

Data Supplements

Mechanistic inferences on metabolic dysfunction in PTSD from an integrated model and multi-omic analysis:

Role of glucocorticoid receptor sensitivity

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Methods: Detail protocols for assays

Clinical assessments, neuroendocrine (plasma and urine), metabolomics and cytokine assays

Demographics and group differences (Related to statistical analysis)

Table S1: Demographics of the cohort

Table S2: Results for statistical analysis

Mathematical model development

Table S3: Molecular interactions used for model integration (Related to Figure 3)

Table S4: Parameters for the model

Metabolic control analysis

Table S5: Metabolic concentration response coefficients (Related to Figure 4)

Correlational Analysis (Related to Figure 6)

Table S6A: Statistically significant SCCs in controls and PTSD subjects and fold change in SCCs

Table S6B: Spearman correlation coefficients between metabolites and regulatory states for entire cohort

Causal inference

Table S7: Population average causal effects along with statistics and the sensitivity analysis (Related to Figure 7A)

Table S8: Results for causal mediation analysis for the cohort (Related to Figure 7C)

Supplementary Figures

FigureS1. Qualitative validation of model response (Related to model development)

FigureS2. Results for mediation analysis (Related to Figure 7C)

References

Methods: Detailed protocols for biochemical assays

Clinical Assessments: All participants had exposure to a warzone-related DSM-IV PTSD Criterion a trauma while deployed and the presence of a diagnosis of PTSD was determined by a doctoral level psychologist using the Clinician Administered PTSD Scale (CAPS). Participants in the no-PTSD group were required to have a current (past month) CAPS scores ≤ 20 and had never met criteria for PTSD in the past. Participants in the PTSD group were required to have a current (past month) CAPS score ≥ 40 and to meet full DSM-IV criteria for PTSD. Participants were also asked to report their symptoms during the month when their symptoms were most distressing (lifetime). All cases were adjudicated in weekly consensus meetings across the two recruitment sites. The Structured Clinical Interview for DSM-IV (SCID) was used by the same clinician to determine other DSM-IV diagnoses. Participants with a lifetime history of any psychiatric disorder with psychotic features, bipolar disorder, current alcohol dependence, current drug abuse or dependence or obsessive-compulsive disorder, prominent suicidal or homicidal ideation or a suicide attempt in the past year were excluded. Medical exclusions included neurological disorder, loss of consciousness greater than 10 minutes, or other systemic illness affecting CNS function. Participants taking medications for psychiatric or medical conditions had to report consistent use for more than two months to be eligible to participate.

Blood sample collections and assays: Participants reported to the laboratory at JJP VAMC or ISMMS between 7:30 and 8:00 after an overnight fast. Vital signs, weight, height and waist-hip ratio were measured and then approximately 160 cc of whole blood was collected and processed for subsequent assays for neuroendocrine variables.

Neuroendocrine assays

Dexamethasone Suppression Test: Participants received a 0.50 mg tablet of Dexamethasone to ingest at 11:00 pm and returned the following morning (post-Dex) for collection of 10cc of blood. Blood samples were delivered to a CLIA certified lab at ISMMS or JJP VAMC for assessment of a variety of clinical labs (e.g., gamma-glutamyl transferase (GGT), high-sensitivity C-reactive protein (hs-CRP)).

Lysozyme IC₅₀-DEX : For the lysozyme IC₅₀-DEX assay, mononuclear leukocytes were prepared immediately following the blood drawing procedure. For the preparation of mononuclear leukocytes, platelet-rich plasma was separated by low speed centrifugation. After collecting plasma, the remaining cells were diluted by the sample volume with Hanks' Balanced Salt Solution (HBSS) and the lymphocytes were isolated by density centrifugation utilizing Ficoll-Paque (GE Healthcare) and washed twice in PBS according to the method of Boyum (6). The final cell pellet was re-suspended in a medium (RPMI-1640) containing 10% fetal calf serum, penicillin, streptomycin, and L-glutamate (Life Technologies, Grand Island, NY) at a density of $1.75\text{--}2.00 \times 10^6$ cells/ml. The test for examining the inhibition of lysozyme synthesis and release was carried out in 96-well culture plate in a total volume of .22 mL, modified from (62). Lysozyme activity was measured by turbidometric method using *Micrococcus lysodeikticus* (Sigma) as the substrate. *Micrococcus lysodeikticus* was prepared in 0.1 mol/L phosphate buffer, pH 6.3, at a concentration of .05% and homogenized with a tissue grinder equipped with a Teflon pestle (Wheaton, St. Millville, New Jersey) with 3 strokes. 20 μL of supernatant of cell culture was incubated with 150 μL of substrate in a 96-well plate at 37°C for 7–10 min with shaking and then kinetically read by a microplate reader at 450

nm for 20 min. Cells ($3.5\text{--}4.0 \times 10^5$) were incubated with 0, .5, 1, 2.5, 5, 10, 50, and 100 nmol/L of dexamethasone (DEX) (Sigma) at 37°C in a humidified atmosphere with 5% CO₂ for 3 days. Each concentration of DEX was incubated in triplicate. After centrifuging the plate, 120 µL of supernatant were removed and pooled from each triplicate well. The standards were prepared using pure lysozyme from chicken egg white (Sigma) dissolved in RPMI-1640 as used for the cell culture. The inhibition curve was drawn as concentration of DEX versus relative activity of lysozyme. Results were expressed as IC₅₀-DEX (nmol/L) based on the concentration of DEX at which 50% of lysozyme activity was inhibited. The intra- and inter-assay coefficients of variation for the measurement of lysozyme activity were 6.9% and 9.8% respectively (79).

Plasma Cortisol: Cortisol levels in plasma were assayed using Cortisol ELISA Kit from IBL-America (Minneapolis, MN), a solid phase enzyme-linked immunosorbent assay, based on the principle of competitive binding. The microtiter wells were coated with a monoclonal antibody directed towards an antigenic site on the cortisol molecule. Endogenous cortisol from an unknown competes with a cortisol-horseradish peroxidase conjugate for binding to the coated antibody. After incubation the unbound conjugate was washed off. The amount of bound peroxidase conjugate is inversely proportional to the concentration of cortisol in the unknown. After addition of the substrate solution, the intensity of color developed is inversely proportional to the concentration of cortisol in the unknown. Assay sensitivity: 2.5 ng/mL. The intra-assay and inter-assay coefficients of variation for this assay 5.3% and 9.8%, respectively. Two blood samples were assayed for the determination of cortisol before and after DEX administration. Decline of cortisol from Day 1 to Day 2 was used as a measure of DEX suppression.

Plasma ACTH: ACTH levels in plasma was assayed by using ACTH ELISA kit (ALPCO Diagnostics, Windham NH). In this assay, calibrators and research samples were simultaneously incubated with the enzyme labeled antibody and a biotin coupled antibody in a streptavidin-coated micro plate well. At the end of the assay incubation, the microwell was washed to remove unbound components and the enzyme bound to the solid phase was incubated with the substrate, tetramethylbenzidine (TMB). An acidic stop solution was added to stop the reaction and convert the color to yellow. The intensity of the yellow color is directly proportional to the concentration of ACTH in the sample. A dose response curve of absorbance unit vs. concentration was generated using results obtained from the calibrators. Concentrations of ACTH present in the samples was determined directly from this curve. Assay sensitivity: 0.5 pg/mL. The intra-assay and inter-assay coefficients of variation for this assay 5.7% and 8.0%, respectively. Two blood samples were assayed for the determination of ACTH before and after DEX administration.

Plasma DHEA: DHEA and DHEA-S were measured using ALPCO ELISA DHEA and DHEA-S kits (ALPCO Diagnostics, Windham NH). Both kits utilize a competitive immunoassay specifically designed and validated for the in vitro diagnostic measurement of dehydroepiandrosterone (DHEA) and dehydroepiandrosterone sulfate (DHEA-S) in human blood. Assay sensitivity for DHEA: 0.1 ng/mL. The intra-assay and inter-assay coefficients of variation for this assay 3.6% and 6.1%, respectively. Assay sensitivity for DHEA-S: 5.0 pg/ml. The intra-assay and inter-assay coefficients of variation for this assay 5.7% and 10.0%, respectively.

24-hour Urine Collection: At the end of the first study visit, subjects were given instructions and materials to collect urine at home over 24 hours. Urine was kept in a freezer for the duration of the collection and kept frozen until it was returned to the laboratory.

Urinary catecholamines: Urinary catecholamines (E, NE, and DA) were extracted using Urinary Catecholamine Kit developed by Bioanalytical Systems, Inc (BAS). Extraction of catecholamines from 0.5 ml of urine sample was performed on the Solid Phase Extraction (SPE) Columns using the company's proprietary reagents. 12µl of dihydroxybenzoic acid (DHBA) was added to each sample as an internal standard. HPLC analysis of the elute was performed on Thermo Scientific Dionex UltiMate 3000 with an autosampler and Dionex Coulochem III electrochemical detector. Quantitation was performed by integrating peak areas and comparing the ratios of the analyte to those of the internal standard with reference to a calibration curve across the range of concentrations using Chromeleon 7 Chromatography Data System.

Metabolomics and cytokine data

The subjected reported to the laboratory in the morning 7.30 AM under fasting condition and the blood samples were called around 8 AM. The metabolic profiling of the blood samples were performed by Metabolon, Inc. (Durham, NC). The primary metabolic data and details of the sample collection and metabolic profiling are reported in *Mellon et al.*, (in review at PLOS one). The cytokine data was obtained as per our previous reports (49).

Demographics and group differences (Related to statistical analysis)

Table S1. Demographic and clinical measures of combat veterans with PTSD and controls

Demographics	PTSD - (N:82)	PTSD + (N:83)	Demographics	PTSD - (N:82)	PTSD + (N:83)
Sociodemographic			Medication use (n)		
Gender	All males	All males	Sedatives	4	16
Age (Mean±SD)	32.29 ± 7.60	33.20 ± 8.12	Statins	1	4
Years of Education (Mean±SD)	14.78 ± 2.32	13.81 ± 1.93	Anti-depressants	4	24
Hispanic/Non-Hispanic (n)	26/56	38/45	Anticonvulsants	0	9
Smoking (n)	18	33	Anti-inflammatories	6	9
Alcohol use (Mean±SD)	1.65 ± 1.08	1.38 ± 1.22	Anti-diabetics	2	2
Biometric measurements (Mean± SD)			Anti-hypertensives	5	6
BMI	28.44 ± 4.79	30.02 ± 5.047	Antacids	3	3
Weight	192.78 ± 35.46	205.09 ± 37.77	Anti-allergics	4	5
Height	69.05 ± 2.89	69.26 ± 2.84	Pain medicines	4	10
Waist to Hip ratio	0.88 ± 0.15	0.89 ± 0.16	Comorbid diseases (n)		
Pulse	64.68 ± 11.21	72.65 ± 10.33	Clinical hypertension	7	15
Metabolic measurement (Mean±SD)			Heart attack	1	1
HbA1c	5.37 ± 0.44	5.39 ± 0.85	Stable angina	1	3
Cholesterol	171.35 ± 27.44	180.21 ± 35.97	Diabetics	2	4
LDL	49.79 ± 13.08	47.27 ± 12.05			
HDL	100.56 ± 25.12	107.96 ± 32.49			
Clinical measures (Mean±SD)					
CAPS total current	9.24 ± 8.39	91.55 ± 15.8			
CAPS total lifetime	3.73 ± 5.01	69.42 ± 16.91			
PCLSCORE	25.93 ± 8.95	61.51 ± 11.84			
MCS	64.34 ± 14.21	118.53 ± 19.69			
PSQI	5.19 ± 4.02	7.46 ± 5.72			
ETISR	5.98 ± 3.77	13.25 ± 3.28			
Number of deployment	1.77 ± 0.89	1.82 ± 0.84			
MDD diagnosis (n)	1	47			

Table S2 : The features with statistically significant difference in controls and PTSD subjects with $p \leq 0.05$ and $q \leq 0.01$. (*) sign in suffix indicate additional features (with $0.05 < p \leq 0.1$) that were included in analysis due to their association with significantly different pathways.

