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Supplemental information

Coordinated human sleeping brainwaves map peripheral body glucose homeostasis

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Supplementary Tables

Table S1. Demographics of the Cleveland Family Study (CFS; visit 5). Related to STAR Methods.

Variables	Statistics
No. unique participants	647
No. unique families	144
Age (yrs)	44.73 ± 17.39 (range = 15-89)
Sex	359 F / 288 M
BMI (kg/m^2)	33.47 ± 9.17 (range = 17-85)
Race/ethnicity	350 African / 280 Caucasian / 17 Other
Smoking status	324 No / 169 Yes / 154 Missing
Hypertension status	428 No / 211 Yes
Diabetes status	530 No / 115 Yes
Fasting glucose (mg/dl)	100.56 ± 25.65 (range = 66-246)
log(HOMA-IR)	0.99 ± 0.77 (range = -1-4)
log(HOMA-B)	4.81 ± 0.63 (range = 3-8)
Apnea-hypopnea index (AHI)	13.78 ± 20.17 (range = 0-125)
% of participants with AHI >30	13.6%
Sleep efficiency (SE, %)	81.18 ± 12.74 (range = 27-99)
Sleep period time (SPT, min)	459.13 ± 82.01 (range = 52-660)
Total sleep time (TST, min)	369.83 ± 74.26 (range = 40-576)
N1 (% of TST)	5.32 ± 4.72 (range = 0-63)
N2 (% of TST)	58.55 ± 12.41 (range = 21-100)
N3 (% of TST)	17.71 ± 10.99 (range = 0-57)
REM (% of TST)	18.41 ± 7.61 (range = 0-44)
SO density (per min of NREM)	2.50 ± 1.98 (range = 0-11)
Spindles density (per min of NREM)	3.28 ± 1.37 (range = 0-7)
Proportion of SO with significant coupling	87.60 ± 3.35 (range = 72-100)
SO—spindle coupling strength	0.32 ± 0.02 (range = 0.25-0.39)
SO—spindle preferred phase (°)	-12.15 ± 28.32

SO = slow oscillations.

Table S2. Slow oscillation—spindle coupling quantity significantly predicts next-day fasting blood glucose in the CFS dataset. Related to Figure 2.

Predictors	β	Standardized β	95% CI	p
Proportion of NREM SO with significant coupling	-3.88	-0.12	-6.16 – -1.60	**0.001**
Age	0.01	0.15	0.00 – 0.01	**<0.001**
Male	0.41	0.19	0.26 – 0.57	**<0.001**
Race/ethnicity [Black]	0.15	0.14	-0.04 – 0.34	0.128
Race/ethnicity [Other]	0.18	0.16	-0.34 – 0.69	0.502
BMI	0.03	0.28	0.02 – 0.04	**<0.001**
Hypertension	0.44	0.19	0.25 – 0.62	**<0.001**
Apnea-hypopnea index (AHI)	-0.00	-0.06	-0.01 – 0.00	0.158
Sleep efficiency	-0.01	-0.07	-0.01 – 0.00	0.105
Sleep period time	-0.01	-0.02	-0.07 – 0.05	0.686

The number of participants with complete data included in the multilevel regression analysis was 623. Family ID was set as a random effect (n=144 unique groups). The dependent variable, fasting blood glucose, was transformed using a square root transformation to reduce skewness. The reference category for race/ethnicity was White. Age, sex, BMI, and hypertension were all significant predictors of fasting blood glucose levels. Being a male, older, having a higher BMI, and having hypertension were all associated with higher levels of next-day fasting blood glucose. Race, sleep duration, sleep efficiency, and AHI were not significant predictors of next-day fasting blood glucose.

Table S3. Slow oscillation—spindle coupling strength significantly predicts next-day fasting blood glucose in the CFS dataset. Related to Figure 2.

