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Mitochondrial Biomarkers and Metabolic Syndrome in Bipolar Disorder

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A R T I C L E I N F O

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A B S T R A C T

The object of this study is test whether mitochondrial blood-based biomarkers are associated with markers of metabolic syndrome in bipolar disorder, hypothesizing higher lactate but unchanged cell-free circulating mitochondrial DNA levels in bipolar disorder patients with metabolic syndrome. In a cohort study, primary testing from the FondaMental Advanced Centers of Expertise for bipolar disorder (FACE-BD) was conducted, including 837 stable bipolar disorder patients. The I-GIVE validation cohort consists of 237 participants: stable and acute bipolar patients, non-psychiatric controls, and acute schizophrenia patients. Multivariable regression analyses show significant lactate association with triglycerides, fasting glucose and systolic and diastolic blood pressure. Significantly higher levels of lactate were associated with presence of metabolic syndrome after adjusting for

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potential confounding factors. Mitochondrial-targeted metabolomics identified distinct metabolite profiles in patients with lactate presence and metabolic syndrome, differing from those without lactate changes but with metabolic syndrome. Circulating cell-free mitochondrial DNA was not associated with metabolic syndrome. This thorough analysis mitochondrial biomarkers indicate the associations with lactate and metabolic syndrome, while showing the mitochondrial metabolites can further stratify metabolic profiles in patients with BD. This study is relevant to improve the identification and stratification of bipolar patients with metabolic syndrome and provide potential personalized-therapeutic opportunities.

1. Introduction

Clinical outcomes for bipolar disorder (BD) encompass a spectrum of comorbidities including high cardiovascular mortality(Goldfarb et al., 2022). This mood disorder is intimately associated with metabolic aberrations, such as high fasting glucose(Miola et al., 2023), insulin resistance(Miola et al., 2023), cholesterol levels(Goldfarb et al., 2022), leading to double rates of metabolic syndrome (MetS)(Goldfarb et al., 2022; Leboyer et al., 2022). While several biological theories have been envisaged, compelling evidence of mitochondrial metabolic changes continue to grow. Henneman et al., as early as 1954, noted altered mitochondrial metabolism in psychotic patients, evidenced by increased blood lactate after glucose intake(Henneman et al., 1954). Kato and colleagues(Kato, 2022; Kato et al., 1992) studies reinforced this by identifying mitochondrial dysfunction in BD, observed through various markers in post-mortem brain tissues. Later studies confirmed these results, revealing gene expression changes in mitochondrial pathways and distinct brain imaging alterations. Studies also showed gene dysregulation in mitochondrial pathways for both BD and MDD(Andreazza et al., 2013; Kim et al., 2015; Konradi et al., 2004; Scola et al., 2013; Sun et al., 2006). Mitochondrial morphology were observed in BD post-mortem brain tissues, suggesting altered mitochondrial dynamics (Cataldo et al., 2010), further confirmed by Choi et al. by using advanced data analysis leading to identify specific genes that categorize BD subgroups(Choi et al., 2021), collectively underscoring mitochondrial dysfunction as a convergence pathway underpinning these metabolic clinical manifestations.

Dysfunctional mitochondria may arise from multifactorial origins leading to a metabolic shift, with consequent alterations of lipid biosynthesis and fatty acid oxidation(Lowell and Shulman, 2005; Muoio and Newgard, 2008; Petersen et al., 2004). This shift causes cells to be reliant on glycolysis for energy production, causing a build-up in lactate, which can act in competition with glucose as a fuel source and affect glucose uptake, which is implicated in the emergence of metabolic syndrome and may lead to the development of glucose intolerance (Broskey et al., 2020; Montgomery and Turner, 2015). Concurrently, damaged mitochondrial structures result in release of mitochondrial DNA, known as circulating cell free mitochondrial DNA (ccf-mtDNA) to the periphery. Ccf-mtDNA is recognized as damage-associated molecular patterns (DAMPs).(Zhou et al., 2021, 2023) This aberrant mitochondrial DNA outside the mitochondria triggers the TLR9 signaling cascade, amplifying/inducing NFKB-mediated pro-inflammatory gene expression and the activation of the NLRP3 inflammasome, culminating in chronic low-grade inflammation. MetS and inflammation are highly know to be trans-nosographically associated in patients with BD and other psychiatric diseases(Park et al., 2022).

Therefore, to further investigate the relationship between mitochondrial dysfunction and metabolic syndrome in BD, we examined key biological markers of mitochondrial dysfunction, lactate, along with mitochondrial targeted metabolomics, and ccf-mtDNA in patients with BD and determine the association of these markers with metabolic markers, clinical outcomes and MetS. Here, we included patients from the FondaMental Advanced Centers of Expertise in Bipolar Disorders (FACE-BD) cohort, a large and well-phenotype French cohort with stable BD patients and a smaller validation and replication cohort (I-GIVE) including stable and acute BD patients, as well as acute schizophrenia (SCZ) patients and non-psychiatric controls. We hypothesized that higher lactate and ccf-mtDNA levels will be associated with metabolic syndrome and c-reactive protein, as a marker of inflammation, respectively. Exploring biological markers that are easily translatable may ultimately demonstrate new ways for clinicians and researchers to potentially identify and treat metabolic changes, while offering new patient-specific therapeutic possibilities.

2. Methods

Study Population: The participant cohort included individuals undergoing evaluation at a collective of French healthcare facilities specializing in BD, a system instituted with the endorsement and financial aid of the French Ministry of Health and orchestrated by the FondaMental Foundation. The primary testing cohort (FACE-BD, Fig. 1) include stable outpatients diagnosed with BD(N = 837) within the FondaMental Advanced Centers of Expertise (FACE-BD) cohort. Full description of population, characteristics and treatments can be found elsewhere(Brodeur et al., 2021; Godin et al., 2021, 2023, 2020; Leboyer et al., 2022). The replication and validation cohort, were recruited as part of the French National granted I-GIVE (Immuno-Genetics, Inflammation, retro-Virus, Environment) cohort, for full description see (Angrand et al., 2021). The I-GIVE cohort (N = 237) (Fig. 1) consists of a variety of participants including patients with stable BD, acting as our validation group within the cohort (N = 26). The replication group, within the I-GIVE cohort includes participants with acute BD (N = 75 acute), participants with acute SCZ (N = 79) and non-psychiatric community controls (N = 57). Patients were evaluated, during hospitalization, for mania using the Young Mania Rating Scale (YMRS)(Young et al., 1978), the Montgomery-Asberg Depression Rating Scale (MADRS) for depression(Montgomery and Asberg, 1979) and Positive and

