Normative Values for Colonic Transit Time and Patient Assessment of Constipation in Adults With Functional Constipation: Systematic Review With Meta-Analysis

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ABSTRACT: Availability of normative patient outcome data may assist in designing experiments and estimating sample sizes. The purpose of this review was to determine normative ranges for colonic transit time (CTT), Patient Assessment of Constipation-Symptoms (PAC-SYM), and Patient Assessment of Constipation-Quality of Life (PAC-QOL) in adults diagnosed with functional constipation per Rome III guidelines. Pooled estimates were derived from random-effects meta-analysis. Meta-regression was used to explore sources of heterogeneity among studies. A total of 24 studies (3786 patients) were included in the review. In 10 studies with 1119 patients, pooled CTT was 58 hours (95% confidence interval [CI]: 50-65 hours). Publication bias was not evident (Egger $P = .51$); heterogeneity was high ($I^2 = 92\%$, $P < .001$). In meta-regression, geographical location explained 57% of the between-study variance, with CTT significantly longer in studies conducted in Europe (71 hours) compared with Asia (49 hours) or the Americas (44 hours). In 9 studies with 2061 patients, pooled PAC-SYM was 1.70 (95% CI: 1.58-1.83). Publication bias was not evident (Egger $P = .44$). Heterogeneity was high ($I^2 = 90\%$, $P < .001$); however, no study or patient factor influenced PAC-SYM in meta-regression. In 12 studies with 1805 patients, pooled PAC-QOL was 1.97 (95% CI: 1.70-2.24). Publication bias was not evident (Egger $P = .28$); heterogeneity was high ($I^2 = 98\%$, $P < .001$). In meta-regression, age explained 52% of the between-study variance, with older age associated with lower PAC-QOL scores. Overall, in adults diagnosed with functional constipation per Rome III criteria, significant heterogeneity in CTT, PAC-SYM, and PAC-QOL exists among studies. Variability among studies may be explained by geography and patient factors.

KEYWORDS: Colonic transit, constipation, functional, meta-analysis, patient assessment, systematic review, Rome III

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Introduction

Functional constipation (FC) is a common disorder of colonic or anorectal function affecting 14% of adults worldwide.[1] Functional constipation is responsible for a large economic burden[2] and decreased quality of life[3] in affected individuals. Although the Rome III Diagnostic Criteria[4] were developed to improve standardization of diagnosis among functional gastrointestinal disorders, patients with FC present a range of different symptoms, some of which overlap with other functional bowel disorders.[5] Variability in patient symptomatology may be problematic when designing clinical trials focused on FC therapies because estimating baseline symptom severity with reasonable accuracy is necessary for power analysis and sample size calculations. In accordance with International Council for Harmonisation E6 guidance,[6] normative test values for outcomes should be established prior to conducting a clinical trial. We previously published a systematic review and meta-analysis that established reference ranges for stool frequency and form values in patients with FC.[7] Colonic transit time (CTT), Patient Assessment of Constipation-Symptoms (PAC-SYM), and Patient Assessment of Constipation-Quality of Life (PAC-QOL) are also common end points in FC clinical trials. An integral component of power analysis calculations in clinical trials is accurate estimation of the pretreatment mean and variability for an outcome. Furthermore, factors that may introduce variation to these estimates should be identified to appropriately refine study designs and appropriate inclusion criteria. Therefore, the objective of this systematic review and meta-analysis was to determine normative ranges for CTT, PAC-SYM, and PAC-QOL in adults diagnosed with FC per Rome III criteria.

Methods

Literature search

This study was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).[8] We systematically searched Medline (including in-process citations), Embase, and Scopus databases for studies, regardless of study design, that reported CTT, PAC-SYM, or PAC-QOL in adults diagnosed with FC using Rome III criteria. Search terms included "bowel function," "chronic constipation," "constipat*," "functional constipation," "functional gastrointestinal disorder," "idiopathic constipation," and "Rome III." We also manually searched the Directory of Open Access Journals, Google Scholar, and the reference lists of included papers and other relevant meta-analyses. Searches were restricted to papers published since

2006, which coincides with development of the Rome III guidelines. The final search was conducted in April 2017.

