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Mitochondria in the Crossfire: How Early-Life Interventions Shape Lifelong Health

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Abstract

This review examines early-life interventions in mice and their lasting impact on development, mitochondrial function, lifespan, healthspan, and aging, with potential implications for human health. Mitochondria, as central regulators of cellular energy, metabolism, and stress responses, are increasingly recognized as critical mediators of how early-life experiences shape long-term physiological outcomes. We first review studies employing diverse early-life interventions, including dietary modifications, hormonal treatments, and pharmacological interventions, and also explore their effects on aging, longevity, and mitochondrial integrity. These interventions can modify mitochondrial activity, bioenergetics, morphology, and oxidative stress resilience, thereby influencing organismal health across the lifespan. The review further highlights critical factors that modulate the efficacy of early-life interventions, such as timing, duration, sex, genetic background, and environmental context, all of which can dictate mitochondrial responses and downstream physiological consequences. By integrating insights from mitochondrial biology, developmental programming, and aging research, this review underscores the promise of early-life interventions not only for enhancing lifespan and healthspan in model organisms but also for informing interventions that may mitigate the long-term consequences of early-life adversity in humans.

Keywords: Early life interventions, Sexual dimorphism, Mitochondrial function, Aging

Introduction

Accumulating evidence shows that mitochondria play a critical role in cellular energy production and overall physiological regulation. These organelles are essential for generating the energy needed for growth, development, and cellular maintenance, and their function can be influenced by early-life conditions. Early-life interventions, such as nutritional support, environmental enrichment, or pharmacological treatments, have the potential to shape mitochondrial function, promoting optimal cellular metabolism and long-term health outcomes. Understanding the impact of these interventions on mitochondria during critical periods of development could reveal important strategies for enhancing health and resilience across the lifespan.

Stress and Mitochondrial Function

Mitochondrial dysfunction can lead to a range of health problems, including aging, and many other age-related disorders such as neurodegenerative diseases, cardiovascular issues, and metabolic disorders [1, 2]. Some studies have investigated the potential correlation between stressful events during early life

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Adlimoghaddam A., Fortune J Health Sci 2026
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and a decline in mitochondrial function [3-5]. For example, individuals who experienced maltreatment during childhood or suffered the loss of a parent before the age of 18 tend to have a lower number of copies of mitochondrial DNA (mtDNA) compared to those who did not experience such adverse circumstances [6]. Another study shows that even after accounting for factors such as stress, depressive symptoms, and anxiety, the association between childhood adverse events and the quantity of mtDNA copies remained significant [7]. Another study demonstrated that healthy middle-aged individuals when subjected to a brief psychological challenge on two distinct occasions, demonstrated a 2-3-fold rise in their mtDNA but no alteration observed in nuclear DNA [8]. Since mtDNA contains genetic instructions necessary for the synthesis of proteins that are crucial in cellular respiration and other energy-producing functions. Therefore, adverse experiences in early or middle life may impact mitochondrial function, potentially affecting overall energy metabolism and cellular processes. Additionally, a recent study by Duchowny et al. shows that individuals who had experienced adverse life events in childhood showed compromised ATP production and mitochondrial respiration in their muscles [9]. Collectively, these results provide supporting evidence indicating that stressful experiences in early life influence mitochondrial function.

Another study reported that early life stress increases the susceptibility to develop metabolic disorders [10]. They measured the effects of metabolic parameters and multiple aspects of mitochondrial biology (i.e., mitochondrial electron transport chain (ETC) complex activity, mtDNA copy number, and expression of genes relevant to mitochondrial function) in muscle, hypothalamus, and hippocampus at P9 and late adulthood (10–12 months of age). Their research revealed that early-life stress affects glucose levels at P9 but not in late adulthood. Specifically, at P9, early life stress affects both muscle and hypothalamic ETC activity. In the hippocampus, it alters the expression of genes related to mitochondrial fission. In adulthood, alterations in ETC complex activity occur in the hypothalamus, while in muscle and hippocampus, early life stress affects the expression of genes linked to mitophagy and mitochondrial fission, respectively. This study reported that early life stress influences both peripheral and central mitochondrial biology throughout the lifespan of mice [10]. Overall, studies employing metabolomic, proteomic, and transcriptomic approaches have suggested that stressful experiences can impact mitochondrial components in rodents [11].