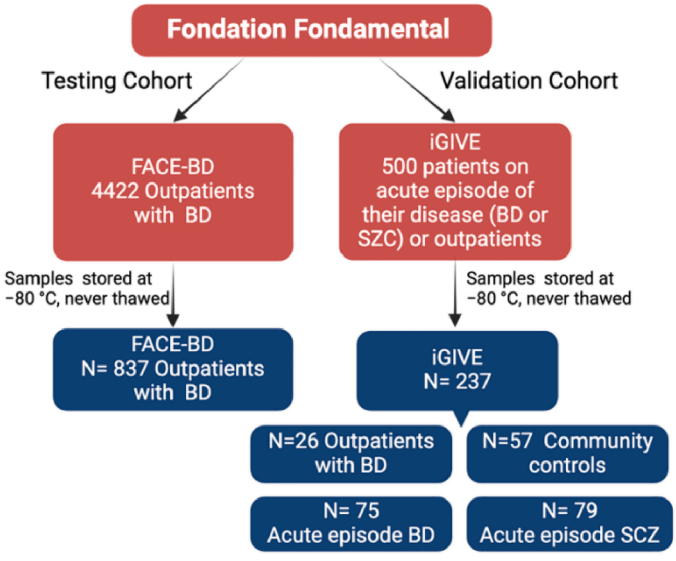


Fig. 1. Sample inclusion of testing cohort and validation cohort
Fig. 1: Testing cohort (FACE-BD) and secondary cohort (I-GIVE) sample inclusion. FACE-BD (N = 837). I-GIVE (N = 237). Number of samples included in the study were based on biological sample and biological marker availability.

Negative Syndrome Scale (PANSS) was used to assess presence of psychotic symptoms(Kay et al., 1987). IGIVE cohort subjects with acute phase had scores of MADRS above 17, YMRS above 8 or PANSS above 60 (Angrand et al., 2021). Fig. 1 and **eTables 1** and **2** shows the study design and clinical and demographics characteristics, respectively. After clinical phenotyping, biological plasma samples were collected (after fasting) and processed by the biological research repository where samples were stored at −80 °C until assayed. Plasma lactate was blindly collected, measured, and analyzed**.**

Metabolic Syndrome: MetS was defined according to the criteria of the International Diabetes Federation(Alberti et al., 2005), and requires the presence of ≥3 of the following criteria: high waist circumference (>90 cm for men and > 80 cm for women), hypertriglyceridemia (≥ 1.7 mmol/L or on lipid-lowering medication), low HDL cholesterol level (< 1.03 mmol/L in men and < 1.29 mmol/L in women), high blood pressure (≥ 130/85 mmHg or on antihypertensive medication), and high fasting glucose concentration (≥ 5.6 mmol/L or on glucose-lowering medication).

Framingham Risk Score: The Framingham Risk Score is calculated using a point system, in which different scores are assigned to age, HDL-C, total cholesterol, blood pressure, diabetes and smoking status. This score is dependent on sex and current treatment and determines an individual's 10-year CVD risk and heart age(Tzoulaki et al., 2009).

Circulating-cell free mitochondrial DNA (ccf-mtDNA) was quantified in plasma using PCR amplification of ND1 and ND4, with methodological details described in **eMethods**. Experimenters were conducted blinded as well as raw analyses.

Measurement of Lactate. Concentration of L-Lactate was measured using Cayman Chemical's L-Lactate assay kit (Product number 700,510) as per the manufacturer's protocol for plasma samples and published elsewhere[22]. Experimenters were conducted blindly, and raw data was blindly analyzed as well. All plasma samples were frozen promptly after collection at −80 °Celsius and were securely preserved until samples were thawed for experiments.

Metabolomics. Prior to conducting metabolomics, lactate samples were binarized. This was based upon visualization of lactate levels distribution across participants with bipolar disorder, in which 320 participants had levels lower than 1 mmol/L and 82 showed higher levels than 1.8 mmol/L (N = 43 higher than 2 mmol/L). Considering the acceptable range of lactate varies from 1–2 mmol/L we selected 50 individuals from each end of the range for metabolomics **(eFig1).** Plasma metabolomics profiling was conducted with collaborators at the University of Ottawa's Metabolomics Core Facility. Targeted mitochondrial metabolomics were conducted for over 20 selected metabolites (**eTable3**), and were quantified by liquid chromatography mass spectrometry (LC-MS). Experimenters were blinded when conducting metabolomics and raw analyses. Plasma samples used for metabolomics all underwent a single-freeze thaw cycle, and were compared relatively to one another.

Statistical Analyses. Demographic and clinical variables were described in mean ± standard deviation or n (%). Fisher's exact test and ANOVA was used to describe group-wise differences, where raw p-values are reported. The quantified ccf-mtDNA by copies of ND1 and ND4 showed linear correlation (Supplementary Methods Material), and natural-log transformation was applied to quantified ND1 (copies/μL) for statistical analyses. T-test, ANOVA, and Pearson's correlation was used to statistically describe the relationship between lactate and ccf-mtDNA with demographic variables. Multivariable linear regression was used to describe the relationship between lactate, ccf-mtDNA and clinical variables, adjusting for age, sex, and BMI, where resulting p values were adjusted using Benjamini-Hochberg procedure. Pearson's correlation test was used for the analysis of the correlation between metabolic markers. The threshold of $p < 0.05$ was used to determine statistical significance. Heatmap was visualized using seaborn (v0.12.2) in Python 3.8.5, where metabolites were z-transformed, then aggregated as group mean for visualization. Metabolomics hierarchical clustering was performed using Euclidian distance metric in Seaborn v0.12.2. Metabolome network was visualized in CytoScape, MetScape, and StringApp, and Pearson's correlation matrix was used as the input for correlation mapping. Kruskal-Wallis tests & additional post-hoc analysis was conducted for a clinical characterization of each strata.

3. Results

3.1. Participant demographics

Of 837 patients in the testing cohort (FACE-BD), 556 (66.58%) are female, 46.66% (N = 388) have a diagnosis of BD-type I. Among the FACE-BD cohort, the frequency of MetS was estimated to 17.76% (**eTable 1**). In the IGIVE cohort, demographical and clinical characteristics can be found in **eTable 2**.

3.2. Levels of blood-based mitochondrial biomarkers in the face-bd cohort

Regression analyses (Fig. 2a,b) adjusted for age, sex, and BMI, indicate that lactate is significantly associated with various markers related to MetS, including fasting glucose (**e**Fig. 2a) triglycerides (**e**Fig. 2c), and systolic and diastolic blood pressure (Fig. 2a). Significantly higher levels of lactate were also associated with frequency of MetS (Fig. 2**c**) whereas no significant association with clinical scales or CRP was observed.

Measures of ccf-mtDNA did not model the same associations with MetS. Ccf-mtDNA was not associated with MetS or with other metabolic markers (Fig. 2a,b). ccf-mtDNA was negatively correlated to one biological marker, specifically C-Reactive Protein (CRP) (Fig. 2**a**). ccf-mtDNA levels were positively associated (Fig. 2b) with manic symptoms (YMRS) while lactate levels did not demonstrate this. CRP and ccf-mtDNA were positively correlated with BMI (Pearson's $R = 0.30$, $p < 0.0001$).