Metabolites	p values	q values	median (Fold)	Cohen's d	Metabolites	p values	q values	median (Fold)	Cohen's d
Glycolysis					5-oxoproline	0.002	0.027	1.104	-0.522
Lactate	2.36E-07	3.42E-05	1.301	-0.867	Gamma glutamyltyrosine	0.008	0.056	1.102	-0.331
Pyruvate	0.001	0.024	1.308	-0.453	Sphingosine 1phosphate	0.015	0.076	1.128	-0.327
Citrate*	0.039	0.138	0.949	0.346	Stearoyl sphingomyelin	0.006	0.055	1.085	-0.437
Amino acids					Other				
Alanine	0.015	0.076	1.123	-0.371	Threonate	0.010	0.061	0.828	0.362
Glutamine	0.021	0.099	0.969	0.423	Transurocanate	0.003	0.035	0.778	0.446
Tyrosine	0.005	0.050	1.074	-0.483	Bilirubin EE	0.018	0.089	0.854	0.389
Isoleucine*	0.044	0.138	1.048	-0.168	Glycerate*	0.028	0.111	0.908	0.369
leucine*	0.090	0.184	1.034	-0.236	3-Hydroxybutyrate (BHBA)	0.008	0.056	0.804	0.287
Valine*	0.086	0.182	1.039	-0.152	Cytokines				
Urea cycle					IL6	2.00E-04	0.007	1.308	-0.441
Arginine*	0.067	0.164	0.973	0.386	TNF α	0.005	0.031	1.077	-0.498
Ornithine	0.011	0.061	1.097	-0.331	Clinical Labs				
Long chain fatty acids					Insulin	0.002	0.017	1.122	-0.497
10-Nonadecenoate 19:1 (ω -9)	0.004	0.047	0.775	0.460	Glucose	0.002	0.017	1.023	-0.375
10-Undecenoate 11:1 (ω -1)	0.006	0.054	0.821	0.371	HOMA-IR	3.96E-04	0.007	1.146	-0.553
17-Methylstearate	0.001	0.026	0.881	0.441	Triglyceride	0.027	0.067	1.055	-0.274
2-Hydroxypalmitate	0.008	0.056	0.933	0.407	Total protein	0.001	0.012	1.015	-0.490
Nonadecanoate 19:0	3.02E-05	0.002	0.815	0.595	Albumin	0.015	0.048	1.011	-0.286
Arachidonate 20:4 (ω -6)	0.010	0.061	0.815	0.371	Alkaline phosphatase	0.006	0.031	1.037	-0.375
Stearate 18:0	0.007	0.056	0.911	0.376	GGT	3.70E-04	0.007	1.131	-0.513
Essential fatty acids					hs-CRP	0.016	0.048	1.298	-0.455
Dihomolinoleate 20:2 (ω -6)	0.008	0.056	0.806	0.429	Pottassium (K)	0.006	0.031	1.025	-0.391
Dihomolinolenate 20:3 (ω -3 or ω -6)	1.84E-04	0.009	0.785	0.504	Chlorine (Cl)	0.015	0.048	1.001	-0.424
Docosahexaenoate (DHA) 22:6 (ω -3)	0.001	0.024	0.812	0.479	White blood cells (WBC)	0.009	0.036	1.049	-0.444
Docosapentaenoate (DPA) 22:5 (ω -3)	0.001	0.024	0.730	0.480	Red blood cells (RBC)	0.011	0.041	1.018	-0.371
Eicosapentaenoate (EPA) 20:5 (ω -3)	0.006	0.055	0.821	0.323	Platelets	0.014	0.048	1.015	-0.327
Eicosenoate 20:1	0.002	0.026	0.801	0.472	MPV	0.030	0.068	1.009	-0.377
Linolenate 18:3 (ω -3 or ω -6)	0.002	0.027	0.808	0.425	Neuro-endocrine features				
Carnitines					ACTH	0.036	0.074	1.069	-0.281
Decanoylcarnitine	0.011	0.061	1.234	-0.328	Cortisol suppression	0.005	0.031	1.021	-0.388
Octanoylcarnitine	0.021	0.099	1.093	-0.343	Urinary epinephrine	0.050	0.092	1.226	-0.285
Palmitoylcarnitine*	0.044	0.138	1.103	-0.268	Cortisol*	0.069	0.114	1.056	-0.290
Energy deficit and oxidative stress					IC50-Dex*	0.082	0.123	0.913	0.284
Hypoxanthine	2.38E-04	0.009	1.354	-0.557					

Mathematical model development (Related to model development and Figure 3)

Table S3: Regulatory interactions implemented in the integration of sub-models for signaling and transcription regulation of metabolism, HPA axis, inflammation and hypoxia.

Regulatory Interactions	References for regulatory interaction	Experimental organism	KO mutants/ dose response	Fold change/ +/-	Parameter estimates for Hill functions		
					V_{max} AU	km/ki AU	n
Metabolic regulation by glucocorticoids							
GR mediated effects on gluconeogenesis (Pck1 and G6pc)	(7)	Human HepG2 cells,	Gene expression	~5 (PEPCK)			
	(16)	Mice	Prednisone treated	~1.5-4 (several genes)			
Activation of lipogenesis	(19)	Human Chub-S7 cell culture	DEX treatment	~2-4 (FAS and ACC)	5	20	2
	(45)	Mice liver	GR mutants	~1.2-1.5 (TG)			
Inhibition of β -oxidation	(68)	Human	Hydrocortisone infusion	~2	2	10	3
	(46)	Mice	DEX treatment	~1.25~2 (enzymes)			
Activation of proteolysis and plasma amino acids	(78)	Murine Myoblasts	DEX treatment	~1.25-2	3	20	1
	(50)	Human	Prednisolone treated	~1.25-2 (several plasma amino acids)			
Activation of urea cycle	(61)	Human serum and Mouse	Liver GR mutant	~1.25-2.5 (Arginine/ Ornithine / urea)	3	20	1
	(22)	Rat hepatocytes	Hydrocortisone treated	~10 (arginase activity)			
Inhibition of insulin secretion	(30)	Rat pancreatic Islets	DEX treated	~3	0.25	20	2
	(44)	Mouse islets	DEX treated	~3			

Transcription regulation by glucocorticoids							
Activation of CREB	(57)	Human pre B cell lines	DEX treated (1µm for 72 hrs)	~4	5	20	2
	(28)	Rat H4IIE Hepatocytes	DEX treated (0.5µm, 4 hrs)	~3			
	(63)	Rat L6 myoblasts	DEX treated (0.1µm, 48 hrs)	~1.5			
Activation of FOXO	(52)	Mice	DEX treated	~2	5	20	2
	(81)	Mice C2C12 cells	Mutant	~1.5			
	(31)	Mice	DEX treated (0.1µm, 24 h)	~2.5			
Activation of CEBP	(11) (64)	Rat hepatocytes	DEX treated	~2	5	20	2
	(55)	Rat hepatocytes	DEX treated	~2			
Activation of PGC1	(39)	Rat liver and myocytes	DEX treated , Gene expression	~2	5	20	2
	(16)	Mice	Prednisone treated	~3			
	(24)	Human HepG2 hepatocytes	DEX treated (0.1µm)	~4			
Signaling regulation by glucocorticoids							
Activation of adrenergic receptors/GPCR	(23)	Rat	DEX treated Adrenalectomy	~2 (Gi/Gs protein)	3	20	2
	(29)	Rat	DEX treated (0.1µm, 24 hrs)	~2			
Inhibition of mTORC1	(73)	Rat	Gene Expression	~1.5-2	1.1	30	2
	(77)	Rat	DEX treated	~1.5-2			
	(35)	Mice C2C12 cell culture	DEX/Cortisol Treated	~1.25-1.5			

Inhibition of IRS/PI3k	(43)	Mice C57BL/6, C2C12 cell culture	Gene expression	~1.5-2	1.25	20	2
	(66)	Rat Liver/ Muscle	DEX treatment	~1.2-1.5			
	(20)	Rat	Cortisone treatment	~2			
Regulation by TNF and IL6/ Inflammation							
Inhibition of Insulin signaling by TNF) (tyrosine phosphorylation of IRS)	(25) (37)	Murine 3T3-L1 cells Mice Liver	TNF treated IL6 treated	~4 ~5	5	100	4
TNF and IL6 inhibits PGC1 α	(47) (75)	LO2 cell culture and Rat Liver Human Hep3B cells and mice liver	Mutants/Gene expression LPS treated	~5 ~2	5	100	2
Inflammatory cytokines activates HPA axis components	(3) (5) (32)	Mice/ Human adrenal cells Mice	IL6 stimulation/ mutant LPS treated	~2-3 (ACTH/ Cortisol) ~2-3 (ACTH/ Cortisol)	Reported and modified as per source models and Spiga et al. (2017) (2, 74)		
Inflammatory cytokine /phagocytes activates HIF α	(15) (76)	Human Cell lines: monocyte THP-1 Human HEK293 cells	LPS treated NF-kb treated	~2 ~2-3	5	1.00E+05	2
Inflammation inhibits oxidative phosphorylation	(67) (13)	Mouse Liver tissue, Murine H2.35 cells Rats livers	TNF treated LPS treated	~2 (CcO activity) ~3-4 (ATP depletion)	1	50	2
Inflammation induces ROS production/ATP depletion	(34)	Human hepatic Hepa1-6, Murine hepatocytes	TNF treated	~2-3			
Regulation by HIFα/ hypoxia							

Alpha-ketoglutarate inhibits HIF α by activation of PHD	(38)	Human HEK293 cells	Hypoxia induced	~2-3	2.5	0.4	2
	(53)	Human HEK293 cells	Plasmid infected	Dose dependent			
Succinate activates HIF α by inhibiting PHD	(69)	Human HEK293 cells	Plasmid infected	~2-3	2.5	1.6	2
	(38)	Human HEK293 cells	Hypoxia induced	~2-3			
HIF α upregulates glycolysis	(72) (10)	Human HeLa and Hep3B cells	Hypoxia induced Gene expn.	~3-8 (ALDA,PGK1, enolase, PFK)	5	0.25	2
	(60)	Human T98G and U-87 cell lines	Hypoxia treated	~10 (PFK2 and GLUT1)			
HIF α downregulates mitochondrial biogenesis transcription/PGC1	(80)	Human RCC4 cells	Mutant	~2 (C-MYC)	1	0.5	2
HIF α inhibits Pyruvate dehydrogenase (activation of PDK)	(51)	Human HeLa cells	Gene expression	~3-4 (PDK3)	1	0.25	2
	(36)	Mice: Mouse embryonic fibroblasts	Gene expression	~3-4 (PDK1)			
HIF α activates lactate dehydrogenase	(14)	Human HeLa cells	Gene expression	~2	3	0.25	3
	(71)	Human Hep3B cells	Mutant	~4			
HIF α inhibits oxidative phosphorylation/ Respiratory chain complex	(8)	Human HCT116 cells	Gene expression	~2 (COX1)	1	0.25	2
	(17) (70)	Human HeLa, 293T cells	Gene expression	~5 (COX4-1)			
HIF α activates inflammatory cytokines/phagocytosis	(1)	Mice: Murine macrophages	Hypoxia treated	~2	5	0.5	2
	(42)	Human cells:HMEC-1	Hypoxia treated	~3			
HIF α activates ROS generation	(4)	Human hepatocytes	Hypoxia treated	~4	1	0.5	1
HIF α induce triglyceride accumulation	(58)	Mice	Mutant	~2	3	0.25	2
	(65)	Mice	Mutant	~2			
HIF α inhibits beta oxidation and lipogenesis	(65)	Mice	Mutant	~2.5-4	1	0.5	2
	(27)	Mice	Mutant	~2			
	(26)	Human Hep3B cells	Gene expression	~2			