Diet, Sex, and Mitochondrial Function

A body of experiments reported that a low-protein and caloric-restriction diet can modulate mitochondrial function *via* interference with dynamics (i.e., fusion and fission), respiration, and related oxidative stress. It has been shown that maternal diet is a critical factor that determines the trajectory of growth and early development of the offspring [12]. Numerous experimental and epidemiological studies suggest a correlation between a maternal low-protein diet and a heightened risk of metabolic diseases later in adulthood [13-16]. It has been shown that animals exposed to protein restriction during fetal and early postnatal stages showed decreased levels of mtDNA, particularly in their skeletal muscles, along with downregulation of genes encoded by mitochondria [17]. This suggests that inadequate protein intake during critical developmental periods can negatively affect the integrity or abundance of mtDNA within skeletal muscle cells [18]. This finding highlights the impact of maternal low-protein diet during pregnancy on the expression of mitochondrial genes in offspring skeletal muscles, emphasizing the importance of maternal nutrition for proper mitochondrial function and muscle development in offspring. Additionally, research indicates that offspring born to mothers on a low-protein diet exhibit reduced birth weight and develop exacerbated glucose intolerance and insulin resistance as they age compared to control groups. Notably, sex-based variations were observed among offspring exposed to the gestational low-protein diet. Specifically, females exhibited diminished glucose homeostasis compared to males. Moreover, a previous study revealed that a low-protein diet during gestation induces glucose intolerance and insulin resistance in adult offspring [19]. Notably, sex-based differences were found in molecular signaling pathways related to insulin-induced glucose transport function [19]. Additionally, it resulted in notable dysregulation of key genes related to mitochondrial biodynamics (fission and fusion) and oxidative phosphorylation (OXPHOS) [1-7] .

Another study found that the skeletal muscles of newborn mice exposed to a low-protein diet revealed a significant decrease in the expression of mitochondrial genes associated with OXPHOS [23]. Another research reported that a prenatal low-protein diet followed by a postnatal high-fat diet decreased skeletal muscle mitochondrial oxidation [17]. Furthermore, low protein diet helps alleviate uremic symptoms and delay the advancement of renal failure in patients with chronic kidney disease [24]. Preclinical studies show that a low-protein diet, especially a very-low-protein diet, can ameliorate oxidative stress, inflammation, fibrosis, and apoptosis by decreasing the accumulation of abnormal mitochondria through decreased activity of the mammalian target of rapamycin complex 1 (mTORC1) in animal models of type 2 diabetes and obesity [25, 26]. Consequently, based on animal studies, implementing a very low-protein diet could potentially yield more beneficial outcomes for advanced diabetic kidney disease.

Adlimoghaddam A., Fortune J Health Sci 2026
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Another study demonstrated that mice consuming a diet low in protein but high in carbohydrates (5% protein, 75% carbohydrate, energy 13 KJ/g food) exhibited tendencies towards increased food consumption and body fat accumulation. However, they displayed indicators of favorable health outcomes, including low levels of HOMA (a measure of insulin resistance), blood pressure, and LDL cholesterol, aligning with the notion of "healthy obesity." Furthermore, these mice exhibited enhanced mitochondrial function [27].

Calorie restriction has been proven to increase both the average and maximum lifespans of several lower species, including rats and mice [28]. In addition to slowing down the aging process, caloric restriction also diminishes the production of mitochondrial reactive oxygen species (MitROS) and reduces oxidative stress in the postmitotic tissues of rats [8]. Another study found that during a 6–7week period on a 40% protein-restricted diet without reducing calorie intake, there is a noticeable decrease in MitROS production, particularly at mitochondrial complex I. This dietary regimen also reduces the rate of mtDNA damage in rat liver mitochondria [29]. The same research team also discovered that 6–7 weeks of methionine restriction, without reducing calorie intake, leads to a decrease in MitROS generation, mtDNA, and specific markers indicating protein oxidative modification in mitochondria of rat liver and heart tissues [29]. Various lines of evidence also propose that methionine may be involved in aging and longevity [30, 31, 32]. These findings indicate that reduction in methionine intake during caloric and protein restriction might lead to less MitROS production and damage to mtDNA, possibly contributing to about half of the longer lifespan seen with caloric restriction [33]. The elevated methionine levels that are present in the typical Western diet could potentially be a factor contributing to the onset or progression of cardiovascular disease in humans. Similar adverse effects of methionine supplementation have been observed in rats fed with 2% methionine and 50% protein diets for a duration of two years [34]. Studies have shown that high-protein diets (consisting of 50% protein for one week), especially those rich in casein, lead to increased levels of plasma protein carbonyls and are associated with elevated cholesterol levels and atherosclerosis in rats [35]. Notably, casein contains a higher methionine content than soybean protein, and protein oxidation appears to play a role in the development of atherosclerosis and other degenerative diseases [36].

