*Psychological Medicine*

**cambridge.org/psm**

# Metabolomic profiles of 38 acylcarnitines in major depressive episodes before and after treatment

Abd El Kader Ait Tayeb[1,2], Romain Colle[1,2], Kenneth Chappell[1], Khalil El-Asmar[1,3], Cécile Acquaviva-Bourdain[4], Denis J. David[1], Séverine Trabado[5,6], Philippe Chanson[5,7], Bruno Feve[8], Laurent Becquemont[1,9], Céline Verstuyft[1,6,*] and Emmanuelle Corruble[1,2,*]

[1]CESP, MOODS Team, INSERM UMR 1018, Faculté de Médecine, Univ Paris-Saclay, Le Kremlin Bicêtre, Paris, F-94275, France; [2]Service Hospitalo-Universitaire de Psychiatrie de Bicêtre, Hôpitaux Universitaires Paris-Saclay, Assistance Publique-Hôpitaux de Paris, Hôpital de Bicêtre, Le Kremlin Bicêtre, Paris, F-94275, France; [3]Department of Epidemiology and Population Health, Faculty of Health Sciences, American University of Beirut, Beirut, Lebanon; [4]Service de Biochimie et Biologie Moléculaire; Unité Médicale Pathologies Héréditaires du Métabolisme et du Globule Rouge; Centre de Biologie et Pathologie Est; CHU de Lyon; F-69500 Bron, France; [5]INSERM UMR-S U1185, Physiologie et Physiopathologie Endocriniennes, Faculté de Médecine, Univ Paris-Saclay, Le Kremlin Bicêtre, Paris, F-94275, France; [6]Service de Génétique Moléculaire, Pharmacogénétique et Hormonologie de Bicêtre, Hôpitaux Universitaires Paris-Saclay, Assistance Publique-Hôpitaux de Paris, Hôpital de Bicêtre, Le Kremlin Bicêtre, F-94275, France; [7]Université Paris-Saclay, Assistance Publique-Hôpitaux de Paris, Hôpital Bicêtre, Service d'Endocrinologie et des Maladies de la Reproduction, Centre de Référence des Maladies Rares de l'Hypophyse, Hôpital de Bicêtre, Le Kremlin Bicêtre, F-94275, France; [8]Sorbonne Université-INSERM, Centre de Recherche Saint-Antoine, Institut Hospitalo-Universitaire ICAN, Service d'Endocrinologie, CRMR PRISIS, Hôpital Saint-Antoine, Assistance Publique-Hôpitaux de Paris, Paris, F-75012, France and [9]Centre de recherche clinique, Hôpitaux Universitaires Paris-Saclay, Assistance Publique-Hôpitaux de Paris, Hôpital de Bicêtre, Le Kremlin Bicêtre, Paris, F-94275, France

## Abstract

**Background.** Major depression is associated with changes in plasma L-carnitine and acetyl-L-carnitine. But its association with acylcarnitines remains unclear. The aim of this study was to assess metabolomic profiles of 38 acylcarnitines in patients with major depression before and after treatment compared to healthy controls (HCs).

**Methods.** Metabolomic profiles of 38 plasma short-, medium-, and long-chain acylcarnitines were performed by liquid chromatography-mass spectrometry in 893 HCs from the VARIETE cohort and 460 depressed patients from the METADAP cohort before and after 6 months of antidepressant treatment.

**Results.** As compared to HCs, depressed patients had lower levels of medium- and long-chain acylcarnitines. After 6 months of treatment, increased levels of medium- and long-chain acylcarnitines were observed that no longer differed from those of controls. Accordingly, several medium- and long-chain acylcarnitines were negatively correlated with depression severity.

**Conclusions.** These medium- and long-chain acylcarnitine dysregulations argue for mitochondrial dysfunction through fatty acid $\beta$-oxidation impairment during major depression.

## Introduction

Major depressive disorder (MDD) is the first leading cause of disability worldwide. By affecting over 350 million individuals, MDD is a public health priority inducing a high cost for society (Malhi & Mann, 2018). However, its clinical outcome after treatment remains poor and its physiopathology is poorly understood (Malhi & Mann, 2018; Trivedi et al., 2006).

Recent data suggest impairments of energy availability and mitochondrial metabolites in MDD (Giménez-Palomo et al., 2021). Moreover, changes in plasma L-carnitine (C0) and acetyl-L-carnitine (C2) have been shown during a major depressive episode (MDE) before and after antidepressant treatment (Ait Tayeb et al., 2023; Nasca et al., 2018). However, there are only few data regarding the metabolomic profiles of short-, medium-, and long-chain acylcarnitines in MDE (from C3 to C18) whereas in other brain-related diseases, such as mental disorders (e.g. schizophrenia, autism) or Alzheimer's disease, studies identified associations with acylcarnitines (Frye, Melnyk, & MacFabe, 2013; Horgusluoglu et al., 2021; Kriisa et al., 2017). In daily clinical practice, metabolomic profiles of acylcarnitines allow for the assessment of fatty acid $\beta$-oxidation (FAO), a main mitochondrial pathway leading to energy production, and for the diagnosis of inborn errors of metabolism related to it (Houten & Wanders, 2010;

## Original Article

*These authors contributed equally to this work.

**Cite this article:** Ait Tayeb AEK *et al* (2024). Metabolomic profiles of 38 acylcarnitines in major depressive episodes before and after treatment. *Psychological Medicine* **54**, 289–298. https://doi.org/10.1017/S003329172300140X

Received: 10 May 2022
Revised: 17 April 2023
Accepted: 26 April 2023
First published online: 25 May 2023

**Keywords:**
Acylcarnitines; antidepressant; fatty acid oxidation; major depressive disorder; major depressive episode; mitochondria

**Corresponding author:**
Emmanuelle Corruble;
Email: emmanuelle.corruble@aphp.fr

© The Author(s), 2023. Published by Cambridge University Press

Merritt, Norris, & Kanungo, 2018). Of note, short-, medium-, and long-chain acylcarnitines are specific to mitochondrial FAO (online Supplementary Fig. S1).

Decreased plasma levels of acylcarnitines are observed in patients with a MDE (Liu et al., 2015) and individuals with depressive symptoms (Cassol et al., 2015; Mukerji et al., 2021; Zacharias et al., 2021). Besides, changes of acylcarnitine metabolic profiles have been shown after antidepressant treatment in 3 clinical cohorts of depressed patients. Indeed, increased levels of short-chain acylcarnitines and decreased levels of medium- and long-chain acylcarnitines were observed after an 8-week treatment with escitalopram/citalopram in 2 samples of 92 and 136 patients (Ahmed et al., 2020; MahmoudianDehkordi et al., 2021). Moreover, a decrease of short-chain acylcarnitines and an increase of medium- and long-chain acylcarnitines were observed 2 h after a ketamine/esketamine treatment in a sample of 53 depressed patients (Rotroff et al., 2016).

Nonetheless, to the best of our knowledge, there are no data comparing healthy subjects with depressed patients before and after 6 months of antidepressant treatment.

Hence, the first goal of this study was to assess plasma metabolomic profiles of acylcarnitines in depressed patients before and after antidepressant treatment as compared to healthy controls (HCs). The second goal was to assess the association between acylcarnitines and clinical outcomes of depressed patients.

## Material and methods

### Patients with major depression

This study was conducted in the METADAP cohort (Corruble et al., 2015), a 6-month prospective, multicenter (6 French university hospitals), naturalistic, treatment study, including patients suffering from a current MDE in the context of MDD (DSM-IV-TR criteria), and requiring a new antidepressant treatment. The antidepressant treatment had to be a monotherapy. The choice of drug and its dose were left to the treating psychiatrist using 'real-world' treatment options. Written informed consent was obtained from all patients participating in this study, which was approved by the Ethics Committee and registered by the French National Agency for Medicine and Health Products Safety (ANSM) and the Commission Nationale de l'Informatique et des Libertés (CNIL) (ClinicalTrials.gov Identifier: NCT00526383).

