Epidemiological and pathophysiological aspects of abdominal pain predominant functional gastrointestinal disorders in children and adolescents: a Sri Lankan perspective

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Chapter 5

Irritable bowel syndrome in children and adolescents in Asia: a systematic review and meta-analysis of the epidemiology

This chapter of the thesis was published as

Devanarayana NM, Rajindrajith S, Pathmeswaran A, Abegunasekara C, Gunawardena NK, Benninga MA.

ABSTRACT

Objectives: Several cross-sectional surveys have been conducted to study the prevalence of irritable bowel syndrome (IBS) in children. The aim of this study was to conduct a systematic review and a meta-analysis of published literature to provide better understanding of the prevalence of IBS among Asian children.

Method: A computer assisted search of MEDLINE, EMBASE, psycINFO and regional data bases of Asia was carried out. Selected articles were reviewed in depth and data were extracted. Pooled prevalence, gender differences as well as 95% confidence intervals were calculated. Heterogeneity of the studies was assessed using I2 test.

Results: Sixteen cross sectional studies which reported prevalence of IBS (in children and adolescents) and qualified to be included, were taken into the final analysis containing 38,076 subjects. Selected studies are from China, Korea, Japan, Iran, Sri Lanka, and Saudi Arabia. Studies showed a marked heterogeneity with I2 of 98.59 (p<0.0001). Prevalence of IBS ranges from 2.8% to 25.7%, with a pooled prevalence of 12.41% (95% CI 9.87-14.95%). Prevalence risk ratio of female: male is 1.39. Prevalence of subtypes is diverse and varies between studies.

Conclusions: The published data indicate that IBS is a significant problem among Asian children and adolescents. Female gender predisposes children and adolescents to develop IBS.
INTRODUCTION

Irritable bowel syndrome (IBS) in children is characterized by chronic abdominal pain and changing bowel habits including frequency of defecation and stool consistency in the absence of organic disease.\textsuperscript{1} It is a common problem in pediatric practice and according to office-based practice, between 21-45% children with chronic abdominal pain have IBS.\textsuperscript{2,4}

This malady could lead to reduction in quality of life and poor quality of school work.\textsuperscript{5,6} In addition, it is well known fact that a sizeable proportion of children suffering from pain predominant functional gastrointestinal diseases (FGIDs), including IBS, grow up to be adults with similar problem.\textsuperscript{7} With the very limited number of therapeutic options available, pediatricians and pediatric gastroenterologists face a daunting task to manage these children.

Initial epidemiological studies from Western countries have shown that 15% of school children in the USA, 14-24% in Russia, and 2% in the UK are suffering from IBS, perhaps promulgating the notion that IBS is a disease of the Western World.\textsuperscript{8-10} However, in the recent past, a new wave of epidemiological research has emerged in Asia and increased the depth and width of knowledge on IBS in this region. Despite these efforts, there remain difficulties to differentiate the true regional and global nature of IBS, its epidemiological facts and predisposing factors, details which are crucial for practicing clinicians.

Asia is the home for over 50% of the world’s childhood population. In addition, most of Asian countries are going through a rapid change in socio-economic status and their cultural foundations are constantly being challenged by globalization. In that light, we believe that studying epidemiological patterns of IBS in Asian children in a systematic way will provide a greater perspective for understanding the burden of IBS, its epidemiological distribution, and patterns of subtypes. Therefore the aim of this study was to conduct a systematic review and meta-analysis of published literature to estimate the prevalence of IBS among Asian children.

METHOD

\textit{Literature search strategy}

A detailed literature search was carried out (from 1948 to October 2014) using MEDLINE, PsycINFO, EMBASE, Global Index Medicus, Index Medicus for South East Asia, East Mediterranean Index Medicus and West Pacific Index Medicus to identify epidemiological studies that reported on the prevalence of IBS in children/adolescents aged 18 years or less in Asia. Search strategy used the following terms; irritable bowel syndrome [MeSH Terms] \textit{OR} irritable bowel syndrome[Text Word] \textit{OR} Irritable Bowel disease*[Text Word] \textit{OR} irritable
colon OR irritable colon syndrome OR mucous colitis OR spastic colon OR spastic colitis OR Functional Gastrointestinal Disorder OR Functional Gastrointestinal Disorders combined with epidemiology OR epidemiologic study OR epidemiologic studies OR frequent OR occur.

