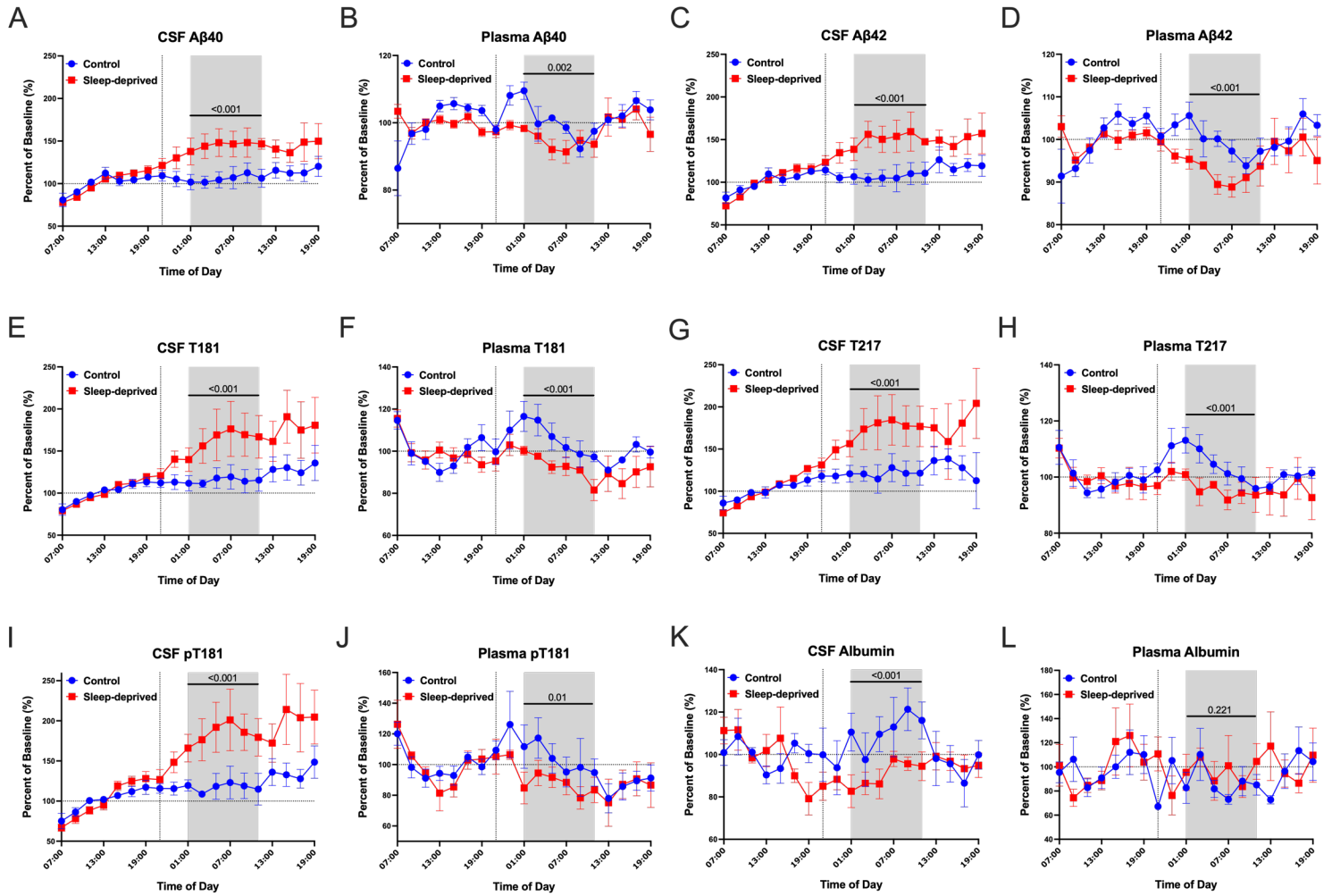
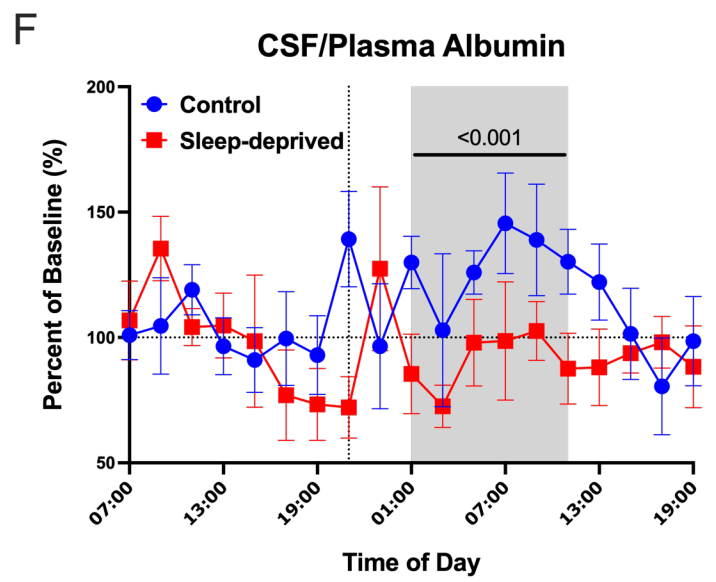
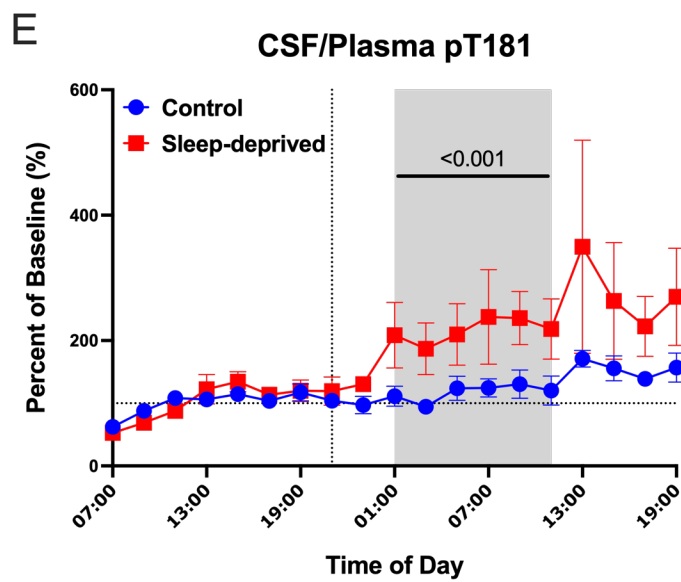
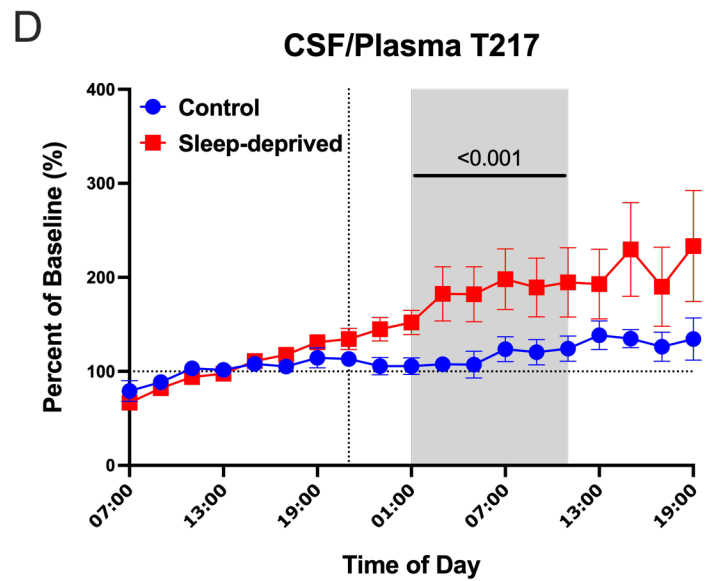
