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TITLE PAGE

Title: Global Prevalence of Functional Constipation According to the Rome criteria: Systematic Review and Meta-analysis.

Short "running" title: Functional Constipation: Systematic Review and Meta-analysis.

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Abbreviations:

CI	confidence interval
FC	functional constipation
FGID	functional gastrointestinal disorder
IBS-C	irritable bowel syndrome with constipation
MeSH	medical subject headings
OR	odds ratio

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ABSTRACT

Background: Functional constipation (FC) is a common functional bowel disorder in the community, whose prevalence varies across cross-sectional surveys. We performed a contemporaneous systematic review and meta-analysis of studies using comparable methodology, and all iterations of the Rome criteria, to estimate global prevalence.

Methods: MEDLINE, EMBASE, and EMBASE Classic were searched (from 1990 to 31st December 2020) to identify population-based studies reporting the prevalence of FC in adults (≥18 years old) according to Rome I, II, III, or IV criteria. Prevalence of FC was extracted, according to criteria used to define it. Pooled prevalence, according to study location and certain other characteristics, odds ratios (OR), and 95% confidence intervals (CIs) were calculated.

Findings: Of 8,174 citations evaluated, 45 studies fulfilled eligibility criteria, representing 80 separate populations, containing 275,260 subjects. Pooled prevalence was 15.3% (95% CI 8.1% to 24.4%, I^2 = 99.4%) in studies defining FC according to the Rome I criteria, 11.2% (95% CI 7.9% to 14.9%, I^2 = 99.6%)) using Rome II, 11.4% (95% CI 6.5% to 14.9%, I^2 = 99.8%)) with Rome III, and 10.1% (95% CI 8.7% to 11.6%, I^2 = 98.2%)) when Rome IV criteria were used. Prevalence of FC was up to two times higher in women, irrespective of definition used. There was significant heterogeneity between studies in all our analyses, which persisted even when the same criteria were applied and similar methodology used.

Interpretation: Even when uniform symptom-based criteria are used to define the presence of FC, prevalence varies between countries. Thus, environmental, cultural, ethnic, dietary, or genetic factors may influence reporting of symptoms. Future studies should aim to elucidate reasons for this geographical variability.

Funding: None

Evidence before this study

Constipation, characterised by unsatisfactory defaecation as a result of infrequent stools, difficult stool passage, or both, is common in the community. The term functional constipation (FC) has been proposed and defined by the Rome Foundation to help standardise a diagnosis of chronic constipation in the absence of physiological abnormality. It is 10 years since the last meta-analysis that synthesised all population-based prevalence studies in this field, to assess the burden of FC globally. This study reported a pooled prevalence of FC of 14.0%. However, prevalence is now likely to be lower, as the Rome criteria for FC have become more restrictive with successive iterations. A comprehensive search of the medical literature using MEDLINE, EMBASE, and EMBASE Classic from 1990 to 31st December 2020, and including foreign language articles, identified multiple studies published since the conduct of this prior meta-analysis, which reported prevalence of FC in numerous countries according to the different iterations of the Rome criteria, thus providing a rationale for this updated systematic review and meta-analysis.

Added value of this study

We did a contemporaneous systematic review of population-based cross-sectional studies reporting the prevalence of FC in ≥50 adults (≥90% aged ≥18 years) according to the Rome I, II, III, or Rome IV criteria, to estimate global prevalence of FC. Pooled prevalence was higher with the Rome I criteria, at 15.3%, compared with 10.1% using the Rome IV criteria. For each iteration of Rome, pooled prevalence was lower when a validated Rome questionnaire was applied, while it was higher when the Rome criteria were approximated using another questionnaire. Studies using the Rome I or II criteria reported a higher prevalence of FC when an interview-administered questionnaire was used. Conversely, studies that applied the Rome III or IV criteria demonstrated a higher pooled prevalence of FC when a self-completed questionnaire was administered. The odds of FC were significantly higher in females, compared with males, irrespective of the definition used. There

were no significant differences in prevalence of FC according to age or socioeconomic status, although data were sparse in these analyses.

