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Gastrointestinal symptoms in the peri- and postmenopause: a protocol for a scoping review

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Abstract

Objective:

This scoping review aims to systematically map research on gastrointestinal (GI) symptoms in the peri- and postmenopause, with consideration of the extent of available evidence, how research has been conducted, and the variables studied that could influence women's experiences of GI symptoms.

Introduction

Perimenopause is a phase starting before a woman's final menstrual period and ending 12 months afterwards. This phase is associated with a range of symptoms that may impact quality of life. However, researchers argue there are significant gaps in knowledge about (peri)menopause, with GI symptoms proposed as one such area of uncertainty. Exploratory searches identified studies with conflicting results, few systematic reviews, and a lack of inclusion in menopause guidelines.

Inclusion criteria

Primary or secondary research investigating GI symptoms (nausea, vomiting, bloating, abdominal pain, constipation, gastroesophageal reflux, and faecal incontinence) during peri-, or postmenopause will be included.

Methods

JBI scoping review methodology will be used to systematically search, select, and extract data from relevant studies. Results from comprehensive searches of 10 bibliographic databases, grey literature and citation-chasing will be assessed for relevance against pre-specified criteria. A standardized template will be used to extract data applicable to review objectives. An additional reviewer will assist with study selection and data extraction, minimising potential for bias or error.

Data will be analysed using descriptive statistics, and presented in tables and diagrams, providing a summary of available research and evidence gaps. This will enable researchers and funders to identify where future research is needed on GI symptoms in the (peri)menopause.

Keywords
menopause; perimenopause; postmenopause; gastrointestinal symptoms;

(250 words

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Abbreviations

DGBI	Disorders of gut brain interaction
FMP	Final menstrual period
IBD	Inflammatory bowel disease
IBS	Irritable bowel syndrome
GI	Gastrointestinal
GP	General practitioner
HRT	Hormone replacement therapy
ILL	Interlibrary loan
JBI	Joanna Briggs Institute
MeSH	Medical Subject Headings
NICE	National Institute for Health and Care Excellence
OSF	Open Science Framework
PCC	Population, Concept, Context framework
PRISMA	Preferred Reporting Items Systematic Reviews (PRISMA) Statement
PRISMA-ScR	Preferred Reporting Items Systematic Reviews (PRISMA) Statement – Scoping Review extension
STRAW	Stages of Reproductive Ageing Workshop

1. Introduction, literature review, and review aim

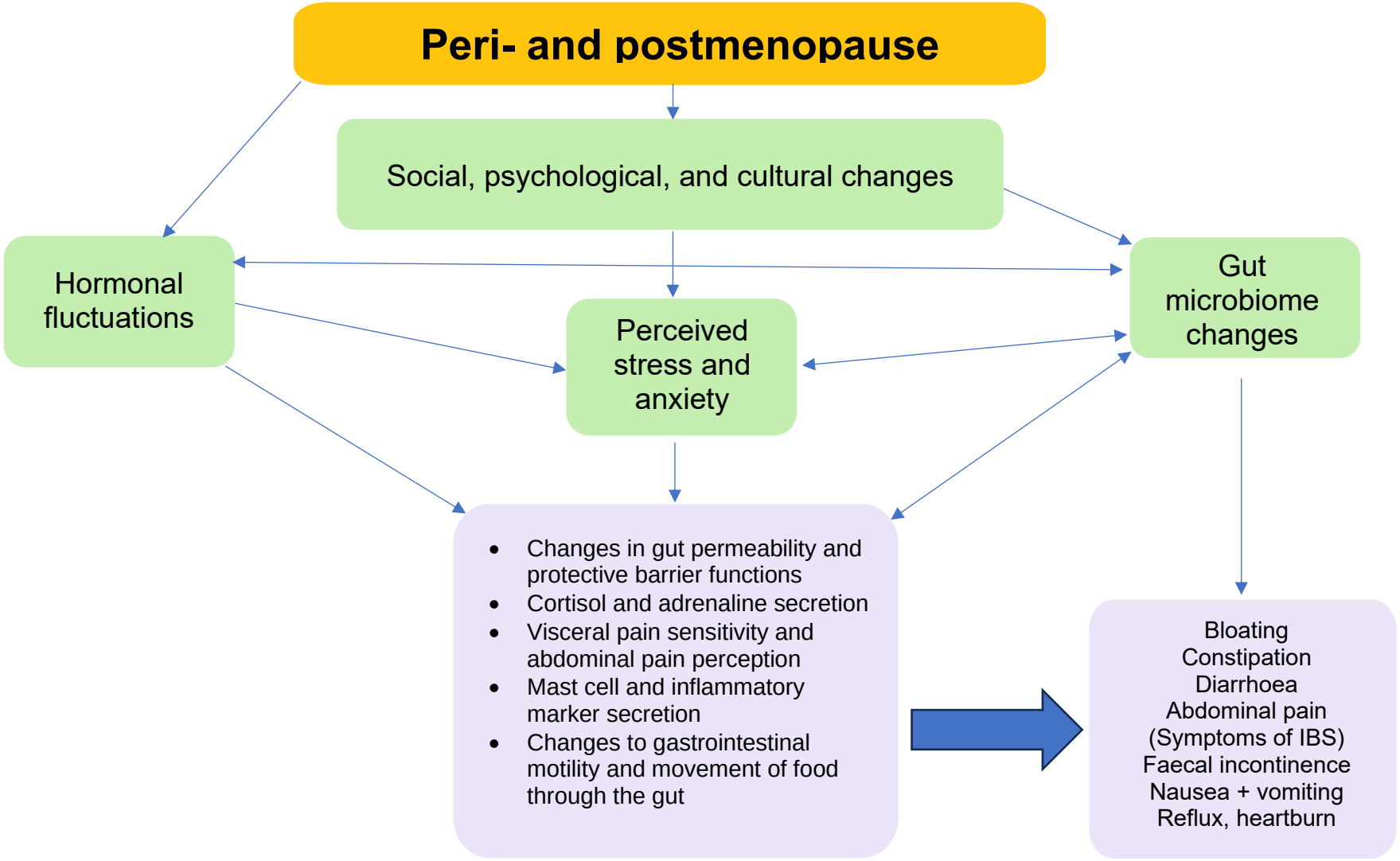
Natural menopause, or the end of a woman's reproductive life, is reached when an individual has not had a menstrual period in the prior 12 months, due to loss of ovarian function linked to ageing. The final menstrual period (FMP) usually occurs between the ages of 44 and 54 (Laisk *et al.*, 2019). However, menopause is considered a 'process' rather than an event (Fraser *et al.*, 2020), with the transition from the reproductive period to one year after the FMP defined as the 'perimenopause' (Harlow *et al.*, 2012). Perimenopause is characterised by irregularity in menstrual cycles, and significant fluctuations in levels of sex hormones (Monteleone *et al.*, 2018). This "reproductive hormonal milieu" followed by a gradual decline in sex hormone levels in postmenopause, has been linked to a cascade of symptoms (Santoro *et al.*, 2021, p.1), including hot flushes, night sweats, disrupted sleep, joint pain, sexual dysfunction, memory disturbances, anxiety and depression (Monteleone *et al.*, 2018). Symptoms are reported to affect 80-90% of menopausal women (British Menopause Society, 2022), though studies point to individual, ethnic, and geographical variation in their frequency and severity (Crandall, Mehta and Manson, 2023). Furthermore, symptoms may persist for more than 10 years (Santoro *et al.*, 2021), with negative impacts on work, quality of life, relationships, and mental health (Harper *et al.*, 2022). Despite 13 million women estimated to be peri- or post-menopausal in the UK (Harper *et al.*, 2022) and evidence of associated social and economic costs (Brewis *et al.*, 2017), researchers argue there are still significant gaps in our understanding of the menopause and the factors that influence symptom presentation (Department of Health and Social Care, 2022; Menopause Priority Setting Partnership, 2023).

