

# Parental, Perinatal, and Childhood Risk Factors for Development of Irritable Bowel Syndrome: A Systematic Review

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## Background/Aims

Adverse early life experiences are associated with the development of stroke, cancer, diabetes, and chronic respiratory and ischemic heart diseases. These negative experiences may also play a role in the development of irritable bowel syndrome (IBS)—a functional gastrointestinal disease. This review discusses the research to date on the parental, perinatal, and childhood risk and protective factors associated with the development of IBS.

## Methods

A literature search was completed for studies published between 1966 and 2018 that investigated premorbid factors occurring during the perinatal and childhood periods as well as parental factors that were associated with the development of IBS.

## Results

Twenty-seven studies fulfilled the review criteria. Risk factors that appeared in more than one study included: (1) parental IBS, substance abuse, parental punishment, and rejection as parental risk factors; (2) low birth weight as a perinatal risk factor; and (3) crowded living conditions in low-income families, childhood anxiety, depression, or child abuse as childhood risk factors. Protective factors for IBS were emotional warmth from the parents and being born to an older mother.

## Conclusions

More effort is needed to identify what fetal and maternal factors are associated with low birth weight and IBS. A well-executed prospective birth cohort with a collection of bio-samples and functional data will provide a better understanding of how adversity and the interplay between genetics, epigenetics, and numerous risk factors affect the development of IBS.

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## Key Words

Infant; Irritable bowel syndrome; Maternal-child nursing; Mother-child relations; Perinatal care

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## Introduction

Irritable bowel syndrome (IBS) is one of the most common functional gastrointestinal disorders (FGIDs) which is characterized by recurrent abdominal pain associated with an abnormal bowel habit. Patients with IBS often complain of abdominal discomfort or bloating and irregular bowel habits like diarrhea, constipation or mixed bowel habits.<sup>1</sup>

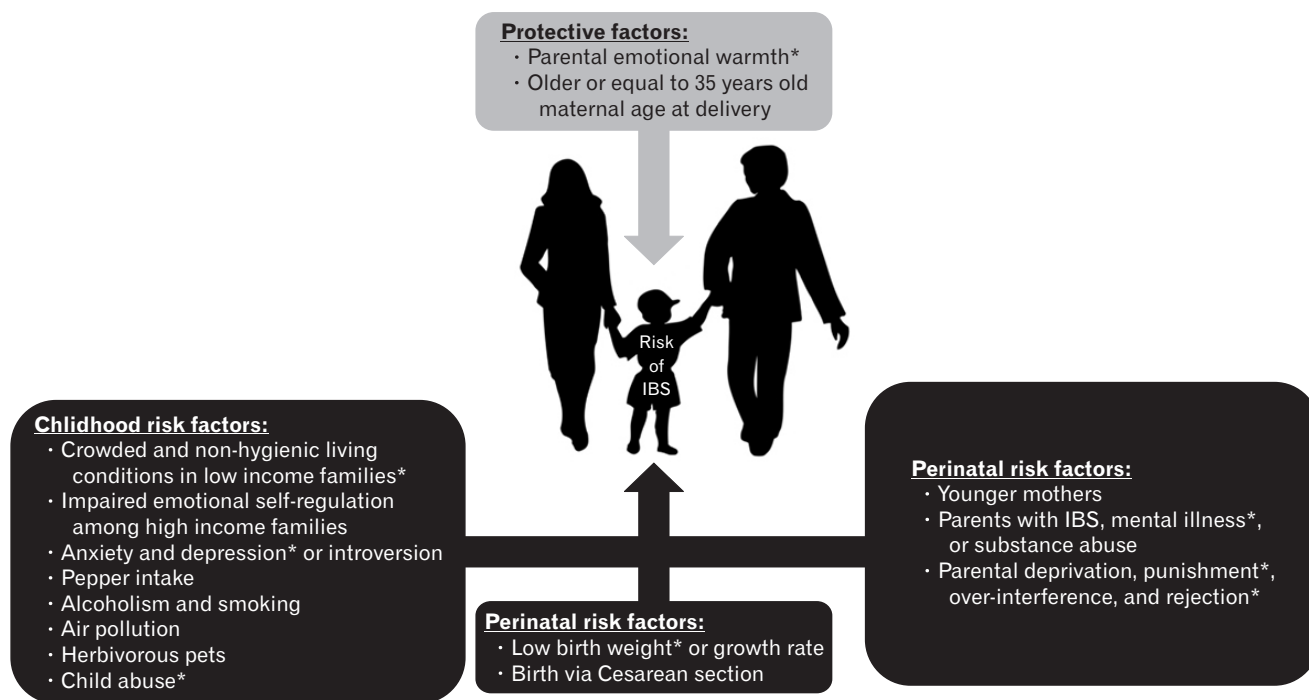
The Rome Foundation performed the first global study of the epidemiology and impact of the FGIDs in 33 countries. The survey was completed by 73 076 respondents. The overall IBS prevalence was 3.8% by Rome IV criteria and 10.1% by Rome III criteria (by internet survey), and the pooled IBS prevalence rates were 1.5% using Rome IV and 3.5% using Rome III (by household survey).<sup>2</sup> For a long time, children with symptoms of IBS were more likely to be diagnosed as having recurrent abdominal pain. This changed in 1995 when an international group of pediatric gastroenterologists defined the diagnostic criteria for FGIDs in childhood. These criteria were published 4 years later as part of the Rome II criteria and have since been updated in Rome IV. The prevalence of IBS in American children ranges from 1.2% to 2.9%.<sup>3</sup> IBS also bears a significant burden on society and individuals. In the United States, IBS accounts for an estimated \$1.7 billion and \$20.0 billion in di-