Finally, we utilized relevant data to calculate the Framingham Risk score, a predictive tool developed for coronary heart disease, for individuals of the FACE-BD cohort(Tzoulaki et al., 2009). While there is nominal elevation of ccf-mtDNA copies with higher Framingham Risk Score, no significant association where observed (Fig. 2b). To investigate the effect of medication (lithium and valproate) on lactate and ccf-mtDNA, we assessed plasma medication levels and medication status. Both presence and plasma concentrations were not associated with lactate ($p_{lithium}$= 0.54, $p_{lithium\ concentration}$= 0.23, $p_{valproate}$= 0.06, $p_{valproate\ concentration}$= 0.12) and ccf-mtDNA ($p_{lithium}$= 0.84, $p_{lithium\ concentration}$= 0.54, $p_{valproate}$= 0.77, $p_{valproate\ concentration}$= 0.73).

3.2.1. Mitochondrial-Targeted metabolomics in FACE-BD

In efforts to further elucidate the metabolic relationship present between lactate and MetS, we conducted mitochondrial targeted metabolomics to examine, several relevant metabolites involved in mitochondrial metabolism in stable BD patients. In total, this subgroup analysis included 100 patients, 50 with clinically defined low levels of lactate (<1 mmol/L) and 50 patients with high lactate levels (>1.8 mmol/L) (Fig. 3**A**). Just over 20 metabolites were selected for examination, but ultimately 16 metabolites were included in our final analyses due to a lack of signal (**eTable 3**). The frequency of MetS was almost 2 times higher in the high lactate group compared to the low lactate group although not significantly associated (x^2=3.05; p = 0.08) (Fig. 3**A**). While stratifying by metabolic syndrome or lactate levels alone yielded no significant mitochondrial associations (Fig. 3**B**), combining both factors pinpointed specific mitochondrial metabolites (Fig. 3**C**). Ultimately, stratification by lactate levels or the presence/absence of metabolic syndrome individually (Fig. 3B) does not significantly alter the metabolomic profile of these individuals, however when metabolic syndrome and lactate levels are used together to stratify patients, distinct metabolic profiles emerge **(**Fig. 3**C).** Notably, patients with elevated lactate and metabolic syndrome had higher citrate and alpha-

A

FACE-BD Regression: Biological Variables

Variables		*Lactate*				*Ccf-mtDNA (ln)*			
Dependent Variable	Covariates	Estimate	Std. Err	Raw P	P adjust	Estimate	Std. Err	Raw P	P adjust
HDL	Age, Sex, BMI	-0.010845	0.044787	0.808737	0.81	0.092928	0.091538	0.31039	0.70
TC	Age, Sex, BMI	0.031313	0.017887	0.080487	0.18	0.0710128	0.0366697	0.05323	0.16
LDL	Age, Sex, BMI	0.007732	0.021401	0.71801	0.81	0.009399	0.043627	0.82950	0.91
TG	Age, Sex, BMI	0.072015	0.022505	0.00144	**0.0065**	0.014168	0.046368	0.76004	0.91
Glucose	Age, Sex, BMI	0.1221213	0.0252300	1.63e-06	**0.000015**	0.014602	0.051736	0.77784	0.91
K	Age, Sex, BMI	-0.0003614	0.0010599	0.733241	0.81	0.0002325	0.0021514	0.91397	0.91
Iron	Age, Sex, BMI	0.001348	0.000562	0.0168	*0.050*	0.002571	0.001149	0.02566	0.12
CRP (log)	Age, Sex, BMI	0.018	0.017	0.28	0.50	-0.12	0.033	0.00044	**0.0040**
Hb1Ac	Age, Sex, BMI	0.051442	0.055981	0.35898	0.54	0.034600	0.105332	0.7428	0.091

B

FACE-BD Regression: Clinical Variables

Variables		*Lactate*				*Ccf-mtDNA (ln)*			
Dependent Variable	Covariates	Estimate	Std. Err	Raw P	P adjust	Estimate	Std. Err	Raw P	P adjust
SBP	Age | Sex | BMI	0.003456	0.001274	0.00683	**0.031**	0.002769	0.002628	0.2923	0.42
DBP	Age | Sex | BMI	0.009499	0.001658	1.49e-08	**1.3e-7**	0.005222	0.003477	0.1335	0.24
Hosp/Duration	Age | Sex | BMI	0.015	0.023	0.52	0.52	0.005969	0.044822	0.89	0.89
MADRS	Age | Sex | BMI	0.0021	0.0017	0.24	0.36	0.003476	0.003537	0.33	0.42
PSQI	Age | Sex | BMI	0.0036	0.0046	0.44	0.52	0.007054	0.009165	0.44	0.50
FAST	Age | Sex | BMI	0.0023	0.0012	0.06	0.18	0.0051	0.0025	0.039	0.087
YMRS	Age | Sex | BMI	0.0058	0.0049	0.24	0.36	0.028	0.0098	0.0051	**0.046**
FRS	BMI	0.010	0.0063	0.10	0.23	0.025	0.012	0.037	0.088
Age of onset	Age | Sex | BMI	0.0017	0.0026	0.51	0.52	-0.011	0.0053	0.033	0.088

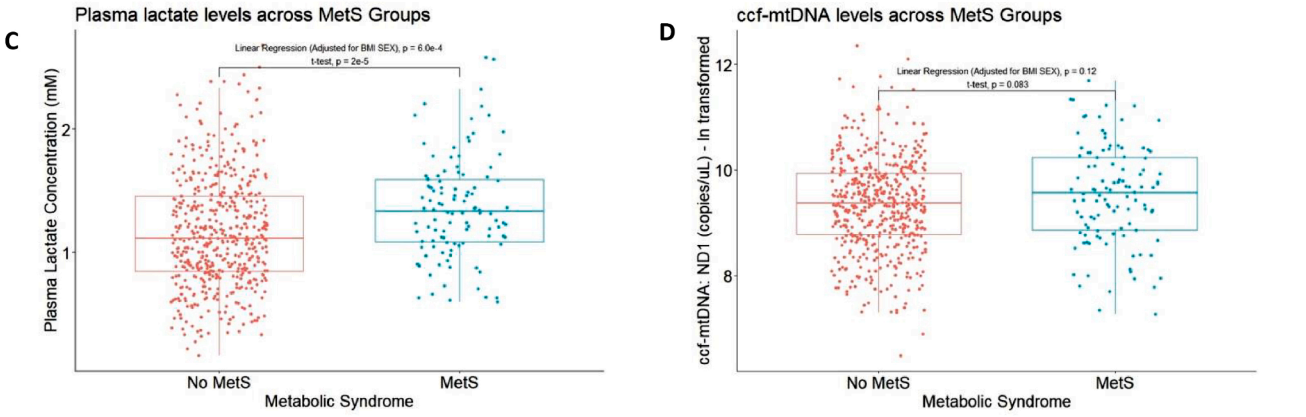


Fig. 2. Regression analysis model for various associations of mitochondrial-blood based biomarkers within the FACE-BD cohort.

