Supplementary Information: Table of Contents

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Supplementary Methods/Results:

Tests	Methods
Abbreviation List:	BMI=Body Mass Index (=kg/m^2), IDS-SR=Inventory for the Severity of Depression (Self-Report Version), Anhedonia=Summary scores from 4 anhedonia items of IDS-SR items, MGH-ATRQ=Massachusetts General Hospital-Antidepressant Treatment Response Questionnaire, CSF=cerebrospinal fluid, KYN/TRP=kynurenine/tryptophan, KYN=kynurenine, KYNA=kynurenic acid, 3HKYN=3-hydroxy-kynurenine, AA=anthranilic acid, 3HAA=3-hydroxy-anthranilic acid, QA=quinolinic acid, TNF=tumor necrosis factor, TNFR2=soluble tumor necrosis factor receptor 2, IL1ra= IL1b-receptor antagonist, IL6sr=IL6-soluble receptor.
Overview & Working Model:	A schematic of overview and working model is provided in **Figure S1**. Assay details including coefficient of variation and lower limits of detection are described in **Table S1.**
Preprocessing:	All immune and kynurenine pathway metabolite data were quantile-normalized following tests of normality and examination of histograms.
Outlier estimation:	Outlier analysis indicated that none of the quantile-normalized values of individual markers exceeded threshold for outliers (3 x interquartile range).
Missing Data: **(Table S2)**	All missing values were due to assay limits falling below detection limits. CSF 3-hydroxy anthranilic acid (CSF 3HAA) was excluded as 60% of the values were missing. Missing data was excluded from analyses other than in the confirmatory factor analysis models - as described below.
Covariates	Age, sex, ethnicity (Caucasian versus African American) and BMI
Software	Statistical calculations were performed in STATA-16 (College Station, TX, USA) and SAS-9.4 (SAS Institute, Cary, NC, USA).
Descriptive Analysis – **(Table S3)**	Seventy-two subjects with both blood and CSF samples were included in the analyses. **Table 1** in main text provides data on clinical and selected biomarker variables that survived correction for false-discovery rate (FDR). A complete list is provided in **Table S3**.
Bivariate analyses – **(Table S4)**	Pairwise-correlations between plasma and CSF kynurenine pathway metabolites as well as their association with plasma and CSF immune measures are depicted as a correlation heatmap in Figure 1. KP metabolites in the plasma strongly correlated with each other (all $p<0.01$), while several KP metabolites in the plasma strongly correlated with KP metabolites in the CSF. Plasma KYN/TRP was similarly robustly associated with CSF KYN/TRP, KYN, AA, KYNA and QA (Pearson r=0,77, 0.72, 0.60 and 0.52 respectively (all $p<0.0001$, Figure 2A-D). In addition, significant correlations were found between plasma and CSF AA as well as plasma and CSF QA (all $p<0.0001$). Plasma 3HKYN was also significantly associated CSF QA ($p<0.0001$). Of the plasma immune markers, plasma TNF and TNFR2 were strongly associated with KYN and QA in the plasma, while plasma 3HKYN was correlated only with plasma TNFR2 (all $p<0.0001$). **Table S4** lists all pairwise correlations that survived Bonferroni correction.
Confirmatory Factor Analysis (CFA) (**Table S5A-C)**	a) **Rationale:** CFA was used in STATA-16 to extract 4 summary factors scores representing plasma kynurenine and immune pathways because of its ability a. to control correlative interdependencies, b. to extract factors with greater precision,

c. to decrease measurement error by isolating shared from unique variations of different markers
d. modeling the whole of the underlying biological pathway.

Thus, the extracted common factors could be used as inputs in a path model that assume that all inputs have minimal or no measurement errors.

b) **Methods:** To minimize errors and improve fit, only markers with insignificant loadings (z tests) upon their component factors were excluded. Modification indices were used to identify and correct correlated error terms *only* if supported by previous biological data. "Full Information Maximum Likelihood Estimation (FIML) via "maximum likelihood with missing values (MLMV)" was used to address missing data.

c) **Results:** CFA yielded 4 summary factor scores representing kynurenine pathway (Plasma-KP, CSF-KP) and immune (Plasma-IMM, CSF-IMM) analytes in the plasma and CSF respectively (Supplemental Table 5A-C). All four models demonstrated robust goodness-of-fit measures (non-significant likelihood chi-sq $p>0.05$ vs fully saturated model, root mean squared error of approximation (RMSEA)<0.05, standardized residual root mean squared residual (RMR)<0.05). The Raykov coefficient of item reliability (=Cronbach's alpha) was >0.7 and the mean r-square of the individual loadings on all 4 factors were greater than the a priori effect size threshold of 0.25. Details of each individual extraction is explained below.

1. **Plasma-KP**: Allowing the error terms between KYNA/3HKYN and AA/3HAA to be correlated demonstrated substantial modification index value and made conceptual sense based on biology. A satisfactory fit was obtained with a chi-sq(7)=7.361, p=0.361, RMSEA=0.03, CFI=1 and SRMR=0.03 Plasma-KP factor with an internal consistency (alpha) of 0.88 and an average r-squared=0.5. Plasma KP included TRP, KYN, KYNA, 3HKYN, HAA, AA and QA (Plasma KP factor, total=7/7 markers).
2. **CSF-KP:** Allowing the error terms between 3HKYN/QA and AA/KYNA to be correlated demonstrated substantial modification index value and made conceptual sense based on biological understanding. A satisfactory fit was obtained with a chi-sq(3)=3.36, p=0.34, RMSEA<0.04, CFI=0.99 and SRMR=0.04. All individual markers loaded significantly on the putative common CSF-KY factor with an internal consistency (alpha) of 0.69 and an average r-squared=0.42. CSF KP included TRP, KYN, KYNA, 3HKYN, AA and QA (CSF KP factor, total=6/6 markers).
3. **Plasma-IMM:** Plasma IL10 and IL1b were excluded due to insignificant loadings onto the hypothesized latent factor. Allowing the error terms between 3 pairs of items (TNF/TNFR2, IL6/CRP, IL6/MCP) to be correlated demonstrated substantial modification index value and made conceptual sense. A satisfactory fit was obtained with a chi-sq(11)=4.74, p=0.94, RMSEA<0.001, CFI=1 and SRMR=0.04. All individual markers loaded significantly on the common Plasma-IMM factor with an internal consistency (alpha) of 0.72 and an average r-squared=0.3. Variables loading significantly to plasma immune factor included TNF, TNFR2, IL6, IL6sr, IL1ra and MCP1 (Plasma-IMM factor, total=7/9 markers)
4. **CSF-IMM:** CSF IL1b and IL10 were excluded following insignificant loadings on to the hypothesized latent factor.

