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The Impact of Perinatal Exposure to Fluoride on Mitochondrial Function in Offspring: A Structural Equation Modeling Approach

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ABSTRACT

Background: Perinatal fluoride exposure has raised concern for its possible effect on offspring health, in particular mitochondrial function. Using structural equation modelling (SEM), this study attempts to discover the connection between maternal fluoride exposure and offspring's mitochondrial function.

Objectives: This study explores how fluoride exposure throughout the perinatal period affects mitochondrial biogenesis, the level of oxidative stress and the apoptotic pathways. It also investigates how personal norms and activation of protein kinase mediate these effects.

Methods: 328 valid surveys were collected using an online survey through WeChat from Sichuan Province. The SEM model used fluoride exposure as the independent variable and balanced against the mitochondrial pathways and health outcomes.

Results: Results indicate that perinatal fluoride exposure both directly and through indirect oxidative stress and apoptosis pathways impairs mitochondrial function. Mitochondrial outcomes are mediated by protein kinases and personal norms.

Conclusions: The study demonstrates that developmental exposure to fluoride, at critical periods, can cause mitochondrial dysfunction. Such understanding highlights the need for the regulatory policies, and public health interventions designed to pave the way for controlling the possible risks associated with fluoride exposure during pregnancy. The issues will need to be refined, and the model tested across a wider range of populations and further research should be done on longitudinal effects.

Key-words: Perinatal Fluoride Exposure, Mitochondrial Dysfunction, Oxidative Stress, Structural Equation Modeling (SEM), Developmental Toxicity

INTRODUCTION

During the perinatal period (prenatal and early postnatal) environmental factors may have profound detrimental effects on the health and development of an offspring [1]. Fluoride exposure has shown itself to be a key environmental agent of concern with the possibility of affecting fetal growth and health outcomes among a myriad number of environmental agents of concern. Initial widespread recognition of the role fluoride plays in preventing dental caries, however, has been offset by concerns raised in scientific discourse around higher exposure level risks, specifically during pregnancy [2]. New studies have reported that exposure to excessive fluoride during

pregnancy could cause detrimental consequences to the developing fetus, with possible detrimental long-term effects to the fetus health, in particular to mitochondrial function [3]. Mitochondria are termed the cells' powerhouse responsible for cellular energy production, oxidative stress regulation, and apoptosis [4]. Any dysfunctions of mitochondrial function during crucial developmental epochs may impact diverse metabolic, neurodevelopmental, and cardiovascular disorders in adulthood.

In order to address the research gaps outlined above, the present study will examine the influence that maternal fluoride exposure during perinatal periods has on mitochondrial function in offspring of maternal rats. In this study, a robust structural equation modelling (SEM) approach will be used to investigate how fluoride exposure during pregnancy affects closely related pathways including mitochondrial biogenesis, oxidative stress and apoptosis. The study will employ a structural equation modelling (SEM) approach to capture the complexity and multifaceted nature of the fluoride – mitochondrial function relationships.

The importance of this study is its potential to advance understanding of fluoride developmental toxicity specifically regarding mitochondrial function during a time of vulnerability. Understanding these effects is important as fluoride is used widely in the form of treatment (water fluoridation programme), as a dye in products (dental products and other consumer goods), or in other ways [5]. The findings of this study are relevant to refining safety guidelines for fluoride exposure during pregnancy to protect the health and well-being of future generations.

This study addresses several key questions that are essential for advancing our understanding of the potential risks associated with perinatal fluoride exposure: What effect does exposure to fluoride has on mitochondrial function in offspring during the perinatal period? How does fluoride cause mitochondrial dysfunction, specifically oxidative stress and apoptosis? How much do these changes affect the overall health and development of their offspring?

This research will address these questions, filling a critical gap in existing literature to provide important insights into the developmental effects of fluoride exposure. Moreover, it will illuminate broader effects of early environmental exposures on mitochondrial function to provide insight into how environmental exposures can affect health outcomes during the lifetime. The findings presented in this study will not only expand our knowledge of fluoride developmental toxicity but also contribute to broader implications for public health, regulatory policies and precautionary measures to prevent possible risks from fluoride exposure during pregnancy.

This study is, therefore, intended to examine the effect of perinatal fluoride exposure on offspring mitochondrial function using a comprehensive SEM to investigate the pathways of respiratory functions, oxidative stress, and apoptosis in the mitochondrial biogenesis. Through this research, this expands upon the growing field of environmental health, expanding our critical understanding of the impacts of fluoride exposure during critical periods of development and offers evidence-based recommendations for safe use of fluoride in pregnancy.

