Sleep Disturbance, Sleep Duration, and Inflammation: A Systematic Review and Meta-Analysis of Cohort Studies and Experimental Sleep Deprivation

Supplemental Information

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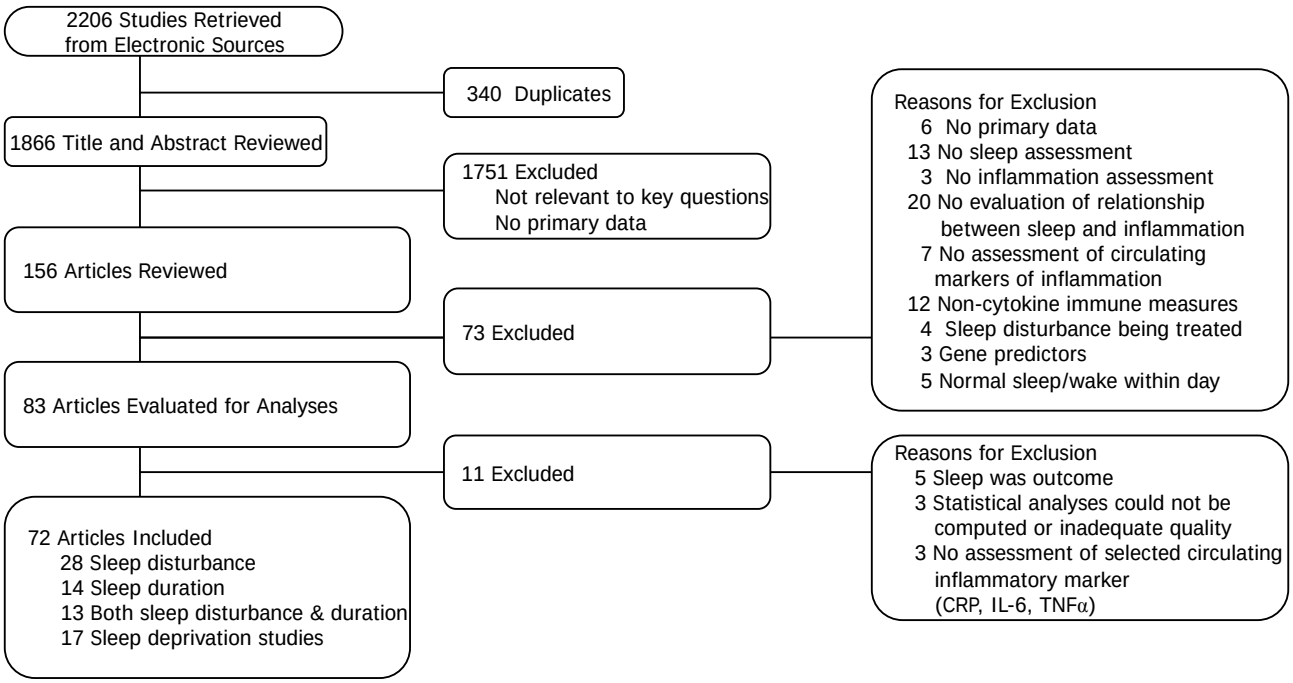

Figure S1. Summary of Literature Search

Table S1. Description of studies evaluating sleep disturbance and inflammation as indexed by C-reactive protein (CRP) and circulating levels of interleukin-6 (IL-6). Sleep disturbance was associated with CRP and IL-6 as a significant increase (+), significant decrease (-) or no difference (0). Sleep disturbance was assessed by single item (Item); symptom reporting (SX); questionnaire (Qu); polysomnography (PSG); or clinical diagnosis (DX).