Predictors	β	Standardized β	95% CI	p
SO—spindle coupling strength	-4.90	-0.08	-9.04 – -0.77	**0.020**
Age	0.01	0.16	0.00 – 0.02	**<0.001**
Male	0.41	0.18	0.25 – 0.56	**<0.001**
Race/ethnicity [Black]	0.16	0.15	-0.03 – 0.35	0.102
Race/ethnicity [Other]	0.18	0.16	-0.34 – 0.69	0.502
BMI	0.03	0.29	0.03 – 0.04	**<0.001**
Hypertension	0.44	0.19	0.25 – 0.62	**<0.001**
Apnea-hypopnea index (AHI)	-0.00	-0.05	-0.01 – 0.00	0.164
Sleep efficiency	-0.00	-0.05	-0.01 – 0.00	0.198
Sleep period time	-0.01	-0.01	-0.07 – 0.05	0.746

The number of participants with complete data included in the multilevel regression analysis was 623. Family ID was set as a random effect (n=144 unique groups). The dependent variable, fasting blood glucose, was transformed using a square root transformation to reduce skewness. The reference category for race/ethnicity was White. Age, sex, BMI, and hypertension were all significant predictors of fasting glucose levels. Being a male, older, having a higher BMI, and having hypertension were all associated with higher levels of next-day fasting blood glucose. Race, sleep duration, sleep efficiency, and AHI were not significant predictors of next-day fasting blood glucose.

Table S4. Demographics of the MESA sleep study. Related to STAR Methods.

Variables	Statistics
No. unique participants	1996
Age (yrs)	68.43 ± 9.17 (range = 54-93)
Sex	359 F / 288 M
BMI (kg/m^2)	28.64 ± 5.49 (range = 17-56)
Race/ethnicity	729 Caucasian / 550 African / 478 Hispanic / 239 Asian
Smoking status	930 Never / 912 Former / 142 Current
Gap between PSG and glucose Measures (days)	341 ± 200 (range = 0-1024)
Hypertension status	1130 Yes / 866 No
Diabetes status	1197 Normal / 409 Impaired / 356 Treated / 34 Untreated
Fasting glucose (mg/dl)	100.46 ± 21.81 (range = 62-249)
log(HOMA-IR)	0.99 ± 0.77 (range = -1-4)
log(HOMA-B)	4.81 ± 0.63 (range = 3-8)
Apnea-hypopnea index (AHI)	19.73 ± 18.54 (range = 0-111)
% of participants with AHI >30	21.8%
Sleep efficiency (SE, %)	78.53 ± 13.44 (range = 10-99)
Sleep period time (SPT, min)	462.20 ± 91.48 (range = 94-1084)
Total sleep time (TST, min)	359.89 ± 82.15 (range = 32-601)
N1 (% of TST)	14.18 ± 9.16 (range = 0-79)
N2 (% of TST)	58.00 ± 11.05 (range = 19-100)
N3 (% of TST)	9.98 ± 9.05 (range = 0-51)
REM (% of TST)	17.84 ± 6.92 (range = 0-59)
SO density (per min of NREM)	1.48 ± 1.18 (range = 0-13)
Spindles density (per min of NREM)	2.68 ± 1.43 (range = 0-12)
Proportion of SO with significant coupling	86.34 ± 4.44 (range = 67-100)
SO—spindle coupling strength	0.32 ± 0.02 (range = 0.23-0.41)
SO—spindle preferred phase (º)	-12.15 ± 28.32

SO = slow oscillations.

Table S5. Slow oscillation—spindle coupling quantity significantly predicts next-day fasting blood glucose in the MESA dataset. Related to Figure 3.

Predictors	β	Standardized β	95% CI	p
Proportion of NREM SO with significant coupling	-1.04	-0.05	-2.00 – -0.08	**0.034**
Age	0.00	0.02	-0.00 – 0.01	0.390
Male	0.22	0.11	0.13 – 0.30	**<0.001**
Race/ethnicity [Black]	0.02	0.02	-0.09 – 0.13	0.688
Race/ethnicity [Asian]	0.37	0.38	0.23 – 0.51	**<0.001**
Race/ethnicity [Hispanic]	0.36	0.37	0.25 – 0.47	**<0.001**
BMI	0.04	0.20	0.03 – 0.04	**<0.001**
Hypertension	0.23	0.12	0.14 – 0.32	**<0.001**
Apnea-hypopnea index (AHI)	0.00	0.03	-0.00 – 0.00	0.201
Sleep efficiency	0.00	0.01	-0.00 – 0.00	0.698
Sleep period time	-0.00	-0.02	-0.00 – 0.00	0.380

The number of participants with complete data included in the multilevel regression analysis was 1966. The dependent variable, fasting blood glucose, was transformed using a square root transformation to reduce skewness. The reference category for race/ethnicity was White. Sex, race BMI, and hypertension were all significant predictors of fasting blood glucose levels. Being male, being Asian, being Hispanic, having a higher BMI, and having hypertension were all associated with higher levels of next-day fasting blood glucose. Age, sleep duration, sleep efficiency, and AHI were not significant predictors of fasting blood glucose.

