ECONOMIST IMPACT

Sex, gender and the brain:

Towards an inclusive research agenda

Commissioned by

WOMEN'S BRAIN PROJECT®

Contents

About this report

"Sex, gender and the brain: Towards an inclusive neurological research agenda" is a white paper by Economist Impact, a project that was envisioned by the Women's Brain Project and commissioned to Economist Impact. The Women's Brain Project provided expert counsel and guidance in the delivery of this project. The white paper presents the role of sex and gender in brain diseases and our research on how these factors are critical for the creation of an inclusive research agenda, which, in turn, is key to reducing the burden of neurological conditions for all. It provides a thematic review of identified sex and gender-based differences across five select brain diseases, and concludes with a series of recommendations that policymakers, researchers and institutions should consider in efforts to improve sex and gender-specific neurological research.

Alongside the white paper are conceptual frameworks, which outline a theory of change for greater investment in sex and gender-inclusive neurological research, and the impact of such investments on nations' economic profile. While this report was written by Economist Impact, we could not have developed the research without the input and support of key opinion leaders in this field.

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Interview list

The list below (in alphabetical order) includes the experts involved in this research:

- **Dr. Cheryl Carcel**, Neurologist and early career researcher leading the sex differences in stroke group at the George Institute for Global Health, University of New South Wales, Australia
- **Dr. Janine Clayton**, Director, National Institutes of Health (NIH) Office of Research on Women's Health; Associate Director for Research on Women's Health, NIH, United States
- **Anna Dé**, Policy Advisor, Women's Brain Project, Switzerland
- **Dr. Tarun Dua**, Head of the Brain Health Unit in the Department of Mental Health and Substance Use, World Health Organization, Switzerland
- **Dr. Maria Teresa Ferretti**, Co-founder and Chief Scientific Officer, Women's Brain Project, Switzerland
- **Professor Martin Knapp**, Professor of Health and Social Care Policy, London School of Economics and Political Science, United Kingdom
- **Dr. Antonella Santuccione Chadha**, Co-founder and CEO of the Women's Brain Project and Chief Medical Officer, Altoida, Switzerland
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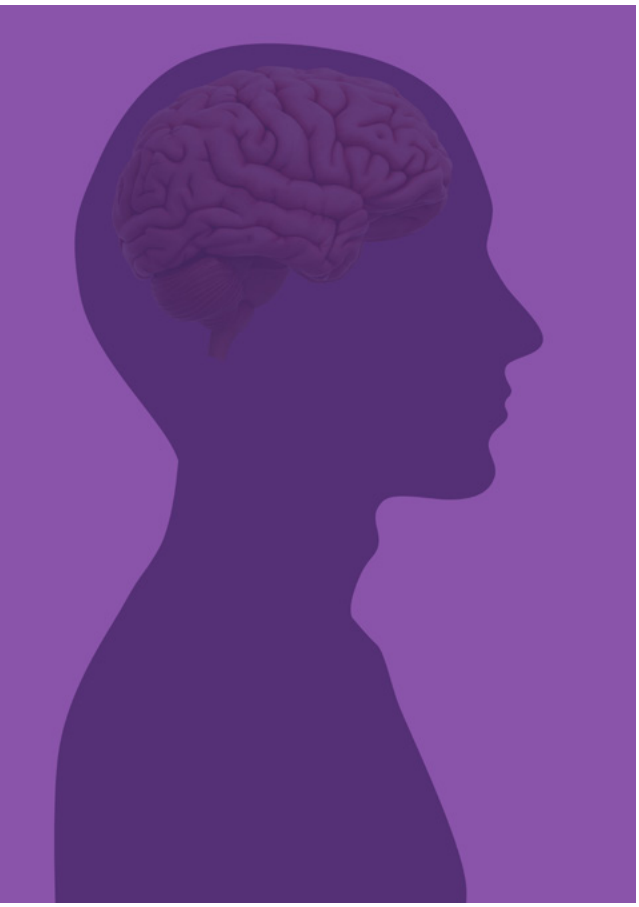
Economist Impact bears sole responsibility for the content of this report. The findings and views expressed in the report do not necessarily reflect the views of the sponsor, nor of the experts who kindly gave their time to advise us.

The research was led by Emi Michael. The research team consisted of Shaileen Atwal and Jocelyn Ho.

Executive summary



The burden of death and disability from brain diseases is a global health challenge, costing over US$800bn in the United States (US) alone, exceeding that of cancer and cardiovascular disease.[1,2,3] Brain disorders have been described as a pandemic far worse than Covid-19, with one in three people having some form of these conditions.[4]

The level of risk, rate of progression, severity of disease and management approach for brain diseases are influenced by, among other factors, an individual's sex, (denoted by characteristics that are biologically defined) and gender (denoted by socially constructed features). Yet, data detailing the influence of sex and gender on brain diseases are limited as these variables are rarely investigated or disaggregated. This gap in clinical research leads to inequitable service provision, from delayed diagnosis to inappropriate treatment and caregiving.

This Economist Impact white paper, informed by expert interviews, presents an economic impact framework to examine how sex and gender differences manifest across five brain diseases: Multiple Sclerosis, Stroke, Parkinson's Disease, Alzheimer's Disease and Migraine. The paper also explores the economic impact of proposed precipitating factors, consequences of differences in disease outcomes, and the most promising solutions to address the imbalance in research – which is, currently, primarily informed by clinical trial data dominated by male participation. This is the first phase of a research programme to create a modelling framework that quantifies the economic implications of sex and gender differences in brain diseases, and to build an evidence-based case for investment.

Key highlights from the report include:

- Brain diseases are growing in prevalence, mirroring the global ageing population. One in three people worldwide live with a brain disease and the total number of people who have died from them has increased significantly over the last 30 years, costing US$1.7trn in the US and Europe.[5]
- The paucity of effective therapies requires new approaches to clinical research and drug development. The economic impact of brain diseases on individuals, their families, social networks, and health systems are sizeable, and there are no curative treatments for many of these conditions including Multiple Sclerosis, Alzheimer's disease, and Parkinson's disease. The economic impact of these conditions is shaped by factors including age of onset, promptness and accuracy of diagnosis, and the burden of caregiving. The human and economic cost calls for an increase in more inclusive and advanced scientific research.
- Both sex and gender influence the prevalence, onset, and progression of brain diseases. Sex can modulate responses to treatment and disease progression, while gender influences factors such as communication between patients and healthcare providers, perceptions, stigma, and individual health-seeking behaviours. Most brain diseases have a higher prevalence among females: Multiple Sclerosis is twice as common in females than males, Migraine is two to three times more common, and two-thirds of the Alzheimer's Disease burden occurs among females. However, Parkinson's Disease is more prevalent among males.
- The economic burden of brain diseases is vast, thereby paralysing global markets and stunting international development. The growing burden and longevity of brain disorders will economically impact individuals, their families and society for years to come. Symptoms can make maintaining a job difficult and often lead to both patients and caregivers, who are primarily women, having poor educational attainment as well as leaving the labour force. To provide perspective, the health expenditure on brain diseases totalled US$800bn in 2017 in the US alone, and this is projected to rise significantly due to an ageing population. Tackling brain diseases therefore is not just a health problem, but also an economic one.
- Females are 'missing' from science. They are under-represented in clinical trials and data are generally extrapolated and deemed suitable for all. Despite the significant role played by sex and gender in disease outcomes, there is a dearth of nuanced analysis into how differences should be accounted for and uncovered in research, as well as a general lack of definitional clarity on sex and gender. Barriers include lack of knowledge and skills, inadequate funding, institutional cultures, and research norms.
- Biases are persistent in clinical research but there are tools to reveal and overcome them. More inclusive clinical trial design, as well as the recruitment and inclusion of sex and gender sensitivity as a requirement for research funding are examples of tools that can be used to enable a more inclusive brain research and policy agenda. More equitable preclinical and clinical research that tackle the biases that emerge from narrow trial populations would provide data to improve treatment protocols, adherence to drug regimens and overall disease outcomes.

Chapter one: The rising impact of brain disorders

The World Health Organization (WHO) defines brain disorders as diseases of the central and peripheral nervous system: structures like the brain, spinal cord and peripheral nerves. These include epilepsy, Alzheimer's Disease (AD) and other dementias, cerebrovascular diseases including stroke, migraine and headache disorders, Multiple Sclerosis (MS), Parkinson's Disease (PD), neuroinfections, brain tumours, traumatic disorders of the nervous system due to head trauma, and neurological disorders as a result of malnutrition.[6] These conditions, often chronic and disabling, are correlated with significant mental health challenges like anxiety and depression.[7]

Brain diseases will be a defining global health challenge in the next two decades. The Global Burden of Disease (GBD) Study in 2019 ranks brain diseases as the leading cause of disability, accounting for 276m disability-adjusted life years (DALYs) and the second leading cause of death worldwide (9m deaths).[8] One in three people worldwide suffer from a brain disorder, ranging from migraine to stroke and dementia[9], and the total number who died globally from brain disorders has increased by 61% (from 5.5m in 1990 to 8.8m in 2019)[5] over the last three decades, costing US$1.7trn in the US and Europe alone, almost twice the global burden of cardiovascular disease.[1,10,11] In 2019, they were the cause of over 530,000 deaths in North and South America and the Caribbean, 60% of which were female.[12] This burden is projected to grow due to an ageing population, with exponential growth expected in low-and middle income countries (LMICs), who are undergoing the epidemiological transition from the predominance of infectious diseases to non-communicable diseases (NCDs).[8,9,13]

Brain diseases will be a defining global health challenge in the next two decades.

Age and incidence of brain disorders increase in lockstep. With the number of people over 60 expected to increase from 962m in 2017 to 2.1bn by 2050, the incidence of brain disorders is set for a worrying escalation.[14] This growth will be especially severe in LMICs, where the incidence of stroke, for example, more than doubled in the preceding 40 years, driven by an ageing population, sedentary lifestyles, and increased prevalence of risk factors such as hypertension, obesity and diabetes mellitus.[15]

Covid-19 has also played a differential role in the trajectory of brain disease, from complications related to the infection to the secondary impact of control measures on access to specialist neurological services.[16,17] While new evidence on the causes of Covid-19-related complications is nascent, a recent study found substantial neurological and psychiatric morbidity in patients six months after a Covid-19 infection, with the greatest risk seen in patients who experienced severe infection.[18] Common symptoms post-infection include fatigue, brain fog, pain, anxiety and depression.[19]

Lack of awareness around sex and gender cascades within health research, resulting in the application of non-representative findings across sex/gender groups, and amplifying health inequalities.

The growing burden of brain disorders will impact individuals, their families and society, imposing both human and economic costs. Symptoms can make maintaining a job difficult, leading individuals and caregivers to drop out of the workforce altogether. Furthermore, accessing care for neurological diseases can be expensive, with many barriers beyond an individual's control. Although there is no recent evidence quantifying the global economic burden of brain diseases, to provide perspective, the health expenditure on brain diseases totalled US$800bn in 2017 in the US alone and this is projected to rise significantly due to an ageing population.[1] The breakdown of costs – both direct and indirect – pertaining to some of the brain diseases in our review include: US$170bn to AD, US$109.6bn to stroke, US$24.2bn to MS, and US$15.5bn to PD.[1] Tackling brain disease is thus an economic priority as well as a public health one.

Sex and gender: The missing perspective

Determinants of health, such as age, socioeconomic status, educational level, living and working conditions, all influence the quality of one's health; sex and gender are no exception, but are often overlooked in health research.[20] Sex can modulate disease progression and response to treatment, while gender influences communication between patients and healthcare providers, non-pharmacological disease management, stigma and an individual's need for assistance.[21]

Defining sex and gender

The impact of sex and gender on prevalence, burden and progression of brain diseases is gaining attention, but the terms are often used interchangeably in health research, and hence definitional clarity is necessary. According to the WHO, sex is defined as "the different biological and physiological characteristics of males and females, such as reproductive organs, chromosomes, hormones, etc.", whereas gender is defined as "the socially constructed characteristics of women and men – such as norms, roles and relationships of and between groups of women and men".[22]

This definition and other definitions found in research are limited because they reduce sex and gender identity to only male and female or man and woman, thereby neglecting the spectrum of biological sex and gender identities – including non-binary and transgender. Furthermore, the definition of gender overlooks the characteristics of behaviours and identities, and how they influence self-perception and interaction with society. This lack of awareness around sex and gender cascades within health research, resulting in the application of non-representative findings across sex/gender groups, and amplifying health inequalities.

While we understand that sex and gender differences between men/males and women/females are only part of the story, and that other sex and gender groups also face similar challenges, the data we have access to mostly focus on the binary groups. Hence, for the purpose of this report, we use the terms "males" and "females" when referring to biological sex differences, and the terms "men" and "women" when referring to gender differences.

Sex and gender in context

Females are disproportionately under-represented in research, specifically clinical trials, relative to the burden of disease in the population,[23,24] and have been consistently under-represented in brain diseases trials over the last two decades.[25] Disease burden and progression are different between males and females. In females, stroke is the third leading

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cause of death, with sex-specific risk factors such as pregnancy, pre-eclampsia and hormone replacement therapy;[26] the burden of MS and migraine is twice as high in females as compared to males, and there is possibly a higher incidence of some types of epilepsy in females.[27] It is therefore critical that the make-up of study populations reflects the distribution of disease.

