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Risk Factors for Abdominal Pain–Related Disorders of Gut–Brain Interaction in Adults and Children: A Systematic Review

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Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at http://dxdoi.org/10.1053/j.gastro.2022.06.028.

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Conflicts of interest

These authors disclose the following: Laurie Keefer is on the Rome Foundation Board of Directors. Lin Chang is a member of Rome Foundation Board of Directors, and has received grant funding from National Institutes of Health (U54 DK123755). The remaining authors disclose no conflicts.

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Abstract

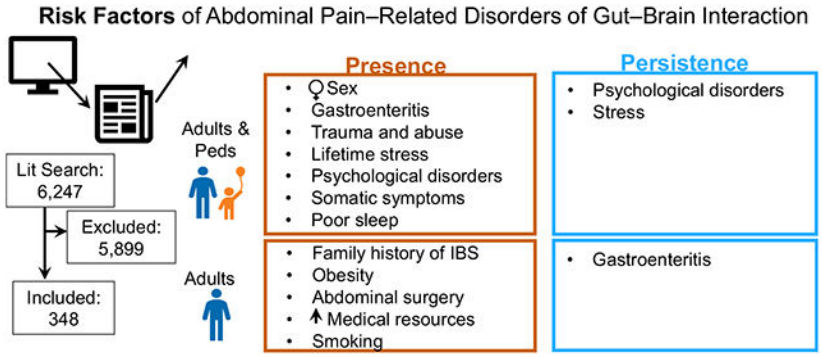
BACKGROUND & AIMS: Many studies have assessed risk factors of irritable bowel syndrome (IBS) and other abdominal pain–related disorders of gut–brain interaction (AP-DGBI); however, the role of these factors is unclear due to heterogeneous study designs. The aim of this systematic review was to extensively evaluate the literature and determine clinical risk and protective factors for the presence and persistence of AP-DGBI in children and adults.

METHODS: A PubMed search identified studies investigating potential risk and protective factors for AP-DGBI in adults and children. Inclusion criteria included fully published studies with a control group; exclusion criteria included poor-quality studies (using a validated scale). For each factor, the proportion of studies that found the factor to be a risk factor, protective factor, or neither was summarized. The number of studies, diagnostic criteria, number of subjects, and average study quality rating provided further context. Whenever possible, a meta-analysis generated pooled odds ratios or mean difference.

RESULTS: The systematic review included 348 studies. Female sex, gastroenteritis, abuse, stress, psychological disorders, somatic symptoms, and poor sleep were consistent risk factors for developing AP-DGBI in adults and children. In adults, additional risk factors included obesity, smoking, and increased use of medical resources. Protective AP-DGBI factors in adults included social support and optimism; no studies for protective factors were found for children.

CONCLUSIONS: There are multiple risk factors for AP-DGBI in adults and children. These include female sex, gastroenteritis, abuse, stress, poor sleep, obesity, psychological disorders, and somatic symptoms. Additional studies are needed in children, on protective factors, and on factors associated with persistence of AP-DGBI.

Graphical Abstract



Keywords

Irritable Bowel Syndrome; Recurrent Abdominal Pain; Functional Gastrointestinal Disorders

Functional gastrointestinal disorders, more recently termed *disorders of gut–brain interactions* (DGBI), are characterized by gastrointestinal (GI) symptoms related to

abnormalities in motility, visceral sensitivity, intestinal permeability, immune activation, neuroendocrine function, central nervous system processing, and the gut microbiota.[1] Abdominal pain–related DGBI (AP-DGBI) include disorders such as irritable bowel syndrome (IBS), functional dyspepsia, recurrent abdominal pain (RAP), and centrally mediated abdominal pain syndrome. IBS is defined by recurrent abdominal pain and alterations in stool form and frequency[2] and represents one of the most common AP-DGBI, with a prevalence reaching approximately 4.1%–11% worldwide.[3,4] Acute GI infection denotes one of the strongest risk factors for development of IBS and has subsequently been defined as a separate entity known as "post-infection IBS" (PI-IBS).[5] Many observational studies have evaluated the effects of additional risk factors, such as sex, early adverse life events, stress, psychiatric history, sleep disturbance, somatic symptoms, and diet on the development of IBS and other AP-DGBI. However, there is marked variability in the literature regarding the impact of these risk factors, given differences in study design, methodology, definitions used to define AP-DGBI, and sample size, and few studies have assessed all risk factors collectively or over time. One recently published systematic review evaluated cumulative risk factors for IBS, but this review included prospective, population-based cohorts only and was limited to adults.[6] The influence of each of these factors is likely to differ between children and adults.

The aim of this systematic review was to more broadly evaluate the current literature, using population-based, non–population-based, retrospective, and prospective studies, to determine clinical risk and protective factors for and against the development and persistence of AP-DGBI in children and adults.

Materials and Methods

Search Strategy and Study Selection

A literature search restricted to the English language was performed using PubMed (before March 2019) to identify articles reporting protective and/or risk factors for AP-DGBI. The medical literature was searched by combining terminologies for "AP-DGBI" and "protective and risk factors" with the set operator AND/OR (for specific terms, please see Supplementary Methods). AP-DGBI included the following search terms: *functional colonic diseases, recurrent abdominal pain, Rome criteria, Manning criteria, functional abdominal pain, functional gastrointestinal disorders, functional bowel disorders, spastic colitis, irritable colon, spastic colon, altered bowel habits*, and *irritable gut syndrome*. We excluded any study in which the primary study population was DGBI without a significant abdominal pain component (exclusion criteria below). If a study investigated more than 1 DGBI, we only included findings relevant to the AP-DGBI study population; we did not report findings for any DGBI without AP. To ensure we had a comprehensive systematic review, a recursive search was also performed for each separate protective and risk factor using the bibliographies of all relevant review articles and by performing a separate PubMed search within the past 5 years.

Studies were identified for this systematic review with a 3-step process: (1) title screening, (2) abstract review, and (3) complete article review. After our literature search, 2 reviewers (J.B., J.Z.) independently screened the resulting titles ($\kappa = 0.78$). The reviewers (J.Z.,

J.B.) then independently reviewed all resulting abstracts and determined those that should be excluded ($\kappa = 0.91$). To be eligible for complete article review, the abstract had to be published after 1987, be peer-reviewed, include patients with AP-DGBI as its primary study population (eg, IBS, functional dyspepsia, and functional abdominal pain in adults or children or RAP in children), and be relevant to the study's aims. Due to the scope of our systematic review, we excluded studies investigating the efficacy of a AP-DGBI treatment, studies in which the primary study population was DGBI without a significant abdominal pain component (eg, functional diarrhea, chronic idiopathic constipation), review articles, and studies that did not include a comparison group without significant GI comorbidities. Finally, the reviewers (J.B., J.Z.) independently reviewed the complete article for inclusion using the same abstract inclusion criteria, but also excluded an article if it was not within the scope of our review or had a quality rating of evidence score of ≤3, as adapted by Sanderson et al[7] (Supplementary Table 1). During each step, any disagreements regarding the titles, abstracts, and complete articles were reviewed by all authors and resolved.

Each author was assigned to a set of risk and protective factors to extract outcomes for the following aims of our study: development and persistence of AP-DGBI. The following data were extracted for each study: country of origin, diagnostic criteria for AP-DGBI, study design, number of AP-DGBI and control subjects, measures used to evaluate risk and protective factors, and quality ratings of evidence score (Supplementary Table 1).[7] The characteristics and outcomes for each individual risk and protective factor were consolidated into tables to summarize whether the majority of the studies found the specific factor to be a risk factor, protective factor, or not associated with an AP-DGBI or its persistence (Supplementary Tables 2–63). As the nomenclature of AP-DGBI in children changed over time, we specify the nomenclature used in each study in our Supplementary Tables 2–63; we referred collectively to these different nomenclatures as AP-DGBI when grouped together.

Meta-analysis was performed for a subset of factors for which pooling of data was appropriate. Data were not pooled for factors when there was significant heterogeneity in study design or measure or when the number of studies with extractable data was fewer than 4. For factors included in the meta-analysis, data were extracted by 2 investigators (G.H. or C.C. and E.J.V.). Studies were included if the following data were reported or able to be calculated: number of AP-DGBI in the sample with and without risk factor and sample size with and without the risk factor. When possible, we combined numbers for AP-DGBI diagnoses (eg, IBS or functional dyspepsia); however, if it was not clear whether these numbers included overlap (eg, IBS+functional dyspepsia), we included subjects with IBS only. Any discrepancies regarding individual study inclusion, data extraction, and interpretation were resolved by means of group consensus before the final analysis. Statistical analysis was performed in RevMan, version 5.4. Pooled odds ratios (OR) or mean difference for AP-DGBI in those with vs without the risk factor were determined with random-effects meta-analysis.[8]

Results

Our study assessed the association of multiple risk and protective factors with having an AP-DGBI (Tables 1 and 2) and its persistence (Tables 3 and 4) in adults and children.

Our search identified 6164 citations. Of these, 348 studies met all of the study's eligibility criteria and were included in this systematic review (Figure 1). Results were organized by each factor; we summarized the number of studies that found the factor to be a risk factor, protective factor, or neither for the presence (Figures 2 and 3) or persistence of AP-DGBI. If there were no studies that measured the association of specific factors and persistence of AP-DGBI, it was not mentioned. The individual studies are detailed and referenced in Supplementary Tables 2–63. For factors where meta-analysis was performed (Figures 4–7, Supplementary Figures 1–3), the pooled OR or mean difference and 95% CI were reported. A summary of meta-analysis results is shown in Supplementary Table 64.

Sex

Adults.—Seventy-nine studies examined the relationship between sex and development of AP-DGBI (Supplementary Table 2). Independent of the criteria used to define AP-DGBI, the majority of studies found that female sex was a risk factor for development of AP-DGBI. The studies in which no association with sex was found were mostly from Asia. Two studies conducted in Asia reported that AP-DGBI were more common in males compared with females, although in 1 study the difference was not significant. Pooled OR for developing AP-DGBI in females vs males was 1.56 (95% CI, 1.4–1.7; Figure 4A).

Persistence of abdominal pain–related disorders of gut–brain interaction.: Seven prospective studies evaluated the association between sex and persistence of AP-DGBI (Supplementary Table 3); 71% (5 of 7 studies) found no significant association between sex and persistence of AP-DGBI, including PI-IBS. Follow-up periods ranged from 1 to 8 years.

Children.—Eight of the 14 studies exploring the relationship between sex and AP-DGBI found a positive association between female sex and AP-DBGI, and the remaining 6 found no association (Supplementary Table 4). The pooled OR for developing AP-DGBI in female vs male children was 1.45 (95% CI, 1.26–1.67; Figure 4B).

Persistence of abdominal pain–related disorders of gut–brain interaction.: Five of the 7 pediatric cohort studies identified in this aim found that female sex was a risk factor for the persistence of AP-DBGIs (Supplementary Table 5).

Race and Ethnicity

Adults.—Studies with a primary aim to evaluate race and ethnicity in AP-DGBI found mixed results (Supplementary Table 6). The studies were from North American and the Middle East.

Persistence of abdominal pain–related disorders of gut–brain interaction.: Three cohort studies evaluated the relationship between race and ethnicity and persistence of AP-DGBI worldwide and found mixed results (Supplementary Table 7). Two studies found no association, and 1 study conducted in Israel found that being of Middle Eastern or African, compared with Western, origin was protective against the persistence of AP-DGBI symptoms.

Children.—Two population-based cohort studies from Europe considered race and ethnicity as factors for development of RAP in children. One UK study reported slightly lower risk of developing RAP at 6¾ -year follow-up among White compared with non-White children (although this was a predominantly White study population). In the Swedish study, having at least 1 immigrant parent increased the risk of developing RAP at age 12 years (Supplementary Table 8).

Body Mass Index

Adults.—Sixteen studies evaluated the relationship between body mass index (BMI) and presence of AP-DGBI (Supplementary Table 9). Six studies investigated BMI as separate categories (eg, nonobese and obese), 8 as a mean value, and 2 as both a mean value and as categories.