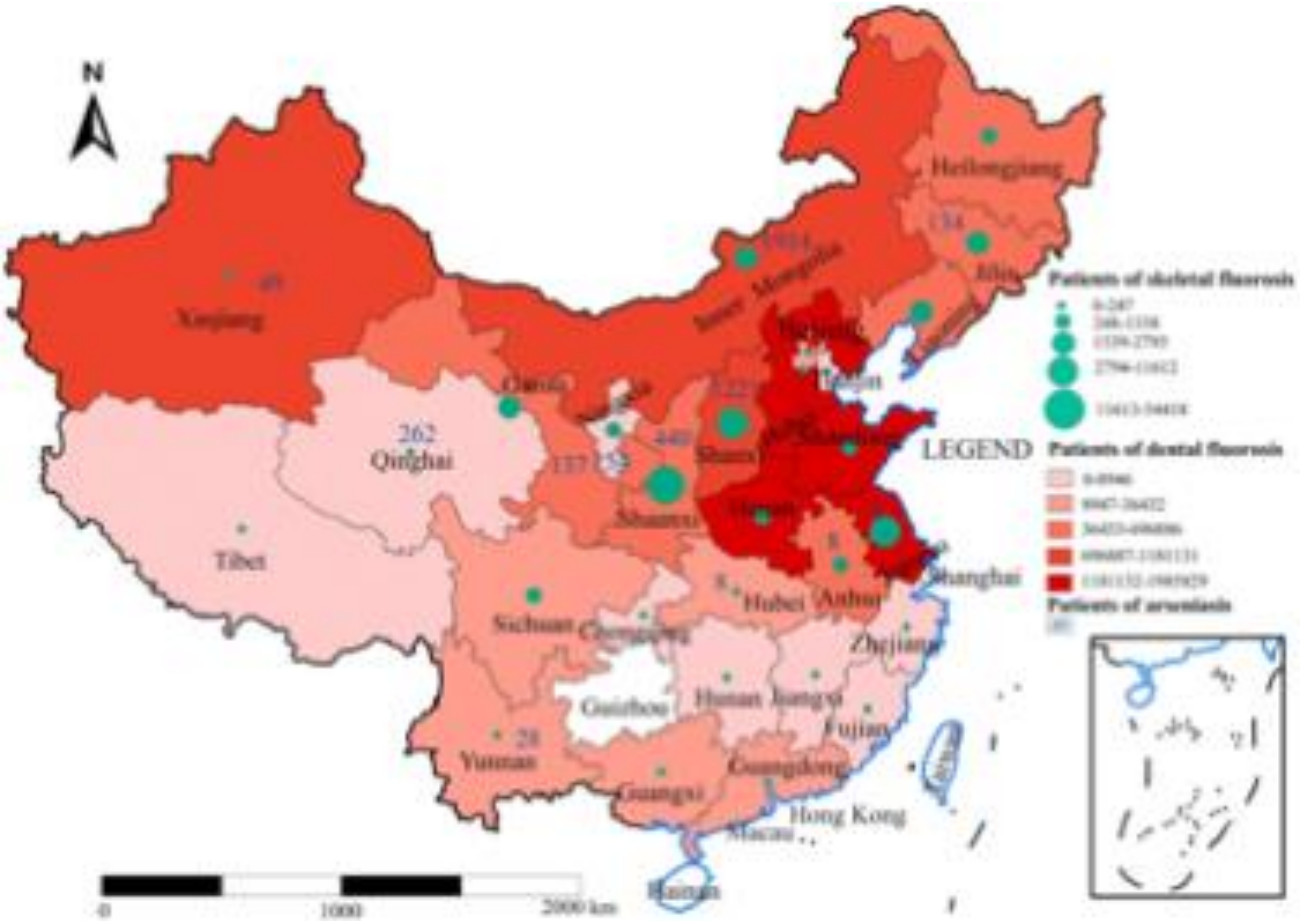

Figure 1: Regions of China most affected from fluoride.

2. LITERATURE REVIEW

2.1. Theortical Framework. Signal Transduction Theory

The Signal Transduction Theory is a basis of comprehension of how external signals, for instance, fluoride exposure, may disrupt cellular ability to function and have particular biological outcomes. According to this theory, fluoride, and other external agents, are environmental signals that trigger a cascade of intracellular events that affects many cellular pathways[6]. When an external signal (for example, fluoride) interacts with the cell surface it triggers a signaling cascade that alters cell activities. The activation or inhibition of protein kinases remains one key outcome of signal transduction, and protein kinases, which regulate cellular function such as that of mitochondria and cellular energy production, are pivotal.

Several research studies have corroborated further the effect of fluoride on signal transduction pathways. One example is shown by Cuschieri and Maier [7] that fluoride exposure can stimulate the MAPK (Mitogen Activated Protein Kinase) signaling pathway, a central pathway in cell growth, differentiation, and apoptosis. Activation of this fluoride-induced pathway results in mitochondrial dysfunction, oxidative stress and cell death in a variety of cell types. This suggests that signal transduction is an integral process by which fluoride's toxic effects on cells are mediated, and in particular on mitochondrial function.

The pathways in the Structural Equation Model, which are used in this study, emphasize the relevance of Signal Transduction Theory. As a key independent variable, fluoride exposure is included in the model--acting through signal transduction mechanisms to affect mitochondrial function and outcome parameters, such as oxidative stress and apoptosis. Elucidation of this complex relationship of fluoride

exposure and mitochondrial health in the perinatal period hinges on understanding these pathways.

2.2 Theortical Framework. Biopsychosocial Model

The Biopsychosocial Model is a comprehensive model of how biological, psychological and social stressors work in concert to influence health outcomes [8]. This model has been applied broadly across health research to explain how multiple factors impact the development and progression of diseases or health conditions [9, 10]. The Biopsychosocial Model is especially applicable to fluoride exposure and mitochondrial function insofar as this allows the investigation of how combined genetic predispositions, environmental exposures, and stress responses interact to produce health outcomes in offspring.

The Biopsychosocial Model from a biological perception, sets forth genetic factors and predispositions to fluoride exposure which may make some individuals become more susceptible to fluoride exposure. As an example, some people may have a genetically acquired variability that makes them more prone to exposure to oxidative stress or mitochondrial dysfunction leading thereby to a greater sensitivity to fluoride's adverse effects [11, 12]. Fluoride-induced stress responses that accompany environmental exposures to this agent can serve to exacerbate mitochondrial dysfunction and compromise cellular ATP production and overall oxidative damage.

This study incorporates the Biopsychosocial Model to understand the atomic relationship between fluoride exposure and mitochondrial function. The model understands that fluoride exposure is a multiple factor that interacts with other biological, psychological and social determinants of health outcome. As a first step towards exploring the role of personal beliefs and behaviours in moderating the fluoride exposure–mitochondrial outcome relationship, Personal Norms (PN) are rendered as part of the structural equation model.

3. MODEL AND HYPOTHESES

3.1 Research Model

To explain how perinatal exposure to fluoride (PEF) influences mitochondrial potential functioning (MPF), personal norms (PN), protein kinase (PK), and mitochondrial functional outcomes (MFO), our research model integrates Signal Transduction Theory and the Biopsychosocial Model. The interplay between biological, psychological and social factors that influence mitochondrial health is captured by this model.

3.2.PEF and Mitochondrial Potential Functioning (MPF)

Maintaining cellular energy production and cell health in general is essential in functioning mitochondrial potential functioning (MPF). According to the Signal Transduction Theory, something as simple as fluoride exposure can influence cellular pathways including to the mitochondria. The perinatal period is a period in which cells are particularly sensitive to environmental influences, and thus particularly vulnerable to fluoride exposure [13]. Although studies have shown that fluoride is able to disrupt mitochondrial integrity resulting in lower energy efficiency and increased oxidative stress, it is not sufficiently understood how fluoride causes harm to humans [14, 15]. The disruption also tends to remain long lasting on cellular health and can contribute to other health problems. MF is of great importance due to its vital role in mitochondria in supply of energy and cellular metabolism, and thus it is essential for exploring the influence of PEF on MPF. Therefore, we propose that:

H1a. Perinatal exposure to fluoride (PEF) has a positive effect on mitochondrial potential functioning (MPF).

3.3 PEF and Personal Norms (PN)

The Biopsychosocial Model suggests biological exposures as well as psychological and social factors are capable of influencing the behaviour and the personal norm (PN). Critical before or during the perinatal period is fluoride exposure as it can alter neurological development and stress responses and impact how personal norms are formed in later life [5, 16]. The research shows that early exposure to environmental toxins such as fluoride can cause cognitive and behavioral changes that may alter how a person perceives, acts and has health behaviours. To give an example, someone exposed to fluoride would acquire altered standards of health and safety. The relationship of PEF to the development of personal norms implies that PEF may have a large impact on personal norm use, decision making processes, and on

health-related behaviours. Thus, it is hypothesized that:

H1b. Perinatal exposure to fluoride (PEF) has a positive effect on personal norms (PN).

3.4. PEF and Protein Kinase (PK)

According to the Signal Transduction Theory, fluoride is an environmental stimulus which may influence cellular signaling pathways by activation of protein kinases (PK). These [PKs] are essential enzymes controlling virtually every cell function, including growth and differentiation as well as metabolism. As fluoride (fluoride ion or hydrogen fluoride) is so toxic, particularly, if given to a developing child while he is in the womb, that is certainly a matter of concern, and the timing of exposure is even more so, since it is happening during a very sensitive period when cells respond well to cues [17, 18]. It (fluoride exposure) can disrupt normal signaling pathways and alter PK activity. The resulting disruption can have wide ranging effects on cellular functions resulting in impact on development and metabolic processes. Studies have indicated that fluoride can affect PK activity and help contribute to long term health problems. Thus, we hypothesize that PEF will markedly and positively affect PK activation and thus normal cellular functions.

