**Supplementary Tables and legends**

| | **HC (n=45) Mean (SD)** | **MDD (n=71) Mean (SD)** |
|---|---|---|
| **Age** | 38.1 (9.9) | 40.8 (13.3) |
| **Height (cm)** | 170 (11.4) | 170 (10.9) |
| **Weight (Kg)** | 77.5 (18.1) | 78 (18.4) |
| **BMI** | 26.7 (4.8) | 27 (5.6) |
| **Sex** | 51% (M) | 49% (M) |
| **MADRS** | 1.4 (2.4) | 32.9 (4.7)*** |
| **HAM-17** | 0.6 (1.1) | 20.2 (3.3)*** |
| **Age of Onset** | - | 22.1 (12.5) |
| **Length of Current Depressive Episode** | - | 21.3 (21.3) |
| **Number of Past Depressive Episodes** | | |
| 1 | - | 22.5% |
| 2 | - | 9.9% |
| ≥3 | - | 67.6% |
| **Psychiatric Comorbidities** | - | 42.3% |
| **Psychotropic Medications** | - | 25.4% |
| Antidepressants | - | 18.3% |
| Other psychotropic meds | - | 18.3% |
| **Acetyl-L-carnitine (LAC)** | 8.3 (3.4) | 6.1 (2.1)*** |
| **Free-carnitine** | 33 (9.2) | 32 (9.7) |

**Table SI 1. Demographic and clinical characteristics for the 116 subjects.** Sex is reported as % of men. *indicates significant comparisons with HC. ***$p<0.001$ at Student's two-tailed t-tests and chi-square as appropriate ($\alpha=0.05$). Psychiatric comorbidities included anxiety disorders as for DSM-IV, such as Post-Traumatic Stress Disorders (PTSD), Generalized Anxiety Disorder (GAD) and panic disorder. Other psychotropic medications included antipsychotics, mood stabilizers, benzodiazepines, and estrogen and thyroid hormone modulators.

| | Center | | | |
|---|---|---|---|---|
| | C | | S | |
| | **HC (n=26) Mean (SD)** | **MDD (n=37) Mean (SD)** | **HC (n=19) Mean (SD)** | **MDD (n=34) Mean (SD)** |
| **Age** | 38.5 (10) | 42.7 (13.7) | 37.7 (9.9) | 38.6 (12.7) |
| **Height (cm)** | 170.6 (11.6) | 171.8 (11.3) | 168.9 (11.3) | 168 (10.4) |
| **Weight (Kg)** | 78.5 (18.4) | 80 (19.4) | 76.3 (18.1) | 76.2 (17.3) |
| **BMI** | 26.7 (4.7) | 26.8 (5.4) | 26.6 (5.1) | 27.2 (5.9) |
| **Sex** | 54% (M) | 49% (M) | 47% (M) | 50% (M) |
| **MADRS** | - | - | 1.4 (2.4) | 32.9 (4.7) |
| **HAM-17** | 0.6 (1.1) | 20.4 (3.4) | - | 19.7 (3.1) |
| **Age of Onset** | - | 25.3 (13.7) | - | 18.4 (10) |
| **Length of Current Depressive Episode (months)** | - | 15.3 (16.5) | - | 27 (24) |
| **Number of Past Depressive Episodes** | | | | |
| 1 | - | 16.2% | - | 29.4% |
| 2 | - | 8.1% | - | 11.8% |
| ≥3 | - | 75.7% | - | 58.8% |
| **Psychiatric Comorbidities** | - | 62.2% | - | 20.6% |
| **Psychotropic Medications** | - | 21.6% | - | 29.4% |
| Antidepressants | - | 21.6% | - | 14.7% |
| Other psychotropic meds | - | 8.1% | - | 29.4% |
| **Acetyl-L-carnitine (LAC)** | 8.4 (3.5) | 6.1 (2.2) | 8.3 (3.4) | 6.1 (2) |
| **Free-carnitine** | 34.8 (9.2) | 32 (10.5) | 30.6 (8.9) | 31.2 (8.9) |

**Table SI 2. Demographic and clinical characteristics by study center, showing similarities across patient samples at both recruitment sites (C: Weill Cornell School of Medicine; S: Mount Sinai School of Medicine).** Sex is reported as % of men. *indicates significant comparisons with HC. ***$p<0.001$ at Student's two-tailed t-tests and chi-square as appropriate ($\alpha=0.05$).