Study	Design	Sample	N	Age	M/F	Sleep Assessment	Inflammation Assessment	Findings
Afshar et al., 2011 (49)	Experimental	End stage renal disease	28	51.9(20.2)	28/0	Qu	CRP	CRP+
Almeida et al., 2011 (26)	Epidemiologic	Community sample	3906	70-90	3906/0	SX	CRP	CRP 0
Bornivelli et al., 2008 (50)	Naturalistic	End stage renal disease	45	59 (16.2)	32/13	Qu	CRP	CRP+
Bower et al., 2009 (33)	Naturalistic	Breast / prostate cancer	48	62.7 (29-75)	20/28	Qu	CRP/IL-6*	CRP=0/IL-6=0
Bower et al., 2011 (51)	Naturalistic	Breast cancer	103	51.2(32-66)	0/103	Qu	CRP*	CRP 0
Burgos et al., 2006 (34)	Naturalistic	Insomniacs/Healthy controls	22	26-58	4/18	Qu/PSG	IL-6	IL6=+
Chiu et al., 2009 (35)	Naturalistic	End stage renal disease	114	56.8 (11.8)	60/54	Qu	CRP/IL-6/TNF*	CRP+/IL-6=0/TNF=+
Christian, 2011 (36)	Naturalistic	Caregivers/non-caregivers	250	63.8 (13.7)	65/185	Qu	CRP/IL-6	CRP+/IL-6=0
Clevenger et al., 2012 (	Naturalistic	Ovarian cancer	136	60.4(12.39)	0/136	Qu	IL-6	IL-6+
Dowd et al., 2011 (38)	Epidemiologic	>53 yo	1020	66.1 (10.4)	540/480	Qu	CRP/IL-6	CRP 0/IL-6=0
Erten et al., 2005 (20)	Naturalistic	End stage renal disease / Healthy	18	39.4	14/4	SX	IL-6/TNF*	IL-6=0/TNF=+
Friedman et al., 2005 (39)	Naturalistic	Community sample	78	73.4 (6.9)	0/78	Qu/PSG	IL-6	IL-6+
Graff et al., 2011 (52)	Naturalistic	Inflammatory bowel disease	318	43 (14.1)	127/191	Qu	CRP	CRP=0
Heffner et al., 2011 (40)	Naturalistic	Chronic lower back pain/ Healthy	50	30.8(11.4)	20/30	Qu	IL-6	IL-6=0
Heffner et al., 2012 (41)	Naturalistic	Community sample	83	61.2 (8.8)	38/45	Qu	IL-6	IL-6=0
Hong et al., 2005 (21)	Naturalistic	Community sample	70	35.7(7.6)	36/34	PSG	IL-6	IL-6=0
Jackowska et al.,2013(27)	Epidemiologic	Community sample	2916	65.9	2916	SX	CRP	Mixed
Laugsand et al., 2012 (28)	Epidemiologic	Community sample	8547	43.4 - 53.7	3266/3744	SX	CRP	CRP+
Lavie et al., 2007 (29)	Case Control	Shift workers	129	56.3 (8.5)	129/0	SX	CRP	CRP-
Lee, et al., 2009 (22)	Naturalistic	End stage renal disease	30	56.1 (10.7)	21/9	PSG	CRP/IL-6	CRP=0/IL-6=0
Li et al., 2012 (53)	Naturalistic	End stage renal disease	212	49.9 (16.7)	114/98	Qu	CRP	CRP+

*Studies that have evaluated sleep disturbance and inflammation as indexed by other cytokines including interleukin-1β (IL-1) (*n* = 4) (1-4); IL-1 receptor antagonist (IL-1ra) (*n* = 3) (1, 2, 5); soluble IL-6 receptor (sIL6R) (*n* = 2) (5, 6); IL-8 (*n* = 5), tumor necrosis factor receptor I (TNFRI) (*n* = 1) (7); and TNFRII (*n* = 1) (1).

See references in main text for studies described in the table.

Table S1 continued.

