Table 1.

Summary of main findings for selected studies investigating inflammatory biomarkers and sex hormones in affective disorders.

Study	Population	Design	Major Findings: Association between sex hormones and inflammatory markers	Other Findings
Almeida et al., 2011	Poor quality of sleep, older men Sex: male N: 5127 Age: range 70–90	Longitudinal population-based study	**Testosterone, hs-CRP**: including hs-CRP, free testosterone and total plasma homocysteine in the statistical analyses did affect the results.	**Sleep quality and depressive symptoms:** 60% of older men report having problems with their sleep. Significant association between poor quality of sleep and development of depressive symptoms.
Canning et al., 2010	PMS Sex: female N: 36 (34 completed) Age: range 18–45; mean 35.3 (SD 5.9)	Randomized, double-blind, placebo-controlled, crossover study: 1) hypericum perforatum; 2) placebo	/	**Sex hormones, inflammatory biomarkers, depressive symptoms:** hypericum perforatum did not show significant effects on mood-related PMS symptoms, on hormones (FSH, LH, E2, progesterone, prolactin, testosterone) levels and on cytokine (IL-1β, IL-6, IL-8, IFN-γ and TNF-α) levels. Hypericum perforatum associated with improvement in physical and behavioural symptoms.
Eisenberg et al., 2009	Healthy subjects Sex: male, female N: 39 (36 completed fMRI) Age: range 18-36; mean 21.8 (SD 3.4)	Randomized, double-blind, placebo-controlled study, fMRI study: 1) endotoxin; 2) placebo	**Menstrual cycle markers**: baseline E2 and progesterone levels before endotoxin/placebo administration did not affect the association between IL-6 and depressed mood.	**Sex differences in the association between inflammation and depression:** in the endotoxin group, increased IL-6 levels significantly correlated with increased self-report depressive symptoms in female but not in male subjects. In the endotoxin group, increased IL-6 levels correlated with greater social pain-related neural activity. Association between increased IL-6 levels and increased depressive symptoms mediated by social pain-related neural activity in female but not in male subjects.

Study	Population	Design	Major Findings: Association between sex hormones and inflammatory markers	Other Findings
Haenisch et al., 2015	BD (mixed mood state, mania) Sex: male, female N: 99 [current manic (N 29), mixed (N 17) mood state; controls (N 53)] Age: controls mean 35.4 (SD 11.9); mania group mean 34.1 (SD 13.7); mixed group mean 34.9 (SD 11.8)	Cross-sectional,case-control study	/	**Clinical symptoms**: no associations between severity of the symptoms and the altered biomarkers in the two patient groups. **Progesterone and insulin:** significantly increased in mania group; statistical trend in mixed mood state in comparison with controls. **Cancer antigen 125**: significantly increased in the mixed mood state group; statistical trend in mania group in comparison with controls. **C-peptide:** significantly increased in both BD groups in comparison with controls showing an association with insulin in all the three groups. **Peptide YY and sortilin:** significantly higher in mania group in comparison with mixed mood state group and controls. **Haptoglobin, Chemokine CC4 and matrix metalloproteinase 7:** increased in the mixed mood group.
Keshri et al., 2018	BD Sex: male N: 82 [BD in remission (N 41); controls (N 41)] Age: range 18–45; controls mean 34.27 (SD 8.1); BD mean 34.27 (SD 8.1)	Cross-sectional,case-control study	**Testosterone:** BD patients in remission showed significantly increased IL-17 and significantly decreased testosterone levels in comparison with controls with IL-17 negatively correlated with testosterone levels.	**Inflammation and BD:** IL-17 positively correlated with the duration of the disease. **Suicidal behaviour, testosterone, and inflammation**: no significant differences in IL-17 and testosterone levels between patients with and without suicidal behaviour.