Gastrointestinal (GI) symptoms in peri- and postmenopause could be considered one such area of uncertainty. GI symptoms include nausea, vomiting, diarrhoea, abdominal pain, constipation, bloating, gastroesophageal reflux, and faecal incontinence, and may have significant impacts on quality of life, being associated with embarrassment and stigma (Almario *et al.*, 2018). Recent media articles and patient information websites propose an association between peri- and postmenopause and increased risk or severity of GI symptoms (Denby, 2023; Valdesolo, 2023). However, GI symptoms are not recognized as key menopausal

symptoms in international and UK guidelines, and this may be due to the limited availability of high-quality evidence (NICE, 2019; North American Menopause Society, 2023) (**Appendix B**). Furthermore, many menopausal symptom assessment scales commonly used in research and practice do not include GI symptoms (Greene, 1976; Heinemann *et al.*, 2004) (**Appendix C**). These omissions may have led to a lack of awareness of GI symptoms among health professionals and the public, resulting in underdiagnosis of perimenopausal status and undertreatment, with a significant number of women potentially affected. Indeed, Harper *et al.* (2022) highlights concerns expressed by women about their GP's lack of knowledge and sympathy about menopausal symptoms, and challenges with access to appropriate support (RCOG, 2019).

Evidence indicates potential mechanisms by which menopause may contribute to the development of GI symptoms (**Figure 1**). Hormonal fluctuations, such as those characteristic of perimenopause, may influence perceptions of pain (Heitkemper and Chang, 2009), normal gastrointestinal functions, including the movement of food through the gut (Zia and Heitkemper, 2016), intestinal permeability (Shieh *et al.*, 2020), as well as immune and inflammatory processes (Nie, Xie and Tuo, 2018). Research also indicates a bidirectional relationship between the gut microbiome and sex hormones, with microbial composition of the GI system impacted by hormonal changes, and gut microbes also contributing to sex hormone metabolism (Yoon and Kim, 2021). Changes within the gut could contribute to new GI symptoms (Collins, 2014; Drossman, 2016) or exacerbations in women with irritable bowel syndrome (IBS) or inflammatory bowel diseases (IBD) (Khalili, 2016), however, Yang, Heitkemper and Kamp (2021) suggest further research is required to understand these mechanisms in the menopause.

Psychological and social variables may also contribute to GI symptoms. Menopause is often experienced at time of personal change, with care responsibilities for elderly parents, bereavement, children leaving home, alongside changing work roles and identities (Dare, 2011). These changes may influence perceived stress and anxiety (Thomas, Mitchell and Woods, 2019), which in turn could trigger or exacerbate GI symptoms (Drossman, 2016)



[Sources: (Coquoz, Regli and Stute, 2022; Drossman, 2016; Hogan *et al.*, 2009; Meleine and Matricon, 2014; Mulak, Taché and Larauche, 2014; Nie, Xie and Tuo, 2018; Shieh *et al.*, 2020; Thomas, Mitchell and Woods, 2019; Zia and Heitkemper, 2016)

Figure 1: Possible mechanisms for increased risk of GI symptoms in peri- and postmenopause

Exploratory searches were conducted (February 2024) to gauge available evidence on GI symptoms in the peri- and postmenopause (**Appendix A**). Searches identified few evidence syntheses, with only one systematic review (Adeyemo, Spiegel and Chang, 2010) examining the relationship between menopausal stage and irritable bowel syndrome (IBS), a disorder characterized by abdominal discomfort and changes in bowel habits (NICE, 2017). While this review concluded there was insufficient evidence for an association, searches only included one database and may not have identified all relevant evidence. Furthermore, additional studies have been published since the search date in 2010, with inconsistent findings regarding the prevalence or severity of IBS, as well as other GI symptoms during peri- and postmenopause. For example, in a survey of 947 women, 41.8% reported bloating, and 33.2% other digestive issues (Harper *et al.*, 2022). Similarly, Craig and Mitchell (2016) identified abdominal pain and vomiting in menopausal women, with value placed on relief from these symptoms. In contrast, Callan *et al.* (2018), did not find menopausal stage was a predictor for abdominal pain. Conflicting findings could be due to use of varied study designs, or a failure to differentiate between perimenopausal women within one year of their final menstrual period, and those at a later postmenopausal stage (Ambikairajah, Walsh and Cherbuin, 2022; Anaya, Culbert and Klump, 2023).

Hormone replacement therapy (HRT) is recommended for management of menopausal symptoms such as hot flashes (NICE, 2019). However, two systematic reviews highlight inconsistent findings, with HRT use shown to be both protective and as increasing risk of the GI symptoms of faecal incontinence and gastroesophageal reflux (Aldhaleei *et al.*, 2023; Bach, Sairally and Latthe, 2020). Both reviews noted limitations with included studies, characterised by small sample sizes and high heterogeneity in the type and delivery of HRT. Few randomized controlled trials were identified, with potential for confounding, and the possibility that women with more severe symptoms are prescribed HRT, rather than HRT causing GI symptoms.

A lack of investment into women's health research has resulted in knowledge gaps related to menopause (Department of Health and Social Care, 2022; Menopause Priority Setting Partnership, 2023; Mirin, 2021). Initial searches suggest the topic of

gastrointestinal symptoms in peri- and postmenopause could be one important area of uncertainty that requires further primary research and evidence synthesis. To identify future research priorities and avoid duplication, it is essential to first explore the available evidence to determine the types of GI symptoms that have been investigated and how research has been conducted. Searches of MEDLINE, Epistemonikos, OSF and JBI Evidence Synthesis in February 2024 (**Appendix A**) did not identify any existing or ongoing evidence syntheses with this goal, with one scoping review investigating oral symptoms only (Lenell *et al.*, 2022). In consequence, this scoping review *aims to systematically search for, select and map research on GI symptoms in natural peri- and postmenopause to identify gaps in the evidence and inform future research*.

This will be achieved by addressing the following research questions:

- What is the **extent** of evidence examining seven key categories of GI symptom (nausea, vomiting, bloating, constipation, diarrhoea, gastrooesophageal reflux and faecal incontinence) in natural peri- and postmenopause?
- How has research on GI symptoms in natural peri- and postmenopause been **conducted** (for e.g., study designs; measures of GI symptoms; populations and interventions studied; funding sources)?
- What **key variables** measured in research on GI symptoms in natural peri- and postmenopause (for e.g., correlates or predictors of GI symptoms, sex hormone levels, gut microbiome composition, body mass index, perceived stress, ethnicity)?