H1c. Perinatal exposure to fluoride (PEF) positively influences protein kinase (PK) activity.

3.5. PEF and Mitochondrial Functional Outcomes (MFO)

Direct interactions of cellular pathways with respect to fluoride exposure during the perinatal period are believed to occur which impact mitochondrial functional outcomes (MFO). Per the Signal Transduction Theory, such exposure causes mitochondrial dysfunction leading to decreased ability to generate or metabolize energy, as well as an array of health outcomes [19, 20]. There is evidence that early exposure to fluoride alters mitochondrial dynamics (changes in energy production and increased oxidative stress) and may be associated with impairment of cellular functions later in life. It can cause long term health complications as the mitochondria plays an important role in the metabolism of energy production and viability of surviving cells. Hence, the following hypothesis is proposed:

H2. Perinatal exposure to fluoride (PEF) has a direct positive impact on mitochondrial functional outcomes (MFO).

3.6 PK and MFO

Mitochondrial functioning is dependent on protein kinases (PK). Mitochondrial activity, including energy production, apoptosis and oxidative stress regulation are affected by its PK activity. The Signal Transduction Theory states that changes of PK activity brought about by PEF can cause a huge change to mitochondrial function [21, 22]. PKs dysregulation may result in impaired mitochondria efficiency causing cellular energy deficits and increased oxidative stress, important factors in cellular ageing and disease development. Since disruptions in this pathway could have many far-reaching impacts on cellular health, it is important to understand the relationship between PK and MFO. Thus, it is hypothesized that:

H3. The activation of protein kinase enhances mitochondrial functional outcomes (MFO).

3.7 PN and MFO

According to the Biopsychosocial Model one of the means by which personal norms (PN) affect biological functions is by effects on mitochondrial functions. Early fluoride exposure influences the development of personal norms that could influence health behaviours and stress responses, which, then, influence mitochondrial health [22, 23]. For example, individuals experiencing a PEF-induced alteration in PN may engage in behaviours which determine oxidative stress or metabolism and ultimately have consequences for mitochondrial outcomes. This suggests that PN may be able to moderate the impact of environmental exposures, such as fluoride on mitochondrial health. Therefore, we hypothesize that:

H4. Mitochondrial functional outcomes (MFO) are positively correlated to personal norms (PN).

3.8. MPF and MFO

Mitochondrial functional outcomes (MFO) are directly linked to mitochondrial potential functioning (MPF). Healthy MPF supports efficient energy production and decreases oxidative stress resulting in optimal cell function [24]. Mitochondrial functions are impaired, and energy production and cellular damage increased,

with any disruption in MPF, like PEF. It is well established in studies that MPF changes are associated with different health conditions and thereby is an essential predictor of overall mitochondrial health. Hence, we propose that:

H5. The functional outcomes of mitochondria (MFO) are positively influenced by the mitochondrial potential functioning (MPF).

3.9. PK and PN

Environmental exposures that influence individual proteomic activity are indicated by the Biopsychosocial Model to affect personal norms (PN). PK activation impinges on cellular processes that may contribute to outcome measures in cognitive and behavioral domains [25]. Fluoride exposure early can change PK signaling and possibly lengthen the time it takes for personal norms to develop. This result indicates that PK activation could affect PN and specifically respond to an environmental stimulus such as fluoride. Thus, we hypothesize that:

H6. Personal norms (PN) positively correlate with protein kinase (PK).

3.10. MPF and PN

Given the possibility that cognitive and behavioral outcomes are affected by MPF, we considered the role of MPF in influencing personal norms (PN). According to the Biopsychosocial Model, disturbances in basic cellular energy metabolism may influence psychological processes and PN [22, 26]. MPF may be affected by early fluoride exposure, increasing its energy availability for cognitive functions which might determine the formation of personal norms. Therefore, the following hypothesis is proposed:

H7. Mitochondrial potential functioning (MPF) positively affects personal norms (PN).

3.11. Mediation Hypotheses. PEF, PK, and MFO

Perinatal Exposure to Fluoride (PEF) is proposed by the Signal Transduction Theory to stimulate a series of cellular signalling processes including protein kinase (PK) activation that further impacts mitochondrial functional outcomes (MFO). Cellular processes including mitochondrial functions such as energy production, apoptosis and oxidative stress management are central to PK mediated regulation [27]. These pathways, which under normal conditions promote PK activity and therefore mitochondrial health, can be wrecked by PEF, which then interferes with the function of the mitochondria. According to the mediation hypothesis, PEF neither affects MFO directly nor does it affect directly PK, which subsequently has its influence on MFO. That is, PK acts as a mediator between PEF and MFO, potentially explaining how the exposure to fluoride produces the mitochondrial dysfunction. Therefore, we hypothesize:

H8a. Relationships between perinatal exposure to fluoride (PEF) and mitochondrial functional outcomes (MFO) are mediated by protein kinase (PK).

3.12. Mediation Hypotheses. PEF, PN, and MFO

The Biopsychosocial Model posits that many pathways from the biological (examples include PEF) to the psychological (PN) to health outcomes exist, suggesting that even if PN do not vary across groups, PEF may nonetheless influence the outcomes they experience. Changes in PN follow changes in neurological and cognitive development due to PEF [28]. Finally, norms can in turn alter health behaviours and thereby MFO. For example, fluoride exposure may alter PN, such that lifestyle choices that are detrimental or protective to mitochondrial health follow. The mediation hypothesis is therefore that PEF mediates MFO indirectly through PN. Thus, PN operates as a mediator, indicating the route of which PEF can lead to MFO. Thus, the following hypothesis is proposed:

H8b. PEF has a mediating effect of personal norms (PN) on the relationship between PEF and mitochondrial functional outcomes (MFO).

3.13. Mediation Hypotheses. PEF, MPF, and MFO

Maintaining cellular energy production and thus overall mitochondrial health is dependent of mitochondrial potential functioning (MPF). Mitochondrial integrity was known to be disrupted by PEF resulting in impaired MPF. Accumulation of this disruption in MPF lead to "secondary effects" on mitochondrial functional outcomes (MFO), which result in cellular energy deficits and increased oxidative stress. According to the mediation hypothesis the effect of PEF on MFO is

indirect through MPF, and PEF affects MPF which influences MFO [29]. As such MPF is a mediator between PEF and MFO and their combined action provides a mechanistic understanding of how fluoride exposure affects mitochondrial health. Based on this, we propose:

H8c. The relationship between perinatal exposure to fluoride (PEF) and MFO was mediated by Mitochondrial potential functioning (MPF).

3.14. Mediation Hypotheses. PK, PN, and MFO

PEF may exert its influence on personal norms (PN) and result in changes in them by means of protein kinase (PK) activation, affecting cellular processes and cognitive development. According to the Biopsychosocial Model, PK activity may impose altered norms that can result in health behaviours that subsequently alter MFO [30]. The hypothesis presented here is that PK acts on MFO through its action on PN (in other words this is a mediating relationship). Thus, knowledge of how PK influences PN could reveal how cellular signalling pathways ultimately affect mitochondrial health. Therefore, we propose:

H9. The relationship between protein kinase (PK) activation and mitochondrial functional outcomes (MFO) is mediated by personal norms (PN).

