Sex differences in neurology: a scoping review

Ginette Moores, Patrick E Steadman, Amirah Momen, Elena Wolff, Aleksandra Pikula, Esther Bui

ABSTRACT

Objective  Historically, neurology research has demonstrated a sex bias with mainly male subjects included in clinical trials as well as lack of reporting of data by sex. In recent years, emphasis has been placed on increased participation of female participants and explicit declaration/evaluation of sex differences in clinical research. We aimed to review the available literature examining sex differences across four subspecialty areas in neurology (demyelination, headache, stroke, epilepsy) and whether sex and gender terms have been used appropriately.

Design  This scoping review was performed by searching Ovid MEDLINE, Cochrane Central Registry of Controlled Trials, EMBASE, Ovid Emcare and APA PsycINFO databases from 2014 to 2020. Four independent pairs of reviewers screened titles, abstracts and full texts. Studies whose primary objective was to assess sex or gender differences among adults with one of four neurological conditions were included. We report the scope, content and trends of previous studies that have evaluated sex differences in neurology.

Results  The search retrieved 22745 articles. Five hundred and eighty-five studies met the inclusion criteria in the review. The majority of studies were observational, often examining similar concepts designed for a different country or regional population, with rare randomised controlled trials designed specifically to assess sex differences in neurology. There was heterogeneity observed in areas of sex-specific focus between the four subspecialty areas. Thirty-six per cent (n=212) of articles used the terms sex and gender interchangeably or incorrectly.

Conclusions  Sex and gender are important biological and social determinants of health. However, the more explicit recognition of these factors in clinical literature has not been adequately translated to significant change in neuroscience research regarding sex differences. This study illustrates the ongoing need for more urgent informed action to recognise and act on sex differences in scientific discovery and correct the use of sex and gender terminology.

Trial Registration  The protocol for this scoping review was registered with Open Science Framework.

INTRODUCTION

The term sex refers to biological differences between males and females (eg, chromosomal, genetic, hormonal and anatomical differences). Sex is usually categorised as male, female or intersex.1 Gender refers to individuals’ identities which are influenced by socially constructed roles, cultural norms, behaviours and expressions. When gender is categorised as binary, it is characterised as man, woman.1 Both sex and gender are independently important in health and disease, interacting throughout an individual’s life course and resulting in different health and disease outcomes. Despite their distinctions, it can be challenging to separate sex and gender. This is further complicated by the often-interchangeable use of the terms sex and gender in medical literature. This can result in misinterpretation of results and impacts the translation of research into real-world conditions.

Biologically, males and females are different. Sex-based and gender-based differences have been identified in the epidemiology, pathophysiology, clinical presentation and outcomes of several medical conditions. Moreover, there remain sex-specific considerations at different life stages for females, such as puberty, pregnancy, ageing and menopause. Sex-based and gender-based analyses have been increasingly recognised as important in scientific evidence. In 2009, the Canadian Institutes of Health Research asked researchers to consider how sex and gender apply to research design and analysis.2 Then in 2016, the US National Institutes of Health designed awards to promote integration of sex as a biological variable into clinical studies.3 The European Commission

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews guidelines were followed with preregistered study protocol.

⇒ Studies were restricted to those published since 2014.

⇒ Only English studies were included.

⇒ No formal assessment of publication bias or study quality was performed.
also integrated gender-based and sex-based analysis into its research and innovation programme which came into effect in 2015–2016. These policies and regulations have fostered female enrolment and sex-specific analysis as well as addressing gender equality in research, although for the purpose of this review the focus will be on sex and not gender.

