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Letter to the Editor

The hormonal effects of childhood trauma in adult women with and without schizophrenia

Inflammation-mediated health sequelae of childhood trauma are well-established and may be particularly salient for women, given baseline immunologic and metabolic sex differences (Thompson et al., 2004). Inflammation is also implicated in psychopathology, with robust evidence supporting a role of early stress and inflammation in schizophrenia (Dennison et al., 2012). Chronic stress may induce hypothalamic-pituitary-adrenal (HPA) axis dysfunction and alter cortisol levels, as well as increase body mass indices (BMI) and affect adipokine secretion. The adipokines leptin and adiponectin are higher in women than men at baseline and may be influenced by early trauma (Joung et al., 2014; Lehto et al., 2012). Childhood trauma is also linked to reproductive pathology, decreased estradiol and increased follicle-stimulating hormone (FSH) levels in women (Allsworth et al., 2001), which may be especially relevant in schizophrenia where estrogen appears protective against severe symptomatology (da Silva and Ravindran, 2015). Altogether, vulnerabilities to inflammatory and metabolic effects of early trauma in women could be exacerbated in schizophrenia, leading to more pronounced hormonal aberrancies than in healthy controls.

We performed a secondary data analysis of 40 female participants (20 with a DSM-IV diagnosis of schizophrenia [SZ] and 20 healthy controls [HC]) ages 30 to 70 (mean age 46.13 ± 10.14 years) from a study on menopause and cognition in schizophrenia that measured adiponectin, leptin, cortisol, estradiol, FSH and luteinizing hormone (LH). We aimed to determine whether hormonal effects of childhood trauma differed in women with and without schizophrenia, with the hypothesis that effects would be more pronounced in those with schizophrenia. Thirty-five percent were premenopausal, 22.5 % perimenopausal and 42.5 % postmenopausal as determined by the Study of Women's Health Across the Nation (SWAN) criteria (El Khoudary et al., 2020). Exclusion criteria were current pregnancy or hormonal contraceptive use within the last 60 days. Participants completed a one-time visit at the Maryland Psychiatric Research Center comprised of fasting serum and saliva collection and clinical questionnaires. Serum adiponectin and leptin were measured by Luminex multianalyte assays (Core Cytokine Laboratory, University of Maryland, Baltimore, MD, USA). Serum FSH, LH, estradiol and progesterone were measured by electrochemiluminescence immunoassays. Salivary cortisol was measured with liquid chromatography/tandem mass spectrometry (ZRT Lab, Beaverton, OR, USA). Aside from higher BMI in the SZ versus HC group (37.97 vs 31.43, $p = 0.039$), there were no statistically significant differences in baseline biological measures, including hormone levels. All but one of the SZ groups participants were on at least one antipsychotic medication.

Trauma history was assessed with the Childhood Trauma Questionnaire (CTQ), a 28-item retrospective self-report questionnaire with scores for overall abuse and 5 subdomains (emotional, sexual and physical abuse and emotional and physical neglect). Independent samples *t*-tests showed similar trauma scores in the SZ and HC groups, with the exception of higher physical neglect scores in the SZ group (8.3 vs 6.8, $p = 0.048$). We created dichotomous trauma predictor variables using validated cut-off scores in each subdomain indicating trauma exposure (Bernstein and Fink, 1998) for simple linear regression analyses assessing whether exposure predicted hormone levels. Hormone levels and continuous CTQ scores were log transformed to correct for skewness and bivariate Pearson correlations were used to assess for dose-dependent relationships between CTQ scores and hormones predicted by trauma. Analyses were completed for the SZ and HC groups separately with regression results reported in Table 1.