Abstracts of all the articles meeting the above search criteria were reviewed by 2 independent investigators (SR, NMD) and full texts of studies were retrieved when they were eligible for inclusion according to the following criteria. 1) Cross sectional surveys from Asia. 2) School or community samples. 3) Included children from 0-18 years. 4) Defined diagnostic criteria. 5) Published in English language as full papers. All possibly relevant full text articles were again independently reviewed by the same authors and consensus was reached on each of the articles. Diagnosis of IBS was made by Rome II (adult/children), or Rome III (adult/children) criteria. Quality assessment of all included studies was conducted using the method described by Al-Jader LN, et al. Data extraction was also done independently by SR and NMD. We used Microsoft Excel spreadsheet (Microsoft, Redmond, WA) to enter data in a systematic manner. The data that were included were year of the publication, country of origin, method of data collection, nature of the sample, sample size, definition used to diagnose IBS, sub-typing (when available), age range and sex of the subjects, and prevalence of IBS.

Statistical analysis and mapping
The prevalence of IBS and the sample size of each of the selected studies were used to calculate the standard error of the prevalence. The individual study results were pooled using a random effect model as there was a high level of heterogeneity between the studies. Heterogeneity was measured using the I2 statistic. The prevalence of IBS among males and females was compared by calculating the prevalence risk ratio. Meta-analysis was performed in Stata version 12 (College Station, Texas, USA) using ‘metaan’ package. Mapping was done using ArcGIS 10.2 (ESEI, Readlands, CA).
RESULTS

**Literature search**

The literature search identified 1212 citations. There were 18 studies that fulfilled the eligibility criteria. Two studies were excluded due to duplication of data. Therefore 16 studies were included in the final analysis (Figure 5.1). The total number of subjects in these studies was 38076. Details of these studies are provided in Table 5.1.

![](image)

**Figure 5.1: Flow chart summarizing the study methodology**

All studies are cross sectional surveys. They were conducted in Japan (n=2), Korea (n=3), China (n=6), Iran (n=1), Saudi Arabia (n=1) and Sri Lanka (n=3). One paper from Japan reported data from two separate studies and we could clearly identify prevalence of IBS in children and adolescents in both studies. Therefore, in the analysis they were considered as two separate studies. The study conducted by Devanarayana et al. had given prevalence of IBS according to both Rome II and Rome III criteria for children. We
selected the prevalence rate obtained using Rome III criteria for the statistical analysis. The two studies from Korea\textsuperscript{19,28} included only females in their samples. Study from Saudi Arabia included only males.\textsuperscript{24}

**Prevalence of IBS in Asian children**

The pooled prevalence of IBS in all 16 studies with a total of 38076 subjects was 12.4\% (95\% CI 9.9-15.0) with a statistically significant heterogeneity between studies ($I^2$ 98.6\%, $P<0.0001$). The lowest prevalence (2.8\%) was reported from Sri Lanka and the highest (25.7\%) from South Korea which included only females.\textsuperscript{25,28} Figure 5.2 shows the forest plot of data from selected studies. Figure 5.3 illustrates the mapping data of prevalence of all Asian studies.

**Prevalence of IBS according to age groups**

Only five studies have studied the age related prevalence.\textsuperscript{6,16,19,26,29} The age groups reported were diverse and therefore could not fit into an analytical model. However, one study has shown a reduction of mean predicted probability of developing IBS with increasing age.\textsuperscript{18}

**Prevalence of IBS according to sex**

Eleven studies have provided prevalence of IBS according to sex.\textsuperscript{6,16-18,20-22,25-27,29} Out of these studies, 5 had found a significantly higher prevalence of IBS in girls (Table 5.1).\textsuperscript{6,16,21,27,29} The pooled prevalence for females was 13.9\% (95\% CI 10.0\%-17.7\%) and for males 9.4\% (95\% CI 6.6\%-12.3\%). Prevalence risk ratio of female to male was, 1.39 indicating that females have a higher tendency to develop IBS (Figure 5.4). When analyzed the 11 studies that have both male and female prevalence separately (excluding single sex studies) the prevalence risk ratio was 1.30.

