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Terror Death of Election Officials: What Are the Effects of Stress and Hypoxia?: A Literature Review

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Abstract

Background: This essay examines the most recent news, namely the passing of a voting committee member (PPS) in the general election (Pemilu), which included candidates for president, vice president, and legislature (Caleg). PPS saw 35 fatalities and 3.909 illnesses. Given that the counting and recapitulation process is still in progress, the likelihood of deaths and illnesses will only rise. **Objective**: The aim of this research is to find the relationship between hypoxia and stress in PPS officers who died due to physical exhaustion during election activities in Indonesia **Methods:** Articles containing information on hypoxia, comorbidity, stress, physical exhaustion, and its connection to death were included as inclusion criteria. There was a total of 25 papers that met the inclusion criteria after the literature analysis procedure was completed. **Result:** Along with the comorbid status, physical exhaustion, and stress play a significant part (comorbidities). This connection arises from the fact that physical exhaustion and stress induce hypoxia, which in turn affects immunity. The drop in blood oxygen levels, or hypoxia, disrupts and dysregulates the innate and adaptive immune systems. The chance of dying can rise when hypoxia and ongoing stress are present. Writing this paper proposes more investigation into the role that hypoxia and stress play as death risk factors. **Conclusion:** Hypoxia results from stress. what makes HIF the primary transcription factor active. When PPS officers activate their HIF in order to fulfill their mandate and fulfill their obligations under Law Number 7 of 2017 concerning General Elections, there is an elevated risk of death and morbidity.

Keywords: Hypoxia condition, Hypoxia Inducible Factor (HIF), Stress, President-Vice President-Legislative Candidates General Elections, Immunology

Review Article

INTRODUCTION

Following the general election process on February 14, 2024, which selected candidates for president, vice president, and legislative parties to hold seats in the People's Representative Council (DPR), the Regional People's Representative Council (DPRD) at the Provincial, City, and Regency level, and the Regional Representative Council (DPD) for the election period 2024–2029, the number of deaths and illnesses among members of the Voting Committee (PPS) has continued to rise. At the moment, 3,909 individuals are ill (with details: 119 PPK people, 596 PPS people, 2,878 PPS Chairmen, and 316 PPS security personnel) and 35 people have died (with details: 3 PPS persons, 23 PPS Chairmen, and 9 PPS security people) (www.bbc.com). This occurrence is identical to those that happened in the US during the 2016 and 2020 presidential elections. The Indonesian general election incident was most likely the result of an acute myocardial infarction that developed minutes to hours after being impacted by overexertion. Acute myocardial infarction (AMI) and stroke risk factors might emerge hours to days following stress exposure, which is linked to a drop in blood oxygen levels (hypoxia) (Mefford et al., 2020; Mefford et al., 2022).

This figure is anticipated to rise because of the General Election Commission (KPU) having a timeline that is being followed by the chairman and voting committee members (PPS), in accordance with Law figure 7 of 2017's mandate for general elections. Specifically, article 413 paragraphs 1 through 3 state that: The KPU shall ascertain the results of the national election and the votes received by candidate pairs, the votes received by political parties for candidates seeking DPR seats, and the votes obtained for candidates seeking DPD seats no later than 35 (thirty-five) days following the day of voting; The Provincial KPU shall ascertain the results of political party votes for candidates seeking Provincial DPRD seats no later than (Law Number 7 Year 2017).

Due to Law Number 7 of 2017's deadline for the general elections, KPU members—particularly PPS members—have had to put in extra effort to fulfill the law's mandate. Anything that is done above and beyond or "forced" will cause stress. Numerous articles have discussed and highlighted the detrimental impacts of stress; yet, stress can also be a catalyst for growth and development, in which case it is both beneficial and necessary. Stress is defined as the sensation of being burdened when an issue is too big for an individual to handle. On the other hand, an excessive amount of stress can cause disorders like poor adjustment, physical disease, and an incapacity to deal. We only feel stress when we believe the pressure from the stressor to be greater than our ability to handle it. Stress is felt when our equilibrium is upset. Stress is not real until it can no longer be sustained; however, when pressure from the same stressor or other stressors increases at the same time, stress becomes real and can be felt (Ng JS, 2021).

