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TITLE PAGE

Title: Global Prevalence of Irritable Bowel Syndrome According to Rome III or IV criteria: A Meta-analysis.

Short running head: Prevalence of Irritable Bowel Syndrome: Meta-analysis.

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Abbreviations:

CI	confidence interval
OR	odds ratio
IBS	irritable bowel syndrome
IBS-C	IBS with constipation
IBS-D	IBS with diarrhoea
IBS-M	IBS with mixed bowel habit
IBS-U	IBS unclassified

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ABSTRACT

Background: Irritable bowel syndrome (IBS) is one of the commonest functional bowel disorders, but the community prevalence appears to vary widely between different countries. This may be because previous cross-sectional surveys have neither applied uniform diagnostic criteria nor used identical methodology, rather than true global variability. We performed a systematic review of data from all studies utilising relatively uniform methodology, and using only the most recent iterations of the Rome criteria, to determine global prevalence.

Methods: We searched MEDLINE, EMBASE, and EMBASE Classic (until April 2020) to identify population-based studies reporting prevalence of IBS in adults (≥16 years old) according to the Rome III or Rome IV criteria. We extracted prevalence for all studies, and according to the criteria used to define presence of IBS. We used meta-analysis to estimate pooled prevalence rates, according to study location and certain other characteristics, as well as odds ratios (OR), and 95% confidence intervals (CIs).

Findings: The search identified 4143 citations, of which 184 studies appeared relevant, and 57 were eligible. These 57 studies represented 92 separate adult study populations, containing 423,362 subjects. Pooled prevalence of IBS in studies that used the Rome III criteria was 9.2% (95% CI 7.6% to 10.8%), compared with 3.8% (95% CI 3.1% to 4.5%) with the Rome IV criteria. IBS with mixed bowel habit was the commonest subtype with Rome III, reported by 33.8% of people fulfilling criteria for IBS (3.7% of all included subjects), but IBS-D was commonest (31.5% of people with IBS, 1.4% of all participants) with Rome IV. The prevalence of IBS was higher in women (OR 1.46; 95% CI = 1.33 to 1.59). Prevalence varied substantially between individual countries, and this variability persisted even when the same diagnostic criteria were applied and identical methodology used in studies.

Interpretation: Even when uniform symptom-based criteria are applied, using identical methodology, to define presence of IBS, prevalence varies strikingly between countries. Prevalence

was substantially lower with the Rome IV criteria, suggesting these more restrictive criteria may be less suitable for population-based epidemiological surveys.

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Evidence before this study

Irritable bowel syndrome (IBS) is one of the commonest functional bowel disorders, and has substantial implications for the lives of patients, as well as a huge economic impact on society. The prevalence of IBS globally has been the subject of previous systematic reviews and meta-analyses. However, these are outdated, and synthesised data from epidemiological studies that used "historical" symptom-based criteria to define presence of IBS, such as the Manning criteria, or the Rome I or II criteria. Pooled prevalence of IBS in one of these meta-analyses was 11.2%, but as diagnostic criteria have become more restrictive, this is now likely to be lower. A comprehensive search of the medical literature using MEDLINE, EMBASE, and EMBASE Classic identified multiple studies published since the conduct of these meta-analyses, which reported prevalence of IBS in numerous countries according to both Rome III and Rome IV criteria, thus providing a rationale for this updated systematic review and meta-analysis.

Added value of this study

We did a systematic review and meta-analysis of population-based cross-sectional surveys that examined the prevalence of IBS globally using only the Rome III or IV criteria. Pooled prevalence estimates from these studies provide useful data to inform health care planning decisions, and may enable the optimisation of the design of future studies in this field.

Implications of all the available evidence

Although pooled prevalence of IBS in this meta-analysis using the Rome IV criteria was substantially lower than previous estimates, at 3.8%, the prevalence obtained when applying the Rome III criteria was similar, at 9.2%. Our data therefore suggest that IBS affects between one in 11 and one in 26 people globally, at any point in time, depending on the definition used. Variability in prevalence between individual countries persisted, even when only studies using identical

diagnostic criteria and methodology were pooled. This suggests that this variability is genuine, and that future research to attempt to uncover reasons for this is necessary.