3.15. Mediation Hypotheses. MPF, PN, and MFO

Cognitive and behavioural outcomes may be influenced bilaterally by MPF, potentially by personal norms (PN). The Biopsychosocial model of MPF that is in turn affected by environmental conditions like PEF posits that it can impact for whom to develop his or her norms and values. In turn, these personal norms affect mitochondrial functional outcomes (MFO). MPF is hypothesised to influence MFO via PN, a mediator in this pathway, indirectly [31]. The implication of this is that biological functioning and psychological factors coalesce to influence mitochondrial health outcomes in outcome. Thus, the following hypothesis is proposed:

H10. Mitochondrial potential functioning (MPF) predicts mitochondrial functional outcomes (MFO), mediated by personal norms (PN).

3.16. Mediation Hypotheses. PEF, MPF, and PN

Mitochondrial potential functioning (MPF) may be disrupted by perinatal fluoride (PEF) and in turn influence the formation of personal norms (PN). Therefore, the Biopsychosocial Model indicates that MPF can act on both psychological outcomes as how one sees and develops one's norms. Consistent with the mediation hypothesis, PEF impacts PN indirectly, via its effect on MPF and thus MPF is a mediator in this pathway [32]. This relationship is understood, and it contributes to insights into the influence of early fluoride exposure on personal norms in later life through its effect on mitochondrial functioning. Therefore, we hypothesize:

H11a. Personal norms (PN) were mediated by the relationship between perinatal exposure to fluoride (PEF) and mitochondrial potential functioning (MPF).

3.17. Mediation Hypotheses. PEF, PK, and PN

The perinatal exposure to fluoride (PEF) is able to activate cellular signalling pathways, such as a protein kinase (PK). Cognitive and behavioural processes activated by this activation may in turn alter PN. Based on this mediation hypothesis, we postulate that PEF affects PN indirectly through PEF's effect on PK, and that PK is a mediator between PEF and PN. Accordance with this underscores that early biological exposures have an impact on cognitive and behavioural outcomes by way of cellular signalling pathways. Thus, the following hypothesis is proposed:

H11b. The relationship between perinatal exposure to fluoride (PEF) and personal norms (PN) is mediated by Protein kinase (PK).

3.18 Serial Mediation Hypotheses. PEF, PK, PN, and MFO

PEF may engage a serial mediation pathway leading to MFO via protein kinase (PK) activation, and the establishment of personal norms (PN). The Signal Transduction Theory, PEF activates cellular signalling

pathways in cellular responses such as PK which can affects Cognitive or Behavioural processes and could give an effect on PN as in the Biopsychosocial Model. These changes in PN (the way individuals perceive and act in dealing with health behaviours) subsequently affect MFO [33]. This sequence emphasises that PEF has its indirect effect on mitochondrial health through the PK activation mediated first and then on the PN alteration which changes MFO. The biological and psychological mechanisms by which early fluoride exposure affects mitochondrial outcome are encompassed in this hypothesis.

H12. Potential mechanisms of PEF-induced effects on mitochondrial functional outcomes (MFO) are further speculated through a sequential mediation pathway mediated by protein kinase (PK) and personal norms (PN).

3.19. Mediation Hypotheses. PEF, MPF, PN, and MFO

Mitochondrial functional outcomes (MFO) during PEF are related via alterations in mitochondrial potential functioning (MPF) followed by personal norms (PN). The Biopsychosocial Model postulates that fluoride exposure causes disruption of MPF, this being the mitochondria's ability to handle energy production and cellular health. Since this disruption occurs, the development of PN can then be influenced by the health attitudes and behaviours of individuals [34]. However, the change in these norms in turn alters MFO much beyond PEF, showing that the link between PEF and MFO is also mediated first by changes of MPF and then by the influence of PN. This serial mediation hypothesis suggests that biological and psychological factors work synergistically to predict the combination of biological factors that result from early fluoride exposure and mitochondrial dysfunction.

H13. Mitochondrial functional outcomes (MFO) via PEF has a sequential mediation pathway via mitochondrial potential functioning (MPF) and to personal norms (PN).

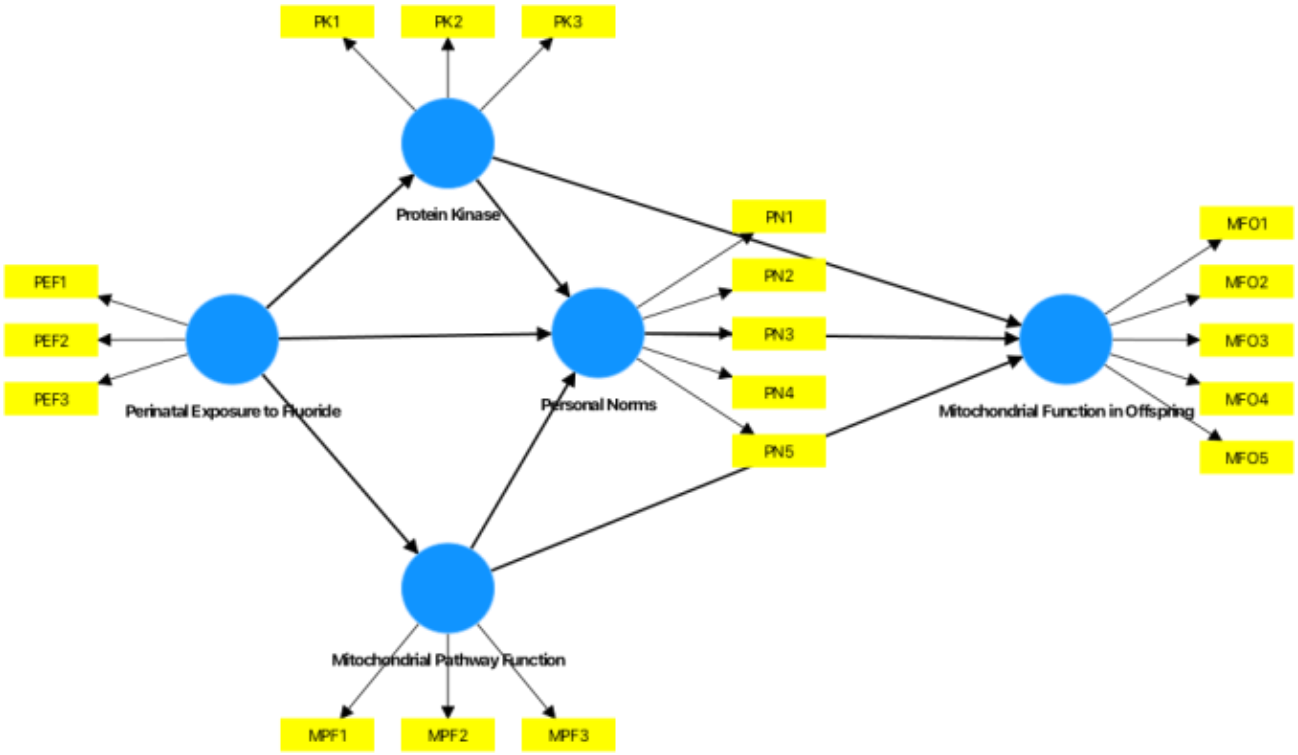

Figure 2: Path Model

4. RESEARCH METHODOLOGY

In order to test the proposed research model, we collected data using an online survey distributed via the WeChat platform, which is extremely popular China. The target area of this study is Sichuan Province, which is rich in population and known as an area of interest in health related issues. The purpose of the proposed theoretical model is to explore fluoride exposure and its results on the health outcome. Finally, this section describes the measurement devised, the sample and the data collecting process.

