Supplementary Online Content

Goff DC, Zeng B, Ardekani BA, et al. Association of hippocampal atrophy with duration of untreated psychosis and molecular biomarkers during initial antipsychotic treatment of first-episode psychosis. *JAMA Psychiatry*. Published online February 21, 2018. doi:10.1001/jamapsychiatry.2017.4595

This supplementary material has been provided by the authors to give readers additional information about their work.

eAppendix 1: Antipsychotic medication
All FEP participants were medication naïve at the time of enrollment. Four FEP participants received 1-4 doses prior to the baseline blood draw. Antipsychotic dosages administered during the study to FEP patients were converted to mean daily chlorpromazine (CPZ) equivalent dosages in milligrams [1]. 22 FEP patients received a single second generation antipsychotic medication and 8 FEP participants received a combination of second generation antipsychotics. The mean (SD) total daily dose was 532 (310.9) mg in CPZ equivalents.

[1] Gardner DM, Murphy AL, O'Donnell H, Centorrino F, Baldessarini RJ. International consensus study of antipsychotic dosing. Am J Psychiatry 2010;167(6):686-693.

eAppendix 2: Imaging
FEP subjects and healthy controls were scanned at baseline and at follow up using a 3.0 T Siemens Verio MRI scanner (Erlangen, Germany) with a 32-channel head coil located at Shanghai Mental Health Center. 3D structural images were acquired using a T1-weighted MPRAGE sequence (TR/TE = 2300 ms/2.96 ms, FOV= 256 × 256 mm^2, FOV phase=93.8%, acquisition matrix = 256 × 256, voxel size = 1 × 1 × 1 mm^3, slice thickness = 1 mm, 192 sagittal slices).

eAppendix 3: Computation of the hippocampal volumetric integrity
Hippocampal volumetric integrity (HVI) is a normalized measure with values between 0 and 1 that is computed automatically from raw 3D T1-weighted inversion recovery structural MRI scans (henceforth referred to as 'MRI volume') without any pre-processing other than a DICOM to NIFTI format conversion. From each MRI volume two HVI values are computed; one from the left hemisphere (LHVI) and one from the right hemisphere (RHVI). HVI is intended as a surrogate marker of hippocampal atrophy and has proven highly reproducible in test-retest evaluations. It has particularly been useful in longitudinal studies for quantifying the rate of hippocampal degeneration. The rate of change of HVI, for example, predicts conversion from mild cognitive impairment to Alzheimer's disease [1]. This section provides an overview of the method for computing HVI. A software implementation of this technique (KAIBA) can be found at www.nitrc.org/projects/art.

KAIBA relies on an automatic method of obtaining an affine transformation based on landmark detection of the MRI volume. The affine transformation is a composite of a 6-parameter rigid-body transformation followed by a 12-parameter structure-specific affine transformation. The 6-parameter rigid-body transformation is intended to standardize the orientation of the MRI volume. It uses published algorithms that automatically detect the brain's mid-sagittal plane (MSP) [2] and the anterior and posterior commissures (AC/PC) on the MSP [3] to obtain the transformation matrix. To obtain the 12-parameter affine transformation, a large number of landmarks (~100) in the vicinity of the structure of interest, in this case the hippocampus, are detected. The corresponding transformation matrix is then estimated by least-squares fit of the detected landmarks to their expected average locations which have been determined *a priori* based on a set of example MRI volumes. Thus, the composite affine transformation (6-parameter global rigid-body and 12-parameter local affine) transforms an MRI volume into a new space designed to create a high degree of overlap between the hippocampi across subjects. Note that this procedure is performed twice, once for each hemisphere.

KAIBA uses probabilistic regions of interest (ROIs) determined based on 65 MRI volumes from young healthy individuals on which the hippocampi were manually delineated. These 65 MRI volumes were registered using the affine transformations obtained using the method described in the previous paragraph. The transformations were applied to the corresponding hippocampi labels thus projecting them onto a common space. The probabilistic ROIs are then obtained by averaging the 65 transformed labels. Again, this process is done twice, once for each hemisphere yielding two ROIs for the left and right hippocampi.

In order to determine the HVI on a test MRI volume, the first step is to determine the composite affine transformation using the landmark detection method described above. Then the inverse affine transformation is applied to the probabilistic ROI described in the previous paragraph to project the ROI onto the native space of the test MRI volume. Figure 1 shows the left ROI projected onto the space of a given test MRI volume. Since the probabilistic ROI is derived from young healthy brains, the algorithm is based on landmarks where in the native space of the test MRI volume we expect to find an intact healthy hippocampus. HVI aims to capture the extent to which this expectation is not met by the region underlying

the ROI. The MRI volume itself is not adjusted in any way and no interpolation is performed on the volume because the ROI is projected onto the native space of the MRI.

In the final stage of the algorithm, KAIBA determines the histogram of the voxel intensities underlying the probabilistic ROI. The histogram is usually noisy. Therefore, a smooth function comprised of a mixture of five Gaussian curves is fitted to the histogram using the expectation maximization (EM) algorithm [4]. An example is shown in Figure 2 where the histogram of the voxel intensities comprising the left hippocampus ROI in a test volume is shown (thin blue jagged line) along with a 5-component Gaussian mixture model fit using the EM algorithm (thick red smooth line). Smooth fitting allows KAIBA to estimate the gray matter peak location I_{gm} (indicated by the "Max" line) from which it determines the location of a CSF intensity threshold $\mathrm{I}_{\mathrm{CSF}}$ (indicated by the "Thld" line). Finally, HVI is defined as the fraction of the supra-threshold voxels, or equivalently, the area under the histogram for intensities above $\mathrm{I}_{\mathrm{CSF}}$. More details about the algorithm can be found in [5].

To evaluate the test-rerest reliability of KAIBA, we used data from 63 subjects from the MIRIAD public domain dataset [6]. These data were comprised of back-to-back independent MRI scans from the same subjects on the same day. We computed the HVI on these cases. The intra-class correlations (ICC) for the left and right hippocampi were 0.998 and 0.997, respectively.

[1] Ardekani BA, Bermudez E, Mubeen AM, Bachman AH; Alzheimer's Disease Neuroimaging Initiative. Prediction of Incipient Alzheimer's Disease Dementia in Patients with Mild Cognitive Impairment. J Alzheimer's Dis. 2016 Nov 1;55(1):269-281. PubMed PMID: 27662309.

[2] Ardekani BA, Kershaw J, Braun M, Kanno I. Automatic detection of the mid-sagittal plane in 3-D brain images. IEEE Trans Med Imaging. 1997 Dec;16(6):947-52. PubMed PMID: 9533596.

[3] Ardekani BA, Bachman AH. Model-based automatic detection of the anterior and posterior commissures on MRI scans. Neuroimage. 2009 Jul 1;46(3):677-82. doi:10.1016/j.neuroimage.2009.02.030. PubMed PMID: 19264138; PubMed Central PMCID: PMC2674131.

[4] Schroeter P, Vesin JM, Langenberger T, Meuli R. Robust parameter estimation of intensity distributions for brain magnetic resonance images. IEEE Trans Med Imaging. 1998 Apr;17(2):172-86. PubMed PMID: 9688150.

[5] Ardekani BA, Convit A, Bachman AH. Analysis of the MIRIAD Data Shows Sex Differences in Hippocampal Atrophy Progression. J Alzheimers Dis. 2016;50(3):847-57. doi: 10.3233/JAD-150780. PubMed PMID: 26836168.

[6] Malone IB, Cash D, Ridgway GR, MacManus DG, Ourselin S, Fox NC, Schott JM. MIRIAD--Public release of a multiple time point Alzheimer's MR imaging dataset. Neuroimage. 2013 Apr 15;70:33-6. doi: 10.1016/j.neuroimage.2012.12.044. PubMed PMID: 23274184; PubMed Central PMCID: PMC3809512.

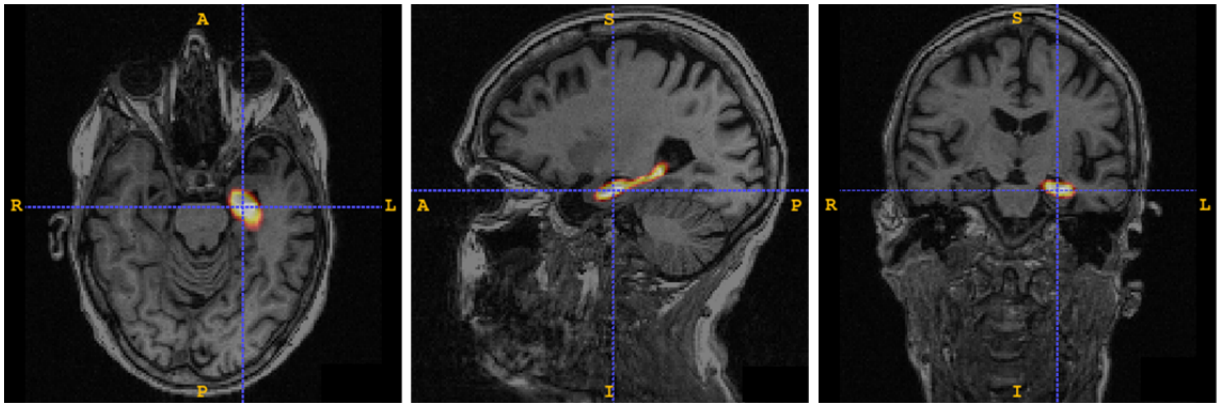


Figure 1: Axial (left), sagittal (center), and coronal (right) views through the automatically detected probabilistic VOI of the left hippocampus in a study participant.

