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BMJ Open Abdominal massage for chronic constipation in the elderly: a systematic review and meta-analysis protocol

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ABSTRACT

Introduction Chronic constinution (CC) is a highly prevalent health challenge that is particularly challenging to treat in elderly patients. Although lifestyle guidance and laxative therapy often yield positive outcomes, patients occasionally struggle with maintaining dietary control. Therefore, identifying an economical and safe alternative therapy to the existing treatment methods documented in the international literature is necessary. This systematic review and meta-analysis aims to evaluate the efficacy and safety of abdominal massage in elderly patients with CC to provide a basis for future mechanistic research. Methods and analysis Electronic searches will be conducted to identify clinical randomised controlled trials in various databases, including Web of Science, PubMed, Cumulated Index to Nursing and Allied Health Literature, Cochrane Library, Embase, Airiti Library, Chinese National Knowledge Infrastructure Databases, Chinese Science and Technology Periodical Database (VIP), Chinese Biomedical Literature Database and Wan Fang Database. Relevant data will be extracted, and a meta-analysis will be conducted using Reviewer Manager V.5.4. Quality and risk assessments of the included studies will be performed, and the outcome indicators of the trials will be observed. This review will evaluate abdominal massage as a treatment option for relieving symptoms and improving quality of life in elderly patients with CC. Moreover, it will provide additional insights for clinical treatment and mechanistic studies. The search will be performed following the publication of this protocol (estimated to occur on 30 December 2023).

Ethics and dissemination As this is a literature review, ethics approval will not be required. We will disseminate the findings of this study to publications in peer-reviewed journals as well as presentations at relevant national and international conferences.

PROSPERO registration number CRD42023408629.

INTRODUCTION

Chronic constipation (CC) is characterised by difficult-to-pass and hard stools, reduced frequency of bowel movements and a feeling of incomplete defecation. The main diagnostic criteria are the Rome IV criteria and self-reported symptoms. 12 The prevalence of CC is 16% for men and 26% for women aged ≥65 years.³ In individuals aged ≥84 years,

STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ All types of clinical studies on chronic constipation across all elderly age groups will be included without language limitations.
- ⇒ The use of Cochrane quality assessment tools will ensure rigorous and standardised methodology.
- ⇒ The systematic review will rely solely on published data, potentially excluding relevant although unpublished studies.

the prevalence is reportedly as high as 26% and 34% for men and women, respectively.⁴ Decreased contractile motility of the detrusor and smooth muscle of the colon and atrophy of the gastrointestinal mucosa with reduced fluid secretion are the mechanisms that make constipation more common in the elderly.⁵ Ageing-related changes in diet and physical activity, lifestyle factors, arthralgia, osteoporosis, laxative dependence, and long-term use of anticholinergic agents, opioid analgesics,⁶ calcium supplements, and non-steroidal antiinflammatory drugs are risk factors for CC in elderly individuals.

Constipation not only significantly affects **©** the quality of life of the elderly but can also cause many diseases and consume a substantial amount of healthcare resources. Faecal retention can result in disruptions of gut microbiota and the production of harmful flora metabolites that induce cardiovascular, neurocognitive and other diseases. 89 The difficulties with defecation experienced by elderly patients may lead to cardiovascular and cerebrovascular accidents, thereby increasing the risk of sudden death. ¹⁰ Concurrently, CC also serves as a risk factor for severe conditions such as colon cancer. 11 12 The main treatments for CC are laxative use and lifestyle modifications.¹³ However, drug therapy may occasionally lead to dependency, potentially exacerbating symptoms or causing complications. 13 Although existing treatment methods



have received positive feedback, identifying safe, effective and economical treatments is necessary due to the high costs, side effects and, in some cases, the ineffectiveness of current interventions.

As an auxiliary complementary therapy, abdominal massage is considered a convenient and cost-effective option in clinical practice. ¹⁴ Abdominal massage has the potential to improve blood circulation in the gastrointestinal tract and stimulate gastrointestinal motility. Previous studies explored the effectiveness of abdominal massage on digestive function and bowel disorders. ^{15–17} However, specific studies on elderly patients with constipation are lacking. Given the increased prevalence of CC in older adults and its specific pathological mechanisms, exploring this condition in an age-restricted manner is necessary.

