associated with risk for autoimmune diseases, such as autoimmune thyroiditis, Graves' hyperthyroidism, primary biliary cirrhosis, and Sjögren's syndrome [2] (Table S2).

A second prediction generated by the PCH is that differences in disease rates between sexes should manifest only once the immune system fails to experience pregnancy, during reproductive years. Therefore, under the PCH, these differences should be observed only after reaching reproductive age, and not in children. However, this prediction is also not supported by data: studies find higher risk for cancer [3] (Table S3) and lower risks for autoimmune diseases (Table S4) in boys compared with girls.

In summary, while the second part of the PCH proposes an unlikely mechanism and is inconsistent with observations, the first part suggests an evolutionary adaptation to hemochorial placentation. The processes leading to immune sexual dimorphism need not necessarily involve modern societal trends, and may be purely evolutionary (Figure 1). The main idea is that increased placental invasiveness may have induced a selection pressure for female immune tolerance to invading fetal cells. For immune sexual dimorphism to evolve, this immune tolerance would have likely involved costs that were not incurred by males. One such cost for females could have been an increased risk for autoimmune diseases. Decreased cancer rates could have also, although not necessarily, resulted from the same evolutionary process, but may not have fully countered the costs of autoimmune diseases, under a hunter-gatherer lifestyle. While the underlying mechanisms of such immune sexual dimorphisms are unknown, future studies that would adopt an evolutionary perspective to study differences in disease rates between sexes could prove insightful.

Supplemental Information

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Letter

Evolution of Immune Sexual Dimorphism in Response to Placental Invasiveness: A Reply to Greenbaum and Greenbaum

Angela R. Garcia,[1,2] Heini Natri,[1,2] Kenneth H. Buetow,[1,2] Benjamin C. Trumble,[2,3] and Melissa A. Wilson[1,2,*]

While we appreciate Greenbaum and Greenbaum's intent to evaluate predictions from the Pregnancy Compensation Hypothesis (PCH) [1] within the existing literature, we disagree with their mischaracterizations of the PCH and its predictions and disagree with their interpretations of the current literature. As discussed in our original paper [1], we are not trying to explain all autoimmune diseases or all cancers, rather we are attempting to explain the sexual dimorphism in relative risk for different types of immune-related diseases. Under the PCH, we hypothesize that the patterning of sex differences in disease observed in industrialized environments can be explained, in part, by sex differences in immune function evolved due to pressures imposed by invasive placentation on the female immune system, mediated by the evolution of gene content and dosage, and regulated proximally by reproductive hormones.

When discussing immune mechanisms, Greenbaum and Greenbaum claim that because there is evidence of the immune system being primed during childhood, they do not see how there could be a mechanism for the onset of change in immune function during adulthood. However, this shift towards autoimmunity across the life course is exactly what is observed across multiple studies [2,3]. We do not dispute the accuracy of the Greenbaum and Greenbaum's description of some of the mechanisms that influence autoimmune disease during development, however, we want to point out that autoimmunity is a consequence of both genetic susceptibilities and environmental triggers that persist throughout the life course. There is evidence that differential exposure to certain environmental stimuli, both early and later in life, can trigger autoimmune diseases. Rook *et al.* [4], outline a number of studies in which a lack of exposure to environmental

pathogens and microbes is associated with higher 'resting' levels of immunological correlates of autoimmune disease (e.g., C-reactive protein, immunoglobulins-1b and 6, TNF). Moreover, Greenbaum and Greenbaum's supposition that the PCH requires privations in adulthood to explain sexual dimorphism in immune function and autoimmune disease is incorrect, as we next address.

In their interpretation of the PCH, Greenbaum and Greenbaum confound evolutionary time with developmental time. They inappropriately claim that the PCH requires pregnancy in modern society to elicit the evolved sex difference. Rather, we claim that the millions of years of evolution of the placenta and pregnancy have shaped sex differences, which will exist now, regardless of whether a person becomes pregnant or not. We provided potential genetic mechanisms, including gene content and regulation on the sex chromosomes, that predict initial sex differences to be exhibited as early as conception and throughout childhood, well before gonadal hormones become predominant, or pregnancy even possible. Consistent with this is evidence about sex differences in early life, including some of the Greenbaum and Greenbaum citations. This work actually supports our claims of evolved sex differences with genetic mechanisms (Figure 4 in [1]).

Further, the critique the authors lobby about industrialization not being a contributing factor to sex differences in disease fails to acknowledge that an additional feature of industrialization is the massive shifts in energetic (i.e., caloric) availability and related shifts in hormone levels, which could proximally be exacerbating immune sex differences. Gonadal hormone levels are already implicated in immune function, and people living urban industrialized lifestyles have increased gonadal hormone levels compared with those living subsistence lifestyles [5,6]. Under the PCH, we assert that at an ultimate level, sexual dimorphism in immune function is in part a consequence of selection on immunomodulation specific to females over millions of years, to deal with the foreign placenta and fetus, and at a proximate level, this dimorphism is mediated in part through the actions of hormones on immune function. In modern, low parity urban industrialized societies, the overall prevalence of cancer and autoimmune diseases likely increase (Figure 2) and dimorphism may be exacerbated due to the lack of hormonal modulation that occurs during pregnancy. The positive association between caloric availability and disease in industrialized societies may be particularly true of cancers, for which excess body fat is a major risk factor for nearly all (htttp://www.cancer.gov).

In regards to the authors' statement that correlations between parity and disease are not supported by epidemiological evidence, we would like to highlight two major issues: (i) an incomplete summarization of the research, and (ii) that the populations in these studies are not natural fertility populations (all but one are from the Danish cohort study). The most notable inaccuracy in their summary of these papers is that it does not, in fact, find all autoimmune diseases increase with parity. Rather, some do not change, some increase, and others, like systemic lupus erythematosus, decrease with parity. To the second point, Danish women still have a very low fertility rate, ranging from 2.57 in 1960 to 1.67 in 2017 (WorldBank data), compared with what would approximate 'near-constant' pregnancy throughout most of human history. Evidence from natural fertility populations would suggest that an average total fertility rate is likely closer to eight or nine children [7–9] across the lifespan. Though scant, research among two of these natural fertility populations (the Hutterites and Hadza) suggests overall lower rates of autoimmune diseases [10,11]. Principally, when discussing why female immune systems are in general more upregulated compared with males, we hypothesize that it may have evolved as a consequence of the persistent state of pregnancy that females likely endured for the majority of our human evolutionary history. Thus, under the PCH, it is likely that the difference between nulliparous and low parity may not be sufficient to result in reduced rates of autoimmune disease and rather, high parity, consistent with natural fertility populations, may be required.

Finally, as noted in the opening statement of this letter, we are not purporting to explain all cases of disease, rather, we are attempting to explain overall sexual dimorphism in relative risk for different types of immune-related diseases. We appreciate that there are complex interactions between genetic and lifestyle factors, parity, immune function, and disease risk, and that the underlying etiology of a disease may vary substantially. The PCH lays out an organizing framework that integrates multileveled theory and empirical data to explain sex differences in disease risk and serves as a null hypothesis for testing predictions.

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