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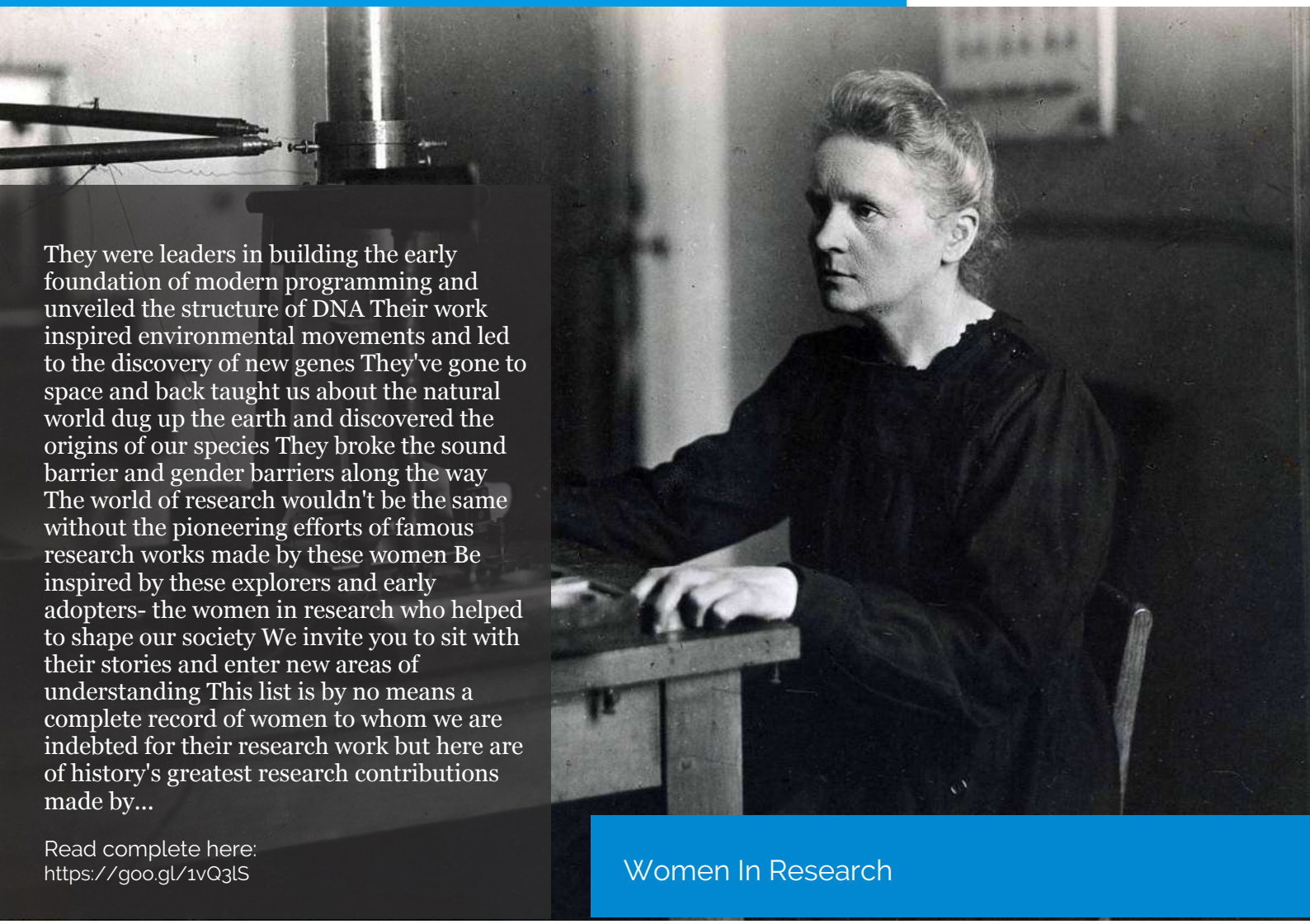

They were leaders in building the early foundation of modern programming and unveiled the structure of DNA Their work inspired environmental movements and led to the discovery of new genes They've gone to space and back taught us about the natural world dug up the earth and discovered the origins of our species They broke the sound barrier and gender barriers along the way The world of research wouldn't be the same without the pioneering efforts of famous research works made by these women Be inspired by these explorers and early adopters- the women in research who helped to shape our society We invite you to sit with their stories and enter new areas of understanding This list is by no means a complete record of women to whom we are indebted for their research work but here are of history's greatest research contributions made by...

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The Serotonin Hypothesis for Depression: A Comprehensive Study

Antonelli, C. C., Pereira, M. E. C. & Carvalho, J. E.

State University of Campinas

ABSTRACT

It has been observed a sharp growth in the number of diagnoses of depression (under the MDD [Major Depressive Disorder] spectrum) in the last decades, accompanied by a similarly increase in sales of antidepressants in several societies, leading to depression being currently considered an epidemic (WHO). The predominant understanding of the cause for depression, the serotonin hypothesis, conveyed by 80% of the population, dates back to the 1960s, when the first antidepressants were being developed. This article sought to verify this state of affairs from the main literature available, starting from the original pharmacological development of antidepressants and their implication in the body's physiology. Most of the literature gathered for this study did not validate the hypothesis as the most plausible main cause for depression, while nonetheless, this continues to be widespread by pharmaceutical industries and most medical practitioners as such.

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I. INTRODUCTION

The biochemical hypothesis relating depression to low levels of neurotransmitters in the central nervous system (CNS) is linked to the millennial use of *Rawolfia serpentina*. Due to the similarity of its roots with vipers, and following the theory of signatures, the ancient Hindu medicine used this species to treat snake and insect bites. The name Rawolfia was given in honor of the German physician Leonard Rauwolf who exhaustively studied the properties of this plant. Ayurvedic medicine also used the roots of this species to treat insomnia and some types of insanity. Mahatma Gandhi took an infusion of these roots every night to treat his insomnia. In 1931, the first work on the therapeutic use of the Rauwolfia root in the treatment of hypertension and psychosis was published, but with little repercussion (Alonso, 1998).

Later, reserpine was highlighted as one of its active principles, and its association with the decrease in the production of dopaminergic neurotransmitters (dopamines) affirmed (Mabey, 1988).

1.1 The Pharmacology in the Origin of Antidepressants

In 1932 the alkaloid reserpine was isolated, and started to be used with great success in the treatment of hypertension. However, in the long-term treatment, reserpine produced depressant effects that limited its use (Mabey, 1988). In addition to depressant effects, reserpine treatment could cause tremors similar to those produced by Parkinson's disease.

Subsequent studies revealed that reserpine produced the release of noradrenaline, adrenaline, dopamine, and serotonin from the nerve endings where these neurotransmitters are synthesized and released. At high doses, reserpine cause marked depletion of these neuro-transmitters and prevented their reuptake by neuronal storage granules, markedly decreasing their neuronal stores. Severe hypotension, bradycardia, gastric ulcer, tremors, fatigue and

"depression" were the symptoms produced by reserpine at high doses (Shore, 1971). These combined effects including the depressive state led researchers to the conclusion that reserpine would be a good tool for experimental studies in the search for new drugs for depression.

However, when we observe the effects it produces in experimental animals it is impossible to conclude that they are related to depression. After 24 hours of a high dose of reserpine, "to induce depression," the animals are in a deplorable state with piloerection (fur erection), elevated hypotension, salivation, intense diarrhea, gastric ulcer, and locomotor ataxia (an impairment of voluntary movements). It is really not possible to claim that these intense effects would be characteristic of a depressive condition.

Therefore, this experimental model of depression has been contested by some authors. Because of its hypotensive effects, by depleting the noradrenaline present in the endings of the sympathetic system responsible for the control of blood pressure, reserpine has been indicated for the treatment of blood pressure, evidently in doses much lower than those used in laboratory animals. However, even at low doses, reserpine, despite lowering blood pressure very effectively, produces orthostatic hypotension (the excessive drop in blood pressure), which has greatly limited its use, since the patient can barely stand upright. In fact, a person with very low blood pressure and dizziness will appear "depressed".

In the 1950s, as with many chance discoveries, researchers observing the clinical effects of iproniazid in tuberculosis patients noted that this drug produced a significant improvement in their mood. What was apparently just a side effect, in reality revealed the discovery of the first group of antidepressants, which acted by inhibiting monoamine oxidase (MAO), responsible for the metabolization of catecholamines (adrenaline, noradrenaline and dopamine) and serotonin, causing accumulation of these neurotransmitters in the nerve endings where they are predominant. In the same decade, another group of researchers, studying derivatives of chlorpromazine, an antipsychotic that originated from the antihistamine promethazine, arrived at the imipramine molecule, which had no antipsychotic effect, but rather an antidepressant one, giving rise to a new class of substances. Subsequent studies revealed that imipramine and derivatives acted by inhibiting the neuronal reuptake of catecholamines and serotonins. Because they have tricyclic chemical structure they were also known as tricyclic antidepressants (Pereira e Hiroaki-Sato, 2018). Meanwhile, experimental studies in animals found that the administration of tryptophan, a precursor of serotonin, potentiated the antidepressant effect of MAO inhibitors and tricyclic antidepressants (Coppen et al., 1963). These experiments gave rise to the monoaminergic theory and the search for drugs that would specifically inhibit serotonin reuptake.

The company Eli Lily constitutes a group of researchers that then began the search for a specific serotonin reuptake inhibitor. Again, from the molecule of antihistamines, they synthesized dozens of molecules until they came to fluoxetine (Prozac), the most potent in inhibiting the reuptake of serotonin in synaptosomes (isolated synaptic terminals of neurons) in mice (Wong et al., 1974). However, conclusions about the mechanism of action of antidepressants have always been based on *in vitro* studies, such as with synaptosomes in experimental models with laboratory animals. Transposing these studies to humans diagnosed with depression is very difficult and unlikely. Experimental models for studies of drugs that act on CNS disorders are very limited, since it is impossible to isolate the brain of an animal and monitor its function, as is done, for instance, with the heart. One can remove the heart from an animal, keep it in perfect functioning and quantitatively register the alterations produced by several substances. The same is not possible with the human brain. Therefore, conclusions about the mechanism of action of drugs in the brain are always risky to extrapolate from *in vitro* studies and behavioral observations of laboratory animals, to the human brain.

There are basically four experimental models used for studies that seek antidepressants' mechanisms of action. One of them is the study of the

potentiation of the effects of noradrenaline in the periphery, in organs stimulated by the sympathetic nervous system, such as the heart. Another model evaluates the potentiation of the central stimulant effects of amphetamine, which acts by releasing noradrenaline. The reduction of the "depressant" effects of reserpine is another model used, besides the one that studies the *in vitro* blockade of neurotransmitter capture.

These are very restricted models (*in vitro* or in animal brains) which, in our understanding, do not allow a safe transposition of their results to the complexity of the human brain.

1.2 The Adverse Effects of Antidepressant Drugs

When studying the various pharmacological effects of antidepressants, we can conclude that the actions observed are far beyond inhibition of reuptake or on neurotransmitter metabolism.

Monoamine oxidase inhibitors (MAOI) cause accumulation of serotonin, norepinephrine, and dopamine in the nerve endings where these neurotransmitters are produced and released. However, contrary to expectations, hypotension is a common side effect, and pargiline, one of the MAOIs, was used for some time as an antihypertensive drug.

The contradiction lies in the fact that MAO inhibition causes an accumulation of noradrenaline at the sympathetic endings, which are responsible for blood pressure control. Thus, with more noradrenaline the greater the chance of hypertension. This accumulation is proven by the hypertension caused by tyramine (produced by fermentation of some cheeses) in patients under MAOI treatment[1].

In the current literature, the role of acetylcholine as an important neurotransmitter in the CNS, through its action on muscarinic receptors, is not sufficiently discussed for depression. Cholinergic neurons are widely distributed in the CNS, being responsible for alertness, learning, and memory. Evidently, the blocking of muscarinic receptors of acetylcholine in the CNS by MAOIs produces alterations in brain function. The amnesia produced by atropine and derivatives is well known. This variety of pharmacological effects automatically questions the theory that the actions on mood are associated exclusively with MAO inhibition.

These same problems are observed when we analyze the adverse effects of tricyclic antidepressants (TADs), which act, according to the literature, by inhibiting the reuptake of serotonin, noradrenalin, and dopamine. Therefore, these substances act by increasing the concentrations of these amines at the sites where they are released. It is reported that in non-depressed individuals these substances cause sedation, confusion, and lack of motor coordination. These effects also occur in patients medicated with TADs, but may diminish with prolonged treatment. As with the MAOI, the TADs also act by blocking the muscarinic receptors of acetylcholine, producing effects such as xerostomia (dry mouth), blurred vision, intestinal constipation, and urinary retention. They cause postural hypotension as well, which, by the proposed mechanism of action, should not happen. On the contrary, the increase in noradrenaline concentration in the sympathetic terminals would produce an increase in blood pressure, mainly because the vasomotor tonus is maintained by the sympathetic, with continuous release of noradrenaline. TADs also have an antihistaminic effect, contributing to the observed sedation. This effect is also expected, because this group of substances was synthesized from the antipsychotic chlorpromazine, a derivative of promethazine, one of the most potent antihistamines. In the CNS, histamine is a neurotransmitter involved in several functions. In the cortex and reticular activating system histamine contributes to arousal and alertness. Therefore, histamine H1 receptor antagonists, such as promethazine, produce sedation, as do

[1] Known as the cheese reaction: the patient may have a severe hypertensive crisis, accompanied by intense pulsating headache (migraine), which can sometimes produce intracranial haemorrhage. These contradictory effects, so far, have not been explained. MAOIs also block the muscarinic acetylcholine receptors, which at the peripheral level produce xerostomia (dry mouth) by decreasing saliva production; cyclopaedia (blurred vision), urinary retention and intestinal constipation, among other effects.

antipsychotics and TADs. Antipsychotics are drugs that are widely used to treat nausea and vomiting, especially when they are consequences of chemotherapy[2].

The adverse effects common to selective serotonin reuptake inhibitors (SSRIs) - nausea, insomnia, loss of libido and of appetite, among others -[3], also observed in the use of MAOIs and TADs, classified as adverse, involve other CNS mediators besides serotonin and other systems in the body, such as the autonomic. Other antidepressant drugs that inhibit the reuptake of noradrenaline and/or serotonin, such as venlafaxine, reboxetine and bupropion, also have similar adverse effects.

In the CNS, serotonin influences numerous functions such as sleep, cognition, sensory perception, motor activity, temperature regulation, nociception (sensory capture), mood, appetite, sexual activity and hormone secretion. In the gastrointestinal system (GIT), serotonin stimulates peristalsis and intestinal secretions. In the cardiovascular system (CVS), serotonin has a complexity of effects that can produce an increase in blood pressure by the contraction of vascular smooth muscle, bradycardia (low heart rate) by vagal stimulation, or an increase in heart rate by direct activity in the heart. In platelets, serotonin stimulates their aggregation, and when there is deep vascular injury, it causes vasoconstriction, contributing to haemostasis (the stopping of blood flow) (Rang and Dale, 2020).

Other factors that, finally, contradict the serotonin hypothesis are related to the distribution of serotonin in the body and its physiological effects through the currently 14 different types of receptors, involved in the actions of this neurotransmitter. At the time of the formulation of the serotonin theory of depression, little was known about its distribution, effects and only two receptors were known at the time. About 90% of the body's serotonin is concentrated in the GIT and the rest (10%) is between the CNS and platelets and cardiovascular system. Considering that the serotonin reuptake mechanism is the same in all these systems, it would be expected that blocking its reuptake would stimulate all of its peripheral effects as well.

Therefore, in addition to the actions on the CNS, the selective blockade of its reuptake should stimulate all other peripheral effects on the TGI, SCV and platelets, which is not observed during treatment with SSRIs. Considering that 90% of serotonin is in the GIT, inhibition of its reuptake would provoke intense stimulating effects on gastrointestinal activity. Thus, the hypothesis does not hold when analysing the “adverse” effects of antidepressants and the physiological effects of this neurotransmitter throughout the body (Ibid.).

At last, we question whether these are in fact adverse effects as usually claimed, or characteristics of action of these substances that act in a very comprehensive way in the organism, which seems to be the case. And in this case, it seems that the sum of effects on CNS histamine, acetylcholine, serotonin and catecholamines would lead to the outcomes that antidepressants have in the treatment of depression.