rect and indirect medical costs annually.<sup>4</sup> IBS patients have reflected a significantly impaired quality of life comparable to that of patients with other chronic diseases such as ischemic heart disease and diabetes mellitus.<sup>5</sup>

Multiple factors are thought to play a role in the pathophysiology of IBS. These factors include visceral hypersensitivity, dysbiosis of the gut microbiota, immune activation, and alterations in brain function. IBS may be triggered by stress, mood disorders, gastrointestinal infection, and adverse early life experiences.<sup>6,7</sup> This systematic review aims to summarize the current understanding of early life experiences (including parental, perinatal, and childhood risk factors) that may contribute to the development of IBS. We also discuss the possible links between these risk factors with potential pathophysiological mechanisms.

## Methodology

We performed a computer-assisted literature search of Cochrane databases, PubMed, Web of Science, and Embase from year 1966 to 2018. Please refer to the Supplementary Figure for the PRISMA flow diagram for this systematic review. Using medical subject heading (MeSH) and title words for the (“Colonic Diseases, Functional” [Mesh] or “Irritable Bowel Syndrome” [Mesh]) AND (“risk factors” OR “risk”) AND (“Prenatal Care” [Mesh]



**Figure 1.** Summary of early life protective and risk factors for irritable bowel syndrome (IBS). \*Demonstrated in > 1 study.

OR “Perinatal Care” [Mesh] OR “Infant” [Mesh] OR “Child Care” [Mesh] OR “Child” [Mesh] OR “Maternal Exposure” [Mesh] OR “Maternal-Child Nursing” [Mesh] OR “Maternal-Fetal Exchange” [Mesh] OR “Mother-Child Relations” [Mesh] OR “Maternal-Fetal Relations” [Mesh] OR “Mothers” [Mesh] OR “Maternal Behavior” [Mesh] OR “Maternal Health” [Mesh]) revealed 554 results. We also searched for reference lists of relevant articles to identify additional relevant citations and found another 88 studies. We included studies that (1) were conducted in adolescents or adults with IBS, (2) investigated premorbid and comorbidity factors occurring specifically during the early childhood and perinatal periods as well as parental risk factors that were associated with the development of IBS.

Reference lists of relevant articles were reviewed for additional citations. Articles had to be in English, and full manuscripts had to be retrievable. The titles and abstracts of all citations identified by the literature search were reviewed. Potentially relevant studies were retrieved, reviewed in full, and the selection criteria were applied. All studies conducted in both clinical settings and population-based samples were considered. Two investigators independently screened for eligible studies based on the selection criteria, and any discrepancies were resolved by consensus.