In the field of neurology, like most other areas of medicine, there has historically been a male bias with fewer females included in clinical trials and the absence of sex-based analysis. Increased recognition of sex-based differences has been observed in a wide range of neurological diseases, including migraine, genetic epilepsies, ischaemic stroke, demyelination, Alzheimer’s disease and Parkinson’s disease. Preclinical evidence suggests that sex steroid hormones affect brain development, modulate synaptic transmission, regulate neural plasticity and interact with many neurotransmitters. Furthermore, a neuroprotective effect of oestrogens and androgens has been proposed. Considerations for sex-based and gender-based differences advance our understanding of disease mechanisms and precision-based therapeutics, highlight disparities in care and outcomes, and inform policy changes aimed towards greater equity.

This scoping review aimed to comprehensively capture and conceptualise sex-based research pertaining to female health in four subspecialty areas of neurology: epilepsy, headache, demyelination and stroke. These subspecialties were chosen as they are some of the larger areas of neurology and these conditions may affect individuals throughout the lifespan. Specifically, we sought to better understand existing sex-based research in neurology as it pertains to three key aspects: (1) appropriate use of sex-based and gender-based terminology, (2) geographical hubs of sex-based research, (3) research focus as it applies to (A) life stage of population studied and (B) main theme of research, that is, epidemiology, pathophysiology, diagnostic, therapeutic or outcomes-based research. While we recognise intersex and other non-binary gender terms, these were not included due to the scope of the paper and specific focus on most common women’s neurology issues.

This review, encompassing multiple subspecialty areas of neurology, will be the first of its kind to summarise the volume of literature and significant advances made in the field of sex-based medicine. The electronic search strategy was developed with the assistance of a medical librarian and included terms for sex or gender, headache, demyelination, stroke and epilepsy. The complete list of specific terms that were used can be found in online supplemental appendix A1. Both sex and gender terminology were used at the initial search stage due to the interchangeable use of the terms in medical literature. However, only sex was included for the purposes of study inclusion. A manual search for articles included in reference lists of the included studies was performed.

Study selection
All studies were imported into Covidence for removal of duplicates and screening. Articles were included in the review if they were reviews or primary research with a primary objective of examining sex-specific differences in one of four neurological subspecialties of interest, regardless of terminology used. Studies were excluded if they were not original research studies, were conference abstracts, editorials, letters to the editor, non-human studies, paediatric studies or published in a non-English language. Table 1 provides the inclusion and exclusion criteria for studies in this review. Two reviewers independently evaluated eligibility of titles, abstracts and full texts for inclusion. Any disagreements were discussed between the pair of reviewers and a third-party reviewer was consulted if consensus was not reached. The PRISMA flow diagram demonstrating study selection process is shown in online supplemental file 2.

Data extraction and synthesis
Specific data were extracted independently by two authors from full-text articles included in the final sample. Extracted information included title, authors, publication year, journal, purpose, methods and conclusions. The average impact factor was calculated for all journals in which included articles were published. Disagreements between reviewers were handled by consensus and, if agreement was not reached, a final decision was made by a third-party reviewer. Due to the heterogeneity of the study methods, populations and objectives, meta-analysis was not appropriate for this review. The main outcomes were categorised into themes. The frequencies of each category are presented below in table 2.
In reviewing the appropriate usage of the sex and gender terminology, we categorised publications into three groups: correct usage, interchangeable usage and incorrect usage. When the terms sex and gender were used in the correct context, this was categorised as correct usage. In contrast, it was considered interchangeable use when sex and/or gender terminology were used equivalently throughout the text, and incorrect use when articles used the term sex or gender under the wrong word definition.

**Patient and public involvement**

Patients were not involved in the design or completion of this study.

**RESULTS**

The systematic searches of the five databases initially identified 22,745 articles. After duplicates were removed and title and abstract screening complete, 869 articles remained for full-text review. On full-text review, 585 articles met all inclusion criteria and were included in the final review. Articles were obtained from a variety of different journals with subspecialty-specific journals being the most represented.