A human study by Civitarese et al. reported that a calorie-restricted diet stimulates the production of more mitochondria, particularly in skeletal muscle [37]. Additionally, mice subjected to a 30% reduction in calorie intake for three months revealed significant increases in mitochondrial numbers across various tissues, including the brain, liver, heart, skeletal muscle, and white adipose tissue (WAT). This rise in mitochondrial content was confirmed by elevated levels of mtDNA, increased expression of mitochondrial complex IV, increased ATP, and oxygen consumption in several tissues, particularly WAT. Moreover, there was an increase in the expression of transcription factors involved in regulating mitochondrial biogenesis, such as peroxisome proliferator-activated receptor–γ coactivator 1α (PGC-1α), mitochondrial transcription factor A (Tfam), and nuclear respiratory factor–1 (NRF-1) [38]. These findings collectively suggest that restricting calorie intake can prompt the production of more mitochondria, essential for cellular energy generation, across diverse body tissues. In addition, reducing calorie intake in mice for two weeks at 10%, followed by two weeks at 35%, boosts the levels of the mitochondrial biogenesis-associated protein (PGC-1α) in both normal and db/db mice aged 12–14 weeks [39]. Another study conducted on rat hearts revealed that caloric restriction, both in short periods (6 weeks) and long periods (1 year), led to a decrease in mitochondrial free radical generation at the level of the respiratory chain [40]. A separate study involving 60-day-old Wistar rats found that a combined regimen of intermittent fasting and high-intensity intermittent exercise over 8 weeks resulted in an increased O2 flux rate associated with ATP production [41]. A long-term (12-month) 40% calorie-restricted diet reduced the rate of mitochondrial H2O2 generation by 45% and decreased oxidative damage to mtDNA by 30% in aged (12-month-old) Wistar rats [42]. Likewise, a short-term (3-week) intervention decreased the rate of mitochondrial H2O2 generation in 6-week-old Swiss mice [43].

Also, a 40% calorie-restricted diet for one month in 6 weeks and 14-week-old C57BL/6 mice resulted in reductions in the capacity for MitoROS production with no significant impact observed on the enzymatic activity of the electron transport chain [44, 45].

Long-term caloric restriction is recognized for its ability to slow down the aging process in numerous organisms, including mammals. A study has shown that lifelong implementation of a 40% caloric restriction in B6D2F1 mice aged 30-31 months diminishes oxidative stress, thus preventing arterial aging and the associated age-related increase in blood pressure. [46]. Furthermore, a 30% caloric restriction reverses vascular endothelial dysfunction in 28–30-month-old B6D2F1 mice by augmenting nitric oxide levels and diminishing oxidative stress. [47]. On the other hand, a severe 60% reduction in calorie intake over two weeks resulted in endothelial dysfunction in mesenteric arteries, as well as ischemia-reperfusion-induced arrhythmias and cardiac pathology in male Fischer rats [48]. In addition, a 40% caloric restriction over 6 months delays cardiac aging in 24-month-old Sprague-Dawley rats, reducing oxidative damage and enhancing mitochondrial function [49]. Additionally,