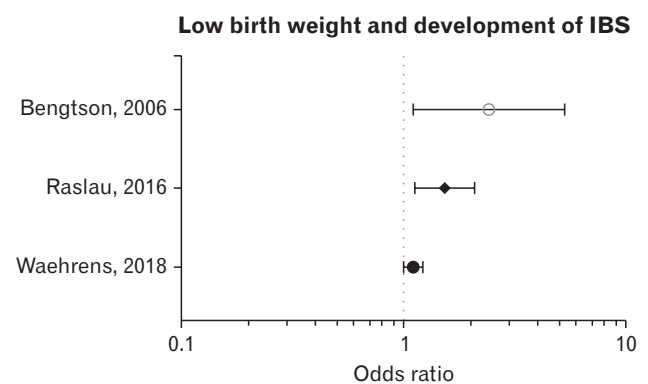
## Results

Twenty-seven articles met the inclusion criteria. We separated the studies into 3 early life factors: perinatal, parental, and childhood factors (Fig. 1).

### Perinatal Factors

Potential perinatal risk factors include a shorter period of

breastfeeding, low birth weight,<sup>8-10</sup> Caesarean birth,<sup>10</sup> and gastric suction at birth<sup>11</sup> (Table 1). It is not understood whether delayed utero growth directly results in low birth weight and in turn leads to IBS, or if low birth weight is a prospective indicator for subsequent early life problems that can lead to IBS. Figure 2 shows the forest plot of association between low birth weight and development of IBS. It has been hypothesized that visceral irritation by gastric suction at birth promotes long-term visceral hypersensitivity and cognitive hypervigilance, leading to an increased prevalence of functional



**Figure 2.** Forest plot shows the association between low birth weight and development of irritable bowel syndrome. Bengtson et al<sup>8</sup> (2006) found low birth weight below 1500 g to be significantly associated with higher irritable bowel syndrome (IBS) risk after adjustment for gestational age and history of same health issues in both twins. Raslau et al<sup>9</sup> (2016) found lower birth weight to be associated with increased odds of IBS. Waehrens et al<sup>10</sup> (2018) found birth weight below 2500 g to be associated with increased risk of IBS after adjusting for sex, birth year, gestational age, fetal growth, birth order, delivery mode, multiple birth status, maternal age at delivery, maternal marital status, paternal length of education, maternal length of education as well as parental history of anxiety, depression, and IBS.

**Table 1.** Perinatal Factors and Development of Irritable Bowel Syndrome

Study	Population	IBS diagnosis	Methodology	Sample size	Risk factors
Anand et al, <sup>11</sup> 2004, Sweden	Birth records	IBS symptoms	Matched case-control	96	Gastric suction at birth
Bengtson et al, <sup>8</sup> 2006, Norway	Norway Birth Registry	Self-completed Questionnaire	Retrospective	345	Low birth weight (< 1500 g)
Raslau et al, <sup>9</sup> 2016, USA	Survey responders	Survey, self-report Talley, Rome	A population-based nested case-control study	89	Low birth weight
Koloski et al, <sup>12</sup> 2015, Australia	Survey responders	Self-completed Questionnaire Rome I	Prospective data collection Recollection	130	Shorter duration of breastfeeding
Waehrens et al, <sup>10</sup> 2018, Sweden	Swedish Birth Registry	ICD Codes – Record Review	Longitudinal Birth Cohort	24 633	Caesarean, low birth weight

IBS, irritable bowel syndrome; ICD, International Classification of Diseases.

intestinal disorders later in life (odds ratio 2.99).<sup>11</sup> Koloski et al<sup>12</sup> reported that a shorter period of breastfeeding was significantly associated with IBS (5.6 months vs 8.1 months,  $P = 0.009$ ). This may be due to the colonization by beneficial bacteria in breast milk that stifles the growth of pathogens like *Clostridium difficile*.<sup>9</sup>