Implications of all the available evidence

Global prevalence of FC ranged from 15.3% using the Rome I criteria to 10.1% when the Rome IV criteria were applied. Our data, therefore, suggest that FC affects between one in six and one in 10 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

Constipation is a common gastrointestinal condition characterised by unsatisfactory defaecation as a result of infrequent stools, difficult stool passage, or both.[1] Mentioned as a clinical entity by the Egyptians in the 16th century BC,[2] constipation continues to negatively impact quality of life and generate major healthcare-associated costs, estimated at approximately £162 million in the UK National Health Service from 2017 to 2018.[3] Constipation can be caused by a wide variety of precipitating factors, with definitions of the condition influenced by variations in geography, language, culture, and level of education. This can create difficulties in interpretation and standardisation of prevalence rates obtained from cross-sectional studies. The term functional constipation (FC) has been proposed and defined by the Rome Foundation to help standardise the diagnosis of chronic constipation in the absence of physiological abnormality.[4,5] Over the last two decades, the Rome criteria have been used with increasing frequency in cross-sectional studies to estimate the prevalence of FC globally.[6] Such consistency is desirable, particularly when comparison of rates of constipation using alternative, or informal, criteria may yield variability in prevalence in excess of 40%.[6,7]

Building on improved diagnostic capabilities and experience gained from previous versions, the Rome IV criteria have been refined to consider constipation as a feature of several distinct, but occasionally overlapping, disorders of gut-brain interaction.[4] This continuum includes FC, irritable bowel syndrome with constipation (IBS-C), opioid-induced constipation, and functional defaecation disorders, all of which result in problematic and unsatisfactory defaecation.[4,8] Published 10 years after their predecessor, the Rome IV criteria also acknowledge non-predominant pain or bloating to be acceptable components of FC, further illustrating the potential for overlap between these different conditions.[4]

In addition to updates within the criteria themselves, technological advances have enhanced and expanded methods of data collection. Marking a change from the most recent meta-analysis on the prevalence of FC conducted in 2011,[6] cross-sectional studies are now being conducted more

frequently using online versions of the Rome criteria, in addition to postal and in-person interviews.[9] Efforts at determining the global prevalence of FC have accelerated over the last decade, in particular through multinational studies using a combination of data collection techniques.[9,10]

Cross-sectional population-based studies using internationally accepted diagnostic criteria for FC remain the gold-standard for understanding the epidemiology of FC which, given the associated cost and morbidity, is essential. In the 10 years since the last study to synthesise all available data in this field, there have been a plethora of epidemiological studies published using accepted symptom-based criteria for FC. We have, therefore, conducted an updated systematic review and meta-analysis to examine the prevalence of FC in the community, using all iterations of the Rome criteria, to gain an accurate understanding of its epidemiology worldwide.

METHODS

Search Strategy and Study Selection

We searched the medical literature using MEDLINE (1990 to 31st December 2020), EMBASE and EMBASE Classic (1990 to 31st December 2020) to identify only cross-sectional surveys that reported the prevalence of FC in adults (≥90% aged ≥18 years) according to the Rome I, II, III, or Rome IV criteria, detailed in the appendix (page 1).[4,5,11,12] We limited the search from 1990 to the present, as the Rome criteria were first described in 1991. To identify studies published only in abstract form, we hand-searched conference proceedings (Digestive Diseases Week, American College of Gastroenterology, United European Gastroenterology Week, and the Asian Pacific Digestive Week). Studies were required to recruit participants from the general population or community. Those that reported the prevalence of FC in convenience samples, such as university students, employees at an institution, or people attending screening clinic health check-ups, or primary care clinics for another reason, were deemed ineligible. To be eligible, studies also had to recruit at least 50 participants. These eligibility criteria, which were defined prospectively, are provided in Box 1.

We used the following terms to search the medical literature: *constipation* or *gastrointestinal transit* (both as medical subject headings (MeSH) and free text terms), as well as *functional constipation*, *chronic constipation*, or *idiopathic constipation* as free text terms. We used the set operator AND to combine these with studies identified with the terms: *Rome I*, *Rome 1*, *Rome II*, *Rome 2*, *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 to examine them in more detail. We used the bibliographies of all eligible articles to perform a recursive search. 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 authors to obtain supplementary information and, therefore, maximise available studies. We performed eligibility assessment independently, using pre-designed eligibility forms. This was done by two investigators (BB and CJ). We resolved any disagreements by discussion with a third investigator (ACF) and used the kappa statistic to measure the degree of agreement. Ethical approval was not required.