Study	Design	Sample	N	Age	M/F	Sleep Assessment	Inflammation Assessment	Findings
Liukkonen et al., 2007(30)	Epidemiologic	Community cohort	4011	31	2104/1907	SX	CRP	CRP+
Matthews et al., 2010(54)	Epidemiologic	Community sample	340	52 (IQR 3)	0/340	Qu/PSG	CRP	CRP+
McDade et al., 2006(31)	Naturalistic	Community sample	188	59.5(4.3)	45/55	Qu	CRP	CRP=0
Mills et al., 2007 (23)	Naturalistic	Community sample	124	38.6 (6.8)	59/65	Qu	IL-6	IL-6+
Okun et al., 2007a (63)	Naturalistic	Pregnant	35	31.0 (3.7)	0/35	Qu	CRP/IL-6/TNF*	CRP 0/IL-6=0/TNF+
Okun et al., 2009 (42)	Naturalistic	Healthy controls	43	28.2(5.2)	0/43	Qu	CRP/IL-6/TNF*	CRP +/IL-6=0/TNF=0
Okun et al., 2011 (58)	Naturalistic	4 groups	128	74.3 (6.6)	54/74	DX	IL-6	IL-6=0
Prather et al., 2009 (44)	Prospective	Hepatitis C	95	47.3 (11.8)	64/31	Qu	IL-6	IL-6=0
Razeghi et al., 2012(55)	Epidemiologic	End stage renal disease	108	56 (15)	62/46	Qu/DX	CRP	CRP+
Song et al., 1998 (59)	Experimental	3 groups	24	42.3	15/9	DX	IL-6*	IL-6+
Sabbagh et al., 2008 (56)	Epidemiologic	End stage renal disease	46	61.9(16.9)	30/16	Qu	CRP	CRP=0
Sprod et al., 2010 (4)	Experimental	Breast/Prostate cancer	38	60(12.1)	11/27	Qu	IL-6/TNF*	IL-6=0/TNF=0
Suarez, 2008 (45)	Epidemiologic	Community sample	210	28.9 (9.7)	115/95	Qu	CRP/IL-6	CRP=0/IL-6=0
Valentine et al., 2009 (57)	Epidemiologic	Community sample 60+	127	70.5 (5)	47/80	Qu	CRP	CRP=0
Valentine et al., 2011 (46)	Epidemiologic	Community sample 60+	182	69.2(6.7)	98/84	Qu	CRP/IL-6*	CRP+/IL-6=0
van Mark et al., 2010 (47)	Experimental	Shift/daytime workers	274	37.8 (8.7)	NA	Qu	IL-6/TNF	IL-6=0/TNF=0
Vgontzas et al., 2002 (60)	Experimental	Insomnia/controls	22	29.4(6.6)	14/8	DX/PSG	IL-6/TNF	IL-6=0/TNF-
von Kanel et al., 2006(25)	Experimental	Caregivers/non-caregivers	100	70.7 (7.9)	30/70	PSG	IL-6	IL-6+
von Kanel et al., 2010 (48)	Experimental	Caregivers/non-caregivers	145	70.9(8.1)	104/41	Qu/PSG	CRP/IL-6	CRP=0/IL-6=0
Zhang et al., 2013 (32)	Epidemiologic	National sample	10908	20-85+	5295/5613	SX	CRP	CRP+

*Studies that have evaluated sleep disturbance and inflammation as indexed by other cytokines including interleukin-1β (IL-1) (*n* = 4) (1-4); IL-1 receptor antagonist (IL-1ra) (*n* = 3) (1, 2, 5); soluble IL-6 receptor (sIL6R) (*n* = 2) (5, 6); IL-8 (*n* = 5), tumor necrosis factor receptor I (TNFRI) (*n* = 1) (7); and TNFRII (*n* = 1) (1).

See references in main text for studies described in the table.

Table S2. Description of studies evaluating sleep duration and inflammation as indexed by C-reactive protein (CRP) and circulating levels of interleukin-6 (IL-6). Sleep duration was associated with CRP and IL-6 as a significant increase (+), significant decrease (-) or no difference (0). Sleep duration was assessed by single item (Item); symptom reporting (SX); questionnaire (Qu); polysomnography (PSG); or clinical diagnosis (DX).