	Allowing the error terms between two pairs of items (TNF and TNFR2 with MCP1) to be correlated demonstrated substantial modification index value and made conceptual sense. A satisfactory fit was obtained with a chi-sq(12)= 8.63, p=0.7, RMSEA<0.001, CLI=1 and SRMR= . All individual markers loaded significantly on the putative common CSF-IMM factor with an internal consistency (alpha) of 0.76 and an average r-squared=0.35. Variables loading significantly to CSF immune factor included TNF, TNFR2, IL6, IL6sr, IL1ra, CRP and MCP1 (CSF-IMM factor, total=7/9 markers).
Mediation/Path Analysis: **(Tables S6A-D)** **(Figure S2)**	a) **Rationale:** All four extracted factors were entered as inputs into a meditational path analysis model with the SEM module of Stata. The goal is to examine the hypothesized directionality of effects from Plasma-IMM to Plasma-KP to CSF-KP. b) **Methods:** Use of the full SEM protocol was avoided and instead a simplified, non-recursive path regression model was used. Plasma-KP and CSF-KP were entered as endogenous (response) variables and Plasma-IMM and CSF-IMM factors were entered as exogenous (predictors). Finally, BMI, age and race were entered as covariates. Sex was removed from the model after it failed to demonstrate significant associations with the endogenous/response variables. All paths including feed-forward feed-back paths were examined to test alternative hypotheses. c) **Results:** Model convergence was achieved after 2 iterations and a satisfactory fit was obtained with a chi-sq(5)=5.40, p=0.37, RMSEA<0.034, CFI=0.99 and SRMR=0.04. The overall path effects were robust with an average r-squared=0.42. As specified in the main body of the text, **Figure 3** and in Supplemental Tables 4 A-D. 1. Paths linking Plasma-IMM to Plasma-KP (chi2(1)=10.69,p=0.001); Plasma-KP to CSF-KP (chi2(1)=10.86,p=0.001); and Plasma-IMM to Plasma-KP to CSF-KP (chi2(1)=12.74,p<0.001) were all significantly stronger than the path from CSF-IMM to CSF-KP. 2. Strong direct effects were noted between Plasma-IMM and Plasma-KP and from Plasma-KP to CSF-KP (p<0.001), and the indirect association between Plasma-IMM and CSF-KP was exclusively mediated by Plasma-KP (p<0.001). 3. **Figure 3** provides a graphic summary of standardized direct, indirect, and total effects, and **Supplemental Tables 6A-D** provides detailed analytic information. d) **Power:** An overall power=0.9 for the path model was obtained using estimated effect sizes (Cohen's f=0.43 and 0.82, partial r-squared=0.33 and 0.45 for Plasma- and CSF-KP factors, respectively) with tested/total predictors=1/7 (including covariates), alpha=0.007 (0.05/7) and sample size=72 (Supplementary Figure 2).
Lasso-selection Models: **(Tables S7A-B.)**	a) **Rationale:** Plasma KYN/TRP ratio was used as an index of IDO-activation by immune markers. Associations between immune markers and KYN/TRP in the plasma was examined using least absolute shrinkage, and selection estimator (lasso)-based variable selection methods were used as these methods were able to handle

	large number of intercorrelated predictors (linear, quadratic, interactive) effects between predictors. b) **Methods:** Least absolute shrinkage and selection estimator (lasso)-based variable selection methods after randomly splitting the data into 'training' and 'validation' sets (n=36 each). A total of 22 effects (including linear and quadratic) effects of 9 immune markers and 4 covariates were tested using a 9 lasso selection models (lasso, elasticnet and square-root lasso with adaptive minimal BIC, k(10)Fold-cross-validation, hetero- and homoscedastic plugin cross-validation techniques). Variables selected by most/all the models and by models with the least prediction error were considered most relevant. More specifically, variables consistently selected by a consensus panel of 9 different lasso/elasticnet/ridge models and by those models performing best in the validation set were used (least prediction error, best out-of-sample r-squared) considered as most relevant predictors. The sample was randomly split into discovery (training) and validation (holdout) sets (n=36 each) all models were run the discovery set and retested subsequently in the validation sample. All processes and procedures were run according to published guidelines [1]. c) **Bayesian-Lasso:** To simultaneously examine linear, quadratic and interaction effects between immune markers (a total of 56 effects), while controlling for unknown variations in prior probabilities; we used a Stochastic search variable (SSVS) variable selection algorithm using Markov-Chain Monte-Carlo (MCMC) estimation to estimate the best set/combination of predictors. Bayesian methods were used to account for model uncertainty by differentially weighting predictors by weighting with binary indicator variables =1 or 0 to yield a Dirichlet distribution. The resultant model provided an anticorrelated set of differentially weighted predictors and enabled toggling between presence and absence of the variable. This model also allowed for inbuilt auto-validation due to the completely anticorrelated weighting by binary indicators. The model was resampled n=1000 times to identify the frequency with which each predictor was selected (marginal inclusion probability, MIP). A null factor was included in the model and MIP had to exceed both null factor and prior probability threshold of >0.5. This was set to control for a high level of false positives due to many predictors. Methods are per published guidelines [2]. **d) Results:** As specified in the main text and **Supplemental Tables 7 A-B.** In addition, BVLR linear and quadratic association between plasma TNF and KYN/TRP ratio had the greatest MIP>0.9 exceeding all other linear, quadratic and interactional effects linking immune marker and KYN/TRP in the plasma.
Polynomial effects	a) **Rationale:** Linear and quadratic effects were both selected above and hence these effects were further examined to guide further analysis. b) **Methods:** Slope estimates of linear and quadratic effects obtained using simple curve-fitting were compared. c) **Pieced regression:** The sample was split across the sample mean of plasma TNF (5.67 pg/ml) and independent regression models were run for above and below this cut-off. Both the slopes and intercepts were compared above and below this point. d) **Results:**

	1. **Figure 4A** in the main text presents comparison of the linear and quadratic fit of the relationship between plasma TNF and KYN/TRP indicating that the curved (quadratic/polynomial) fit was significantly stronger than the linear fit (linear/nonlinear slope difference [F(1,69)=11.3, p=0.001]. 2. A pieced regression breaking the quadratic slope into two linear fits indicated a non-significant slope between TNF and KYN/TRP below the mean of TNF<5.67 pg/ml [beta=0.11, t=0.93, p=0.36] compared to a sharply ascendant and a highly significant linear slope at TNF>5.67 pg/ml [beta=0.75,t=6.95, p<0.001] despite comparable intercepts (p>0.05). 3. This examination (along with evidence of clustering among residuals) indicated differential associations between immune and kynurenines at differing TNF levels suggested clustering effects between TNF and KYN/TRP at various levels of immune activation.
K-means clustering **(Supplementary Table 8)** **(Supplemental Figure 3)**	a) **Rationale:** K-means clustering was used to partition the sample into groups with concurrently increased immune and kynurenine markers (high) and contrasted to those subjects without such concurrent increases (low) TNF-KYN/TRP grouping. b) **Method:** Iterative k-means clustering as described in 'FASTCLUS' module of SAS 9.4 was used examine cluster sizes ranging from 2-12 and the cluster with the best Cubic Clustering Criterion (CCC) was selected. c) **Results:** 1. **Cluster Number**: Based on CCC values, a two-group solution with optimal CCC=1.95 was chosen to partition subjects into two groups - a high TNF-KYN/TRP group (n=17) and a low TNF-KYN/TRP group (n=55). **Supplementary Table 8** details the range of CCC values. 2. **Cluster separation** was retested in a new data table containing simulated cluster observations (n=10000) of Plasma TNF and KYN/TRP in accordance with recent recommendations [3]. 3. **Cluster reproducibility:** K-means cluster was performed on the training sample after hiding/excluding the validation sample. The Cluster formula generated by the training set was concatenated and applied to the validation set and used to generate probabilities of membership in each cluster. Upon comparison, the clustering predicted group membership in the validation sample with 100% accuracy. 4. **Cluster validation:** After controlling for multiple comparisons high plasma TNF-KYN/TRP status was associated with differences among several markers illustrated in **Supplement**al **Figure 3.**
Lasso-inferential methods	a) **Rationale:** Lasso-inferential models were used to examine associations between TNF-KYN/TRP group status and clinical symptom rating scores after partialing out the effects of covariates. b) **Methods:** Cross-validation was accomplished concurrently using both k(10)-fold repetition and n=10 resampling (amounting to 100 repetitions). The primary covariates of the study - age, sex, BMI and ethnicity (Caucasian vs African American) - were entered as control

variables and hence were partialed out prior to testing key variables of interest.

c) Results:

