

Sex hormones skew outcomes in clinical trials—here's how

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Clinical research often excludes females from their trials under the assumption that "one size fits all," that a painkiller or antidepressant will be equally effective in subjects of either sex, but a growing number of scientists are criticizing this approach. In an Essay published August 9 in *Cell Metabolism*, one group argues that hormones and other variables make a difference in how potential therapeutics behave, and both males and females must be accounted for in trials to move medical advances forward.

"Right now, when you go to the doctor and you are given a prescription, it might not ever have been specifically tested in females," says Deborah J. Clegg, a Professor of Biomedical Science at Cedars-Sinai Hospital in California. "Almost all basic research—regardless of whether it involves rodent models, dogs, or humans—is predominately done in males. The majority of research is done with the assumption that men and women are biologically the same."

One reason females are excluded from studies, she says, is that across the menstrual cycle there are fluctuations in hormones such as estrogens and progesterone, in essence creating a different hormonal milieu or profile depending on the phase of cycle, which may potentially impact the research. Often overlooked in male-only studies, these [sex](#) hormones are implicated in all biological processes, including sensitivity to fatty acids, or the ability to metabolize simple sugars. These differences have implications for all [clinical trials](#), whether they are testing the effects of a drug or a body's ability to tolerate an organ transplant.

It is important to remember that chromosomal differences also exist between the sexes, says Clegg. There is little research examining whether drugs behave differently in the presence of an XX chromosome as opposed to an XY chromosome. Even genome-wide studies often don't take chromosomes into account, even though [sex chromosomes](#) are an integral piece of an individual's genomic makeup.

While researchers appreciate that there are sex differences in disease risk, less is known about how or why these sex differences occur or how they extend to the transsexual community. Clegg's lab is currently investigating the impact of gender reassignment surgery on [cardiovascular disease risk](#). Women are traditionally protected against cardiovascular diseases when compared to men; however, it is unclear whether a transsexual woman (a man who has transitioned to become a woman) is at a lower or higher risk for heart disease due to the presence of endogenous male chromosomes overlaid with exogenous female hormones.

"This is an important population of individuals to study, as they will begin to enlighten us about the optimal hormonal profile to protect us from disease risk not only in this population, but also with respect to men and women. It is important to begin to understand if there is a role for hormones, chromosomes, and/or their interactions with respect to disease risk.

The NIH has only recently begun addressing these issues by instating the Office of Research on Women's Health ([DOI: 10.1038/509282a](#)). Clegg says that though well intended, many researchers don't know how to properly include sex as a variable in their experiments. Often, they will include females in their study without addressing if they're pre- or post-menopause, whether they're on [birth control pills](#), or if they're taking hormone blockers. These are all aspects that can impact the hormonal profile, adding another variable that's not accounted for in the

experiment's outcome. "Without addressing all of these variables in your analysis, you're still not accurately reflecting the impact of hormones and chromosomes in your research," she adds.

Clegg is hopeful that in the future, clinical trials can change. "It would be great if there were drugs that were specifically tested and dosed based on sex," she says. "There are so many variables in medical research that can't be solved by placing all women, regardless of age, into one category and certainly can't be solved by excluding us completely. With the goal of personalized medicine, it is important to begin to address and focus on sex as a biological variable."

More information: Morselli et al., "Sex and Gender: Critical Variables In Pre-Clinical and Clinical Medical Research," *Cell Metabolism* (2016). [www.cell.com/cell-metabolism/f ...](http://www.cell.com/cell-metabolism/fulltext/S1550-4131(16)30363-1)
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