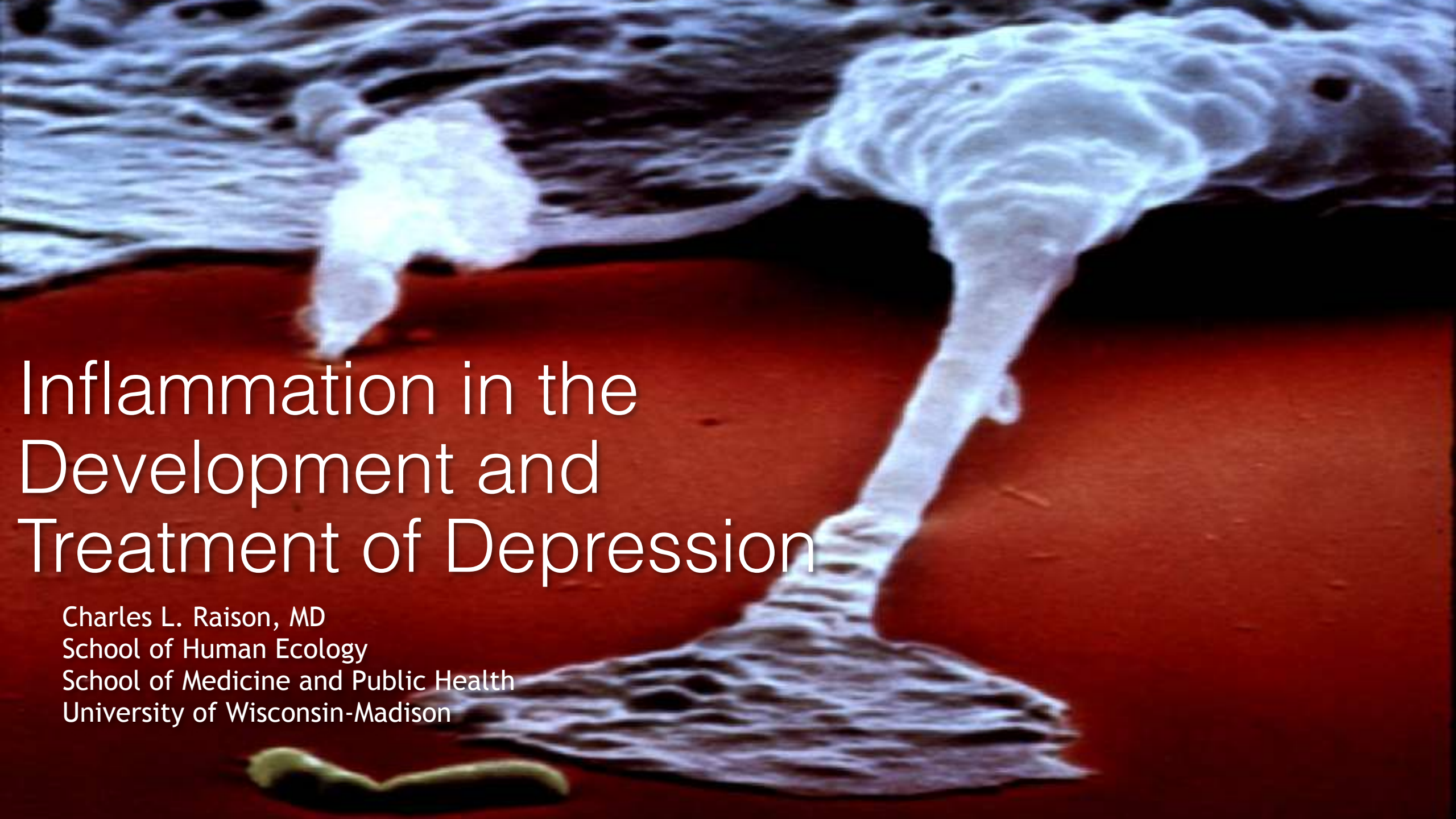

Inflammation in the Development and Treatment of Depression

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Faculty Disclosure

- **Dr. Raison:** Consultant—Alfasigma, Emory Healthcare, Novartis, Usona Institute.

Inflammation May Cause Depression Because It First Caused Sickness

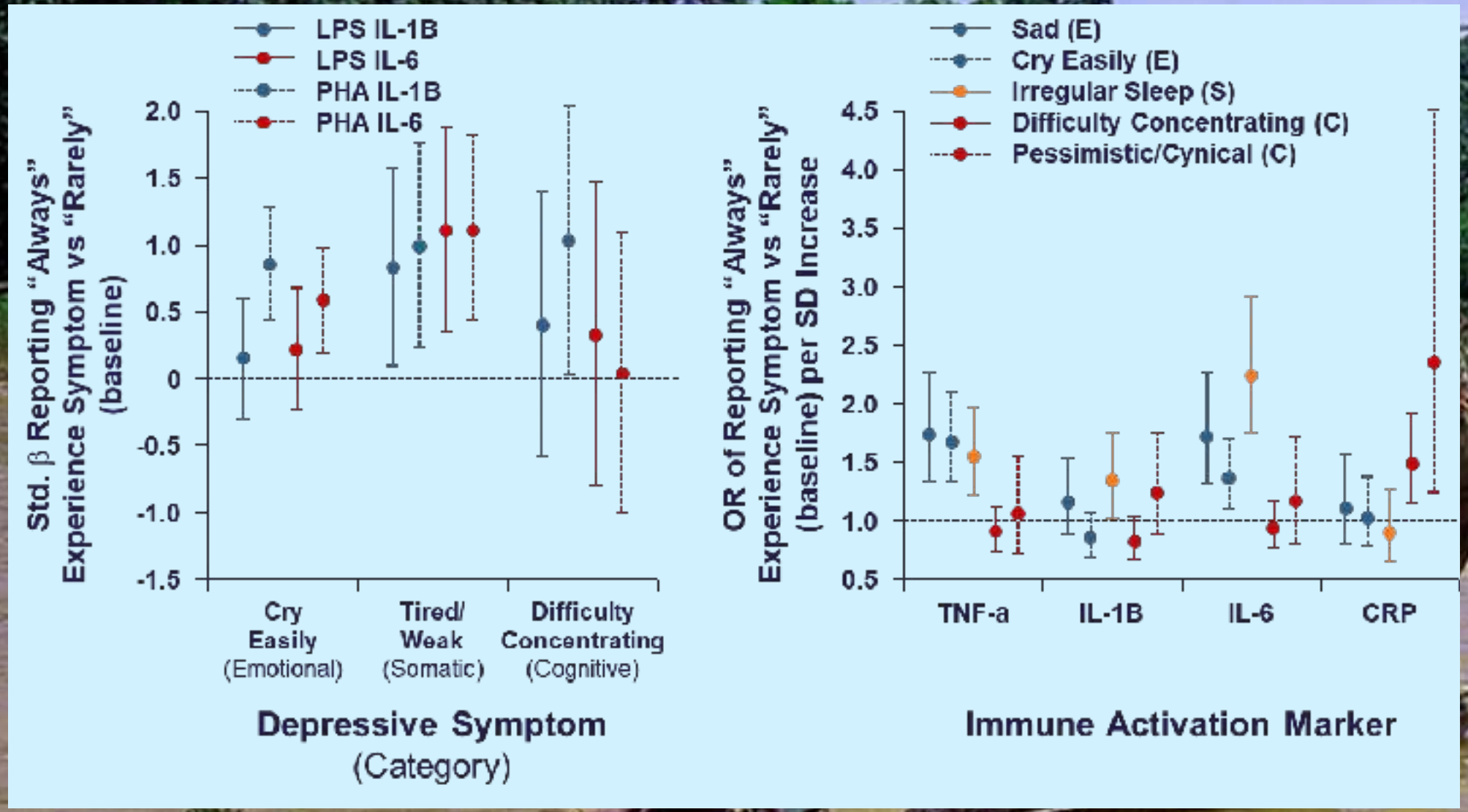
SICKNESS

- Loss of pleasure*
- Loss of appetite*
- Weight loss*
- Cognitive disturbance*
- Decreased sexual energy*
- Fatigue*
- Physical slowness*
- Sleep disturbance*
- Social isolation*
- Increased pain*
- Fever*
- Sad mood†
- Suicidal ideation†
- Worthlessness/guilt†

