

**The George Institute for Global Health, Imperial College London
Submission to the Women's Health Strategy: Call for Evidence, June 2021**

Addressing the leading causes of death and disability for women in the UK

Summary

- **Four of the five leading causes of death for women in the UK are non-communicable diseases (NCDs)**, including dementia, acute coronary syndromes (ACS), cerebrovascular diseases (e.g. stroke) and chronic lower respiratory diseases (e.g. chronic obstructive pulmonary disease, COPD).
- We and others have shown that **the way women and men develop and experience NCDs can differ significantly**, including how they are managed within the health system.
- However, as we and others have shown, **recognition of these differences is not routinely reflected in policies, clinical guidelines or practice**, nor in the training of those involved with the provision of healthcare, including in preventative care.
- Furthermore, **women continue to be under-represented as participants in research**, including in clinical trials, and the **disaggregation of analyses by sex and/or gender** to reveal health patterns in women and men separately **is not yet routine**.
- As a result, we and others have documented numerous examples where, compared to men, women are more likely to experience non-evidence-based treatments for NCDs and have worse health outcomes than would be expected if care was equitable between genders.

Opportunities

Women's health can be improved through the **routine use of sex- and gender-disaggregated analyses**, which can help us better understand the role of both biological and socio-cultural factors in disease incidence, prevention and management, and develop treatments and interventions that appropriately address the needs of women and men. To facilitate this, actions that the Department of Health & Social Care (DHSC) should take include:

- **Prioritise the disaggregation of health data by sex and gender**, where possible and appropriate.
- Ensure that the NIHR **prioritises funding for sex- and gender-disaggregated analyses in research**, and stipulates that funded studies should be powered to show outcomes by sex and/or gender.
- Work with providers to set **national minimum standards for medical training and education programmes**, including an understanding of sex and gender differences in disease.
- Ensure that the **NICE clinical guideline development process includes an assessment of the extent to which sex and gender have been considered** in the underlying evidence base.
- Prioritise research into the **associations between female-specific conditions and NCD risk and presentation**, and support the translation of this research into guidelines and practice.
- Prioritise and resource research into the **integration of NCD prevention and treatment into routine reproductive, maternal, child and adolescent services** provided by the NHS.
- Prioritise research that addresses evidence gaps on **sex- and gender-related differences** in the burden, causes and management of NCDs **at different stages of the life course**.

- Mandate that UK government-funded trials **should not exclude pregnant women** unless there is a valid *a priori* reason not to do so.
- Ensure funding is available to **boost the number of women in government-funded clinical trials**.
- Ensure that Clinical Trial Authorisation requires that specific **approval is sought by investigators who do not plan to include equal percentages of women and men** in their trial.

Introduction

The George Institute for Global Health at Imperial College London welcomes the Government's commitment to developing a women's health strategy, and appreciates the opportunity to submit evidence to this consultation.

Despite remarkable advances in maternal, reproductive and sexual health over the last 100 years, a full appreciation of women's health, extending to the leading causes of death and disability for women - namely NCDs - is yet to be realised. Here we provide evidence on how the experiences of women and girls have been largely overlooked in medical research and practice, leading to health inequities between genders. We highlight the urgent need for the use of **sex- and gender-disaggregated analyses to better understand the role of both biological and socio-cultural factors in disease incidence, prevention and management, and inform the development of treatments and interventions that appropriately address the needs of women and men.**

Sex- and gender-disaggregated analysis refers to analyses in which data are collected, analysed and interpreted for women and men separately such that the similarities and differences between the sexes/genders becomes a central consideration.

For brevity, we have used the terms 'women and girls' and 'men and boys' in this submission. However, sex and gender are not synonymous; 'female/male' are the appropriate terms when referring to sex, and 'women/men' better reflects socially constructed gender roles. It's also important to recognise that this binary distinction of women and men does not reflect the true diversity of sex and gender in our society, and that 'women' encompasses cis-women, intersex women and women with a transgender experience.

While it is not a focus of our submission, it is important to also note that gender intersects with other factors, including ethnicity and socio-economic status, to drive health inequities.

Evidence

Theme 1: Women's voices

Sub-themes addressed:

- *Evidence of male experience of symptoms being treated as default ('typical') and the impact of this on women's experience of health services and health outcomes*
- *Evidence on the training and education provided to clinicians on sex and gender differences*

The result of having a health system largely designed by men is that the male experience of a disease is often seen as 'typical', and women's symptoms may be missed or misdiagnosed. This leads to women being more likely than men to experience non-evidence-based treatments for many NCDs, and to having worse health outcomes than would be expected if care was equitable between genders.