1. **Comparison of plasma TNF or KYN/TRP and their interaction term (TNF*KYN/TRP) with TNF-KYN/TRP clustering:** First, it was examined if either plasma TNF or KYN/TRP alone or their interaction term (TNF*KYN/TRP) explained depressive symptom severity (measured using IDS-SR scores) better than clustered groupings of TNF-KYN/TRP. A cross-fit, partialing-out, lasso-inferential model demonstrated that high TNF-KYN/TRP group status (Wald z=1.91, p=0.05) explained IDS-SR scores better than plasma TNF (z=-3.93, p=0.22) or KYN/TRP ratio (z=0.15, p=0.95) alone or their interaction term (z=1.93, p=0.45). Following this, an examination was conducted to examine t*he strength of association* between TNF-KYN/TRP grouping and IDS-SR after *controlling for covariates*.
2. **Plasma TNF-KYN/TRP and depression severity:** After partialing out the effects of covariates, high TNF-KYN/TRP status was strongly associated with IDS-SR scores (Wald z=3.21, p=0.001) in the cross-fit lasso inferential model. The 8.17-point IDS-SR score difference (95%CI=3.18-13.2) seen in the high-low TNF-KYN/TRP group contrast had a strong effect size d(95%)=0.90(0.34-1.47). A power analysis comparing r-squared values of the full model (4 covariates+ TNF-KYN/TRP=0.22) with that from the reduced model (only TNF-KYN/TRP grouping = 0.13) yielded a power of (1-beta) of 0.81 for the current samples size of 72. Notably, Caucasian ethnicity was associated IDS-SR scores (PE=5.37, t=2.51, p=0.014) and Caucasians in the high TNF-KYN/TRP group experienced significantly greater symptom-severity scores than African-Americans with high TNF-KYN/TRP status [F(1,66)=6.41, p=0.01] and Caucasians with low TNF-KYN/TRP status [F(1,66)=0.02].
3. **Plasma TNF-KYN/TRP and anhedonia severity:** The summated individual scores of four anhedonia items selected from IDS-SR scale combined reliability with a Cronbach's alpha of 0.73. The cross-fit, partialing out lasso indicated that high TNF-KYN/TRP group was associated with greater anhedonia scores on the 4-item subscale (Wald z=2.88, p=0.004). The 1.89-point Anhedonia score difference (95%CI=0.60-3.17) seen in the high-low TNF-KYN/TRP group contrast had a strong effect size d(95%)=0.85(0.29-1.41). A power analysis using r-squared comparison between the full (0.24) and reduced (0.12) model indicated a power of 0.91 with the current sample size of 72. Caucasian ethnicity was again associated with greater anhedonia scores (PE=1.30, t=2.43, p=0.02) and Caucasians in the high TNF-KYN/TRP group experienced greater severity of anhedonia than African-Americans in the same group [F(1,66)=5.91, p=0.02} and Caucasians in the low TNF-KYN/TRP group.
4. **TNF-KYN/TRP and antidepressant treatment response:** MGH-ATRQ scores were not available for 4 subjects (3 subjects in high and 1 in low TNF-KYN/TRP groups respectively) and hence data was available only 68 of 72 subjects. The MGH-ATRQ scores ranged between 0-12.5

	with a mean of 1.68 (SD=2.97). Due to the high degree of kurtosis (=6.97), MGH-ATRQ scores were recalibrated into 3 groups of treatment non-response namely 0 (no previous trials), 1 (score range=1-3) and 2 (scores >3) and an increasing score from 0 to 3 indicating increasing treatment resistance. Of note, MGH-ATRQ scores >3 has been demonstrated as indicating treatment resistance in several previous studies [40-42]. After partialing out covariates, high TNF-KYN/TRP group was significantly associated with increased MGH-ATRQ ratings (Wald z=2.59, p=0.009) yielding an effect size of 0.78(0.18-1.39). Comparisons of full (r-squared=0.16) with reduced model (r-squared=0.08) yielded a 1-beta estimate of 0.72. None of the covariates were associated with modified MGH-ATRQ ratings on post hoc analysis.
Rigor/reproducibility	a) **Method:** The stability of estimates linking TNF-KYN/TRP status with clinical variables across discovery and validation were examined using classification probabilities generated using logistic models. First, logistic models using group status as dependent variable and clinical variables are predicted were used to generate predicted probabilities (p). The distribution of p was compared across randomly generated discovery and validation sets using sing area-under- the curve (AUC) generated using receiver operating curves (ROC)-curves linking TNF-KYN/TRP grouping (reference variable) to classification variable (clinical measures). b) **Results:** Comparison of AUC across discovery and training sets indicated good stability of estimates and replicability across sample sets for the association between TNF-KYN/TRP groups and 1. IDS-SR scores (0.73 vs 0.77, chi2(1)=0.11, p=0.74), 2. anhedonia (0.71 vs 0.77, chi2(1)=0.15, p=0.69) and 3. modified MGH-ATRQ scores (0.66 vs 0.67, chi2(1)=0, p=0.98)
Power Analysis of clinical variables (**Figure S4**)	The r-squared of the reduced model (0.13, 0.12 and 0.08) and full model r-squared values (including TNF-KYN/TRP grouping + 4 covariates) were (0.22, 0.24 and 0.16) for total IDS-SR scores, Anhedonia and MGH-ATRQ scores respectively.

References:

1. Tibshirani R. Regression shrinkage and selection via the lasso: a retrospective. Journal of the Royal Statistical Society: Series B (Statistical Methodology). 2011;73(3):273-82.
2. Guan Y, Stephens M. Bayesian variable selection regression for genome-wide association studies and other large-scale problems. The Annals of Applied Statistics. 2011;5(3):1780-815.
3. Newell MA, Cook D, Hofmann H, Jannink J-L. An algorithm for deciding the number of clusters and validation using simulated data with application to exploring crop population structure. The Annals of Applied Statistics. 2013;7(4):1898-916.

Table S1: Estimation Parameters for Kynurenine-Pathway Metabolites

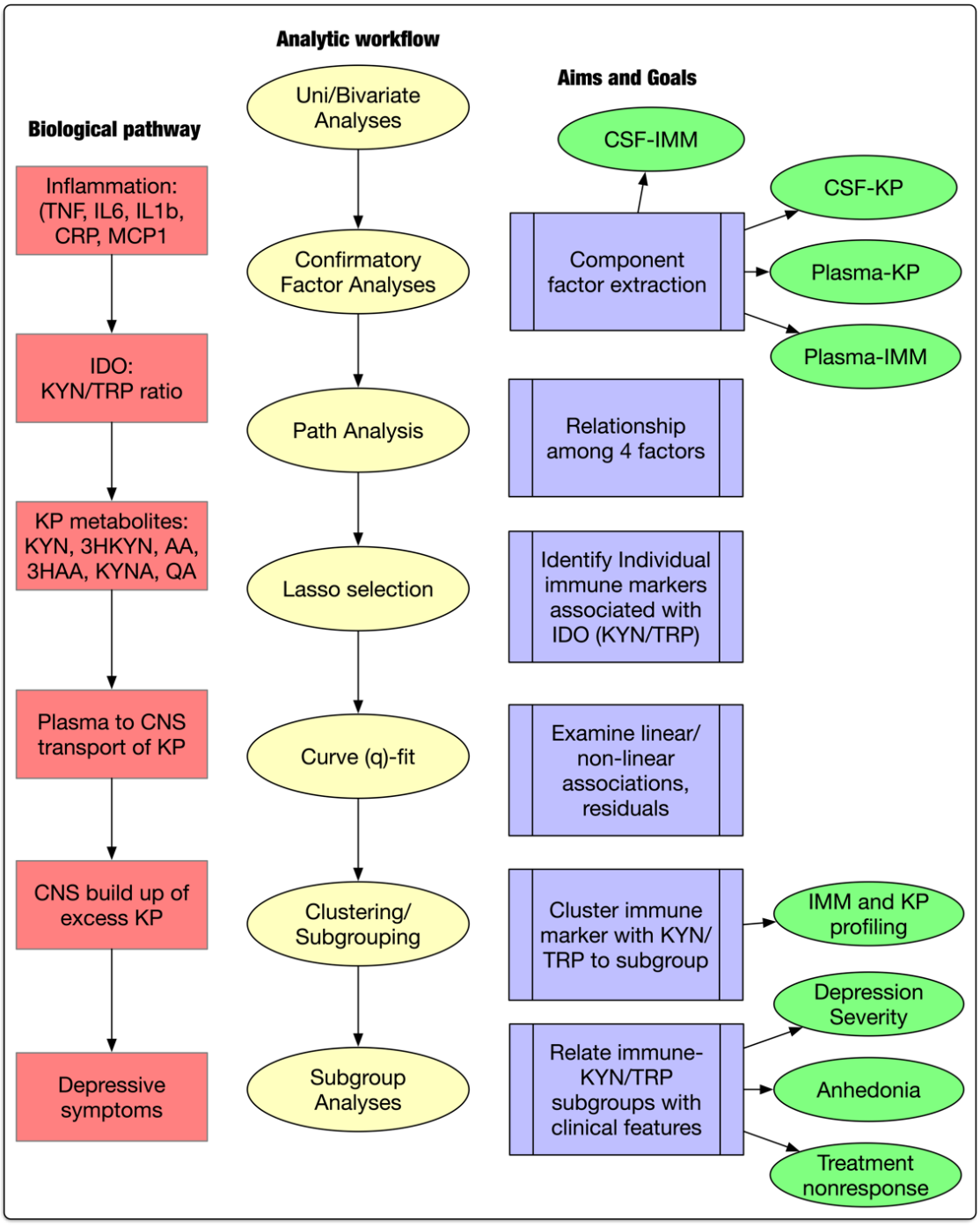
Analyte	Plasma		CSF	
	LLOQ	%CV	LLOQ	%CV
TRP	3 µM	2.3	0.12 µM	3.82
KYN	0.225 µM	1.84	12 nM	4.22
KA	7.5 nM	4.18	0.6 nM	3.56
AA	3 nM	6.46	120 nM	3.82
3HKYN	5 nM	4.54	1.2 nM	4.59
3HAA	10 nM	6.27	1.2 nM	6.3
QA	100 nM	4.89	5 nM	4.72