DEPRESSION

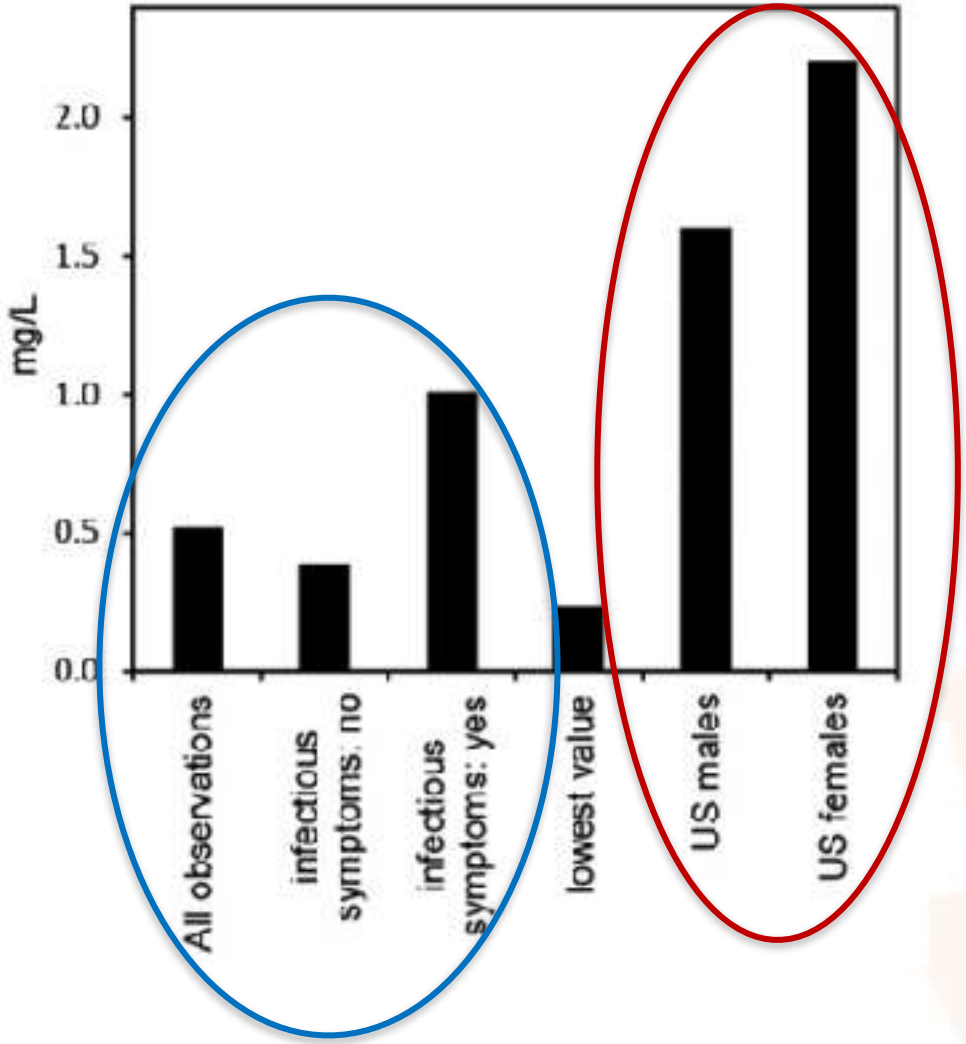
- Loss of pleasure*
- Loss of appetite*
- Weight loss*
- Cognitive disturbance*
- Decreased sexual energy*
- Fatigue*
- Physical slowness*
- Sleep disturbance*
- Social isolation*
- Increased pain complaints*
- Increased body temperature*
- Sad mood†
- Suicidal ideation†
- Worthlessness/guilt†

Raison CL, et al. *Semin Clin Neuropsychiatry*. 2001;6(4):277-294.



CRP = C-reactive protein; IL = interleukin; LPS = lipopolysaccharide; PHA = phytohaemagglutinin; TNF-α = tumor necrosis factor alpha.
Stieglitz J, et al. *Brain Behav Immun*. 2015;49:130-139.

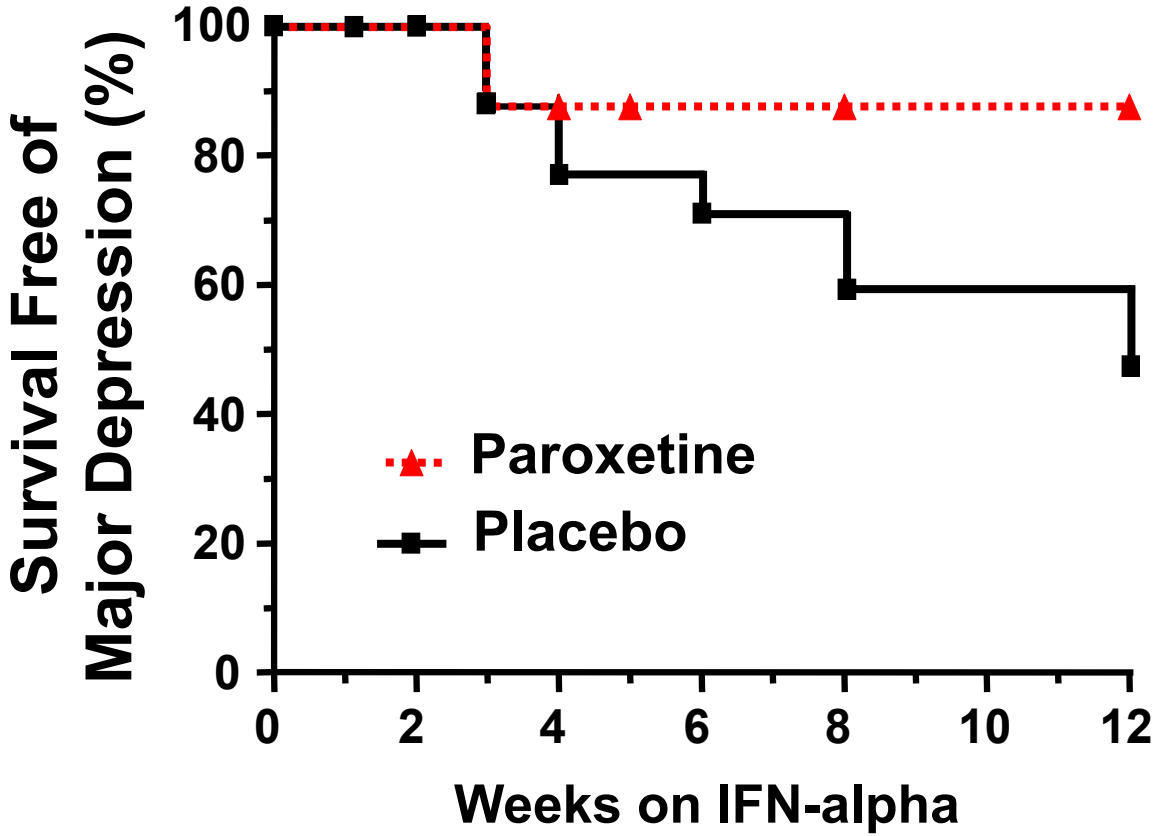
Inflammation:
Modern vs Across Evolutionary Time

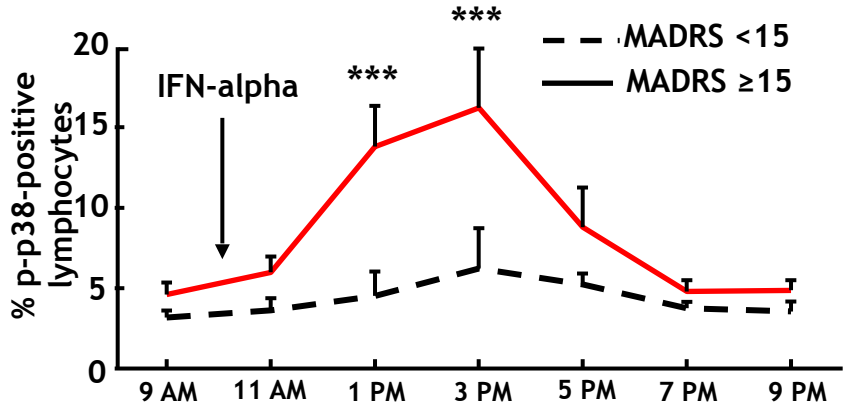


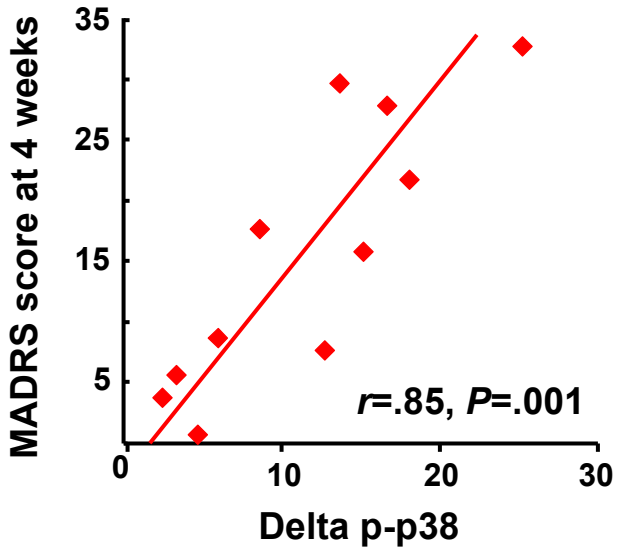
CRP levels were measured repeatedly over 4 weeks in 52 individuals living a traditional lifestyle in the Amazon basin. Levels rose and fell with infectious status but were far lower overall than seen in the United States, and no cases of chronically-elevated CRP were observed, as is common in the developed world.