Psychiatric comorbidities included anxiety disorders as for DSM-IV, such as Post-Traumatic Stress Disorders (PTSD), Generalized Anxiety Disorder (GAD) and panic disorder. Other psychotropic medications included antipsychotics, mood stabilizers, benzodiazepines, and estrogen and thyroid hormone modulators.

**Supplementary figures and legends**

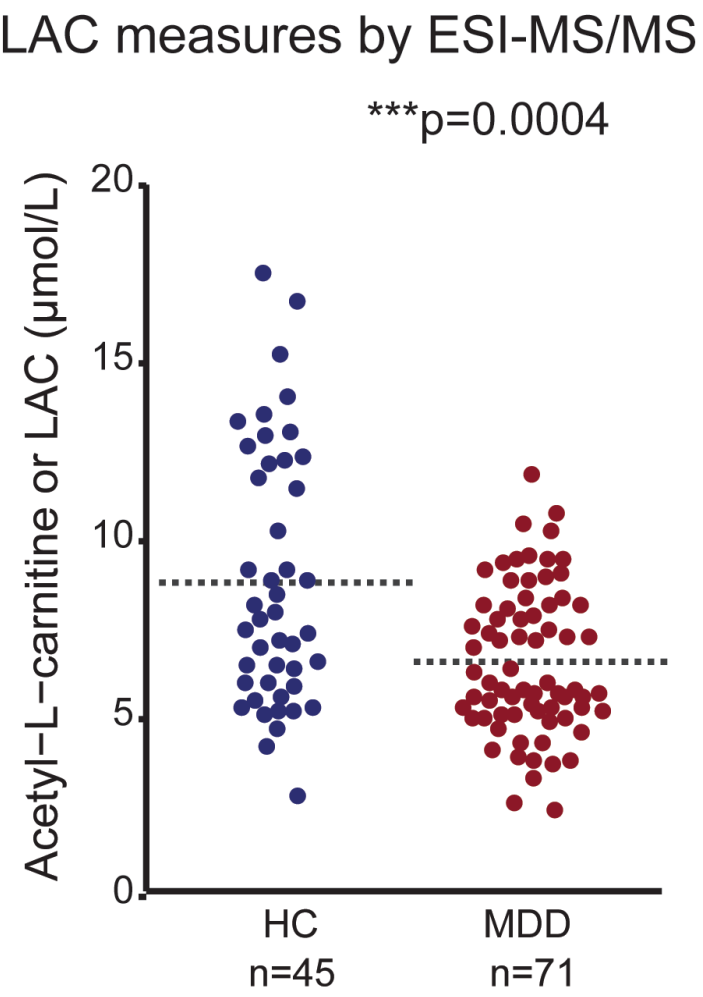


**Fig.SI1. LAC measures by stable isotope dilution electrospray-tandem mass spectrometry (ESI-MS/MS).** Plasma LAC measurements by ESI-MS/MS in the same 116 samples showing a methodological validation of reduced LAC in patients with MDD as compared to age- and sex-matched healthy controls (HC). *indicates significant comparisons with HC. Dashed bars indicate group mean.