Data Analysis

Two investigators (BB and CJ) extracted data independently 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 (self-completed postal questionnaire, self-completed questionnaire given to the participant at an appointment, self-completed internet-based questionnaire, or interviewer-administered questionnaire, either face-to-face or over the telephone), criteria used to define FC, whether the study used the Rome I, II, III, or IV diagnostic questionnaires, or approximated these definitions of FC using another questionnaire, the total number of subjects providing complete data, the mean age of subjects, the number of subjects with FC, the number of male and female subjects, and the number of male and female subjects with FC. Where FC prevalence was reported according to more than one set of criteria within an individual study, the number of subjects with FC according to each individual definition was extracted.

We used a random effects model to combine the proportion of individuals with FC in each study to give a pooled prevalence of FC for all studies, according to the Rome I, II, III, or IV criteria. We used the I^2 statistic with a cut off of 50%, and the χ^2 test with a P value <0.10, used to define a statistically significant degree of heterogeneity between studies.[13] We conducted subgroup analyses according to country, whether the Rome I, II, III, or IV criteria were defined strictly, or approximated via another questionnaire, how the questionnaire was completed (self-completed versus interview-administered), sex, age, and socioeconomic status, where reported. Finally, we

compared the prevalence of FC according to sex, age group, and socioeconomic status using an odds ratio (OR), with a 95% confidence interval (CI). We generated Forest plots of pooled prevalences and pooled ORs with 95% CIs using StatsDirect version 3.2.7 (StatsDirect Ltd, Sale, Cheshire, England). We applied Egger's test to funnel plots of odds ratios,[14] to assess for evidence of publication bias, where a sufficient number of studies were available.[15]

Role of the Funding Source

No funding was received. All authors had full access to all of the data and accept responsibility to submit for publication.

RESULTS

The search strategy generated 8,174 citations. From these we identified 168 that appeared to be relevant to the study question. In total, 45 of these articles fulfilled the eligibility criteria,[9,10,16-58] representing 80 separate adult study populations (Figure 1) and containing 275,260 subjects recruited from 43 different countries worldwide. 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,[10] and a multi-national survey conducted in 33 different countries.[9] Agreement between investigators for assessment of study eligibility was good (kappa statistic = 0.72). Detailed characteristics of all included studies are provided in the appendix (pages 2 to 5). The lowest prevalence of FC reported was 0.2% (95% CI 0.1% to 0.3%) in one German study that administered the Rome III questionnaire during a face-to-face interview.[49] The highest prevalence was 30.7% (95% CI 28.5% to 33.0%),[26] reported in an Australian study that used the Rome II criteria in a validated self-administered questionnaire.

Prevalence of FC According to Criteria Used to Define its Presence

In total, seven studies stated that they used the Rome I criteria in 6 separate countries,[16-19,23,25,40] 17 the Rome II criteria in 12 separate countries,[20-31,35,36,41,45] 18 the Rome III criteria in 14 separate countries,[32-34,37,39,42-44,46-53,55,58] and five the Rome IV criteria in 35 separate countries.[9,10,54,56,57] The pooled prevalence of FC, according to the criteria used to define its presence, is provided in Table 1. Pooled prevalence was highest when the Rome I criteria were used (15.3%; 95% CI 8.1% to 24.4%), and lowest when the Rome IV criteria were used (10.1%; 95% CI 8.7% to 11.6%). Figures 2a to 2dsummarise pooled data for the prevalence of FC worldwide, according to country, using all iterations of the Rome criteria.

The pooled prevalence in individual countries, according to the Rome I, II, III, or IV criteria, is provided in the appendix (page 6). When the Rome I criteria were used, prevalence of FC was lowest in Australia at 7.8%,[19] and highest in South Korea at 24.3%.[18] According to Rome II,

prevalence was lowest in China at 4.8%,[22,38] and highest in Turkey at 24.5%.[29] Using the Rome III criteria, prevalence of FC was lowest in Germany at 0.2%,[49] and highest in the Netherlands at 24.5%.[53] Finally, when the Rome IV criteria were used prevalence was lowest in Honduras at 1.1%,[56] and highest in Ghana at 26.1%.[9] The continued disparity in prevalence of FC by country in these analyses suggests that geographical variation was not related solely to the diagnostic criteria used in each study. We therefore conducted further analyses to explore reasons for this variability.