There are generally three different kinds of stress: physiological, chemical, and physical stress. Too-high or too-low temperatures, too-loud noises, too-bright light, or an electric shock all contribute to physical stress. Strong acids, medications, poisonous substances, hormones, or gasses can all lead to chemical stress. Diseases can also be brought on by stress brought on by microbiological agents, such as bacteria, viruses, and parasites. Disturbances in the structure and operation of tissues, organs, or systemic illnesses that result in aberrant bodily functioning are the causes of physiological stress. Impaired growth and development from infancy to old age is the source of stress during the growth and development process. According to (Cheng *et al.,* 2022; Kelly *et al.*, 2019; Vielma *et al*., 2018) there are three forms of stress that can affect the body: 1. The central nervous and endocrine systems; 2. The respiratory and cardiovascular systems; and 3. The digestive system. Another link between excessive stress and hypoxia, or low blood oxygen levels, is hypoxia. Hypoxia-inducible factor (HIF), a gene that functions as an autocrine signal that enhances cell survival and incites paracrine signals, will be expressed in response to hypoxia. It's linked to the hypoxia factor because the main point of view of the literature review so the main actor in this literature review is hypoxia.

Hypoxia Inducible Factor (HIF) comes in three varieties: HIF 1, HIF 2, and HIF 3. Of these, HIF 1 is associated with the angiogenesis process, whereas HIF 3 has no bearing on angiogenesis and HIF 2's functions overlap with HIF 1's. There are two different forms of HIF 1 isoforms: HIF 1α and HIF 1β. To function, HIF 1 has to bind with two cofactors: cAMP response element binding protein (CREB) and p300 cofactor. Since oxygen levels control the stability and activation of the HIF 1 protein, there are two different kinds of oxygen sensors that control HIF 1, namely: 1. Asparaginyl hydroxylase, which suppresses HIF 1 via asparagine residues; 2. Prolyl-hydroxylase domain proteins (PHDs), hydroxylate two residues in the oxygen-dependent degradation portion. HIF 1 will translocate to the nucleus to perform functions through activation of gene transcription factors through binding to the hypoxia response element with the consensus sequence 5'-RCGTG-3', where R is a purine residue. Hypoxia causes stabilization between the bonds of HIF 1α and HIF 1β. HIF is linked to genes that are involved in angiogenesis's metabolism and cell survival.

The most recent research on the connection between excessive stress and the hypoxia and deaths that PPS members experience while performing their duties will be included in this narrative review, along with the date of the announcement of the actual election results in 2024 that will determine the president, vice president, and members elected legislative candidates for the 2024–2029 term.

METHODS

The primary goal of the literature review is to learn more about the connection between stress and risk factors for disease and death as experienced by PPS members doing their duties in accordance with Law Number 7 of 2017 concerning General Elections, a literature review was conducted. Using PubMed, Science Direct, and Google Scholar articles, the following MeSH terminology and keywords were used to search for articles pertaining to the mentioned keywords: ("hypoxia"[MeSH Terms] OR "hypoxia inducible factor"[All Fields]) AND ("stress"[All Fields] OR "stressed"[All Fields] OR "stressful"[All Fields] OR "stressfulness"[All Fields] OR "stressing"[All Fields]). Figure 1 will demonstrate the article analysis procedure. The files that were searched were from 2014 to 2024. Through full-text articles, more papers from other databases were accessed. The abstract was used to filter articles after they were initially chosen based on their title. The inclusion criteria of the articles were the range of the year between 2014 to 2024, it had to review about hypoxia related stress, and they had to open access. The exclusion criteria were: the article was closed access and they had not review hypoxia related stress. The number of exclude and include articles were explained deeply through figure 1. The articles were excluded due to their poor usefulness for the study's topic and the unavailability of their whole texts. We arrived at our conclusion in this article by taking into account and combining the findings and conclusions from the other articles. Because this is just a literature study, no statistical analysis was done to determine the results.