II. THE LITERATURE OF DEPRESSION

Following this series of preliminary pharmacological studies, in 1965 Joseph Schildkraut published the hypothesis that low levels of monoamines would be related to the cause of depression, associated with low levels of norepinephrine, referring essentially to catecholamines (Schildkraut, 1965). Short after, another group of researchers ratified that serotonin was the neurotransmitter of interest in

[2] Another adverse effect of TADs is the induction of cardiac arrhythmias by blocking sodium and potassium channels, similar to that produced by phenothiazine, such as promethazine, used in the treatment of schizophrenia (Vieweg et al., 2004). Probably, the same chemical origin of these substances is related to this activity, which increases the chances of sudden death in patients treated with these drugs. This activity in cardiac conduction tissue can certainly be present in CNS neurons, increasing the possibilities of interference in the conduction of the nervous action potential, essential for communication between neurons.

[3] Still according to the Prozac package insert, also diarrhoea, fatigue, headache, flu syndrome, pharyngitis, sinusitis, palpitations, blurred vision, xerostomia, dyspepsia, arrhythmias also due to increased QT interval, attention disorder, vertigo, dysgeusia, tremor, abnormal dreams (nightmares), anxiety, pollakiuria, hyperhidrosis, pruritus, hives and flushing with hot flashes.

this hypothesis, which would be in deficit in cases of depression, and that it could be reversed with antidepressants that would restore its function in depressed patients (Coppen, 1967). Coppen's thesis remains one of the most frequently cited in the history of psychiatry (Healy et al., 2001).

In the following years, several attempts were made to identify reproducible neurochemical changes in the nervous system of patients diagnosed with depression. Researchers compared levels of serotonin metabolites in the cerebrospinal fluid of clinically depressed and potentially suicidal patients for control, but this early literature is mixed and crossed by methodological difficulties such as too small sample sizes and uncontrolled confounding variables (Lacasse and Leo, 2005). In a recent review of these studies, the chairman of the German Medical Board and his colleagues stated, "Reported associations of suicidal behavior in subgroups with low concentrations of 5-hydroxyindoleacetic acid (5-HIAA) [the serotonin metabolite] in cerebrospinal fluid (CSF) are likely to represent somewhat premature translations of findings from studies that are flawed in methodology" (Ibid., p. 1211). Attempts have also been made to induce depression by depleting serotonin levels in humans, but these experiments have not yielded consistent results either. Similarly, they found that even huge increases in brain serotonin levels - achieved by administering high doses of L-tryptophan - were ineffective in alleviating depression.

Despite little verifiable evidence, "the hypothesis" prevailed. Cowen and Browning (2015) argue that in biological psychiatry, pathophysiological hypotheses are usually not so easily disproved. More often, they simply seem to become irrelevant as new models of causality take their place. In the case of depression, a new explanatory model has not taken place yet; possibly because of its high complexity, variability, and likely multifactorial cause. "In an era of neural networks and systems-level neuroscience, theories of depression with a single neurotransmitter seem increasingly implausible" (p. 158).

In traditional etiological studies diagnosis and therapy always seem to rely on a common point, a so-called biological marker. Even though attempts have been made to determine the level of brain serotonin as a marker, this does not seem to have remained sufficiently consensual (Cowen and Browning, 2015). On the other hand, contemporary neuroscientific research has failed to confirm serotonin lesions in any mental disorder, and, on the contrary, has provided significant counter evidence to the explanation of a simple neurotransmitter deficiency (Lacasse and Leo, 2005). While at the same time, they have been showing that the brain is very complex and poorly understood.

While the field of neuroscience is knowingly rapidly advancing, proposing that one can objectively identify a chemical imbalance at the molecular level is indeed not compatible (Ibid., p. 1212). "In fact, *there is no scientifically established ideal serotonin chemical balance,* much less an identifiable pathological imbalance" (Ibid., emphasis added). The biological marker,

> This reliable witness is absent in psychiatric illnesses in general and in depression in particular, and for this very reason, it is necessary to find explanatory strategies different from those that characterize classical etiological studies (Caponi, 2009, p. 2).

However, as here mentioned, even without proven biological markers or a new explanatory hypothesis, that first comprehension (dating from the 1960s) has endured as the sustainer of the medication related to its claimed pathology. That is, the SSRIs, which have the specific function of regulating the chemical imbalance of this neuron in the brain, according to the original hypothesis, remains the most sold antidepressant (Quevedo et *al.*, 2019).

However, there is a great interest of the pharmaceutical industry in developing drugs that act on the histamine receptor (H3) in the CNS, given that they have potential for the treatment of several pathologies: Alzheimer's, Parkinson's, schizophrenia, attention deficit hyperactivity disorder, obesity, narcolepsy (chronic sleep

disorder). One of them is the reported TAD, with an important use in the treatment of chronic pain, i.e. fibromyalgia, headaches and migraines, as well as pain of neuropathic origin.[4]

Related to the latter, there is an important curious fact: studies report that many chronic pain patients are often diagnosed with depression, likely in consequence of their suffering while according to some authors, the proposed mechanism of antidepressant action is not associated with an analgesic effect (Rang and Dale, 2020). However, in ancient times, opium was used for the treatment of depression, suggesting a correlation between pain and depression (Weber and Emrich, 1988).

Anxiety/anguish, its affective correlates (to pain), are widely reported by numerous patients diagnosed as depressed, in different intensities: from the exclusively psychic/emotional reported anguishes, to the somatised (registered in the body) ones, as in fibromyalgia, panic crises and physical pains (Berlinck, 1999, p. 50). One of the consequences of this fundamental observation about the human psychic and physiological apparatus is that depression, pain, and anguish are often indistinguishable, given that they are sensations referred to as extensive helplessness.

As the literature also shows, depression seems to have had distinct expressions from the origin of its mapping to the present days. Although these expressions overlap each other to some extent, nowadays authors (mostly from psychoanalysis) point to especially present bodily clinical pictures: fatigue, generalized and non-localized pain - as in the here above mentioned fibromyalgia -, chronic fatigue, insomnia, and the inertias of the body.

2.1 The Neurobiology Of Depression

In May 2011, a two-day conference entitled "The neurobiology of depression - revisiting the 5-HT hypothesis" (hydroxytryptamine, the serotonin neuron) was held at the University of Montreal, Canada, counting the 33rd International Symposium of the CNS Research Group (*Groupe de Recherche sur le Système Nerveux Central*), which annually brings together leading researchers from around the world to discuss a specific, pre-chosen topic. As defined by its organizers from three Canadian universities, Laurent Descarries (*Université de Montréal*), Chawki Benkelfat (McGill University) and Paul R. Albert (University of Ottawa), the objective of that year's meeting was to gather experts from different disciplines to review current knowledge on the neurobiology of depression - and in particular the serotonin hypothesis, including its most recent results. The twenty lectures then delivered were the basis for the publication of two special issues.[5]

Among these lectures, the authors confirm that a variety of functional deficits of serotonin in the brain circuits known to regulate emotions, whether primary or secondary, have been consistently associated with Major Depressive Disorder (MDD)[6] , as suggested by post-modern genetic, neurochemical, neuroimaging, and pharmacological studies (p. 2379). They further state that more recently, relatives of MDD patients are reported to be more sensitive to serotonin deficits, and there is evidence that altered serotonin functions are still present in MDD patients in remission, suggesting that being found with altered or low serotonin levels may represent a risk factor and trait diathesis increasing vulnerability to MDD (Ibid.).

Some authors in the above mentioned publication report, furthermore, that over the years, the serotonin hypothesis of depression would have been refined to take into account new knowledge.

[4] SSRIs and MAOIs also have certain analgesic action, but of lesser efficacy than the one produced by TADs.

[5] Philosophical Transactions of the Royal Society B: Biological Sciences (Albert, Benkelfat & Descarries, 2012).

[6] Major Depressive Disorder (MDD) is characterized by two or more weeks of depressed mood or diminished interest, associated with symptoms such as disturbed sleep, decreased appetite and libido, psychomotor changes, reduced concentration, excessive guilt, and suicidal thoughts or attempts. It is insidious and often recurring, with each episode increasing the likelihood of a new one by 16 percent. MDD is the second leading cause of disability worldwide, in the 15–44 age group for both sexes combined, second only to heart disease. The financial cost involved in this diagnosis and treatment is billions of dollars per year (Albert et al., 2012, p. 2378).

However, they reiterate some original inconsistencies, exemplifying that induction of a transient CNS serotonin reduction obtained experimentally in healthy control cases revealed only modest effects on mood, *"if any"*. (Ibid., p. 2379, emphasis added).

> Today, it is generally accepted that a variety of genetic, environmental, and neurobiological factors are implicated in depression. All areas of neuroscience, from molecules to mind, from genes to behavior, and from the laboratory to the bedside, are actively engaged in attempts to elucidate the physiology of depression, as well as the mechanisms underlying the efficacy of antidepressant treatments (Ibid.).

And add, "The model of a mental disorder based exclusively on the dysregulation of a determined neurotransmitter system is obviously simplistic and open to criticism" (Ibid.).

2.2 Rise and Shining of Antidepressants

When Kuhn and Kline in the late 1950s announced the "discovery" that promised to treat depression, the new drugs (antidepressants) would not have become famous and immensely profitable from the start. Herzberg (2010) argues that these were first marketed only in psychiatric publications as a treatment for severe and lifelong depression; early advertisements, for example, described these drugs as substitutes for electroconvulsive therapies. It was only in the early 1960s that (mental health) experts in the United States began to spread the word about depression. Then depression - and no longer anxiety -, was responsible for the new epidemic wave of mental illness and its associated physical symptoms (Herzberg, 2010; Horwitz and Wakefield, 2010), from the belief (once hypothetical) of low levels of serotonin.

Herzberg will further reiterate from Healy (1997) that, however, this hope for brain chemical simple answers were indeed precariously supported by evidence. The author clarifies:

> Whatever psychotropic drugs are doing, they are not correcting any observable imbalance in dopamine, serotonin, or norepinephrine. Even the initial observation that reserpine caused depression turned out to be largely anecdotal and misleading, or totally incorrect (...). In the case of antidepressants, no one has explained why it takes two weeks for the drugs to work, even though they increase monoamine levels immediately, or why the drugs work only for a relatively small portion of depressed patients. Even the most positive studies preferred by drug manufacturers show improvement in approximately 60% of patients, barely more effective than a placebo (Herzberg, 2010, p. 167).

This and other mysteries, claims Herzberg (2010), do not diminish the importance of biology to emotional and mental illness, but they are simplistic and devastating models when equalizing moods with the amount of a few monoamines in the brain. The author alludes finally to other possible, more complex models, such as one in which the brain would resemble the (meteorological) weather, sufficiently complex and self-influencing, and absolute precision and control would be impossible, even in theory. Another model, also considered, would emphasize the difficulty in determining the causality of a system based on interactions between genes, biology, and one's experiences. Thus, the author understands that chemical substances would indeed play a role in moods and emotions, but it cannot be affirmed that they cause them (ibid.).

Authors consider that the possible reason why simplistic explanations such as serotonin depletion would have survived is not because they have been proven true - once they have not - but because they would have been very useful for almost everyone involved in this story: the pharmaceutical industry, which used it to prove efficacy to the Food and Drug Administration (FDA) and general advertisements; psychiatric professionals, who used them to claim a "true understanding" of their patients' psychic pain, while highlighting the drug power prescription; insurance companies, who benefited from the "objectivity of causal diagnosis"; and last but not least, the patients themselves, who often preferred a supposed physical (biological) illness to a

mental/psychiatric one, becoming consequently "grateful for the simple cure" (ibid. , p. 168).

In this direction, while antidepressants did not achieve celebrity at first (as previously stated), they were nevertheless a gateway to the awakening of the popularization of the "new brain sciences." Accompanied by simple explanations of brain functions and their "correction" such as by antidepressants, these became a prime example of the relatively objective theories of brain chemistry favored by commercial medicine (Herzberg, 2010).

Schildkraut, forerunner of the neuronal default hypothesis, himself would have recognized:

> Even if drugs are effective in treating a disorder, this does not necessarily mean that their mode of action implies that the latent abnormality will be corrected (1965, apud Horwitz and Wakefield, 2010, p.198).

In this sense, even if the hypothesis of serotonin deficiency were proven, it would explain only a part of the cases of depression, as Schildkraut, himself again, would have recognized years earlier (Ibid). On the other hand, we find in Nathan Klein, also a "discoverer" of an antidepressant produced from iproniazid, the genesis of the belief that these new drugs would do more than cure diseases: they would enhance/improve emotional states, beyond the cure. An example of this, was when in an interview with the New York Times in 1957, Klein would claim that "the beneficial action of the drug would not be limited to sick individuals, but could improve the ordinary performance (...) of essentially normal people" (1957, in Herzberg, 2010, p. 170).

The serotonin hypothesis, the driving force behind antidepressants that "corrected the deficient levels of this neurotransmitter", pointed in its early days to the (today common) idea of enhancement of the human kind: an area of pharmacology that aims at the improvement of the so-called normal human performance (without intervention), as in the sexual, intellectual and emotional human spheres.

An article in Maclean's Magazine[7] recorded the delight of some researchers of the time: *"Improve your memory! Increase your sexual potency! Relieve your anxiety! End your depression! Maximize your powers of concentration! Get rid of agonizing physical pain!* " (Ibid., p. 171); or, in some other advertisements, *"No fun? No desire? Antidepressants can bring new life to your life! "* (Ibid., p. 174).

Voices like these grew in the 1980s, with the idea of "a new brain" amenable to psychopharmacological remodeling, and the popularization of these new neurological/brain sciences were crucial to the turning point of the so-called biological revolution (ibid., p. 173). This is what the subscription magazines of the time used to publish in their cover advertisements, and sold massively in many countries.

However, at the same time (1970s and 1980s), other researchers were also reexamining the crucial question: do people diagnosed with depression suffer from a chemical imbalance that can be corrected by medication? Were the new drugs really antidotes to something chemically wrong in the brain? (Whitaker, 2017).

2.3 Returning To The Chemical Imbalance Hypothesis

> *Although SSRIs are considered antidepressants, they are FDA-approved treatments for eight separate psychiatric diagnoses, ranging from social anxiety disorder to obsessive-compulsive disorder and premenstrual dysphoric disorder.*
>
> J.R. Lacasse and J. Leo

A recurring criticism made is that supposed deficiencies of serotonin or other brain chemicals could even be consequences, rather than causes, of depression. To many authors, the most serious conceptual problem with "the hypothesis" is that there are no proper benchmarks for normal and pathological levels of serotonin or other amines, just as there are for other biological markers for

[7] Maclean's is a Canadian weekly news magazine. It was launched in 1905 under the name The Business Magazine. Its weekly circulation is 350,000 magazines. (Wikipedia)

biological diseases (Horwitz and Wakefield, 2010; Dunker, 2021).

The Clinical Science Laboratory of the US National Institute of Mental Health (NIMH), regarding "the hypothesis", in a statement made by researchers from this institute, further states that "the demonstrated efficacy of SSRIs cannot be used as primary evidence for serotonin dysfunction in the pathophysiology of these disorders" (Lacasse and Leo, 2005, p. 1211). In this sense, Cowen and Browning (2015) restate this uncertain state of affairs: to these psychiatrists the hypothesis eventually achieved the status of a "conspiracy theory whose purpose was to allow the industry to market SSRIs to a gullible public" (p. 158).

The explanation for the cause of depression (in all its intensities, from mild to a severe and chronic MDD) remains in fact unknown or at least quite controversial among different theoretical and clinical bodies, while, nevertheless, the idea that neurotransmitter imbalances cause depression is still vigorously promoted by pharmaceutical companies and psychiatric practice in general.

Consequently, today SSRIs are the most prescribed class of antidepressants in the world, besides the other classes of antidepressants[8] which, altogether, indeed report clinical efficacy.

However, in several studies, they strongly compete with placebos; as in an important study that verified a large number of clinical trials of antidepressants submitted to the FDA, showing an impressive 80% response rate to placebos[9]. However, another critic commonly made by researchers is that, lacking a biological marker, it is from the mediation of the antidepressant that an explanatory causal network is then built. "This kind of explanation is possible because there is no 'reliable witness' that allows translating human sufferings to the controlled world of the laboratory" (Pignarre in Caponi, 2009, p. 3).

