Title

Systematic Review and Meta-analysis Protocol: Association of Mitochondrial Dysfunction and Schizophrenia.

Authors

Fausak, Erik Davis
Bapu, Saanvi
Belambe, Amruta
et al.

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A Protocol for Meta-analytic assessment of the Association of Mitochondrial Dysfunction and Schizophrenia with Preliminary Results.

Erik Fausak[1], Saanvi Bapu[2], Amruta Belambe[2], Melissa Corea[2], Summer Duron[2], Johnathan Espinoza[2], Benjamin Horner[2], Kasidy Johnston[2], Gabriana La[2], Tianna Le[2], Zoe Lee Greenblatt[2], Jessie Li[2], Megan Li[2], Angela Min[2], Yash Rathi[2], Ellie Raymond[2], Oscar Rodriguez[2], Lena Rohan[2], Elvis Sandoval[2], Luis Santiago[2], Iman Shafaie[2], Anya Singh[2], Armando Tabales[2], Kaitlyn Thomas[2], Huy-An Tran[2], Nidhi Vadulas[2] , Maccabee Veder[2], Aldo Vorkapich[2], Jianan Wang[2], Frederich Zeller[2], Cecilia Giulivi[2*]

[1] University Library, University of California, Davis.m

[2] Department of Molecular Biosciences, School of Veterinary Medicine and MIND Institute.

*Correspondence: Dr. Cecilia Giulivi , cgiulivi@ucdavis.edu

Author Contributions: guarantor: Cecilia Giulivi

is the guarantor (responsible for quality and typically associated with correspondence), contributed to risk of bias and selection criteria, developed the search strategy, provided content expertise, provided statistical expertise (if meta-analysis).

Abstract:

Background:

Objectives: The objective of this study is to identify different primary studies that investigate the relationship between schizophrenia and mitochondrial dysfunction. Study inclusion is research that exclusively addresses schizophrenia and any objective measure of mitochondrial function. Comparable studies will be included into meta-analytic analysis.

Design: A comprehensive and replicable search was conducted across six literature databases to discover studies that examine mitochondrial dysfunction and schizophrenia, based on inclusion criteria and PRISMA guidelines [1].

Registration: This has been submitted to eScholarship, University of California (https://escholarship.org/) on 9 December 2021. Amendment has been updated 15 November 2023.

Amendments from Original Protocol:

New authors are contributing to project and outcome of study has been changed to measuring energy output instead of phases of electron transport chain and DNA copy number. Since all studies were observational (case-control), Risk of Bias was conducted using the Newcastle-Ottawa scale.

Funding and Support:

No funding to report.

Role of Sponsor or Funder:

No role applicable

Introduction

Rationale

Schizophrenia affects approximately 1% of the world population. Presentation of clinical signs typically manifest in young adults in their late teens to early twenties. Symptoms of those presenting include feelings of suspiciousness, hallucinations, perplexity, bizarre ideas, and depersonalization [2–5].

While not fully understood, evidence suggests schizophrenia has genetic and environmental factors. Environmental causes are believed to play a smaller role than genetic causes. Prenatally, poor nutrition and maternal infections are both linked to increased risk of schizophrenia. Postnatally, infection, nutritional deficits, neurotoxins, head injury, epilepsy, autoimmune diseases, and cannabis use in adolescence all pose an increased risk of developing schizophrenia. Additionally, developed countries and urban areas have a higher incidence rate whereas undeveloped countries and rural areas have lower incidence rates, due to increased risk of exposure to toxins or infection in these environments. Genetically, schizophrenia is estimated to have eighty percent inheritability. Schizophrenia is considered highly polygenic and pleiotropic, overlap has also been found between schizophrenia, bipolar disorder, and autism [6–8].

Diagnosis of Schizophrenia is usually made by utilization of the Diagnostic and Statistical Manual of Mental Disorders. Diagnosis occurs with identification of two or more events for more than six months and ruling out depressive or bipolar disorders [9]. There is currently no diagnostic imaging methodology to diagnose schizophrenia but it is currently being investigated [10]. Recent evidence suggests that mitochondrial dysfunction may be associated with a number of neurological disorders including schizophrenia [11,12]. Identifying the relationship of mitochondria and schizophrenia may aid and assist future prevention, diagnosis and treatment of the disease.