Patients were included based on the following criteria: aged 18–65 years, with a minimum score of 18 on the Hamilton Depression Rating Scale-17 items (HDRS-17) (Hamilton, 1960). Patients with psychotic symptoms, bipolar disorders, psychotic disorders, eating disorders, current substance abuse or dependence, organic brain syndromes, severe unstable medical conditions, or pregnancy were excluded from this study. Patients receiving antipsychotics or mood stabilizers before inclusion and/or for 4 months or more during the last year were not included. Of the 624 patients of the METADAP cohort, blood samples for metabolomic analyses from 164 patients of a single center were not available. Thus, 460 patients were analyzed. Patients were assessed at inclusion before treatment (M0), and three (M3) and six months (M6) after beginning treatment. Among depressed patients, 175 (38.5%) were treated with a selective serotonin reuptake inhibitor (SSRI), mainly escitalopram and citalopram, 177 (38.5%) were treated with a serotonin-norepinephrine reuptake inhibitor (SNRI), mainly venlafaxine, 38 (8.3%) were treated by tricyclic antidepressant (TCA), and 70 (15.2%) with another one (Table 1). The specific antidepressant treatments received by patients are reported in online Supplementary Table S1 (online Supplementary Table S1). 282 patients dropped out from the study. The main reasons were antidepressant drug changes for insufficient effectiveness /tolerance and loss to follow-up.

Clinical assessments were performed by the same senior psychiatrist for each visit. The HDRS-17, and the Quick Inventory of Depressive Symptomatology – Self-Report (QIDS-SR) (Rush et al., 2003), a self-questionnaire, were used to assess severity of MDE symptoms. Response and remission were defined as recommended by the American College of Neuropsychopharmacology Task Force (Rush et al., 2006). Response was based on a decrease of at least 50% from baseline in the HDRS score. Remission was based on a HDRS score lower or equal to 7. After 3 months of treatment, 132 patients (54.1%) were responders and 69 (28.3%) were remitters, while after 6 months, 119 patients (66.9%) were responders and 77 (43.3%) were remitters. There were no missing values at baseline, 8 at M3, and none at M6 for the HDRS-17. For the QIDS-SR, there were 14 missing values at baseline, 13 at M3, and none at M6.

### Healthy controls

HCs were part of VARIETE, a cross-sectional study in the general population (Chanson et al., 2016; Trabado et al., 2017). This study was approved by the French National Agency for Medicine and Health Products Safety (ANSM) and the Ethics Committee (ClinicalTrials.gov Identifier: NCT01831648). To be included in the study, adult subjects (aged between 18 and 89 years) had to be healthy according to medical and psychiatric history, without any current diseases or disorders, including psychiatric disorders, assessed during a medical examination, and standard biological tests performed after an overnight fast. The exclusion criteria were history of a medical condition or psychiatric disorder, substance use, pregnancy or breastfeeding, and a history of blood transfusion or donation within the 3 months prior to inclusion. The VARIETE cohort included 895 subjects, but 2 blood samples were not available. Thus, 893 subjects were analyzed.

### Metabolomic profiles of plasma acylcarnitines

EDTA blood samples were obtained from each subject in fasting standardized conditions for both depressed patients and HCs. Blood samples were obtained before any drug intake between 8:00 and 10:00 a.m. after an overnight fast and were prepared and analyzed as previously described (Ait Tayeb et al., 2023). Briefly, blood was centrifuged immediately (10 min, 2000 g at 4 °C) and plasma was aliquoted into separate polypropylene tubes that were immediately stored at −80 °C. Each aliquot was further divided into the volumes required for different analytical methods. One 10-$\mu$L aliquot was analyzed with the Biocrates AbsoluteIDQ p180 kit (Biocrates Life Science AG®, Innsbruck, Austria). The plasma samples were processed as recommended by the manufacturer and analyzed on an API 4000 Q-TRAP mass spectrometer (AB Sciex®, Darmstadt, Germany) coupled to an ACQUITY UPLC I Class system (Waters Corporation®, Milford, MA, USA) equipped with an Agilent $C_{18}$ HPLC column.

The identification and the quantification of metabolites were performed as previously published (Trabado et al., 2017).

https://doi.org/10.1017/S003329172300140X Published online by Cambridge University Press

**Table 1.** Sociodemographic and clinical characteristics of healthy controls and depressed patients at baseline

| | Healthy controls | Depressed patients | p |
|---|---|---|---|
| Subject characteristics | | | |
| Number of subjects (n) | 893 | 460 | <0.00001 |
| Age (years) (m(s.d.)) | 39.8 (18.6) | 46.0 (13.0) | <0.00001 |
| Women (n (%)) | 436 (48.8) | 315 (68.6) | <0.00001 |
| BMI (kg/m$^2$) (m(s.d.)) | 23.1 (2.4) | 24.1 (5.0) | <0.00001 |
| Lipidic and glycemic profiles | | | |
| Total cholesterol (mmol/l (s.d.)) | 4.94 (1.12) | 5.17 (1.14) | <0.00001 |
| Glycemia (mmol/l (s.d.)) | 4.68 (0.60) | 5.00 (1.07) | <0.00001 |
| MDD characteristics | | | |
| MDD onset (years (m(s.d.)) | – | 35.4 (14.4) | |
| Recurrent MDD (n (%)) | – | 362 (74.0) | |
| HDRS-17 at baseline (m(s.d.)) | – | 24.0 (4.5) | |
| MDD treatment (n (%)) | | | |
| SSRI | – | 175 (38.0) | |
| SNRI | – | 177 (38.5) | |
| TCA | – | 38 (8.3) | |
| Others | – | 70 (15.2) | |

Student's *t* tests were performed to compared healthy controls and depressed patients – BMI, Body mass index; MDD, Major depressive disorder; HDRS-17, 17-item Hamilton Depression Rating Scale; n, number of subjects; SD, Standard deviation; SSRI, Selective serotonin reuptake inhibitors; SNRI, Serotonin-norepinephrine reuptake inhibitors; TCA, Tricyclic antidepressant.

Briefly, the Biocrates AbsoluteIDQ p180 kit allows for the identification and measurement of more than 180 metabolites, including acylcarnitines. Acylcarnitines were analyzed using flow injection analysis (FIA) coupled to tandem mass spectrometry. Identification and quantification were performed based on internal standards and multiple reactions monitoring detection. After a pre-processing step (peak integration and concentration determination from calibration curves) with Multiquant software (AB Sciex, Darmstadt, Germany), data were uploaded into Biocrates MetIDQ software (included in the kit). Then, metabolite concentrations were directly calculated in MetIDQ.

EDTA sample management, plasma metabolomic analyses with Biocrates AbsolutIDQ p180 kit, and plasma sample processing were performed for HCs and depressed patients at each study time point (M0, M3, and M6) (Ait Tayeb et al., 2023). There were no missing biological data in HCs and in depressed patients at baseline, and 14 and 5 missing data at M3 and M6, respectively, in depressed patients. To prevent potential storage and batch effects, biological samples were assayed at the same time (randomly mixing both cohorts (METADAP and VARIETE) independently of the evaluation time for depressed patients) in the same laboratory using the same techniques for all subjects.

Thirty-eight acylcarnitines were measured, of which 12 were short chain acylcarnitines (from C3 to C5), 11 were medium chain (from C6 to C12) and 15 were long chain (from C14 to C18) (Table 2). Metabolites with less than 40% of values below the lower limit of quantification (LLOQ) at each time point in depressed patients and in HCs were analyzed as quantitative variables (MahmoudianDehkordi et al., 2021) and were described as 'acylcarnitines with continuous values'. Metabolites with 40% or more values below the LLOQ at any time point in depressed patients or in HCs were analyzed as qualitative variables (above or under the LLOQ) and were described as 'acylcarnitines with discretized dichotomized values'. Thus, among the 38 acylcarnitines, 12 were analyzed as quantitative variables and 26 as qualitative variables. For quantitative variables, values of acylcarnitines below the LLOQ were imputed as LLOQ/$\sqrt{2}$ (Colle et al., 2020). The plasma concentrations of acylcarnitines with continuous values in depressed patients during follow-up and in HCs are reported in online Supplementary Table S2 (online Supplementary Table S2). Concentrations of acylcarnitines with continuous values were $\log_2$ transformed for statistical analyses (MahmoudianDehkordi et al., 2021).