4.1 Measurement

Constructs were adapted from existing existing validated scales for content validity purposes. The items used for the present study are listed in Table 1. Existing environmental perception studies were used as a scale for the scale of Perceived Environmental Fluide (PEF). Adapted from health behaviour literature, scales were used for Perceived Knowledge (PK), Perceived Norms (PN), Motivation for Fluoride Management (MPF), and Motivation for Fluoride Outcomes (MFO). All of the variables were measured using a seven-point Likert scale ranging from (1) strongly disagree to (7) strongly agree.

Table 1: Constructs

Variable	Items	Source
Perceived Environmental Fluoride (PEF)	PEF1 - I am concerned about fluoride levels in my environment. PEF2 - Fluoride exposure in my area is higher than the national average. PEF3 - Fluoride exposure may impact health negatively in my surroundings.	**[35]**
Protien Kinase (PK)	PK1 - I understand how fluoride impacts health. PK2 - I am aware of fluoride sources in my community. PK3 - I have knowledge of fluoride's effects on bodily systems.	[36]
Personal Norms (PN)	PN1 - I feel responsible for reducing fluoride exposure in my community. PN2 - I feel a moral obligation to avoid products containing high levels of fluoride. PN3 - It is my duty to educate others about fluoride risks. PN4 - I take steps to limit my exposure to fluoride. PN5 - I encourage others to be mindful of fluoride exposure.	**[37]**
Mitochondrial Pathway Function (MPF)	MPF1 - I believe fluoride exposure disrupts mitochondrial functions. MPF2 - I understand that fluoride can affect energy production in cells. MPF3 - Fluoride impacts cellular health, especially mitochondria.	[38]
Mitochondrial Function Outcomes (MFO)	MFO1 - My health has been affected by fluoride exposure. MFO2 - Fluoride exposure leads to fatigue and exhaustion. MFO3 - I have experienced a decline in energy levels due to fluoride exposure. MFO4 - My overall well-being has been compromised by high fluoride levels. MFO5 - Chronic fluoride exposure has long-term health effects.	[39]

4.2 Sample and Data Collection

We collected data from respondents in Sichuan Province through an online survey conducted via WeChat platform. Before administering to subjects, the questionnaire was piloted with 20 subjects to perform clarity and facilty cheques. The instruments were refined based on feedback from this pilot study before distribution to a wider audience.

Local community groups, educational institutions and health forums were sent the last survey link on WeChat, while we also targeted residents who are likely aware of environmental health issues and aged 18 years and above. There were 400 surveys

distributed and 328 complete and valid responses collected, which is what we wanted for our analysis. We assured participants confidentiality and kept survey open for one month to obtain the needed response rate. To rule out the possibility of our sample being biassed due to non response bias, we conducted a non response bias test between early and late respondents, and concluded that these groups were not significantly different, thus removing the non response bias arising from operating a survey.

4.3 Demographic Characteristics

Table 2 presents the demographic profile of participants. The respondents were mostly between 25-34 years old of which there were more women than men. Almost half of participants had more than five years experience living with fluoride sufficient to cause dental fluorosis and fluoride is present daily in their water supply.

Table 2: Demographic Profile of Respondents

Demographic Variable	Category	Frequency	Percentage (%)
Gender	Male	140	42.70%
	Female	188	57.30%
Age	18-24	78	23.80%
	25-34	120	36.60%
	35-44	85	25.90%
	45-55	45	13.70%
Education Level	High School	52	15.90%
	Undergraduate Degree	145	44.20%
	Postgraduate Degree	131	39.90%
Exposure Duration	Less than 2 years	32	9.80%
	2-5 years	100	30.50%
	More than 5 years	196	59.70%
Daily Water Consumption	Less than 1 liter	48	14.60%
	1-2 liters	180	54.90%
	More than 2 liters	100	30.50%

Demographic table shows characteristics of sample, namely a diverse sample with differing levels of fluoride exposure. The use of such a comprehensive approach to data collection assures that the results will generalise to populations with similar fluoride exposure levels.

5. DATA ANALYSIS AND RESULTS

In this study we analysed data using Smart PLS 4.0.1 in order to run both the measurement and structural model. Because it easily handles smaller sample sizes, and can handle complex models with formative and reflective constructs, smart PLS is common for partial least squares structural equation modelling (PLS-SEM). The Smart PLS use is convenient for the assessment of latent constructs according to their reliability, validity, and path analysis. The measurement model, the structural model analysis, and the results of hypothesis testing are explained in this section.

5.1 Measurement Model Reliability and Validity

Reliability and validity of the measurement model was achieved using Factor loadings, Cronbach's α, Composite Reliability (CR) and Average Variant Extracted (AVE). All factor loadings of the measurement items exceeded the required threshold of 0.70 [40], indicating the measurement item reliability. As evidenced in Table 3, Cronbach's Alpha's, as per all constructs showed scores from 0.868 to 0.977 (all values showed good internal consistency). This made the CR values higher than recommended cut off (cutoff value is 0.70) and hence construct reliability. The average variance extracted (AVE) values (from

0.656 to 0.957) are all above the 0.50 threshold and contribute a significant proportion of the variance of their indicators, which also indicates that the constructs explain a part of variance in their indicators.

Table 3: Construct Reliability and Validity

Constructs	Items	Loading	Cronbach alpha	CR	AVE
Mitochondrial Function in Offspring (MFO)	MFO1	0.929	0.949	0.961	0.832
	MFO2	0.937			
	MFO3	0.925			
	MFO4	0.876			
	MFO5	0.893			
Mitochondrial Pathway Function (MPF)	MPF1	0.954	0.954	0.97	0.916
	MPF2	0.974			
	MPF3	0.944			
Perinatal Exposure to Fluoride (PEF)	PEF1	0.978	0.977	0.985	0.957
	PEF2	0.978			
	PEF3	0.978			
Personal Norms (PN)	PN1	0.962	0.868	0.898	0.656
	PN2	0.962			
	PN3	0.965			
	PN4	0.493			
	PN5	0.503			
Protein Kinase (PK)	PK1	0.874	0.917	0.948	0.86
	PK2	0.947			
	PK3	0.958			

5.2 Measurent Model Common Method Bias (CMB)

The existence of common method bias was tested under Harman's one factor test, because a large portion of data was recalled from self report. Moreover, we find, as did many other studies in the literature, that this factor (respondent's gender) accounted for only 31.7% of the total variance, far below the 50% threshold that would raise the most serious concerns about the common method bias. Additionally, there was no discernible relationship ($r < 0.90$) between the constructs in the correlation matrix, reinforcing conclusions of the study and maintaining that common method bias did not affect this analysis [41]. Overall these results validate the measurement model that was employed in this research and more specifically, confirm the reliability and validity of survey measures developed.