Study	Design	Sample	N	Age	M/F	Sleep Assessment	Inflammation Assessment	Findings
Burgos et al., 2006 (34)	Naturalistic	Insomniacs/Healthy controls	22	26-58	4/18	Qu/PSG	IL-6	IL6 mixed
Dowd et al., 2011 (38)	Epidemiologic	>53 yo	1020	66.1 (10.4)	540/480	Item/Qu	CRP/IL-6	Mixed
Ferrie et al., 2013 (71)	Epidemiologic	Civil service	5003	49.3	3592/1411	Item	CRP/IL-6	CRP+/IL6+
Friedman et al., 2005 (39)	Naturalistic	Community sample	78	73.4 (6.9)	0/78	Qu/PSG	IL-6	IL-6=0
Hong et al., 2005 (21)	Naturalistic	Community sample	70	35.7(7.6)	36/34	PSG	IL-6	IL-6 mixed
Jackowska et al., 2013(27)	Epidemiologic	Community sample	2916	65.9	2916	Item	CRP	CRP mixed
Larkin et al., 2005 (70)	Naturalistic	Adolescents(13-18) w/wo SDB	143	13.8(0.8)	72/71	Item/PSG	CRP	CRP +
Lee et al., 2009 (22)	Naturalistic	End stage renal disease	30	56.1 (10.7)	21/9	PSG	CRP/IL-6	CRP=0/IL-6+
Marsland et al., 2008 (61)	Naturalistic	Community sample	76	45(6.5)	32/44	Item	IL-6	IL-6=0
Martinez-Gomez, 2011 (62)	Naturalistic	Adolescents (13-17)	183	14.8 (1.3)	95/88	Item	CRP/IL-6	CRP+/IL-6=0
Matthews et al., 2010 (54)	Epidemiologic	Community sample	340	52 (IQR 3)	0/340	Qu/PSG	CRP	CRP mixed
McDade et al., 2006 (31)	Naturalistic	Community sample	188	59.5(4.3)	45/55	Qu	CRP	CRP=0
Miller et al., 2009 (71)	Epidemiologic	Civil service	4624	49.1(5.9)	3382/0	Item	CRP/IL-6	CRP+/IL-6+
Motivala et al., 2005 (67)	Case Control	Depression/controls	40	42.6(8.3)	40/0	PSG	IL-6*	IL-6=0
Okun et al., 2007a (63)	Naturalistic	Pregnant	35	31.0 (3.7)	0/35	Qu	CRP/IL-6/TNF*	CRP=0/IL-6=0/TNF=0
Okun et al., 2009 (42)	Naturalistic	Healthy controls	43	28.2(5.2)	0/43	Qu	CRP/IL-6/TNF*	CRP=0/IL-6=0/TNF=0
Patel et al., 2009 (73)	Epidemiologic	OSA and non-OSA	614	46.1(14.4)	275/339	Item/PSG	CRP/IL-6/TNF*	Mixed
Ramey et al., 2012 (64)	Epidemiologic	Police officers (shift work)	85	39.6 (9.0)	85/0	Item/Qu	CRP	CRP-
Rief et al., 2010 (68)	Naturalistic	Community sample	130	34.9(9.6)	74/56	Qu/PSG	CRP/IL-6*	CRP=0/IL-6=0
Sprod et al., 2010 (24)	Experimental	Breast/Prostate cancer	38	60(12.1)	11/27	Qu	IL-6/TNF	IL-6 -
Suarez, 2008 (45)	Epidemiologic	Community sample	210	28.9 (9.7)	115/95	Qu	CRP/IL-6	CRP=0/IL-6=0
Stenholm et al., 2011(74)	Epidemiologic	>=65	751	72.9 (6.0)	335/416	Item	CRP/IL-6/TNF	Mixed
Taheri et al., 2007 (65)	Epidemiologic	Community sample	907	52.5(8.1)	500/407	Item/PSG	CRP	CRP=0/TNF=0
Taveras et al., 2011 (66)	Epidemiologic	Post-partum females	479	37.8(5.1)	0/479	Item	CRP/IL-6	CRP=0/IL-6=0
Tuomilehto et al., 2009 (75)	Experimental	Overweight with IGT	515	55(7)	230/285	Item	CRP/IL-6	CRP+/IL-6=0
Vgontzas et al., 1997 (69)	Experimental	4 groups	41	33.1(2.5)	31/10	PSG	IL-6/TNF*	IL-6+/TNF+
von Kanel et al., 2006 (25)	Experimental	Caregivers/non-caregivers	100	70.7 (7.9)	30/70	PSG	IL-6	IL-6=0

*Studies that have evaluated sleep duration and inflammation as indexed by other cytokines including interleukin-1β (IL-1) (*n* = 2) (8, 9), IL-1 receptor antagonist (IL-1ra) (*n* = 0), soluble IL-6 receptor (sIL6R) (*n* = 1) (10); IL-8 (*n* = 0); tumor necrosis factor receptor I (TNFRI) (*n* = 1) (11); and TNFRII (*n* = 0).

See references in main text for studies described in the table.

Table S3. Description of studies evaluating sleep duration as experimentally shortened, i.e., sleep deprivation or sleep restriction, and inflammation as indexed C-reactive protein (CRP) and circulating levels of interleukin-6 (IL-6). Sleep deprivation as partial night sleep deprivation (PSD) or total night sleep deprivation (TSD) was associated with CRP and IL-6 as a significant increase (+), significant decrease (-) or no difference (0).