### Statistical analyses

The statistical analyses were performed using R 4.0.3.

Bivariate analyses were performed to compare depressed patients and HCs for socio-demographical (chi$^2$ tests for qualitative variables and Student's *t* tests or Wilcoxon tests for quantitative variables).

Linear regressions (for quantitative variables) and logistic regressions (for qualitative variables) adjusted for age, gender, body mass index (BMI), blood total cholesterol, and glycemia were performed to compare plasma acylcarnitine levels between depressed patients and HCs and between depressed patients at each time point. In the event of a significant difference in linear regressions between HCs and depressed patients at baseline, receiver operating characteristic (ROC) curves were performed to explore the potential diagnostic relevance of the acylcarnitine.

Then, changes of acylcarnitines with continuous values after treatment were assessed with mixed-effect models for repeated measures adjusted for age, gender, BMI at baseline, HDRS at

https://doi.org/10.1017/S003329172300140X Published online by Cambridge University Press

**Table 2.** The 38 acylcarnitines studied

| Metabolites | Abbreviations | Type of analyses | |
|---|---|---|---|
| | | Quantitative | Qualitative |
| Short-chain acylcarnitines | | | |
| Propionylcarnitine | C3 | + | |
| Hydroxypropionylcarnitine | C3-OH | | + |
| Propenoylcarnitine | C3:1 | | + |
| Butyrylcarnitine | C4 | + | |
| Hydroxybutyrylcarnitine /Malonylcarnitine | C4-OH (C3-DC) | + | |
| Butenylcarnitine | C4:1 | | + |
| Valerylcarnitine | C5 | + | |
| Glutarylcarnitine /Hydroxyhexanoylcarnitine | C5-DC (C6-OH) | | + |
| Methylglutarylcarnitine | C5-M-DC | | + |
| Hydroxyvalerylcarnitine /Methylmalonylcarnitine | C5-OH (C3-DC-M) | | + |
| Tiglylcarnitine | C5:1 | | + |
| Glutaconylcarnitine | C5:1-DC | | + |
| Medium-chain acylcarnitines | | | |
| Hexanoylcarnitine | C6 (C4:1-DC) | + | |
| Hexenoylcarnitine | C6:1 | | + |
| Pimeloylcarnitine | C7-DC | | + |
| Octanoylcarnitine | C8 | | + |
| Nonaylcarnitine | C9 | + | |
| Decanoylcarnitine | C10 | + | |
| Decenoylcarnitine | C10:1 | | + |
| Decadienylcarnitine | C10:2 | | + |
| Laurylcarnitine /Dodecanoylcarnitine | C12 | | + |
| Dodecanedioylcarnitine | C12-DC | | + |
| Dodecenoylcarnitine | C12:1 | | + |
| Long-chain acylcarnitines | | | |
| Tetradecanoylcarnitine | C14 | | + |
| Tetradecenoylcarnitine | C14:1 | + | |
| Hydroxytetradecenoylcarnitine | C14:1-OH | | + |
| Tetradecadienylcarnitine | C14:2 | | + |
| Hydroxytetradecadienylcarnitine | C14:2-OH | | + |
| Palmitoylcarnitine /Hexadecanoylcarnitine | C16 | + | |
| Hydroxyhexadecanoylcarnitine | C16-OH | | + |
| Hexadecenoylcarnitine | C16:1 | | + |
| Hydroxyhexadecenoylcarnitine | C16:1-OH | | + |
| Hexadecadienylcarnitine | C16:2 | | + |
| Hydroxyhexadecadienylcarnitine | C16:2-OH | | + |
| Stearoylcarnitine / Octadecanoylcarnitine | C18 | + | |
| Oleoylcarnitine/ Octadecenoylcarnitine | C18:1 | + | |
| Hydroxyoctadecenoylcarnitine | C18:1-OH | | + |
| Octadecadienylcarnitine | C18:2 | + | |

Abbreviations were the name of acylcarnitines in the form 'C(n)' – Quantitative analyses were performed for metabolites with <40% of measurements under the lower limit of quantification in healthy controls and depressed patients at baseline, 3 months, and 6 months – Qualitative analyses were performed for other metabolites

https://doi.org/10.1017/S003329172300140X Published online by Cambridge University Press

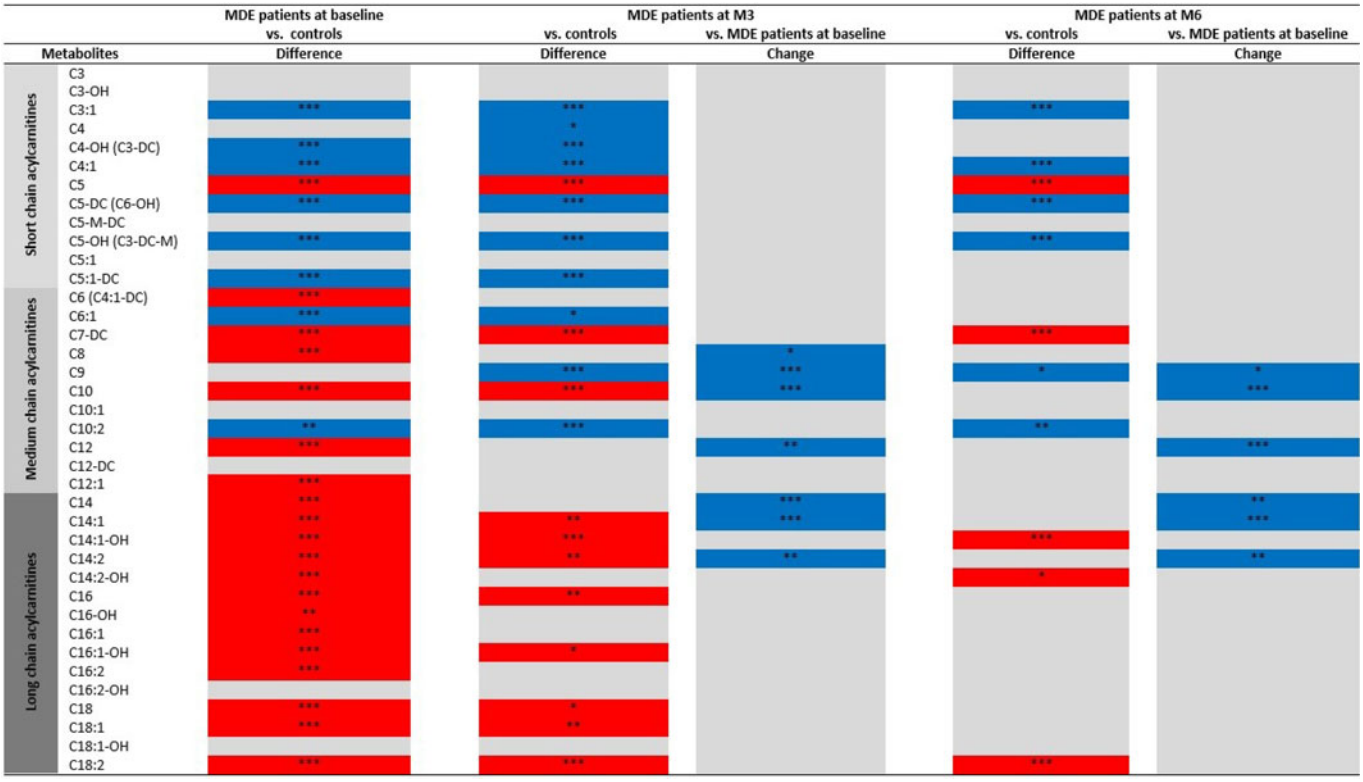


**Figure 1.** Plasma levels of acylcarnitines in healthy controls and in depressed patients during follow-up. Logistic regression adjusted for age, gender, BMI, HDRS score, total blood cholesterol, glycemia, and antidepressant class were performed for qualitative variables – Linear regression adjusted for age, gender, BMI, HDRS scores, total blood cholesterol, glycemia, and antidepressant class were performed for quantitative variables – MDE: Major depressive episode – M3: at 3 months – M6: at 6 months – Metabolite abbreviations and quantitative/qualitative variables are defined in Table 2 – : Statistically lower/decreased – : Statistically higher/increased – : No statistical difference – *: Significance after Bonferroni corrections ($p < 0.00131$) – **: $p < 0.0001$ – ***: $p < 0.00001$.