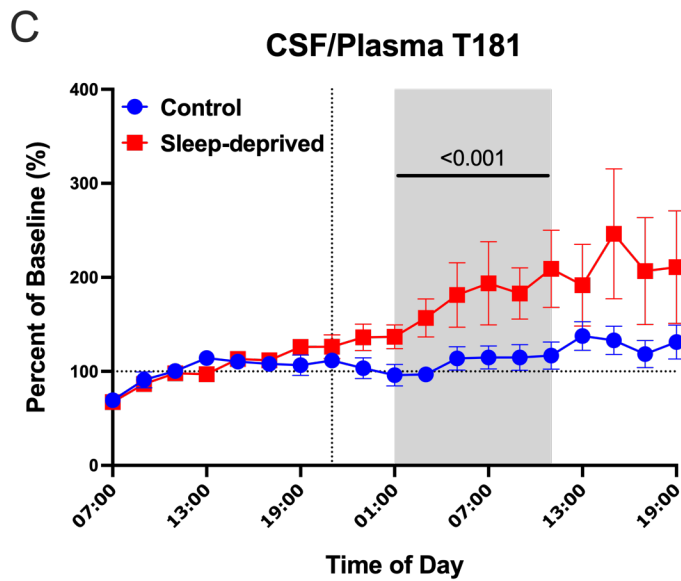
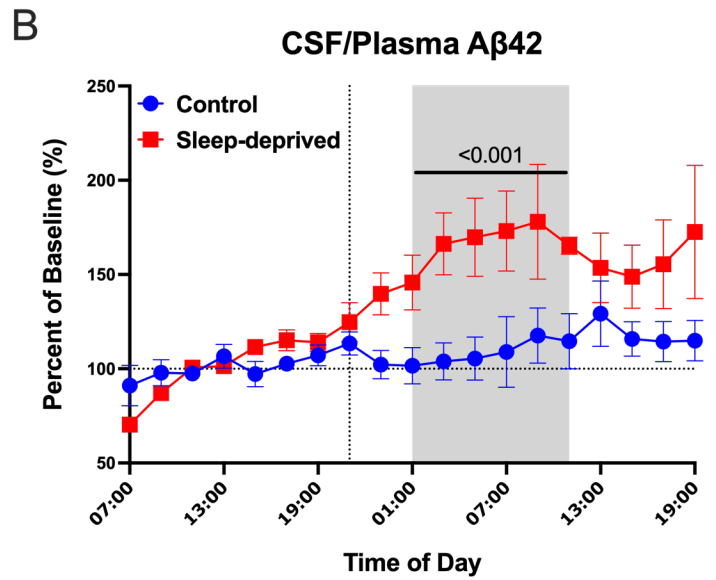
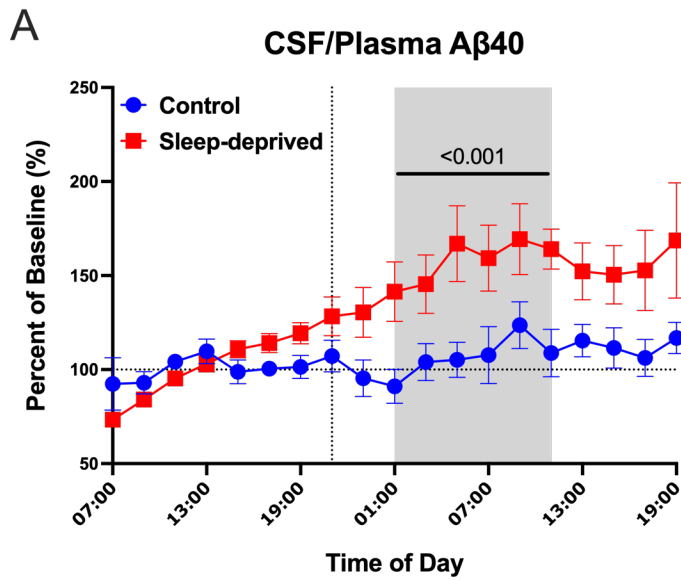