Adlimoghaddam A., Fortune J Health Sci 2026
DOI:10.26502/fjhs.410

diabetic cardiomyopathy was regulated in 12–14-week-old wild-type or db/db mice through a regimen of 10% caloric restriction for 2 weeks, followed by 35% caloric restriction for another 2 weeks. This regulation was characterized by the attenuation of angiotensin 2-induced hypertension in diabetic mice, improvement in lipid profiles, and reduction in cardiac fibrosis, oxidative stress, and inflammation [39]. Research reveals that subjecting 24-month-old Sprague-Dawley rats to a 40% caloric restriction for six months effectively delays cardiac aging [49]. This intervention achieves this by reducing oxidative damage and enhancing mitochondrial function. Alternate-day fasting was initiated in a study with a rodent model of 2-month-old Sprague Dawley rats, continuing until they reached the ages of 6, 12, or 24 months. This fasting regimen effectively shielded the rat heart from age-induced inflammation and fibrosis by inhibiting mitochondrial oxidative damage [50].

A different study aimed to evaluate the effect of calorie restriction on mitochondrial respiration in the aging brain. It found that calorie restriction could decrease the age-related stiffening of cell membranes and restrict the production of harmful oxygen radicals when mitochondria were metabolically stimulated with succinate [51]. Another study revealed that calorie restriction (initiated with a 20% reduction for 2 weeks, followed by a 40% caloric restriction for 13 months) notably affects mitochondrial biodynamics (fusion) and mitochondrial morphology in the muscular tissue of Sprague–Dawley rats. This intervention resulted in reduced age-related fragmentation of mitochondria and an elevation in the muscle expression of mitochondrial fusion protein MFN2 [52].

Sex-dependent differences have been reported in response to early-life interventions. For example, when UM-HET3 mice received rapamycin supplementation during the first 45 days after birth, a significant increase in lifespan was observed in males, whereas females showed no measurable benefit [53]. Furthermore, sex-specific patterns have been stated in studies involving hormonal manipulation. In Ames dwarf mice, administering GH from two to eight weeks after birth shortened lifespan in both males and females. In contrast, when GH treatment was given from one to seven weeks after birth, only males experienced a significant reduction in lifespan, while females remained unaffected. These findings suggest that the effects of early-life interventions are shaped not only by the timing of exposure but also by how treatment timing interacts with sex. Additionally, it has been shown that dietary restriction in UM-HET3 mice, increasing litter size from eight to twelve pups per dam, significantly extended lifespan in females, whereas males did not exhibit a similar longevity benefit.

Notably, shifts in the timing of female reproductive development appear to be linked to longevity. Females that reach sexual maturity at an earlier age have been reported to produce smaller litters and higher mortality within the first six months of life [54]. Also, sensory exposure during early life seems to affect female lifespan. It has also been reported that contact with odor cues from adult females significantly increases longevity in female mice [55]. However, males do not exhibit changes in lifespan when exposed to odor cues from either adult females or males. Taken together, these observations indicate that the connection between reproductive maturation and lifespan is evident in females but not in males, pointing toward sex-specific biological pathways that regulate aging.

Eagleson et al., 2025 [56] reported that disruption of maternal care during the first postnatal week produces lasting, sex-specific changes in mitochondrial function, as demonstrated using the limited-bedding and nesting (LBN) model of early-life adversity (ELA). ELA increased complex I activity as well as mitochondrial oxidative phosphorylation in juveniles reduced both measures in adulthood, showing sex-based differences in adult outcomes. Notably, early-life mitochondrial dysfunction and female-specific behavioral deficits were reversed by post-weaning treatment with the mitochondrial-targeted antioxidant (MitoQ). These findings suggest that early-life treatment can restore mitochondrial health in a sex-dependent manner, underscoring the role of mitochondria in shaping lasting susceptibility and adaptive capacity.

Sex differences in lifespan can reflect underlying disease vulnerabilities, as seen in Non-obese diabetic (NOD) mice a widely used model for diabetes, which show sex-specific susceptibility to the disease. Female NOD mice are significantly more prone to autoimmune diabetes compared to males [57]. It has been reported that androgen treatment can reduce disease risk in female NOD mice, highlighting a connection between sex-specific disease susceptibility and lifespan regulation [58]. This underscores the importance of considering sex as a key variable in early-life intervention studies with NOD mice, as ignoring these differences could lead to biased or misleading results. It has been reported that androgen treatment can lessen this risk in females [115]. This suggests a potential link between sex-specific susceptibility to certain diseases and lifespan regulation.

