

Scientists develop new hypothesis to explain sex differences in human diseases

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The Pregnancy Compensation Hypothesis suggests that evolution shaped men's and women's immune systems differently. It also suggests that in modern, industrialized populations, the reduced amount of time women spend pregnant and lactating, and other environmental effects on hormone levels, explains sexual differences in the risk for autoimmune diseases and certain cancers. Credit: Jacob Sahertian/ASU VisLab

Women get autoimmune diseases, such as multiple sclerosis, lupus and rheumatoid arthritis eight times more than men do. On the other hand, women have a smaller risk of getting non-reproductive cancers such as

melanoma, colon, kidney and lung cancer.

And while there are some exciting developments in cancer treatments, such as immunotherapies, research is showing that women are responding more favorably than men to this type of intervention.

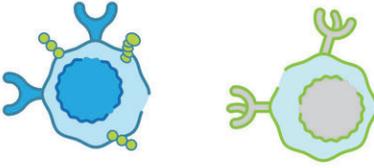
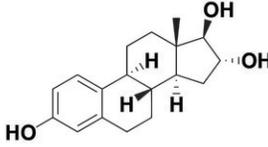
So why is there such a big difference between women and men when it comes to human diseases?

An interdisciplinary team of scientists at Arizona State University believes it may have the answer.

In a paper published today in the scientific journal *Trends in Genetics*, the team presents a new hypothesis to explain the phenomenon, setting the stage for novel research avenues focused specifically on treating [autoimmune diseases](#) and cancer.

"Until now, the differences between women and men in regards to human diseases have not been explained by existing theories," said Melissa Wilson, assistant professor with ASU's School of Life Sciences and senior author of the paper. "We are proposing a new theory called The Pregnancy Compensation Hypothesis.

"Basically, women's immune systems evolved to facilitate their survival during the presence of an immunologically invasive placenta and pregnancy, and compensate so they could also survive the assault of parasites and pathogens. But now, in modern, industrialized societies, women are not pregnant all the time so they don't have a placenta pushing back against the immune system. The changes in their reproductive ecology exacerbate the increased risk of autoimmune [disease](#) because immune surveillance is heightened. At the same time, we see a reduction in some diseases, like cancer," Wilson said.

Sex-differences in disease	
Evolutionary	Proximate
<p>Function</p>  <p>Immune system</p>	<p>Mechanism</p> <div style="display: flex; justify-content: space-around;"> <div style="text-align: center;">  <p>Reproductive hormones</p> </div> <div style="text-align: center;">  <p>Sex chromosome dosage</p> </div> </div>
<p>Phylogeny</p>  <p>Placentation</p>	<p>Development</p> <div style="display: flex; justify-content: space-around;"> <div style="text-align: center;">  <p>Industrialized</p> </div> <div style="text-align: center;">  <p>Nonindustrialized</p> </div> </div>

There are longer-term evolutionary explanations and more immediate explanations for sexual dimorphism in immune function. The female immune system must compensate for the unique DNA of the placenta and immune-modulation during pregnancy. The placenta is phylogenetically shared across therian mammals, but with additional unique evolutionary pressures including invasive hemochorial placentas in eutherian mammals. Dimorphism in immune function in response to placentation and pregnancy occurs via the direct impact of reproductive hormones on immune function, as well as through heritable variation in sex chromosome gene content and dosage. Although evolution has shaped these sex differences over millions of years, industrialized urban populations experience exacerbated sex differences in hormone mechanisms as well as reduced pregnancies compared with non-industrialized populations.

Credit: *Trends in Genetics*

Heini Natri, the lead author of the study and a postdoctoral scholar with the ASU Center for Evolution and Medicine, said because the immune system varies between the sexes, it should be considered when developing immunotherapies and other treatments.

"We think the Pregnancy Compensation Hypothesis can explain why there's a big sex difference in these diseases. Going forward, understanding the evolutionary origin of the sex bias in these diseases can help us better understand the mechanisms and particular pieces of the immune system we can target," said Natri. "Our goal is to actually make treatments better for everyone. We are realizing that cancer is different in men and women. In the study of most cancers and other diseases, and so far in the development of cancer treatments, that has not really been taken into account."

Effects of industrialization

Another factor that may exacerbate this situation is living a modern-day, urban lifestyle.

In industrialized communities, autoimmune diseases appear to occur at a much higher rate than in non-industrialized populations. The researchers believe the human immune system evolved expecting a given load of parasites. In the modern environment, exposure to those parasites has diminished so the immune system has fewer foreign targets. With this reduced load, the [immune system](#) attacks 'self.'