When BMI was investigated categorically, 4 of the 8 studies found no association of AP-DGBI with BMI, 3 studies found an association with obesity, and 1 study found an association with nonobesity. The pooled OR for developing AP-DGBI in obese vs nonobese individuals was 1.31 (95% CI, 1.03–1.68; Figure 5A), indicating an increased risk of AP-DGBI in obesity. Of note, 3 Asian studies defined obesity as BMI ≥25 kg/m^2.

When BMI was investigated as a mean value, 6 of the 10 studies found no association of AP-DGBI with BMI, 3 found an association with lower BMI, and 1 found an association with higher BMI. Two of the 3 studies that found lower mean BMI associated with AP-DGBI were conducted in Asia. The pooled mean difference in BMI between patients with AP-DGBI and controls was not significant: 0.4 (95% CI, −0.14 to 0.93; Figure 5B).

Persistence of abdominal pain–related disorders of gut–brain interaction.: Of the 1 study identified, no association was found between BMI and persistent AP-DGBI (Supplementary Table 10).

Children.—Two of 5 studies found an association between obese/overweight BMI and AP-DGBI (Supplementary Table 11).

Diet-Related Factors and Food Allergies and Intolerances

Adults.—Thirty-three studies examined the association of diet-related factors and AP-DGBI (Supplementary Table 12). Eleven studies evaluated the association between food allergies, hypersensitivities, intolerances, and/or avoidance and AP-DGBI, and most concluded that these aforementioned factors were associated with an increased risk of AP-DGBI. However, only 1 study defined food allergies by skin prick and serologic testing. Seven studies evaluated the association of regular or irregular meal patterns and AP-DGBI and found mixed results. Finally, 23 studies evaluated the consumption of specific foods and diets and development of AP-DGBI and demonstrated mixed results.

Persistence of abdominal pain–related disorders of gut–brain interaction.: Three studies evaluated the association between diet and persistence of AP-DGBI (Supplementary Table 13), with conflicting results. A Danish study, which followed the largest number of patients for up to 5 years, found no association between coffee consumption and persistent AP-DGBI

symptoms, and a US study found that coffee consumption was associated with persistent AP-DGBI symptoms during a 5-year period.

Children.—Ten studies, mostly retrospective, examined the association between diet (eg, food allergies, irregular feeding patterns, and specific food groups) and AP-DGBI in children (Supplementary Table 14). The results were inconclusive, given the significant variability within these studies.

Gastroenteritis

Adults.—There were 32 studies, predominantly cohort studies conducted in Europe or North America, relevant to this aim (Supplementary Table 15); 75% found that infectious gastroenteritis was a risk factor for development of AP-DGBI. Data could be extracted from 29 studies for a pooled OR of 3.53 evaluating gastroenteritis as a risk factor for developing AP-DGBI (95% CI, 2.52–4.95; Figure 6A). Frequent diarrheal episodes, vomiting, and high somatization scores were strong and independent PI-IBS risk factors. For up to 1 year, the prevalence of AP-DGBI increased significantly in exposed compared with unexposed subjects.

Persistence of abdominal pain–related disorders of gut–brain interaction.: All 6 studies relevant to this aim found gastroenteritis to be associated with persistent AP-DGBI (Supplementary Table 16). Of note, 1 Norway study also found a higher intake of water before *Giardia* outbreak as a significant risk factor for persistent AP-DGBI.

Children.—Four of 5 cohort studies found a significant relationship between gastroenteritis and AP-DGBI (Supplementary Table 17). The only study that did not find gastroenteritis to be a risk factor for developing AP-DGBI was specifically evaluating rotavirus. The pooled OR for developing AP-DGBI after gastroenteritis was 2.86 (95% CI, 1.88–4.37; Figure 6B).

Family History

Adults.—All 4 studies found that a family history positive for IBS was associated with development of adult-onset IBS (Supplementary Table 18). Meta-analysis yielded a pooled OR of 2.69 (95% CI, 2.16–3.36; Supplementary Figure 1). Having an adoptive parent with IBS was not a risk factor.

Persistence of abdominal pain–related disorders of gut–brain interaction.: A single study demonstrated that a family history of GI symptoms was independently associated with persistent IBS (Supplementary Table 19).

Children.—Three European studies were included (Supplementary Table 20). All 3 studies found higher psychological distress in parents of children with RAP. Mothers of children with RAP had higher anger and hostility scores, more negative life events, worse family functioning, higher levels of separation anxiety, illness in pregnancy, depression after childbirth, and depression in general. Both parents had higher levels of anxiety and hypochondriasis.

Persistence of abdominal pain–related disorders of gut–brain interaction.: Two population-based studies found that maternal anxiety was associated with persistence of RAP and 1 of them also found that mothers had higher scores of depression and somatic symptoms (Supplementary Table 21).

Familial Co-Aggregation (Twin Studies)

Adults.—Of the 5 twin studies evaluating the relationship between familial co-aggregation and development of AP-DGBI (Supplementary Table 22), 4 studies reported significantly higher concordance rate of AP-DGBI among monozygotic than dizygotic twins.

Birth and Early-Life Conditions

Adults.—There were 4 population-based studies that evaluated the association between birth and early-life conditions and presence of AP-DGBI (Supplementary Table 23). Collectively, these studies recognized birth and early-life conditions as risk factors for the presence of AP-DGBI. Complicated deliveries, fetal growth >1 standard deviation above the mean, lower birth length, lower maternal age at delivery, lower parental education level, and shorter duration of breastfeeding were associated with AP-DGBI. There were mixed results regarding the association of AP-DGBI and gestational age at birth and birth weight. With respect to childhood factors, 1 study found that a history of chronic diarrhea or functional abdominal pain in childhood was higher in adults with AP-DGBI.

Trauma and/or Abuse History

Adults.—There were 15 studies evaluating the association of trauma and abuse and presence of AP-DGBI, mostly from North America (Supplementary Table 24).

Childhood general trauma.: Five studies demonstrated that greater exposure to traumas (eg, family death, serious accidents, or illness) during childhood was associated with an increased risk of AP-DGBI in adulthood. Interestingly, 1 of these studies found that confiding in others regarding the traumatic event at the time of occurrence decreased the odds of developing AP-DGBI.

Childhood emotional and verbal abuse.: All 8 studies found that childhood emotional and verbal abuse was associated with an increased risk of developing AP-DGBI in adulthood. However, 1 of these studies found that, after controlling for verbal abuse, emotional abuse items did not significantly contribute to AP-DGBI. Emotional neglect was also found to be a risk factor for AP-DGBI. The pooled OR from these 8 studies was 2.16 (95% CI, 1.7–2.76; Figure 7A).

Childhood sexual abuse.: Of the 12 studies, one-half found that sexual abuse during childhood was associated with development of AP-DGBI in adulthood. Of the remaining studies, 3 showed a numerically higher prevalence of sexual abuse in the patients with AP-DGBI compared with controls, but this was not statistically significant. However, the pooled OR from these 12 studies was 1.92 (95% CI, 1.58–2.33; Figure 7B).

Childhood physical abuse.: Of the 12 studies, 5 found that physical punishment or being a victim of violence during childhood was associated with development of AP-DGBI in adulthood. The prevalence of physical abuse was higher in patients with AP-DGBI compared with controls in these studies, but not after controlling for confounders (eg, psychological distress). The pooled OR from these 12 studies was 1.56 (95% CI, 1.25–1.94; Figure 7C).

Adulthood abuse.: Eight studies evaluating adulthood abuse demonstrated mixed results. One study found that adulthood abuse was associated with AP-DGBI, but the type of abuse was not specified. Two studies found that emotional abuse in adulthood was significantly associated with AP-DGBI and 3 studies found no significant relationship. Sexual abuse in adulthood was associated with AP-DGBI in 2 studies, but was not associated with AP-DGBI in the other 5 studies when adjusted for confounders. Finally, physical abuse in adulthood was associated with DGBI in 2 studies, but not in 4 other studies.

Combined childhood and adulthood trauma and abuse.: Two population-based studies evaluated the combined effects of childhood and adulthood trauma/abuse and the subsequent risk of AP-DGBI. One study found that childhood and adulthood abuse (ie, sexual or emotional and verbal abuse but not physical abuse) was associated with IBS. The second study found that a history of emotional, physical, and sexual trauma was associated with an increased risk of AP-DGBI plus fibromyalgia, but not AP-DGBI alone.

Children.—Two studies examined the relationship between abuse and unexplained or functional abdominal pain in children (Supplementary Table 25). Both studies found that physical, psychological, and/or sexual abuse in childhood were associated with an increased risk of developing abdominal pain. However, in 1 study, when the results were adjusted for psychological distress, the association between self-reported symptoms of abuse and unexplained abdominal pain was no longer present in logistic regression.

Stressful Life Events and Perceived Stress

Adults.—There were 36 relevant studies for this aim (Supplementary Table 26).

Stressful life events (excluding wartime only).: Seventeen studies evaluated the effects of stressful life events (eg, death of a spouse, change in work or financial situation) over the past year and the risk of AP-DGBI. Fifteen studies showed that a greater number and/or impact of negatively perceived life events was associated with an increased risk of AP-DGBI.

Wartime exposure.: Of the 4 studies, 3 assessed combat-related stressors in military personnel, fear of being in danger or of being killed, seeing killed or wounded people, or discharging a weapon. These wartime stressors increased the risk of AP-DGBI, including PI-IBS, although 1 study found this relationship was no longer significant on multivariate analysis. The fourth study was population-based in the Netherlands and found that those with early-life exposure to wartime conditions up to 1.5 years of age had an increased risk of AP-DGBI compared with those who did not have an early exposure to wartime.

Perceived or daily stress.: Fifteen studies assessed the relationship between perceived stress (eg, emotional or work stress, increased sensitivity to stress) and risk of AP-DGBI. The majority found that increased stress was a significant risk factor for development of AP-DGBI. Three studies failed to find an association between stress and AP-DGBI, but used nonvalidated questionnaires.

Persistence of abdominal pain–related disorders of gut–brain interaction.: Five of the 7 studies relevant to this aim demonstrated that stress, including negatively perceived life events, was associated with persistence of AP-DGBI (Supplementary Table 27). One study demonstrated that a reciprocal, rather than causal, relationship existed between daily stress and AP-DGBI symptoms during a 4-week period. Wartime stressors were associated with persistent AP-DGBI over a period of 3 and 16 years.

Children.—Ten studies evaluated the relationship between stress and risk of AP-DGBI in children or adolescents (Supplementary Table 28). Three studies found that a greater number of negatively perceived life events or bullying were associated with development of AP-DGBI. Three other studies showed no association between negative life events and AP-DGBI on multivariate analysis. Higher levels of perceived stress or daily stress also correlated with AP-DGBI in a population of both adolescents and adults.

Persistence of abdominal pain–related disorders of gut–brain interaction.: Three prospective cohort studies relevant to this aim found that a greater number of negatively perceived life events were associated with the persistence of AP-DGBI at follow-up (Supplementary Table 29).

Psychological Disorders

Adults.—Thirty-four worldwide studies studied the association of psychological factors and AP-DGBI (Supplementary Table 30). Depression and anxiety were more prevalent in the AP-DGBI group in the majority of studies, although the data were more compelling for anxiety than depression. Psychiatric comorbidity in treatment-seeking populations was as high as 58%; however, the relationship between psychiatric comorbidity and AP-DGBI could be bidirectional, with 1 population-based study reporting that patients with IBS without depression and anxiety at baseline were more likely to be depressed and anxious 12 years later. Anxiety about health was also commonly associated with AP-DGBI and appeared to be a risk factor distinct from depression and anxiety. Hypochondriasis and negative attentional bias to bodily sensations emerged as independent risk factors for AP-DGBI.

Symptomatic anxiety and depression scores based on questionnaires instead of diagnostic codes were significantly elevated compared with healthy controls. Independent of a personal history of psychiatric comorbidity, a family history of psychiatric illness, including anxiety; depression; and substance abuse, also doubled the risk of AP-DGBI.