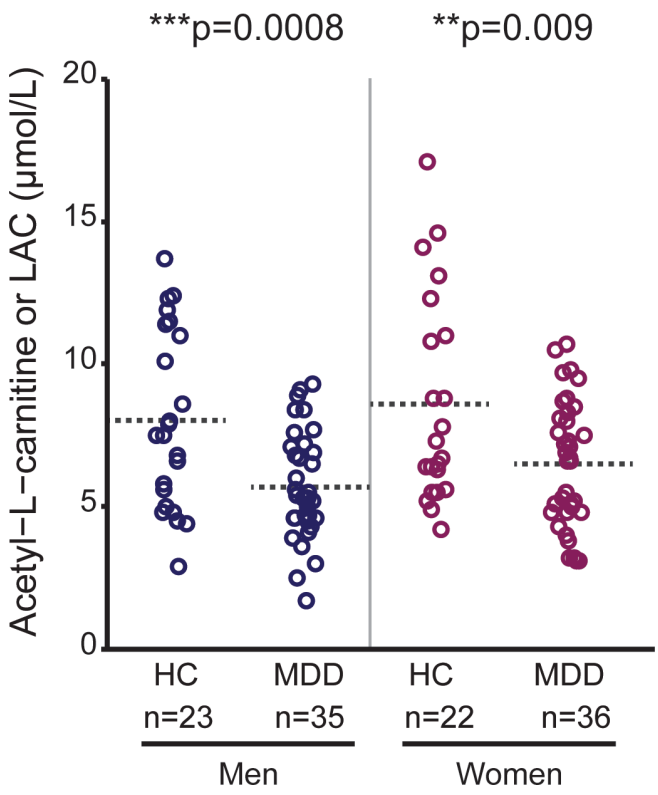


**Fig.SI2. LAC levels differ between HC and MDD groups in both men and women.** Plasma LAC levels in HC and MDD subjects (men in blue; women in pink) as assessed by UPLC-MS/MS. *indicates significant comparisons with HC. ***p<0.001 at Student's two-tailed t-tests (α=0.05). Dashed bars indicate group mean.