Fig. 2. Regression analysis model for association of mitochondrial-blood based biomarkers with biological (A) and clinical (B) variable in the FACE-BD cohort. Association of peripheral levels of lactate (C) and circulating cell free mitochondrial DNA (ccf-mtDNA, D) with metabolic syndrome (MetS) in stable patients with bipolar disorder. High-density lipoprotein (HDL), total cholesterol (TC), triglycerides (TG), potassium (K), c-reactive protein (CRP), hemoglobin A1C (HbA1C), systolic blood pressure (SBP), diastolic blood pressure (DBP), hospitalization (Hosp); Young Mania Rating scale (YMRS); Functional Assessment Short Test (FAST); Framingham risk score (FRS).

ketoglutarate (AKG) levels than those with lower lactate (Fig. 3**C**). Alternatively, individuals with lower lactate levels with metabolic syndrome, had elevated levels of kynurenine and tryptophan **(**Fig. 3**C).** A metabolite correlation analysis emphasizes the association of AKG in this pathway (Fig. 3**E**). Mitochondrial metabolites showed a general trend towards inverse relationships with YMRS (**eFig. 3**). A clinical characterization of each strata was conducted and all variables were compared across the groups. While no significant differences were found across the variables after correcting for multiple testing, MADRS was nominally associated with the strata (p-value = $X^2 = 10.91$, $p_{adjusted} = 0.069$). A post-hoc analysis indicated higher MADRS scores in the MetS and high lactate group, compared to those with no MetS and low lactate group (X^2=3.28, FDR = 0.0031; **eTable 4**).

3.3. Replication analysis

Mitochondrial Biomarkers in FACE-BD & I-GIVE. To strengthen our analysis, we conducted a replication analysis utilizing age and sex-matched stable BD patients from a separate cohort, the I-GIVE cohort. Throughout the study, our inter- and intraplate variability remains relatively low for both lactate and ccf-mtDNA (Fig. 4**A**). Then we selected age and sex matched stable BD patients from both cohorts, it is evident that both plasma lactate (Fig. 4**B**) and ccf-mtDNA (Fig. 4**C**) levels remain consistent throughout both BD populations. Finally, we compare among the same individuals ($N = 100$), we compared the lactate levels measured via mass spectroscopy and spectrophotometry, which showing a strong positive correlation (Fig. 4**D**).

3.4. Validation analysis: blood-based mitochondrial biomarkers in I-GIVE

Further we investigated the levels of lactate and ccf-mtDNA in patients with BD or SCZ during acute phase of the illness (**eTable 5**). Intriguingly, acute BD patients of showed significantly elevated lactate levels in comparison to stable BD patients and non-psychiatric controls (Fig. 5**A**). Notably, when compared to non-psychiatric controls lactate levels were also elevated in stable BD patients (Fig. 5**A**). Acute SCZ patients showed similar levels of lactate when compared to acute BD patients (Fig. 5**A**). We explored the relationship of lactate levels and clinical presentation of depression, hypomania or mania and observed no relationship due to insufficient power (**eTable 6**). No differences were observed for ccf-mtDNA levels in patients compared to non-psychiatric controls. Finally, in the I-Give cohort we evaluated, whether mitochondrial DNA copy number (previously published in these patients(Angrand et al., 2021)) could affect the release of ccf-mtDNA, by creating a mt copy number to ccf-mtDNA ratio, no significant differences were observed across participants groups. To further explore sensitivity and specificity of lactate, we performed a receiver operating characteristic curve (ROC) showing that lactate differentiated between patients with acute psychiatric disorder compared to non-psychiatric controls (Fig. 5**B-D, eFig4)**.

4. Discussion

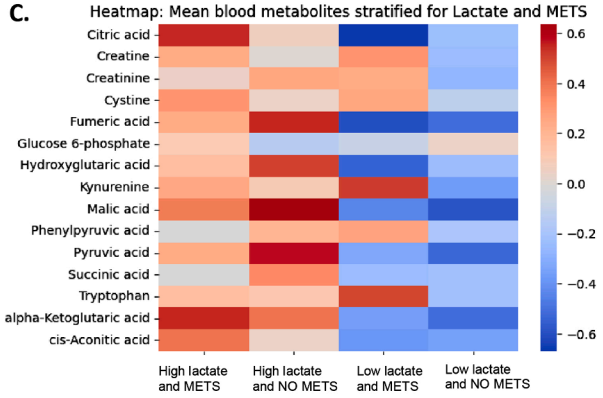
In the first study of its kind, utilizing a large cohort of stable BD patients, we were able to describe the utility of lactate as a biomarker in

A.

Demographics	<1 mmol/L (n=50)	>1.8 mmol/L (n=50)	Statistics
Age (mean, sd)	31.5 (9.2)	38.7 (11.9)	t = 3.41, p = 0.00097
Sex (F/M)	34/16	26/24	χ^2 = 2.04, p = 0.153
Diagnosis (BD-I/BD-II/unspecific)	15/33/2	30/17/3	χ^2 = 10.32, p = 0.0057
Metabolic Syndrome (present out of, n=76)	9 of 37 (24%)	18 of 39 (46%)	χ^2 = 3.05, p = 0.08
BMI (mean, sd)	25.0 (4.0)	28.4 (6.7)	t = 2.91, p = 0.0048
Smoker (n, % of n=87)	23 (53%)	25 (56%)	χ^2 = 0.0093, p = 0.923

B.

	Metabolic Syndrome				Lactate Stratification			
	estimate	std.error	statistic	p.value	estimate	std.error	statistic	p.value
Cystine	0.312965	0.255102	1.22682	0.224456	0.519533	0.404918	1.283057	0.328071
Creatine	0.437343	0.28442	1.537669	0.129137	-0.600749	1.296316	-0.463428	0.6886
Kynurenine	0.363891	0.23905	1.522236	0.132954	0.833148	1.936729	0.430183	0.708981
Glucose 6-phosphate	0.134247	0.21465	0.625422	0.533953	0.298956	0.435754	0.686066	0.563527
Fumeric acid	0.080396	0.25165	0.319474	0.750424	1.349197	0.061222	22.03763	0.002053
Hydroxyglutaric acid	-0.106785	0.244313	-0.437084	0.663545	-0.07772	0.796836	-0.097536	0.931195
alpha-Ketoglutaric acid	0.398046	0.250632	1.588172	0.117254	0.676018	1.712744	0.394699	0.731179
Phenylpyruvic acid	0.194459	0.249263	0.780133	0.438234	0.434621	1.564485	0.277804	0.807246
Tryptophan	0.292895	0.253268	1.156462	0.251859	0.477267	1.248485	0.382277	0.739055
Pyruvic acid	0.248733	0.168205	1.478744	0.144192	1.789916	0.160511	11.15136	0.007946
Succinic acid	0.017673	0.211483	0.083568	0.933665	1.014703	0.489557	2.072695	0.173961
Malic acid	0.239772	0.252647	0.949039	0.346227	1.621747	0.826521	1.962136	0.188755
cis-Aconitic acid	0.343278	0.261661	1.311919	0.194308	2.680053	2.672449	1.002846	0.421556
Creatinine	0.094095	0.21736	0.432898	0.666567	-0.336298	0.166704	-2.017336	0.181165
Citric acid	0.242702	0.271201	0.894915	0.374239	0.757945	1.753085	0.432349	0.70764



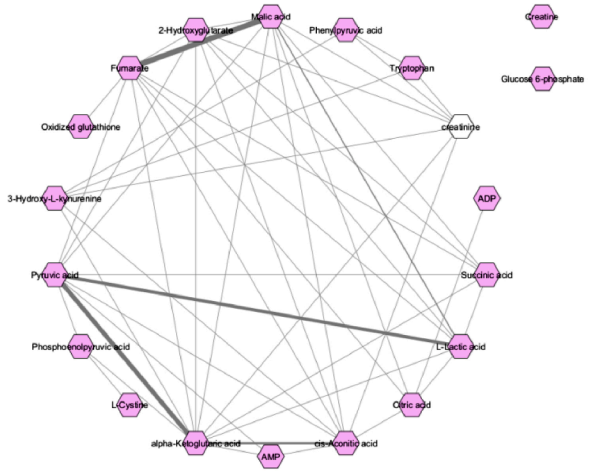


Fig. 3. Mitochondrial targeted metabolomics in patients with bipolar disorder (FACE-BD).

