Table 2.

Summary of main findings for selected studies investigating inflammatory biomarkers and sex hormones in menopause and postpartum.

Study	Population	Design	Major Findings: Association between sex hormones and inflammatory markers	Other Findings
Amini et al., 2020	PPD N: 81 (76 completed) Age: range 18-45; mean 28.35 (SD 1.43)	Randomized double-blind placebo controlled clinical trial: 1) 50,000 IU vitamin D3 + 500 mg calcium carbonate 2) 50,000 IU vitamin D3 + placebo of calcium carbonate 3) placebo of vitamin D3 + placebo of calcium carbonate	/	**Sex hormones and inflammation:** no significant differences in E2 and in IL-6, TNF-α between the three groups. **Depressive symptoms:** group 1 and group 2 showed greater reduction in depressive symptom in comparison with group 3. Group 2 showed greater reduction in depressive symptoms in comparison with group 1.
Davis et al., 2006	Post-menopause N: 76 (60 completed, 30 in each group) Age: group 1 mean 53.8 (SD 7.2); group 2 mean 54.2 (SD 5.7)	Randomized double-blind placebo controlled clinical trial: 1) transdermal testosterone therapy + latrazole; 2) transdermal testosterone therapy + placebo. (* The authors merged the two treatment groups in the statistical analyses).	**Testosterone**: increased total and free testosterone levels. No significant associations between testosterone therapy and changes in SHBG, E2, cholesterol (total, LDL, HDL), triglycerides, lipoprotein(a), hs-CRP.	**Sex hormones and inflammation after treatment:** No significant differences after treatment in immune and endocrine profiles (E2, SHBG, lipids, total cholesterol, HDL, LDL, triglycerides, lipoprotein(a), hs-CRP) between the groups. **Clinical symptoms after treatment:** no significant effect of treatment allocation in clinical profiles (SSS, BDI, PGWB) between the groups. **Clinical symptoms after treatment (combined sample):** improvement in BDI, SSS and PGWB Index clinical scales, but no associations with significant changes in inflammatory profile.

Study	Population	Design	Major Findings: Association between sex hormones and inflammatory markers	Other Findings
Figueroa-Vega et al., 2015	Post-menopause N: 60 (early post-menopause N 36; late post-menopause N 24). Age: early post-menopause group mean 52.4 (SD 4.2); late post-menopause group mean 54.9 (SD 4.7)]	Cross-sectional study	**FSH**: negative association with LPS-induced NO production and with CD62L expression by lymphocytes (negative association with BMI, annexin V+ microparticles, and LPS-induced NO in adjusted model). **E2**: positive association with IL-6 (positive association with BMI and negative association with age in adjusted model).	**Depressive symptoms**: moderately elevated in early and late post-menopause. Depression showed negative association with PSGL-1 expression by lymphocytes, positive association with LPS-induced NO concentrations. **BMI**: increased in late post-menopause. **E2**: lower levels in late post- menopause. **ICAM-1 expression on isolated lymphocytes**: increased in late post-menopause. **CD62L+ peripheral lymphocytes**: significant decreased in late post- menopause. **CD14+CD11c+ monocytes:** significantly lower in late post-menopause **Membrane-bound TNF-α on peripheral CD14+ monocytes:** significantly higher in late post- menopause
Haren et al., 2007	Menopause; peri-menopause; non-menopause N:244 [menopause group N 180; peri- or non-menopause N 64] Age: mean 56.9 (SD 4.4)	Cross-sectional study	**E2**: positive association with leptin, SHBG, DHEA-S, BMI and inversely correlated with adiponectin and sTNFr1. **DHEA-S, testosterone, FAI**: positive association with CRP and BMI. **DHEA-S, testosterone and E2**: negative association between DHEA-S with SHBG levels, adiponectin, sTNFr1, sTNFr2, and positively correlated with total-testosterone, FAI and E2 levels.	**E2:** positive association with better clinical outcome (MMSE and CESD). **Testosterone, FAI:** negative association with adiponectin. No significant associations with neuropsychological functions. **DHEA-S**: negative association with clinical outcome. (The association was no more significant in adjusted analyses for ethnicity, site, age, smoking and log waist circumference). **DHEA-S and E2**: both showed an age-related decline.
Karaoulanis et al., 2014	peri-menopause N: 65 (depressed (taking and not taking SSRI) N 39; controls N 26) Age: range 40-58; [depressed mean 50.10 (SD 3.95); controls mean 48.29 (SD 10.95)]	Cross-sectional case-control study	**E2, FSH, LH:** no significant associations with inflammatory biomarkers. **E2 and SSRI:** E2 exhibited a positive association with haptoglobin in the sub-group of depressed women who were not taking SSRI.	**Inflammation:** the acute-phase response proteins (transferrin, a1-antitrypsin, haptoglobin, complement protein 3 and complement protein 4, CRP) did not show significant differences between depressed patients and controls or between groups. **Inflammation and depressive symptoms:** no significant associations with acute-phase response proteins and depressive symptoms.