Personality factors also increased risk for AP-DGBI, particularly neuroticism, pessimism, and alexithymia, or difficulty expressing emotions and feelings. Other factors that were associated with AP-DGBI included having a lower resilience to stress; interpersonal

difficulties (eg, people pleasing); dysfunctional attitudes, including need for approval from others and over-responsibility or having a sense of urgency to meet demands. A few protective factors against development of AP-DGBI also emerged, including social support, optimism, and an active coping style.

Persistence of abdominal pain–related disorders of gut–brain interaction.: Eleven studies investigated the association of psychological factors and persistent AP-DGBI (Supplementary Table 31). A pre-existing comorbid mental disorder, particularly anxiety, had a 3- to 6-fold increased risk of persistent AP-DGBI symptoms. Notably, anxiety at the time of acute gastroenteritis was a predictor of continuing AP-DGBI symptoms for up to 8 years. In another study, participants with lower anxiety at baseline were more likely to report themselves as "better" at 5 years.

Children.—The majority of the 7 pediatric studies found depression and anxiety associated with development of AP-DGBI (Supplementary Table 32). Two negative studies from the United States and Thailand found no difference between AP-DGBI and controls on psychiatric history. A third study from Greece found that children with RAP had more psychiatric diagnoses than controls. One study suggested that anxiety and depression before age 7 years was associated with a >2-fold increased risk of AP-DGBI.

Persistence of abdominal pain–related disorders of gut–brain interaction.: There were 3 relevant studies. Psychological factors, such as anxiety or depression, were associated with chronicity and persistence of AP-DGBI (Supplementary Table 33), although maternal reports of these symptoms did not match these outcomes. Children who had resolution of their AP-DGBI symptoms were 4-fold less likely to have depression or anxiety disorders at admission compared with those who experienced continued symptoms of AP-DGBI. Similarly, children with psychological elevations at baseline were more likely to have continuing symptoms of AP-DGBI. Several temperament and behavioral factors also influenced persistence of AP-DGBI, including poorer emotional regulation skills, lower self-worth, early hyperactivity, and conduct problems.

Somatic Symptoms

Adults.—Thirty-three studies evaluated the relationship between somatic symptoms and development of AP-DGBI (Supplementary Table 34). Increased somatic symptoms (eg, fatigue, headache, and backaches) and/or scores were associated with development of AP-DGBI. For studies with validated scores reported, the mean somatic symptom scores were significantly higher in patients with AP-DGBI vs controls, with a pooled mean difference of 4.29 (95% CI, 3.52–5.05; Supplementary Figure 2).

Persistence of abdominal pain–related disorders of gut–brain interaction.: Three studies evaluated the relationship between somatic symptoms and persistence of AP-DGBI and results were mixed (Supplementary Table 35).

Children.—Fifteen studies evaluated the relationship between somatic symptoms and AP-DGBI (Supplementary Table 36) and consistently found that somatic symptoms, such as

multidimensional somatic symptoms, headaches or extraintestinal pain, and fatigue were associated with AP-DGBI. One study found that children with IBS-like symptoms had a higher prevalence of back pain and fibromyalgia, and 1 study reported contradictory results on the relationship between limb pain and RAP.

Persistence of abdominal pain–related disorders of gut–brain interaction.: Seven studies consistently found that the levels and/or number of somatic symptoms were risk factors for persistent AP-DGBI (Supplementary Table 37). Among these studies, 2 studies specified the somatic symptoms, namely headaches and limb pain.

Sleep

Adults.—Twenty-one studies evaluated the relationship between sleep and the presence of AP-DGBI (Supplementary Table 38). The majority found that sleep disturbance (ie, poor sleep quality, insomnia) was a risk factor for developing AP-DGBI. However, only 2 studies found less self-reported total sleep time was associated with development of AP-DGBI.

Children.—Six pediatric studies examined the relationship between sleep disturbances and AP-DGBI (Supplementary Table 39). Five of these studies that used questionnaires for sleep assessment found that poor sleep was associated with development of AP-DGBI, but when actigraphy was used to assess sleep, no group differences were seen.

Other Factors

We also reviewed studies that evaluated specific medical conditions (Supplementary Tables 40–42), surgery (Supplementary Table 43), medications (Supplementary Tables 44 and 45), use of medical resources (Supplementary Tables 46 and 47), pets (Supplementary Tables 48 and 49), living environment (Supplementary Tables 50 and 51), education (Supplementary Tables 52 and 55), physical activity (Supplementary Tables 56 and 57), occupation and socioeconomics (Supplementary Tables 58 and 60), and use of tobacco and alcohol (Supplementary Tables 61 and 63) as potential risk factors for the presence and persistence of AP-DGBI. Pooled data from 20 studies (n = 45,061) showed that being a current smoker vs never smoker was associated with a small but significant increase in the risk of AP-DGBI (OR, 1.15; 95% CI, 1.05–1.25; Supplementary Figure 3).

Discussion

This systematic review included 348 published peer-reviewed studies from 41 countries identifying risk and protective factors for AP-DGBI and its persistence in children and adults. Overall, consistent risk factors for developing AP-DGBI were female sex; gastroenteritis; trauma and abuse; lifetime stress; psychological disorders, such as depression and anxiety; increased somatic symptoms; and poor self-reported sleep. In adults, other consistent risk factors included a family history of IBS, familial co-aggregation, abdominal surgery, obesity, smoking, and increased use of medical resources. Whether other factors, such as race and ethnicity, birth characteristics, living environment, presence of pets, and physical activity, serve as risk or protective factors in development and persistence of AP-DGBI is less clear. In this review, we found greater attention to studies on risk factors

for AP-DGBI relative to its persistence. There were more studies conducted in adult than pediatric populations. Social support, optimism, and confiding in others about a traumatic event in childhood were identified as protective factors.

This review provided positive, negative, or no associations regarding AP-DGBI risk and protective factors and persistence based on 22 previously identified factors associated with AP-DGBI. The articles included in this review met specific inclusion and exclusion criteria. Reviewer agreement regarding eligibility of studies was consistent. For the most part, included studies used validated criteria for IBS (eg, Rome and Manning). However, it is worth noting that none of the studies used Rome IV criteria (established in 2016).

By taking a comprehensive search approach to examine all of the data-based literature and using robust quality evaluations, this review extends prior reviews of AP-DGBI risk factors in that risk and protective factors for persistent AP-DGBI were also included and evaluated across the lifespan when possible.[3,5,6,9] For example, the Creed[6] systematic review included prospective adult studies for IBS only. It did not include any cross-sectional or case–control studies, pediatric studies, AP-DGBI diagnoses outside of IBS, or protective factors. Creed also used general search terms for risk factors (eg, *epidemiology*, *incidence*), whereas our review used specific risk and protective factors search terms (eg, *stress*, *trauma*). Due to these differences, our review analyzed 310 more studies than Creed's systematic review and investigated 11 more factors of AP-DGBI (eg, family history and education). Of the overlapping risk factors investigated, our findings were consistent with Creed's: female sex, anxiety, depression, gastroenteritis, stress, frequent health care use, and poor sleep were found to be consistent risk factors for AP-DGBI in adults.

Given the worldwide scope of this review, differences were noted between Western countries and other parts of the world. For example, studies derived from Western countries consistently demonstrated that female sex is a risk factor for AP-DGBI regardless of criteria used to diagnose AP-DGBI. The 2 studies that found an increase risk in males were from Korea and Pakistan. In the Korean study, this finding was not statistically significant, and in the Pakistan study, this was only among males in the 16- to 30-year age group.

We only included studies in which race and/or ethnicity were the primary focus. Although these studies demonstrated mixed results, targeted studies to measure race and ethnicity and health disparity differences within a country are needed. For example, a recent retrospective U.S. study found that patients self-identified as Hispanic, Black, or Asian were more likely to have more IBS-related primary care visits and gastroenterology-focused procedures performed.[10] Whether this is unique to the United States or present in other countries requires further study. A recent global epidemiology study was conducted in which the prevalence of AP-DGBI was measured (Rome III/IV criteria)[4] and provided a better assessment of the cross-cultural differences in the prevalence of IBS. In general, IBS prevalence rates were similar among most countries, although there were a couple of outliers (eg, Singapore and Egypt), and there was more variability if criteria were evaluated with household surveys rather than internet surveys.

We reviewed studies that measured an association of BMI with AP-DGBI and the findings differed depending on how BMI was investigated: as a mean value or in categories (eg, nonobese, obese). Although there was only a trend for higher mean BMI and presence of AP-DGBI, obesity as a dichotomous outcome was significantly associated with AP-DGBI in adults when data were pooled. This emphasizes that mean BMI alone may not adequately represent body composition and that other such parameters need to be included in future studies. For example, in 1 of the studies that reported BMI as both a mean and categorical variable, there was no association between mean BMI and AP-DGBI, but there was an association between higher visceral adipose tissue and waist circumference and IBS.[11] Prior studies in liver and cardiovascular disease have also demonstrated that waist to hip ratio is superior to BMI in its significant association with chronic disease.[12]

Similar to a systematic review and meta-analyses conducted in 2017,[5] we found that gastroenteritis was a risk factor for development and persistence of AP-DGBI. Based on that systematic review of 45 studies, the authors found a pooled prevalence of IBS at 12 months after infectious enteritis of 10.1% (95% CI, 7.2%–14.1%).[5] Our analysis only included studies with a nonexposed control group, and we found that gastroenteritis was associated with an OR of approximately 3 in both adults and children. The prevalence of PI-IBS increased in those samples studied beyond 12 months. The pathophysiological mechanisms accounting for PI-IBS are likely multifactorial and involved dysmotility, visceral hypersensitivity, neuroimmune activation, increased intestinal permeability, and genetic predisposition.

Evidence supports that AP-DGBI is a stress-sensitive disorder. Studies support that general trauma and emotional, sexual, and physical abuse in childhood increase the risk of having AP-DGBI. Delineating the independent relationship between stressful life events and AP-DGBI by taking into account psychological distress was performed in some but not all studies, and this may have contributed to variable results. Furthermore, various methodologies to measure stress and abuse were used, which contributed to a lack of standardized assessment. Generally, a history of any type of abuse in adulthood was not as strong a risk factor for AP-DGBI as history of abuse in childhood. Most studies found that other stressful life events and wartime exposure in adulthood were associated with increased risk of AP-DGBI. The relationship between traumatic events is complex with a combination of factors potentially affecting the risk of having AP-DGBI (ie, peri-traumatic fear increases risk[13] and confiding in others reduces risk[14]).

Psychological disorders, particularly anxiety, GI symptom anxiety and depression, as well as somatic symptoms and poor sleep, emerged as risk factors for development of AP-DGBI in the majority of studies. It is notable that many of these studies were cross-sectional between AP-DGBI and healthy control groups and this connection may be more associative than predictive. Even after controlling for demographic characteristics and presence of a *Diagnostic and Statistical Manual of Mental Disorders*, 4th Edition,[15] disorder, the increased odds of a sleep disorder in those with AP-DGBI remained significant.[16] There is also fairly robust data that personality characteristics, such as neuroticism and alexithymia, could impact risk for AP-DGBI. Social support, interpersonal relationships, and resilience emerged as protective factors when present and as risk factors when absent or decreased,

respectively. Based on multiple longitudinal and prospective cohort studies, anxiety seems to drive the persistence of AP-DGBI symptoms over time. Less is known about the impact of depression and other psychiatric comorbidities on persistence of AP-DGBI. A recent report based on a National Comorbidity Survey-Replication study from more than 5000 respondents found that the odds of having insomnia-related symptoms and/or hypersomnolence-related symptoms were higher in those with IBS than controls.[16] Such findings support the need to consider the patient's history of psychological distress and somatic symptom severity in health care–seeking behavior and symptom management for AP-DGBI.