Table S4: Parameters for the mathematical Model (Related to model development)

Parameter	Value	Units	Parameter	Value	Units	Parameter	Value	Units
Parameters for integrated HPA axis-inflammation model								
n	1	-	$kphg$	4.9956E7	kg/hr/pg	$xil6il10$	1.1818	pg/ml
Ki_{n1}	1.2	nM/ml	$kptnf$	12.94907	-	$dil6$	0.43605	/h
K_{strs}	1	μg/dL/min	$xnTNF$	1693.9509	pg/ml	$il6b$	0.25	pg/ml. h
$n3$	2	-	$xTGF$	0.07212	pg/ml	$q1$	0.5	ml/pg.h
$Vs3$	0.032	/min	$xIL10$	147.68	pg/ml	$q2$	625	μg/dL
$Kp2$	0.41	/min	dpg	0.144	/h	$kmpi3k$	1.4	AU
$Vs4$	0.016	/min	$ktgf$	0.15625E-8	ml/pg.U.h	$kmcres$	0.75	AU
$Vs5$	0.0266	/min	$dtgf$	0.03177	/h	$fpi3k$	5	-
$kp4$	45E-4	/min	$ktnf$	25.5194	pg/ml.h	$fcreb$	5	-
$q3$	2.8014	pg/mL.min	$TNFn$	550E4	U	wt	0.66	-
$q4$	11.2	pg/mL.min	$xtntg$	0.1589*1.25	pg/ml	$fmtor$	5	-
$q5$	40	pg/mL	$ktnff$	3.5514E4	pg/ml.h	$kIL10$	267480	pg/ml. h
$q6$	7	pg/mL	$kmator$	2	-	$kil6$	5E2	pg/ml. h
$q8$	40	pg/mL	$dtnf$	0.0307	ml/pg. h	$xil6$	33E4	pg/ml
$ksynt_{rm}$	3.625	/h	sil	1187.2	pg/ml.h	$kil6tnf$	4.4651	pg/h.ml.U
nkm_{Grn}	26	nM/mg protein	xil	8.0506E7	U	$xil6tnf$	1211.3	pg/ml
$kdeg_{rm}$	0.1124	/h	dil	98.932	/h	It	1E-6	U
$ksynt_{rp}$	1.2	/h	$kiltg$	43875	pg/ml.h	$kmtnf$	100	pg/ml
vp_{rp}	0.0279	/h	$xiltg$	0.38*2	pg/ml	dlp	1.35E-7	/h.U
kon	0.00329	nM/h	$vtnf$	1	nM/h	$nf1$	4	-
deg_{rp}	0.0572	/h	kp_{tnf}	10	pg/ml	$nf4$	3	-
krt	0.63	/h	m	4	-	$n4$	2	-
kre	0.57	/h	nx	1	-	$nf2$	6	-
$taup$	0.1401	H	$nf3$	2	-			
Parameters for transcriptional regulatory network								
nf_{gcr}	5	AU	K_{ATP}	2.8	mM	$fFFA1$	5	-
$s2$	2	-	$AMPKt$	1	AU	$kmffa1$	1.15	mM
$Kmgcr$	20	μg/dL	$kcb1$	0.003	AU/min	$fpgc$	5	-
$ksr1$	3E-3	AU/min	$kcb2$	0.02	/min	$kmpgc$	2	AU
$ksr2$	5E-3	/min	$kcb0$	0.016	AU /min	$fpka2$	10	-
$ksr0$	8E-3	AU /min	$kpc1$	8E-4	AU /min	$kmpka2$	3	AU

<i>kprg1</i>	9E-3	<i>AU /min</i>	<i>kpc2</i>	0.02	<i>/min</i>	<i>fakt2</i>	3	-
<i>kprg2</i>	0.02	<i>/min</i>	<i>kpc0</i>	0.016	<i>AU /min</i>	<i>kmakt2</i>	2	<i>AU</i>
<i>kprg0</i>	0.03	<i>AU /min</i>	<i>ktr1</i>	1.65E-3	<i>AU /min</i>	<i>fglu</i>	5	-
<i>kprg3</i>	5E-3	<i>AU /min</i>	<i>ktr2</i>	0.02	<i>/min</i>	<i>kmglu</i>	10	<i>mM</i>
<i>kpra1</i>	2.5E-3	<i>AU /min</i>	<i>ktr0</i>	0.014	<i>AU /min</i>	<i>fpka3</i>	5	-
<i>kpra2</i>	0.02	<i>/min</i>	<i>fs6k</i>	0.5	-	<i>kmpka3</i>	2	<i>AU</i>
<i>kpra0</i>	0.012	<i>AU /min</i>	<i>kms6k</i>	1	<i>AU</i>	<i>fampk1</i>	1.25	-
<i>kpra3</i>	5E-3	<i>AU /min</i>	<i>fcAMP</i>	2	-	<i>kiampk</i>	0.4	<i>AU</i>
<i>khr1</i>	0.02	<i>AU /min</i>	<i>kicAMP</i>	3.2E-6	<i>mM</i>	<i>fglnac</i>	5	-
<i>khr2</i>	0.02	<i>/min</i>	<i>fAMPK</i>	1.25	-	<i>kmglnac</i>	0.05	<i>mM</i>
<i>khr0</i>	2.5E-3	<i>AU /min</i>	<i>kiAMPK</i>	0.5	<i>AU</i>	<i>fakt3</i>	3	-
<i>kcr1</i>	5E-3	<i>AU /min</i>	<i>kiFOXO</i>	0.5	<i>AU</i>	<i>kmakt3</i>	2.2	<i>AU</i>
<i>kcr2</i>	0.03	<i>/min</i>	<i>fins</i>	5	-	<i>fpparg</i>	1.25	-
<i>CREBt</i>	1	<i>AU</i>	<i>kins</i>	2	-	<i>kmpparg</i>	2	<i>AU</i>
<i>kfr11</i>	2.5346E-3	<i>AU/min</i>	<i>kmffa</i>	1.7	<i>mM</i>	<i>fakt4</i>	5	-
<i>kfr0</i>	1.215E-3	<i>AU/min</i>	<i>fFFA</i>	12.5	-	<i>kmakt4</i>	2	<i>AU</i>
<i>kfr2</i>	0.0215	<i>/min</i>	<i>fakt1</i>	5	-	<i>fpka4</i>	5	-
<i>kam1</i>	1	<i>AU</i>	<i>kmakt1</i>	2	<i>AU</i>	<i>kmpka4</i>	2	<i>AU</i>
<i>Kam2</i>	1.1925	<i>AU</i>	<i>fFoxo</i>	1.25	-	<i>fpkc1</i>	3	-
<i>K_{AMP}</i>	0.16	<i>mM</i>	<i>fpka</i>	5	-	<i>kmpkc</i>	3	<i>AU</i>
<i>fppar</i>	5	-	<i>kmcreb1</i>	0.5	<i>AU</i>	<i>fcAMP1</i>	10	-
<i>kmppar</i>	2	<i>AU</i>	<i>fampk1</i>	5	-	<i>kmcAMP1</i>	3	<i>AU</i>
<i>fpgc1</i>	5	-	<i>ftnfil6</i>	5	-	<i>ffoxo1</i>	5	-
<i>kmpgc1</i>	2	<i>AU</i>	<i>kmtnfil6</i>	100	<i>pg/ml</i>	<i>kmfoxo1</i>	0.5	<i>AU</i>
<i>PKA_b</i>	9E-6	<i>mM</i>	<i>fpi3k</i>	4	-	<i>fakt5</i>	3	-
<i>cAMP_b</i>	3.2E-6	<i>mM</i>	<i>kmpi3k</i>	1.25	<i>AU</i>	<i>kmakt5</i>	2.25	<i>AU</i>
<i>kmpka</i>	2	<i>AU</i>	<i>fpkc2</i>	2	-	<i>kmhif</i>	0.5	<i>AU</i>
<i>s3</i>	3.5	-	<i>kmpkc2</i>	2	<i>AU</i>	<i>fcreb1</i>	5	-

Metabolic Control Analysis (Related to Figure 4)

Table S5: Metabolic concentration response coefficients for the model parameters that reproduced MD signature. (-) prefix indicates reduction in the parameter resulted in MD signature. The list includes parameters that yielded the MCRC of at least 0.001 for each of the 12 metabolites in the MD signature. The table includes the 34 parameters reported in Figure 2B (MCRC of at least 0.1).

Model Parameters	MCRCs	Model Parameters	MCRCs
Metabolic fluxes			
α -ketoglutarate dehydrogenase flux	0.317	Activation of TNF	0.014
Glycerol phosphorylation	0.179	Saturation constant of phagocytes on TNF	0.182
(-) Lipolysis	0.028	Rate of TNF positive feedback	0.142
Triglyceride synthesis	0.175	(-) Degradation of TNF	0.183
(-) Alanine to protein synthesis	0.041	Plasma Endotoxin concentration	0.203
Protein breakdown to amino acids	0.032	(-)Rate of TGF activation by PI3k	0.003
Plasma glycerol levels	0.173	Activation of TNF by CREB/NFkb	0.134
Plasma Amino acid (except glutamine)	0.490	(-) Sensitivity of anti-inflammatory effect of TGF on TNF	0.070
(-) Degradation rate of SREBP1c	0.340	Saturation constant for effect of TGF on TNF	0.308
GPCR signaling pathway		HPA-axis and GCR signaling	
(-) Saturation constant of glucagon secretion	0.442	(-) Activation of anti-inflammatory response by GCR	0.504
Catecholamine/ Glucagon secretion	0.494	Saturation constant of GCR for anti-inflammatory action	0.405
(-)Degradation of Catecholamine	0.334	Sensitivity of GCR negative feedback on inflammation	0.838
(-) β -adrenergic receptor-ligand dissociation constant	0.252	(-) Sensitivity of GCR central negative feedback	0.710
(-)Rate of GPCR sequestration	0.258	Inhibitory constant of HPA negative feedback	0.383
(-)Rate of G-protein deactivation	0.260	Stress parameter at CRH (HPA axis)	0.192
Degradation of GPCR activated PLC	0.306	(-) Sensitivity of HPA axis to inflammatory cytokines	0.253
Activation of calcium signaling by G-protein	0.485	(-)Degradation of CRH	0.334
(-) Suppression pf calcium signaling	0.336	Activation of ACTH by CRH	0.304
Inflammatory signaling pathway		(-)Degradation of ACTH	0.342
Rate of phagocyte activation	0.207	Activation rate of CRH by TNF	0.142
(-)Rate of TGF activation by phagocytes	0.003	(-) Activation threshold of HPA axis by TNF	0.042
Degradation of TGF anti-inflammatory cytokine	0.410	Sensitivity of GCR negative feedback (central + immune)	1.005

Correlational Analysis (Related to Figure 6)

Table S6 (A): The statistically significant ($p \leq 0.05$) spearman correlation coefficients in controls and PTSD. The fold change in statistically significant correlation coefficients in PTSD with respect to controls (the coefficients in controls were taken based on p -values ≤ 0.05 in PTSD). The correlations highlighted in red are the positive associations and the correlations highlighted in green are the negative associations. The correlations of zero indicate statistically insignificant correlations.