## Parental Factors

Parental support and maternal maturity had been shown to influence the development of IBS. These factors were recently explored by Waehrens et al<sup>10</sup> in a study of 25 000 patient records from Sweden's national birth registry.<sup>10</sup> They found that the children of mothers who were young, divorced or widowed, and with an education of 10-14 years were at higher risk for developing IBS. These factors may reflect the importance of parenting skills, and available socioeconomic and support network provided by a traditional nucleus family. Parental reinforcement, modeling of symptoms, coping strategies, and psychological distress during childhood have been shown to influence the development of IBS (Table 2). Interestingly, a parental history of IBS was associated with depression and anxiety, suggesting a shared, familial risk factor.<sup>10</sup> A similar finding was made by van Tilburg et al<sup>16</sup> who found a marked tendency for IBS to cluster within families, especially those with mothers suffering

from anxiety, depression, and stress. A twin study found that social learning may contribute to IBS to an equal or higher degree than genetic factors.<sup>13</sup> Parenting behaviors may also have a significant impact on IBS; parental punishment, over interference, rejection, and over-protection can put children at risk for IBS.<sup>19,20</sup> Receiving emotional warmth from the parents may protect children from IBS.<sup>14,15</sup>

## Childhood Factors

Studies on early life risk factors for the development of IBS have focused on the role of socioeconomic factors, environmental factors, and antecedent diseases (Table 3). There had been contradicting findings of the risk of socioeconomic status. An Africa-based study among school children found an association between a lower socioeconomic status and a history of gastroenteritis.<sup>19</sup> Several studies have looked at adult IBS patients' childhood recollections to evaluate early risk factors for IBS. Mendall and Kumar<sup>20</sup> investigated 421 adult subjects attending a general practice health screening clinic in the United Kingdom and found that adults were at greater risk of developing IBS if they had grown up with a father working in manual labor or in a home with a living density of more than one person per room.

**Table 2.** Parental Factors and Development of Irritable Bowel Syndrome

Study	Population	IBS diagnosis	Methodology	Sample size	Risk factors	Protective factors
Hislop, <sup>17</sup> 1979, Australia	Medical records	Physician-diagnosed IBS	Recollection	333	Childhood parental deprivation (parental loss, alcoholic, unsatisfactory relationships)	
Levy et al, <sup>13</sup> 2001, USA	Population – Twins	Self Questionnaire	Prospective data collection	6060	Mother/father with IBS	
Lackner et al, <sup>15</sup> 2004, USA	Clinic referrals	Self Questionnaire Rome II + Physician	Prospective data collection	81	Paternal parenting behaviors (rejection or hostility)	
Xing et al, <sup>14</sup> 2014, China	School students	Self Questionnaire Rome III	Prospective data collection	96	Parental punishment, Paternal rejection, Maternal over-interference, Paternal overprotection	Parental emotional warmth
Knight et al, <sup>18</sup> 2015, USA	Medical records	Self Questionnaire Talley	Nested Case-control	287	Family history of mental illness/ alcohol, substance abuse problems	
van Tilburg et al, <sup>16</sup> 2015, USA	Clinic visits	Self Questionnaire Rome I	Retrospective	296	Mothers with psychological traits (anxiety, depression, and somatization), Family stress	
Waehrens et al, <sup>10</sup> 2018, Sweden	Swedish Birth Registry	ICD Codes – Record Review	Longitudinal Birth Cohort	24 633	Young maternal age < 20 years old, Maternal marital status (divorced/widowed), Maternal education of 10-14 years old, Parental history of IBS, anxiety, depression	≥ 35 years old maternal delivery

IBS, irritable bowel syndrome; ICD, International Classification of Diseases.