A scoping review methodology was selected as an appropriate approach to address these research objectives. In contrast to systematic reviews that consider focused research questions, scoping reviews are deemed suitable for broad questions aiming to explore and summarise the extent of available research (Munn *et al.*, 2018). Scoping reviews can prevent future research waste, by identifying gaps in the evidence, and highlighting future priorities for primary research, or areas requiring evidence synthesis to answer targeted questions. In turn, this future research could inform evidence-based recommendations (Khalil *et al.*, 2022).

2. Research approach and research methods

2.1 Scoping review methodology

The review will adhere to JBI guidance for the conduct of scoping reviews (Peters *et al.*, 2020; Pollock *et al.*, 2023), using systematic, rigorous, and reproducible methods for the identification and mapping of relevant studies, to minimize bias. JBI guidance was selected as building on existing frameworks (Arksey and O'Malley, 2005; Levac, Colquhoun and O'Brien, 2010). Reporting will align with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Scoping Review extension (PRISMA-ScR, 2018) to ensure methods are transparent and replicable. Deviations from pre-specified methods described in this protocol will be reported, with justification, in the final review.

2.2. Inclusion/exclusion criteria

Inclusion/exclusion criteria have been defined to clarify the focus of the scoping review, inform search strategy development, and facilitate assessment of the relevance of records identified through comprehensive searches (Peters *et al.*, 2020). The JBI Participant, Concept, Context framework (PCC) has been used to organise inclusion criteria, with additional information provided in **Table 1** on types of evidence, dates, and language of publication (Peters *et al.*, 2022). Further clarification is outlined in **2.2.1-2.2.6**.

Table 1: Inclusion/exclusion criteria

	Include	**Exclude**
Population	Individuals* described as experiencing: • 'natural' perimenopause (characterized by variability in menstrual cycle length experienced before the final menstrual period (FMP), plus the year after FMP) (Harlow *et al.*, 2012), or • the menopause transition (the period leading up to the final menstrual period), or menopausal, • postmenopause (i.e., when periods have not occurred in the prior 12 months). *Including those described as perimenopausal and postmenopausal that do not identify as women including transgender and non-binary people.	Individuals experiencing: • hysterectomy or surgical menopause (surgical removal of the uterus, or removal of both ovaries performed prior to natural menopause), • radiotherapy-induced or drug-induced menopause (tamoxifen, chemotherapy) or women also undergoing treatment for cancer as these interventions can influence menstrual cycles. • chronic illness that influences menstrual cycles (e.g., polycystic ovary syndrome). • primary ovarian insufficiency or premature menopause. Studies that focus only on individuals described as pre-menopausal (<40 years AND still experiencing regular periods). If studies include a mix of participants experiencing 'natural' and surgical, radiotherapy or drug-induced menopause, these studies will be excluded if separate data is not provided.
Concept	Studies focusing on patient-reported GI symptoms from Spiegel *et al.* (2014) including: • bloating, abdominal pain, constipation, diarrhoea, nausea, vomiting, reflux, faecal incontinence (see also **Appendix D**) • the above GI symptoms associated with disorders of gut brain interaction (DGBI) (also known as functional gastrointestinal disorders) that occur in the absence of recognized diagnostic pathology (e.g., irritable bowel syndrome, functional dyspepsia) • the above GI symptoms associated with organic gastrointestinal disorders with an underlying diagnostic pathology (e.g., inflammatory bowel diseases, such as ulcerative colitis and Crohn's disease) • the above GI symptoms associated with hormone replacement therapy (HRT) taken by perimenopausal or postmenopausal individuals.	Studies that focus: • only on menopausal symptoms not related to the gastrointestinal system (e.g., vasomotor, skin, genitourinary, mood symptoms). • only on oral symptoms (dry mouth, swallowing difficulties), or symptoms not covered by the NIH PROMIS GI Scale (e.g., disordered eating, increased food intake) (Spiegel *et al.*, 2014). • on non-patient reported measures **only** (e.g., electrophysiological measures, anorectal physiology, gut motility, transit time or tests of visceral pain sensitivity, other structural changes to the gut, or gut microbiome composition). • on GI symptoms as an adverse effect of drug or medical interventions (e.g. raloxifene for osteoporosis)
Context	All countries	-
Types of evidence	Ongoing and published primary research studies (including epidemiological, interventional, and qualitative studies) and evidence syntheses (described as systematic reviews, scoping reviews or rapid reviews) published in journals, theses, dissertations, reports, and other grey literature.	Animal studies, laboratory studies, editorials and commentary, case studies, case reports, narrative and literature reviews, conference abstracts (due to limited detail provided of methods and measures)
Language	English-language publications	Non-English language publications
Publication date	All years	No restriction on publication date

2.2.1. Population

As this review focuses on GI symptoms in 'natural' peri- or postmenopause, studies focusing on surgical or medically induced menopause will be excluded. 'Natural' perimenopause is associated with significant hormonal fluctuations, followed by a gradual decline in sex hormones (Harlow *et al.*, 2012). In contrast, medically induced or surgical menopause can result in a rapid reduction in sex hormones (Crandall, Mehta and Manson, 2023), and these women may experience more severe menopausal symptoms (British Menopause Society, 2021). In addition, as menopausal stage of women with polycystic ovary syndrome, or those who have undergone hysterectomy cannot be determined using menstrual cycle criteria (Harlow *et al.*, 2012), studies focusing on these populations will be excluded.

Inconsistencies have been noted in the definitions used to characterize menopausal stage in research (Ambikairajah, Walsh and Cherbuin, 2022). The term 'pre-menopause' can refer to both a period of 1-2 years prior to menopause, and the entire reproductive period up until the final menstrual period. For clarification, studies that include pre-menopausal women only (aged <40 years who are experiencing regular periods), will be excluded.

2.2.2. Concept

This scoping review will include a range of patient-reported GI symptoms occurring from the oesophagus to the anus will be included, based on seven key groups of GI symptoms outlined in the NIH Patient Reported Gastrointestinal Symptom Scale (Spiegel *et al.*, 2014) (**Appendix D**). A recent scoping review focused on oral symptoms in menopause (Lenell *et al.*, 2022), so these will be excluded to avoid duplication. Studies that report only electrophysiological measures will be excluded, as this review focuses on *patient-reported* GI symptoms.

2.2.3. Context

Existing research indicates there may be cultural and geographic differences in the experience of menopausal symptoms (Richard-Davis and Wellons, 2013). As this scoping review intends to identify key variables assessed that could be related to GI symptoms (including ethnicity), primary studies from all geographical locations will be included.

2.2.4. Language

Non-English publications will be excluded due to translation costs, and the potential for language bias is noted (Higgins *et al.*, 2023). As recommended by Pieper and Puljak (2021), language limits will not be applied to searches. Instead, non-English publications will be identified and excluded during screening, with citations reported in the final review for transparency.

2.2.5. Publication dates

As this review intends to determine the extent of evidence on this topic area, studies from all publication dates will be included.

2.2.6. Types of evidence

Scoping reviews can include a broad range of literature and study designs (Peters *et al.*, 2020). This review will include published and ongoing quantitative and qualitative primary research studies, and evidence syntheses to align with objectives to determine the extent of available evidence and how research has been conducted.