Correlations Metabolites	Controls								PTSD								Fold change in PTSD							
	Cort. Supp	IC50	CORT	HOMAIR	hsCRP	GGT	HYPOX	Urn.EPN	Cort. Supp	IC50	CORT	HOMAIR	hsCRP	GGT	HYPOX	Urn.EPN	Cort. Supp	IC50	CORT	HOMAIR	hsCRP	GGT	HYPOX	Urn.EPN
Glucose	0.281	-0.263	0.000	0.559	0.000	0.276	0.249	0.000	0.000	0.000	0.000	0.549	0.224	0.000	0.000	0.000	0.000	0.000	0.000	0.981	2.726	0.000	0.000	0.000
Pyruvate	0.000	0.000	0.278	0.404	0.000	0.000	0.374	0.000	0.000	0.000	0.000	0.000	0.000	0.251	0.584	0.000	0.000	0.000	0.000	0.000	0.000	1.298	1.561	0.000
Lactate	0.000	-0.221	0.304	0.437	0.000	0.000	0.327	0.000	0.311	0.000	0.000	0.450	0.000	0.347	0.470	0.000	1.435	0.000	0.000	1.031	0.000	2.217	1.438	0.000
Citrate	0.000	0.000	0.000	-0.340	-0.344	-0.270	-0.232	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
Arginine	0.000	0.000	0.000	0.000	0.000	0.000	0.000	-0.221	0.000	0.000	0.000	0.000	0.000	0.000	0.216	0.000	0.000	0.000	0.000	0.000	0.000	0.000	-7.086	0.000
Ornithine	0.000	0.000	-0.230	0.261	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	-0.340	0.000	0.000	0.000	0.000	0.000	0.000	0.000	75.793
Alanine	0.287	0.000	0.000	0.354	0.000	0.000	0.000	0.000	0.334	0.000	0.000	0.000	0.000	0.000	0.000	0.000	1.162	0.000	0.000	0.000	0.000	0.000	0.000	0.000
Glutamine	0.000	0.000	0.000	0.000	-0.267	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
Tyrosine	0.000	0.000	0.000	0.282	0.000	0.264	0.000	0.000	0.240	0.000	0.000	0.392	0.260	0.518	0.222	0.000	1.126	0.000	0.000	1.389	1.410	1.960	1.256	0.000
Isoleucine	0.000	0.000	0.000	0.391	0.281	0.222	0.000	0.000	0.000	0.000	0.000	0.265	0.230	0.349	0.000	-0.220	0.000	0.000	0.000	0.680	0.820	1.577	0.000	-4.118
Leucine	0.000	0.000	0.000	0.323	0.237	0.000	0.252	0.000	0.000	0.000	0.000	0.320	0.265	0.338	0.220	0.000	0.000	0.000	0.000	0.990	1.117	2.049	0.871	0.000
Valine	0.000	0.000	0.000	0.264	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.254	0.247	0.296	0.246	0.000	0.000	0.000	0.000	0.962	1.746	2.187	2.356	0.000
Undecenoate.11n1.	0.000	0.000	0.000	0.000	0.000	0.000	0.261	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.277	0.000	0.000	0.000	0.000	0.000	0.000	0.000	1.283
X17.methylstearate	0.000	0.000	0.000	-0.271	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
X2.hydroxypalmitate	0.000	0.000	0.000	0.000	0.231	0.000	0.000	0.221	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.292	0.000	0.000	0.000	0.000	0.000	0.000	0.000	1.321
Arachidonate..20.4n6.	0.000	0.000	0.000	-0.238	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.243	0.000	0.000	0.000	0.000	0.000	0.000	0.000	-4.236
Nonadecenoate.19n9.	0.000	0.000	0.000	-0.220	0.000	0.000	0.000	0.237	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.274	0.000	0.000	0.000	0.000	0.000	0.000	0.000	1.154
Nonadecanoate..19.0.	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.277	0.000	0.000	0.000	0.000	0.000	0.000	0.000	1.296
Stearate..18.0.	0.000	0.000	0.000	0.000	0.000	0.000	0.244	0.000	0.000	0.000	0.000	0.000	0.246	0.000	0.000	0.248	0.000	0.000	0.000	0.000	1.703	0.000	0.000	1.542
Carnitine	0.000	0.000	0.000	0.000	0.000	0.000	-0.220	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
Decanoylcarnitine	0.000	0.000	0.365	0.000	0.000	0.000	0.267	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
Octanoylcarnitine	0.000	0.000	0.297	0.000	0.000	0.000	0.219	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
Palmitoylcarnitine	0.000	0.000	0.292	0.000	0.000	0.000	0.316	0.000	0.000	0.000	0.000	0.232	0.000	0.304	0.328	0.000	0.000	0.000	0.000	37.600	0.000	3.565	1.037	0.000
Glycerate	0.000	0.000	0.000	-0.314	-0.255	-0.241	-0.352	0.000	0.000	0.000	0.000	-0.291	-0.225	-0.443	-0.396	0.000	0.000	0.000	0.000	0.929	0.883	1.835	1.128	0.000
Triglyceride	0.312	0.000	0.000	0.653	0.348	0.296	0.000	0.000	0.000	0.000	0.000	0.468	0.507	0.432	0.000	0.000	0.000	0.000	0.000	0.717	1.457	1.461	0.000	0.000
Gamaglutamyltyrosine	0.304	0.000	0.000	0.341	0.231	0.283	0.000	0.000	0.000	0.000	0.000	0.226	0.318	0.335	0.222	0.000	0.000	0.000	0.000	0.664	1.376	1.184	2.963	0.000
Oxoproline	0.000	0.000	0.000	0.000	0.000	-0.219	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	-0.277	0.000	0.000	0.000	0.000	0.000	0.000	0.000	2.374	0.000
Stearoyl.sphingomyelin	0.000	0.000	0.000	0.230	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.240	0.000	0.000	0.000	0.000	0.000	0.000	0.000	1.268	0.000	0.000
IL6	0.241	0.000	-0.236	0.233	0.496	0.000	0.000	0.000	0.000	0.241	-0.236	0.260	0.270	0.243	0.000	0.000	0.000	2.728	0.999	1.115	0.545	1.894	0.000	0.000
TNF	0.000	0.000	0.000	0.000	0.248	0.000	0.000	-0.219	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
Sphingosine.1.phosphate	0.000	-0.226	0.000	0.229	0.000	0.000	0.374	0.000	0.000	0.000	0.000	0.000	0.262	0.218	0.300	0.000	0.000	0.000	0.000	0.000	16.423	2.123	0.802	0.000
Albumin	0.000	0.000	0.305	0.000	0.000	0.000	0.364	0.000	0.000	0.000	0.000	0.242	0.000	0.000	0.000	0.000	0.000	0.000	0.000	1.387	0.000	0.000	0.000	0.000
Alkaline.phosphatase	0.256	0.000	0.000	0.374	0.344	0.335	0.000	0.247	0.000	0.000	0.000	0.396	0.000	0.480	0.000	0.000	0.000	0.000	0.000	1.059	0.000	1.433	0.000	0.000
Bilirubin.E.E.	0.000	0.000	0.000	-0.448	-0.360	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
Total protein	0.000	0.000	0.414	0.300	0.297	0.329	0.312	0.000	0.000	0.000	0.000	0.257	0.309	0.318	0.000	0.000	0.000	0.000	0.000	0.854	1.042	0.966	0.000	0.000
Cortisol Suppression	NA	0.000	0.000	0.301	0.000	0.000	0.000	0.000	NA	0.000	0.000	0.271	0.000	0.251	0.000	0.000	NA	0.000	0.000	0.902	0.000	1.618	0.000	0.000
IC50	0.000	NA	0.000	0.000	0.000	0.000	0.000	0.000	0.000	NA	0.000	0.000	0.000	0.000	0.000	0.000	0.000	NA	0.000	0.000	0.000	0.000	0.000	0.000
Cortisol	0.301	0.000	NA	0.000	0.000	0.000	0.268	0.000	0.000	0.000	NA	0.000	0.000	0.000	0.000	0.000	0.000	0.000	NA	0.000	0.000	0.000	0.000	0.000
HOMAIR	0.000	0.000	0.000	NA	0.334	0.584	0.000	0.000	0.271	0.000	0.000	NA	0.313	0.490	0.246	0.000	0.902	0.000	0.000	NA	0.937	0.840	1.140	0.000
hsCRP	0.000	0.000	0.000	0.334	NA	0.312	0.000	0.000	0.000	0.000	0.000	0.313	NA	0.512	0.226	0.000	0.000	0.000	0.000	0.937	NA	1.640	3.620	0.000
GGT	0.000	0.000	0.000	0.584	0.312	NA	0.000	0.000	0.251	0.000	0.000	0.490	0.512	NA	0.297	0.000	1.618	0.000	0.000	0.840	1.640	NA	2.656	0.000
Hypoxanthine	0.000	0.000	0.268	0.000	0.000	0.000	NA	0.000	0.000	0.000	0.000	0.246	0.226	0.297	NA	0.226	0.000	0.000	0.000	1.140	3.620	2.656	NA	-21.112
Urn.Epinephrine	0.000	0.000	0.000	0.000	0.000	0.000	NA	0.000	0.000	0.000	0.000	0.000	0.000	0.226	NA	0.000	0.000	0.000	0.000	0.000	0.000	-21.112	0.000	NA

Table S6 (B): Regulatory correlates of metabolic dysfunction in entire cohort (PTSD+Controls). Red and yellow shade highlights the p and q values <=0.05 and between 0.05 and 0.1, respectively.

