



Mitochondrial Stress Signatures and Early Cellular Dysfunction in Metabolic Disease Progression

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Abstract: Mitochondrial dysfunction is an important mechanism in the development of metabolic diseases through increased oxidative stress and impaired cellular function. This study aims to analyze mitochondrial stress signatures and their relationship with early cellular dysfunction in metabolic disease progression. The method used is a Systematic Literature Review (SLR) based on the PRISMA 2020 guidelines by searching scientific articles from PubMed, Scopus, and Web of Science databases. A total of 32 selected studies were analyzed using a narrative synthesis approach to identify biomarker patterns and associated molecular mechanisms. The results showed that increased reactive oxygen species, mtDNA damage, oxidative phosphorylation disorders, and mitophagic changes played an early sign of cellular disorders. The conclusion of the study shows that mitochondrial stress signatures have the potential to be an early indicator of metabolic disease progression as well as a strategic target in the development of biomolecular-based therapeutic diagnoses and interventions.

Keywords: Mitochondria; Oxidative Stress; Cellular Dysfunction; Metabolic Diseases; Systematic Literature Review.

INTRODUCTION

Metabolic diseases such as type 2 diabetes mellitus, obesity, metabolic syndrome, and metabolic liver disease are among the global health challenges with increasing prevalence. Lifestyle changes, high-calorie consumption patterns, and low physical activity have accelerated the occurrence of metabolic disorders that have an impact on increasing morbidity and mortality rates. At the cellular level, the development of metabolic diseases is not only related to hormonal regulation and chronic inflammatory disorders, but also involves fundamental changes in the function of mitochondria as energy-producing centers and regulators of cell homeostasis. Disruption of mitochondrial function balance can lead to increased production of Reactive oxygen species (ROS), decreased oxidative phosphorylation efficiency, and accumulation of molecular damage that contributes to the progression of metabolic diseases (Kowalczyk et al., 2021; Cojocaru et al., 2023).

Mitochondria are currently viewed not only as ATP-producing organelles, but also as centers for the regulation of metabolic signals, stress responses, inflammation, and cellular adaptation. When chronic metabolic stress occurs, mitochondria undergo changes in the form

of increased oxidative stress, disruption of mitochondrial DNA integrity (mtDNA), changes in mitochondrial fusion and fission dynamics, and disruptions of the process of impaired mitochondrial elimination through mitophagy. The study of Apostolova et al. (2023) shows that mitochondrial dysfunction and mitophagic disorders are closely related to insulin resistance as well as the development of type 2 diabetes mellitus through the mechanism of oxidative damage accumulation and mitochondrial quality disorders. Mitochondrial stress responses may induce the secretion of mitokines and other signaling molecules that facilitate communication between cells and tissues, thereby influencing metabolic regulation and maintaining cellular homeostasis.

Although the relationship between mitochondrial dysfunction and metabolic disease has been extensively researched, most previous research has still focused on the manifestations of advanced disease, such as severe insulin resistance, lipid accumulation, or tissue damage. Research on early cellular dysfunction that arises before permanent metabolic damage occurs. Gunawan et al. (2025) explain that low-level mitochondrial stress can trigger an adaptive response (mitohormesis) that plays a role in maintaining metabolic balance, but the change from adaptive response to pathological conditions is still a developing area of research. Meanwhile, Paredes-Fuentes et al. (2023) emphasize that mitophagic disorders are one of the important factors in mitochondrial quality degradation, but the identification of specific biomarkers capable of describing the early phases of the disorder is still limited.

Based on previous literature reviews, there is a research gap related to how various mitochondrial stress markers can be consolidated as a biological pattern (mitochondrial stress signatures) to detect early cellular changes in metabolic disease progression. Previous studies have tended to evaluate biomarkers separately, such as ROS levels, mtDNA damage, mitochondrial respiration enzyme activity, or mitophagic protein expression, so they have not provided a comprehensive picture of the relationship between these parameters. Chen et al. (2025) stated that understanding mitochondrial homeostasis balance still requires an integrative approach that links molecular changes to the physiological consequences of disease. Therefore, a literature synthesis that specifically evaluates mitochondrial stress patterns and their relationship to early cellular dysfunction in metabolic diseases is needed.