Study	Sleep deprivation	Sample	N	Age	M/F	Inflammation Assessment	Findings
Abedelmalek et al., 2012 (82)	PSD	Tunisian athletes	12	21.2 (1.2)	12/0	IL-6	IL-6+
Bollinger et al., 2010 (83)	TSD	German	6	21-32	6/0	IL-6/TNF*	IL-6=0/TNF=0
Chennaoui et al., 2011 (78)	TSD	French	12	29.1(3.3)	12/0	CRP/IL-6/TNF*	CRP=0/IL-6=0/TNF=0
Faraut et al., 2011 (79)	PSD/napping	Belgian	40	18-27	40/0	CRP*	CRP=0
Frey et al., 2007 (80)	TSD		19	28.1(8.6)	10/9	CRP/IL-6*	CRP=0/IL-6=0
Haack et al., 2002 (84)	TSD	German	12	28.1(4.6)	12/0	IL-6	IL-6=0
Haack et al., 2007 (89)	PSD 12 days		18	27.3(5.8)	12/6	CRP/IL-6	CRP=0/IL-6=0
Irwin et al., 2004 (85)	PSD	Alcoholics, controls	50	40.6 (7.7)	50/0	IL-6/TNF	IL-6=0/TNF=0
Meier-Ewert et al., 2004 (90)	TSD/PSD		10	27.2	10/0	CRP	CRP=0
Redwine et al., 2000 (86)	PSD		31	35.8 (10.1)	31/0	IL-6	IL-6=0
Sauvet et al., 2010 (81)	TSD	French	12	29.1(3.3)	12/0	CRP/IL-6/TNF*	CRP=0/IL-6=0/TNF=0
Schmid et al., 2011 (92)	PSD	German/Swiss	15	27.1(1.3)	15/0	IL-6	IL-6=0
Shearer et al., 2001 (93)	TSD		21	28.7 (21-47)	21/0	IL-6/TNF*	IL-6=0/TNF=0
van Leeuwen et al., 2009 (91)	PSD	Finnish	19	23.1(2.5)	19/0	CRP	CRP=0
Vgontzas et al., 1999 (87)	TSD		8	23.6(1.0)	8/0	IL-6	IL-6=0
Vgontzas et al., 2004 (94)	PSD		25	25.2 (3.7)	12/13	IL-6/TNF	IL-6=0/TNF=0
Vgontzas et al., 2007 (88)	TSD		41	23.3 (0.7)	20/21	IL-6/TNF*	IL-6=0

*Studies that have evaluated sleep duration as experimentally shortened and inflammation as indexed by other cytokines including interleukin-1β (IL-1) (*n* = 2) (12, 13), IL-1 receptor antagonist (IL-1ra) (*n* = 1) (12), soluble IL-6 receptor (sIL6R), IL-8 (*n* = 1) (14); tumor necrosis factor receptor I (TNFRI) (*n* = 1) (15-17), and TNFRII (*n* = 1) (16).

See references in main text for studies described in the table.