Abbreviations: LLOQ = lower limits of quantification, %CV= coefficient of variability of the assay, TRP=tryptophan, KYN=kynurenine, KA=kynurenic acid, AA=anthranilic acid, 3HKYN=3-hydroxy kynurenine, 3HAA=3-hydroxy anthranilic acid, QA=quinolinic acid

Note: Estimation Parameters for immune markers have been provided as Supplements to our previously published papers.

1. Felger JC, Haroon E, Patel TA, Goldsmith DR, Wommack EC, Woolwine BJ, et al. What does plasma CRP tell us about peripheral and central inflammation in depression? Mol Psychiatry. 2018.
2. Felger JC, Li Z, Haroon E, Woolwine BJ, Jung MY, Hu X, et al. Inflammation is associated with decreased functional connectivity within corticostriatal reward circuitry in depression. Mol Psychiatry. 2016;21(10):1358-65.

Figure S1: Working Model and Analytic Pathway



Abbreviations: TNF=tumor necrosis factor, IL6=interleukin-6, IL1b=interleukin 1-beta, CRP= c-reactive protein, MCP1=monocyte chemoattractant protein-1, TRP=tryptophan, KYN=kynurenine, KYNA=kynurenic acid, AA=anthranilic acid, 3HKYN=3-hydroxy-kynurenine, HAA=3-hydroxy anthranilic acid, QA=quinolinic acid

Table S2: Missing Data

	n-missing	sample	%
MGH-ATRQ scores	4	72	6
Plasma KYNA (nM)	1	72	1
Plasma AA (nM)	1	72	1
Plasma 3HAA (nM)	4	72	6
CSF KYNA (nM)	11	72	15
CSF3HAA [nM]	43	72	60
CSF QA (nM)	5	72	7
Plasma IL10 (pg/ml)	1	72	1
CSF TNF (pg/ml)	1	72	1
CSF TNFR2 (pg/ml)	1	72	1
CSF IL6 (pg/ml)	1	72	1
CSF IL6sr (pg/ml)	1	72	1
CSF IL1b (pg/ml)	1	72	1
CSF IL10 (pg/ml)	1	72	1
CSF IL1ra (pg/ml)	1	72	1
CSF CRP (ng/ml)	1	72	1
CSF MCP1 (pg/ml)	1	72	1

Abbreviations: MGH-ATRQ=Massachusetts General Hospital - Antidepressant Treatment Response Questionnaire, CSF=cerebrospinal fluid, KYNA=kynurenic acid, AA=anthranilic acid, 3HAA=3-hydroxy anthranilic acid, QA=quinolinic acid, IL10=interleukin-10, TNF=tumor necrosis factor, TNFR2=soluble tumor necrosis factor receptor 2, IL6=interleukin-6, IL6sr=IL6 soluble receptor, IL1b=interleukin 1-beta, IL1ra= IL1b receptor antagonist, CRP= c-reactive protein and MCP1=monocyte chemoattractant protein-1.

Table S3: Descriptive Table of Measures in All Subjects and Contrasts of Across Low versus High TNF-KYN/TRP groups