Metabolic pathways	Regulations		Cortisol		Cortisol suppression				IC50		Urinary Epinephrine		
	Metabolites	p	p-value	q-value	p	p-value	q-value	p	p-value	q-value	p	p-value	q-value
Glycolysis and TCA Cycle	Glucose	0.103	0.188	0.314	0.214	0.006	0.020	-0.073	0.353	0.476	0.109	0.164	0.282
	Pyruvate	0.197	0.011	0.036	0.175	0.024	0.067	-0.147	0.059	0.129	0.120	0.126	0.231
	Lactate	0.216	0.005	0.020	0.323	2.31E-05	1.72E-04	-0.151	0.053	0.119	0.121	0.122	0.225
	Citrate	0.093	0.235	0.364	-0.157	0.044	0.101	0.070	0.373	0.497	0.050	0.524	0.653
Urea Cycle	Arginine	-0.012	0.876	0.913	0.001	0.986	0.992	-0.049	0.530	0.658	-0.111	0.156	0.271
	Ornithine	-0.075	0.338	0.465	0.223	0.004	0.015	-0.032	0.679	0.758	-0.139	0.076	0.154
Glucogenic	Alanine	0.089	0.257	0.390	0.333	1.20E-05	9.87E-05	-0.038	0.624	0.720	-0.100	0.203	0.325
amino acids	Glutamine	0.126	0.107	0.204	0.017	0.830	0.884	-0.031	0.696	0.769	-0.049	0.535	0.658
	Tyrosine	0.147	0.059	0.129	0.254	0.001	0.005	-0.081	0.301	0.426	-0.052	0.509	0.639
Branched chain	Isoleucine	0.010	0.894	0.926	0.196	0.012	0.036	-0.084	0.285	0.413	-0.048	0.541	0.658
amino acids	Leucine	0.056	0.471	0.603	0.134	0.085	0.172	-0.070	0.372	0.497	-0.040	0.613	0.712
	Valine	0.083	0.291	0.419	0.142	0.070	0.144	-0.128	0.101	0.197	0.000	0.999	1.000
Long chain fatty acids	Undecenoate..11n1.	-0.075	0.340	0.465	-0.183	0.018	0.054	0.037	0.636	0.727	0.013	0.870	0.910
	X17.methylstearate	0.048	0.544	0.658	-0.096	0.220	0.346	0.116	0.137	0.245	0.185	0.017	0.051
	X2.hydroxypalmitate	0.117	0.136	0.245	-0.090	0.252	0.383	0.165	0.034	0.085	0.061	0.434	0.559
	Arachidonate..20.4n6.	0.063	0.423	0.550	-0.112	0.151	0.267	0.209	0.007	0.024	0.206	0.008	0.027
	Nonadecenoate..19n9.	0.048	0.540	0.658	-0.173	0.026	0.070	0.102	0.194	0.318	0.175	0.024	0.067
	Nonadecanoate..19.0.	-0.039	0.621	0.719	-0.162	0.038	0.091	0.167	0.032	0.082	0.151	0.053	0.119
	Stearate..18.0.	0.009	0.913	0.937	-0.088	0.262	0.394	0.175	0.025	0.067	0.129	0.098	0.195
Carnitines	Carnitine	-0.068	0.388	0.514	0.180	0.020	0.059	0.092	0.241	0.371	-0.041	0.599	0.704
	Decanoylcarnitine	0.272	4.02E-04	0.002	-0.019	0.808	0.869	-0.134	0.086	0.174	0.179	0.021	0.060
	Octanoylcarnitine	0.209	0.007	0.024	-0.084	0.284	0.413	-0.101	0.196	0.318	0.164	0.035	0.086
	Palmitoylcarnitine	0.141	0.071	0.146	0.036	0.646	0.734	-0.074	0.347	0.471	0.034	0.661	0.745
Triglycerids metabolism	Glycerate	-0.087	0.268	0.399	-0.074	0.342	0.467	0.055	0.481	0.608	-0.083	0.290	0.419
	Triglyceride	-0.031	0.691	0.767	0.261	0.001	0.003	0.060	0.447	0.574	-0.008	0.917	0.937
	Gamaglutamyltyrosine	0.167	0.032	0.082	0.230	0.003	0.012	-0.013	0.868	0.910	-0.076	0.333	0.462
Oxidative stress	Oxoproline	0.145	0.063	0.133	0.169	0.030	0.078	-0.055	0.487	0.613	-0.018	0.817	0.873
and Inflammation	Stearyl.sphingomyelin	-0.077	0.327	0.455	0.146	0.061	0.131	-0.103	0.187	0.314	0.115	0.142	0.251
	IL6	-0.159	0.042	0.099	0.233	0.003	0.011	0.104	0.186	0.314	0.117	0.136	0.245
	TNF	-0.082	0.296	0.422	0.082	0.293	0.420	0.021	0.787	0.854	-0.126	0.107	0.204
	Sphingosine.1.phosphate	0.041	0.600	0.704	0.080	0.306	0.431	-0.181	0.020	0.058	0.082	0.297	0.423
Hepatic function	Albumin	0.278	2.95E-04	0.002	0.104	0.185	0.314	-0.073	0.353	0.476	0.041	0.603	0.705
	Alkaline.phoshatase	0.079	0.313	0.440	0.244	0.002	0.007	0.088	0.261	0.394	0.161	0.039	0.092
	Bilirubin.E.E.	-0.077	0.324	0.453	-0.190	0.014	0.044	0.100	0.203	0.325	-0.015	0.847	0.899
	Total protein	0.275	3.48E-04	0.002	0.179	0.021	0.060	-0.087	0.267	0.399	0.100	0.201	0.324
Regulatory components	Cortisol	1.000	0.000	0.000	0.047	0.552	0.660	-0.167	0.032	0.082	0.084	0.285	0.413
	Cortisol.supp	0.047	0.552	0.660	1.000	0.000	0.000	-0.125	0.110	0.205	-0.025	0.746	0.812
	IC50	-0.167	0.032	0.082	-0.125	0.110	0.205	1.000	0.000	0.000	-0.048	0.541	0.658
	Urinary epinephrine	0.084	0.285	0.413	-0.025	0.746	0.812	-0.048	0.541	0.658	1.000	0.000	0.000
	HOMAIR	0.006	0.934	0.948	0.328	1.67E-05	1.28E-04	-0.047	0.550	0.660	-0.020	0.800	0.863
	hsCRP	0.026	0.745	0.812	0.142	0.068	0.142	-0.065	0.406	0.534	0.129	0.099	0.195
	GGT	-0.010	0.902	0.929	0.265	0.001	0.003	-0.094	0.231	0.359	-0.014	0.859	0.904
	Hypoxanthine	0.103	0.190	0.314	0.097	0.216	0.343	-0.164	0.036	0.086	0.170	0.029	0.077

Table S6 (B) (continued)

Metabolic pathways	Regulations		HOMA1R			hsCRP			GGT			Hypoxanthine	
	Metabolites	p	p-value	q-value	p	p-value	q-value	p	p-value	q-value	p	p-value	q-value
Glycolysis and TCA Cycle	Glucose	0.609	4.01E-18	1.53E-16	0.232	0.003	0.011	0.263	0.001	0.003	0.217	0.005	0.019
	Pyruvate	0.363	1.71E-06	1.84E-05	0.196	0.012	0.036	0.315	3.88E-05	2.78E-04	0.525	4.78E-13	1.26E-11
	Lactate	0.518	1.08E-12	2.64E-11	0.193	0.013	0.040	0.348	4.54E-06	4.34E-05	0.460	5.14E-10	1.04E-08
	Citrate	-0.202	0.009	0.031	-0.233	0.003	0.011	-0.243	0.002	0.007	-0.164	0.035	0.086
Urea Cycle	Arginine	-0.091	0.245	0.376	-0.199	0.010	0.034	-0.084	0.281	0.413	0.056	0.474	0.604
	Ornithine	0.190	0.014	0.044	0.037	0.634	0.727	0.101	0.196	0.318	0.005	0.945	0.956
Glucogenic amino acids	Alanine	0.328	1.65E-05	1.28E-04	0.146	0.061	0.131	0.173	0.027	0.071	0.164	0.035	0.086
	Glutamine	-0.174	0.026	0.070	-0.200	0.010	0.034	-0.229	0.003	0.012	-0.159	0.041	0.098
	Tyrosine	0.388	2.71E-07	3.73E-06	0.267	0.001	0.003	0.437	4.44E-09	8.03E-08	0.246	0.001	0.007
Branched chain amino acids	Isoleucine	0.364	1.58E-06	1.75E-05	0.279	2.81E-04	0.002	0.320	2.76E-05	2.02E-04	0.180	0.021	0.059
	Leucine	0.346	5.14E-06	4.78E-05	0.269	4.73E-04	0.003	0.283	2.32E-04	0.001	0.245	0.002	0.007
	Valine	0.283	2.28E-04	0.001	0.198	0.011	0.035	0.224	0.004	0.015	0.215	0.006	0.020
	Undecenoate..11n1.	-0.212	0.006	0.022	-0.125	0.109	0.205	-0.048	0.541	0.658	-0.111	0.157	0.271
Long chain fatty acids	X17.methylstearate	-0.005	0.952	0.961	0.043	0.580	0.689	0.000	1.000	1.000	0.026	0.737	0.812
	X2.hydroxypalmitate	-0.197	0.011	0.036	0.034	0.667	0.750	-0.156	0.045	0.103	-0.151	0.053	0.119
	Arachidonate..20.4n6.	-0.122	0.118	0.219	0.063	0.421	0.550	-0.069	0.376	0.500	-0.091	0.246	0.376
	Nonadecenoate..19n9.	-0.043	0.581	0.689	0.062	0.430	0.557	0.033	0.674	0.755	0.147	0.060	0.130
	Nonadecanoate..19.0.	-0.140	0.074	0.151	-0.014	0.859	0.904	-0.144	0.066	0.139	-0.103	0.190	0.314
	Stearate..18.0.	0.011	0.885	0.920	0.150	0.054	0.119	0.032	0.686	0.763	0.158	0.042	0.099
Carnitines	Carnitine	0.071	0.366	0.491	0.042	0.589	0.696	0.133	0.087	0.175	0.008	0.918	0.937
	Decanoylcarnitine	-0.037	0.636	0.727	0.056	0.477	0.605	0.040	0.611	0.712	0.107	0.172	0.294
	Octanoylcarnitine	0.019	0.813	0.871	0.051	0.517	0.646	0.063	0.422	0.550	0.102	0.192	0.316
	Palmitoylcarnitine	0.150	0.055	0.121	0.128	0.102	0.198	0.222	0.004	0.015	0.344	6.04E-06	5.47E-05
Triglycerids metabolism	Glycerate	-0.334	1.18E-05	9.87E-05	-0.263	0.001	0.003	-0.387	2.83E-07	3.74E-06	-0.393	1.84E-07	2.64E-06
	Triglyceride	0.570	1.41E-15	4.05E-14	0.450	1.28E-09	2.45E-08	0.430	8.14E-09	1.33E-07	0.112	0.153	0.268
Oxidative stress and Inflammation	Gamaglutamyltyrosine	0.337	9.36E-06	8.05E-05	0.302	8.E-05	0.001	0.349	4.32E-06	4.25E-05	0.186	0.017	0.050
	Oxoproline	-0.035	0.659	0.745	-0.112	0.153	0.268	-0.127	0.104	0.199	-0.119	0.129	0.237
	Stearoyl.sphingomyelin	0.223	0.004	0.015	0.238	0.002	0.009	0.306	6.24E-05	4.38E-04	0.128	0.102	0.198
	IL6	0.288	1.80E-04	0.001	0.411	4.23E-08	6.33E-07	0.247	0.001	0.006	0.036	0.643	0.733
	TNF	0.155	0.047	0.108	0.117	0.135	0.245	0.076	0.335	0.462	-0.086	0.274	0.406
	Sphingosine.1.phosphate	0.229	0.003	0.012	0.158	0.043	0.099	0.187	0.016	0.049	0.370	1.E-06	1.E-05
Hepatic function	Albumin	0.270	4.51E-04	0.003	0.094	0.231	0.359	0.244	0.002	0.007	0.262	0.001	0.003
	Alkaline.phosphatase	0.424	1.44E-08	2.25E-07	0.302	8.E-05	0.001	0.433	6.12E-09	1.05E-07	0.234	0.002	0.010
	Bilirubin.E.E.	-0.340	7.95E-06	7.01E-05	-0.235	0.002	0.010	-0.188	0.016	0.048	-0.116	0.138	0.246
	Total protein	0.357	2.55E-06	2.65E-05	0.352	3.45E-06	3.49E-05	0.366	1.36E-06	1.56E-05	0.292	1.44E-04	0.001
	Cortisol	0.006	0.934	0.948	0.026	0.745	0.812	-0.010	0.902	0.929	0.103	0.190	0.314
	Cortisol.suppl	0.328	1.67E-05	1.28E-04	0.142	0.068	0.142	0.265	0.001	0.003	0.097	0.216	0.343
Regulatory components	IC50	-0.047	0.550	0.660	-0.065	0.406	0.534	-0.094	0.231	0.359	-0.164	0.036	0.086
	Urinary epinephrine	-0.020	0.800	0.863	0.129	0.099	0.195	-0.014	0.859	0.904	0.170	0.029	0.077
	HOMA1R	1.000	0.000	0.000	0.372	8.78E-07	1.08E-05	0.600	1.76E-17	5.51E-16	0.292	1.44E-04	0.001
	hsCRP	0.372	8.78E-07	1.08E-05	1.000	0.000	0.000	0.488	2.82E-11	6.06E-10	0.196	0.012	0.036
	GGT	0.600	1.76E-17	5.51E-16	0.488	2.82E-11	6.06E-10	1.000	0.000	0.000	0.258	0.001	0.004
	Hypoxanthine	0.292	1.44E-04	0.001	0.196	0.012	0.036	0.258	0.001	0.004	1.000	0.000	0.000

Causal Inference (Related to Figure 7A)

Table S7: Population level average causal effects. Sensitivity coefficient τ_1 representing the coefficient of unobserved confounder at which ACE=0, sensitivity coefficient τ_2 representing the coefficient of unobserved confounder at which ACE becomes statistically insignificant ($p>0.05$). Red, yellow and green shade highlights the p and q values <0.05 , between 0.05 and 0.1 and $\tau_2 >0.2$, respectively.