METHODS AND ANALYSIS Study registration

This systematic review protocol is registered with the International Prospective Register of Systematic Reviews (registration number: CRD42023408629). The reporting of this protocol adheres to the guidelines outlined in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P) statement. ¹⁸ The review will be reported in accordance with the PRISMA-P guidelines.

Inclusion criteria for study selection

Type of study

All randomised controlled trials that fulfil the inclusion criteria will be included in this systematic evaluation and meta-analysis to assess the safety and efficacy of abdominal massage therapy (performed by nurses, nurse aides, caregivers or doctors) for the treatment of CC among the elderly.

Type of participant

Participants aged 65 years or older diagnosed with CC will be included, regardless of sex, race, education or economic status. The diagnostic criteria for CC are as follows:

- 1. Clinical diagnostic criteria (eg, Rome IV criteria). 19
- 2. Diagnostic criteria defined by the authors or defined by the clinician.
- 3. Participants' self-reported constipation. The exclusion criteria are as follows:
- 1. Severe cognitive impairment that hinders understanding of the trial.
- 2. Belonging to specific clinical population groups (eg, pregnant women, intensive care unit patients, postoperative patients).

Type of intervention and comparisons

Abdominal massage includes any type of pressure applied to the abdominal region, such as Swedish abdominal massage, acupressure (abdominal acupoint massage) and aromatic abdominal massage. No limits will be placed

on massage time or frequency. The comparison group consists of individuals who received either no intervention, a placebo intervention or other medicinal treatments, such as osmotic or stimulant laxatives, elobixibat, linaclotide, lubiprostone, mizagliflozin, naronapride, plecanatide, prucalopride, tegaserod, tenapanor or velusetrag.²⁰

Type of outcome measure

The primary efficacy outcomes will be the frequency of bowel movements, related scales and symptoms of constipation. Constipation symptom questionnaires, such as the Demographic Characteristics Questionnaire, Rome criteria and related Conk Assessment Scales, will be used to measure constipation symptoms. Secondary efficacy outcomes will include the influence of constipation on the quality of life and laxative use. The safety outcomes include the monitoring of adverse events.

Search methods for identification of studies

Electronic data sources

The following electronic databases will be searched from their inception dates up to 30 December 2023: Web of Science, PubMed, Cumulated Index to Nursing and Allied Health Literature, Cochrane Library, Embase, Airiti Library, Chinese National Knowledge Infrastructure Databases, Chinese Science and Technology Periodical Database (VIP), Chinese Biomedical Literature Database and Wan Fang Database. After excluding publication restrictions, we will review randomised clinical trials to investigate the effectiveness of abdominal massage on CC in older adults who meet the eligibility criteria.

Searching other resources

The reference lists of potentially missing eligible studies will be reviewed, and relevant conference proceedings will also be examined.

Search strategy

The search strategy is summarised in online supplemental appendix 1. The following search keywords will be used: abdominal massage (eg, "tuina", "massage", "Chinese massage"); constipation (eg, "Dyschezia" or "Colonic Inertia"); and randomized controlled trial (eg, "randomized controlled trial", "random allocation", "randomized", "randomly", "double-blind method", "single-blind method" or "clinical trial"). Equivalent search keywords were used in Chinese databases. Additional studies will be identified from the reference lists of the selected articles, and the authors will be contacted for any unclear information.

Data collection and analysis

Selection of studies

The titles and abstracts of all retrieved studies will undergo independent review and screening by two reviewers (QY and XW) to identify eligible trials and exclude duplicate or irrelevant studies. The selected studies will be imported using the document management software EndNote V.X9

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Figure 1 Flow diagram of study selection process.

(Clarivate, London, UK). The initial screening, based on titles and abstracts, will be performed, and suitable studies will be selected based on the inclusion criteria. Subsequently, full texts of all potentially eligible studies will be obtained for rescreening. In case of discrepancies between the inclusion and exclusion criteria, discussions with the corresponding authors will occur to resolve these differences. A PRISMA-P flow chart (figure 1) will be used to illustrate the study selection process.

Data extraction and management

The following data will be extracted from the selected studies by two independent reviewers (QY and XW) using a standard data extraction sheet: year of publication, country, general information, participant characteristics, inclusion and exclusion criteria, sample size, randomisation, blinding methods, methods, controls, outcome measures, results, adverse reactions, conflicts of interest, ethical approval and other information. The extracted data will be entered into an electronic database, and

differences will be verified by the corresponding authors (JL and HW).