Mitochondrial dysfunction is implicated in the pathophysiology of major psychiatric disorders, such as bipolar disorder (BD) [13] and schizophrenia (SZ) [14], as well as neurodegenerative disorders, such as Alzheimer disease (AD) [15], Parkinson disease (PD) [15], and FXTAS [16–18] . Mitochondria are intracellular organelles that produce adenosine triphosphate (ATP), the main source of cellular energy. Prior to the generation of ATP, the electrons extracted from nutrients are transported along the electron transport chain (ETC) through Complexes located on the inner mitochondrial membrane and the energy released is directed into a transmembrane

proton which is utilized for the synthesis of ATP [19]. Impaired mitochondrial function results in energy failure, apoptosis, impaired calcium buffering, and oxidative stress [19–21].

Most studies investigated mitochondrial function once the disorder is already established (with the exception of one study) [22], when actually mitochondrial dysfunction is present before the onset of psychosis remains known [23].
A meta-analysis summarizing the mitochondrial findings in schizophrenia could not be found in the literature. Complex I and IV were mainly studied, with the remaining complexes II (succinate dehydrogenase), III (cytochrome c reductase) and V (ATP synthase) either have not been studied, or they have been studied to a much smaller degree in these five disorders, compared with complex I and IV, and thus there are too few data for a meta-analysis.

Objectives

The objective of this study is to identify different primary studies that investigate the relationship between schizophrenia and mitochondrial dysfunction. The objective is to answer the research question, *In populations of diagnosed schizophrenia, does mitochondrial dysfunction occur more than the general population*? Study inclusion is research that exclusively addresses schizophrenia and any objective measure of mitochondrial function. Comparable studies will be included into meta-analysis.

Methods

Eligibility Criteria:

Study Designs: Any primary research in human or animal populations including ex vivo or clinical research.

Participants: All studies must have a schizophrenic population with a comparison population.

Interventions and Comparators: Any interventions including: Mitochondrial DNA copy number, Oxidative phosphorylation, activity/ATP, mtDNA deletions, gene expression/transcriptome, proteomes, metabolites, enriched mitochondrial fraction/cytoplasmic extract, Mitochondria number/volume, Intracellular dopamine, polarized mitochondria/membrane potential, ROS Production/superoxide or hydrogen peroxide, calcium buffering/dynamics, heme metabolism and Krebs cycle (PDHC, CS, aconitase, AKGDH, OGDH, SDH, FH, NDH).

Outcomes: Primary studies using the above interventions will be incorporated, if feasible, into meta-analytic review.

Inclusion Criteria/ Exclusion criteria:

Studies for Inclusion	*Studies for Exclusion*
Is it original research? Is it about schizophrenia? Does it measure mitochondrial energy output in the data? Is it in English or Spanish? In methods, did the study get IRB (Internal Review Board), ethics committee, or IACUC approval? If it is tissue, do they clearly state where they got the tissues from (other university, which one)? If it is tissue, did they say when they collected it? Tissue of schizophrenic patient PMI (post-mortem interval), harvesting has to be mentioned	Is it a review article? Book chapter? Conference proceeding? Does it measure SNP (single nucleotide polymorphism)? Case report? Just one family? Editorial or commentary? Meta-analysis? Is it about other diseases or psychoses in general? Is it about the treatment or care of schizophrenia (intervention like drugs or behavioral therapy)? Tissues are used of non schizophrenic patients? Protocol (how to do it versus looking at disease in a population)? Mitochondrial dna variants Mitochondrial dna polymorphisms Mitochondrial dna haplotype PMI not mentioned

Include definitions.

Information Sources:

Database	**Interface**
Medline	Pubmed
PsycInfo	ProQuest
Scopus	Scopus
Biosis	Web of Science

Embase	Elsevier
Scifinder	SciFinder-N

Search Strategy:

evidence that mitochondrial is associated with Schizophrenia?

.

Databases and Interfaces Searched:

PRISMA-S Template (based on v1.0 retrieved from https://osf.io/2ybwn/)

(Literature and information being sought)

Mitochondrial involvement with Schizophrenia that looks at ATP production, ROS production, dynamics (morphology and distribution), Membrane potential, and tissue, brain samples, lymphoblasts, PBMNCs Skin or muscle biopsies, amniotic or placental fluid, CSF, ASD Mode, proteomics.

