

The Big Read Medical science

## How medical research is failing women

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For years, the process for developing and testing new drugs has focused disproportionately on male bodies — to the detriment of female patients

**Sarah Neville** in London AUGUST 2 2024

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Kate Womersley was a medical student at Cambridge university, nervously dissecting her first cadaver, when she noticed an odd lacuna in her anatomy course handbook: there was no mention of breasts.

Puzzlement swiftly turned to anger. Not until 2016, a year after she and a female classmate first raised concerns, were their entreaties heeded and the curriculum adjusted.

Womersley, now a doctor in psychiatry, remains shocked that a hugely significant organ for women's health — after the lung, the second most common site of fatal cancer in females — had been disregarded until so recently at one of the world's most prestigious medical schools. "Having breasts seemed not to be an experience that was reflected in this teaching at all," she says.

The episode changed the trajectory of her career. In 2022, she co-founded the Medical Science Sex and Gender Equity (Message) project at the George Institute for Global Health, which has major centres around the world. The initiative campaigns for policies to ensure sex and gender are accounted for across every stage of the research cycle, from study design and recruitment of participants to data analysis and the reporting of findings.

Womersley is among a band of scientists and clinicians who believe the biological and societal factors that shape women's health have long failed to receive adequate attention from researchers, educators and clinicians.

Bias starts to creep in at the development stage, years before drugs reach patients. Scientists say that pre-clinical testing has sometimes focused disproportionately on male animals and male cells. Then, when the medicines reach human trials, women are persistently under-represented.

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## The gap between women suffering from conditions and their representation in trials

**Category** Female share of Phase I trial\* participation (%)  
Female share of US prevalence (%)

FINANCIAL TIMES

Sources: Aggregate Analysis of ClinicalTrials.gov database, US Census Bureau, IQVIA Institute analysis • \*2014-2023

This partly reflects concern about testing a drug on those of child-bearing age. The scandal of the anti-morning sickness drug thalidomide, which caused devastating birth defects in babies more than 60 years ago, casts a long shadow. Study organisers may fear additional complications and expense from including women. More prosaically, caring responsibilities may make it harder for women to carve out the time commitment a study often demands.

The result is that women are being prescribed drugs that are not simply less effective, but sometimes less safe than they would be for men, researchers argue.

Jill Fisher, professor of social medicine at the University of North Carolina's centre for bioethics, who has extensively researched how clinical trials are conducted, says: "When you're using male bodies to do safety and tolerability studies, essentially you're creating doses of these drugs that are based on the male body . . . generally speaking, larger, heavier bodies, but also bodies that have different fat content."

Data backs up the notion that women suffer disproportionately from a male-centric approach to drug development. Since 2000, women in the US taking approved medicines have reported "total adverse events" — defined as "any untoward medical occurrence" — 52 per cent more frequently than men, and serious or fatal events 36 per cent more frequently, according to Food and Drug Administration information gathered by the McKinsey Health Institute.



Kate Womersley of the Royal Edinburgh Hospital is hopeful that the climate is changing in favour of more gender-inclusive research © Gary Doak/FT

Healthcare professionals in the US reported 4.4mn serious or fatal events for women, compared with 3.8mn for men in 2022. Meanwhile, an examination of medicines withdrawn for safety reasons — a process that the institute says requires objective scientific review — found that since 1980 products were three and a half times more likely to be removed because of safety risks in women than in men.

“Historically the white male body has been seen as the scientific norm, so there’s a sense that ‘whatever we find in men will apply to women,’” says Fisher. This assumption — equally evident in the lack of racial diversity in drug trials — is “something that’s been very difficult to change in the culture of science”.

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**That has not stopped professionals** from trying. Pioneering female researchers first began raising concerns about gender balance in the late 1980s — with some success.

In 1993, the game-changing NIH Revitalisation Act was passed in the US, requiring women to be included in clinical studies funded by the federally backed National Institutes of Health. Around half of participants in the trials it supports are now female, the organisation says.

Teresa Woodruff, president emerita and MSU Foundation professor at Michigan State University, led the push for an equivalent policy in 2016, mandating that female cells must be considered in pre-clinical research before a drug moves into human trials.

