REVIEW

Prevalence of, and Risk Factors for, Chronic Idiopathic Constipation in the Community: Systematic Review and Meta-analysis

Nicole C. Suares, MBChB¹ and Alexander C. Ford, MBChB, MD, MRCP^{1,2}

- OBJECTIVES: Chronic idiopathic constipation (CIC) is a common functional gastrointestinal disorder in the community, yet no previous systematic review and meta-analysis has estimated the global prevalence, or potential risk factors for the condition.
- METHODS: MEDLINE, EMBASE, and EMBASE Classic were searched (up to December 2010) to identify population-based studies reporting the prevalence of CIC in adults (≥15 years), according to self-report, questionnaire, or specific symptom-based criteria. The prevalence of CIC was extracted for all studies, and according to country, age, gender, socioeconomic status, and presence or absence of irritable bowel syndrome (IBS) where reported. Pooled prevalence overall, and according to study location and certain other characteristics, as well as odds ratios (ORs), with 95% confidence intervals (CIs) were calculated.
- RESULTS: Of the 100 papers evaluated, 45 reported the prevalence of CIC in 41 separate study populations, containing 261,040 subjects. Pooled prevalence of CIC in all studies was 14% (95% CI: 12–17%). The prevalence of CIC was lower in South East Asian studies, and in studies using the Rome II or III criteria. The prevalence of CIC was higher in women (OR: 2.22; 95% CI: 1.87–2.62), and increased with age and lower socioeconomic status. The prevalence was markedly higher in subjects who also reported IBS (OR: 7.98; 95% CI: 4.58–13.92), suggesting common pathogenic mechanisms.
- CONCLUSIONS: Pooled prevalence of CIC in the community was 14%, and of similar magnitude in most geographical regions. Rates were higher in women, older individuals, and those of lower socioeconomic status. Presence of IBS was strongly associated with CIC.

Am J Gastroenterol 2011; 106:1582-1591; doi:10.1038/ajg.2011.164; published online 24 May 2011

INTRODUCTION

Constipation is characterized by the difficult or infrequent passage of stool, often accompanied by straining or a sensation of incomplete evacuation. It is a common complaint in the general population, and contributes considerably to physician visits and other costs to the health service (1). Chronic idiopathic constipation (CIC) is a functional gastrointestinal disorder (FGID), and although its symptoms are similar to the above definition, there is usually no demonstrable underlying physiological abnormality (2). It is thought to be more common in women, elderly people, and those of lower socioeconomic status (3,4), and sufferers report a degree of impairment in health-related quality of life that is comparable with that for some chronic organic conditions (5). The prevalence of constipation has been reported in numerous population-based cross-sectional surveys (3,6,7), and the implicit assumption in studies such as these is that, as organic disease in the community is rare, the majority of individuals reporting symptoms compatible with constipation will have CIC. Many of these community surveys have used either self-report of symptoms or a questionnaire to diagnose the disorder. However, studies conducted over the last decade have increasingly used one of the three iterations of the Rome criteria (2,8,9), which were developed initially to aid recruitment of homogenous groups of patients into clinical trials, with the diagnosis of the various FGIDs reached via symptom-based criteria.

Another FGID with some symptoms that are common to CIC is constipation-predominant irritable bowel syndrome (IBS).

¹Leeds Gastroenterology Institute, Leeds General Infirmary, Leeds, UK; ²Leeds Institute of Molecular Medicine, University of Leeds, Leeds, UK. **Correspondence:** Alexander C. Ford, MBChB, MD, MRCP, Leeds Gastroenterology Institute, Leeds General Infirmary, D Floor, Clarendon Wing, Great George Street, Leeds LS1 3EX, UK. E-mail: alexf12399@yahoo.com

Received 8 March 2011; accepted 19 April 2011

The American Journal of GASTROENTEROLOGY

VOLUME 106 | SEPTEMBER 2011 www.amjgastro.com

Bausch Health Ireland Exhibit 2054, Page 1 of 10 Mylan v. Bausch Health Ireland - IPR2022-00722 Each of these is a distinct condition according to the Rome criteria (2), with the presence of either abdominal pain or discomfort, which are required to meet diagnostic criteria for IBS, used as the main features to distinguish between the two. Recently, however, there has been some evidence to suggest a degree of overlap between the two conditions, and a lack of stability in either diagnosis during follow-up, suggesting that IBS and CIC are not entirely separate conditions (10).

Despite a growing number of cross-sectional surveys examining the prevalence of CIC, some of which have been conducted across several countries worldwide (11,12), the prevalence of CIC according to geographical location has not been well studied to date. Nor has any single study synthesized all the available evidence to examine potential risk factors for CIC, or the degree of overlap between CIC and IBS. We have therefore conducted a systematic review and meta-analysis of the prevalence of CIC in the community to examine these issues.

METHODS

Search strategy and study selection

A search of the medical literature was conducted using MEDLINE (1950 to December 2010), EMBASE, and EMBASE Classic (1947 to December 2010) to identify population-based cohort studies, case–control studies, cross-sectional surveys, or randomized controlled trials that reported the prevalence of CIC in adults aged 15 years or over. Studies conducted among convenience samples, such as university students or hospital employees, were not eligible for inclusion. The diagnosis of CIC could be on the basis of symptoms self-reported by the individual, defined according to a questionnaire, based on the Rome I, II, or III criteria (2,8,9), or according to a physician's diagnosis. Studies were only eligible for inclusion if they contained \geq 50 individuals. Detailed eligibility criteria for study inclusion, which were defined prospectively, are provided in **Box 1**.