McDade TW, et al. *Am J Hum Biol*. 2012;24(5):675-681.

Evidence That Inflammation Can Cause Depression

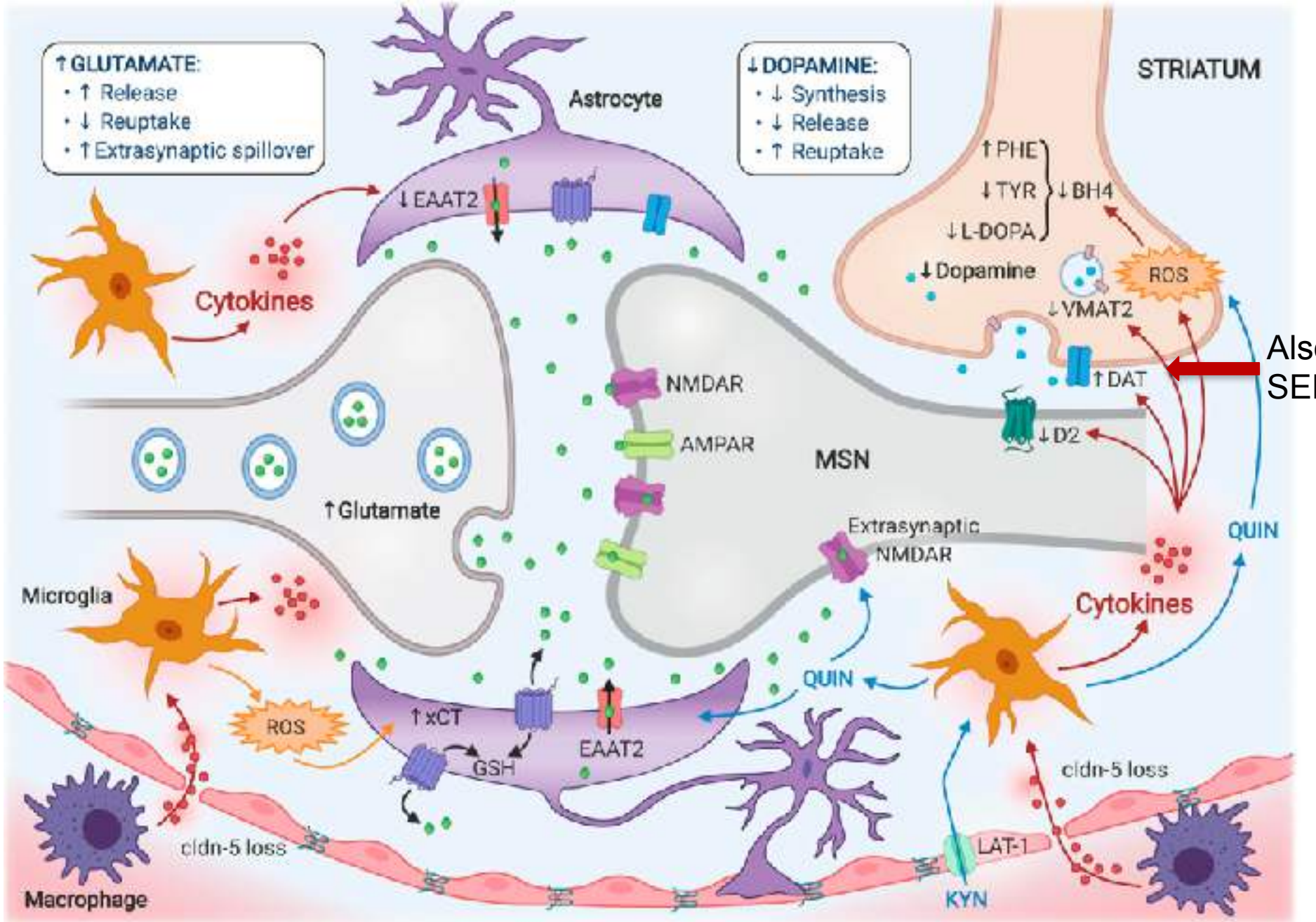






MADRS = Montgomery-Asberg Depression Rating Scale.

Musselman DL, et al. *N Engl J Med*. 2001;344(13):961-966.
Felger JC, et al. *Brain Behav Immun*. 2011;25(6):1094-1098.

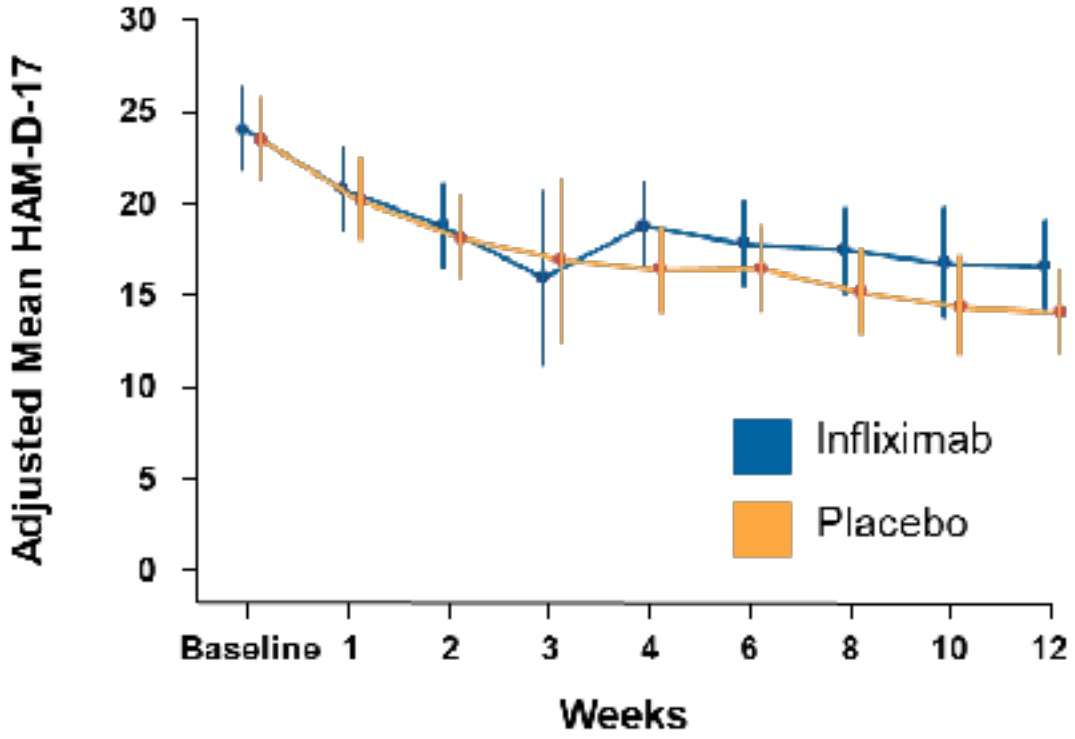


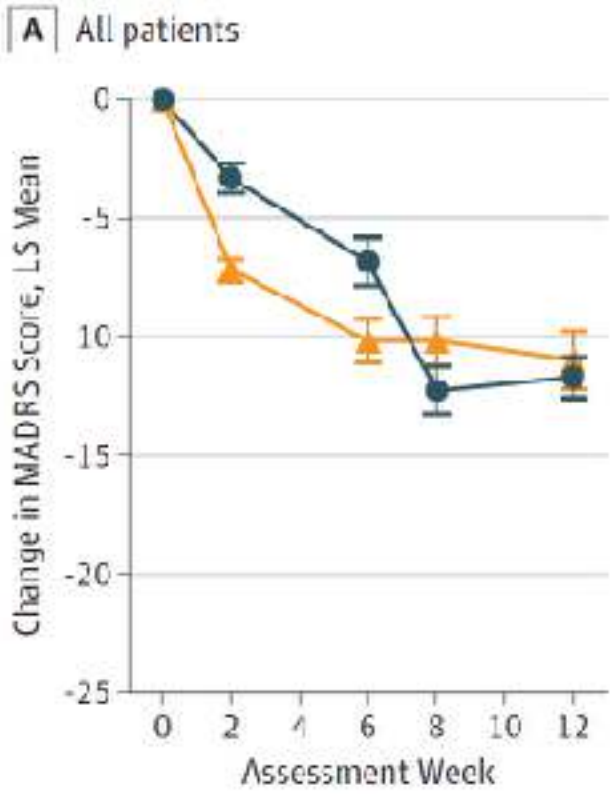
Also increases SERT and NET

SERT = serotonin reuptake transporter; NET = norepinephrine transporter.
Lucido MJ, et al. *Pharmacol Rev*. 2021;73(3):1084-1117.

