

# BMJ Open Sex differences in neurology: a scoping review protocol

Ginette Moores , Elena Wolff, Aleksandra Pikula, Esther Bui

**To cite:** Moores G, Wolff E, Pikula A, *et al.* Sex differences in neurology: a scoping review protocol. *BMJ Open* 2022;**12**:e054513. doi:10.1136/bmjopen-2021-054513

► Prepublication history and additional supplemental material for this paper are available online. To view these files, please visit the journal online (<http://dx.doi.org/10.1136/bmjopen-2021-054513>).

Received 16 June 2021

Accepted 09 March 2022

## ABSTRACT

**Introduction** Sex and gender are independently important in health and disease but have been incompletely explored in neurology. This is in part contributed to by the pre-existing male bias in scientific literature that results in fewer females being included in clinical research and the often interchangeable use of sex and gender in the literature. This scoping review intends to identify the advances as well as under-explored aspects of this field to provide a road map for future research. This paper outlines the methods for a scoping review of published, peer-reviewed literature on sex and gender differences in four subspecialty areas of neurology: demyelination, stroke, epilepsy and headache.

**Methods and analysis** A detailed search strategy will be used to search five databases pertaining only to sex differences. Specific inclusion and exclusion criteria will be applied to capture relevant literature published from 2014 to 2020. Data will be collected and synthesised to provide an overview of information retrieved, a narrative synthesis of each subspecialty area and map of results.

**Ethics and dissemination** Research ethics board approval was not required for this study. This study will aid in mapping recent trends in sex differences in four major neurological conditions and will help identify areas for further research. A manuscript will be compiled for publication and presentations of findings.

**Registration details** The final protocol is registered with the Open Science Framework (<https://osf.io/n937x/>).

## INTRODUCTION

Medicine has moved away from a ‘one size fits all’ model of care in favour of a targeted, precision-based medicine approach that recognises the importance of population variables in health and disease. Of particular note are sex and gender, which have historically been used interchangeably or omitted as a variable in research design.<sup>1</sup> With the National Institutes of Health’s (NIH) policy change requiring sex to be defined as a biological variable, research is moving towards an increasing understanding of how sex influences neurological illness and treatment.

The interchangeable use of sex and gender in medical literature disregards distinctions between biological factors and sociocultural norms. Sex refers to biological differences between males and females (eg, hormonal

## Strengths and limitations of this study

- This will be one of the most comprehensive studies to date to summarise the available literature on sex and gender differences in four of the largest neurology subspecialties across diverse periods of hormonal changes.
- Both quantitative and qualitative studies will be assessed.
- The review will cover five databases (Ovid MEDLINE, PsychINFO, Embase, Central Registry of Controlled Trials, Ovid Emcare).
- Grey literature, commentaries, cases and pilot studies will not be included in the literature search.
- Due to the vast literature and broad topic, only studies published within the past 5 years will be included.

and genetic differences).<sup>2</sup> Sex differences play an important role in disease prevalence, presentation and outcomes, as well as in treatment efficacy and tolerability.<sup>3 4</sup> Gender refers to socially constructed roles, behaviours, expressions and identities of individuals (eg, risk-taking behaviour, treatment by others).<sup>2</sup> Gender differences have been implicated in health behaviours and disease outcomes.<sup>3</sup> Both sex and gender are independently important in health and disease, interacting through an individual’s life course and resulting in different health and disease outcomes.

The extent of sex and gender differences in neurology is incompletely explored. There has historically been a male bias in scientific literature, particularly in neuroscience, with females excluded from clinical trials or fewer females than males recruited to clinical trials.<sup>1</sup> Although this discrepancy has been reduced in recent years, gaps in studies examining sex and gender differences remain in the literature. Despite recent research indicating that 85.5% of human neuroscience studies include both male and female participants, 73.5% of these studies did not analyse data by sex.<sup>1</sup> As well, males are exclusively studied four times as often as females.<sup>1</sup> To optimise care for patients with neurological



© Author(s) (or their employer(s)) 2022. Re-use permitted under CC BY-NC. No commercial re-use. See rights and permissions. Published by BMJ.

Division of Neurology, Faculty of Medicine, University of Toronto, Toronto, Ontario, Canada

### Correspondence to

Dr Ginette Moores;  
[ginette.moores@medportal.ca](mailto:ginette.moores@medportal.ca)

conditions, it is important to understand how sex and gender each impact health and disease outcomes.

Therefore, this protocol is appropriately set for a scoping review of sex and gender differences across four neurology subspecialties: demyelination, stroke, headache and epilepsy. These four subspecialty areas were chosen as they are among the largest subspecialties in neurology. Furthermore, these conditions commonly affect younger adults, allowing for further evaluation of sex differences during periods of hormonal changes (ie, menstruation, pregnancy, menopause). The aims of the scoping are: (1) to systematically map the research conducted in these areas and (2) to identify any existing gaps in knowledge. These findings may inform future research and ultimately enable implementation of sex- and gender-specific strategies in clinical practice.