**Table 3.** Childhood Factors and Development of Irritable Bowel Syndrome

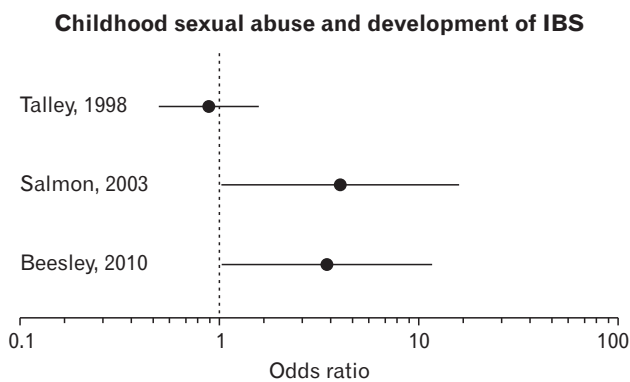
Study	Population	IBS diagnosis	Methodology	Sample size	Risk factors
Walker et al, <sup>27</sup> 1993, USA	GI clinic (adults)	Physician-diagnosed IBS	Prospective data Recollection	28	Severe Childhood sexual abuse
Talley et al, <sup>28</sup> 1994, USA	Survey (adults)	Self Questionnaire BDQ	Prospective data Recollection	130	Childhood abuse
Mendall and Kumar, <sup>20</sup> 1998, UK	GP clinic (adults)	Self Questionnaire Manning	Prospective data Recollection	48	Antibiotic use Privileged childhood living conditions
Talley et al, <sup>29</sup> 1998 Australia	Voters (adults)	Self Questionnaire BSQ	Prospective data Recollection	90	Childhood abuse
Salmon et al, <sup>22</sup> 2003, UK	Clinic visits (adults)	Self Questionnaire + Physician	Prospective data Recollection	64	Childhood sexual, physical and psychological abuse
Howell et al, <sup>21</sup> 2004 Australia	Birth Registry	Self Questionnaire BSQ	Longitudinal Birth Cohort	157	Affluent childhood environment
Dong et al, <sup>25</sup> 2005, China	Students	Self Questionnaire Rome II	Prospective data collection	716	Anxiety, depression, introverted, food habits (excessive pepper), personal habits (smoking/alcoholism), bad exterior environment (abdominal operation, abuse of antibiotics, exposure to coldness, and fatigue), single parent
Son et al, <sup>30</sup> 2009, S Korea	Females students	Self Questionnaire Rome II	Prospective data collection	104	Higher stress, anxiety, and depression
Beesley et al, <sup>23</sup> 2010, UK	Clinic visits (adults)	Physician Rome III	Prospective data Recollection	75	Childhood sexual abuse A tendency to suppress anger, anxious emotional abuse
Tietjen et al, <sup>24</sup> 2010, USA	Clinic visits (adults)	Self-report + Physician	Prospective data Recollection	418	
Zhou et al, <sup>31</sup> 2012, China	Students	Interview Questionnaire less	Prospective data collection	268	Poor sleep
Koloski et al, <sup>12</sup> 2015, Australia	Survey responders (adults)	Self Questionnaire Rome I	Prospective data Recollection	130	Sharing bedroom to 5 years old Exposure to herbivore pet (horse/ bird) to 5 years old
Adeniyi et al, <sup>19</sup> 2017 Nigeria	Students	Self Questionnaire, Rome III	Prospective data collection	62	Lower socioeconomic status Past history of gastroenteritis
Tan et al, <sup>32</sup> 2017, Taiwan	National Health Insurance Research Database	Physician-diagnosed IBS	Retrospective	11 242	Antecedent allergic diseases, allergic rhinitis, higher clinical allergy burden.
Rajindrajith et al, <sup>33</sup> 2018, Sri Lanka	Students	Self Questionnaire, Rome III	Prospective data collection	1972	Exposure to physical, emotional and sexual abuse
Tan et al, <sup>26</sup> 2019, Taiwan	National Health Insurance Research Database	Physician-diagnosed IBS	Retrospective	3537	Air pollutants

IBS, irritable bowel syndrome; GI, gastrointestinal; GP, general practitioner; BDQ, Bowel Disease Questionnaire; BSQ, Bowel Screening Questionnaire.

Conversely, Howell et al<sup>21</sup> showed that children raised in an affluent environment were at greater risk of developing IBS. The authors postulated that the emphasis on academic achievement and behavioral self-regulation within this echelon of society might

impair children's coping mechanisms, causing them to internalize stress. Another well-studied childhood risk factor for IBS is child abuse. Children are at an increased risk of developing IBS if they had been abused sexually,<sup>22,23</sup> emotionally,<sup>24</sup> physically, or psycho-

logically<sup>22</sup> during childhood. Figure 3 shows the forest plot of association between childhood sexual abuse and development of IBS. A study on school children in China found that certain psychological factors (anxiety, depression, and introverted personality), food habits (excessive intake of pepper), personal habits (alcoholism and smoking), adverse environmental exposures (history of dysentery, abdominal operation, overuse of antibiotics, exposure to coldness, and fatigue), and family dynamics (poor care by only a single parent) put children at higher risk of developing IBS.<sup>25</sup> Koloski et al<sup>12</sup> performed a population survey in Sydney which showed that adults who grew up sharing a bedroom or raising an herbivorous pet—both of which may allow increased exposure of the gut to various microbes—were at greater risk of developing IBS.