Treatment Implications of the Inflammation-Depression Connection: *Anti-Inflammatory Strategies*

No Evidence That Tumor Necrosis Factor Inhibition Works in Major or Bipolar Depression

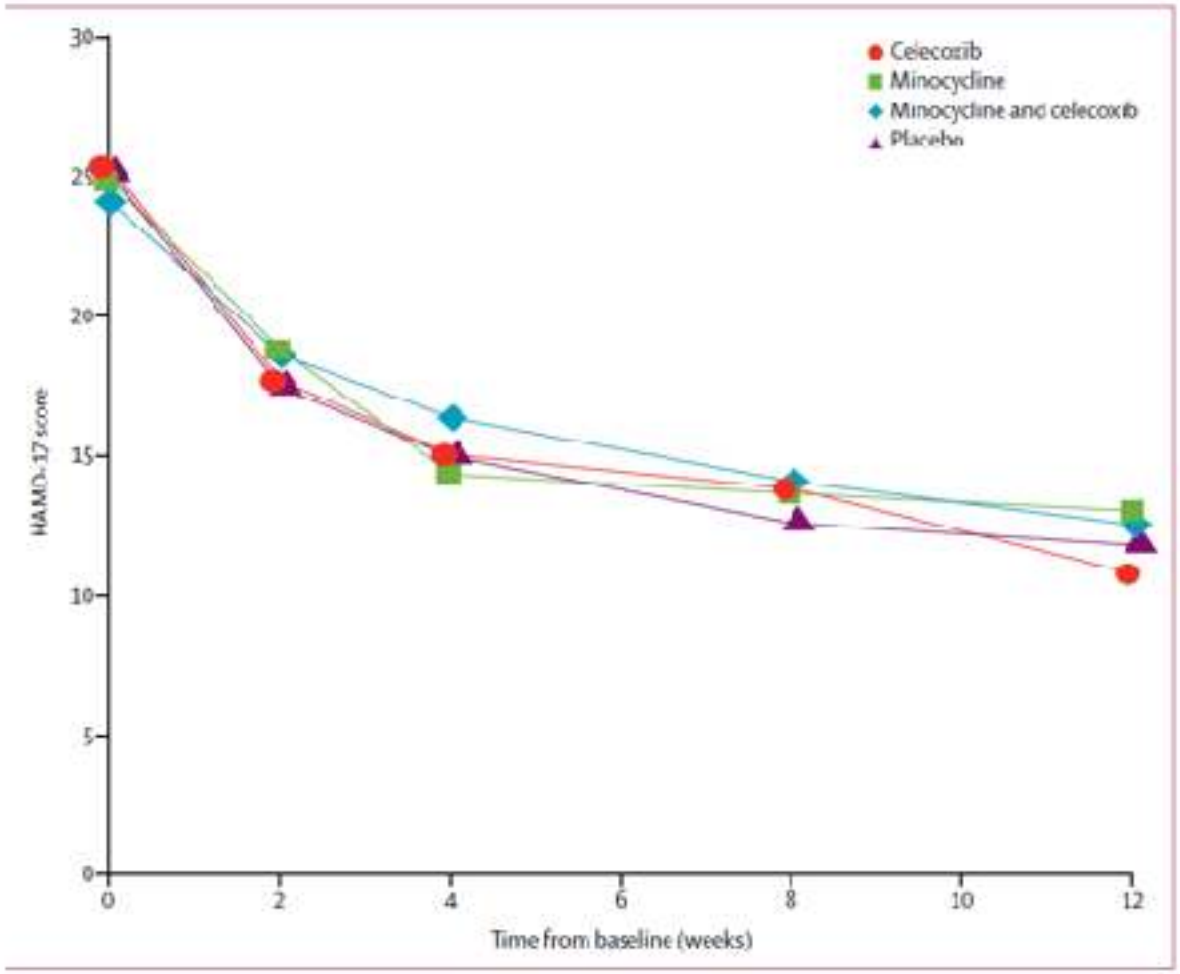




No effect of 3 infusions of infliximab vs placebo in 60 medically-healthy patients with major depression (Left). No effect of 3 infusions of infliximab vs placebo in 60 patients with bipolar I or II disorder (Right).

Raison CL, et al. *JAMA Psychiatry*. 2013;70(1):31-41. McIntyre RS, et al. *JAMA Psychiatry*. 2019;76(8):783-790.

No Strong Evidence That Minocycline or Celecoxib Work in Major or Bipolar Depression



A double-blind, 12-week, randomized, placebo-controlled trial in Pakistan. Eligible participants were adults (aged 18–65 years) with *DSM-5* bipolar disorder (type I or II) and a major depressive episode. In a 2 × 2 factorial design, participants were randomly assigned (1:1:1:1) to receive either active minocycline + active celecoxib, active minocycline + placebo celecoxib, placebo minocycline + active celecoxib, or placebo minocycline + placebo celecoxib. The primary outcome was the mean change from baseline to week 12 in score on the 17-item Hamilton Depression Rating Scale (HAMD-17). 266 (17%) of 1542 patients assessed between May 1, 2016, and March 31, 2019, were randomly assigned to receive **minocycline + celecoxib (n=68)**, **minocycline + placebo (n=66), celecoxib + placebo (n=66), or placebo + placebo (n=66). No effect of minocycline or celecoxib, or their combination when compared to placebo.**

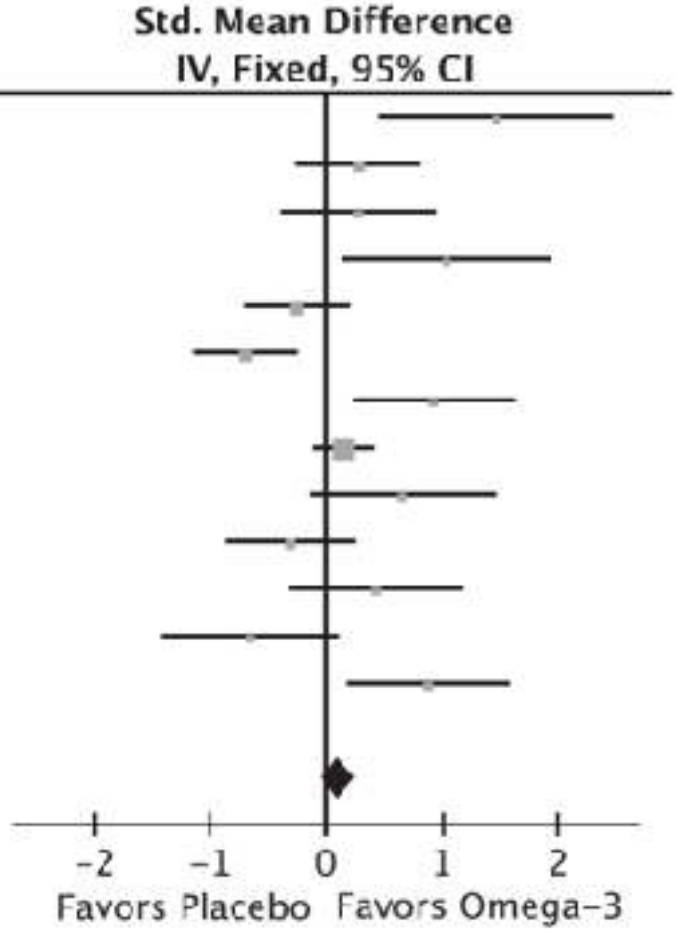
Husain MI, et al. *Lancet Psychiatry*. 2020;7(6):515-527.

