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Perspectives

Female Health Across the Tree of Life: Insights at the Intersection of Women's Health, One Health and Planetary Health

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Abstract

Across the tree of life, female animals share biological characteristics that place them at risk for similar diseases and disorders. Greater awareness of these shared vulnerabilities can accelerate insight and innovation in women's health. We present a broadly comparative approach to female health that can inform issues ranging from mammary, ovarian, and endometrial cancer to preeclampsia, osteoporosis, and infertility. Our focus on female health highlights the interdependence of human, animal, and environmental health. As the boundaries between human and animal environments become blurred, female animals across species are exposed to increasingly similar environmental hazards. As such, the health of female animals has unprecedented relevance to the field of woman's health. Expanding surveillance of animal populations beyond zoonoses to include noncommunicable diseases can strengthen women's health prevention efforts as environmental factors are increasingly implicated in human mortality. The physiology of nonhuman females can also spark innovation in women's health. There is growing interest in those species of which the females appear to have a level of resistance to pathologies that claim millions of human lives every year. These physiologic adaptations highlight the importance of biodiversity to human health. Insights at the intersection of women's health and planetary health can be a rich source of innovations benefitting the health of all animals across the tree of life.

Keywords: Women's Health, One Health, Planetary Health, Evolutionary Medicine, Biomimicry

> "In nature nothing exists alone."
> Rachel Carson, *Silent Spring*, 1962.

Across the tree of life, female animals share biological characteristics placing them at increased risk for similar diseases and disorders. (The term 'female' is expanding to include a broader range of individuals. For the purpose of this paper, the term denotes individuals who produce larger gametes with the corresponding reproductive physiology.) These shared vulnerabilities can be a source of insight and innovation in women's health, promoting collaborations benefiting the health of females across species. Despite this promise, many of these connections remain essentially unexamined. As anthropogenic environmental change increasingly threatens life on Earth, the health of female animals has unprecedented significance for the health of human females. (In this manuscript, the term 'animals' is used to describe nonhuman animals and the term 'human' to describe human animals.)

While a similar nexus of vulnerabilities also connects the health of male animals, women's health research—historically under-resourced—has emerged as a global priority (1–4). Evidence that the health effects of climate change and accelerated environmental degradation disproportionately impact women and girls, reinforces the importance and urgency of a female focus (1). Examining unique health vulnerabilities of female animals also aligns with conservation concerns (5). Female fertility is often the critical limiting factor in population growth and species survival. Emerging threats to female fertility should, therefore, inform and shape efforts to mitigate the high rate of species extinction and loss of global biodiversity (5, 6).

Awareness of these shared, species-spanning female health vulnerabilities can improve women's health in several ways. First, it can accelerate the identification of environmental hazards endangering human females. The health of female mammals,

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birds, reptiles, and fish living in and around human communities has become increasingly relevant to women's health as anthropogenic changes blur the boundaries that once demarcated human versus animal environments. In the 21st century, all female animals—including every human female—have become canaries and the Earth, a shared, planetary coal mine (7).

Examining shared vulnerabilities across species can also help to identify species in which females have evolved a level of resistance to pathological processes. The biological diversity found in nature has been shaped by challenges encountered in wide-ranging ecologies. Physiologic adaptations have evolved to counter these challenges and optimize survival and reproduction. These optimized solutions can serve as a blueprint for developing novel and more effective approaches to both female and male health concerns (8–12).

For insights arising from either disease vulnerability or resistance in other species to emerge, however, human health communities must recognize the critical relevance of animal health to the care of human patients. This calls for the integration of evolutionary, ecological, conservation, and veterinary perspectives into the education of human medical professionals and paraprofessionals (13).

Shared Vulnerability

For nearly a century, British miners carried canaries into mineshafts to detect carbon monoxide leaks. Animal sentinels have since become an important source of information about environmental dangers for humans (14). However, sentinels have not been used to specifically identify hazards that place women, girls, and other female animals at increased risk. While the zoonotic origins of COVID-19 focused global attention on the interdependence of human and animal health, the connections extend far beyond infectious disease. The disproportionate impact of anthropogenic environmental change on the health of human females includes rising rates of noncommunicable diseases (NCDs) (1, 4, 15). Many of the NCDs impacting the health of women may also develop in other female animals (16). While socioeconomic disparities and the inequitable distribution of power are recognized as promoters of disease and disability in women (2, 4), less well-examined are the ancient biological pathways that connect female lives and health vulnerabilities.