	All Subjects			Low TNF-KYN/TRP			High TNF-KYN/TRP		
	N	Miss	Mean(SD)	N	Miss	Mean(SD)	N	Miss	Mean(SD)
Clinical									
IDS-SR score	72	0	36.79(9.7)	55	0	34.87(9)	17	0	43(9.49)
Anhedonia	72	0	6.36(2.36)	55	0	5.91(2.15)	17	0	7.82(2.51)
MGH-Raw	68	4	1.68(2.97)	54	1	1.42(2.94)	14	3	2.71(2.99)
MGH-Modified	68	4	0.63(0.86)	54	1	0.5(0.77)	14	3	1.14(1.03)
Plasma-KP									
Plasma KYN (μM)	72	0	1.59(0.44)	55	0	1.42(0.28)	17	0	2.14(0.4)
Plasma TRP (μM)	72	0	50.1(8.98)	55	0	50.95(9.42)	17	0	47.34(6.91)
Plasma KYN/TRP	72	0	32.27(9.59)	55	0	28.11(4.56)	17	0	45.71(9.31)
Plasma KYNA (nM)	70	2	35.51(15.45)	53	2	31.67(10.38)	17	0	47.46(21.89)
Plasma AA (nM)	71	1	6.12(2.26)	54	1	5.56(1.94)	17	0	7.91(2.34)
Plasma 3HKYN (nM)	72	0	30.88(11.32)	55	0	27.09(7.21)	17	0	43.12(13.6)
Plasma 3HAA (nM)	68	4	20.01(8.76)	51	4	17.88(7.32)	17	0	26.41(9.81)
Plasma QA (nM)	72	0	442.97(141.94)	55	0	392.91(101.62)	17	0	604.94(134.38)
Plasma QA/KYNA	70	2	13.69(4.88)	53	2	13.33(4.42)	17	0	14.79(6.13)
CSF-KP									
CSF KYN (nM)	72	0	31.3(13.74)	55	0	27.22(10)	17	0	44.49(16.04)
CSF TRP (μM)	71	1	1.58(0.33)	54	1	1.57(0.33)	17	0	1.58(0.32)
CSF KYN/TRP	71	1	20.13(8.28)	54	1	17.63(7.05)	17	0	28.07(6.84)
CSF KYNA (nM)	61	11	1.5(0.77)	44	11	1.36(0.81)	17	0	1.85(0.56)
CSF AA (nM)	72	0	2.56(0.72)	55	0	2.38(0.67)	17	0	3.11(0.61)
CSF 3HKYN (nM)	72	0	4.39(4.47)	55	0	4.21(4.05)	17	0	4.97(5.73)
CSF QA (nM)	67	5	19.49(9.47)	50	5	17.11(6.8)	17	0	26.48(12.59)
CSF QA/KYNA	57	15	14.94(8.33)	40	15	14.5(7.26)	17	0	15.97(10.62)
Plasma-IMM									
Plasma TNF (pg/ml)	72	0	5.67(2.32)	55	0	4.8(1.6)	17	0	8.51(2.01)
Plasma TNFR2 (ng/ml)	72	0	2.48(0.88)	55	0	2.21(0.67)	17	0	3.34(0.93)
Plasma IL6 (pg/ml)	72	0	1.71(1.25)	55	0	1.59(1.2)	17	0	2.13(1.33)
Plasma IL6sr (ng/ml)	72	0	15.7(2.76)	55	0	15.3(2.78)	17	0	16.99(2.33)
Plasma IL1b (pg/ml)	72	0	0.41(0.17)	55	0	0.4(0.16)	17	0	0.46(0.2)
Plasma IL1ra (ng/ml)	72	0	1.99(2.82)	55	0	1.43(2.05)	17	0	3.82(4.05)
Plasma IL10 (pg/ml)	68	4	0.51(0.35)	55	0	0.49(0.33)	13	4	0.63(0.41)
Plasma CRP (mg/l)	72	0	2.51(2.73)	55	0	2.14(2.72)	17	0	3.73(2.49)
Plasma MCP1 (pg/ml)	72	0	130.34(44.84)	55	0	126.02(40.82)	17	0	144.34(55.01)
CSF-IMM									
CSF TNF (pg/ml)	72	0	1.22(0.41)	55	0	1.18(0.43)	17	0	1.35(0.31)
CSF TNFR2 (pg/ml)	72	0	121.31(67.48)	55	0	108.4(56.38)	17	0	163.11(83.95)
CSF IL6 (pg/ml)	70	2	2.55(1.32)	54	1	2.44(1.27)	16	1	2.95(1.42)
CSF IL6sr (pg/ml)	72	0	708(355.92)	55	0	624.47(278.77)	17	0	978.24(445.3)
CSF IL1b (pg/ml)	71	1	0.28(0.1)	55	0	0.28(0.1)	16	1	0.26(0.07)
CSF IL10 (pg/ml)	70	2	6.21(3.01)	53	2	5.79(2.89)	17	0	7.52(3.11)
CSF IL1ra (pg/ml)	72	0	0.42(0.15)	55	0	0.41(0.16)	17	0	0.45(0.07)
CSF CRP (ng/ml)	72	0	13.85(18.01)	55	0	11.78(17.42)	17	0	20.54(18.77)
CSF MCP1 (pg/ml)	72	0	292.39(129.57)	55	0	287.77(139.57)	17	0	307.35(91.83)

Abbreviations: IDS-SR= Inventory for the Severity of Depression (Self-Report Version), Anhedonia: Summary scores from anhedonia items of IDS-SR items, MGH-ATRQ= Massachusetts General Hospital - Antidepressant Treatment Response Questionnaire, KYN/TRP= kynurenine/tryptophan ratio, TRP=tryptophan, KYN=kynurenine, KA=kynurenic acid, AA=anthranilic acid, 3HKYN=3-hydroxy-kynurenine, 3HAA=3-hydroxy anthranilic acid, QA=quinolinic acid, TNF=tumor necrosis factor, TNFR2=soluble tumor necrosis factor receptor 2, IL6=interleukin-6, IL6sr=IL-6-soluble receptor.

Table S4: Pairwise Correlations Between Markers – Bonferroni-corrected for multiple comparisons [@].

Variable 1	Variable 2	Correlation	Count	Lower 99.99%	Upper 99.99%	p-value
CSF QA	CSF 3HKYN	0.64	66	0.27	0.85	<.0001
CSF QA/KYNA	CSF 3HKYN	0.58	56	0.13	0.83	<.0001
CSF IL1ra	CSF IL6sr	0.50	70	0.07	0.77	<.0001
CSF AA	CSF KYN	0.67	71	0.33	0.86	<.0001
CSF KYN/TRP	CSF KYN	0.82	71	0.60	0.93	<.0001
CSF QA	CSF KYN	0.52	66	0.09	0.79	<.0001
Plasma TNF	CSF KYN	0.47	71	0.04	0.75	<.0001
CSF AA	CSF KYN/TRP	0.51	71	0.08	0.77	<.0001
CSF AA	CSF KYNA	0.55	61	0.10	0.81	<.0001
CSF IL6sr	CSF KYNA	0.52	61	0.07	0.80	<.0001
CSF QA/KYNA	CSF KYNA	-0.66	56	-0.87	-0.25	<.0001
CSF TNFR2	CSF KYNA	0.53	61	0.07	0.80	<.0001
CSF QA/KYNA	CSF QA	0.53	56	0.06	0.81	<.0001
Plasma TNFR2	CSF QA	0.57	66	0.15	0.81	<.0001
CSF IL1ra	CSF TNFR2	0.54	70	0.12	0.79	<.0001
CSF IL6sr	CSF TNFR2	0.81	72	0.59	0.92	<.0001
CSF MCP1	CSF TNFR2	0.54	72	0.13	0.79	<.0001
Plasma QA	Plasma 3HAA	0.58	68	0.19	0.82	<.0001
CSF KYN	Plasma 3HKYN	0.50	71	0.08	0.77	<.0001
CSF QA	Plasma 3HKYN	0.64	66	0.26	0.85	<.0001
Plasma 3HAA	Plasma 3HKYN	0.54	68	0.12	0.80	<.0001
Plasma QA	Plasma 3HKYN	0.70	72	0.38	0.87	<.0001
Plasma TNFR2	Plasma 3HKYN	0.50	72	0.07	0.77	<.0001
CSF AA	Plasma AA	0.47	70	0.04	0.76	<.0001
CSF KYN/TRP	Plasma AA	0.48	70	0.04	0.76	<.0001
Plasma 3HKYN	Plasma AA	0.55	70	0.14	0.80	<.0001
Plasma QA	Plasma AA	0.48	70	0.05	0.76	<.0001
CSF CRP	Plasma CRP	0.85	72	0.66	0.94	<.0001
Plasma CRP	Plasma IL1ra	0.54	72	0.14	0.79	<.0001
CSF CRP	Plasma IL6	0.47	72	0.04	0.75	<.0001
Plasma CRP	Plasma IL6	0.60	72	0.22	0.82	<.0001
CSF IL6sr	Plasma IL6sr	0.48	72	0.06	0.76	<.0001
CSF AA	Plasma KYN	0.61	72	0.23	0.82	<.0001
CSF KYN	Plasma KYN	0.60	71	0.21	0.82	<.0001
CSF KYN/TRP	Plasma KYN	0.58	71	0.18	0.81	<.0001
CSF QA	Plasma KYN	0.63	66	0.24	0.84	<.0001
Plasma 3HAA	Plasma KYN	0.61	68	0.23	0.83	<.0001
Plasma 3HKYN	Plasma KYN	0.68	72	0.34	0.86	<.0001
Plasma AA	Plasma KYN	0.58	70	0.18	0.81	<.0001
Plasma KYN/TRP	Plasma KYN	0.79	72	0.54	0.91	<.0001
Plasma KYNA	Plasma KYN	0.48	70	0.05	0.76	<.0001
Plasma QA	Plasma KYN	0.78	72	0.52	0.91	<.0001
Plasma TNF	Plasma KYN	0.54	72	0.14	0.79	<.0001
Plasma TNFR2	Plasma KYN	0.49	72	0.06	0.76	<.0001
CSF AA	Plasma KYN/TRP	0.60	72	0.22	0.82	<.0001
CSF KYN	Plasma KYN/TRP	0.72	71	0.41	0.88	<.0001
CSF KYN/TRP	Plasma KYN/TRP	0.77	71	0.50	0.90	<.0001
CSF QA	Plasma KYN/TRP	0.52	66	0.08	0.79	<.0001
Plasma 3HKYN	Plasma KYN/TRP	0.63	72	0.26	0.84	<.0001