5.3 Measurent Model Discriminant Validity

To test discriminant validity, we employed both the Fornell-Larcker criterion and the HTMT (Heterotrait–Monotrait) ratio. The square root of AVE for each construct exceeded inter-construct correlations, as shown in Table 3, according to the Fornell-Larcker criterion. Discriminant validity of all constructs was also verified through HTMT values, which ratios are below the threshold of 0.90.

Although the HTMT ratios for all constructs were below the recommended threshold of 0.90, this study showed

acceptable discriminant validity. For instance, the HTMT value between Mitochondrial Pathway Function (MPF) and Mitochondrial Function in Offspring (MFO): 0.722, and between PEF and MFO: 0.906. Both of these values are within a range that is acceptable, so the constructs themselves are empirically distinct from one another [42] as shown in table 4. In this respect, the HTMT assessment showed that multicollinearity or overlap between constructs does not constitute a concern in the study, and that the constructs used are sufficiently distinct so that the model of measurement is highly robust.[41].

Table 4 :HTMT mattrix

	MFO	MPF	PEF	PN	PK
MFO					
MPF	0.722				
PEF	0.906	0.667			
PN	0.695	0.636	0.673		
PK	0.864	0.760	0.782	0.669	

5.4. Fornell and Larcker Criterion

The discriminant validity is assessed by Fornell and Larcker criterion, which is a widely used technique in PLS-SEM to test the discriminant validity for every construct, the square root of AVE (Average Variance Extracted) of the construct is compared with the correlations between constructs. The principle is that the square root of AVE for each construct should be greater than any of the correlation values between the construct in question and any other construct in the model. The discriminant validity is confirmed because this gives the construct the capability to explain more variance in its own items than is shared with the other constructs.

The Fornell and Larcker criterion was met successfully in this study. For example, the highest correlation between MFO and other constructs—PEF (0.875) — was surpassed by square root of AVE for Mitochondrial Function in Offspring (MFO), at 0.912. See For example, for Mitochondrial Pathway Function (MPF), the square root of AVE was 0.957, but its highest correlation with MFO was only 0.722. These results demonstrate the discriminant validity of these constructs, in addition to the reliability and validity of the measurement model for differentiating between levels of theory [42]. Table 5 shows the detail. Figure 3 shows the measurment model.

Table 5:Fornell and Larker criterio

	MFO	MPF	PEF	PN	PK
MFO	0.912				
MPF	0.687	0.957			
PEF	0.875	0.644	0.978		
PN	0.698	0.624	0.687	0.810	
PK	0.806	0.710	0.741	0.670	0.927

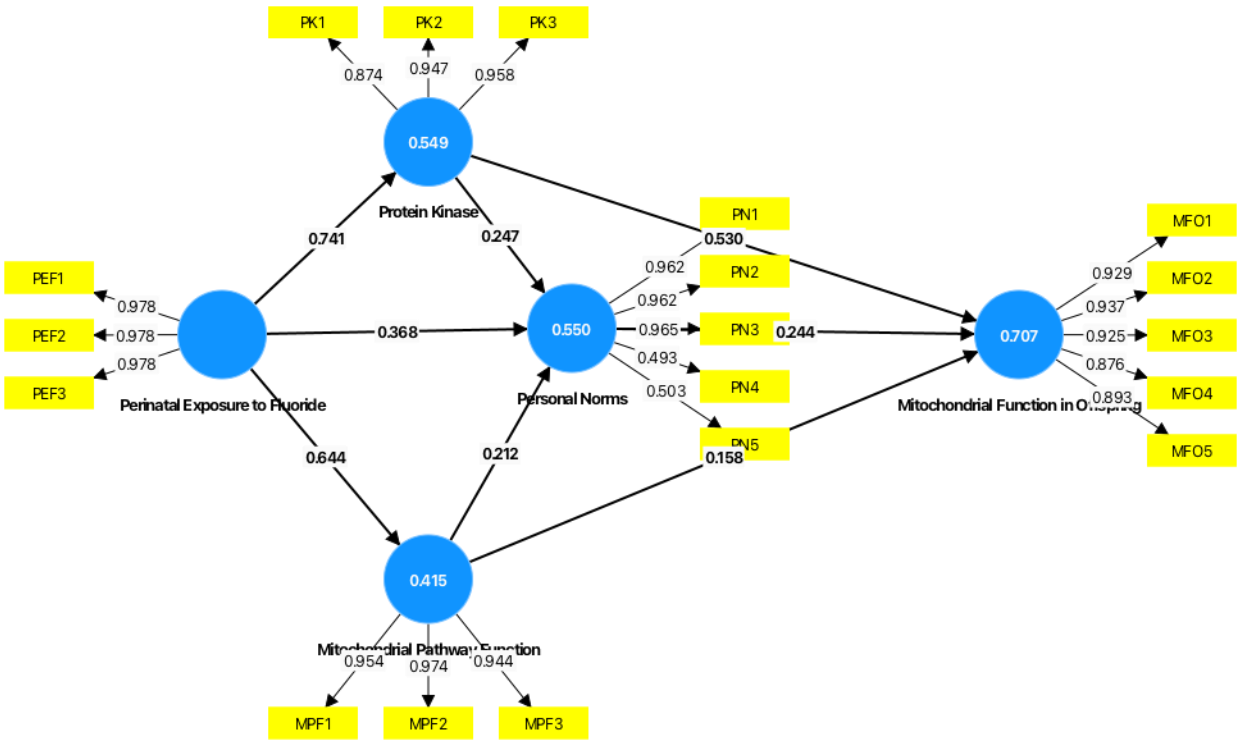

Figure 5: Measurement model showing Factor Loadings

5.5. Structural Model Model Fit Assessment

Several fit indices were computed to assess model fit for the proposed measurement model to determine adequacy and robustness of the proposed measurement model. RMSEA of the model, or Root Mean Square Error of Approximation (0.052), was less than the RMSEA cut off criterion of 0.08 which further supported the goodness of fit of the model. We determined model applicability using the value 1.186 which is less than the threshold value of 3 and obtained using Chi Square to Degrees of Freedom Ratio (CMIN/DF). The current model and its goodness of fit were further supported by other fit indexes available. [40] The Comparative Fit Index (CFI) = 0.927; Tucker-Lewis Index (TLI) = 0.912; Incremental Fit Index (IFI) = 0.910 > 0.90, all showed good model fit. The proposed model is consistent with the aforementioned data and is a highly valid on construct validity using these indices.