Nevertheless, the message that consumers take home when buying an antidepressant by viewing the ads for SSRIs, is that they work by normalizing neurotransmitters that have gone wrong or are below the proper level in their brain. "This was a hopeful notion 30 years ago, but it is not an accurate reflection of the current scientific evidence" (Lacasse and Leo, p. 1214). Also according to these authors, what remains unmeasured, is how many people seek the help of their doctor because they have been convinced that they suffer from an insufficiency of serotonin. "These advertisements present a seductive concept of cure for an imbalance that these same people would not otherwise have access to" (Ibid.).

Thus, the paradox goes on. Nowadays the American Psychiatric Press Textbook of Clinical Psychiatry addresses serotonin deficiency as an unconfirmed hypothesis, stating, "Additional experience has not confirmed the hypothesis of monoamine depletion," while in a contemporary advertisement one could read: "Celexa helps restore the brain's chemical balance by restoring the supply of a chemical messenger called serotonin", thus revealing the contrast between the official guide, and the advertisement.

In the United States, between 1991 and 2000, the diagnosis of depression doubled in parallel with the introduction of SSRI drugs. According to publications, these drugs were not marketed by explaining the problematic correlational data; instead, "they were sold as remedies for the chemical imbalance that caused depression" (Lacasse and Leo, 2005, p. 35).

At last, scholar Nikolas Rose in an interview (Spink, 2010), questions research programs in the psycho/neuro/pharmacological field that would be "path-dependent," as when related to serotonin levels at the synapse as a deficit or abnormality of the serotonin system. He argues that "this was a very potent heuristic device for psycho-pharmacology and later for psychiatry, but almost

[8] According to MD.Saúde on 02/20/2021 https://www.mdsaude.com/

[9] Kirsch, I., Moore T. J., Scoboria, A., Nicholls, S. S. (2002) The emperor's new drugs: An analysis of antidepressant medication data submitted to the U.S. Food and Drug Administration. Prev Treat 5: article 23. Available at: https://psycnet.apa.org/record/2002-14079-003 Accessed by Lacasse and Leo on 10/14/2005; and by the authors of this article on 01/19/2022.

certainly, if this is not completely wrong, it's quite wrong (p. 9)".

Rose summarizes that in a certain kind of biological psychiatric thinking and research –presumably the prevalent kind world wide-, this (assumption-dependent research) provided a gateway and a model for understanding a number of other issues that were occurring in the transmission between neurons, but that "the hypothesis" would have remained "assumed".

> ( ) Everybody thought that the locus of the disorder was the brain; somehow it was a brain thing - maybe a gene thing; maybe a neurotransmitter thing. Nobody talked about it, it was an assumption (...) There is a psychology underpinned by neurobiology. And if you talk to people, they also think of themselves as people with a neurobiology and not just brains on legs. They don't think of their minds as what their brains do, but, not surprisingly, they think they are more than that. (Rose in Spink, p. 311).

2.4 The Serotonin Cause for Depression: A Hypothesis or a Persisting Myth?

There are possibly one hundred billion neurons in the human brain. A single neuron would have between one thousand and ten thousand synaptic connections, and the adult brain altogether around 150 trillion synapses. According to experts, the brain's serotonin system is the largest brain system known and can be characterized as a gigantic neuronal system (Azmitia, 1991). However, the chemical imbalance theory of mental disorders reduces this enormity and complexity to a simple pathological mechanism that is relatively easy to describe and grasp. As mentioned, in depression, the problem would be that serotonin neurons release too little serotonin into the synaptic cleft and, therefore, the brain's serotonin pathways become underactive. Thus, antidepressants would raise and normalize serotonin levels in these clefts, allowing these pathways to transmit messages at a, now, appropriate rate.

Since the hypothesis said that this low level of serotonin caused depression, consequently, anyone with this diagnosis should have low levels of serotonin, or "lower than normal" (without knowing exactly what the cut-off level was), in their cerebrospinal fluid.

In 1969, Malcolm Bowers at Yale University, became the first to report on whether or not depressed patients had low levels of serotonin metabolites. In a study of eight depressed patients (all previously on antidepressants), Bowers announced that their serotonin levels were lower than normal, but "not significantly so" (Bowers in Whitaker, 2017, p. 85).

Two years later, other researchers, from McGill University stated that they too had not found a "statistically significant" difference in the serotonin levels of depressed patients, and that they had also found no correlation between serotonin levels and the severity of depressive symptoms.

In 1974, Bowers returned with an improved follow-up study, with a very thought-provoking result: depressed patients who had not taken antidepressants, exhibited "perfectly normal 5-HT levels" (Bowers, 1974).
In other words,

> The literature reviewed here strongly suggests that a reduction in brain norepinephrine, dopamine, or serotonin is not sufficient, by itself, to account for the development of the clinical syndrome of depression (Mendels, 1974, in Whitaker, 2017, p. 85).

Yet, other researches continued to credit the serotonin hypothesis in a positive way, and soon American psychiatrists were writing that 30% of depressed patients had low serotonin levels, while other Japanese studies revealed that 24% of patients diagnosed with depression "had high serotonin levels" (Nagayama, 1986).

Following the studies of those decades focused on this task, in 1984 researchers at the NIMH investigated the hypothesis once again, seeking to see if the biological subgroup of depressed patients with low serotonin levels responded best to an antidepressant, amitriptyline, which blocked

its reuptake. Sometime later, wrote James Maas, the team leader of these researchers:

Contrary to expectations, no relationships were found between cerebrospinal 5-HIAA and the response to amitriptyline (...). Elevations or decreases in serotonin system function, by themselves, do not tend to be associated with depression. (in: Whitaker, 2017, p. 87).

In light of the recurring lack of evidence since the inception of the stated hypothesis and, conversely, numerous counter evidence, we end up wondering, in echo with the counter evidence, whether it is still today "worth thinking of serotonin as a primary causative factor in depression" (Lacasse and Leo, 2008).

In an article from Harvard Health Publishing, a 2019 Harvard Medical School publication titled "What Causes Depression?"[10] the author designates the chemical imbalance hypothesis as a figure of speech:

> It is often said that depression results from a chemical imbalance, *but this figure of speech fails to capture the complexity of the disease*. Research suggests that depression does not arise simply by having too much or too little of certain brain chemicals. Instead, there are many possible causes for depression, including impaired mood regulation by the brain, genetic vulnerability, stressful life events, medications, and medical problems. Several of these forces are believed to interact to cause depression. (Ibid., emphasis added).

In current articles concerning depression - whether in the field of psychiatry, psychoanalysis, descriptive or fundamental psychopathology, or even in the neurosciences - in their different views and conceptualizations, the serotonin level is hardly ever addressed as a proven causal factor[11]. However, as previously stated here, the prescription of a SSRI type antidepressant is the usual response to the symptoms reported and classified in some category of MDD, whose first causative logic would be the serotonin hypothesis – not only unproven but also to some extent, currently silenced.

In our understanding, MDD or depression in its various forms would indeed not be explained by the serotonin level, but this hypothesis would be "respected" by most, crediting it with the possibility of the reason for depressive conditions. While, on the other hand, nothing proves it otherwise.

When the first antidepressants were manufactured, depression was perceived as relatively rare. "The idea that there should be a depression that could be treated on the basis of drugs had to be invented, as well as that of an antidepressant," states Healy (1997, introduction).

Interestingly, in Japan, this phenomenon that came to occur more recently than in the West, since the SSRIs were introduced to the Japanese market only in 1999; however, already accompanied by intense "disease awareness" propaganda from the beginning. Soon after, in 2000, public opinion started to perceive depression as a "common, everyday" form of mental illness; a perception strengthened by Japanese popular sayings such as *kokoro no kaze*, an expression that characterizes depression as "a common cold of the soul" (Okuda, 2015).

> Depression has become more widespread in Japanese society in the last 10-20 years, and the growing number of people with depression in Japan today is becoming a social problem (...) We find a marked change in treatment models, referred to in this article as bio medicalization and pharmaceuticalization of mental health (...). As a consequence of these trends, an inordinate number of campaigns for disease awareness have emerged as part of the promotional efforts of pharmaceutical companies to increase sales of prescription drugs. These campaigns seem to have had a significant impact on people's behavior about depression (Ibid., p. 633).

[10] What causes depression? - Harvard Health accessed on 11/11/2021

[11] In the main academic search engines: Scielo, Google Scholar/Scholar google, VHL, MeSH, EMBASE, BDTD; WorldWideScience, PubMed Central, Research Gate, among others.

The author reports that prior to the entry of SSRIs into the Japanese market, the size of antidepressant sales remained relatively low, at around 17 billion/year. With the entry of SSRIs - underpinned by the serotonin hypothesis - this same market began to skyrocket, and by 2012 had reached 137.7 billion/year - a more than eight-fold increase over the 12 years measured since their inception in Japanese pharmacies (Okuda, 2015). Okuda's publication seems to illustrate clearly, as in a mirror, the dynamics that starts to be installed with the very installation of SSRI antidepressants in the market, supported by an expanded diagnostic system (through the western standardized diagnostic manuals), which until then kept some reserve and circumscription in Japanese society. Since then, the numbers of work leaves due to depression in the country have increased considerably. Okuda names the phenomenon he observes and studies as the fabrication and contagion of a disease (Ibid., p. 637).

It is possible that the construction of a logic that made sense - that is, a failure or lack in the conduct of brain neurotransmitters that would be in the constructed hypothesis, responsible for triggering depression, remediable with antidepressants - occupies today a certain place of myth, even if not so named: the myth of the origin of depression.

Ever since, this myth - the hypothesis - is equally accepted and appropriated by society, to whom it also explains and justifies its malaise.

Rose, in the aforementioned interview with Spink (2010), reports:

> We know, for example, in the field of psychopathology, that in the last ten years there have been written, by more or less well-known people, narratives where the story is more or less this: they fell into depression (...) and the resolution, in the end, is always that they accepted their psychiatrists' view that it was a biological disorder and they medicated themselves and got better (p. 310).

Recently a new antidepressant substance, esketamine, in fact a derivative of the ketamine, has been approved by some regulatory agencies. The drugs made from ketamine have no effect on the reuptake of neurotransmitters, but inhibit the activity of glutamate, a stimulating neurotransmitter in the CNS. Since ketamine is very old and cheap, a derivative was produced to enable an abusive price tag for "a new promise for treating depression".[12]

III. CONCLUSION

“The hypothesis” has been widely assumed since its origin, already more than half a century ago, bringing about a massive manufacture of antidepressant drugs, namely the SSRIs. Fluoxetine, launched in the market in 1986 (broadly referred to as *Prozac*, its gigantic successful representative in sales), came in for the so desired reestablishment of this neuronal lack, supposedly the cause of depression.

However, pharmacological studies of antidepressant substances reveal that their adverse effects interfere with the activity of several other neurotransmitters such as histamine, acetylcholine and noradrenaline, in addition to serotonin. Furthermore, the distribution of serotonin in the body and its peripheral physiological effects oppose the hypothesis of selective inhibition of serotonin reuptake, which is widely distributed in the CNS, in the SCV and especially in the GIT, which concentrates 90% of the body's serotonin. Therefore, with the inhibition of its reuptake, whose mechanism is the same in all these systems, intense adverse effects would also be expected to happen in the BMS and in the GIT, which is not observed.

The effects of the three groups of antidepressants on histamine, acetylcholine and noradrenaline receptors are observed peripherally and classified as adverse. Nevertheless, the peripheral adverse effects, resulting from selective inhibition of serotonin reuptake, which would necessarily be intense in the digestive and cardiovascular

[12] The Antidepressant Conundrum | Super (abril.com.br) accessed on 02/11/2022.

system, are simply not observed, raising more doubts about this alleged selectivity. Moreover, the possible side effects of real selective serotonin reuptake inhibitors would be incompatible for the treatment of depression.

The literature also reveals that in fact there are no established biological markers for good levels of serotonin. There are also certain categories of antidepressants (such as TADs) that also act on physical pain, which seems to bring relief to many patients diagnosed as depressed.

Neurobiological studies also point to the complexity of the human brain and the CNS, ruling out the possibility of a hypothesis that would focus on the functions of a single neurotransmitter (serotonin), amidst the trillions of synapses that would occur, resulting from the thousands of synaptic connections of a single brain neuron, among the possible one hundred billion mapped by studies in this area.

There are also studies that question whether the supposed low levels of serotonin are in fact the cause, or the consequence, of depressed states. For all these evidences it becomes difficult to relate depression to a single neurotransmitter, as sustained until today.

Critical authors claim that a logic is established as supposedly true: since the treatment of depression starts from the serotonin hypothesis, when the patient is relieved of his pain - physical or mental - with the use of antidepressants (generally approximately 60% of medicated patients are reported to respond to antidepressants, while 40% to placebo), it is as if the hypothesis was confirmed, even though it has never been effectively proven; and it seems, in fact, to be increasingly distant from a proof.

The serotonin hypothesis has finally been proposed as *a figure of speech*, by a study at Harvard Medical School (2021). We believe it is important that this category be distinguished from a hypothesis postulated and conveyed as factual, given that it has never been fully confirmed.

Lastly, do the announcements of the World Health Organization (WHO) alarm us, or to what extent do they fulfill the prophecy? Twenty years ago the projections were that by 2020 depression would be the second most numerous disease, preceded only by heart diseases. The projections now in 2022 are that by 2030 depression is expected to be the largest in number of people affected. How much would the serotonin hypothesis for depression, sustained on the foundation of old, precarious and never proven parameters, be helping or, instead, hindering the understanding of this complex and currently rampant picture?

Our understanding is that there is something still quite unknown and misunderstood about the clinical picture of depression, being therefore, neglected; leading it, inevitably, to its ungoverned, epidemic status.

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Newborn Survival Analysis: Neonatal Mortality between 2019 and 2021 in Burundi

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ABSTRACT

Progress towards the fourth Millennium Development Goal - to reduce child mortality under the age of 5, to which all countries are committed - has been slow in several countries in the Central African region in recent years. This study includes 2,886 observations from Burundi between 2019 and 2022. Early neonatal mortality (0 - 6 days) accounts for 50% of neonatal deaths in the country. Through survival analysis, I identified several key risk factors- Caesarean section, malaria, and fetal distress-as the primary causes of early neonatal mortality. Contrary to conventional wisdom, most of these health problems can be managed with cost- effective, evidence-based interventions that do not require sophisticated skills or technologies in countries with high infant mortality. By improving the health of the mother, through adequate nutrition during pregnancy, correct management of childbirth and appropriate care of the newborn, 32.9% of infant deaths can be avoided.

Keywords: cox model, kaplan-meier model, survival analysis, statistics, neonatal mortality, burundi.

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Keywords: cox model, kaplan-meier model, survival analysis, statistics, neonatal mortality, burundi.

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I. INTRODUCTION

Maternal health in Burundi remains a critical concern, with alarmingly high maternal, neonatal, and child mortality rates, significantly surpassing the targets set by the Sustainable Development Goals. According to the 2021 report from the Congress of the Obstetrics and Gynecology Association, the country has a maternal mortality ratio of 334 deaths per 100,000 live births, a neonatal mortality rate of 23 per 1,000 live births, and an infant and child mortality rate of 78 per 1,000 live births (EDSB III 2016-2017). These high mortality rates are primarily driven by complications during pregnancy, childbirth, and the postpartum period. Burundi's healthcare system is underdeveloped, grappling with limited resources, poverty, food insecurity, and inadequate access to healthcare, particularly in rural areas. The country faces challenges such as insufficient infrastructure, a lack of trained healthcare professionals, and inadequate neonatal care, including the shortage of essential equipment like incubators and resuscitation tools. Many women in rural areas also lack proper prenatal care, and traditional birth attendants often lack the skills to manage serious complications during childbirth. In the same context, statistics collected by the WHO indicate that approximately 830 women die every day worldwide due to complications related to pregnancy or childbirth [1]. According to the same statistics, half of these deaths occur in Sub-Saharan Africa. Following all these observations, the following questions arise:

- "How can survival time for newborns be increased during the first four weeks after birth ?"
- "How do neonatal deaths evolve during the first four weeks after birth?"
- "Does the survival time of the newborn differ depending on whether the mother was exposed to a disease before childbirth?"