Plasma AA	Plasma KYN/TRP	0.56	70	0.16	0.80	<.0001
Plasma QA	Plasma KYN/TRP	0.63	72	0.27	0.84	<.0001
Plasma TNF	Plasma KYN/TRP	0.51	72	0.10	0.78	<.0001
Plasma TNFR2	Plasma KYN/TRP	0.48	72	0.06	0.76	<.0001
Plasma 3HAA	Plasma KYNA	0.50	67	0.06	0.78	<.0001
Plasma 3HKYN	Plasma KYNA	0.67	70	0.33	0.86	<.0001
Plasma QA	Plasma KYNA	0.56	70	0.16	0.80	<.0001
Plasma QA/KYNA	Plasma KYNA	-0.62	70	-0.84	-0.25	<.0001
CSF KYN	Plasma QA	0.49	71	0.06	0.76	<.0001
CSF QA	Plasma QA	0.55	66	0.13	0.80	<.0001
Plasma TNF	Plasma QA	0.53	72	0.12	0.78	<.0001
Plasma TNFR2	Plasma QA	0.49	72	0.06	0.76	<.0001
Plasma TNFR2	Plasma TNF	0.60	72	0.22	0.82	<.0001

[@] Pairwise Pearson Product-Moment correlation coefficients and their 99% confidence intervals [r(99%CI)] were used to estimate linear associations between using a conservative Bonferroni-correction threshold ($p<0.0001$ for 595 correlated pairs).

*** p-value threshold < 0.05/575 = 0.0001

Abbreviations: CSF=cerebrospinal fluid, TNF=tumor necrosis factor, TNFR2=soluble tumor necrosis factor receptor 2, IL6=interleukin-6, IL6sr=IL6 soluble receptor, IL10=interleukin-10, IL1b=interleukin 1-beta, IL1ra= IL1b receptor antagonist, CRP= c-reactive protein, MCP1=monocyte chemoattractant protein-1, TRP=tryptophan, KYN=kynurenine, KA=kynurenic acid, AA=anthranilic acid, 3HKYN=3-hydroxy-kynurenine, 3HAA=3-hydroxy anthranilic acid, QA=quinolinic acid.

Table S5A: Confirmatory Factor Analysis – Factor Loadings Table

CSF-IMM Factor	Loading	CSF-KP Factor	Loading
CSF-IMM-→CSF TNFR2	**0.919*** **	CSF-KP→CSF KYN	**0.946*** **
CSF-IMM→CSF IL6sr	**0.874*** **	CSF-KP→CSF AA	**0.712*** **
CSF-IMM→CSF IL1ra	**0.326** **	CSF-KP→CSF QA	**0.635*** **
CSF-IMM→CSF MCP1	**0.571*** **	CSF-KP→CSF KYNA	**0.569*** **
CSF-IMM→CSF CRP	**0.238***	CSF-KP→CSF 3HKYN	**0.293***
CSF-IMM→CSF IL6	**0.404** **	CSF-KP→CSF TRP	**0.287***
CSF-IMM→CSF TNF	**0.368** **		
var(e.CSF TNFR2)	**0.141**	var(e.CSF KYN)	**0.0917**
var(e.CSF IL6sr)	**0.221** **	var(e.CSF AA)	**0.479*** **
var(e.CSF IL1ra)	**0.877*** **	var(e.CSF QA)	**0.677*** **
var(e.CSF MCP1)	**0.653*** **	var(e.CSF KYNA)	**0.692*** **
var(e.CSF CRP)	**0.930*** **	var(e.CSF 3HKYN)	**0.900*** **
var(e.CSF IL6)	**0.826*** **	var(e.CSF TRP)	**0.904*** **
var(e.CSF TNF)	**0.850*** **	var(CSF-KP)	**1**
var(CSF-IMM)	**1**		
cov(e.CSF TNFR2,e.CSF MCP1)	**0.161***	cov(e.CSF QA,e.CSF 3HKYN)	**0.181**
cov(e.CSF MCP1,e.CSF TNF)	**-0.236***	cov(e.CSF KYNA,e.CSF TRP)	**0.526*** **
		cov(e.CSF AA,e.CSF KYNA)	**-0.210***
Observations	**72**	Observations	**72**

Table S5B: Factor Loadings Table - Continued

Plasma-IMM Factor	Loading	Plasma-KP Factor	Loadings
Plasma-IMM→Plasma TNF	**0.461*** **	Plasma-KP→Plasma KYN	**0.875*** **
Plasma-IMM→Plasma CRP	**0.707*** **	Plasma-KP→Plasma QA	**0.832*** **
Plasma-IMM→Plasma TNFR2	**0.506*** **	Plasma-KP→Plasma 3HKYN	**0.772*** **
Plasma-IMM→Plasma IL1ra	**0.741*** **	Plasma-KP→Plasma HAA	**0.674*** **
Plasma-IMM→Plasma IL6	**0.568*** **	Plasma-KP→Plasma KYNA	**0.627*** **
Plasma-IMM→Plasma IL6sr	**0.381** **	Plasma-KP→Plasma AA	**0.615*** **
Plasma-IMM→Plasma MCP1	**0.287***	Plasma-KP→Plasma TRP	**0.324** **
var(e.Plasma TNF)	**0.774*** **	var(e.Plasma KYN)	**0.220*** **
var(e.Plasma CRP)	**0.486*** **	var(e.Plasma QA)	**0.294*** **
var(e.Plasma TNFR2)	**0.730*** **	var(e.Plasma 3HKYN)	**0.388*** **
var(e.Plasma IL1ra)	**0.437*** **	var(e.Plasma HAA	**0.537*** **
var(e.Plasma IL6)	**0.655*** **	var(e.Plasma KYNA)	**0.633*** **
var(e.Plasma IL6sr)	**0.841*** **	var(e.Plasma AA)	**0.610*** **
var(e.Plasma MCP1)	**0.904*** **	var(e.Plasma TRP)	**0.877*** **
var(Plasma-IMM)	**1**	var(Plasma-KP)	**1**
cov(ePlasma TNF,e.Plasma TNFR2)	**0.358** **	cov(e.Plasma KYN,e.Plasma KYNA)	**0.174***
cov(e.Plasma CRP,e.Plasma IL6)	**0.172**	cov(e.Plasma 3HKYN,e.Plasma TRP)	**-0.153***
cov(e.Plasma IL6, e.Plasma MCP1)	**-0.227***	cov(e.Plasma HAA,e.Plasma AA)	**-0.119**
		cov(e.Plasma HAA,e.Plasma TRP)	**0.177**
Observations	**72**	Observations	**72**

Table S5C: Confirmatory Factor Analysis – Goodness-of-Fit

Factor	LR Chi, (df), p	RMSEA (p)	CFI	Reliability	mean r2
CSF-IMM	8.45, (12), 0.75	<0.001	1	0.76	0.35
CSF-KYN	3.64, (6), 0.72	<0.001	1	0.71	0.38
Plasma-IMM	4.74, (11), 0.94	<0.001	1	0.71	0.3
Plasma-KP	11.46, (10), 0.32	0.04	0.99	0.85	0.49

Abbreviations

CSF=cerebrospinal fluid, TNF=tumor necrosis factor, TNFR2=soluble tumor necrosis factor receptor 2, IL6=interleukin-6, IL6sr=IL6 soluble receptor, IL10=interleukin-10, IL1b=interleukin 1-beta, IL1ra= IL1b receptor antagonist, CRP= c-reactive protein, MCP1=monocyte chemoattractant protein-1, TRP=tryptophan, KYN=kynurenine, KYNA=kynurenic acid, AA=anthranilic acid, 3HKYN=3-hydroxy-kynurenine, 3HAA=3-hydroxy anthranilic acid, QA=quinolinic acid. Plasma-IMM= plasma immune factor,
Plasma-KP= plasma kynurenine pathway factor, CSF-IMM=CSF immune factor
CSF-KP=CSF kynurenine pathway factor
*** p=<0.001, **p=<0.01, *=<p<0.05