In the SZ group, sexual abuse negatively predicted leptin level with large effect size ($\beta = -0.564$, $p = 0.010$). Physical abuse approached significance as a negative predictor of leptin with moderate effect size ($\beta = -0.436$, $p = 0.055$). Models for other trauma subdomains were nonsignificant, though all showed negative relationships with leptin. In controls, relationships between abuse and leptin were also negative but nonsignificant. Pearsons correlations in the SZ group revealed significant negative correlations between leptin and physical abuse ($r = -0.463$, $p = 0.040$), emotional abuse ($r = -0.581$, $p = 0.007$), sexual abuse ($r = -0.522$, $p = 0.018$) and emotional neglect ($r = -0.491$, $p = 0.028$) scores, suggesting a dose response. Correlations with overall abuse ($r = -0.558$, $p = 0.100$) and physical neglect ($r = -0.257$, $p = 0.274$) scores were nonsignificant. These results conflicted with two existing studies reporting increased leptin in relation to childhood maltreatment (Joung et al., 2014; Lehto et al., 2012). However, animal studies have demonstrated both increased and decreased leptin following early stress (Kaufman et al., 2007; Llorente et al., 2011).

Significant positive predictors of FSH in the SZ group included any abuse ($\beta = 0.584$, $p = 0.017$), physical abuse ($\beta = 0.509$, $p = 0.044$), emotional abuse ($\beta = 0.584$, p = 0.017) and emotional neglect ($\beta = 0.584$, p = 0.017), all with large effect sizes. Correlations were positive and significant between FSH and emotional abuse ($r = 0.541$, $p = 0.031$) and neglect ($r = 0.617$, $p = 0.011$) scores, again suggesting a dose response. Correlations were positive but nonsignificant between FSH and overall abuse ($r = 0.465$, $p = 0.069$), physical abuse ($r = 0.332$, $p = 0.209$), sexual abuse ($r = 0.276$, $p = 0.301$) and physical neglect ($r = 0.133$, $p = 0.622$) scores. No significant predictors were found in controls. There is only one study we are aware of examining childhood abuse in relation to FSH, which also showed a positive correlation between the two (Allsworth et al., 2001).

Although there were no significant findings for other hormones studied, there were several trends. In both groups, abuse appeared negatively related to adiponectin, consistent with existing literature (Lehto et al., 2012). Estradiol and abuse appeared negatively related in the SZ group, consistent with previous findings (Allsworth et al., 2001),

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Table 1
Linear regression results for trauma predictors of hormone levels.