Metabolic pathways	Regulators	Cortisol Suppression						IC ₅₀ Dex-lysozyme suppression						HOMAIR					
	Metabolites	ACE (Y)	Std. error	p-value	q-value	τ_1	τ_2	ACE (Y)	Std. error	p-value	q-value	τ_1	τ_2	ACE (Y)	Std. error	p-value	q-value	τ_1	τ_2
Glycolysis and TCA Cycle	Glucose	0.020	0.031	0.513	0.671	0.000	0.000	0.008	0.010	0.420	0.579	0.000	0.000	0.100	0.016	1.94E-09	4.76E-08	0.519	0.405
	Pyruvate	1.156	0.674	0.089	0.210	0.000	0.000	-0.217	0.232	0.352	0.535	0.000	0.000	1.416	0.391	4.06E-04	0.004	0.450	0.310
	Lactate	0.407	0.281	0.149	0.306	0.000	0.000	-0.035	0.094	0.712	0.804	0.000	0.000	0.813	0.145	9.70E-08	2.17E-06	0.507	0.407
	Citrate	-0.534	0.187	0.005	0.026	0.457	0.259	0.013	0.063	0.832	0.902	0.000	0.000	-0.204	0.111	0.067	0.180	0.000	0.000
Urea Cycle	Arginine	0.080	0.207	0.698	0.795	0.000	0.000	0.012	0.069	0.866	0.915	0.000	0.000	0.165	0.127	0.194	0.366	0.000	0.000
	Ornithine	0.380	0.318	0.233	0.416	0.000	0.000	0.111	0.113	0.327	0.503	0.000	0.000	0.462	0.188	0.015	0.061	0.387	0.119
Glucogenic amino acids	Alanine	0.483	0.228	0.036	0.115	0.403	0.167	0.069	0.079	0.382	0.560	0.000	0.000	0.395	0.130	0.003	0.017	0.410	0.218
	Glutamine	-0.088	0.105	0.403	0.579	0.000	0.000	-0.029	0.035	0.422	0.579	0.000	0.000	-0.063	0.063	0.312	0.494	0.000	0.000
	Tyrosine	0.313	0.184	0.091	0.212	0.000	0.000	-0.005	0.062	0.932	0.959	0.000	0.000	0.275	0.118	0.021	0.080	0.379	0.195
Branched chain amino acids	Isoleucine	0.281	0.162	0.086	0.207	0.000	0.000	-0.005	0.055	0.926	0.957	0.000	0.000	0.205	0.100	0.041	0.123	0.361	0.094
	Leucine	0.143	0.137	0.299	0.483	0.000	0.000	0.000	0.044	0.992	0.995	0.000	0.000	0.128	0.082	0.120	0.260	0.000	0.000
	Valine	0.077	0.149	0.607	0.729	0.000	0.000	-0.018	0.051	0.723	0.805	0.000	0.000	0.116	0.089	0.195	0.366	0.000	0.000
Long chain fatty acids	10-Nonadecenoate 19:1 (o-9)	0.003	0.324	0.992	0.995	0.000	0.000	-0.087	0.111	0.432	0.590	0.000	0.000	-0.450	0.190	0.019	0.076	0.371	0.180
	10-Undecenoate 11:1 (o-1)	-0.141	0.353	0.691	0.795	0.000	0.000	0.151	0.118	0.201	0.375	0.000	0.000	-0.118	0.199	0.554	0.704	0.000	0.000
	17-Methylstearate	-0.050	0.156	0.749	0.830	0.000	0.000	0.055	0.052	0.291	0.478	0.000	0.000	-0.261	0.091	0.005	0.025	0.402	0.183
	2-Hydroxypalmitate	-0.542	0.287	0.061	0.169	0.000	0.000	0.166	0.100	0.099	0.223	0.000	0.000	-0.385	0.164	0.020	0.079	0.359	0.092
	Nonadecanoate 19:0	-0.876	0.388	0.025	0.091	0.413	0.142	0.094	0.127	0.461	0.624	0.000	0.000	-0.502	0.233	0.033	0.107	0.349	0.123
	Arachidonate 20:4 (o-6)	-0.462	0.244	0.060	0.169	0.000	0.000	0.157	0.081	0.055	0.158	0.000	0.000	-0.251	0.144	0.082	0.207	0.000	0.000
	Stearate 18:0	-0.224	0.201	0.268	0.456	0.000	0.000	0.169	0.067	0.013	0.055	0.430	0.189	-0.164	0.120	0.174	0.344	0.000	0.000
Carnitines	Carnitine	0.062	0.116	0.592	0.720	0.000	0.000	0.047	0.038	0.222	0.402	0.000	0.000	-0.008	0.069	0.911	0.949	0.000	0.000
	Decanoylcarnitine	0.497	0.708	0.484	0.647	0.000	0.000	-0.212	0.237	0.374	0.560	0.000	0.000	-0.462	0.430	0.284	0.469	0.000	0.000
	Octanoylcarnitine	0.299	0.685	0.663	0.781	0.000	0.000	-0.189	0.232	0.417	0.579	0.000	0.000	-0.258	0.425	0.546	0.703	0.000	0.000
	Palmitoylcarnitine	-0.175	0.268	0.516	0.671	0.000	0.000	-0.051	0.087	0.554	0.704	0.000	0.000	-0.019	0.164	0.910	0.949	0.000	0.000
Triglycerids metabolism	Glycerate	-0.154	0.230	0.503	0.665	0.000	0.000	-0.030	0.076	0.697	0.795	0.000	0.000	-0.340	0.133	0.011	0.049	0.380	0.162
	Triglyceride	0.213	0.088	0.017	0.070	0.403	0.135	0.063	0.030	0.038	0.118	0.375	0.111	0.235	0.050	5.31E-06	8.71E-05	0.475	0.340
Oxidative stress and Inflammation	Gamaglutamyltyrosine	0.362	0.201	0.073	0.190	0.000	0.000	0.070	0.069	0.315	0.494	0.000	0.000	0.300	0.131	0.024	0.088	0.383	0.195
	5-Oxoproline	0.134	0.132	0.310	0.494	0.000	0.000	-0.016	0.045	0.720	0.805	0.000	0.000	-0.033	0.083	0.689	0.795	0.000	0.000
	Stearoyl sphingomyelin	0.275	0.262	0.294	0.480	0.000	0.000	-0.003	0.085	0.971	0.987	0.000	0.000	0.314	0.153	0.043	0.127	0.353	0.121
	IL6	1.234	0.547	0.026	0.091	0.415	0.255	0.001	0.178	0.994	0.995	0.000	0.000	0.002	0.334	0.995	0.995	0.000	0.000
	TNF α	0.261	0.213	0.221	0.402	0.000	0.000	0.080	0.073	0.278	0.465	0.000	0.000	-0.068	0.132	0.607	0.729	0.000	0.000
Hepatic function	Sphingosine 1 phosphate	-0.144	0.381	0.705	0.800	0.000	0.000	-0.127	0.125	0.314	0.494	0.000	0.000	0.186	0.229	0.419	0.579	0.000	0.000
	Albumin	0.041	0.029	0.156	0.314	0.000	0.000	-0.006	0.009	0.495	0.658	0.000	0.000	0.066	0.016	6.11E-05	0.001	0.473	0.335
	Alkaline phosphatase	0.162	0.053	0.003	0.016	0.478	0.306	0.033	0.018	0.068	0.180	0.000	0.000	0.101	0.033	0.002	0.015	0.428	0.236
	Bilirubin EE	-1.154	0.425	0.007	0.038	0.454	0.188	-0.033	0.153	0.828	0.901	0.000	0.000	-0.997	0.248	9.25E-05	0.001	0.472	0.341
	Total protein	0.056	0.023	0.014	0.058	0.429	0.198	0.003	0.008	0.664	0.781	0.000	0.000	0.040	0.013	0.003	0.017	0.410	0.185
Regulators	Cortisol suppression							-0.016	0.027	0.559	0.705	0.000	0.000	0.156	0.048	0.001	0.010	0.437	0.287
	IC50-Dex	-0.135	0.247	0.586	0.720	0.000	0.000							-0.029	0.150	0.848	0.912	0.000	0.000
	HOMA-IR	0.411	0.134	0.003	0.016	0.419	0.291	0.027	0.048	0.576	0.719	0.000	0.000						
	hs-CRP	1.808	0.683	0.009	0.042	0.428	0.315	0.097	0.227	0.671	0.782	0.000	0.000	0.343	0.392	0.383	0.560	0.000	0.000
	GGT	0.362	0.134	0.008	0.038	0.428	0.298	0.011	0.042	0.799	0.882	0.000	0.000	0.304	0.074	5.94E-05	0.001	0.442	0.307
	Hypoxanthine	0.74	0.56	0.18	0.36	0.00	0.00	-0.11	0.20	0.59	0.72	0.00	0.00	0.73	0.34	0.03	0.10	0.36	0.09

Table S7 (continued)