Female fish, amphibians, reptiles, and birds share significantly overlapping health vulnerabilities. In a range of vertebrate species, for example, rising temperatures can accelerate aging of female oocytes, promoting embryo loss and reducing the likelihood of conception and successful gestation (17, 18). Especially strong connections can be found between human and nonhuman female mammals who are particularly vulnerable to rising levels of environmental toxins and pollutants (19–21). Hormonal contraceptives and endocrine-disrupting chemicals bind to estrogen receptors and are highly lipophilic. Female mammals—whose percentage of body fat mass exceeds that of males—therefore, accumulate higher concentrations of these contaminants over their lifetimes (20). This not only disproportionately exposes females themselves to carcinogenic and other disease-promoting agents, it endangers their offspring. Maternal exposures raise the risk of congenital syndromes (21, 22) and expose newborns to concentrated chemicals released with lactation (21, 23–25). Because environmental exposures during gestation and early life can shape adult and some intergenerational health vulnerabilities, the reproductive health of females often plays a central role in shaping the overall health and stability of species (6, 26).

These shared vulnerabilities should serve as a call to action for every healthcare professional to deepen their engagement in initiatives focused on protecting ecosystems, biodiversity, and local environments. Yet, human health professionals may lack awareness of these connections and their importance to the health of their female (and male) human patients.

To increase awareness, we surveyed vertebrate lineages to identify the phylogenetic range of species in which pathologies impacting human females have also been identified in nonhuman females. Cases of mammary carcinoma were identified in nearly every mammalian order, and endometrial pathologies (including cancers) were identified in a phylogenetically wide range of mammalian species. Ovarian cancer cases were identified in not only mammalian species but within avian, reptilian, and piscine taxa. The occurrence of these pathologies across the tree of life points to an ancient origin of vulnerabilities as well as the interdependence of environments, genes, and species-specific genomes in shaping disease risk (Fig. 1).

The Case for Expanded Surveillance

In recent decades, a heightened understanding of the interdependence of human, animal, and environmental health has fueled interest in and the adoption of One Health initiatives. Surveillance of animals living in key ecological contexts for emerging infectious diseases (EIDs) that may spill into the human population exemplifies how a One Health approach can protect lives. The zoonotic origins of the recent pandemic cast light on the value of One Health surveillance efforts (27–32) focused on zoonotic (communicable) diseases (30, 31, 33–35). NCDs have not been a central focus. Yet, some currently running EID surveillance programs (30, 31, 33–35) have infrastructure that could also identify respiratory diseases, congenital abnormalities, neurological disorders, and other NCDs linked to environmental contaminants in free-ranging animals (36). Expansion of surveillance efforts may provide early warning of novel environmental hazards, an increasingly urgent concern given the growing number of contaminants and exposures implicated in human (4, 15, 36), and in some cases especially female, deaths (1). While this is a global challenge, the urgency is greatest in regions suffering disproportionate levels of ecological degradation.

Specific outbreaks of NCDs in females have already drawn the attention of human health professionals, providing critical information for women's health. Unexpectedly high rates of adenocarcinoma, including mammary carcinoma among wild beluga whales in St. Lawrence Estuary between 1983 and 1999, for example, were linked to carcinogenic contaminants and higher cancer rates among local women (37, 38). Similarly, increased identification of cervical and other urogenital carcinomas in California sea lions exposed to both the herpesvirus and organochlorides (38–40) has heightened awareness of parallel and combined cancer exposures risks in human communities (36, 41, 42).