GH and Mitochondrial Function

Growth hormone (GH) may increase the demands on mitochondria due to its role in promoting growth and protein synthesis, which are energy-demanding processes requiring ATP. Recent findings suggest that GH interacts with the GH receptor (GHR), triggering the production of insulin-like growth factor 1 (IGF1). IGF-1 enhances the synthesis of mitochondrial proteins such as cytochrome c oxidase

Adlimoghaddam A., Fortune J Health Sci 2026
DOI:10.26502/fjhs.410

and UCP, impacting mitochondrial respiration [59]. Mice with lifelong congenital reductions in the GH/IGF-1 axis activity were found to have extended lifespans [60]. The GH-GHR-IGF1 axis has been recognized to play significant roles in mitochondrial activity by overseeing mitochondrial biogenesis, biodynamics, and mitophagy (reviewed by z. Oxygen consumption (VO2), and respiratory quotient significantly increased in the long-lived Ames dwarf mice and GH receptor knock-out (GHRKO) mice [61, 62] Conversely, VO2 decreased in the short-lived bovine GH-overexpressing transgenic (bGH TG) mice [61]. Another study shows that in Ames dwarf mice, the activity of complex proteins associated with (OXPHOS), specifically complex IV, increased in the liver and kidney [9]. The increased expression of mitochondrial OXPHOS in Ames mice was associated with a decrease in H2O2 production during both state 3 (ATP production) and state 4 (reflecting mitochondrial leak) of respiration in liver mitochondria [63].

The IGF-1 haploinsufficiency (IGF-$1^{+/-}$) in mice led to mitochondrial dysfunction, marked by elevated intramitochondrial ROS levels in hepatocytes [64]. This dysfunction manifested as reduced mitochondrial membrane potential and impaired OXPHOS. However, treatment with IGF-1 resolved these deficits. In aging Wistar rats, IGF-1 administration restored mitochondrial membrane potential, oxygen consumption, ATP production, and enzyme activities in liver mitochondria. Furthermore, 30 days of IGF-1 therapy countered age-related increases in mitochondrial ROS production, restored mitochondrial membrane potential, oxygen consumption rate, proton leak, ATP production, as well as the activities of cytochrome oxidase and ATPase complexes in mitochondria isolated from the livers of elderly Wister rats (103 weeks old) [65]. Overall, these findings underscore the crucial role of IGF-1 in maintaining mitochondrial function and mitigating age-related cellular damage.

Another study demonstrates that medium-dose recombinant human growth hormone (rhGH) supplementation administered before standard ovarian stimulation regimens enhances oocyte quality in aged mice, potentially by enhancing mitochondrial function [66]. A human study shows that administering a 14-hour infusion of GH to healthy individuals enhances mitochondrial oxidative capacity and boosts the abundance of various mitochondrial genes. However, it does not seem to affect the rate of mitochondrial protein synthesis [67]. Moreover, a case study involving a patient diagnosed with acromegaly, characterized by an overproduction of GH, demonstrated that surgical intervention (hypophysectomy) resulted in the correction of structural irregularities observed in muscle mitochondria [68].

Chemical Treatments and Mitochondrial Function

Rapamycin, by inhibiting mTOR, interrupts the signals that coordinate cellular activities in response to nutrient cues [65]. This disruption leads to significant changes in autophagy, mitochondrial biogenesis, lipid synthesis, translation, and cell survival [69]. Previous studies have reported that rapamycin dietary treatment extends longevity when initiated in young [70], middle-aged mice [71], or mixed-age mice [72]. Rapamycin has been demonstrated to extend lifespan in several neurodegenerative mice models, particularly in a model of mitochondrial disease stemming from the removal of the thymidine kinase 2 (TK2), which is involved in mitochondrial DNA replication and nucleus-encoded gene responsible for producing the [NADH dehydrogenase (ubiquinone) Fe-S protein 4 (Ndufs4) subunit of the OXPHOS complex I [73, 74]. In addition, Ndufs4 knockout mice that received rapamycin treatment exhibited enhancements in neurological symptoms and metabolic changes, particularly a shift in energy production from glycolysis to amino acid metabolism, which could be beneficial given the OXPHOS dysfunction. [73]. Another study reported that rapamycin could trigger mitophagy as a strategy to decrease levels of the heteroplasmic mtDNA G11778A mutation and partial restoration of ATP levels [75]. Interestingly, short-term (10 weeks) rapamycin treatment reversed pre-existing age-dependent cardiac hypertrophy and diastolic dysfunction in 24-26-month-old C57BL/6 female mice [76]. This was achieved by inducing autophagy during the initial week of treatment, which then returned to baseline levels by the second week and thereafter. In agreement with this, indicators of mitochondrial biogenesis rise during the initial two weeks of treatment and then revert to baseline levels. This temporary boost in autophagy and mitochondrial biogenesis implies that damaged mitochondria are substituted with newly generated ones, aiding in the restoration of mitochondrial balance [76].