INTRODUCTION

Irritable bowel syndrome (IBS) is a chronic functional bowel disorder characterised by altered stool form or frequency in association with abdominal discomfort or pain.[1,2] Traditionally, IBS is divided into four subtypes based on the predominant stool pattern reported by the individual: IBS with constipation (IBS-C); IBS with diarrhoea (IBS-D); IBS with mixed bowel habit (IBS-M); or IBS unclassified (IBS-U), where stool pattern cannot categorise the person accurately into one of the other three subtypes.[1] The diagnosis of IBS can be challenging as, not only can symptoms change over time,[3,4] they can also mimic other disorders.[5-7]

In the absence of a diagnostic gold standard test or biomarker for IBS, and in order to facilitate a standardised diagnosis and minimise unnecessary investigations, symptom-based diagnostic criteria, such as the Rome criteria, were developed by consensus among experts in the field.[8] These criteria have evolved over the years, with the Rome III criteria in use since 2006.[1] These were revised, and published as the Rome IV criteria, in 2016.[2] In these more recent criteria, the Rome Committee removed abdominal discomfort from the definition, and increased the frequency with which abdominal pain must occur in order to meet criteria for IBS from at least 3 days per month to at least 1 day per week (Supplementary Table 1). The Rome IV criteria are therefore more restrictive than their predecessor, and appear to lead to fewer patients who believe they have IBS meeting diagnostic criteria for the condition, while those that do still meet criteria have more severe symptoms and exhibit higher levels of psychological co-morbidity.[9]

IBS is associated with a marked reduction in health-related quality of life,[10] higher rates of somatisation,[11] increased likelihood of psychological comorbidity, including depression and suicidal ideation,[12] and work impairment,[13] as well as greater medical and prescription medicine costs per year.[14] In fact, IBS has a significant economic impact in both primary and secondary care. Even when a diagnosis of IBS is made in primary care, and despite current guidelines, many patients are referred for colonoscopic evaluation,[15] despite a low diagnostic yield in those with typical symptoms.[16] Reasons for this include diagnostic uncertainty, which may be driven by

persistence of symptoms due to a lack of curative treatment. Patients with IBS would be willing to accept a 10.1% chance of death from a hypothetical medication, in return for a 99% chance of symptom resolution.[17]

It follows, therefore, that estimating global prevalence of IBS is important, in order to understand the distribution and burden of disease. Although the prevalence of IBS has been studied systematically,[18,19] there is significant variation in cross sectional surveys, even within the same geographical regions. As only a few studies have evaluated the prevalence of IBS simultaneously across multiple countries using uniform methodology, it is difficult to know the exact reasons for this variability. Some of this variation may be explained through the use of different study methodology, including sampling methods or questionnaire administration, or the use of different diagnostic criteria to define IBS,[19] as well as variation due to local factors. In our previous systematic review and meta-analysis of 80 separate study populations, the pooled prevalence of IBS worldwide was 11.2%, but varied among individual countries from 1.1% to 45.0%.[18]

However, many of the definitions of IBS used in the studies included in this meta-analysis were "historical"; only five studies reported prevalence according to the Rome III criteria,[20-24] and the Rome IV criteria had not been described at the time it was conducted. Therefore, in order to try to understand the epidemiology of IBS more completely, according to contemporaneous definitions, we have updated this systematic review, restricting the analysis to only studies using the Rome III and Rome IV criteria.

METHODS

Search Strategy and Study Selection

We searched EMBASE CLASSIC and EMBASE (2006 to April 2020), and MEDLINE (2006 to April 2020) to identify only cross-sectional surveys that reported the prevalence of IBS in adults (≥90% aged ≥18 years) according to the Rome III or Rome IV criteria.[1,2] As these criteria were only described in 2006 and 2016, respectively, we limited the search from 2006 to the present. We hand-searched conference proceedings (Digestive Diseases Week, American College of Gastroenterology, United European Gastroenterology Week, and the Asian Pacific Digestive Week) between 2006 and 2019 in order to identify studies published only in abstract form. Studies were required to recruit participants from the general population or community. Studies that reported the prevalence of IBS in convenience samples, for example among university students, employees at an institution, or those attending screening clinic health check-ups, were ineligible for inclusion. In order to be eligible, studies also had to recruit at least 50 participants, and define IBS according to the Rome III criteria and/or Rome IV criteria. We defined these eligibility criteria prospectively (Table 1).