**Study design**

Study characteristics are summarised in table 2. The majority of sex-based articles identified were in the stroke literature (57.2%, n=335/585), followed by demyelination (17.4%, n=102/585), epilepsy (15.9%, n=93/585) and headache (9.4%, n=55/585), respectively. Most were cohort or cross-sectional-based studies (64.4%, n=377/585) with only 7.8% (n=46/585) with a randomised controlled trial design. The average impact factor of articles was 4.6. Articles with a sex-based research focus have been published at an unchanging rate annually from 2014 to 2020 apart from a slight decrease in numbers in 2020. This is likely a reflection of the earlier stop date of September 2020 due to date of data acquisition.

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**Table 1** Inclusion and exclusion criteria

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Inclusion</th>
<th>Exclusion</th>
</tr>
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<tbody>
<tr>
<td>Language</td>
<td>English</td>
<td>Any other language</td>
</tr>
<tr>
<td>Type of article</td>
<td>Reviews, primary research (ie, qualitative, quantitative, mixed methods)</td>
<td>Abstracts, commentaries, editorials, letters to the editor, case reports, case series, and animal studies, phase 1 and 2 studies, pilot studies, duplicate studies, irrelevant studies, studies with a wrong aim, availability in abstract form only, and multiple articles from the same study</td>
</tr>
<tr>
<td>Population</td>
<td>Primary condition is one of: Demyelination (neuromyelitis optica (NMO), multiple sclerosis, myelin oligodendrocyte glycoprotein (MOG), acute disseminated encephalomyelitis (ADEM), transverse myelitis, optic neuritis) Stroke (haemorrhagic, ischaemic or cerebral venous sinus thrombosis) Primary headache disorder (migraine, tension-type, cluster headache, trigeminal autonomic cephalgias) Epilepsy or seizure</td>
<td>Any other group</td>
</tr>
<tr>
<td>Participants</td>
<td>Adults ≥18 years</td>
<td>Humans &lt;18 years</td>
</tr>
<tr>
<td>Reporting measures</td>
<td>Provide sex-specific data as a primary objective/outcome of the study</td>
<td>Primary objective was not a sex-specific endpoint</td>
</tr>
</tbody>
</table>

**Table 2** Study characteristics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Categories</th>
<th>N</th>
<th>%</th>
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<tbody>
<tr>
<td>Subspecialty</td>
<td>Demyelination</td>
<td>102</td>
<td>17.4</td>
</tr>
<tr>
<td></td>
<td>Epilepsy</td>
<td>93</td>
<td>15.9</td>
</tr>
<tr>
<td></td>
<td>Headache</td>
<td>55</td>
<td>9.4</td>
</tr>
<tr>
<td></td>
<td>Stroke</td>
<td>335</td>
<td>57.3</td>
</tr>
<tr>
<td>Study design</td>
<td>Cohort</td>
<td>256</td>
<td>43.4</td>
</tr>
<tr>
<td></td>
<td>Cross-sectional</td>
<td>121</td>
<td>20.5</td>
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<tr>
<td></td>
<td>Case-control</td>
<td>44</td>
<td>7.5</td>
</tr>
<tr>
<td></td>
<td>Narrative or comprehensive review</td>
<td>2</td>
<td>0.3</td>
</tr>
<tr>
<td></td>
<td>RCT</td>
<td>46</td>
<td>7.8</td>
</tr>
<tr>
<td></td>
<td>Systematic review/meta-analysis</td>
<td>100</td>
<td>16.9</td>
</tr>
<tr>
<td></td>
<td>Other</td>
<td>17</td>
<td>2.9</td>
</tr>
<tr>
<td>Impact factor</td>
<td>Average</td>
<td>4.6</td>
<td></td>
</tr>
<tr>
<td>Year of publication</td>
<td>2014</td>
<td>76</td>
<td>13.0</td>
</tr>
<tr>
<td></td>
<td>2015</td>
<td>77</td>
<td>13.2</td>
</tr>
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<td></td>
<td>2016</td>
<td>82</td>
<td>14.0</td>
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<td></td>
<td>2017</td>
<td>100</td>
<td>17.1</td>
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<td></td>
<td>2018</td>
<td>91</td>
<td>15.6</td>
</tr>
<tr>
<td></td>
<td>2019</td>
<td>94</td>
<td>16.1</td>
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<tr>
<td></td>
<td>2020</td>
<td>64</td>
<td>10.9</td>
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</table>