Table S6A: Path Analysis – Path Loadings Table

Paths	Unstandardized Loadings	Std Loadings
Plasma-KP		
Plasma-IMM→Plasma-KP	1.05***	0.51
Caucasian-->Plasma-KP	0.40*	-0.23
CSF-KP		
Plasma-KP→CSF-KP	0.61***	0.57
CSF-IMM→CSF-KP	0.08	0.08
Age→CSF-KP	0.02**	0.25
Variances		
var(e.Plasma-KP)	0.46***	0.67
var(e.CSF-KP)	0.44***	0.55
var(BMI)	52.86***	1.00
var(Plasma-IMM)	0.16***	1.00
var(CSF-IMM)	0.77***	1.00
var(Age)	125.66***	1.00
var(Caucasian)	0.24***	1.00
Covariance		
cov(BMI,Plasma-IMM)	1.58***	0.54
cov(BMI,CSF-IMM)	-0.05	-0.01
cov(BMI,Age)	4.25	0.05
cov(BMI,Caucasian)	0.61	0.17
cov(Plasma-IMM,CSF-IMM)	0.09*	0.25
cov(Plasma-IMM,Age)	0.65	0.14
z	0.01	-0.05
cov(CSF-IMM,Age)	4.03**	0.41
cov(CSF-IMM,Caucasian)	0.20***	-0.46
cov(Age,Caucasian)	0.1	0.02
Sample		
Observations	72	

Table S6B: Path Analysis – Goodness of Fit

Description	Measure	value	a priori threshold
Model vs. saturated (LR Chi(df), p)	saturated	6.1, (6), 0.40 (NS)	>0.05
Baseline vs. saturated (LR Chi(df), p)	baseline	79.7, (11), <0.001	<0.05
Root mean squared error of approximation	RMSEA	0.018	<0.05
Standardized root mean squared residual	SRMR	0.047	<0.08
Comparative fit index	CFI	1	1
Effect size (R-squared)	Plasma-KP	0.33	0.25
	CSF-KP	0.45	0.25

Table S6C: Path Analysis – Total, Direct and Indirect Effects

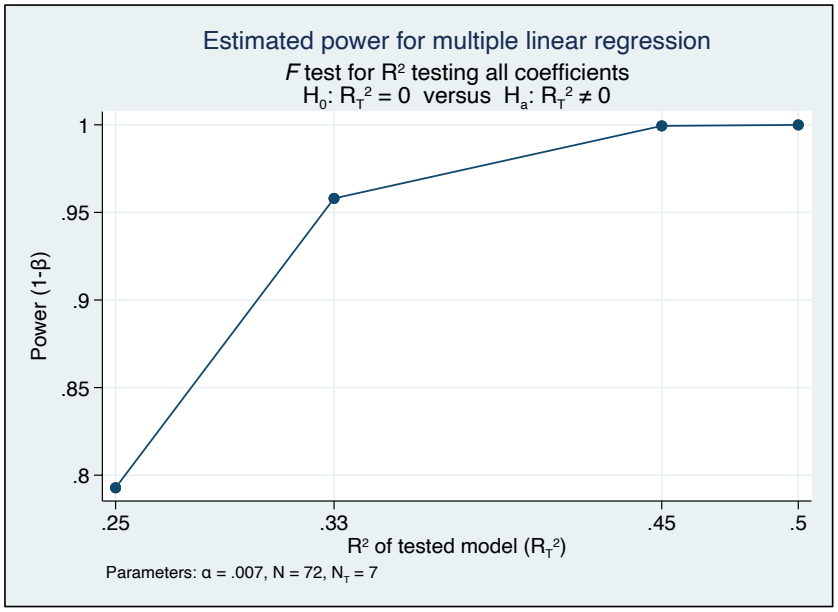
Paths	Total	Direct	Indirect
Plasma-IMM→Plasma-KP	0.51***	0.51***	---
Caucasian-→Plasma-KP	0.23*	0.23*	---
Plasma-KP→CSF-KP	0.57***	0.57***	---
Plasma-IMM→CSF-KP	0.29***	---	0.29***
CSF-IMM→CSF-KP	0.08	0.08	---
Age→CSF-KP	0.25*	0.25*	---
Caucasian→CSF-KP	0.13*	---	0.13*

Table S6D: Path Analysis – Path Contrast Analysis

Path 1: [To]From	(minus) Path 2: [To]From	chi2(df=1)
Plasma-KP→CSF-KP	null	83.8***
Plasma-IMM→Plasma-KP	null	39.3***
CSF-IMM→CSF-KP	null	0.42
Plasma-IMM→CSF-IMM	null	5.4*
Plasma-IMM→Plasma-KP	CSF-IMM→CSF-KP	7.7**
Plasma-KP→CSF-KP	Plasma-IMM→Plasma-KP	0.39
Plasma-IMM→>Plasma-KP-->CSF-KP	CSF-IMM→CSF-KP	32.1***
Plasma-IMM→Plasma-KP-->CSF-KP	Plasma-IMM<-->CSF-IMM→CSF-KP	12.5***
BMI←→Plasma-IMM→Plasma-KP→CSF-KP	Age+Cacausian+Plasma-IMM←→CSF-IMM→→CSF-KP	22.5***

Abbreviations: Plasma-IMM= plasma immune factor, Plasma-KP= plasma kynurenine pathway metabolites factor, CSF-IMM=CSF immune factor, CSF-KP=CSF kynurenine pathway metabolites factor. *** p=<0.001, **p=<0.01, *=<p<0.05.

Figure S2: Power Analysis Curve for Path Analysis



Legend: An overall power=0.9 for the path model was obtained using estimated effect sizes (Cohen's f=0.43 and 0.82, partial r-squared=0.33 and 0.45 for Plasma- and CSF-KP factors, respectively) with #tested/total predictors=1/7 (including covariates).

Table S7A: Lasso-based Variable Selection to Identify Plasma Immune Predictors of Plasma KYN/TRP – Model Comparison

	CV Lasso	Min BIC	Adaptive Lasso	Plugin1	Plugin2	Elastic Net	Ridge	Squareroot Lasso	Manual
PTNF#PTNF	x	x	x	x	x	x	x	x	x
Age	x	x	x	x		x	x	x	x
PIL6sr#PIL6sr	x	x	x			x	x	x	x
PIL1ra#PIL1ra	x	x	x			x	x	x	x
PTNFR2#PTNFR2	x	x		x		x	x		x
PIL6sr						x	x		x
PTNF						x	x		x
PIL1ra						x	x		x
PTNFR2						x	x		x
PMCP1#PMCP1						x	x		
PMCP1							x		
BMI							x		
PIL1b							x		
PCRP							x		x
Sex							x		
PIL6#PIL6							x		x
PCRP#PCRP							x		
PIL6							x		
PIL10#PIL10							x		
PIL10							x		
Race							x		
PIL1b#PIL1b							x		

Table S7B: Lasso-based Variable Selection to Identify Plasma Immune Predictors of Plasma KYN/TRP – Cross-Validation Table.