More females are recruited into clinical trials for migraine than males, making it harder to extrapolate results for males with migraines and leaving them more prone to sub-optimal outcomes.[28] Such biases impact the quality of research and application of the findings. For instance, despite a growing commitment to reduce disparities in healthcare, information on gender identity is not routinely collected and can be misclassified by healthcare workers.[29,30] Women have to try longer and harder before getting a medical diagnosis, and are diagnosed at a later stage than men in more than 700 diseases.[31]

Sex- and gender-based biases and blind spots in research lead clinicians to perpetuate disparities in outcomes.[32] A Danish study, for example, found that doctors viewed men with chronic pain as "stoic" or "brave", whereas women were seen as "emotional" or "hysterical", and received less effective pain medication and more mental health referrals than men.[33] A separate analysis of 1,648 patients found that despite having similar clinical presentations, women were less likely than men to receive a diagnosis of stroke,[34] leading to undertreatment and poorer outcomes.[35] A recent retrospective study of patients in Ottawa found sex-specific differences in transient ischaemic attack (TIA)/ stroke diagnosis based on features such as duration, suddenness of symptom-onset, unilateral sensory loss, and pain; only 12% of women reporting pain were diagnosed with TIA/stroke, in comparison to 58% of men with the same complaint.[36] While organisations, including the WHO and the UN, have focused on mainstreaming gender as a relational concept that intersects with other drivers of inequalities at a global level, this has fallen short, with gender equality still largely treated as a separate issue or delegated to specialist agencies.[37]

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Health-seeking behaviours also differ based on sex and gender. For example, women in India reportedly prefer informal care where it is easier to communicate and avoid stigma, while men seek formal care due to ease of access, better quality of treatment, and better outcomes in some regions.[38] In Europe, men are less likely than women to seek help for health issues, a result of socio-cultural expectations of self-reliance and difficulty in expressing emotions.[39,40] Social beliefs about masculinity, which encourage men to project strength and hide vulnerability, translate into fewer healthcare encounters, delayed attention to symptoms and unwillingness to discuss medical concerns.[41] Greater awareness of sex and gender differences, and better clinical guidelines, are therefore imperative to avoid misconceptions amongst healthcare workers.

Research outlook

A strong evidence-based understanding of the role of sex and gender in brain disorders is critical to recognising variations in disease manifestations and health outcomes.[42] Progress in such understanding has improved in areas like cardiology,[43] leading to improved outcomes; for example, the UK and Ireland made significant reductions in cardiovascular mortality of more than 60% between 1980 and 2009.[44] This was partly due to a greater focus on the specific, unmet needs of females – for example, greater awareness of symptomatic differences (such as lower likelihood of central chest pain during a myocardial infarction)[45] and better adherence to treatment guidelines.[46]

Although sex differences are gaining more attention in research, gender is less frequently explored.[47] Barriers to including gender in health

research amongst researchers include: lack of knowledge and skills, not knowing how to quantify and measure gender, lack of applicability and feasibility, institutional cultures and inadequate funding.[48] Institutions such as the European Research Council (ERC), for example, dedicate less than 1% of their total budget (€924m) to investigating sex- and gender-specific brain research.[49] However, a recent report by the non-profit organisation Women's' Health Access Matters (WHAM) shows that the return on investment in sex-specific research is high. The report found that investing US$300m in women's health research for AD and other NCDs could generate a return on investment (ROI) of US$13bn through reduced burden of disease and lower societal costs and can generate US$930m in economic gains, as well as save 3,500 years of nursing home care and costs.[25]

To build the case for investing in sex- and gender-specific brain research, this report outlines how these two determinants impact five brain diseases: MS, Stroke, AD, PD, and Migraine. It explores how the economic impact of these diseases on patients and their caregivers varies based on factors such as prevalence, age of diagnosis, and the significance of informal care, and builds an economic impact model. The paper argues the need for greater efforts on sex- and gender-specific brain research based on the beneficial economic consequences of early and more reliable diagnosis, prevention, more effective treatments, and disease management, all of which could mitigate the impact of these conditions on individuals, families, and society at large.

Economic return

The economic impact of excluding sex- and gender-specific outcomes from biomedical research is complex, but can influence productivity, as well as national economic outcomes, both directly and indirectly. "Women live longer than men do, but women also live more years disabled than men do. Women are also more likely to provide unpaid caregiving to family members. Both disability and caregiving responsibilities can limit full participation in the workforce," says Dr Janine Clayton, Director of the National Institutes of Health (NIH) Office of Research on Women's Health and Associate Director for Research on Women's Health at the NIH. Healthy women are more productive in paid and unpaid work, take fewer sick days, and promote economic well-being and progress by raising their children in emotionally stable environments.[50]

In a recent report published by the RAND Corporation, the societal impact of increasing funding for dementia research in females was explored using microsimulation models. These models were used to measure the effect of enhanced investment in women's health research in the US, particularly the health and economic well-being of women and wider society. The findings indicate that investing US$280m in AD research that is focused on females can save 6,000 years with AD and AD-related dementias across a 30-year period, with significant gains in health-related quality of life, a drop in nursing home costs by more than US$360m; doubling investment could generate a ROI of 224%.[51]

Barriers to including gender in health research amongst researchers include: lack of knowledge and skills, not knowing how to quantify and measure gender, lack of applicability and feasibility, institutional cultures and inadequate funding.

Defining a conceptual framework for investment in sex and gender research

To make an economic case for greater investment in sex and gender inclusive brain research, Economist Impact has developed five novel conceptual frameworks, which convey how sex- and gender-specific research can impact a nation's overall gross domestic product (GDP), for each of the brain diseases included in this report: MS, Stroke, AD, PD and Migraine.

The framework development process began with an extensive literature review that focused on the sex and gender differences in the five select brain diseases and how they impact health and social expenditure. We assumed that a lack of data on sex and gender differences was the main driver of sex and gender inequalities in brain diseases; therefore, we assume that if we increase funding for better data generation and analysis of sex and gender variables, this will lead to better health outcomes for both males/men and females/women. We consulted five experts from across the world in the brain diseases field and conducted semi-structured interviews to gain insights and validate our approach. Experts were identified and selected based on their contributions to brain diseases, and included those who represent the following areas: academia, research and medicine, and policy.

We started with a conceptualisation of a general framework for brain diseases (see Figure 1), which we then adapted to build five frameworks according to disease-specific outcomes, where parameters were selected based on the availability of data. The parameters used in the framework were validated by our experts. The conceptual frameworks will inform the second stage of this two-step research programme which includes the development of an economic model that aims to quantify the disease-specific outcomes detailed within them.

For each brain disorder, the key objective is to fill the knowledge gaps in understanding the diagnosis, prevention and risk factors, based on sex- and gender-based presentations. As shown in Figure 1, there are two streams to achieve this. The first stream (Figure 1, left side) focuses on redefining clinical research priorities to mandate thorough exploration of sex and gender differences and reduce data gaps in disease epidemiology, pathophysiology, clinical manifestation and prognosis. The second stream (Figure 1, right side) is based on the need for better representation of males and females in clinical drug trials (reflective of the epidemiological data of the relevant disease) to ensure that clinical innovations can be applied based on the response of individual sexes in trial outcomes.

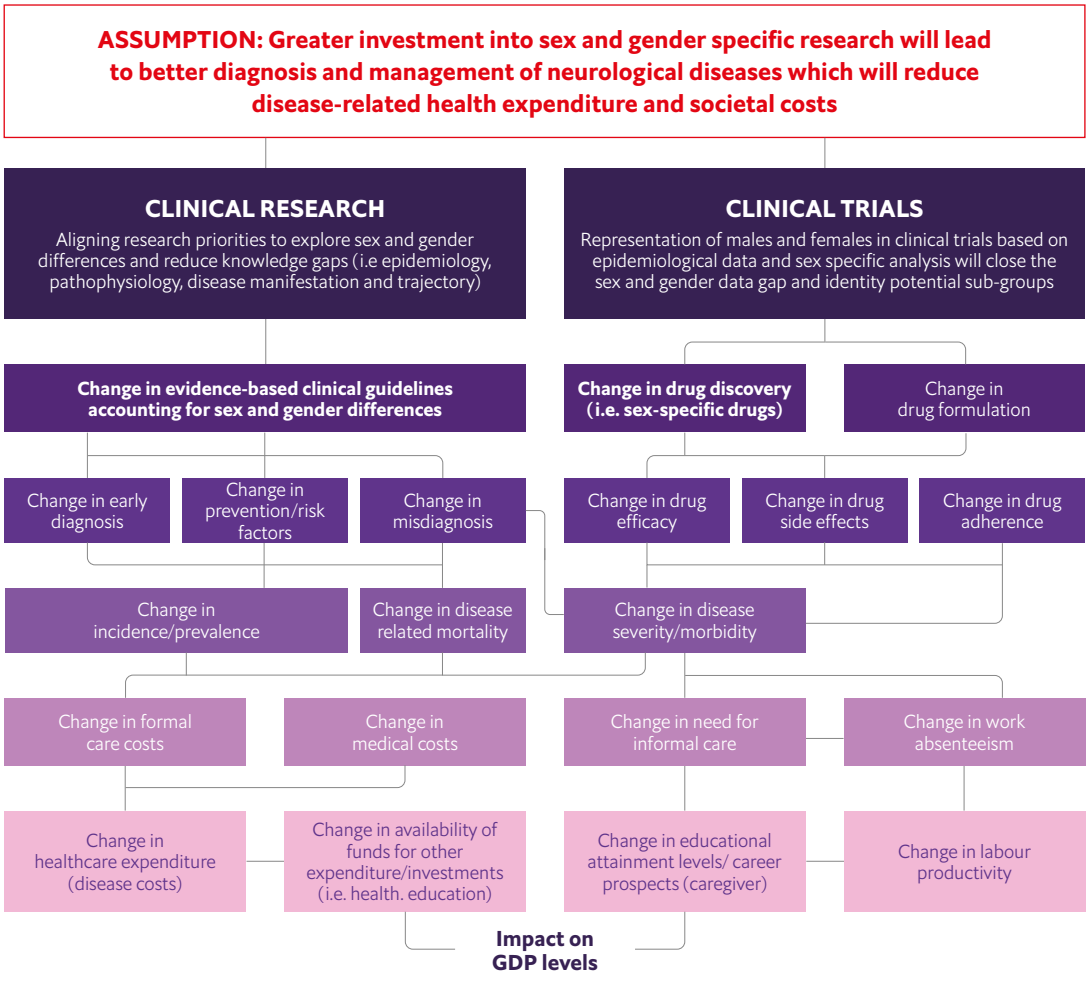
Stream 1 would see the realignment of research priorities towards including sex and gender differences, which would result in better-informed clinical guidelines that equip clinicians with the knowledge to make earlier diagnosis, and reduce misdiagnosis of brain disorders. It would also allow for sex-specific risk factors to be identified allowing for better preventive measures to be introduced. For instance, the American Heart Association published sex-specific guidelines for stroke prevention strategies in 2014, which resulted in an improvement in the treatment of females for acute stroke, as sex-specific research identified that females had a better response to aspirin than males.[52] Prevention, in the case of brain diseases, would result in reduced incidence of disease, whereas early and accurate diagnosis would result in more effective treatment which would reduce disease severity, hence decreasing disease-related disability and mortality.

Stream 2 would enable sex-specific analysis to close the sex and gender data gap, and help identify potential sub-groups for treatments. Sex-specific drugs would improve the efficacy of treatment for both males and females, as well as provide a mechanism to conduct further research into reducing the adverse drug effects predominantly experienced by women. Dr Cheryl Carcel, a neurologist and Lead of the Sex Differences in Stroke group at the George Institute in Sydney, Australia, reiterates that "[The consequence] of not enrolling enough women in a trial is that there isn't enough safety and efficacy data for both sexes. So, the trial will

need to be done again, costing millions of dollars. And [another] economic impact would be the withdrawal of medications [which are] deemed to have more serious side effects in women."

The framework goes on to define how improvements in clinical guidelines, drug development and efficacy would change the course of the diseases through better clinical management – possibly reducing disease-related severity and mortality, and thereby reducing work absenteeism or the need for informal care. Considering the substantial costs associated with chronic brain diseases, particularly those identified at late stages, and the cost of formal and informal care, the positive knock-on effect would result in reduced healthcare expenditure. Additionally, the impact extends to caregivers, who would now have better opportunities for educational attainment and career prospects, thereby strengthening the overall labour force. Furthermore, the presumed cost-savings would indirectly feed into a country's GDP, thus having a broader impact on a nation's economic development.