Similar steps have been taken in other important drug development markets. In 2010, the Canadian Institutes of Health Research introduced mandatory reporting of sex and gender design on application forms for funding, among other steps designed to improve diversity. Since 2021, one of the core aims of Horizon Europe, a major funder of research across the EU, is “integration of the gender dimension in research and innovation content”. Both the FDA and the European Medicines Agency have underscored the importance of diversity in clinical trials so differences in how the two different genders respond can be detected.

## 4.4mn

Number of serious or fatal events for women taking approved medicines in the US in 2022, compared with 3.8mn for men

But overall, progress has been insufficient to counter decades in which the primacy of male bodies went largely unchallenged, campaigners argue.

This underrepresentation is particularly glaring when judged against the proportion of women with the condition that a particular medicine is designed to address. Global data, analysed for the Financial Times by the IQVIA Institute for Human Data Science, reveals that in Crohn's disease, for example, women made up about 45 per cent of participants in phase 1 studies that test for safety, but comprise 84 per cent of all cases of the condition in the US.

“We're including, by and large, [both] men and women in clinical trials, but we're not doing it in a manner which is balanced or reflective of the prevalence of the disease,” says Melina Kibbe, a surgeon who is dean of the University of Virginia's School of Medicine and a longtime advocate of gender inclusive research.

This disparity is especially noticeable in trials of immunotherapy drugs, often considered the gold standard for treatment of advanced cancer.

In the 10 years from 2014, the percentage of women in clinical trials ranged between 37 and 42 per cent, the IQVIA data shows. This is partly because the trials commonly exclude those with a previous history of immune diseases, “substantially penalising women” who make up about 80 per cent of that cohort, says Fabio Conforti, chief of the breast oncology unit at Humanitas Gavazzeni Hospital in Bergamo, Italy.



Globally, lung cancer is more common in women © Science Photo Library/Alamy

In 2019, he analysed the combined findings of all randomised clinical trials testing immunotherapy in the past 10 years, spanning 11,000 patients. In 19 out of 20 trials, men's survival rate was double that seen in women.

Conforti emphasises that women continue to derive substantial benefit from the treatment, compared with chemotherapy alone. But his team is now conducting parallel trials in men and women to identify a drug, or a combination of drugs, that would work better in female cancer patients.

He is aiming to control for any differences in lifestyle and behaviour between the two groups, which other researchers have suggested could have been a factor in women's poorer results.

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The importance of considering sociological as well as biological factors when thinking about why illness and drug treatment may manifest differently in men than women is underlined by Charles Swanton, deputy clinical director at the Francis Crick Institute, and one of the world's most respected cancer researchers.

He is studying a subset of lung cancer patients who develop the disease despite having never smoked, after making the "fascinating and worrying observation"

that globally the condition is more common in women. A European Research Council grant will help him explore the reasons why, including his hypothesis that women tend to spend more time at the stove than men.

"The answer to this question could be just as simple, and concerning, as cooking oil exposure," Swanton says, adding that oils might behave like air pollutants which his work has previously demonstrated contribute to the development of lung cancer.

Alternative explanations could be that oestrogen, a female sex hormone, heightens a predisposition to lung cancer, or other genetic differences might affect immune cell activation in response to lung tissue injury, he notes.

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**But ensuring gender parity** in trials is just the first battle. The next challenge is to ensure that findings are regularly broken down by gender, campaigners say.

Regulators are paying more attention to subgroup differences but the UNC's Fisher suggests there is little evidence that this is yet "translating into any differences in clinical recommendations and certainly not preventing drugs from getting to the market".

Antipsychotics prescribed to treat some mental health conditions are one example, says Womersley. While treatment is effective in both sexes, women suffer far more side effects.

As with other areas of medicine, paying greater attention to sex or gender-specific research would spare patients from complications "some of which are just annoying and affect quality of life but some of which are dangerous", she says.