RCT, randomised controlled trial.
Appropriate use of sex-based and gender-based terminology

The appropriate usage of the terms sex and gender is highlighted in figure 1. Despite the absence of clear definitions, review of the original manuscripts confirmed that only 63.6% accurately used the terms ‘sex’ or ‘gender’ in the context of the stated primary outcome. Among these, only 37.1% correctly applied this definition to a uniform population, that is, females or males and women or men. For example, in one study, the authors correctly identified that sex and not gender differences were being assessed regarding the epidemiology, clinical features and pathophysiology of migraine. However, in the publication text, sex terminology (ie, females) were interchangeably used with gender-based terminology (ie, women). This pattern was seen consistently across all the subspecialty areas examined.

Geographical hubs of sex-based research

Most of the research originated from three countries: USA (32.3%, n=189/585), China (7.0%, n=41/585) and Canada (5.5%, n=32/585). Articles originated from a total of 51 countries, as illustrated in figure 2. Conversely, there was a relative paucity of sex-based research originating from Africa, Southeast Asia, Oceania and South America.

Research focus

Our scoping review identified dominant aspects of research among the population studied as well as themes of research, as summarised in figure 3. These dominant aspects of research varied among the four specialties.

Demyelination

There were 103 studies that examined sex differences in demyelination. In 28 of these studies, sex was included solely as a risk factor for demyelination, stratified or adjusted for sex across a population. One systematic review examining sex differences for approved disease modifying therapy in multiple sclerosis found that no clinical trial performed a preplanned sex-based analysis of adverse events. There was an overall lack of research regarding sex differences in clinical characteristics of participants in trials and response to disease modifying therapy.
Among the remaining studies, most described demyelinating disease among females or for female-specific considerations (eg, puberty, pregnancy). Seven studies assessed the disease characteristics and imaging findings for testosterone levels among men with demyelinating disease. Of these, one phase 2 study found that testosterone treatment decreased grey matter loss in the brains of 10 males with active relapse remitting multiple sclerosis.

Twenty-seven studies examined puberty, disease course peripartum and treatment recommendations during pregnancy. Demyelination literature in the ageing population was lacking with no studies specifically examining individuals older than 60. Furthermore, literature in the perimenopausal period was sparse: one cross-sectional, one case–control, nine narrative/expert opinion and one systematic review. There were conflicting results with regard to the effect of menopause on Expanded Disability Status Scale (EDSS) and disease perception. One case–control study analysing differences in brain structure found that prior to menopause females had higher total brain, cortical and brainstem volumes compared with men. However, these differences were not observed during the postmenopausal period.

**Headache**

Among the 55 studies, there were 63 primary headache types reported as some studies addressed more than 1 headache disorder. Almost three-quarters of these focused on migraine (n=46, 73.0%). Sex differences in clinical presentation and treatment were the two main themes in the headache literature.

In migraine, eight case–control and cohort studies describe headaches of longer duration, increased pain intensity, with more associated clinical symptoms among females than males. A systematic review of cluster headache found that females were more likely to have an atypical presentation with more associated nausea but no other differences in associated migraine symptoms. Females were more likely to be misdiagnosed with an average 6.6-year delay to cluster headache diagnosis. One cohort study of 210 people with tension-type headache found that females had more active trigger points than males. The authors speculate that this difference may explain the differential response to trigger point injections observed.