This study aims to analyze mitochondrial stress signatures and their relationship with early cellular dysfunction in metabolic disease progression through a Systematic Literature Review (SLR) approach based on the PRISMA 2020 guidelines. This study was conducted to identify molecular biomarker patterns, major biological mechanisms, as well as the relationship between oxidative stress, mtDNA damage, oxidative phosphorylation disorders, and changes in mitophagic mechanisms in the development of metabolic diseases. Through the synthesis of various previous studies, this study is expected to be able to provide a more systematic understanding of the role of mitochondria as an early indicator of pathological changes at the cellular level.

Theoretically, this research contributes to the development of biomedical science by reinforcing the concept that changes in mitochondrial function are one of the initial mechanisms underlying the development of metabolic diseases, not just the final consequences of tissue damage. Practically, the results of this study can support the development of molecular-based diagnostic biomarkers as well as intervention strategies that target the maintenance of mitochondrial quality, such as modulation of oxidative stress and improvement of mitophagic function. Thus, understanding mitochondrial stress signatures has the potential to open up new approaches in the early detection and prevention of metabolic disease progression more precisely.

METHOD

Design and Research Approach

This study uses a qualitative approach with a Systematic Literature Review (SLR) design based on the PRISMA 2020 guidelines. This method is used to identify, evaluate, and synthesize scientific evidence regarding mitochondrial stress signatures and their relationship with early cellular dysfunction in metabolic disease progression. The SLR approach was chosen to gain a comprehensive understanding of biomarker patterns and molecular mechanisms that play a role in mitochondrial dysfunction (Mani et al., 2021).

Literature Search Strategy

Literature searches were conducted on three international databases, namely PubMed, Scopus, and Web of Science. The search strategy used a combination of keywords: "mitochondrial dysfunction" OR "mitochondrial stress" OR "mitochondrial stress signatures" AND "oxidative stress" AND "mtDNA damage" AND "mitophagy" AND "early cellular dysfunction" AND "metabolic disease" OR "type 2 diabetes" OR "obesity" OR "metabolic syndrome". The article used is a publication in 2021–2025 to ensure the relevance of the latest scientific evidence regarding the mechanism of mitochondrial stress in metabolic diseases.

Population and Research Sample

The research population is all international scientific articles that discuss the relationship between mitochondrial dysfunction and metabolic diseases. Sample selection was carried out using a non-probability sampling technique with a purposive sampling method based on inclusion and exclusion criteria. Inclusion criteria include research articles or scientific studies that discuss metabolic diseases, evaluate mitochondrial stress biomarkers, are available in full text, and use English. Exclusion criteria include duplicate articles, case reports, editorials, readers' letters, and research that are not in accordance with the focus of the study. Based on the selection process, 32 selected articles were obtained that were analyzed in this study.