Resilience: Evolved Adaptations

In some species, females have evolved adaptations which may confer resistance to diseases of women and girls. Understanding the biology underlying these adaptations can guide innovation in women's health (Fig. 2). This is a biomedical application of biomimicry, an approach to addressing human challenges by

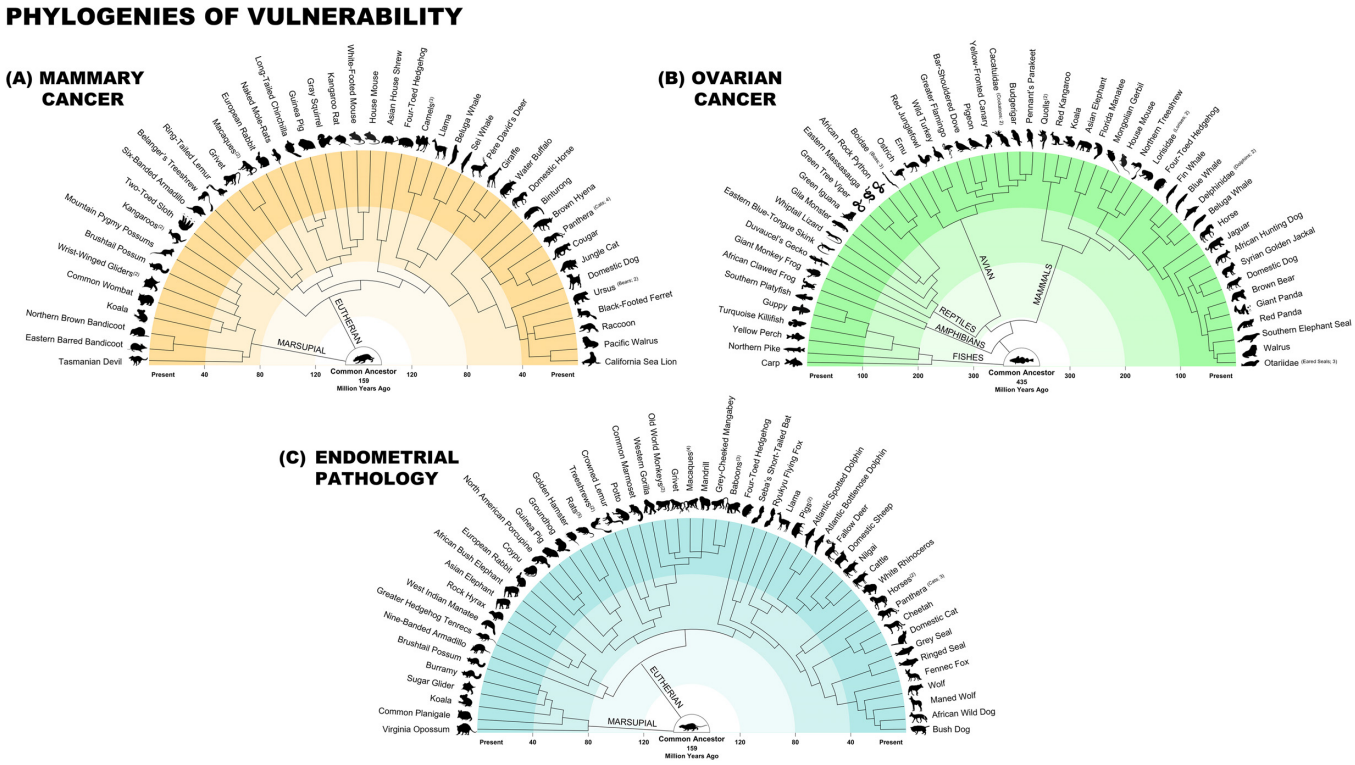

Fig. 1. Vulnerability to challenges in women's health exists across a phylogenetically wide range of species. These phylogenies feature selected species (rather than a comprehensive taxonomy) to illustrate the ancient origins and phylogenetically widespread nature of vulnerability to common challenges in women's health. (A) Vulnerability to mammary cancer is found across a wide range of mammalian species. (B) Vulnerability to ovarian cancer is found across vertebrate lineages. (C) Vulnerability to common human endometrial pathologies can be found in phylogenetically diverse species. Species lists were uploaded to TimeTree (http://www.timetree.org/) and images were created and annotated in Interactive Tree of Life (iTOL, https://itol.embl.de/). Superscript numbers indicate the number of species with vulnerabilities in the grouping. Species images were obtained from Phylopic.org. Full image credits and species references are listed in the Supplementary Materials.