Of the 23 articles discussing treatment, 13 (56.5%) focused on differences in response to various headache medications and treatment patterns. The remaining studies focused on the management of menstrual migraine or reviewed the safety of pharmacological headache management during pregnancy. Females were more likely to seek medical care and be given prescription medication for their migraine headaches. A systematic review and meta-analysis found only 19 studies providing sex-specific results to triptan treatment. Trials largely enrolled female participants (85.9%). There was no difference in pain freedom between sexes, however, females were more likely to experience pain recurrence and adverse effects. Another study did not find any differences in pain response to over-the-counter medications. There was an absence of literature examining sex differences in preventative treatment strategies, especially the
new highly effective therapies. Only two studies assessed sex differences in complementary medicine treatment of headaches. The study argued that sex differences in the relationship between stress, sleep anxiety and headaches should lead to different management strategies between the sexes, with a focus on treatment of sleep and underlying depression in males and physical therapy and psychological/emotional approaches in females.

Among the women’s health topics, most focused on menstrual-related migraine, the use of hormonal therapy and the perimenopausal transition. Headache literature in vitro fertilisation was sparse with only one systematic review of headache in pregnancy that discussed the increased risk of headache with in vitro fertilisation.

**Stroke**

Of the 335 cerebrovascular disease studies, 276 studies examined risk factors, outcomes and for cerebrovascular disease, most of which included sex as a covariate or stratifying variable.

Some studies focused on more than one stroke subtype. Over three-quarters of these focused on ischaemic stroke (77.0%). The second most common subtype was haemorrhagic stroke (17.3%). Most other topics including cerebral venous sinus thrombosis, subarachnoid haemorrhage and reversible cerebral vasoconstriction syndrome received little attention.

There are sex differences in the prevalence and impact of major stroke risk factors between the sexes. Females have a higher prevalence of hypertension, obesity, congestive heart failure and atrial fibrillation while males have higher rates of diabetes, dyslipidaemia, smoking and coronary artery disease. A history of diabetes confers a greater risk of stroke for females than males. Similarly, females with atrial fibrillation have a 24% increase in relative risk of stroke compared with males with atrial fibrillation. Hypertension carries a greater risk of stroke among females at a lower threshold compared with males.

A systematic review and meta-analysis that included 78 studies with a total of 10,187,549 individuals identified the additional presence of sex-specific risk factors for ischaemic and haemorrhagic stroke such as hypertensive disorder in pregnancy, orchietomy, androgen deprivation therapy, testosterone therapy and late menopause.

Studies analysing sex differences in stroke treatment found conflicting results. For example, in a large retrospective cohort study of 55,947 people with a new diagnosis of atrial fibrillation, rivaroxaban decreased the risk of stroke in males compared with both warfarin and dabigatran use without a significant difference in the risk of bleeding. In females, there was no difference in risk of stroke between anticoagulants, however, rivaroxaban was associated with a significantly increased risk of bleeding (HR 1.20, 95% CI 1.09 to 1.48). By contrast, a systematic review and meta-analysis that included three post hoc analyses and one cohort study found that new oral anticoagulants were more effective in males (OR 1.19, 95% CI 1.06 to 1.33); however, females had less adverse effects of major bleeding (OR 0.90, 95% CI 0.82 to 0.99). Similarly, there remains controversy in sex differences for thrombolysis, while sex differences are only now being explored for tenecteplase use in stroke.

**Epilepsy**

Ninety-one studies evaluated sex differences in epilepsy. Ten studies discussed sex differences in pharmacokinetics of antiseizure medication. Of these studies, five cohort studies, three cross-sectional, one systematic review, one narrative review and two post hoc analysis of clinical trials reported differences for levetiracetam, valproic acid, Dilantin, lamotrigine, lacosamide and perampanel. One post hoc analysis of 1478 individuals found that oral clearance of perampanel was 17% lower among females. Adverse effects differed between males and females; however, females were more likely to discontinue the medication due to adverse effects. A cohort study of Dilantin and post hoc analysis of lacosamide both found that females were exposed to higher concentrations of antiseizure medications, possibly due to lower body weight.