Overall, fewer studies examined factors associated with persistence of AP-DGBI symptoms. In our review, persistence was denoted by follow-up assessment of AP-DGBI presence at anywhere from 6 months to 8 years. Stress and psychological disorders, in particular anxiety, were also associated with persistence of symptoms in both adults and children. In children only, other consistent risk factors for the persistence of AP-DGBI included female sex and increased somatic symptoms.

This was the first review to investigate risk and protective factors for AP-DGBI in both adults and children. Although the number of studies conducted in children was smaller compared with adults, the overall conclusions were similar. There was a striking paucity of studies across the lifespan. Few studies in children focused on the persistence of symptoms and there were almost no studies on protective factors. These are important gaps in the literature considering that approximately 1 in 4 children with RAP will evolve into adults with IBS.[17] A better understanding of the protective and risk factors in pediatrics could not only improve the quality of life for children and families, but also help prevent the progression of symptoms into adulthood.

Limitations

Most of the studies were performed in North America, Europe, and Asia. As such, findings about factors such as medication use, health care visits, and somatic symptoms may not be generalizable to other parts of the world. In addition, using electronic patient records to collect data on patients' race and ethnicity necessitates relying on the providers' documentation and may result in bias. Only studies reported in English were included. The high heterogeneity across study populations, methodologies, sample sizes, measures used to diagnose AP-DGBI, tools used to assess risk and protective factors, and persistence may have impacted consistency of the results and are inherent limitations to this review.

The validated scale (adapted by Sanderson et al[7]) used to evaluate study quality did not specifically address potential confounding factors or bias. We excluded studies of poor-quality scores, but our analysis did not weigh the likelihood of the conclusions made for each factor based on average quality scores or specific components of the quality rating (eg, adequately powered study, appropriate measures used for assessing factors). Although we chose to highlight factors with most studies and higher study quality ratings, this limitation may have allowed smaller, less adequately powered studies to be weighed similarly to larger, more well-powered studies.

The primary objective of this study was to undertake a comprehensive systematic review. A rigorous meta-analysis for each of the factors is beyond the scope of our study. Where appropriate, we have provided pooled ORs to supplement our descriptive results; however, there are important limitations to these results. These limitations arise from not contacting authors for data and thus only including studies for which data were readily extractable and not performing subgroup or sensitivity analyses. Importantly, although the pooled effect measures can be used to provide an estimate of the association between a factor and AP-DGBI, in many cases, the majority of studies were case–control, which do not define cohorts based on the risk factor but rather based on the outcome. Specifically, more data from prospective or retrospective cohort studies are needed to corroborate our findings suggesting that obesity and tobacco are associated with an increased risk of IBS.

Conclusions

To our knowledge, this is the most comprehensive systematic review assessing a wide range of risk and protective factors for AP-DGBI to date in an adult and pediatric populations. A number of factors appear to increase the risk of developing AP-DGBI in adults and children: female sex, gastroenteritis, abuse, stress, psychological disorders, somatic symptoms, and poor sleep. There are a limited number of studies in children and protective factors, and factors associated with the persistence of AP-DGBI. Well-designed, multicenter, and multinational prospective studies evaluating predictors of AP-DGBI onset and its persistence in children and adults are needed.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

The authors acknowledge the assistance of Cara Axelrod and Mariya Klymenko in reviewing papers and editing the manuscript.

Data Availability

All data, analytic methods, and study materials will be made available to other researchers on request.

Abbreviations used in this paper:

AP-DGBI	abdominal pain–related disorders of gut–brain interaction
BMI	body mass index
GI	gastrointestinal
IBS	irritable bowel syndrome
OR	odds ratio
PI-IBS	post-infection irritable bowel syndrome

RAP recurrent abdominal pain

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WHAT YOU NEED TO KNOW

BACKGROUND AND CONTEXT

Previous studies have assessed risk factors for irritable bowel syndrome and other disorders of gut–brain interaction, but their influence is unclear due to variable study designs and populations.

NEW FINDINGS

Risk factors associated with abdominal pain–related disorders of gut–brain interaction include female sex, obesity, smoking, and a history of gastroenteritis, trauma or abuse, lifetime stress, psychological disorders, somatic symptoms, and poor sleep.

LIMITATIONS

Most studies were performed in North America, Europe, and Asia with heterogeneity in study methodologies, measures, and populations, which may impact the consistency of the results. There were fewer studies examining factors in children, protective factors, and factors associated with the persistence of symptoms.

IMPACT

This comprehensive systematic review identifies risk and protective factors for abdominal pain–related disorders of gut–brain interaction and symptom persistence, which should be considered in the management of adults and children.

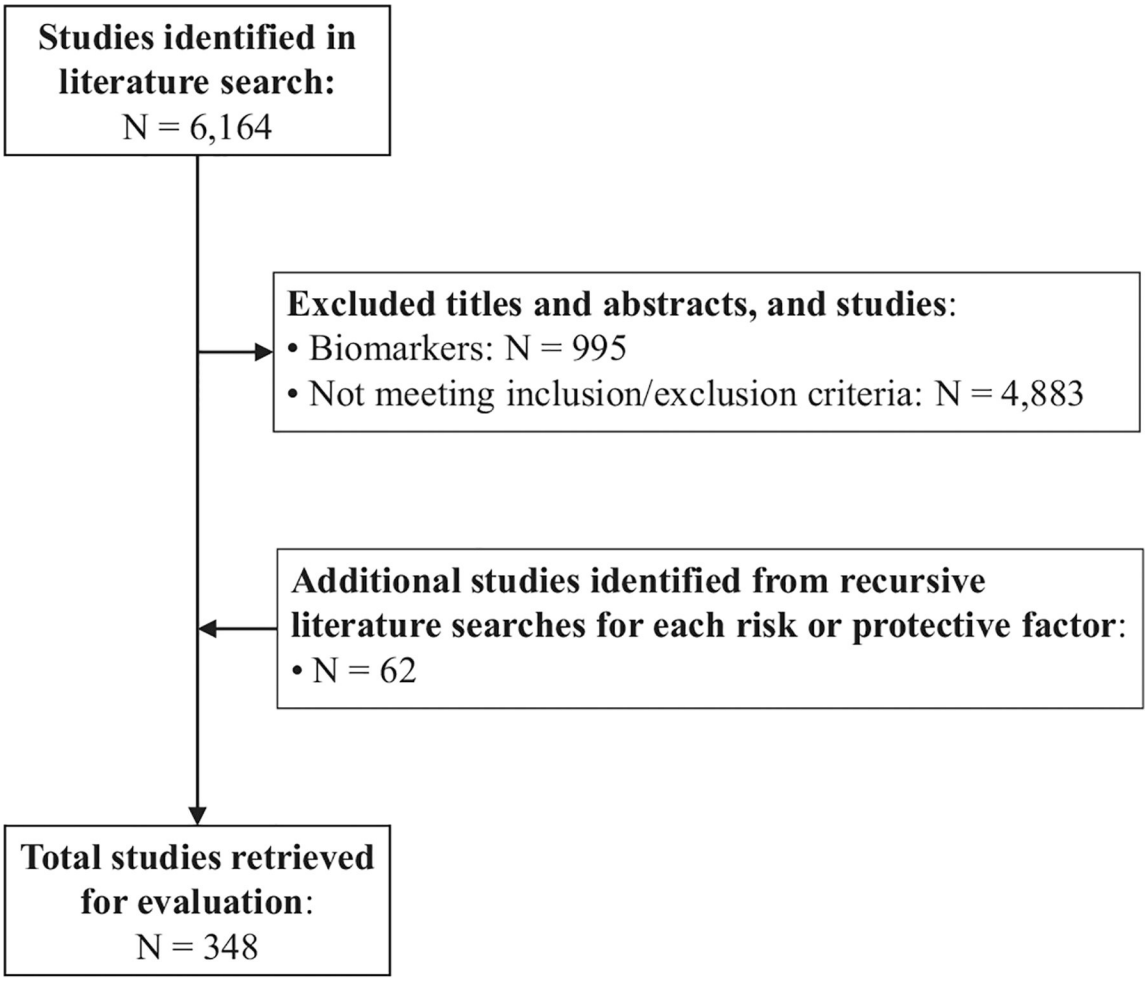

Figure 1.
Flow diagram of assessment of studies identified in systematic review.

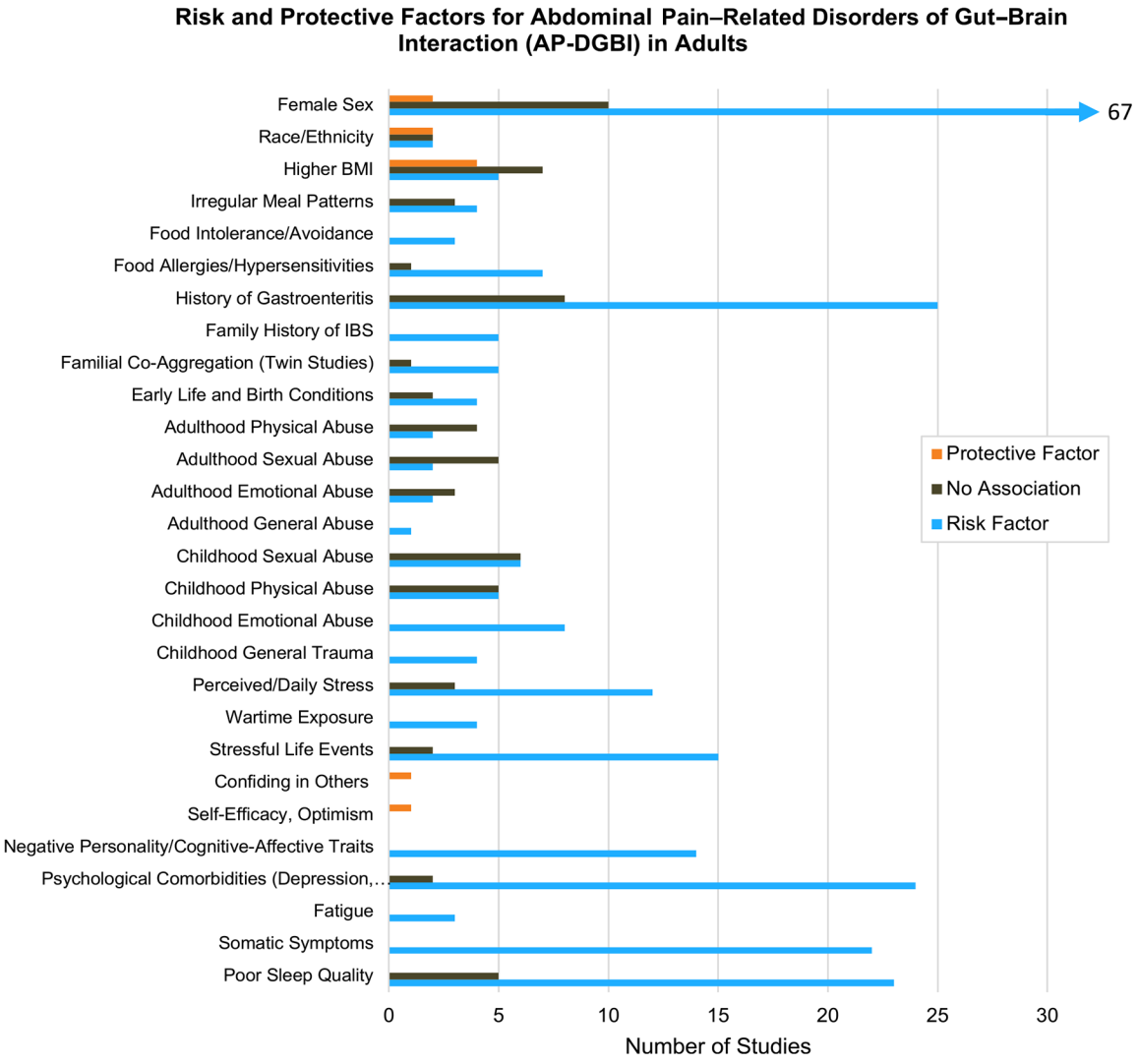

Figure 2.