Study selection and data extraction

Two researchers independently selected studies for inclusion in the review. Disagreements were resolved by consensus. Titles and abstracts were screened to exclude all non-English papers, review articles, commentaries, letters, case reports, and obviously irrelevant manuscripts. Full texts of the remaining manuscripts were retrieved and reviewed. Studies were included that enrolled patients with FC per Rome III criteria and reported CTT, PAC-SYM, or PAC-QOL. Studies were excluded if patients were less than 18 years of age; FC was secondary to disease, surgery, or medication use; Rome III diagnostic criteria were not applied; or Rome III diagnostic criteria were modified to additionally include CTT thresholds for study inclusion. An initial database was developed, pilot tested, and refined to maintain consistency with outcomes reported in the literature. Data were extracted from eligible peer-reviewed articles by one researcher and then verified by a second researcher. Data extraction discrepancies were resolved by consensus. Baseline outcome data were extracted from longitudinal studies. In studies with multiple groups, baseline data from each group were pooled into a single estimate for each outcome.

Outcomes

Main outcomes were CTT, PAC-SYM, and PAC-QOL. Colonic transit time was preferentially extracted from studies that used radiopaque markers or wireless motility capsule. Studies that reported transit geometric mean at specific time intervals were excluded given different units of measure. The PAC-SYM is a 12-question survey that comprised 3 subscales (stool symptoms, rectal symptoms, and abdominal symptoms) that measures the severity of constipation symptoms over the past 2 weeks.[9] For each question, patients are asked to rate symptom severity as absent (0), mild (1), moderate (2), severe (3), and very severe (4). The range of possible scores on this questionnaire is 0 to 48, with higher scores indicative of greater symptom severity. The PAC-QoL is a 28-question survey that measures the impact that constipation has on daily life over the past 2 weeks. The questions comprised 4 subscales (worries and concerns, physical discomfort, psychosocial discomfort, and satisfaction) and an overall scale.[10] For each question, patients are asked to rate the impact of constipation on quality of life using a 0 to 4 scale, where higher scores represent a greater burden. The range of possible scores on this questionnaire is 0 to 112, with higher scores indicative of a greater burden of constipation on quality of life. The PAC-SYM and PAC-QOL total scores were normalized to a common 0 to 4 scale for analysis purposes.

Data analysis

For each outcome, the pooled estimate and 95% confidence interval (CI) were calculated using a random-effects model given the a priori assumption that outcome estimates among studies were heterogeneous. A forest plot was used to illustrate the individual study findings and the random-effects meta-analysis results. Publication bias was visually assessed with funnel plots (not shown) and quantitatively assessed using the Egger regression test.[11] We assessed heterogeneity with the I^2 statistic, which reflects the amount of heterogeneity among studies in relation to sampling variation; I^2 values of ≤25%, 50%, and ≥75% represent low, moderate, and high heterogeneity, respectively.[12] A random-effects meta-regression using the method of Knapp and Hartung[13] was undertaken to examine the impact of moderator variables on outcome estimates using regression-based techniques. *P* values were 2-sided with a significance level <.05. Statistical analyses were performed using Comprehensive Meta-Analysis version 3.3 (Biostat, Englewood, NJ, USA).

Results

Study selection

After screening 426 records for eligibility, 24 studies representing 3786 unique patients were included in the meta-analysis.[5,14-36] The most common reasons for study exclusion were attributable to absence of main outcome reporting or Rome III FC diagnosis. A flow diagram of study identification and selection is shown in Figure 1.

Study and patient characteristics

Median patient characteristic values were age 47 (range: 23-76) years, 80% women (range: 0%-100%), body mass index 24 (range: 23-27) kg/m^2, and 8 years symptom duration (range: 1-17 years), with the latter 2 variables reported inconsistently among studies. Functional constipation was diagnosed by a physician in 15 (63%) studies or via questionnaire only in 9 (37%) studies. Colonic transit was assessed by the Bouchoucha method[37] in 5 studies, the Metcalf method[38] in 2 studies, custom radiopaque marker ingestion protocols in 2 studies, and wireless motility capsule in 1 study (Table 1).