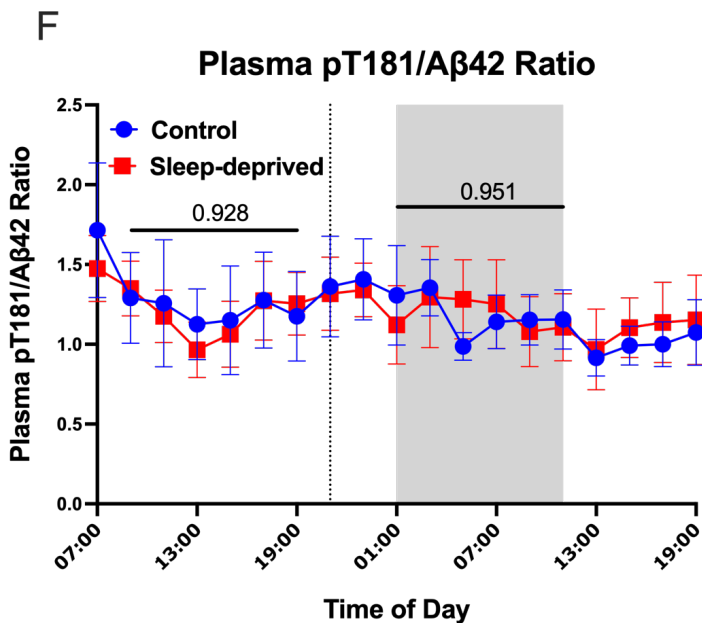
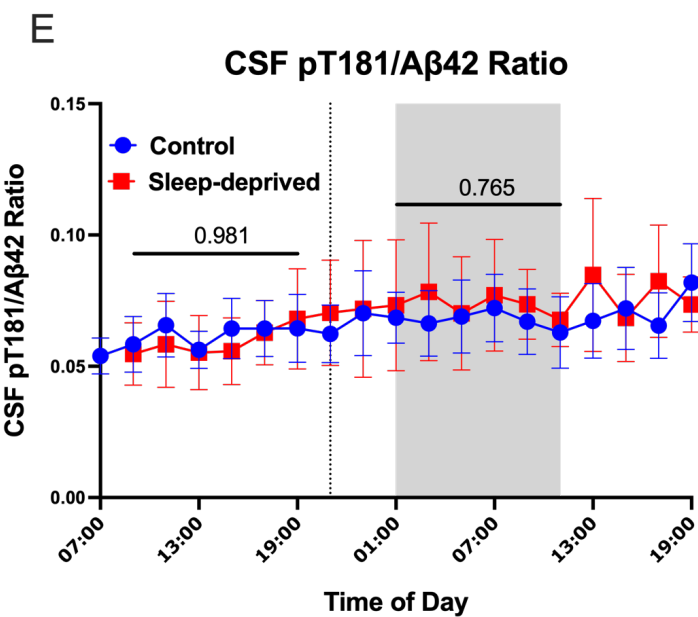
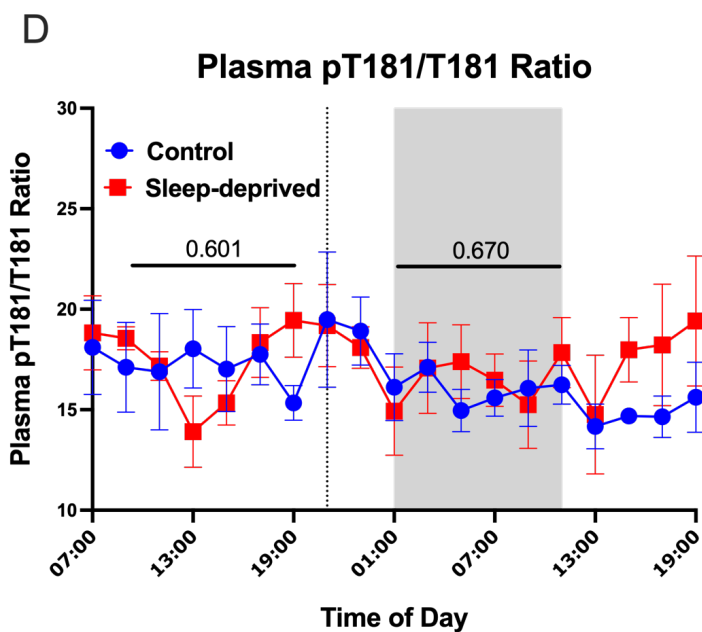
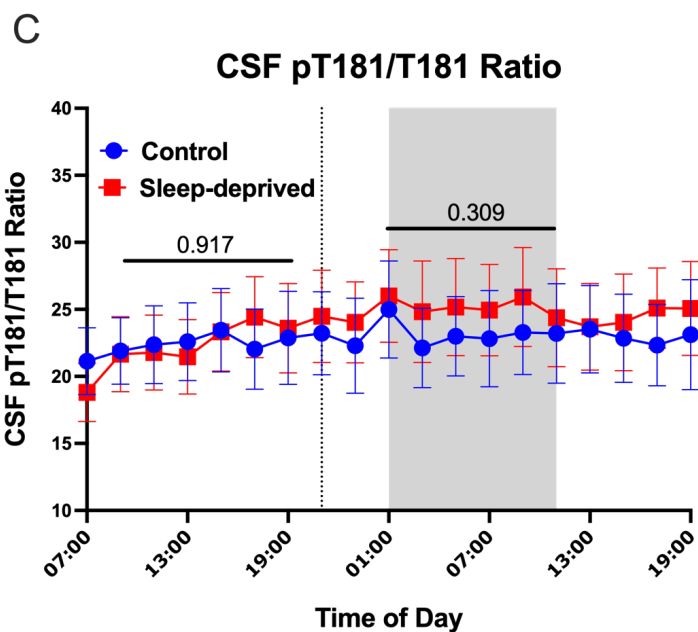
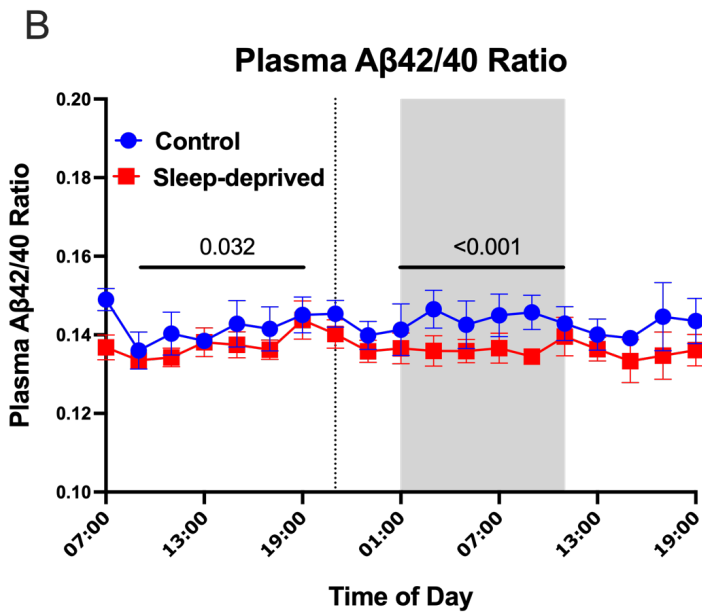
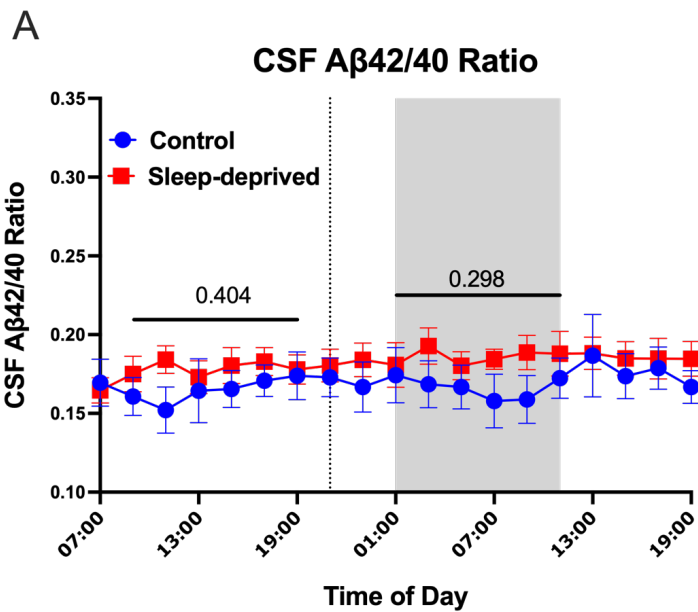
Supplementary Figure 1: Sleep loss decreases plasma but increases CSF AD biomarkers. Mean overnight A β , tau and phosphorylated tau (p-tau) concentration normalized to a baseline of the average concentrations over hours 0-12 (07:00-19:00) in cerebrospinal fluid (CSF) and plasma. Sleep deprivation increased overnight A β ₄₀, A β ₄₂, T181, T217, and pT181 levels by 35-65% from baseline during sleep deprivation compared with controls. In plasma, sleep deprivation decreased overnight A β ₄₀, A β ₄₂, T181, T217, and pT181 by 5-15% in plasma compared to participants in the control group (A-J). The overnight albumin level in CSF decreased ~20% from baseline during sleep deprivation, but in plasma was not significantly different in the sleep-deprived group compared with the control (K, L). The overnight period during the intervention night was defined as hours 18 to 28 (01:00–11:00) to account for the transit time of CSF from the brain to the lumbar catheter (shaded area). Blue: control; Red: sleep-deprived; Error bars indicate standard error. The vertical dashed line is the intervention start time. The horizontal dashed line is at 100% of baseline. P-values are shown.