Fig. 3. Mitochondrial targeted metabolomics in patients with BD (FACE-BD). A. Demographic distribution of patients with low (<1 mmol/L) and high (> 1.8 mmol/L) levels of lactate. B. Statistical analysis of mitochondrial metabolites by stratification via metabolic syndrome or lactate levels. C. Heatmap of mitochondrial blood metabolites stratified by lactate and metabolic syndrome (METS). D. Metabolites correlation analysis.

BD and the potential of mitochondrial metabolites to identify a distinct signature between patients with MetS and elevated levels of lactate compared to those with MetS only. Furthermore, lactate levels remain consistent among stable BD patients in both the FACE-BD and I-GIVE cohorts but are notably significantly lower in non-psychiatric controls and higher in both acute BD patients and acute SCZ patients (I-GIVE cohort). While identifying that ccf- mtDNA may not be a strong marker of metabolic shift in patients with BD, it is hypothesized to be a marker of chronic inflammation in this cohort. The underlying mechanisms and modulations are depicted in Fig. 6, representing a proposed model that warrants even further investigation (Fig. 6). This data collectively suggests a potential association of lactate with metabolism and ccf-mtDNA with clinical symptomatology, and demonstrates the importance of mitochondrial metabolites in identifying homogenous patient groups likely to benefit from targeted mitochondrial metabolic interventions and personalized therapeutics.

Lactate is a well-known product of glycolysis, that is critical in the homeostasis of metabolism(Ferguson et al., 2018; Li et al., 2022). However, in a state of mitochondrial dysfunction and anaerobic conditions, there is a decrease in efficiency of the Krebs cycle and electron transport chain, forcing glycolysis to compensate to produce sufficient ATP for the organism to function(Broskey et al., 2020). In this case, pyruvate is reduced by NADH into lactate in high amounts and intracellular and extracellular lactate accumulation occurs, and this relationship is emphasized in the correlation analysis conducted(Rabinowitz and Enerbäck, 2020). While this process is well established, lactate has also been demonstrated to generate under fully aerobic conditions and in many cases is described as the fulcrum of metabolism fulfilling roles such as an energy source for mitochondrial metabolism, and potentially neurons in the brain, a gluconeogenic precursor and a signalling molecule with hormone-like effects that shuttles throughout the body in many different processes(Brooks, 2020; Brooks et al., 2021; Fillenz, 2005). There are many publications outlining the vast physiological roles of lactate, but the reason behind elevated lactate is not as thoroughly understood. This likely due to the fact that lactate production is complex, and the elevation is patient and disease specific(Andersen et al., 2013; Brooks, 2020; Brooks et al., 2021). In psychiatric diseases, including mood disorders, autism and schizophrenia, elevated lactate levels have consistently been demonstrated in serum, brain and cerebrospinal fluid(Dogan et al., 2018; Kuang et al., 2018). In individuals with T2D plasma lactate levels were raised compared to non-disease controls, and associated with increased fasting glucose levels, lower HDL cholesterol levels and triglycerides(Broskey et al., 2020; Jones et al., 2019). Despite the various occurrences in which lactate can be elevated, the elevation of lactate is associated to higher risk of mortality and morbidity(Andersen et al., 2013).

A finding within this study that we want to highlight is the association of lactate with fasting blood glucose and not HbA1c. While fasting blood glucose levels and HbA1c were correlated in the FACE-BD participants, with low correlation coefficient (Pearson's $R = 0.23$, $p < 0.0001$), this does not alter lactate's association with HbA1c. This is likely due to the fact that fasting glucose levels and HbA1c are not identical markers and should not be treated as such. Fasting blood glucose measures blood glucose levels after fasting, for typically 12 h, in one snapshot in time, ultimately acting as a measure of baseline metabolism(Ho-Pham et al., 2017). This measure can fluctuate and is dependent on several factors including time fasted, meals prior to blood collection, techniques used, exercise, etc. HbA1c was a measure discovered late and has been demonstrated to be a better indicator of type 2 diabetes and overall hyperglycemic control(Ho-Pham et al., 2017). While HbA1c can be affected by race and sex, it is a long-term indicator of glycemic exposure and can provide a more robust measure of glucose in humans for diagnostic purposes(Ho-Pham et al., 2017). These findings demonstrate that lactate is associated with

A.

Interplate Variability - Lactate	
Average	2847 uM
St. dev	432.4 uM
%CV	15.1%
Intraplate Variability - Lactate	
%CV	3.7 %
Interplate Variability - ccf-mtDNA	
%CV	15.1%
Intraplate Variability - ccf-mtDNA	
%CV	4.0 %