Is there solid evidence that mitochondrial is associated with Schizophrenia?

.

Databases and Interfaces Searched:

Database	Interface	Date Coverage	Date Searched
PsycInfo	ProQuest	1840 to Present	16 October 2023
Medline (Included products: Medline, in process citations, "ahead of print" citations, out-of-scope citations, journals indexing prior to medline inclusion, pre-1966 citations, PubMed Central, author manuscripts NIH funding, NCBI Bookshelf)	PubMed	1948 to present	16 October 2023
Embase	Embase	1974 to present	16 October 2023
SciFinder	American Chemical Society	1907 to present	16 October 2023
Biosis	Web of Science	1926 to present	16 October 2023
Scopus	Elsevier	1996-present	16 October 2023

Simultaneous Searches:
None performed
Item 2: Other Online Resources (As Needed):
Not applicable

Manual Searching (searching relevant journals Table of Contents):

Not Applicable

Citation Searching And Text Analysis:

Article Citation:
Takami, G., Ota, M., Nakashima, A., Kaneko, Y. S., Mori, K., Nagatsu, T., & Ota, A. (2010). Effects of atypical antipsychotics and haloperidol on PC12 cells: only aripiprazole phosphorylates AMP-activated protein kinase. *Journal of neural transmission (Vienna, Austria : 1996)*, *117*(10), 1139–1153. https://doi.org/10.1007/s00702-010-0457-9
Dogan, A. E., Yuksel, C., Du, F., Chouinard, V. A., & Öngür, D. (2018). Brain lactate and pH in schizophrenia and bipolar disorder: a systematic review of findings from magnetic resonance studies. *Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology*, *43*(8), 1681–1690. https://doi.org/10.1038/s41386-018-0041-9

Process: Searching was performed using keywords and utilizing database indexing with librarian (EF) and content expert (CG)

Contacts (Researchers contacted for additional information):
N/A

Additional Methodologies Not Listed Above:

N/A

Limits and Restrictions

Date and Time Period: Not restricted

Language: English/Spanish
Publication status: Published/peer reviewed

Species Included: Any

Study Design: ex vivo/in vitro, prospective experimental studies, Cohort, Case-contol, cross-sectional

Database Subset: N/A

Pre-specified cut-off or saturation point for results: N/A

Other Restrictions: N/A

Search Filters:

Database	Interface	Search Filters Applied
Medline	PubMed	Review, English, Spanish
Scifinder	Scifinder	English, Spanish, Journal, Review
Biosis	Web of Science	English, Spanish,Journal, Review

Full Search Strategy:

Search Database: PubMed

Search ID	Terms (copy and paste)	Results
#1	**"Schizophrenia/anatomy and histology"[Mesh] OR "Schizophrenia/blood"[Mesh] OR "Schizophrenia/cerebrospinal fluid"[Mesh] OR "Schizophrenia/enzymology"[Mesh] OR "Schizophrenia/etiology"[Mesh] OR "Schizophrenia/genetics"[Mesh] OR "Schizophrenia/metabolism"[Mesh] OR "schizophren*"[Title/Abstract]**	**138,970**
#2	**"Mitochondria"[Mesh] OR "mitochondri*"[Title/Abstract]**	**360,904**
#3 Energy	**"ATP production"[Tiab] OR "ATP generation"[tiab] OR**	**1,039,956**