II. RESEARCH METHODOLOGY

- This research aims to model the time remaining before the death of a newborn, presenting the relevance and interpretation of survival curves.

The survival analysis of patients relies on robust biostatistical techniques, such as the Kaplan-Meier model or Cox regression. We focus on the occurrence of an event over time, and in the case of death, this goal involves attempting to increase the survival duration of patients (the newborns).

In practice, estimating the average survival times in hospitals proves impossible in many situations, as it is rare to follow all patients until the event occurs. To address this difficulty, survival analysis techniques have been developed [2].

For this purpose, a proportional hazards model (Cox Model) will be used, which is a class of survival models in Statistics. Survival models relate the time that elapses before an event occurs based on the survey data collected [3].

Survival analysis was performed using the R software, and SPSS software was used for descriptive analysis.

III. DATA SOURCES

The data from DHIS2 is used by the Ministry of Public Health and the Fight Against AIDS of Burundi. This system is installed in all health centers across the country, and the data is reported daily to the national server. The censoring in the dataset was random.

IV. CHOICE OF VARIABLE

Statistics indicate that female babies are generally more resilient, while male babies face higher risks of death, as they are more susceptible to infections, according to the WHO [1].

Approximately 830 women die each day worldwide due to complications related to pregnancy or childbirth. In 2015, 303,000 women died during or after pregnancy, with the majority of these deaths occurring in low-income countries, many of which could have been avoided. The risk of maternal mortality is higher among adolescents under the age of 15. Pregnancy and childbirth complications are among the leading causes of death among adolescents in most developing countries, according to the WHO [1].

A well-known case study documenting the severe consequences of Plasmodium falciparum malaria during pregnancy, particularly highlighting higher rates of maternal anemia and low birth weight [4].

Fetal distress refers to signs before and during birth indicating that the fetus is in trouble. It usually occurs when the fetus does not receive enough oxygen. Each year, between 4 and 9 million newborns develop asphyxia. It is estimated that one million newborns die annually from birth asphyxia in many developing countries, with causes such as cord compression, placental abruption with retroplacental hematoma, and excessive uterine contractions [1].

The study concluded that gestational diabetes mellitus (GDM) is a condition with profound effects on both maternal and fetal health. Women with GDM are at increased risk of maternal anemia, and their infants are at higher risk for low birth weight due to placental insufficiency. Poorly controlled glucose levels during pregnancy increase the risk of pregnancy complications, including preterm birth, neonatal hypoglycemia, and fetal distress [5].

A study titled “Maternal mortality and severe morbidity associated with low risk planned cesarean delivery versus planned vaginal delivery at term” [6], examined the risks associated with planned cesarean deliveries in low-risk women. The study found that while the overall in-hospital maternal mortality rate was not significantly different between the planned cesarean and planned vaginal delivery groups, the planned cesarean group had an increased risk of severe maternal morbidity, with an adjusted odds ratio of 3.1.

V. SURVIVAL ANALYSIS

5.1 Survival Estimation: Kaplan-Meier Method

The survival curve is the most commonly used representation to describe the dynamics of death occurrences over time. It is a curve that represents the survival rate S (the probability of surviving at least until time t) as a function of time. The estimation of survival curves primarily uses the Kaplan-Meier technique 1, a nonparametric method (i.e., one that does not use a model where the distribution of survival durations is a function of time) in which an estimate of the survival probability is calculated at each occurrence of the event of interest (e.g., death). In the Kaplan-Meier method, the observed participation time is divided into time intervals, starting at the time when a death occurs and ending just before the next death. Survival is estimated for each time interval, giving the curve a "staircase" appearance [7].

5.2 Cox

The proportional hazards regression model proposed by Cox in 1972 to study the relationship between the time to occurrence of an event (e.g., death) and a set of explanatory variables (e.g., genes) has had a significant impact on survival data analysis, both theoretically and practically, and has quickly become the most widely used model. However, it assumes (like any multiple linear regression model) that there are more observations than variables, complete data, and variables that are not strongly correlated with each other. These assumptions are often impossible to meet in practice [8].

Cox's semi-parametric regression (estimating the influence of exogenous factors without assumptions about the baseline distribution) is the standard method for analyzing longitudinal data from cohort studies or clinical trials. The goal is to model the logarithm of the instantaneous risk as a function of a set of explanatory variables x that may change over time [8].

$$\ln h\,t\,x(\,,\,) = \beta 0(t) + \sum_{k=0} \beta kXk\,t(\,) \ln h\,t$$

$$x(\,,\,) = \beta 0(t) + X'\beta$$

Equivalently:

$$h\,t\,x(\,,\,) = 0(\,)^{\Sigma_{k=0}^{1}\beta kXk(t)}\,h \qquad t\,e$$

$$h\,t\,x(\,,\,) = h0(t\,e)^{X'\beta}$$

The term ho(t) is a baseline hazard independent of the explanatory factors of the model. No assumption is made about the duration distribution, i.e., the form of ho(t). As with a survival curve, two special variables are required to estimate the Cox model: the follow-up times and the event indicator (whether or not the event occurred).

VI. DATA PROCESSING

6.1. Survival Curves by Sex of Newborns

We use the median time rather than the mean time here because as soon as some of the observations are censored, we cannot calculate a mean time [7].

The Kaplan-Meier method shows the survival curve of infants over the 30 days following birth, with a survival probability ranging from 0 to 1 (100%).

Additionally, the median time, which corresponds to a 50% survival chance, is equal to 3 days, meaning that from the 3rd day, these newborns have a 50% chance of dying within the next 30 days. Although very close, it is observed that the survival curve for female infants is higher than that for male infants.

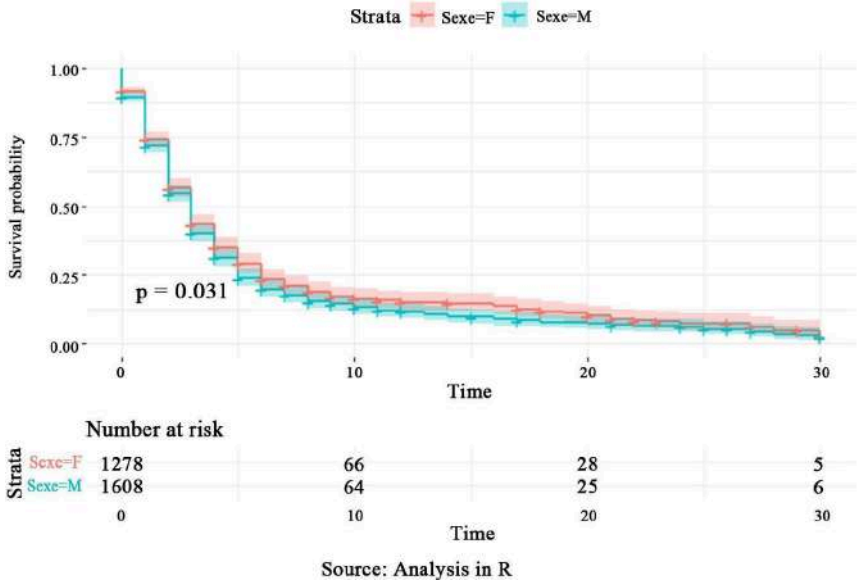

Figure 1: Survival Curves by Sex of Newborns

Figure 1 shows that among 1,278 female infants, 653 (51.09%) died, while 854 (53.10%) of the 1,608 male infants died. Do neonatal death rates differ significantly based on the infant's sex? We will now test whether this difference is statistically significant. Hypotheses:

- *Ho:* No difference in survival between the two studied groups, meaning neonatal deaths affect both girls and boys equally;
- *Ha:* Difference in survival between the two studied groups, meaning neonatal deaths affect girls and boys differently.

Table 1: Sex of Newbzorns

		Observed	Expected	(O – E)^2 /E	(O – E)^2 /
Sex = F	1278	653	3	2.05	4.64
Sex = M	1608	854	3	1.74	4.64
	Chisq = 4.6 on 1 degrees of freedom, p =0.03				

Table 1 shows that the Chi-squared value is 4.6, with 1 degree of freedom (df), and a p-value of 0.03, which is less than 0.05. Therefore, we reject the null hypothesis (H0) at the 5% significance level. This indicates that boys are more affected by neonatal mortality compared to girls.

6.2 Survival Curves of Newborns Based on Whether the Mothers Have Malaria

Figure 2 shows that newborns of mothers not affected by malaria have a better survival curve, indicating improved survival outcomes compared to those whose mothers were affected by malaria. Furthermore, the median time is on the 2nd day for newborns of mothers with malaria, and for mothers without malaria, the median time for their newborns is on the 3rd day. However, the survival curve for newborns of mothers with malaria stops at the 23rd day, meaning that from the 23rd day these newborns have a 0% chance of survival.

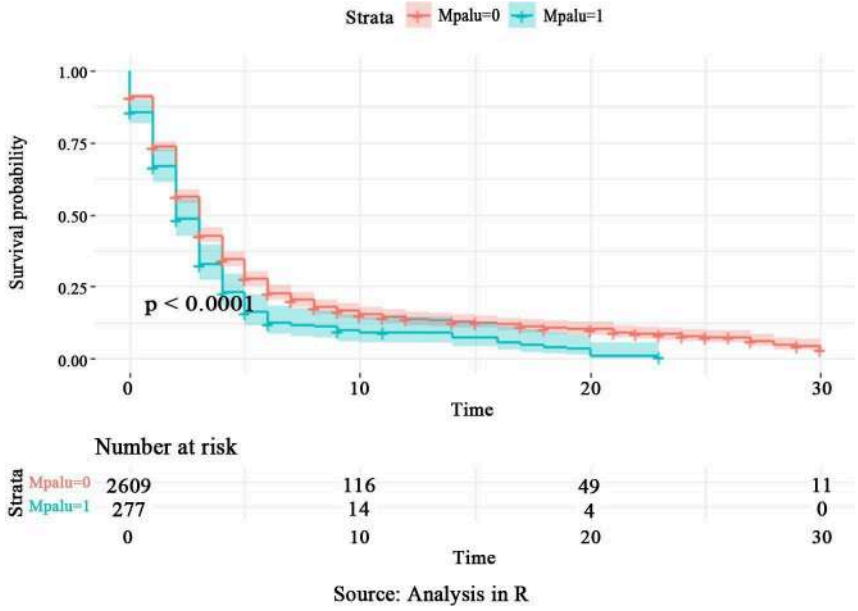

Figure 2: Survival Curves by Malaria in Mothers

It is observed that a large majority of mothers (2609) were not sick with malaria, and only a small minority of mothers (277) had malaria. Note that 1299, or 48.9%, of newborns died among mothers who did not have malaria, while 208, or 75.1%, died among mothers who were affected by malaria.

Table 2: Malaria in Mothers

	N	Observed	Expected	(O – E)^2 /E	(O – E)^2 /E
Malaria = 0	2609	1299	1345	1.55	17.7
Malaria = 1	277	208	162	12.80	17.7

Chisq = 17.7 on 1 degrees of freedom, p = 3e-05

Table 2 shows that the Chi-squared = 17.7, df = 1, p-value = 3e-05 < 0.05, we reject H0 at 5%. There is a statistically significant difference in neonatal mortality between newborns with mothers who have malaria and those whose mothers are not sick.

6.3 Survival Curves of Newborns based on Diabetic Mothers

Figure 3 shows that the median survival time for newborns of diabetic mothers is between the 3rd and 4th days, while for mothers who are not diabetic, the median time is 3 days. It is observed that newborns of diabetic mothers show a better survival curve until the 20th day because these women received quality medical follow-up during their pregnancy. However, it is observed that the two survival curves for newborns converge after the 20th day, but with a sharp drop at the 27th day for newborns of diabetic mothers, meaning that from the 27th day, these newborns have a 0% chance of survival.

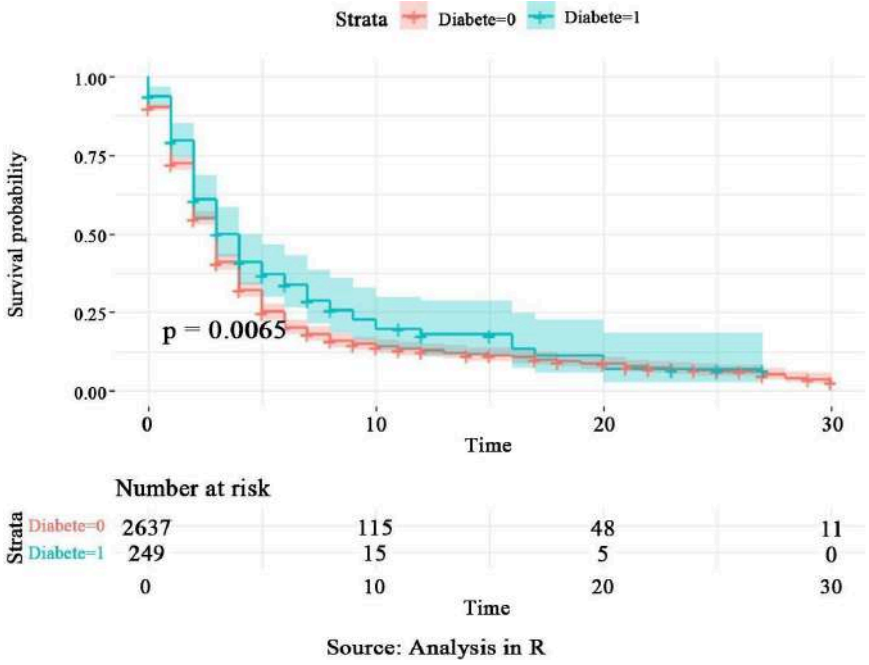

Figure 3: Survival Curves by Diabetes in Mothers

It is observed that the vast majority of mothers (2835) did not suffer from diabetes, but a small minority of them (249) were diabetic. It is worth noting that 1385, or 52.2%, of newborns died among mothers without diabetes, and 122, or 49.0%, of deaths occurred among diabetic mothers. I will test whether this difference is significant or not.

Table 3: Diabetes in Mothers

	N	Observed	Expected	(O – E)^2 /E	(O – E)^2/E
Diabetes = 0	2637	1385	1356	0.601	7.4
Diabetes = 1	249	122	151	5.415	7.4
	Chisq = 7.4 on 1 degrees of freedom, p = 0.007				

Table 3 shows that the Chi-squared = 7.4, df = 1, p-value = 0.007 < 0.05, we reject Ho at 5%. Therefore, there is a statistically significant difference in neonatal deaths between newborns of diabetic and non-diabetic mothers.

6.4. Survival Curves of Newborns based on Fetal Distress

Figure 4 shows that the median survival time corresponding to a 50% chance of survival is 3 days for both groups, meaning that from the 3rd day these infants have a 50% chance of dying within the 30 days. Although it is very close, we observe that the survival curve for fetuses without fetal distress is higher than that of fetuses showing signs of fetal distress.

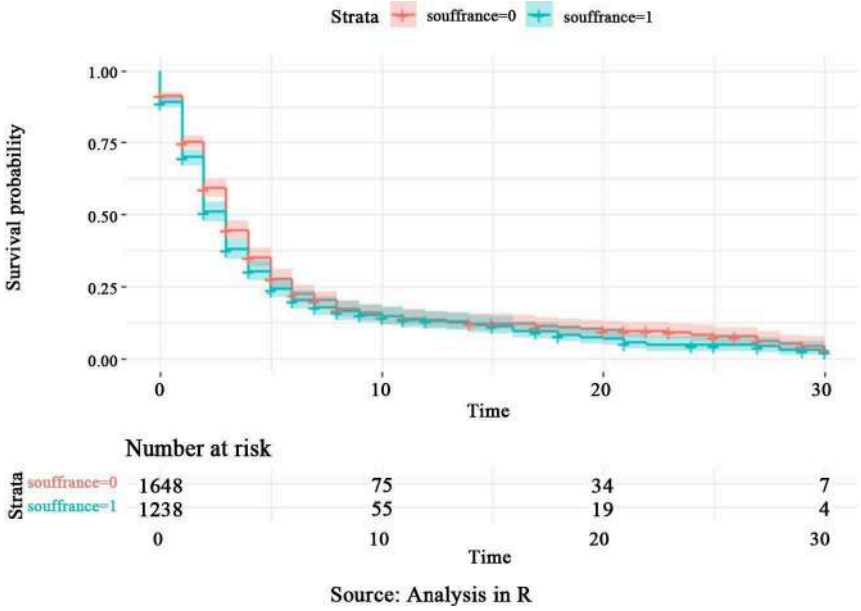

Figure 4: Survival Curves by Fetal Distress

We observe that 1238 refers to the fetuses that showed signs of fetal distress, and 700, or 56.5%, of the newborns died among them. While 807, or 49.0% of the deaths among the 1648 newborns, showed no signs of fetal distress.