For example, in 2019, 8% of all deaths in women in England and Wales were the result of ACS.(1) We have shown that both women and men with ACS present most often with chest pain (74% of women and 79% of men), but women are more likely than men to present with pain between the shoulder blades, nausea or vomiting, and shortness of breath.(2) Despite the huge burden of ACS in women, and the fact that sex differences in symptoms for patients with confirmed ACS have been evident since the early 2000s, women's symptoms, where they differ from men's, continue to be labelled 'atypical' in international guidelines.(3, 4)

The impact of this on women's experiences of health services and health outcomes is troubling. One UK study found that women presenting to hospital with ACS symptoms less frequently received 13 of the 16 components of guideline-recommended care.(5) In the same study, women were more likely to die than men within 30 days of experiencing an acute event such as a heart attack. Using these findings, the authors estimated that 8,243 deaths in women who had a heart attack in the UK between 2003 and 2013 could have been prevented, had the quality of their care been equal to that of men.

Our team has also found that risk-factor management for the secondary prevention of coronary heart disease is generally worse in women than in men.(6) Women are less likely to achieve treatment targets for total cholesterol, LDL cholesterol, HDL cholesterol or glucose. They are also less likely to be physically active or non-obese, or to have attended cardiac rehabilitation. This could in part explain our finding in a separate study that the risk of experiencing a coronary event is more similar between women and men who have already had a heart attack than between women and men without this history.(7)

Another example of men's experience of a condition being treated as the default is with COPD. Research shows that, compared to men with COPD, women are more likely to be diagnosed with asthma and are less likely to be formally diagnosed using spirometry (the gold standard for measuring lung function), even when presenting with symptoms compatible with the disease.(8-10) This is particularly concerning given that women diagnosed with COPD tend to experience it more severely (11) and have more rapid disease progression than men.(12) Despite clear sex differences in the risk and progression of COPD, the Global guidelines for Obstructive Lung Disease (GOLD) do not address these.(13)

Not surprisingly, male bias is also an issue with less common conditions, such as abdominal aortic aneurysm (AAA). Guidelines for the best treatment of AAAs are based on what works for men, as they are more likely to develop the condition.(14, 15) However, using these guidelines, women are more likely to die or suffer complications from elective AAA repair, or to be turned down for treatment.(16) AAAs are more likely to burst at a smaller size in women, who are less likely to be offered endovascular surgery, and who respond differently to the stress of surgery. Our colleagues at Imperial are investigating why outcomes for AAA in women are worse than in men, to try to identify ways of better treating women.

The extent to which training and education about sex and gender differences is incorporated into UK medical curricula has not been systematically studied. Anecdotally, however, recent medical graduates report not having been taught any sex- and gender-based medicine in their courses. Moreover, surveys from the US and Europe indicate that sex- and gender-based content which moves beyond sex and gender differences in reproduction is currently lacking.(17, 18)

Opportunities:

Reducing the burden of NCDs and other conditions in women would be greatly accelerated by a better understanding of sex and gender differences in disease and how these can be addressed. To facilitate this, the DHSC should:

- **Prioritise the disaggregation of health data by sex and gender, where possible and appropriate.**
- **Ensure that the NIHR prioritises funding for sex- and gender-disaggregated analyses in research, and stipulates that funded studies should be powered to show outcomes by sex and gender.**

Ensuring that an understanding of sex and gender differences in disease is included in all UK medical curricula would prevent the male experience being seen as 'typical', and would greatly improve women's experience of health services and the quality of care they receive. To facilitate this, the DHSC should:

- **Work with medical education and training providers to set national minimum standards for training and education programmes, including an understanding of sex and gender differences in disease and the implications for clinical practice as a key component.**
- **Ensure that the NICE clinical guideline development process includes an assessment of the extent to which sex and gender have been considered in the underlying evidence base, and that guidelines highlight to health professionals where this is lacking.**

Theme 2: Information and education on women's health

Sub-themes addressed:

- *Evidence on women's awareness of health issues*
- *Evidence on healthcare practitioners' awareness and understanding of conditions affecting women*

Just as there are gaps in our understanding of how conditions affecting both genders impact women in different ways, there are also gaps in our understanding of how risk factors and determinants of health exert a different influence on health outcomes for women and men. This has implications for both healthcare practitioners' ability to provide evidence-based information and effective advice, and women's awareness of the health risks they face and their ability to take appropriate measures in response.