Colonic transit time

In 10 studies with 1119 patients,[5,15,17-19,28-30,32,35] pooled CTT was 58 hours (95% CI: 50-65 hours) (Figure 2). Publication bias was not evident (Egger $P = .51$). Heterogeneity in CTT was high among studies ($I^2 = 92\%$, $P < .001$). In meta-regression, geographical location explained 57% of the between-study variance (Figure 3). Pooled CTT was significantly longer in studies performed in Europe (71 hours) compared with Asia (49 hours) or the Americas (44 hours). No other study or patient factor influenced CTT (Table 2).

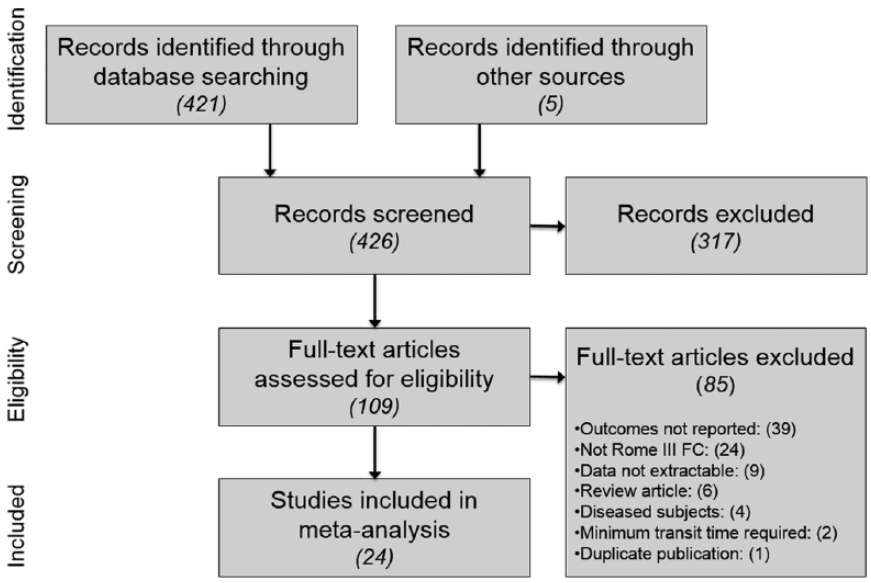

Figure 1. Study flow diagram. FC indicates functional constipation.

Patient Assessment of Constipation–Symptoms

In 9 studies with 2061 patients,[16,17,20,23,25-27,34,36] pooled PAC-SYM was 1.70 (95% CI: 1.58-1.83) (Figure 4). Publication bias was not evident (Egger $P = .44$). Heterogeneity in PAC-SYM was high among studies ($I^2 = 90\%$, $P < .001$). In meta-regression, no study or patient factor influenced PAC-SYM (Table 2).

Patient Assessment of Constipation–Quality of Life

In 12 studies with 1805 patients,[14,16,17,21,22,24-26,31,33,34,36] pooled PAC-QOL was 1.97 (95% CI: 1.70-2.24) (Figure 5). Publication bias was not evident (Egger $P = .28$). Heterogeneity in PAC-QOL was high among studies ($I^2 = 98\%$, $P < .001$). In meta-regression, age explained 52% of the between-study variance where older age was associated with lower PAC-QOL scores (Figure 6). No other study or patient factor influenced PAC-QOL (Table 2).

Discussion

To our knowledge, this is the first meta-analysis that reports pooled CTT, PAC-SYM, or PAC-QOL values in patients diagnosed with FC per Rome III guidelines. The main findings of this systematic review and meta-analysis were that despite the use of consistent diagnostic guidelines for FC, significant heterogeneity in CTT, PAC-SYM, and PAC-QOL exists among studies. In our analysis, CTT was significantly associated with geography and PAC-QOL was inversely associated with patient age; no covariates were associated with PAC-SYM.

