The words of the 1979 Pink Floyd classic *Another brick in the wall* describe an educational system that rigidly imposes a single view of education, one that prefers to promote the development of conformed students rather than tailoring education to allow everyone to thrive.

Parallels can be drawn for healthcare. Medical and scientific communities have tended to think of healthcare as a one-size-fits all endeavour rather than recognise difference and tailor healthcare accordingly. This is particularly evident when it comes to sex and gender, the topic of a recent article in *Clinical Oncology* [1].

The concepts of sex and gender are often incorrectly used interchangeably. Sex refers to the biological characteristics of humans and animals, whereas gender refers to the socially constructed roles, behaviours, and identities of humans. Male/female/intersex refer to sex as a biological variable; man/woman/non-binary refer to gender. Much biomedical research concentrates only on the study of male participants, ignoring the effects of sex differences and gender expression.

Consider the laboratory-based life sciences. Studies conducted in cells very rarely identify the sex of the cells used [2]. Additionally, animal studies have mainly been conducted in male animals for fear that the hormonal levels observed in females might "get in the way" and alter the results, or that including female animals would substantially increase costs [3]. This trend continues in clinical research involving human participants. Many clinical studies have been conducted with predominantly male participant populations based on the assumption that the results will apply to everyone and that the inclusion of female participants might require more complex research designs due, again, to hormonal fluctuations [4]. In a recent study of 27 drugs for example, all participants were administered a standard drug dose, but the pharmacokinetics of those drugs differed significantly between sexes. Despite consuming the same drug dose, the actions of the drugs once in the body varied, exposing females to higher concentrations of drug metabolites for an extended period of time, compared to males, making them more prone to experience adverse reactions and/or side effects [5].

The assumption that research involving any one sex can apply to all sexes can be far from correct. Evidence suggests sexual dimorphism in terms of disease manifestation and progression is not rare. Diabetes and its associated cardiovascular complications are examples. Premenopausal females are less likely to develop diabetes and its cardiovascular complications, compared to males or postmenopausal females [6–8]. After menopause, women have an increased risk of developing diabetes and suffer from increased mortality, and more severe complications, from diabetes-associated cardiovascular diseases [6,8,9]. Sex differences have been seen in susceptibility to viral immunity, with women appearing to be less susceptible than men to viral infections such as hepatitis B (HBV) and C (HCV) as well as COVID-19 (9). Conversely, women are more prone to be infected with cytomegalovirus (CMV) or herpes simplex type virus 2 (HSV2) [10]. Sex differences have also been observed in autoimmune diseases, with

females having up to a four-fold greater risk of developing disorders such as rheumatoid arthritis, multiple sclerosis and systemic lupus erythematosus, compared to males [11,12].

Sex and gender differences also affect diagnosis and therapeutic strategies. A study on paroxysmal supraventricular tachycardia showed that even though women tend to have more symptoms, they are often misdiagnosed as symptoms of anxiety leading to a later referral compared to men [13]. A recent cohort study in family practice showed that women are prescribed fewer diagnostic tests than men, leading to divergent diagnostic paths [14]. In terms of therapeutic strategies, females are twice as likely to experience side effects from treatments compared to males and that these differences are not explained by differences in body weight [5,15].

In short, sex matters. Greater efforts need to be taken towards a more inclusive way of designing, conducting, analysing and reporting research and the article by *X* and colleagues is a step in this direction.

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Their work focuses on evaluating sex effects in people with non-small cell lung cancer (NSCLC) treated with immunotherapics PD-1 and PD-L1 by synthesising the results of randomised controlled trials that presented their results by sex. The authors clearly acknowledge the presence of sex differences between males and females with respect to cancer survival and immunological profiles, providing evidence from epidemiological and scientific studies. X *et al* concluded that there were no significant differences in clinical response and overall survival between sexes. We are less sure there are no differences for progression-free survival: the hazard ratios and confidence intervals do, to us, suggest the possibility of a difference in favour of better progression-free survival in males. Perhaps with more participants, the confidence interval would have tightened. But readers can draw their own conclusions, the key point is that these authors have spent time considering the effect of sex on treatment effect and present data on this.

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The study highlights two important points. The first is an acknowledgement of the presence of sex differences, which is supported by both clinical and laboratory evidence. Laboratory evidence provided by studies in animals and cells is an important component of translational knowledge. These studies represent a useful way to test sex differences in disease phenotypes and learn more about the influence of sex in the mechanisms underlying their manifestation and progression. Secondly, the study by X *et al* is a sign of the shift toward a more inclusive mindset when conceptualising research design. This study is one of the few that focuses on analysing the effects of sex on a clinical outcome. Being inclusive in research does not just mean incorporating gender diverse participants in the study: it also means analysing the effects of biological sex and gender on study outcomes. As the United States' National Institutes of Health (NIH) explains, this involves a more thorough consideration of sex and gender in study design, the collection of data and its analysis; and with solid reasons being given should sex and gender not be included [16,17].

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NIH has required that studies include women and members of underrepresented groups in clinical trials since 1993 and in 2015 a new mandate was established to include the analysis of sex as a biological variable as well as gender in research design, analysis, and reporting [4]. Despite this, a cross-sectional study of US-based clinical trials still shows that women are underrepresented in trials across medical disciplines such as cardiology, immunology, and oncology [16]. Very few trials analyse the effects of sex as a biological variable [16]. Unlike NIH, the UK's National Institute for Health and Care Research (NIHR) does not have a mandate for including women and underrepresented groups in the research it funds. NIHR's INCLUDE initiative, which aims to improve the representativeness of NIHR research [18], is however now shining a spotlight on inclusivity during the funding process.

Inclusion of sex and gender in scientific and clinical research analysis is not a chore but an opportunity. The work by X *et al* is an example of grasping this opportunity. Rather than adding more bricks to the existing wall of bias, we need a more inclusive, tailored approach to design and analysis.

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