

Supplementary Materials for

Impact of *APOE* $\epsilon 4$ and $\epsilon 2$ on plasma neurofilament light chain and cognition in autosomal dominant Alzheimer's disease

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Table S1

Distribution of APOE variants

	<i>PSEN1</i> E280A Carriers	<i>PSEN1</i> E280A Non-Carriers
$\epsilon 2/\epsilon 2$	4	2
$\epsilon 2/\epsilon 3$	96	62
$\epsilon 2/\epsilon 4$	16	16
$\epsilon 3/\epsilon 3$	511	421
$\epsilon 3/\epsilon 4$	139	137
$\epsilon 4/\epsilon 4$	14	12

Table S2

ANOVA output from NfL group differences using 3 groups

Predictor	F-value	<i>p</i> -value	Eta squared
<i>PSEN1</i>	7.07	.008	.080
<i>APOE</i>	3.44	.032	.002
Age	1203.70	<.001	.074
Sex	11.26	.001	
<i>PSEN1</i> * <i>APOE</i>	2.90	.055	.001

Post-hoc pairwise *t*-tests comparing NfL across *APOE* variant groups were not statistically significant

Table S3

Linear regression output of APOE (excluding $\epsilon 2/\epsilon 4$) and plasma NfL as predictors of API composite score

PSEN1 E280A Carriers		
Predictor	β	p-value
NfL	-0.28	< .001
APOE $\epsilon 2+$	-0.16	.070
APOE $\epsilon 4+$	0.18	.056
Age	-0.48	< .001
Sex	-0.04	.190
NfL* APOE $\epsilon 2+$	0.20	.021
NfL* APOE $\epsilon 4+$	-0.19	.051
PSEN1 E280A Non-Carriers		
Predictor	β	p-value
NfL	-0.03	.608
APOE $\epsilon 2+$	0.14	.376
APOE $\epsilon 4+$	0.21	.207
Age	-0.09	.082
Sex	0.02	.640
NfL* APOE $\epsilon 2+$	-0.24	.138
NfL* APOE $\epsilon 4+$	-0.17	.309

APOE $\epsilon 3/\epsilon 3$ used as the reference group; plasma NfL values were log-transformed; standardized beta weights reported

Table S4

Participant demographics by APOE $\epsilon 2$ group

All participants						
	PSEN1 E280A Carriers			PSEN1 E280A Non-Carriers		
	APOE $\epsilon 2+$ (n=114)	APOE $\epsilon 2-$ (n=664)	Group difference	APOE $\epsilon 2+$ (n=80)	APOE $\epsilon 2-$ (n=570)	Group difference
Age (years)	36.65 $\pm$ 12.74	35.78 $\pm$ 12.32	$t(776) = -0.69, p = .491$	35.14 $\pm$ 12.24	35.77 $\pm$ 12.55	$t(648) = 0.42, p = .674$
Sex (% female)	58.8%	55.7%	$\chi^2(1) = 0.37, p = .544$	62.5%	55.6%	$\chi^2(1) = 1.35, p = .245$
Education (years)	7.25 $\pm$ 4.36	7.30 $\pm$ 4.42	$t(775) = 0.10, p = .921$	8.06 $\pm$ 4.81	8.42 $\pm$ 4.68	$t(644) = 0.64, p = .526$

Subset of participants with cognitive data						
	<i>PSEN1</i> E280A Carriers			<i>PSEN1</i> E280A Non-Carriers		
	<i>APOE</i> ϵ 2+ (n=102)	<i>APOE</i> ϵ 2- (n=572)	Group difference	<i>APOE</i> ϵ 2+ (n=73)	<i>APOE</i> ϵ 2- (n=521)	Group difference
Age (years)	35.40 $\pm$ 11.55	33.89 $\pm$ 11.11	$t(672) = -1.26, p = .208$	33.93 $\pm$ 11.45	35.15 $\pm$ 12.07	$t(592) = 0.81, p = .416$
Sex (% female)	56.9%	54.4%	$\chi^2(1) = 0.22, p = .641$	64.4%	54.7%	$\chi^2(1) = 2.43, p = .119$
Education (years)	7.33 $\pm$ 4.42	7.44 $\pm$ 4.38	$t(672) = 0.23, p = .820$	7.97 $\pm$ 4.81	8.27 $\pm$ 4.68	$t(592) = 0.51, p = .610$
API Composite	64.80 $\pm$ 18.65	63.73 $\pm$ 21.06	$t(672) = -0.48, p = .630$	68.31 $\pm$ 15.94	71.59 $\pm$ 13.45	$t(86.97) = 1.67, p = .098$