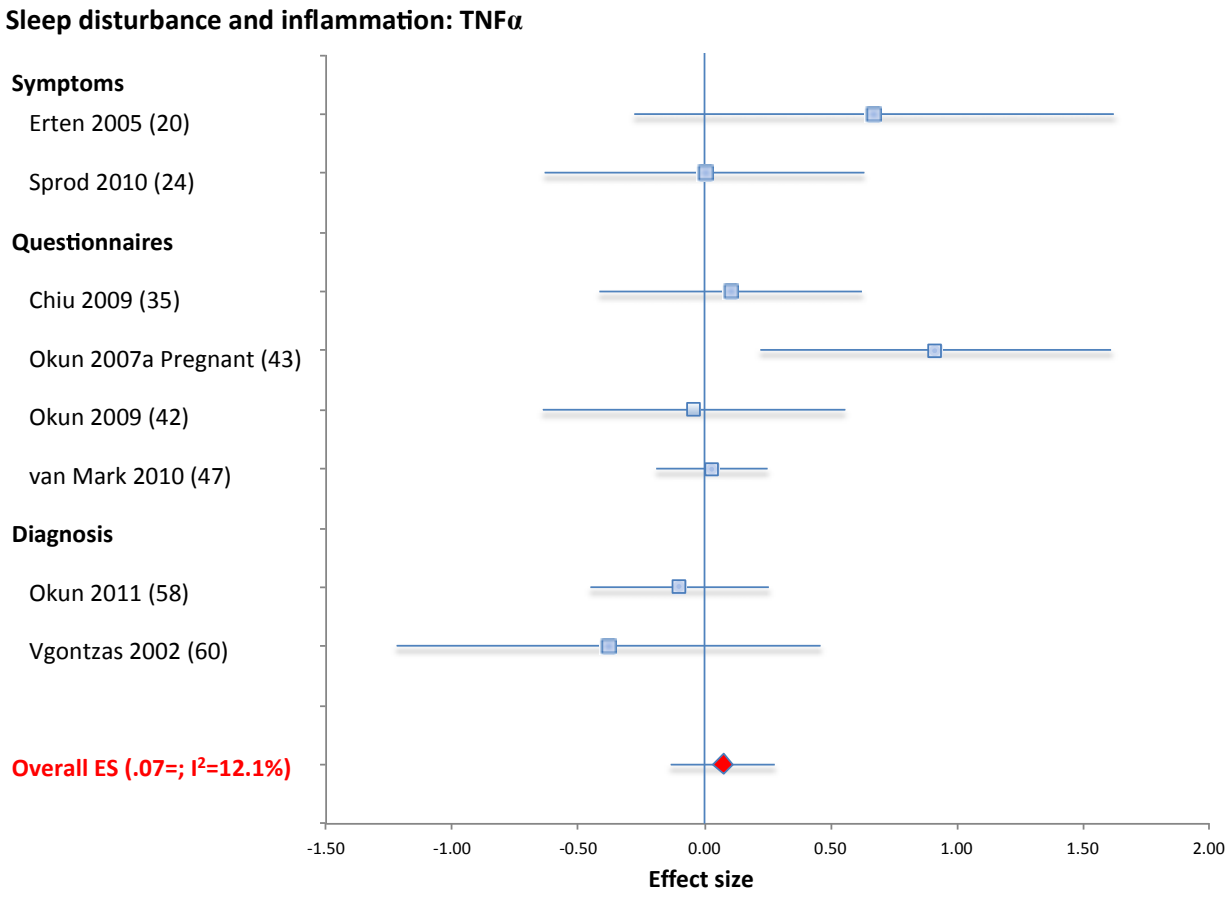

Figure S2. Forest plot of sleep disturbance associated with inflammation as indexed by circulating levels of tumor necrosis factor (TNF)-α. Sleep disturbance is assessed by self-reported symptoms and questionnaires. Results are expressed as effect sizes (ES) and 95% confidence intervals (95% CI). See references in main text for studies included in the figure.