Evolutionary Novel Environments: Sedentary Industrial Populations	Traditional Human Environments: Active Subsistence Populations
Low parasite and pathogen load: may increase risk of autoimmune disorders	High parasite and pathogen load: Th2 biased immunity may reduce autoimmune risk
Calorically unlimited: high rates of obesity and metabolic disease	Calorically Limited: high rates of stunting and wasting
Low Parity: higher proportion of time cycling, few pregnancies, shorter lactational amenorrhea	High Parity: Females spend most of reproductive ages pregnant or lactating
High Reproductive Hormones: increased risk of reproductive linked cancers	Low Reproductive Hormones: decreased risk of reproductive linked cancers



Although humans evolved in a mosaic of different environments, sedentary industrialized urban environments are evolutionarily novel. ASU scientists predict that these shifts in the environment may contribute to mismatches between how our immune systems have been shaped by natural selection to respond to the environment and how they are now responding, resulting in human disease. Credit: *Trends in Genetics*

"There is a mismatch between the ancestral environment humans were adapted to, and the industrialized environment many people currently live in. In terms of an evolutionary timescale, our environment has changed incredibly fast," said Angela Garcia, also a postdoctoral research fellow with the center.

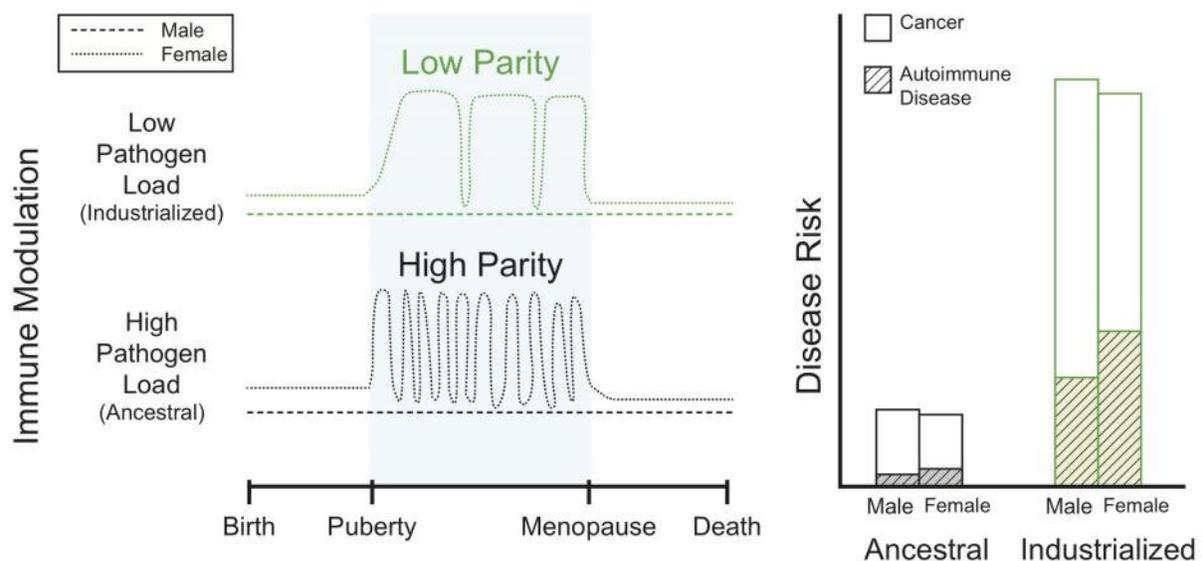
"We have also shifted from an active lifestyle to a sedentary one. We now have an overabundance of calories available, which potentially allows us to maintain excessive levels of hormones, including the female

hormone estradiol. Maintaining such high levels of hormones may increase the chance of triggering autoimmune diseases," she said.

Future treatments

The researchers suggest that by framing future research within the Pregnancy Compensation Hypothesis, scientists could dive deeper into the characterization of genes, [environmental context](#) and the longitudinal history of people.

"We think this is more than a hypothesis. By using modern molecular biologic techniques in genetics and genomics, we can look at the differences between male and female immune systems, and between modern immune profiles and those in pre-industrial populations. By doing so, we may find new ways to prevent [cancer](#) and autoimmune diseases," Ken Buetow, a professor with the school and co-author of the study.



An illustration of the expected immune differences between high and low parity (layered on top of high/low pathogen load). The study suggests that low pathogen load (hygiene hypothesis) affects immune function in both men and women (green lines), making everyone more susceptible to autoimmune disease, whereas low parity will only affect the immune system in women, exacerbating the immune compensation that evolved in response to tolerating an internal pregnancy, further increasing the immune risk for women in industrialized regions. Credit: Arizona State University

The researchers also suggest there are places where genes are regulated uniquely in males and females, as well as across environmental contexts.

"Going forward, we need to systematically collect environmental variables like pathogenic exposure, levels of stress and reproductive hormones, and parity. We have to understand these areas better," said Wilson.

More information: Heini Natri et al, The Pregnancy Pickle: Evolved Immune Compensation Due to Pregnancy Underlies Sex Differences in Human Diseases, *Trends in Genetics* (2019). [DOI: 10.1016/j.tig.2019.04.008](https://doi.org/10.1016/j.tig.2019.04.008)

Provided by Arizona State University

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