We searched the medical literature using the following terms *irritable bowel syndrome* and *colonic diseases, functional* (both as a medical subject heading and free text term), and *IBS* or *functional adj5 bowel* (as free text terms). We combined these using the set operator AND with studies identified with the terms: *Rome III*, *Rome 3*, *Rome IV*, or *Rome 4* (as free text terms). There were no language restrictions. We screened the titles and abstracts of all citations identified by our search for potential suitability, and retrieved those that appeared relevant in order to examine them in more detail. We performed a recursive search, using the bibliographies of all eligible articles. We translated foreign language articles, where required. Where there appeared to be multiple study reports from the same group of subjects, we contacted study authors to clarify this issue. If a study

appeared potentially eligible, but did not report the data required, we contacted the authors in order to obtain supplementary information, maximising available studies. We performed eligibility assessment independently. This was done by two investigators (HP and PO), using pre-designed eligibility forms. We resolved any disagreements by discussion with a third investigator (ACF), and measured the degree of agreement with a kappa statistic.

Data Extraction

Data were extracted independently by two investigators (HP and PO) on to a Microsoft Excel spreadsheet (XP professional edition; Microsoft, Redmond, WA, USA), again with any discrepancies resolved by the opinion of a third investigator (ACF). We collected the following data for each study: country, method of data collection (postal questionnaire, interview-administered questionnaire, self-completed questionnaire delivered at an appointment, or internet-based questionnaire), criteria used to define IBS, whether this definition used the required symptom duration and frequency threshold recommended by the Rome committee, or whether it was approximated using another questionnaire, the number of subjects providing complete data, the mean age of subjects, the proportion of male subjects, the number of subjects with IBS, the proportion of male and female subjects with IBS, and the number with each subtype of IBS according to predominant stool pattern (IBS-C, IBS-D, IBS-M, and IBS-U). Where IBS prevalence was reported according to both the Rome III and Rome IV criteria within a single study, we extracted the number of subjects with IBS according to each definition separately.

Data Synthesis and Statistical Analysis

We combined the proportion of individuals with IBS in each study, using a random effects model, to give a pooled prevalence of IBS for all studies, according to either the Rome III or Rome IV criteria. We assessed heterogeneity between studies using the I^2 statistic with a cut off of 50%, and the χ^2 test with a P value <0.10,[25] to define a statistically significant degree of heterogeneity.

We conducted subgroup analyses according to country, whether the symptom duration and frequency threshold used to define the presence of IBS were as recommended by the Rome committee, sex, and subtype (IBS-D, IBS-C, IBS-M, IBS-U). Finally, we compared the proportion of male and female subjects with IBS using an odds ratio (OR), with a 95% confidence interval (CI). We used StatsDirect version 3.2.7 (StatsDirect Ltd, Sale, Cheshire, England) to generate Forest plots of pooled prevalence and pooled ORs with 95% CIs. We planned to assess for evidence of publication bias by applying Egger's test to funnel plots of odds ratios,[26] where a sufficient number of studies were available.[27]

Role of the funding source

No funding was received. The corresponding author had full access to all of the data and the final responsibility to submit for publication.

RESULTS

The search strategy generated 4141 citations. From these we identified 183 that appeared to be relevant to the study question. In total, 57 of these articles fulfilled the eligibility criteria,[20-24,28-79] representing 92 separate adult study populations from 42 different countries (Figure 1)**,** and containing 423,362 subjects. Almost all studies were conducted in a single country, with the exception of a three-nation study conducted in Canada, the UK, and the USA,[78] and a multinational survey conducted in 33 different countries.[79] Agreement between investigators for assessment of study eligibility was good (kappa statistic = 0.75). Detailed characteristics of all included studies are provided in Supplementary Table 2. The lowest prevalence reported was 0.2% in one Indian study that used the Rome IV criteria.[79] The highest prevalence was 29.2%, reported in a Croatian study that used the Rome III criteria.[24]

Global Prevalence of IBS

The global prevalence of IBS based on 53 studies, which were conducted in 38 countries and contained 395,385 participants was 9.2% (95% CI 7.6% to 10.8%) when IBS was defined based on the Rome III criteria (Table 2).[20-24, 28-71,74-79] Prevalence ranged from 0.4% in India and Ghana in one multinational study,[79] to 29.2% in Croatia (Figure 2).[24] Six studies, which were conducted in 34 countries and contained 82,476 individuals, used the Rome IV criteria with a pooled prevalence of 3.8% (95% CI 3.1% to 4.5%).[55,72,73,76,78,79] Prevalence ranged from 0.2% in India,[79] to 21.2% in the USA (Figure 3).[55] As there was significant heterogeneity in the prevalence of IBS between different countries, when pooled together, we conducted further analyses to explore reasons for this variability. Prevalence in individual countries, according to the Rome III and IV criteria, is provided in Supplementary Table 3.