No Strong Evidence That Omega-3 Fatty Acids Work in Major or Bipolar Depression

Study or Subgroup	Weight	Std. Mean Difference IV, Fixed, 95% CI	Year
Nemets B	2.2%	1.47 [0.45, 2.48]	2002
Peet	7.7%	0.28 [-0.26, 0.82]	2002
Marangell	5.0%	0.28 [-0.39, 0.94]	2003
Su-MDD	2.7%	1.04 [0.13, 1.94]	2003
Silvers	11.1%	-0.25 [-0.70, 0.20]	2005
Grenyer	11.4%	-0.69 [-1.13, -0.25]	2007
Su-PD	4.7%	0.93 [0.24, 1.62]	2008
Rogers	31.7%	0.15 [-0.12, 0.41]	2008
Rees	3.6%	0.66 [-0.14, 1.45]	2008
Freeman	7.3%	-0.31 [-0.86, 0.25]	2008
da Silva	4.1%	0.43 [-0.31, 1.17]	2008
Lucas	3.9%	-0.66 [-1.41, 0.10]	2009
Mischoulon	4.6%	0.88 [0.18, 1.58]	2009
Total (95% CI)	**100.0%**	**0.11 [-0.04, 0.26]**	

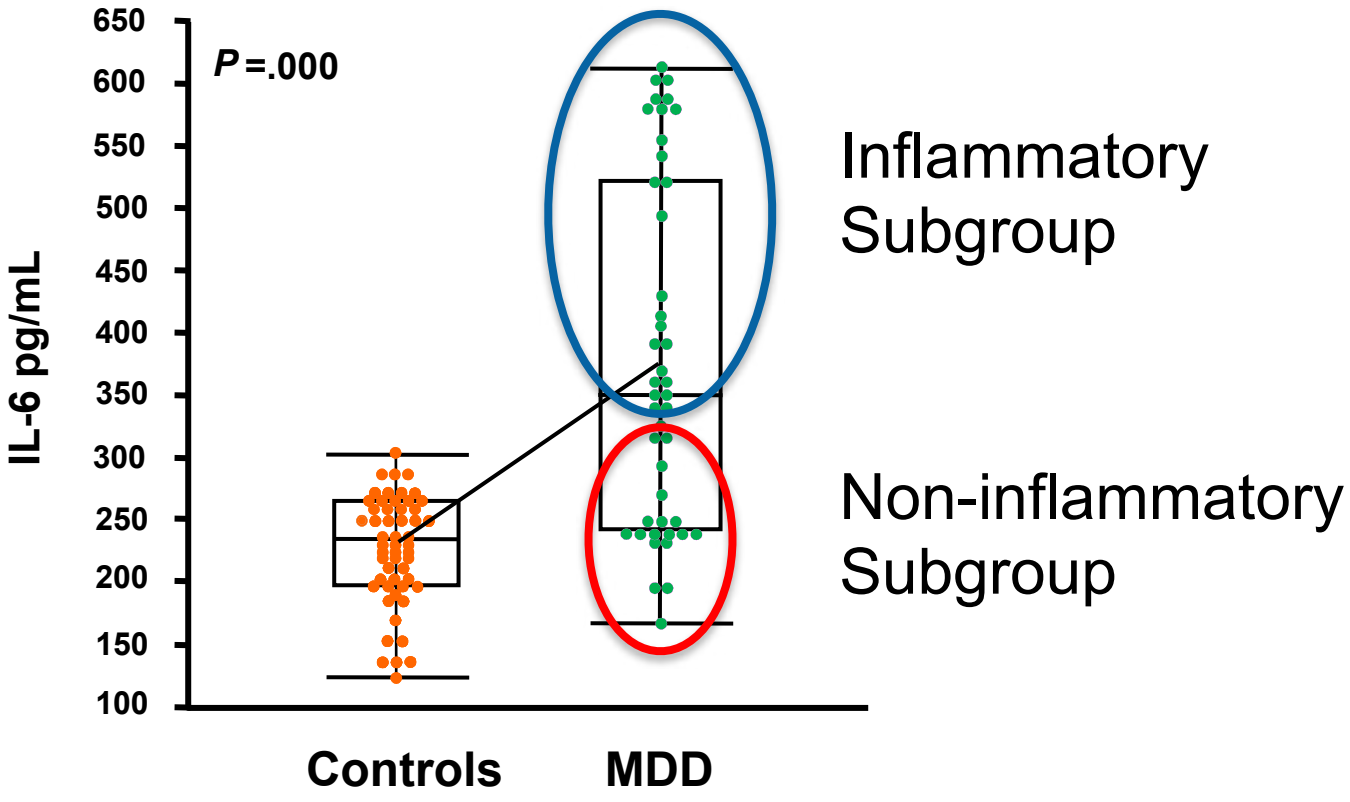
Heterogeneity: $Chi^2 = 45.26$, $df = 12$ ($P < 0.00001$); $I^2 = 73\%$

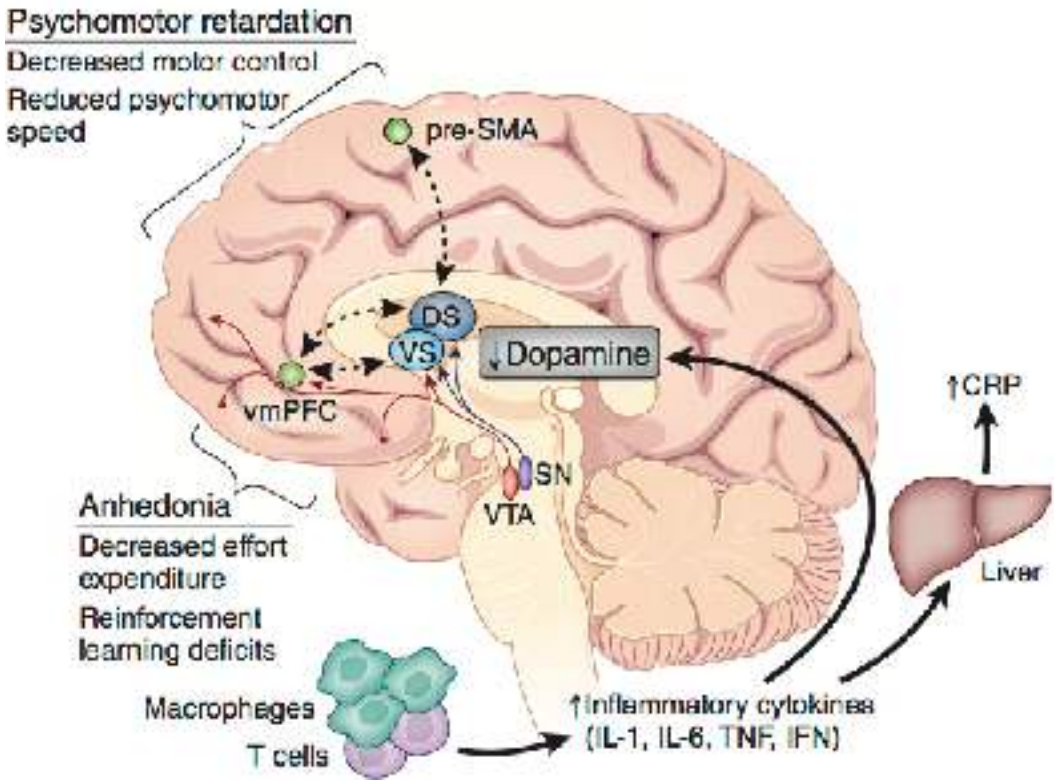
Test for overall effect: $Z = 1.47$ ($P = 0.14$)



Rapaport MH, et al. *Mol Psychiatry*. 2016;21(1):71-79.