The following evidence sources will be excluded: animal studies, laboratory studies, editorials and commentary, case studies, case reports, narrative/literature reviews, and conference abstracts (due to limited detail provided of methods and measures).

2.3. Study identification

As recommended by JBI guidance (Peters *et al.*, 2020), searches will be conducted following a three-stage process, and reported in alignment with PRISMA-ScR (2018) guidance.

2.3.1. Initial scoping searches

A provisional search strategy for Ovid MEDLINE (**Appendix E**) has been developed by an Information Specialist (IS) with expertise in searching for evidence syntheses, and peer reviewed using the PRESS checklist (McGowan *et al.*, 2016). Text analysis of relevant articles from exploratory searches supported identification of synonyms and controlled vocabulary (e.g., MeSH in MEDLINE) for the population (i.e., peri- and postmenopause) and concept (i.e., GI symptoms).

2.3.2. Full database searches

Bibliographic databases (**Table 2**) will be searched from inception, without date or publication type limitations to identify published and ongoing studies. Search

strategies will be adapted for each database using appropriate syntax and vocabulary.

Table 2: Bibliographic database sources

Bibliographic database/source	**Platform/ Publisher**	**Dates of coverage**
MEDLINE ® and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations, Daily and Versions	Ovid	1946-present
Embase	Ovid	1974- present
APA PsycINFO	Ovid	1806- present
Cochrane Database of Systematic Reviews	Wiley	1996- present
Cochrane Central Register of Controlled Trials (CENTRAL)	Wiley	1908- present
CINAHL Plus with Full Text	EBSCO	1937- present
AMED (The Allied and Complementary Medicine Database)	EBSCO	1995- present
Scopus	Elsevier	1788- present
Web of Science Core Collection including: • Science Citation Index Expanded • Social Sciences Citation Index • Arts & Humanities Citation Index • Conference Proceedings Citation Index – Science • Conference Proceedings Citation index – Social Science & Humanities • Emerging Sources Citation Index	Clarivate Analytics	 1970- present 1970- present 1975- present 1990- present 1990- present 2015- present
ProQuest Dissertations & Theses	ProQuest	1743- present
ClinicalTrials.gov (available at https://clinicaltrials.gov)	National Library of Medicine	2000- present
WHO International Clinical Trials Registry Platform (ICTRP) (available at: https://www.who.int/clinical-trials-registry-platform)	World Health Organization	2006- present

2.3.3. Supplementary search methods

Grey literature (including reports and theses) will be identified by browsing key websites (British Menopause Society), and searches of Google and Google Scholar. Simplified search strategies will be used, with the first ten pages of each search screened by one reviewer for feasibility. Reference lists of key review articles will be

checked, and forwards/backwards citation chasing of included studies will be completed using CitationChaser (Haddaway, Grainger and Gray, 2022).

2.3.4. Management of search results

All records from searches will be exported to EndNote X9.3.3 (Clarivate Analytics) and de-duplicated using EndNote functionality and manual checks.

2.4. Study selection

2.4.1. Pilot screening

Study selection will be guided by pre-specified inclusion/exclusion criteria (**2.2**). A random sample (100 records) will be used to pilot criteria, with two reviewers reviewing titles/abstracts of records to independently assess eligibility in Rayyan (Ouzzani *et al.*, 2016), discussing disagreements, and refining screening documentation where necessary (Peters *et al.*, 2022).

2.4.2. Title/abstract and full-text screening

Screening by two independent reviewers is recommended to minimize risk of bias or human error (Waffenschmidt *et al.*, 2019). As this is resource intensive, to ensure feasibility, one reviewer will screen 100% of records, with a second reviewer screening 50%, assessing titles/abstracts against eligibility criteria, followed by the full-text articles. Articles not accessible through University library services will be excluded, but citations noted in review Appendices. Disagreements at both screening stages will be resolved through consensus, or discussion with a third reviewer. Records excluded at the full-text screening stage will be reported with reasons (PRISMA-ScR, 2018).

2.5. Data extraction

A standardised template for Microsoft Excel will be developed to extract data items relevant to the review question and objectives. This will be structured to align with the PCC framework (Campbell *et al.*, 2023) (**Table 3**). As this review does not aim to synthesise findings, study results will not be extracted. Additional items may be added iteratively as reviewers become familiar with the included literature. Justifications for deviations from the protocol will be provided (Pollock *et al.*, 2023).

The researcher notes that included primary studies may also be cited within identified evidence syntheses. To minimise the impact of double counting data from these studies, limited data extraction of evidence syntheses will be completed (see Table 3). (Pollock *et al.*, 2023)

The data extraction template will be piloted by two reviewers on ten included studies covering a range of evidence types. Independent data extraction by two reviewers is considered good practice (Pollock *et al.*, 2023), however, to balance feasibility with accuracy, one reviewer will extract data from all studies, with a second reviewer checking 10% of records for errors and completeness.

Table 3: Data extraction draft template

	Data item	Types of evidence
Study information	Author(s)	Evidence syntheses and primary research
	Year of publication	
	Journal/source	
	Aims/objectives of study	
	Source of funding	
	Study design	
Population (P)	Total number of participants (sample size)	Primary research only
	Gender (female, transgender, non-binary, other)	Primary research only
	Menopausal stage (i.e., perimenopause, early or late postmenopause)	Evidence syntheses and primary research
	Criteria used to define menopausal stage (e.g., STRAW 10+ (Harlow *et al.*, 2012); menstrual calendar data; self-report of number of skipped periods, changes in cycle length, flow, report of hot flashes/night sweats (vasomotor symptoms))	Primary research only
	Ethnicity	Primary research only
	Socioeconomic status	Primary research only
	Educational level	Primary research only
	Age	Primary research only
	Diagnosis of a Disorder of Gut Brain Interaction (DGBI) or organic gastrointestinal disease (self-reported; medical records; confirmation by a health care professional)	Primary research only
	HRT use (oestrogen, progestogen, testosterone)	Primary research only
	HRT use (route of administration: vaginal, systemic, anal, dermal)	Primary research only
	Urine or serum assay of sex hormones (e.g., oestrogen, progesterone, testosterone, follicle stimulating hormone, lutenizing hormone, gonadotrophin releasing hormone	Primary research only
	Assay of stress hormones (e.g., urinary cortisol) or catecholamines (epinephrine and norepinephrine)	Primary research only
	Perceived stress, anxiety, depression, tension, quality of life measures	Primary research only
	Gut microbial composition, abundance, and diversity measures	Primary research only
	Obstetric history; mode of delivery	Primary research only
	Other variables, correlates, risk factors or predictors of GI symptoms not yet identified.	Primary research only
Concept (C)	Types of gastrointestinal symptom assessed (domains from (Spiegel *et al.*, 2014) including bloating, abdominal pain, constipation, diarrhoea, nausea, vomiting, reflux, faecal incontinence)	Evidence syntheses and primary research
	Measure used for gastrointestinal symptom assessment (e.g., symptom scale, diary)	Primary research only
	Type of symptom assessment: symptom severity; frequency; onset	Primary research only
	Analysis of symptom clusters to determine co-occurrence of gastrointestinal symptoms	Primary research only
Context (C)	Geographical location	Primary research only
Data extracted for interventional studies only	Type of intervention (e.g., hormone replacement therapy)	Interventional studies only (e.g., randomised controlled trials, controlled before and after studies)
	Comparator	
	Duration of treatment	
	Dosage of treatment and mode of delivery	

2.6. Quality assessment

Quality assessment of included studies is not a mandatory step in scoping reviews (Peters *et al.*, 2022), and in consequence, this may limit the review's ability to inform policy and practice (Grant and Booth, 2009). As this review's rationale is to inform future research, quality assessment of included studies is not considered necessary.