While the pooled mean for CTT was 58 hours, the reported mean in individual studies ranged from 41 to 88 hours. The finding that CTT was notably higher in European studies should be interpreted cautiously. On one hand, it is plausible that the association of geography on CTT is influenced by factors that were not measured in this review such as ethnicity, diet, activity, and stress levels. Another plausible explanation for this finding is due to cultural or geographic differences in interpretation and reporting of patient symptoms. On the other hand, the stability of these estimates may be questionable given the inclusion of only 5 European studies and 5 non-European studies that reported CTT.

A limitation of the Rome III guidance for FC is that there is no delineation of rapid, normal, and slow transit. In fact, in the American Gastroenterological Association technical review on constipation, the subset of patients with slow-transit constipation is not considered to be truly functional.[39] Furthermore, accurate diagnosis is complicated by the significant overlap of symptoms in those with FC and irritable bowel syndrome.[40] Clinical trials of FC treatments that use CTT as a primary end point may benefit by additionally stipulating minimum CTT thresholds for study entry. Although such a design may limit generalizability of findings, it could exclude patients with normal transit and presumably little potential for further improvement.

Pooled mean patient assessment values were 1.7 for PAC-SYM and 2.0 for PAC-QOL. For reference, these questionnaires are scored from 0 to 4, where a higher value corresponds to worse symptom severity and constipation-specific quality of life, respectively. These data suggest that patient assessment total scores may not accurately reflect the burden of FC. Given the heterogeneous nature of FC and that the patient assessment questionnaires comprise multiple domains, these total scores may have limited responsiveness to therapy in patients who exhibit worse scores in some, but not all, subdomains of these questionnaires. As with CTT, the responsiveness of PAC-SYM and PAC-QOL to treatment may be somewhat blunted given that the pooled total scores do not suggest severe patient burden.

Table 1. Study and patient characteristics.

STUDY	COUNTRY	N	AGE, Y	FEMALE, %	BMI, KG/M^2	SYMPTOM DURATION, Y	PHYSICIAN DIAGNOSIS	REPORTED OUTCOME		
								CTT	PAC-SYM	PAC-QOL
Abbott et al[14]	US	100	46	75	—	—	No	No	No	Yes
Bazzocchi et al[15]	Italy	29	40	86	—	—	Yes	Yes[a]	No	No
Bellini et al[16]	Italy	549	53	79	[24]	[>10]	Yes	No	Yes	Yes
Belvaux et al[17]	France	11	[49]	100	[25]	[>10]	Yes	Yes[a]	Yes	Yes
Bouchoucha et al[18]	France	151	43	74	25	[15]	Yes	Yes[a]	No	No
Camilleri et al[19]	US	158	43	87	—	—	No	Yes[a]	No	No
Choopani et al[20]	Iran	35	48	91	27	—	No	No	Yes	No
Da et al[21]	China	67	37	81	—	10	No	No	No	Yes
Dupont et al[22]	France	244	42	100	24	—	No	No	No	Yes
Fateh et al[23]	Iran	60	23	0	—	1	No	No	Yes	No
Gürsen et al[24]	Turkey	50	39	92	24	8	Yes	No	No	Yes
Iqbal et al[25]	UK	20	39	80	—	6	Yes	No	Yes	Yes
Jiang et al[26]	China	126	51	72	—	—	No	No	Yes	Yes
Neri et al[27]	Italy	878	50	80	24	17	Yes	No	Yes	No
Park et al[28]	Korea	88	[56]	[55]	—	—	Yes	Yes[b]	No	No
Polymeros et al[29]	Greece	39	56	87	24	—	Yes	Yes[a]	No	No
Rao et al[30]	US	27	71	52	—	—	Yes	Yes[c]	No	No
Ruiz-López and Coss-Adame[31]	Mexico	25	51	76	—	—	No	No	No	Yes
Saberi et al[32]	Iran	52	37	81	—	[3]	Yes	Yes[a]	No	No
Shekhar et al[5]	UK	11	38	100	23	—	Yes	Yes[d]	No	No
Wong et al[33]	US	231	76	70	—	—	Yes	No	No	Yes
Yiannakou et al[34]	International[e]	370	58	0	—	9	Yes	No	Yes	Yes
Zhang et al[35]	China	553	42	48	—	5	Yes	Yes[d]	No	No
Zhang et al[36]	China	12	60	67	—	—	No	No	Yes	Yes