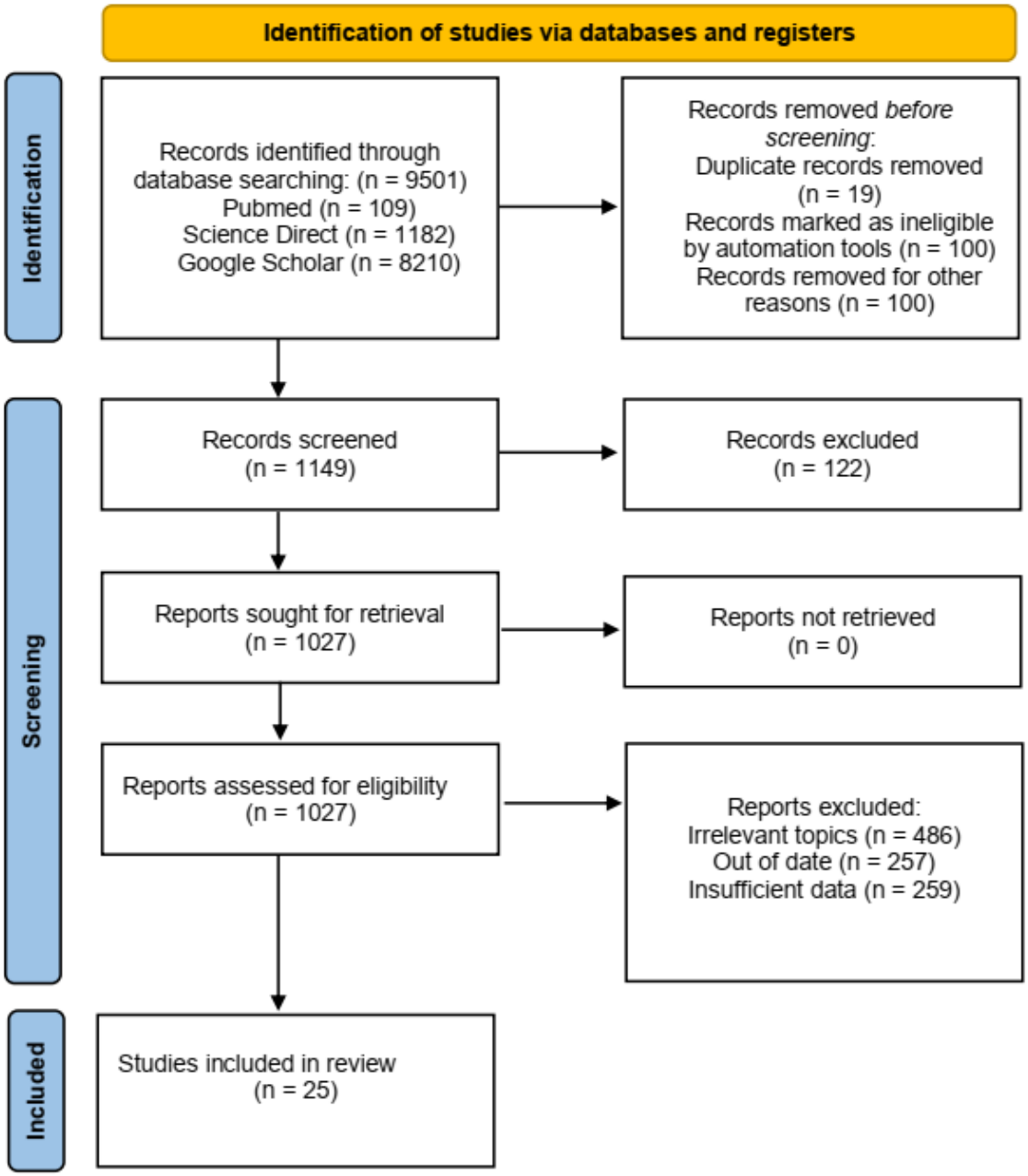

Figure 1. The process of screening and selecting articles to be reviewed

RESULTS

When searching using the terms "hypoxia-inducible factor," "stress," "comorbid," and "pathophysiology of stress-related hypoxia through hypoxia-inducible factor," 122 articles in all were found at the beginning of the search. 1027 titles were chosen following the filtering procedure based on the abstracts and titles. The next twenty-five articles were manually removed because they did not pertain to the topic under discussion, based on the article's overall substance. Only 25 publications, all of which concentrate on the discussion studies that should be included in the preparation of the systematic review, remain after the inclusion process has been completed.

Of the 25 articles that were chosen, the majority were chosen due to their discussion of the pathophysiology of stress associated with hypoxia through factors that induce hypoxia, including pathophysiological processes that begin with cell entry and result in the release of pro-inflammatory cytokines and their subsequent pathophysiological effect. This systematic review's discussions of all the studies are theoretical investigations founded on review articles.

Each article's description is predicated on a review of pathophysiological research and how stress and hypoxia, in the form of secretomes and exosomes, are related:

1. A theoretical investigation based on review articles discovered that pro-inflammatory cytokines (TNF-α, IL-6, and IL-1) were all associated with the development of organ damage.
2. A review paper on the pathophysiology of the molecular basis of stress-induced hypoxia caused by hypoxia-inducible factor.
3. Research on the connection between hypoxia and stress as one explanation for the PPS group's demise during the presidential, vice presidential, and legislative elections

Publications that meet the inclusion category's requirements are:

1. Articles about stress, comorbid conditions, hypoxia, and the presidential election have been published since 2010. They also discuss hypoxia, comorbid states, and hypoxia-inducible factors;
2. 2. Explain the function of hypoxia and the hypoxia-inducible factor receptor;
3. 3. Talk about stress-induced hypoxia via hypoxia-inducible factors. You should also talk about the connections between these factors and the pathophysiological mechanisms that underlie them;