**Prevalence of sub-types of IBS**

Table 5.2 shows the prevalence of the different IBS sub-types. Studies from China\textsuperscript{22,26} have indicated untyped IBS (IBS-U) as the commonest sub-type, while studies from Sri Lanka and one study from Korea have shown approximately an even distribution of all four sub-types.\textsuperscript{18,25,28} The study from Iran has found higher prevalence of constipation predominant IBS (IBS-C) in their population.\textsuperscript{27}
<table>
<thead>
<tr>
<th>Study and reference</th>
<th>Year</th>
<th>Location of Survey</th>
<th>Population</th>
<th>Age Range (years)</th>
<th>Sample Size</th>
<th>Method of Data collection</th>
<th>Case Ascertainment</th>
<th>Case definition</th>
<th>Total prevalence %</th>
<th>Age specific Prevalence</th>
<th>Male Prevalence %</th>
<th>Female Prevalence %</th>
</tr>
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<tbody>
<tr>
<td>1. Devanarayana et al&lt;sup&gt;15&lt;/sup&gt;</td>
<td>2014</td>
<td>Sri Lanka</td>
<td>School based</td>
<td>13-18</td>
<td>1850</td>
<td>Cross sectional survey</td>
<td>Subject questionnaire</td>
<td>Rome III (Child)</td>
<td>4.9</td>
<td>No</td>
<td>-</td>
<td>-</td>
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<td>2. Zhu et al&lt;sup&gt;16&lt;/sup&gt;</td>
<td>2014</td>
<td>China</td>
<td>School based</td>
<td>8-13</td>
<td>7472</td>
<td>Cross sectional Survey</td>
<td>Subject questionnaire</td>
<td>Rome II</td>
<td>10.81</td>
<td>8 years: 13.4</td>
<td>9 years: 12.7</td>
<td>10 years: 11.2</td>
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<td>3. Xing et al&lt;sup&gt;17&lt;/sup&gt;</td>
<td>2014</td>
<td>China</td>
<td>School based</td>
<td>11-18</td>
<td>1714</td>
<td>Cross sectional survey</td>
<td>Subject questionnaire</td>
<td>Rome III (Child)</td>
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<td>4. Sagawa et al&lt;sup&gt;6&lt;/sup&gt;</td>
<td>2013</td>
<td>Japan</td>
<td>School based</td>
<td>10-17</td>
<td>3976</td>
<td>Cross sectional survey</td>
<td>Subject questionnaire</td>
<td>Rome III (Child)</td>
<td>5.9</td>
<td>10-11 years: 3.7</td>
<td>12-14 years: 6.3</td>
<td>15-17 years: 12.8</td>
</tr>
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<td>5. Rajindrajith and Devanarayana</td>
<td>2012</td>
<td>Sri Lanka</td>
<td>School based</td>
<td>10-16</td>
<td>2163</td>
<td>Cross sectional survey</td>
<td>Subject questionnaire</td>
<td>Rome III (Child)</td>
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<td>1.9</td>
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<td>Study Design</td>
<td>Age Group</td>
<td>Sample Size</td>
<td>Methodology</td>
<td>Questionnaire</td>
<td>Symptom Criteria</td>
<td>Prevalence (%)</td>
<td>Age Group Prevalence</td>
<td>Other Notes</td>
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<tr>
<td>6. Song et al&lt;sup&gt;19&lt;/sup&gt;</td>
<td>2012</td>
<td>Korea</td>
<td>School based</td>
<td>12-17</td>
<td>820</td>
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<td>Subject questionnaire</td>
<td>Rome II (Adult)</td>
<td>12.8%</td>
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<td>7. Endo et al&lt;sup&gt;20&lt;/sup&gt;</td>
<td>2011</td>
<td>Japan</td>
<td>School based Study 1 (2004)</td>
<td>15</td>
<td>1721</td>
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<td>School based Study 2 (2009)</td>
<td>14</td>
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<td>Subject questionnaire</td>
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<td>7.1</td>
<td>11.6</td>
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<td>8. Park and Lim&lt;sup&gt;21&lt;/sup&gt;</td>
<td>2011</td>
<td>Korea</td>
<td>School based</td>
<td>12-18</td>
<td>3671</td>
<td>Cross sectional survey stratified, randomized study</td>
<td>Self-reported Questionnaire</td>
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<td>19</td>
<td>7.7</td>
<td>11.2*</td>
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<td>10. Zhou et al&lt;sup&gt;23&lt;/sup&gt;</td>
<td>2011</td>
<td>China (sleep)</td>
<td>School based</td>
<td>12-17</td>
<td>1175</td>
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<td>Self-reported Questionnaire</td>
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<td>9.2</td>
<td>No</td>
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<td>11. Alhzami et al&lt;sup&gt;24&lt;/sup&gt;</td>
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<td>19</td>
<td>7.7</td>
<td>11.2*</td>
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<td>12. Devanarayana et al&lt;sup&gt;25&lt;/sup&gt;</td>
<td>2010</td>
<td>Sri Lanka</td>
<td>Semiurban school sample</td>
<td>12-16</td>
<td>427</td>
<td>Cross sectional survey</td>
<td>Subject questionnaire</td>
<td>Rome III (Child)</td>
<td>7.0</td>
<td>No</td>
<td>6.5</td>
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<td>Type of Study</td>
<td>Age Range</td>
<td>Sample Size</td>
<td>Data Collection Method</td>
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<td>Zhou et al.</td>
<td>2010</td>
<td>South China (Shanghai)</td>
<td>School based</td>
<td>10-18</td>
<td>2013</td>
<td>Randomly selected sample</td>
<td>Subject questionnaire</td>
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<td>Subject Questionnaire</td>
<td>Rome II (Adults)</td>
<td>4.1</td>
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<td>2.6</td>
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<td>Korea</td>
<td>School based</td>
<td>15-17</td>
<td>405</td>
<td>Cross sectional descriptive design</td>
<td>Subject Questionnaire</td>
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<td>25.7</td>
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<td>Dong et al.</td>
<td>2005</td>
<td>China (Shanghai and Heilongjiang provinces)</td>
<td>School based</td>
<td>6-18</td>
<td>5403</td>
<td>Stratified, random cluster sample</td>
<td>Subject questionnaire</td>
<td>Rome II (Child)</td>
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<td>(8-9 years: 14.78)</td>
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<td>20.9*</td>
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<td>&gt;=13 years: 11.44</td>
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<td>(15-16 years: 17.35)</td>
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<tr>
<td>Study</td>
<td>Criteria</td>
<td>IBS-C (%)</td>
<td>IBS-D (%)</td>
<td>IBS-M or IBS-A (%)</td>
<td>IBS- Untyped (%)</td>
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<td>Zhou <em>et al.</em> (2011)</td>
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<td>20.11</td>
<td>17.8</td>
<td>10.3</td>
<td>51.1</td>
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<td>Park <em>et al.</em> (2011)</td>
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<td>15.7</td>
<td>66.0</td>
<td>7.3</td>
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<td>Sohrabi <em>et al.</em> (2010)</td>
<td>Rome II – adult</td>
<td>52.5</td>
<td>11.8</td>
<td>18.6</td>
<td>-</td>
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<tr>
<td>Son <em>et al.</em> (2008)</td>
<td>Rome II- adult</td>
<td>34.6</td>
<td>26.9</td>
<td>38.5</td>
<td>-</td>
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</table>
Figure 5.2 – Pooled prevalence of IBS in all of the studies, (*) Studies with only females, (**) Studies with only males. CI – confidence interval; IBS – irritable bowel syndrome
Figure 5.3 - Prevalence of IBS according to country
IBS = irritable bowel syndrome

