic regulation of the glucocorticoid receptor in human brain associates with childhood abuse. Nat Neurosci 2009;12:342–348.
34. Videlock EJ, Adeyemo M, Licudine A, et al. Childhood trauma is associated with hypothalamic-pituitary-adrenal axis responsiveness in irritable bowel syndrome. Gastroenterology 2009;137:1954–1962.
35. Leserman J, Drossman DA, Li Z, et al. Sexual and physical abuse history in gastroenterology practice: how types of abuse impact health status. Psychosom Med 1996;58:4–15.
36. Leserman J, Li Z, Drossman DA, et al. Selected symptoms associated with sexual and physical abuse history among female patients with gastrointestinal disorders: the impact on subsequent health care visits. Psychol Med 1998;28: 417–425.
37. Barsky AJ, Borus JF. Functional somatic syndromes. Ann Intern Med 1999;130:910–921.
38. Salmon P, Skaife K, Rhodes J. Abuse, dissociation, and somatization in irritable bowel syndrome: towards an explanatory model. J Behav Med 2003;26:1–18.
39. Hunt MG, Moshier S. Catastrophizing the consequences of gastrointestinal symptoms in irritable bowel syndrome. J Cogn Psychother 2009;23:160–173.
40. Van Oudenhove L, Vandenberghe J, Vos R, et al. Risk factors for impaired health-related quality of life in functional dyspepsia. Aliment Pharmacol Ther 2011;33:261–274.
41. Nemeroff CB, Heim CM, Thase ME, et al. Differential responses to psychotherapy versus pharmacotherapy in patients with chronic forms of major depression and childhood trauma. Proc Natl Acad Sci U S A 2003;100:14293–14296.

Reprint requests

Address requests for reprints to: Lin Chang, MD, Center for Neurobiology of Stress, David Geffen School of Medicine at the University of California Los Angeles, 10833 Le Conte Avenue, CHS 42-210, Los Angeles, California 90095-7378. e-mail: linchang@ucla.edu; fax: (310) 825-1919.

Conflicts of interest

The authors disclose no conflicts.

Funding

Supported by National Institutes of Health grant P50 DK64539.

Supplementary Table 1. Prevalence of Early Life Trauma in IBS Patients and Healthy Controls

Early life traumatic events	IBS, % (n = 294)	Controls, % (n = 435)	*P* value
General trauma	78.5	62.3	**<.001**
Were you ever exposed to a life-threatening natural disaster?	13.7	10.1	.31
Were you involved in a serious accident?	18.2	11.7	.03
Did you ever suffer a serious personal injury or illness?	22.3	11.8	.02
Did you ever experience the death or serious illness of a parent or a primary caretaker?	23.3	11.8	.06
Did you experience the divorce or separation of your parents?	31.2	27.7	.36
Did you experience the death or serious injury of a sibling?	10.7	4.1	.02
Did you ever experience the death or serious injury of a friend?	28.9	23.3	.67
Did you ever witness violence toward others, including family members?	33.8	19.4	**<.001**
Did anyone in your family ever suffer from mental or psychiatric illness or have a "breakdown?"	28.3	13.6	**<.001**
Did your parents or primary caretaker have a problem with alcoholism or drug abuse?	18.1	12.9	.28
Did you ever see someone murdered?	3.8	2.1	.19
Physical punishment	60.6	49.2	**<.001**
Were you ever slapped in the face with an open hand?	41.8	29.2	.01
Were you ever burned with hot water, a cigarette, or something else?	6.8	5.5	.34
Were you ever punched or kicked?	28.5	19.4	.01
Were you ever hit with an object that was thrown at you?	26.1	18.4	.003
Were you ever pushed or shoved?	46.2	35.8	.005
Emotional abuse	54.9	27.0	**<.001**
Were you often put down or ridiculed?	39.9	19.8	**<.001**
Were you often ignored or made to feel that you did not count?	34.1	12.7	**<.001**
Were you often told you were no good?	20.8	10.6	.009
Most of the time were you treated in a cold, uncaring way or made to feel like you were not loved?	16.8	5.5	**<.001**
Did your parents or caretakers often fail to understand you or your needs?	34.8	14.5	**<.001**
Sexual abuse	31.2	17.9	**<.001**
Were you ever touched in an intimate or private part of your body (eg, breast, thighs, genitals) in a way that surprised you or made you feel uncomfortable?	24.9	13.1	.003
Did you ever experience someone rubbing their genitals against you?	16.8	11.5	.13
Were you ever forced or coerced to touch another person in an intimate or private part of their body?	13.7	4.4	**<.001**
Did anyone ever have genital sex with you against your will?	9.3	2.1	**.001**
Were you ever forced or coerced to perform oral sex on someone against your will?	7.2	1.6	.02
Were you ever forced or coerced to kiss someone in a sexual rather than an affectionate way?	7.8	2.8	.04

NOTE. *P* values set in bold remained significant after adjusting for Bonferroni correction.