Using a methodology developed by members of our team,(19) we have shown that several major risk factors for coronary heart disease (e.g. diabetes, smoking, socioeconomic background and adiposity) have a larger effect on the risk of coronary heart disease in women than they do in men. For example, we have shown that, while having diabetes doubles the chance of a future heart attack in men, it triples the chance in women.(20) Similar findings have been observed for other associations between risk factors and diseases; for example, between blood pressure and vascular dementia,(21) smoking and COPD,(22, 23) adiposity and heart attack,(24) and between diabetes and stroke,(25) kidney failure,(26) and heart failure.(27) This increasing body of evidence dismantles the commonly held assumption that major known risk factors have a similar effect on disease outcomes in women and men.

Women-specific reproductive factors have also been shown to be associated with a higher risk of cardiovascular disease (CVD), but are not currently included in the QRISK risk tool recommended by NICE for the assessment of CVD risk.(28, 29) For example, we found that early menarche, early

menopause, earlier age at first birth, and a history of miscarriage, stillbirth or hysterectomy were each associated with a higher risk of CVD in later life.(30) Similarly, early and late menarche, earlier age at first birth, and hysterectomy were found to be associated with a higher risk of dementia,(31) while women who have a late menopause (≥ 55 years of age) are more than twice as likely to experience a haemorrhagic stroke later in life than those who experience natural menopause between 50 and 54 years of age.(32)

This significant and growing body of evidence highlights the urgent need to raise awareness among both women and healthcare practitioners of women-specific risk factors and risk factor associations, and to develop preventive health interventions that are tailored to women and take these risks into account.

Opportunities:

Improved awareness of how they are differentially affected by risk factors for NCDs would empower women to make more informed decisions about their health. To facilitate this, the DHSC should:

- **Ensure that public health messaging and NCD prevention campaigns are routinely designed with a sex and gender lens in order to target both women and men with effective messaging.**

Improved awareness among healthcare practitioners of how female-specific conditions, including reproductive factors, are associated with risks for NCDs later in life would improve the quality of support, diagnosis and treatment they are able to provide. To facilitate this, the DHSC should:

- **Prioritise more and better research into the associations between female-specific conditions and NCD risk and presentation, and support the translation of this research into clinical guidelines and practice.**

Theme 3: Women's health across the life course

Sub-themes addressed:

- *How the needs of healthcare services vary between different demographic characteristics*
- *Evidence on intervention points that are under-explored*
- *Opportunities for targeted action and evidence on the potential benefits*
- *Examples of innovation in service delivery which take a life course approach or have improved women's access to services*

There is growing evidence that health status and outcomes in later life are influenced by women's health status in early life and pregnancy, and that these life stages therefore offer opportunities for interventions that are under-explored.

Of specific concern is evidence that women who have diabetes, hypertension and anaemia during pregnancy have a heightened risk of future diabetes or cardiovascular disease.(33-35) For example, otherwise healthy women who develop gestational diabetes mellitus (GDM) have 10 times the risk of developing type 2 diabetes in the 10 years after delivery compared to those not affected by GDM.(36) Similarly, gestational hypertension doubles a women's risk of ACS and stroke in the 10 years following pregnancy.(37) Conversely, we have found that breastfeeding is associated with a lower risk of type 2 diabetes, particularly in women with gestational diabetes,(38) and that women who breastfeed for 24 months or longer have a 17% lower risk of stroke than women who have never breastfed.(39)

These findings highlight both a critical need – to identify women at risk, and manage their healthcare in order to reduce premature deaths – and an opportunity: to integrate prevention and treatment of conditions such as heart disease and stroke into reproductive, maternal, child and adolescent health services, recognising that this engagement of women with health services may not be repeated.(40, 41) At The George Institute, we are currently trialling a digital clinical decision-making support tool that can be used by community health workers to perform risk factor identification for future CVD risk among pregnant women in India.(42) This tool has been used successfully in non-pregnant adults,(43) and could be evaluated in high-income settings such as the UK.

Careful consideration of the healthcare services needs of women in older age is also needed. In 2019, dementia and stroke – two ageing-related diseases – were among the three leading causes of death for women in the UK.(44) The morbidity burden of these diseases is also considerable. An estimated 400,000 women in the UK are stroke survivors. Nearly half of stroke survivors suffer significant disability - ranging from physical to cognitive - and emotional ill-health, and women are disproportionately affected.(45) For example, we found that, compared to men who had survived a stroke, women survivors experienced more problems related to mobility, self-care, pain/discomfort and anxiety/depression.(46) In the same study, we found that women were less likely to die within 3-6 months after an ischemic stroke. This evidence has clear implications for healthcare services.