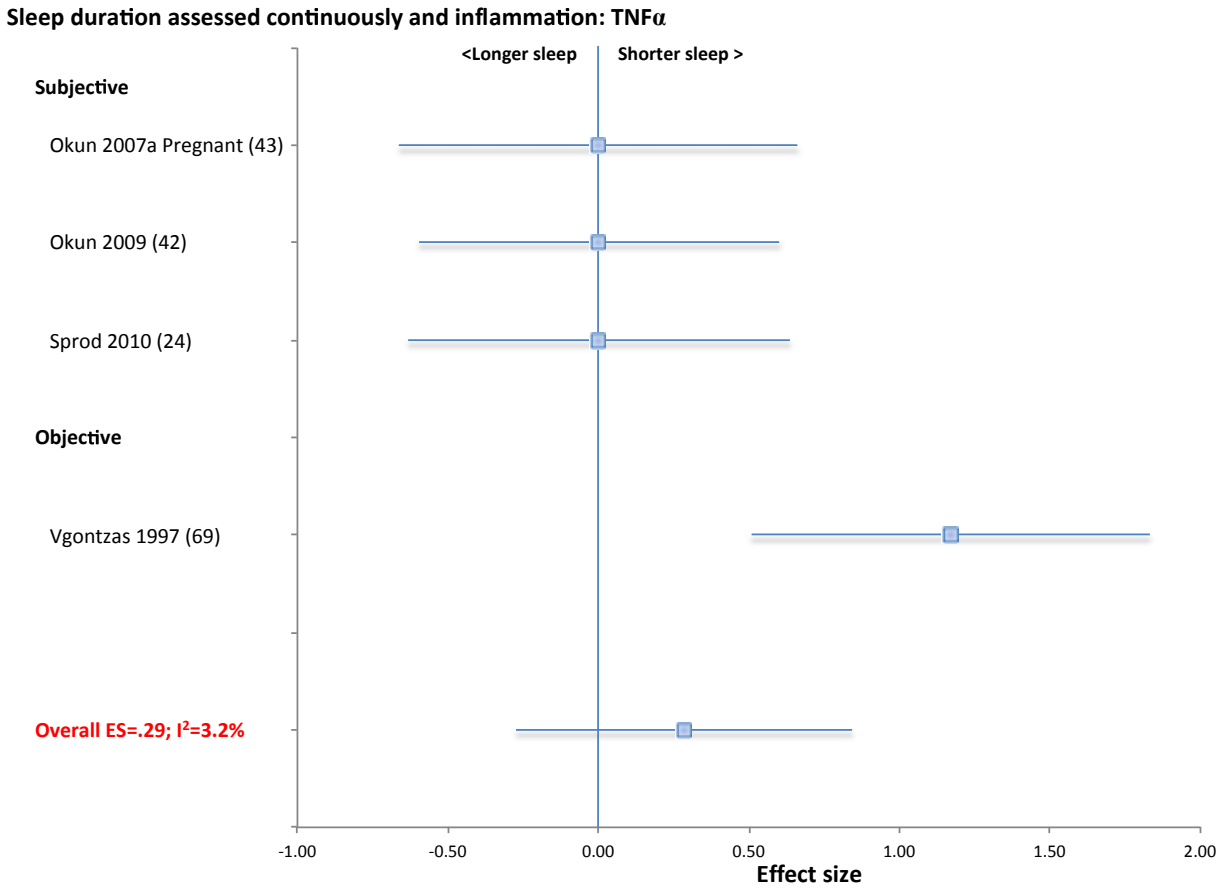

Figure S3. Forest plot of sleep duration associated with inflammation as indexed by circulating levels of tumor necrosis factor-α. Sleep duration is assessed continuously by subjective and objective measures. Results are expressed as effect sizes (ES) and 95% confidence intervals (95% CI). See references in main text for studies included in the figure.

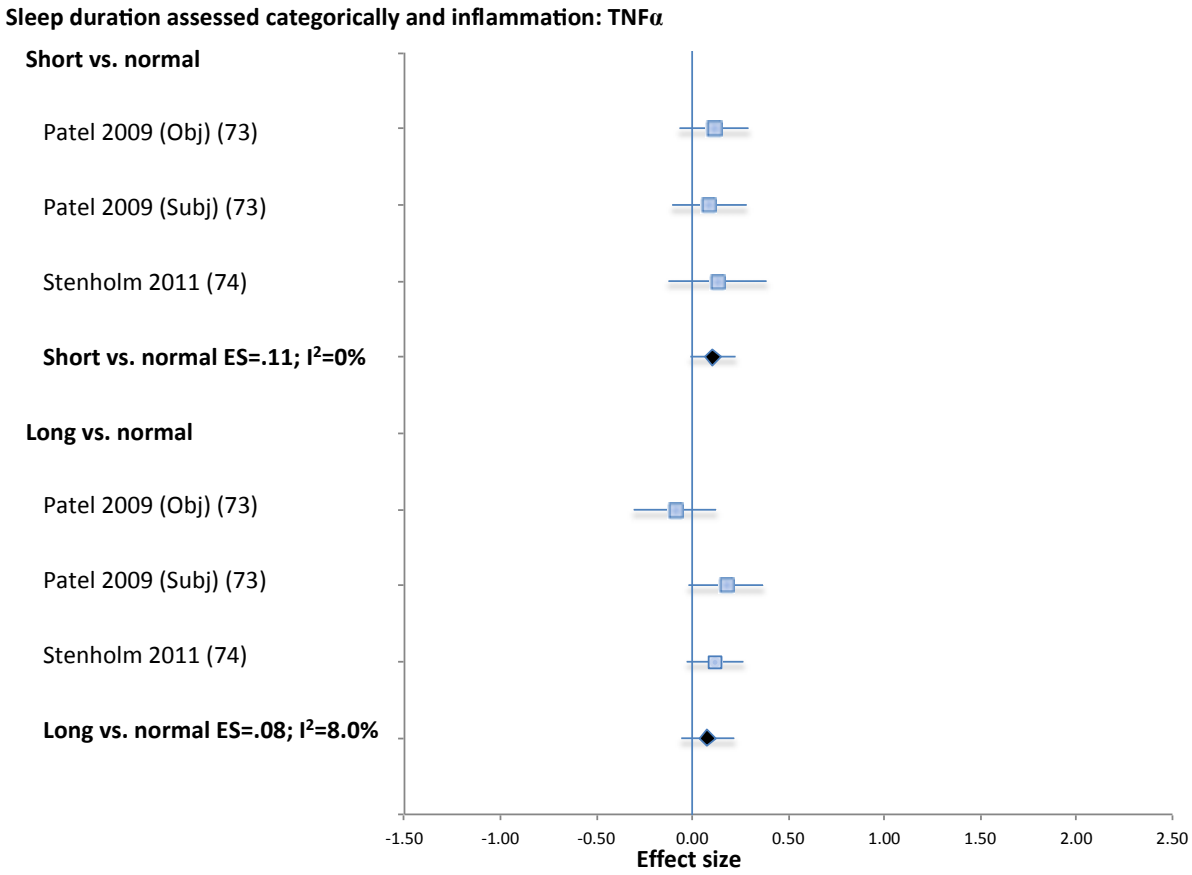

Figure S4. Forest plot of sleep duration associated with inflammation as indexed by circulating levels of tumor necrosis factor-α. Sleep duration is assessed categorically with normal sleep being defined by sleep duration 7-8 h per night, and short sleep as < 7 h per night, and long sleep as > 8 h per night. Results are expressed as effect sizes (ES) and 95% confidence intervals (95% CI). See references in main text for studies included in the figure.