Healthy controls	Adiponectin	Leptin	Cortisol	Estradiol	FSH	LH
Abuse (model); (predictor)	(R^2 = 0.018, F(1,17) = 0.314, p = 0.582); (β = −0.135, *p* = 0.582)	(R^2 = 0.085, F(1,17) = 1.578, p = 0.226); (β = −0.291, *p* = 0.226)	(R^2 = 0.023, F(1,14) = 0.330, *p* = 0.575); (β = −0.152, p = 0.575)	(R^2 = 0.065, F(1,17) = 1.180, *p* = 0.293); (β = 0.255, p = 0.293)	(R^2 = 0.146, F(1,8) = 1.365, p = 0.276); (β = −0.382, *p* = 0.276)	(R^2 = 0.047, F(1,8) = 0.392, p = 0.549); (β = −0.216, *p* = 0.549)
Physical abuse (model); (predictor)	(R^2 = 0.053, F(1,17) = 0.943, p = 0.345); (β = −0.229, *p* = 0.345)	(R^2 = 0.039, F(1,17) = 0.685, p = 0.419); (β = −0.197, *p* = 0.419)	(R^2 = 0.042, F(1,14) = 0.611, *p* = 0.447); (β = −0.205, p = 0.447)	(R^2 = 0.166, F(1,17) = 3.382, *p* = 0.083); (β = 0.407, p = 0.083)	(R^2 = 0.146, F(,) = 1.365, p = 0.276); (β = −0.382, *p* = 0.276)	(R^2 = 0.047, F(1,8) = 0.392, p = 0.549); (β = −0.216, *p* = 0.549)
Emotional abuse (model); (predictor)	(R^2 = 0.002, F(1,17) = 0.041, p = 0.843); (β = 0.049, *p* = 0.843)	(R^2 = 0.006, F(1,17) = 0.100, p = 0.756); (β = −0.076, *p* = 0.756)	(R^2 = 0.006, F(1,14) = 0.085, *p* = 0.776); (β = −0.077, *p* = 0.776)	(R^2 = 0.007, F(1,17) = 0.124, *p* = 0.729); (β = 0.085, p = 0.729)	(R^2 = 0.146, F(1,8) 1.365=, p = 0.276); (β = −0.382, *p* = 0.276)	(R^2 = 0.047, F(1,8) = 0.392, p = 0.549); (β = −0.216, *p* = 0.549)
Sexual abuse (model); (predictor)	(R^2 = 0.037, F(1,17) = 0.660, p = 0.428); (β = −0.193, *p* = 0.428)	(R^2 = 0.155, F(1,17) = 3.121, p = 0.095); (β = −0.394, *p* = 0.095)	(R^2 = 0.039, F(1,14) = 0.565, *p* = 0.465); (β = −0.197, *p* = 0.465)	(R^2 = 0.003, F(1,17) = 0.049, *p* = 0.828); (β = 0.054, *p* = 0.828)	(R^2 = 0.000, F(1,8) = 0.001, p = 0.982); (β = −0.008, *p* = 0.982)	(R^2 = 0.106, F(1,8) = 0.949, p = 0.358); (β = 0.326, *p* = 0.358)
Emotional neglect (model); (predictor)	(R^2 = 0.065, F(1,17) = 1.181, p = 0.292); (β = −0.255, *p* = 0.292)	(R^2 = 0.069, F(1,17) = 1.259, p = 0.278); (β = −0.263, *p* = 0.278)	(R^2 = 0.018, F(1,14) = 0.259, *p* = 0.619); (β = −0.135, *p* = 0.619)	(R^2 = 0.002, F(1,17) = 0.027, *p* = 0.872); (β = 0.040, *p* = 0.872)	(R^2 = 0.146, F(1,8) = 1.365, p = 0.276); (β = −0.382, *p* = 0.276)	(R^2 = 0.047, F(1,8) = 0.392, p = 0.549); (β = −0.216, *p* = 0.549)
Physical neglect (model); (predictor)	(R^2 = 0.142, F(1,17) = 2.816, p = 0.112); (β = −0.377, *p* = 0.112)	(R^2 = 0.060, F(1,17) = 1.078, p = 0.314); (β = −0.244, *p* = 0.314)	(R^2 = 0.003, F(1,14) = 0.042, *p* = 0.841); (β = −0.054, *p* = 0.841)	(R^2 = 0.011, F(1,17) = 0.184, *p* = 0.673); (β = −0.103, *p* = 0.673)	(R^2 = 0.000, F(1,8) = 0.001, *p* = 0.982); (β = −0.008, *p* = 0.982)	(R^2 = 0.106, F(1,8) = 0.949, *p* = 0.358); (β = 0.326, *p* = 0.358)