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

Table 1 shows how the pooled prevalence varied based on the method used to define the presence of FC. When a validated Rome questionnaire was used, the highest prevalence was found in four studies that used the Rome I criteria (11.8%; 95% CI 3.8% to 23.5%),[16,19,23,40] while the prevalence was lowest in 17 studies using the Rome III criteria (9.9%; 95% CI 6.0% to 14.6%).[10,32-34,39,42-44,46-49,51-53,55,58] Among the studies that approximated the Rome criteria using another questionnaire, the prevalence was highest when the Rome I criteria were used in three studies (20.5%; 95% CI 16.9% to 24.3%),[17,18,25] while it was lowest in six studies using the Rome II criteria (12.5%; 95% CI 5.3% to 22.2%).[21,24-26,28,31]

When a self-completed questionnaire was administered, the pooled prevalence of FC was highest according to the Rome III criteria (12.3%; 95% CI 6.2% to 20.2%) in eight studies,[10,33,44,47,51,53,55,58] and lowest with Rome II in ten studies (11.0%; 95% CI 6.4% to 16.7%).[20-23,25,26,28,30,35,38] When an interview-administered questionnaire was used the highest prevalence was again found with Rome I in one study (24.3%; 95% CI 20.3% to 28.7%),[18] and lowest with Rome IV in three studies (7.3%; 95% CI 3.8% to 11.8%).[9,54,56]

Prevalence of FC According to Sex, Age, and Socioeconomic Status

Overall, the prevalence of FC according to sex of the participants was reported in four,[16,18,23,25] eleven,[20,23-27,29,31,38,41,45] and nine[32-34,39,46,47,52,53,58] studies using the Rome I, II, or III criteria respectively. No study using the Rome IV criteria reported these data. The pooled prevalence of FC was higher in women compared with men, irrespective of the definition used (Table 2). There were 11 studies reporting the prevalence of FC according to age that provided extractable data.[16,23-26,33,38,45,46,53,58] However, the different age bands used to report prevalence of FC limited the available data for pooling. Overall, the prevalence of FC according to age <45 years and ≥45 years was reported in one,[16] one,[26] and two studies[33,58] using the Rome I, II, or III criteria respectively. Two studies reported prevalence of FC according to age <50 years and ≥50 years using Rome I,[23,25] and three studies Rome II (Table 2).[23-25] Irrespective of age cut off or criteria for FC, there were no significant differences in prevalence of FC in younger versus older individuals. Finally, there were four studies reporting the prevalence of FC according to socioeconomic status, of which one used both Rome I and II criteria and three the Rome II criteria.[21,23,24,26] When data from these studies were pooled, people of higher socioeconomic status tended to have a lower prevalence of FC, although again this was not statistically significant (Table 2). There were an insufficient number of studies to examine for funnel plot asymmetry in all these analyses.

DISCUSSION

This systematic review and meta-analysis has assembled data from 45 population-based cross-sectional surveys that reported prevalence of FC in the community using all iterations of the Rome criteria. It has demonstrated that, even when the same definitions are applied, and similar methodology utilised, the prevalence of FC varies widely between countries, from less than 1% to more than 30%. Pooled prevalence was higher with the Rome I criteria, at 15.3%, compared with 10.1% using the Rome IV criteria. For each iteration of Rome, pooled prevalence was lower when a validated Rome questionnaire was applied, while it was higher when an approximation of the Rome criteria was arrived at using another questionnaire. Studies using the Rome I or II criteria reported a higher prevalence of FC when an interview-administered questionnaire was used. Conversely, studies that applied the Rome III or IV criteria demonstrated a higher pooled prevalence of FC when a self-completed questionnaire was administered. Finally, the odds of FC were significantly higher in females, compared with males, irrespective of the definition used, but there were no significant differences detected according to either age or socioeconomic status, although the number of studies reporting these data were small.

We used a broad search strategy to maximise the likelihood of identifying pertinent literature. The judging of study eligibility and data extraction were carried out by two investigators independently, with discrepancies resolved by consensus. We also included data from eligible foreign language articles, after translation, to be as inclusive as possible. We used a random effects model to pool data to provide a more conservative estimate of the prevalence of FC, and planned to assess for publication bias, if sufficient studies were identified. Finally, we limited studies to those based in the general population, and excluded those conducted among convenience samples, meaning that the likelihood that the prevalence of FC has been inflated has been minimised, and the data we report should therefore be generalisable to individuals living in the community.