*note: years of education was unavailable for 1 *PSEN1* carrier and 4 *PSEN1* non-carriers

Table S5

Comparison of demographics of PSEN1 carriers with and without cognitive data

	<i>APOE</i> ϵ 4+		<i>APOE</i> ϵ 2+	
	With cognitive data (n = 141)	Without cognitive data (n = 28)	With cognitive data (n = 102)	Without cognitive data (n = 12)
Age (years)	33.7 $\pm$ 10.9	46.8 $\pm$ 13.2	35.4 $\pm$ 11.6	47.3 $\pm$ 17.5
Sex (% female)	55.3%	57.1%	56.9%	75%
Education (years)	8.1 $\pm$ 4.0	6.32 $\pm$ 4.2	7.3 $\pm$ 4.4	6.6 $\pm$ 3.9
Log plasma NfL	1.0 $\pm$ 0.3	1.5 $\pm$ 0.6	1.0 $\pm$ 0.3	1.35 $\pm$ 0.5

Table S6*Participant characteristics, after excluding 3 outliers*

		All participants						
	PSEN1 E280A Carriers				PSEN1 E280A Non-Carriers			
	APOE ε4+ (n=169)	APOE ε4- (n=609)	Group difference		APOE ε4+ (n=163)	APOE ε4- (n=484)	Group difference	
Age (years)	35.87 ± 12.28	35.92 ± 12.41	t (776) = -0.05	p = 0.961	36.90 ± 12.67	35.36 ± 12.44	t (645) = 1.36	p = 0.175
Sex (% female)	55.62%	56.32%	χ ² (1) = 0.03	p = 0.871	60.12%	54.95%	χ ² (1) = 1.32	p = 0.250
Education (years)	7.80 ± 4.04	7.15 ± 4.50	t (776) = 1.74	p = 0.082	8.45 ± 4.92	8.25 ± 4.66	t (645) = 0.45	p = 0.651
Log10 NFL levels	1.06 ± 0.43	1.03 ± 0.39	t (776) = 0.89	P = 0.374	0.86 ± 0.26	0.83 ± 0.24	t (645) = 0.99	p = 0.320
		Subset of participants with cognitive data						
	PSEN1 E280A Carriers				PSEN1 E280A Non-Carriers			
	APOE ε4+ (n=141)	APOE ε4- (n=533)	Group difference		APOE ε4+ (n=147)	APOE ε4- (n=445)	Group difference	
Age (years)	33.70 ± 10.89	34.23 ± 11.27	t (672) = -0.50	p = 0.616	35.59 ± 11.80	34.84 ± 12.08	t(590) = 0.65	p = 0.514
Sex (% female)	55.32%	54.60%	χ ² (1) = 0.02	p = 0.878	59.86%	54.38%	χ ² (1) = 1.34	p = 0.246
Education (years)	8.01 ± 3.96	7.25 ± 4.47	t(672) = 2.06	p = 0.040	8.39 ± 4.74	8.16 ± 4.68	t(590) = 0.51	p = 0.613
API Composite	57.28 ± 22.85	57.12 ± 21.18	t(672) = 0.08	p = 0.938	65.38 ± 14.33	63.87 ± 13.32	t(590) = 1.17	p = 0.242

Means ± standard deviations given for continuous variables

Note: years of education was unavailable for 1 *PSEN1* carrier and 4 *PSEN1* non-carriers

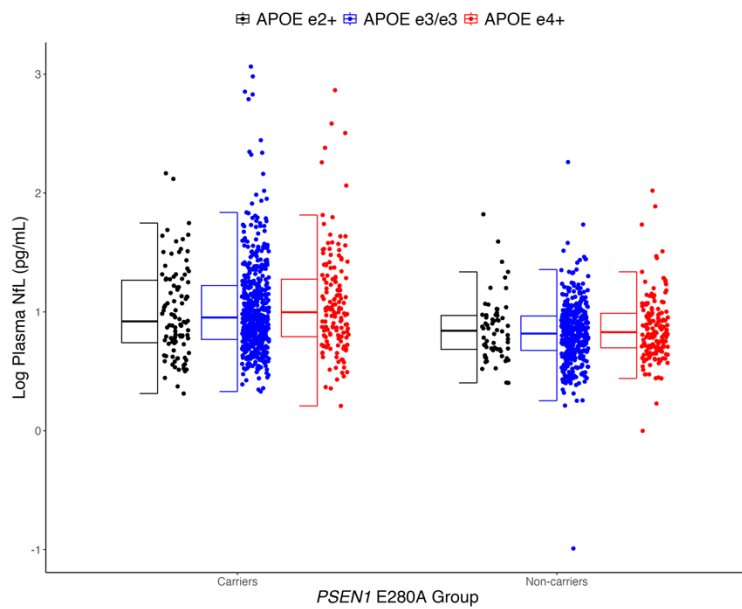


Figure S1. Log-transformed plasma NfL as a function of *APOE* and *PSEN1*, excluding *APOE* $\epsilon 2/\epsilon 4$ variants.