Schizophrenia	Adiponectin	Leptin	Cortisol	Estrogen	FSH	LH
Abuse (model); (predictor)	(R^2 = 0.118, F(1,18) = 2.413, p = 0.138); (β = −0.344, p = 0.138)	(R^2 = 0.101, F(1,18) = 2.016, *p* = 0.173); (β = −0.317, p = 0.173)	(R^2 = 000, F(1,17) = 0.002, *p* = 0.965); (β = −0.011, p = 0.965)	(R^2 = 0.030, F(1,18) = 0.555, *p* = 0.466); (β = −0.173, p = 0.466)	(R^2 = 0.341, F(1,14) = 7.257, *p* = 0.017)*; (β = 0.584, p = 0.017)*	(R^2 = 0.242, F(1,14) = 4.468, *p* = 0.053); (β = 0.492, p = 0.053)
Physical abuse (model); (predictor)	(R^2 = 0.009, F(1,18) = 0.156, *p* = 0.697); (β = −0.093, *p* = 0.697)	(R^2 = 0.190, F(1,18) = 4.222, p = 0.055); (β = −0.436, p = 0.055)	(R^2 = 0.017, F(1,17) = 0.293, *p* = 0.595); (β = −0.130, p = 0.595)	(R^2 = 0.010, F(1,18) = 0.188, *p* = 0.669); (β = −0.102, p = 0.669)	(R^2 = 0.260, F(1,14) = 4.908, *p* = 0.044)*; (β = 0.509, p = 0.044)*	(R^2 = 0.153, F(1,14) = 2.531, *p* = 0.134); (β = 0.391, p = 0.134)
Emotional abuse (model); (predictor)	(R^2 = 0.048, F(1,18) = 0.903, *p* = 0.355); (β = −0.219, *p* = 0.355)	(R^2 = 0.133, F(1,18) = 2.767, p = 0.114); (β = −0.365, p = 0.114)	(R^2 = 0.001, F(1,17) = 0.012, p = 0.913); (β = −0.027, *p* = 0.913)	(R^2 = 0.075, F(1,18) = 1.451, *p* = 0.244); (β = −0.273, p = 0.244)	(R^2 = 0.341, F(1,14) = 7.257, *p* = 0.017)*; (β = 0.584, p = 0.017)*	(R^2 = 0.242, F(1,14) = 4.468, *p* = 0.053); (β = 0.492, p = 0.053)
Sexual abuse (model); (predictor)	(R^2 = 0.074, F(1,18) = 1.441, p = 0.246); (β = −0.272, p = 0.246)	(R^2 = 0.318, F(1,18) = 8.390, *p* = 0.010); (β = −0.564, p = 0.010)*	(R^2 = 0.016, F(1,17) = 0.270, *p* = 0.610); (β = 0.125, p = 0.610)	(R^2 = 0.012, F(1,18) = 0.221, *p* = 0.644); (β = −0.110, p = 0.644)	(R^2 = 0.173, F(1,14) = 2.932, *p* = 0.109); (β = 0.416, p = 0.109)	(R^2 = 0.136, F(1,14) = 2.209, *p* = 0.159); (β = 0.369, p = 0.159)
Emotional neglect (model); (predictor)	(R^2 = 0.118, F(1,18) = 2.413, p = 0.138); (β = −0.344, p = 0.138)	(R^2 = 0.101, F(1,18) = 2.016, p = 0.173); (β = −0.317, p = 0.173)	(R^2 = 0.000, F(1,17) = 0.002, p = 0.965); (β = −0.011, *p* = 0.965)	(R^2 = 0.030, F(1,18) = 0.555, p = 0.466); (β = −0.173, p = 0.466)	(R^2 = 0.341, F(1,14) = 7.257, *p* = 0.017)*; (β = 0.584, p = 0.017)*	(R^2 = 0.242, F(1,14) = 4.468, *p* = 0.053); (β = 0.492, p = 0.053)
Physical neglect (model); (predictor)	(R^2 = 0.114, F(1,18) = 2.313, p = 0.146); (β = −0.337, p = 0.146)	(R^2 = 0.173, F(1,18) = 3.760, p = 0.068); (β = −0.416, p = 0.068)	(R^2 = 0.007, F(1,17) = 0.113, *p* = 0.741); (β = 0.081, p = 0.741)	(R^2 = 0.001, F(1,18) = 0.018, p = 0.895); (β = −0.031, *p* = 0.895)	(R^2 = 0.080, F(1,14) 1.220=, p = 0.288); (β = 0.283, p = 0.288)	(R^2 = 0.085, F(1,14) = 1.294, p = 0.274); (β = 0.291, *p* = 0.274)

* Significant at $p < 0.05$.

but positively related in controls. There were weak to moderate positive relationships between abuse and LH in the SZ group and mixed findings in controls, but there is little existing literature with which to compare these findings. Cortisol appeared negatively related to most abuse predictors. Existing literature has shown both higher and lower baseline cortisol levels associated with abuse in people with schizophrenia (Aas et al., 2019; Braehler et al., 2005).

Our analysis was limited by small sample size, but is the first to our knowledge to examine hormonal effects of childhood trauma in a sample of only women and in a subcohort of women with schizophrenia, as well as one of the few studies addressing endocrine effects of trauma subdomains. Our main findings were that early trauma predicted leptin and FSH levels in a dose-dependent fashion in adult women with schizophrenia but not in controls, suggesting that women with schizophrenia are more vulnerable to the metabolic and inflammatory effects of childhood trauma. This is consistent with known predispositions to metabolic pathology in schizophrenia (De Hert et al., 2009), and could have significant health implications for women with schizophrenia and history of early adversity. Our analysis is hypothesis-generating and further studies would include larger samples allowing for multiple regression models including menopausal status, medications and other covariates.

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Declaration of competing interest

Dr. Deanna L. Kelly serves as a consultant for Alkermes, Lyndra Therapeutics and Sunovion Pharmaceuticals.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.schres.2023.03.043.

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