Table S6. Slow oscillation—spindle coupling strength significantly predicts next-day fasting blood glucose in the MESA dataset. Related to Figure 3.

Predictors	β	Standardized β	95% CI	p
Proportion of NREM SO with significant coupling	-2.57	-0.06	-4.56 – -0.59	**0.011**
Age	0.00	0.02	-0.00 – 0.01	0.464
Male	0.22	0.11	0.13 – 0.30	**<0.001**
Race/ethnicity [Black]	0.02	0.02	-0.09 – 0.13	0.710
Race/ethnicity [Asian]	0.37	0.38	0.23 – 0.51	**<0.001**
Race/ethnicity [Hispanic]	0.36	0.37	0.25 – 0.47	**<0.001**
BMI	0.03	0.19	0.03 – 0.04	**<0.001**
Hypertension	0.23	0.12	0.14 – 0.32	**<0.001**
Apnea-hypopnea index (AHI)	0.00	0.03	-0.00 – 0.00	0.210
Sleep efficiency	0.00	0.01	-0.00 – 0.00	0.691
Sleep period time	-0.00	-0.02	-0.00 – 0.00	0.387

The number of participants with complete data included in the multilevel regression analysis was 1966. The dependent variable, fasting blood glucose, was transformed using a square root transformation to reduce skewness. The reference category for race/ethnicity was White. Sex, race BMI, and hypertension were all significant predictors of fasting blood glucose levels. Being male, being Asian, being Hispanic, having a higher BMI, and having hypertension were all associated with higher levels of next-day fasting blood glucose. Age, sleep duration, sleep efficiency, and AHI were not significant predictors of fasting blood glucose.

Table S7. Slow oscillation—spindle coupling quantity significantly predicts next-day HOMA-IR in the CFS dataset. Related to Figure 4.

Predictors	β	Standardized β	95% CI	p
Proportion of NREM SO with significant coupling	-2.20	-0.10	-3.73 – -0.68	**0.005**
Age	-0.0	0.02	-0.00 – 0.00	0.660
Male	0.17	0.11	0.07 – 0.27	**0.001**
Race/ethnicity [Black]	0.14	0.19	0.02 – 0.27	**0.025**
Race/ethnicity [Other]	0.13	0.17	-0.21 – 0.47	0.458
BMI	0.04	0.44	0.03 – 0.04	**<0.001**
Hypertension	0.23	0.14	0.11 – 0.35	**<0.001**
Apnea-hypopnea index (AHI)	0.00	0.01	-0.00 – 0.00	0.826
Sleep efficiency	-0.00	-0.01	-0.01 – 0.00	0.797
Sleep period time	-0.03	-0.05	-0.07 – -0.01	**0.141**

The number of participants with complete data included in the multilevel regression analysis was 626. Family ID was set as a random effect (n=144 unique groups). The dependent variable, HOMA-IR, was log-transformed to reduce skewness. The reference category for race/ethnicity was White.

Table S8. Slow oscillation—spindle coupling strength significantly predicts next-day HOMA-IR in the CFS dataset. Related to Figure 4.

Predictors	β	Standardized β	95% CI	p
SO—spindle coupling strength	-3.39	-0.08	-6.14 – -0.64	**0.016**
Age	0.00	0.02	-0.00 – 0.00	0.580
Male	0.17	0.11	0.06 – 0.27	**0.002**
Race/ethnicity [Black]	0.15	0.19	0.03 – 0.27	**0.018**
Race/ethnicity [Other]	0.14	0.18	-0.20 – 0.48	0.428The
BMI	0.04	0.44	0.03 – 0.04	**<0.001**
Hypertension	0.23	0.14	0.11 – 0.35	**<0.001**
Apnea-hypopnea index (AHI)	0.00	0.01	-0.00 – 0.00	0.829
Sleep efficiency	0.00	0.00	-0.00 – 0.00	0.973
Sleep period time	-0.03	-0.05	-0.07 – -0.01	**0.170**

The number of participants with complete data included in the multilevel regression analysis was 626. Family ID was set as a random effect (n=144 unique groups). The dependent variable, HOMA-IR, was log-transformed to reduce skewness. The reference category for race/ethnicity was White.

Table S9. Multilevel regression between sleep features and next-day fasting blood glucose in the CFS dataset. Related to Figure 5.