**Figure 3.** Forest plot shows the association between childhood sexual abuse and development of irritable bowel syndrome (IBS). Talley et al<sup>29</sup> (1998) did not find childhood sexual abuse below 14 years to be associated with IBS after controlling for gender, age, psychological morbidity, and neuroticism. Salmon et al<sup>22</sup> (2003) found childhood sexual abuse below 14 years to be a significant predictor of IBS as compared to physical disease. Beesley et al<sup>23</sup> (2010) showed that IBS patients had a higher likelihood of remembering childhood sexual abuse occurring below 14 years as compared to Crohn’s disease patients after controlling for gender.

In addition to these psychological, social, and environmental factors, allergic diseases have also been explored for their contribution to IBS. To date, there is conflicting evidence as to whether or not children with allergies are more susceptible to developing IBS. A study in Taiwan by Tan et al<sup>32</sup> found that preschoolers with a history of allergic disease had an increased risk of subsequently developing IBS at school age.

Air pollution may put children at higher risk of IBS. The 2019 study by Tan et al<sup>26</sup> showed that children exposed to higher concentrations of air pollution have an increased risk of IBS. The correlation persisted even after adjustment for monthly income, urban environments, number of consultations with or visits to a physician per year, and allergic diseases. This indicates that a crowded or stressful environment and the frequency of physician visits for other diseases were not confounding factors. Further studies are required to better elucidate the contribution of environmental and allergic factors in the pathogenesis of IBS.

### Post-infectious Irritable Bowel Syndrome

Two population-based studies have been published on the relationship between childhood gastrointestinal infections and the development of IBS, also known as post-infectious IBS (PI-IBS; Table 4). Cremon et al<sup>34</sup> studied 204 children exposed to salmonella contaminated tuna sauce and compared them with a healthy cohort. They found that childhood cases of gastroenteritis related to salmonella infection were at greater risk of subsequently developing IBS. Thabane et al<sup>35</sup> studied a population exposed to a contaminated water supply and found that acute bacterial gastroenteritis was associated with subsequent cases of IBS in children and adults.

### Discussion

Figure 1 summarizes the early life protective and risk factors for IBS, which we have discussed so far. Compared to other inflam-

**Table 4.** Risk Factors Associated With Post-Infectious Irritable Bowel Syndrome Patient

Study	Population	IBS diagnosis	Methodology	Sample size	Risk factors
Thabane et al, <sup>35</sup> 2010, Canada	Outbreak of GE (water supply)	Interview + self Questionnaire Talley	Prospective cohort	33 IBS of 467 exposed	Acute bacterial gastroenteritis ( <i>Escherichia coli</i> , <i>Campylobacter</i> ), diarrheal illness lasting more than 7 days, weight loss > 10 pounds, and antibiotic use during the outbreak
Cremon et al, <sup>34</sup> 2014, Italy	Outbreak of GE in schools	Self Questionnaire Rome III	Prospective controlled cohort	75 IBS of 204 exposed	Salmonella-induced gastroenteritis during childhood (not adulthood)

IBS, irritable bowel syndrome; GE, gastroenteritis.



matory and organic diseases, the study of early life experiences in patients with IBS has received little attention. Reported studies have been retrospective in nature, and have relied on patients' own recollection of events in order to build a better picture of the childhood risk factor. This may lead to a potential bias in recall. For example, the research on early life risk factors for IBS that were collected by Chitkara et al<sup>36</sup> in their 2008 review had relied heavily on questionnaires that recorded participants' own recollections of childhood. Nonetheless, compared to parental and perinatal factors, the childhood risk factors of IBS have been better studied.