finding effective biological solutions evolved in other species (9, 10, 43). While evolutionary tradeoffs and constraints may limit this approach, biological systems regulating female physiology are highly conserved across the metazoan lineage creating the potential for translating evolved adaptations in other species into strategies countering human pathology. There is growing interest in medical biomimicry (sometimes referred to as bioinspired medicine). In recent years, a number of species have been identified in which the physiology of females appears to confer a level of resistance to women's health challenges from infertility and cardiovascular disease to cancer, osteoporosis, and gestational hypertension (8, 10, 44–46).

Infertility

Embryo preservation is a central challenge for many advanced reproductive technologies (47). In over 130 mammals, blastocyst development may become delayed or arrested during what is called embryonic diapause. Embryonic diapause provides reproductive benefit by providing some flexibility (delay) in the timing of offspring birth. Diapause has been identified in a phylogenetically wide range of mammals from nine-banded armadillos and bears, to pinnipeds and fruit bats. Many of the pathways and genes associated with embryonic diapause in other species are conserved in humans and may, therefore, guide innovation in embryo preservation strategies for women undergoing fertility treatments (48).

Reproductive Senescence

Reproductive senescence limits female fertility, imposing medical, occupational, and social constraints on women. By contrast, notable reproductive longevity (minimal decline in fertility with age) is found in a number of both mammalian and nonmammalian species from the tundra vole (49) and naked mole rat (6, 11, 50) to the Greenland shark (51). The biological pathways underlying reproductive longevity in these species may guide innovation in women's fertility preservation.

Osteoporosis

In women, especially postreproductive women, prolonged physical inactivity increases the risk of bone loss and osteoporosis (12, 52, 53). In comparison, brown and black bears, yellow-bellied marmots (54), Arctic squirrels (55), and other hibernating mammals have evolved adaptations, which provide them with some resistance to bone loss despite lengthy periods of inactivity. A number of investigators are exploring the biological mechanisms underlying this resistance.

Heart Failure with Preserved Ejection Fraction (HFpEF)

Hypertension, diagnosed in humans with systolic or diastolic blood pressures exceeding 130 mmHg or 80 mmHg, respectively (56), contributes to two of the most significant health concerns