Sleep predictors	Std. beta	n	p
Proportion of coupled SO	-0.109	639	**0.002**
REM alpha	0.097	626	**0.01**
NREM theta	-0.088	647	**0.013**
SO–spindle coupling strength	-0.079	639	**0.026**
REM delta	-0.059	626	0.107
NREM delta (SWA)	0.058	647	0.1
N1	-0.057	647	0.11
REM sigma	0.056	626	0.161
NREM slow delta	0.056	647	0.11
TIB	-0.055	647	0.112
SO density	0.055	647	0.23
Arousal index	-0.049	640	0.197
REM theta	0.049	626	0.171
%N1	-0.047	647	0.2
SME	-0.047	647	0.231
REM fast delta	-0.046	626	0.233
N2 latency	-0.044	647	0.214
NREM alpha	-0.041	647	0.245
REM slow delta	-0.039	626	0.266
SOL	-0.039	647	0.274
WASO	0.037	647	0.333
NREM	-0.034	647	0.354
Spindles frequency	-0.033	647	0.346
N2	-0.033	647	0.349
N3 latency	0.032	617	0.37
TST	-0.032	647	0.392
N3	0.029	647	0.483
N1 latency	-0.028	640	0.438
%N3	0.027	647	0.502
AHI	-0.027	647	0.491
SO frequency	-0.021	647	0.601
NREM beta	-0.02	647	0.56
SO amplitude	-0.02	647	0.664
NREM power	0.019	647	0.58
%REM	0.017	647	0.614
%NREM	-0.017	647	0.616
%N2	-0.015	647	0.696
Spindles power	0.013	647	0.736

REM power	-0.013	626	0.718
NREM fast delta	-0.011	647	0.75
REM	-0.008	647	0.823
REM beta	-0.007	626	0.851
SE	-0.007	647	0.86
REM latency	0.004	626	0.918
Spindles density	-0.004	647	0.921
NREM sigma	-0.003	647	0.927
SPT	0.001	647	0.988

All regressions were adjusted for age, sex, BMI, race/ethnicity, hypertension and family ID. Regressions are sorted in descending order of significance. NREM refers to N2 + N3 sleep (N1 excluded). Sleep features that significantly predict *higher* levels of fasting glucose = worse outcome) are highlighted in red. A total of 47 sleep parameters were included in the correlation analysis. Two-sided p-values were not corrected for multiple comparisons. The spectral frequency bands are: slow delta (0.5-1.25 Hz), fast delta (1.25-4 Hz), delta (0.5-4 Hz), theta (4-8 Hz), alpha (8-12 Hz), sigma (12-16 Hz), beta (16-30 Hz), and total power (in microvolts-squared, 0.5-30 Hz). AHI = Apnea–hypopnea index, SE = sleep efficiency, SO = slow oscillations, SME = sleep maintenance efficiency, SOL = sleep onset latency, SPT = sleep period time, TST = total sleep time, WASO = wake after sleep onset.

Table S10. Multilevel regression between sleep features and next-day insulin resistance (HOMA-IR) in the CFS dataset. Related to Figure 5.

Sleep predictors	Std. beta	n	p
SO density	0.11	647	**0.012**
Proportion of coupled SO	-0.096	639	**0.004**
SO–spindle coupling strength	-0.084	639	**0.014**
REM alpha	0.083	626	**0.022**
NREM fast delta	-0.081	647	**0.017**
NREM slow delta	0.079	647	**0.019**
Spindles density	-0.072	647	**0.039**
NREM theta	-0.072	647	**0.035**
REM theta	0.068	626	**0.047**
SO amplitude	0.067	647	0.124
REM delta	-0.059	626	0.099
%N1	-0.059	647	0.095
N1	-0.058	647	0.095
%N3	0.056	647	0.145
SPT	-0.052	647	0.123
REM	-0.05	647	0.147
REM fast delta	-0.05	626	0.178
TST	-0.049	647	0.182
SOL	0.047	647	0.175
N3	0.045	647	0.256
SO frequency	-0.041	647	0.297
NREM delta (SWA)	0.039	647	0.252
NREM power	0.039	647	0.246
N3 latency	0.039	617	0.274
REM slow delta	-0.037	626	0.285
N1 latency	0.036	640	0.297
N2	-0.036	647	0.292
REM latency	0.035	626	0.314
SE	-0.033	647	0.356
NREM	-0.028	647	0.436
N2 latency	0.027	647	0.427
NREM beta	-0.022	647	0.511
AHI	0.022	647	0.561
Spindles frequency	-0.022	647	0.526
SME	0.021	647	0.571
WASO	-0.02	647	0.583
REM sigma	0.02	626	0.605
REM power	0.017	626	0.615