Summary of the number of studies finding a factor to be a risk factor, protective factor, or neither for AP-DGBI in adults. The *blue arrow* depicts that the number of studies finding female sex as a risk factor for the presence of AP-DGBI was 67 studies (over the displayed maximum x-axis value of 30).

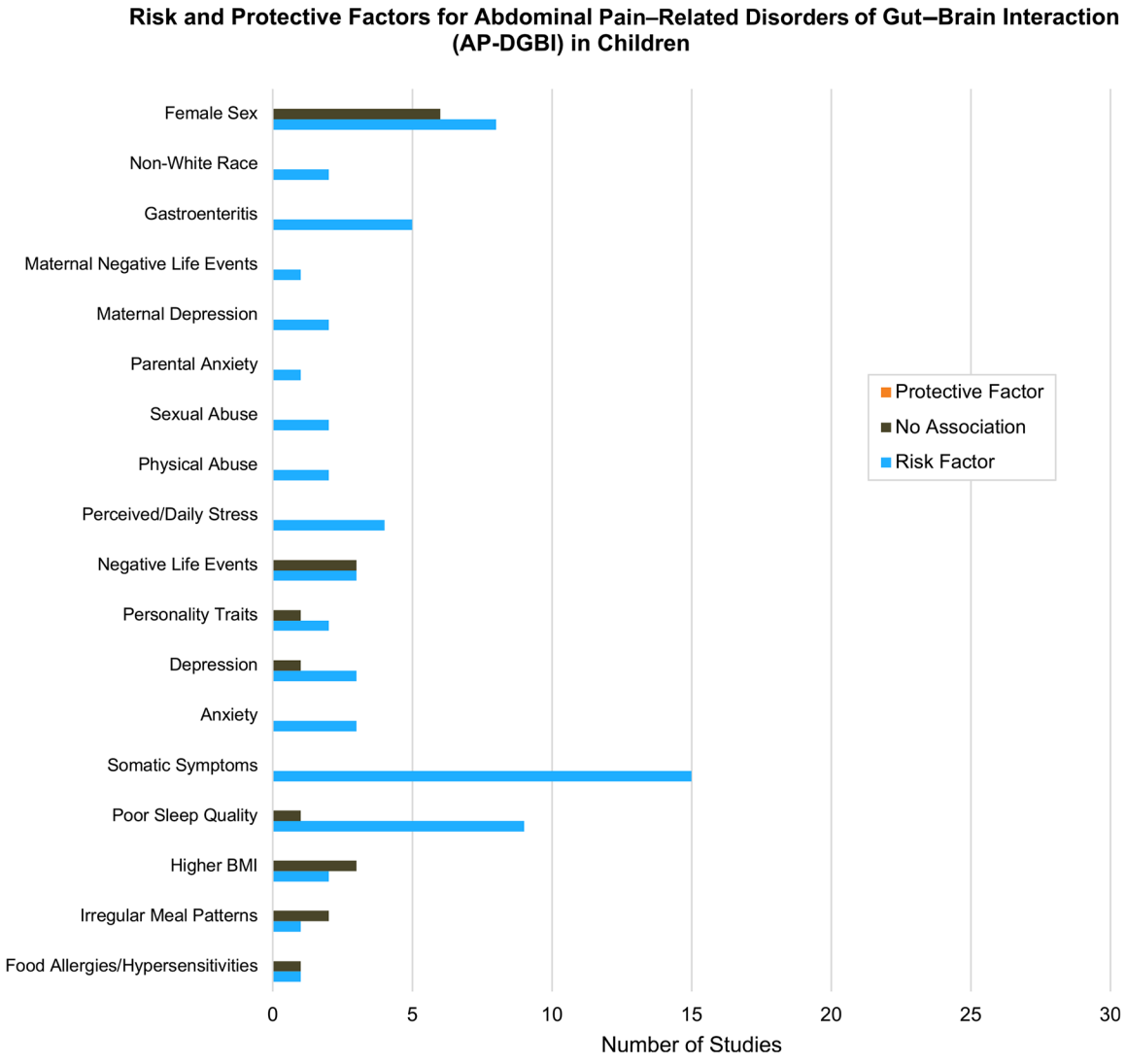

Figure 3.

Summary of the number of studies finding a factor to be a risk factor, protective factor, or neither for AP-DGBI in children.

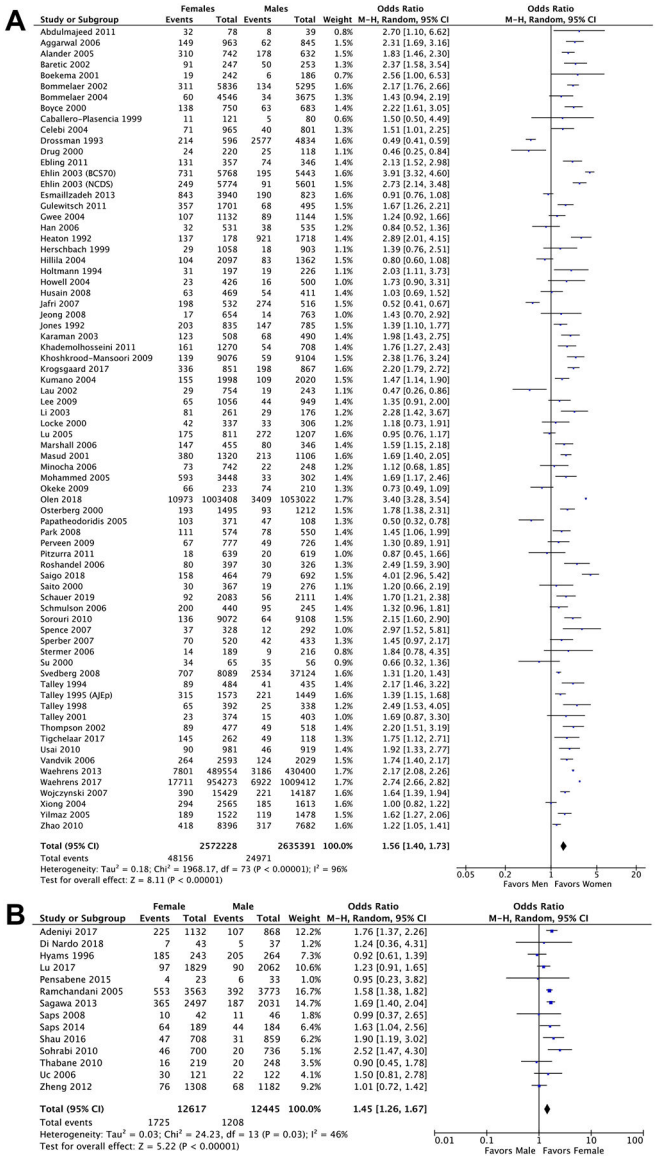

Figure 4.

Forest plots showing ORs for AP-DGBI (formerly termed *functional gastrointestinal disorders*) in female vs male adults (*A*) or children (*B*). M-H, Mantel-Haenszel.

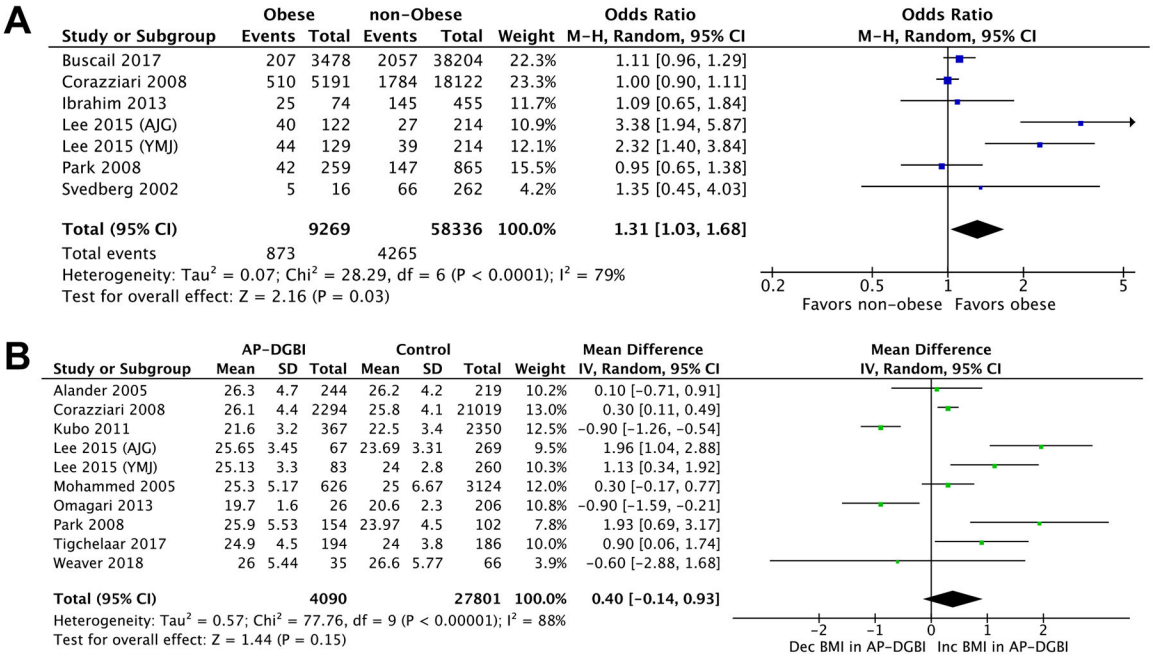

Figure 5.

Forest plots showing ORs for AP-DGBI in obese vs nonobese adults (*A*) and mean BMI in AP-DGBI (formerly termed *functional gastrointestinal disorders*) vs controls (*B*). Dec, decreased; Inc, increased; IV, inverse variance; M-H, Mantel-Haenszel.

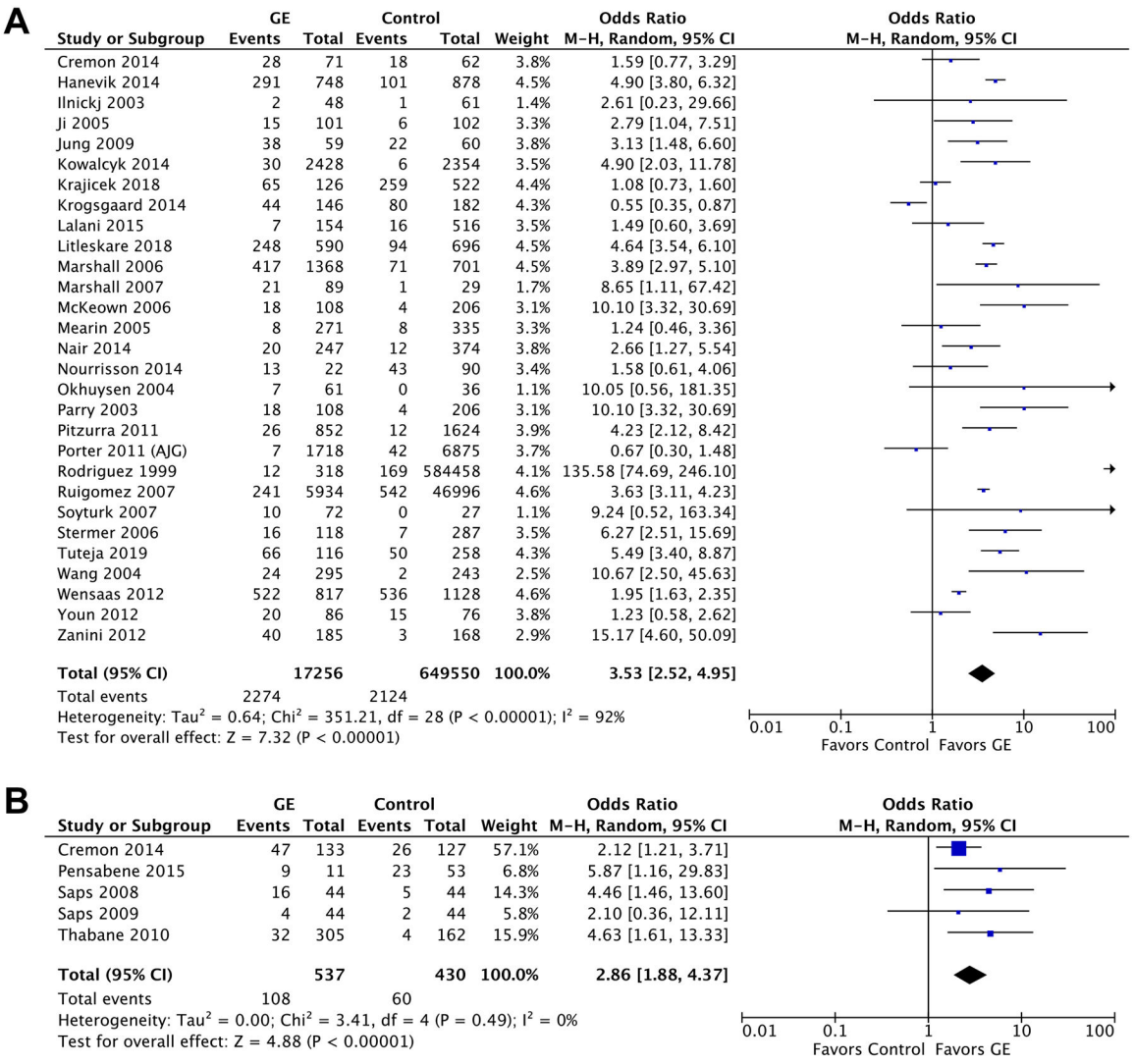

Figure 6.