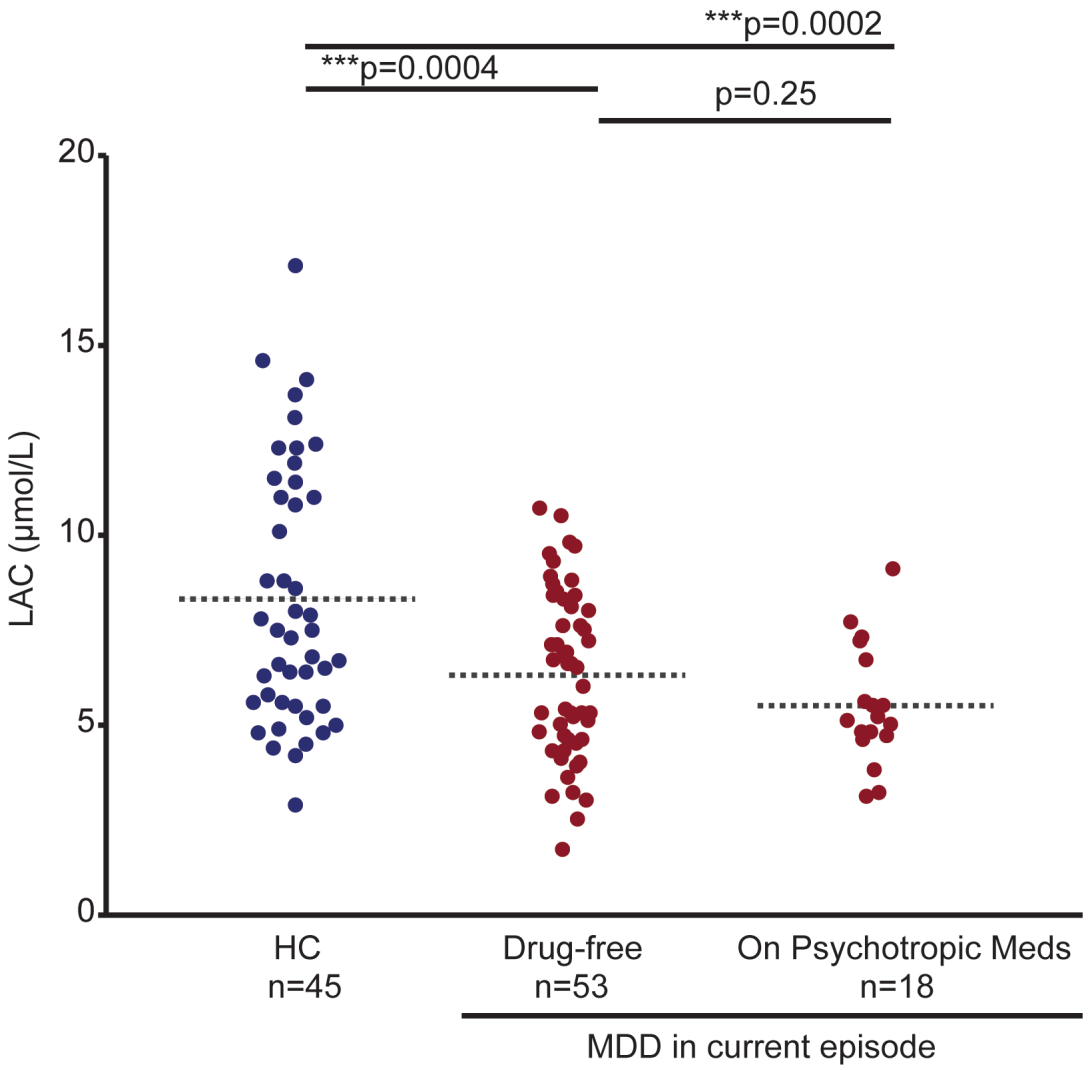


**Fig.SI3. The association between LAC and MDD persists upon use of psychotropic medications.** Plasma LAC concentrations in HC and in patients with MDD, in an acute depressive episode during study participation, broken down by use of psychotropic medications (patients not-receiving treatment at the time of study participation: 53; patients with MDD on psychotropic medications: 18). All patients were in acute depressive episode at the time of study participation. ***p<0.001 at Student's two-tailed t-tests (α=0.05). Dashed bars indicate group mean.

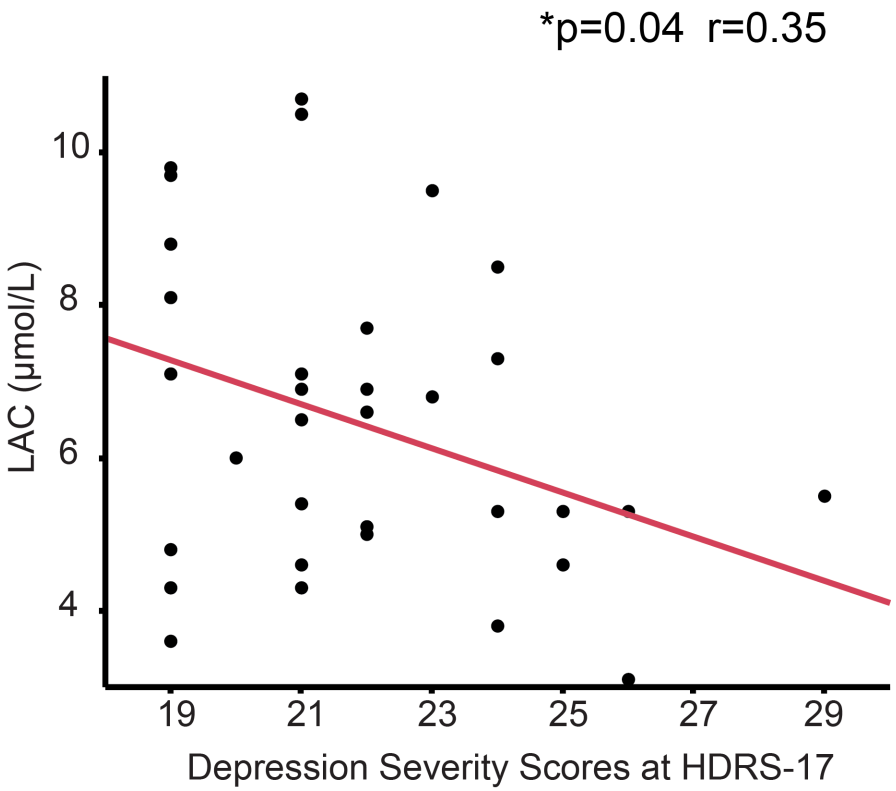


**Fig.SI4. LAC is lower in patients who exhibit greater severity.** Pearson correlation between LAC concentrations and depression severity scores at HDRS-17 among patients with moderate to severe depression (cutoff ≥19 at HDRS-17). *p<0.05 using Pearson correlation (α=0.05). Regression line is indicated in red.