baseline, blood total cholesterol, glycemia, and antidepressant class. Using mixed-effect models, a patient with missing data on a specific visit/time-point will not result in a complete loss of information for that patient and an average estimation can still be calculated based on the remaining non-missing data points (Mallinckrodt et al., 2003). Covariables of the multivariate models were selected based on differences in bivariate analyses, with a significance threshold of $p < 0.05$. Spearman's correlation tests and linear regressions adjusted for age, gender, BMI, blood total cholesterol, and glycemia were used to test associations between levels of acylcarnitines with continuous values and MDE severity (according to HDRS total scores and QIDS-SR total scores). Finally, logistic regressions adjusted for age, gender, BMI, blood total cholesterol, glycemia, and antidepressant class were performed to compare acylcarnitine levels according to response/remission after 3 and 6 months of antidepressant treatment. All tests were two-tailed. Bonferroni corrections were applied. Based on the 38 metabolites measured, the significance threshold retained was $p < 0.00131$, except for analyses of acylcarnitine levels according to clinical outcomes and MDE severity, based on the 12 acylcarnitines with continuous values, for which the significance threshold retained was $p < 0.00417$.

## Results

### Socio-demographic and clinical characteristics

Socio-demographic and clinical characteristics of the 460 depressed patients and 893 HCs are shown in Table 1. At baseline, depressed patients and HCs differed with respect to age, gender, BMI, blood total cholesterol, and glycemia (Table 1).

### Metabolomic profiles of acylcarnitines in MDE patients at baseline and HCs

Among the 12 short-chain acylcarnitines, 6 were increased (C3:1, C4-OH, C4:1, C5-DC, C5-OH and C5:1-DC) and one was decreased (C5) in depressed patients compared to HCs. There was no significant difference for 5 of them (C3, C3-OH, C4, C5:1, C5-M-DC). Among the 11 medium-chain acylcarnitines, 6 were decreased (C6, C7-DC, C8, C10, C12 and C12:1) and 2 were increased (C6:1 and C10:2) in depressed patients compared to HCs. There was no significant difference for 3 of them (C9, C10:1, C12-DC). Among the 15 long-chain acylcarnitines, 13 were decreased (C14, C14:1, C14:1-OH, C14:2, C14:2-OH, C16, C16-OH, C16:1, C16:1-OH, C16:2, C18, C18:1 and C18:2) in depressed patients compared to HCs. There was no significant difference for 2 of them (C16:2-OH, C18:1-OH) (Fig. 1 and online Supplementary Tables S3 and S4). The performed ROC curves were associated with the diagnosis of MDE for C4-OH (area under the curve (AUC): 0.644; $p < 0.0001$), C5 (AUC: 0.654; $p < 0.0001$), C6 (AUC:0.604; $p < 0.0001$), C10 (AUC: 0.740; $p < 0.0001$), C14:1 (AUC: 0.732; $p < 0.0001$), C16 (AUC: 0.667; $p < 0.0001$), C18 (AUC: 0.632; $p < 0.0001$), C18:1 (AUC: 0.584; $p < 0.0001$), and C18:2 (AUC: 0.657; $p < 0.0001$). The performed ROC curves were described in the online Supplementary Figure S2 (online Supplementary Fig. S2).

https://doi.org/10.1017/S003329172300140X Published online by Cambridge University Press

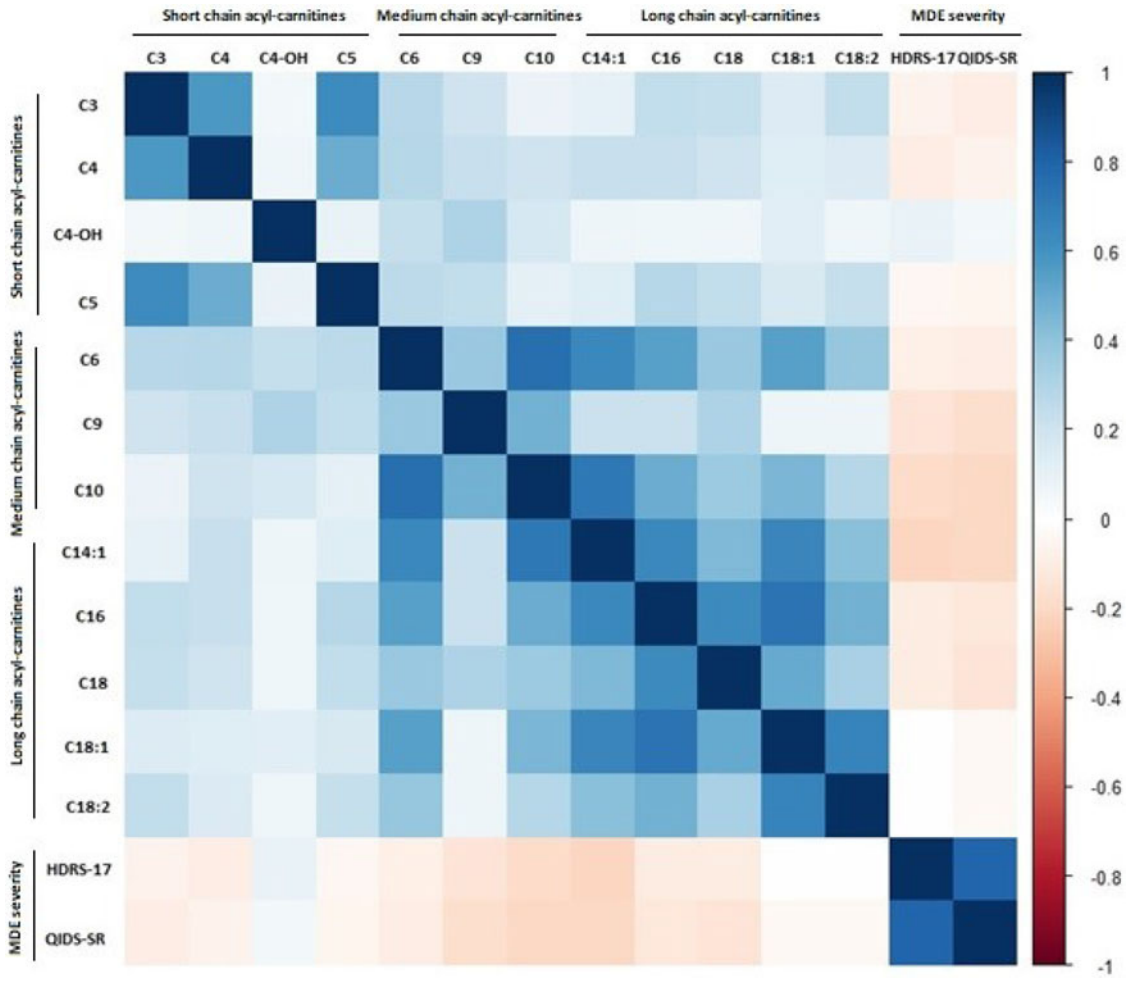


**Figure 2.** Correlation plot of acylcarnitines and depression severity in depressed patients. Blue represents positive correlations and red represents negative correlations – Acylcarnitine concentrations were $log_2$ transformed – The first cluster (C3, C4, C4-OH, C5) was short-chain acylcarnitines – The second cluster (C6, C9, C10, C14:1, C16, C18, C18:1, C18:2) was medium- and long-chain acylcarnitines – The third cluster (HDRS-17, QIDS-SR) was scales of depression severity – Metabolite abbreviations are defined in Table 2 – MDE, Major depressive episode; HDRS-17, 17-item Hamilton Depression Rating Scale; QIDS-SR, Quick Inventory of Depressive Symptomatology-Self-Report.