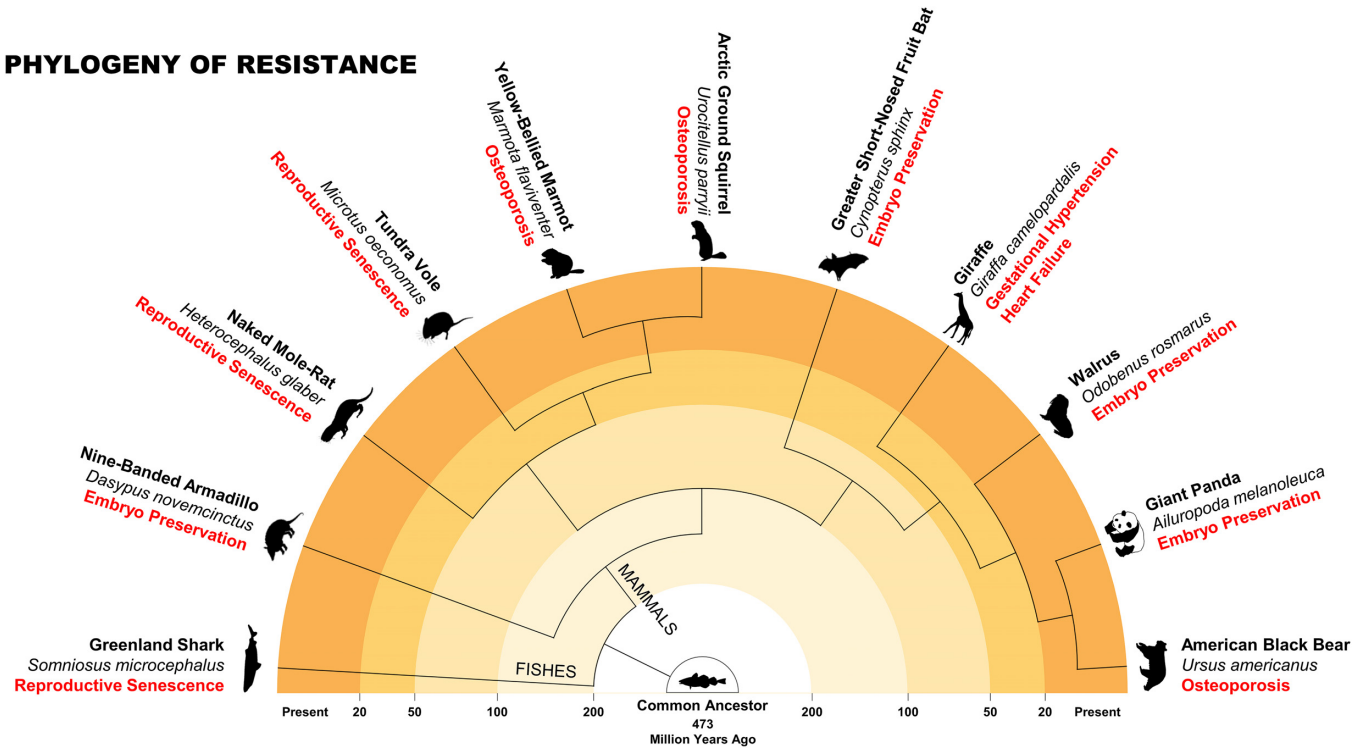

Fig. 2. Bioinspired medicine and women's health. Evolved physiologic adaptations in other species may confer a level of resistance to challenges in women's health. The biological pathways underlying resistance can be a source of innovative solutions for women's health issues ranging from infertility, reproductive senescence, and cardiovascular disease to cancer, osteoporosis, and gestational hypertension. Species images were obtained from Phylopic.org. Full image credits and species references are listed in the Supplementary Materials.

in women: heart failure with preserved ejection fraction (HFpEF) and gestational hypertension. Blood pressure in adult giraffes may exceed 250 mmHg (57). Yet, giraffe appear to have evolved adaptations protecting their hearts from the adverse effects of longstanding hypertension that play a central role in the pathogenesis of HFpEF, the leading cause of heart failure in women (58). Identifying the mechanisms through which this resistance occurs may provide a guide for HFpEF prevention strategies in women.

Gestational Hypertension

In humans, gestational hypertension (with or without associated preeclampsia) is defined as abnormally high blood pressure (systolic or diastolic blood pressure $\geq$ 140 mmHg and 90 mmHg, respectively) arising after 20 weeks of pregnancy (59). Gestational hypertension is associated with significantly worsened fetal and maternal outcomes (60). Pregnant giraffe appear to have evolved adaptations which protect both mother and calf from the consequences of blood pressure levels which would seriously endanger human pregnancies (56, 59). The unique characteristics of giraffe gestation, placentation, or placental function could inspire the development of protective strategies for women with pre-eclampsia and other forms of gestational hypertension.

While these examples present certain species as potentially helpful for women's health challenges, the critical insight is that biodiversity itself is an invaluable resource for biomedical innovation. However, the natural world can only be an enduring source of lifesaving insights if our efforts to understand it, do not destroy it. Protecting, rather than exploiting other species, is the path to a healthy human future (12, 53–55, 61, 62).

Women's Health Meets One Health, Meets Planetary Health

Over sixty years ago, *Silent Spring*, Rachel Carson's pathbreaking book, launched the modern environmental movement. Within two years of its publication Carson would die from complications of breast cancer, a pathology now linked to the same chemicals she had implicated in the devastation of reproduction in female birds (62). "In nature, nothing exists alone" (63) she cautioned. Carson's words remain as prescient and powerful today as they were decades ago when she drew the world's attention to the interdependent health of all life on Earth (Fig. 3).