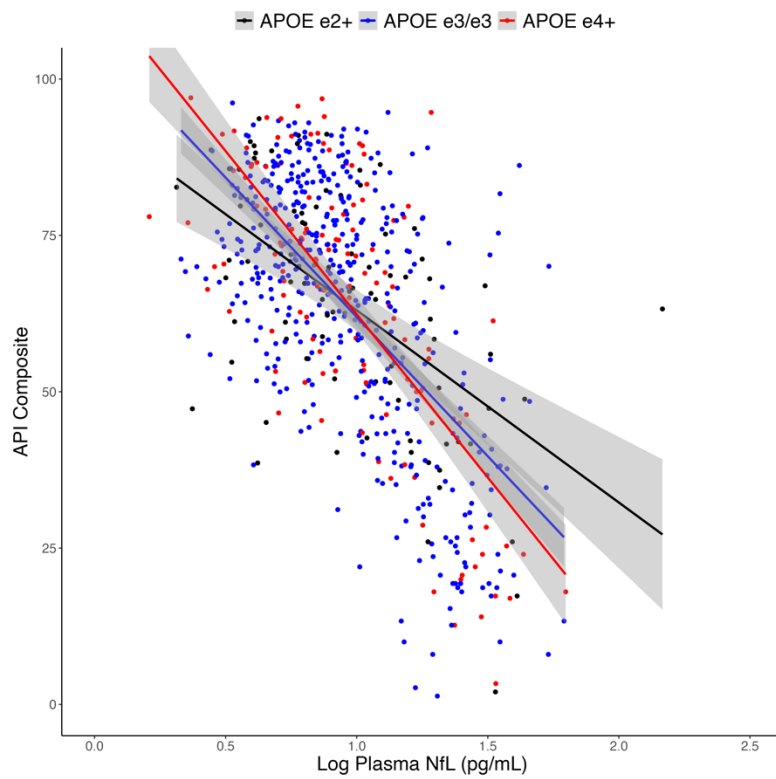


Figure S2. Association between plasma NfL and API Composite score as a function of *APOE*, excluding *APOE* $\epsilon 2/\epsilon 4$ variants