	“energy metabolism”[tiab] OR “oxygen uptake”[tiab] OR “oxygen consumption”[tiab] OR “oxygen”[tiab] OR “ATP”[tiab] OR “AMP”[tiab] OR “ATP/AMP ratio”[tiab] OR “AMP/ATP”[tiab] OR “lactate”[tiab] OR “lactic acid”[tiab] OR “pyruvic acid”[tiab] OR “pyruvate”[tiab] or “lactate to pyruvate ratio”[tiab]	
#4	**#3 AND AND (english[Filter] OR spanish[Filter])**	**274**
#5	**#4 NOT Review[filter]**	**196**
Copy and paste:	**(("Oxidative Phosphorylation"[MeSH Terms] OR "lactic acid/metabolism"[MeSH Terms] OR "adenosine triphosphate/biosynthesis"[MeSH Terms] OR "ATP production"[Title/Abstract] OR "ATP generation"[Title/Abstract] OR "energy metabolism"[Title/Abstract] OR "oxygen uptake"[Title/Abstract] OR "oxygen consumption"[Title/Abstract] OR "oxygen"[Title/Abstract] OR "ATP"[Title/Abstract] OR "AMP"[Title/Abstract] OR "ATP/AMP ratio"[Title/Abstract] OR "AMP/ATP"[Title/Abstract] OR "lactate"[Title/Abstract] OR "lactic acid"[Title/Abstract] OR "pyruvic acid"[Title/Abstract] OR "pyruvate"[Title/Abstract] OR "lactate to pyruvate ratio"[Title/Abstract] OR "Oxidative Phosphorylation"[Title/Abstract] OR "oxphos"[Title/Abstract]) AND ("Mitochondria"[MeSH Terms] OR "mitochondri*"[Title/Abstract]) AND ("schizophrenia/anatomy and histology"[MeSH Terms] OR "schizophrenia/blood"[MeSH Terms] OR "schizophrenia/cerebrospinal fluid"[MeSH Terms] OR "schizophrenia/enzymology"[MeSH Terms] OR "schizophrenia/etiology"[MeSH Terms] OR "schizophrenia/genetics"[MeSH Terms] OR "schizophrenia/metabolism"[MeSH Terms] OR**	

	"schizophren*"[Title/Abstract]) AND ("english"[Language] OR "spanish"[Language])) NOT ("review"[Publication Type])	

Search Database: Scifinder
Ellie Raymond, Tianna Le, Luis Santiago

Search ID	Terms (copy and paste)	Results
#1	mitochrondi* in References	579,130
#2	schizophren* in References	1,372
#3	"Oxidative Phosphorylation" OR "Lactic Acid/metabolism" OR "Adenosine Triphosphate/biosynthesis" OR "ATP production" OR "ATP generation" OR "energy metabolism" OR "oxygen uptake" OR "oxygen consumption" OR "oxygen" OR "ATP" OR "AMP" OR "ATP/AMP ratio" OR "AMP/ATP" OR "lactate" OR "lactic acid" OR "pyruvic acid" OR "pyruvate" OR "lactate to pyruvate ratio" OR "oxidative phosphorylation" OR "oxphos"	
#4	#1 AND #2 AND #3	528
#5	#4 and Filter by Language: English and Spanish	507
#4	#3 and Filter by Document Type: Journal and Exclude: Review	286
Copy and paste	mitochondri* AND schizophren* AND ("Oxidative Phosphorylation" OR "Lactic Acid/metabolism" OR "Adenosine Triphosphate/biosynthesis" OR "ATP production" OR "ATP generation" OR "energy metabolism" OR "oxygen uptake" OR "oxygen consumption" OR "oxygen" OR "ATP" OR "AMP" OR "ATP/AMP ratio" OR "AMP/ATP" OR "lactate" OR "lactic acid" OR "pyruvic acid" OR	

	“pyruvate” OR “lactate to pyruvate ratio” OR “oxidative phosphorylation” OR “oxphos”) And (filters)	

919

Search Database: Biosis

Yash Rathi, Benjamin Horner Armando Tabales

Search ID	Terms (copy and paste)	Results
#1	TS=schizophren*	126,826
#2	TS=mitochondri*	458,187
#3	TS=("Oxidative Phosphorylation" OR "Lactic Acid/metabolism" OR "Adenosine Triphosphate/biosynthesis" OR "ATP production" OR "ATP generation" OR "energy metabolism" OR "oxygen uptake" OR "oxygen consumption" OR oxygen OR ATP OR AMP OR "ATP/AMP ratio" OR AMP/ATP OR lactate OR "lactic acid" OR "pyruvic acid" OR pyruvate OR "lactate to pyruvate ratio" OR "oxidative phosphorylation" OR oxphos)	1,509,426
#4	#1 AND #2 AND #3	313
#5	#4 AND LA=(English OR Spanish)	310
#6	#5 AND Refine by: NOT Literature Types: Literature Review	258
#7	TS=schizophren* AND TS=mitochondri* AND TS=("Oxidative Phosphorylation" OR "Lactic Acid/metabolism" OR "Adenosine Triphosphate/biosynthesis" OR "ATP production" OR "ATP generation" OR "energy metabolism" OR "oxygen uptake" OR "oxygen consumption" OR oxygen OR ATP OR AMP OR "ATP/AMP ratio" OR AMP/ATP OR lactate OR "lactic acid" OR "pyruvic acid" OR pyruvate OR "lactate to pyruvate ratio" OR "oxidative phosphorylation" OR oxphos) AND LA=(English OR Spanish)	