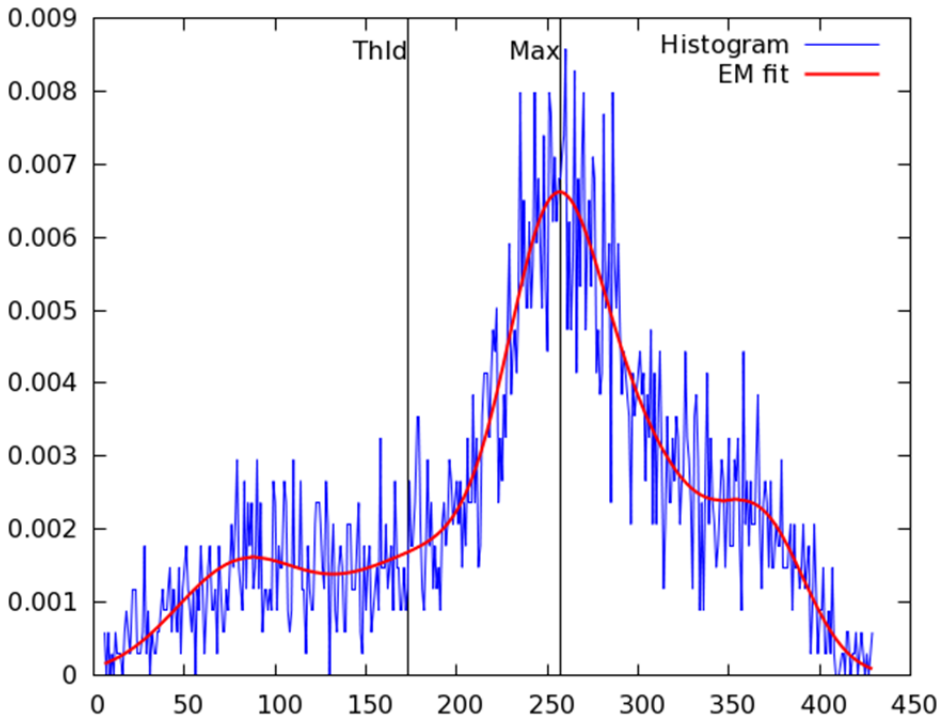


Figure 2: Histogram analysis using the EM algorithm. The histogram of the voxel intensities comprising the left hippocampus ROI in a subject is shown (thin jagged line) along with a 5-component Gaussian mixture model fit using the EM algorithm (thick smooth line). Smooth fitting allows us to estimate the gray matter peak location I_{gm} (indicated by the "Max" line) from which we determine the location of a CSF intensity threshold I_{CSF} (indicated by the "Thld" line). HVI is defined as the fraction of the supra-threshold voxels, or equivalently, the area under the histogram for intensities above I_{CSF}.

eAppendix 4: Medical and psychiatric assessments

All subjects were first assessed by study staff for capacity to participate in the study. Subjects were then assessed with the Structured Clinical Interview for DSM Disorders (SCID) to verify the diagnosis of schizophrenia or schizophreniform disorder and to exclude other Axis I diagnoses, such as psychosis due to drug use. We also completed a demographics form for each subject, a physical exam, a comprehensive medical history evaluation, a psychiatric history evaluation including past medications and hospitalizations, and vital signs assessment. We performed laboratory tests at the Screening Visit which included complete blood count, electrolytes, creatinine, BUN, glucose, liver enzymes, calcium, phosphate, magnesium, albumin, prolactin level, and urinalysis. All subjects were evaluated for drug use with a urine toxicology test and female subjects were tested for pregnancy. For inpatients, full medical evaluations from hospital records were also used to evaluate medical status to participate.

eAppendix 5: Sample collection and preparation

Fasting blood samples were obtained at baseline from FEP participants and healthy controls and at follow up from FEP participants. Plasma samples were obtained from venous blood using from EDTA anticoagulant and were centrifuged at 3000rpm for 20min before being frozen at -80 degree. Plasma protein quantification was performed using enzyme-linked immunosorbent assay (ELISA) or protein arrays. All samples were batched and all assays were performed in one run after completion of sample collection.

eAppendix 6: Blood biomarker assays

Cytokines: The human cytokines CRP, BDNF, IL-1beta, IL-8, IFNγ, S100B and TNF alpha were quantified using the Customized Human Cytokine Antibody Array (RayBiotech, Norcross, GA, USA). The assay was based on the sandwich immunoassay principle and was performed according to the manufacturer's instructions by Wayen Biotechnology (Shanghai, China). In brief, antibodies targeting the selected cytokines are immobilized in specific locations on the surface of the array surface, and fifty micro liters of sample was 2-fold diluted and applied to each block in duplicate. Cytokines present in the samples are captured by the corresponding antibodies and a collection of biotinylated antibodies is added to detect the bound cytokines. The signals were visualized using fluorescent dye conjugated with streptavidin (cy3 equivalent) and were detected with a GenePix 4000B system (Axon Instruments, Foster City, CA, USA). GenePix Pro 6.0 software (Axon Instruments) was used for densitometric analysis of the spots.

Enzyme-linked immunosorbent assay (ELISA): Thioredoxin 1 (unit: pg/ml) and 5-Methyltetrahydrofolate (unit: ng/ml) were measured using specific ELISA kits (Mybiosource, Southern California, USA) based on sandwich enzyme immunoassay, with a corresponding dilution of 1:2 and 1:1 respectively. Homocysteine (unit: μmol/L) was measured using an ELISA kit (Mybiosource, Southern California, USA) based on competitive enzyme immunoassay, with a dilution of 1:8. All assays were performed according to the manufacturer's instructions by Wayen Biotechnology (Shanghai, China). All samples were analyzed repeatedly (CV<20).

Colorimetric Assay: L-Lactate, L-Glutamate and L-Aspartate were quantitatively measured using specific kits (Biovision, San Francisco,USA) based on colorimetric methods. The plasma sample was directly tested as a dilution of 1:20 for L-Lactate (unit: nmol/μl) and 1:1 for L-Glutamate (unit: nmol/μl). For L-Aspartate (unit: nmol/μl), a 100μl plasma sample was first deproteinized by centrifuging 10 min with a 10 kDa spin filter (BioVision, San Francisco,USA) and then a 30μl deproteinized sample was directly used in the assay. All tests were performed according to the manufacturer's instructions by Wayen Biotechnology (Shanghai, China). All samples were analyzed repeatedly (CV<20%).

eAppendix 7: KASP (Kompetitive Allele Specific PCR) genotyping assays

The human SNPs of rs12742393, rs1344706, rs1360780, rs1801133, rs202676, rs2301022, rs2391191, rs2494732, rs41279104, rs4680, rs5522, rs6265, rs6490121, rs778294, rs4818, rs1801131 were tested using KASP genotyping assays (LGC, UK) performed according to the manufacturer's instructions by South Gene Technology (Shanghai, China). KASP genotyping assays were based on competitive allele-specific PCR and enable bi-allelic scoring of single nucleotide polymorphisms (SNPs) at specific loci. In brief, the KASP Assay mix contains three assay-specific non-labeled oligos: two allele-specific forward primers and one common reverse primer. The allele-specific primers each harbor a unique tail sequence that corresponds with a universal FRET (fluorescence resonant energy transfer) cassette; one labeled with FAM dye and the other with HEX dye. The KASP Master mix contains the universal FRET cassettes, ROX passive reference dye, taq polymerase, free nucleotides and MgCl2 in an optimized buffer solution. During thermal cycling, the relevant allele-specific primer binds to the template and elongates, thus attaching the tail sequence to the newly synthesized strand. The complement of the allele-specific tail sequence is then generated during subsequent rounds of PCR, enabling the FRET cassette to bind to the DNA. The FRET cassette is no longer quenched and emits fluorescence. Bi-allelic discrimination is achieved through the competitive binding of the two allele-specific forward primers. If the genotype at a given SNP is homozygous, only one of the two possible fluorescent signals will be generated. If the genotype is heterozygous, a mixed fluorescent signal will be generated. The signals were detected with a 7900HT system (Applied Biosystems, USA). SDS Software 2.3 was used for densitometric (Applied Biosystems, USA) analysis of the spots.

eAppendix 8: Salivary cortisol

Three saliva samples were collected throughout the day on two consecutive days: at 8:00 AM, 12:00 AM and 20:00 PM. Participants were instructed to chew on a piece of cotton, store it in a tube. Samples were stored in the participant’s home freezer until collection of 3 samples, and subsequently were sent back to our laboratory and were frozen at -80 degrees. After thawing and centrifugation at 1500rpm for 15min, cortisol levels were measured using Salimetrics High Sensitivity Salivary Cortisol ELISA KIT (Salimetrics, Suffolk, UK). The analytical sensitivity was 0.012μg /dl, and the inter- and intra-assay coefficients ranged from 3% to 7% and 3% to 11%, respectively.

