Fatigue and Mitochondrial Dysfunction in Neurodevelopmental and Psychiatric Disorders: A Structured Literature Review

1. Introduction

Mitochondrial dysfunction has emerged as a significant factor in the pathophysiology of both neurodevelopmental and psychiatric disorders, with fatigue being a prominent and often debilitating symptom across these conditions. Evidence from systematic reviews, clinical studies, and mechanistic research highlights that mitochondrial abnormalities—ranging from impaired ATP production to increased oxidative stress—are frequently observed in disorders such as autism spectrum disorder (ASD), attention-deficit/hyperactivity disorder (ADHD), depression, bipolar disorder, and schizophrenia (Payares et al., 2024; Morris & Berk, 2015; Tanaka et al., 2022; Ni et al., 2022; Spritzler & Deloudi, 2025; Rose et al., 2018; Rezin et al., 2009; Kim et al., 2019). Fatigue, cognitive impairment, mood disturbances, and other neuropsychiatric symptoms are commonly reported in patients with primary mitochondrial diseases as well as those with secondary mitochondrial dysfunction associated with psychiatric or neurodevelopmental diagnoses (Payares et al., 2024; Morris & Berk, 2015; Tanaka et al., 2022; Anitha et al., 2023). The literature also points to shared mechanisms involving oxidative stress, inflammation, genetic mutations affecting mitochondrial function, and environmental triggers that exacerbate energy deficits in the brain (Morris & Berk, 2015; Tanaka et al., 2022; Mantle et al., 2024). While the association between mitochondrial dysfunction and fatigue is well-documented in chronic fatigue syndrome (CFS) and post-viral fatigue syndromes (Mantle et al., 2024), similar bioenergetic impairments are increasingly recognized in classic psychiatric and neurodevelopmental disorders (Payares et al., 2024; Morris & Berk, 2015; Tanaka et al., 2022). However, questions remain regarding causality versus correlation, specificity of mitochondrial alterations to particular diagnoses, and the potential for targeted metabolic therapies (Kim et al., 2019; Morris et al., 2018). This review synthesizes current findings on the interplay between mitochondrial dysfunction, fatigue, and neuropsychiatric/neurodevelopmental disorders.

Is mitochondrial dysfunction associated with fatigue in neurodevelopmental and psychiatric disorders? N = 6

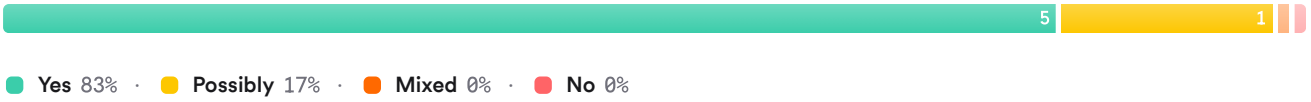

FIGURE 1 Consensus meter visualizing agreement on whether mitochondrial dysfunction is linked to fatigue in these disorders.

2. Methods

A comprehensive search was conducted across over 170 million research papers indexed by Consensus—including Semantic Scholar, PubMed, Scopus, Cochrane Library, and additional sources. The search strategy included foundational concepts linking mitochondria to neuropsychiatric/neurodevelopmental disorders; focused queries on fatigue; alternative terminology for both constructs; critical/contradictory perspectives; adjacent topics like CFS; and disorder-specific breakdowns. In total, 1,513,581 papers were identified through initial queries. After multi-phase filtering for relevance and quality (screening 249 papers), 133 were deemed eligible. The final review includes the top 50 most relevant papers.