TIB	-0.017	647	0.616
NREM alpha	-0.014	647	0.677
%NREM	0.013	647	0.703
%REM	-0.013	647	0.706
Spindles power	0.012	647	0.738
%N2	-0.011	647	0.752
REM beta	-0.008	626	0.812
NREM sigma	0.004	647	0.9
Arousal index	-0.001	640	0.978

All regressions were adjusted for age, sex, BMI, race/ethnicity, hypertension and family ID. Regressions are sorted in descending order of significance. NREM refers to N2 + N3 sleep (N1 excluded). Sleep features that significantly predict *higher* HOMA-IR values (= worse outcome) are highlighted in red. A total of 47 sleep parameters were included in the correlation analysis. Two-sided p-values were not corrected for multiple comparisons. The spectral frequency bands are: slow delta (0.5-1.25 Hz), fast delta (1.25-4 Hz), delta (0.5-4 Hz), theta (4-8 Hz), alpha (8-12 Hz), sigma (12-16 Hz), beta (16-30 Hz), and total power (in microvolts-squared, 0.5-30 Hz). AHI = Apnea–hypopnea index, SE = sleep efficiency, SO = slow oscillations, SME = sleep maintenance efficiency, SOL = sleep onset latency, SPT = sleep period time, TST = total sleep time, WASO = wake after sleep onset.

Supplementary Figures

Figure S1. Assessment of insulin resistance (IR) and pancreatic beta cells function (B) using the standardized homeostasis assessment model (HOMA). A) HOMA-IR is positively correlated with fasting glucose. B) HOMA-B is negatively correlated with fasting glucose. Related to STAR Methods.

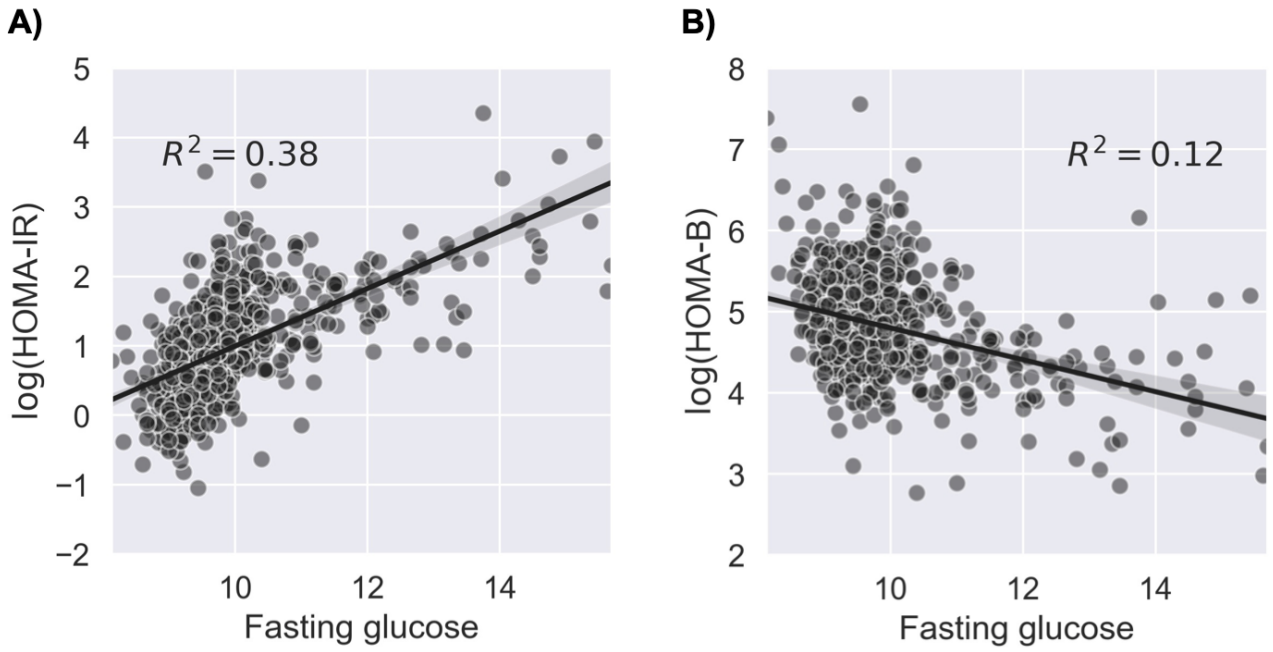

Figure S2. Mediation analysis demonstrated that the link between SO-spindle coupling and improved next-day fasting glucose is, in part, explained by increased heart rate variability, in the MESA dataset. A) A significant association between the proportion of SO-spindle coupling and increased heart rate variability (HRV), which in turn predicted lower (improved) fasting glucose values. B) A significant association between the strength of SO-spindle coupling and increased HRV, which in turn predicted lower (improved) fasting glucose values. Related to Figure 3.