Inflammation Causes Depression, But Depression is Not an Inflammatory Disorder

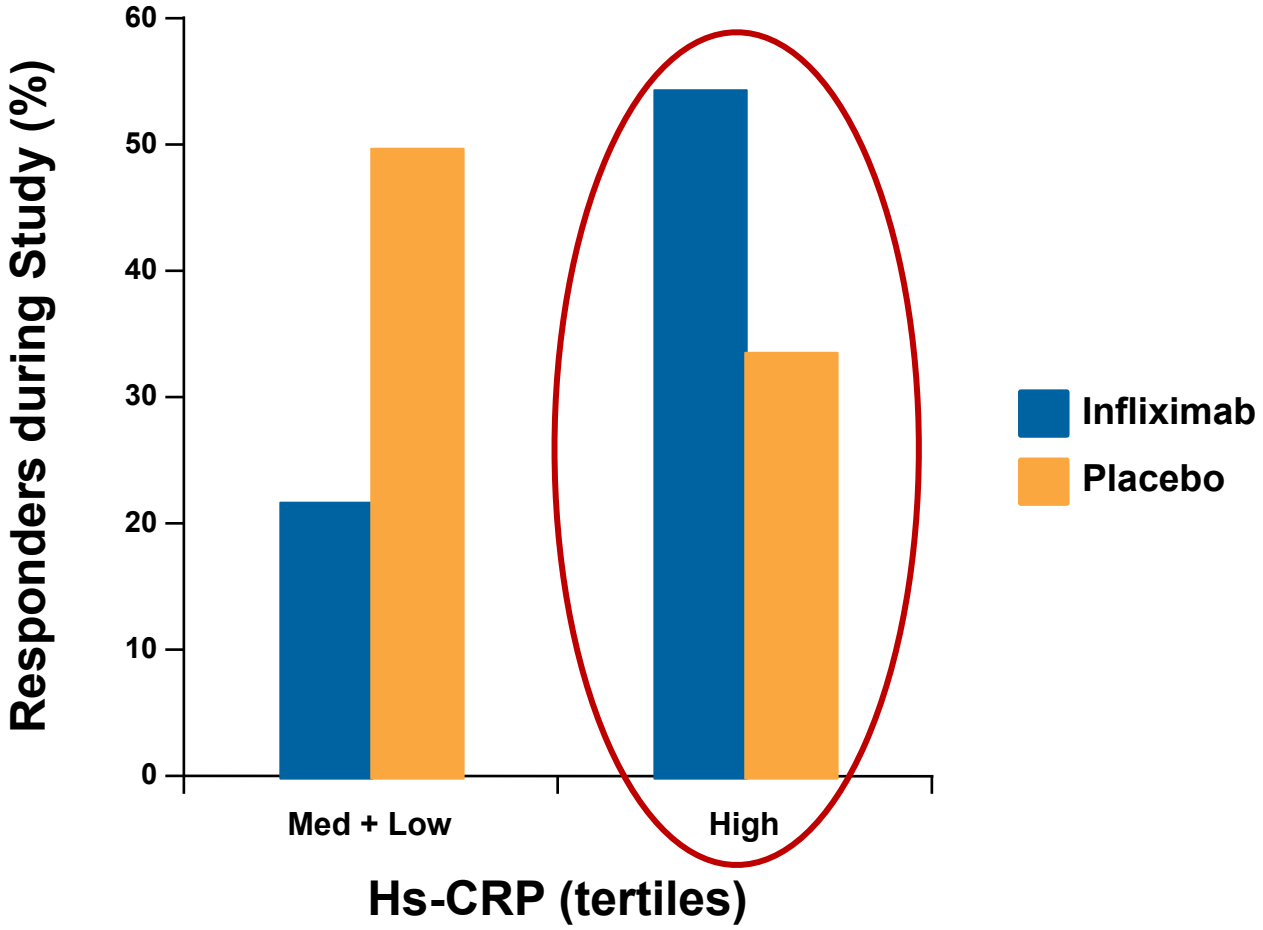


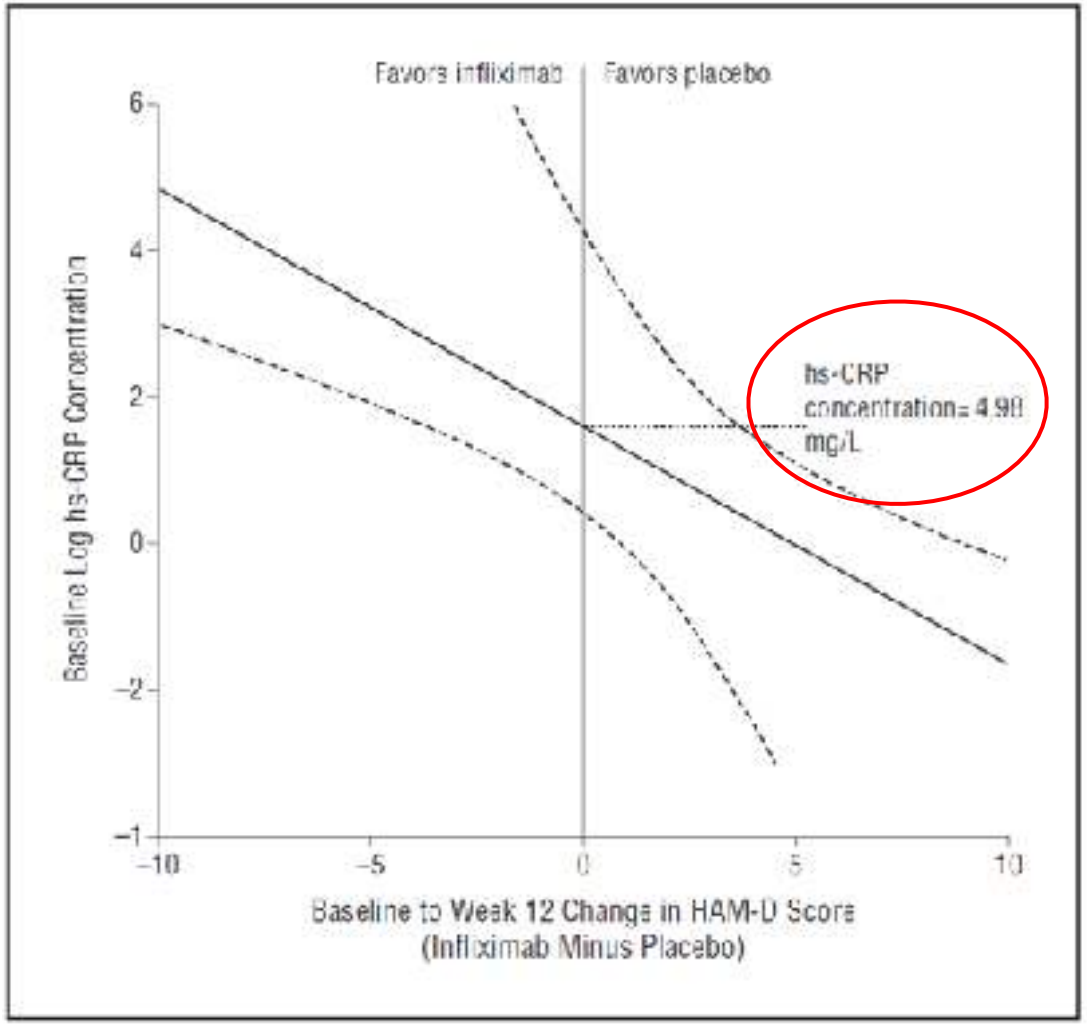


DS = dorsal striatum; IL = interleukin; TNF = tumor necrosis factor; IFN = interferon; SMA = supplementary motor area; SN = substantia nigra; vmPFC = ventromedial prefrontal cortex; VS = ventral striatum; VTA = ventral tengmental area; CRP = c-reactive protein.

Kim YK, et al. Prog Neuropsychopharmacol Biol Psychiatry. 2007;31(5):1044-1053; Felger JC, et al. *Neuropsychopharmacology*. 2017;42(1): 216-241.

Cytokine Antagonism Only Works in MDD Patients with Chronic Inflammation





Hs-CRP = high-sensitivity CRP.

Raison CL, et al. *JAMA Psychiatry*. 2013;70(1):31-41.

Omega-3 Fatty Acids Only Work in MDD Patients with Chronic Inflammation

Table 2. Change in HAM-D 17 total score from baseline to treatment week 8 by number of 'high' biomarkers at baseline[a]

Number of biomarkers reflecting 'high' inflammation	Change from baseline to treatment week 8				Standardized treatment effect size[b] at treatment week 8			Paired comparison of groups at treatment week 8			Significance of treatment-by-time interaction	
		EPA	DHA	PLA	EPA vs PLA	DHA vs PLA	EPA vs DHA	EPA vs PLA	DHA vs PLA	EPA vs DHA		
4 or 5 Biomarkers (N=21)	LS mean (s.e.m.) [N]	−11.14 (1.79) [10]	−4.90 (2.17) [7]	−5.02[c] (2.52) [4]	ES (95% CI)	−1.11 (−2.35 to 0.13)	+0.02 (−1.21 to 1.25)	−1.10 (−2.14 to −0.05)	t	2.01	+0.04	2.13	F	0.94
									df[d]	34.4	31.9	31.5	df[d]	2, 79.8
									P-value	0.052	0.972	0.041	P-value	0.396
2 or 3 Biomarkers (N=38)	LS mean (s.e.m.) [N]	−12.38 (1.47) [13]	−11.52 (1.35) [13]	−9.43 (1.35) [12]	ES (95% CI)	−0.59 (−1.39 to +0.21)	−0.44 (−1.23 to +0.36)	−0.17 (−0.94 to +0.60)	t	−1.48	−1.09	−0.42	F	0.70
									df[d]	82.2	82.2	82.1	df	2, 135
									P-value	0.142	0.279	0.672	P-value	0.498
1 Biomarker (N=50)	LS mean (s.e.m.) [N]	−11.78 (1.28) [13]	−7.81 (1.10) [21]	−10.80 (1.10) [29]	ES (95% CI)	−0.20 (−0.90 to +0.50)	+0.73 (+0.06 to +1.40)	−0.97 (−1.73 to −0.20)	t	−0.57	+2.23	−2.62	F	1.20
									df	122	122	120	df	2, 177
									P-value	0.569	0.027	0.010	P-value	0.303
Any (1–5) biomarkers (N=109)	LS mean (s.e.m.) [N]	−11.46 (0.82) [36]	−8.59 (0.77) [37]	−9.57 (0.80) [36]	ES (95% CI)	−0.39 (−0.85 to +0.08)	+0.21 (−0.25 to +0.67)	−0.60 (−1.07 to −0.13)	t	1.66	0.88	2.55	F	0.86
									df	251	249	250	df	2, 405
									P	0.099	0.381	0.011	P	0.423
No biomarker (N=46)	LS mean (s.e.m.) [N]	−7.78 (0.85) [16]	−11.65 (0.96) [14]	−10.85 (0.83) [16]	ES (95% CI)	+0.91 (+0.13 to +1.64)	−0.23 (−0.95 to +0.49)	+1.11 (+0.33 to +1.88)	t	+2.80	−0.63	+3.03	F	4.09
									df	215	215	215	df	2, 215
									P-value	0.013	0.528	0.003	P-value	0.018
All subjects with 5 baseline biomarkers (N=155)	LS mean (s.e.m.) [N]	−10.14 (0.57) [52]	−9.61 (0.57) [51]	−9.79 (0.55) [52]	ES (95% CI)	−0.09 (−0.47 to +0.30)	+0.04 (−0.34 to +0.43)	−0.13 (−0.52 to +0.26)	t	−0.44	+0.27	−0.65	F	0.17
									df	716	716	716	df	2, 716
									P-value	0.661	0.823	0.513	P-value	0.849