These risk factors span from a patient's clinical history to psycho-developmental factors and environmental factors. Regarding clinical history, antibiotic usage lasting more than 7 days,<sup>20</sup> weight loss of more than 10 pounds,<sup>35</sup> poor sleep,<sup>31</sup> antecedent allergic disease,<sup>32</sup> and antecedent gastroenteritis (eg, salmonella infection) were strongly associated with an increased risk of IBS.<sup>34,35</sup> Psycho-developmental factors predisposing to IBS included child abuse (ie, emotional, sexual, or physical abuse)<sup>22,23</sup> as well as psychological traits like anxiety and depression.<sup>16</sup> Childhood environmental factors found to play an important role in the development of IBS include growing up within an affluent lifestyle,<sup>21</sup> air pollution,<sup>26</sup> and keeping herbivorous pets in the household.<sup>12</sup> We think that these opposing findings may be secondary to geographical difference of the studies. A low socioeconomic status in developing countries with possible poor access to clean water or food may increase the chance of gastroenteritis and later post-infectious IBS. High socioeconomic status in developed countries bring with its own sets of issues such as academic stress.

### Pathophysiology: Hygiene and Gut Dysbiosis

The hygiene and gut microbiota hypothesis postulate that early life exposure to microbial diversity regulates the composition of the gut microbiome and immunity. The gut microbiota plays an important role in IBS. The gut microbiota develops in early infancy, and the composition of gut microbiota is affected by the usage of antibiotics and gastroenteritis, which are known risk factors of IBS. Bokulich et al<sup>37</sup> suggested that intestinal bacterial flora of infants aged 1 to 24 months are the most sensitive to disturbances from infections or antibiotic usage. During this period, even a transient and small alteration can have a lasting impact on the composition of the gut microbiome well into adulthood. Children treated with antibiotics have been shown to have intestinal microbiota with decreased stability and diversity<sup>38</sup> and delayed maturation<sup>37</sup> compared to children not exposed to antibiotics. Hygiene factors associated with IBS include the sharing of bedrooms and exposure to pets.<sup>39</sup> The

hygiene and microflora hypothesis postulate that early life exposure to microbial diversity regulates the composition of the gut microbiome and immunity.

There are conflicting results as to the relationship between IBS and obesity.<sup>40,41</sup> Pickett-Blakely et al<sup>42</sup> found the prevalence of IBS in obese patients to range from 11.6% to 24.0%. We do not yet understand if IBS is associated with affluence, and more studies are needed to examine the relationship between IBS and various markers of affluence such as education, obesity, and diet.

It is not known whether changes in the gut microbiota are markers or consequences of IBS. Both luminal and mucosal samples of IBS patients show reduced bacterial diversity compared to healthy individuals. Many studies have demonstrated that several microbial alterations are associated with IBS, including an increased ratio of Firmicutes/Bacteroidetes at the phylum level, increased relative abundance of fecal *Ruminococcus torques*-like phylotype, and reduced fecal Lactobacilli abundance.<sup>43,44</sup> Childhood adversity and stress may predispose individuals to IBS through their effects on the gut microbiome,<sup>25</sup> and these may mediate the pathogenesis of IBS. Taken together, IBS may be mediated by gut dysbiosis in early life.

### Pathophysiology: Mood and Emotional Disturbances

Children are at increased risk of developing IBS if they were born to young mothers or if they were raised by parents with a history of IBS, mental illness, and substance abuse, anxiety, depression, and negative parenting styles. Given this finding, there may be a psychosocially-based transmission of somatic symptoms from parents to children. In a study by van Tilburg et al,<sup>16</sup> psychological distress among children was found to correlate with the psychological distress of their mothers. In this study, children's own psychological traits, such as anxiety and depression, were associated with increased symptom reports of their parents. In Amsterdam, Zeevenhooven et al<sup>45</sup> compared parents of 91 children with IBS or functional abdominal pain to parents of 74 healthy children. They found a difference in physical health of parents and their child-rearing styles when parents of healthy controls were compared to children with IBS. The only protective parental factors against IBS were parental emotional warmth and older maternal age. Psychosocial aspects contributing to IBS were further evaluated by Gerson et al<sup>46</sup> in a study of 239 adult IBS patients across 8 countries. IBS symptoms were found to be directly associated with parents having relationship conflicts, but inversely associated with a deep and supportive relationship.