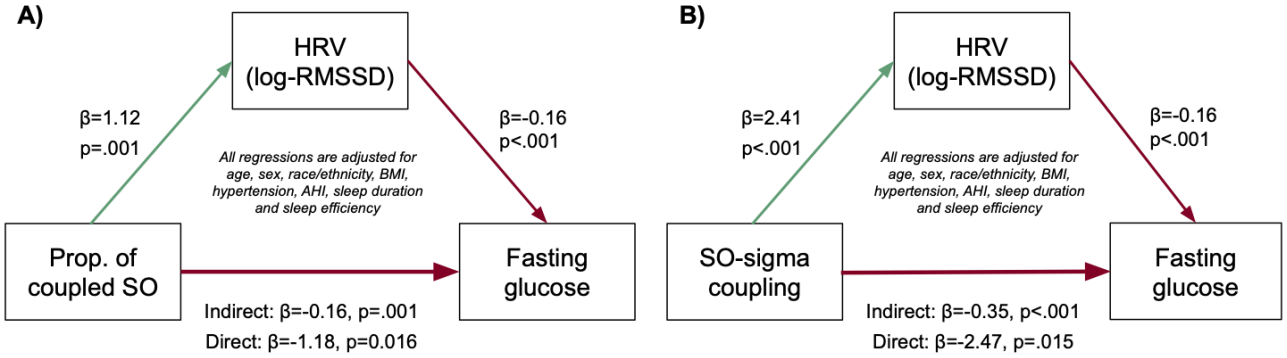

Figure S3. Mediation analysis demonstrated that the link between SO-spindle coupling and improved next-day fasting glucose is not, in part, explained by increased heart rate variability, in the CFS dataset. A) A significant association between the proportion of SO-spindle coupling and lower (improved) fasting glucose values is not mediated by HRV. B) A significant association between the strength of SO-spindle coupling and lower (improved) fasting glucose values is not mediated by HRV. Related to Figure 2.

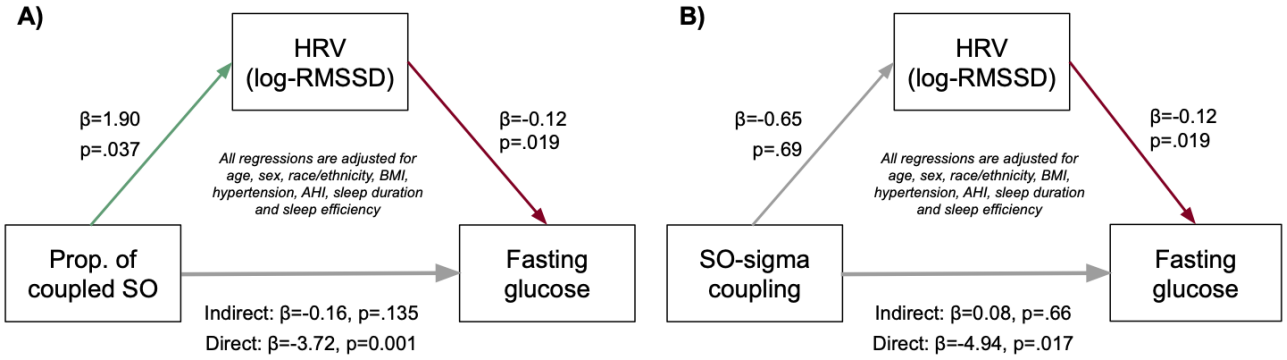

Figure S4. Mediation analysis demonstrated that the link between SO-spindle coupling and next-day insulin resistance is modestly explained by increased heart rate variability, in the CFS dataset. A) A trending significant association between the proportion of SO-spindle coupling increased heart rate variability (HRV), which in turn predicted lower (better) insulin resistance values. B) A significant association between the strength of SO-spindle coupling and lower (better) insulin resistance values is not mediated by HRV. Related to Figure 2.