155 participants with *DSM-IV* MDD, a baseline HAM-D-17 score ≥15 and baseline biomarker data (IL-1ra, IL-6, hs-CRP, leptin, and adiponectin) were randomized to 8 weeks of double-blind treatment with EPA-enriched n-3 1060 mg day(-1), DHA-enriched n-3 900 mg day(-1), or placebo. Although overall treatment group differences were negligible (ES=-0.13 to +0.04), participants with any "high" inflammation improved more on EPA than placebo (ES=-0.39) or DHA (ES=-0.60) and less on DHA than placebo (ES=+0.21); furthermore, EPA-placebo separation increased with increasing numbers of markers of high inflammation.

DHA = docosahexaenoic acid; EPA = eicosapentaenoic acid.

Rapaport MH, et al. *Mol Psychiatry*. 2016;21(1):71-79.

More Evidence That Anti-Inflammatory Strategies Only Work in the Inflamed: Minocycline

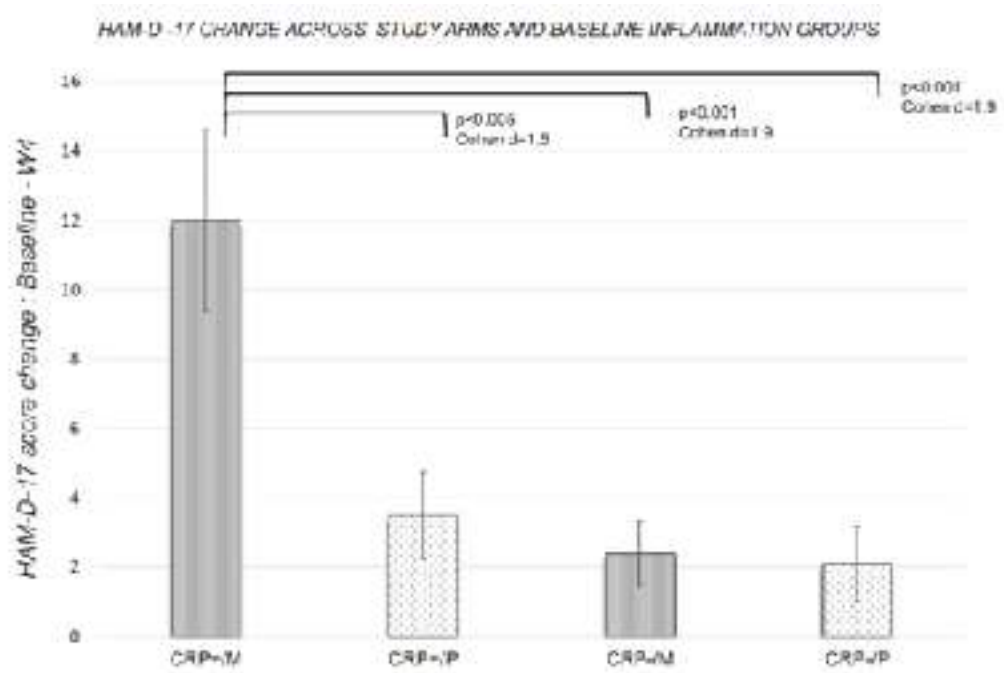


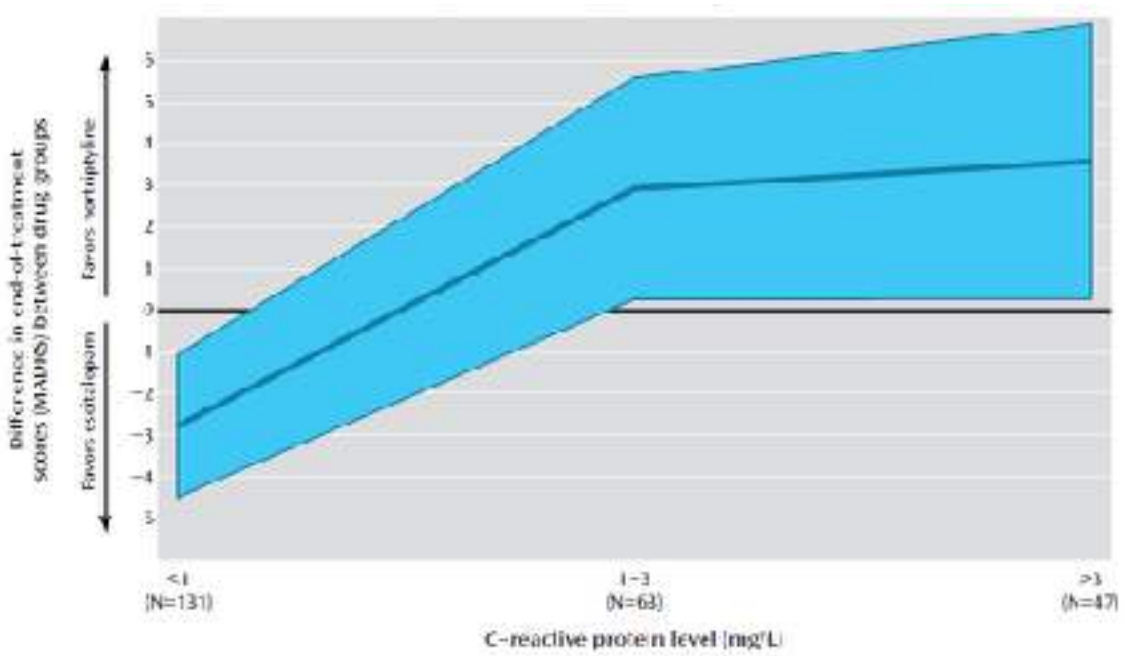
Fig. 1 **Difference in HAM-D-17 mean change, calculated as baseline scores minus week 4 scores, between patients divided by Study Arm X baseline hsCRP.** Patients with hsCRP levels ≥ 3 mg/L and taking minocycline (CRP^{+}/M) showed a significantly larger improvement compared with all other patients. HAM-D-17 = Hamilton Depression Rating Scale. CRP^{+} = baseline hsCRP levels ≥ 3 mg/L. CRP^{-} = baseline hsCRP levels <3 mg/L. M = Minocycline, P = Placebo.