With an ageing population comes an increasing burden of multimorbidity: the existence of multiple medical conditions in a single individual.(47) It is estimated that by 2035, two-thirds of UK adults who are aged 65 or older will be living with multimorbidity, and that almost 20% will live with four or more different conditions. Women, with their longer mean life expectancy (83.1 years compared with 79.4 years in men), can be expected to experience a higher multimorbidity burden, both in terms of the prevalence of multimorbidity and the number of years they live with multiple conditions. However, whether this is compounded or offset by gender differences in the age of onset is unknown. There are significant knowledge gaps around the burden, causes and management of multimorbidity – both in the overall population and by sex/gender – as highlighted in a 2018 report from The Academy of Medical Sciences.

Efficient planning and cost-effective resourcing of healthcare services requires a comprehensive understanding of differing disease burdens and their impacts in men and women at different stages of their lives.

Opportunities:

Reproductive, maternal, child and adolescent health services offer an opportunity to reach women who may not engage with the NHS at other times and put in place measures that have the potential to improve their health outcomes later in life, and create efficiency savings over the long term. To facilitate this, the DHSC should:

- **Prioritise and resource research into the integration of prevention and treatment services for NCDs such as diabetes and hypertension into routine reproductive, maternal, child and adolescent services provided by the NHS.**

A comprehensive understanding of differing disease burdens and their impacts in men and women at different stages of their lives would enable more efficient planning and resourcing of healthcare services adequate to meet needs. To facilitate this, the DHSC should:

- **Ensure that the NIHR prioritises funding for research that addresses evidence gaps on sex- and gender-related differences in the burden, causes and management of NCDs at different stages of the life course, including multimorbidity.**

Theme 5: Research, evidence and data

Sub-themes addressed:

- *Aspects of health or medical research that overlooks or neglects women's perspectives or experiences and the consequences of this*
- *How research and evidence are used by healthcare professionals and/or patients*

Women continue to be under-represented in many areas of health and medical research, including in clinical trials, which provide the highest standard of evidence for new treatments and interventions. The evidence is therefore all too often 'male by default'. However, what constitutes the best treatment and care may differ between women and men, for both safety and efficacy reasons. For example, guidelines for the treatment of heart failure are similar for women and men, but there is evidence that giving women lower doses of blood pressure-lowering medications than men may increase their chances of survival.(48) Knowing whether a treatment offers similar protection to both women and men against adverse health outcomes, or indeed has a similar safety profile, is equally important to guide effective clinical decision-making.(49)

We can only know whether sex differences in treatment efficacy or safety exist if sufficient numbers of both women and men are included in all phases of clinical trials, and if results are publicly reported in a sex- and/or gender-disaggregated way. However, in stroke clinical trials, for example, we have previously found that women make up only around 42% of all patients, (50) despite women accounting for half of all those affected by stroke.(51) Similar results have been found for coronary heart disease, ACS and heart failure.(52)

During the COVID-19 pandemic, we have seen examples where small numbers of women participants in clinical trials has led to inconclusive evidence for the efficacy of certain treatments in this subgroup, making it difficult to translate the evidence into tailored guidance. In addition, a review of WHO-registered COVID-19 clinical trials found that all nine vaccine trials explicitly excluded pregnant women.(53) This led to mixed and confusing policy messages around the safe use of vaccines in pregnant and lactating women. However, as we and others have argued, the absence of women in COVID-19 vaccine trials simply shifted experimentation from the relatively safe and controlled setting of clinical trials to the poorly controlled setting of real-world implementation.(54)

Despite clear evidence of the need to embed sex and gender in health and medical research, we have found, through preliminary scoping work (unpublished), that none of the leading health and medical research funding charities in the UK currently have sex and gender policies for the research they support. This represents a clear opportunity to improve sex and gender equality in research, and we are currently working with a number of these funders to co-create a UK gold standard for sex and gender integration in health and medical research.

Opportunities

Integrating sex and gender into health and medical research and presenting disaggregated data has been shown to improve the relevance and validity of findings to inform clinical practice and provide

the most robust evidence to inform equitable interventions and healthcare planning. To facilitate this, the DHSC should:

- **Mandate that UK government-funded trials should not exclude pregnant women unless there is a valid *a priori* reason not to do so.**
- **Ensure that funding is available to boost the number of women in government-funded clinical trials.**
- **Ensure that Clinical Trial Authorisation from the Medicine and Healthcare products Regulatory Agency requires that specific approval is sought by investigators who do not plan to include equal percentages of women and men in their trial, with reasonable justification for this decision.**
- **Continue to support endeavours such as Trial Forge, which has been set up to better understand recruitment and retention in clinical trials.**

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