Management of missing data

The cause of missing data will be determined to solve this problem. If this investigative approach proves unsuccessful, the authors will be contacted to request the missing data. This process will be documented, and in the absence of the missing data, the available data will be extracted and analysed.

Risk of bias assessment

The Cochrane Collaboration tool will be used to assess the risk of bias in each study, including six types of bias: random sequence generation, allocation concealment, participant and personal blinding, outcome assessment blinding, incomplete outcome data, selective reporting, as well as other sources of bias.²² The quality of the reports will be divided into three levels: low, unclear and

high risk. Differences will be resolved through group discussion.

Statistical analysis

Data will be analysed using Review Manager V.5.3 (The Cochrane Collaboration, London, England). The relative risk will be used to evaluate dichotomous variables, with 95% CIs. The standardised mean difference and 95% CI will be used to evaluate continuous variables. The X² test and I² statistic will be used to confirm heterogeneity. The former checks for heterogeneity, whereas the latter reflects the degree of heterogeneity using a specific value. I²>50% will indicate considerable heterogeneity among the studies. Consequently, a subgroup analysis will be performed to investigate the potential causes.

Subgroup analysis

If significant heterogeneity is observed, subgroup analyses will be conducted to explore the sources of heterogeneity. These subgroup analyses will be conducted based on the characteristics of the included studies, including the publication time, geographical scope of the study, participant sex and control interventions. Regarding interventions, we will explore the impact of massage modality, duration and frequency on efficacy.

Sensitivity analysis

A sensitivity analysis will be conducted to test the robustness of the conclusions, examining the impact of sample size, study design, methodological quality and missing data.

Grading the quality of evidence

The Grading of Recommendations Assessment, Development and Evaluation approach will be used to judge the quality of evidence for all outcomes. Risks of bias, heterogeneity, indirectness, imprecision and publication bias were assessed. The assessments were classified into four levels: high, moderate, low or very low.

Ethics and dissemination

Because this study is based exclusively on published literature, ethics approval and informed consent will not be required. The outcomes of this review will be shared through peer-reviewed journals and conference reports.

Patient and public involvement

Patients will not be involved in the design, conduct, reporting or dissemination of this research.

DISCUSSION

This is the first protocol for a systematic review and metaanalysis intended to evaluate the effectiveness and safety of abdominal massage therapy for CC in elderly patients. We aim to objectively and comprehensively evaluate the therapeutic effects of abdominal massage on constipation in elderly patients. The results of this review will provide physical therapists, gastroenterologists and patients with additional information on complementary treatment options for CC in the elderly population. Furthermore, the credibility of existing clinical evidence provides new directions for future research.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

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REFERENCES

- 1 Bharucha AE, Pemberton JH, Locke GR. American Gastroenterological Association technical review on constipation. Gastroenterology 2013;144:218–38.
- 2 Siah KTH, Gong X, Yang XJ, et al. Rome foundation-Asian working team report: Asian functional gastrointestinal disorder symptom clusters. Gut 2018;67:1071–7.
- 3 Milosavljevic T, Popovic DD, Mijac DD, et al. Chronic constipation: gastroenterohepatologist's approach. Dig Dis 2022;40:175–80.
- 4 Gallegos-Orozco JF, Foxx-Orenstein AE, Sterler SM, et al. Chronic constipation in the elderly. Am J Gastroenterol 2012;107:18–25;
- 5 Bharucha AE, Lacy BE. Mechanisms, evaluation, and management of chronic constipation. *Gastroenterology* 2020;158:1232–49.
- 6 Katakami N, Oda K, Tauchi K, et al. Phase IIb, randomized, doubleblind, placebo-controlled study of naldemedine for the treatment