Studies on CIC were identified using the search terms: *constipation* or *gastrointestinal transit* (both as medical subject headings (MeSH) and as free text terms), as well as *functional constipation*, *chronic constipation*, or *idiopathic constipation* as free text terms. These were combined with the set operator AND with studies identified with the search term *prevalence* as both a MeSH and free text term. There were no language restrictions. All abstracts identified by the search were evaluated for appropriateness to the study question, and all potentially relevant papers were obtained and assessed in detail. A recursive

search of the literature was conducted using the bibliographies of all eligible studies. Foreign language papers were translated where required. Studies were assessed independently by two investigators, using pre-designed eligibility forms, according to the eligibility criteria. All disagreements were resolved by consensus.

Data extraction

Data were extracted independently by two investigators onto a Microsoft Excel spreadsheet (XP professional edition; Microsoft, Redmond, WA), with discrepancies resolved by consensus. The following data were collected for each study: type of study, year(s) conducted, country and geographical region, method of data collection (postal questionnaire, interview-administered questionnaire, face-to-face interview, telephone interview), criteria used to define CIC, symptom duration used to define the presence of CIC, total number of subjects recruited, and number of subjects with CIC. We also extracted the number of subjects with CIC according to age group, gender, socioeconomic status, and IBS symptom status, in order to examine any effect of these factors on the prevalence of CIC.

Data synthesis and statistical analysis

The proportion of individuals with CIC in each study was combined to give a pooled prevalence of CIC for all studies. Heterogeneity between studies was assessed using the l^2 statistic with a cutoff of 50% (13), and the χ^2 test with a *P* value < 0.10, used to define a statistically significant degree of heterogeneity. We planned to conduct sensitivity analyses according to geographical region, criteria used to define the presence of CIC, study publication year, validation status of the questionnaire (where used), symptom duration used to define the presence of CIC, age, gender, and IBS symptom status to examine whether this had any effect on the pooled prevalence of CIC. The prevalence of CIC was also compared according to age group, gender, socioeconomic status, and IBS symptom status using an odds ratio (OR), with a 95% confidence interval (CI).

Data were pooled using a random effects model (14), to give a more conservative estimate of the prevalence of CIC and the odds of CIC in these various groups. StatsDirect version 2.7.2 (StatsDirect, Sale, Cheshire, UK) was used to generate Forest plots of pooled prevalences and pooled ORs with 95% CIs. We planned to assess for the evidence of publication bias by applying Egger's test to funnel plots of ORs (15).

Box 1. Eligibility criteria

Cohort studies, case–control studies, cross-sectional surveys, or randomized controlled trials Recruited adults (>90% of participants aged ≥15 years) Participants recruited from the general population/community (convenience samples excluded) Reported prevalence of chronic idiopathic constipation (according to self-report, questionnaire data, specific diagnostic criteria (Rome I, II, or III criteria), or a physician's opinion) Sample size of ≥50 participants

© 2011 by the American College of Gastroenterology

The American Journal of GASTROENTEROLOGY

Bausch Health Ireland Exhibit 2054, Page 2 of 10 Mylan v. Bausch Health Ireland - IPR2022-00722



Figure 1. Flow diagram of assessment of studies identified in the systematic review and meta-analysis.

RESULTS

The search strategy identified 3,278 citations (**Figure 1**). From these we identified 100 papers that appeared to be relevant to the study question. Of these, 45 studies reported the prevalence of CIC in 41 separate adult study populations (3,6,7,11,12,16–55). Agreement between investigators for assessment of study eligibility was excellent (κ statistic=0.88). Detailed characteristics of all included studies are provided in **Table 1**.

Most studies were cross-sectional surveys, but two were casecontrol studies conducted among diabetic patients and nondiabetic controls from the general population (33,41). For the purposes of the present analysis, only data for the non-diabetic controls were extracted from these two studies. Three of the studies were multi-national surveys (11,12,25), and two of these also provided data according to each individual country studied (11,12). The pooled prevalence of CIC in all 41 studies containing 261,040 participants, using the primary definition for CIC in each study, was 14.0% (95% CI: 12.0–17.0%), with statistically significant heterogeneity between studies (I^2 =99.7%, P<0.001).

Global prevalence of CIC

The majority of studies were conducted in North America or Northern Europe. There were no identified studies conducted in

The American Journal of GASTROENTEROLOGY

South Asia, Africa, or Central America, and only a few studies from South America and the Middle East (11,12,18,40,44). The pooled prevalence of CIC according to geographical location of the study is provided in **Table 2**. There was statistically significant heterogeneity between studies in all of these analyses, but the prevalence was remarkably similar in all of the regions studied, with the lowest prevalence occurring in South East Asia (11.0%) and the highest in South America (18.0%). The prevalence according to individual country studied is shown in **Figure 2**.

Prevalence of CIC according to criteria used to define its presence

The majority of studies used a questionnaire to define the presence of CIC. Eleven studies used the Rome II criteria (18–20,23,26,28, 32,34,35,37,43), 10 used self-report of symptoms (7,28–30,37,42–45,51), six used the Rome I criteria (3,7,24,28,38,43), and only two used the Rome III criteria (42,44). The pooled prevalence of CIC according to the various criteria used to define its presence is provided in **Table 3**. The prevalence of CIC was similar with all definitions, with the exception of when the Rome II or III criteria were used to define its presence, with a prevalence of 11.0 and 6.8%, respectively.

Prevalence of CIC according to study year

Of the identified and eligible studies, seven were conducted between 1981 and 1990 (3,6,16,29,30,33,50), 16 between 1991 and 2000 (17,20,22,24,25,27,28,31,36,38,40,43,45–48), and 18 between 2001 and 2010 (11,12,18,21,23,26,32,34,35,37,39,41,42,44,49,51,52,54). The prevalence of CIC was generally lower in studies conducted between 1981 and 1990 (11.0%), compared with those conducted from 1991 to 2000, and from 2001 to 2010 (15.0%) (**Table 3**).