Women are persistently under-represented in medical trials, partly because of concerns about testing a drug on those of child-bearing age © Dzmitry Kliapitski/Alamy

What is being taught in medical schools is a decade behind what is being discovered in the laboratory and in research "but we can't really afford to wait that long for sex and gender disaggregated findings to change the way we practise. In almost every field of medicine, there are harms that are playing out because of this," she adds.

The position of pregnant women is especially sensitive. Since the 1990s, says the UNC's Fisher, the FDA has allowed human clinical trials to start before all animal studies have been completed, particularly those designed to measure so-called reproductive toxicity. The result is that initially researchers "may have no idea how an investigational drug might affect a developing fetus".

In recent years, the FDA has said it is safe for women of "child-bearing potential" to join studies before animal-testing is completed, provided they are monitored, including for pregnancy. But Fisher says that researchers would often "rather just restrict the participation of women [of child-bearing age] than inform them: 'Please don't get pregnant during this clinical trial' and trust that they won't do so."

Yet by excluding small numbers of women from clinical trials in an environment where trouble is quite quickly dealt with "you're just moving that experiment to the real world, with many more women exposed and very little surveillance", Womersley adds. "We're missing an opportunity to capture data, and we're probably introducing a huge amount of risk in the process."

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**The idea that treatments** should be tailored to reflect genetic differences has become something of an article of faith among clinicians and health policymakers.

Yet some scientists believe this approach, known as "personalised medicine" or its near-cousin "precision medicine", is still failing to take gender into account.

Alberto Mantovani, a globally renowned immunologist who is scientific director at the hospital where Conforti is researching gender and cancer, says that one area that is far too rarely viewed through a gender lens is obesity. It seems to affect the male and female immune systems differently and could be among the factors affecting the response to immunotherapy, he suggested.

Woodruff argues that gender, along with ethnicity, must be elements of any bespoke treatment approach. "People will say, well, it's too costly to do that. My answer is, it's too costly not to. Personalised medicine represents the revolution that we're all hoping for, that drugs will be tailored for me — and for you and you and you — so let's get it right, starting with sex as a biological variable," she adds.



**It opens our vista so much wider to opportunities for understanding and exploring fundamental mechanisms, because you have two cell types that you can ask questions about**

The amount that remains unknown about female biology should be a massive lure for scientists, she argues, opening up new fields for inquiry and potential breakthroughs.

“All of a sudden you have the opportunity to study things that nobody has seen before: in the immune system, in kidney health, in inflammation,” she says.

“It opens our vista so much wider to opportunities for understanding and

exploring fundamental mechanisms, because you have two cell types that you can ask questions about.”