Figure 1: A conceptual framework for investing in sex- and gender-specific research in the area of brain disorders



Sex- and gender-based differences in select brain disorders

Multiple Sclerosis

Definition and overview of the burden

MS is an inflammatory and neurodegenerative condition that targets the brain and spinal cord, affecting over 2.8m people worldwide.[53] Although in many cases it is possible to treat the symptoms of MS, without a cure it remains a lifelong condition that can result in severe disability.[54] Average life expectancy is slightly reduced for people with MS, and its prevalence varies significantly across demographic groups and regions.[55,56,57,58,59,60,61,62,63,64,65] MS is the most common disabling neurological disease in young people, with the average age of diagnosis being 30 years; the economic consequences are therefore considerable since the condition significantly impacts those within the working age population.[53]

The prevalence of MS differs between males and females; MS is more prevalent amongst females, who bear approximately two-thirds of the global burden.[53,56,66,67,68,69,70,71,72,73] According to the 2019 GBD Study, the prevalence amongst males is 15 per 100,000 persons, compared to 31 per 100,000 persons for females. MS can can limit participation in activities of daily living (ADL) and reduce independence, leading to females spending more years living with disability than males.[57,74] In terms of disability-adjusted life years (DALYs), MS causes 19 DALYs per 100,000 persons in females, in comparison to 11 DALYs per 100,000 persons in males.[75]

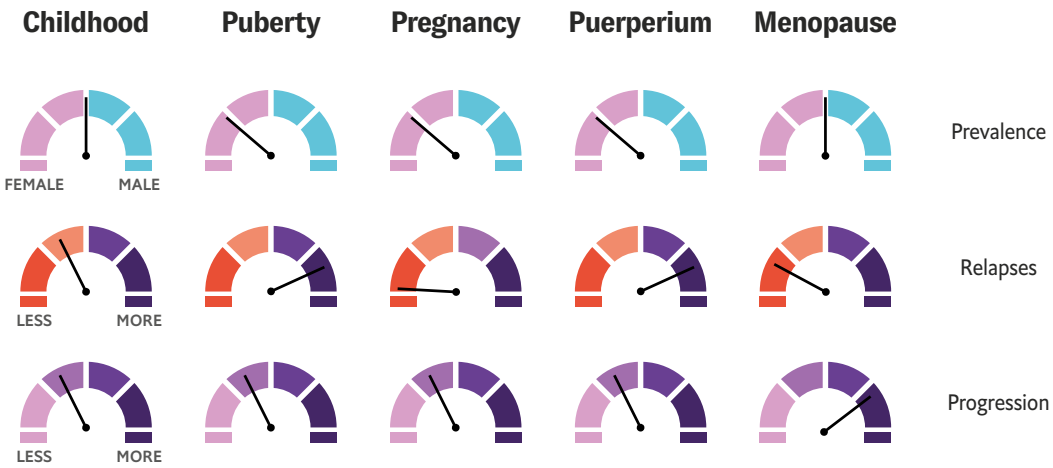
Sex (and gender) differences in clinical presentation, diagnosis and management of MS

The disease trajectory for MS varies from person to person, and the patterns of symptoms can be classified into the following types: relapsing-remitting (RRMS), primary-progressive (PPMS) and secondary-progressive (SPMS). Although MS affects more females at an aggregate level, males have a higher risk of developing PPMS which is associated with greater disability.[60,63,69] The factors behind these differences are not entirely understood, but researchers have started to investigate sex and gender differences in MS, with several studies exploring the effect of sex and sex hormones on the risk and severity of the disease.[66,69-71,73,76,77]

Changes in the levels of sex hormones have long been associated with changes in the course of MS (see Figure 2). Studies suggest that sex hormones, such as oestrogen, provide a protective effect by reducing neuro-degeneration and the severity of symptoms.[78,79,80] Conversely, females who receive a MS diagnosis over the age of 50 tend to have a similar disease progression to males, which can be related to reduced oestrogen levels during menopause.[77] Furthermore, the effect of pregnancy on MS disease outcomes has been widely explored.[69,73,81,82,83] In comparison to pre-pregnancy, pregnant women in the second half of their pregnancy have less relapses and women in the third trimester have a 70% lower relapse rate.[77] However, this effect is limited in duration, with women experiencing higher rates of relapse during the post-partum period, particularly within three months of childbirth.[77] The effect of rapid changes in post-partum oestrogen levels on MS activity have been investigated, but the evidence on the causality is largely inconclusive.[77]

Behavioural and lifestyle choices, such as smoking, poor diet and lack of physical activity, have been shown to lead to greater risk of MS,

Figure 2: Changes in MS based on the female reproductive cycle.
Before puberty, prevalence is similar between boys and girls, but rates in girls are three times higher after they begin their periods. During pregnancy, there is a decrease in relapse rates that reverses after delivery. Worsening of symptoms is suggested at menopause.[84]



Source: Ysrraelit & Correale, 2019

but the extent of this risk differs between men and women.[85,86] For example, high body mass index (BMI) and obesity are both known to be associated with an increased susceptibility to MS in early adulthood, particularly between the ages of 18 and 25.[87,88] The risk of developing MS doubles for obese females with a BMI greater than 30, but this effect is not seen in males.[87,89] As with obesity, smoking increases the risk of developing MS, due to its association with chronic inflammation.[90,91,92,93,94] While evidence on the gendered effect of smoking on MS is not well established, it is important to highlight the fact that increased prevalence of MS in females has coincided with an increased rate of female smoking over the last decade.[95]

Early diagnosis of MS is a predictive factor of the prognosis of the disease, and misdiagnosis and delayed diagnosis are more common in women than men.[96,97,98,99] Misdiagnosing MS can prevent access to disease modifying treatments (DMTs), thereby worsening the severity of symptoms and accelerating disease progression as well as contributing to the economic burden associated with the disease.[99,100] A retrospective study in Argentina evaluated the medical records of 572 patients with MS and found that 16% of patients were misdiagnosed and women had an 83% higher risk of misdiagnosis.[101]

DMTs can reduce relapses and slow disease progression in MS patients; men have better adherence to DMTs, and therefore better outcomes than women.[102] Several studies have found that women report a higher number of adverse drug events than men, which may cause the lower adherence rates.[103,104,105,106,107,108] Steroids are routinely used in the treatment of MS to reduce inflammation, but their prolonged use increases the risk of developing osteoporosis, which is more common in women than men.[103]

Interactions between MS drugs and other medications can result in multiple side effects, which could impact regular life, particularly among females.[96] For example, common drugs used in the treatment of MS, such as antibiotics, can reduce the effectiveness of hormonal birth control pills, thus increasing the risk of unplanned pregnancy.[109] Additionally, women who have prolonged immobility as a result of MS have a higher risk of developing blood clots when taking combined hormonal contraceptives.[96] While early treatment of

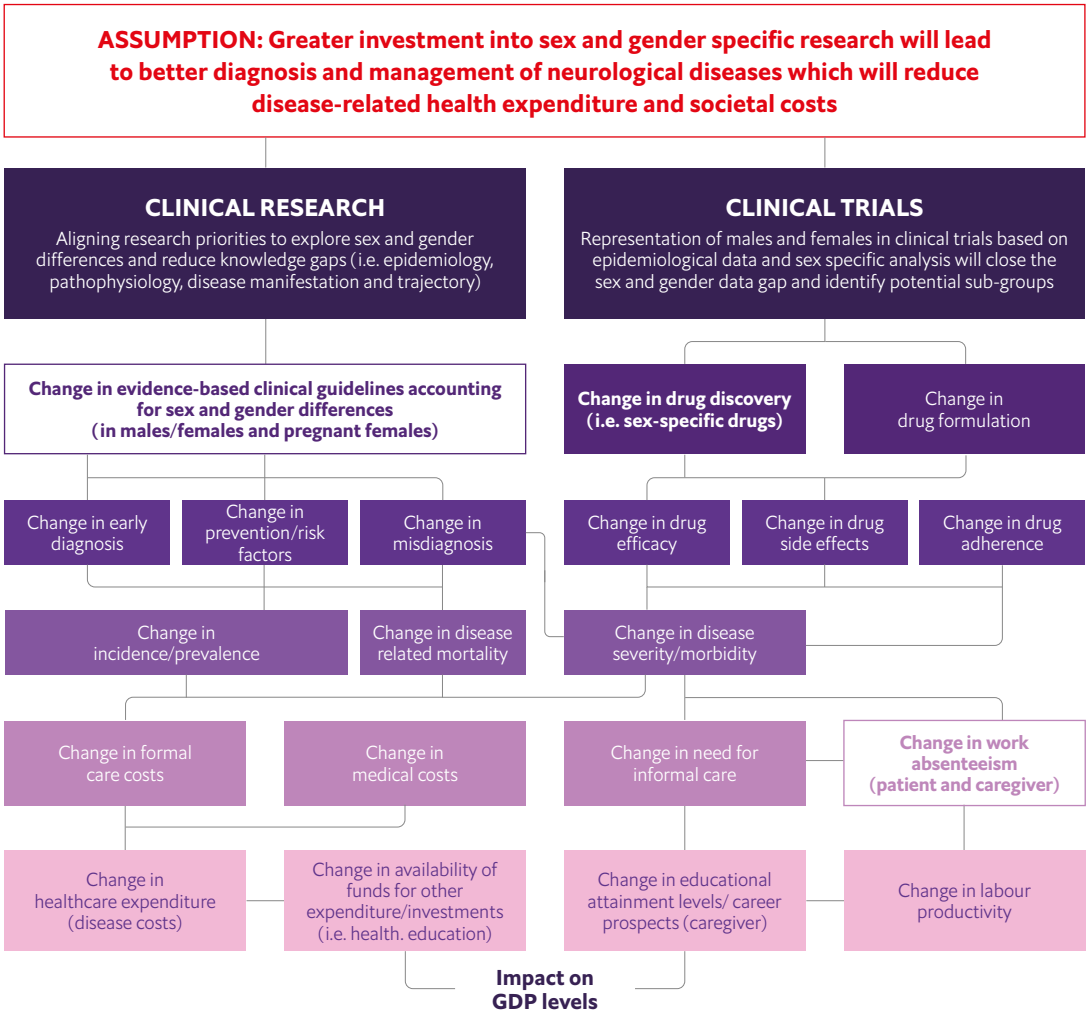
MS is critical for the prevention of long-term disability, women who plan to have children are often required to alter treatment courses because some DMTs, including Fingolimod and Teriflunomide, are considered to be unsafe during pregnancy.[110]

Specialist rehabilitation, including physiotherapy, is currently the most cost-effective treatment for patients with MS because it aims to optimise function and independence and improve outcomes related to quality of life.[111] However, rehabilitation has received limited attention in research, and further work is needed to explore sex and gender differences in the adherence rates to such programmes and the self-management of MS. The presence of sex and gender differences in current MS treatments also warrants the need to shift to a more precise approach, which is based on individual needs, to improve health outcomes for all patients with MS.

Economic impact

People living with MS suffer from various forms of disability that have downstream effects on employment status.[16] In the US alone, the cost of MS equates to US$85.4bn, of which 66% is from medications.[112] This economic cost is exacerbated

Figure 3: A conceptual framework for investing in sex and gender-specific research in the area of Multiple Sclerosis



by various indirect costs, such as productivity losses and the cost of paid and unpaid care, which equal US$22.1bn.[67] The cost of MS also differs by gender; while men (US$70,603) incur higher per-person costs than women ($63,896), the latter have more than double the total direct medical cost (US$45,890m) than the former (US$17,438m) as a result of a higher prevalence of the disease.[112]

Figure 3 shows a conceptual framework for investing in sex- and gender-specific MS research. It captures the assumption of how greater investment in sex and gender-specific MS research has the potential to lead to better diagnosis and management of the disorder, reducing health expenditure and social costs. It highlights specific patient populations that would benefit from the increased momentum in research on sex and gender differences in MS, such as females who bear most of the epidemiological disease burden. Pregnant females can also expect to see more treatment options as, currently, most DMTs are not certified for use during pregnancy, due to the lack of reliable evidence of their effect on humans and the data on adverse effects obtained only from animal reproduction studies.[113] As a result, females with MS who become pregnant often need to discontinue treatments. This, coupled with the disproportionate incidence of MS in females, particularly those of reproductive age, highlights the clear need for clinical research priorities to include the identification of sex-specific subgroups in tandem with better drug discovery and safer drug formulation.

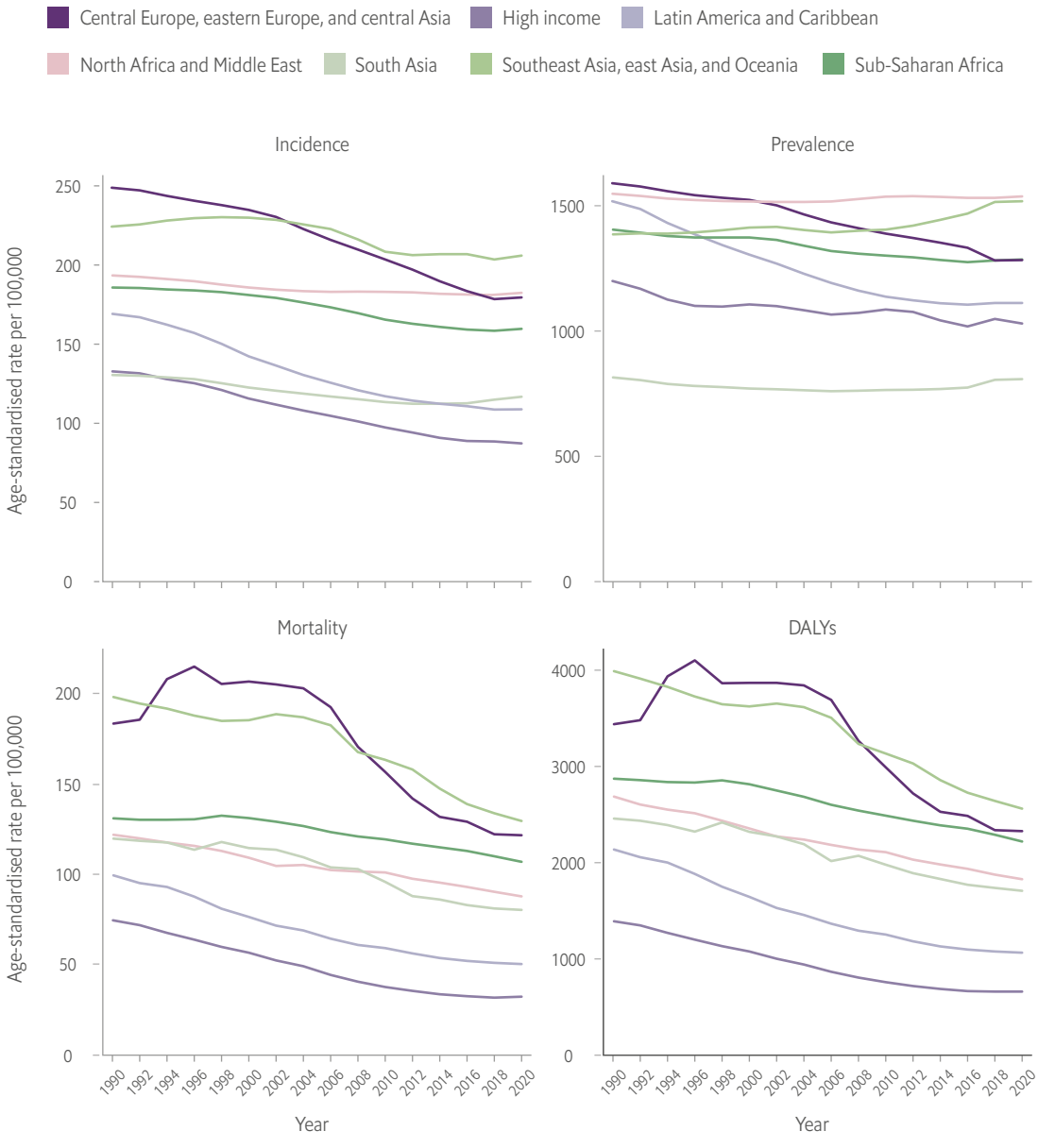
Although it can develop at any age, MS is most commonly diagnosed in individuals in their 20s, 30s and 40s, representing a significant portion of the productive workforce, thus impacting GDP.[54] In Spain, a study of 189 patients with MS, 71.4% of whom were female, reported an absence from work of 14.3 working days over a three-month period.[114] This study also found absenteeism to be correlated with anxiety and depression, and presenteeism correlated with fatigue and severe symptoms.[114] This observation of the interaction between depression and MS also highlights how the complex relationship between brain and mental health disorders creates an additional economic burden on people with MS and societies alike. In the US, studies[115] have shown that people with MS have higher productivity losses, with significantly more missed workdays in a year on average compared to the general population. Patients using DMTs have increased annual indirect costs due to absenteeism, short-term and long-term disability averaging US$6,474, US$2,368, and US$280 respectively.[116] The fact that women are more likely to shoulder the bulk of domestic and caregiving responsibilities indicates a significant knock-on effect of MS on households, a consequence that ultimately affects the country's GDP through reduced productivity of the female workforce who may also have poorer career prospects due to reduced time spent in education. Indeed, people with MS lose substantial amounts in earning potential; the average retirement age of someone with MS in the UK has been quoted as 42,[117] and failing to address the absence of effective treatments through investment in sex- and gender-specific research would likely lead to more negative effects on a nation's economy.[118]