Prevalence of CIC according to questionnaire validation status

Of the 41 studies, 40 used a questionnaire to capture CIC symptom data, and 27 of these used a validated instrument (3,6,16–18,20–27,31,32,34–37,39,42–44,46,47,49,50). The prevalence of CIC was almost identical in studies that used a validated, compared with a non-validated questionnaire (**Table 3**).

Prevalence of CIC according to duration of symptoms

Twenty-six studies reported the duration of symptoms required to meet diagnostic criteria for CIC, with eight using 3 months (3,16,17,20,21,25,37,45), 16 using 12 months (7,11,12,23,28,29, 31,32,35,36,38,46–48,52,54), and two using both 3 and 12 months (42,43). The prevalence of CIC was only slightly higher, 15.0 vs. 13.0%, in studies that used 12 months compared with those that used 3 months (**Table 3**).

Prevalence of CIC according to age

There were 12 studies reporting the prevalence of CIC according to age, which provided extractable data (3,11,12,16,17,21,23,28, 29,32,42,43). However, due to different age bands used to report the prevalence of CIC, data available for pooling were limited. Three studies used identical age bands to report prevalence (11,12,42), and these studies were therefore pooled accordingly.

VOLUME 106 | SEPTEMBER 2011 www.amjgastro.com

Bausch Health Ireland Exhibit 2054, Page 3 of 10 Mylan v. Bausch Health Ireland - IPR2022-00722

Table 1. Onaracteristics o	i included stadio				
Study	Country	Method of data collection	Criteria used to define CIC	Sample size	Number with CIC (%)
Talley et al. (6)	USA	Postal questionnaire ^a	Questionnaire-defined	835	140 (16.8)
Talley et al. (7)			Self-reported	690	86 (12.5)
			Rome I	690	126 (18.3)
Jones and Lydeard (36)	UK	Postal questionnaireª	Questionnaire-defined	1,620	333 (20.6)
Walker et al. (50)	USA	Interview-administered questionnaireª	Questionnaire-defined	18,571	1,794 (9.7)
Drossman et al. (3)	USA	Postal questionnaire ^a	Rome I	5,430	197 (3.6)
Heaton <i>et al.</i> (30)	UK	Interview-administered questionnaire	Self-reported	1,892	452 (23.9)
Janatuinen <i>et al.</i> (33)	Finland	Postal questionnaire	Questionnaire-defined	588	107 (18.2)
Agreus et al. (16)	Sweden	Postal questionnaireª	Questionnaire-defined	1,156	92 (8.0)
Talley et al. (46)	Australia	Postal questionnaire ^a	Questionnaire-defined	99	23 (23.2)
Harari <i>et al.</i> (29)	USA	Interview-administered questionnaire	Self-reported	42,375	1,433 (3.4)
Frexinos et al. (27)	France	Postal questionnaire ^a	Questionnaire-defined	4,817	1,686 (35.0)
Ho <i>et al.</i> (31)	Singapore	Interview-administered questionnaireª	Questionnaire-defined	696	29 (4.2)
Talley et al. (47)	Australia	Postal questionnaire ^a	Questionnaire-defined	726	103 (14.2)
Enck <i>et al.</i> (25)	Multi-national	Interview-administered questionnaire ^a / telephone interview	Questionnaire-defined	5,581	564 (10.1)
Stewart et al. (45)	USA	Telephone interview	Self-reported	10,018	1,466 (14.6)
Chen <i>et al.</i> (22)	Singapore	Interview-administered questionnaire ^a	Questionnaire-defined	271	16 (5.9)
Choo et al. (24)	South Korea	Interview-administered questionnaireª	Rome I	420	102 (24.3)
Koloski <i>et al.</i> (38)	Australia	Postal questionnaire	Rome I	2,910	227 (7.8)
Koloski <i>et al.</i> (53)					
Boyce <i>et al.</i> (19)			Rome II	762	22 (2.9)
Bytzer <i>et al.</i> (20); Bytzer <i>et al.</i> (55)	Australia	Postal questionnaire ^a	Rome II	8,608	313 (3.6)
Fang <i>et al.</i> (26)	China	Self-administered questionnaireª	Rome II	1,952	73 (3.7)
Pare <i>et al.</i> (43)	Canada	Postal questionnaire ^a	Self-reported	1,149	312 (27.2)
			Rome I	1,149	192 (16.7)
			Rome II	1,149	171 (14.9)
Tangen Haug <i>et al.</i> (48)	Norway	Postal questionnaire	Questionnaire-defined	60,998	2,248 (3.7)
Walter et al. (51)	Sweden	Postal questionnaire	Self-reported	1,610	232 (14.4)
Cheng et al. (23)	Hong Kong	Telephone interview with questionnaire ^a	Rome II	3,282	458 (14.0)
Mjornheim <i>et al.</i> (41)	Sweden	Postal questionnaire	Questionnaire-defined	242	76 (31.4)
Garrigues et al. (28)	Spain	Postal questionnaire	Self-reported	349	103 (29.5)
			Rome I	349	67 (19.2)
			Rome II	349	49 (14.0)
Wang et al. (52)	China	Interview-administered questionnaire	Questionnaire-defined	2,532	292 (11.5)
Locke <i>et al.</i> (39)	USA	Postal questionnaire ^a	Questionnaire-defined	643	109 (17.0)
Aro et al. (17)	Sweden	Self-administered questionnaire ^a	Questionnaire-defined	1,001	239 (23.9)
Howell et al. (32)	Australia	Postal questionnaire ^a	Rome II	1,673	514 (30.7)
Jun <i>et al.</i> (37)	South Korea	Interview-administered questionnaire ^a	Self-reported	1,029	170 (16.5)
			Rome II	1,029	95 (9.2)
Mendoza-Sassi et al. (40)	Brazil	Interview-administered questionnaire	Questionnaire-defined	1,259	268 (21.3)