eAppendix 9: SNPs and associated pathways

Gene	SNP	Pathway
Glutamate cysteine ligase modifier (GCLM)	rs2301022	Oxidative stress
Nitric oxide synthase 1 (NOS1)	rs41279104 rs6490121	Glutamatergic NMDA transmission; Oxidative stress
Nitric oxide synthase 1 adaptor protein (NOS1AP)	rs12742393	Glutamatergic NMDA transmission; Oxidative stresss
Brain-derived neurotrophic factor (BDNF)	rs6265	Growth factor
Zinc finger protein 804A (ZNF804A)	rs1344706	Dopamine signaling
AKT serine/threonine kinase 1 (AKT1)	rs2494732	Dopamine signaling (intracellular)
Methylenetetrahydrofolate reductase (MTHFR)	rs1801133	Folate/homocysteine metabolism
D-amino acid oxidase activator (DAOA)	rs2391191 rs778294	Glutamatergic NMDA transmission
Folate hydrolase 1 (FOLH)	rs202676	Folate/homocysteine metabolism
Catechol-O-methyltransferase $Val^{158}Met$ (COMT Val158Met)	rs4680	Dopamine signaling
FK506 binding protein 5 (FKBP5)	rs1360780	Stress and cortisol
Nuclear receptor subfamily 3 group C member 2 (NR3C2)	rs5522	Stress and cortisol

eAppendix 10: Tests of effects of hemispheric laterality on HVI findings

To examine the effect of hemispheric laterality on baseline HVI and change from baseline in HVI, given the non-normal distribution of the HVI data, we conducted a Wilcoxon matched pairs signed rank test to determine whether there was a difference in the ranking of left and right HVI values and annualized change in left and right within FEP participants and HC. Results suggest that at baseline there was not a significant difference between left and right HVI for FEP participants, z=-.258, p=.796. However RHVI was significantly larger than LHVI for HC at baseline, z=-3.526, p=.001. We repeated this analysis for annualized change in left and right HVI. Results from this analysis did not show a significant difference between left and right annualized HVI change for FEP participants, z=-.771, p=.400 or HC, z=-.098, p=.922.

eAppendix 11: LASSO regression

Least Absolute Shrinkage and Selection Operator (LASSO) regression shrinks the coefficients of non-associated variables towards 0, allowing for the variance of associated variables to be identified and irrelevant variables to be removed from the analysis [1]. To explore the significant associations from the correlational analyses, LASSO regression was applied in two models: the first used LHVI at baseline and the second used change in LHVI as the dependent variable. In each model baseline values of peripheral biomarkers that correlated with baseline LHVI or with change in LHVI at a level of $p < .10$ were examined by LASSO regression. This permissive threshold was utilized because LASSO is more robust for detecting relationships between non-normally distributed variables than Spearman correlations and to maximize power to detect potential relationships without overloading the statistical model. Variables that were entered included baseline levels of CRP, INFγ, IL8, S100B, TNFα, thioredoxin, DUP and the following genotypes: NOS1 (rs41279104), BDNF (rs6265), ZFN804A (rs1344706) and COMT Val158Met (rs4680). In addition, two-way interactions with DUP were examined. Results that were significant at a level of $p < .05$ are presented in Table 3. Complete regression results of models of baseline LHVI and LHVI change are summarized in eTable 7 and eTable 8, respectively.

[1] Tibshirani R. Regression shrinkage and selection via the Lasso. *J Royal* Statis *Soc, Series B (Methodological).* 1996;58(1):267-288.

eAppendix 12: Excluded subjects

At baseline, images from seven FEP patients and one healthy control were excluded due to motion prior to processing. At follow up, images from one FEP patient and three healthy controls were also excluded due to motion.

eAppendix 13: Test-retest reliability comparison with FreeSurfer v.6

Macleren et al. [1] provide a unique publicly available dataset to assess the repeatability of brain segmentation and analysis methods. The dataset consists of 120 T1-weighted structural MRI volumes from 3 subjects (40 volumes/subject) acquired in 20 sessions in a span of 31 days. Each subject was scanned twice within each session, with repositioning between the two scans, allowing determination of both intra-session and inter-session test-retest reliability. The authors in [1] computed the total coefficient of variation (CV_t) for sum of left and right hippocampal volume (HV) estimated using FreeSurfer v.5.1 to be 2.92% and the intra-session coefficient of variation (CV_s) to be 2.77%. The difference CV_t- CV_s was not significant (p=0.41) assessed using a Monte Carlo permutation test where the scan order of all 40 volumes for each subject was randomly permutated 100,000 times.

We implemented the exact same computational procedure for the HV estimated using the longitudinal stream of FreeSurfer v.6. We calculated CV_t=1.03% and CV_s=1.04%. The difference CV_t- CV_s was not statistically significant (p=.54). We repeated the procedure for the sum of left and right hippocampal volumetric integrity (HVI) obtained using KAIBA which yielded CV_t=.43% and CV_s=.35%. The difference CV_t- CV_s was found to be statistically significant (p=.002).

There are two sources of variation in the estimated quantities: (1) the variance due to different subject positioning and random MRI noise; and (2) actual day-to-day variations, e.g., due to hydration level or time of day. The above analysis indicates that HVI (CV_t=.43%) is substantially more reproducible than the HV computed using either FreeSurfer v.5.1 (CV_t=2.92%) or FreeSurfer v.6 longitudinal stream (CV_t=1.03%). Furthermore, the inter-session variability of HVI significantly exceeded intra-session variability (p=.002).

These results support the finding in this paper that HVI is more sensitive than FreeSurfer v.6.0 computed HV in detecting HC vs FEP group difference in hippocampus atrophy progression over the period of 8 weeks.

The means and total standard deviations for each subject and each method are given in the following table. The CV_t for each subject can be obtained from these numbers. The pooled CV_t reported above is obtained by taking the root-mean-square average of the CV_t data from each subject as done in [1].

	Subject 1	Subject 2	Subject 3
FreeSurfer v.6 HV	8741.8 (97.2)	8662.9 (76.9)	8581.4 (93.4)
KAIBA HVI	1.9135 (0.0089)	1.9148 (0.0078)	1.9048 (0.0079)

Mean (SD) of the total left + right HV (obtained from FreeSurfer v.6) and left + right HVI obtained from KAIBA for each of the three subjects.

[1] Maclaren J, Han Z, Vos SB, Fischbein N, Bammer R. Reliability of brain volume measurements: a test-retest dataset. *Scientific data.* 2014;1:140037.

eAppendix 14: Correlations between intra-cranial volume and FreeSurfer v.6 hippocampal volumes and HVI

A source of inter-subject variance is that measurements may be associated with intra-cranial volume which is variable across subjects. To illustrate this, we computed the average hippocampal volume (HV) measured using FreeSurfer v.6 (average of left and right and both scans) and similarly the average hippocampal volumetric integrity (HVI) measured using KAIBA for all HC and FEP subjects with imaging data at baseline. We then computed the bivariate correlations between these measures and the estimated total intra-cranial volume (eTIV) obtained from FreeSurfer v.6. The HV was strongly associated with eTIV ($r=.690$, $p<.10^{-16}$), however, the association between HVI and eTIV was weaker ($rs=-.19$, $p=.05$). These results indicate HVI is less affected by inter-subject variance due difference in intra-cranial volume.

eTable 1: Comparison of baseline measures between FEP completers and non-completers

		FEP participants completers (*n*=31)		FEP participants non-completers (*n* =40)	Test Statistic	*p* Value
Characteristic:	n	M (*SD*) or %	n	M (*SD*) or %	$t/X^2/U$ (df)	
Age	31	23.97 (*7.02*)	40	26.00 (*8.09*)	-1.11 (69)	*.27*
Women, No. (%)	31	18 (58.1)	40	21 (52.5)	X^2 (1) = *.219*	*.64*
DUP	29	23.81 (*16.08*)	32	26.90 (*25.85*)	*t*(59)=-.554	*.58*
BPRS Total Score	31	51.77 (*13.07*)	39	45.03 (*7.94*)	2.53 (46.99)	*.01*
BPRS Agitation Subscale	31	11.06 (*5.31*)	40	8.33 (*2.65*)	2.62 (41.75)	*.01*
BPRS Positive Subscale	31	20.10 (*5.51*)	40	18.33 (*4.05*)	1.54 (68)	*.13*
BPRS Negative Subscale	31	6.13 (*3.77*)	40	5.56 (*2.84*)	.716 (68)	*.48*
SANS Composite Total	31	22.32 (*19.87*)	39	19.49 (*16.43*)	.654 (68)	*.52*
MCCB Composite Total	31	34.45 (*13.64*)	38	36.24 (*13.85*)	-.536 (67)	*.59*
LHVI median Baseline (IQR)	27	.9239 (*.8256-.9689*)	30	.9387 (*.8546-.9687*)	*U*=347.00	*.35*

Abbreviations: DUP = duration of untreated psychosis; BPRS = Brief Psychiatric Rating Scale; SANS = Scale for the Assessment of Negative Symptoms; MCCB = MATRICS Consensus Cognitive Battery.

eTable 2. Baseline characteristics of study participants with baseline imaging that met quality standards