Limitations of this study include the paucity or absence of studies reporting prevalence of FC from geographical regions such as Africa, South America, or Central America, and the

relatively small number of studies reporting prevalence of FC according to sex, age, or socioeconomic status. In addition, there was some variability in methods used to collect symptom data. It may be that these different approaches to collecting data, such as face-to-face or telephone interview, versus self-completed internet-based or paper questionnaires, led to different estimates of the prevalence of FC. This certainly appeared to be the case in the Rome Foundation global survey, which used both interview-administered and internet-based questionnaires.[9] There was significant heterogeneity between studies in all our analyses, which was not explained by any of the subgroup analyses we conducted. Given that the heterogeneity persisted even when the analysis was limited to studies that applied the same diagnostic criteria, and used an identical method of data collection, this suggests the variation in prevalence of FC observed between studies conducted in different countries is genuine. Reasons for this are speculative. It could be that environmental, genetic, ethnic, dietary, or cultural differences between individual study populations influence prevalence of symptoms, or likelihood of symptom-reporting by individuals. Another possible explanation for the variation in prevalence between countries could be that, as the Rome criteria have been written in English, the translation into other languages, or interpretation of the questions by non-English speakers leads to increased or decreased symptom-reporting. Whether the Rome criteria should be used as a gold-standard to estimate prevalence of disorders like FC is perhaps a matter of debate, as there may be individuals in these studies who were constipated but did not meet criteria for FC, but whose symptoms are equally troublesome, and who may respond equally well to available treatments. Although we found that prevalence of FC was higher in women than men, individual studies did not provide information on whether the questionnaire response rates were equal among males and females. Finally, the findings of our study could be criticised as being superfluous, given the recent publication of a definitive 33-nation global study conducted by the Rome Foundation, using the Rome IV criteria to estimate prevalence of FC.[9] However, given the variation in prevalence rates observed between countries, even in this study, which used uniform methodology,

we feel that a contemporaneous evidence synthesis of all available population-based cross-sectional surveys, using all definitions of the Rome criteria, still has merit.

There have been few previous systematic reviews examining the prevalence of FC in the community. The most recent of these, to our knowledge, was our own meta-analysis, which included population-based studies reporting the prevalence of FC in adults published up to 2010. The literature search that informed this meta-analysis is therefore over 10 years out of date, and the eligibility criteria also allowed for the inclusion of studies that used any definition of FC, including self-reported symptoms, according to any questionnaire, or according to a physician's opinion that constipation was present. In this previous meta-analysis, pooled prevalence both overall and according to the Rome I criteria was 14% but was lower in studies using the Rome II or III criteria. In keeping with the more restrictive nature of the Rome criteria, versus some of the less stringent definitions of FC used in studies included in this prior meta-analysis, prevalence of FC observed in the current meta-analysis was lower with all iterations of Rome at 10.1% to 11.2%, except for when the Rome I were used, where it was 15.3%. The previous meta-analysis reported that pooled prevalence of FC increased significantly according to increasing age, across 10-year age bands, from 12.0% in those age <29 years to 17.0% in those aged ≥60 years.[6] However, these data were from only three studies, and when age was dichotomised at 45 years and ≥45 years (five studies), or <50 years and ≥50 years (seven studies), there were no significant differences in prevalence of FC, as we observed in the current meta-analysis.

There have been two large multi-national cross-sectional surveys published in the intervening years since this meta-analysis, one a three-nation survey,[10] and the other a 33-nation global study,[9] both of which were conducted by the Rome Foundation, and are included in the current meta-analysis. Even in these two studies, which applied the Rome IV criteria using near identical methodology, the prevalence of FC varied according to country. Participants in some of the countries included in the 33-nation study received an interview-administered questionnaire. In these countries, prevalence varied from 1.8% in India and 1.9% in Turkey, to 11.8% in Bangladesh

and 26.1% in Ghana.[9] Using an internet survey, prevalence of FC ranged from 7.7% in Australia and 8.6% in the UK, to 14.5% in France and 16.6% in Japan. However, pooled prevalence of FC was higher at 11.7% in the internet-based survey in 26 countries, compared with 6.6% using an interview-administered questionnaire in nine countries.[9]

The findings of our study have implications for both clinical practice and future research. These data suggest that FC affects somewhere between one in six and one in ten people in the community at any point in time, depending on which iteration of the Rome criteria is used to define its presence. However, prevalence data for FC in certain geographical regions are lacking and should be the subject of future studies. From a research perspective, it appears that the method of questionnaire administration affects the likelihood of reporting of symptoms compatible with FC, and therefore the prevalence in the community. In addition, studies that report the prevalence of FC according to the Rome criteria, but approximate this using another questionnaire, rather than using the validated Rome questionnaires, appear to overestimate prevalence. As a result, standardising methodology of future population-based cross-sectional surveys should be considered, to facilitate direct comparisons between them. Finally, data mining of the 33-nation global study conducted by the Rome Foundation may allow valuable insights into why prevalence of FC varies between countries, even when identical criteria and methods are used to define its presence.[9] For example, information concerning diet, physical activity, mood, and medication use may be relevant to prevalence of FC.