Supplementary Table 2. ETI-SF Scores in IBS Patients and Controls

	IBS		Controls		
	Mean	SE	Mean	SE	*P* value
All subjects					
General trauma	2.325	0.125	1.484	0.081	<.001
Physical abuse	1.496	0.09	1.088	0.068	<.001
Emotional abuse	1.464	0.1	0.629	0.061	<.001
Sexual abuse	0.795	0.089	0.354	0.046	<.001
Total score	6.072	0.3	3.557	0.186	<.001
Men					
General trauma	2.326	0.3	2.047	0.195	.630
Physical abuse	2.367	0.213	1.693	0.168	.013
Emotional abuse	1.508	0.224	0.891	0.145	.016
Sexual abuse	0.483	0.159	0.23	0.066	.228
Total score	6.656	0.655	4.86	0.406	.022
Women					
General trauma	2.324	0.137	1.314	0.085	<.001
Physical abuse	1.27	0.094	0.904	0.069	.002
Emotional abuse	1.453	0.111	0.55	0.066	<.001
Sexual abuse	0.876	0.104	0.392	0.056	<.001
Total score	5.923	0.338	3.159	0.205	<.001

SE, standard error.

Supplementary Table 3. Prevalence of Early Life Trauma in Male IBS Patients and Healthy Controls

Early life traumatic events	IBS, % (n = 61)	Controls, % (n = 101)	*P* value	Odds ratio
General trauma, %	77.0	75.2	.85	1.05
Were you ever exposed to a life-threatening natural disaster?	16.4	12.9	.64	1.29
Were you involved in a serious accident?	15.0	23.8	.23	0.59
Did you ever suffer a serious personal injury or illness?	18.0	20.0	.84	0.92
Did you ever experience the death or serious illness of a parent or a primary caretaker?	19.7	13.9	.38	0.96
Did you experience the divorce or separation of your parents?	29.5	38.6	.31	0.71
Did you experience the death or serious injury of a sibling?	13.3	6.9	.26	2.26
Did you ever experience the death or serious injury of a friend?	36.7	28.7	.30	1.21
Did you ever witness violence toward others, including family members?	36.1	24.0	.11	1.95
Did anyone in your family ever suffer from mental or psychiatric illness or have a "breakdown?"	18.0	16.8	.83	1.10
Did your parents or primary caretaker have a problem with alcoholism or drug abuse?	21.3	12.9	.19	2.06
Did you ever see someone murdered?	8.2	5.9	.75	1.18
Physical punishment, %	80.0	65.3	.05	1.34
Were you ever slapped in the face with an open hand?	56.7	39.6	.05	2.47
Were you ever burned with hot water, a cigarette, or something else?	11.5	10.9	.99	1.21
Were you ever punched or kicked?	51.7	39.6	.14	1.80
Were you ever hit with an object that was thrown at you?	41.7	24.8	.03	2.62
Were you ever pushed or shoved?	75.0	54.5	.011	2.66
Emotional abuse, %	54.1	36.6	.03	1.21
Were you often put down or ridiculed?	41.0	28.7	.12	1.41
Were you often ignored or made to feel that you did not count?	39.3	15.8	**.001**	**3.01**[a]
Were you often told you were no good?	23.0	14.9	.21	1.48
Most of the time were you treated in a cold, uncaring way or made to feel like you were not loved?	14.8	7.9	.19	1.90
Did your parents or caretakers often fail to understand you or your needs?	32.8	21.8	.14	1.61
Sexual abuse, %	21.7	14.9	.29	1.39
Were you ever touched in an intimate or private part of your body (eg, breast, thighs, genitals) in a way that surprised you or made you feel uncomfortable?	14.8	8.9	.30	2.09
Did you ever experience someone rubbing their genitals against you?	15.0	9.9	.45	2.15
Were you ever forced or coerced to touch another person in an intimate or private part of their body?	6.6	2.0	.19	2.92
Did anyone ever have genital sex with you against your will?	3.3	1.0	.56	3.17
Were you ever forced or coerced to perform oral sex on someone against your will?	6.6	0.0	.02	—
Were you ever forced or coerced to kiss someone in a sexual rather than an affectionate way?	3.3	1.0	.56	3.45

NOTE. *P* values or odds ratios set in bold remained significant after adjusting for Bonferroni correction. The odds ratio for each individual ETI-SF question was obtained from logistic regressions controlling for age, education (did not graduate from college vs college graduate), and race (white vs nonwhite).