		FEP Participants[a]		Healthy Controls[a]	Test Statistic	*p* Value
Characteristic	*n*	M (SD) or %	*n*	M (SD) or %	$t/\chi^2/U$ (*df*)	
Age	57	25.49 (7.29)	54	24.78 (6.445)	*t (109)* = .545	*.59*
Women, No. (%)	57	31 (54.4)	54	30 (55.6)	$\chi^2(1)$ = .015	*.53*
Education Parental Education	57	12.51 (2.73) 7.86 (5.93)	54	13.09 (2.29) 10.06 (3.83)	*t (109)* = -1.22 *t*(*109)* = -2.31	*.23* *.02*
Married, No. (%)	57	13 (22.8)	54	18 (33.3)	$\chi^2(1)$ = 1.53	*.15*
Employed, No. (%)	57	18 (31.6)	54	27 (50.0)	χ^2 (*2*) = 10.23	*.006*
Tobacco use, No. (%)	57	1 (1.8)	54	0 (0.0)	χ^2 (*2*) = 1.26	*.53*
DUP	53	25.42 (22.32)		NA		
BPRS Total Score	56	47.21 (11.09)		NA		
BPRS Agitation Subscale	56	9.13 (4.23)		NA		
BPRS Positive Subscale	56	18.86 (4.87)		NA		
BPRS Negative Subscale	56	5.70 (3.16)		NA		
SANS Composite	56	20.29 (17.85)		NA		
MCCB Composite	57	35.23 (13.47)	54	44.87 (9.24)	*t*(*109)*) = -4.418	*.001*
CRP, median (IQR)	57	7678.90 (6789.31-9476.76)	53	7484.70 (6680.51-8921.00)	*U* = 1358	*.36*
IL-1B, median (IQR)	57	74.62 (42.34-166.58)	53	73.75 (40.95-225.11)	*U* = 1462	*.77*
IL-8, median (IQR)	57	73.47 (50.71-86.40)	53	60.51 (50.08-82.46)	*U* = 1308	*.23*
IFNγ, median (IQR)	57	93.71 (73.44-113.86)	53	88.96 (64.69-125.78)	*U* = 1394	*.49*
TNFa, median (IQR)	57	95.99 (77.77-108.09)	53	91.06 (72.25-103.23)	*U* = 1258	*.13*
Salivary Cortisol, median (IQR)[b]	39	6.19 (4.02-8.59)	46	4.88 (3.19-7.32)	*U* = 657	*.03*
Aspartate, median (IQR)	57	4.05 (2.62-6.13)	53	3.07 (2.38-4.07)	*U* = 1153	*.03*
Glutamate, median, (IQR)	57	5.70 (5.00-6.45)	53	5.28 (4.83-6.26)	*U* = 1342	*.31*
Lactate, median (IQR)	57	4.39 (3.14-5.74)	52	3.69 (2.73-5.17)	*U* = 1257	*.17*
HCY, median (IQR)	57	4.80 (4.51-5.24)	53	4.80 (4.44-5.38)	*U* = 1478	*.85*
BDNF, median (IQR)	57	351.08 (160.63-1101.97)	54	317.21 (153.79-742.37)	*U* = 1431	*.52*
Thioredoxin, median (IQR)	57	412.17 (302.83-626.50)	53	495.83 (317.33-637.67)	*U* = 1380	*.44*
S100B, median (IQR)	57	126.12 (76.71-211.93)	53	130.89 (54.53-250.15)	*U* = 1489	*.90*

Abbreviations: DUP = duration of untreated psychosis in weeks; BPRS = Brief Psychiatric Rating Scale; SANS = Scale for the Assessment of Negative Symptoms; MCCB = MATRICS Consensus Cognitive Battery; CRP = c-reactive protein; IQR = interquartile range; IL-1B = interleukin-1 beta; IL-8 = interleukin-8; IFNγ = interferon gamma;

TNFa = tumor necrosis factor alpha; HCY = homocysteine; BDNF = brain derived neurotrophic factor; S100B = S100 calcium binding protein B;
[a]Comparisons between FEP participants and healthy controls were adjusted for parental education level.
[b]Units of plasma concentration levels for all biomarkers are pg/mL except salivary cortisol which is measured in µg/dL.

eTable 3: Comparison of FEP and HC participants who completed follow up imaging

	FEP Participants (*n*=24)	HC Participants (*n*=32)	Test Statistic	*p* Value
	M (SD) or %	M (SD) or %		
Age	23.79 (5.32)	25.25 (7.40)	*t(54)=-.858*	*.40*
Women, No. (%)	12 (50.0)	19 (59.4)	$X^2(1)$=.488	*.59*
Education	12.75 (2.51)	13.03 (2.52)	t(54)=-.414	*.68*
Week 8 MCCB Composite score	40.46 (10.35)	50.28 (7.69)	*t(54)=-4.08*	*.001*

Abbreviation: MCCB = MATRICS Consensus Cognitive Battery.

eTable 4. Comparison between FEP participants and HC in baseline hippocampal volume and change from baseline of hippocampal volume calculated by the longitudinal stream of FreeSurfer v. 6

		Baseline LHV			Baseline RHV				Change LHV			Change RHV		
	n	M (*SD*)	*t*	*p* Value	M (*SD*)	*t*	*p* Value	*n*	M (*SD*)	*t*	*p* Value	M (*SD*)	*t*	*p* Value
FEP	57	3979.29 (*382.34*)	-1.27	*.21*	4200.77 (*353.92*)	-.46	*.65*	24	-20256.75 (*5039.96*)	-1.65	*.11*	-21149.23 (*5260.69*)	-1.73	*.09*
HC	54	4065.64 (*330.21*)			4232.62 (*375.77*)			32	-18153.25 (*4490.77*)			-18819.97 (*4789.58*)		

Abbreviations: LHV = left hippocampal volume; RHV = right hippocampal volume.

eTable 5: Comparison of peripheral biomarkers at baseline between healthy controls and FEP patients who were medication free

	FEP Participants (medication free) *(n*=65)	Healthy Controls *(n*=61)	Test Statistic	*p* Value
Biomarker:	Median (*IQR*)	Median (*IQR*)	*U*	
CRP (pg/mL)	7686.12 (*3120.81-10682.08*)	7610.08 (*4168.24-10837.24*)	*U=1739*	*.64*
IL-1B (pg/mL)	74.76 (*18.43-1631.57*)	75.76 (*20.36-2432.81*)	*U*=1726	*.59*
IL8 (pg/mL)	71.30 (*49.79-83.26*)	63.41 (*50.77-82.46*)	*U=1810*	*.40*
IFNγ (pg/mL)	89.29 (*48.55-751.75*)	88.96 (*51.72-1650.50*)	*U*=1755	*.70*
TNFa (pg/mL)	94.67 (*64.97-221.57*)	92.03 (*58.27-414.46*)	*U*=1681	*.44*
Salivary Cortisol (µg/dL)	6.19 (*1.82-15.31*)	4.88 (*1.16-16.75*)	*U*=892	*.05*
Aspartate (pg/mL)	4.08 (*.90-17.03*)	3.07 (*.83-9.71*)	*U*=1371	*.02*
Glutamate (pg/mL)	5.71 (*3.59-10.04*)	5.25 (*3.91-9.70*)	*U*=1510	*.098*
Lactate (pg/mL)	4.38 (*1.58-12.35*)	3.69 (*1.33-12.89*)	*U=1487*	*.10*
HCY (pg/mL)	4.84 (*3.51-6.43*)	4.79 (*3.68-6.57*)	*U=1808*	*.91*
BDNF (pg/mL)	297.77 (*31.95-6498.98*)	287.37 (*35.12-12697.51*)	*U*=1750	*.57*
Thioredoxin (pg/mL)	422.33 (*113.67-10835.17*)	492.33 (*106.83-12818.83*)	*U*=1718	*.56*
S100B (pg/mL)	123.78 (*28.98-834.46*)	130.44 (*30.03-2854.11*)	*U*=1824	*.98*

Abbreviations: CRP = c-reactive protein; IL-1B = interleukin-1 beta; IL-8 = interleukin-8; IFNγ = interferon gamma; TNFa = tumor necrosis factor alpha; HCY = homocysteine; BDNF = brain derived neurotrophic factor; S100B = S100 calcium binding protein B.

eTable 6: Change in peripheral biomarkers with analysis restricted to FEP participants who were medication free at baseline

Biomarker	Baseline	Follow up	Test Statistic	*p* Value
CRP (pg/mL)	7541.41 (*5539.32-10397.16*)	7687.25 (*5911.16-11496.23*)	*Z*=-.260	*.79*
IL-1B (pg/mL)	89.11 (*29.81-624.88*)	57.01 (*44.63-218.34*)	*Z*=-.071	*.94*
IFNγ (pg/mL)	94.63 (*60.55-326.52*)	74.74 (*44.63-218.34*)	*Z*=-.071	*.94*
TNFa (pg/mL)	95.59 (*68.02-164.17*)	81.90 (*62.96-153.26*)	*Z*=-.213	*.83*
Salivary Cortisol (µg/dL)	7.41 (*1.82-15.31*)	4.36 (*1.11-12.24*)	*Z*=-1.82	*.07*
Aspartate (pg/mL)	4.21 (*1.50-9.11*)	4.56 (*1.87-8.66*)	*Z*=-.639	*.52*
Glutamate (pg/mL)	5.36 (*4.17-7.51*)	5.31 (*3.44-7.39*)	Z=-.402	*.69*
Lactate (pg/mL)	4.49 (*2.25-10.42*)	4.28 (*1.40-7.17*)	*Z=-.450*	*.65*
HCY (pg/mL)	4.59 (*3.69-5.66*)	4.93 (*4.16-6.01*)	*Z=-1.68*	*.09*
BDNF (pg/mL)	351.08 (*31.95-5665.72*)	285.60 (*68.57-3390.16*)	*Z*=-.497	*.62*
Thioredoxin (pg/mL)	393.67 (*159.17-10835.17*)	378.33 (*158.83-12501.83*)	*Z*=-.544	*.59*
S100B (pg/mL)	203.86 (*44.27-834.46*)	149.40 (*28.09-947.79*)	*Z*=-.450	*.65*