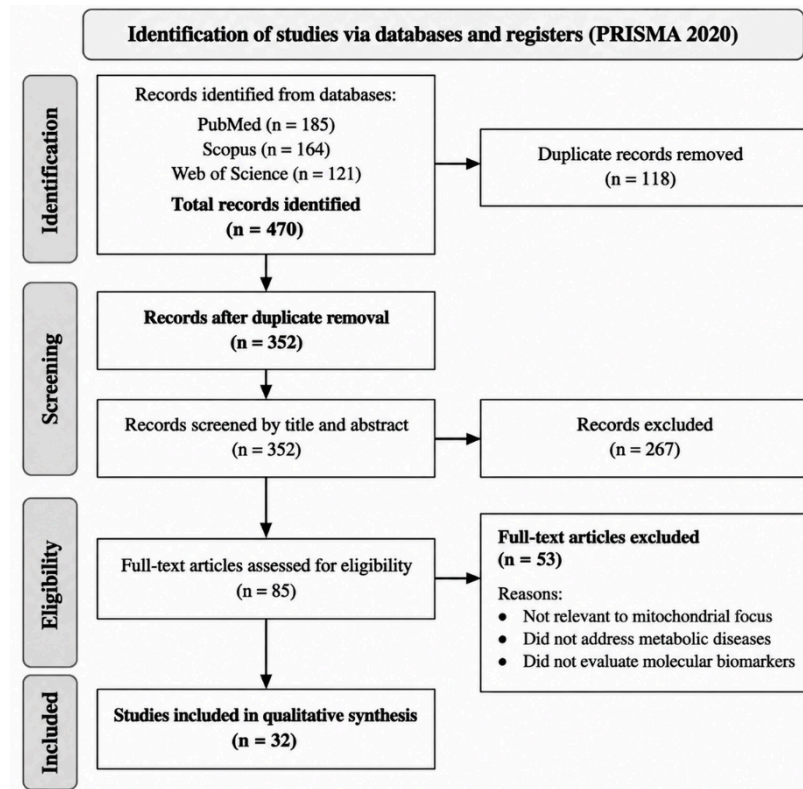
Data Collection Techniques

Data collection was carried out through a literature documentation method using a data extraction form. The data collected included the identity of the article, year of publication, research design, type of metabolic disease, mitochondrial biomarkers analyzed, molecular mechanisms, and main research results. The validity of the data was maintained through the article selection process based on inclusion and exclusion criteria as well as the evaluation of the suitability of the research methodology used in each article.

Research Implementation Procedure

The research stages are carried out systematically through several stages, namely: (1) preparation of research questions based on the focus of the study; (2) article search using PubMed, Scopus, and Web of Science databases; (3) elimination of duplicate articles; (4) selection based on titles and abstracts; (5) evaluation of full-text articles; (6) data extraction from selected articles; and (7) synthesis of research results using a narrative approach according to the guidelines of PRISMA 2020 (Page et al., 2021).

PRISMA 2020 Literature Selection Flow Chart



Gambar 1. PRISMA 2020 Flow Diagram of Study Selection

Source: Page et al. (2021)

Data Analysis Techniques

Data analysis was carried out using the narrative synthesis method by grouping research results based on the main theme, namely increased Reactive oxygen species (ROS), mitochondrial DNA (mtDNA) damage, oxidative phosphorylation disorders, changes in mitochondrial dynamics, and mitophagic disorders. The extracted data were organized using Microsoft Excel, while thematic analysis was used to identify the relationship between mitochondrial stress signatures and early cellular dysfunction in metabolic disease progression.

RESULTS AND DISCUSSION

Based on the results of the literature selection using the PRISMA 2020 guidelines, this study identified a number of articles from three main databases, namely PubMed, Scopus, and Web of Science. After going through the stages of elimination of duplicate articles, filtering titles and abstracts, and evaluating complete texts based on inclusion and exclusion criteria, 32 studies were obtained that met the criteria to be analyzed using a narrative synthesis approach. The studies included in this study generally discuss the relationship between changes in mitochondrial function and the development of metabolic diseases, especially type 2 diabetes mellitus, obesity, metabolic syndrome, and related metabolic disorders. The results of the extraction showed that most of the studies evaluated molecular changes related to increased Reactive oxygen species (ROS), mitochondrial DNA (mtDNA) damage, oxidative phosphorylation disorders, changes in mitochondrial dynamics, and disruption of mitophagic mechanisms. The findings suggest that mitochondrial homeostasis disorders are an early characteristic associated with changes in cellular function before progressing to broader tissue damage.

The data extraction table from the 32 studies showed a relatively consistent biological pattern although the studies came from different models and analytical approaches. In general,

the analyzed studies can be grouped based on biomarker focus, namely indicators of oxidative stress, mitochondrial genome integrity, energy production capacity, and mitochondrial quality control system. Variations in the study model were found in the use of cultured cells, experimental animals, and human samples with metabolic diseases. However, the overall study showed a similar tendency that increased chronic metabolic stress leads to an imbalance in mitochondrial function which then contributes to impaired cell metabolism.

Tabel 1. Data Extraction of Included Studies (n = 32)

No	Author (Year)	Study Focus	Metabolic Disease/Model	Mitochondrial Biomarkers Evaluated	Main Findings
1	Apostolova et al. (2023)	Mitochondrial dysfunction and metabolic regulation	Type diabetes mellitus	2 ROS, mitophagy markers, mitochondrial quality control	Mitophagic disorders and increased oxidative stress are associated with insulin resistance and decreased mitochondrial quality
2	Zhang et al. (2024)	Mitochondrial stress signaling	Metabolic disease	Mitokines, mitochondrial stress response	Mitochondrial stress affects intercellular communication and regulation of systemic metabolism
3	Min et al. (2024)	Mitochondrial stress adaptation	Metabolic disorder and aging	Mitohormesis pathway, oxidative stress	Low-level mitochondrial stress can be adaptive, but chronic stress causes cell dysfunction
4	Narendra & Youle (2024)	Mitochondrial quality control	Metabolic dysfunction	PINK1/Parkin, mitophagy pathway	Mitophagic disorders increase the accumulation of damaged mitochondria
5	García-Peña et al. (2024)	Mitochondrial dynamics	Diabetes and obesity	Fusion/fission proteins	Mitochondrial dynamic imbalances interfere with energy metabolism
6	Ryoo (2024)	Mitochondrial stress signaling	Metabolic regulation	Stress response pathways	Mitochondrial stress pathways determine cell