### *Metabolomic profiles of acylcarnitines and severity of MDE*

In correlation plots, two clusters of acylcarnitines were identified in depressed patients. The first comprised short-chain acylcarnitines, while the second comprised medium- and long-chain acylcarnitines (Fig. 2). Of note, similar clusters were identified in HCs (online Supplementary Fig. S3). In depressed patients at baseline, M3, and M6, correlation plots show that HDRS total scores were negatively correlated with medium- and long-chain acylcarnitines, but not with short- ones (Fig. 2). Accordingly, negative correlations were observed between HDRS total scores and C6, C9, C10, C14:1, C16, and C18 (respectively rho = −0.105; $p = 0.002$ – rho = −0.141; $p = 3.1E\text{-}5$ – rho = −0.201; $p = 2.3E\text{-}9$ – rho = −0.247; $p = 1.9E\text{-}13$ – rho = −0.116; $p = 0.0006$ – rho = −0.129; $p = 0.0001$) (online Supplementary Table S5). In multivariate analyses adjusted for age, gender, BMI, blood total cholesterol, and glycemia, these associations remained statistically significant for C9, C10, and C14:1. Similar correlations were identified with the QIDS-SR total scores. Moreover, in bivariate analyses, negative correlations were observed between HDRS total scores and C6, C9, C10, C14:1, C16, and C18 (respectively rho = −0.099; $p = 0.004$ – rho = −0.169; $p = 7.2E\text{-}7$ – rho = −0.206; $p = 1.5E\text{-}9$ – rho = −0.215; $p = 2.4E\text{-}10$ – rho = −0.133; $p = 1.0E\text{-}4$ – rho = −0.150; $p = 1.5E\text{-}6$). In multivariate analyses adjusted for age, gender, BMI, blood total cholesterol, and glycemia, these associations remained statistically significant, except for C6 (online Supplementary Table S5).

### *Metabolomic profiles of acylcarnitines after treatment in depressed patients*

In mixed models for repeated measures adjusted for age, gender, BMI at baseline, HDRS at baseline, blood total cholesterol, glycemia, and antidepressant class, only one short-chain acylcarnitine with continuous values (C4) among the 4 analyzed increased over time after 3 and 6 months of treatment. Among the 8 medium- and long-chain acylcarnitines with continuous values, 6 increased (C6, C9, C10, C14:1, C16 and C18) over the 6 months of treatment, while there was no significant change for the other 2 (Table 3).

Moreover, the differences in acylcarnitine levels between HCs and depressed patients decreased progressively until a normalization after 6 months of treatment (Fig. 1 and online Supplementary Tables S3 and S4). In analyses at each time

https://doi.org/10.1017/S003329172300140X Published online by Cambridge University Press

**Table 3.** Mixed model analyses for repeated measures for plasma levels of acylcarnitines in depressed patients over time

| | Coefficient (change/months) | 95CI | *p* |
|---|---|---|---|
| Short-chain acylcarnitines | | | |
| **C3** | 0.006 | [−0.003 to 0.015] | 0.22 |
| **C4** | 0.019 | [0.008–0.029] | **0.0006** |
| **C4-OH** | −0.026 | [−0.043 to −0.010] | **0.002** |
| **C5** | 0.007 | [−0.004 to 0.018] | 0.19 |
| Medium-chain acylcarnitines | | | |
| **C6** | 0.031 | [0.017–0.045] | $\mathbf{1.3 \times 10^{-5}}$ |
| **C9** | 0.030 | [0.017–0.043] | $\mathbf{8.0 \times 10^{-6}}$ |
| **C10** | 0.063 | [0.046–0.081] | $\mathbf{1.6 \times 10^{-12}}$ |
| Long-chain acylcarnitines | | | |
| **C14:1** | 0.050 | [0.038–0.061] | $\mathbf{<2 \times 10^{-16}}$ |
| **C16** | 0.020 | [0.011–0.030] | $\mathbf{1.7 \times 10^{-5}}$ |
| **C18** | 0.022 | [0.012–0.032] | $\mathbf{1.8 \times 10^{-5}}$ |
| **C18:1** | 0.006 | [−0.005 to 0.017] | 0.29 |
| **C18:2** | 0.004 | [−0.007 to 0.014] | 0.50 |

Mixed model analyses were adjusted for age, gender, BMI at baseline, HDRS at baseline, blood total cholesterol at baseline, glycemia at baseline, and antidepressant class – Metabolite concentrations were log2 transformed – CI: Confidence interval – Metabolite abbreviations are defined in Table 2 – **Bold *p*-value**: Significance after Bonferroni corrections

point during follow-up, there was an increase in the levels of several medium- and long-chain acylcarnitines, but not in the levels of short-chain acylcarnitines compared to baseline (Fig. 1 and online Supplementary Tables S4 and S6).

### *Acylcarnitines and clinical outcomes after treatment in depressed patients*

Plasma acylcarnitine values did not differ between responders and non-responders or remitters and non-remitters at baseline or during follow-up (online Supplementary Tables S7 and S8).

## Discussion

This study compared the plasma metabolomic profiles of 38 acylcarnitines in depressed patients and HCs and described their changes after treatment in depressed patients. Depressed patients had lower levels of medium- and long-chain acylcarnitines. Globally, these acylcarnitine levels were normalized after 6 months of treatment. Nonetheless, these changes were not associated with clinical outcomes.

First, we showed that plasma levels of medium- and long-chain acylcarnitine were lower in MDE patients as compared to controls. This result is consistent with previous clinical data. Indeed, in a sample of 135 depressed patients and 111 controls, medium- and long-chain acylcarnitine levels were lower in MDE patients (Liu et al., 2015). Cassol et al., showed that the levels of all acylcarnitines decreased, though it did not specifically focus on MDE in the context of MDD, but rather on depressive symptoms in a specific sample of 104 HIV-positive and HIV-negative patients compared to controls (Cassol et al., 2015). In another specific sample of 99 HIV-positive patients, plasma acylcarnitine levels decreased while depressive symptoms increased (Mukerji et al., 2021). Accordingly, in 2 large samples of 1411 and 968 participants, subjects with depressive symptoms had lower levels of medium-chain acylcarnitines (Zacharias et al., 2021).

Our result suggests an increase of FAO in depressed patients (Warren et al., 2014). Indeed, medium- and long-chain fatty acids enter mitochondria through the carnitine shuttle in the form of acylcarnitines to be converted into acyl-CoA, which is essential for FAO (Houten & Wanders, 2010). Consequently, reduced levels of acylcarnitines reveal an upregulation of FAO. Interestingly, in schizophrenia, enhanced FAO has also been reported among 110 patients and 190 healthy subjects (Yang et al., 2017). In line with our results, a meta-analysis of peripheral metabolites showed an alteration of fatty acid metabolism in MDE patients (Pu et al., 2021).