## Intrauterine Growth Restriction and Irritable Bowel Syndrome

Our review showed that low birth weight and intrauterine growth restriction (IUGR) might have played important roles in IBS. Low birth weight was defined as less than 2500 g, while very low birth weight was below 1500 g. Raslau et al<sup>47</sup> studied the perinatal factors of IBS in a population-based nested, case-controlled study in Olmsted County. They reported that lower birth weight increased the odds of IBS. Using the birth registry of Sweden, Waehrens et al<sup>10</sup> found that low birth weight (< 2500 g) was a significant risk factor for IBS. Similarly, in a twin study performed by Bengtson et al<sup>8</sup> in Sweden, low birth weight (< 1500 g) had higher risk of IBS. In this study, the results were only significant when adjusted for gestational age, suggesting that intrauterine growth retardation (IUGR) contributed to IBS.<sup>8</sup> IUGR describes a condition whereby a fetus cannot achieve its genetically determined potential size; a prenatal finding of restriction of growth. Genetic factors, placental factors, fetal factors, and maternal factors can all contribute to IUGR.<sup>48</sup> It is commonly linked to preterm birth, diseases of prematurity and impairment of cognitive and motor development.<sup>49</sup> Identification of various causes of low birth weight and IUGR may discover novel pathogenetic mechanisms involved in IBS.

## The Clinical Implications of the Study

Our studies reinforce the importance of the early growing-up period in determining the risk of IBS development. In particular, the role that a warmth family plays in the protection of a child from long term suffering of IBS. More emphasis should be given to marital counseling and early recognition of psychological well-being of a child. More doctors, especially primary physicians, should be trained to pick up anxiety, depression, and sign of abuse in the very young. So that timely intervention can be executed and tackle those children in their early presentation. From the aspect of further research purposes, this study can provide a good reference for future hypothesis-driven research. As it provides evidence of the important correlation between the above-mentioned risk factors and IBS, this might encourage creating a program with a large validated database that is rigorously phenotyped; a parallel, linkable biorepository; dedicated resources for further studies.<sup>50</sup>

## Limitations

Many of the included studies relied on participants' recollection

of childhood experiences (eg, the onset of symptoms, parenting patterns, and history of abuse), which were subject to recall bias. Also, these studies did not use a shared, standardized definition of IBS. Compared to childhood factors, even fewer studies investigated the paternal and perinatal factors that might have influenced IBS. Our review may also suffer from selection bias, as some of the study populations included a large number of survey respondents who might have exhibited health-seeking behaviors. This review is necessarily qualitative in nature; the studies available are too heterogeneous in terms of the patient population and study design to combine for any sort of meta-analysis.

## Conclusion

Our review showed that the early life period impacts the development of IBS. In fact, it strongly suggests the importance of further mechanistic studies. To improve our understanding of how each risk factor may interact and influence IBS, we will need to start at the very beginning. A life-course approach that studies both the mother and child is required to understand the link between early-life risk factors and IBS. Many common mental disorders, such as anxiety and depression, typically begin in adolescence.<sup>50</sup> A longitudinal study of children and adults with IBS, encompassing key time points throughout life to improve the science of IBS.<sup>51</sup> More mechanistic studies are needed to elucidate the role of various risk factors in the pathogenesis of IBS. We also need bio-samples to provide functional data (microbiome, metabolome, and immune regulation) which will enhance the understanding on mechanisms at the molecular and microbial level, and how external factors influence pathogenesis of IBS. These will guide the development of interventions targeted at the at-risk population to alter disease trajectory. Some of these interventions include improvement of prenatal care, family counseling for supportive parent-child relationship and timely response to child symptoms and safe environment for healthy development may help to lessen the burden of IBS.

## Supplementary Material

Note: To access the supplementary figure mentioned in this article, visit the online version of *Journal of Neurogastroenterology and Motility* at <http://www.jnmjournal.org/>, and at <https://doi.org/10.5056/jnm20109>.

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