Metabolic pathways	Regulators	hs-CRP						GGT						Hypoxanthine					
	Metabolites	ACE (Y)	Std. error	p-value	q-value	τ_1	τ_2	ACE (Y)	Std. error	p-value	q-value	τ_1	τ_2	ACE (Y)	Std. error	p-value	q-value	τ_1	τ_2
Glycolysis and TCA Cycle	Glucose	-0.005	0.003	0.094	0.215	0.000	0.000	-0.004	0.017	0.803	0.882	0.000	0.000	0.000	0.004	0.965	0.985	0.000	0.000
	Pyruvate	0.014	0.072	0.849	0.912	0.000	0.000	0.797	0.370	0.033	0.107	0.360	0.135	0.695	0.089	1.07E-12	3.29E-11	0.699	0.583
	Lactate	-0.017	0.028	0.542	0.702	0.000	0.000	0.196	0.150	0.192	0.366	0.000	0.000	0.248	0.031	3.19E-13	1.12E-11	0.619	0.532
	Citrate	-0.084	0.022	1.82E-04	0.002	0.489	0.350	-0.379	0.101	2.67E-04	0.003	0.461	0.315	-0.034	0.025	0.169	0.337	0.000	0.000
Urea Cycle	Arginine	-0.050	0.025	0.050	0.145	0.365	0.211	0.093	0.114	0.414	0.579	0.000	0.000	0.065	0.029	0.030	0.101	0.392	0.211
	Ornithine	-0.043	0.043	0.317	0.494	0.000	0.000	0.454	0.175	0.011	0.046	0.398	0.222	-0.048	0.043	0.262	0.451	0.000	0.000
Glucogenic amino acids	Alanine	-0.004	0.024	0.860	0.912	0.000	0.000	0.142	0.125	0.257	0.448	0.000	0.000	0.086	0.029	0.004	0.021	0.429	0.231
	Glutamine	-0.026	0.011	0.023	0.088	0.379	0.101	-0.112	0.058	0.054	0.158	0.000	0.000	-0.021	0.014	0.126	0.268	0.000	0.000
	Tyrosine	0.023	0.019	0.211	0.391	0.000	0.000	0.368	0.099	2.99E-04	0.003	0.454	0.313	0.084	0.025	0.001	0.006	0.457	0.192
Branched chain amino acids	Isoleucine	0.032	0.018	0.074	0.190	0.000	0.000	0.446	0.089	1.52E-06	2.87E-05	0.538	0.300	0.045	0.020	0.028	0.097	0.380	0.165
	Leucine	0.015	0.015	0.336	0.514	0.000	0.000	0.244	0.071	0.001	0.006	0.448	0.184	0.057	0.017	0.001	0.006	0.458	0.309
	Valine	0.012	0.019	0.514	0.671	0.000	0.000	0.218	0.081	0.008	0.038	0.409	0.219	0.055	0.018	0.003	0.018	0.435	0.237
Long chain fatty acids	10-Nonadecenoate 19:1 (ω -9)	-0.108	0.040	0.008	0.040	0.439	0.229	0.101	0.185	0.585	0.720	0.000	0.000	-0.070	0.044	0.117	0.255	0.000	0.000
	10-Undecenoate 11:1 (ω -1)	0.044	0.039	0.262	0.451	0.000	0.000	-0.255	0.189	0.178	0.344	0.000	0.000	-0.021	0.048	0.663	0.781	0.000	0.000
	17-Methylstearate	0.020	0.017	0.239	0.420	0.000	0.000	-0.156	0.085	0.067	0.180	0.000	0.000	-0.034	0.021	0.113	0.250	0.000	0.000
	2-Hydroxypalmitate	0.027	0.032	0.409	0.579	0.000	0.000	-0.315	0.152	0.040	0.123	0.348	0.142	-0.016	0.038	0.675	0.783	0.000	0.000
	Nonadecanoate 19:0	-0.006	0.045	0.900	0.946	0.000	0.000	-0.187	0.209	0.371	0.559	0.000	0.000	0.046	0.056	0.416	0.579	0.000	0.000
	Arachidonate 20:4 (ω -6)	0.012	0.026	0.635	0.759	0.000	0.000	-0.200	0.133	0.135	0.284	0.000	0.000	-0.059	0.034	0.083	0.207	0.000	0.000
Carnitines	Stearate 18:0	0.041	0.022	0.061	0.169	0.000	0.000	-0.104	0.105	0.323	0.500	0.000	0.000	0.044	0.027	0.106	0.236	0.000	0.000
	Carnitine	-0.019	0.012	0.126	0.268	0.000	0.000	0.015	0.064	0.821	0.897	0.000	0.000	0.010	0.016	0.555	0.704	0.000	0.000
	Decanoylcarnitine	-0.083	0.075	0.271	0.456	0.000	0.000	-0.336	0.403	0.405	0.579	0.000	0.000	0.180	0.101	0.078	0.200	0.000	0.000
	Octanoylcarnitine	-0.099	0.073	0.175	0.344	0.000	0.000	-0.334	0.396	0.400	0.578	0.000	0.000	0.218	0.095	0.024	0.088	0.407	0.276
Triglycerids metabolism	Palmitoylcarnitine	-0.033	0.030	0.282	0.468	0.000	0.000	0.128	0.148	0.388	0.565	0.000	0.000	0.144	0.033	2.40E-05	3.69E-04	0.528	0.359
	Glycerate	-0.053	0.024	0.029	0.099	0.367	0.146	-0.450	0.120	2.67E-04	0.003	0.460	0.283	-0.147	0.030	3.58E-06	6.30E-05	0.558	0.422
Oxidative stress and Inflammation	Triglyceride	0.020	0.009	0.030	0.102	0.344	0.127	0.216	0.050	2.82E-05	4.09E-04	0.482	0.074	0.011	0.012	0.380	0.560	0.000	0.000
	Gamaglutamyltyrosine	0.039	0.021	0.067	0.180	0.000	0.000	0.425	0.114	2.92E-04	0.003	0.466	0.320	0.040	0.027	0.138	0.288	0.000	0.000
	5-Oxoproline	-0.008	0.015	0.579	0.719	0.000	0.000	-0.078	0.076	0.305	0.490	0.000	0.000	-0.031	0.018	0.092	0.213	0.000	0.000
	Stearoyl sphingomyelin	0.015	0.029	0.594	0.720	0.000	0.000	0.394	0.132	0.003	0.019	0.420	0.298	0.002	0.035	0.951	0.975	0.000	0.000
	IL6	0.373	0.057	1.04E-09	2.85E-08	0.620	0.422	-0.107	0.299	0.720	0.805	0.000	0.000	-0.053	0.070	0.452	0.614	0.000	0.000
	TNF α	-0.021	0.030	0.473	0.636	0.000	0.000	-0.192	0.114	0.094	0.215	0.000	0.000	-0.053	0.031	0.085	0.207	0.000	0.000
Hepatic function	Sphingosine 1 phosphate	0.057	0.039	0.142	0.293	0.000	0.000	-0.248	0.208	0.236	0.417	0.000	0.000	0.252	0.046	2.45E-07	5.02E-06	0.576	0.428
	Albumin	-0.004	0.003	0.228	0.410	0.000	0.000	0.030	0.014	0.038	0.118	0.338	0.118	0.010	0.004	0.010	0.045	0.414	0.183
	Alkaline phosphatase	0.010	0.006	0.086	0.207	0.000	0.000	0.099	0.029	0.001	0.007	0.449	0.212	0.025	0.007	0.001	0.009	0.473	0.192
	Bilirubin EE	-0.055	0.050	0.269	0.456	0.000	0.000	-0.346	0.242	0.154	0.313	0.000	0.000	-0.105	0.060	0.084	0.207	0.000	0.000
Regulators	Total protein	0.003	0.002	0.177	0.344	0.000	0.000	0.020	0.012	0.089	0.210	0.000	0.000	0.010	0.003	0.001	0.009	0.455	0.283
	Cortisol suppression	0.022	0.009	0.010	0.044	0.395	0.158	0.131	0.045	0.004	0.022	0.426	0.257	0.021	0.010	0.040	0.123	0.374	0.193
	IC50-Dex	-0.016	0.028	0.572	0.718	0.000	0.000	-0.214	0.136	0.117	0.255	0.000	0.000	-0.030	0.034	0.382	0.560	0.000	0.000
	HOMA-IR	-0.018	0.014	0.215	0.394	0.000	0.000	0.307	0.075	7.44E-05	0.001	0.428	0.237	0.051	0.019	0.008	0.040	0.376	0.163
	hs-CRP							1.251	0.349	4.54E-04	0.004	0.429	0.218	0.017	0.096	0.859	0.912	0.000	0.000
	GGT	0.053	0.013	1.03E-04	0.001	0.442	0.308							-0.002	0.018	0.916	0.951	0.000	0.000
	Hypoxanthine	0.03	0.06	0.67	0.78	0.00	0.00	0.06	0.32	0.86	0.91	0.00							

Causal mediation analysis: (Related to Figure 7C)

Table S8: The table reports the estimates and statistics for natural direct, natural indirect and total causal effect of glucocorticoid receptor sensitivity assessed by DEX suppression test on metabolites. Red and yellow shade highlights the p and q values <0.05 and between 0.05 and 0.1, respectively.

Metabolic pathways	Natural Effects			Natural Direct Effect						Natural Indirect Effect						Total Causal Effect			
	Metabolites	NDE (wd)	Std. error	CI-lower	CI-upper	p-value	q-value	NIE (vi)	Std. error	CI-lower	CI-upper	p-value	q-value	TCE (wt)	Std. error	CI-lower	CI-upper	p-value	q-value
Glycolysis and TCA Cycle	Glucose	0.002	0.025	-0.047	0.051	0.938	0.984	0.012	0.011	-0.011	0.034	0.304	0.380	0.014	0.023	-0.031	0.058	0.544	0.732
	Pyruvate	0.181	0.413	-0.628	0.990	0.662	0.896	0.644	0.207	0.238	1.050	0.002	0.007	0.825	0.404	0.032	1.617	0.041	0.138
	Lactate	0.000	0.230	-0.450	0.450	0.999	0.999	0.319	0.088	0.146	0.493	3.01E-04	0.002	0.319	0.216	-0.105	0.743	0.140	0.273
	Citrate	-0.347	0.204	-0.747	0.054	0.090	0.492	-0.134	0.048	-0.228	-0.039	0.006	0.016	-0.480	0.195	-0.864	-0.097	0.014	0.098
Urea Cycle	Arginine	-0.065	0.170	-0.398	0.268	0.701	0.896	0.024	0.059	-0.092	0.140	0.686	0.774	-0.041	0.163	-0.361	0.279	0.801	0.852
	Ornithine	0.292	0.210	-0.119	0.703	0.164	0.492	0.110	0.089	-0.065	0.286	0.218	0.294	0.402	0.199	0.012	0.793	0.044	0.138
Glucogenic amino acids	Alanine	0.347	0.224	-0.091	0.785	0.121	0.492	0.125	0.077	-0.025	0.275	0.103	0.172	0.472	0.189	0.100	0.843	0.013	0.098
	Glutamine	-0.047	0.107	-0.258	0.163	0.659	0.896	-0.053	0.028	-0.108	0.002	0.060	0.116	-0.100	0.100	-0.297	0.097	0.318	0.506
	Tyrosine	0.141	0.176	-0.204	0.487	0.423	0.779	0.189	0.041	0.108	0.270	4.34E-06	1.52E-04	0.330	0.177	-0.016	0.676	0.061	0.161
Branched chain amino acids	Isoleucine	0.123	0.120	-0.111	0.358	0.302	0.621	0.162	0.047	0.070	0.254	0.001	0.003	0.285	0.123	0.045	0.526	0.020	0.110
	Leucine	0.036	0.103	-0.165	0.237	0.728	0.896	0.123	0.037	0.051	0.196	0.001	0.004	0.159	0.104	-0.044	0.362	0.124	0.256
	Valine	-0.007	0.121	-0.245	0.231	0.952	0.984	0.093	0.039	0.017	0.169	0.016	0.036	0.086	0.120	-0.149	0.321	0.472	0.661
Long chain fatty acids	10-Nonadecenoate 19:1 (ω-9)	0.139	0.280	-0.410	0.688	0.619	0.896	-0.127	0.099	-0.320	0.066	0.198	0.278	0.012	0.268	-0.513	0.538	0.964	0.964
	10-Undecenoate 11:1 (ω-1)	-0.117	0.357	-0.817	0.583	0.742	0.896	0.032	0.098	-0.159	0.223	0.744	0.814	-0.086	0.345	-0.762	0.591	0.804	0.852
	17-Methylstearate	0.040	0.142	-0.239	0.319	0.777	0.903	-0.070	0.040	-0.147	0.008	0.080	0.140	-0.029	0.135	-0.293	0.235	0.828	0.852
	2-Hydroxypalmitate	-0.484	0.327	-1.125	0.156	0.139	0.492	-0.019	0.081	-0.178	0.140	0.813	0.862	-0.503	0.305	-1.100	0.094	0.098	0.215
	Nonadecanoate 19:0	-0.869	0.453	-1.758	0.019	0.055	0.435	0.004	0.090	-0.174	0.181	0.968	0.968	-0.866	0.445	-1.739	0.007	0.052	0.151
	Arachidonate 20:4 (ω-6)	-0.390	0.276	-0.931	0.152	0.158	0.492	-0.070	0.065	-0.197	0.057	0.280	0.363	-0.460	0.264	-0.976	0.057	0.081	0.190
	Stearate 18:0	-0.276	0.214	-0.694	0.143	0.197	0.492	0.036	0.053	-0.068	0.140	0.494	0.577	-0.239	0.206	-0.643	0.164	0.245	0.412
Carnitines	Carnitine	0.035	0.138	-0.235	0.305	0.800	0.903	0.004	0.031	-0.057	0.066	0.889	0.916	0.039	0.132	-0.220	0.299	0.767	0.852
	Decanoylcarnitine	0.690	0.599	-0.484	1.864	0.249	0.582	-0.234	0.160	-0.547	0.080	0.144	0.219	0.456	0.590	-0.700	1.613	0.439	0.641
	Octanoylcarnitine	0.437	0.581	-0.703	1.576	0.453	0.792	-0.201	0.153	-0.500	0.099	0.189	0.275	0.236	0.574	-0.888	1.360	0.681	0.796
	Palmitoylcarnitine	-0.249	0.275	-0.789	0.291	0.366	0.712	0.104	0.069	-0.032	0.240	0.132	0.211	-0.145	0.272	-0.678	0.389	0.595	0.744
Triglycerides metabolism	Glycerate	0.136	0.261	-0.375	0.648	0.602	0.896	-0.239	0.063	-0.363	-0.116	1.49E-04	0.001	-0.103	0.252	-0.597	0.390	0.682	0.796
	Triglyceride	0.058	0.083	-0.105	0.221	0.486	0.810	0.112	0.026	0.061	0.163	1.55E-05	2.72E-04	0.170	0.084	0.006	0.334	0.042	0.138
Oxidative stress and Inflammation	Gamma-glutamyltyrosine	0.203	0.188	-0.166	0.572	0.281	0.615	0.177	0.051	0.077	0.277	0.001	0.003	0.380	0.188	0.012	0.748	0.043	0.138
	5-Oxoproline	0.182	0.136	-0.085	0.448	0.181	0.492	-0.066	0.031	-0.126	-0.005	0.033	0.068	0.116	0.130	-0.138	0.371	0.371	0.565
	Stearoyl sphingomyelin	0.011	0.206	-0.392	0.415	0.955	0.984	0.205	0.063	0.081	0.329	0.001	0.004	0.217	0.187	-0.150	0.583	0.247	0.412
	IL6	0.733	0.355	0.037	1.429	0.039	0.435	0.433	0.180	0.080	0.786	0.016	0.036	1.166	0.327	0.524	1.808	3.70E-04	0.013
	TNFi	0.370	0.197	-0.016	0.756	0.060	0.435	-0.044	0.060	-0.162	0.073	0.459	0.553	0.326	0.176	-0.019	0.670	0.064	0.161
	Sphingosine 1 phosphate	-0.470	0.357	-1.169	0.229	0.187	0.492	0.288	0.111	0.071	0.505	0.009	0.025	-0.182	0.342	-0.852	0.488	0.595	0.744
Hepatic function	Albumin	0.009	0.025	-0.040	0.058	0.717	0.896	0.019	0.007	0.004	0.033	0.012	0.030	0.028	0.023	-0.018	0.073	0.232	0.412
	Alkaline phosphatase	0.092	0.049	-0.005	0.189	0.062	0.435	0.050	0.013	0.025	0.074	7.11E-05	0.001	0.142	0.048	0.047	0.237	0.003	0.058
	Bilirubin EE	-0.995	0.499	-1.973	-0.017	0.046	0.435	-0.221	0.120	-0.457	0.015	0.066	0.122	-1.216	0.472	-2.142	-0.291	0.010	0.098
	Total protein	0.031	0.023	-0.013	0.076	0.163	0.492	0.019	0.006	0.006	0.031	0.003	0.011	0.050	0.022	0.007	0.093	0.022	0.110