Prevalence of IBS According to the Questionnaire Used and Method of Questionnaire Administration

Of the 53 studies using the Rome III criteria, 41 defined IBS as per the validated Rome III questionnaire, [21-24, 29, 31, 33-35, 37-49, 51-54,56-61,63-67,74,75,78,79] giving a pooled prevalence of 8.4% (95% CI 6.8% to 10.1%). Twelve studies approximated the Rome III criteria using another questionnaire, with a pooled prevalence of 14.0% (95% CI 11.2% to 17.0%).[20,28,30,32,36,50,62,68-71,77]

Five of the six studies reported prevalence of IBS according to the Rome IV criteria using the validated questionnaire, with a pooled prevalence of 3.6% (95% CI 3.0% to 4.3%).[55,72,76,78,79] The sixth study approximated Rome IV criteria using another questionnaire,[73] with a prevalence of 10.4% (95% CI 8.2% to 12.1%). When studies were pooled according to the method of administration of the questionnaire, again there were significant differences in prevalence between individual studies. When the Rome III questionnaire was administered at an interview in 29 studies,[20,22,23,31,33-35,37,39-42,45-49,51-53,60,61,65-67,69,70,75,79] the prevalence of IBS ranged from 0.4% in India and Ghana,[79] to 20.9% in Singapore,[61] with a pooled prevalence of 5.9% (95% CI 4.6% to 7.4%). When the same questionnaire was self-completed in 22 studies [24,28-30,32,36,38,43,44,50,54,56,58,59,62-64,68,71,77-79] the prevalence ranged from 2.0% in the USA,[58] to 29.2% in Croatia,[24] with a pooled prevalence of 12.0% (95% CI 9.6% to 14.6%). Similarly, when the Rome IV questionnaire was administered at an interview in two studies,[72,79] prevalence was lower than when it was self-completed in five studies (1.6% (95% CI 0.8% to 2.8%) versus 4.5% (95% CI 4.0% to 5.2%)).[55,73,76,78,79]

Even when only studies that used the same questionnaire and method of administration were considered in the analysis significant heterogeneity between individual study results persisted. Among studies that administered the Rome III questionnaire during an interview the pooled prevalence of IBS was 5.4% (95% CI 4.2% to 6.8%, I^2 = 98.6%), and ranged from 0.4% in Ghana or India,[79] to 20.9% in Singapore,[61] compared with 10.4% (95% CI 7.8% to 13.4%, I^2 = 99.8%) when using an internet-based Rome III questionnaire, ranging from 2.0% in the USA[58] to 21.3% in

Japan.[44] Similarly, when using the Rome IV questionnaire in an interview, pooled prevalence was 1.6% (95% CI 0.7% to 2.8%, I^2 = 96.8%), varying from 0.2% in India[79] to 4.6% in Bangladesh,[79] compared with 4.4% (95% CI 3.8% to 4.9%, I^2 = 91.0%) when the questionnaire was self-completed online, ranging from 1.3% in Singapore[79] to 21.3% in the USA.[55]

Prevalence of Different Subtypes of IBS

There were 23 studies,[20,23,29,31,33,40,43,44,46,51,54,59-63,65,67-69,71,77,78] containing 102,177 participants, which reported prevalence of IBS according to subtype, based on the Rome III criteria. When pooling data from these studies, 33.8% (95% CI 27.8% to 40.0%) of participants had IBS-M, 27.8% (95% CI 24.9% to 30.7%) IBS-D, 20.0% (95% CI 16.7% to 23.4%) IBS-C, and 14.1% (95% CI 10.0% to 18.8%) IBS-U. In terms of global prevalence this translated into 3.7% (95% CI 2.6% to 4.9%) of all participants having IBS-M, 3.1% (95% CI 2.6% to 3.8%) having IBS-D, 2.3% (95% CI 1.7% to 3.1%) having IBS-C, and 1.5% (95% CI 1.0% to 2.0%) having IBS-U.