Stroke

Definition and overview of the burden

Stroke is the second leading cause of death and a leading cause of disability worldwide.[119] Annually, close to 14m people suffer from stroke globally, resulting in significant levels of disability and over 6.5m deaths.[9,75] Although there are more than 100m people living with stroke, over time, stroke incidence and mortality are decreasing.[9,75,120,121] Considerable improvements in stroke management have reduced the burden of stroke over the past 30 years (see Figure 4), but this is predominantly seen in high income countries (HICs); in LMICs, the burden of stroke is expected to increase as the epidemiological transition progresses.[9,122,123,124] Stroke incidence in the UK and US has increased over the years for particular segments of populations, including those aged 15-44 years or those of minority ethnicities, but the reason for these specificities remains under-researched.[122,123,125]

Figure 4: Global trends in stroke incidence, prevalence, mortality and DALYs, 1990-2020.[9]



Source: Feigin et al, 2019

According to the 2019 GBD Study, females have a higher stroke prevalence rate (1,463 per 100,000 population) than males (1,160 per 100,000 population) and make up approximately 55% of the global burden.[75] Although more females live with stroke, males spend more years living in ill-health, disability and premature death (1,980 DALYs per 100,000 population) than females (1,720 DALYs per per 100,000 population).[75] Additionally, females develop the most cardiovascular risk factors during the menopausal transition, with the risk of stroke doubling during the ten years after menopause.[126] While longevity in females can be used to explain the difference in stroke prevalence rates to some extent, researchers have started to explore other sex differences in stroke further.[127,128,129,130,131,132,133,134,135,136,137,138,139,140,141,142,143,144,145,146,147]

Sex and gender differences in the clinical presentation, diagnosis and management of Stroke

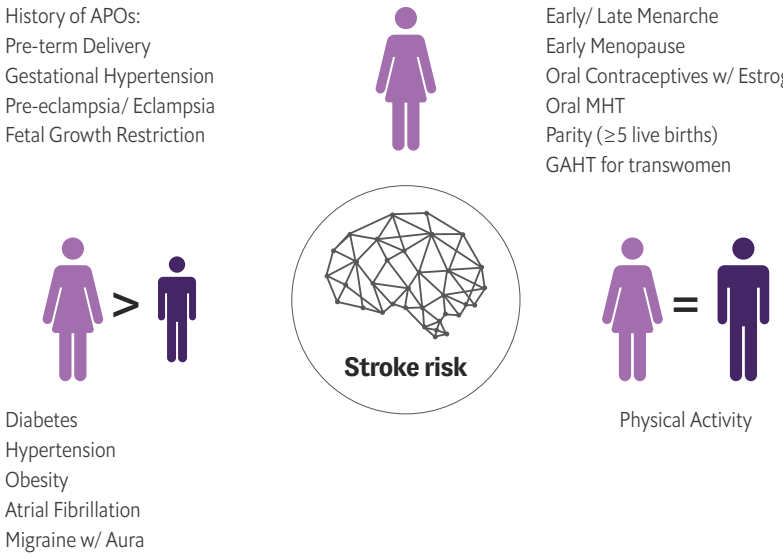
Stroke can be classified into two types: ischaemic and haemorrhagic, with the former resulting from blood clots and the latter caused by bleeding in the brain.[148] Approximately 87% of all strokes are ischaemic, which is associated with lower mortality and better clinical interventions than haemorrhagic strokes.[149] Studies show that ischaemic strokes are more common in females aged 18-44 in comparison to their male counterparts.[150,151] The decrease in stroke incidence over time has been predominantly driven by reductions in ischaemic stroke among males, suggesting that the improvements made in this field have been disproportionate, and continue to neglect females as they continue to have higher stroke incidence than males.[147,152,153]

Females have a higher risk of developing stroke than males. The causes of this higher risk is complex and can be associated with multiple factors including ethnicity, comorbidities, age, pregnancy, preeclampsia, atrial fibrillation (AF), contraceptive use, hormonal therapy and migraine with aura (see Figure 5).[35,126,149,152,154,155,156,157,158] AF causes irregular heartbeats and is a critical comorbidity that more than doubles the risk of stroke; females with AF have a higher incidence of stroke, experience more severe stroke, and have higher mortality compared to males with AF.[159,160] Several studies have also found that the underuse of oral anticoagulants (blood thinning medication) in controlling AF is more common in females, thus elevating their stroke risk profile.[34,161,162] Lifestyle-related behaviours such as smoking also increase the risk of stroke. Smoking is more prevalent in males than females, and the risk of stroke increases by 54% in smoking males as compared to non-smoking males;[161] in female smokers, on the other hand, the risk of stroke rises by 88% as compared to female non-smokers.[161]

Misdiagnosis of stroke is more common in women than men. Only 12% of women who reported pain were diagnosed with TIA/stroke in comparison to 58% of men presenting with the same complaint, resulting in delayed access to treatment and ultimately poorer long-term outcomes.[34,35,36,163] Furthermore, women are more likely to receive a diagnosis of stroke mimic, rather than a stroke diagnosis, which includes fainting, seizures and migraine, despite having similar symptoms as men.[34] The reasons for women having a higher stroke misdiagnosis are unclear, but a contributing factor is that women have a higher frequency of atypical stroke symptoms, such as dizziness and headaches.[133]

Women are also more likely to experience delayed prescription for preventive treatments, side effects from medication and interference with everyday life. Anticoagulants are the most commonly used treatment for ischaemic stroke, but they are chronically under-prescribed to women.[159] Females have more sex-specific side-effects from anticoagulation therapy, such as heavy vaginal bleeding during and

Figure 5: Sex differences in stroke risk factors.
APOs: Adverse Pregnancy Outcomes, GAHT: Gender-Affirming Hormone Therapy and MHT: Menopausal Hormone Therapy.[152]



Source: Rexrode et al, 2022

between periods.[164] Additionally, females on anticoagulants are required to stop their treatment during pregnancy due to risks to foetal health.[165,166] Statins are also commonly prescribed to control cholesterol levels and prevent stroke. Studies indicate that women who were eligible for statin therapy were likely to either receive a lower-than-needed dose or none at all, compared to men.[167,168] Women were also more likely to decline and discontinue statins due to safety concerns and side effects, highlighting the need for more drug development trials on women to better understand their side effects, as well as better stroke education for women.[168]

Rehabilitation is a key part of recovery as it can help patients regain function and independence following a stroke.[169] Research into the sex and gender differences in stroke rehabilitation is either lacking or poor in quality, further emphasising the need for more action in this area. A Danish study found that after two weeks of intensive stroke rehabilitation, females had higher disability scores when performing ADL in comparison to males.[170] However, this was a retrospective study of medical records, which, because of the missing data, could not account for the intensity or quality of individual therapy provided.

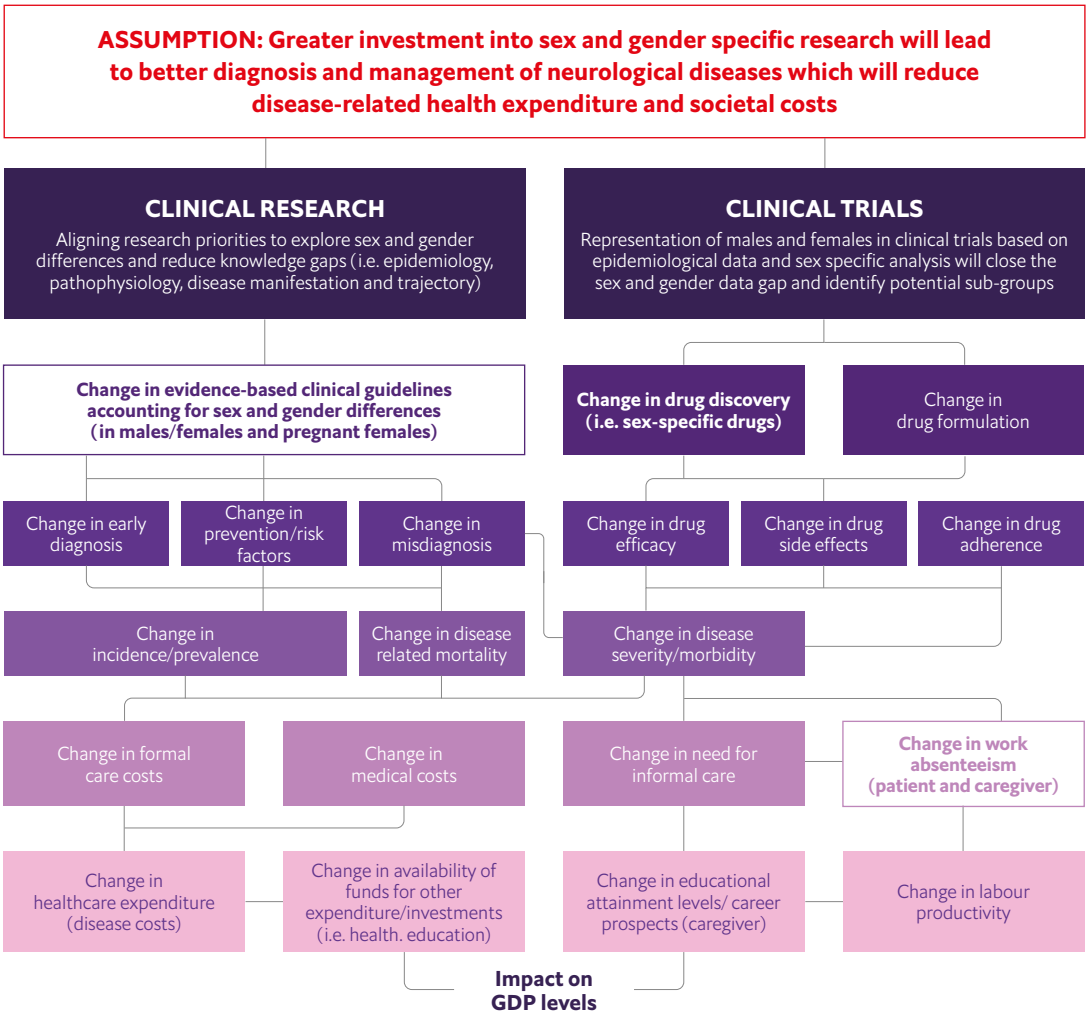
About 33% of stroke patients suffer with depression.[171] In a study following 2,313 people for five years after the onset of stroke symptoms, a team of researchers from King's College London found that 20% of women suffered from severe depression post-stroke, as compared to 10% of men. The researchers also found that higher mortality rates were associated with long-term symptoms of depression.[172] The intersectionality of mental health and brain disorders is once again highlighted; psychiatric illness increases the burden of stroke for patients, with a knock-on effect on the wider economy.