Abbreviations: CRP = c-reactive protein; IL-1B = interleukin-1 beta; IL-8 = interleukin-8; IFNγ = interferon gamma; TNFa = tumor necrosis factor alpha; HCY = homocysteine; BDNF = brain derived neurotrophic factor; S100B = S100 calcium binding protein B.

eTable 7: Change from baseline to week 8 in FEP participants

	Baseline[a]	Follow up[a]	*n*	Test Statistic	*p* Value
Characteristic:	Mean (SD)	Mean (SD)		*Z*/*t*(df)	
BPRS Total Score	51.77 (13.07)	33.48 (7.17)	31	*t(30)* = 8.19	*.001*
BPRS Agitation Subscale	11.06 (5.31)	7.61 (2.25)	31	*t(30)* = 4.51	*.001*
BPRS Positive Subscale	20.10 (5.51)	10.19 (3.54)	31	*t(30)* = 8.78	*.001*
BPRS Negative Subscale	6.13 (3.77)	5.23 (2.26)	31	*t(30)* = 1.72	*.10*
SANS Composite	22.32 (19.87)	16.94 (12.93)	31	*t(30)* = 1.94	*.06*
MCCB Composite	33.90 (13.52)	39.40 (11.58)	30	*t*(29) = 3.06	*.01*
CRP, median (IQR)	7541.41 (5539-10397)	7627.60 (5704.38-11841.01)	29	*Z* = -.508	*.61*
IL-1B, median (IQR)	104.75(29.81-624.88)	60.11 (19.52-554.56)	29	*Z* = -.314	*.75*
IL-8, median (IQR)	74.34 (50.02-93.98)	65.79 (51.16-82.38)	29	*Z* = -.638	*.52*
IFNγ, median (IQR)	94.95 (60.55-326.52)	70.50 (44.63-263.68)	29	*Z* = -.162	*.87*
TNFa, median (IQR)	101.31(68.02-164.17)	78.78 (62.96-153.26)	29	*Z* = -.314	*.75*
Salivary Cortisol, median (IQR)[b]	6.57 (1.82-15.31)	4.47 (1.11-12.24)	19	*Z* = -1.89	*.06*
Aspartate, median (IQR)	4.29 (1.50-9.11)	4.43 (1.87-8.66)	29	*Z* = -2.37	*.02*
Glutamate, median (IQR)	5.41 (4.22-7.51)	5.40 (4.50-7.39)	29	*Z* = -.57	*.57*
Lactate, median (IQR)	4.49 (3.11-5.21)	3.95 (2.75-6.11)	29	*Z* = -.076	*.94*
HCY, median (IQR)	4.54 (3.69-5.66)	4.87 (4.16-5.85)	29	*Z* = -2.47	*.01*
BDNF, median (IQR)	351.44 (31.95-5665.72)	300.36 (68.57-3390.16)	29	*Z* = -.703	*.48*
Thioredoxin, median (IQR)	398 (159.17-10835.17)	385.58 (158.83-12501.83)	28	*Z* = -.660	*.51*
S100B, median (IQR)	174.77 (44.27-834.46)	135.73 (28.09-947.79)	27	*Z* = -.270	*.79*
LHVI, median (IQR)	.9323 (.8343-.9789)	.9297 (.8083-.9763)	24	*Z* = -3.29	*.001*
RHVI, median (IQR)	.9277 (.8623-.9678)	.9238 (.8575-.9597)	24	*Z* = -2.60	*.01*

Abbreviations: BPRS = Brief Psychiatric Rating Scale; SANS = Scale for the Assessment of Negative Symptoms; MCCB = MATRICS Consensus Cognitive Battery; CRP = c-reactive protein; IQR = interquartile range; IL-1B = interleukin-1 beta; IL-8 = interleukin-8; IFNγ = interferon gamma; TNFa = tumor necrosis factor alpha; HCY = homocysteine; BDNF = brain derived neurotrophic factor; S100B = S100 calcium binding protein B; LHVI = left hippocampal volumetric integrity; RHVI = right hippocampal volumetric integrity.
[a]Comparisons between FEP participants and HC were adjusted for parental education level.
[b]Units of plasma concentration levels for all biomarkers are pg/mL except salivary cortisol which is measured in µg/dL.

eTable 8: Spearman correlations between antipsychotic dose, DUP and HVI in FEP participants

	n	r_s	*p* Value
Bsl LHVI x DUP	53	.038	*.80*
∆LHVI x DUP	23	-.61	*.002*
Bsl RHVI x DUP	53	.065	*.64*
∆RHVI x DUP	23	-.071	*.75*
CPZ x Wk8 LHVI	24	.193	*.367*
CPZ x Wk8 RHVI	24	.199	*.35*
CPZ x ∆LHVI	24	-.050	*.82*
CPZ x ∆RHVI	24	.185	*.39*

Abbreviations: LHVI = left hippocampal volumetric integrity; DUP = duration of untreated psychosis; RHVI = right hippocampal volumetric integrity; CPZ = mean daily chlorpromazine equivalent.

eTable 9: Spearman correlations between LHVI and clinical variables at baseline

Variable:	*n*	r_s	*p* Value
DUP (weeks)	53	.04	*.80*
BPRS Total Score	56	-.33	*.01*
BPRS Agitation Subscale	56	-.31	*.02*
BPRS Positive Subscale	56	-.25	*.06*
BPRS Negative Subscale	56	.005	*.97*
SANS Composite Total	56	-.13	*.36*
MCCB Composite Total	57	-.08	*.57*

Abbreviations: DUP = duration of untreated psychosis; BPRS = Brief Psychiatric Rating Scale; SANS = Scale for the Assessment of Negative Symptoms; MCCB = MATRICS Consensus Cognitive Battery.

eTable 10: Spearman correlations between change in LHVI and clinical assessments

Assessments:	*n*	r_s	*p* Value
BPRS Total Score	24	.21	*.33*
BPRS Agitation Subscale	24	.45	*.03*
BPRS Positive Subscale	24	.25	*.25*
BPRS Negative Subscale	24	-.41	*.05*
SANS Composite Total	24	.13	*.55*
MCCB Composite Total	24	.05	*.82*

Abbreviations: DUP = duration of untreated psychosis; BPRS = Brief Psychiatric Rating Scale; SANS = Scale for the Assessment of Negative Symptoms; MCCB = MATRICS Consensus Cognitive Battery.

eTable 11: Lasso regression – baseline LHVI

Variable:	Parameter Estimate	Standard Error	95% CI	*p* Value
CRP (pg/mL)	-0.000003	2.9508e-6	-8.779e-6-2.7882e-6	*.31*
IL8 (pg/mL)	-0.000273	0.0001146	-0.00049-4.816e-5	*.02*
IFNγ (pg/mL)	0.0003771	0.0001557	7.1923e-0.0006822	*.02*
TNFa (pg/mL)	0	0	0	*1.00*
Thioredoxin (pg/mL)	3.3597e-6	1.8589e-6	-2.926e-7-6.994e-6	*.07*
S100B (pg/mL)	0	0	0	*1.00*
DUP	0	0	0	*1.00*
NOS1 (CC)	0.0295961	0.0093529	0.0112649-0.0479274	*.002*
NOS1 (TC)	0	0	0	*1.00*
BDNF (GG)	0.0235826	0.0091729	0.005604-0.0415612	*.01*
BDNF (AA)	0	0	0	*1.00*
ZFN804A (GG)	0.0084336	0.0097114	-0.0106 - 0.0274677	*.38*
ZFN804A (GT)	0.0128578	0.0081179	-0.003053-0.0287685	*.11*
COMT (GG)	0	0	0	*1.00*
COMT (GA)	-0.00868	0.0100054	-.028290-0.0109305	*.39*
CRP x DUP	0	0	0	*1.00*
IFNγ x DUP	1.3282e-5	6.3559e-6	8.2421e-7-2.574e-5	*.04*
IL8 x DUP	7.2689e-5	0.0000127	4.7779e-5- 0.0000976	*.001*
S100B x DUP	0	0	0	*1.00*
TNFa x DUP	0	0	0	*1.00*
Thioredoxin x DUP	0	0	0	*1.00*
NOS1 (CC) x DUP	0.0021139	0.0005374	0.0010606-0.0031673	*.001*
NOS1 (TC) x DUP	0	0	0	*1.00*
BDNF (GG) x DUP	0.0009341	0.0007839	-0.000602-0.0024706	*.23*
BDNF (AA) x DUP	0.002997	0.0009478	-0.004855-0.001139	*.002*
ZFNA804A (GG) x DUP	0.0012497	0.0002708	0.000719-0.0017803	*.001*
ZFN804A (GT) x DUP	0	0	0	*1.00*
COMT (GG) x DUP	0	0	0	*1.00*
COMT (GA) x DUP	-.00142	0.000502	-0.002404-0.000437	*.005*

Abbreviations: CRP = c-reactive protein; IL-8 = interleukin-8; IFNγ = interferon gamma; TNFa = tumor necrosis factor alpha; S100B = S100 calcium binding protein B; DUP = duration of untreated psychosis; NOS1 = nitric oxide synthase 1; BDNF = brain derived neurotrophic factor; ZFN804A = zinc finger protein 804A; COMT = catechol-o-methyltransferase.