[a]Significant at the 1% level.

Supplementary Table 4. Prevalence of Early Life Trauma in Female IBS Patients and Healthy Controls

Early life traumatic events	IBS, % (n = 233)	Controls, % (n = 334)	*P* value	Odds ratio
General trauma, %	78.9	58.4	**<.001**	**1.30**[a]
Were you ever exposed to a life-threatening natural disaster?	12.9	9.3	.17	1.41
Were you involved in a serious accident?	19.0	8.1	**<.001**	**2.31**
Did you ever suffer a serious personal injury or illness?	23.4	9.3	**<.001**	**2.24**
Did you ever experience the death or serious illness of a parent or a primary caretaker?	24.2	11.1	**<.001**	**1.70**
Did you experience the divorce or separation of your parents?	31.6	24.4	.067	1.60
Did you experience the death or serious injury of a sibling?	10.0	3.3	.002	2.36
Did you ever experience the death or serious injury of a friend?	26.8	21.6	.16	1.09
Did you ever witness violence toward others, including family members?	33.2	18.0	**<.001**	**2.31**[a]
Did anyone in your family ever suffer from mental or psychiatric illness or have a "breakdown?"	31.0	12.6	**<.001**	**2.94**[a]
Did your parents or primary caretaker have a problem with alcoholism or drug abuse?	17.2	12.9	.180	1.20
Did you ever see someone murdered?	2.6	0.9	.170	3.58
Physical punishment, %	55.6	44.3	.01	1.17
Were you ever slapped in the face with an open hand?	37.9	26.3	.004	1.37
Were you ever burned with hot water, a cigarette, or something else?	5.6	3.9	.420	1.68
Were you ever punched or kicked?	22.5	13.3	.004	1.52
Were you ever hit with an object that was thrown at you?	22.1	16.5	.100	1.55
Were you ever pushed or shoved?	38.8	30.1	.040	1.38
Emotional abuse, %	55.2	24.0	**<.001**	**1.43**[a]
Were you often put down or ridiculed?	39.7	17.1	**<.001**	**2.69**[a]
Were you often ignored or made to feel that you did not count?	32.8	11.7	**<.001**	**3.00**[a]
Were you often told you were no good?	20.3	9.3	**<.001**	**2.14**
Most of the time were you treated in a cold, uncaring way or made to feel like you were not loved?	17.3	4.8	**<.001**	**3.32**[a]
Did your parents or caretakers often fail to understand you or your needs?	35.3	12.3	**<.001**	**3.04**[a]
Sexual abuse, %	33.6	18.9	**<.001**	**1.29**[a]
Were you ever touched in an intimate or private part of your body (eg, breast, thighs, genitals) in a way that surprised you or made you feel uncomfortable?	27.6	14.4	**<.001**	**1.99**[a]
Did you ever experience someone rubbing their genitals against you?	17.2	12.0	.09	1.44
Were you ever forced or coerced to touch another person in an intimate or private part of their body?	15.5	5.1	**<.001**	**3.14**[a]
Did anyone ever have genital sex with you against your will?	10.8	2.4	**<.001**	**4.65**[a]
Were you ever forced or coerced to perform oral sex on someone against your will?	7.3	2.1	.005	2.81
Were you ever forced or coerced to kiss someone in a sexual rather than an affectionate way?	9.1	3.3	.005	2.31

NOTE. *P* values or odds ratio set in bold remained significant after adjusting for Bonferroni correction. The odds ratio for each individual ETI-SF question was obtained from logistic regressions controlling for age, education (did not graduate from college vs college graduate) and race (white vs nonwhite).

[a]Significant at the 1% level.

Supplementary Table 5. Psychological Factors Associated With IBS

Psychological measure	Coefficient (standard error)	Odds ratio	Interpretation
HAD anxiety	0.28 (0.03)	1.32	For every unit increase in the HAD anxiety score, the odds of having IBS is increased by 32%
HAD depression	0.35 (0.04)	1.42	For every unit increase in the HAD depression score, the odds of having IBS is increased by 42%
PHQ score	0.71 (0.06)	1.73	For every unit increase in the PHQ score, the odds of having IBS is increased by 73%
Trait anxiety	0.08 (0.01)	1.08	For every unit increase in trait anxiety, the odds of having IBS is increased by 8%
VSI score	0.18 (0.01)	1.19	For every unit increase in the VSI score, the odds of having IBS is increased by 19%

NOTE. Each odds ratio was statistically significant ($P < .001$) and was adjusted for age, sex, education, and race using logistic regression.