Abbreviations: CTT, colonic transit time; PAC-QOL, Patient Assessment of Constipation-Quality of Life; PAC-SYM, Patient Assessment of Constipation-Symptoms.
The values in brackets represent estimated values.
[a]Assessed by Bouchoucha method.[37]
[b]Assessed by Metcalf method.[38]
[c]Assessed by wireless motility capsule.
[d]Assessed by custom radiopaque marker ingestion protocol.
[e]European study.

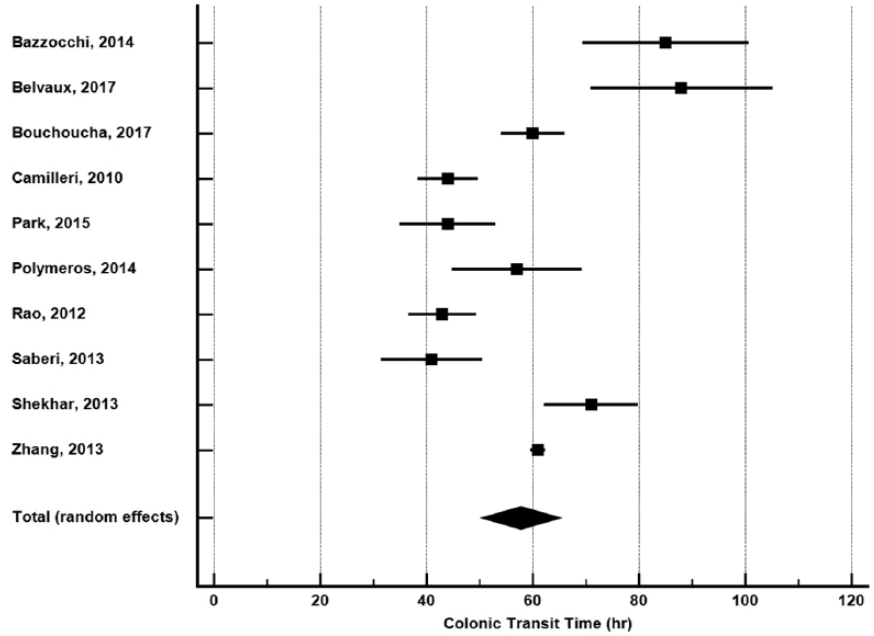

Figure 2. Colonic transit time in adults with functional constipation. Colonic transit time estimates from random-effects meta-analysis. The mean and 95% confidence interval are plotted for each study. The pooled estimate is represented by the diamond apex (58 hours) and the 95% confidence interval is represented by the diamond width (50-65 hours). Publication bias: Egger $P = .51$. Heterogeneity: $I^2 = 92\%$, $P < .001$.