eTable 12: Lasso regression – change in LHVI

Variable:	Parameter Estimate	Standard Error	95% CI	*p* Value
CRP (pg/mL)	-0.000226	0.0008955	-0.001982-0.0015288	*.80*
IL8 (pg/mL)	0	0	0	*1.00*
IFNγ (pg/mL)	0	0	0	*1.00*
TNFa (pg/mL)	0	0	0	*1.00*
Thioredoxin (pg/mL)	0	0	0	*1.00*
S100B (pg/mL)	-0.016025	0.0016714	-0.019301- (-0.012749)	*.001*
DUP	0	0	0	*1.00*
NOS1 (CC)	1.3784267	1.7338788	-2.019913-4.7767667	*.43*
NOS1 (TC)	0	0	0	*1.00*
BDNF (GG)	0	0	0	*1.00*
BDNF (AA)	0	0	0	*1.00*
ZFN804A (GG)	0	0	0	*1.00*
ZFN804A (GT)	0	0	0	*1.00*
COMT (GG)	0	0	0	*1.00*
COMT (GA)				
CRP x DUP	0	0	0	*1.00*
IFNγ x DUP	0	0	0	*1.00*
IL8 x DUP	0	0	0	*1.00*
S100B x DUP	-0.000801	0.000159	-0.001112 – (-0.000489)	*.001*
TNFa x DUP	0	0	0	*1.00*
Thioredoxin x DUP	-0.000159	2.7019e-5	-0.000212 – (-0.000106)	*.001*
NOS1 (CC) x DUP	-0.241284	0.0811758	-0.400386 – (-0.082182)	*.003*
NOS1 (TC) x DUP	0	0	0	*1.00*
BDNF (GG) x DUP	0	0	0	*1.00*
BDNF (AA) x DUP	0	0	0	*1.00*
ZFNA804A (GG) x DUP	0	0	0	*1.00*
ZFN804A (GT) x DUP	-0.114129	0.0934451	-0.297278-0.0690204	*.22*
COMT (GG) x DUP	0	0	0	*1.00*

Abbreviations: CRP = c-reactive protein; IL-8 = interleukin-8; IFNγ = interferon gamma; TNFa = tumor necrosis factor alpha; S100B = S100 calcium binding protein B; DUP = duration of untreated psychosis; NOS1 = nitric oxide synthase 1; BDNF = brain derived neurotrophic factor; ZFN804A = zinc finger protein 804A; COMT = catechol-o-methyltransferase.

eTable 13: Spearman correlations between change in LHVI and baseline biomarkers

Biomarker:	*n*	r_s	*p* Value
CRP (pg/mL)	24	-.34	*.11*
IL-1B (pg/mL)	24	-.10	*.66*
IL8 (pg/mL)	24	-.45	*.03*
IFNγ (pg/mL)	24	-.41	*.045*
TNFa (pg/mL)	24	-.40	*.053*
Salivary Cortisol (µg/dL)	19	-.28	*.24*
Aspartate (pg/mL)	24	-.004	*.98*
Glutamate (pg/mL)	24	-.08	*.71*
Lactate (pg/mL)	24	-.08	*.71*
HCY (pg/mL)	24	-.04	*.86*
BDNF (pg/mL)	24	-.34	*.11*
Thioredoxin (pg/mL)	24	-.16	*.46*
S100B (pg/mL)	24	-.60	*.002*

Abbreviations: CRP = c-reactive protein; IL-1B = interleukin-1 beta; IL-8 = interleukin-8; IFNγ = interferon gamma; TNFa = tumor necrosis factor alpha; HCY = homocysteine; BDNF = brain derived neurotrophic factor; S100B = S100 calcium binding protein B.

eTable 14: Spearman correlations between change in LHVI and change in biomarkers

Biomarker:	*n*	r_s	*p* Value
CRP (pg/mL)	24	.22	*.32*
IL-1B (pg/mL)	23	.49	*.02*
IL8 (pg/mL)	23	.29	*.18*
IFNγ (pg/mL)	23	.38	*.07*
TNFa (pg/mL)	23	.29	*.18*
Salivary Cortisol (µg/dL)	17	.26	*.31*
Aspartate (pg/mL)	23	.18	*.41*
Glutamate (pg/mL)	23	-.01	*.95*
Lactate (pg/mL)	23	.33	*.12*
HCY (pg/mL)	23	.19	*.39*
BDNF (pg/mL)	21	-.15	*.52*
Thioredoxin (pg/mL)	23	-.28	*.20*
S100B (pg/mL)	23	.37	*.09*

Abbreviations: CRP = c-reactive protein; IL-1B = interleukin-1 beta; IL-8 = interleukin-8; IFNγ = interferon gamma; TNFa = tumor necrosis factor alpha; HCY = homocysteine; BDNF = brain derived neurotrophic factor; S100B = S100 calcium binding protein B.

eTable 15: Comparison of LHVI between FEP participants grouped by genotype

Genotype	Median (IQR)	Median (*IQR*)	Test Statistic	*p*-value
GCLM[a]	GG (*n*=35) .9257(*.9111-.9456*)	AA/GA (*n*=13) .9273 (*.8892-.9601*)	*U*=208	*.65*
NOS1[b]	CC (*n*=36) .9289 (*.9171-.9524)*	TC/TT (*n*=15) .9250 (*.8631-.9458*)	*U*=207	*.19*
NOS1[c]	AA (*n*=19) .9250 (*.9171-.99504)*	AG/GG (*n*=32) .9289 (*.8836-.9506)*	*U*=303	*.98*
NOS1AP[d]	AA (*n*=27) .9230 (*.8796-.9456*)	AC/CC (*n*=23) .9424 (*.9172-.9509*)	*U*=230	*.12*
BDNF[e]	GG (*n*=13) .9304 (*.9115-.9500*)	AA/AG (*n*=37) .9257 (*.8892-.9506*)	*U=223*	*.70*
ZNF804A[f]	GG (*n*=14) .9280 (*.9156-.9471*)	GT/TT (*n*=12) .8958 (*.8683-.9263*)	*U=45*	*.045*
AKT1[g]	CC (*n*=29) .9249 (*.8847-.9452*)	TC/TT (*n*=21) .9424 (*.9172-.9511*)	*U=249*	*.28*
MTHFR[h]	CC (*n*=23) .9336 (*.8796-.9513*)	TC/TT (*n*=28) .9245 (*.8986-.9450*)	*U=288*	*.52*
DAOA[i]	AA (*n*=20) *.9248* (*.9087-.9450*)	AG/GG (*n*=6) .9249 (*.8736-.9460*)	*U*=54	*.72*
DAOA[j]	GG (*n*=41) .9304 (.9115-.9506)	AG/AA (*n*=9) .9231 (*.8653-.9492*)	*U=147*	*.36*
FOLH[k]	TT (*n*= 21) .9424 (*.9010-.9547)*	CT/CC (*n*=28) .9265 (*.8821-.9502*)	*U*=252	*.40*
COMT Val158Met[l]	GG (*n*=27) .9249 (*.8741-.9446*)	AA/GA (*n*=19) .9424 *(.9231-.9523*)	*U=219*	*.08*
FKBP5[m]	CC (*n*=26) .9256 (.8942-.9467)	TC/TT (*n*=9) .9304 (*.8552-.9527*)	*U= 117*	*1.00*
NR3C2[n]	TT (*n*=32) .9253 (*.9072-.9458*)	CT/CC (*n*=16) .9424 (*.8887-.9528*)	*U=276*	*.59*