- of opioid-induced constipation in patients with cancer. *J Clin Oncol* 2017;35:1921–8.
- 7 Ness J, Hoth A, Barnett MJ, et al. Anticholinergic medications in community-dwelling older veterans: prevalence of anticholinergic symptoms, symptom burden, and adverse drug events. Am J Geriatr Pharmacother 2006;4:42–51.
- 8 Travagli RA, Browning KN, Camilleri M. Parkinson disease and the gut: new insights into pathogenesis and clinical relevance. *Nat Rev Gastroenterol Hepatol* 2020;17:673–85.
- 9 Sumida K, Molnar MZ, Potukuchi PK, et al. Constipation and risk of death and cardiovascular events. Atherosclerosis 2019;281:114–20.
- 10 Tse G, Lai ETH, Lee APW, et al. Electrophysiological mechanisms of gastrointestinal arrhythmogenesis: lessons from the heart. Front Physiol 2016;7:230.
- 11 Peng Y, Liu F, Qiao Y, et al. Association of abnormal bowel health with major chronic diseases and risk of mortality. Ann Epidemiol 2022;75:39–46.
- 12 Staller K, Olén O, Söderling J, et al. Chronic constipation as a risk factor for colorectal cancer: results from a nationwide, case-control study. Clin Gastroenterol Hepatol 2022;20:1867–76.
- 13 Vriesman MH, Koppen IJN, Camilleri M, et al. Management of functional constipation in children and adults. Nat Rev Gastroenterol Hepatol 2020;17:21–39.
- 14 Wang G, Zhang Z, Sun J, et al. Abdominal massage: a review of clinical and experimental studies from 1990 to 2021. Complement Ther Med 2022;70:102861.

- 15 Wang X, Sun J, Li Z, et al. Impact of abdominal massage on enteral nutrition complications in adult critically ill patients: a systematic review and meta-analysis. Complement Ther Med 2022;64:102796.
- 16 Wang J, Chen Y, Xue H, et al. Effect of abdominal massage on feeding intolerance in patients receiving enteral nutrition: a systematic review and meta-analysis. Nurs Open 2023;10:2720–33.
- 17 Dai N, He Q, Liu X, et al. Therapeutic massage/Tuina for treatment of functional dyspepsia: a systematic review and meta-analysis of randomized controlled trials. Qual Life Res 2023;32:653–67.
- 18 Shamseer L, Moher D, Clarke M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ 2015;350:g7647.
- 19 Aziz I, Whitehead WE, Palsson OS, et al. An approach to the diagnosis and management of Rome IV functional disorders of chronic constipation. Expert Rev Gastroenterol Hepatol 2020;14:39–46.
- 20 Luthra P, Camilleri M, Burr NE, et al. Efficacy of drugs in chronic idiopathic constipation: a systematic review and network metaanalysis. Lancet Gastroenterol Hepatol 2019;4:831–44.
- 21 Coffin B, Caussé C. Constipation assessment scales in adults: a literature review including the new bowel function index. Expert Rev Gastroenterol Hepatol 2011;5:601–13.
- 22 Higgins JPT, Altman DG, Gøtzsche PC, et al. The Cochrane collaboration's tool for assessing risk of bias in randomised trials. BMJ 2011;343:d5928.

Appendix 1 Search strategies for databases

Web of Science

```
#1: TS=("constipation")
#2: TS=("dyschezia" OR "colonic inertia" OR "functional constipation" OR "primary constipation"
OR "chronic constipation" OR "idiopathic constipation" OR "slow transit constipation" OR
"constipated" OR "defecation disorder*" OR "evacuation disorder*" OR "gastrointestinal transit"
OR "gut transit" OR "slow transit" OR "hard stool*" OR "lumpy stool*" OR "hard feces" OR
"straining" OR "incomplete evacuation" OR "infrequent bowel movement" OR "Constipation")
#3: TS=("Massage")
#4: TS=("massage" OR "tuina" OR "tui na" OR "chinese massage" OR ("rubbed" OR "rubbing"
OR "rubbings"))
#5: TS=("Randomized Controlled Trial" OR "randomized controlled trial" OR "controlled clinical
trial" OR "random allocation" OR "randomized" OR "randomly" OR "double blind method" OR
"single blind method" OR "clinical trial")
#6: #1 OR #2
#7: #3 OR #4
#8: #5
#9: #6 AND #7 AND #8
```