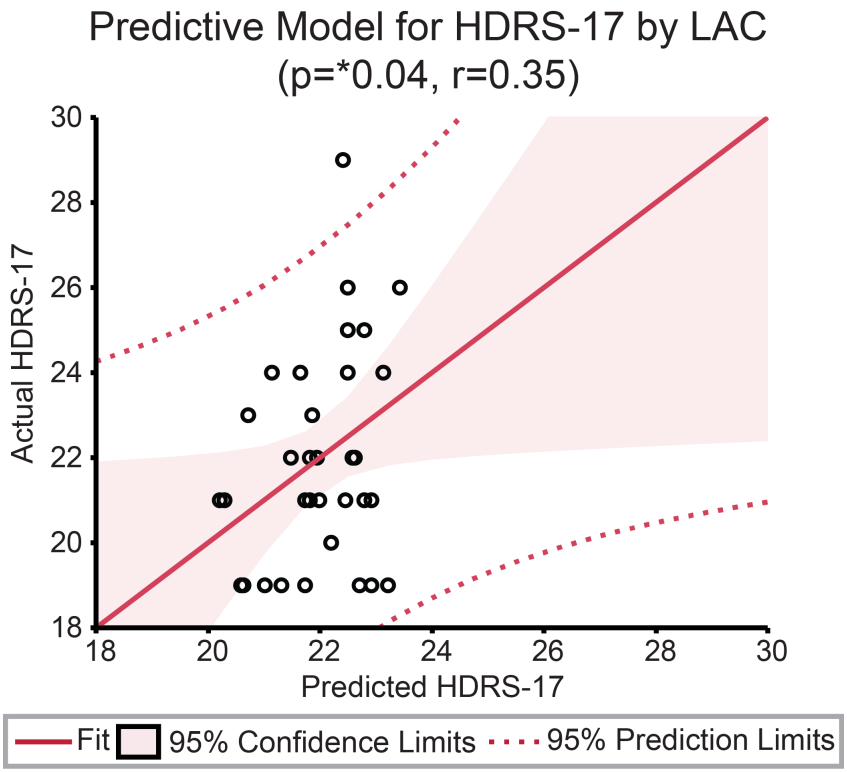


**Fig.SI5. LAC levels predict MDD severity scores at HDRS-17.** Prediction model analysis of depression severity scores at HDRS-17 by LAC in patients with moderate to severe MDD. In x-axis: depression severity scores at HDRS-17 as predicted by the model; in y-axis: depression severity scores at HDRS-17 self-reported by patients. *p<0.05 using multiple regression analysis.