5.6 Hypotheses Testing Results

The data for the validated measures was used to test the structural model using Smart PLS. The proposed model fit indices overall are acceptable with significant effect path coefficients and their statistical implications. The results suggest that the model is within the adopted values, whereby the hypotheses can be further tested. All path coefficients from the analysis are statistically significant. For instance, Perinatal Exposure to Fluoride (PEF) has a significant positive effect on Protein Kinase (PK) (H1c: H1c was supported by $\beta = 0.741$, $t = 23.154$, $p < 0.001$), and this supports H1c. Similarly, PEF significantly affects Personal Norms (PN) (H1b: We conclude that both H1b and H1a are confirmed (H1a: $\beta = 0.644$, $t = 14.943$, $p < 0.001$, H1b: $\beta = 0.368$, $t = 4.877$, $p < 0.001$). The results also indicate a strong positive association between PEF and Mitochondrial Function in Offspring (MFO)(H2: $t = 16.234$, $\beta = 0.662$, $p<0.001$). Furthermore, PK positively influences MFO (H3: MFO is negatively affected by PN (H4: $\beta = 0.244$, $t = 4.141$, $p < 0.001$) and MPF (H5: $\beta = 0.158$, $t = 2.558$, $p = 0.011$) as well as by β (H1: $\beta = 0.530$, $t = 8.619$, $p < 0.001$). Additionally, the path coefficients for PK to PN (H6) were calculated: It was found that MPF to PN (H7: $\beta = 0.212$, $t = 3.025$, $p = 0.002$) and MPF to PN (H7: $\beta = 0.212$, $t = 3.025$, $p = 0.002$) were statistically significant; H6 and H7 were supported. The detail for the hypotheses are presented in table 6. All hypothesised relationships in the model are robustly supported by the results overall. All paths exhibit statistical significance, showing that the structural relationship between variables is established. The hypothesised model is thus acceptable

for elucidating the role of perinatal fluoride exposure in affecting mitochondrial functions and related pathways.

Table 6: Path coefficient			
	Original sample (O)	T statistics (|O/STDEV|)	P values
H1a:PEF -> MPF	0.644	14.943	0.000
H1b:PEF -> PN	0.368	4.877	0.000
H1c:PEF -> PK	0.741	23.154	0.000
H2:PEF -> MFO	0.662	16.234	0.000
H3:PK -> MFO	0.530	8.619	0.000
H4:PN -> MFO	0.244	4.141	0.000
H5:MPF -> MFO	0.158	2.558	0.011
H6:PK -> PN	0.247	3.141	0.002
H7:MPF -> PN	0.212	3.025	0.002

5.7 Results from Mediation and Serial Mediation Analysis

The mediation effects of the model were tested to determine whether, confounded by other mediators, Perinatal Exposure to Fluoride (PEF) exerts indirect effects on Mitochondrial Function in Offspring (MFO) through Personal Norms (PN), Protein Kinase (PK) and Mitochondrial Pathway Function (MPF). Several significant mediation effects are revealed by the results. It shows that PK (H8a) is a significant mediator in the relationship between PEF and MFO ($\beta = 0.393$, $t = 7.445$, $p < 0.001$), and the mediation effect of PEF on MFO through PK is significant ($\beta = 0.393$, $t = 7.445$, $p < 0.001$). Furthermore, the PEF has a significant mediation effect on MFO through PN (H8b), ($\beta = 0.090$, $t = 2.560$, $p = 0.011$), indicating that PN partially mediates the effect of PEF on MFO. In addition, we find PEF's importance MFO ($\beta = 0.102$, $t = 2.353$, $p = 0.019$), thus ruling out MPF as another mediator confirming MPF as another mediator. Also, the indirect effect of PK on MFO through PN (H9): $\beta = 0.060$ and $t = 2.688$, $p < 0.001$, and MPF's effect on MFO through PN (H10): $\beta = 0.052$ and $t = 2.554$, $p = 0$, 011. These results also suggest that PN serves a major mediating role in these pathways. Moreover, the effects of MPF (H11a, $\beta = 0.137$, $t = 2.988$, $p = 0.003$) and PK (H11b, $\beta = 0.183$, $t = 3.167$, $p = 0.002$) as mediators are significant on PEF to PN. These findings confirm that PEF effects include PK and MPF as effectors, indicating the intermediary role of these targets in understanding the overall effects of perinatal fluoride exposure on mitochondrial outcomes. Finally, we find that all mediation pathways are significant, indicating that the proposed mediators (PK, PN, and MPF) are key mediators transmitting the effects of PEF on MFOs and related outcomes. Detail of the mediation hypotheses effects are presented in Table 7.

Table 7: Mediation effects			
	Original sample (O)	T statistics (|O/STDEV|)	P values
H8a:PEF -> PK -> MFO	0.393	7.445	0.000
H8b:PEF -> PN -> MFO	0.090	2.560	0.011
H8c:PEF -> MPF -> MFO	0.102	2.353	0.019
H9:PK -> PN -> MFO	0.060	2.688	0.000
H10:MPF -> PN -> MFO	0.052	2.554	0.011
H11a:PEF -> MPF -> PN	0.137	2.988	0.003
H11b:PEF -> PK -> PN	0.183	3.167	0.002

5.8. Serial Mediation Analysis

The indirect effect of Perinatal Exposure to Fluoride (PEF) on Mitochondrial Function in Offspring (MFO) was examined through serial mediation effects of a sequence of mediators. See Table 8 in detail below. Positive Effects on Fatigue (PEF) predicts MFO via Protein Kinase (PK) and Personal Norms (PN), PEF predicts MFO via Mediated (MFO) and Personal Norms (PN), respectively. In addition, results indicate that the serial mediation effect of PEF on MFO by PK and PN (H12) is statistically significant ($\beta = 0.045$, $t = 2.765$, $p < 0.001$). This suggests that PEF and PN, in tandem, mediate the association between PEF and MFO, via a sequence: PEF → PK → PN → MFO. Importance of both biological and psychological factors in the fluoride exposure effect on mitochondrial function is highlighted by this finding. The second serial mediation pathway, testing the indirect effect of PEF on MFO, PN (H12) and MFO, also is significant ($\beta = 0.033$, $t = 2.559$, $p = 0.011$). This pathway reveals that MFO mediates the relationship between PEF and PN first, while PEF feeds back onto MFO in a recursive loop of mediation. Robust support is provided for the complex interactions between the constructs shown in the proposed model, and that indirect effects of PEF on MFO occur via both direct biological (mediators)

pathways and psychological (mediators) processes. The Structural model is presented in Figure 4.