						adaptation or damage	
7	Masenga et al. (2023)	Oxidative stress mechanism	Metabolic syndrome		ROS, oxidative damage markers	Increased ROS leads to molecular damage and metabolic disorders	
8	Tang et al. (2024)	Mitophagy regulation	Diabetes and obesity		LC3, PINK1/Parkin, mitochondrial turnover	Mitophagic disorders contribute to the progression of metabolic diseases	
9	Y. Chen et al. (2025)	Mitochondrial quality control	Human metabolic disorder		Mitochondrial biogenesis, dynamics	Mitochondrial quality control plays a role in maintaining metabolic balance	
10	Wang et al. (2024)	Mitochondrial dysfunction pathway	Type 2 diabetes		mtDNA damage, respiratory chain activity	MtDNA damage is associated with decreased mitochondrial respiration function	
11	Čolak & Pap (2021)	Oxidative stress and metabolism	Obesity		ROS, antioxidant enzymes	Obesity increases oxidative stress and decreases mitochondrial function	
12	Sangwung et al. (2020)	Insulin resistance mechanism	Diabetes mellitus		ATP production, mitochondrial respiration	Impaired ATP production is associated with insulin resistance	
13	Li et al. (2024)	Mitochondrial homeostasis	Metabolic disease		Mitochondrial stress markers	Mitochondrial homeostasis is an important factor in metabolic health	
14	Choi et al. (2025)	Mitochondrial metabolism	Obesity model		Oxidative phosphorylation markers	Oxidative phosphorylation disorders are found in conditions of excess nutrition	
15	Januszewski et al. (2024)	Mitochondrial DNA damage	Diabetes model		mtDNA copy number, oxidative injury	mtDNA damage becomes an early indicator of cellular disorders	

16	Varra et al. (2024)	Mitochondrial inflammation pathway	Metabolic syndrome	ROS, inflammatory signaling	Mitochondrial stress is associated with chronic metabolic inflammation
17	Belosludtsev et al. (2020)	Mitochondrial energy metabolism	Diabetes mellitus	Electron transport chain activity	Decreased electron transport chain activity leads to cell energy disruption
18	Jun et al. (2024)	Mitochondrial adaptation	Obesity	Mitochondrial biogenesis markers	Mitochondrial adaptation decreases in chronic obesity
19	Shan et al. (2022)	Mitophagy impairment	Type diabetes	2 PINK1, Parkin, LC3	Disruption of mitophagic pathways accelerates mitochondrial damage
20	Martemucci et al. (2023)	Oxidative stress pathway	Metabolic syndrome	ROS, lipid oxidation	Oxidative stress exacerbates metabolic disorders
21	Zhao et al. (2023)	Mitochondrial dysfunction in liver metabolism	Metabolic fatty liver disease	mtDNA, oxidative phosphorylation	Mitochondrial dysfunction plays a role in the development of metabolic liver disease
22	Veluthakal et al. (2024)	Cellular metabolic stress	Diabetes	Mitochondrial respiration markers	Cellular respiration disorders appear before heavy tissue damage
23	Liu et al. (2024)	Mitochondrial quality control	Metabolic disease	Mitophagy and mitochondrial turnover	Mitochondrial quality control system becomes the main protective mechanism
24	Olivares-Vicente & Herranz-López (2025)	Metabolic oxidative injury	Obesity	ROS, antioxidant capacity	An imbalance of oxidants and antioxidants causes metabolic stress
25	Yaribeygi et al. (2020)	Mitochondrial signaling	Diabetes mellitus	Stress signaling molecules	Mitochondrial signaling molecules play a