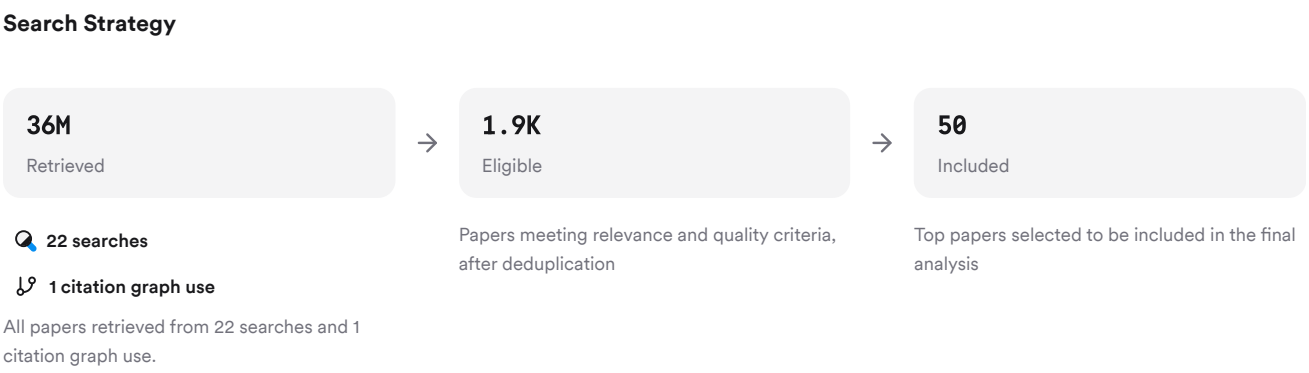

FIGURE 2 Flow diagram of paper selection process for this review.

Six unique search strategies were used to ensure broad coverage of foundational theory, symptom focus (fatigue), terminology variation, critique/contradiction, adjacent syndromes (e.g., CFS), and disorder-specific evidence.

3. Results

3.1 Mitochondrial Dysfunction Across Disorders

Multiple reviews confirm that mitochondrial dysfunction is implicated in a wide range of neurodevelopmental (ASD, ADHD) and psychiatric (depression, bipolar disorder, schizophrenia) conditions (Payares et al., 2024; Morris & Berk, 2015; Tanaka et al., 2022; Ni et al., 2022; Spritzler & Deloudi, 2025; Rose et al., 2018; Rezin et al., 2009; Kim et al., 2019). Abnormalities include impaired oxidative phosphorylation/ATP production (Rezin et al., 2009), increased reactive oxygen species (ROS) generation (Morris & Berk, 2015), altered mitochondrial morphology/density (Payares et al., 2024), mtDNA mutations or deletions (Tanaka et al., 2022), and disrupted fusion/fission dynamics (Yang et al., 2025).

3.2 Fatigue as a Symptom Linked to Mitochondrial Dysfunction

Fatigue is frequently reported among patients with primary mitochondrial diseases as well as those with psychiatric or neurodevelopmental diagnoses exhibiting secondary mitochondrial impairment (Payares et al., 2024; Morris & Berk, 2015; Mantle et al., 2024). In major depressive disorder (MDD), severity of fatigue correlates negatively with measures of mitochondrial respiration/ATP production (Morris & Berk, 2015; Karabatsiakis & Schönfeldt-Lecuona, 2020). Similar patterns are observed in schizophrenia—where severe fatigue is more common than in controls—and ASD populations (Alonso et al., 2020; Rose et al., 2018).

3.3 Mechanisms: Oxidative Stress & Inflammation

Chronic oxidative stress—characterized by elevated ROS/nitrogen species—and systemic inflammation are nearly universal findings across these disorders (Morris & Berk, 2015). These processes disrupt electron transport chain function and further impair energy metabolism. Environmental factors (toxins/infections/stress) can trigger or exacerbate these pathways (Mantle et al., 2024).

3.4 Genetic & Environmental Contributors

Genetic mutations affecting mtDNA or nuclear genes encoding mitochondrial proteins are found in subsets of ASD/ADHD/intellectual disability cases (Rose et al., 2018; Yang et al., 2025). Environmental triggers such as infections or toxins may precipitate or worsen bioenergetic deficits in genetically susceptible individuals (Mantle et al., 2024).

