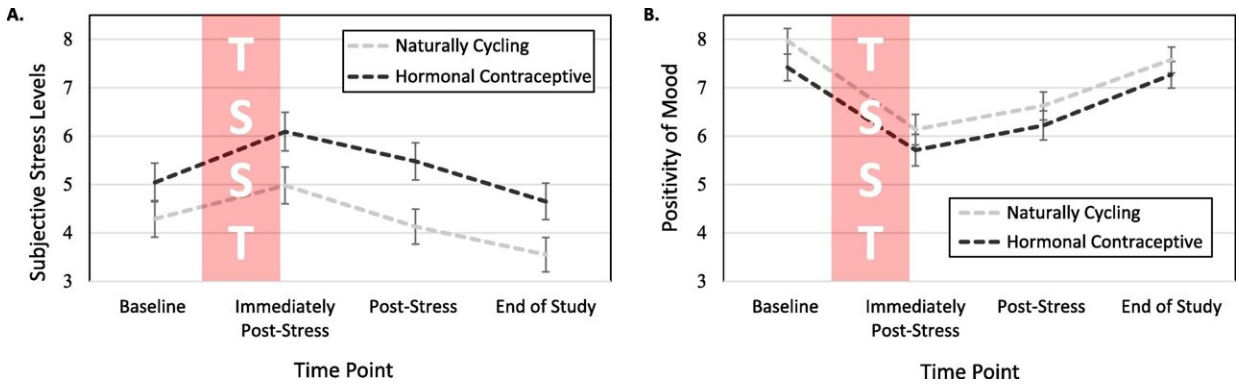
Hormonal contraceptive users process stress differently at the molecular and psychological level, finds study

December 6 2023



Subjective stress levels and positivity of moods before and after the Trier Social Stress Test (TSST). Women reported increased stress and decreased positivity of moods in response to the TSST. (A) HC users reported more TSST-induced stress than did NC women. (B) There were no differences in positivity of mood between HC users and NC women. Credit: *Brain, Behavior, and Immunity* (2023). DOI: 10.1016/j.bbi.2023.10.033

A new UCLA Health study is shedding light on how using hormonal contraceptive pills may affect women's responses to stress and their risk for inflammation-related illnesses.

The study, published in the journal *Brain, Behavior, and Immunity*, is the first to directly measure differences in hormonal contraceptive users' and

non-users' psychological and immune responses to socially stressful situations.

Researchers at the UCLA Department of Psychiatry and Biobehavioral Sciences' Laboratory for Stress Assessment and Research found contraceptive users and non-users processed stress differently at the molecular level, with contraceptive users also reporting a more negative psychological response to stress compared to non-users.

Study lead author Summer Mengelkoch said the findings could help researchers uncover the mechanisms underlying the interactions between birth control pills, stress responses, and inflammation, potentially improving health outcomes for the hundreds of millions of women who use birth control pills around the world.

"I hope this research is the beginning of work that can advance a precision medicine-based approach to hormonal contraceptive use so that women and their doctors can make truly informed decisions about their health," said Mengelkoch, a UCLA postdoctoral fellow.

"To do this, we need basic science research that investigates how both endogenous sex steroid hormones that women already have in their bodies and exogenous sex steroid hormones from contraceptives impact their stress processing, inflammation, and risk for inflammation-related disorders."

Although hormonal contraceptives are safely used by more than 300 million women worldwide (as of a 2019 study by the United Nations), there has been minimal research on their downstream physiological and behavioral effects.

Past research has found hormonal contraceptive pills may increase women's risk for chronically elevated inflammation, which carries the

long-term risk of developing illnesses such as cancer, cardiovascular disease, and autoimmune disorders, as well as potential mood disorders, including depression. However, the mechanisms behind this association have remained understudied and unclear, Mengelkoch said.

Hormonal contraceptive users have been shown in past research to have higher levels of C-reactive protein (CRP), which is a marker of systemic inflammation, compared to non-users. At the same time, past research has also found no differences in the basal, or resting, levels of other markers of inflammation, including cytokines, between users and non-users. Cytokines are immune-response proteins that increase inflammation in response to stress and can contribute to systemic inflammation over time.

Mengelkoch and fellow researchers, including her UCLA faculty mentor, Dr. George Slavich, sought to test for differences in these proinflammatory cytokines in response to stress between hormonal contraceptive users and non-users.

In the study, nearly 130 women—60 women using hormonal contraceptive pills and 67 being naturally cycling, or free from hormonal contraceptive use—provided researchers a saliva sample and then rated their mood and stress levels.

Each participant then underwent a stress test in which they gave a five-minute speech about their dream job to a stone-faced researcher who did not react or provide positive affirmation. Following this speech, the participant was surprised with a mental math task in which they had to count backward from 1,022 in intervals of 13 for five minutes. If the participant made a mistake, they were told to start again.

Following the test, participants provided a second saliva sample as well as rated their mood and stress levels.

Researchers found that women who use contraceptives had higher levels of an inflammatory cytokine called TNF-alpha both before and after the stress test. Mengelkoch said this cytokine may be associated with a more "male-typical" response to stress. In comparison, naturally cycling women had a more "female-typical" response to stress, with higher levels of the cytokine known as interleuken-6 rising alongside increases in cortisol.

There are different types of synthetic hormones in different contraceptive pills which have been found to bind with different types of receptors in the body. Mengelkoch said the findings of this study suggest that synthetic hormones in some contraceptives that bind more to androgen receptors—sites in the body where testosterone usually binds—may be causing differences in inflammatory stress response for some contraceptive users.

The findings also found that women who used contraceptives reported a more negative emotional response to the stress as their levels of cortisol—a steroid hormone that works to reduce inflammation—rose.

"Cortisol gets a bad rap, but increases in cortisol in response to stress help the body manage stressful situations," Mengelkoch said. "If women on the pill are having these increases in cortisol but their mood is getting worse, it could mean that the pill is preventing their bodies and minds from returning to normal following stress."

More information: Summer Mengelkoch et al, Hormonal contraceptive use is associated with differences in women's inflammatory and psychological reactivity to an acute social stressor, *Brain, Behavior, and Immunity* (2023). DOI: 10.1016/j.bbi.2023.10.033