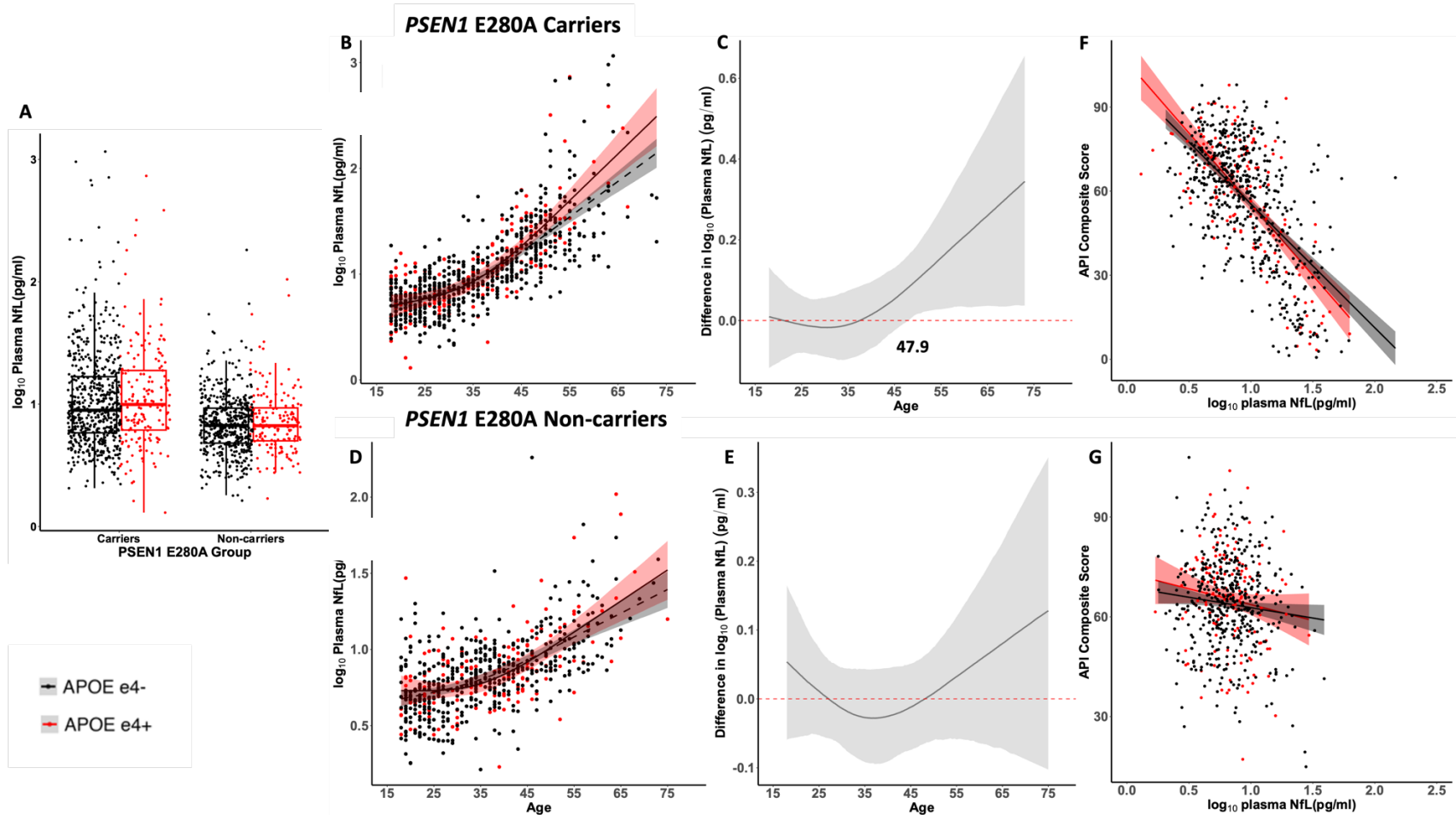


Figure S3. Plasma NfL as a function of APOE $\epsilon 4$, after excluding three outliers. (A) Boxplot showing log-transformed plasma NfL concentrations (pg/mL) in *PSEN1* E280A carriers and non-carriers as a function of APOE $\epsilon 4$ group (black: APOE $\epsilon 4^-$, red: APOE $\epsilon 4^+$). (B) Log-transformed plasma NfL concentrations of *PSEN1* E280A mutation carriers who are APOE $\epsilon 4^+$ and APOE $\epsilon 4^-$ as a function of age. (C) Differences in NfL concentrations between APOE $\epsilon 4^+$ and $\epsilon 4^-$ *PSEN1* E280A mutation carriers as a function of age. (D) Log-transformed plasma NfL concentrations of *PSEN1* E280A mutation non-carriers who are APOE $\epsilon 4^+$ and APOE $\epsilon 4^-$ as a function of age. (E) Differences in NfL concentrations between APOE $\epsilon 4^+$ and $\epsilon 4^-$ *PSEN1* E280A mutation non-carriers as a function of age. (F) API composite score plotted by log-transformed plasma NfL concentrations in *PSEN1* E280A mutation carriers stratified by APOE $\epsilon 4$ group. (G) API composite score plotted by log-transformed plasma NfL concentrations in *PSEN1* E280A mutation non-carriers stratified by APOE $\epsilon 4$ group. In panels C and E, the shaded areas of each plot represent the 99% credible intervals around the model estimates drawn from the distributions of model fits derived by the Hamiltonian Markov chain Monte Carlo analyses. In panels F and G, plots show regression line with shaded standard error bands.

