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Commentary

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Human Population Density and Reproductive Health: A Changing World Needs Endocrinology

Chelsea A. Weitekamp[1] and Hans A. Hofmann[2,3,4]

[1]Center for Public Health and Environmental Assessment, U.S. Environmental Protection Agency, Research Triangle Park, 109 TW Alexander Dr, Durham, NC 27709, USA; [2]Department of Integrative Biology, The University of Texas at Austin, 2415 Speedway - C0930, Austin, TX 78745, USA; [3]Institute for Cellular and Molecular Biology, The University of Texas at Austin, 2415 Speedway - C0930, Austin, TX 78745, USA; and [4]Institute for Neuroscience, The University of Texas at Austin, 2415 Speedway - C0930, Austin, TX 78745, USA

ORCiD number: 0000-0001-6392-7784 (C. A. Weitekamp); 0000-0002-3335-330X (H. A. Hofmann).

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Over the past century, many countries around the world have experienced a historical decline in birth rates and infant mortality concurrent with an increase in education and economic development. The negative correlation between fertility rate and economic development is one of the most robust findings in the social sciences. Maybe not surprisingly, this "demographic transition" is commonly attributed to social factors, such as increased access by women to education and workforce participation. In addition to socio-technological changes, population density also increases with economic development, as a consequence of both urbanization and overall population growth. It has therefore been suggested that population density should be included in models of human fertility rates (1). In fact, population density and fertility rates were found to be negatively correlated within and across 174 countries (2).

Drawing on animal studies in the laboratory and in the wild, a recent review by Suvorov (3) calls attention to our lack of insight into the behavioral and physiological mechanisms that might mediate the effects of increasing population densities on human fertility. Such density-dependent reproduction (ie, reduced reproductive rate at high population densities) has been documented across a wide range of species, from insects to elephants, as well as in primates. While there are likely species-specific ecological variables that drive these patterns, there may also be mediating mechanisms that are shared across species. As the author suggests, one mechanism through which this could occur is activation of the hypothalamic-pituitary-adrenal axis. Often referred to as the "stress" axis, this neuroendocrine system controls the body's reaction to stress and regulates many physiological systems. While excessive or chronic activation of the stress axis is well-known to inhibit reproduction in mammals (4), the existence of an explicit link between population density, the stress axis, and fertility remains an open question.

Suvorov asks whether excessive social interactions could be contributing to the declining rates of human reproduction via changes in neuroendocrine signaling. This is contingent upon the assumption that the observed decline in reproductive output (fertility rate) is related, in part, to a reduced physiological potential to reproduce (what demographers call fecundity). Whether or not human fecundity is actually changing is challenging to address (5). Several markers indicate it may be declining, such as heightened demand for infertility treatments, a high prevalence of

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polycystic ovarian syndrome, poor semen quality, and serum testosterone decline in men. Some of these outcomes have been related to other factors, including obesity, inadequate nutrition, and exposure to environmental pollutants, such as endocrine disrupting chemicals. Nonetheless, as Suvorov points out, there is plenty of room for complementary hypotheses.

Population density, commonly defined as the number of individuals of a species per unit area, may be insufficient for quantifying social interactions in modern human societies, yet developing an appropriate metric is critical to testing these hypotheses. If population density were simply the number of people around, it would be difficult to separate confounding factors that come along with higher density. For example, compared to rural areas, cities have higher amounts of air pollution and less greenspace, factors that are also known to activate the stress axis. Self-sorting also likely plays a role, as density and fertility could be correlated due to the choices individuals make in where to live – for example, people who (plan to) have fewer children may be more likely to move to densely populated cities. However, if density is instead defined by the number of social interactions per unit of time (ie, an encounter rate), many of these confounding factors could potentially be untangled, especially if modeled within a social network framework. Such an approach would also enable us to take into account the quality of individual encounters. A social encounter rate may be modified by wealth or resource availability with different physiological effects occurring within harsh or benign environments, as observed in other animal species.

Social interactions can take many different forms and can now occur both in real life and on social media platforms. Understanding how these interactions differ could be critical for appropriately defining density. For example, for a social interaction to be encoded in the brain, neuronal activity must exceed a threshold to trigger lasting changes in gene expression. If an interaction lacks salience, it is unclear how these encounters would be processed and, ultimately, affect physiology. Furthermore, the valence of social interactions (eg, whether representative of challenge or opportunity) can affect the encoding of experience and an individual's internal state, with the potential for interactions that involve repeated social defeat to impair reproductive function. Much of the embedding of social interactions likely occurs within the social decision-making network, an evolutionarily conserved network of brain regions that mediate social behavior (6). Within this network, the preoptic area of the hypothalamus serves as a neuroendocrine relay center central to the integration of stress physiology and reproductive behavior, thus making it a prime candidate in which to examine the mechanistic basis of how density is translated in the brain.

Many neuroendocrine signaling pathways that regulate social behavior act as neuromodulators within the social decision-making network and interact with the stress axis (7), offering additional routes through which population density could affect fecundity. For example, the neuropeptides oxytocin and vasopressin mediate social interactions, such as social recognition and affiliation. The biogenic amine dopamine encodes the salience and rewarding properties of social stimuli. Similarly, sex steroid hormones such as androgens and estrogens modulate reproductive social behaviors. Mapping the interactions between these pathways in response to population density (defined as social interactions per unit time) could lead to novel insights.

Uncovering the relationships between population density, social interactions, neuroendocrine signaling, and reproductive physiology is critical for understanding and treating infertility. In addition, accurately estimating human fecundity is important for modeling changes in population growth, which itself is critical for informed decision-making in a changing world under a changing climate (8). It is high time for social scientists, endocrinologists, and neuroscientists to begin collaborating toward understanding and solving these historical challenges to humanity.

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Additional Information

Correspondence: Hans A Hofmann, PhD, The University of Texas at Austin, Department of Integrative Biology, 2415 Speedway - C0930, Austin, TX 78745, USA. Email: hans@utexas.edu.

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