In nature, no female animal exists alone. A species-spanning sisterhood promises new knowledge, innovation, and hope. There are many benefits to moving beyond anthropocentric and androcentric traditions in medicine. Foremost among these is the clarity of vision to recognize the key to safeguarding the future of animals across the tree of life: protecting the planet and the biodiversity it supports.

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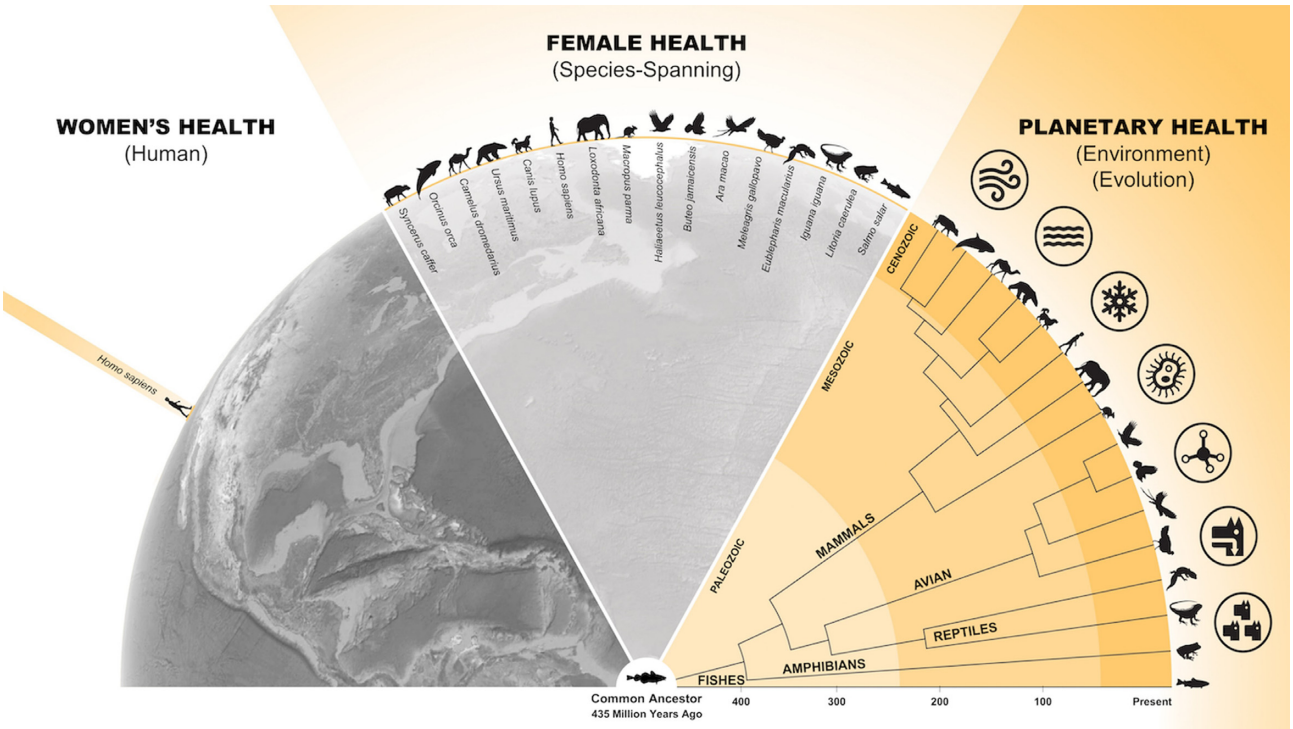

Fig. 3. Expanded perspectives provide insight for innovation in women's health. Moving beyond human-centered and male-centered traditions in medicine can strengthen our understanding of the causes of disease and guide development of effective therapeutic and prevention strategies. Novel insights emerge from perspectives that traverse species, sex, and gender and are deeply informed by evolution and the environment. Figure designed by B. Natterson-Horowitz and Oliver Uberti.

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Supplementary Material

Supplementary material is available at *PNAS Nexus* online.

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Authors' Contributions

All authors contributed to the conception, drafting, and finalization of the manuscript.

Data Sharing

There is no original data in this work.

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