Economic impact

The economic burden of stroke on health services and societies is vast across the world. In Europe, informal care costs following stroke were €1.3bn, while the cost for healthcare was €27bn, and productivity losses amounted to €12bn in 2017.[173] These figures were even greater in the US, with indirect costs forming up to 66% of the total costs (US$103.5bn), costs associated with productivity losses amounting to US$38.1bn and premature death costing US$30.4bn.[174] In the UK, 2015 data indicated that even though the majority of stroke survivors are over 65, productivity losses still cost £1.6bn annually.[175] In exploring the extent to which productivity is affected by stroke, researchers in Portugal reported that in the first year following a stroke, the mean loss in productivity was 76.4 days for patients and caregivers combined. Sick leave and hospitalisation of patients accounted for 73% of this, but presenteeism made up 11% of the losses.[176]

Figure 6 shows a conceptual framework for investing in sex and gender-specific stroke

Figure 6: A conceptual framework for investing in sex- and gender-specific research in the area of Stroke



research. This is particularly important given that the lower mortality but increased incidence of stroke in people in their 50s and 60s leads to an increase in the prevalence of working-age stroke survivors.[177] Stroke survivors are less likely to be employed; 35.3% in the cited study were employed and were paid less than the general population. Men are more likely to die from stroke, meaning that more women are affected by non-fatal stroke events.[178]

Differences in how stroke affects men and women is under-addressed in clinical trials, despite the unique risks to females, such as the use of the oral contraceptives, pregnancy, menopause and hormone replacement therapy.[179] With pregnancy, the risk of stroke for females rises well into the early postpartum period,[180,181] and is magnified in females with gestational hypertension and preeclampsia.[182] Stroke is the most common cause of serious long-term disability after a pregnancy, requiring prolonged hospitalisation and possibly additional care, both of which are associated with an economic burden.[182]

Post-stroke recovery is also associated with strenuous caregiving demands which, due to the sudden and unpredictable onset of a stroke, often means that informal caregivers are unprepared for the physical, social, psychological and financial impact on their lives.[183] Most change from full-time to part-time employment or leave their job completely, creating a sudden loss of income which has a knock-on effect, particularly when the caregiver has children younger than 18 years of age.[184] This could mean reduced career prospects for both carers and their children who might experience a negative impact on their schooling. These generational losses in productivity would undoubtedly have a significant impact on the country's GDP, and further emphasises the need for investment in sex- and gender-specific research to prevent and improve stroke outcomes.

Alzheimer's Disease

Definition and overview of the burden

The prevalence of dementia has increased significantly over the past 30 years, and now over 55m people worldwide live with the condition.[185] This number will almost double every 20 years, reaching 78m in 2030 and 139m in 2050, driven by an ageing population and improved detection.[186,187] AD is the most common form of dementia making up 60-80% of all cases, and predominantly impacting older females who constitute approximately two-thirds of the burden.[188] Furthermore, global estimates of the number of people with AD across the continuum, including those in the early stages (prodromal and preclinical), have been projected at 416m, accounting for 22% of the population aged over 50 years.[189] The disease progression of AD can be rapid, with most people living an average of four to eight years following diagnosis.[190]

People with AD can develop considerable memory loss, as well as cognitive and behavioural challenges, thus requiring significant care and support, and utilising substantial health and care resources.[185] Women account for almost 60% of AD caregivers, and often have to quit their jobs in order to meet the full-time care needs of people with AD, resulting in significant indirect costs.[188]

Sex (and gender) differences in the clinical presentation, diagnosis and management of AD

AD is a progressive, neurodegenerative condition, which predominantly impacts older adults.[191] In its early stages, people with AD may only have a mild cognitive impairment (MCI), but as the disease advances, symptoms include loss of speech, reduced control of movement, and unresponsiveness to the environment.[192] Along with women, people from ethnic minority and lower income groups are disproportionately impacted by AD.[193] Several studies have shown that men and women from ethnic minority groups, such as African or Latino, are twice as likely to develop AD than any other ethnic group, but gaps in understanding why remain. Further research is required to understand such variations in AD.[194,195,196]

Multiple risk factors have been identified for AD and dementia including biomarkers, socio-demographic variables, lifestyle-related factors, comorbidities, medications and environmental triggers.[197] As a result of the sex disparities in the prevalence of AD, research has focused on identifying sex and gender differences in the risk factors.[190,198,199,200,201,202]

Ageing is the primary risk factor for AD.[203] Genetic risk factors, in particular, the Apolipoprotein E (APOE) ε4 gene increases the risk of developing AD and also at an earlier age.[204] Males and females with the APOE ε3/ε4 genotype have a similar risk of developing AD between 55 and 85 years, but the risk is higher in females aged 65-75 years.[205]

Comorbidities such as type 2 diabetes, cardiovascular disease, depression and gastrointestinal diseases have also been found to increase the risk of AD.[185,206,207] Cardiovascular conditions increase the risk of cognitive decline in both males and females, but some conditions have differential outcomes based on sex; coronary heart disease, for example, leads to cognitive decline only in females, while congestive heart failure leads to cognitive decline only in males.[208] People with depression have an increased risk of AD, but the evidence on how this risk differs between males and females is mixed.[209] In a systematic review of seven studies, found that two studies showed an increased AD risk in males with depression, two indicated an increased AD risk in females, and three reported no sex differences.[210] In addition, this review also found that most studies do not routinely provide disaggregated data on sex and gender; therefore, accounting for these variables in future study designs would allow for better analysis of the sex-specific effect of depression on AD risk.

Various social and economic factors, such as alcohol consumption and educational attainment, have also been shown to have an association with AD.[211,212] Lower educational levels have been associated with an increased risk of AD; this is relevant to sex-specific risks because historically, women have had fewer opportunities to pursue higher level education which may therefore increase their risk of developing AD, in comparison to men.[211,213] A study in Japan, found that the risk of developing dementia was higher for individuals with a lower education level and for those from a lower socioeconomic background.[214] Contrary to European studies, lifestyle-related risk factors such as high alcohol consumption were not associated with dementia risk in this Japanese population, indicating variations in AD risk factors across regions.[215,216]

Sex differences in the clinical presentation of AD varies according to the disease stage. Females show faster cognitive decline after diagnosis of MCI or AD dementia.[217] A study in the US compared the brain scans of males and females with MCI and found that females had twice the amount of tau protein than their male counterparts, providing a potential explanation for more rapid AD decline in females than males.[218] Another study found that females with MCI perform better on verbal memory tests in comparison to males, despite having similar AD presentations.[219] While this indicates that females may have better cognitive functioning during the early stages of the disease, a disadvantage is that it may mask the condition and prevent early diagnosis of AD, leading to delays in treatment.

Like many other neurological diseases, there is currently no cure for AD and approved drugs are directed at alleviating symptoms. The National Institute for Health and Care Excellence (NICE) recommends the use of acetylcholinesterase (AChE) inhibitors in people with mild to moderate AD, while memantine monotherapy is recommended for managing moderate to severe AD.[220] Evidence on the sex and gender differences in adherence to AChE inhibitors is limited, but a US Food and Drug Administration (FDA) medical review found that females taking oral rivastigmine reported greater side effects, including vomiting and weight loss, than males.[221] The differences in body structure, liver metabolism, elimination pathways and hormonal changes between males and females could be why females experience more of these side effects, irrespective of drug type and dosage. While female enrolment is higher in clinical drug trials for AD, very few trials reported the sex differences in outcomes or drug adherence.[222]

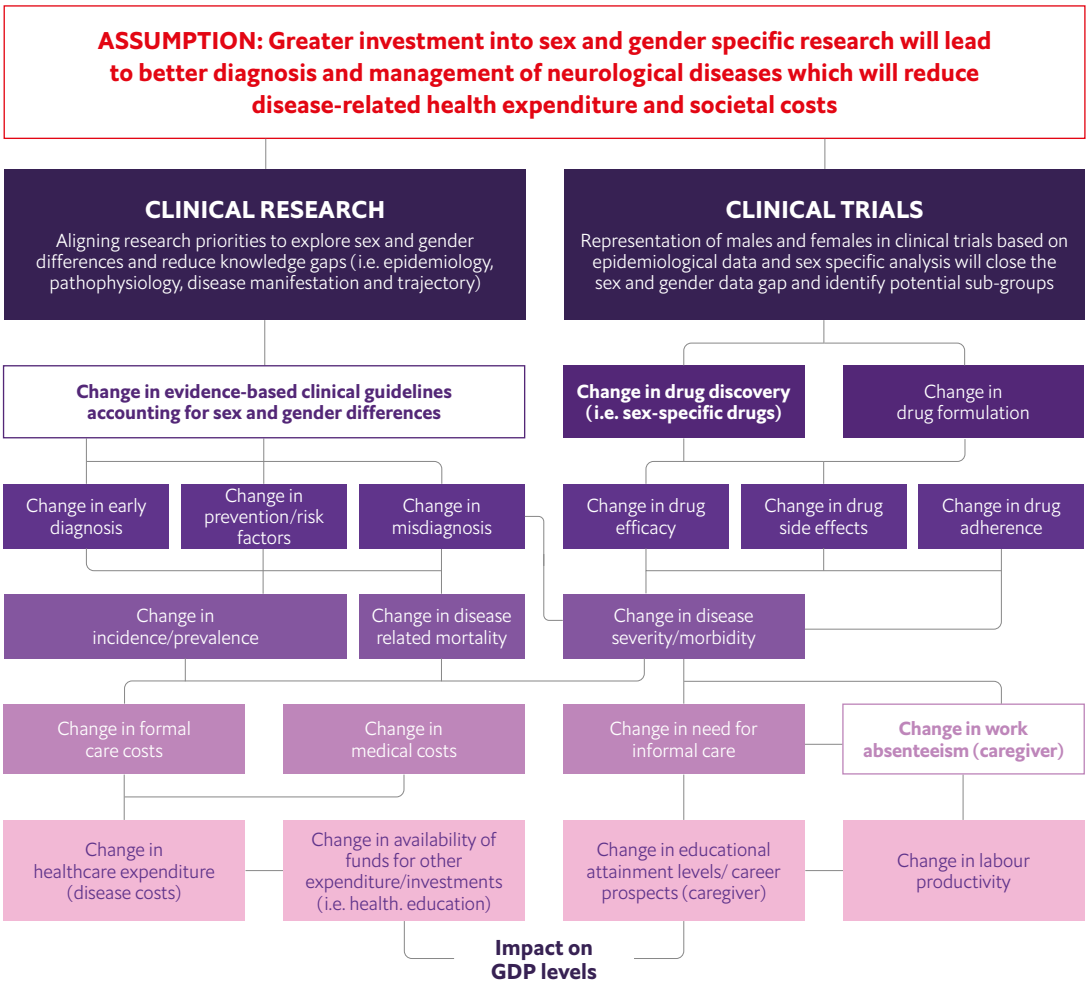
Like with other brain disorders, mental illness is also common in those with AD. Depression commonly occurs in 20-30% of patients with AD, and recent research further suggests that depressive symptoms in older adults with unimpaired cognition may serve as a target for delaying the onset of AD symptoms.[223] This adds to the growing body of evidence suggesting that depression is a risk factor for AD, although the relationship is complex and poorly understood and would benefit from further research.[224]

Economic impact

AD imposes the greatest economic burden of all the brain disorders, with total healthcare costs from treatment alone standing at US$305bn in the US, and expected to increase to US$1trn with the ageing of the population.[225] Total lifetime costs for an American with dementia is around US$341,840, 70% of which is the cost of family care.[226]

Unlike the other brain diseases in this study, AD is a disease primarily found in older people, making it one of the major drivers of demand for elderly care; statistics suggest that caregivers take the brunt of the impact of AD in terms of earnings and productivity. In the US, nearly 15m people provide informal care to persons with AD and other dementias, equating to 17bn hours of unpaid care work valued at over US$202bn. A majority of these informal caregivers are women (60%), aged between 35 and 64 years old (67%),

Figure 7: A conceptual framework for investing in sex- and gender-specific in research in the area of Alzheimer's Disease



with several reporting the need to take a leave of absence from work, change their working hours, go from working full-time to part-time and even quitting their jobs altogether.[227]

Women are both disproportionately affected by AD and bear the bulk of the caregiving burden resulting in poorer educational and career prospects. Therefore, there is a pressing need to better understand and provide for female patients and caregivers. Figure 7 shows a conceptual framework on the benefits of sex- and gender-specific research into AD. This economic model suggests that investing in this area will improve diagnosis and management of AD, and help reduce the burden on all patients and caregivers. In addition to the absence of DMTs and females showing a poor response to existing medicines, sex- and gender-specific research is further needed in the area of therapeutics to help boost the productivity of those affected, and reduce the economic impact on carers, and by extension, the drain on the country's GDP.

Males have earlier onset of PD, more severe and progressive motor symptoms, and greater cognitive decline than females.