Second, we showed that plasma medium- and long-chain acylcarnitine levels significantly increased over time after antidepressant treatment in depressed patients until a normalization after 6 months of treatment. In preclinical studies using various rodent models of depression, the antidepressant fluoxetine normalized plasma acylcarnitine alterations (Chen et al., 2014; Hamilton et al., 2020; Xue et al., 2020). However, previous clinical data are still contentious. In two samples of depressed patients treated with escitalopram or citalopram for 8 weeks, there were changes in acylcarnitine levels after treatment (Ahmed et al., 2020; Rotroff et al., 2016; MahmoudianDehkordi et al., 2021). Recently, decreased levels of medium- and long-chain acylcarnitines and increased levels of short-chain acylcarnitines have been shown in a small sample of 136 depressed patients (Ahmed et al., 2020; MahmoudianDehkordi et al., 2021). Another study exploring acylcarnitines in 53 MDE patients treated with ketamine or esketamine showed increased plasma long chain acylcarnitine levels after treatment (Rotroff et al., 2016). Of note, none of these studies had a control group of healthy subjects.

Third, we showed a negative correlation between medium- and long-chain acylcarnitines and depression severity. Consistent results have been described previously for 11 acylcarnitines,

https://doi.org/10.1017/S003329172300140X Published online by Cambridge University Press

whereas we show a complete metabolomic profile (Liu et al., 2015). Nevertheless, a previous study showed increased levels of acylcarnitines in MDE patients in remission compared to HCs, whereas we show no difference in acylcarnitine levels according to remission in MDE patients after antidepressant treatment, nor between MDE patients after treatment and HCs (Mocking et al., 2021).

Finally, we found different changes according to the size of acylcarnitines, with short-chain acylcarnitines on one hand and medium- and long-chain acylcarnitines on the other. Similar differences were observed in previous studies that explored antidepressant effects on acylcarnitines levels (Ahmed et al., 2020; MahmoudianDehkordi et al., 2021), antipsychotic treatment in psychotic disorders (Kriisa et al., 2017), autism (Frye et al., 2013) and neurological disorders such as Parkinson's disease (Saiki et al., 2017) and Alzheimer's disease (Horgusluoglu et al., 2021). Unlike medium- and long-chain fatty acids, short-chain fatty acids do not need the carnitine shuttle to enter mitochondria. Moreover, short-chain acylcarnitines reflect the metabolism of some amino acids, such as leucine, valine, or isoleucine (MahmoudianDehkordi et al., 2021). Consequently, they are less in line with FAO and should be further explored. Effects on medium- and long-chain acylcarnitines were stronger among medium-chain acylcarnitines. This result was consistent with those of previous studies showing that even medium-chain acylcarnitines are the main biomarkers of FAO activity (Lehmann et al., 2010).

Relations between plasma acylcarnitine concentrations on the one hand and brain metabolism and cerebral acylcarnitine concentrations on the other hand are still unclear (Dambrova et al., 2022). Nevertheless, hypotheses can be raised and several mechanisms could underly our results. Recent evidence suggests the implication of mitochondrial and energy metabolic disturbances and a reduced metabolic flexibility in psychiatric disorders including MDD (Lin & Beal, 2006; Moore, Christensen, Lafer, Fava, & Renshaw, 1997). In preclinical models, depression-like behavior is related to a decreased level of acetyl-CoA (the final product of FAO, which is important for ATP production via the citric acid cycle) (Kubota, Goto, Hagiya, Chohnan, & Toyoda, 2016; Xie et al., 2020) and consequently decreased energy availability. In line with this hypothesis, decreased FAO could be expected during MDE. Nevertheless, we observed an upregulation of FAO (Houten & Wanders, 2010). This upregulation might be an attempt to restore acetyl-CoA levels. In the brain, the FAO is largely based in astrocytes to support neurons, probably by regulating the concentrations of cerebral neurotransmitters and should be further explored (Bartlett & Eaton, 2004; Souza, Almeida, Souza, & Zimmer, 2019; White et al., 2020). Equally, the FAO is based in the hypothalamus (Lam, Schwartz, & Rossetti, 2005). Of note, MDD is known to be related with hypothalamic and astroglial abnormalities (Malhi & Mann, 2018). Therefore, MDE could be related to FAO dysregulation in the brain. Moreover, during stress or cerebral diseases, there is an increased hepatic production of ketone bodies by FAO upregulation to support brain metabolism (Jensen, Wodschow, Nilsson, & Rungby, 2020; McGarry, Robles-Valdes, & Foster, 1975). Hence, the observed FAO upregulation in MDD could be systemic, as suggested by plasma modifications of medium- and long-chain acylcarnitines (online Supplementary Fig. S1) (Saiki et al., 2017). However, FAO upregulation leads to increased oxidative stress and inflammation characterized by a production of reactive oxygen species (Jensen et al., 2020; White et al., 2020), which could maintain the MDD.

The present study has some limitations. First, there were differences with respect to socio-demographic characteristics and biological parameters between MDE patients and HCs. Furthermore, patients were treated with different antidepressant classes. Thus, the models used were adjusted on these potentially cofounding factors. Second, data regarding food intake were not evaluated, though it could influence acylcarnitine concentrations. However, we showed in a previous analysis of the same cohorts an increase in plasma L-carnitine (C0) levels in depressed patients compared to HCs (Ait Tayeb et al., 2023). This result does not suggest a deficiency in total carnitine levels (L-carnitine and acylcarnitines) in depressed patients, but rather a change in metabolomic profiles. Even if a decreased appetite is observed in MDE, the constant levels of total carnitines argue against acylcarnitine deficiency in the food intake of depressed patients, and observed abnormalities were in line with FAO disturbances (Reuter & Evans, 2012). Third, some metabolite levels were below the LLOQ and were either imputed for analysis or were analyzed as qualitative variables. Fourth, targeted metabolomic profiles of acylcarnitines were performed instead of a large-scale metabolomic profile. However, this allowed for the study of a specific pathway with a clear rationale, the FAO. Moreover, acylcarnitines are currently used in daily practice and could have earlier clinical implications after replication and determination of specific pathologic thresholds adapter for MDD. Finally, the attrition rate was high and could limit the power of the study. However, it is close to those of other similar cohorts, like the STAR*D cohort (Trivedi et al., 2006).

This study has several strengths. First, the number of MDE patients compared to controls is the largest to assess the whole metabolomic profile of plasma acylcarnitines. This sample confers a reasonable confidence and generalizability of the results. Second, it is also a naturalistic study of 'real-life' patients, which reduces the gap between research and practice. Third, it offers the first extensive quantification of plasma acylcarnitine metabolomic profiles in depressed patients assessed in a central laboratory with controlled sampling and pre-analytical procedures. Hence, it provides a reliable picture of FAO in depressed patients. Finally, to the best of our knowledge, it is the first case-control study exploring the whole plasma metabolomic profiles of acylcarnitines in MDE in the context of MDD before and after antidepressant treatment.

To conclude, this study is the largest to explore the association between acylcarnitine metabolomic profiles, major depression, and long-term outcome after treatment. It provides new insights into the biological mechanisms of major depression. MDE in the context of MDD is associated with lower levels of plasma medium- and long-chain acylcarnitines, which are normalized after treatment. These results suggest an implication of FAO in MDD and should be further investigated.

**Supplementary material.** The supplementary material for this article can be found at https://doi.org/10.1017/S003329172300140X.

**Acknowledgements.** Centre de Ressources Biologiques Paris-Saclay (CRB PARIS SACLAY) for the METADAP biobank's storage (BRIF Number: BB-0033-00089).

**Financial support.** This work was supported by the Programme Hospitalier de Recherche Clinique (PHRC) from the French Ministry of Health

https://doi.org/10.1017/S003329172300140X Published online by Cambridge University Press

(AOM06022:PC and AOM09122:EC); and the Assistance Publique – Hôpitaux de Paris (P060219:EC).

**Conflict of interest.** Abd El Kader AIT TAYEB, Romain COLLE, Kenneth CHAPPELL, Khalil EL-ASMAR, Cécile ACQUAVIVA-BOURDAIN, Séverine TRABADO, Phillipe CHANSON, Bruno FEVE, Laurent BECQUEMONT, Céline VERSTUYFT, and Emmanuelle CORRUBLE had no conflict of interest to disclose.

Denis J. DAVID serves as a consultant for Lundbeck Inc, received compensation from Lundbeck and named on non-provisional patent applications for the prophylactic use of RS67333 against stress-related psychiatric disorders.