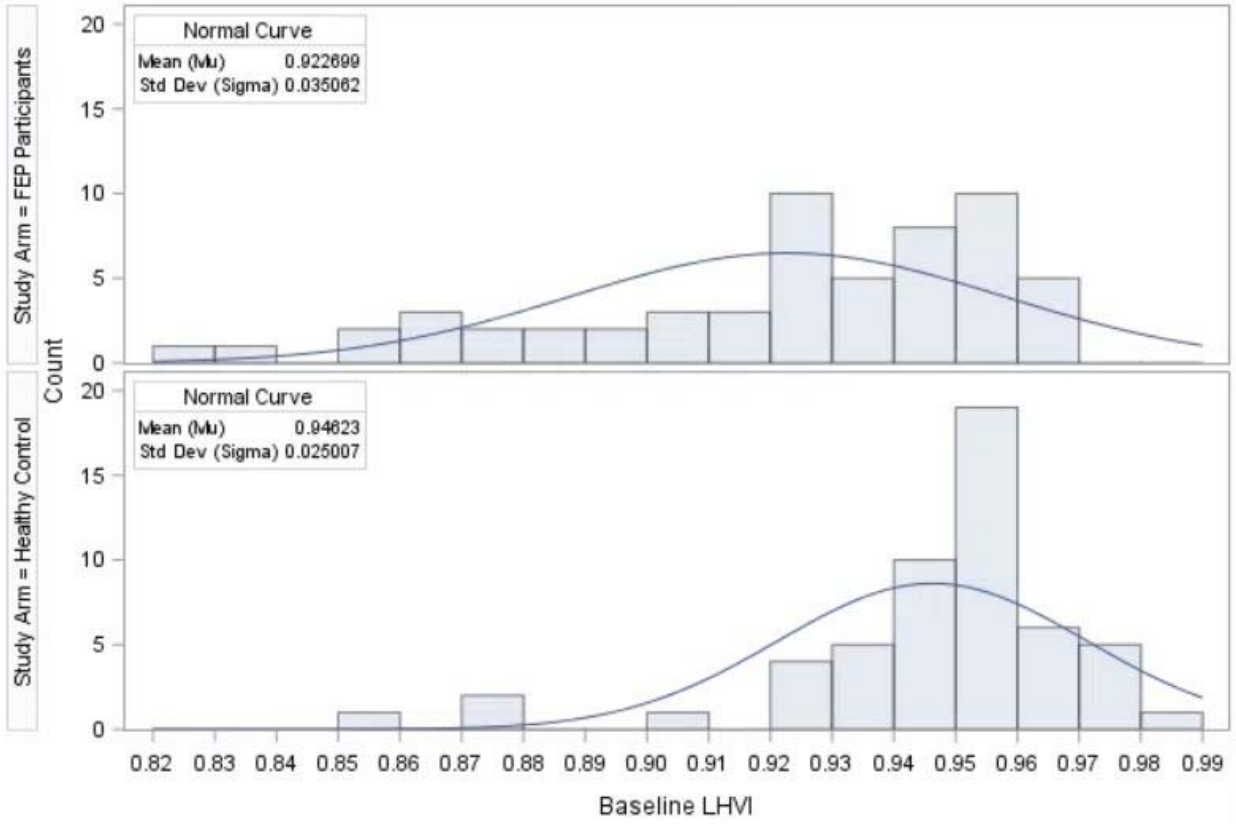
[a]rs2301022 Glutamate cysteine ligase modifier; [b]rs41279104 Nitric oxide synthase 1; [c]rs6490121 Nitric oxide synthase 1; [d]rs12742393 Nitric oxide synthase 1 adaptor protein; [e]rs6265 Brain-derived neurotrophic factor; [f]rs1344706 Zinc finger protein 804A; [g]rs2494732 AKT serine/threonine kinase 1; [h]rs1801133 Methylenetetrahydrofolate reductase; [i]rs2391191 D-amino acid oxidase activator; [j]rs778294 D-amino acid oxidase activator; [k]rs202676 Folate hydrolase 1; [l]rs4680 Catechol-O-methyltransferase Val[158]Met; [m]rs1360780 FK506 binding protein 5; [n]rs5522 Nuclear receptor subfamily 3 group C member 2

eTable 16: Comparison of percent change in LHVI between FEP participants grouped by genotype

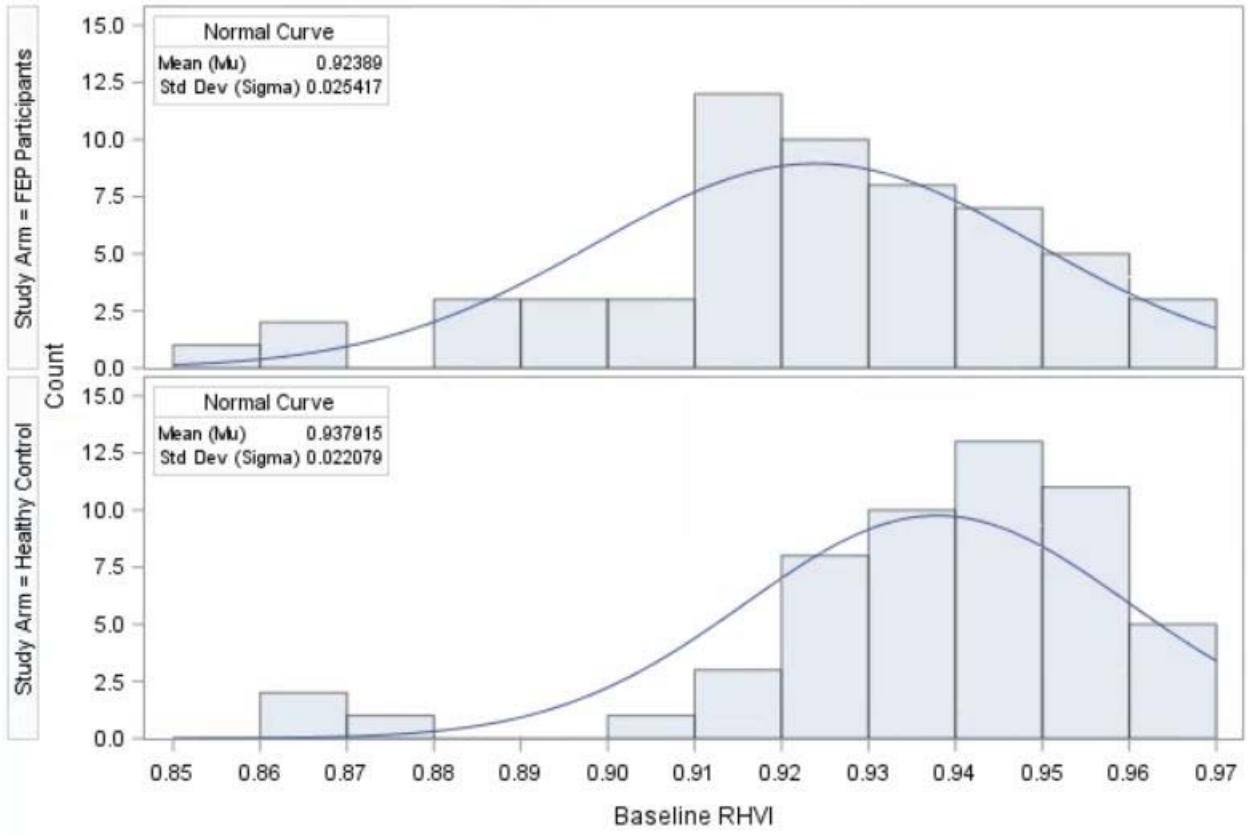
Genotype	Median (*IQR*)	Median (*IQR*)	Test Statistic	*p*-value
GCLM[a]	GG (*n*=13) -3.85 (*-6.52-.8285*)	AA/GA (*n*=7) -7.91 (*-16.00- -.1619*)	*U*=33	*.32*
NOS1[b]	CC (*n*=17) -3.73 (*-5.94-.9270*)	TC/TT (*n*=5) -11.13 (*-24.99- -4.31*)	*U*=16	*.04*
NOS1[c]	AA (*n*=8) -5.20 (*-7.58- -.2542*)	AG (*n*=14) -1.53 (*-5.18-.8890*)	*U=52*	*.79*
NOS1AP[d]	AA (*n*=15) -3.85 (*-16.00-.9046*)	AC/CC (*n*=7) -3.96 (*-6.44- -.8763*)	*U*=49	*.81*
BDNF[e]	GG (*n*=6) -.0844 (*-4.41-1.12*)	AA/AG (*n*=16) -5.07 (*-14.79- -.6668*)	*U*=24	*.08*
ZNF804A[f]	GG (*n*=5) .7076 (*-6.38-1.2774)*	GT/TT (*n*=6) -8.87 (*-17.16- -.4199)*	*U*=7	*.14*
AKT1[g]	CC (*n*=14) -3.02 (*-5.94-.7568*)	TC/TT (*n*=8) -6.52 (*-14.79- .3050*)	*U*=47	*.54*
MTHFR[h]	CC (*n*=7) -3.96 (*-5.28- -.1619*)	TC/TT (*n*=15) -3.85 (*-11.13-.9046*)	*U*=49	*.81*
DAOA[i]	AA (*n*=10) -4.41 (*-6.93-.9158*)	AG/GG (*n*=2) -1.17 *(-2.18- -.1.17*)	*U*=7	*.52*
DAOA[j]	GG (*n*=19) -3.85 (*-6.60-.7076*)	AG/AA (*n*=3) -20.63 *(-29.07-* .20.68)	*U*=18	*.32*
FOLH[k]	TT (*n*=10) -3.84 (*-12.35-.7680)*	CT/CC (*n*=11) -3.85 (*-7.91-.9046)*	*U*=53	*.89*
COMT Val158Met[l]	GG (*n*=13) -3.73 (*-8.87-.2728*)	GA (*n*=9) -3.96 (*-11.96-1.2324)*	*U*=58	*.97*
FKBP5[m]	CC (*n*=10) -2.30 (*-8.71-.7568*)	TC/TT (*n*=4) -3.73 (*-6.15-.1667)*	*U*=20	*1.00*
NR3C2[n]	TT (*n*=16) -3.90 (*-10.33-.8554*)	CT/CC (*n*=6) -3.73 (*-8.95-.3340)*	*U*=46	*.88*

[a]rs2301022 Glutamate cysteine ligase modifier; [b]rs41279104 Nitric oxide synthase 1; [c]rs6490121 Nitric oxide synthase 1; [d]rs12742393 Nitric oxide synthase 1 adaptor protein; [e]rs6265 Brain-derived neurotrophic factor; [f]rs1344706 Zinc finger protein 804A; [g]rs2494732 AKT serine/threonine kinase 1; [h]rs1801133 Methylenetetrahydrofolate reductase; [i]rs2391191 D-amino acid oxidase activator; [j]rs778294 D-amino acid oxidase activator; [k]rs202676 Folate hydrolase 1; [l]rs4680 Catechol-O-methyltransferase Val[158]Met; [m]rs1360780 FK506 binding protein 5; [n]rs5522 Nuclear receptor subfamily 3 group C member 2