Parkinson's Disease

Definition and overview of the burden

Over the last three decades, the global prevalence of PD has more than doubled as a result of the ageing population; furthermore, people with PD live longer with potentially greater exposure to environmental toxins.[228,229] Over 8m people globally have been diagnosed with PD, but this likely underestimates the true burden.[229,230,231,232,233] Unlike the other brain diseases in this report, PD is more prevalent among males than females; globally, 4.6m males are living with PD as compared to 3.8m females.[233] The hallmark symptoms of PD include tremor, bradykinesia (slowness of movement) and limb rigidity, which can cause varying levels of disability and dependence.[234,235] Non-motor symptoms of PD include, but are not limited to, cognitive changes, constipation and nausea, sleep disturbances, pain, fatigue and mood changes.[236] Males with PD experience a higher rate of DALYs (94 per 100,000 persons) in comparison to females (68 per 100,000 persons), indicating that they spend more years living with disability and ill-health, and have a higher risk of premature death.[233]

People with PD need significant healthcare resources.[229] As the disease progresses, people with PD may have difficulties with ADL, thereby increasing their dependence on caregivers.[231,232] A multi-national study of 7,209 PD patients found that men were more likely to receive informal unpaid care support from family and friends, while women were more likely to use formal paid care services, suggesting that gender norms primarily place women as caregivers rather than care receivers.[237]

Sex (and gender) differences in the clinical presentation, diagnosis and management of PD

PD is a neurodegenerative condition that inhibits the production of dopamine, a neurotransmitter in the brain, leading to impaired function and reduced independence. PD is classified into three types: idiopathic PD (most common), early-onset PD (occurs in people younger than 50 years), and familial PD (caused by inherited genetic mutations).[238] Disease predictors and risk factors for PD include age, sex, genetics and environmental factors.[232, 235, 236,239,240] Advancing age is considered a key risk factor for developing PD since most people living with PD are over the age of 60.[241,242,243,244] As a result of the higher prevalence in males, sex is considered to be an important risk factor, with incidence rates significantly peaking in males between the ages of 60 and 80.[239, 243,245]

In addition to the higher rate of incidence and prevalence, males have earlier onset of PD, more severe and progressive motor symptoms, and greater cognitive decline than females.[246] Differences between males and females have also been observed in cognition; females perform better on long-term memory tests, whereas males demonstrate better visuospatial skills. However, these differences become less significant as the disease progresses.[247] Sociocultural gender norms place more men in high-risk occupation groups that increase their susceptibility to developing PD.[248,249] For example, exposure to chemicals, such as pesticides, solvents, metals and environmental toxins, increases the risk of developing PD, with certain occupation groups including wood workers, painters, metallurgy and medical workers being at a greater risk.[248,249] Women are less inclined to take on roles associated with these occupational risks, thereby reducing their risk of developing PD.[250]

Figure 8: Non-motor conditions and comorbidities associated with PD.
Drugs to treat type 2 diabetes, depression, anaemia and cancer are currently being tested in clinical trials for PD (in pink).[255]

Source: Santiago et al, 2017

As shown in Figure 8, the prevalence of PD is altered by the presence or absence of certain comorbidities, but the extent of this change may differ between males and females. Risk of PD increases for people with hypertension by 33.17%, cerebrovascular disease by 42.53%, and diabetes by 10.60%.[251] Type 2 diabetes is also a predictor of disease severity due to its positive correlation with progressive motor symptoms and cognitive decline.[252] Females with diabetes have an odds ratio of 1.71 of being diagnosed with PD compared to those without; whereas males with diabetes have an odds ratio of 1.46 when compared to those without, significantly lower than for females.[253,254] PD is also associated with a greater risk of secondary diseases, such as dementia, with the outcomes being much worse for females. The risk of developing dementia is greater in people with PD than in those without, and it increases with age and disease duration.[240] Although dementia is more common in male patients with PD than their female counterparts, females have significant reductions in life expectancy with a higher excess mortality rate of 1.45, indicating that current treatments provide females with sub-optimal outcomes in comparison to males.[256]

Although the evidence is limited, the negative impact of PD symptoms on daily life is shown to be greater for females. Females with PD have poorer quality of life outcomes, such as physical functioning and psychosocial health, which refers to the ability to manage emotions, reactions and relationships, and report more symptoms in general than males.[257,258,259] In addition, females are more severely affected by fatigue, depression, restless legs, constipation, pain, loss of taste or smell, weight change and excessive sweating; males, on the other hand, suffer from more daytime sleepiness, dribbling saliva and sexual dysfunction.[260]

The drug levodopa is considered the gold standard treatment of PD, but its chronic use is associated with a deterioration in motor symptoms, particularly towards the end of the treatment course, also known as the weaning-off period.[261] A study found that females on levodopa therapy had an 80% increased risk of both motor and non-motor symptoms during the weaning-off period, when compared with their male counterparts.[262] For example, females had more mood changes and fatigue during the weaning-off than males, for the

same levodopa intake, suggesting that females may be under-dosed.[263] Since clinical trial data inform drug treatments for PD, and males are more represented in clinical trials, they benefit more from better drug responses and fewer side effects to drugs, including levodopa. A systematic review found that females were consistently under-represented in over half of all major PD trials.[264]

Non-motor symptoms associated with PD include impaired cognition, constipation, mood disorders, depression and anxiety, pain, and sleep disturbances.[265] Depression is one of the most common neuropsychiatric complications of PD and is associated with increased disability and reduced quality of life.[266] At least 50% of PD patients will experience depression during their illness and 40% will experience anxiety,[267] again highlighting how closely intertwined brain and mental health disorders are. Anxiety and depression are more associated with females,[268] while impulse control disorders are more associated with males.[269] Recognising depression in PD, it must be noted, can be quite difficult since some symptoms may be masked by the slowed movements and facial expressions characteristic of PD.

There is evidence suggesting that PD patients can have poor sleep quality and daytime sleepiness, and treatment options remain limited.[270] A study of hospitalised men and women found that men are more likely to experience insomnia or parasomnia, while women are more likely to experience a sleep disorder and sleep-related movement disorders such as restless legs syndrome.[265] Sleep disturbances have been further linked to impaired visual learning and memory,[271] which will undoubtedly have implications for employed PD patients and their ability to maintain productivity.

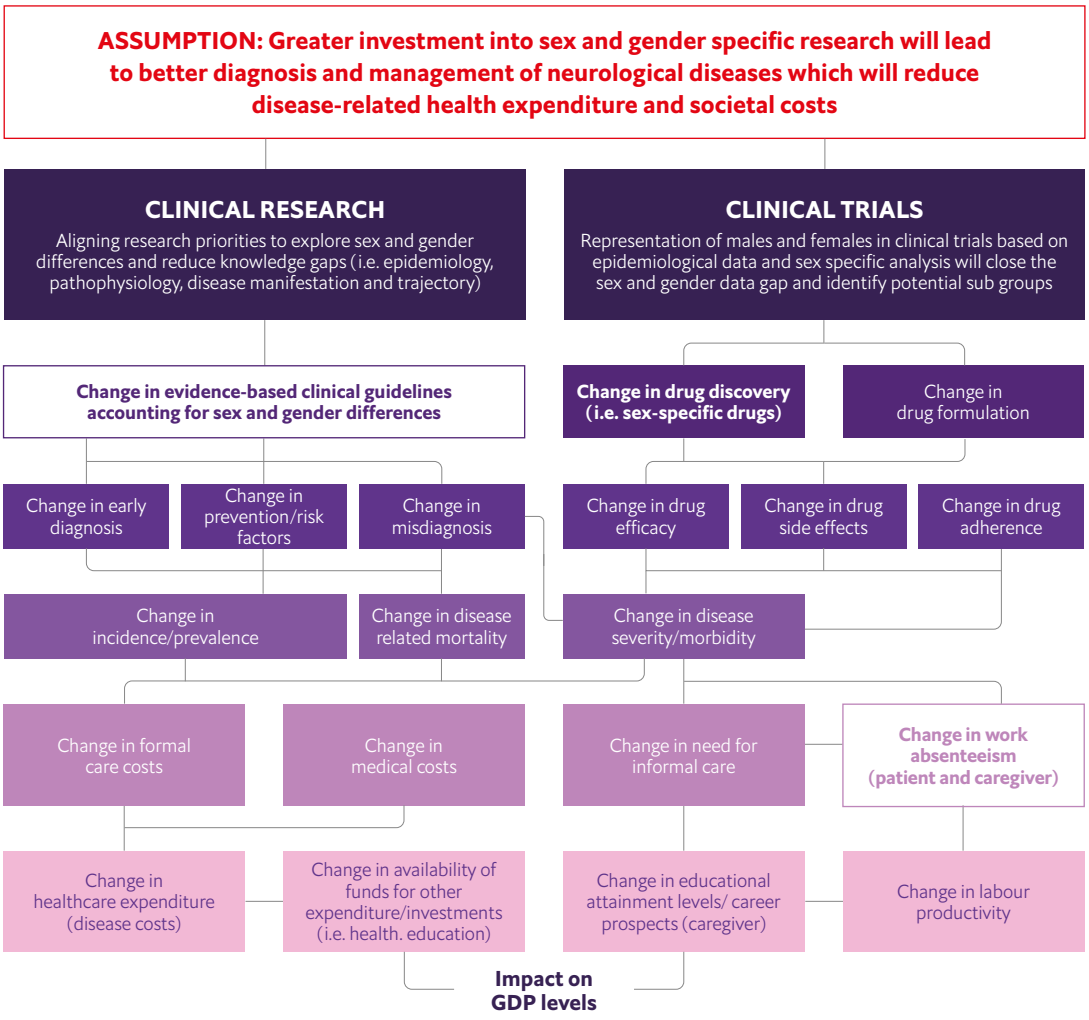
Economic impact

Costs related to PD are significant and the most current data on these costs are more readily available for the US than other countries. In 2017, for the one million people living with PD in the US, the cost was estimated at US$51.9bn, including direct medical costs of US$25.4bn[272] and indirect costs of US$26.5bn.[229] Costs are expected to increase to $79bn by 2037 as PD prevalence exceeds 1.6m in the US.[272] Older data from Europe estimated PD costs at €13.9bn.[273]

For patients with PD, apart from the financial benefits, employment is key for social interaction and other indicators such as self-esteem. However, patients with PD are 70% less likely to be in employment than their peers,[274] causing those diagnosed during their working life to lose years of potential employment. Most do not receive early intervention to manage issues such as fatigue, which makes them leave employment prematurely, and several patients would benefit from adaptations at work to allow for flexible working. Although males have a higher incidence of PD, being a female is one of the factors associated with loss of employment, on par with socioeconomic status;[275] this is perhaps indicative of the increased severity of symptoms and faster disease progression.[235]

Figure 9 shows a conceptual framework for the benefits of sex- and gender-specific research into PD. Sex- and gender-specific research in PD would lead to better diagnosis and management of PD, thereby reducing the economic and social impacts of the disease. Although males are more likely to be diagnosed with PD, females appear to have more negative effects and worse reactions to existing medicines; this could improve with the inclusion of females in clinical studies to determine symptoms unique to women in the early stages of the disease to allow for early detection, and effective therapies for both sexes. More research into the understanding of symptoms, such as sleep

Figure 9: A conceptual framework for investing in sex and gender-specific research in the area of Parkinson's Disease



disturbances and cognitive difficulties, would allow both male and female patients to better manage them, which would, in turn, improve absenteeism and presenteeism in the workforce. As with AD, optimised treatments and better control of symptoms would also benefit caregivers by easing their burden of care and allowing them to continue educational activities and jobs. Ultimately, the investment in sex- and gender-specific PD research will have a positive impact on a country's GDP.

Migraine

Definition and overview of the burden

Migraine is one of the most prevalent and disabling brain disorder, with over 1.04bn people suffering from the condition globally.[276] The 2016 GBD study discovered that migraine was the second-most disabling condition worldwide, preceded only by lower back pain.[276] Because it typically affects adults aged 20-55 years, the prime productive years spent in employment, migraine imposes significant economic costs.[277,278] Migraine incidence is exacerbated by its association with the following comorbidities: asthma, anxiety, depression, insomnia, gastric ulcers, angina and chronic pain.[279]

Similar to many other brain disorders, there are sex differences in the epidemiology of migraine as it is two to three times more prevalent in females than males.[28,277,280,281,282,283,284] The apparent sex disparity in migraine is partly mediated by differences in ovarian hormones, such as oestrogen and progesterone, but the exact mechanisms are not entirely understood.[75,284] Females also have significantly higher DALYs (685 per 100,000 persons) due to migraine than males (403 per 100,000 persons), and experience a more significant impact on day-to-day functions.[276] The findings of a recent survey of 700 women with migraine showed that 80% of respondents felt that migraine had impacted their ability to work, while 31% felt it had influenced their decision to reduce their contracted working hours (30% decided to work part-time), and 17% were no longer able to work.[285] Hence, not only does migraine exacerbate health inequalities between the sexes, but it also leads to greater gender inequality in the labour force as more women with migraine are forced to abandon their careers in their prime working years.[284]

Sex (and gender) differences in the clinical presentation, diagnosis and management of migraine

Migraine is a common neurovascular disorder that manifests as a moderate-to-severe throbbing pain (headache), lasting between four and 72 hours, usually accompanied by sensitivity to light, sound, nausea and vomiting.[283] There are two types of migraine: migraine with aura (a series of sensory disturbances such as visual disturbances and flashing lights that occurs right before a headache) and migraine without aura (the most common type, which occurs without warning).[283] Although the exact causes of migraine are unknown, there is reliable evidence that environmental, hormonal, emotional, physical, medicinal and dietary factors can trigger migraines, and these triggers vary between males and females. For instance, the top three migraine triggers reported by women were menstruation, stress and bright lights, while bright lights, sleep deprivation and stress commonly led to migraine attacks in men.[286] Additionally, not only do females report more migraine triggers, but their migraines also last longer, with an increased risk of recurrence, greater disability and longer time taken to recover, suggesting that female sex hormones have a key influence in migraine risk and manifestations.[28,285] Females are prone to experiencing catamenial (menstrual) migraines, which occur regularly in at least two of three consecutive menstrual cycles and usually manifest on Day 1 or 2 of menstruation (may range from two days before the cycle to Day 3 of menstruation).[287] Menstrual migraines affect around 20-25% of females with migraines, and are associated with greater disability, longer duration, and are more difficult to treat than non-menstrual migraine attacks.[287,288]

The burden of migraine is greater in females, who also have a higher prevalence of comorbidities that are associated with migraine risk, including psychiatric illnesses such as

anxiety and depression.[279,286] Additionally, the risk of ischaemic stroke is almost double in people who suffer from migraine with aura; this risk is elevated in females experiencing migraine with aura who also take contraceptive medication and engage in risky behaviours such as smoking.[289,290,291]

Despite the high prevalence of migraine, it is severely underdiagnosed, partly due to misdiagnosis or patients not seeking healthcare services, both of which result in poor management of the condition and ultimately poorer health outcomes.[292] A multi-national study conducted across seven countries that surveyed over 1,000 patients who suffered from migraine found that poor migraine awareness existed in both patients and physicians; only 8% of general practitioners (GPs) and 35% of specialists gave a correct migraine diagnosis.[293] The findings of the Chronic Migraine and Epidemiology Outcomes (CaMEO) study, which surveyed over 16,000 people with migraine (only ~25% of whom were males) in the US, showed that men (42%) were less likely to receive a correct migraine diagnosis in comparison to women (58%).[286, 294]