Pubmed

```
#1 "constipation" [MeSH Terms]
#2 "dyschezia"[Title/Abstract] OR "colonic inertia"[Title/Abstract] OR "functional
constipation"[Title/Abstract] OR "primary constipation"[Title/Abstract] OR "chronic
constipation"[Title/Abstract] OR "idiopathic constipation"[Title/Abstract] OR "slow transit
constipation"[Title/Abstract] OR "constipated"[Title/Abstract] OR "defecation
disorder"[Title/Abstract] OR "evacuation disorder*"[Title/Abstract] OR "gastrointestinal
transit"[Title/Abstract] OR "gut transit"[Title/Abstract] OR "slow transit"[Title/Abstract] OR
"hard stool*"[Title/Abstract] OR "lumpy stool*"[Title/Abstract] OR "hard feces"[Title/Abstract]
OR "straining" [Title/Abstract] OR "incomplete evacuation" [Title/Abstract] OR "infrequent bowel
movement"[Title/Abstract] OR "Constipation"[Title/Abstract]
#3 #1 OR #2
#4 "Massage"[MeSH Terms]
#5 "massage"[Title/Abstract] OR "tuina"[Title/Abstract] OR "tui na"[Title/Abstract] OR "chinese
massage"[Title/Abstract] OR (("rubbed"[Title/Abstract] OR "rubbing"[ Title/Abstract] OR
"rubbings"[Title/Abstract])
#6 #4 OR #5
#7 "Randomized Controlled Trial" [Publication Type]
#8 "randomized controlled trial"[Title/Abstract] OR "controlled clinical trial"[Title/Abstract] OR
"random allocation" [Title/Abstract] OR "randomized" [Title/Abstract] OR
```

"randomly"[Title/Abstract] OR "double blind method"[Title/Abstract] OR "single blind method"[Title/Abstract] OR "clinical trial"[Title/Abstract] #9 #7 OR #8

CINAHL-Plus with full text (EBSCOhost Research Databases)

#1: MH "Constipation"

#10 #3 AND #6 AND #9

#2: "dyschezia" OR "colonic inertia" OR "functional constipation" OR "primary constipation" OR "chronic constipation" OR "idiopathic constipation" OR "slow transit constipation" OR "constipated" OR "defecation disorder*" OR "evacuation disorder*" OR "gastrointestinal transit" OR "gut transit" OR "slow transit" OR "hard stool*" OR "lumpy stool*" OR "hard feces" OR "straining" OR "incomplete evacuation" OR "infrequent bowel movement" OR "Constipation" #3: MH "Massage"

#4: "massage" OR "tuina" OR "tui na" OR "chinese massage" OR ("rubbed" OR "rubbing" OR "rubbings")

#5: PT "Randomized Controlled Trial" OR "randomized controlled trial" OR "controlled clinical trial" OR "random allocation" OR "randomized" OR "randomly" OR "double blind method" OR "single blind method" OR "clinical trial"

#6: #1 OR #2

#7: #3 OR #4

#8: #5

#9: #6 AND #7 AND #8

Cochrane library

#1: MeSH descriptor: [Constipation]

#2: "dyschezia" OR "colonic inertia" OR "functional constipation" OR "primary constipation" OR "chronic constipation" OR "idiopathic constipation" OR "slow transit constipation" OR "constipated" OR "defecation disorder*" OR "evacuation disorder*" OR "gastrointestinal transit" OR "gut transit" OR "slow transit" OR "hard stool*" OR "lumpy stool*" OR "hard feces" OR "straining" OR "incomplete evacuation" OR "infrequent bowel movement" OR "Constipation"

#3: MeSH descriptor: [Massage]

#4: "massage" OR "tuina" OR "tui na" OR "chinese massage" OR ("rubbed" OR "rubbing" OR "rubbings")

#5: "Randomized Controlled Trial" OR "randomized controlled trial" OR "controlled clinical trial" OR "random allocation" OR "randomized" OR "randomly" OR "double blind method" OR "single blind method" OR "clinical trial"

#6: #1 OR #2 #7: #3 OR #4 #8: #5

#9: #6 AND #7 AND #8

Embase(Ovid)

#1: "constipation"/exp

#2:"dyschezia" OR "colonic inertia" OR "functional constipation" OR "primary constipation" OR "chronic constipation" OR "idiopathic constipation" OR "slow transit constipation" OR "constipated" OR "defecation disorder*" OR "evacuation disorder*" OR "gastrointestinal transit" OR "gut transit" OR "slow transit" OR "hard stool*" OR "lumpy stool*" OR "hard feces" OR "straining" OR "incomplete evacuation" OR "infrequent bowel movement" OR "Constipation"

#3: #1 OR #2

#4: "Massage"/exp

#5: "massage" OR "tuina" OR "tui na" OR "chinese massage" OR ("rubbed" OR "rubbing" OR "rubbings")

#6: #4 OR #5

#7: "Randomized Controlled Trial"/exp

#8:"randomized controlled trial" OR "controlled clinical trial" OR "random allocation" OR "randomized" OR "randomly" OR "double blind method" OR "single blind method" OR "clinical trial"

#9: #7 OR #8

#10: #3 AND #6 AND #9