Search Database:Scopus* -Melissa Corea, Oscar Rodriguez, Frederich Zeller**

Search ID	Terms (copy and paste)	Results
#1	TITLE-ABS-KEY (schizophren*)	202,163
#2	TITLE-ABS-KEY (mitochondri*)	449,902
#3	TITLE-ABS-KEY("Oxidative Phosphorylation") OR TITLE-ABS-KEY("Lactic	2,031,979

	Acid/metabolism") OR TITLE-ABS-KEY("Adenosine Triphosphate/biosynthesis") OR TITLE-ABS("ATP production") OR TITLE-ABS("ATP generation") OR TITLE-ABS("energy metabolism") OR TITLE-ABS("oxygen uptake") OR TITLE-ABS("oxygen consumption") OR TITLE-ABS(oxygen) OR TITLE-ABS(ATP) OR TITLE-ABS(AMP) OR TITLE-ABS("ATP/AMP ratio") OR TITLE-ABS(AMP/ATP) OR TITLE-ABS(lactate) OR TITLE-ABS("lactic acid") OR TITLE-ABS("pyruvic acid") OR TITLE-ABS(pyruvate) OR TITLE-ABS("lactate to pyruvate ratio") OR TITLE-ABS("oxidative phosphorylation") OR TITLE-ABS(oxphos)	
#4	#1 AND #2 AND #3	**276**
#5	#4 AND (LIMIT-TO (LANGUAGE , "English") OR LIMIT-TO (LANGUAGE , "Spanish"))	
Copy and Paste	(schizophreni*:ab,ti OR 'schizophrenia'/exp) AND (mitochondri*:ab,ti OR 'mitochondrion'/exp) AND ('oxidative phosphorylation'/exp OR 'lactic acid/metabolism' OR 'adenosine triphosphate/biosynthesis' OR 'atp production':ti,ab OR 'atp generation':ti,ab OR 'energy metabolism':ti,ab OR 'oxygen uptake':ti,ab OR 'oxygen consumption':ti,ab OR oxygen:ti,ab OR atp:ti,ab OR amp:ti,ab OR 'atp/amp ratio':ti,ab OR 'amp/atp':ti,ab OR lactate:ti,ab OR 'lactic acid':ti,ab OR 'pyruvic acid':ti,ab OR pyruvate:ti,ab OR 'lactate to pyruvate ratio':ti,ab OR 'oxidative phosphorylation':ti,ab OR oxphos:ti,ab) AND [article]/lim AND ([english]/lim OR [spanish]/lim)	

Search Database: Embase (Summer Duron, Gabriana La, Angela Min)

Search ID	Terms (copy and paste)	Results
#1*	**schizophreni*:ab,ti AND 'schizophrenia'/exp**	**151,112**
#2*	**mitochondri*:ab,ti AND 'mitochondrion'/exp**	**170,769**
#3*	**#1 AND #2**	**341**
#4	**#3 AND articles**	**142**

Search Database: PsycInfo

Search ID	Terms (copy and paste)	Results
#1	**ab(schizophren*) OR MJMAINSUBJECT.EXACT("Schizophrenia") OR ti(Schizophren*)**	**131359**
#2	**ab(mitochondri*) OR MAINSUBJECT.EXACT("Mitochondria") OR ti(mitochondri*)**	**9588**

#3	**(ab(schizophren*) OR MJMAINSUBJECT.EXACT("Schizophrenia") OR ti(schizophren*)) AND (ab(mitochondri*) OR MJMAINSUBJECT.EXACT("Mitochondria") OR ti(mitochondri*))**	**325**
#4	**(ab(schizophren*) OR MJMAINSUBJECT.EXACT("Schizophrenia") OR ti(schizophren*)) AND (ab(mitochondri*) OR MJMAINSUBJECT.EXACT("Mitochondria") OR ti(mitochondri*)) AND (la.exact("ENG") AND yr(2010-2029) AND PEER(yes))**	**193**

Results:

Total Records	Total Records after deduplication	Deduplication software/methodology
760	**393**	**Endnote**
393	**393**	**Covidence**

Updates: N/A

Search Designers: Librarian(EF) and content expert(CG) built the original search strategy and all other authors helped translate to other databases. All authors then used PRESS checklist to review the search strategy. SR accelerator (Bond University, Australia) was used to find keywords with WordFreq and translation was done using Polyglot. All records were deduplicated with SR Accelerator and then deduplicated again with Covidence (Australia).