Table 4: Fetal Distress

	N	Observed	Expected	(O – E)^2 /E	(O – E)^2 /
Fetaldistress = 0	1648	861	861	3.37	9.2
Fetaldistress = 1	1238	700	646	4.48	9.2
	Chisq = 8.1 on 1 degrees of freedom, p = 0.002				

Table 4 shows that the Chi-squared = 8.1, df = 1, p-value = 0.002 < 0.05, we reject H0 at 5%. There is a statistically significant difference in newborn deaths between fetuses born with fetal distress and those born without it.

6.5 Survival Curves of Newborns According to Mothers who Received Fetal Iron Supplement

Figure 5 shows that the median survival time corresponding to a 50% chance of survival is 3 days for both groups, meaning that from the 3rd day these infants have a 50% chance of dying within the 30 days. Although it is very close, it is noted that the survival curve for fetuses whose mothers received fetal iron supplements is lower than that of fetuses whose mothers did not receive fetal iron supplements from the 2nd day to the 15th day. Indeed, iron accumulates in the body, and its excess can cause severe poisoning: joint pain, diabetes, heart disorders, liver cirrhosis, and even colon and rectal cancers. However, from the 15th day to the 30th day, the two curves cross and therefore have the same survival probability.

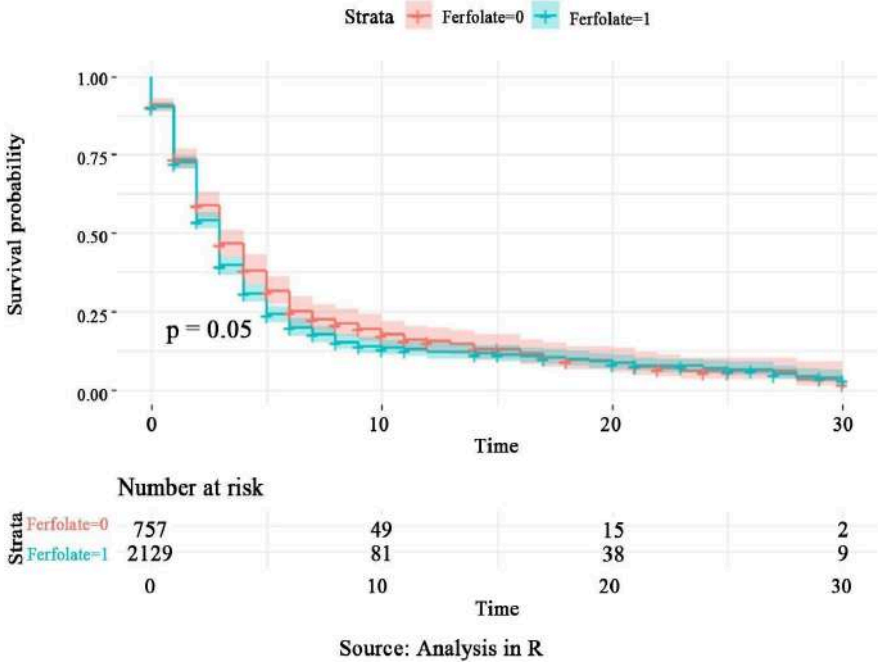

Figure 5: Survival Curves According to Maternal Fetal Iron Supplement

It is observed that the majority of mothers (2129) received iron supplements, but only a small proportion (757, or 35.5%) did not receive them. It is worth noting that 413, or 56.4% of the fetuses died among the mothers who did not receive iron supplements, and 1094, or 51.4% of the deaths were recorded among the fetuses whose mothers received iron supplements.

Table 5: Fetal Iron

	N	Observed	Expected	(O – E)^2 /E	(O – E)^2 /E
Fetal Iron = 0	757	413	444	2.205	3.85
Fetal Iron= 1	2129	1094	1063	4.48	3.85
	Chisq = 8.1 on 1 degrees of freedom, p = 0.002				

Table 5 shows that the Chi-squared = 3.9, df = 1, p-value = 0.05, we reject H0 at 5%. There is a statistically significant difference in newborn deaths between fetuses whose mothers received fetal iron supplementation and those who did not.

6.6 Survival Curves According to the Type of Delivery

Figure 6 shows that the survival curves for cesarean and eutocic births are very similar. However, we can see that the survival curve for newborns born by vacuum or forceps is much higher than the cesarean and eutocic curves. The median time corresponding to a 50% chance of survival is 3 days for newborns whose mothers had a eutocic or cesarean delivery, meaning that from the 3rd day, these newborns have a 50% chance of dying within 30 days. On the other hand, newborns born by vacuum or forceps have a median time of 6 days, meaning that from the 6th day, these newborns have a 50% chance of dying.

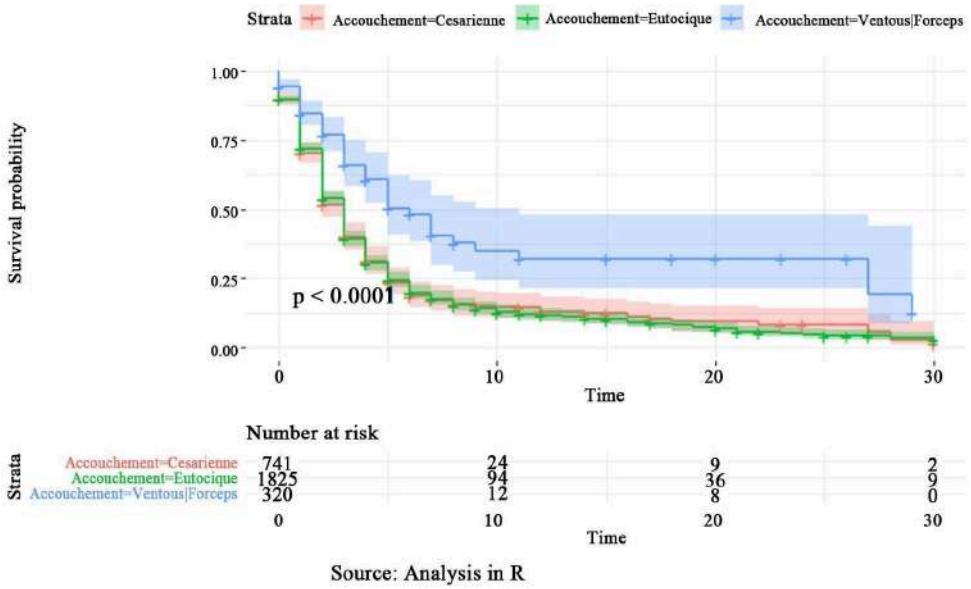

Figure 6: Survival Curves According to the Type of Delivery

We have 741 newborns who were born by cesarean section, of which 48.9% died. While 1065, or 58.4% of the newborns, died among the 1825 newborns who were born eutocically. It should be noted that 80, or 25% of the deaths, were recorded among the 320 newborns born by vacuum or forceps.

Table 6: Type of Delivery

	N	Observed	Expected	(O – E)^2 /E	(O – E)^2 /
Vacuum|Forceps = 0	320	80	152	33.95	46.05
Caesarean = 1	741	362	342	1.21	1.91
Eutocic = 2	1825	1065	1014	2.61	9.79
Chisq = 46.1 on 2 degrees of freedom, p = 1e-10					

Table 6 shows that the Khi2 = 46.1, ddl = 2, the calculated probability = 1e-10 < 0.05, we reject Ho at 5%. There is a statistically significant difference in deaths according to the type of delivery used.

VII. ESTIMATION OF THE COX MODEL: SELECTION OF SIGNIFICANT VARIABLES USING THE STEPWISE PROCEDURE

First, we will focus on selecting the variables that should be included in our model and those that do not need to be retained. To do this, I will use the Stepwise procedure, which also retests all variables (whether included or not in the model) at each step and can re-enter or remove a variable that was previously removed or entered but whose significance has changed.

STEPWISE in R :

Model 1 :
Start : AIC=20592.11
Surv(dureeHop, statut) ~ Sexe + AgeM + Mpalu + mpresentation + Vaccantitetanique + Diabete + Accouchement + ProfessionMere + SitMat + Ferfoetale + souffrance

	Df	AIC
mpresentation	1	20589
ProfessionMere	1	20589
Vaccantitetanique	1	20589
SitMat	1	20589
<none>		20591
Sexe	1	20593
AgeM	1	20594
Ferfoetale	1	20595
souffrance	1	20599
Diabete	1	20599
Mpalu	1	20603
Accouchement	2	20640

Model 2 :
Step : AIC=20590.11
Surv(dureeHop, statut) ~ Sexe + AgeM + Mpalu + Vaccantitetanique + Diabete + Accouchement + ProfessionMere + SitMat + Ferfoetale + souffrance

	Df	AIC
ProfessionMere	1	20587
Vaccantitetanique	1	20587
SitMat	1	20587
<none>		20589
Sexe	1	20591
AgeM	1	20592
Ferfoetale	1	20593
souffrance	1	20597
Diabete	1	20597
Mpalu	1	20601
Accouchement	2	20638

Model 3 :
Step : AIC=20588.2
Surv(dureeHop, statut) ~ Sexe + AgeM + Mpalu + Vaccantitetanique +Diabete + Accouchement + SitMat + Ferfoetale + souffrance

	Df	AIC
Vaccantitetanique	1	20585
SitMat	1	20585
<none>		20587
Sexe	1	20589
AgeM	1	20590
Ferfoetale	1	20591
souffrance	1	20595
Diabete	1	20595
Mpalu	1	20600
Accouchement	2	20636

Model 4 :
Step : AIC=20586.41
Surv(dureeHop, statut) ~ Sexe + AgeM + Mpalu + Diabete + Accouchement + SitMat + Ferfoetale + souffrance

	Df	AIC
SitMat	1	20584
<none>		20585
Sexe	1	20587
AgeM	1	20588
Ferfoetale	1	20590
souffrance	1	20593
Diabete	1	20593
Mpalu	1	20598
Accouchement	2	20634

Model 5 :
Step : AIC=20583.51
Surv(dureeHop, statut)~ Sexe + AgeM + Mpalu + Diabete + Accouchement + Ferfoetale + souffrance

	Df	AIC
<none>		20584
Sexe	1	20585
AgeM	1	20587
Ferfoetale	1	20588
souffrance	1	20591
Diabete	1	20592
Mpalu	1	20596
Accouchement	2	20633

7.1 Partial Schoenfeld Residuals

- In a traditional linear regression model, residuals measure the difference between the observed values of the dependent variable and the values predicted by the model;
- In the case of a Cox model, it is the instantaneous risk that is explained, and the notion of residual does not make sense, because there is no way to calculate a difference between observed and predicted values;
- Schoenfeld residuals primarily concern the covariates and not the instantaneous risk function;
- These residuals only concern uncensored cases. The Schoenfeld residual represents the deviation between the value taken by this

covariate for an individual at the time of the event's occurrence and the mean of this covariate among all individuals exposed to the risk at that moment.

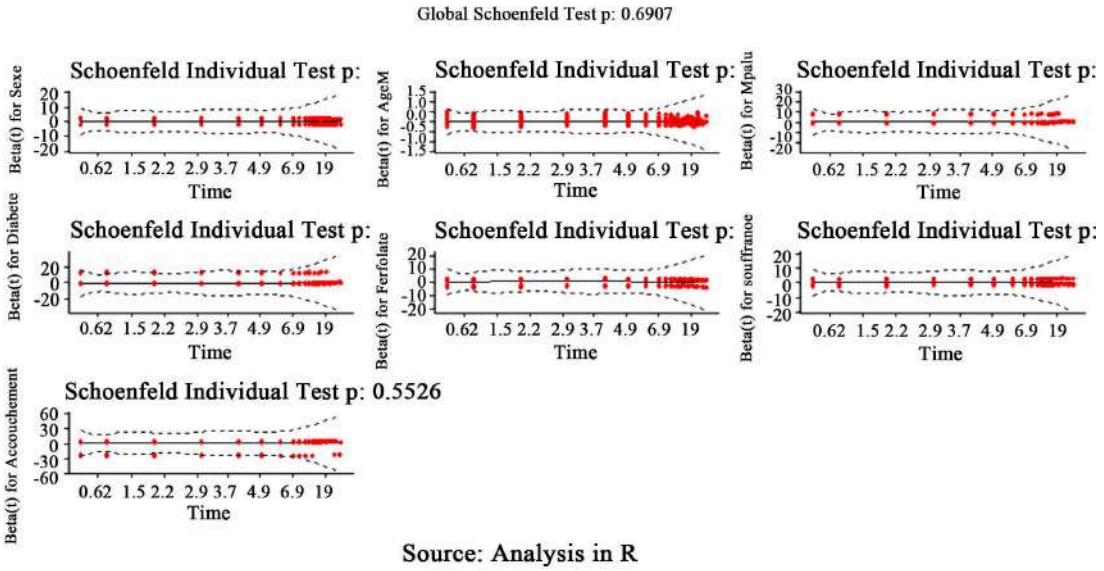

Figure 7: Survival Curves According to the Type of Delivery

Figure 7 shows that the residuals are normally distributed around 0 for each variable, indicating that the data follows a normal distribution. However, the evolution of the Schoenfeld residuals over time did not allow for a graphical verification of the proportional hazards assumption for the variables in this model, as the proportionality of the hazards over time is difficult to see on the survival curve (survival rate S(t) versus time). More simply, it is often considered that as long as the survival curves from different groups do not cross, the proportional hazards assumption is "acceptable".

Test of Residuals :

	chisq	df	p
Sex	0.0529	1	0.818
AgeM	0.0968	1	0.756
Mpalu	0.9119	1	0.340
Diabetes	0.5006	1	0.479
Folate	0.1161	1	0.733
Suffering	2.8490	1	0.091
Delivery	1.1863	2	0.553
GLOBAL	*5.6115*	*8*	*0.691*

A variation in risk over time can lead to contradictory conclusions [7]. Test the Proportional Hazards Assumption of a Cox Regression allows testing whether the condition of independence of the explanatory variables Xi over time is met. In my case, a p-value less than 5% indicatesand text heads. That the hypothesis of independence of the explanatory variables over time is not verified. It appears that p is greater than 5% (0.69 > 0.05) overall and for each variable individually, so the hypothesis of independence of the explanatory variables over time is verified. Therefore, my model is valid.

7.2 Test of Influential Observations

To test for influential observations or outliers, I can visualize either:

- The deviance residuals or;
- The dfbeta values.

By specifying the argument type = "dfbeta", we trace the estimated changes in the regression coefficients when each observation is removed one at a time; similarly, type = "dfbetas" produces the estimated changes in the coefficients divided by their standard errors.