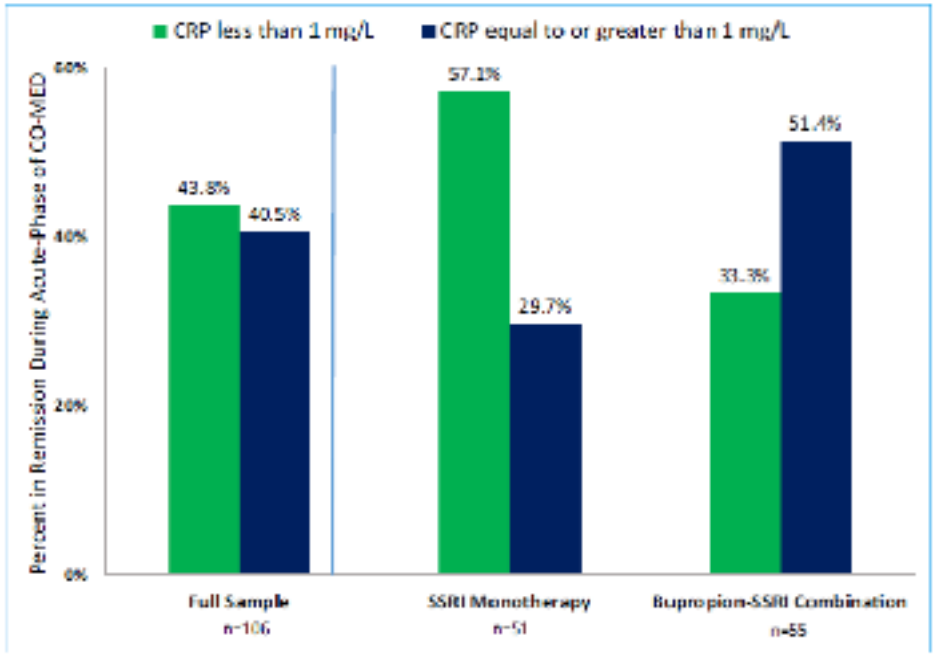
A 4-week, placebo-controlled, randomized clinical trial of minocycline (200 mg/day) added to antidepressant treatment in 39 patients selected for elevated levels of serum C-reactive protein (CRP ≥1 mg/L), n=18 randomized to minocycline (M) and n=21 to placebo (P). The main outcome was the change in HAM-D-17 score from baseline to week 4, in the overall sample and after further stratification for baseline CRP ≥3 mg/L. After stratification for CRP levels <3 mg/L (CRP−) or ≥3 mg/L (CRP+), **CRP+/M patients showed the largest changes in HAM-D-17 scores (mean ± SD = 12.00 ± 6.45) compared with CRP-/M (2.42 ± 3.20, *P*<.001), CRP+/P (3.50 ± 4.34, *P*=.003) and CRP−/P (2.11 ± 3.26, *P*=.006) patients, and the largest proportion (83.3%, *P*=.04) of partial treatment response at week 4.** The threshold point for baseline CRP to distinguish responders from nonresponders to minocycline was 2.8 mg/L. Responders to minocycline had higher baseline IL-6.

Nettis MA, et al. *Neuropsychopharmacology*. 2021;46(5):939-948.

Treatment Implications of the Inflammation-Depression Connection: *Standard Psychotropic Agents*

CRP Predicts Response and Nonresponse to Antidepressants



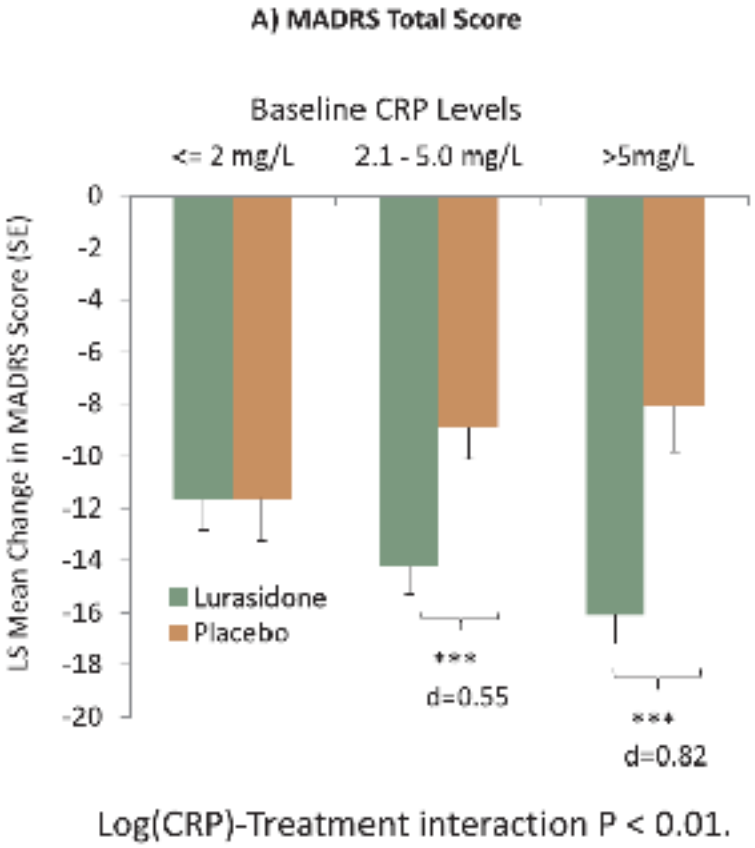


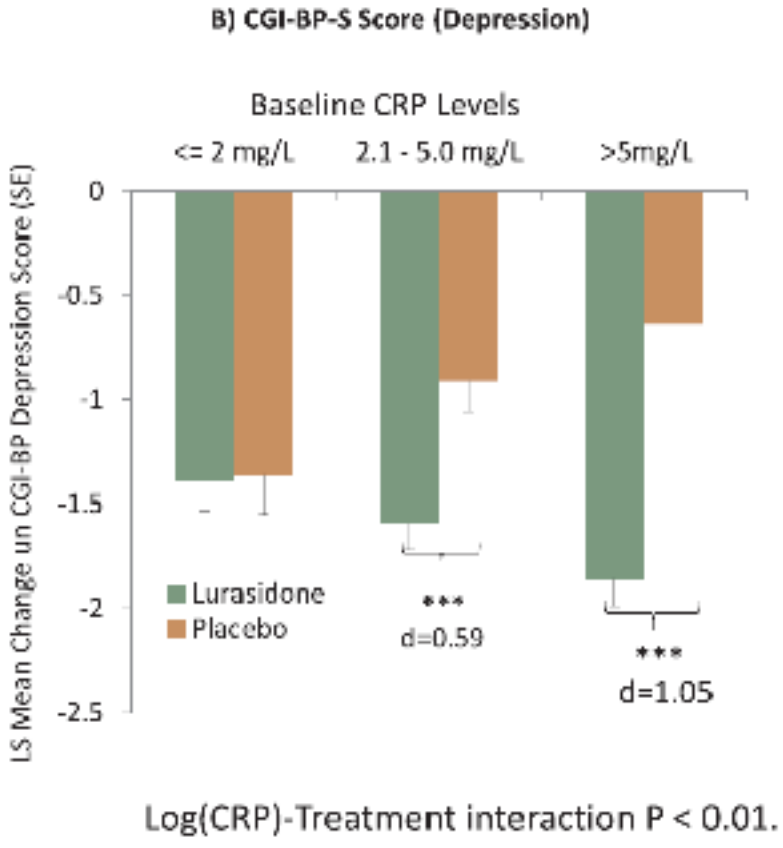
In a multicenter open-label randomized clinical trial. CRP was measured with a high-sensitivity method in serum samples from 241 adult men and women with MDD randomly allocated to 12-week treatment with escitalopram (n=115) or nortriptyline (n=126). CRP level at baseline differentially predicted treatment outcome with the 2 antidepressants (CRP-drug interaction: β = 3.27, 95% CI = 1.65, 4.89). For patients with low levels of CRP (<1 mg/L), improvement on the MADRS score was 3 points higher with escitalopram than with nortriptyline. For patients with higher CRP levels, improvement on the MADRS score was 3 points higher with nortriptyline than with escitalopram. CRP and its interaction with medication explained more than 10% of individual-level variance in treatment outcome.

CO-MED = Combining Medications to Enhance Depression Outcomes; SSRI = selective serotonin reuptake inhibitor.

Uher R, et al. *Am J Psychiatry* 2014;171(12):1278-1286. Jha MK, et al. *Psychoneuroendocrinol* 2017;78:105-113.

CRP Predicts Response to Lurasidone in Bipolar Depression





Serum CRP concentration was measured prior to, and following, 6 weeks of treatment in 485 outpatients with bipolar I depression. Patients were randomized to receive monotherapy with lurasidone 20–60 mg/day (n=161), lurasidone 80–120 mg/day (n=162), or placebo (n=162). Increasing pre-treatment wr-CRP level predicted a larger overall antidepressant response to lurasidone, as well as an increased response for a number of individual depressive symptoms. These moderating effects of pre-treatment wr-CRP remained significant after adjustment for potential confounds (eg, baseline BMI and weight change). Treatment with lurasidone did not affect serum concentrations of CRP compared to placebo.

********P*<.001 for lurasidone vs placebo.**
BMI = body mass index; wr-CRP = wide-ranging CRP.
Raison CL, et al. *Brain Behav Immun*. 2018;73:717-724.

Take Away Points

- The link between inflammation and depression is ancient and may have arisen from enhancing protection against death from infection
- Inflammation causes changes in brain function that predispose to depression.
- However, depression is not an inflammatory condition and reducing inflammation only benefits depressed patients with elevated inflammation
- Inflammatory biomarkers may hold promise for the development of precision medicine approaches to treating depression