Peer Review:
PRESS checklist was used by authors (N = 15) that did not translate original strategies.

Records Screened:

Not completed on date of protocol
Prisma Diagram:

Updates: N/A

Search Designers: Librarian(EF) and content expert(CG) built the original search strategy and all other authors helped translate to other databases.

Peer Review:
Students translated search from a broadly designed search strategy, librarian (EF) reviewed the search strategies.

Records Screened:

393

Study Records:

SR Accelerator(Bond University, Australia) and Covidence (Australia) was used to deduplicate.

Selection Process:

2 screeners with inclusion and exclusion criteria went through records in title/abstract phase and full screen phases using Covidence Systematic Review Software (Veritas Health Innovation, Melbourne, Australia. Available at www.covidence.org)

Data Collection Process:

Data were collected from full text and extracted in pairs via Excel (Microsoft, USA) with review of extraction data by a pair that did not extract data. Finally, expert review (CG) was conducted of all data for final extraction. Form details included: author, study date, study title, study populations (including species, sex and age), types of cells/tissues examined/brain regions,presence of control and sample size (control and schizophrenic populations), studied protein/genes and outcomes.

Outcomes and Prioritization:

Data that has comparable outcomes with sufficient power for meta-analysis. Outcomes being considered:

Mitochondrial ATP production
Oxidative phosphorylation activity/ATP
Lactate/pyruvate ratio

ATP/ADP ratio
AMP/ATP ratio
Energy charge
Mitochondrial mass

Risk of bias in Individual Studies:

Risk of bias will be performed using Newcastle-Ottawa Scale[50] since all studies included were observational.

Data Synthesis:

Meta-analysis was conducted using OpenMeta(Analyst)(Center of Evidence Based Medicine, Brown University) using continuous data results of Complex 1 (see figure 1) and mtDNA copy number.

Confidence in Cumulative Evidence:

Qualitative analysis and assessment were applied to included studies.

Discussion:

In performing a meta-analysis finding connections between mitochondrial dysfunction and schizophrenia, we utilized various databases for review,SR accelerator (Bond University, Australia) to compile our results and deduplicate, and Covidence to deduplicate and aid in the review process narrowing down relevant articles. Using keyword searches related to mitochondria and schizophrenia, we limited our search results to articles in English or Spanish and excluded review articles, in the following databases: PudMed, Embase, Scifinder, Biosis, Scopus, and Psycinfo. A total of 760 articles were compiled in SR Accelerator, in which 367 duplicates were removed, leaving a total of 393 articles for further screening. Each article underwent title and abstract screening via Covidence, resulting in 216 articles for full text review. We set our inclusion criteria to ensure that only articles with original research and a clear connection between mitochondria and schizophrenia were included. As part of our inclusion criteria, the study must note that patients or test subjects were treated ethically with some form of written consent and/or approval from an ethics committee, such as the Internal Review Board (IRB) or Institutional Animal Care and Use Committee (IACUC). Additionally, when discussing samples or test subjects in the study, the article must explicitly note the difference between a control group and patients with schizophrenia within their methods and data collection, and for studies utilizing post-mortem brain samples or tissues, the article must state where samples came from and include information regarding the post-mortem interval (PMI). Articles were excluded if they did not meet the above criteria or if they met any of the exclusion criteria. There were 125 studies included in the review process for data

extraction; however, only 5 studies [24–28] were considered for the results of this protocol (see figure 1 for forest plot).