## References


Ahmed, A. T., MahmoudianDehkordi, S., Bhattacharyya, S., Arnold, M., Liu, D., Neavin, D., … Kaddurah-Daouk, R. (2020). Acylcarnitine metabolomic profiles inform clinically-defined major depressive phenotypes. *Journal of Affective Disorders*, *264*, 90–97. https://doi.org/10.1016/j.jad.2019.11.122.

Ait Tayeb, A. E. K., Colle, R., El-Asmar, K., Chappell, K., Acquaviva-Bourdain, C., David, D. J., … Corruble, E. (2023). Plasma acetyl-l-carnitine and l-carnitine in major depressive episodes: A case–control study before and after treatment. *Psychological Medicine*, *53*(6), 2307–2316. https://doi.org/10.1017/S003329172100413X.

Bartlett, K., & Eaton, S. (2004). Mitochondrial beta-oxidation. *European Journal of Biochemistry*, *271*(3), 462–469. https://doi.org/10.1046/j.1432-1033.2003.03947.x.

Cassol, E., Misra, V., Morgello, S., Kirk, G. D., Mehta, S. H., & Gabuzda, D. (2015). Altered monoamine and acylcarnitine metabolites in HIV-positive and HIV-negative subjects with depression. *JAIDS Journal of Acquired Immune Deficiency Syndromes*, *69*(1), 18–28. https://doi.org/10.1097/QAI.0000000000000551.

Chanson, P., Arnoux, A., Mavromati, M., Brailly-Tabard, S., Massart, C., & Young, J., … for the VARIETE Investigators. (2016). Reference values for IGF-I serum concentrations: Comparison of six immunoassays. *The Journal of Clinical Endocrinology & Metabolism*, *101*(9), 3450–3458. https://doi.org/10.1210/jc.2016-1257.

Chen, S., Wei, C., Gao, P., Kong, H., Jia, Z., Hu, C., … Xu, G. (2014). Effect of Allium macrostemon on a rat model of depression studied by using plasma lipid and acylcarnitine profiles from liquid chromatography/mass spectrometry. *Journal of Pharmaceutical and Biomedical Analysis*, *89*, 122–129. https://doi.org/10.1016/j.jpba.2013.10.045.

Colle, R., Masson, P., Verstuyft, C., Fève, B., Werner, E., Boursier-Neyret, C., … Becquemont, L. (2020). Peripheral tryptophan, serotonin, kynurenine, and their metabolites in major depression: A case–control study. *Psychiatry and Clinical Neurosciences*, *74*(2), 112–117. https://doi.org/10.1111/pcn.12944.

Corruble, E., El Asmar, K., Trabado, S., Verstuyft, C., Falissard, B., Colle, R., … Becquemont, L. (2015). Treating major depressive episodes with antidepressants can induce or worsen metabolic syndrome: Results of the METADAP cohort. *World Psychiatry*, *14*(3), 366–367. https://doi.org/10.1002/wps.20260.

Dambrova, M., Makrecka-Kuka, M., Kuka, J., Vilskersts, R., Nordberg, D., Attwood, M. M., … Schiöth, H. B. (2022). Acylcarnitines: Nomenclature, biomarkers, therapeutic potential, drug targets, and clinical trials. *Pharmacological Reviews*, *74*(3), 506–551. https://doi.org/10.1124/pharmrev.121.000408.

Frye, R. E., Melnyk, S., & MacFabe, D. F. (2013). Unique acyl-carnitine profiles are potential biomarkers for acquired mitochondrial disease in autism spectrum disorder. *Translational Psychiatry*, *3*(1), e220–e220. https://doi.org/10.1038/tp.2012.143.

Giménez-Palomo, A., Dodd, S., Anmella, G., Carvalho, A. F., Scaini, G., Quevedo, J., … Berk, M. (2021). The role of mitochondria in mood disorders: From physiology to pathophysiology and to treatment. *Frontiers in Psychiatry*, *12*, 546801. https://doi.org/10.3389/fpsyt.2021.546801.

Hamilton, M. (1960). A rating scale for depression. *Journal of Neurology, Neurosurgery & Psychiatry*, *23*(1), 56–62. https://doi.org/10.1136/jnnp.23.1.56.

Hamilton, P. J., Chen, E. Y., Tolstikov, V., Peña, C. J., Picone, J. A., Shah, P., … Nestler, E. J. (2020). Chronic stress and antidepressant treatment alter purine metabolism and beta oxidation within mouse brain and serum. *Scientific Reports*, *10*(1), 18134. https://doi.org/10.1038/s41598-020-75114-5.

Horgusluoglu, E., Neff, R., Song, W., Wang, M., Wang, Q., & Arnold, M., … the Alzheimer Disease Metabolomics Consortium. (2021). Integrative metabolomics-genomics approach reveals key metabolic pathways and regulators of Alzheimer's disease. *Alzheimer's & Dementia*, *18*(6), 1260–1278. https://doi.org/10.1002/alz.12468.

Houten, S. M., & Wanders, R. J. A. (2010). A general introduction to the biochemistry of mitochondrial fatty acid $\beta$-oxidation. *Journal of Inherited Metabolic Disease*, *33*(5), 469–477. https://doi.org/10.1007/s10545-010-9061-2.

Jensen, N. J., Wodschow, H. Z., Nilsson, M., & Rungby, J. (2020). Effects of ketone bodies on brain metabolism and function in neurodegenerative diseases. *International Journal of Molecular Sciences*, *21*(22), 8767. https://doi.org/10.3390/ijms21228767.

Kriisa, K., Leppik, L., Balõtšev, R., Ottas, A., Soomets, U., Koido, K., … Zilmer, M. (2017). Profiling of acylcarnitines in first episode psychosis before and after antipsychotic treatment. *Journal of Proteome Research*, *16*(10), 3558–3566. https://doi.org/10.1021/acs.jproteome.7b00279.

Kubota, Y., Goto, T., Hagiya, Y., Chohnan, S., & Toyoda, A. (2016). Decreased hepatic contents of coenzyme A molecular species in mice after subchronic mild social defeat stress. *Stress (Amsterdam, Netherlands)*, *19*(2), 192–197. https://doi.org/10.3109/10253890.2015.1137558.

Lam, T. K. T., Schwartz, G. J., & Rossetti, L. (2005). Hypothalamic sensing of fatty acids. *Nature Neuroscience*, *8*(5), 579–584. https://doi.org/10.1038/nn1456.

Lehmann, R., Zhao, X., Weigert, C., Simon, P., Fehrenbach, E., Fritsche, J., … Niess, A. M. (2010). Medium chain acylcarnitines dominate the metabolite pattern in humans under moderate intensity exercise and support lipid oxidation. *PLoS One*, *5*(7), e11519. https://doi.org/10.1371/journal.pone.0011519.

Lin, M. T., & Beal, M. F. (2006). Mitochondrial dysfunction and oxidative stress in neurodegenerative diseases. *Nature*, *443*(7113), 787–795. https://doi.org/10.1038/nature05292.

Liu, X., Zheng, P., Zhao, X., Zhang, Y., Hu, C., Li, J., … Xu, G. (2015). Discovery and validation of plasma biomarkers for major depressive disorder classification based on liquid chromatography–mass spectrometry. *Journal of Proteome Research*, *14*(5), 2322–2330. https://doi.org/10.1021/acs.jproteome.5b00144.

MahmoudianDehkordi, S., Ahmed, A. T.,Bhattacharyya, S., Han, X., Baillie, R. A., Arnold, M., … The Mood Disorders Precision Medicine Consortium (MDPMC). (2021). Alterations in acylcarnitines, amines, and lipids inform about the mechanism of action of citalopram/escitalopram in major depression. *Translational Psychiatry*, *11*(1), 153. https://doi.org/10.1038/s41398-020-01097-6.