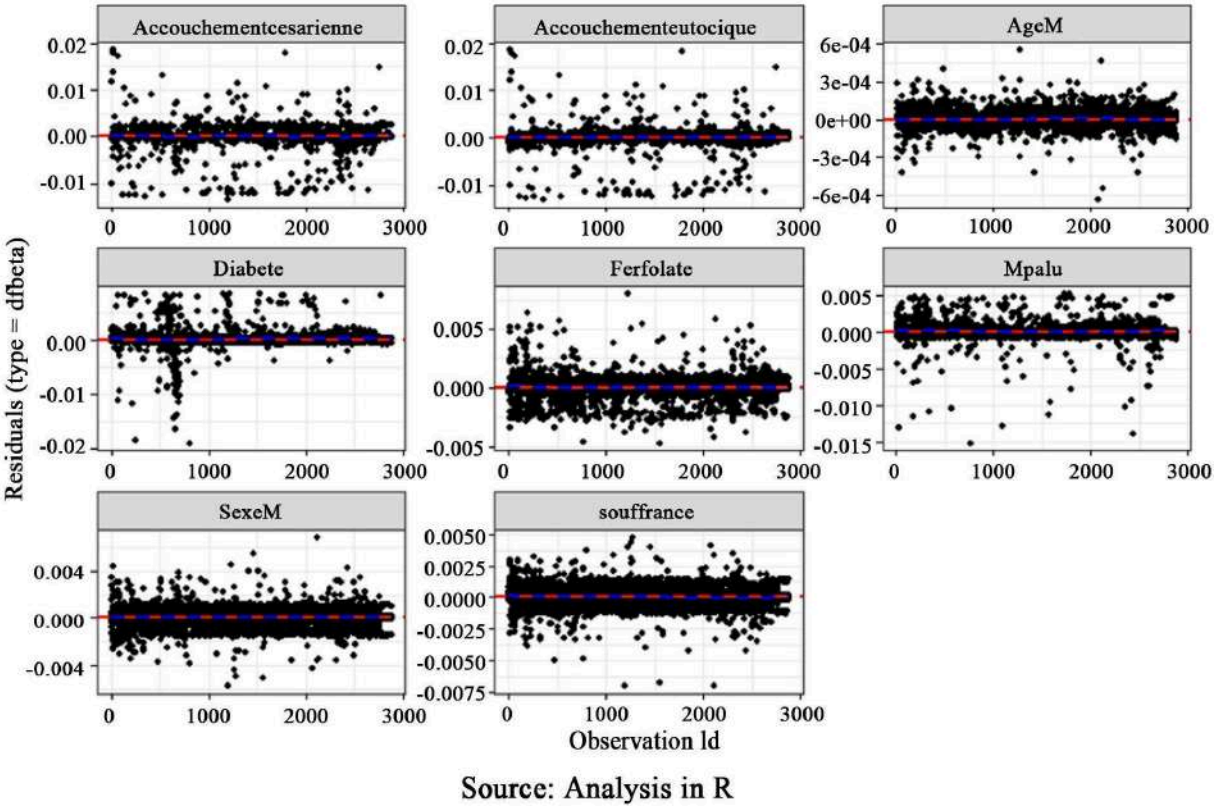

Figure 8: Representation of Influential Observations

The index plots above (Figure 8) show that the comparison of the amplitudes of the largest dfbeta values with the regression coefficients suggests that none of the observations are particularly influential individually, even though some dfbeta values for delivery (amplitudes between 0.02 and −0.01) and diabetes (amplitudes between 0.009 and −0.02) are important compared to others. It is also possible to check outliers by visualizing the deviance residuals. The deviance residual is a normalized transformation of the martingale residual. These residuals should be approximately symmetrically distributed around zero with a standard deviation of 1.

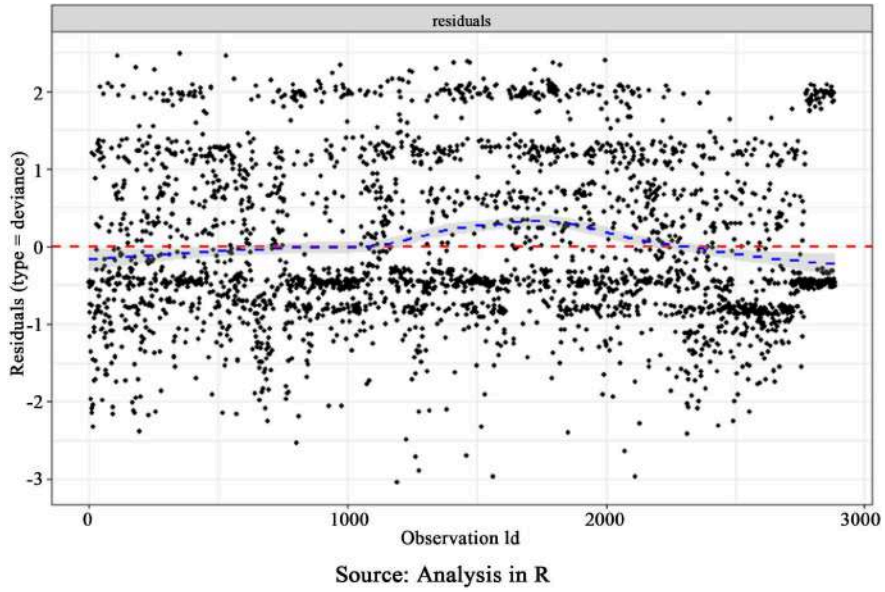

Figure 9: Representation of Deviance Residuals

1. Positive values correspond to individuals "who died too early" compared to the expected survival durations;
2. Negative values correspond to individuals who "lived too long"; 3) Very large or small values are outliers, poorly predicted by the model.

The deviance residuals of the model appear quite symmetric around 0 in Figure 9.

7.3 Martingale Residuals

In the Cox model, the relationship between instantaneous risk and covariates is loglinear. Often, it is assumed that continuous covariates have a linear form. However, this assumption should be verified. Plotting the martingale residuals against the explanatory variables included in the model can be used to indicate whether certain variables need to be transformed before being incorporated into the model. To do this, a smoothed curve is added over the points obtained. The functional form is then suggested by the shape of the smoothed curve. Thus, a slow growth of the curve suggests a logarithmic or root transformation. Conversely, a rapid growth suggests a power transformation with a power greater than 1 [8].

The fitted line has a flatter function; it is linear to satisfy the assumptions of the Cox proportional hazards model. The martingale residuals are therefore linear (Figure 9).

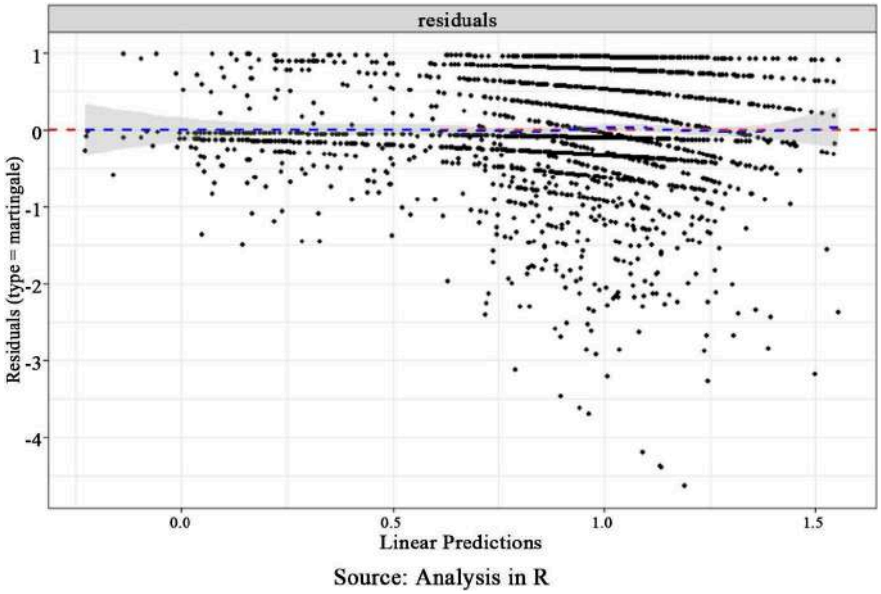

Figure 10: Model Visualization and Interpretation

7.4 Model Visualization and Interpretation

Figure 11 shows that the survival probability is highest at the beginning of the cycle, but the risk of death increases with the duration of hospitalization. The estimated model indicates that the median time for a 50% survival chance within the 30-day period is 4 days. This probability is reached on the 4th day because nearly half of the newborns die before this time, due to factors such as hypothermia (body temperature below 35˚C), hypoglycemia (abnormal drop in blood sugar from insufficient breastfeeding), fetal infections, and other complications. By day 30, the survival probability of newborns drops to less than 10%.

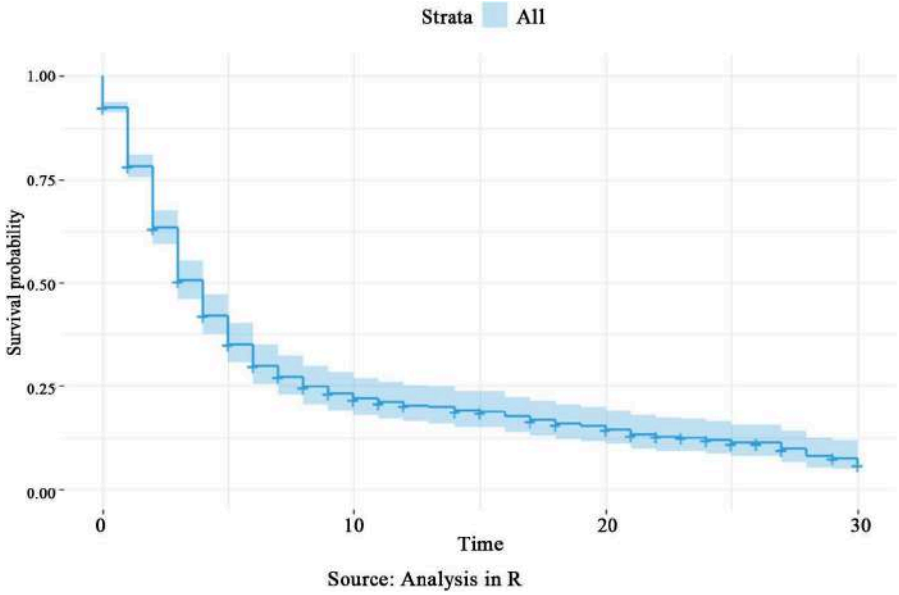

Figure 11: Survival Curve from the final Model

Estimated Model:

$$h\,t\,xi(\,,\,) = e0.10SexM\ -0.009AgeM\ -0.29Diabetes+0.29Mpalu+0.15FetalFolate+0.16Suffering-0.75VacuumForceps$$

The model is globally significant (Wald statistic of 93.52 with a p-value of 2e16 < 0.05). The Concordance = 0.584, meaning a concordance of 58.4%. This percentage also helps verify the model's strength, indicating that it is correct 58.4% of the time. In other words, the predictions from this model align with reality 58.4% of the time.

Likelihood ratio test = 103.6, this value can roughly be interpreted as the distance between the predictions made by this model and the observations. However, this value alone doesn't tell us much but is useful as a reference for judging the contribution of explanatory factors introduced later.

We see that the estimated effect of the child's sex has a logarithmic hazard ratio β equal to 0.102790. Since its coefficient is positive, higher risks are associated with male infants. In other words, at any given moment in time, the risk of death for male infants is over 10% higher than for female infants, as they are more prone to infections. Very significant and negative (β = −0.009108), the mother's age coefficient reduces the risk of death for newborns, meaning that regardless of time t, each additional. Year of life for the mother decreases the overall risk of newborn death by a factor of 0.990934 (1%) per year.

For malaria, significant at the 5% level (6.74e-05 < 0.05), the value 1.349314 indicates that at any given time, newborns of mothers with malaria are estimated to have a 34.9% higher risk of death compared to newborns of mothers without malaria.

Although significant (0.00996 < 0.05), the fetal iron supplementation for mothers, at any moment during the first 4 weeks after birth, increases the risk of death for newborns by a factor of 1.162351, meaning the risk of death for newborns whose mothers received iron supplementation is 16% higher than for those whose mothers did not receive this treatment. In fact, iron accumulates in the body, and its excess can lead to severe poisoning: joint pain, diabetes, heart issues, liver cirrhosis, and even colon and rectum cancers.

Significant at the 5% level (0.00166 < 0.05), the effect of fetal distress in newborns, at any time, increases the risk of death for newborns by a factor of 1.177144, about 17.7% higher risk of death for distressed newborns. Also significant at the 5% level (0.00189 < 0.05), the effect of diabetes in mothers, at any time, reduces the risk

of death for newborns by a factor of 0.744649, meaning the neonatal mortality risk in the group of diabetic mothers is 0.74 times lower than in the group of non-diabetic mothers. Since diabetic mothers and their children receive high quality medical care (prenatal care), this contributes to reducing the risk of death.

Vaginal delivery (eutocic) is found to be non-significant in my model and has no effect on the neonatal death risk. However, assisted delivery by vacuum or forceps is significant at the 5% level (1.28e-09 < 0.05), and the value 0.4718794 indicates that at any time, newborns born via assisted delivery with vacuum or forceps have a 52.8% lower risk of death than newborns born via caesarean section.

VIII. GENERAL CONCLUSION AND DISCUSSION OF RESULTS

8.1 Iron Supplementation and Mortality Risk

The study challenges the common belief that iron is crucial for neonatal health by suggesting that iron supplementation may actually increase the risk of neonatal mortality. This discrepancy could be due to a range of factors, such as the dosage of iron, the timing of supplementation, and underlying comorbidities, which may contribute to negative outcomes, including iron toxicity. The risk of iron overload is a well-established concern, particularly for newborns, and studies provide additional evidence supporting this hypothesis [9].

One study emphasized that excessive iron intake can lead to oxidative stress and damage to vital organs, which may have severe consequences for neonates, particularly in regions where healthcare monitoring is inadequate. Another study similarly found that iron overload can impair antioxidant defenses in neonates, increasing susceptibility to various infections and diseases, thereby negatively affecting survival. On the other hand, several studies have highlighted the importance of iron supplementation in preventing iron deficiency anemia, one of the leading causes of poor neonatal health outcomes. Other studies demonstrated that iron supplementation helps reduce the risks of preterm birth, low birth weight, and developmental delays when properly administered. This indicates that the timing, dosage, and method of supplementation are key factors in determining whether iron supplementation is beneficial or harmful.

8.2 The Protective Effect of Diabetic Mothers

The finding that maternal diabetes may offer a protective effect for neonatal outcomes is intriguing but likely reflects the quality of prenatal care received rather than a direct protective benefit of the condition itself. As the study suggests, more intensive prenatal care for diabetic mothers could lead to better neonatal outcomes, skewing results and potentially leading to a false assumption of protection.

Studies like those by Schoenleber et al. and Radaelli et al. have shown that better management of maternal diabetes, through blood glucose control and close monitoring, can reduce the risks of neonatal complications. However, they also caution that the underlying risks of maternal diabetes—such as preterm birth, macrosomia (large birth weight), and fetal hypoglycemia—remain significant despite improved care. This suggests that while intensive prenatal care can improve outcomes, diabetes itself is not inherently protective.

8.3 Malaria and Neonatal Mortality

The study also highlights the well-documented link between maternal malaria and increased neonatal mortality. Malaria is a leading cause of neonatal death, especially in sub-Saharan Africa, due to its association with preterm birth, low birth weight, and intrauterine growth restriction. This finding is consistent with studies by Mwakagile et al. and Akinmoladun et al., which reported higher rates of neonatal mortality in malaria-endemic regions. Mwakagile noted that maternal malaria during pregnancy significantly impairs placental function, leading to poor fetal development and increased susceptibility to infections after birth. This reinforces the need for malaria prevention and treatment interventions to reduce neonatal mortality in malaria-endemic areas.

8.4 Caesarean Delivery and Neonatal Mortality

Perhaps one of the most surprising findings is that caesarean sections, generally considered protective for neonatal health by preventing complications associated with vaginal delivery, appear to increase the risk of neonatal mortality in this study. While caesarean sections are essential in cases of obstructed labor, fetal distress, or other complications, unnecessary or non-medically indicated caesarean sections can be associated with increased neonatal risks. Research by Guise et al. and Barros et al. supports this concern, showing that elective caesarean deliveries in low-risk pregnancies may expose newborns to greater respiratory complications, infections, or longer recovery times, particularly in settings with limited access to specialized neonatal care. It's also important to consider that caesareans are often performed in higher-risk pregnancies, which may inherently carry a higher risk of adverse neonatal outcomes. This suggests that the apparent increase in neonatal mortality may be linked to factors such as underlying maternal health conditions, complications during pregnancy, or the context in which the caesarean is performed.

8.5 Data Limitations and Implications for Policy

A significant limitation of the study, as acknowledged by the authors, is the reliance on retrospective data, which may introduce biases due to inaccurate or incomplete records. Retrospective studies, particularly those relying on administrative data from systems like DHIS2, are susceptible to data entry errors, inconsistencies in reporting, and lack of standardized monitoring. These issues could undermine the validity of the findings, as seen in previous studies examining maternal and neonatal outcomes based on administrative records. Future prospective studies with more rigorous data collection and standardization could provide more reliable insights into the relationships between iron supplementation, maternal health conditions, and neonatal outcomes.