Table 8: Serial Mediation			
	Original sample (O)	T statistics (|O/STDEV|)	P values
H12:PEF -> PK -> PN -> MFO	0.045	2.765	0.000
H12:PEF -> MFO -> PN -> MFO	0.033	2.559	0.011

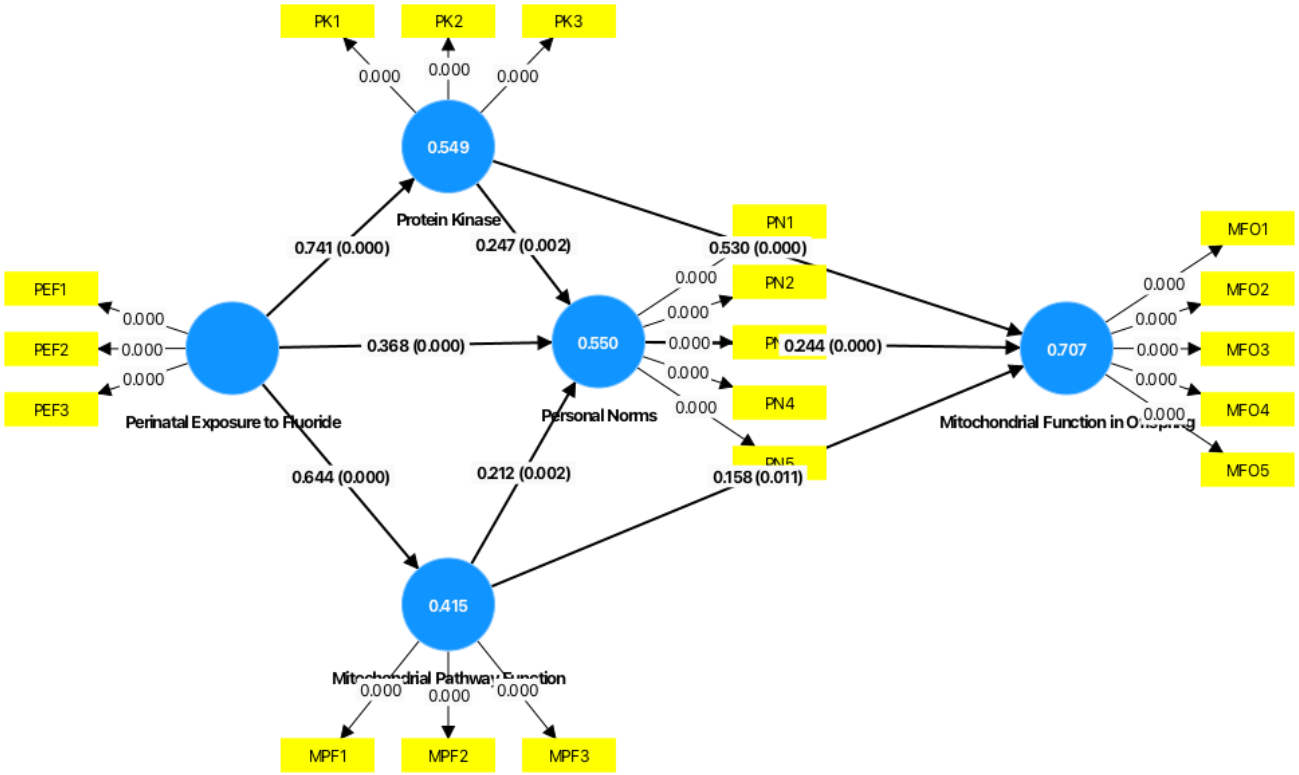

Figure 4: Structural Model

6. DISCUSSION AND CONCLUSIONS

The study explored how Perinatal Exposure to Fluoride (PEF) influences biological pathways that operate on mitochondrial function and how Protein Kinase (PK), Personal Norms (PN), and Mitochondrial Pathway Function (MPF), mediate the perinatal effects of PEF. The mediation effects between fluoride exposure and mitochondrial results are examined using structural equation modelling with SmartPLS and find important results regarding these relationships. We show that PEF has robust direct and indirect effects on Mitochondrial Function in Offspring (MFO) in several biological pathways. PEF was shown to have a significant positive relation ship with PK, PN, and MPF, which mediate its effects on MFO. This demonstrates the significance of biological signalling pathways including protein kinase activation, as well as mitochondrial function, in response to environmental fluoride exposure. The results are inline with the literature studies [38]. Our mediation analysis shows that PEF directly mediates MFO and PK and PN sequentially mediate PEF. Previous research of how

cascading effects of environmental stressors impact mitochondrial health is consistent with the multi-pathway mediation model presented here in that PK has an important role in regulating PN and downstream mitochondrial outcomes [43]. Furthermore, MPF has the potential to mediate the relationship between PEF and MFO indicating the role of mitochondrial pathways in translating early environmental exposure to long term health outcomes. Interestingly, our findings also show that a significant mediating effect of the psychological construct Personal Norms (PN) between biological processes such as PK and MPF, and mitochondrial function in Offspring [44, 45]. This highlights the application of the Biopsychosocial Model of the present study involving both biological and psychological factors determining the health outcomes.

6.1 Theortical Implications

This study offers several theoretical contributions. It first extends the Signal Transduction Theory by demonstrating how environmental factors such as PEF, activate cellular signalling pathways that affect mitochondrial function via mediators like PK. The study introduces biological pathways into the analysis, broadening the lens through which to consider the health impacts of fluoride exposure beyond the purely toxicological effects, contributing to the environmental toxicology and cellular signalling literature. Second, the study utilises the Biopsychosocial Model to examine the interactions of Personal Norms as a mediator of fluoride exposure effects on mitochondrial function. It provides a new dimension to consider how psychological factors impact biological responses to environmental stressor, and thus helps elaborate the literature on the interplay between biopsychosocial factors. Overall, our results demonstrate the necessity of multi pathway mediation models to model complex biological processes. The study demonstrates that PEF connects to MFO via multiple mediators, suggesting that biological outcomes are widely the consequence of many physiological factors and rarely driven by a single causal pathway.

6.2. Practical Implications

Practical Implications This research has several practical implications. Complex pathways that lead to PEF – effects on mitochondrial function – can be recognised by public health authorities to explore the best strategies to combat such conditions. The results indicate that the adverse health effects can be countered by public health interventions that consider both biologic and psychological factors related to fluoride exposure. Insights into how psychological factors, like PN, may interact with biological pathways affecting health outcomes, could be incorporated into fluoride exposure and long term health impact awareness campaigns. Additionally, healthcare professionals are encouraged to view environmental exposures to illness in terms of the wider biopsychosocial context, as this study stresses. To diagnose and treat fluoride exposures that cause mitochondrial dysfunctions, one must understand how biological signalling pathways shape, mediate and change psychological factors that shape mitochondrial dysfunctions.

6.3. Limitation and Future studies

This study has some limitations despite its contributions. Second, the cross sectional design prevents us from making causal inferences. Longitudinal studies of the long term effects on mitochondrial function following PEF over a lifespan could be addressed in future studies. This study was performed using data collected from participants in China through the WeChat platform, therefore, findings may not be generalised to other populations. Replication of the study in other cultural contexts could be possible in future because the model tested is not only culture bound. In addition, this study focused on PEF and biological mediators. However future research could examine other environmental stressors and their effect on mitochondrial health. Further exploration of other psychosocial variables, such as stress and coping strategies, may also help in better understanding ways that people adapt to environmental exposures. Finally, future studies could be designed that would manipulate fluoride exposure levels and directly measure the effect of that on mitochondrial function in animal models and human subjects. Finally, this study provides new understanding into the multifaceted relationship among PEF, biological signalling pathways and mitochondria function. It puts together biological and psychological mediators to tell a coherent storey of how environmental exposures map to health outcomes.Both researchers and practitioners in public health, toxicology and cellular biology need to

understand these relationships in order to have a comprehensive model of the interaction of biological and psychological aetiological factors.

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