Supplementary Figure 2: Blood-CSF transport impaired by sleep loss. CSF/Plasma Protein Ratio normalized to a baseline of the average ratio over hours 0-12 (07:00-19:00). The CSF/plasma ratio increased for A β 40, A β 42, T181, T217, and pT181 during the overnight period in the sleep-deprived group compared with the control (A-E). The CSF/plasma albumin ratio, a marker of blood-CSF permeability, was decreased overnight during sleep deprivation (F). The overnight period during the intervention night was defined as hours 18 to 28 (01:00–11:00). Blue: control; Red: sleep-deprived; Error bars indicate standard error. The vertical dashed line is the intervention start time. The horizontal dashed line is at time 0. P-values are shown.



Supplementary Figure 3: No effect of sleep on Alzheimer's disease biomarker ratios. Both daytime and overnight A β 42/40 ratios were not significantly different between the sleep-deprived and control groups in CSF, but they did differ in plasma (A, B). The CSF A β 42/40 ratio for one participant's time course under the control condition was abnormally high compared to the same participant's time course under the sleep-deprived condition and was excluded. Although plasma A β 42/40 ratios were higher in the control group than the sleep-deprived group, there were no evidence of an effect from sleep loss. Both day and night ratios of pT181/T181 and pT181/ A β 42 in CSF and plasma were not significantly different between groups (C-F). The overnight period during the intervention night was defined as hours 18 to 28 (01:00–11:00) (Shaded area). The day period was defined as 09:00 – 19:00. Blue: control; Red: sleep-deprived; Error bars indicate standard error. The vertical dashed line is the intervention start time. P-values are shown.