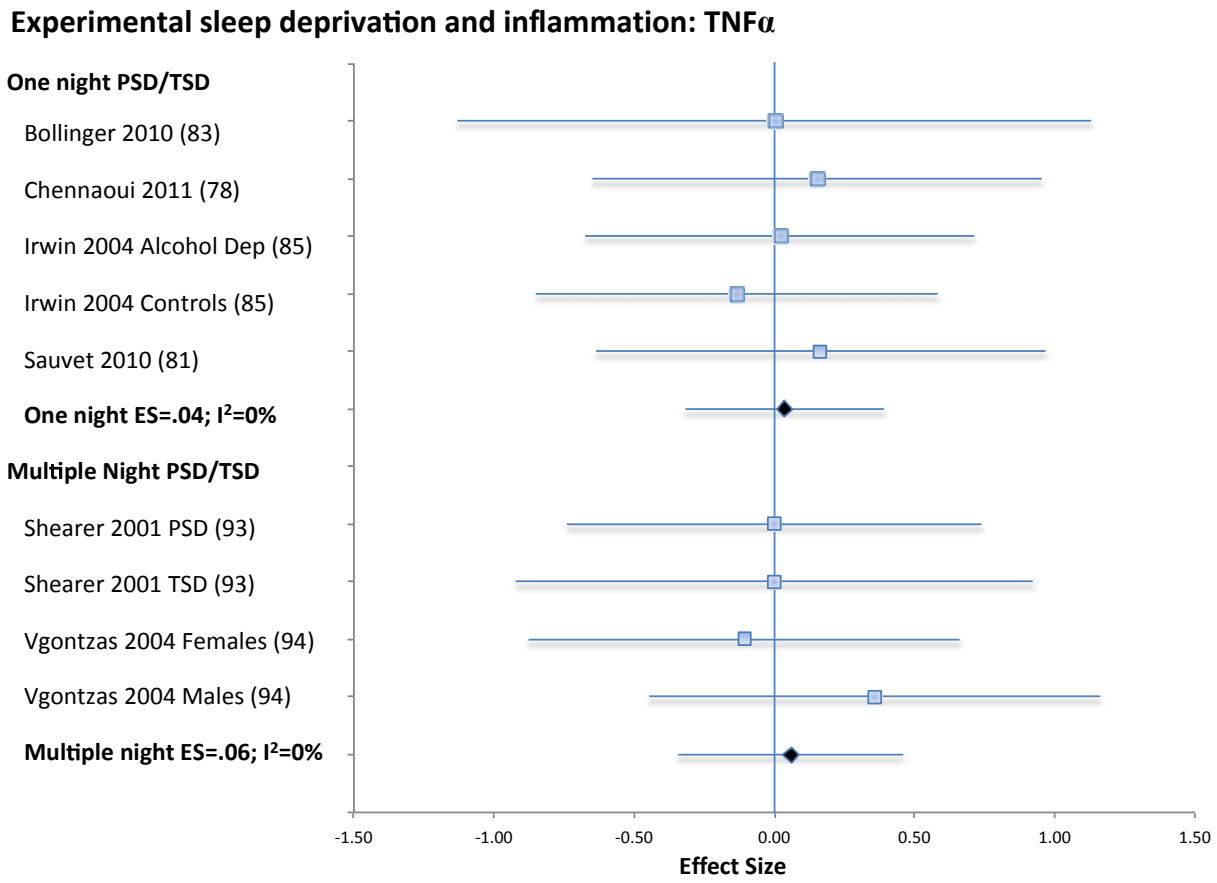

Figure S5. Forest plot of experimentally shortened sleep duration associated with inflammation as indexed by circulating levels of tumor necrosis factor-α. Sleep duration was shortened by either partial- or total night sleep deprivation for one night or for multiple nights. Results are expressed as effect sizes (ES) and 95% confidence intervals (95% CI). See references in main text for studies included in the figure.

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