Table 1. Characteristics of included studies

Continued on following page

© 2011 by the American College of Gastroenterology

The American Journal of GASTROENTEROLOGY

Bausch Health Ireland Exhibit 2054, Page 4 of 10 Mylan v. Bausch Health Ireland - IPR2022-00722

Table 1. Continued

REVIEW

Study	Country	Method of data collection	Criteria used to define CIC	Sample size	Number with CIC (%)
Siproudhis <i>et al.</i> (54)	France	Postal questionnaire	Questionnaire-defined	7,196	1,611 (22.4)
Chang <i>et al.</i> (21)	USA	Postal questionnaire ^a	Questionnaire-defined	523	93 (17.8)
Johanson <i>et al.</i> (35)	USA	Self-administered questionnaireª	Rome II	24,090	4,680 (19.4)
Basaranoglu <i>et al.</i> (18)	Turkey	Interview-administered questionnaireª	Rome II	707	173 (24.5)
Jeong <i>et al.</i> (34)	South Korea	Interview-administered questionnaireª	Rome II	1,417	37 (2.6)
van Kerkhoven <i>et al.</i> (49)	Holland	Postal questionnaire ^a	Questionnaire-defined	1,616	230 (14.2)
Wald <i>et al.</i> (11)	Multi-national	Interview-administered questionnaire/ telephone interview	Questionnaire-defined	13,879	1,712 (12.3)
Papatheoridis <i>et al.</i> (42)	Greece	Self-administered questionnaire*	Self-reported	1,000	140 (14.0)
			Rome III	1,000	132 (13.2)
Sorouri <i>et al.</i> (44)	Iran	Interview-administered questionnaireª	Self-reported	18,180	1,145 (6.3)
			Rome III	18,180	445 (2.4)
Wald <i>et al.</i> (12)	Multi-national	Interview-administered questionnaire/ telephone interview	Questionnaire-defined	8,100	1,293 (16.0)
CIC obranic idianathic constin	ation				

^aValidated questionnaire.

The prevalence of constipation increased modestly with increasing age in these three studies (Table 4).

We also dichotomized the reported age groups for all studies. Five studies provided data according to age <45 years, or ≥45 years (3,11,12,32,42). The prevalence of CIC in those aged ≥45 years was not significantly higher than in those aged <45 years (OR: 1.10; 95% CI: 0.93–1.29), with significant heterogeneity between studies (F=74.6%, P=0.003), but no evidence of funnel plot asymmetry (Egger test, P=0.59). Seven studies provided data according to an age threshold of ≥50 years compared with <50 years (16,17,21,23,28,29,43). Again, there was no significant difference detected between the prevalence of CIC in those aged ≥50 years compared with those aged <50 years (OR: 1.16; 95% CI: 0.87–1.54), with significant heterogeneity between studies (F=87.6%, P<0.001), and evidence of funnel plot asymmetry or other small study effects (Egger test, P=0.03).

Prevalence of CIC according to gender

There were 26 studies that reported the prevalence of CIC according to the gender of participants (3,11,12,16–19,21–24,28–34,37,42–45,47,49,51). Overall, the pooled prevalence of CIC was higher in women compared with men (17.4% (95% CI: 13.4–21.8%) vs. 9.2% (95% CI: 6.5–12.2%)). The OR for CIC in women was 2.22 (95% CI: 1.87–2.62) (Figure 3), with significant heterogeneity between studies (F = 90.4%, P < 0.001), but no evidence of funnel plot asymmetry (Egger test, P=0.83).

Prevalence of CIC according to socioeconomic status

There were six studies reporting the prevalence of constipation according to socioeconomic status (11,12,23,32,43,55). When

The American Journal of GASTROENTEROLOGY

data from these studies were pooled, there was a modest increase in the prevalence of CIC in those of lower socioeconomic status, compared with those of higher socioeconomic status, but no difference between those of medium socioeconomic status and those of higher socioeconomic status (Table 5).

Prevalence of CIC according to IBS symptom status

There were five studies that collected data on both IBS and CIC and that reported the prevalence of CIC according to the IBS symptom status of participants (6,36,39,44,53). Two studies used the Manning criteria to define IBS (6,36), two the Rome I criteria (39,53), and one the Rome II criteria (44). Overall, the pooled prevalence of CIC was higher in individuals with IBS (44.0%; 95% CI: 36.0–53.0%) compared with those without (9.0%; 95% CI: 7.0–12.0%). The OR for CIC in those with IBS was 7.98 (95% CI: 4.58–13.92) (Figure 4), with significant heterogeneity between studies (I^2 =92.2%, P<0.001), but no evidence of funnel plot asymmetry (Egger test, P=0.95).