4. Articles written in English.

Table 1. Summary of the *stress related hypoxia* studies

No	References	Methods	General outcomes
1	Ng et al, 2021	Article review Potential mechanisms linking psychological stress to bone health	Stress can be linked to the bone health
2	Kelly et al, 2019	Impacts of Psychological Stress on Osteoporosis based on Clinical Implications and Treatment Interactions	Psychological stress strongly affected the osteoporosis condition
3	Vielma et al, 2015	Pathophysiology of osteoporosis is related to genes, oxidative stress, and immunopathogeny. A qualitative systematic review	Pathophysiology osteoporosis is linked to genes, oxidative stress and immunopathogeny
4	Mefford et al, 2020	Association of the 2020 US Presidential Election with Hospitalizations for Acute Cardiovascular Conditions	The presidential election had a great effect with the acute cardiovascular conditions

DISCUSSION

Four perspectives are commonly used to define stress: stress as a stimulus, reaction, interaction between a person and their surroundings, and relationship between a person and a stressor. Stress is a stimulation that permeates the environment and causes people to feel stressed while they are in it. According to this theory, the person is a dependent variable and stress is an independent variable. The competitive atmosphere around us, such as in airports and train stations near Eid, might provide as an example of stress as a stimulus. People in this setting, whether they are potential passengers or members of the bus or train personnel, find it challenging to avoid these tense circumstances. A person's response or reaction to current pressures is what is meant by the concept of stress. Stress is an independent variable in this situation, whereas stress is a dependent variable. A person's reaction to a stressor can be divided into two categories: psychological (such as surprise, worry, shame, panic, and uneasiness) and physiological (such as rapid heartbeat, nausea, dry mouth, and profuse sweating). Strain is the term for the physiological and psychological reaction to stimuli. Individual responses to the same stressor at various periods are described by the idea of stress as an interaction between the individual and the environment.

