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Study reveals how sex 'blindspot' could misdirect medical research

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The sex of animals frequently has an effect in biomedical research and therefore should be considered in the study of science, report scientists

from the Wellcome Trust Sanger Institute and the International Mouse Phenotyping Consortium. In the largest study of its kind, researchers found that the differences between male and female mice had an effect that could impact research results in more than half of their studies.

The study, published today (26 June) in *Nature Communications*, quantified the differences between males and females - known as sexual dimorphism. The results have implications for the design of future animal studies which underpin research into treatments for human diseases.

Historically, a woman has been thought of as a small man in medicine and biomedical research. Even today, medical practice is less evidence-based for women than for men due to a bias towards the study of males in biomedical research.

Sex influences the prevalence, course and severity of the majority of common diseases and disorders, including cardiovascular diseases, autoimmune diseases and asthma. In spite of this, the usual approach in biomedical research is to ignore sex or to analyse only one sex and assume the results apply to the other sex.

In this new study, researchers have quantified the difference between male and female mice, looking across multiple experiments and institutes. In the largest study of its kind, scientists analysed up to 234 physical characteristics of more than 50,000 mice.

The team found that in the standard group of mice - the control mice - their sex had an impact on 56.6 per cent of quantitative traits, such as bone mass, and on 9.9 per cent of qualitative traits, including whether the shape of the head was normal or abnormal. In mice that had a gene switched off - the mutant mice - their sex modified the effect of the mutation in 13.3 per cent of qualitative traits and up to 17.7 per cent of

quantitative traits.

Dr Natasha Karp, lead author who carried out the research at the Wellcome Trust Sanger Institute, and now works in the IMED Biotech Unit at AstraZeneca, said: "This was a scientific blindspot that we really thought needed exploration. A person's sex has a significant impact on the course and severity of many common diseases, and the consequential side effects of treatments - which are being missed. Now we have a quantitative handle on how much sexual dimorphism has an impact in biomedical research. In the movement towards precision medicine, we not only have to account for genetic differences between people when we consider disease, but also their sex."

In the study, scientists analysed 14,250 control mice and 40,192 mutant mice from 10 centres that are part of the International Mouse Phenotyping Consortium (IMPC). At each institution, scientists studied up to 234 physical characteristics of the mice, including body composition, metabolic profile, blood components, behavioural traits and whole body characterisation - whether the head shape, coat, paws and other areas of their bodies were normal or abnormal.

In the first half of the study, scientists studied the differences between the physical traits of control male and female mice to see if their sex had an effect.

In the second part of the study, scientists then looked at how the sex of a mouse impacted on the effect of a genetic modification. For example, researchers switched off a gene and assessed whether any differences in the resulting trait depended on the sex of the mice.

Professor Judith Mank, an author of the study from University College London, said: "This study illustrates how often sex differences occur in traits that we would otherwise assume to be the same in males and

females. More importantly, the fact that a mouse's sex influenced the effects of genetic modification indicates that males and females differ right down to the underlying genetics behind many traits. This means that only studying males paints half the picture."

This study presents implications for the design of future animal studies and clinical trials. It has been more than twenty years since it became a requirement that women were included within clinical trials in the US. Whilst more women are taking part in clinical trials, increasing from 9 per cent in 1970 to 41 per cent 2006, women are still under-represented.

The bias is even stronger in the earlier stages of biomedical research. A review of international animal research between 2011 and 2012 found that 22 per cent of studies did not state the sex of the animals, and of those that did, 80 per cent of studies used solely males and only 3 per cent included both males and females.

Professor Steve Brown, an author of the study who is Director of the MRC Harwell Institute and Chair of the International Mouse Phenotyping Consortium Steering Committee, said: "It is likely that important scientific information is missed by not investigating more thoroughly how males and females differ in biomedical research. Rather than extrapolate the results to account for the opposite sex, these results suggest designing experiments to include both sexes in the study of disease. This study is a major step to highlighting the impact of sex differences in research and will help in accounting for those differences in the future of biomedicine."

More information: Natasha Karp et al. (2017) Prevalence of sexual dimorphism in mammalian phenotypic traits. *Nature Communications*. DOI: 10.1038/NCOMMS15475

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