DISCUSSION

This is the first systematic review and meta-analysis of studies, to our knowledge, examining the global prevalence of CIC, risk factors for CIC, and relationship between CIC and IBS in the community. We have demonstrated a pooled prevalence of CIC across all included studies of 14%. The pooled prevalence of CIC was remarkably stable according to geographical location, though was slightly lower in South East Asian studies, and generally higher in South American studies. There were a paucity of data from the Middle East, Africa, and Central America. Similar pooled

VOLUME 106 | SEPTEMBER 2011 www.amjgastro.com

Bausch Health Ireland Exhibit 2054, Page 5 of 10 Mylan v. Bausch Health Ireland - IPR2022-00722

Table 2.	Pooled	prevalence of	CIC	according	to	geographical	location
Tuble L	i ooicu	pretuiciliee or	0.0	according		ScoBraphicar	location

	Number of studies	Number of subjects	Pooled prevalence	95% Confidence interval	/² (%)	P value for I ²
All studies	41	261,040	14.0	12.0–17.0	99.7	< 0.001
North American studies	10	105,634	14.0	9.0-20.0	99.8	< 0.001
North European studies	14	88,615	16.0	10.0-24.0	99.8	< 0.001
South European studies	3	3,349	16.0	7.0-27.0	98.1	< 0.001
Middle Eastern studies	2	18,887	14.0	2.0-36.0	N/A	N/A
South East Asian studies	11	17,699	11.0	7.0-15.0	98.3	< 0.001
South American studies	4	7,259	18.0	15.0-22.0	94.1	< 0.001
Australasian studies	5	14,016	14.0	5.0-27.0	99.6	< 0.001
Multinational studies	3	27,560	13.0	10.0-16.0	98.2	<0.001

CIC, chronic idiopathic constipation.

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



Figure 2. Prevalence of chronic idiopathic constipation according to country.

prevalence rates were also found according to definition of CIC, with the exception of the Rome III criteria, for which the prevalence was lower at around 7%. This lower prevalence with Rome III was driven by one study (44), which reported a prevalence of only 2.4%, compared with 13.2% in the other study that used these criteria (42). Studies performed in the 1980s demonstrated a slightly lower pooled prevalence of CIC, but duration of symptoms and validation status of the questionnaire used appeared to have little impact on pooled prevalence of CIC in our analyses. Data for pooled prevalence of CIC according to age, gender, and socioeconomic status support previous assertions that the condition is commoner in females, older individuals, and those of lower socioeconomic status, although ORs were only modestly increased in these groups. Finally, and most strikingly, the odds of CIC in those with IBS were almost eightfold greater than that of individuals without IBS.

This study was strengthened by our rigorous methodology. The literature search, judging of study eligibility, and data extraction were carried out by two investigators independently, with discrepancies resolved by consensus. Foreign language papers were translated where required. Use of a random effects model to pool data provided a more conservative estimate of prevalence of CIC, and publication bias was assessed using funnel plots. We were careful to include only population-based studies conducted with participants recruited from the community, who were therefore representative of the general population in each study country, in order not to inflate the pooled prevalence of CIC. This was done to ensure that the results are generalizable to the general population.

© 2011 by the American College of Gastroenterology

The American Journal of GASTROENTEROLOGY

Bausch Health Ireland Exhibit 2054, Page 6 of 10 Mylan v. Bausch Health Ireland - IPR2022-00722 duration of symptoms

	Number of	Number of	Pooled	95% Confidence	12 (%)	Pivalue for 12
	studies	subjects	prevalence	Interval	1- (76)	P value for I-
All studies	41	261,040	14.0	12.0–17.0	<i>99.7</i>	<0.001
Criteria used to define CIC						
Questionnaire-defined	22	132,949	15.0	11.0-20.0	99.7	< 0.001
Rome II	11	45,018	11.0	6.0-18.0	99.6	< 0.001
Self-reported	10	78,292	15.0	10.0-21.0	99.7	< 0.001
Rome I	6	10,948	14.0	18.0-22.0	98.9	< 0.001
Rome III	2	19,180	6.8	0.3-20.9	N/A	N/A
Study year						
1981–1990	7	70,847	11.0	6.0–16.0	99.7	<0.001
1991–2000	16	100,522	15.0	10.0-22.0	99.8	< 0.001
2001–2010	18	89,671	15.0	12.0-19.0	99.5	< 0.001
Validation status of question	naire					
Validated	27	107,092	14.0	11.0-18.0	99.6	< 0.001
Not validated	13	143,930	15.0	11.0-20.0	99.8	< 0.001
Duration of symptoms						
3 months	10	35,495	13.0	8.0-18.0	99.4	< 0.001
12 months	18	173,364	15.0	11.0-20.0	99.8	< 0.001

Table 3. Pooled prevalence of CIC according to criteria used to define its presence, study year, validation status of questionnaire, and

CIC, chronic idiopathic constipation.

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

Table 4. Pooled prevalence of CIC according to age						
Age band	Number of subjects	Pooled prevalence of CIC (95% confidence interval)	Odds ratio for CIC (95% confidence interval)			
<29 years	7,153	12.0 (10.0–14.0)	1.0			
30-44 years	7,092	15.0 (12.0–19.0)	1.20 (1.09–1.33)			
45–59 years	5,314	16.0 (11.0–21.0)	1.31 (1.09–1.58)			
≥60 years	3,443	17.0 (13.0–22.0)	1.41 (1.17–1.70)			
CIC chronic idiopathic constinution						

Limitations of this study arise from the available studies and the reporting of data within them. When calculating pooled prevalence, there was a notable absence of studies conducted in certain

lence, there was a notable absence of studies conducted in certain geographical regions making it difficult to accurately estimate true global prevalence. There was also considerable heterogeneity across all the analyses we conducted, which our pre-specified sensitivity analyses did not reveal any clear explanation for. The reasons for this, therefore, remain speculative, but may relate to individual inconsistencies and variations in the definition of constipation used in studies that defined CIC according to either self-report or on the basis of questionnaire data, differences in demographic characteristics of recruited individuals, or cultural differences.

The American Journal of GASTROENTEROLOGY

There have been two previous systematic reviews of the epidemiology of constipation conducted (56,57). The earlier of these restricted its focus to population-based studies conducted in North America, and only included 10 English language publications (56). The authors reported prevalence rates between 2 and 27%, with an average of 14.8%, and a higher prevalence with self-reported symptoms than with either the Rome I or II criteria. They also reported a higher prevalence in females (median femaleto-male ratio of 2.2:1) and those of lower socioeconomic status, while data according to age were conflicting across the various studies they identified. The second systematic review, conducted in 2008, included epidemiological studies conducted in Europe and Oceania (57). However, the authors employed less stringent inclusion criteria, accommodating convenience samples in their review. They reported a mean prevalence of constipation in all studies of 22%, while the mean prevalence in Europe was 17%, and that in Oceania was 15% and, as with our study, there was a female preponderance of symptoms. Other potential risk factors were not analyzed systematically by the authors.