Pregnancy was the most studied women’s health topic with a predominant focus on complications, antiseizure medication exposure/clearance and fetal outcomes. A single study investigated males with epilepsy during a partner’s pregnancy. This retrospective cross-sectional study found that fathers with epilepsy more frequently had new-onset anxiety and depression compared with fathers without epilepsy (OR 1.8). Results were not adjusted for social factors or other comorbidities that could impact the development of psychiatric disease.

Five observational studies highlighted a change in attitudes and prescriptions for females with epilepsy with decreased use of valproic acid and other first-generation antiseizure medications and trend towards use of second-generation medications since the early 2000s.

**DISCUSSION**

This scoping review provides a large-scale synthesis of research involving sex differences in neurology, identifying overarching themes in four subspecialty areas. Despite the new policies and regulations designed to foster sex equality in research, we did not identify any change in the number of annual articles considering sex-based differences after 2014. The lower number of articles published in 2020 likely reflects our study endpoint (September 2020) as opposed to a true decrease in publications.

Although knowledge of sex-based medicine continues to grow, we highlighted the ongoing use of sex and gender terms interchangeably with very limited separation between the use of the biological sex terms and social gender terms. Even when sex and gender constructs were appropriately used, language such as women and men or male and female was often used interchangeably. While this does not change the presence or the
absence of sex-related findings, this can potentially lead to incorrect interpretation of results and measurements bias. This highlights the need for precision in the use of related terminology in future research. Journal editors should also be informed and attentive to the precise use of related terminology.

Our scoping review also identified a lack of diversity of countries of study origin. Most research originated in North America and China, with few studies from Africa, Southeast Asia, South America and Oceania. However, studies not published in English language were excluded from this scoping review, leading to the potential for geographical bias. Previous research has explored the potential impact of excluding non-English language literature and did not identify evidence of systemic bias based on this exclusion criteria. As such, our observations raise the concern that sex-based neurological data are over-represented by three main regions and under-represented by some of the most populous dense regions in the world that may have unique biological and cultural influences on sex-based and gender-based research in neurology.

Sex-based research varied between the different neurological subspecialties. These differences are likely related to the age at onset of each condition, as individuals often develop headache, demyelination and epilepsy at younger ages than stroke. Therefore, more individuals with conditions emerging at younger age are likely to encounter concerns regarding pregnancy, hormones and contraception. Regarding hormonal-related analysis, we noted that most articles examining hormonal influences related to neurological conditions focused on female participants. Testosterone was examined to a much lesser extent than oestrogen and progesterone for both males and females. Despite age being captured in most studies, explicit research of sex differences in the ageing and geriatric population was lacking. This is most surprisingly seen in the field of stroke, where age-related factors contribute markedly to stroke incidence and prevalence. With the ageing baby boomer population, greater understanding and awareness of sex differences in the ageing population is necessary. This approach to sex integration would make recommendations applicable to a broader population.

In conditions where males are under-represented, findings may not be applicable to male patients. For example, there is a predominance of females in most demyelination trials likely reflecting the lower prevalence of demyelination in males. The lack of evidence regarding sex differences in response to management makes applicability of the results to males challenging. The CLAdRihne Tablets treating multiple sclerosis orally (CLARITY) study found that cladribine treatment significantly reduced the annual relapse rate in relapsing remitting multiple sclerosis. Subsequent post hoc analysis stratifying the efficacy of therapy based on baseline demographic characteristics, including sex, there was a greater reduction in annual relapse rate observed in males compared with females (68.4% vs 48.4%). These results were never intended for a direct sex-based comparison or adjusted for other possible confounding variables, and therefore, must be interpreted with caution.

In the field of headache, few studies have investigated sex differences in response to approved treatments for migraine, as well as their use in women who may be pregnant or lactating. Headache is a common adverse effect of in vitro fertilisation Furthermore, a pre-existing history of migraine increases the risk of ovarian hyperstimulation syndrome and rarely stroke. Despite this, few studies were found to specifically examine the relationship between headache and in vitro fertilisation or strategies to mitigate this risk.