Prognostic factors for men with migraine are poorly understood by healthcare professionals, resulting in sub-optimal clinical management.[286] The CaMEO study also found that men were less likely to consult a doctor for their symptoms than women, highlighting well known differences in health-seeking behaviour between genders.[286] Stigma towards migraine, which arises from the notion that migraines are "invisible", also prevents people from accessing healthcare.[294] This is particularly true for men, who are known to seek healthcare less frequently when suffering from "invisible" conditions such as mental illness.[39,295,295] Another explanation for men not seeking help is based on the notion that migraine is predominantly considered to be a "female disorder".[296] Comparatively, women with migraine experience a different type of stigma; a recent survey revealed that 36% of women felt discriminated against at work due to migraine.[285] The breadth of stigma also extends into health systems – women with migraines are routinely undertreated because they are often stigmatised by doctors who view them as drug seekers that are exaggerating their symptoms.[295]

Drugs such as ergotamine and triptans are commonly used to treat migraines; while the former is more widely available, the latter is proven to have greater efficacy but costs more.[297] Women tend to use more prescription drugs, and are 1.4 times more likely to use triptans than men.[28] However, a recent meta-analysis revealed that despite higher exposure to triptans, females still had higher migraine recurrence rates and more adverse events than males, which may be due to them experiencing longer lasting attacks.[298] Although the number of studies reporting sex differences in migraine treatments has increased over time, most studies looking into the effects of triptans recruit more females than males and do not report the response efficacy disaggregated by sex.[28,299]

Calcitonin gene-related peptide (CGRP) is a new class of drugs recommended for the prevention of migraine.[300] The new CGRP-based drugs have demonstrated high levels of effectiveness in reducing the frequency of migraines, headache days and the use of medications.[301,301,302] Furthermore, in the clinical trials evaluating the effectiveness of CRGP-based drugs in the prevention of migraine, more than 80% of the participants are female, demonstrating that recruitment of a participant pool that reflects the true burden of disease (in this case, more females) can provide more robust data with the potential for better drug discovery.[302,303,303] Despite the promising results of CGRP, the reality is that only seven drugs have been approved for use, and access remains a huge issue as they can only be prescribed by headache specialists.[304,305]

While migraine researchers have made progress in recruiting more females into clinical

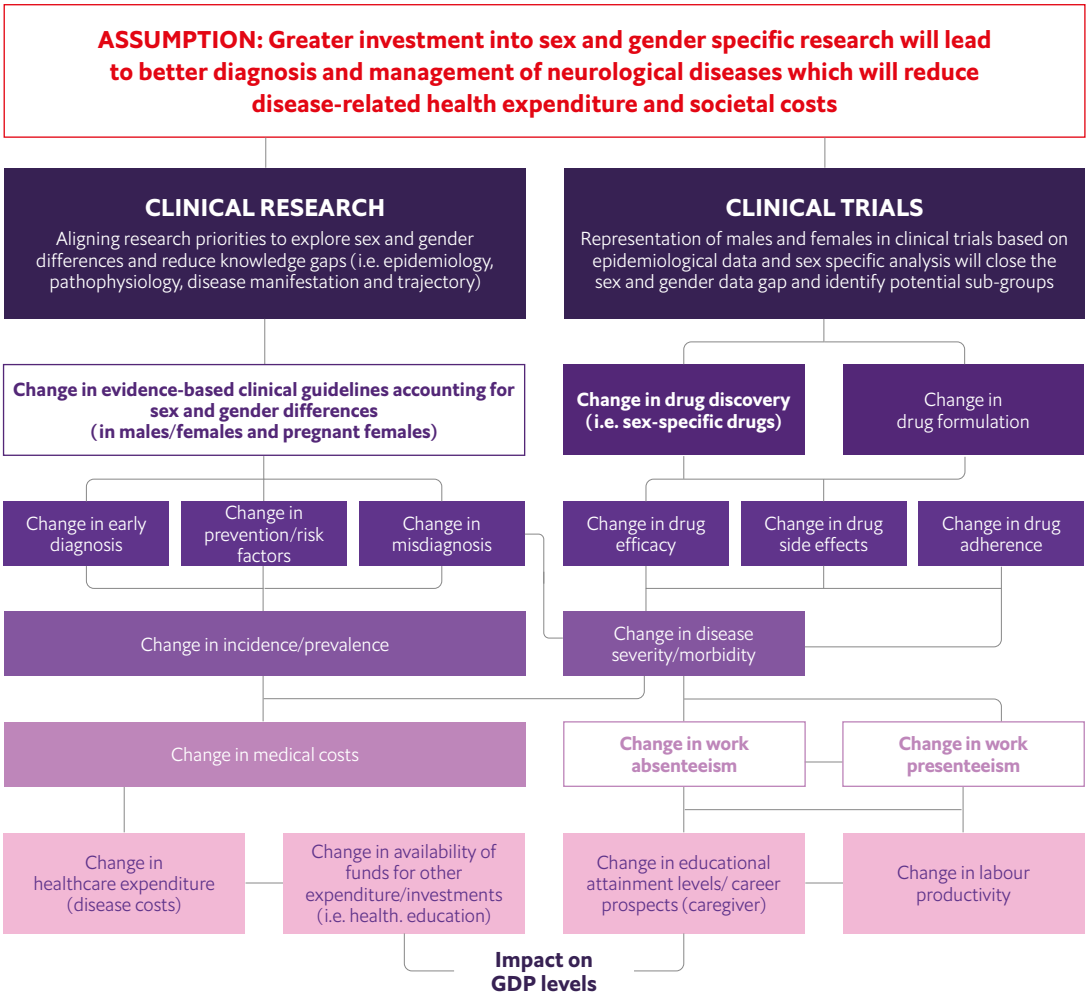
trials, more needs to be done to ensure a fair representation of males in these trials, given the evidence that males with migraines are underdiagnosed and undertreated.[306]

Like other brain disorders, depression affects 80% of migraine sufferers,[307] with studies showing an increase in depressive symptoms during a migraine headache.[308] Reports on the sex and gender differences in the effect of depression on migraine are sparse. One study found that middle-aged women are 40% more likely to become depressed if they experience migraines, with the risk remaining elevated even after the cessation of pain; a link not seen in men.[309]

Economic impact

The impact of migraine on workforce productivity is substantial; in a survey of 11,000 people across 31 countries (across North and South Americas, Europe, the Middle East and Northern Africa, and the Asia-Pacific region) who suffer from migraine, 52% reported absenteeism and presenteeism.[310] The US

Figure 10: A conceptual framework for investing in sex and gender-specific research in the area of Migraine



spends US$19.3bn in indirect costs, of which 81% is attributable to absenteeism.[311] In Europe, direct and indirect annual costs of migraine are estimated at €95bn, of which 93% comes from productivity losses.[312] The average annual healthcare expenditure on migraine is greater in women (€1,517) than men (€1,274).[313]

Although not fatal, migraine is the leading cause of missed workdays among people aged under 50 years because about a third of attacks occur during workdays and two-thirds of migraine attacks result in significant productivity losses. Chronic migraine sufferers lose four times as much productive time as their counterparts who have infrequent headaches.[314] Women are two to three times more likely than men to have migraines, meaning they disproportionately suffer the economic impact. The condition typically hits hardest during one's thirties, an important decade in which women are building their careers and earning potential, and possibly starting families.[315] Research has also shown that migraine, a debilitating disorder, can be an 'invisible' or easily dismissed condition, often wrongly seen as 'just a headache'.[316] Where such presumptions exist on the part of employers, there is a risk that women may not take time off for fear of losing their jobs or promotions. Figure 10 shows a conceptual framework for the benefits of sex- and gender-specific research in migraine. Investments in treatments would have a substantial impact on the debilitating effects of migraine, improving both the health and productivity of patients, and ultimately impacting the GDP of a country.

Chapter two: The case for investing in sex- and gender-based brain research

Preclinical and clinical trials, drug discovery and diagnosis

While advances in science have led to improvements in treatments for some brain disorders, such as stroke, most are still not curable, despite significant drug development research, because underlying pathways and mechanisms are too little understood.[317] Brain conditions are highly variable in how they affect patients, which further complicates the design of clinical trials.[318] However, sex and gender biases are prevalent from the very early stages of preclinical research as there are 5.5 times more animal studies using only male animals than studies that include female animals.[319] These biases later cascade down into human studies as an estimated 85.5% of human neuroscience studies include both male and female participants, and 73.5% of these studies do no analysis disaggregated by sex. Furthermore, historically brain disease research has consistently favoured the use of males over females.[320]

Multiple factors account for uneven participation in clinical research. In the past, women were routinely excluded from clinical trials due to the unfounded belief that hormonal fluctuations made them problematic study subjects; similarly, women of childbearing potential were excluded due to concerns around possibly harming the foetus.[321] Trial designs further exclude female participation. Researchers in Germany found that an upper age limit for their study would have excluded only 19% of male participants, but 44% of females.[322] Hard-to-reach clinical sites are a barrier for women, who are more likely to identify transportation challenges such as cost and time as obstructing factors.[323] Patient-specific issues are also at play. Family dynamics, such as caring responsibilities and the lack of self-autonomy, could impact women's decision-making (such as being more likely to seek approval from a spouse to participate than vice-versa). Men and women express different reasons for participating in clinical trials, an insight which could inform more strategic communications to drive up participation.[324]

Unequal representation has hindered analysis disaggregated by sex and created assumptions that drugs will work in the same way in females as they do in males.[325] Unfortunately, this is clearly not the case, with women experiencing adverse drug reactions almost twice as frequently as men. One report also found that side effects such as nausea, headache, depression, cognitive deficits, seizures, hallucinations, agitation and cardiac anomalies were worse in 90% of females studied.[326]

Pharmacokinetics (what the body does to a drug) and pharmacodynamics (what the drug does to the body) differs between males and females due to several factors; for example, increased acidity in the male

stomach enhances drug dissolution, the distribution of subcutaneous fat on females slows absorption for intramuscular injections, and drug transporters vary based on gonadal hormones.[327] For Zolpidem, a sleeping tablet,[328] females had double the levels present after receiving the same dose as males because of sex-based differences in the way the drug was metabolised. These findings led the FDA to initiate weight-based dosing for females and males, demonstrating the importance of recognising sex as a variable that contributes to varying responses to drugs in patients, along with the importance of using research data to make decisions.[319]

There has been some progress towards gender equity in clinical trials. With regards to the safety concerns for females of child-bearing potential, the FDA's 1977 regulations that excluded females from Phase 1 and 2 drug studies until fertility and teratogenicity (the propensity for foetal defects) studies were widely criticised, leading to a reversal in 1993. This was followed by a rule in 1998 giving the FDA authority to refuse any New Drug Application (NDA) that does not analyse the safety and efficacy data appropriately by sex. An NDA must also include efficacy data based on age, sex and racial subgroups,[319] and studies show that female representation is increasing.[329]

As a consequence of higher male participation in trials, data are incorrectly generalised to females, leading to sub-optimal outcomes and putting patients at risk of harm.[330] Women are known to report more side effects than men, and in some instances these are more severe.[331] The hormonal state of a female – whether she is pregnant, menstruating or in menopause – are all important when considering drug distribution and elimination from the body.[332]

Dr Carcel highlights this need for more women to be enrolled in clinical trials and for the increased reporting of sex and gender differences in observational data. Borrowing a quote from Professor Londa Schiebinger, Director of Gendered Innovations at Stanford University, Dr Carcel explains why sex- and gender-based research was beneficial, saying, "Intersectional analysis, which includes sex and gender, but also age and important sociodemographic variables, is doing good science. We need to analyse and report our trial and real-world data by sex and gender, and this can improve reproducibility and efficiency. Ultimately, the aim would be to improve health outcomes and reduce bias. These findings would provide a shift in how clinicians treat their patients and an avenue to start the discussion on a personalised approach to the treatment of women and men. This research encourages precision medicine as is the aim of the Women's Brain Project."

To optimise care for patients with brain diseases, it is important to increase the enrolment of both sexes into clinical research and drug trials that is reflective of the sex distribution of the epidemiological burden. Better efficacy and safety of drugs, as well as fewer side effects – which would all result from more equitable clinical trial research – would improve adherence to treatment protocols for both males and females.

Prediction and prevention

Because treatments for brain diseases are limited, with no current curative treatments, and therapies typically taking about 15 years of development and often failing in late-stage clinical trials, prevention and disease management is central to healthcare efforts.[333]

Despite the obvious sex and gender differences in presentation, diagnosis and responses to treatment, males and females with brain disorders are often treated in a similar manner clinically.[334] There are large knowledge gaps in terms of how these differences arise mechanistically; the recognition that sex hormones could be influencing factors has not yet translated into clinical recommendations for disease management.

Dr Tarun Dua, Head of the Brain Health Unit in the Department of Mental Health and Substance Use at the WHO, argues that "with greater knowledge about the causes and risk factors of neurological disorders, they can be more effectively prevented. Stroke and dementias are among the conditions that could be prevented, forestalled or made less severe through the promotion of brain health across the life course".

A valuable intervention is greater awareness about pathological changes that could lead to clinical expression, which can be present decades before the clinical onset for some conditions. Biomarkers could also improve prediction and prevention by identifying biological type and severity of neurodegeneration, both before and after clinical onset. A population strategy in which onset is delayed to a more advanced age would have a significant public health impact.[335]

Sex and gender research can offer important predictive and preventive insights. A life course approach to women's health, for instance, could contribute to a better understanding of biological differences in the presentation of brain diseases. Such an approach investigates the long-term effects on health and disease of biopsychosocial exposures from gestation, through childhood, adolescence, and young adulthood. Simply put, such an approach focuses on whether early intervention could reduce disease risk or severity later in life.[336]

Dr Clayton thinks that the menstrual cycle is one factor that should be included in these considerations far more than is currently the case. "We know that if you are diagnosed with anxiety and depression in puberty, you are more likely to have it in menopause. We [also] know that the cessation of the menstrual cycle (menopause) is associated with neuro-endocrinological changes and we are learning more and more through brain imaging techniques, what's actually happening there," she explains. Dr Clayton argues that sex- and gender-aware care requires understanding about every stage of the person's life, including pregnancy history. While asking an older female about any prior incidence of preeclampsia may seem odd, the condition increases the risk of stroke, thus presenting the argument for embedding menstrual and pregnancy history in every electronic health record system.