From a policy perspective, the study advocates for improving prenatal and postnatal care, with a focus on providing effective interventions, such as iron supplementation and malaria prevention, tailored to the specific needs of mothers and newborns. Addressing the quality of healthcare services, expanding access to care, and ensuring accurate data collection should be central to policies aimed at reducing neonatal mortality, particularly in low-resource settings. Additionally, strengthening surveillance during pregnancy and the postpartum period, as well as ensuring high-quality neonatal care in the first days of life, could significantly improve survival rates.

IX. CONCLUSION

In summary, while this study offers important insights into the factors affecting neonatal mortality, including the role of iron supplementation, caesarean delivery, and maternal diabetes, it also underscores the complexity of neonatal health outcomes. Further research is needed to clarify the causality of these associations, especially with respect to the timing and dosage of interventions like iron supplementation, the true impact of maternal health conditions, and the consequences of caesarean deliveries. The study also highlights the need for improved data accuracy and healthcare policies that prioritize equitable access to high-quality prenatal, delivery, and neonatal care, particularly in resource-limited settings.

Conflicts of Interest

The author declares no conflicts of interest regarding the publication of this paper.

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Phrenic Nerve Paralysis: Effects on Diaphragm Mobility

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ABSTRACT

Phrenic nerve paralysis is a severe clinical condition with significant repercussions on respiratory mechanics and patient quality of life. It results from the interruption of diaphragmatic innervation, compromising the physiology of the muscle, reducing pulmonary expansion, and leading to alveolar hypoventilation. The phrenic nerve originates from the cervical roots C3 to C5, following a complex anatomical pathway that makes it vulnerable to iatrogenic injury during cervical or thoracic surgeries or anesthetic blocks. This study reviewed scientific evidence from the past decade, without language restrictions, using databases such as PubMed and SciELO and search terms including "phrenic nerve paralysis," "iatrogenesis," and "neurotization." The analysis integrated data from prospective studies and systematic reviews, highlighting diagnostic techniques such as dynamic ultrasonography and electroneuro- myography.

Keywords: denervation, atrophy, fibrosis, hypoventilation, and neurostimulation.

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ABSTRACT

Phrenic nerve paralysis is a severe clinical condition with significant repercussions on respiratory mechanics and patient quality of life. It results from the interruption of diaphragmatic innervation, compromising the physiology of the muscle, reducing pulmonary expansion, and leading to alveolar hypoventilation. The phrenic nerve originates from the cervical roots C3 to C5, following a complex anatomical pathway that makes it vulnerable to iatrogenic injury during cervical or thoracic surgeries or anesthetic blocks. This study reviewed scientific evidence from the past decade, without language restrictions, using databases such as PubMed and SciELO and search terms including "phrenic nerve paralysis," "iatrogenesis," and "neurotization." The analysis integrated data from prospective studies and systematic reviews, highlighting diagnostic techniques such as dynamic ultrasonography and electroneuromyography. Therapeutic strategies ranged from conservative approaches to surgical interventions, including neurotization with autologous grafts and diaphragmatic plication. The findings conclude that preventing iatrogenic injuries requires standardized protocols, intraoperative monitoring, and equitable access to therapies. These measures are essential to reduce morbidity and mortality and improve clinical outcomes, particularly in vulnerable populations such as the elderly and patients with neuromuscular comorbidities.

Keywords: denervation, atrophy, fibrosis, hypoventilation, and neurostimulation.

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I. INTRODUCTION

Phrenic nerve paralysis is a serious clinical condition with systemic repercussions on the patient's health[1] . It results from the interruption of diaphragmatic innervation, severely affecting respiratory mechanics and compromising the physiological contraction of the diaphragm, which prevents its ideal flattening and, consequently, decreases lung expansion[2].

The phrenic nerve is a mixed nerve, usually originating from the cervical roots C3, C4, and C5 [3,4]. However, in some cases, there are anatomical variations in its origin or path, which considerably increases the risk of surgical iatrogenesis in the absence of preoperative imaging studies[4].

Its path begins at the neck, descending anteriorly to the anterior scalene muscle and posteriorly to the internal jugular vein and subclavian artery[3,4]. Upon crossing the mediastinum, it branches to innervate both hemidiaphragms, synchronizing their contractions during inspiration[4].

It is important to note that there is anatomical asymmetry between the right and left sides: on the right, the nerve accompanies the superior vena cava and the right atrium[5]. In some cases, the proximity of the nerve to the subclavian vein increases the risk of injury during venous procedures in the region[4]. On the left side, it crosses the aortic arch and continues over the left ventricle[5]. This relationship explains the incidence

of postoperative phrenic paralysis in cardiac surgery[9].

This superficial and complex path exposes the nerve to iatrogenic trauma, especially during cervical, thoracic, or cardiac surgery[9]. Interscalene brachial plexus blocks are associated with 15.4% transient diaphragmatic paralysis[10]. Other causes include compression by mediastinal neoplasia's and neuromuscular diseases, such as amyotrophic lateral sclerosis[7]. Rare cases, such as granulomatosis with polyangiitis, may also manifest with phrenic paralysis as an initial symptom[6].

Anatomically, the diaphragm acts as a dynamic barrier between the thoracic and abdominal cavities, being the main motor of respiration[5]. The exclusive innervation of the diaphragm by the phrenic nerve highlights the interdependence between neural structure and muscle function[5]. When this connection is interrupted, the balance of intrathoracic and abdominal pressures is disturbed, resulting in alveolar hypoventilation and dyspnea[8].

These changes can be evidenced by imaging tests, such as X-rays and ultrasounds, which reveal unilateral or bilateral elevation of the diaphragm and reduced respiratory excursion These changes can be evidenced by imaging tests, such as X-rays and ultrasounds, which reveal unilateral or bilateral elevation of the diaphragm and reduced respiratory excursion[8]. Clinically, a paradoxical movement is observed, in which the affected diaphragm is elevated during inspiration, exacerbating hypoxia[1,8].

Therapeutic management varies according to etiology and severity. Conservative strategies include respiratory physiotherapy and non-invasive ventilation in most cases[1,4]. In acute traumatic injuries, neurotization with autologous grafts is indicated, achieving functional recovery in half of patients over the course of one year[11]. Techniques such as diaphragmatic stimulation are a promising therapeutic option in bilateral paralysis, although their high cost limits their accessibility[11,13,14].

This study aims to integrate current evidence on phrenic nerve injury, addressing two fundamental axes. First, the correlation between anatomical variations and risk of iatrogenesis. Second, we evaluate diagnostic methods with an emphasis on their clinical applicability and accuracy.

II. MATERIALS AND METHODS

The bibliographic method was used to collect scientific data from the last five years from medical sources in Portuguese, Spanish, and English, using the following platforms: SciELO, Google Scholar, and PubMed. Keywords such as 'Denervation,' 'Atrophy,' 'Fibrosis,' 'Hypoventilation,' and 'Neurostimulation' were searched. The study included a comparative table addressing the main causes of paralysis, anatomical alterations, histological changes and the associated functional impact.

Classical reference works were also consulted, such as Gray's Anatomy (Gray H. et al., 42nd ed., Elsevier, 2020), Ross MH, Pawlina W. Histology: Text and Atlas. 8th ed. Barcelona: Wolters Kluwer; 2023. and Clinical Embryology (Moore KL., 11th ed., Elsevier, 2021). In addition, guidelines from the American Thoracic Society (ATS) and studies from the National Institutes of Health (NIH) on nerve regeneration were included.

III. RESULTS

The review revealed findings consistent with the literature and medical epidemiology. It provides a systematic overview of cases of phrenic nerve injuries. Such injuries directly compromise diaphragmatic dynamics, resulting in physiological and systemic dysfunctions. Table 1 summarizes crucial data from the main studies, highlighting the type of study, sample, etiology of the injury, and clinical outcome.

Table 1: Phrenic Nerve Paralysis: Comparative Summary of Clinical Studies

Author/Year	Type of Study	Sample	Etiology of the Injury	Clinical Outcome
Saba-Santiago et al. (2022)[10]	Prospective	78 patients	Interscalene block of the brachial plexus	Spontaneous recovery in most cases
Hu et al. (2024)[9]	Integrative review	Data from 107 references	Surgical procedures (cardiac/thoracic)	Reduction of complications with intraoperative monitoring
Boussuges et al. (2020)[8]	Systematic review	Data from 102 references	Diaphragmatic dysfunction	Accurate diagnosis via dynamic ultrasound
Supra & Agrawal (2023)[11]	Narrative review	Data from 94 references	Traumatic injury to the phrenic nerve	Moderate success of nerve grafts
Dubé et al. (2016)[13]	Clinical review	65 surgical cases	Irreversible chronic paralysis	Symptomatic improvement after plicature

Prospective data, such as those from Saba-Santiago et al, highlighted that 15.4% of interscalene blocks resulted in transient diaphragmatic paralysis, with spontaneous resolution in most cases[10]. On the other hand, cardiothoracic surgical interventions, analysed by Hu et al, showed a reduction in complications when accompanied by intraoperative monitoring, reinforcing the importance of preventive strategies[9].

In addition, advanced ultrasound techniques, such as speckle tracking, allow for more accurate assessment of diaphragmatic micro-movements compared to conventional ultrasound[15]. This approach is particularly useful in the early detection of subclinical dysfunctions, such as in patients with chronic comorbidities that predispose them to diaphragmatic weakness[16].

As for therapeutic options, autologous nerve grafts, reviewed by Supra & Agrawal, achieved functional success in 50% of cases, but with heterogeneity in the evaluation criteria between studies[11].

At the same time, electroneuromyography of the phrenic nerve, performed with electrical stimuli near the C3-C5 roots and intramuscular recording in the diaphragm, allows parameters such as latency and amplitude of the muscle action potential to be quantified[18].

Additionally, esophageal manometry assists in the assessment of transdiaphragmatic pressure, whose optimal difference (≥10 cmH_2O) reflects preserved function[17,19]. These findings corroborate the central hypothesis of the study, the complexity and anatomical variability of the phrenic nerve.

IV. DISCUSSION

Phrenic nerve paralysis is not just a technical complication, but a reflection of structural gaps in the safety of routine medical procedures[1]. The incidence of 15.4% of transient paralysis after interscalene block is not merely a statistical fact, but rather an alarming indicator of how anesthetic protocols underestimate the anatomical vulnerability of the nerve[2].

The emphasis on 'spontaneous recovery' in cases of transient paralysis masks an underlying problem, the normalization of iatrogenic risk[2]. Patients may recover diaphragmatic function, but sequelae such as chronic muscle fatigue and exercise intolerance are often overlooked[1]. Studies such as that by Hu et al, which celebrate a 30% reduction in complications with intraoperative monitoring, fail to question why 70% of cases are still exposed to predictable risks [1,9].

The 95% sensitivity of dynamic ultrasound contrasts sharply with the reality of healthcare systems that still rely on static X-rays to assess respiratory dynamics[4,20]. Meanwhile, electro-neuromyography, the gold standard for neuropathies, remains inaccessible in regions without specialists, deepening inequalities in the quality of care[18].

The 50% success rate of nerve grafts is a warning sign: half of patients undergoing invasive procedures are left with functional sequels, often without access to pulmonary rehabilitation or psychological support[19]. Diaphragmatic plication, despite improving symptoms in 80% of cases, is a palliative solution that does not restore respiratory physiology, perpetuating dependence on medical interventions[20].

The ability of bulboprotuberal centers to mask symptoms through accessory muscles is not a physiological detail[22]. While young patients adapt to unilateral dysfunction, elderly patients or those with neuromuscular comorbidities face abrupt decompensation, which is often fatal [23].

V. FINAL CONSIDERATIONS

Phrenic nerve paralysis not only paralyses a muscle, but also chains the body to a silent struggle, where breathing becomes an act of resistance. Those who suffer from it face days marked by constant fatigue, the anguish of not being able to fill their lungs, and the fear that a simple movement will aggravate their weakness. It is a condition that robs them of their most basic autonomy, turning everyday life into a challenge.

However, amid this reality, there is a clear path forward: accurate diagnosis and timely treatment. An ultrasound revealing diaphragmatic elevation, adapted physiotherapy, or a properly placed pacemaker are not just medical procedures, but bridges to the recovery of a full life. Each successful step in managing this disease not only repairs a nerve, but also restores the freedom to breathe without fear.

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Neurological Manifestation of Chikungunya Virus and its Implication in the Pathogenesis of Guillain-Barré Syndrome: A Systematic Review of Clinical and Mechanistic Evidence

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ABSTRACT

Chikungunya virus (CHIKV) infection has been linked to severe neurological outcomes, notably Guillain-Barré Syndrome (GBS). This systematic review highlights clinical and mechanistic evidence associating CHIKV with autoimmune polyradiculoneuropathies. Findings reveal the virus's neurotropism and support its role as a triggering factor for GBS. Despite methodological heterogeneity among studies, the evidence underscores important implications for diagnosis, clinical surveillance, and patient management. Deeper understanding of this relationship is essential to improve preventive and therapeutic health strategies.

Keywords: chikungunya, guillain-barré syndrome, peripheral neuropathies, arboviruses.

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Manifestação nervosa pelo vírus chikungunya e sua implicação na patogênese da Síndrome de Guillain-Barré: Uma revisão sistemática das evidências clínicas e mecanísticas

Manifestaciones neurológicas del virus chikungunya y su implicación en la patogenia del síndrome de Guillain-Barré: una revisión sistemática de la evidencia clínica y mecanística

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RESUMO

A infecção pelo vírus Chikungunya (CHIKV) pode desencadear manifestações neurológicas graves, incluindo a Síndrome de Guillain-Barré (SGB). Esta revisão sistemática identificou evidências clínicas e mecanísticas que apontam para a relação entre o CHIKV e polirradiculoneuropatias autoimunes. Os achados demonstram o tropismo neurológico do vírus e reforçam a hipótese de sua participação como fator precipitante da SGB. Apesar de limitações metodológicas nos estudos, a associação sugere implicações relevantes para diagnóstico, vigilância e manejo clínico. A compreensão aprofundada dessa correlação é fundamental para estratégias terapêuticas e preventivas em saúde pública.

Palavras-Chave: chikungunya, síndrome de guillain-barré, neuropatias periféricas, Arboviroses.

ABSTRACT

Chikungunya virus (CHIKV) infection has been linked to severe neurological outcomes, notably Guillain-Barré Syndrome (GBS). This systematic review highlights clinical and mechanistic evidence associating CHIKV with autoimmune polyradiculoneuropathies. Findings reveal the virus's neurotropism and support its role as a triggering factor for GBS. Despite methodological heterogeneity among studies, the evidence underscores important implications for diagnosis, clinical surveillance, and patient management. Deeper understanding of this relationship is essential to improve preventive and therapeutic health strategies.

Keywords: chikungunya, guillain-barré syndrome, peripheral neuropathies, arboviruses.

RESUMEN

La infección por el virus Chikungunya (CHIKV) se ha relacionado con manifestaciones neurológicas graves, especialmente el síndrome de Guillain-Barré (SGB). Esta revisión sistemática evidenció asociaciones clínicas y mecanísticas que vinculan al CHIKV con polirradiculoneuropatías autoinmunes. Los hallazgos muestran un claro tropismo neurológico del virus y respaldan su papel como

desencadenante de la SGB. A pesar de las limitaciones metodológicas de los estudios, la evidencia tiene implicaciones relevantes para el diagnóstico, la vigilancia y el manejo clínico. Comprender esta relación es crucial para optimizar las estrategias preventivas y terapéuticas en salud pública.

Palabras Clave: chikungunya, síndrome de guillain-barré, neuropatías periféricas, arbovirus.