The stroke literature has demonstrated that risk factors affect sexes differently and despite no difference in those risk factors prevalence, however, knowledge translation into clinical practice guidelines is limited. We identified a paucity of research pertaining to pathophysiology. For example, there is a lack of understanding of why diabetes confers a greater risk of stroke among mid-age females than males of the same age or why this risk is present at lower fasting blood glucose levels for females. Without understanding the underlying differences, guidelines recommend routine screening, with the same target levels for both sexes. This suggests the need for further research to elucidate the underlying biological and behavioural mechanisms involved, hence, to improve clinical practice for preventive stroke strategies.

In epilepsy research, pregnancy and contraception have been a main focus. The increased recognition and understanding of cognitive and teratogenic effects of valproic acid has led to decreased usage over time for females. Without understanding the underlying differences, guidelines recommend routine screening, with the same target levels for both sexes. This suggests the need for further research to elucidate the underlying biological and behavioural mechanisms involved, hence, to improve clinical practice for preventive stroke strategies.

Despite an increasing recognition in the importance of sex and gender as biological and health variables, this has not yet translated into sex-based research within these four specialties. Future studies should integrate sex in relation to all biological and age milestones, not only solely focusing on transient periods, such as pregnancy or menstruation, but also on developmental and transitional periods, such as childhood or menopause. There are known sex differences is brain development and anatomy from early childhood to late adolescence. Furthermore, adolescence is a period of increased sex hormones. Understanding how these biological changes may affect disease development, presentation and response to treatment will allow for individualised medicine. Females live longer than males, however, they are often more frail towards the end of life. Therefore, greater understanding of sex differences in older adults will serve to better understand and effectively treat age-related decline and diseases.
Strenghts and limitations
This scoping review follows the PRISMA guidelines. The study protocol was registered with OSF prior to title and abstract screening and protocol published to ensure transparency of the process and reduce potential bias. A comprehensive search strategy developed by a medical librarian was employed. This review was not without limitations. Although our scoping review focused on binary terms of male and female, men and women, we recognise that sex and gender issues in the neurosciences reflect a spectrum, including transgender, intersex and non-binary identities as examples of the diversity that truly reflects the greater population.

While efforts were made to include all relevant literature, it is possible that studies were missed due to electronic databases used. We restricted studies to those published since 2014 due to the significant progress in the recognition of sex considerations in medicine and research within the past decade. In addition, only studies published in the English language were included. We did not perform a formal assessment of publication bias or study quality. Therefore, it is possible that our results do not represent the current state of sex-based primary research in the field of neurology.

CONCLUSIONS
This review provides a first-ever up-to-date overview of the recently published sex-based primary research pertaining to four subspecialty areas of neurology. There are known sex differences in the epidemiology, risk factors, clinical presentation and management of neurological disorders. We highlighted limitations in current research with inappropriate application of sex and gender in clinical research. Integration of sex considerations has the potential to tailor clinical practice more specifically to individuals considering basic biological differences between males and females. Future research should consider more higher-quality trials. Researchers should consider how sex is used in analyses with a preference for mediation analyses, assessing if sex is an effect modifier rather than controlling for it as a confounding variable. This can, in turn, lead to improved health outcomes, patient experiences and reduced disparities in care.

Contributors All authors were involved in screening of literature and data extraction. GM was the main author of this work responsible for study design and coordination of the research team. GM is the guarantor of the study. GM and EB conceptualised this work. AP and EB were responsible for supervision of the research and critical revision of the manuscript. GM, EB, AP, PES, AM and EW were involved in screening of literature and data extraction. GM and PES were responsible for drafting of the manuscript. All authors helped with critical review of the manuscript for important intellectual content.

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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 applicable.

Ethics approval Research ethics approval was not required for this study as it is a summary of already-published literature.

Provenance and peer review Not commissioned; externally peer reviewed.

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