Supplementary Table 1: Mixed Model Results for Differences in Daytime (09:00 – 19:00) CSF and Plasma Alzheimer Disease Biomarker Ratios: A β 42/40, pT181/T181, and pT181/A β 42

CSF and Plasma AD Biomarker Ratios					
Biomarker Ratio	Factor	Pairwise Comparison	Mean Difference (95% CI)	F (df)	p
CSF A β 42/40	Intervention	Sleep-deprived vs. Control	+0.014 (-0.024, 0.052)	0.789 (1,7)	0.404
	Time of day			1.843 (5,35)	0.130
	Intervention x time			2.560 (5,35)	0.045
Plasma A β 42/40	Intervention	Sleep-deprived vs. Control	-0.003 (-0.007, -0.0003)	4.88 (1,44)	0.032
	Time of day			2.84 (5,44)	0.026
	Intervention x time			0.40 (5,44)	0.847
CSF pT181/T181	Intervention	Sleep-deprived vs. Control	+0.173 (-3.141, 3.488)	0.01 (1,44)	0.917
	Time of day			0.13 (5,44)	0.984
	Intervention x time			0.10 (5,44)	0.993
Plasma pT181/T181	Intervention	Sleep-deprived vs. Control	+0.360 (-1.018, 1.739)	0.28 (1,43)	0.601
	Time of day			0.70 (5,43)	0.624
	Intervention x time			1.97 (5,43)	0.103
CSF pT181/ A β 42	Intervention	Sleep-deprived vs. Control	-0.0005 (-0.044, 0.043)	0.001 (1,8)	0.981
	Time of day			2.579 (5,40)	0.041
	Intervention x time			1.015 (5,40)	0.422
Plasma pT181/ A β 42	Intervention	Sleep-deprived vs. Control	-0.033 (-0.841, 0.775)	0.009 (1,8)	0.928
	Time of day			3.228 (5,40)	0.015
	Intervention x time			0.656 (5,40)	0.659

CSF = cerebrospinal fluid; A β = amyloid- β ; T181 = unphosphorylated tau-181; T217 = unphosphorylated tau-217; pT181 = phosphorylated tau-181; CI = confidence intervals; df = degrees of freedom

Supplementary Table 2: Mixed Model Results for Differences in Overnight (21:00 – 11:00) CSF and Plasma Alzheimer Disease Biomarker Ratios: A β 42/40, pT181/T181, and pT181/A β 42

CSF and Plasma AD Biomarker Ratios					
Biomarker Ratio	Factor	Pairwise Comparison	Mean Difference (95% CI)	F (df)	p
CSF A β 42/40	Intervention	Sleep-deprived vs. Control	+0.011 (0.002, 0.021)	5.54 (1,52.00)	0.022
	Time of day			0.219 (7,50.92)	0.979
	Intervention x time			0.450 (7,50.92)	0.866
Plasma A β 42/40	Intervention	Sleep-deprived vs. Control	-0.007 (-0.009, -0.004)	32.34 (1,60.00)	<0.001
	Time of day			0.862 (7,60.00)	0.542
	Intervention x time			0.801 (7,60.00)	0.590
CSF pT181/T181	Intervention	Sleep-deprived vs. Control	+1.857 (-1.407, 5.121)	1.30 (1,60.00)	0.260
	Time of day			0.098 (7,60.00)	0.998
	Intervention x time			0.021 (7,60.00)	0.999
Plasma pT181/T181	Intervention	Sleep-deprived vs. Control	+0.070 (-1.274, 1.414)	0.011 (1,58.99)	0.917
	Time of day			2.04 (7,58.99)	0.065
	Intervention x time			0.308 (7,58.99)	0.948
CSF pT181/ A β 42	Intervention	Sleep-deprived vs. Control	+0.007 (-0.008, 0.022)	0.884 (1,59.05)	0.351
	Time of day			0.067 (7,59.05)	0.999
	Intervention x time			0.085 (7,59.05)	0.999
Plasma pT181/ A β 42	Intervention	Sleep-deprived vs. Control	-0.033 (-0.141, 0.074)	0.390 (1,59.00)	0.535
	Time of day			1.64 (7,59.00)	0.143
	Intervention x time			0.405 (7,59.00)	0.896