While relatively few of the studies identified in our literature search collected data on prevalence of CIC according to IBS symptom status, the five studies that did report these data showed a marked increase in prevalence of CIC in those with IBS compared with those without (6,36,39,44,53). The issue of overlap between constipation-predominant IBS and CIC has been examined in

VOLUME 106 | SEPTEMBER 2011 www.amjgastro.com

Bausch Health Ireland Exhibit 2054, Page 7 of 10 Mylan v. Bausch Health Ireland - IPR2022-00722



Odds ratio meta-analysis plot [random effects]

Figure 3. Pooled odds ratio for chronic idiopathic constipation in women compared with men.

1.32 (1.11-1.57)

status			
Socio- economic status	Number of subjects	Pooled prevalence of CIC (95% confidence interval)	Odds ratio for CIC (95% confidence interval)
High	8,054	14.0 (8.0-22.0)	1.0
Medium	14,515	15.0 (8.0-23.0)	1.01 (0.92-1.10)

Table 5 Peoled provalence of CIC according to secioeconomic

Low 10,719 18.0 (12.0–25.0)

CIC, chronic idiopathic constipation.

detail recently, in a study that evaluated the ability of the Rome II criteria to distinguish between the two disorders (10). The authors suspended the mutual exclusivity of the two sets of diagnostic crite-

ria, and reported that this led to significant overlap between them, implying that constipation-predominant IBS and CIC may be different subgroups within the same disorder. Our data support this theory, as do the fact that newer therapies that are effective for the treatment of CIC, such as lubiprostone and linaclotide (58–60), also appear to be of benefit in constipation-predominant IBS (61,62).

The findings of this study have implications for both future research and clinical practice. The prevalence of constipation in certain geographical regions, such as Africa, should be studied to enable the global prevalence of CIC to be calculated with greater precision. Population-based studies using the Rome III criteria to define CIC remain scarce. Extracting and analyzing study data on the prevalence of CIC has emphasized the magnitude of this disorder within the community, and thus the implications for health services worldwide. Health-seeking behavior in those affected results in 2.5 million health visits per year in North

The American Journal of GASTROENTEROLOGY

Bausch Health Ireland Exhibit 2054, Page 8 of 10 Mylan v. Bausch Health Ireland - IPR2022-00722



Odds ratio meta-analysis plot [random effects]

Figure 4. Pooled odds ratio for chronic idiopathic constipation in individuals with irritable bowel syndrome compared with those without.

America alone, with a third of these in primary care, leading to significant costs to the health service (63).

Although an association between IBS and CIC has been suggested, the reasons for this are not fully understood. Continued research in this area should focus on longer follow-up and reassessment of participants to support the data from Wong et al. (10) that sufferers of the two disorders may undergo 'switching' of symptoms some months after initial diagnosis. The higher rates of constipation in those with IBS compared with those without, and variations in prevalence depending on definitions used, highlight the need for consistent, and perhaps more accurate, diagnostic criteria. The Rome criteria for functional bowel disorders have been reached through a consensual process, with the third iteration published in 2006 (2). Despite their laudable aims, and the fact that they are accepted as the current gold standard for the diagnosis of the various FGIDs, these criteria have never been subjected to rigorous validation studies, and this issue needs to be addressed in order to assess their true accuracy. In addition, physicians should recognize the potential for overlap between IBS and CIC, and consider the implications of this in their management, particularly where therapies fail.

In conclusion, this systematic review and meta-analysis has demonstrated a global prevalence of CIC of 14%. Rates were higher according to self-report or questionnaire compared with more objective measures, such as the Rome II or III criteria. The condition was commoner in women, older individuals, and those of lower socioeconomic status. Finally, there was a significantly higher prevalence of CIC individuals with IBS, once again calling into question potentially artificial divisions between the FGIDs.

ACKNOWLEDGMENTS

We thank Professor Paul Moayyedi for producing **Figure 2** of the article for us, and Dr Cathy Yuhong Yuan for assisting us with the translation of foreign language articles.

The American Journal of GASTROENTEROLOGY

CONFLICT OF INTEREST

Guarantor of the article: Alexander C. Ford, MBChB, MD, MRCP. **Specific author contributions:** Conceived and drafted the study, collected all data, drafted the manuscript, and commented on drafts of the paper: Nicole C. Suares and Alexander C. Ford; analyzed and interpreted the data: Alexander C. Ford. Both authors have approved the final draft of the manuscript.

Financial support: None.

Potential competing interests: None.