The current finding was based on the perspective stress definition as it involves strains and stresses in addition to the interaction between an individual and their surroundings. A transactional connection is one in which people and their environment interact and influence one another. Stress is viewed as a process in which the individual is also an active middleman so that he can influence the stressor by cognitive and emotional behavioral strategies. Stress is defined as an interaction between

the individual and the environment. Stress is a term that can arise from more than just environmental conditions. In addition to external influences, psychological disputes, bodily injuries, and other personal experiences can also be considered stressors. Relationships between people and stressors—both internal and external—are the source of stress. The current finding was based on these theories. (Kimball *et al.,* 2021; Azuma K, *et al* 2015).

There are three different kinds of stress: physiological, chemical, and physical stress. Too-high or too-low temperatures, too-loud noises, too-bright light, or an electric shock all contribute to physical stress. Strong acids, medications, poisonous substances, hormones, or gasses can all lead to chemical stress. Diseases can also be brought on by stress brought on by microbiological agents, such as bacteria, viruses, and parasites. Anomalous bodily activities resulting from systemic illnesses or disruptions in the structure and function of tissues and organs produce physiological stress. Impaired growth and development from early childhood to old age is the source of stress during the growth and development process. There are three different kinds of stressors: psychological, social, and physiological. Physical impairments, such as lack of function in a bodily part, difficult-to-cure diseases, and improper posture are examples of physiological stressors. Prejudice, anger at not getting what one wants, jealousy, hostile attitudes, interpersonal problems, and aspirations that are unachievable are examples of psychological stressors. Among the social pressures include dysfunctional family dynamics and other (Zaki A, 2020).

There are several strategies or approaches to managing stress, including the homeostasis principle and the coping mechanism. Since stress is unpleasant and generally bad for a person, anyone who encounters stress should attempt to resolve the issue using the homeostasis principle, which is applicable to all living things. According to the principle of homeostasis, an individual should always strive to keep themselves in a balanced condition. This way, in the unlikely event that an unbalanced state arises, an attempt should be made to bring the state back to balance. If an individual is alive, then the principle of homeostasis is applicable, as its major purpose is to preserve the life of the organism. Coping with stress refers to actions taken to reduce or manage stress. Two main strategies are utilized to cope with stress: 1. Emotional coping and 2. Problem-focused coping. To control emotional reactions to stress, employ emotional-focused coping techniques. Through the removal of painful facts from individual conduct, this arrangement is carried out. Learning new techniques or stress-reduction strategies—two approaches exist—is the first step toward problem-focused coping. These strategies are task-oriented and ego defense mechanism-oriented.

The digestive, respiratory, and cardiovascular systems, as well as the central nervous and endocrine systems, can all be impacted by stress. All bodily reactions are controlled by the central nervous system, which is housed in the brain. The brain's hypothalamus controls the release of cortisol and adrenaline, two stress hormones, by the adrenal glands. In an emergency, the heart, muscles, and other vital organs require more blood flow, which is what these two hormone kinds do by raising heart rate. The hypothalamus tells the other organs that were previously in an elevated condition to calm down and return to normal when the stress or fear subsides. When the central nervous system is unable to regulate stress, headaches and sleeplessness may result from a persistent reaction. Because the body breathes more faster during a stress response to quickly distribute blood that carries a lot of oxygen throughout the body, stress can have an impact on the respiratory and cardiovascular systems. Stress can make breathing harder and cause the heart to beat more quickly than usual when it coincides with respiratory issues (such as asthma or emphysema). Stress hormones raise blood pressure by causing blood vessels to constrict. The liver will create blood sugar, or glucose, in stressful circumstances, which can boost energy. Blood sugar that is not used will be reabsorbed by the body. Prolonged stress prevents the body from storing extra glucose, which raises the possibility of type 2 diabetes. In addition to upsetting the digestive system, hormones, fast breathing, and elevated heart rate can cause individuals to have acid reflux or heartburn because of elevated stomach acid (Musradinur, 2016).