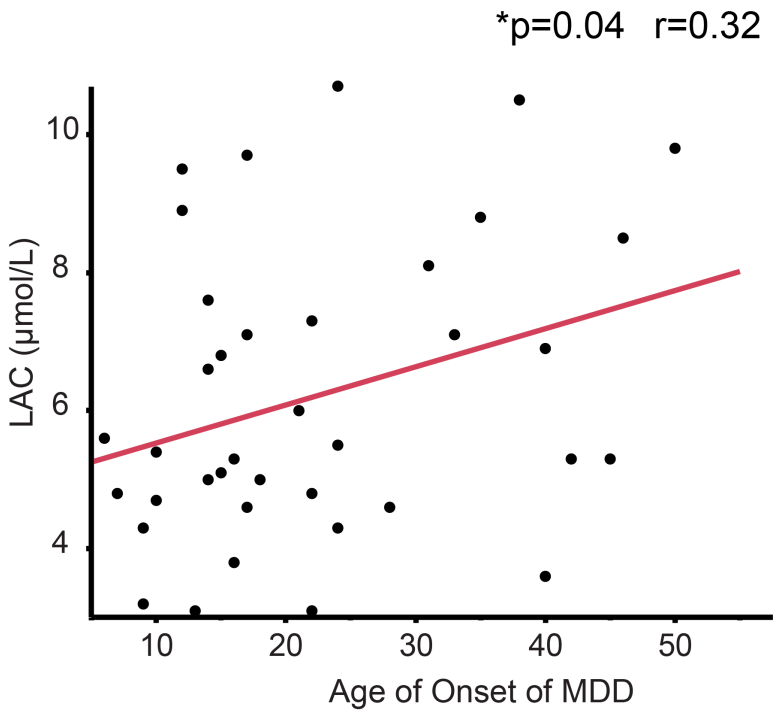


**Fig.SI6. LAC is lower in patients who report earlier onset of the illness.** Pearson correlation between LAC levels and age of onset of MDD among patients with moderate to severe depression (cutoff ≥19 at HDRS-17, ref ). *p<0.05 using Pearson correlation (α=0.05). Regression line is indicated in red.

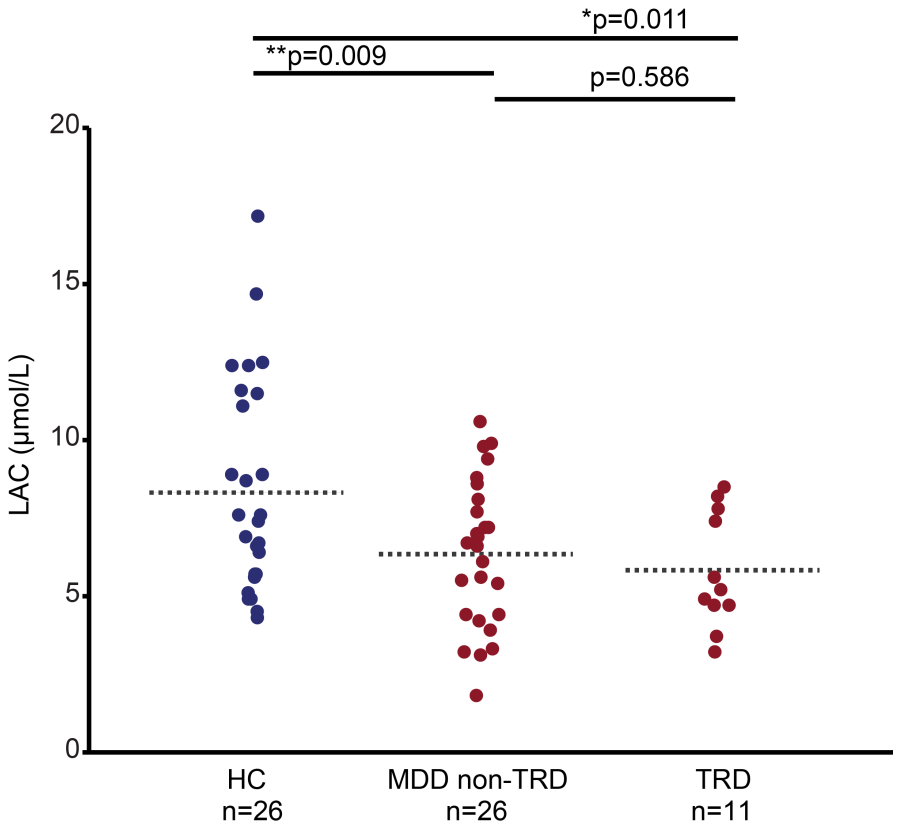


**Fig.SI7. The LAC deficiency is greater in patients with MDD and history of treatment-resistant depression (TRD).** Plasma LAC concentrations across HC and patients with MDD with or without history of TRD, labeled as MDD non-TRD and TRD for the study center C. $F_{2,62}$=5.1, p=0.009. *indicates significant comparisons with HC at Student's two-tailed t-tests (α=0.05). Dashed bars indicate group mean. See also Fig.3 for stepwise analysis in study center S.