REFERENCES

- Choung RS, Branda ME, Chitkara D et al. Longitudinal direct medical costs associated with constipation. Aliment Pharmacol Ther 2011;33:251–60.
- Longstreth GF, Thompson WG, Chey WD et al. Functional bowel disorders. Gastroenterology 2006;130:1480–91.
- Drossman DA, Li Z, Andruzzi E et al. U.S. householder survey of functional gastrointestinal disorders. Prevalence, sociodemography, and health impact. Dig Dis Sci 1993;38:1569–80.
- Everhart JE, Go VL, Johannes RS *et al.* A longitudinal survey of self-reported bowel habits in the United States. Dig Dis Sci 1989;34:1153–62.
- Wald A, Scarpignato C, Kamm MA *et al.* The burden of chronic constipation on quality of life: results of a multinational survey. Aliment Pharmacol Ther 2007;26:227–36.
- Talley NJ, Zinsmeister AR, Van Dyke C et al. Epidemiology of colonic symptoms and the irritable bowel syndrome. Gastroenterology 1991;101:927–34.
- Talley NJ, Weaver AL, Zinsmeister AR et al. Functional constipation and outlet delay: a population-based study. Gastroenterology 1993;105:781–90.
- Thompson WG, Longstreth GF, Drossman DA et al. Functional bowel disorders and functional abdominal pain. Gut 1999;45 (Suppl II): II43–7.
- Whitehead WE, Chaussade S, Corazziari E et al. Report of an international workshop on management of constipation. Gastroenterol Int 1991;4: 99–113.
- Wong RK, Palsson O, Turner MJ et al. Inability of the Rome III criteria to distinguish functional constipation from constipation-subtype irritable bowel syndrome. Am J Gastroenterol 2010;105:2228–34.
- Wald A, Scarpignato C, Mueller-Lissner S *et al.* A multinational survey of prevalence and patterns of laxative use among adults with self-defined constipation. Aliment Pharmacol Ther 2008;28:917–30.

VOLUME 106 | SEPTEMBER 2011 www.amjgastro.com

Bausch Health Ireland Exhibit 2054, Page 9 of 10 Mylan v. Bausch Health Ireland - IPR2022-00722

- with self-defined constipation in South America and Asia: a comparison of six countries. Aliment Pharmacol Ther 2010;31:274–84.
 13. Higgins JPT, Thompson SG, Deeks JJ et al. Measuring inconsistency in
- Higgins JP1, Hompson SG, Deeks JJ et al. Measuring inconsistency in meta-analyses. Br Med J 2003;327:557–60.
- DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials 1986;7:177–88.
- 15. Egger M, Davey-Smith G, Schneider M *et al.* Bias in meta-analysis detected by a simple, graphical test. Br Med J 1997;315:629–34.
- Ágreus L, Svardsudd K, Nyren O *et al.* The epidemiology of abdominal symptoms: prevalence and demographic characteristics in a Swedish adult population. Scand J Gastroenterol 1994;29:102–9.
- Aro P, Storskrubb T, Ronkainen J et al. Peptic ulcer disease in a general adult population. The Kalixanda study: a random population-based study. Am J Epidemiol 2006;163:1025–34.
- Basranoglu M, Celebi S, Ataseven H et al. Prevalence and consultation behavior of self-reported rectal bleeding by face-to-face interview in an Asian community. Digestion 2008;77:10–5.
- Boyce PM, Talley NJ, Burke C et al. Epidemiology of the functional gastrointestinal disorders diagnosed according to Rome II criteria: an Australian population-based study. Intern Med J 2005;36:28–36.
- Bytzer P, Talley NJ, Leemon M et al. Prevalence of gastrointestinal symptoms associated with diabetes mellitus. Arch Intern Med 2001;161:1989–96.
- Chang JY, Locke GR, Schleck CD et al. Risk factors for chronic constipation and a possible role of analgesics. Neurogastroenterol Motil 2007;19:905–11.
- Chen LY, Ho KY, Phua KH. Normal bowel habits and prevalence of functional bowel disorders in Singaporean adults—findings from a community based study in Bishan. Singapore Med J 2000;41:255–8.
- Cheng C, Chan AOO, Hui WM *et al.* Coping strategies, illness perception, anxiety and depression of patients with idiopathic constipation: a population-based study. Aliment Pharmacol Ther 2003;18:319–26.
- 24. Choo KY, Choi MG, Choi H *et al.* The prevalence of gastrointestinal symptoms in a rural community in Korea. Korean J Gastrointest Motil 2000;6:31–43.
- Enck P, Dubois D, Marquis P. Quality of life in patients with upper gastrointestinal symptoms: Results from the domestic/international gastroenterology surveillance study (DIGEST). Scand J Gastroenterol 1999; 34 (Suppl 231): 48–54.
- Fang X, Lu S, Pan G. An epidemiologic study of bowel habit in adult nonpatient population in Beijing area. Natl Med J China 2001;81:1287–90.
- Frexinos J, Denis P, Allemand H et al. Descriptive study of functional digestive symptoms in the French general population. Gastroenterol Clin Biol 1998;22:785–91.
- Garrigues V, Galvez C, Ortiz V et al. Prevalence of constipation: agreement among several criteria and evaluation of the diagnostic accuracy of qualifying symptoms and self-reported definition in a population-based survey in Spain. Am J Epidemiol 2004;159:520–6.
- Harari D, Gurwitz JH, Avorn J et al. Bowel habit in relation to age and gender. Findings from the National Health Interview Survey and clinical implications. Arch Intern Med 1996;156:315–20.
- Heaton KW, Cripps HA. Straining at stool and laxative taking in an English population. Dig Dis Sci 1993;38:1004–8.
- Ho KY, Kang JY, Seow A. Prevalence of gastrointestinal symptoms in a multiracial Asian population, with particular reference to reflux-type symptoms. Am J Gastroenterol 1998;93:1816–22.
- 32. Howell SC, Quine S, Talley NJ. Low social class is linked to upper gastrointestinal symptoms in an Australian sample of urban adults. Scand J Gastroenterol 2006;41:657–66.
- Janatuinen E, Pikkarainen P, Laakso M et al. Gastrointestinal symptoms in middle-aged diabetic patients. Scand J Gastroenterol 1993;28:427–32.
- Jeong J-J, Choi M-G, Cho Y-S *et al.* Chronic gastrointestinal symptoms and quality of life in the Korean population. World J Gastroenterol 2008;14:6388–94.
- 35. Johanson JF, Kralstein J. Chronic constipation: a survey of the patient perspective. Aliment Pharmacol Ther 2007;25:599–608.
- Jones R, Lydeard S. Irritable bowel syndrome in the general population. Br Med J 1992;304:87–90.
- Jun DW, Park HY, Lee OY *et al.* A population-based study in bowel habits in a Korean community: prevalence of functional constipation and self-reported constipation. Dig Dis Sci 2006;51:1471–7.
- Koloski NA, Talley NJ, Boyce PM. The impact of functional gastrointestinal disorders on quality of life. Am J Gastroenterol 2000;95:67–71.