Caregiving and disease management

Sex and gender do not only influence the clinical dynamics of the brain disease onset, they also manifest in disease management, logistics and caregiving. Professor Wiesje van de Flier, Scientific Director at the Alzheimer Center Amsterdam, Amsterdam UMC, thinks that awareness of sex and gender differences is advancing. "We are stepping up and interest is developing in sex and gender differences and the most important starting point is that AD is more common in females than males. We're not entirely sure why that is, but for other dementias, particularly Dementia with Lewy Bodies, it is the opposite. Sex and gender inclusive research is therefore very relevant", she explains, adding that "In the end it is about treatment and for AD, current treatment is mostly organising care, and there are clearly great gender issues involved as appropriate care is different for men and women. More importantly, there are gender inequality issues in caregiving, with female partners providing more care than male partners."

"Despite having universal health systems and pretty well-funded responses to ageing [in the UK] compared to the rest of the world, and

having good awareness of dementia and what happens in older age, unpaid and informal care is very heavily gendered towards women," says Professor Martin Knapp, Professor of Health and Social Care Policy at the London School of Economics and Political Science. However, there have been positive changes, Prof Knapp goes on to say, "such as men living longer and therefore now able to provide care for their wives or partners who have had a stroke". Also, women are now more open to allowing their sons to carry out personal care tasks; however, despite this changing dynamic, the reality is that 70% of informal care for brain diseases is in fact provided by women.[337]

Progressive diseases, including brain disorders, put substantial pressure on caregivers who tend to have poorer emotional well-being, more difficulty with tasks, and more distress in general.[338] Brain disorders that cause higher levels of impairment, such as AD and PD, tend to be associated with greater caregiver burden, which is also tied to how well the family functions as a unit.[339] The caregivers may have fears and insecurities about their future, may experience feelings of guilt, sadness, and frustration, negative changes in their lifestyle such as limits to how much they can work and socialise, as well as a deteriorating financial situation due to loss of income.[340] In the UK, the work of an informal (and therefore unpaid) caregiver during Covid-19 was valued at £193bn per year, more than the country's annual spend on healthcare.[341] The needs of these caregivers should therefore be carefully assessed and steps taken to reduce the burden.

Chapter three: Tools to improve sex- and gender-specific brain disease research

Addressing biases in healthcare

Confronting norms through policy change

Sex- and gender-based biases impact how healthcare professionals and clinical researchers make decisions and carry out research, and there are tools to expose and address these biases and blind spots effectively. Standardised protocols, the development of sex- and gender-specific data, and the use of all-women healthcare teams for female patients are among the solutions tabled.[342] Across Europe, countries foster equality and equity across regulatory, organisational and informational domains.[343] These include duty laws to promote equality and enhanced organisational strategies, such as gender budgeting, to ensure financial allocations are designed and evaluated for their impact on gender-responsive public governance.[344] The European Commission requires all higher education and research organisations to have a gender equality plan in place before they can receive research funding.[345] Improved informational strategies could also provide gender-sensitive health indicators that identify key differences between women and men in relation to health and the social determinants of health to support policy changes.[341]

Impact assessments in research can promote sex and gender equity by analysing the social and economic impact of brain disorder research findings, driven by the 4As: Advocacy, Accountability, Analysis and Allocation.[346] Advocacy highlights the benefits of sex- and gender-based research; accountability – more specifically to the public – would ensure that research funding is well spent as researchers need to account for how public money is allocated; analysis suggests the need to challenge biases and devise policies that change or eliminate them; and allocation would ensure equitable representation from all sex and gender identities in research.[347]

To be effective, such approaches require good data disaggregated by sex and gender, political commitment to change, and an openness to challenge obstructive opinions about females and women in healthcare. Healthcare providers need to recognise the inextricable link between sex and gender and disease prevention, diagnosis, and management.[348]

Clinical research

Boosting recruitment

More representative clinical study populations would produce more rigorous research and better outcomes, such as treatments that work effectively with minimal side effects. Clinical trial design can also be improved at every step, from diagnostic criteria to communications that

ensure better cohort selection, to data analysis disaggregated by sex. "The way we design the study can affect the likelihood that you are going to enroll women or men", explains Dr Clayton. "For example, a lot of the diagnostic criteria for diseases are based on a male pattern of disease, autism is a good example where the diagnostic criteria are for the way boys show up with the disease, not girls." Applicable Phase 3 Clinical Trials are now being required to report results by sex or gender, race and ethnicity into the trial database, clinicaltrials.gov. The FDA also publishes the demographics of their studies, and females are increasingly being incorporated.[349]

Other tools to improve women's participation in clinical trials include providing compensation to offset issues related to transportation and other financial costs associated with participation, as studies show that monetary incentives help boost and retain participant levels in a trial.[350]

Flexibility in research settings could help too; use of telephone interviews scheduled for evenings and weekends have increased female engagement by eliminating the need for transportation or rearranging work schedules and childcare.[351] Engaging the community and working alongside the church, civic groups or community healthcare providers could also boost clinical trial recruitment as people are more likely to be sign up when engaged by trusted members of their community.[352]

Trial logistics could also be optimised. Females can, and do, become pregnant during clinical trials, and researchers should ensure that foetal exposure is minimised. Recommendations from the FDA suggest one approach that can be used in shorter clinical trials is administering the trial drug during or immediately following a woman's menstrual period, after a negative result for human chorionic gonadotropin (HCG). For longer studies, trial subjects could be counselled on the use of reliable birth control.[353]

Access to research funding

Protocols governing access to clinical research funding are an important policy lever for change. US federal law dictates that applications for NIH studies that involve human subjects must address the inclusion of women, under-represented racial and ethnic groups, and children in the proposed research.[354] The NIH Sex As a Biological Variable policy "expects that sex as a biological variable will be factored into research designs, analyses, and reporting in vertebrate animal and human studies," unless there is a clear and strong justification for a single-sex study. "[This] shifts the expectation from one where there wasn't an articulation to one where there is a clear expectation to look at both males and females unless there is a valid reason not to do so" says Dr Clayton.

As a result of the SABV policy – in place now for six years – there is increased awareness of the importance of sex as variable in many disciplines, including brain research. Research in rodent models on ischaemic stroke is showing how different the response is in males and females on a molecular level. One recent example[355] highlighted how inhibiting autophagy in ischaemic stroke was beneficial in male mice and female mice who had their ovaries removed (ovariectomised), but made the effects worse in normal females and ovariectomised ones who were given oestrogen. These differences would not have been realised if data had not been disaggregated by sex.

The Canadian Institutes of Health Research (CIHR) also has a Sex and Gender-Based Analysis (SGBA) in Research Action Plan, which expects research applicants to integrate sex and gender into research design and practices when appropriate.[356] Increasingly, researchers in Canada need to identify their approach to SGBA, and often need to assign a Sex and Gender 'Champion' in order to be eligible for funding.[357]

A 10-year longitudinal evaluation of the mandatory requirement to include SGBA in research grant applications showed that proposals including sex as a variable rose from 22% to 83%, and gender from 12% to 33%, with population health research applications paying the greatest attention to gender (82%).[358]

Female principal investigators were more likely to integrate sex and gender than those who identified as male.

Applications with female principal investigators were more likely to integrate sex and gender than those who identified as male.[359] This latter point is worrying as female researchers are less likely to receive research funding than their male counterparts, and are also more likely to receive less funding than males.[360,361,362,363] Beyond this, the increase in research integrating sex and gender in the design highlights the importance of policies that increase awareness, as well as the need for monitoring to ensure that these policies are followed.

Requirements from the NIH (via their SABV policy), the CIHR (via their SGBA policy), and the European Commission to integrate sex, gender and intersectionality into clinical trial design have all led to a shift in research practices. The Trans-NIH Strategic Plan for Women's Health Research: Advancing Science for the Health of Women will also ensure the integration of sex and gender into biomedical research to allow every woman to receive evidence-based care better suited to her own needs and circumstances through the appropriate representation in the research process.[328]

Increased funding to explicitly support sex- and gender-based research could also redress the imbalances. Programmes such as the "Brain Canada-Women's Brain Health Initiative (WBHI) Expansion Grants: Considering Sex and Gender Program" are helping to make a difference in this area, through the provision of a funding boost of C$ 105,000 to each of the six research teams in a move described as 'a call to action for gender equity in scientific research'.[364]

Greater equity in the number of female scientists leading brain research could also drive improvements in the inclusivity and quality of research outcomes. However, a notable rise in the number of female neurologists over the last half century has not yet translated into more equal authorship of scientific publications.[365] Many obstacles, from the challenge of pursuing academic careers and starting families to biases and stereotypes, have been identified in the neuroscience field, reflecting broader STEM sector trends.[366]

Diagnosis and management

The first step towards improved disease management is an expanded understanding of brain disorders. Borrowing an example from cancer, some successful treatments were only developed after the molecular basis of cancers was discovered.[315] Biomarkers play a vital role in detection and early diagnosis, and can revolutionise the study of brain disorders with recent technological advances allowing measurements of neurological damage.[367] Reliable identification of biomarkers allows for earlier diagnosis, improves selection of participants for clinical trials, and allows effective monitoring of treatment.[368] Sex-specific biomarkers have become a form of identification of brain disorders[369,370] with biomarkers associated with AD showing great promise for personalised medicine.[371] Sex-specific differences in diagnostic accuracy have been explored, where detection of male and female biomarkers showed equivalent specificity,[372] paving the way for more equitable diagnosis and management.

The lack of curative treatments for the brain disorders in this study means that disease management remains the centrepiece of health system responses. This in turn makes caregiving significantly gendered, especially for dementia.[373] Care is mostly provided by women, and the burden tends to be exacerbated in advanced

stages of brain diseases. Studies have shown that positive experiences help to reduce caregiver burden, and they are known to feel better when they feel appreciated;[374] results of these studies should be cascaded to medical and social care settings, for example – through the use of national guidelines, to help ease caregiver burden.

In Austria, for instance, caregivers receive an allowance that increases when their charge develops dementia, and there is an argument for a more comprehensive assessment of caregiver burden to determine what levels of support are adequate for each caregiver. This requires more public and political awareness.[370] Another possible solution is for an alternative approach to care, different from informal caregivers and typical nursing homes.[375] For example, Hogewey in Amsterdam is a non-traditional nursing home that appears like a real neighbourhood with streets, squares, alleys and a park where the residents live in houses with housemates, perform daily tasks, and live as normally as possible.[376]

Prof Knapp advocates greater support for unpaid carers. Using England as an example, he explains that "carers are now entitled by law to an assessment of their needs [under the 2014 Care Act], which provides a better support system compared to the years preceding [the 2014 Care Act]". Also in England, Policy Leeds – an organisation that connects researchers and policy professionals to influence policy change – tabled suggestions for improving the lives of informal carers, such as redefining the term "personalised medicine" to go beyond targeted molecular treatments for disease to encompass targeted interventions that promote health. This would see tailored support provided for the carer based on consultation with both carer and patient. Support services available to carers also need to be highlighted as many do not access these due to their lack of awareness.[339]

In the absence of existing DMTs, sex- and gender-informed healthcare should maintain a strong focus on prevention. For instance, 35% of the risk of AD and other dementias is modifiable. The 12 modifiable risk factors include lower education, hypertension, hearing impairment, smoking, obesity, depression, physical inactivity, diabetes, low social contact, excessive alcohol consumption, traumatic brain injury and air pollution, and these risks could be reduced through targeted programmes that address lifestyle changes.[374] One study in the US found that reductions in stroke mortality were associated with lower stroke incidence rates, resulting from better prevention and control of risk factors such as hypertension, diabetes and smoking, further highlighting the importance of healthy lifestyles.[377]

Conclusion

Brain disorders are a growing public health concern, which blight the lives of patients, their caregivers and families. Extrapolating from current trends, brain disorders will impose a large burden on health systems and economies through increased medical costs and productivity losses (from both the patients and their caregivers), and will have an overall knock-on impact on GDP. The absence of curative treatments means that these disorders will continue to result in significant forms of disability. Further investment in basic scientific and clinical research is needed to allow for therapeutic innovation and improvement in testing that is specific to demographic groups.

Brain disorders have differential causes and impacts on people and their families, based on various individual and environmental factors, including sex and gender. These differences manifest at every stage of disease, from onset to diagnosis to treatment, and shape disease management due to socioeconomic norms. These conditions require a scale-up in research funding to more effectively tackle their prevalence, cost, and the lack of breakthrough therapies.

An increase in funding alone – while welcome – must not exacerbate the long-standing tendency to ignore or underestimate the impact of sex and gender on disease causes and progression. An intersectional approach, taking into account sex, gender and other identities, would generate better science and better outcomes.

Positively, the scientific community has made gains in understanding the role of sex and gender across healthcare more broadly, and this progress now needs to accelerate in the domain of brain diseases. Tools to move brain disease research in the right direction include designing clinical trials and recruitment methodologies in ways that encourage broader participation; tying funding to sex- and gender-informed research design and participation; greater awareness amongst clinicians and healthcare workers on sex and gender differences in the symptoms manifested by brain diseases, their progression and impact; and more funding to drive momentum towards exploring more- sex and gender-based differences in brain disease research.

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