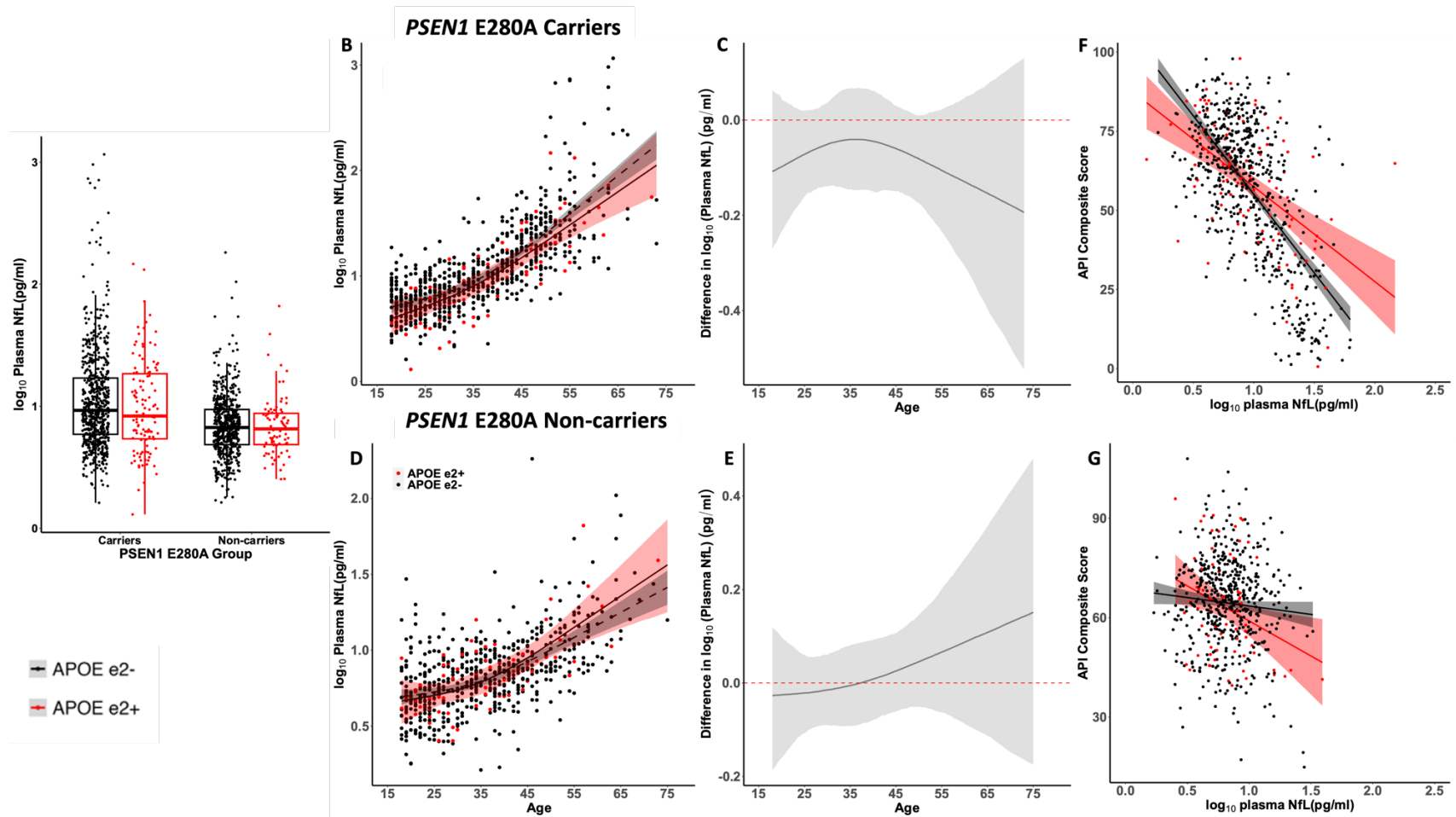


Figure S4. Plasma NfL as a function of APOE $\epsilon 2$, after excluding three outliers. (A) Boxplot showing log-transformed plasma NfL concentrations (pg/mL) in *PSEN1* E280A carriers and non-carriers as a function of APOE $\epsilon 2$ group (black: APOE $\epsilon 2^-$, red: APOE $\epsilon 2^+$). (B) Log-transformed plasma NfL concentrations of *PSEN1* E280A mutation carriers who are APOE $\epsilon 2^+$ and APOE $\epsilon 2^-$ as a function of age. (C) Differences in NfL concentrations between APOE $\epsilon 2^+$ and $\epsilon 2^-$ *PSEN1* E280A mutation carriers as a function of age. (D) Log-transformed plasma NfL concentrations of *PSEN1* E280A mutation non-carriers who are APOE $\epsilon 2^+$ and APOE $\epsilon 2^-$ as a function of age. (E) Differences in NfL concentrations between APOE $\epsilon 2^+$ and $\epsilon 2^-$ *PSEN1* E280A mutation non-carriers as a function of age. (F) API composite score plotted by log-transformed plasma NfL concentrations in *PSEN1* E280A mutation carriers stratified by APOE $\epsilon 2$ group. (G) API composite score plotted by log-transformed plasma NfL concentrations in *PSEN1* E280A mutation non-carriers stratified by APOE $\epsilon 2$ group. In panels C and E, the shaded areas of each plot represent the 99% credible intervals around the model estimates drawn from the distributions of model fits derived by the Hamiltonian Markov chain Monte Carlo analyses. In panels F and G, plots show regression line with shaded standard error bands.