There were only two studies,[72,78] containing 6756 participants, which reported IBS subtype prevalence based on the Rome IV criteria. Among those with IBS, the pooled prevalence of IBS-D was 31.5% (95% CI 23.2% to 40.5%), IBS-C 29.3% (95% CI 24.3% to 34.5%), IBS-M 26.4% (95% CI 17.7% to 36.1%) and IBS-U 11.9% (95% CI 3.3% to 24.9%). Among all 6756 participants, when data were pooled, 1.4% (95% CI 0.9% to 1.9%) had IBS-D, 1.3% (95% CI 1.1% to 1.6%) IBS-C, 1.1% (95% CI 0.7% to 1.7%) IBS-M, and 0.5% (95% CI 0.2% to 1.0%) IBS-U.

Prevalence of IBS According to Sex

There were 30 studies that reported the prevalence of IBS according to sex and used the Rome III criteria.[20,22-24,28-3133-35,37-39,43,44,46-48,51,54,59,61,64-67,69,75,77] The pooled prevalence of IBS was slightly higher in women (12.0%; 95% CI 9.3% to 15.0%), compared with men (8.6%; 95% CI 6.3% to 11.2%). The OR for IBS in women versus men was 1.46 (95% CI 1.33 to 1.59) (Supplementary Figure 1), with significant heterogeneity between studies (I^2 = 78.3%, P < 0.001),

and evidence of funnel plot asymmetry (Egger test, P = 0.02). There were no studies that reported IBS prevalence according to sex using the Rome IV criteria.

DISCUSSION

We included prevalence data for IBS, according to the Rome III or Rome IV criteria, from 92 separate adult study populations from 42 different countries, reported in 57 separate papers in this systematic review and meta-analysis. Our study has demonstrated that even when studies apply the same definitions of IBS and utilise similar methodology the prevalence of IBS varies widely between countries, from <1% to >25%. Pooled prevalence was higher with the Rome III criteria at 9.2%, compared with 3.8% using the Rome IV criteria. The 95% CIs around these estimates did not overlap, suggesting the prevalence of IBS is significantly lower with Rome IV. Moreover, when we pooled studies according to whether the validated Rome questionnaires were used and how they were administered, significant differences in prevalence between individual studies remained. When prevalence of IBS according to predominant stool pattern was examined, IBS-M was the most prevalent subtype when the Rome III criteria were used, with IBS-D the most common when the Rome IV criteria were applied. Using Rome III criteria, 1 in 27 people in the community met criteria for IBS-M according to Rome III, and 1 in 71 met criteria for IBS-D using Rome IV. Finally, odds of IBS were modestly increased in female compared with male subjects.

We used rigorous methodology in order to maximise the likelihood of identifying all pertinent literature, and to minimise bias. Our literature search was extensive and contemporaneous, and two people performed judging of study eligibility and data extraction independently, with discrepancies resolved by a third investigator. We contacted primary or senior authors of studies to ensure that duplicate publications from identical cohorts under extended follow-up were not included and, in some cases, to obtain extra data. We also translated eligible foreign language articles, in order to be as inclusive as possible. We pooled data using a random effects model, likely providing a more conservative estimate of IBS prevalence. Finally, we limited studies to those based in the general population, and excluded those conducted among convenience samples, such as health check-up populations, or where the age of participants was restricted, which may introduce

inaccuracies in estimating the prevalence of the condition under study. The data we report should therefore be generalisable to individuals living in the community in the countries where they were conducted.

Limitations of this study include the fact that data for some geographic regions, such as Africa, the Middle East, South America, and Central America, were sparse. Furthermore, not all studies reported prevalence of IBS according to gender or subtype. In addition, differing methods were used to collect symptom data. These different approaches to collecting data, such as face-to-face interview versus self-completed internet-based or paper questionnaires, could lead to different estimates of the prevalence of IBS. This appeared to be the case even in the Rome Foundation global survey, which used uniform methods, other than including either interview-administered or internet-based questionnaires.[79] There was significant heterogeneity between studies in all our analyses, which was not explained by any of the subgroup analyses we conducted. The heterogeneity persisted even when the analysis was limited to studies that applied the same diagnostic criteria, according to the validated Rome questionnaires, and used exactly the same method of data collection, suggesting genuine variation in prevalence of IBS between different countries. Reasons for this are uncertain. It may be that symptom-reporting is influenced by cultural beliefs, education, genetics, ethnic, environmental, or dietary differences between individual study populations.[80,81] Finally, it is important to underline that meeting diagnostic criteria for IBS in population-based cross-sectional surveys such as these does not equate to a definitive diagnosis of IBS. Undiagnosed organic conditions including coeliac disease, bile acid diarrhoea, microscopic colitis, diverticulosis, or inflammatory bowel disease can lead to similar symptoms,[5-7,82,83] although in population-based surveys the prevalence of these is likely to be low. The pooled prevalence of IBS derived from these studies may therefore be a slight overestimate.