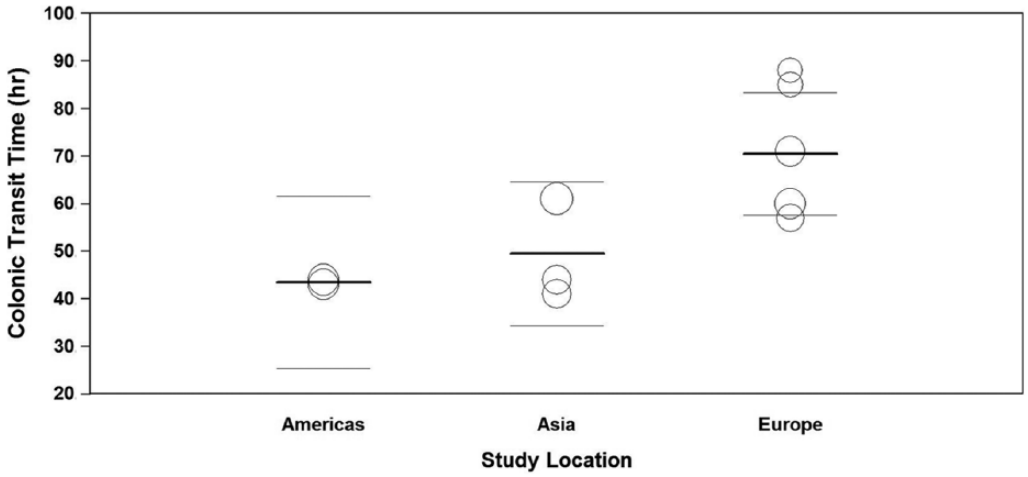

Figure 3. Meta-regression of relationship between geographic location and colonic transit time in adults with functional constipation. Percentage of variance in transit time explained by geography = 57%, $P = .04$. Pairwise comparisons: Europe vs Asia, $P = .04$; Europe vs Americas, $P = .02$. Open circles represent values of individual studies where circle size is proportional to the study weight in the random-effects model. Thick lines represent the pooled mean in each group. Thin lines represent the 95% confidence interval of the pooled mean in each group.

The results of this meta-analysis may be of benefit in the design of future clinical trials on FC. Power analyses and sample size calculations must consider not only the anticipated effect size of treatment but also the baseline mean and the variability around the mean. Our results suggest that patients diagnosed with FC per Rome III guidelines present with only modest CTT delays and constipation-specific complaints using standard questionnaires. Responsiveness of these outcomes may be somewhat limited unless patient entry guidelines are tailored to select those with more severe baseline symptoms.

This meta-analysis was associated with several limitations. Unreported confounding factors such as temporal symptoms, psychological issues, stress levels, diet, hydration, physical activity, and medical history may have influenced outcomes. The results presented here are applicable to adults diagnosed with FC using Rome III guidelines; however, generalizability of these results to constipated adults diagnosed using other methods is unknown. The number of included studies reporting each outcome was minimally sufficient to reliably assess publication bias and sources of heterogeneity. We also excluded body mass index and symptom duration as covariates in meta-regression due to

Table 2. Meta-regression of study-related and patient-related factors on colonic transit time and patient assessment of constipation.

COVARIATE	UNIT OF MEASURE	CTT			PAC-SYM			PAC-QOL		
		INTERCEPT[a]	SLOPE (95% CI)[b]	*P*	INTERCEPT[a]	SLOPE (95% CI)[b]	*P*	INTERCEPT[a]	SLOPE (95% CI)[b]	*P*
Geography	Americas	43.5	Reference		—	—	—	1.487	Reference	
	Asia	43.5	6.0 (−17.6 to 29.6)	.57	1.622	Reference		1.487	0.772 (−0.255 to 1.800)	.12
	Europe	43.5	27.0 (4.8–49.2)	.02	1.622	0.203 (−0.286 to 0.692)	.36	1.487	0.549 (−0.441 to 1.538)	.24
Physician diagnosis	Yes vs no	44.0	16.2 (−23.6 to 55.9)	.38	1.622	0.203 (−0.286 to 0.692)	.36	1.868	0.213 (−0.617 to 1.044)	.58
Sample size	Per 10 patients	59.6	−0.1 (−0.9 to 0.7)	.80	1.786	−0.002 (−0.011 to 0.006)	.58	2.167	−0.001 (−0.037 to 0.012)	.28
Female proportion	Per 1%	25.3	0.4 (−0.2 to 1.0)	.14	1.577	0.003 (−0.004 to 0.009)	.41	1.729	0.003 (−0.014 to 0.020)	.67
Age	Per 1 y	83.0	−0.5 (−1.7 to 0.7)	.34	1.869	−0.003 (−0.027 to 0.021)	.79	4.038	−0.041 (−0.068 to −0.015)	<.01

Abbreviations: CI, confidence interval; CTT, colonic transit time; PAC-QOL, Patient Assessment of Constipation-Quality of Life; PAC-SYM, Patient Assessment of Constipation-Symptoms.
[a]Intercept represents estimated outcome value when covariate value = 0.
[b]Slope represents the magnitude of change in estimated outcome value per unit increase in covariate value.
— indicates no available studies to perform meta-regression.