It has been shown that metformin decreases cellular oxygen consumption by inhibiting mitochondrial complex 1 activity [77, 78]. Also, it has been shown that metformin inhibits mitochondrial respiratory activity (glycerol 3-phosphate dehydrogenase), which may involve the activation of AMPK [79]. Studies on mice have shown that mutations affecting AMPK-targeted phosphorylation sites in acetyl-coenzyme A (CoA) carboxylase 1 and 2 result in insulin resistance. Another study demonstrates that metformin stimulates AMPK activation and mitophagy in peripheral blood mononuclear cells (PBMCs) isolated from individuals with type 2 diabetes [80]. These findings provide support for the proposed mechanism of metformin action through the activation of the AMPK pathway.

Metformin treatment over the course of four months rescues the mitochondrial respiratory chain complex activities, brain ATP production, and levels, as well as a decrease in ROS production in the whole blood of Rett syndrome (RTT) mice. Furthermore, there is a notable increase in PGC-1α-dependent pathways associated with mitochondrial biogenesis in the brains of RTT mice treated with metformin [81]. Another study discovered that 8 weeks of metformin treatment enhances mitochondrial biogenesis and increases the levels of CPT-1, a crucial mitochondrial protein linked to fatty acid utilization and oxidation capacity, in brown adipocytes of C57Bl/6 mice [82].

Another investigation revealed that administering a clinically relevant amount of metformin enhances mitochondrial respiration, membrane potential, and ATP levels in hepatocytes. Furthermore, metformin augments liver mitochondrial density and amplifies complex I activity, leading to improved hyperglycemia in mice subjected to a high-fat diet [83, 84]. Some studies have found that metformin can improve ROS production by reversing electron flow into mitochondrial complex I, repairing the damaged tricarboxylic acid cycle, and stabilizing mitochondrial function in human cancer [10]. Metformin has been shown to enhance mitochondrial respiration by stimulating mitochondrial fission through the AMPK-Mff signaling pathway, resulting in increased mitochondrial fission. This heightened fission supports cellular energy production by preserving mitochondrial health and functionality. Conversely, at supra-pharmacological concentrations, metformin diminishes mitochondrial respiration by reducing levels of adenine nucleotides, including ATP and ADP. These nucleotides are crucial for cellular energy metabolism, and their depletion inhibits mitochondrial respiration, adversely affecting cellular energy production [11]. Overall, metformin's effect on mitochondrial respiration varies depending on the concentration used.

Conclusions

In summary, early-life experiences profoundly shape long-term health, with mitochondrial function emerging as a critical mediator of these effects. Early-life interventions have the potential to influence development, lifespan, healthspan, and aging by modulating mitochondrial activity, energy metabolism, and cellular resilience. The outcomes of such interventions are strongly dependent on biological sex, the timing and duration of treatment, and the specific nature of the intervention, as these factors can differentially affect mitochondrial pathways. Additionally, genetic background and environmental context can further influence how mitochondria respond to early-life treatments. These insights underscore the importance of designing early life treatment that strategically targets mitochondrial function to optimize health trajectories in a sex-specific and developmentally informed manner. Advancing studies in this area, especially those aimed at clinical applications, hold promise for reducing the lifelong health consequences of early-life adversity for many affected individuals.

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Declaration of interests

The author declares no competing interests.

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Adlimoghaddam A., Fortune J Health Sci 2026
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SUPPLEMENTARY FILES

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