

**Table 4.10 Studies on chronic inflammation and coffee drinking in exposed humans**

Tissue	Cell type	End-point	Test	Description of exposure <sup>a</sup> and controls	Response <sup>b</sup> /significance	Comments	Reference
<i>Cross-sectional studies</i>							
Serum	-	hs CRP	Immunonephelometric Detection limit: 0.05 µg/ml	Cross-sectional study; 10 325 (4407 M, 5918 F) healthy Japanese (49–76 y); quintiles of coffee intake (0; < 1 cup/d; 1–3 cup/d; 4–6 cup/d; ≥ 7 cup/d)	Highest quintile vs lowest Men –20% (95% CI, –36%, –0%) [P trend < 0.05] Women –25% (95% CI, –40%, –3%) [P trend = 0.52]	Effect only in men, and limited to high alcohol consumption (≥ 50 g/d)	Maki et al. (2010), Pham et al. (2011)
Serum	-	hs CRP	Latex Agglutination assay Detection limit: 0.1 µg/ml	Cross-sectional study; 7574 (3664 M, 3910 F) healthy Koreans (40–69 y); coffee pattern derived by factor analysis and divided into quartiles (no data on actual coffee intake);	No difference between Q4 and Q1 [P = 0.77]		Lee et al. (2014)
Plasma	-	hs CRP	Immunoturbidimetric Detection limit: no data	Cross-sectional study; 4139 (1921 M, 2218 F) healthy Asians (50 y); quartiles coffee intake (0, < 1 cup/d, 1–2 cup/d, ≥ 3 cup/d)	No effect in multiple regression analysis [P = 0.185]	Adjusted a.o. for tea drinking	Rebello et al. (2011)
Plasma	-	hs CRP	Immunonephelometric Detection limit: no data	Cross-sectional study; 344 healthy women (57 y); quartiles of coffee intake (0; 1 cup/mo- 6 cup/wk; 1 cup/d-13 cup/wk; ≥ 2 cup/wk)	Highest quartile vs lowest –30% (95% CI, –40%, –7%) [P trend = 0.005]	CRP positively associated with BMI; hormone replacement therapy increased CRP	Arsenault et al. (2009)
Serum	-	hs CRP	ELISA detection limit: no data	Cross-sectional study; 114 healthy Japanese, age- and sex-matched (60 y); coffee (≥ 1 cup/d) and non-coffee (< 1 cup/d) drinkers	Comparison between coffee and non-coffee drinkers (control) –25% [P = 0.05]	Small sample size	Kotani et al. (2010)

Plasma	-	CRP, SAA, IL-6, TNF- $\alpha$ ; white blood cell counts	Immunonephelometric (CRP, SAA); ELISA (IL-6, TNF- $\alpha$ )	Cross-sectional study; 1514 healthy men and 1528 healthy women (45 y); quartiles of coffee intake (0; < 200 ml/d; 200–400 ml/d; > 400 ml/d)	<p>Inflammatory markers were positively associated with coffee consumption [<math>P &lt; 0.05</math>]</p> <p>Highest quartile vs lowest (no coffee)</p> <p>Men</p> <p>CRP +35% [<math>P &lt; 0.01</math>]</p> <p>IL-6 +60% [<math>P &lt; 0.01</math>]</p> <p>TNF-<math>\alpha</math> +40% [<math>P &lt; 0.01</math>]</p> <p>SAA +15% [<math>P &lt; 0.05</math>]</p> <p>WBC + 4% [<math>P &lt; 0.05</math>]</p> <p>Women</p> <p>CRP +40% [<math>P &lt; 0.05</math>]</p> <p>IL-6 +60% [<math>P &lt; 0.01</math>]</p> <p>TNF-<math>\alpha</math> +40% [<math>P &lt; 0.01</math>]</p> <p>SAA +50% [<math>P &lt; 0.01</math>]</p> <p>WBC + 7% [<math>P &lt; 0.05</math>]</p>	Stratification for filtered or unfiltered coffee did not change the effects	Zampelas et al. (2004)
Serum	-	CRP, sICAM, E-selectin, sTNF- $\alpha$ -receptor II	ELISA; turbidimetric (CRP)	Cross-sectional study; 1393 women (43–70 y) Nurses' Health Study I; quartiles coffee intake (< 1 cup/mo; 1 cup/mo–4 cup/wk; 5–7 cup/wk; $\geq 2$ cup/d)	<p>Difference (%) per 1 cup/d increment</p> <p>Caffeinated coffee</p> <p><i>non-diabetic</i></p> <p>Not significant: CRP, sICAM, E-selectin, TNF-R2</p> <p><i>diabetic</i></p> <p>E-selectin -3% [<math>P = 0.05</math>]</p> <p>CRP -0% [<math>P &lt; 0.001</math>]</p> <p>Not significant: sICAM, sTNF-R2</p>	Repeated assessment of coffee intake	Lopez-Garcia et al. (2006)