## METHODS

### Scoping review aim

The aim is to conduct a scoping review of sex differences in neurological conditions, using the Preferred Reporting Items for Systematic Reviews and Meta-analysis Protocols (PRISMA-P) guidelines.<sup>5</sup>

### Research objectives

This scoping review will explore how sex differences affect different aspects of patient experiences in four subspecialty areas in neurology: demyelination, stroke, headache and epilepsy. The findings will be used to summarise research conducted in these areas and identify any existing gaps of knowledge.

The broad research question for this review is: How does sex impact the epidemiology, pathophysiology, clinical presentation, response to intervention and disease outcomes in neurological conditions?

### Identifying relevant studies

#### Participants

Studies of participants with primary neurological conditions in one of the four neurology subspecialties (ie, demyelination, stroke, headache, epilepsy) will be included. Primary demyelination conditions will be considered as multiple sclerosis, neuromyelitis optica spectrum disorders and acute disseminated encephalomyelitis. Primary stroke conditions will be considered as ischaemic strokes, haemorrhagic strokes and cerebral venous sinus thrombosis. Primary headache conditions will be considered as migraines, tension-type headaches, cluster headaches, paroxysmal hemicrania, hemicrania continua or short-lasting unilateral neuralgiform headaches/short-lasting unilateral neuralgiform headaches with autonomic symptoms. Primary epilepsy conditions will be considered as any epileptic seizures (ie, non-epileptic events will not be included). Studies of participants with primary diagnoses of neuromuscular conditions, movement disorders, sleep disorders, neuroinfectious diseases, neuro-ophthalmology or neuro-oncologic conditions will not be included.

### Interventions

Studies that explore sex or gender differences in neurology will be included in initial review due to their often-interchangeable use in research. Ultimately, only studies exploring true sex differences will be included. Sex will be defined as the biological differences between males and females (eg, hormonal, genetic). Gender will be defined as social norms for men and women, including social constructs and attitudes.

### Inclusion and exclusion criteria

The scoping review will include (must meet all of the following):

1. Reviews, primary research (ie, qualitative, quantitative, mixed methods).
2. Human adults  $\geq 18$  years.
3. Sex- or gender-specific data as a primary objective of the study.
4. At least one of the four neurological subspecialties of interest (ie, demyelination, stroke, headache, epilepsy).
5. Published in English language.

The scoping review will exclude (must meet one of the following):

1. Abstracts, commentaries, editorials, letters to the editor, case reports, case series, animal studies, phase 1 and 2 studies, pilot studies.
2. Duplicate studies, irrelevant studies, those with a wrong aim, availability in abstract form only and multiple articles from the same study.
3. Humans  $< 18$  years.
4. Primary objective is not sex-specific endpoint.
5. Condition is not in one of the four neurological subspecialties of interest (ie, demyelination, stroke, headache, epilepsy).
6. Not published in English language.

### Search strategy

The search strategy will be designed and conducted by an information specialist using terms for each of the main concepts found within the review's research questions. The search strategy will include broad terms related to each neurological condition, their synonyms, sex or gender. The search strategy will first be validated in MEDLINE (Ovid) and subsequently translated in Cochrane Central Registry of Controlled Trials (Ovid), EMBASE (Ovid), Emcare (Ovid) and PsychINFO (Ovid). See online supplemental file 1 for the search strategy syntax that will be used in MEDLINE (Ovid).

Free-text terms will be run to identify additional relevant studies that were not identified with the controlled classifying terminology. Reference lists of relevant systematic reviews and all included articles will be reviewed to identify additional studies of relevance. Lastly, articles from authors of included studies will be sought for inclusion. Grey literature will not be searched. Given the rapidly evolving field and recent advances in sex and gender differences in person-centred medicine, studies

will be limited to those published between 2014 and 2020. This time frame was chosen as in 2015/2016, the US NIH designed awards to promote the integration of sex and gender into clinical studies.<sup>6</sup> These policies highlighted the importance of considering sex in study design and analysis and subsequently led to a new generation of research. This scoping review focuses on the aftermath of this historical change to provide a review of recent work in this field.

### Data collection and study selection

Searches will be exported into EndNote software, with duplicates identified and removed. Study selection will involve a two-stage process:

1. Title and abstract review
2. Full-text review

For the first stage, two reviewers with the aid of Covidence software will screen the titles and abstracts of articles identified in the search and additional sources described. The inclusion/exclusion criteria will be tested on sample abstraction prior to beginning full abstract review. At the second stage, full-text articles will be obtained and assessed again by two reviewers to determine if they meet inclusion and exclusion criteria. Reasons for exclusion will be documented for all articles at both stages. In the case of disagreement not resolved by discussion, a third reviewer will be consulted. A complete PRISMA flow chart and table of all included studies will be prepared for the final review.<sup>5</sup>