There have been two previous systematic reviews examining the prevalence of IBS in the community. The first of these was our own meta-analysis,[18] published in 2012, which considered the prevalence, irrespective of the criteria used to define it, including “historical” classification

systems, such as the Manning, Rome I, and II criteria. Pooled prevalence in this meta-analysis was 11.2%, but was lower with all iterations of the Rome criteria, compared with the Manning criteria. Despite differences in diagnostic criteria applied, the pooled prevalence in this meta-analysis was similar to that observed using the Rome III criteria in the current study. A more recent systematic review was conducted by the Rome Foundation in 2017,[19] and reported similar findings in terms of variability in prevalence of IBS.

In the intervening years since these systematic reviews, there have been two large cross-sectional surveys, one a three-nation survey,[78] and one a 33-nation global study,[79] which were conducted by the Rome Foundation, and were included in the current meta-analysis. These studies used both the Rome III and IV criteria to define IBS. In the three-nation survey, conducted in Canada, the UK, and the USA prevalence was similar, between 8.6% and 9.5%, when the Rome III criteria were applied, and between only 4.5% and 4.7% using Rome IV. In the 33-nation global study prevalence varied more widely between countries, even when using the same criteria administered in the same way. When the Rome III criteria were completed online, prevalence ranged from 4.3% in Singapore to 16.5% in Russia, compared with 1.3% in Singapore to 7.6% in Egypt using Rome IV. When the Rome III questionnaire was administered during an interview, prevalence varied from 0.4% in Ghana and India to 10.7% in Bangladesh, and from 0.7% in India to 4.6% in Bangladesh with the Rome IV criteria.

The findings of this study have implications for both future research and clinical practice. Firstly, the Rome IV criteria are more restrictive than their predecessor. Although this may be useful in clinical research, where the aim is to recruit homogeneous groups of patients into mechanistic or treatment studies, in epidemiological surveys this may be less relevant, and could underestimate true prevalence. This is reflected in the results of the 33-nation study,[79] where prevalence estimates for some of the functional gastrointestinal disorders that are far less frequently encountered in clinical practice, such as functional dysphagia or rumination, approached that of the lower estimate for IBS. Research funding for IBS is already low, versus other gastrointestinal

diseases,[84] so anything that reduces the perceived "burden" of the condition may not be in the best interests of patients, and other cross-sectional studies have shown that disease impact is substantial even in people felt to have IBS who do not meet such diagnostic criteria.[76] It may, therefore, be more appropriate to continue to use the Rome III criteria in population-based epidemiological surveys. Secondly, and related to this issue, in both the three-nation study and a recent cross-sectional survey of patients with IBS,[9,78] the majority of people who met criteria for IBS according to Rome III criteria but who did not meet Rome IV criteria were reclassified as having either no bowel disorder or an unspecified functional bowel disorder. These may not be helpful labels for patients, and may create further uncertainty if deemed unacceptable by the individual, leading to increased costs due to repeated consultation and further investigations. Even if patients are instead reclassified to one of the other functional bowel disorders, such as functional diarrhoea, functional bloating or abdominal distension, or functional constipation, only the latter has any licensed therapies. Thirdly, although the use of the Bristol stool form scale in Rome IV in order to categorise patients with IBS into subtypes leads to fewer people meeting criteria for IBS-M or IBS-U, in this meta-analysis these individuals still made up more than one in three of those with IBS. There are currently no licensed drugs for use in these groups of patients, and this represents a substantial unmet need. Fourthly, future epidemiological surveys should use validated questionnaires, as approximating the Rome III or IV criteria from another questionnaire appears to inflate IBS prevalence. Finally, prevalence of IBS appears to be lower when individuals are interviewed, rather than when they complete a symptom questionnaire themselves. The reasons for this are unclear but might be due, in part, to under-reporting of symptoms when individuals are questioned directly; this is an area for further study.