					Decaffeinated coffee <i>non-diabetic</i> CRP –8% [ $P = 0.02$ ] Not significant: sICAM, E-selectin, sTNF-R2, <i>diabetic</i> Not significant: CRP, sICAM, E-selectin, sTNF-R2		
Plasma	-	IL-6, PAI-1		Cross-sectional study, hypertensives (43 y); heavy coffee drinkers (> 4 cups/d) ( $n = 30$ ) vs light coffee drinkers (< 1 cup/d) ( $n = 30$ )	IL-6 +120% [ $P < 0.005$ ] PAI-1: +85% [ $P < 0.0001$ ]		Tsioufis et al. (2006)
Serum	-	77 Inflammatory/immune markers	Luminex bead-based assays	Cross-sectional study with 1728 older US non-Hispanic whites	Coffee drinkers (> 2.5 cups/d) vs non-drinkers sTNF-R2 OR, 0.34; (95% CI: 0.15–0.79)		Loftfield et al. (2015)
<i>Prospective studies</i>							
Serum	-	CRP, TNF- $\alpha$ -receptor II	ELISA; turbidimetric (CRP)	Prospective study; follow-up 6 y; 2040 women Nurses' Health Study; quartiles coffee intake (< 1 cup/wk; 1–6 cup/wk; 1–3 cup/d; $\geq 4$ cup/d)	Inverse associations: CRP [ $P = 0.001$ ] TNF-R2 [ $P = 0.03$ ]	Repeated assessment coffee intake	Williams et al. (2008)
Serum /plasma		CRP, IL-6	Turbimetric (CRP), electrochemiluminescence	Prospective nested case-control study; 125 incident cases of hepatocellular carcinoma (HCC); 250 controls; $\geq 4$ cups/d vs < 2 cups/d	IL-6 inverse with coffee drinking, $\beta = -0.18$ (-0.35, -0.02), [ $P = 0.06$ ] CRP not significant	HCC risk coffee drinkers: 0.25 (95% CI: 0.11–0.62) [ $P$ -trend = 0.006]	Aleksandrova et al. (2015)

Randomized controlled trials (RCTs)

Plasma	-	hs CRP, sE-selectin, sVCAM-1, sICAM-1, IL-1 $\beta$ , IL-6, TNF- $\alpha$ , MCP-1, tPAI-1, fibrinogen,	Immunonephelometric (CRP), Luminex bead-based assay (other markers except fibrinogen)	RCT crossover; 20 (6 M, 14 F) healthy non-smoking subjects; 3 cups/d (150 ml) paper-filtered coffee light roasted, 3 cups/d paper-filtered coffee medium roasted; 4 wk, no wash-out in between	Medium roasted vs baseline: fibrinogen + 8% [ $P < 0.01$ ] sVCAM-1 +15% [ $P < 0.05$ ] other markers did not differ Light roasted vs baseline: sVCAM-1 +20% [ $P < 0.05$ ] sE-selectin +10% [ $P < 0.05$ ] other markers did not differ	No placebo	Corrêa et al. (2013)
Serum	-	CRP, IL-6, IL-18, IL-1ra, SAA, MIF	Luminex bead-based assay (IL-18), ELISA (IL-6, IL-1ra, MIF), immunonephelometric (CRP, SAA),	Clinical trial, 3-stage; 47 (11 M, 36 F) subjects (54 y) elevated risk type 2 diabetes; subsequently, no coffee (1 mo), 4 cups/d filtered coffee (1 mo), 8 cups/d filtered coffee (1 mo)	Difference 8 cups vs 0 cups: IL-18 +8% [ $P < 0.01$ ] Not significant: CRP, IL6, IL-1ra, MIF, SAA	No placebo Compliance thoroughly checked	Kempf et al. (2010)
Plasma, serum	-	IL-6, IL-18	ELISA, detection limits: IL-6 0.16 fg/ml; IL-18 ng/ml	RCT, crossover; 16 men (21–39 y); water, 200 ml caffeinated (3 mg caffeine/kg BW), 200 ml decaffeinated coffee; blood drawn every 30 min until 180 min	Serum IL-18 did not change Plasma IL-6 (AUC, IAUC) did not differ between treatments	No placebo	Gavrieli et al. (2011)

<sup>a</sup> unless otherwise specified, the term coffee is used to mean brewed, caffeinated coffee

<sup>b</sup> +, positive; –, negative; differences: coffee vs control

AUC, area under the curve; CI, confidence interval; CRP, C-reactive protein; d, day; GTT,  $\gamma$ -glutamyltransferase; hs CRP, high-sensitivity CRP; HHQ, hydroxyhydroquinone; F, female; IAUC, incremental AUC; IL, interleukin; IL-1ra, IL-1 receptor antagonist; LR, light roast; M, male; min, minute; mo, month; MR, medium roast; MCP-1, monocyte chemoattractant protein-1; MIF, macrophage migration inhibitory factor; NR, not reported; OR, odds ratio; PAI-1, plasminogen activator inhibitor-1; RCT, randomized clinical trial; SSA, serum amyloid-A; sTNF-R2, sTNF- $\alpha$ -receptor II; sICAM-1, soluble intercellular adhesion molecule-1; sVCAM-1, soluble vascular cell adhesion molecule-1; tPAI-1, total TPAI-1; WBC, white blood cell counts; vs, versus; wk, week; y, year

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