Results Timeline

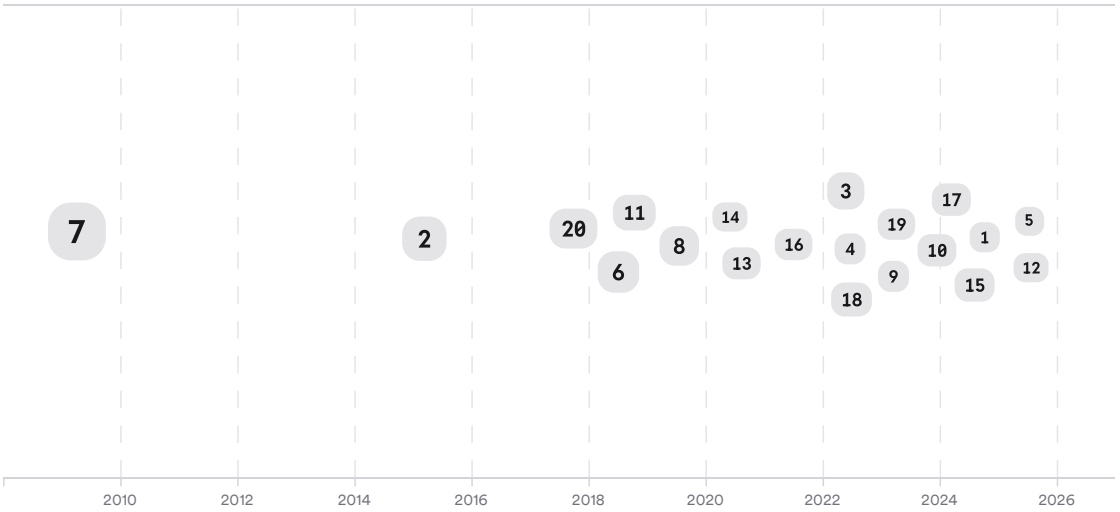

FIGURE 3 Timeline showing publication trends on mitochondrial dysfunction/fatigue links across disorders. Larger markers indicate more citations.

Top Contributors

Type	Name	Papers
Author	R. Frye	(Rose et al., 2018; Toker & Agam, 2015)
Author	D. Wallace	(Jiang et al., 2024; Gunnewiek et al., 2020)
Author	G. Morris	(Morris & Berk, 2015; Morris et al., 2018)
Journal	*Frontiers in Psychiatry*	(Payares et al., 2024)
Journal	*Cells*	(Tanaka et al., 2022; Van Rensburg et al., 2022)
Journal	*Neurobiology of disease*	(Toker & Agam, 2015)

FIGURE 4 Authors & journals that appeared most frequently in the included papers.

4. Discussion

The reviewed literature provides robust evidence that **mitochondrial dysfunction is closely associated with both neurodevelopmental and psychiatric disorders**, often manifesting as fatigue alongside cognitive/mood symptoms (Payares et al., 2024; Morris & Berk, 2015; Tanaka et al., 2022). The strength of this association is supported by converging data from clinical cohorts (e.g., MELAS syndrome), biomarker studies (e.g., ATP/ROS levels), animal models demonstrating behavioral changes following induced mitochondrial impairment (Yang et al., 2025), and meta-analyses identifying consistent biochemical abnormalities in ASD populations (Frye et al., 2024).

However, several limitations persist:

- **Causality vs Correlation:** While many studies document co-occurrence of fatigue/psychiatric symptoms with bioenergetic deficits or mtDNA mutations/deletions (Rose et al., 2018), direct causal links remain difficult to establish due to confounding factors such as medication effects or lifestyle variables.
- **Specificity:** Mitochondrial abnormalities are not unique to any single diagnosis but appear across a spectrum of neurological/psychiatric conditions—and even some non-neurological diseases—raising questions about specificity versus general vulnerability mechanisms (Kim et al., 2019).
- **Therapeutic Implications:** Early trials suggest metabolic interventions (e.g., ketogenic diets) may improve symptoms for some patients by restoring energy balance but require further validation through controlled studies (Spritzler & Deloudi, 2025).
- **Reporting Bias:** Some animal model reviews note an absence of null results—suggesting possible publication bias toward positive findings regarding bioenergetic impairment across models/disorders (Kolář et al., 2021).