Forest plots showing ORs for AP-DGBI (formerly termed *functional gastrointestinal disorders*) in adults (*A*) or children (*B*) with vs without a history of infectious gastroenteritis. GE, gastroenteritis; M-H, Mantel-Haenszel.

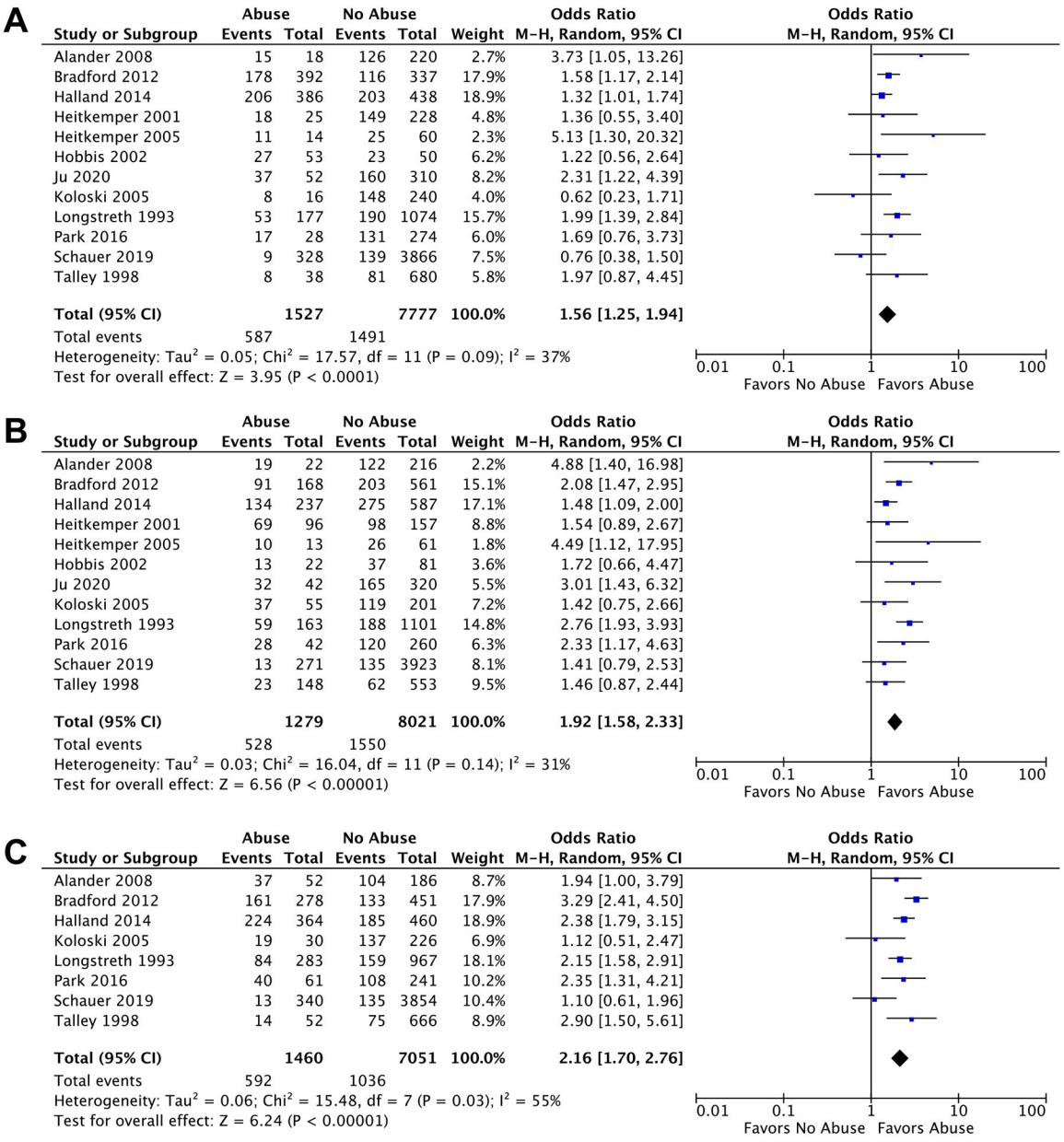

Figure 7.

Forest plots showing ORs for AP-DGBI (formerly termed *functional gastrointestinal disorders*) in adults with history of emotional (*A*), sexual (*B*), or physical (*C*) abuse vs those without any abuse history. M-H, Mantel-Haenszel.

Table 1.

Risk Factors for Developing Abdominal Pain–Related Disorders of Gut–Brain Interaction

Variable	Total studies, n	Total no. of AP-DGBI subjects	Total no. of control subjects	Measure used to define AP-DGBI, no. of studies	Study designs, n	Studies showing variable was a risk factor for AP-DGBI, n (%)	Studies showing no strong association with AP-DGBI, n (%)	Quality rating, mean (range)
Adult studies Variables showing overall risk factor for the presence of AP-DGBI								
Sex	79	72,827	5,138,321	Rome: 56 Manning: 5 Rome+Manning: 9 ICD codes: 4 Clinical diagnosis, questionnaire, or self-report: 5	Case–control: 4 Cross-sectional: 58 Cohort: 17 Population-based: 69 Prospective: 10	Female sex: 67/79 (84.8) Male sex: 2/79 (2.5)	Female sex: 10/79 (12.7)	8 (4–10)
Gastroenteritis	32	7609	655,5801	Rome: 25 ICD codes: 1 Clinical diagnosis, questionnaire, or self-report: 6	Case–control: 5 Cohort: 26 Cross-sectional: 1 Population-based: 7 Prospective: 26	Gastroenteritis: 24/32 (75)	Gastroenteritis: 8/32 (25)	7.5 (4–10)
Family history	5	1566	30,845	Rome: 4 ICD codes: 1	Case–control: 3 Cross-sectional: 1 Case–control+cohort: 1 Population-based: 0 Prospective: 2	Family history of IBS: 4/4 (100.0) Family history of psychiatric illness: 1/1 (100)	Adoptive parent with IBS: 1/1 (100.0)	7.5 (7–8)
Familial co-aggregation	5	4331	52,010	Rome: 2 Clinical diagnosis, questionnaire, or self-report: 3	Case–control: 1 Cross-sectional: 4 Population-based: 5 Prospective: 0	Case-wise concordance between MZ and DZ twin: 3/4 (75.0) Correlations for IBS between MZ and DZ: 2/2 (100)	Case-wise concordance between MZ and DZ twin: 1/4 (25.0)	7 (7–8)
Adverse birth and early-life conditions	4	39,185	3,981,740	Rome: 2 ICD codes: 2	Case–control: 2 Cross-sectional: 2 Population-based: 4 Prospective: 1	Complicated deliveries: 2/2 (100) Early gestational age:1/2 (50.0) Low birth weight: 1/2 (50.0)	Early gestational age:1/2 (50.0) Low birth weight: 1/2 (50.0)	7.5 (6–9)
Trauma and/or abuse history	15 (includes all childhood and adulthood abuse studies (general, emotional,	2577	11,465	Rome: 11 Manning: 2 Clinical diagnosis, questionnaire, or self-report: 2	Case–control: 2 Cross-sectional: 9 Cohort: 4 Population-based: 4 Prospective: 2	Childhood: General trauma: 4/4 (100) Emotional abuse: 8/8 (100) Physical abuse: 5/10 (50.0) Sexual abuse: 6/12 (50.0) Adulthood: General (unspecified) abuse: 1/1 (100) Emotional abuse: 2/5 (40.0) Sexual abuse: 2/7 (28.6) Physical abuse: 2/6 (33.3)	Childhood: General trauma: 0/4 (0) Emotional abuse: 0/8 (0) Physical abuse: 5/10 (50.0) Sexual abuse: 6/12 (50.0) Adulthood: General abuse: 0/1 (0) Emotional abuse: 3/5 (60.0)	7 (6–10)

Gastroenterology. Author manuscript; available in PMC 2022 October 01.

Variable	Total studies, n	Total no. of AP-DGBI subjects	Total no. of control subjects	Measure used to define AP-DGBI, no. of studies	Study designs, n	Studies showing variable was a risk factor for AP-DGBI, n (%)	Studies showing no strong association with AP-DGBI, n (%)	Quality rating, mean (range)
	sexual, and physical)						Sexual abuse: 5/7 (71.4) Physical abuse: 4/6 (66.7)	
Stress	36	21,530	2,076,639	Rome: 29 Manning: 2 Rome+Manning: 1 ICD codes: 1 Clinical diagnosis, questionnaire, or self-report: 3	Case–control: 5 Cross-sectional: 19 Cohort: 12 Population-based: 13 Prospective: 9	Stressful life events: 15/17 (88.2) Wartime exposure: 4/4 (100) Perceived or daily stress: 12/15 (80.0)	Stressful life events: 2/17 (11.8) Wartime exposure: 0/4 (0) Perceived or daily stress: 3/15 (20.0)	7 (4–10)
Psychological disorders	34	687,567	700,971	Rome: 20 Manning: 3 Clinical diagnosis, questionnaire, or self-report: 11	Case–control: 8 Cohort: 6 Cross-sectional: 20 Population-based: 8 Prospective: 4	Comorbidity (depression, anxiety, somatization): 24/26 (92.3) Negative personality/cognitive-affective traits: 14/14 (100)	Comorbidity (depression): 2/26 (7.7)	7 (5–10)
Somatic symptoms	33	148,578	211,607	Rome: 28 Manning: 2 Clinical diagnosis, questionnaire, or self-report: 2 Nonspecified: 1	Case–control: 4 Cohort: 9 Cross-sectional: 20 Population-based: 16 Prospective: 7	Somatic symptoms: 22/22 (100.0) Somatic symptom scores: 9/9 (100.0) Fatigue: 3/3 (100.0)	—	7 (4–10)
Sleep disturbance	21	27,581	87,286	Rome: 19 Clinical diagnosis, questionnaire, or self-report: 1 Nonspecified: 1	Case–control: 3 Cohort: 1 Cross-sectional: 17 Population-based: 11 Prospective: 1	Sleep disturbance: 8/8 (100) Poor sleep quality: 7/7 (100.0) Insomnia symptoms:5/6 (83.3) Self-reported less total sleep time: 2/5 (40.0) Single study: insufficient sleep, late sleep-wake phase, less sleep regularity	Insomnia symptoms: 1/6 (16.7) Self-reported total sleep time: 3/5 (60.0) Single study: actigraphic sleep parameters	7 (4–10)
Specific medical conditions	30	156,728	464,545	Rome: 19 ICD-codes: 5 Clinical diagnosis, questionnaire, or self-report: 6	Case–control: 7 Cross-sectional: 14 Cohort: 9 Population-based: 10 Prospective: 5	Asthma: 6/7 (85.7) Allergies: 6/7 (85.7) Fibromyalgia: 4/5 (80) Migraines: 5/6 (83.3) Arthritis: 4/4 (100) Urticaria 2/2 (100) Non-GI infections: 3/3 (100) GERD: 2/2 (100) Diverticulosis: 2/2 (100) Single studies: psoriasis, sensitive skin syndrome, eczema, chronic pain, bronchitis, metabolic syndrome, endometriosis, hypoglycemia, angina, biliary event, eating disorder, renal disease, OSA, hypothyroidism	Asthma: 1/7 (14.3) Allergies: 1/7 (14.3) Fibromyalgia: 1/5 (20) Migraines: 5/6 (83.3)	8 (6–10)
Surgery	10	119,140	340,518	Rome: 5 Manning: 3 Clinical diagnosis,	Case–control: 1 Cross-sectional: 5 Cohort: 4	Any abdominal surgery: 8/10 (80) Cholecystectomy: 5/7 (71.4)	Any abdominal surgery: 2/10 (20) Cholecystectomy: 2/7	8 (6–10)

