

# Phasing out animal research prematurely will maintain gender inequities in medicine

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**Decades of male bias in animal research have left female biology critically understudied. Prematurely phasing out animal research would lock this inequity into future biomedicine, disproportionately harming women.**

At the international level, there is growing momentum among policy-makers and advocacy organizations toward the progressive – and in some cases complete – phasing out of animal research, for example, through legislation such as the [Directive 2010/63/EU](#) in the European Union and the [FDA Modernization Act 2.0](#) in the USA. These initiatives are typically framed as ethical progress: a long-overdue response to concerns about animal use in research, enabled by advances in ‘new approach methodologies’ (NAMs) such as organoids, organ-on-chip systems, and in silico computational models, including predictive algorithms produced by artificial intelligence (AI), based on machine learning (ML). In this discourse, animal use is treated as the primary moral problem; reducing or abolishing it is considered an almost self-evident ethical good.

What is largely absent from these discussions is a distributive justice perspective: consideration of who benefits, and who might be harmed, if we drastically curtail in vivo experimentation at this specific historical moment.

Preclinical research has been extensively documented as male-biased. For decades, biomedical and, especially, neuroscience studies have relied predominantly on male animals, under the assumption that males are the ‘simpler’ or ‘default’ sex<sup>1,2</sup>. Even after the introduction of the NIH ‘Sex as a biological variable’ (SABV) policy a decade ago, neuroscience continues to struggle with its implementation, and the proportion of female-only studies remains consistently low at approximately 3% (ref. 1). As a result, our mechanistic understanding of disease pathways, drug actions and stress responsivity is systematically better developed for male than female physiology, and many conditions that impose a disproportionate burden on women (such as affective disorders, certain pain syndromes and gynaecological and reproductive disorders) remain mechanistically undercharacterized<sup>3</sup>. This bias is mirrored clinically, as women are more likely than men to experience adverse drug reactions<sup>4</sup>. The consequences of male-default assumptions in preclinical research are well documented: from the teratogenic effects of thalidomide – driven in part by the absence of testing in pregnant animals – to the decades-long overmedication of women with zolpidem, whose slower drug clearance went undetected because foundational pharmacokinetic studies had been conducted exclusively in male rats<sup>5</sup>. Critically, in vivo models remain irreplaceable for capturing sex-specific developmental trajectories

that no current cell-based system can replicate<sup>6</sup>. Early-life adversity, for instance, exerts pronounced and sex-dependent effects on neurodevelopmental outcomes, addiction vulnerability and psychiatric risk in ways that depend critically on gonadal hormone state and developmental timing<sup>7–10</sup>.

These examples reflect a broader and well-documented pattern: across multiple biological domains, sex-dependent mechanisms remain inadequately studied in females, leaving large gaps in mechanistic understanding that disproportionately affect women’s health<sup>1,11</sup>. When left unaddressed, such gaps constitute a form of structural sexism in biomedical knowledge production, whereby the conditions and biological pathways that are most relevant to female health remain systematically under-represented.

However, proponents of a rapid transition toward NAMs argue that emerging in vitro systems will soon replace such in vivo studies. Advocates of NAMs rightly point out that cell-based and organoid models derived from human tissues can, in principle, be tailored to female biology and diverse ancestries<sup>12</sup>. Nevertheless, the same sex bias that has characterized animal research also persists in many in vitro studies<sup>12,13</sup>. As of today, NIH policy does not require investigators to consider SABV in cell culture models<sup>14</sup>. Moreover, NAMs are not yet capable – and probably will not be for a long time – of replacing domains of in vivo work that depend on systemic regulation, developmental context and organism-level plasticity, such as pregnancy, multi-organ pharmacokinetics, chronic stress susceptibility and pain regulation.

In silico NAMs, including ML-based approaches applied to the synthesis of large, publicly available datasets, represent another rapidly expanding alternative to in vivo research. Although these approaches offer clear advantages for hypothesis generation and pattern detection, their outputs are fundamentally constrained by the data on which they are trained. For example, analyses of a deployed medical AI system, the Babylon Health symptom-checking chatbot, identified sex-related discrepancies in triage recommendations, with women’s reported symptoms in some cases assigned lower urgency<sup>15</sup>. These discrepancies were traced to male-biased clinical datasets used for model training. Such cases highlight the broader principle of how data-driven systems can inherit, reproduce and amplify existing representational gaps embedded in clinical and preclinical practice. Although attention to sex-specific diagnostics is increasing, substantial mechanistic ‘unknown unknowns’ remain – sex-dependent pathways that cannot be inferred from existing datasets and can emerge only through in vivo investigation of systemic physiology and development. In domains where sex-specific biology remains undercharacterized, the consequences will extend beyond diagnosis to drug development and therapeutic application.

Against this backdrop, a rapid phase-out of animal research is not a neutral act. Given a history in which male animals dominated preclinical research, ending in vivo work now risks structurally locking sex-related

inequities into the foundation of future ‘animal-free’ biomedicine. Specifically, a premature phase-out may:

- Freeze a mechanistic evidence base that is already male-skewed
- Limit the discovery of systems-level sex-specific vulnerabilities, biomarkers and treatment responses
- Disproportionately harm women, who are already underserved by current medical evidence and clinical innovation

In other words, ending animal research before we have used it to correct human-focused inequities does not erase injustice. It risks creating a new form of structural sexism: one in which moral concern for animals, however genuine, is prioritized over completing the unfinished work of understanding and treating diseases that disproportionately affect women.

To our knowledge, no existing discussion of animal-research phase-out policies has systematically examined the distributive-justice implications for sex-based health inequities. This commentary proposes to fill that gap. We argue that any ethically coherent roadmap for reducing animal use must explicitly:

- Integrate sex as a biological variable and health-disparity considerations into decisions about which areas of *in vivo* research are phased out and when
- Define minimum knowledge thresholds for sex-sensitive mechanisms in key disease domains before endorsing phase-out
- Evaluate NAMs not only on technical performance, but also on their capacity to address, rather than entrench, existing inequities

Our aim is not to defend the status quo of animal research, nor to deny the moral urgency of reducing animal suffering. Rather, we argue that a just transition away from animal models must be temporally and structurally aligned with the project of closing the gender gap in biomedical knowledge. Failing to recognize these distributive consequences turns the phase-out movement’s ethical clarity into a blind spot, in which the effort to protect animals unintentionally

obscures the continued exclusion of women from the benefits of biomedical progress.

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## Author contributions

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## Competing interests

The authors declare no competing interests.