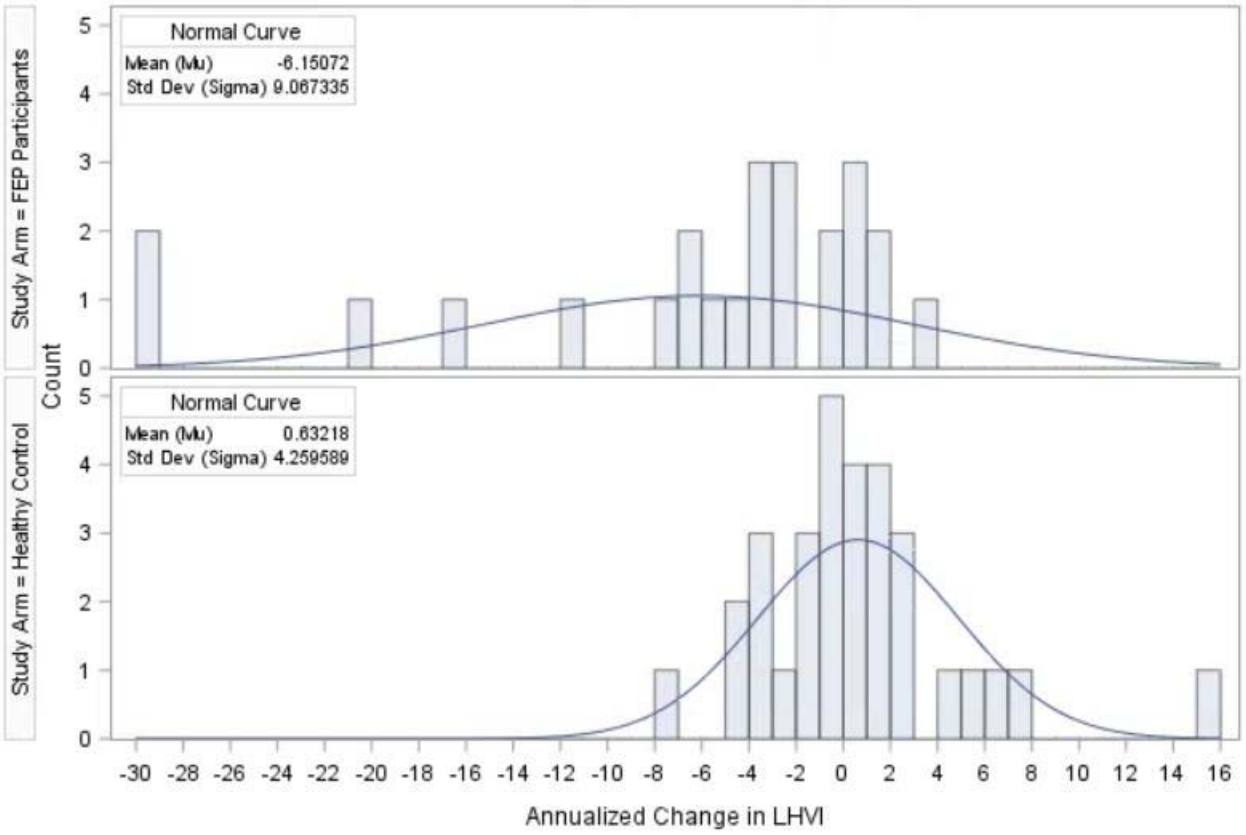
eFigure 1: Histogram of LHVI baseline for FEP participants and HC



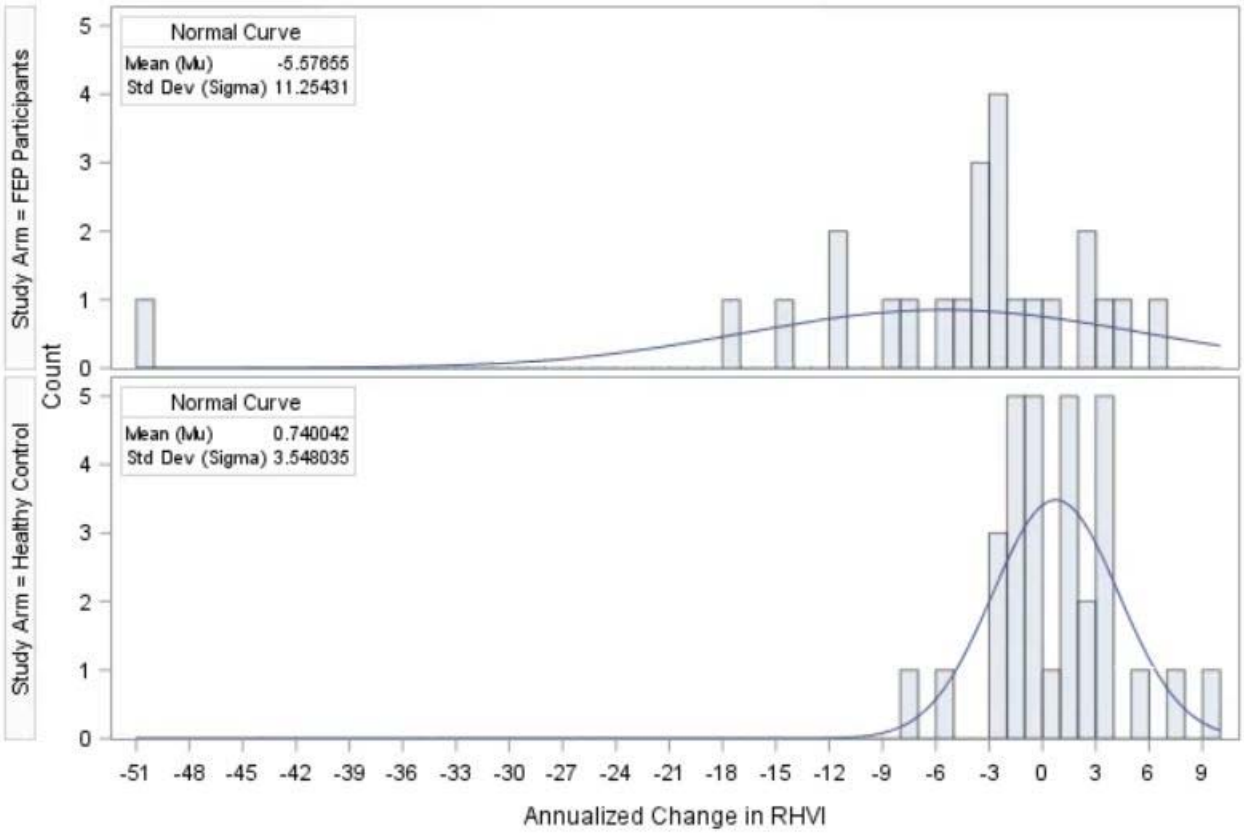
eFigure 2: Histogram of RHVI baseline for FEP participants and HC



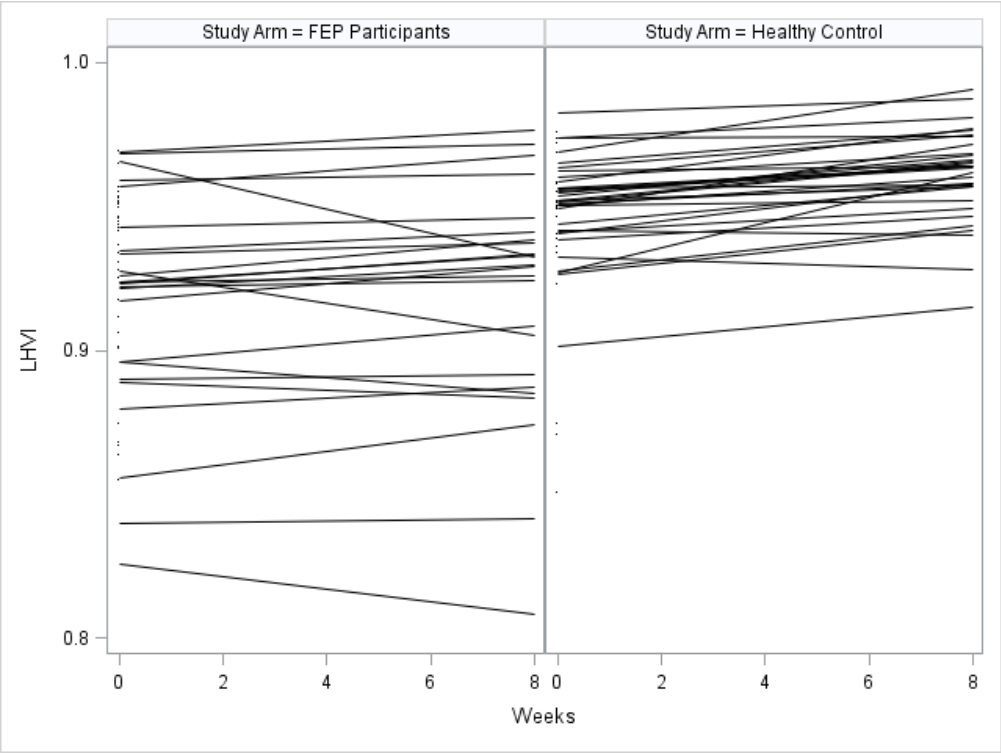
eFigure 3: Histogram of LHVI annualized change rate for FEP participants and HC



eFigure 4: Histogram of RHVI annualized change rate for FEP participants and HC



eFigure 5: LHVI Change from Baseline to Follow Up in FEP Participants and HC



eFigure 6: RHVI Change from Baseline to Follow Up in FEP Participants and HC