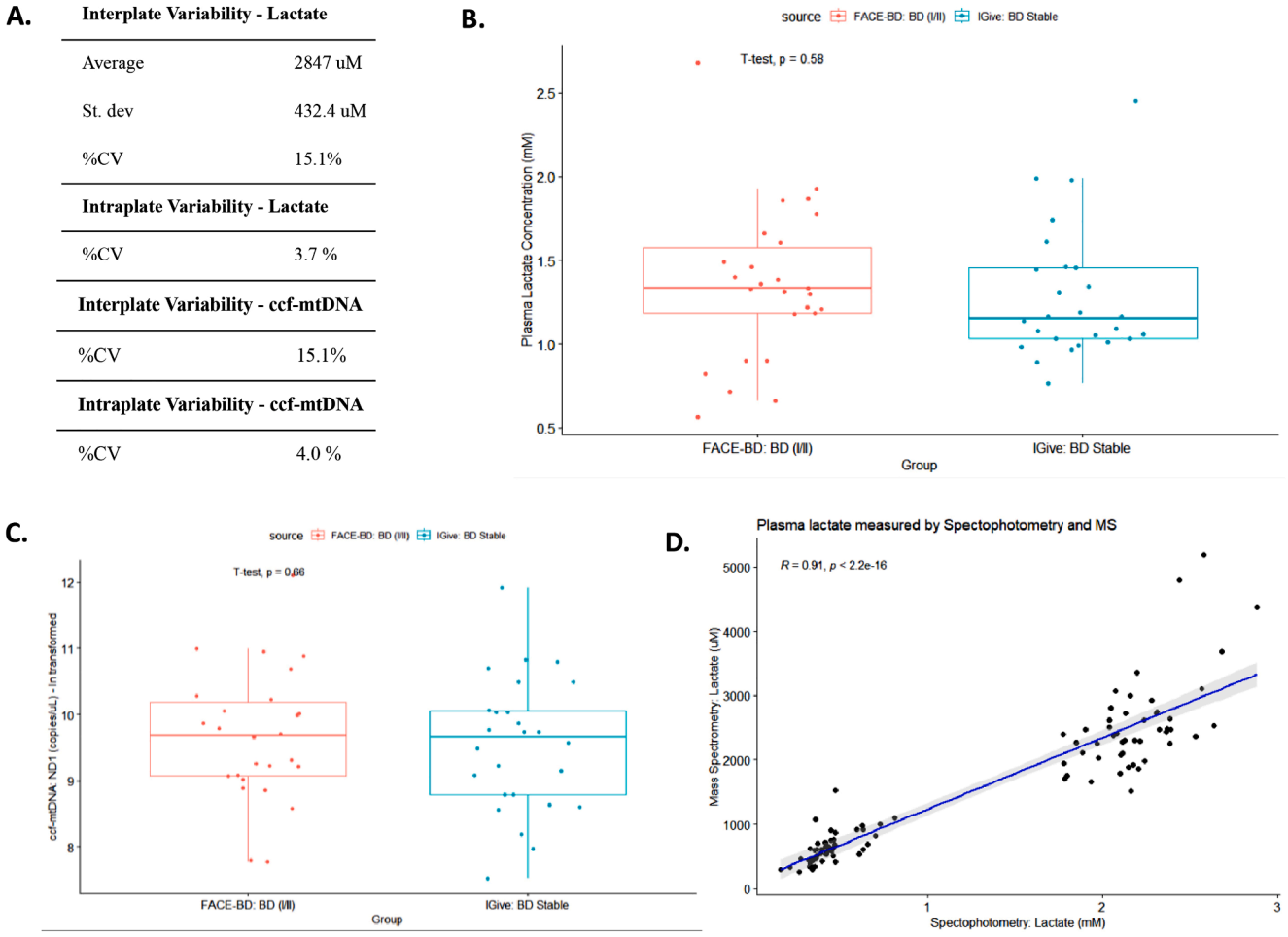


Fig. 4. Age-sex matched replication analysis of mitochondrial-blood based biomarkers.

Fig. 4. Age-sex matched replication analysis of mitochondrial-blood based biomarkers. A. Interplate and intraplate variability of lactate and circulating cell free mitochondrial DNA (ccf-mtDNA). B. Levels of lactate across FACE-BD and iGIVE cohort age-sex matched stable bipolar disorder (BD) patients. C. Levels of ccf-mtDNA across FACE-BD and iGIVE cohort age-sex matched stable bipolar disorder (BD) patients. D. Correlation of lacate levels measured by spectrophotometric measurement and liquid chromatography mass spectrometry (LC-MS).

baseline glycemic control and metabolic flux, and in this context, not with hyperglycemic indicators. It is plausible that this correlation occurs as lactate and glucose metabolism are both dynamic, can act as a source of fuel for energy production and have both been highlighted in the context of psychiatry and metabolism (Caddye et al., 2023). DISC1, a gene associated with various brain diseases, has been linked to astrocyte function and metabolism and moderates glucose utilization and lactate production. Lactate acts as an intermediary between glycolysis and glucose uptake, as well as oxidative phosphorylation. Lactate shuttling is quite common throughout the periphery, helping to replenish glucose or fuel energy production in various tissue types (Caddye et al., 2023; Hui et al., 2017). Several studies have explored the relationship between lactate and glucose, including one study in which the competition between lactate and glucose was assessed in rat hippocampal slice cultures. While results at a physiological dose had no significant changes on glucose when lactate was perfused, at a much higher lactate dose, glucose uptake was suppressed(Gilbert et al., 2006). In a separate study, researchers assessed the metabolic changes of venlafaxine, a commonly used anti-depressant, and highlighted its ability to rescue metabolic changes in the hippocampus of rats exposed to stress and noted the increase of both lactate and glucose(Brivio et al., 2023). Mechanistic studies are warranted, but the correlation between glucose and lactate is a plausible hypothesis that may explain these findings in some capacity (Brooks, 2020).

The metabolomics analysis emphasized the relationship of lactate and MetS, while simultaneously providing insight on potential underlying mechanisms within individuals with BD and MetS. Excess citrate, transported from the mitochondrial matrix to the cytosol, can suppress aerobic glycolysis, TCA cycle, and fatty acid breakdown, influencing metabolic diseases(Noriko Yoshimi et al., 2016). Moreover, heightened AKG levels are known to boost fatty acid production and elevate stored triglycerides(Wu, 2016). AKG acts as a rate limiting step in the TCA cycle as glutamine rewiring can occur to convert AKG back into citrate in hypoxic cells or in the event of dysfunctional mitochondria, which may explain this link exhibited in BD patients with high lactate and metabolic syndrome(Chen 2018; Guo et al., 2022; Gyanwali et al., 2022). In individuals with low lactate with metabolic syndrome, kynurenine and tryptophan were relatively elevated. Tryptophan is an essential amino acid metabolized by the kynurenine pathway, which can lead to the formation of quinolinic acid and nicotinamide adenine dinucleotide (NAD)(Tsuji et al., 2023). The first of two rate limiting enzymes in this pathway, indoleamine-2,3-dioxygenase, has been theorized to play a role in major depressive disorder. The second enzyme, tryptophan 2, 3-dioxygenase, is inhibited by glucose intake in the liver and downstream enzymes have been positively correlated with impaired glucose tolerance(Tsuji et al., 2023). These metabolites have been previously noted to be altered in BD, but not in the context of MetS in BD(Brady Jr et al., 2012).