Although the prevalence of FC in some geographical regions requires further study, data from this meta-analysis re-emphasise the magnitude of this disorder globally, and thus the implications for health services worldwide. In fact, health-seeking behaviour in those affected results in 2.5 million health visits per year in North America alone, with a third of those occurring in primary care, leading to significant costs to the health service.[59] Although efficacious drugs for FC exist,[60,61,62] many patients symptoms are refractory to these, and the efficacy of the majority of these has not been studied in primary care. A recent meta-analysis estimated the global prevalence

of IBS-C according to the Rome IV criteria to be 1.1%,[63] based on two studies,[10,64] compared with a prevalence of FC of 10.1% according to Rome IV in this meta-analysis. This suggests one-in-nine people in the community will have constipation at any one point in time, with FC being much more prevalent than IBS-C. Although distinguishing IBS-C from FC may be an important issue in a research setting, many therapies, such as linaclotide, lubiprostone, plecanatide, and tegaserod,[62,65,66] are effective in both conditions. This suggests that, given the much lower prevalence of IBS-C, more novel therapies, which are expensive to bring to market due to the difficulty in conducting RCTs, should be tested in mixed populations of patients with FC and IBS-C. This has been the case in recent trials of mizagliflozin and elobixibat.[67,68] In addition, although prucalopride is of proven efficacy in RCTs in patients with FC,[61] it may also be worth considering this as a treatment for IBS-C, given the overlap between the two conditions.[69]

In conclusion, this systematic review and meta-analysis has demonstrated that the global prevalence of FC ranged from 15.3% using the Rome I criteria to 10.1% when the Rome IV criteria were applied. Prevalence varied, considerably in some instances, according to country, whether diagnostic criteria were applied strictly, or approximated, and how symptom data were collected 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, similar to that observed in recent meta-analyses of the global prevalence of both IBS and functional dyspepsia.[63,70] Reasons for this variability are unclear and should be the subject of future research. These data provide up to date estimates of the burden of this condition and can be used to inform future healthcare planning, as well as to underline the importance of the treatment of FC as a research priority.

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AUTHOR CONTRIBUTIONS: BB, CJ, EVS, and ACF conceived and drafted the study. BB and CJ collected, analysed and interpreted the data. BB, CJ and ACF drafted the manuscript. All authors commented on drafts of the paper. All authors have approved the final draft of the manuscript.

DECLARATION OF INTERESTS

Brigida Barberio: none. Ciaran Judge: none. Edoardo V. Savarino: none. Alexander C. Ford: none.

ETHICS COMMITTEE APPROVAL

Not required.

DATA SHARING STATEMENT

No additional data available.

Box 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 functional constipation (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 I, II, III, or IV criteria

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FIGURE LEGENDS

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

Figure 2a. Prevalence of Functional Constipation Worldwide Using the Rome I Criteria.

Figure 2b. Prevalence of Functional Constipation Worldwide Using the Rome II Criteria.

Figure 2c. Prevalence of Functional Constipation Worldwide Using the Rome III Criteria.

Figure 2d. Prevalence of Functional Constipation Worldwide Using the Rome IV Criteria.