Figure 5.4 - Pooled prevalence of IBS according to gender
CI = confidence interval; IBS = irritable bowel syndrome
To the best of our knowledge, this is the first systematic review and meta-analysis of epidemiological studies of IBS in Asian children. The pooled prevalence in our study was 12.4 with no clear correlation with age and female sex as a risk factor of developing IBS.

IBS is a disease that affects children across the world. Epidemiological surveys from the Western countries such as UK and the USA have shown a prevalence of 2 to 14%. Prevalence in Russian children was 14%-24%. Recent studies from Colombia noted that 5.1% children suffer from IBS. In this systematic review and meta-analysis the pooled prevalence was noted to be 12.4%. Our data fall within the range of Western and Russian data possibly indicating the true global prevalence. The highest prevalence was reported in Korean females and the lowest was reported from Sri Lanka (with Rome II criteria for children).

Studies have shown a statistically significant heterogeneity. This considerable variation could be due to several reasons. First, variation of the sizes of the samples may have contributed to this variation in prevalence. Sample sizes of the studies included in this study range from 427 to 7472. In addition, obtaining precise data about prevalence was difficult because of the lack of uniform definitions and the absence of a precise biomarker. All studies in this systematic review have used standard Rome criteria (Rome II or III) for the diagnosis of IBS. However, Rome criteria itself are in an evolutionary process and criteria for the diagnosis have been changing from its first iteration to the latest Rome III classification. This is likely to affect the calculated prevalence significantly. Earlier studies have shown that the Rome II criteria are too restrictive in diagnosing FGID in children. Furthermore, some studies have used adult criteria instead of pediatric criteria for diagnostic purpose. Although the clinical features are similar, the time duration before diagnosis in adult criteria is three months whereas they are two months in the pediatric criteria. This would have underestimated the true prevalence in studies that used adult Rome criteria. It is well known that IBS status is influenced by food and food habits. There are marked differences in food preparation and use of spices and other ingredients in different cultures. It is possible that these factors also influence the variation in prevalence.