2.7 Data analysis and presentation

This scoping review will provide a comprehensive map of available evidence on GI symptoms in the peri- or postmenopause, with the intended audience being researchers, priority setting partnerships and funders. The findings may prevent research waste by highlighting where research has been conducted and aid prioritisation of future research through identification of evidence gaps (Peters *et al.*, 2022). Exploratory searches (February 2024) (**Appendix A**) identified approximately 40 primary studies and 3 systematic reviews for inclusion.

The flow of studies through the review will be reported in a narrative description as well as a PRISMA flow diagram (PRISMA-ScR, 2018) (**Appendix E**), outlining numbers of search results, duplicates, records screened at title/abstract, full-text and excluded at each stage, and number of included studies.

The aim of most scoping reviews is not to synthesize study results, but rather to summarize and collate evidence, providing a descriptive overview of the extent of available research (Pollock *et al.*, 2023). In consequence, study findings will not be extracted or reported, and analyses for this review will focus on frequency counts calculated using Excel (Microsoft) (**Table 4**). These will be presented in tabular or visual formats (e.g., a map to illustrate the geographical distribution of studies). Tables will be supplemented with narrative descriptions, with findings organized by review objective.

A summary table of all included studies, outlining brief citation details, population characteristics, GI symptom(s) assessed and study design, will be provided in the review Appendices.

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Table 4: Review analyses: frequency counts by review objective

Review objective	**Frequency counts**
To determine the **extent** of evidence examining GI symptoms in natural peri- and postmenopause.	Overall number of studies included
	Studies by year of publication
	Studies by journal or publication source
	Studies by geographical location
	Studies by GI symptom (mapped to (Spiegel *et al.*, 2014) domains: diarrhoea, constipation, nausea, vomiting, bloating, faecal incontinence, reflux and abdominal pain)
To determine how research on GI symptoms in natural peri- and postmenopause has been **conducted.**	Funding sources
	Study designs (e.g., case-control, observational, randomised control trials, qualitative, systematic reviews): all and categorized by GI-symptom
	Studies by sample size. (Categories will be dependent on sample size range identified in included studies).
	Studies by population characteristic (e.g., gender (females, transgender, and non-binary individuals), age, menopausal stage, ethnicity)
	Measures or criteria used to assess menopausal stage
	Measures used to assess gastrointestinal symptoms (e.g., symptom scales, diaries, assessment of severity, frequency, or impact of GI symptom)
To identify **key variables** measured in research on GI symptoms in natural peri- and postmenopause.	Studies measuring variables (e.g., age, sex hormones, perceived stress, pre-existing irritable bowel syndrome, gut microbial composition) with analyses completed to investigate the relationship between the variable and GI symptom frequency, severity, or prevalence. Variables may be grouped into categories for clarity of presentation.

3. Acknowledgements

This review forms part of the requirements for the lead author's studies for MSc Human Nutrition (University of Plymouth). Naomi Shaw wrote the review protocol, will also conduct all searches, screen 100% of records, carry out data extraction for all included studies, analyse all data, and author the final review report. Dr Clare Pettinger will supervise the review.

A second reviewer will independently screen 50% of records, and quality check 10% of data extraction for included studies

4. Funding

The authors have received no external funding for this review.

5. Conflicts of Interest

The author declares no conflicts of interest.

6. References

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Appendix A: Exploratory searches

(Searches completed 11th February 2024)

Ovid MEDLINE(R) and In-Process, In-Data-Review & Other Non-Indexed Citations <1946 to February 09, 2024>

1 exp Menopause/ 63795
2 (menopaus* or perimenopaus* or peri-menopaus* or postmenopaus* or post-menopaus* or postreproductive or post-reproductive or climacteric).ti,ab. 108322
3 1 or 2 122751 [menopause search terms]
4 Irritable Bowel Syndrome/ 9696
5 exp Inflammatory Bowel Diseases/ 99466
6 exp "signs and symptoms, digestive"/ 170900
7 ((digestive or bowel or gut or gastro* or colonic) adj2 (symptom* or habit* or issue* or issue* or problem* or dysfunction*)).ti,ab. 38141
8 ((digestive or gastro*) adj3 symptom*).ti,ab. 26840
9 IBS.ti,ab. 11494
10 (inflammatory adj bowel).ti,ab. 63350
11 (ulcerative adj colitis).ti,ab. 47950
12 crohn*.ti,ab. 55687
13 (irritable adj bowel).ti,ab. 16348
14 (diarrh* or constipat*).ti,ab. 152871
15 ((loose or watery) adj stool*).ti,ab. 1895
16 ((bowel* or defecat*) adj2 (frequen* or urgen* or infrequen*)).ti,ab. 2740
17 (incomplete adj evacuation).ti,ab. 468
18 (bloating or bloated or gassiness or gaseousness or flatulence or flatulent or flatus or (abdom* adj disten*) or (swollen adj abdom*) or (swelling adj2 abdom*) or (postprandial adj fullness) or (post-prandial adj fullness)).ti,ab. 18869
19 ((gurgling or rumbling) adj2 (abdom* or stomach or gastro*)).ti,ab. 32
20 ((abdom* or stomach or epigastric or rectal or rectum or belly) adj2 (pain* or cramp* or ache* or colic or discomfort)).ti,ab.86233
21 (reflux or GERD or dyspepsia or indigestion or heartburn or regurgitat*).ti,ab. 119996
22 (belch* or burp* or eructation or hiccup*).ti,ab. 3625
23 (nausea* or vomit* or emesis or retching).ti,ab. 114376
24 ((faecal or fecal or anal or bowel) adj2 (incontinen* or leak* or soiling)).ti,ab. 10164
25 ((bowel* adj control*) or encopresis).ti,ab. 1056
26 ((gut or digestive or gastro* or bowel* or colon*) adj2 health*).ti. 1442
27 exp animals/ not humans/ 5191565
28 or/4-26662206 [GI symptoms search terms]
29 3 and 28 2162 [menopause + GI symptoms search terms combined]
30 29 not 27 2141 [excluding animal studies]
31 (metaanalysis or meta-analysis or metasynthesis or meta-synthesis).ti,ab. 248545
32 (systematic adj (review or overview or search*)).ti,ab. 294767
33 (systematically adj (review* or search*)).ab. 38857
34 evidence synthesis.ti,ab. 6857
35 thematic synthesis.ti,ab. 1534
36 (evidence adj2 map*).ti,ab. 1652
37 ((scoping or rapid or realist or mapping or umbrella) adj2 review).ti,ab. 29203
38 (qualitative adj2 synthesis).ti,ab. 5343
39 (qualitative adj2 synthesis).ti,ab. 5343
40 ((mixed-stud* or (mixed adj stud*) or (mixed adj method*) or mixed-method*) adj2 review).ti,ab. 1263
41 cochrane.jw. 16644

42 systematic reviews.jn. 2772
43 systematic review/ 250830
44 "review of reviews".ti,ab. 891
45 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 470457 [evidence synthesis search terms]
46 30 and 45 75 [menopause + GI symptoms + evidence synthesis search terms]

Open Science Framework
https://osf.io/

Searched 19th October 2023; updated 12th December 2023 and 19th February 2024

Search term	Search dates	Number of hits	Number of relevant records
Menopause	19/10/2023; 12/12/2023; 19/02/2024	148; 157; 165	0
Menopausal	19/10/2023; 12/12/2023	148; 157; 165	0
Perimenopause	19/10/2023; 12/12/2023	34; 34; 36	0
Perimenopausal	19/10/2023; 12/12/2023	47; 48; 51	0
Postmenopausal	19/10/2023; 12/12/2023	56; 58; 62	0

JBI Evidence Synthesis
https://journals.lww.com/jbisrir/pages/default.aspx

Searched 20th October 2023; updated 19th February 2024.