Variable	Total studies, n	Total no. of AP-DGBI subjects	Total no. of control subjects	Measure used to define AP-DGBI, no. of studies	Study designs, n	Studies showing variable was a risk factor for AP-DGBI, n (%)	Studies showing no strong association with AP-DGBI, n (%)	Quality rating, mean (range)
				questionnaire, or self-report: 2	Population-based: 7 Prospective: 1	Hysterectomy: 3/5 (60) Single study: surgical abortion, appendectomy, back surgery, genital surgery (men)	(28.6) Hysterectomy: 2/5 (40)	
Medications	19	5847	70,002	Rome: 13 Manning: 2 Rome+Manning: 1 ICD codes: 3	Case–control: 6 Cohort: 6 Cross-sectional: 7 Population-based: 13 Prospective: 4	Antibiotics: 7/8 (87.5) NSAID/aspirin: 2/3 (67) HRT/OCS: 3/4 (75) Laxative: 1/2 (50) Single studies: herbal treatment, anticholinergic drugs, drug intolerance, selective serotonin reuptake inhibitors, acetaminophen	Antibiotics: 1/8 (12.5) NSAID/aspirin: 1/3 (33) HRT/OCs: 1/4 (25) Laxative: 1/2 (50) Single study: antipsychotics, loperamide use	8 (4–10)
Use of medical resources	9	158,551	1,206,798	Rome: 4 ICD codes: 4 Clinical diagnosis, questionnaire, or self-report: 1	Cohort: 4 Cross-sectional: 5 Population-based: 10 Prospective: 1	More frequent health care behaviors/increased medical resources: 8/9 (89)	Frequency of health care behaviors/medical resources: 1/9 (11)	7 (6–10)
Pets	1	130	637	Rome: 1	Cross-sectional: 1 Population-based: 1 Prospective: 0	Exposure to herbivore pets: 1/1 (100)	—	7
Living environment	7	1447	7580	Rome: 4 Rome+Manning: 1 Clinical diagnosis, questionnaire, or self-report: 2	Case–control: 1 Cross-sectional: 6 Population-based: 5 Prospective: 0	Sharing a bedroom: 1/1 (100) Urban residence: 1/2 (50.0) Living in a landed property: 1/1 (100) Living in a school dormitory: 1/1 (100) Exposure to pollutants/ chemicals: 2/2 (100.0)	Urban vs rural residence: 1/2 (50.0)	7 (5–9)
Variables showing no overall association or mixed associations[a] for the presence of AP-DGBI								
Race	5	3289	467,521	Rome: 4 Manning: 1	Cross-sectional: 4 Cohort: 1 Population-based: 1 Prospective: 1	People who migrated to Saudi Arabia: 1/5 (20.0) Jewish or Israeli-born: 1/5 (20.0%)	Non-Hispanic White: 1/5 (20.0) White ethnicity: 1/5 (20.0)	7 (4–9)
BMI	16	10,090	103,832	Rome: 12 Clinical diagnosis, questionnaire, or self-report: 4	Case–control: 1 Cross-sectional: 12 Cohort: 3 Population-based: 6 Prospective: 1	Lower BMI: 4/16 (25) Higher BMI: 5/16 (31.3)	BMI: 7/16 (43.8)	7 (6–10)
Diet-related factors and	33	9717	70,583	Rome: 28 Manning: 1	Case–control: 5 Cross-sectional: 26	Food allergies/ hypersensitivities: 7/8 (87.5)	Food allergies/ hypersensitivities: 1/8	7 (4–10)

Variable	Total studies, n	Total no. of AP-DGBI subjects	Total no. of control subjects	Measure used to define AP-DGBI, no. of studies	Study designs, n	Studies showing variable was a risk factor for AP-DGBI, n (%)	Studies showing no strong association with AP-DGBI, n (%)	Quality rating, mean (range)
food allergies/ intolerances				Rome+Manning: 1 Clinical diagnosis, questionnaire, or self-report: 3	Cohort: 2 Population-based: 14 Prospective: 5	Food intolerance/avoidance: 3/3 (100) Irregular meal patterns: 4/7 (57.1) Specific foods: 23 (mixed results)	(12.5) Irregular meal patterns: 3/7 (42.9) Specific foods: 23 (mixed results)	
Specific medical conditions	9	142,902	149,231	Rome: 5 ICD codes: 1 Clinical diagnosis, questionnaire, or self-report: 3	Case–control: 2 Cross-sectional: 6 Cohort: 1 Population-based: 6 Prospective: 3	Prediabetes/elevated fasting blood glucose: 1/2 (50.0) Hypertension: 1/2 (50.0)	Prediabetes/elevated fasting blood glucose: 1/2 (50.0) Diabetes: 2/2 (100.0) Hypertension:1/2 (50.0) Single studies: scleroderma, gallbladder disorders, hypertriglyceridemia, history of *Helicobacter pylori,* hepatitis B/C, UTI, ear infections, hemorrhoids, urinary troubles	7 (6–8)
Education	25	7478	49,353	Rome: 21 Manning: 1 Rome+Manning: 2 Clinical diagnosis, questionnaire, or self-report: 1	Case–control: 4 Cross-sectional: 18 Cohort: 3 Population-based: 14 Prospective: 3	Higher education: 2/22 9.1) Lower education: 6/22 (27.3) Academic workload: 1/1 (100) Lower cognitive ability/lower global constructive thinking: 2/2 (100)	Education level: 14/22 (63.6)	8 (4–10)
Physical activity	12	2483	8975	Rome: 11 Rome+Manning: 1	Case–control: 1 Cross-sectional: 9 Cohort: 1 Population-based: 2 Prospective: 1	Decreased physical activity: 7/12 (58.3) Increased physical activity: 1/12 (8.3)	Physical activity: 2/12 (16.7)	6 (4–8)
Occupation and socioeconomics	17	4193	35,515	Rome: 15 Rome+Manning: 1 ICD codes: 1	Case–control: 3 Cross-sectional: 10 Cohort: 4 Population-based: 10 Prospective: 4	Occupational status: 1/12 (8.3) Unemployed/lower employment status: 4/12 (33.3) Lower income level: 2/9 (22.2) Higher childhood social class: 1/9 (11.1)	Occupational status: 6/12 (50.0) Parent's occupational status: 1/12 (8.3) Income level: 6/9 (66.7)	8 (5–9)
Tobacco/alcohol use	31	9437	108,387	Rome: 24 Manning: 3 Clinical diagnosis, questionnaire, or self-report: 4	Case–control: 5 Cross-sectional: 23 Cohort: 3 Population-based: 16 Prospective: 2	Tobacco: 7/27 (25.9) Alcohol: 4/24 (16.7)	Tobacco: 21/27 (77.8) Alcohol: 20/24 (83.3)	7 (4–10)
Pediatric studies Variables showing overall risk factor for the presence of AP-DGBI								

Variable	Total studies, n	Total no. of AP-DGBI subjects	Total no. of control subjects	Measure used to define AP-DGBI, no. of studies	Study designs, n	Studies showing variable was a risk factor for AP-DGBI, n (%)	Studies showing no strong association with AP-DGBI, n (%)	Quality rating, mean (range)
Sex	14	3053	21,982	Rome: 12 Apley: 1 Clinical diagnosis, questionnaire, or self-report: 1	Cross-sectional: 9 Cohort: 5 Population-based: 5 Prospective: 4	Female sex: 8/14 (57.1)	No association with sex: 6/14 (42.9)	7 (5–9)
Race/ethnicity	2	1123	9669	Rome: 1 Apley: 1	Cohort: 2 Population-based: 2 Prospective: 0	Non-White: 2/2 (50)	Non-White: 0/2 (0)	8 (7–9)
Gastroenteritis	5	580	488	Rome: 5	Cohort: 5 Population-based: 0 Prospective: 3	Gastroenteritis: 4/5 (80)	Gastroenteritis: 1/5 (20)	9 (7–9)
Family history	3	1054	7436	Apley: 1 Clinical diagnosis, questionnaire, or self-report 2	Cross-sectional: 2 Cohort: 1 Population-based: 1 Prospective: 1	Parental anxiety: 1/1 (100) Maternal depression: 2/2 (100) Maternal negative life events: 1/1 (100)	—	6 (5–8)
Trauma and/or abuse history	2	1150	3204	Rome: 1 Clinical diagnosis, questionnaire, or self-report: 1	Cross-sectional: 1 Cohort: 1 Population-based: 0 Prospective: 1	(100.0) Physical abuse: 2/2 (100.0) Sexual abuse: 2/2 (100.0)	—	5.5 (5–6)
Stress	10	825	3710	Rome: 4 Apley: 4 Clinical diagnosis, questionnaire, or self-report: 2	Cross-sectional: 6 Cohort: 4 Population-based: 1 Prospective: 2	Negative life events: 3/6 (50.0) Perceived or daily stress: 4/4 (100.0)	Negative life events: 3/6 (50.0), 2 of these studies were positive on univariate analysis	6 (5–8)
Psychological disorders	7	9714	89,113	Rome: 1 Apley: 6	Case–control: 4 Cross-sectional: 3 Population-based: 1 Prospective: 1	Anxiety: 3/3 (100) Depression: 3/4 (75) Personality traits: 2/3 (67)	Depression: 1/4 (25) Personality traits: 1/3 (33)	7 (5–9)
Somatic symptoms	15	3648	32,861	Rome: 3 Apley: 8 Rome+Apley: 1 Clinical diagnosis, questionnaire, or self-report: 3	Case–control: 2 Cross-sectional: 7 Cohort: 6 Population-based: 8 Prospective 5	Somatic symptoms: 15/15 (100)	—	7 (4–10)
Sleep disturbance	6	18,412	114,606	Rome: 4 Apley: 2	Case–control: 1 Cross-sectional:4 Cohort: 1 Population-based: 0 Prospective: 0	Sleep disturbance: 2/2 (100) Poor sleep quality: 2/2 (100.0) Insomnia symptoms:1/1 (100) Self-reported less total sleep time: 1/1 (100)	—	7 (5–9)
Education	6	18,394	84,639	Rome: 5 Apley: 1	Cross-sectional: 6 Population-based: 1 Prospective: 0	Private school: 3/5 (60) Higher grade level: 2/2 (100) School absence: 1/1 (100)	Private school: 2/5 (40)	8 (5–9)