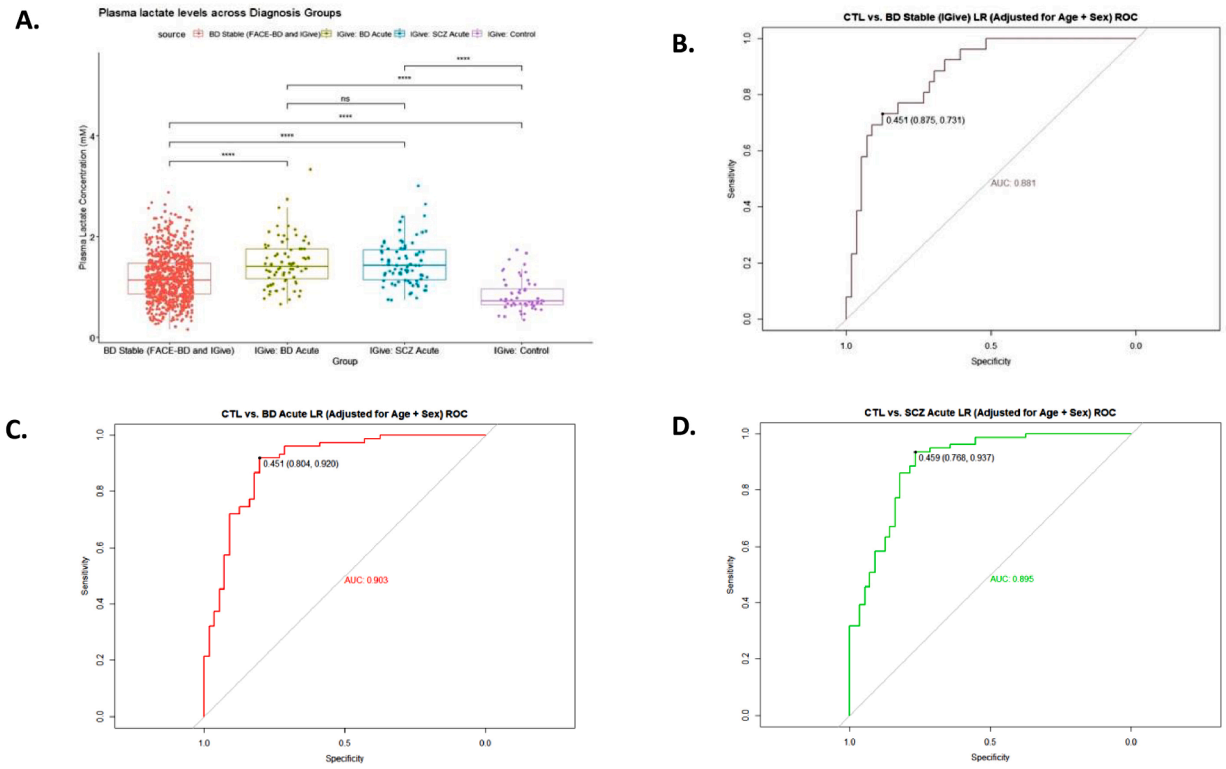


Fig. 5. Validation analysis of mitochondrial blood-based biomarkers in acute bipolar disorder and schizophrenia (I-GIVE).
Fig. 5. Levels of lactate (A) across acute patients with bipolar disorder (BD) and schizophrenia (SCZ) and non-psychiatric controls (controls) and (B - D) sensitivity and specificity analysis.

Circulating-cell free mitochondrial DNA (ccf-mtDNA) occurs when dysfunctional mitochondria fragment and release this fragmented DNA into the periphery(Picca et al., 2018). Increased ROS production can trigger released of its DNA into the cytosol through the mitochondrial transition channel opening(Picca et al., 2018). Cell death occurs, typically via apoptosis, and the mitochondrial DNA accumulates in the periphery and acts as a DAMP triggering the TLR9 signaling cascade and formation of the NLRP3 inflammasome. NLRP3 activation is known to play a role in immune and autoimmune disease, both type 1 and 2 diabetes, cancer, and central nervous system diseases, including BD and SCZ(Qiu et al., 2022). While there was an observed link with ccf-mtDNA and CRP, further exploration in an immune-focused model, incorporating more markers of inflammation, is warranted. CRP is a marker commonly utilized clinically to represent acute phase response and low-grade inflammation in many different physiological and psychiatric diseases(Osimo et al., 2019). It has been demonstrated that CRP is moderately increased in BD and is highest in mania compared to a depressive episode and euthymia(Fernandes et al., 2016). Similarly, CRP has been associated with obesity, type 2 diabetes and cardiovascular risk (Bae et al., 2019; Haffner, 2006; S. et al., 2005; Santos et al., 2005). Lastly, ccf-mtDNA and CRP have been linked previously, specifically in aging populations and dementia, both of which have as established etiology of mitochondrial dysfunction(Nidadavolu et al., 2023). Notably, CRP and ccf-mtDNA were positively correlated with BMI. BMI is noted in this study as a metabolic marker and was a co-variate in the regression analysis to ensure its role is statistically accounted for. CRP and ccf-mtDNA remain significantly correlated even after adjusting for age, sex, and BMI, highlighting the contribution of ccf-mtDNA on inflammatory pathways.

These underlying mechanisms discussed are highly variable and speak to the clinical heterogeneity demonstrated in individuals with bipolar disorder. To best understand the etiology of the disease, and improve therapeutic outcomes, precision medicine requires thoughtful consideration. The utilization of metabolomics is becoming a more common tool utilized in precision medicine and translational psychiatry. In a study be J. Tomasik, ceramides were indicated to be associated to manic episodes in both BD and MDD(Tomasik et al., 2024). In a different study, fibroblast growth factor 21, another marker of mitochondrial dysfunction was significantly increased in both males and females(Pan et al., 2023). While their main study outcome was suicidal ideation in MDD, most of the deregulatory pathways were mitochondria-related and other alterations were in lactate and glutamate, both of which are relevant to our findings(Pan et al., 2023). Finally, a plasma-metabolite targeted metabolomic study in both MDD and BD patients, examined neurotransmitter signatures and noted significant alterations in GABA, dopamine, tyramine and kynurenine, which we noted to be altered in patients with low lactate and metabolic syndrome (Fig. 3**C**)(Pan et al., 2018). Tryptophan and lactate have been closely linked to the gut microbiome, altering their overall metabolism and plasma levels, providing a wide array of therapeutic targets to be explored(Amin et al., 2023; Tsuji et al., 2023). The ketogenic diet has been examined in the context of insulin resistance in BD patients as it provides ketones as an alternative mitochondrial fuel source(Campbell and Campbell, 2020). Finally, the use of AKG as a nutritional supplement has been more commonly investigated to improve ATP supply, but this may only be useful in BD patients without metabolic syndrome, or those with lower