Malhi, G. S., & Mann, J. J. (2018). Depression. *The Lancet*, *392*(10161), 2299–2312. https://doi.org/10.1016/S0140-6736(18)31948-2.

Mallinckrodt, C. H., Sanger, T. M., Dubé, S., DeBrota, D. J., Molenberghs, G., Carroll, R. J., … Tollefson, G. D. (2003). Assessing and interpreting treatment effects in longitudinal clinical trials with missing data. *Biological Psychiatry*, *53*(8), 754–760. https://doi.org/10.1016/S0006-3223(02)01867-X.

McGarry, J. D., Robles-Valdes, C., & Foster, D. W. (1975). Role of carnitine in hepatic ketogenesis. *Proceedings of the National Academy of Sciences*, *72*(11), 4385–4388. https://doi.org/10.1073/pnas.72.11.4385.

Merritt II, J. L., Norris, M., & Kanungo, S. (2018). Fatty acid oxidation disorders. *Annals of Translational Medicine*, *6*(24), 473–473. https://doi.org/10.21037/atm.2018.10.57.

Mocking, R. J. T., Naviaux, J. C., Li, K., Wang, L., Monk, J. M., Bright, A. T., … Naviaux, R. K. (2021). Metabolic features of recurrent major depressive disorder in remission, and the risk of future recurrence. *Translational Psychiatry*, *11*(1), 37. https://doi.org/10.1038/s41398-020-01182-w.

Moore, C. M., Christensen, J. D., Lafer, B., Fava, M., & Renshaw, P. F. (1997). Lower levels of nucleoside triphosphate in the basal ganglia of depressed subjects: A phosporous-31 magnetic resonance spectroscopy study. *American Journal of Psychiatry*, *154*(1), 116–118. https://doi.org/10.1176/ajp.154.1.116.

Mukerji, S. S., Misra, V., Lorenz, D. R., Chettimada, S., Keller, K., Letendre, S., … Gabuzda, D. (2021). Low neuroactive steroids identifies a biological subtype of depression in adults with human immunodeficiency virus on suppressive antiretroviral therapy. *The Journal of Infectious Diseases*, *223*(9), 1601–1611. https://doi.org/10.1093/infdis/jiaa104.

Nasca, C., Bigio, B., Lee, F. S., Young, S. P., Kautz, M. M., Albright, A., … Rasgon, N. (2018). Acetyl- l -carnitine deficiency in patients with major depressive disorder. *Proceedings of the National Academy of Sciences*, *115* (34), 8627–8632. https://doi.org/10.1073/pnas.1801609115.

Pu, J., Liu, Y., Zhang, H., Tian, L., Gui, S., Yu, Y., … Xie, P. (2021). An integrated meta-analysis of peripheral blood metabolites and biological functions in major depressive disorder. *Molecular Psychiatry*, *26*(8), 4265–4276. https://doi.org/10.1038/s41380-020-0645-4.

Reuter, S. E., & Evans, A. M. (2012). Carnitine and acylcarnitines. *Clinical Pharmacokinetics*, *51*(9), 553–572. https://doi.org/10.1007/BF03261931.

Rotroff, D. M., Corum, D. G., Motsinger-Reif, A., Fiehn, O., Bottrel, N., Drevets, W. C., … Kaddurah-Daouk, R. (2016). Metabolomic signatures of drug response phenotypes for ketamine and esketamine in subjects with refractory major depressive disorder: New mechanistic insights for rapid acting antidepressants. *Translational Psychiatry*, *6*(9), e894–e894. https://doi.org/10.1038/tp.2016.145.

Rush, A. J., Kraemer, H. C., Sackeim, H. A., Fava, M., Trivedi, M. H., Frank, E., … Schatzberg, A. F. (2006). Report by the ACNP task force on response and remission in major depressive disorder. *Neuropsychopharmacology*, *31*(9), 1841–1853. https://doi.org/10.1038/sj.npp.1301131.

Rush, A. J., Trivedi, M. H., Ibrahim, H. M., Carmody, T. J., Arnow, B., Klein, D. N., … Keller, M. B. (2003). The 16-Item quick inventory of depressive symptomatology (QIDS), clinician rating (QIDS-C), and self-report (QIDS-SR): A psychometric evaluation in patients with chronic major depression. *Biological Psychiatry*, *54*(5), 573–583. https://doi.org/10.1016/S0006-3223(02)01866-8.

Saiki, S., Hatano, T., Fujimaki, M., Ishikawa, K.-I., Mori, A., Oji, Y., … Hattori, N. (2017). Decreased long-chain acylcarnitines from insufficient $\beta$-oxidation as potential early diagnostic markers for Parkinson's disease. *Scientific Reports*, *7*(1), 7328. https://doi.org/10.1038/s41598-017-06767-y.

Souza, D. G., Almeida, R. F., Souza, D. O., & Zimmer, E. R. (2019). The astrocyte biochemistry. *Seminars in Cell & Developmental Biology*, *95*, 142–150. https://doi.org/10.1016/j.semcdb.2019.04.002.

Trabado, S., Al-Salameh, A., Croixmarie, V., Masson, P., Corruble, E., Fève, B., … Chanson, P. (2017). The human plasma-metabolome: Reference values in 800 French healthy volunteers; impact of cholesterol, gender and age. *PLOS One*, *12*(3), e0173615. https://doi.org/10.1371/journal.pone.0173615.

Trivedi, M. H., Rush, A. J., Wisniewski, S. R., Nierenberg, A. A., Warden, D., & Ritz, L., … STAR*D Study Team. (2006). Evaluation of outcomes with citalopram for depression using measurement-based care in STAR*D: Implications for clinical practice. *American Journal of Psychiatry*, *163*(1), 28–40. https://doi.org/10.1176/appi.ajp.163.1.28.

Warren, B. E., Lou, P.-H., Lucchinetti, E., Zhang, L., Clanachan, A. S., Affolter, A., … Lemieux, H. (2014). Early mitochondrial dysfunction in glycolytic muscle, but not oxidative muscle, of the fructose-fed insulin-resistant rat. *American Journal of Physiology-Endocrinology and Metabolism*, *306*(6), E658–E667. https://doi.org/10.1152/ajpendo.00511.2013.

White, C. J., Lee, J., Choi, J., Chu, T., Scafidi, S., & Wolfgang, M. J. (2020). Determining the bioenergetic capacity for fatty acid oxidation in the mammalian nervous system. *Molecular and Cellular Biology*, *40*(10), e00037–20. https://doi.org/10.1128/MCB.00037-20.

Xie, X., Shen, Q., Yu, C., Xiao, Q., Zhou, J., Xiong, Z., … Fu, Z. (2020). Depression-like behaviors are accompanied by disrupted mitochondrial energy metabolism in chronic corticosterone-induced mice. *The Journal of Steroid Biochemistry and Molecular Biology*, *200*, 105607. https://doi.org/10.1016/j.jsbmb.2020.105607.

Xue, S., Zhou, C., Xue, F., Liu, L., Cai, Y., Luo, J., … Peng, Z. (2020). The impact of repetitive transcranial magnetic stimulation and fluoxetine on the brain lipidome in a rat model of chronic unpredictable stress. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, *102*, 109946. https://doi.org/10.1016/j.pnpbp.2020.109946.

Yang, X., Sun, L., Zhao, A., Hu, X., Qing, Y., Jiang, J., … Wan, C. (2017). Serum fatty acid patterns in patients with schizophrenia: A targeted metabonomics study. *Translational Psychiatry*, *7*(7), e1176–e1176. https://doi.org/10.1038/tp.2017.152.

Zacharias, H. U., Hertel, J., Johar, H., Pietzner, M., Lukaschek, K., Atasoy, S., … Ladwig, K.-H. (2021). A metabolome-wide association study in the general population reveals decreased levels of serum laurylcarnitine in people with depression. *Molecular Psychiatry*, *26*, 7373–7383. https://doi.org/10.1038/s41380-021-01176-0.

https://doi.org/10.1017/S003329172300140X Published online by Cambridge University Press