Variable	Total studies, n	Total no. of AP-DGBI subjects	Total no. of control subjects	Measure used to define AP-DGBI, no. of studies	Study designs, n	Studies showing variable was a risk factor for AP-DGBI, n (%)	Studies showing no strong association with AP-DGBI, n (%)	Quality rating, mean (range)
Occupation and socioeconomics	2	1598	5791	Rome: 1 Clinical diagnosis, questionnaire, or self-report: 1	Cross-sectional: 2 Population-based: 0 Prospective: 0	Low socioeconomic status: 2/2 (100)	Social class alone: 1/1 (100)	6 (5–7)
Variables showing no overall association or mixed associations[a] for the presence of AP-DGBI								
BMI	5	605	2754	Rome: 4 Clinical diagnosis, questionnaire, or self-report: 1	Cross-sectional: 5 Population-based: 0 Prospective: 4	BMI: 2/5 (40)	BMI: 3/5 (60)	7 (4–8)
Diet-related factors and food allergies/ intolerances	10	2979	18,930	Rome: 7 Apley: 1 Clinical diagnosis, questionnaire, or self-report: 2	Cross-sectional: 8 Cohort: 2 Population-based: 3 Prospective: 2	Food allergies/ hypersensitivities: 1/2 (50) Irregular meal patterns: 1/3 (33) Specific foods: 7 (mixed results)	Food allergies/ hypersensitivities: 1/2 (50) Irregular meal patterns: 2/3 (67) Specific foods: 7 (mixed results)	8 (4–9)
Specific medical conditions	14	2272	10,605	Rome: 3 Apley: 7 Clinical diagnosis, questionnaire, or self-report: 4	Cross-sectional: 11 Cohort: 3 Population-based: 1 Prospective: 5	*H pylori*: 2/8 Atopy: 1/2 Single studies: headaches, colic, Henoch-Schonlein purpura	*H pylori*: 6/8 Atopy: 1/2	6 (4–8)
Physical activity	3	356	2234	Rome: 3	Cross-sectional: 3 Population-based: 0 Prospective: 1	Physical activity: 1/3 (33)	Physical activity: 2/3 (66)	5 (4–5)
Tobacco/alcohol	3	18,091	81,545	Rome: 3	Cross-sectional: 3 Population-based: 0 Prospective: 0	Tobacco/alcohol: 1/3 (33)	Tobacco/alcohol: 2/3 (66)	5 (5–8)

DZ, dizygotic; GERD, gastroesophageal reflux disease; HRT/OC, hormone replacement therapy/oral contraceptive; ICD, International Classification of Diseases; MZ, monozygotic; NSAID, nonsteroidal anti-inflammatory drug; OSA, obstructive sleep apnea; UTI, urinary tract infection.

[a] *No overall association* defined as >50% of studies showing no significant relationship between variable and presence of AP-DGBI. *Mixed association* defined as some variable subcategories showing an association with AP-DGBI and other subcategories showing no association.

Table 2.

Protective Factors Against Developing Abdominal Pain–Related Disorders of Gut–Brain Interaction in Adults

Factor	Total studies, n	Total no. of AP-DGBI subjects	Total no. of control subjects	Measure used to define AP-DGBI	Study designs, n	Studies showing a protective association against AP-DGBI, n (%)	Quality rating, mean (range)
Race	1	976	439,846	Rome: 1	Cohort: 1 Population-based: 0 Prospective: 0	Middle Eastern or African origin: 1/1 (100.0)	9
Confiding in others about traumatic experiences	1	197	165	Rome: 1	Cross-sectional: 1 Population-based: 0 Prospective: 0	1/1 (100)	7
Psychological factors: resilience, optimism, and social support	1	401	401	Rome: 1	Cross-sectional: 1 Cohort: 1 Population-based: 0 Prospective: 1	Self-efficacy: 1/1 (100.0) Optimism: 1/1 (100.0)	9
Engaging in sports or regular physical activity	2	318	2242	Rome: 1 Rome+Manning: 1	Cross-sectional: 2 Population-based: 0 Prospective: 0	2/2 (100)	4

Table 3.

Risk Factors for Persistent Abdominal Pain–Related Disorders of Gut–Brain Interaction

Variable	Total studies, n	Measure used to define AP-DGBI, n	Study designs, n	Studies showing variable was a risk factor for AP-DGBI, n (%)	Studies showing no strong association with AP-DGBI, n (%)	Quality rating, mean (range)
Adult studies Variables showing overall risk factor for persistent AP-DGBI						
Gastroenteritis	6	Rome: 4 ICD codes: 1 Clinical diagnosis, questionnaire, or self-report: 1	Cohort: 5 Case–control: 1 Population-based: 1 Prospective: 5	Gastroenteritis: 6/6 (100)	—	7 (6–10)
Family history	1	Rome: 1	Prospective cohort: 1 Population-based: 0 Prospective: 0	Family history of GI symptoms: 1/1 (100)	—	9
Stress	7	Rome: 6 Clinical diagnosis, questionnaire, or self-report: 1	Prospective cohort: 7 Population-based: 2 Prospective: 1	Negative life events: 2/2 (100.0) Daily/monthly stress: 1/3 (33.3) Wartime stressors: 2/2 (100.0)	Daily/monthly stress: 2/3 (66.7)	7 (6–9)
Psychological disorders	11	Rome: 7 ICD codes: 1 Clinical diagnosis or self-report: 3	Case–control: 2 Cohort: 9 Population-based: 5 Prospective: 7	Pre-existing comorbid anxiety disorder: 5/7 (71.4) Pre-existing comorbid depressive disorder: 2/7 (28.6)	Pre-existing comorbid anxiety disorder: 2/7 (28.6) Pre-existing comorbid depressive disorder: 5/7 (71.4)	8 (4–10)
Somatic symptoms	3	Rome: 1 ICD codes: 1 Clinical diagnosis, questionnaire, or self-report: 1	Case–control: 1 Cohort: 2 Population-based: 0 Prospective: 2	Concomitant cramps after acute GE: 1/1 (100.0) Somatic symptoms (eg, extremity pain, migraine, fatigue, chest pain): 1/1 (100.0)	Pelvic pain, chronic headache, and back pain after laparoscopy: 1/1 (100.0)	5 (4–6)
Specific medical conditions	2	Rome: 2	Cohort: 2 Population-based: 0 Prospective: 2	IBS: 1/1 (100) Headaches: 1/1 (100) Non-GI chronic pain: 1/1 (100)	—	7 (4–10)
Medications	4	Rome: 2 Clinical diagnosis, questionnaire, or self-report: 2	Cohort: 4 Population-based: 4 Prospective: 4	Increased prescriptions: 1/1 (100.0) Nsaid use: 1/1 (100.0)	Hormone replacement therapy: 2/2 (100.0) Acetaminophen or aspirin use: 1/1 (100.0)	7.5 (5–9)
Use of medical resources	3	Rome: 1 Manning: 0 Rome+Manning: 0 ICD codes: 1 Clinical diagnosis, questionnaire, or self-report:1	Cross-sectional: 1 Cohort: 2 Population-based: 2 Prospective: 2	More frequent health care behaviors: 3/3 (100)	—	8 (6–10)
Variables showing no overall association or mixed associations[a] for persistent AP-DGBI						

Variable	Total studies, n	Measure used to define AP-DGBI, n	Study designs, n	Studies showing variable was a risk factor for AP-DGBI, n (%)	Studies showing no strong association with AP-DGBI, n (%)	Quality rating, mean (range)
Sex	7	Rome: 5 Clinical diagnosis, questionnaire, or self-report: 2	Cohort: 7 Population-based: 4 Prospective: 7	Female sex: 2/7 (28.6)	No sex association: 5/7 (71.4)	8 (6–9)
Race/ethnicity	3	Rome: 2 Clinical diagnosis or self-report: 1	Cohort: 3 Population-based: 0 Prospective: 2	—	No association with race/nationality: 2/3 (66.7)	8 (5–9)
BMI	1	Rome: 1	Cohort: 1 Population-based: 1 Prospective: 1	—	No association with bmi: 1/1 (100.0)	9
Diet-related factors and food allergies/intolerances	3	Rome: 2 Clinical diagnosis, questionnaire, or self-report: 1	Cohort: 3 Population-based: 2 Prospective: 3	Food allergies/hypersensitivities: 1/1 (100) Specific foods: 2 (mixed results)	Food intolerance/avoidance: 1/1 (100) Specific foods: 2 (mixed results)	8 (6–9)
Pets	1	Rome: 1	Cohort: 1 Population-based: 1 Prospective: 1	—	Pets: 1/1 (100.0)	9
Education	1	Rome: 1	Cohort: 1 Population-based: 1 Prospective: 1	—	Higher education: 1/1 (100)	9
Occupation/economics/social class	2	Clinical diagnosis or self-report: 2	Cohort: 2 Population-based: 2 Prospective: 1	—	Social class: 1/1 (100.0) Sick leave: 1/1 (100.0)	8 (8–8)
Tobacco/alcohol	3	Rome: 2 Manning: 0 Rome+Manning: 0 ICD codes: 0 Clinical diagnosis, questionnaire, or self-report: 1	Cohort: 3 Population-based: 2 Prospective: 3	Tobacco use: 2/4 (50.0) Alcohol use: 1/4 (25.0)	Tobacco use: 2/4 (50.0) Alcohol use: 3/4 (75.0)	8.5 (8–9)
Pediatric studies Variables showing overall risk factor for persistent AP-DGBI						
Sex	7	Rome: 5 Manning: 1 Apley: 1	Cohort: 7 Population-based: 2 Prospective: 7	Female sex: 5/7 (71.4)	Female sex: 2/7 (28.6)	7 (5–9)
Family history	2	Apley: 2	Cohort: 2 Population-based: 0 Prospective: 2	Family history of maternal anxiety: 2/2 (100)	—	7.5 (7–8)
Stress	3	Manning: 1 Clinical diagnosis or self-report: 2	Cohort: 3 Population-based: 0 Prospective: 3	Negative life events: 3/3 (100.0)	—	5 (5–6)
Psychological disorders	3	Apley: 3	Case–control: 1 Cohort: 2	Anxiety: 3/3 (100) Depression: 2/2 (100)	Psychological factors: 2/5 (40)	7 (5–9)

Variable	Total studies, n	Measure used to define AP-DGBI, n	Study designs, n	Studies showing variable was a risk factor for AP-DGBI, n (%)	Studies showing no strong association with AP-DGBI, n (%)	Quality rating, mean (range)
			Population-based: 1 Prospective: 2			
Somatic symptoms	7	Rome: 3 Apley: 1 Clinical diagnosis, questionnaire, or self-report: 3	Cross-sectional: 1 Cohort: 6 Population-based: 1 Prospective: 5	Somatic symptoms: 6/7 (85)	Somatic symptoms: 1/7 (15)	7 (5–8)
Specific medical conditions	13	Rome: 2 Apley: 7 Clinical diagnosis, questionnaire, or self-report: 4	Cross-sectional: 10 Cohort: 3 Population-based: 1 Prospective: 5	—	—	6 (4–8)
Education	1	Rome/Manning: 1	Cohort: 1 Population-based: 0 Prospective: 1	Lower academic competence: 1/1 (100)	—	5

GE, gastroenteritis; ICD, International Classification of Diseases; NSAID, nonsteroidal anti-inflammatory drug.

[a] *No overall association* defined as >50% of studies showing no significant relationship between variable and persistent AP-DGBI. *Mixed association* defined as some variable subcategories showing an association with AP-DGBI and other subcategories showing no association.

Table 4.

Protective Factors Against Persistent Abdominal Pain–Related Disorders of Gut–Brain Interaction in Adults

Factor	Total studies, n	Measure used to define functional disorder, n	Study designs, n	Studies showing protective association with persistence of IBS, n (%)	Quality rating, mean (range)
Psychological disorders	3	Rome: 2 ICD code: 1	Case–control: 1 Population-based: 0 Prospective: 2	Moderate satisfaction with social support: 1 Lower anxiety at diagnosis: 2	7 (5–9)
Living environment	1	Rome: 1	Cohort: 1 Population-based: 0 Prospective: 0	Living in rural settlement: 1/1 (100)	9

ICD, International Classification of Diseases.