CSF = cerebrospinal fluid; A β = amyloid- β ; T181 = unphosphorylated tau-181; T217 = unphosphorylated tau-217; pT181 = phosphorylated tau-181; CI = confidence intervals; df = degrees of freedom

Supplementary Table 3: Mixed Model Results for Change in Overnight (01:00–11:00) CSF and Plasma A β , Tau, Phosphorylated Tau, and Albumin from Baseline

CSF					
Biomarker	Factor	Pairwise Comparison	Mean Difference (95% CI)	F (df)	p
A β 40, % baseline	Intervention	Sleep-deprived vs. Control	+38.631 (27.368, 49.894)	47.84 (1,42.99)	<0.001
	Time of day			0.302 (5,42.99)	0.909
	Intervention x time			0.077 (5,42.99)	0.995
A β 42, % baseline	Intervention	Sleep-deprived vs. Control	+43.324 (29.949, 56.698)	42.68 (1,43)	<0.001
	Time of day			0.249 (5,43)	0.938
	Intervention x time			0.333 (5,43)	0.890
T181, % baseline	Intervention	Sleep-deprived vs. Control	+48.022 (32.875, 63.168)	40.83 (1,44)	<0.001
	Time of day			0.740 (5,44)	0.598
	Intervention x time			0.334 (5,44)	0.890
T217, % baseline	Intervention	Sleep-deprived vs. Control	+53.910 (41.102, 66.718)	71.96 (1,44)	<0.001
	Time of day			0.534 (5,44)	0.750
	Intervention x time			0.421 (5,44)	0.832
pT181, % baseline	Intervention	Sleep-deprived vs. Control	+66.185 (48.835, 83.535)	59.10 (1,44)	<0.001
	Time of day			0.529 (5,44)	0.753
	Intervention x time			0.264 (5,44)	0.930
Albumin, % baseline	Intervention	Sleep-deprived vs. Control	-20.796 (-30.298, -11.295)	19.6 (1,44)	<0.001
	Time of day			1.22 (5,44)	0.315
	Intervention x time			0.311 (5,44)	0.903
Plasma					
Biomarker	Factor	Pairwise Comparison	Mean Difference (95% CI)	F (df)	p
A β 40, % baseline	Intervention	Sleep-deprived vs. Control	-5.48 (-8.898, -2.062)	10.44 (1,44)	0.002
	Time of day			3.1 (5, 44)	0.018
	Intervention x time			1.4 (5,44)	0.243
A β 42, % baseline	Intervention	Sleep-deprived vs. Control	-6.980 (-10.394, -3.566)	16.98 (1,44)	<0.001
	Time of day			1.99 (5,44)	0.099
	Intervention x time			0.67 (5,44)	0.649
T181, % baseline	Intervention	Sleep-deprived vs. Control	-13.31 (-18.717, -7.899)	24.62 (1,43.13)	<0.001
	Time of day			4.76 (5,43.12)	0.001
	Intervention x time			0.387 (5,43.12)	0.855
T217, % baseline	Intervention	Sleep-deprived vs. Control	-8.604 (-13.058, -4.151)	15.16 (1,44)	<0.001
	Time of day			2.84 (5,44)	0.026
	Intervention x time			0.766 (5,44)	0.579
pT181, % baseline	Intervention	Sleep-deprived vs. Control	-16.694 (-29.186, -4.203)	7.26 (1,43.23)	0.010
	Time of day			0.80 (5, 43.22)	0.555
	Intervention x time			0.26 (5,43.22)	0.931
Albumin, % baseline	Intervention	Sleep-deprived vs. Control	+9.431 (-5.882, 24.743)	1.54 (1,42.29)	0.221
	Time of day			1.04 (5,42.11)	0.407
	Intervention x time			0.435 (5,42.11)	0.822