Study	Population	Design	Major Findings: Association between sex hormones and inflammatory markers	Other Findings
Nishi et al., 2020	PPD N: omega 3 group N 49; placebo group N 51. Age: omega 3 group mean 32.8 (SD 5.3); placebo group mean 32.6 (SD 5.3)	Multicenter randomised double-blind, parallel group placebo-controlled trial study: 1) omega-3 PUFA group: 134 mg EPA and 67.7 mg DHA 2) placebo group: 320 mg olive oil and 9.9 mg omega-3 PUFAs.	**E2, inflammatory biomarkers, PUFAs:** no significant association between these factors. **Changes in E2, PUFAs:** no significant association with changes in hs-CRP, IL-6, and adiponectin.	**Depressive symptoms:** negative association with increases in EPA and E2 in the active group. **Adiponectin**: negative association with DHA in the active group.
Okun et al., 2011	PPD N: 56 Age: mean 31.1 (SD 4.1)	Longitudinal study *[the subjects took part in a randomized clinical trial investigating the use of nortriptyline (N 20), sertraline (N 10) or placebo (N 26) after the delivery]	/	**PPD recurrence, sleep, and inflammation:** IL-6 concentrations were available for a subgroup of 33 women at single time point. IL-6 levels and poor sleep quality after the delivery increased the risk for recurrent PPMD among patients with past-history of MDD. **Sleep quality X IL-6:** possible role of the interaction between increased IL-6 and poor quality of sleep after the delivery in increasing the risk of recurrence (statistical trend). **Sleep quality and hormones:** no significant interactions between changes in sleep quality and changes in the biomarker levels (E2, cortisol, prolactin).
Sha et al., 2020	PPD N: 163 (Pine Rest N 87; Spectrum Health N 76); PPD (N 87): non-PPD (N 58). Age: PPD mean 26.7 (SD 5.2); non-PPD mean 28 (SD 6.3)	Longitudinal study	**Oestrogen**: negative association with picolinic acid and kynurenine; positive association with IL-6. **Progesterone**: negative association with quinolinic acid, kynurenine/ tryptophan ratio and kynurenine, IL-1β, nicotinamide.	**Oestrogen**: positive association with BMI. **Sex hormones:** no significant differences between PPD and non-PPD groups. **Oestrogen, progesterone:** positive association with total long-term EPDS score (Spectrum Health cohort) **Progesterone**: positive association with acute depressive symptoms (Spectrum Health cohort).
Stepheson et al., 2013	Peri-/post-menopause N: 75 Age: range 30-70; median 52.3 (SD 9.6)	Longitudinal, closed-label cohort study, BHRT: Bi-Est (80% oestriol/20% E2) 0.25 mg to 0.5 mg; and/or progesterone 20 mg to 60 mg; DHEA 1 mg to 2 mg; testosterone 0.2 mg to 0.5 mg.	**E2, progesterone**: significant increased after BHRT treatment. **CRP, TNF, IL-6, MMP-9, IGF-1:** significant decreases after BHRT treatment.	**Depressive symptoms:** significant decrease after treatment.

Study	Population	Design	Major Findings: Association between sex hormones and inflammatory markers	Other Findings
Stojanovska et al., 2015	Post-menopause N: 34 (29 completed) Age: range 46-59; mean 52.4 (SD 2.7)	Randomized, single-center, double-blind, placebo-controlled, cross-over trial: 1)lepidium meyenii (Maca); 2)placebo	/	**Depressive symptoms**: significant reduction after treatment. **E2, FSH, TSH, SHBG:** no significant variations after treatment. **IL-5, IL-10, and IL-13**: no significant variations after treatment. (*IL-2, IL-4, IL-12, GM-CSF, IFN-γ, TNF-α: concentrations beyond the detectable range and included as zero values).

NOTE: BDI (beck depression inventory); BHRT (); BMI (body mass index); CESD (center for epidemiologic studies depression scale); CRP (C-reactive protein); DHEA (dehydroepiandrosterone); DHEA-S (dehydroepiandrosterone sulphate); E2 (oestradiol, 17-β-oestradiol); EPA (eicosapentaenoic acid); EPDS (Edinburgh Perinatal Depression Rating Scale); DHA (docosahexaenoic acid);FAI (free androgen index); FSH (follicle stimulating hormone); GM-CSF (granulocyte macrophage colony-stimulating factor); HDL (high-density lipoprotein); hs-CRP (high-sensitivity CRP);IGF (insulin-like growth factor); IL(interleukin); INF (interferon); LDL (low-density lipoprotein); LH (luteinizing hormone); LPS (lipopolysaccharide); MMP (matrix metalloproteinase); MMSE (mini-mental state examination); N (number); NO (nitric oxide);PGWB (psychological general well-being index); PPD (postpartum depression); PUFA (polyunsaturated fatty acids); SD (standard deviation);SHBG (sex hormone binding globulin); SSRI (selective serotonin reuptake inhibitor); SSS (sexual satisfaction scale); sTNFr (tumour necrosis factor receptor); TNF (tumour necrosis factor); Vitamin D (25 hydroxyvitamin D; 25[OH]D).