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

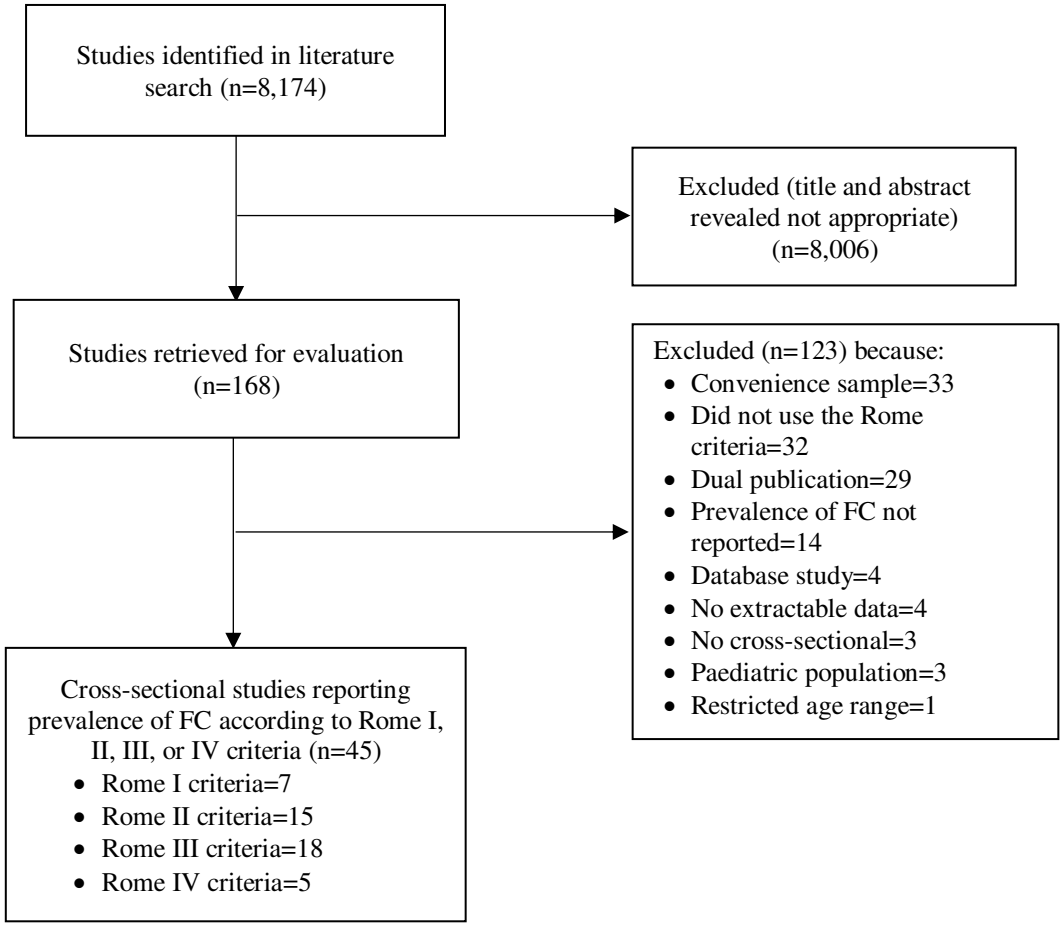

Table 1. Pooled Prevalence of Functional Constipation According to Criteria Used to Define its Presence, Questionnaire Used, and Method of Questionnaire Administration.

	Number of studies	Number of subjects	Pooled prevalence (%)	95% confidence interval	I^2	P value for χ^2
Criteria used to define FC						
Rome I	7	14,068	15.3	8.1 – 24.4	99.4%	<0.0001
Rome II	17	80,302	11.2	7.9 – 14.9	99.6%	<0.0001
Rome III	19	87,215	10.4	6.5 – 14.9	99.8%	<0.0001
Rome IV	5	101,876	10.1	8.7 – 11.6	98.2%	<0.0001
Questionnaire used						
Defined as per Rome I questionnaire	4	12,609	11.8	3.8 – 23.5	99.7%	<0.0001
Approximated Rome I using another questionnaire	3	1,459	20.5	16.9 – 24.3	66.5%	0.051
Defined as per Rome II questionnaire	11	40,883	10.5	7.7 – 13.6	98.7%	<0.0001
Approximated Rome II using another questionnaire	6	39,419	12.5	5.3 – 22.2	99.8%	<0.0001
Defined as per Rome III questionnaire	17	83,864	9.9	6.0 – 14.6	99.8%	<0.0001
Approximated Rome III using another questionnaire	1	2,162	14.6	13.1 – 16.1	*N/A	*N/A
Unclear how Rome III defined	1	1,189	16.5	14.4 – 18.7	*N/A	*N/A
Defined as per Rome IV questionnaire	5	101,876	10.1	8.7 – 11.6	98.2%	<0.0001
Method of questionnaire administration						
Rome I: self-completed questionnaire	5	10,528	12.2	6.3 – 19.7	98.9%	<0.0001