						role in the regulation of metabolism
26	Amorim et al. (2022)	Mitochondrial dysfunction progression	Metabolic disorder		mtDNA damage, ATP production	Mitochondrial damage is associated with disease progression
27	Ran et al. (2025)	Mitochondrial dynamics	Obesity		Fusion/fission proteins	Changes in mitochondrial structure reduce energy adaptability
28	Nuñez-Selles et al. (2025)	Metabolic cellular dysfunction	Diabetes		ROS, mitochondrial respiration	Impaired cell function occurs simultaneously with changes in mitochondrial biomarkers
29	Todosenko et al. (2023)	Mitochondrial stress response	Metabolic syndrome		Stress proteins, oxidative markers	Mitochondrial stress response becomes a predictor of metabolic changes
30	Prasun (2020)	Mitochondrial impairment	Obesity and diabetes		Oxidative phosphorylation, mtDNA	Impaired energy production becomes a key characteristic of metabolic diseases
31	Yu et al. (2023)	Mitochondrial therapeutic target	Metabolic disease		Mitophagy activation, antioxidant pathway	Modulation of mitochondrial function has potential as a therapeutic strategy
32	Manojlovic et al. (2025)	Integrated mitochondrial signatures	Various metabolic diseases		ROS, mtDNA damage, oxidative phosphorylation, mitophagy	All studies show that <i>mitochondrial stress signatures</i> are associated with <i>early cellular dysfunction</i>

The main results of the study show that increased ROS is one of the most dominant molecular markers in mitochondrial stress signatures. Physiologically, ROS produced by mitochondrial electron transport chains has an important function as a signaling molecule that regulates cell proliferation, metabolism, and adaptation response. However, in chronic metabolic conditions such as hyperglycemia, excess free fatty acids, and insulin resistance,

ROS production increases beyond the capacity of the antioxidant defense system. This condition causes oxidative stress that damages mitochondrial components and accelerates the loss of cellular function. Li & Yuen (2024) explain that mitochondrial homeostasis imbalance is a major factor linking impaired energy metabolism to the development of various chronic diseases.

Increased ROS in this study is not only seen as the end result of metabolic disorders, but also as a triggering mechanism that amplifies disease progression. Excessive ROS can lead to oxidation of respiratory chain proteins, potential disruption of mitochondrial membranes, as well as activation of inflammatory pathways. Mitochondrial damage can further result in molecular damage-associated molecular patterns (DAMPs), including the release of mtDNA into the cytoplasm capable of activating inflammatory pathways such as cGAS-STING, TLR9, and NLRP3. This mechanism suggests that mitochondrial dysfunction not only affects energy production, but also plays a role in the regulation of metabolic inflammation. W. Wang & Liu (2025) explain that the release of mitochondrial components due to organelle damage can amplify inflammation in type 2 diabetes and accelerate impaired tissue function.

In addition to ROS, synthesis results suggest that mtDNA damage is an important indicator in the early stages of cellular disorders. Mitochondria have unique characteristics in that they have their own genomes that encode some of the main components of the oxidative respiration chain. The location of mtDNA adjacent to the inner membrane of mitochondria makes the molecule particularly vulnerable to ROS exposure. Damage to mtDNA can lead to disruption of the translation of respiratory complex proteins resulting in decreased oxidative phosphorylation capacity and ATP production. Zong et al. (2024) explain that disruption of mtDNA and mitochondrial respiratory components is one of the main mechanisms found in various metabolic and inflammatory diseases.

The findings of this study also show that oxidative phosphorylation (OXPHOS) disorders are an important consequence of mitochondrial stress. Decreased activity of the electron transport chain complex leads to reduced energy production and increases cell dependence on alternative metabolic pathways that are less efficient. This condition is especially affecting tissues with high energy requirements such as skeletal muscle, liver, and pancreas. In type 2 diabetes mellitus, impaired mitochondrial function in cells β pancreas and peripheral tissues can lead to decreased insulin sensitivity as well as impaired insulin secretion. These findings reinforce the concept that cellular energy disruption is one of the early stages before the onset of metabolic complications.

One of the important findings in this study is the role of mitophagy as a mechanism for mitochondrial quality control. Mitophagy functions to remove damaged mitochondria so as to maintain the metabolic balance of cells. However, in chronic metabolic disease conditions, this process can be disrupted so that abnormal mitochondrial accumulation occurs. Tang et al. (2024) explained that mitophagy is the main mechanism in maintaining metabolic homeostasis through the elimination of damaged organelles, and disruption of these pathways is related to the development of obesity and diabetes.