Search term	Number of results	Number of relevant records
Menopause	30; 31	0
Perimenopausal	5; 5	0
Perimenopause	5; 5	0
Postmenopausal	21; 21	0
Climacteric	5; 5	0

Epistemonikos
https://www.epistemonikos.org/

Searched 20th October 2023; updated 19th February 2024

Search terms	Number of hits	Number of relevant records
Menopause AND digestive	2; 3	0
Menopausal AND digestive	1; 2	0
Perimenopause AND digestive	0; 0	0
Perimenopausal AND digestive	0; 0	0
Menopause AND gut	49; 51	1
Menopausal AND gut	30; 32	0
Perimenopause AND gut	3; 3	0
Perimenopausal AND gut	4; 4	0
Menopause AND gastrointestinal	37; 37	1 (Heitkemper and Chang, 2009) (review)
Menopausal AND gastrointestinal	25; 27	1 (Heitkemper and Chang, 2009) (review)
Perimenopause AND gastrointestinal	4; 4	1 (Heitkemper and Chang, 2009) (review)
Perimenopausal AND gastrointestinal	4; 4	1 (Heitkemper and Chang, 2009) (review)

Menopause AND diarrhoea	6; 6	1 (Adeyemo, Spiegel and Chang, 2010)
Menopausal AND diarrhoea	5; 5	1 (Adeyemo, Spiegel and Chang, 2010)
Perimenopause and diarrhoea	0; 0	0
Menopause AND diarrhea	5; 5	0
Menopausal AND diarrhea	4; 4	0
Perimenopause AND diarrhea	1; 1	0
Perimenopausal AND diarrhea	1; 1	0
Menopause and constipation	10; 11	1 (Adeyemo, Spiegel and Chang, 2010)
Menopausal and constipation	10; 11	1 (Adeyemo, Spiegel and Chang, 2010)
Perimenopause and constipation	1; 1	0
Perimenopausal and constipation	1; 1	0
Menopause AND bowel	17; 18	2 (Adeyemo, Spiegel and Chang, 2010; Heitkemper and Chang, 2009)
Menopausal and bowel	13; 14	2 (Adeyemo, Spiegel and Chang, 2010; Heitkemper and Chang, 2009)
Postmenopausal and digestive	2; 4	0
Postmenopausal and gut	25; 25	0
Postmenopausal and gastrointestinal	37; 38	0

PROSPERO
https://www.crd.york.ac.uk/prospero/

Searched 11th February 2024

#1 MeSH DESCRIPTOR Menopause EXPLODE ALL TREES 222

#2 menopaus* or perimenopaus* or peri-menopaus* or postmenopaus* or post-menopaus* or postreproductive or post-reproductive or climacteric 2682

#3 #1 OR #2 2697

#4 MeSH DESCRIPTOR Irritable Bowel Syndrome EXPLODE ALL TREES 120

#5 MeSH DESCRIPTOR Inflammatory Bowel Diseases EXPLODE ALL TREES 451

#6 MeSH DESCRIPTOR Signs and Symptoms, Digestive EXPLODE ALL TREES 451

#7 ((digestive or bowel or gut or gastro* or colonic) adj2 (symptom* or habit* or issue* or issue* or problem* or dysfunction*)) 1370

#8 ((digestive or gastro*) and symptom*) 4263

#9 IBS 527

#10 inflammatory bowel 1857

#11 crohn* 1364

#12 irritable bowel 703

#13 diarrh* or constipat* 3582

#14 (loose or watery) and stool* 111

#15 (bowel* or defecat*) and (frequen* or urgen* or infrequen*) 1360

#16 incomplete evacuation 40

#17 bloating or bloated or gassiness or gaseousness or flatulence or flatulent or flatus or (abdominal distension) or (distended abdomen) or (swollen abdomen) or (abdominal swelling) or (postprandial fullness) or (post-prandial fullness) 918

#18 (gurgling or rumbling) and (abdom* or stomach or gastro*) 8

#19 (abdom* or stomach or epigastric or rectal or rectum or belly) and (pain* or cramp* or ache* or colic or discomfort) 3467

#20 reflux or GERD or dyspepsia or indigestion or heartburn or regurgitat* 1749

#21 belch* or burp* or eructation or hiccup* 158

#22 nausea* or vomit* or emesis or retching 4760

#23 (faecal or fecal or anal or bowel) and (incontinen* or leak* or soiling) 872

#24 (bowel control) or encopresis 36

#25 ((gut or digestive or gastro* or bowel* or colon*) AND health*):TI 129

#26 #25 OR #24 OR #23 OR #22 OR #21 OR #20 OR #19 OR #18 OR #17 OR #16 OR #15 OR #14 OR #13 OR #12 OR #11 OR #10 OR #9 OR #8 OR #7 OR #6 OR #5 OR #4 15754

#27 #26 AND #3 211

Evidence syntheses identified in exploratory searches

Adeyemo, M.A., Spiegel, B.M. and Chang, L. (2010) 'Meta-analysis: do irritable bowel syndrome symptoms vary between men and women?'. *Alimentary Pharmacology & Therapeutics*, 32(6), pp. 738-755. Available at: https://doi.org/10.1111/j.1365-2036.2010.04409.x.

Aldhaleei, W.A., Bhagavathula, A.S., Wallace, M.B., DeVault, K.R. and Faubion, S.S. (2023) 'The association between menopausal hormone therapy and gastroesophageal reflux disease: a systematic review and meta-analysis'. *Menopause*, 30(8), pp. 867-872. Available at: https://dx.doi.org/10.1097/GME.0000000000002214.

Bach, F.L., Sairally, B.Z.F. and Latthe, P. (2020) 'Effect of oestrogen therapy on faecal incontinence in postmenopausal women: a systematic review'. *International Urogynecology Journal*, 31(7), pp. 1289-1297. Available at: https://dx.doi.org/10.1007/s00192-020-04252-1.

Lenell, C., Pena-Chavez, R., Burdick, R.J. and Rogus-Pulia, N. (2022) 'The relationship between menopause and dysphagia: A scoping review'. *Womens Health Reports*, 3(1), pp. 990-997. Available at: https://doi.org/10.1089/whr.2022.0078.