Hypoxia-inducible factor (HIF) will be expressed in response to hypoxia. There are three different forms of hypoxia inducible factor (HIF): HIF 1, HIF 2, and HIF 3. However, only HIF 1 is associated with the angiogenesis process, as HIF 3 has no bearing on angiogenesis and HIF 2's functions overlap with HIF 1's. There are two different forms of HIF 1 isoforms: HIF 1α and HIF 1β. To function, HIF 1 must bind with two cofactors: cAMP response element binding protein (CREB) and p300 cofactor. There are two types of oxygen sensors to regulate HIF 1, namely: 1. Prolyl-hydroxylase domain proteins (PHDs), which hydroxylate two residues in the oxygen-dependent degradation section; and 2. Asparaginyl hydroxylase, which inhibits HIF 1 via asparagine residues. The stabilization and activation of the HIF 1 protein are regulated by oxygen levels. HIF 1 will translocate to the nucleus to perform functions through activation of gene transcription factors through binding to the hypoxia response element with the consensus sequence 5'-RCGTG-3', where R is a purine residue. Hypoxia causes stabilization between the bonds of HIF 1α and HIF 1β. HIF is linked to genes involved in angiogenesis's metabolic process and cell survival. To determine the relationship between excessive stress and the incidence of illness and death suffered by PPS members, a total of all the articles that have been analyzed in writing narrative reviews have been done so. Many of these articles are based on concepts and relationships and are sourced from the PubMed, Science Direct, and Google Scholar databases. somewhere between "hypoxia" and "stress" (Esch, 2010) (Chen & Holland, 2018; (Kardena *et al*., 2016; Suud *et al*., 2020).

Stress can impact the central nervous system, endocrinological system, and immunological system, making it a physiological reaction to environmental changes and adverse stimuli. These three systems can be upset by stressful situations, which can lead to immunological response dysregulation. Members of the PPS who are hardworking in accordance with Law Number 7 of 2017 for the General Elections are under stress, more precisely, physiological stress. First, using the concepts of homeostasis and the stress-reduction mechanism, the body attempts to overcome the physiological stress that develops. The homeostatic principle, which aims to preserve equilibrium, is applicable as long as a person pursues self-preservation (survival) (Hignasari, 2020; Enayatjazi *et al*., 2015; (Najmuddin, 2020).

The neuroendocrine and autonomic nerve systems, as well as alterations in behavior that result in homeostatic levels, are all involved in the physiological stress response. Stress causes the sympathetic nervous system to become active, which in turn encourages the adrenal medulla to release adrenaline and noradrenaline. These two releases raise blood flow to the skeletal muscles, heart rate, respiration rate, and glucose concentration. The survival process is the main cause of the growing response (Weiyu *et al*., 2020; Pilozzi& Carro, 2021; Smith &Pollak, 2021). A drop in the oxygen concentration required to sustain regular cell function can cause hypoxia, which is the body's reaction. Hypoxia is defined as a drop in oxygen levels. It can result from low oxygen concentrations (normobaric hypoxia) or low barometric pressure (hypobaric hypoxia). The pO_2 sign, which measures the amount of oxygen available in tissues and arteries, indicates the existence of hypoxia. The first phase of exposure to hypoxia, known as acute ambient hypoxia, is characterized by a pathophysiological response and can last anywhere from a few minutes to several days. Chronic hypoxia, on the other hand, can also happen and refers to exposure to hypoxia that occurs either intermittently or continuously after acute hypoxia (from a matter of days to with year). The availability of oxygen levels below the level normally required can be caused by changes in oxygen levels both physiologically (exercising) and pathologically (ischemia, inflammation, cancer). Physiological oxygen levels are required at high levels in oxygen-dependent tissues and can affect cells with specialized functions. The hypoxia value in arterial blood ranges from the specific oxygen requirement = 80-100 mmHg. The specific oxygen requirement in different tissues, namely: the thymus and bone marrow (pO_2) can be considered hypoxic if the oxygen level is < 10 mmHg, the spleen < 4-34 mmHg, and the lymphatic nodules < 4-46 mmHg (Kroemer *et al.,* 2022).