### Data charting process

Reviewers will independently extract data using a standardised data collection form designed for this study. Prior to implementation, the research team will review this form to ensure all relevant information is accurately captured. Data charted will include, but not be limited to: study citation, study methods (eg, aim, design, population, 'n' sample size), key findings, patient characteristics (eg, pregnancy, menopause), neurological condition, and sex-specific and gender-specific information relevant to the patient experience (eg, epidemiology, pathophysiology, risk factors, clinical features, diagnostics, medical and surgical treatments, disease outcomes, psychosocial outcomes and comorbidities). All study outcomes will be reviewed, including both qualitative and quantitative results. Data abstraction will occur concurrently by two independent reviewers. To ensure accuracy, extracted information by each reviewer will be compared and discrepancies will be discussed to ensure consistency between reviewers. Authors of eligible studies will be contacted, if necessary, to obtain further information. The data will be compiled into a single Microsoft Excel spreadsheet.

The methodological quality of studies included for in-depth review will be examined, as applicable, using a modified version of the Critical Appraisal Skills Programme quality assessment tool for qualitative studies.<sup>7</sup> The Confidence in the Evidence from Reviews of

Qualitative research approach will be used to determine how much certainty should be placed on findings from the review's synthesis.<sup>8</sup>

### Results synthesis

The neurology subspecialty areas previously identified will be used as a foundation to organise results as an overview of all of the information retrieved and to establish the extent and nature of the literature. The following presentation strategies will be used for each subspecialty area:

1. Basic overview of amount, type and distribution of included studies
2. Narrative synthesis and mapping of results

A meta-analysis of quantitative results will not be performed as that is not part of scoping review methodology.

### Patient and public involvement

No patient involvement.

### ETHICS AND DISSEMINATION

No ethical approval was required for this study as it is literature-based.

Given that sex and gender differences are not studied with consistent methods, the overview presented by this scoping review may provide clarity regarding what is currently known about sex differences in neurology. This scoping review will map the recent trends observed in sex difference research in neurology and identify subspecialty areas in need of further research. An understanding of sex-differences in neurology is necessary for implementation of sex-specific strategies to optimise patient care.

Knowledge translation will occur through presentation of results at relevant national and international conferences, and publication in a peer-reviewed journal. The study team will use their individual networks to encourage broad dissemination of results.

**Contributors** AP, EB and GM initiated the project. AP and EB advised on study methods and revised the draft paper. EW and GM wrote the first drafts of the paper. All authors were involved in the response to reviewers and approved the final version of the paper.

**Funding** The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

**Competing interests** None declared.

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

**Patient consent for publication** Not required.

**Provenance and peer review** Not commissioned; externally peer reviewed.

**Supplemental material** This content has been supplied by the author(s). It has not been vetted by BMJ Publishing Group Limited (BMJ) and may not have been peer-reviewed. Any opinions or recommendations discussed are solely those of the author(s) and are not endorsed by BMJ. BMJ disclaims all liability and responsibility arising from any reliance placed on the content. Where the content includes any translated material, BMJ does not warrant the accuracy and reliability of the translations (including but not limited to local regulations, clinical guidelines, terminology, drug names and drug dosages), and is not responsible for any error and/or omissions arising from translation and adaptation or otherwise.



**Open access** This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited, appropriate credit is given, any changes made indicated, and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>.

#### ORCID iD

Ginette Moores <http://orcid.org/0000-0002-5824-0563>

#### REFERENCES

- 1 Mamlouk GM, Dorris DM, Barrett LR, *et al.* Sex bias and omission in neuroscience research is influenced by research model and Journal, but not reported NIH funding. *Front Neuroendocrinol* 2020;57:100835.
- 2 What is gender? what is sex? *can. Institutes heal. Res.* 2020. Available: <https://cihr-irsc.gc.ca/e/48642.html> [Accessed 3 May 2021].
- 3 Connelly PJ, Azizi Z, Alipour P, *et al.* The importance of gender to understand sex differences in cardiovascular disease. *Can J Cardiol* 2021;37:699–710.
- 4 Zucker I, Prendergast BJ. Sex differences in pharmacokinetics predict adverse drug reactions in women. *Biol Sex Differ* 2020;11:32.
- 5 Tricco AC, Lillie E, Zarin W, *et al.* PRISMA extension for scoping reviews (PRISMA-ScR): checklist and explanation. *Ann Intern Med* 2018;169:467–73.
- 6 Consideration of sex as a biological variable in NIH-funded research. NIH website, 2015. Available: [https://orwh.od.nih.gov/sites/orwh/files/docs/NOT-OD-15-102\\_Guidance.pdf](https://orwh.od.nih.gov/sites/orwh/files/docs/NOT-OD-15-102_Guidance.pdf)
- 7 Critical Appraisal Skills Programme. *CASP qualitative checklist*. *CASP online*, 2018.
- 8 Lewin S, Glenton C, Munthe-Kaas H, *et al.* Using qualitative evidence in decision making for health and social interventions: an approach to assess confidence in findings from qualitative evidence syntheses (GRADE-CERQual). *PLoS Med* 2015;12:e1001895.