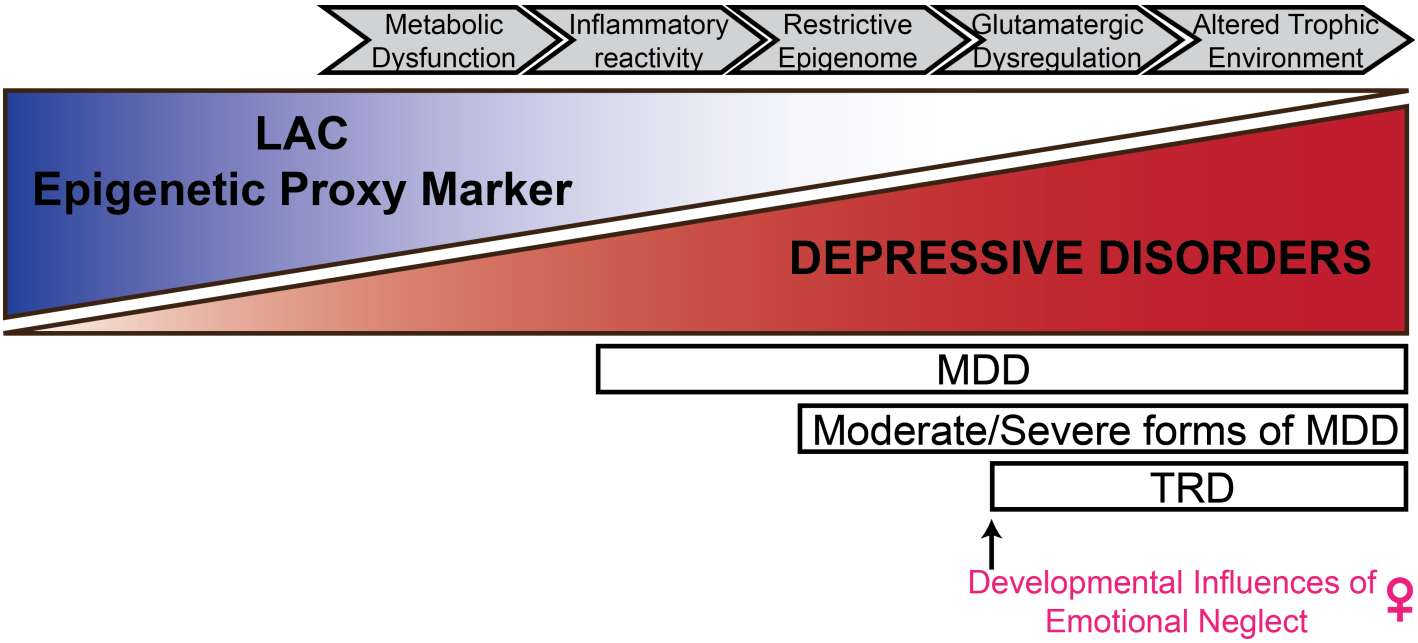


**Fig.SI8. Model featuring the Epigenetic Agent LAC as a candidate biomarker to help the diagnosis of a clinical endophenotype of MDD.** Schematic illustration of a proposed model featuring a kindling-like reduction in LAC toward more severe forms of MDD. The LAC deficiency may represent a proxy target that integrates interdependent biological functions underlying a vicious cycle of metabolic dysfunction, inflammatory reactivity, glutamatergic dysregulation and altered trophic environment in the pathophysiology of MDD. We propose that LAC may serve as a candidate biomarker to help the diagnosis of a bio-behavioral phenotype of MDD characterized by reduced LAC, greater severity and earlier onset as well as a history of childhood trauma in patients with TRD. Together with studies in rodents, these first translational findings demand further exploration of LAC as a therapeutic target that may help to define individualized treatments in biologically-based depression subtype consistent with the spirit of precision medicine.