Study	Population	Design	Major Findings: Association between sex hormones and inflammatory markers	Other Findings
Meier et al., 2018	MDD (remitted or current), BD, controls [combined sample] Sex: male, female N: 480 [controls (N 219); rMDD group (N 42); dMDD (N 151); BD (N 68)] Age: male group (N 130) mean 34.2 (SD 11.3); female group (N 350) mean 34.7 (SD 11.1)	Cross-sectional,case-control study	**Female sex hormones (whole female sample):** E2 positively correlated with progesterone, but neither of them correlated with the inflammatory profile (CRP, KnyA/3HK, KynA/QA, Kyn/TRP). **Exogenous sex hormones:** females taking contraceptives exhibited lower KynA and increased CRP levels in comparison with females not taking contraceptives. Progesterone positively correlated with KynA, KynA/3HK, and KynA/QA only in females taking contraceptives.	**Sex hormones and contraceptives:** lower E2 levels in females taking contraceptives (vs. females not taking contraceptives). No significant differences in progesterone levels between the two groups. **Sex differences in the association between inflammation and depression:** higher CRP levels in women in comparison with men (no statistical significance); females (patients and controls together) showed lower KynA/3HK and KynA/QA ratios vs. males with lower KynA in the female group.
Miller et al., 1999	MDD Sex: female N: 64 [MDD (N 32); controls (N 32)] Age: controls range 20-48, mean 34.4 (SEM 1.5); MDD range 22-48, mean 34.5 (SEM 1.4)	Cross-sectional,case-control study	**E2:** E2 and norepinephrine levels did not correlate with the inflammatory profile (lymphocyte proliferative responses).	**Sex hormones and inflammatory biomarkers**: leukocyte subset, plasma cortisol, epinephrine, progesterone, and urinary cortisol, epinephrine, and norepinephrine, did not differ between patients and controls. **E2:** depressed women showed a statistical trend in higher E2 levels in comparison with controls. **Norepinephrine:** depressed women showed significantly higher circulating levels of norepinephrine in comparison with controls. **Inflammation and clinical symptoms:** patients with greater depressive symptoms had greater numbers of circulating white blood cells and granulocytes.
Roomruangwong et al., 2020	PMS/ MCAS Sex: female N: 41 [PMS (N 14); controls (N 27)] Age: controls mean 31.4 (SD 6.5); PMS/MCAS mean 30.9 (SD 8.2)	Longitudinal study	**PON1 CMPAase activity:** positive association with E2 levels. **AREase activity:** positive association with progesterone (steady state and delta variations). **-SH groups:** positive association with increasing progesterone levels. **AOPP:** inversely predicted by steady state progesterone levels and increases in delta E2 levels. **LOOH, C3:** negative association with progesterone levels. **Hp**: negative association with E2 (steady state). **Hs-CRP, C4 or MDA**: no significant associations with sex hormones.	**PMS/MCAS:** no significant increase in hs-CRP and Hp levels during the premenstrual period. **MCAS:** association with elevated C4 levels at day 21. **Hp, C3 and C4:** significant alterations (not in the inflammatory range). **DRSP total score and depression sub-score**: best predicted by the lagged C4 values (positive association) and PON1 AREase (inverse association) and MDA (inverse association).

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Shattuck and Muehlenbein, 2015	Healthy subjects Sex: male,female N: 11 Age: range 21-27; mean 22.8 (SD NA)	Within-subjects pilot study: rabies vaccine (three doses: day +0, +7, +21)	/	**IL-6:** decrease in IL-6 levels but no significant differences before and after the rabies vaccine. **Testosterone:** Decrease in testosterone levels but no significant differences before and after the rabies vaccine. **Clinical symptoms:** no significant differences in mood before and after the rabies vaccine.
Suarez et al., 2004	Healthy subjects (25% of patients exhibited mild to moderate depressive symptoms) Sex: female N: 44 Age: range 23–49, mean 33.5 (SD 8.2)	Cross-sectional study	**E2**: E2 significantly predicted the expression in vitro (LPS stimulation) of IL-8 monocyte-associated markers in regression analyses.	**Inflammation and depressive symptoms:** positive association between depressive symptoms and greater expression in vitro (LPS stimulation) of TNF-α and IL-8. **Inflammation and hostility:** positive association between hostility scores and greater expression in vitro (LPS stimulation) of IL-1α, IL-1β, IL-8.

NOTE: 3HK (3-hydroxykynurenine acid); BD (bipolar disorder); AOPP (advanced oxidation protein products); AREase (Arylesterase); C-peptide (connecting peptide); CMPA (4- (chloromethyl)phenyl acetate);CRP (C reactive protein); dMDD (current MDD); DRSP (Daily Record of Severity of Problems); E2 (oestradiol, 17-β-oestradiol); fMRI (functional magnetic resonance imaging); FSH (follicle stimulating hormone); Hp (haptoglobin); hs-CRP (high sensitivity CRP); IL (interleukin); KynA (kynurenic acid); LH (luteinizing hormone); LOOH (lipid hydroperoxides); LPS (lipopolysaccharide); MDA (malondialdehyde); MDD (major depressive disorder); N (number); peptide YY (peptide tyrosine tyrosine); PMS (premenstrual syndrome); PMS/MCAS (PMS/menstrual cycle associated symptoms); PON (paraoxonase);QA (quinolinic acid); rMDD (remitted MDD); SD (standard deviation); SEM (standard error of the mean); -SH (sulfhydryl);TNF (tumour necrosis factor);TRP (tryptophan); vs. (versus).