Age groups included in the studies are diverse. They range from 6 to 19 years and the majority included children in their teens. Only five studies reported age specific prevalence. According to them prevalence seems to be increasing with age. However the differences are not statistically significant. Contrary to this, one study from Sri Lanka has shown reduction of the mean predicted probability of prevalence with increasing age. Similar meta-analysis of
epidemiology of IBS in adults have found no statistically significant difference between older and younger age groups (less than 45 against more than 45 years). It is possible that there is no relationship between age and IBS contrast to other FGIDs such as functional constipation.

Asian girls have a higher tendency to develop IBS with a higher risk ratio. One study has shown a higher mean predicted probability of developing IBS in girls of 10-16 years. Similar to this, in a systematic review and meta-analysis, Lovell and Ford reported that adult females have higher Odds Ratios of developing IBS. This systematic review also reported a significant heterogeneity between studies, similar to our review.

Sub-typing of IBS is an important concept, especially because some of the current therapeutic options are based on the predominant bowel pattern of IBS. Sub-typing is described only for adults in both Rome II and Rome III criteria. Although both criteria recognized IBS-C and diarrhea predominant IBS (IBS-D), Rome III criteria only recognize mixed IBS (IBS-M). However, Rome II criteria recognize alternating IBS (IBS-A) which is more or less similar to IBS-M. In addition, Rome III criteria appreciate untyped IBS (IBS-U). Several pediatric studies have used the same classification systems to sub-type IBS in children. Studies from Sri Lanka have shown an even distribution of all four subtypes according to Rome III criteria. However, two studies from China noted that around 50% of their subjects had IBS-U, IBS-C was more prevalent in Iran than the other two types. Prospective studies among adults have shown that sub-types of IBS can be interchanging among patients and there is no stability in the clinical patterns. This concept may be applicable to children and adolescents as well and, perhaps partly explain the diverse variability of sub-types.

There are several strengths of our systematic review and meta-analysis. We have conducted an exhaustive literature search not only through the commonly used databases but also regional databases to identify and include maximum number of studies conducted in Asia. We also used a currently accepted and reliable method to calculate pooled prevalence. In addition, all studies have used well accepted robust definitions (Rome II or Rome III) to diagnose IBS. Finally, all studies are community- or school- based studies and have a higher chance of representing the true burden of IBS in respective countries in Asia.

However, there are a few limitations as well. We included studies published only in the English language. This may have missed studies published in other languages as there is a marked diversity of languages in Asia. Two studies from Korea have only included females in their study population, possibly contributing to over-estimation of gender specific prevalence.
have used a variety of definitions of IBS in children including criteria described for adults. Some of these definitions, especially Rome II criteria and adult Rome II and Rome III criteria, would have underestimated the true prevalence of IBS in some studies.\textsuperscript{11-13} Data from some large geographical regions are not available. Finally, it is important to realize that meeting diagnostic criteria for IBS does not necessarily exclude other possible organic diseases. Diseases such as coeliac disease and inflammatory bowel disease, although rare among the Asians, are a cause for concern. In addition, chronic gastrointestinal infections such as giardiasis and amoebiasis may mimic symptoms of IBS, especially in the developing countries of Asia.

There is a significant heterogeneity between studies included in this systematic review, as previously seen during pooling of epidemiological data.\textsuperscript{32,34} It may possibly be due to differences in ethnicity, subtle application differences in diagnostic criteria, and cultural differences even between areas of the same country. It is not possible to appreciate these factors in a meta-analysis. However, we believe although the above factors are challenges in summarizing data in this fashion, this study is useful to get a greater epidemiological perspective of IBS in Asian children than individual study or a systematic review.

In conclusion, this systematic review and meta-analysis has demonstrated that a sizeable population of young Asians have IBS. However, the prevalence varies according to the country, diagnostic criteria, and age. It is more common among girls compared to boys. Sub-types vary between studies and countries. Further studies using pediatric criteria for IBS is needed to understand the true prevalence, especially in other parts of the Asia with large populations. These studies will help us to understand the epidemiological dynamics and risk factors in a systematic manner so that the preventive strategies could be planned. This will eventually lead the path to minimize suffering of children and young adults.

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