CSF = cerebrospinal fluid; A β = amyloid- β ; T181 = unphosphorylated tau-181; T217 = unphosphorylated tau-217; pT181 = phosphorylated tau-181; CI = confidence intervals; df = degrees of freedom

Supplementary Table 4: Mixed Model Results for Change in Overnight (01:00 – 11:00) CSF/Plasma Ratios of A β , Tau, Phosphorylated Tau, and Albumin from Baseline

CSF/Plasma Ratios					
Biomarker	Factor	Pairwise Comparison	Mean Difference (95% CI)	F (df)	p
A β 40, % baseline	Intervention	Sleep-deprived vs. Control	+50.012 (36.718, 63.306)	57.56 (1,43)	<0.001
	Time of day			1.67 (5,43)	0.163
	Intervention x time			0.18 (5,43)	0.968
A β 42, % baseline	Intervention	Sleep-deprived vs. Control	+56.592 (40.012, 73.173)	47.38 (1,43)	<0.001
	Time of day			0.63 (5,43)	0.676
	Intervention x time			0.23 (5,43)	0.948
T181, % baseline	Intervention	Sleep-deprived vs. Control	+69.414 (47.421, 91.408)	40.51 (1,43)	<0.001
	Time of day			1.75 (5,43)	0.145
	Intervention x time			0.45 (5,43)	0.811
T217, % baseline	Intervention	Sleep-deprived vs. Control	+68.367 (51.409, 85.325)	66.02 (1,44)	<0.001
	Time of day			1.37 (5,44)	0.254
	Intervention x time			0.28 (5,44)	0.920
pT181, % baseline	Intervention	Sleep-deprived vs. Control	+100.695 (61.755, 139.636)	27.20 (1,43)	<0.001
	Time of day			0.45 (5,43)	0.810
	Intervention x time			0.03 (5,43)	0.999
Albumin, % baseline	Intervention	Sleep-deprived vs. Control	-37.858 (-57.544, -18.172)	15.05 (1,42)	<0.001
	Time of day			1.10 (5,42)	0.377
	Intervention x time			0.11 (5,42)	0.991

CSF = cerebrospinal fluid; A β = amyloid- β ; T181 = unphosphorylated tau-181; T217 = unphosphorylated tau-217; pT181 = phosphorylated tau-181; CI = confidence intervals; df = degrees of freedom

Supplementary Table 5: Mixed Model Results for Differences in Overnight (01:00 – 11:00) CSF and Plasma Alzheimer Disease Biomarker Ratios: A β 42/40, pT181/T181, and pT181/A β 42

CSF and Plasma AD Biomarker Ratios					
Biomarker Ratio	Factor	Pairwise Comparison	Mean Difference (95% CI)	F (df)	p
CSF A β 42/40	Intervention	Sleep-deprived vs. Control	0.018 (-0.020, 0.056)	1.263 (1,7)	0.298
	Time of day			0.440 (5,34)	0.818
	Intervention x time			0.933 (5,34)	0.472
Plasma A β 42/40	Intervention	Sleep-deprived vs. Control	-0.008 (-0.011, -0.004)	25.30 (1,44)	<0.001
	Time of day			0.30 (5,44)	0.911
	Intervention x time			0.76 (5,44)	0.586
CSF pT181/T181	Intervention	Sleep-deprived vs. Control	+1.977 (-1.896, 5.850)	1.06 (1,44)	0.309
	Time of day			0.10 (5,44)	0.993
	Intervention x time			0.02 (5,44)	1.0
Plasma pT181/T181	Intervention	Sleep-deprived vs. Control	+0.284 (-1.052, 1.621)	0.18 (1,43)	0.670
	Time of day			0.75 (5,43)	0.589
	Intervention x time			0.51 (5,43)	0.770
CSF pT181/ A β 42	Intervention	Sleep-deprived vs. Control	+0.007 (-0.045, 0.058)	0.096 (1,8)	0.765
	Time of day			0.365 (5,39)	0.869
	Intervention x time			0.497 (5,39)	0.777
Plasma pT181/ A β 42	Intervention	Sleep-deprived vs. Control	-0.019 (-0.718, 0.679)	0.004 (1,8)	0.951
	Time of day			1.243 (5,39)	0.308
	Intervention x time			0.812 (5,39)	0.548

CSF = cerebrospinal fluid; A β = amyloid- β ; T181 = unphosphorylated tau-181; T217 = unphosphorylated tau-217; pT181 = phosphorylated tau-181; CI = confidence intervals; df = degrees of freedom