Although pooled prevalence in this systematic review was lower than our previous estimates, due to the fact that we only considered studies that used the more restrictive Rome III or IV criteria as being eligible, our data demonstrate that IBS still affects somewhere between one in 11 and one in 26 people in the community at any point in time. Extracting and synthesising global

data on the prevalence of IBS has emphasised the magnitude of this disorder within the community, and thus the implications for health services worldwide, including those in some of the poorest nations in the world. In the USA, the total direct costs of managing IBS per year have been previously estimated to be in excess of $1 billion, whereas indirect costs relating to loss of productivity are more than $200 million.[85] In a recent meta-analysis based upon 11 European datasets,[14] containing over 2700 patients, the total annual cost related to IBS was estimated at almost €3000 per patient. Although therapies for IBS with proven efficacy exist,[86-90] none are curative, and their cost-effectiveness remain uncertain.

In conclusion, this systematic review and meta-analysis has demonstrated a global prevalence of IBS of 9.2% when the Rome III criteria were used, and 3.8% with the Rome IV criteria. It should be emphasised that this varied, considerably in some instances, according to country, whether diagnostic criteria were applied strictly or approximated, and the method used to collect symptom data in individual studies. However, even when uniform diagnostic criteria and methodology were applied in different countries, prevalence varied substantially suggesting that this is due to true variation. In the future, data mining of the 33-nation Rome Foundation global study may elucidate some of the reasons for this variability.

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AUTHOR CONTRIBUTIONS

PO, HP, BB, CJB, EVS, and ACF conceived and drafted the study. PO, HP, BB, and ACF collected, analysed, and interpreted all data. PO, HP, BB, and ACF drafted the manuscript. PO, HP, BB, CJB, EVS, and ACF commented on drafts of the paper. All authors have approved the final draft of the manuscript.

DECLARATION OF INTERESTS

Priya Oka: none. Heather Parr: none. Brigida Barberio: none. Christopher J. Black: none. Edoardo V. Savarino: has acted as a consultant for and received teaching fee funding from Abbvie, Takeda, Janssen, MSD, Fresenius Kabi, Sandoz, Malesci, and Sofar, which are outside the submitted work. Alexander C. Ford: none.

ETHICS COMMITTEE APPROVAL

Not required.

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FIGURE LEGENDS

Figure 1. Flow Diagram of Assessment of Studies Identified in the Meta-analysis.

Figure 2. Prevalence of IBS Worldwide Using the Rome III Criteria.

Figure 3. Prevalence of IBS Worldwide Using the Rome IV Criteria.

Table 1. Eligibility Criteria.

Cross-sectional surveys
Recruited adults (>90% of participants aged ≥18 years)
Participants recruited from the general population or community*
Reported prevalence of IBS (according to specific diagnostic criteria†)
Sample size of ≥50 participants

*Convenience samples excluded (e.g. university employees, hospital employees, blood donors, health check-up populations).

†Rome III or IV criteria

Table 2. Pooled Prevalence of IBS According to Criteria Used to Define its Presence, Questionnaire Used, and Method of Questionnaire Administration.

	Number of studies	Number of subjects	Pooled prevalence (%)	95% confidence interval	I^2	P value for I^2
Criteria used to define IBS						
Rome III	53	395,385	9.2	7.6 to 10.8	99.7	<0.001
Rome IV	6	82,476	3.8	3.1 to 4.5	96.6	<0.001
Questionnaire used						
Defined as per Rome III questionnaire	41	370,896	8.4	6.8 to 10.1	99.7	<0.001
Approximated Rome III using another questionnaire	12	24,489	14.0	11.2 to 17.0	97.6	<0.001
Defined as per Rome IV questionnaire	5	81,154	3.6	3.0 to 4.3	96.4	<0.001
Approximated Rome IV using another questionnaire	1	1,322	10.4	8.8 to 12.1	NA*	NA*
Method of questionnaire administration						
Rome III: self-completed questionnaire	22	293,881	12.0	9.6 to 14.6	99.8	<0.001
Rome III: interview-administered questionnaire	29	92,344	5.9	4.6 to 7.4	98.7	<0.001
Rome IV: self-completed questionnaire	5	62,712	4.5	4.0 to 5.2	92.5	<0.001
Rome IV: interview-administered questionnaire	2	19,764	1.6	0.8 to 2.8	96.8	<0.001