Narrative review (identified from Epistemonikos searches) not using systematic methods:

Heitkemper, M.M. and Chang, L. (2009) 'Do fluctuations in ovarian hormones affect gastrointestinal symptoms in women with irritable bowel syndrome?'. *Gend Med*, 6 Suppl 2, pp. 152-167. Available at: http://doi.org/10.1016/j.genm.2009.03.004

Appendix B: UK and international menopause guidelines: inclusion of gastrointestinal symptoms

Organisation	Guidance	GI symptoms in peri- or postmenopause	Reference
National Institute for Health and Care Excellence (NICE)	Menopause: diagnosis and management	Not described	(NICE, 2019)
British Menopause Society (BMS)	What is the menopause? Information for GPs and other health professionals	Not described	(British Menopause Society, 2023)
Royal College of Nursing (RCN)	Menopause. RCN guidance for nurses, midwives and health visitors	Not described	(RCN, 2020)
European Menopause and Andropause Society (EMAS)	Position statement: The essential menopause curriculum for healthcare professionals	Not described	(Rees *et al.*, 2022)
Endocrine Society	Treatment of Symptoms of the Menopause: An Endocrine Society Clinical Practice Guideline	Not described	(Stuenkel *et al.*, 2015)
North American Menopause Society (NAMS)	The 2023 nonhormone therapy position statement of The North American Menopause Society	Not described	(North American Menopause Society, 2023)
Association of the Scientific Medical Societies in Germany (AWMF)	Perimenopause and postmenopause - Diagnosis and Interventions	Not described	(Inwald *et al.*, 2021)
American Association of Clinical Endocrinologists (AACE)	Position Statement on Menopause-2017 Update	Not described	(Cobin and Goodman, 2017)
Society of Obstetricians and Gynaecologists Canada (SOGC)	SOGC/CMS Menopause Guidelines	Not described	(Rowe, 2021)

Appendix C: Gastrointestinal symptom inclusion in menopausal symptom assessment scales

Menopausal symptom assessment scale	**Gastrointestinal symptoms assessed**	**Reference**
Blatt-Kupperman Menopausal Index	None	(Blatt, Wiesbader and Kupperman, 1953)
Cervantes Scale	None	(Pérez-López *et al.*, 2013)
Greene Climacteric Scale	None	(Greene, 1976)
Holte/Mikkelsen Menopause Checklist	None	(Holte and Mikkelsen, 1991)
Women's Health Questionnaire (WHQ)	Abdominal cramps or discomfort; nausea; bloating	(Hunter, 2000)
Menopause Rating Scale (MRS)	None	(Heinemann *et al.*, 2004)
Menopause-specific Quality of Life Questionnaire (MENQOL)	Flatulence or gas pains; feeling bloated	(Hilditch *et al.*, 1996)
MenoScores Questionnaire (MSQ)	Bloating; flatulence; uncontrollable loss of gas or stool; constipation; diarrhoea; loose stools; nausea	(Lund *et al.*, 2018)
Midlife Women's Symptom Index	Bloating; stomach pain; frequent loose bowel movements; constipation; nausea	(Im, 2006)
Neugarten and Kraine's Symptom Checklist	Constipation; diarrhoea	(Neugarten and Kraines, 1965)
Study of Women's Health Across the Nation Menopausal Symptom Scale	None	(Gold *et al.*, 2000)

Appendix D: National Institute for Health (NIH) Patient-Reported Symptom Scales (PROMIS)

GI symptom domains	**Further details and subsymptoms**	**Notes**
Abdominal pain	Belly pain	
Gas/bloat/flatulence	Bloating (appearance of larger abdomen or feelings of pressure or fullness). Flatulence (passing gas). Gurgling, rumbling, bubbling in the abdomen.	
Nausea/vomiting	Feeling sick or queasy, vomiting up contents of your stomach, dry heaves	
Diarrhoea	Loose watery stools, bowel urgency (feeling like you must rush to the toilet), frequent bowel movements. Noticing undigested food in stools.	
Constipation	Incomplete evacuation (feeling unfinished after a bowel movement), straining, infrequent hard stools, anal pain	
Faecal incontinence	Stool leakage or soiling	
Gastrooesophageal reflux (GER)	Reflux (or the backflow of stomach contents into the throat), regurgitation of food, heartburn (sensation of burning in the breastbone area), belching, or hiccups	
[Disrupted swallowing]	*Pain or difficulty swallowing food or liquids. Food getting stuck in throat.*	*As there is a recent scoping review on menopause and dysphagia (Lenell et al., 2022), this symptom domain will not be included in this review.*
(Spiegel, 2013; Spiegel *et al.*, 2014)		

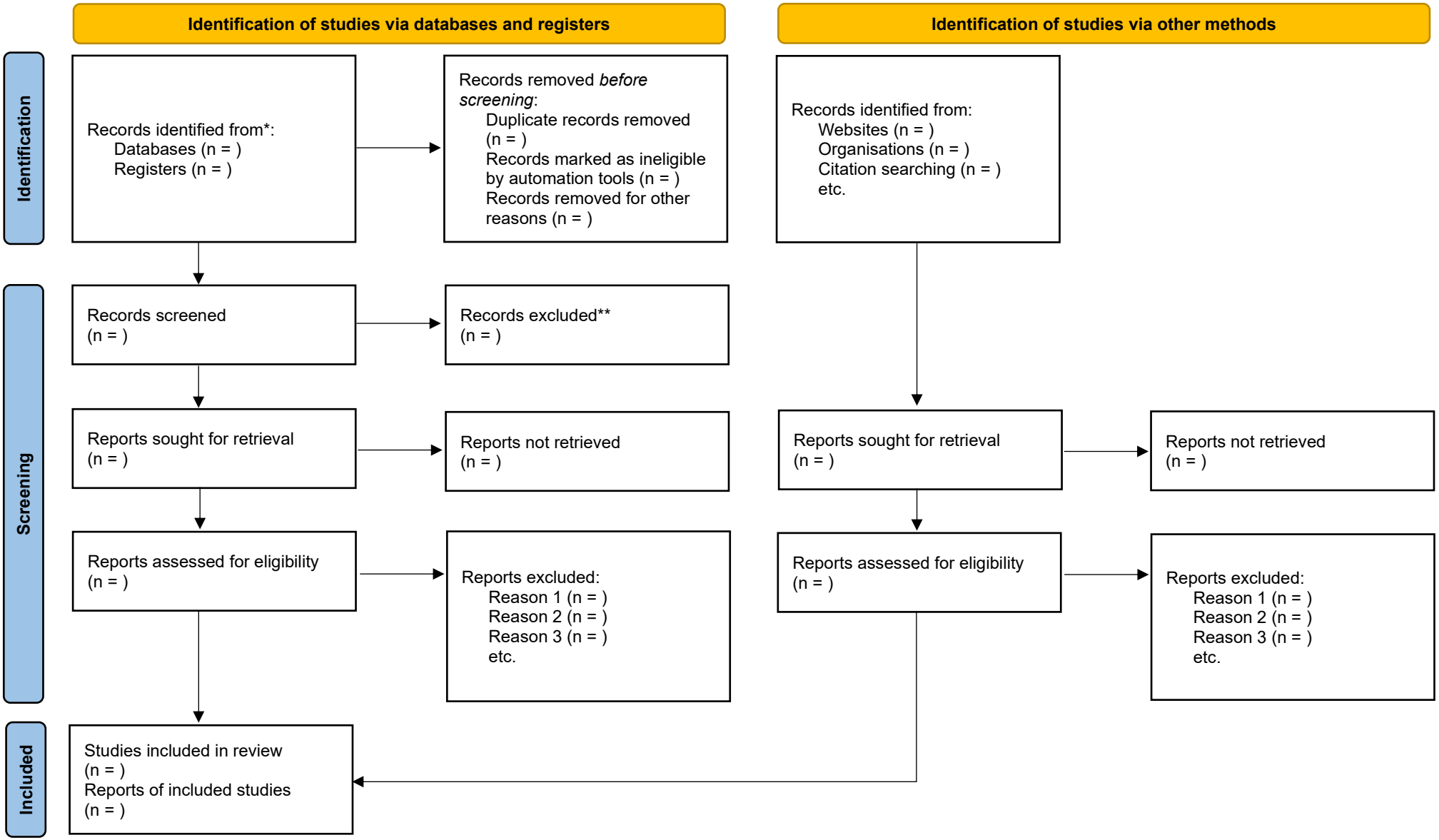
Appendix E: Provisional search strategy for Ovid MEDLINE