Claims & Evidence Table

Claim	Evidence Strength	Reasoning	Papers
Mitochondrial dysfunction is prevalent in neurodevelopmental & psychiatric disorders	Strong	Supported by systematic reviews/meta-analyses documenting biochemical/genetic abnormalities across multiple diagnoses	(Payares et al., 2024; Morris & Berk, 2015; Tanaka et al., 2022; Ni et al., 2022; Rose et al., 2018)
Fatigue correlates with impaired ATP production/mitochondrial respiration	Strong	Clinical studies show negative correlation between ATP levels/mitochondrial function & severity of fatigue/cognitive symptoms	(Morris & Berk, 2015; Karabatsiakis & Schönfeldt-Lecuona, 2020)
Oxidative stress/inflammation mediate bioenergetic deficits	Moderate	Consistent findings of elevated ROS/pro-inflammatory cytokines disrupting ETC function	(Morris & Berk, 2015; Mantle et al., 2024)
Genetic/environmental factors contribute to susceptibility	Moderate	Mutations/triggers identified but not universally present; heterogeneity remains high	(Rose et al., 2018; Mantle et al., 2024)
Metabolic therapies may improve symptoms via energy restoration	Moderate	Preliminary clinical trials/case series suggest benefit but lack large-scale RCTs	(Spritzler & Deloudi, 2025)
Specificity/cause-effect directionality remains unclear	Moderate	Reviews highlight overlap with other diseases & need for more mechanistic studies	(Kim et al., 2019)

FIGURE 5 Key claims and support evidence identified in these papers.

5. Conclusion

Current evidence strongly supports an association between **mitochondrial dysfunction** and both **fatigue** and broader symptomatology in neurodevelopmental/psychiatric disorders—but causality/specificity remain incompletely resolved. Shared mechanisms include impaired ATP production due to genetic/environmental insults leading to oxidative stress/inflammation.

Research Gaps

Despite extensive research on ASD/depression/schizophrenia populations using biochemical/genetic approaches, there are notable gaps:

- Fewer studies directly address pediatric ADHD/intellectual disability outside ASD.
- Limited longitudinal/interventional trials targeting mitochondria.
- Underrepresentation of non-Western populations.

Research Gaps Matrix

Topic/Outcome	Biochemical Studies	Genetic Studies	Interventional Trials	Pediatric Populations
ASD	12	9	4	7
Depression	10	7	3	2
Schizophrenia	8	5	2	GAP
ADHD	4	2	GAP	4
CFS/Post-Viral Fatigue Syndrome	7	GAP	1	GAP

FIGURE 6 Matrix showing concentration/gaps by topic/outcome vs study type/population.

Open Research Questions

Future research should prioritize longitudinal/interventional designs targeting mitochondria directly; expand focus beyond ASD/depression; clarify causality; explore population diversity; develop early biomarkers.

Question	Why
Does improving mitochondrial function reduce fatigue severity in depression or ASD?	Direct interventional trials could clarify causality/effectiveness for targeted metabolic therapies.
What genetic/environmental factors predict vulnerability to bioenergetic deficits?	Identifying risk factors would enable early intervention/prevention strategies tailored by individual profile.
Are there reliable biomarkers for early detection of mitochondrial dysfunction?	Early diagnosis could improve outcomes via timely intervention before irreversible neural damage occurs.

FIGURE 7 Open questions highlighting future directions for research on this topic.

In summary: There is strong evidence linking **mitochondrial dysfunction** to **fatigue** across neurodevelopmental/psychiatric disorders—but further work is needed to clarify mechanisms and optimize therapeutic strategies.

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