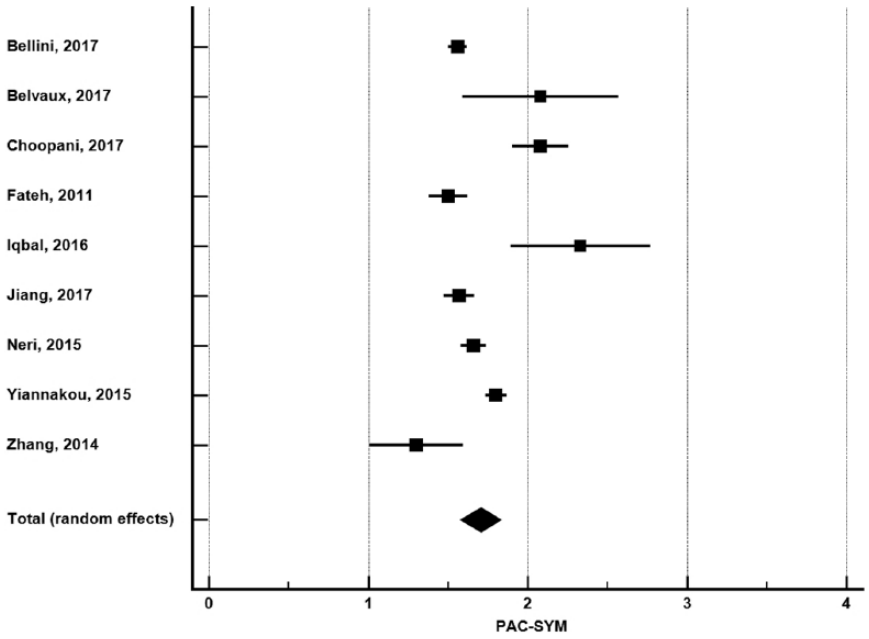

Figure 4. PAC-SYM in adults with functional constipation. PAC-SYM (Patient Assessment of Constipation-Symptoms) estimates from random-effects meta-analysis. The mean and 95% confidence interval are plotted for each study. The pooled estimate is represented by the diamond apex (1.70) and the 95% confidence interval is represented by the diamond width (1.58-1.83). Publication bias: Egger $P = .44$. Heterogeneity: $I^2 = 90\%$, $P < .001$.

insufficient reporting. Furthermore, subgroup analysis and meta-regression results should be considered exploratory and hypothesis-generating. For these reasons, the estimates within may be somewhat unstable and the conclusions prone to change with inclusion of future studies. Finally, we did not conduct a formal risk of bias assessment because data were extracted from cross-sectional studies as well as baseline data from interventional studies, for which no assessment tools are available.

Conclusions

In adults diagnosed with FC per Rome III criteria, significant heterogeneity in CTT, PAC-SYM, and PAC-QOL exists