Ovid MEDLINE(R) and In-Process, In-Data-Review & Other Non-Indexed Citations <1946 to February 09, 2024>

1 exp Menopause/ 63795 2 (menopaus* or perimenopaus* or peri-menopaus* or postmenopaus* or post-menopaus* or postreproductive or post-reproductive or climacteric).ti,ab. 108322 3 1 or 2 122751	**Population search terms**
4 Irritable Bowel Syndrome/ 9696 5 exp Inflammatory Bowel Diseases/ 99466 6 exp "signs and symptoms, digestive"/ 170900 7 ((digestive or bowel or gut or gastro* or colonic) adj2 (symptom* or habit* or issue* or issue* or problem* or dysfunction*)).ti,ab. 38141 8 ((digestive or gastro*) adj3 symptom*).ti,ab. 26840 9 IBS.ti,ab. 11494 10 (inflammatory adj bowel).ti,ab. 63350 11 (ulcerative adj colitis).ti,ab. 47950 12 crohn*.ti,ab. 55687 13 (irritable adj bowel).ti,ab. 16348 14 (diarrh* or constipat*).ti,ab. 152871 15 ((loose or watery) adj stool*).ti,ab. 1895 16 ((bowel* or defecat*) adj2 (frequen* or urgen* or infrequen*)).ti,ab. 2740 17 (incomplete adj evacuation).ti,ab. 468 18 (bloating or bloated or gassiness or gaseousness or flatulence or flatulent or flatus or (abdom* adj disten*) or (swollen adj abdom*) or (swelling adj2 abdom*) or (postprandial adj fullness) or (post-prandial adj fullness)).ti,ab. 18869 19 ((gurgling or rumbling) adj2 (abdom* or stomach or gastro*)).ti,ab. 32 20 ((abdom* or stomach or epigastric or rectal or rectum or belly) adj2 (pain* or cramp* or ache* or colic or discomfort)).ti,ab. 86233 21 (reflux or GERD or dyspepsia or indigestion or heartburn or regurgitat*).ti,ab. 119996 22 (belch* or burp* or eructation or hiccup*).ti,ab. 3625 23 (nausea* or vomit* or emesis or retching).ti,ab. 114376 24 ((faecal or fecal or anal or bowel) adj2 (incontinen* or leak* or soiling)).ti,ab. 10164 25 ((bowel* adj control*) or encopresis).ti,ab. 1056 26 ((gut or digestive or gastro* or bowel* or colon*) adj2 health*).ti. 1442 27 or/4-26662206	**Concept search terms**
28 3 and 27 2162	**Population and concept search terms combined**
29 exp animals/ not humans/ 5191565	

30	28 not 29	2141	**Limit to humans only**

Appendix F: Blank PRISMA flow diagram from PRISMA 2020 (Matthew *et al.*, 2021)



Appendix G: Recommended items to report in a scoping review protocol (Peters *et al.*, 2022): completed checklist

Scoping review protocol			
Section and topic	**Item no**	**Information to report**	**Notes**
TITLE			
Identification	1a	Identify the report as a protocol of a scoping review	p. 1
Update	1b	If the protocol is an update of a previous scoping review, identify it as such	N/A
Registration	2	If registered, provide the name of the registry (such as JBI) and the registration number	
AUTHORS			
Contact	3a	Provide name, institutional affiliation, email address of all protocol authors; provide physical mailing address of corresponding author	p. 1 (Authors)
Contributions	3b	Describe the contributions of the protocol authors and identify the guarantor of the review	p. 21 (Section 3)
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol identify it as such and list changes: otherwise, state plan for documenting important protocol amendments	N.A
SUPPORT:			
Sources	5a	Indicate sources of financial or other support for the review	p. 21 (Section 4)
Sponsor	5b	Provide the name of the review funder and/or sponsor	p. 21 (Section 4)
Role of sponsor or funder	5c	Describe the roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	N/A
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the	p. 10 (Section 1)

		context of what is already known. Consider providing a rationale for conducting a scoping review as compared to other evidence synthesis approaches	
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to the inclusion/exclusion criteria.	p. 10 (Section 1)
METHODS			
Eligibility criteria	8	Specify the study characteristics such as PCC, study design, setting and timeframe) and report characteristics (such as years, consider, language, publication status) to be used as criteria for eligibility for the review	p. 11-14 (Table 1 and Section 2.2)
Information sources	8	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers, or other gray literature sources) with planned dates of coverage	p. 14-16 (Table 2 and Section 2.3)
Search strategy	10	Present a draft of the search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	p. 41-42 (Appendix F)
STUDY RECORDS			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	p. 16 (Section 2.3.4)
Selection process	11b	State that process that will be used for selecting studies (such as 2 independent reviewers) through each phase of review (that is screening, eligibility, and inclusion)	p. 16 (Section 2.4)
Data collection process	11c	Describe the planned method of extracting	p. 16-18 (Section 2.5)

		data from reports (such as piloting forms, done independently, in duplicate), any process for obtaining and confirming data from investigators	
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources) any preplanned data assumptions and simplifications	p. 18 (Table 3)
Outcomes and prioritization	13	Scoping reviews may not extract outcome data, so this can refer to whichever data items are extracted	This review will not extract outcome data from studies.
Risk of bias in individual studies	14	If this is to occur, describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done a the outcome or study leve, or both, state how this information will be used in data synthesis.	This review will not include risk of bias assessment (see Section 2.6)
Data synthesis	15a	Describe criteria under which study data will be presented	p. 19-20 (Section 2.7)
	15b	Describe the planned approach to how extracted data will be presented (such as figures, tables, evidence gap maps)	p. 19-20 (Section 2.7)
	15c	Describe any proposed additional analyses (such as thematic analysis)	N/A
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned synthesis	N/A
Meta-biases	16	Specify any planned assessment of meta-bias(es) such as publication bias across studies, selective reporting within studies	N/A
Confidence in cumulative evidence	17	If this is to occur, the method should be decribed.	N/A