Rome I: interview-administered questionnaire	1	420	24.3	20.3 – 28.7	*N/A	*N/A
Rome I: unclear how administered	1	3,120	23.8	22.3 – 25.3	*N/A	*N/A
Rome II: self-completed questionnaire	10	62,832	11.0	6.4 – 16.7	99.7%	<0.0001
Rome II: interview-administered questionnaire	6	7,440	11.5	6.1 – 18.3	98.4%	<0.0001
Rome II: unclear how administered	1	10,030	11.2	10.6 – 11.8	*N/A	*N/A
Rome III: self-completed questionnaire	8	29,016	12.3	6.2 – 20.2	99.7%	<0.0001
Rome III: interview-administered questionnaire	9	56,712	7.4	3.3 – 12.9	99.8%	<0.0001
Rome III: unclear how administered	3	6,006	15.5	14.6 – 16.5	0.0%	0.59
Rome IV: self-completed questionnaire	3	81,054	11.2	10.4 – 12.0	92.0%	<0.0001
Rome IV: interview-administered questionnaire	3	20,822	7.3	3.8 – 11.8	99.2%	<0.0001

*N/A; not applicable, too few studies to assess heterogeneity

Table 2. Prevalence of Functional Constipation According to Sex, Age, and Socioeconomic Status for Each of the Rome Definitions.

	Rome I	**Rome II**	**Rome III**	**Rome IV**
Sex				
Number of studies	4	11	9	0
Prevalence of FC in men (95% confidence interval)	12.6 (3.1 – 27.2)	10.5 (5.8 – 16.3)	8.6 (4.2 – 14.3)	N/A
Prevalence of FC in women (95% confidence interval)	26.1 (6.5 – 52.9)	18.1 (11.1 – 26.4)	17.3 (9.0 – 27.6)	N/A
Odds ratio for women vs. men (95% confidence interval)	2.40 (2.02 – 2.86)	1.94 (1.46 – 2.57)	2.32 (1.85 – 2.92)	N/A
I^2 (P value for χ^2)	0% (0.55)	87.5% (<0.0001)	85.3% (<0.0001)	N/A
Age <45 years vs. ≥45 years				
Number of studies	1	1	2	0
Prevalence of FC in <45 years (95% confidence interval)	3.7 (3.0 – 4.5)	31.7 (28.6 – 35.0)	20.2 (9.6 – 33.6)	N/A
Prevalence of FC in ≥45 years (95% confidence interval)	3.5 (2.8 – 4.2)	27.5 (24.5 – 30.7)	20.8 (18.7 – 23.0)	N/A
Odds ratio for <45 years vs. ≥45 years (95% confidence interval)	1.06 (0.79 – 1.43)	1.22 (0.99 – 1.52)	0.99 (0.52 – 1.88)	N/A
I^2 (P value for χ^2)	N/A	N/A	90.2% (0.0014)	N/A

Age <50 years vs. ≥50 years				
Number of studies	2	3	0	0
Prevalence of FC in <50 years (95% confidence interval)	18.1 (15.8 – 20.5)	13.8 (12.6 – 15.1)	N/A	N/A
Prevalence of FC in ≥50 years (95% confidence interval)	15.8 (12.7 – 19.2)	14.8 (13.2 – 16.4)	N/A	N/A
Odds ratio for <50 years vs. ≥50 years (95% confidence interval)	1.17 (0.87 – 1.57)	0.92 (0.78 – 1.09)	N/A	N/A
I^2 (P value for χ^2)	0% (0.99)	0% (0.99)	N/A	N/A
Socioeconomic status				
Number of studies	1	4	0	0
Prevalence of FC in lower socioeconomic status (95% confidence interval)	18.8 (12.9 – 26.0)	14.9 (5.4 – 28.0)	N/A	N/A
Prevalence of FC in medium socioeconomic status (95% confidence interval)	16.1 (13.3 – 19.2)	13.9 (4.0 – 28.3)	N/A	N/A
Prevalence of FC in higher socioeconomic status (95% confidence interval)	11.8 (7.0 – 18.2)	12.0 (1.6 – 30.1)	N/A	N/A
Odds ratio for medium vs. low (95% confidence interval)	0.83 (0.51 – 1.37)	0.91 (0.78 – 1.05)	N/A	N/A
I^2 (P value for χ^2)	N/A	0% (0.65)	N/A	N/A
Odds ratio for high vs. low (95% confidence interval)	0.58 (0.28 – 1.16)	0.78 (0.57 – 1.07)	N/A	N/A

I^2 (P value for χ^2)	N/A	56.6% (0.075)	N/A	N/A

N/A; not applicable, no or too few studies.