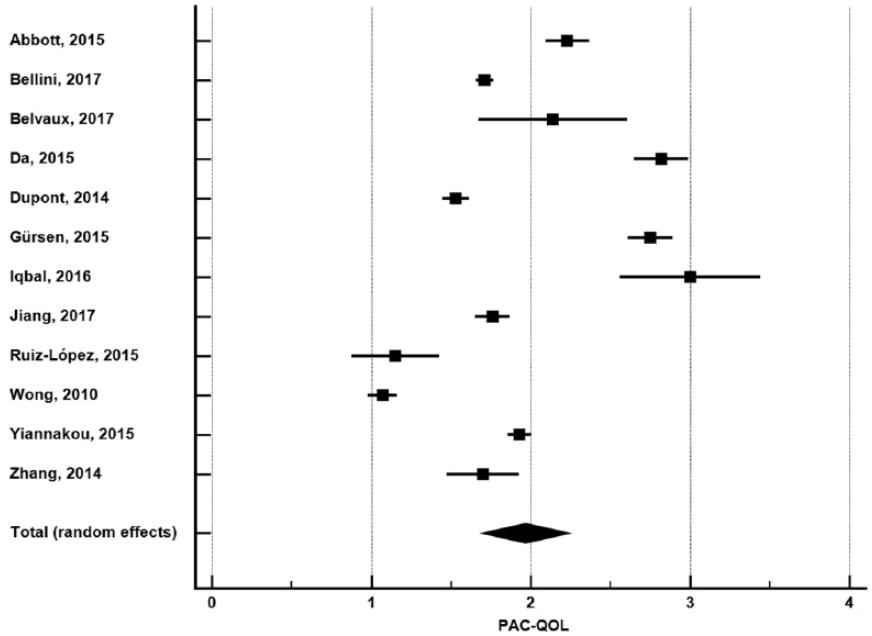

Figure 5. PAC-QOL in adults with functional constipation. PAC-QOL (Patient Assessment of Constipation-Quality of Life) estimates from random-effects meta-analysis. The mean and 95% confidence interval are plotted for each study. The pooled estimate is represented by the diamond apex (1.97) and the 95% confidence interval is represented by the diamond width (1.70-2.24). Publication bias: Egger $P = .28$. Heterogeneity: $I^2 = 98\%$, $P < .001$.

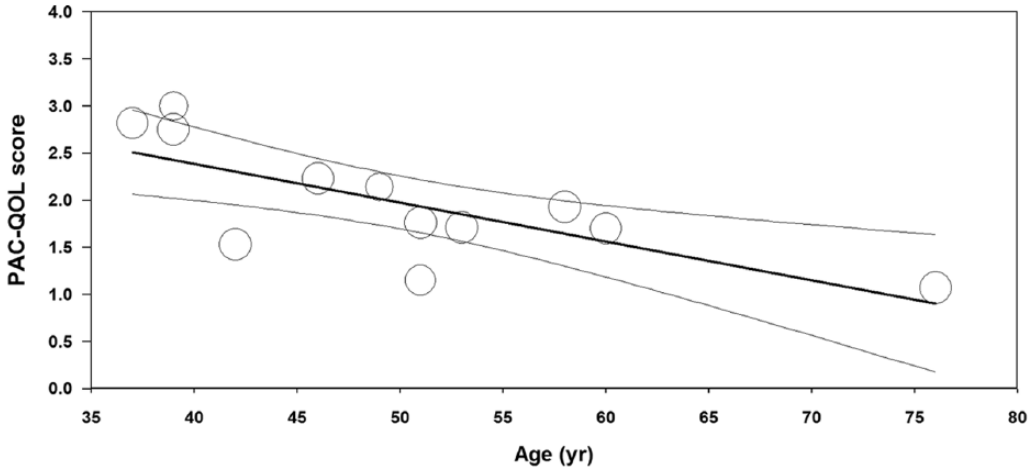

Figure 6. Meta-regression of relationship between age and PAC-QOL score in adults with functional constipation. Percentage of variance in PAC-QOL (Patient Assessment of Constipation-Quality of Life) score explained by age = 52%, $P < .01$. Open circles represent values of individual studies where circle size is proportional to the study weight in the random-effects model. Thick lines represent the regression line of best fit. Thin lines represent the 95% confidence interval of the regression line.

among studies. Variability among studies may be explained by geography and patient factors.

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Author Contribution

LM, AI, and AO contributed to conception and design; analysis and interpretation of the data; critical revision of the article for important intellectual content; and final approval of the article. LM contributed to drafting of the article.

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