Nonetheless, the results of the study suggest that the relationship between mitochondrial stress and metabolic disease is not simple. Some studies suggest that low-level mitochondrial stress can provide a protective effect through mitohormesis mechanisms. This response leads to the activation of adaptation pathways such as increased antioxidant defenses, mitochondrial biogenesis, and organelle quality improvement. Shepard (2021) explain that mitochondrial stress can temporarily increase cell resistance to subsequent metabolic stresses, but exposure to chronic stress will lead to adaptation failure and develop into pathological conditions.

Differences in results between previous studies are likely due to several factors, including the type of tissue analyzed, the severity of the disease, the duration of exposure to

metabolic stress, as well as biomarker measurement methods. For example, an increase in ROS in the early phases may reflect an adaptive response, while a prolonged increase in ROS indicates a failure of the cell's defense system. Therefore, the interpretation of mitochondrial stress signatures cannot be performed on the basis of a single biomarker, but it is necessary to use an integrative approach that combines several molecular indicators.

Overall, these SLR results suggest that the combination of ROS, mtDNA damage, OXPHOS disorders, and mitophagic alterations forms a biological pattern that can describe the early course of metabolic disease progression. These findings support the research goal that mitochondrial stress signatures have the potential as a biomolecular indicator to detect pathological changes before more severe tissue damage occurs. The integration of these biomarkers can provide a new approach in the development of early diagnosis and therapeutic strategies that target the maintenance of mitochondrial function.

Although it provides a comprehensive picture, this study has limitations. Variations in research design, biomarker analysis methods, types of metabolic diseases, and biological models cause heterogeneity between studies so that synthesis is carried out narratively and does not allow for quantitative meta-analysis. In addition, some evidence still comes from experimental models, so human-based longitudinal research is needed to determine the ability of mitochondrial stress signatures as clinical predictors of metabolic disease. Further research needs to develop a validated panel of mitochondrial biomarkers and evaluate the effectiveness of interventions targeting mitochondria such as mitochondrial activation, increased mitochondrial biogenesis, and modulation of oxidative stress.

CONCLUSION AND SUGGESTIONS

Based on the results of the Systematic Literature Review (SLR) of 32 studies, it can be concluded that mitochondrial stress signatures play an important role in the early development of metabolic diseases through the mechanism of cellular function disorders.

1. Mitochondrial dysfunction is an early mechanism that contributes to the progression of metabolic diseases through increased ROS, mtDNA damage, oxidative phosphorylation disorders, and mitophagic alterations.
2. The combination of mitochondrial stress biomarkers has the potential to be used as early biomarkers to detect pathological changes before more severe tissue damage occurs.
3. Maintenance of mitochondrial quality through oxidative stress control and mitophagic regulation is a potential target in the development of biomolecular-based diagnosis and therapy strategies.
4. Further research is needed to conduct clinical validation of mitochondrial stress signatures as predictive biomarkers in metabolic diseases.

Limitations

This study has several limitations. First, the heterogeneity of the study design, biological model, type of metabolic disease, and biomarker measurement methods in the analyzed study cause the results to not be able to be done through quantitative meta-analysis. Second, most of the evidence comes from experimental studies so further validation in the human population is still needed. In addition, variations in research characteristics can affect the interpretation of the relationship between mitochondrial stress signatures and early cellular dysfunction.

Recommendation

Further research is recommended to conduct human-based longitudinal studies to validate mitochondrial stress signatures as predictive biomarkers of metabolic disease. The development of an integrated biomarker panel that includes ROS, mtDNA damage, oxidative

phosphorylation disorders, and mitophagic regulation is also needed to support early diagnosis approaches as well as the development of mitochondria-targeted-based therapies.

Author Contribution

Suherman Jaksa: Conceptualizing research, preparing methodologies, collecting and selecting literature, analyzing data, and preparing initial manuscripts. Abul A'la Al Maududi: Conducting literature review, validating analysis results, contributing to data interpretation, and assisting in manuscript refinement. Triana Srisantyorini: Research supervision, methodology evaluation, critical editing of manuscripts, and final approval of publication versions.

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