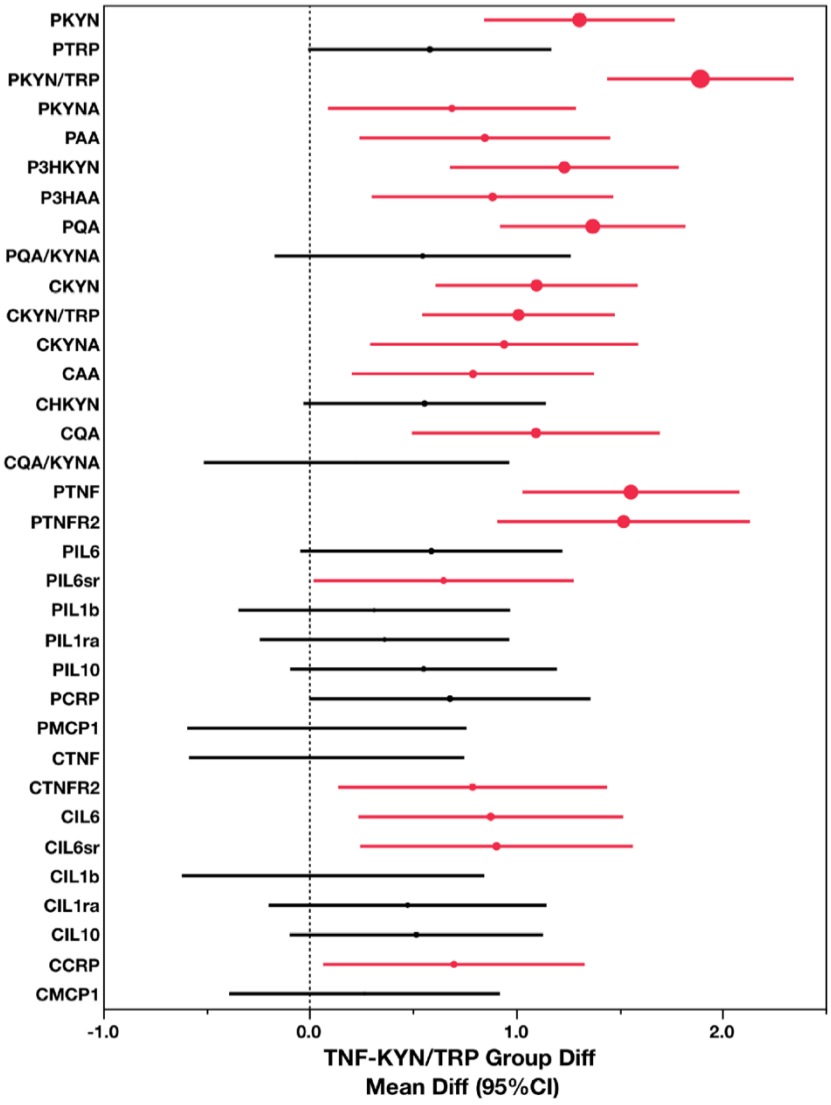
Name	sample	MSE	R-squared	N
CV-Lasso	Training	19.61817	0.6381	36
	Validation	83.88983	0.3399	36
Min BIC	Training	19.61817	0.6381	36
	Validation	83.88983	0.3399	36
Adaptive-Lasso	Training	19.5466	0.6394	36
	Validation	85.28944	0.3289	36
Plugin1*	Training	25.40343	0.5313	36
	Validation	71.84263	0.4347	36
Plugin2 *	Training	31.23075	0.4238	36
	Validation	69.82508	0.4506	36
Elastic Net	Training	21.54317	0.6026	36
	Validation	238.0783	-0.8733	36
Ridge	Training	9.851336	0.8173	35
	Validation	223.6609	-0.7584	33
Square-Lasso	Training	19.5466	0.6394	36
	Validation	85.28944	0.3289	36
Manual	Training	20.70269	0.6181	36
	Validation	244.8864	-0.9269	36

Table S8: K-means Cluster Comparison

Method	N Cluster	CCC	Best
K Means Cluster	2	-1.95	Optimal CCC
K Means Cluster	3	-3.61	
K Means Cluster	4	-2.94	
K Means Cluster	5	-4.38	
K Means Cluster	6	-4.39	
K Means Cluster	7	-4.24	
K Means Cluster	8	-3.64	
K Means Cluster	9	-4.59	
K Means Cluster	10	-4.67	
K Means Cluster	11	-3.96	
K Means Cluster	12	-4.05	

Abbreviations: CCC: Cubic Clustering Criteria

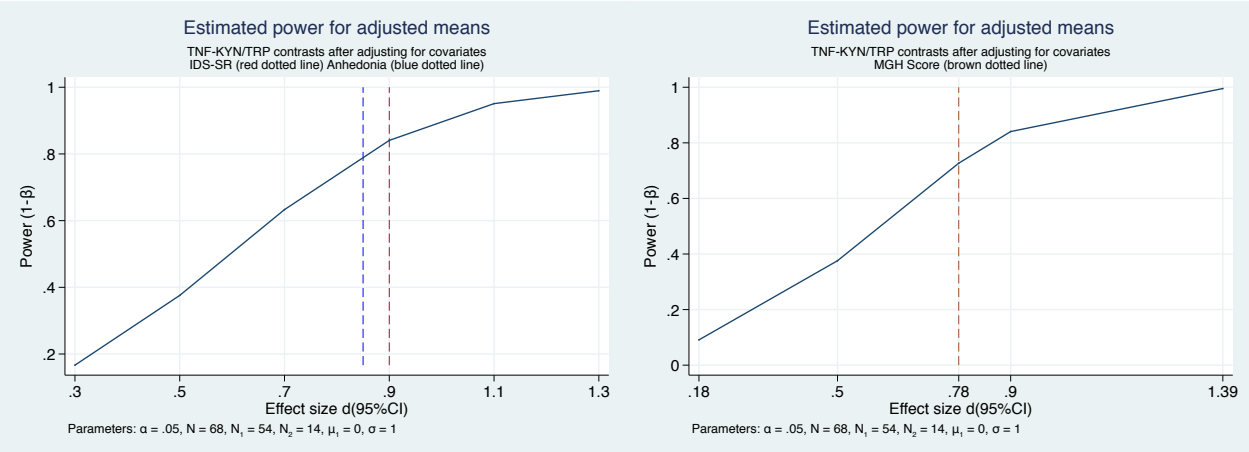
Figure S3. Contrasts between High versus Low KYN/TRP groups.



Legend: Red lines indicate increasing bias of the mean differences towards High TNF-KYN/TRP groups. The size of the red circles at the center indicate the p-value of the findings. Plasma KYN/TRP and TNF are provided for comparison as they were used for grouping.

Abbreviations: P=plasma, C=cerebrospinal fluid, KYN=kynurenine, TRP=tryptophan KYN/TRP=kynurenine/tryptophan, KYNA=kynurenic acid, AA=anthranilic acid, 3HKYN=3-hydroxy-kynurenine, 3HAA=3-hydroxy anthranilic acid, QA=quinolinic acid, QA/KYNA= quinolinic acid/kynurenic acid ratio, TNF=tumor necrosis factor, TNFR2=soluble tumor necrosis factor receptor 2, IL6=interleukin-6, IL6sr=IL6 soluble receptor, IL10=interleukin-10, IL1b=interleukin 1-beta, IL1ra= IL1b receptor antagonist, CRP= c-reactive protein, MCP1=monocyte chemoattractant protein-1.

Figure S4: Power Analysis of the Association between TNF-KYN/TRP Groups and Clinical Variables



Legend: Power was estimated using standardized effect sizes (d) obtained using comparisons of adjusted means derived after partialing out effects of covariates (age, sex, ethnicity, BMI). The plots indicate power estimates over the 95% confidence interval of the d values. A combined plot is provided for IDS-SR and anhedonia scales, and a separate plot for MGH-ATRQ scale is provided due to differing sample sizes for the latter. The red, blue and brown dotted lines represent total IDS-SR scores, Anhedonia and MGH-ATRQ scores respectively. As noted in the text, the power estimates for the association between High TNF-KYN/TRP group membership was 0.81, 0.91 and 0.72 for IDS-SR scores, Anhedonia and MGH-ATRQ scores respectively.