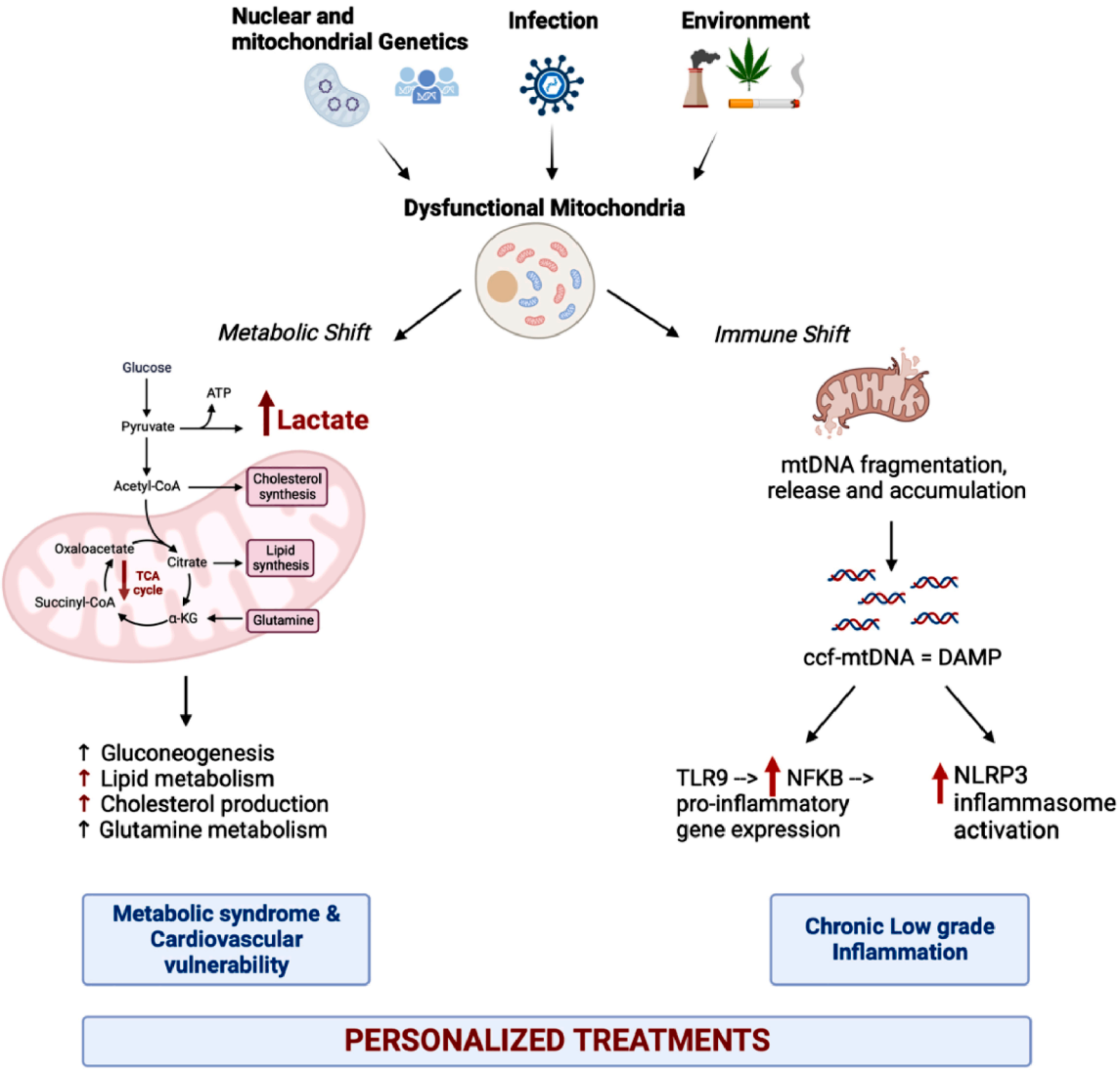


Fig. 6. A model of mitochondrial dysfunction as a convergence pathway leading to metabolic or immune shift: towards personalized treatments.

lactate levels(Gyanwali et al., 2022; Nirenberg et al., 2012).

Within every study there are limitations, thus results should be interpreted with caution through lenses of investigational science. It is important to note that our primary cohort was sufficient in sample size, however our replication and validation cohort were comparatively much smaller, warranting further studies on additional cohorts to strengthen this model. Despite this cohort's sample size and imbalanced distribution of clinical outcomes (etc. MADRS, YMRS, etc.) it was included to provide more informative data on various stages of BD (stable vs. acute). BD is incredibly complex and to only examine those in a stable state is not reflective of the overall course of disease. The I-GIVE cohort also had individuals with acute SCZ woth accessible data that provided a worthwhile analysis, despite the small sample size, as lactate in this small sample size was elevated compared to stable BD and similar compared to acute BD. Finally, including this group highlights the need for further investigation in a larger sample size.

This study did not account for lifestyle factors such as diet and exercise. We also used frozen plasma to collect biomarker measurements, but this plasma did not undergo any freeze-thaw cycles and analyses were performed over ice to ensure quality was maintained. Metabolomic samples underwent a single freeze-thaw cycle, however all samples underwent the same cycle and thus samples were all handled comparatively. To ensure reliability of the experiments we compared levels of mitochondrial biomarkers across cohorts and compared levels of lactate using two different technologies (i.e., mass spectrometry and spectrophotometry) demonstrating accuracy of lactate levels. We performed ROC analysis to explore the sensitivity and specificity of lactate, caution should be applied in absence of additional testing sets the presented data is a statistical description of the cohorts we have examined.

In conclusion, our study marks a significant advancement in bipolar disorder research by revealing the critical role of lactate and mitochondrial metabolites in distinguishing metabolic profiles among patients. Demonstrating consistent lactate levels across BD cohorts and its differential levels among acute versus stable patients and non-psychiatric controls, we highlight its potential as a metabolic surrogate biomarker. Our findings also clarify that circulating cell-free mitochondrial DNA (ccf-mtDNA) does not mark metabolic shifts in BD, adding a new dimension to our understanding of mitochondrial dynamics in psychiatric conditions. These insights pave the way for personalized treatment strategies in bipolar disorder, emphasizing the importance of mitochondrial dynamics in psychiatric and metabolic health. This research opens new avenues for targeted interventions, promising a future of precision medicine tailored to individual metabolic and psychiatric needs[49].

CRediT authorship contribution statement

Kassandra A. Zachos: Writing – review & editing, Writing – original draft, Methodology, Investigation, Formal analysis, Data curation. **Jaehyoung Choi:** Writing – review & editing, Writing – original draft, Methodology, Investigation, Formal analysis, Data curation. **Ophelia Godin:** Writing – review & editing, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Timofei Chernega:** Writing – review & editing, Data curation. **Haejin Angela Kwak:** Writing – review & editing, Data curation. **Jae H. Jung:** Writing – review & editing, Formal analysis, Data curation. **Bruno Aouizerate:** Writing – review & editing. **Valérie Aubin:** Writing – review & editing. **Frank Bellivier:** Writing – review & editing. **Raoul Belzeaux-R:** Writing – review & editing. **Philippe Courtet:** Writing – review & editing. **Caroline Dubertret:** Writing – review & editing. **Bruno Etain:** Writing – review & editing. **Emmanuel Haffen:** Writing – review & editing. **Antoine Lefrere A:** Writing – review & editing. **Pierre-Michel Llorca:** Writing – review & editing. **Emilie Olié:** Writing – review & editing. **Mircea Polosan:** Writing – review & editing. **Ludovic Samalin:** Writing – review & editing. **Raymund Schwan:** Writing – review & editing. **Paul Roux:** Writing – review & editing. **Caroline Barau:** Writing – review & editing. **Jean Romain Richard:** Writing – review & editing. **Ryad Tamouza:** Writing – review & editing. **Marion Leboyer:** Writing – review & editing, Resources, Project administration, Funding acquisition, Conceptualization. **Ana C. Andreazza:** Writing – review & editing, Writing – original draft, Visualization, Supervision, Resources, Project administration, Methodology, Investigation, Funding acquisition, Data curation, Conceptualization.

Declaration of competing interest

Kassandra A. Zachos: none
Jaehyoung Choi: none
Ophelia Godin: none
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Jae H. Jung: none
Bruno Aouizerate: none
Valérie Aubin: none
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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.psychres.2024.116063.

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