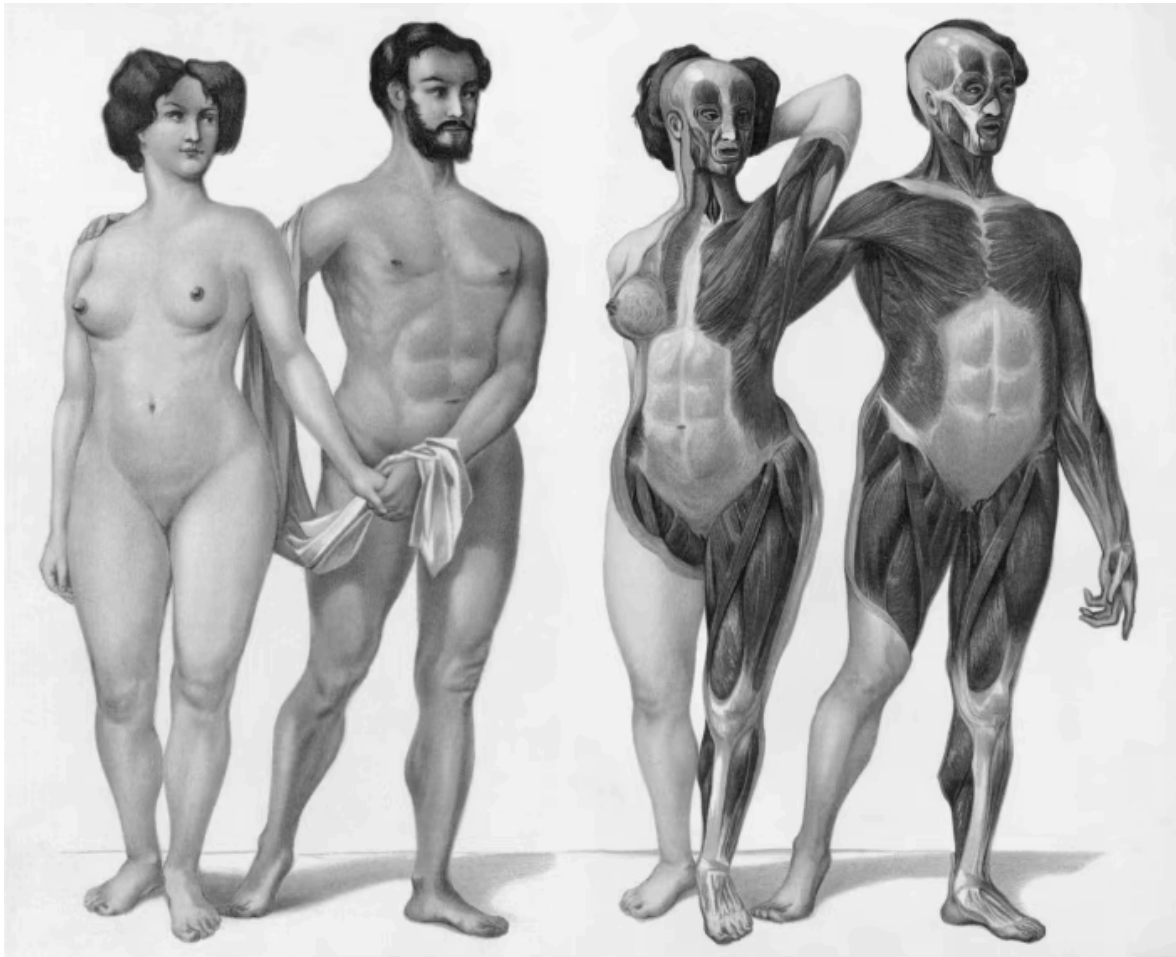
Other obstacles remain. Womersley acknowledges that the politically charged debate around issues of sex and gender may be making it harder to argue the case for female-specific research.

But testing for different outcomes in subgroups can lead to better and more effective treatments across the board, she argues. “At this point there is an emphasis on improving women’s health, but it’s equally important for the health of men, for non-binary, for trans and intersex patients to have this granularity too,” the doctor adds.

Womersley remains hopeful that the climate is changing in favour of more gender-inclusive research.

In 2021, she says, none of the UK organisations that provided money to researchers “had any stipulations that they should recruit women and men to their research, that they should analyse and disaggregate the data, and then compare [the outcomes] to see if there’s a difference”.

Since then, the Medical Research Council, Cancer Research UK and the British Heart Foundation — all backers of the Message project — have introduced diversity guidelines, and a policy framework around sex and gender inclusion in research is being rolled out to funders across the UK. “Starting with funders was a good way to change research right from its beginnings, when hypotheses are made and researchers are coming up with their project ideas,” she adds.



A 19th-century depiction of male and female anatomies © FALKENSTEINFOTO/Alamy

Yet the appetite for change may only shift substantially as female scientists increase in number and more reach senior positions, argues Woodruff, citing research that women are generally more aware than men of the need for gender balance in studies.

An older, largely male generation, which controls grant applications and other key decisions, may still be “imprinting” their attitudes on a rising female generation that needs their patronage to succeed.

She adds: “You might say ‘this is a workforce issue’ [but] . . . it’s about the culture of science that we have to continue to work in and through.”

In the meantime, Woodruff has some simple advice for women being prescribed a new medication — which may ultimately cascade down through the drug development pipeline to ensure their voices resound more loudly.

“People need to ask their physician: was this drug tested for me? The physician needs to ask the drug rep, and then the drug rep needs to ask the pharma company that produced the medicine, and they need to ask the researchers who carried out the fundamental science.”

She adds: “Drug companies — and all of us — need to see that the group most at risk for adverse outcomes is going to be the sex that’s often left out. And that, right now, is women.”

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