Supplementary Figures:

Figure Legends

Figure S1 (Related to model development): Dynamics of fold change (normalized response) in the state variables of the model for input impulses of CHO meal, stress and infection (lipopolysaccharides) starting at the time represented by the arrow on x-axis. (A) Meal response: The model was simulated for 75 gm of carbohydrate meal impulse and the corresponding dynamics of the fold change in the metabolic states are shown. The trends are reproduced as per the source models and observed profiles in experimental data (12, 18, 40). (B) Stress response: The model was simulated for a stress impulse (5 fold change in the stress parameter). The corresponding dynamics of fold change in HPA axis and cytokine state variables are shown. The associated changes in metabolic variables for insulin, glucose and metabolic state are also reported. The trends match the source models and response reported in (41, 48, 54). (C) Response to infection/LPS: The model was simulated for an impulse of LPS (10×10^{-5} AU). The dynamics of the corresponding fold change in pro-inflammatory and anti-inflammatory cytokines are shown, along with the HPA axis and metabolic components. The model reproduces trends from the source models and observations reported in (9, 21, 33, 56, 59).

Figure S2 (Related to Figure 7C): Forest plot representation of the natural indirect effects (joint mediated effects), natural direct effects and total causal effects of GR sensitivity (measured by cortisol suppression test) on 35 metabolites for the causal hypothesis tested on the entire cohort adjusting for the group effects. The error bar represents 95% confidence intervals of the point estimates of the effects. It is noted that the joint mediated effects on pyruvate, lactate, citrate, gluconeogenic and branched chain amino acids, oxidative stress, inflammation and hepatic function components are statistically significant. The total causal effect (TCE) had trend level significance for ornithine, alanine, nonadecenoates, triglycerides, gammaglutamyltyrosine, and hepatic function components. The TCE and NIE were both statistically significant for IL6.

Figure S1

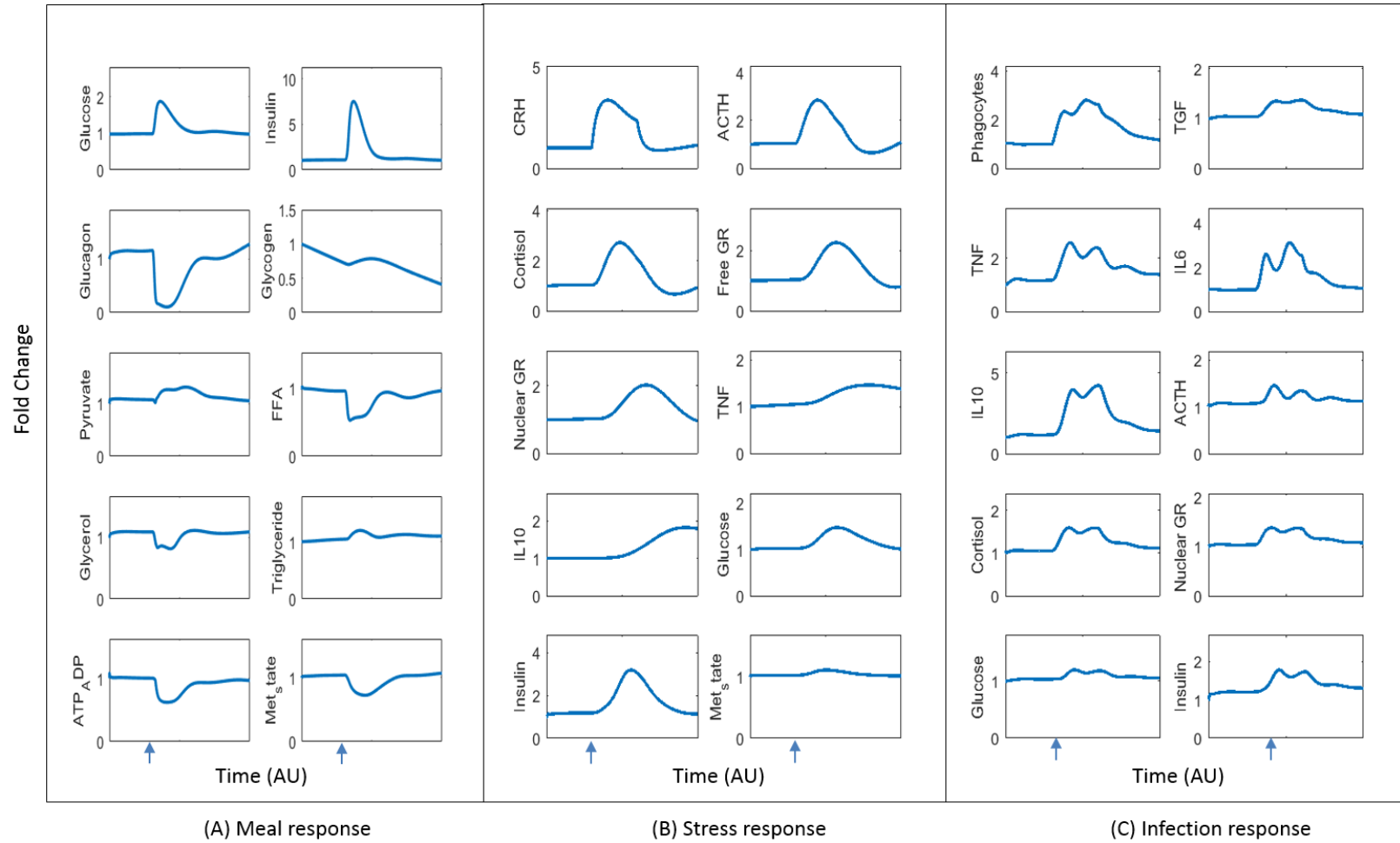
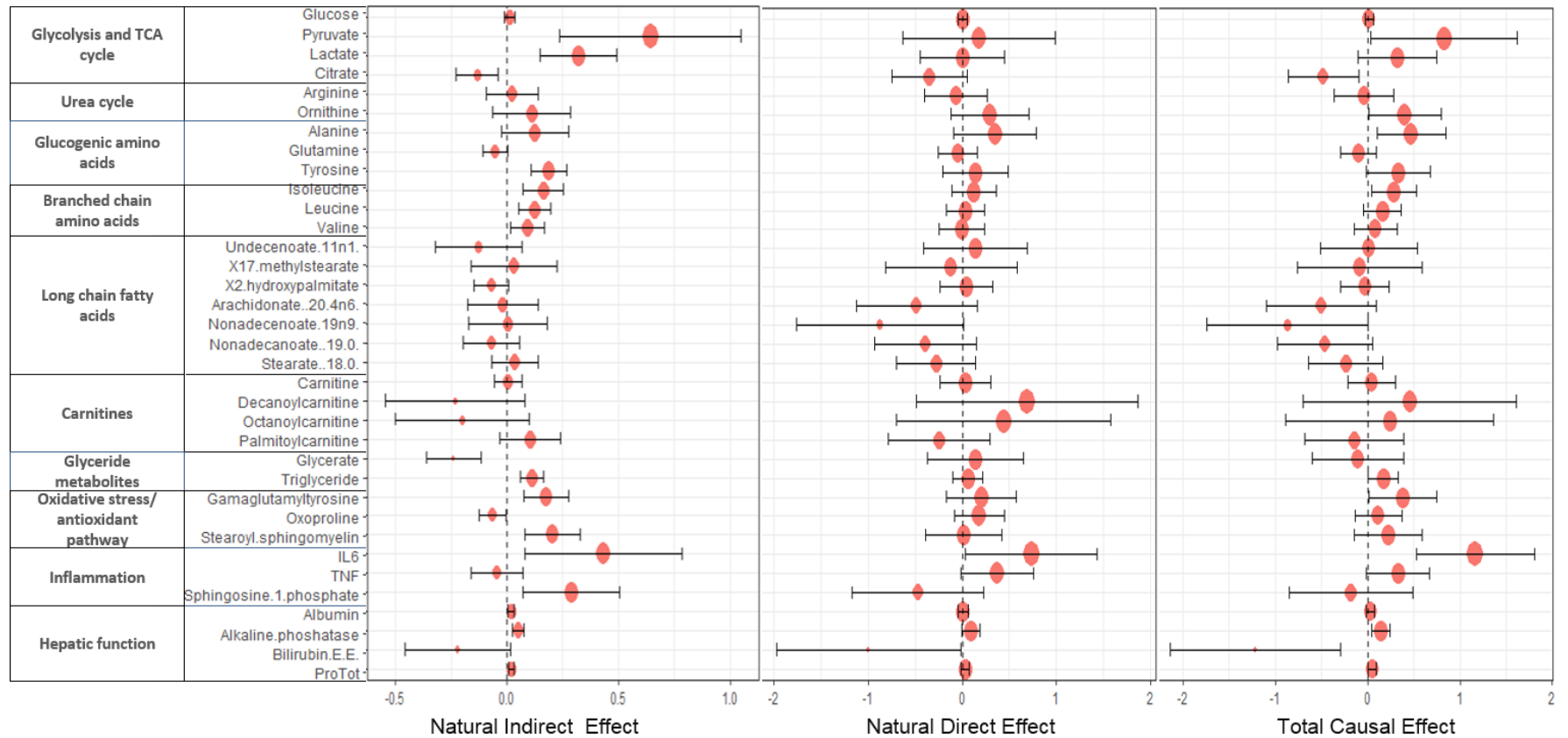


Figure S2



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