Numerous excellent reviews [3,13,14,29] have discussed the details of impairments in Complex activities and subunit assembly in these disorders, including schizophrenia [30]. In addition to their role in energy production, mitochondria are also involved in regulating neuronal development and synaptic plasticity [31]. As such, mitochondrial dysfunction may alter critical neuronal processes underlying abnormal brain development and cognitive impairment in psychosis.
Alterations in mitochondrial function in high-risk subjects of developing schizophrenia [23] and in diagnosed schizophrenic subjects are supported by converging evidence from genetic, enzymatic evaluations in several tissues, and imaging studies [20,31]. Genetic studies have identified single-nucleotide polymorphisms in mtDNA and mitochondrial-related genes as risk factors for schizophrenia [32–35]. Several studies performed on post-mortem biospecimens have reported decreased expression of mitochondrial-related genes [36,37], particularly genes encoding mitochondrial complexes [30,38,39] as well as reduced enzymatic activity in multiple brain regions [40], although others have failed to replicate these findings [41]. Post-mortem studies are confounded by numerous factors including cause of death, duration of illness and long-term medication use. In order to avoid the limitations associated with post-mortem studies, mitochondrial complex function has been measured in peripheral tissues in living patients. Alterations in mitochondrial complex activity have been consistently reported in blood cells of schizophrenia patients. Reduced mitochondrial complex I activity has been reported in lymphocytes and platelets of SCZ patients chronically treated with antipsychotics compared to healthy controls [42,43], with no differences in Complexes II-III activities [27]. Conversely, increased complex I activity was observed in platelets of medicated and unmedicated schizophrenia patients in acute exacerbation [25,26]. In addition, studies have also reported mitochondrial-induced impairments in brain energy metabolism [44]. Phosphorus magnetic resonance studies (31P-MRS) reported lower levels of ATP and phosphocreatine (PCr) in the brains of patients with schizophrenia [45,46]. Additionally, elevated lactate [30,44,47,48] and pyruvate levels [49] have also been reported in schizophrenia patients, consistent with mitochondrial dysfunction and a shift toward anaerobic metabolism.

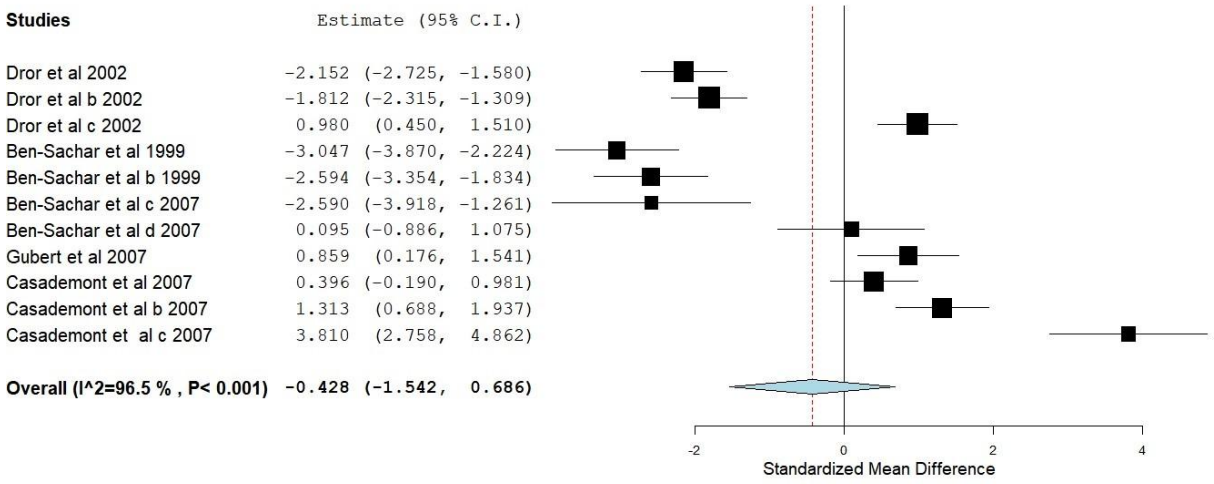

Figure 1: Forest plot based on five studies[24-28] measuring electron transport chain outcomes from 2021.

Acknowledgments:

We would like to acknowledge the University of California, Davis and its Course-based Undergraduate Research Experience (CURE) program for allowing us the opportunity to undergo the meta-analysis process and write this paper. Throughout our time working together, we have gained valuable experience reading, carefully reviewing, and extracting data from scientific literature.

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