Hypoxia-inducible factors (HIFs) are the primary transcriptional master regulators that control the body's metabolic and cellular responses to hypoxia. Oxygen availability is the primary regulator of HIFs, particularly the HIF-α subunit, which is constantly broken down in normoxic environments after

being hydroxylated by prolyl hydroxylases and ubiquitinated by Van Hippel Lindau proteins. A constitutive β subunit heterodimerizes with three isoform HIF-α subunits. In comparison to HIF-3, HIF-1 and HIF-2 ubiquitination (HIF isoforms in cells) is better understood and researched. It affects the expression of many kinds of genes and pathways, including those related to cell proliferation-survival pathways, glycolysis, metabolism, angiogenesis, metastasis, erythropoiesis, apoptosis, and autophagy. Hypoxia is linked to HIF activation, which can lead to hypoxia-related damage and a drop in energy availability that jeopardizes barrier function. Protective factors have been linked to HIF activation. HIF also plays a role in leukocyte cell activation and differentiation, mainly by supplying energy in a hypoxic environment, which enables leukocytes to migrate to target tissues and perform immunological tasks. In addition, HIF controls the transcription and metabolism of immune cells, specifically those belonging to the lymphoid and myeloid lineages (B and T cells and neutrophils, eosinophils, basophils, monocytes, macrophages, and dendritic cells). (Seiler et al., 2022).

While pathophysiological chronic hypoxic conditions are linked to inflammatory conditions, and inflammation can lead to hypoxic conditions caused by increased oxygen consumption, HIF-1, a master regulator in hypoxic conditions, also contributes to the homeostasis of innate and adaptive immune responses under acute and physiological hypoxic conditions. caused by infections, immune cells that have infiltrated the body, inflammatory cells, and reduced oxygen supply because of vascular disease. By stabilizing the conventional route (inhibition of prolyl hydroxylases, which contribute to HIF accumulation), inflammatory hypoxia initiates HIF stabilization. When there is little oxygen available, it is linked to inflammatory cytokines like TNF-α and IL-1β, where the amount of HIF-1 protein can increases DNA binding. HIF is also known as the master regulator of transcription factors, and transcriptional responses to hypoxia. Nuclear factor kappa-light-chain-enhancer in activated B cells (NF-kB) is one of the transcription factors that HIF regulates, and NF-kB is activated in hypoxia. A key regulator of inflammation, NF-kB controls the expression of toll-like receptors (TLRs), HIF transcription, and the relationship between HIF and DNA. (Danesse & Lewis, 2017). The practical implication through publishing to the journal is to prevent the similar case because Indonesia will have general election again in this November 2024 so the PPS must concern to their health and stress management system.

CONCLUSION

Conclusively, an examination of the extant scientific literature indicates that PPS members' primary cause of suffering during the election process and subsequent elections is their heightened work ethic, which causes the body to react with stress. Stress results in hypoxia, and the primary transcription factor HIF is activated when there is hypoxia. Transcriptional factors that are activated during PPS officers' performance of their mandate and duties under Law Number 7 of 2017 concerning General Elections are linked to higher risk factors for death and morbidity.

CONFLICT OF INTEREST

The authors have no conflict of interest to declare

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