© 2011 by the American College of Gastroenterology

- Locke GR III, Zinsmeister AR, Fett SL *et al.* Overlap of gastrointestinal symptom complexes in a US community. Neurogastroenterol Motil 2005;17:29–34.
- Mendoza-Sassi R, Beria JU, Fiori N et al. Prevalence of signs and symptoms, associated sociodemographic factors and resulting actions in an urban center in Southern Brazil. Rev Panam Salud Publica 2006;20: 22–8.
- Mjornheim A-C, Finizia C, Blohme G et al. Gastrointestinal symptoms in type 1 diabetic patients, as compared to the general population. Digestion 2003;68:102–8.
- Papatheoridis GV, Vlachogiannakos J, Karaitianos I et al. A Greek survey of community prevalence and characteristics of constipation. Eur J Gastroenterol Hepatol 2010;22:354–60.
- Pare P, Ferrazzi S, Thompson WG et al. An epidemiological survey of constipation in Canada: definitions, rates, demographics, and predictors of health care seeking. Am J Gastroenterol 2001;96:3130–7.
- Sorouri M, Pourhoseingholi MA, Vahedi M et al. Functional bowel disorders in an Iranian population using Rome III criteria. Saudi J Gastroenterol 2010;16:154–60.
- Stewart WF, Liberman JN, Sandler RS *et al*. Epidemiology of constipation (EPOC) study in the United States: relation of clinical subtypes to sociodemographic features. Am J Gastroenterol 1999;94:3530–40.
- 46. Talley NJ, Boyce PM, Owen BK *et al.* Initial validation of a bowel symptom questionnaire and measurement of chronic gastrointestinal symptoms in Australians. Aust NZ J Med 1995;25:302–8.
- Talley NJ, Boyce P, Jones M. Identification of distinct upper and lower gastrointestinal symptom groupings in an urban population. Gut 1998; 42:690–5.
- Tangen Haug T, Mykeluten A, Dahl AA. Are anxiety and depression related to gastrointestinal symptoms in the general population? Scand J Gastroenterol 2002;37:294–8.
- van Kerkhoven LAS, Eikendal T, Laheij RJ *et al.* Gastrointestinal symptoms are still common in a general Western population. Neth J Med 2008;66: 18–22.
- Walker EA, Katon WJ, Jemelka RP *et al.* Comorbidity of gastrointestinal complaints, depression, and anxiety in the epidemiologic catchment area (ECA) study. Am J Med 1992;92 (Suppl 1A): 26S–30S.
- Walter S, Hallbook O, Gotthard R *et al.* A population-based study on bowel habits in a Swedish community: prevalence of faecal incontinence and constipation. Scand J Gastroenterol 2002;37:911–6.
- Wang J-H, Luo J-Y, Dong L *et al.* Epidemiology of gastroesophageal reflux disease: a general population-based study in Xi'an of Northwest China. World J Gastroenterol 2004;10:1647–51.
- 53. Koloski NA, Talley NJ, Boyce PM. Epidemiology and health care seeking in the functional GI disorders: a population-based study. Am J Gastroenterol 2002;97:2290–9.
- 54. Siproudhis L, Pigot F, Godeberge P *et al*. Defecation disorders: a French population survey. Dis Colon Rectum 2006;49:219–27.
- Bytzer P, Howell S, Leemon M et al. Low socioeconomic class is a risk factor for upper and lower gastrointestinal symptoms: a population based study in 15,000 Australian adults. Gut 2001;49:66–72.
- Higgins PDR, Johanson JF. Epidemiology of constipation in North America: asystematic review. Am J Gastroenterol 2004;99:750–9.
- 57. Peppas G, Alexiou VG, Mourtzoukou E *et al.* Epidemiology of constipation in Europe and Oceania: a systematic review. BMC Gastroenterol 2008;8:5.
- Ford AC, Suares NC. Effect of laxatives and pharmacological therapies in chronic idiopathic constipation: systematic review and meta-analysis. Gut 2011;60:209–18.
- 59. Johanson JF, Morton D, Geene J *et al.* Multicenter, 4-week, double-blind, randomized, placebo-controlled trial of lubiprostone, a locally-acting type-2 chloride channel activator, in patients with chronic constipation. Am J Gastroenterol 2008;103:170–7.
- Lembo AJ, Kurtz CB, MacDougall JE et al. Efficacy of linaclotide for patients with chronic constipation. Gastroenterology 2010;138:886–95.
- 61. Johanson JF, Drossman DA, Panas R *et al.* Clinical trial: phase 2 study of lubiprostone for irritable bowel syndrome with constipation. Aliment Pharmacol Ther 2008;27:685–96.
- 62. Johnston JM, Kurtz CB, MacDougall JE et al. Linaclotide improves abdominal pain and bowel habits in a phase IIb study of patients with irritable bowel syndrome and constipation. Gastroenterology 2010;139:1877–86.
- Sonnenberg A, Koch TR. Physician visits in the United States for constipation: 1958–1986. Dig Dis Sci 1989;34:606–11.

The American Journal of GASTROENTEROLOGY

Bausch Health Ireland Exhibit 2054, Page 10 of 10 Mylan v. Bausch Health Ireland - IPR2022-00722