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I. INTRODUÇÃO

A infecção pelo Vírus Chikungunya (CHIKV), um arbovírus da família Togaviridae transmitido por mosquitos do gênero Aedes, tem sido amplamente reconhecida como causa de febre, artralgia e poliartrite, e sua evolução clínica é dividida em três fases: aguda, subaguda e crônica. A fase aguda, tem duração de aproximadamente 14 dias e é caracterizada por poliartralgia bilateral, predominando nas regiões distais. Em seguida, a fase subaguda manifesta-se pela persistência e agravamento da artralgia, que pode se estender por até três meses. Por último, a fase crônica é marcada por acometimento articular persistente ou recorrente nas articulações previamente afetadas, com duração a partir de três meses, com um impacto direto na vida do paciente. Dentre os sintomas clássicos destacam-se a febre, artralgia, e poliartrite. Alguns pacientes podem apresentar manifestações atípicas como a meningoencefalite, paralisias, neuropatias periféricas, neurite óptica e dentre outras complicações. Entre essas, a Síndrome de Guillain-Barré (SGB) se destaca como uma manifestação mais grave do envolvimento neurológico pós-viral.

A infecção pelo vírus Chikungunya tem sido relacionada, em alguns casos clínicos, como fator desencadeante da Síndrome de Guillain-Barré (SGB). Essa associação se explica tanto pelos mecanismos fisiopatológicos do vírus quanto pelo quadro clínico observado, que favorece a desmielinização progressiva, embora os processos exatos ainda não sejam totalmente compreendidos, estando intimamente ligados à patogênese da SGB. Essa síndrome pode decorrer de modificações epigenéticas ou de gatilhos ambientais que induzem uma resposta imune contra as próprias células do organismo. Por se tratar de uma doença autoimune, é necessário que ocorra a quebra da tolerância imunológica, o que pode acontecer quando o indivíduo entra em contato com agentes infecciosos capazes de romper esse equilíbrio, ativar a resposta imune e favorecer complicações subsequentes.

Entre os mecanismos envolvidos destaca-se o mimetismo molecular, no qual antígenos virais desencadeiam uma resposta imunológica cruzada contra componentes da mielina ou dos axônios periféricos. O resultado dessa agressão é a desmielinização neuronal, que reduz a condução do impulso nervoso, visto que o neurônio perde sua capacidade de condução saltatória. No caso das infecções virais, como a causada pelo CHIKV, há ativação de linfócitos T citotóxicos e expansão clonal de linfócitos B, com produção de autoanticorpos dirigidos contra gangliosídeos, desencadeando várias formas da SGB, podendo elas serem desmielinizantes ou axonais.

Os estudos recentes demonstram que pacientes acometidos pela SGB após infecção pelo CHIKV apresentam sintomas rapidamente progressivos, sugerindo um envolvimento neuroimunológico intenso. A relação do fator causal e do tempo entre a infecção viral e o início da SGB reforça ainda mais a hipótese de que fatores imunopatogênicos mediados ou desencadeados pelo CHIKV desempenham um papel protagonista no desenvolvimento e manifestação dos sinais e sintomas da síndrome.

Alguns estudos prévios identificaram a infecção pelo Zika vírus como o principal fator desencadeante da SGB, resultando em um aumento da identificação da incidência da síndrome durante epidemias. No entanto, a evidência sobre o CHIKV como um agente precipitante da SGB permanece fragmentada e pouco sistematizada, tornando essencial uma revisão abrangente sobre essa relação.

Atualmente, há escassez de revisões sistemáticas que avaliem especificamente o papel do CHIKV na patogênese da SGB, e os estudos disponíveis apresentam metodologias heterogêneas, o que dificulta a obtenção de conclusões para tomada de decisões clínicas ou até mesmo conhecer o perfil da doença e da manifestação. Além disso, a crescente incidência de infecções pelo CHIKV no Brasil reforça a necessidade de compreender melhor as manifestações e complicações neurológicas para aprimorar as estratégias diagnósticas, terapêuticas e preventivas dos serviços de saúde desde o nível primário até os mais avançados. Na última década vem sendo discutido pela comunidade científica o aumento de casos com comprometimentos neurológicos desencadeados pelas arboviroses, especialmente em regiões tropicais e subtropicais. Entre os comprometimentos relatados estão as neuropatias periféricas autoimunes, como a Síndrome de Guillain-Barré. No entanto, atualmente evidenciou-se o rompimento de um problema de saúde global, haja vista a crescente de casos documentados.

O principal objetivo desta revisão sistemática é buscar evidências científicas que embasam a correlação do desenvolvimento da Síndrome de Guillain-Barré a partir da infecção por Chikungunya, incluindo a documentação das mecanísticas da infecção, além de uma perspectiva baseada em evidências sérias para contribuição de manejo e conduta específica.

II. REFERENCIAL TEÓRICO

As arboviroses são classificadas como patologias com eitologias virais e transmitidas na natureza entre os hospedeiros suscetíveis através de artrópodes hematófagos como mosquitos. Esses vírus possuem em seu ciclo uma ampla gama de hospedeiros vertebrados e invertebrados, podendo infectar de mamíferos até mesmo outros insetos. Estima-se que haja mais de 545 espécies de arbovírus, dentre as quais, mais de 150 relacionadas com doenças em seres humanos, sendo a maioria zoonótica (Lopes; Nozawa; Linhares, 2014).

O vírus chikungunya (CHIKV) pertence ao gênero Alphavirus, da família Togaviridae, e possui quatro genótipos: Oeste Africano, Leste-Centro-Sul Africano (ECSA), Asiático e Oceano Índico (IOL). No Brasil, até o momento foram detectadas as linhagens asiática e ECSA (Brasil, 2024a).

A Chikungunya faz parte do grupo das arboviroses, da família *togaviridae* cujo agente etiológico é transmitido pela picada de fêmeas infectadas do gênero Aedes. No Brasil, até o momento, o vetor envolvido na transmissão do vírus Chikungunya (CHIKV) é o Aedes aegypti, que tem hábitos seletivos por horários e condições específicas para sua reprodução e disseminação. Os togavírus constituem uma família de vírus de RNA de fita simples, envelopados e de morfologia esférica. Embora tenham sido inicialmente agrupados com outros vírus transmitidos principalmente por insetos, estudos posteriores permitiram sua reclassificação em uma família própria, composta por dois gêneros: Alphavirus e Rubivirus (Lopes; Nozawa; Linhares, 2014).

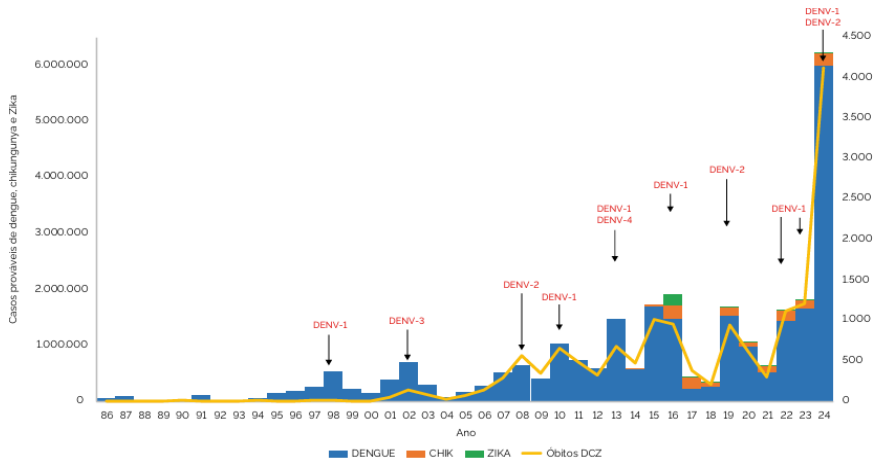
Tabela 1: Classificação dos arbovírus e doenças emergentes e reemergentes no Brasil

Família	Vírus	Sigla	Doença
Adenoviridae	Dengue	*DENV*	Febre Hemorrágica
Flaviviridae	Zika	*ZIKV*	Febre Hemorrárgica
Togaviridae	Chikungunya	*CHIKV*	Artropatia/Tenossinovite febril
Flaviviridae	Rocio	*ROCV*	Encefalite
	Oeste do Nilo	*WNV*	Meningite e Encefalite
	Mayaro	*MAYV*	Doença Febril e Artralgias
Togaviridae	Encefalite Equina do Leste	*EEEV*	Doença neurológica
Bunyaviridae	Oropuche	*OROV*	Febre Hemorrágica e Doença neurológica

Fonte: Adaptado de Lopes; Nozawa; Linhares, 2025

Aproximadamente 50 a 100 milhões de casos de arboviroses de ciclo urbano e silvestre ocorrem todo ano em países endêmicos, mesmo que a maioria não consiga ser documentada formalmente pelos sistemas de saúde, ainda é expressiva a relação de projeção de infecção por arboviroses. Nas Américas, a dengue, do grupo de arboviroses urbanas, ocupa a posição de maior incidência desde 1980. Os países tropicais sulamericanos como Brasil, Argentina, Bolívia e Peru são detentores dos maiores recordes de casos registrados pela Organização Pan-Americana da Saúde - Opas (Brasil, 2024b).

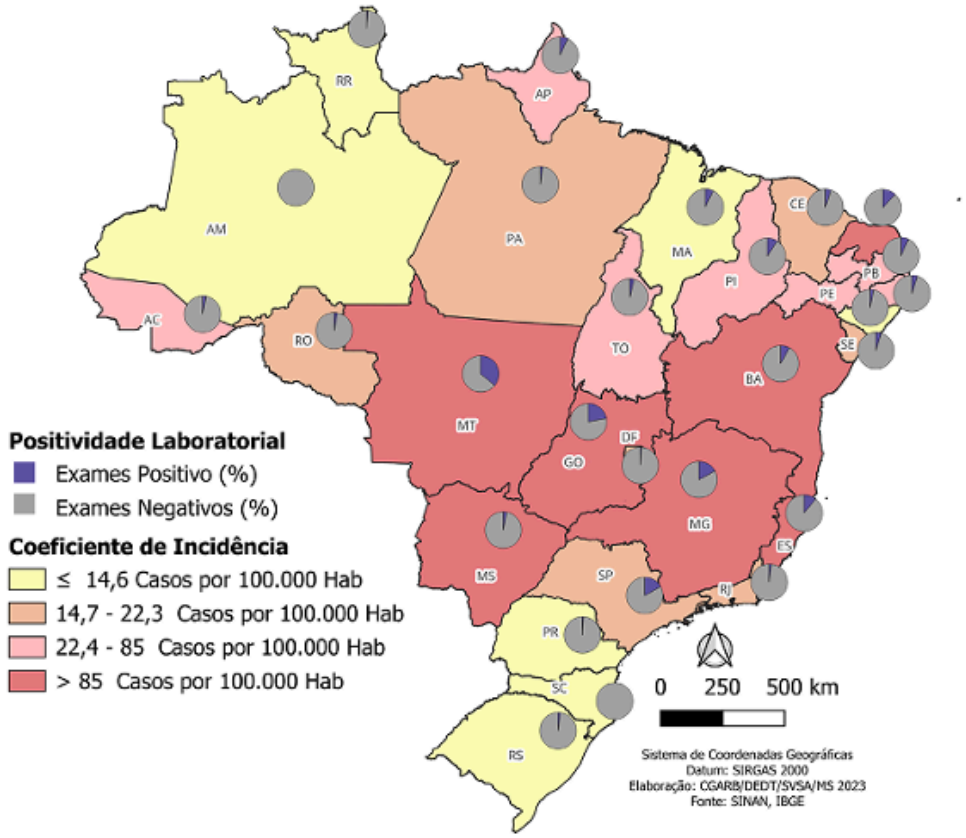
A cada 3 a 5 anos, no Brasil, as arboviroses apresentam picos endêmicos em determinadas regiões, coincidindo com as perspectivas históricas já documentadas nas epidemias mais fortes já documentadas como as de 2004, 2015, 2016 e 2019 em todo o território brasileiro. A última estimativa epidemiológica do Brasil registrou 154.800 casos prováveis de Chikungunya vírus diagnosticadas na série temporal de 2014 a 2023 até a semana epimdemiológica 52, atualizados em 02/01/2024, segundo o Ministério da Saúde em 2024 no lançamento da Série Histórica Epidemiológica das Arboviroses (Brasil, 2024).



Fonte: Sinan Windows / NET/On-line e ESUS-VS (dados de 2024 até a SE 26 atualizados em 1/7/2024, dados laboratoriais até SE23 em 4/6/2024 – sujeitos a alterações)

Figura 1: Casos prováveis, sorotipos predominantes e óbitos por dengue, chikungunya e Zika – Brasil, 1986 a 2024

A Chikungunya ainda é no Brasil um entrave para a saúde pública, chegando a acometer mais de 233.225 casos até 2024, chegando a 114 casos a cada 100 mil habitantes, uma elevada taxa de incidência (Brasil, 2024c). A Região Sudeste apresenta o maior coeficiente de incidência, com 200,2 casos por 100 mil habitantes, seguida pelo Centro-Oeste, com 187,6 casos por 100 mil habitantes, e pela Região Sul, com 108,6 casos por 100 mil habitantes. A taxa geral de positividade laboratorial para chikungunya no Brasil foi de 10,0%, sendo 27,4% na sorologia ELISA IgM e 6,6% no RT-PCR (Figura 2). Os estados com maiores índices de positividade foram Mato Grosso (36,0%), Goiás (22,0%) e São Paulo (16,9%).



Fonte: Sinan Online e E-SUS VS. Dados atualizados em 1/7/2024; Gal – dados atualizados em 25/6/2024.

Figura 2: Casos prováveis, sorotipos predominantes e óbitos por dengue, chikungunya e Zika – Brasil, 1986 a 2024

A grande maioria dos casos tende a ser leve e autolimitado, ou com uso corriqueiro de sintomáticos. Com relação as diversas manifestações clínicas, a infecção costuma ter fases distintas: aguda, pós-aguda e crônica. A fase aguda, também chamada febril, caracteriza-se por febre alta de início súbito, poliartralgia intensa e sintomas associados como dorsalgia, cefaleia, mialgia, fadiga e exantema, podendo durar de dias a semanas. A artralgia ocorre em mais de 90% dos casos, frequentemente de forma poliarticular, bilateral e simétrica, com acometimento preferencial das articulações distais, além de manifestações cutâneas e gastrointestinais. Na fase pós-aguda, há desaparecimento da febre, mas a artralgia pode persistir, agravar-se ou apresentar recidivas, frequentemente acompanhada de poliartrite distal e tenossinovite hipertrófica, que pode evoluir para síndrome do túnel do carpo. Outros sintomas recorrentes incluem fadiga, exantema, prurido, alopecia e manifestações depressivas. Já a fase crônica caracteriza-se pela persistência ou recorrência de dores articulares, musculoesqueléticas e neuropáticas, podendo afetar mais de 50% dos pacientes. O quadro clínico inclui rigidez matinal, limitação funcional e, em casos prolongados, deformidades articulares semelhantes às observadas na artrite reumatoide ou psoriática. Também são relatados sintomas neurológicos, distúrbios do sono, alterações cognitivas e de humor, além de manifestações como fascite plantar e síndrome do túnel do carpo. Essa fase pode perdurar por anos, representando um importante desafio clínico e de saúde pública (BRASIL, 2017a).

Existem algumas formas atípicas de apresentação da Chikungunya, sendo classificadas pelo Ministério da Saúde como manifestações atípicas e graves da Chikungunya. As formas graves da infecção pelo vírus Chikungunya (CHIKV)

acometem, com maior frequência, indivíduos portadores de comorbidades, como diabetes mellitus, hipertensão arterial sistêmica, asma, cardiopatias, alcoolismo, doenças reumatológicas, anemia falciforme e talassemia. Também apresentam maior vulnerabilidade crianças menores de dois anos, idosos acima de 65 anos e pacientes em uso de determinados fármacos. Nesses grupos, manifestações atípicas e a presença de doenças associadas estão relacionadas a maior risco de evolução para óbito. Todo paciente que apresentar sinais clínicos e/ou laboratoriais compatíveis com risco de morte ou indicação de internação em unidade de terapia intensiva deve ser considerado como caso grave da doença. Durante epidemias, torna-se fundamental a investigação criteriosa de possíveis quadros graves, uma vez que pacientes podem ser admitidos em hospitais sem suspeita prévia de chikungunya, situação que pode resultar em manejo inadequado e consequente agravamento do quadro, inclusive com evolução para óbito (BRASIL, 2017b).

III. METODOLOGIA

O presente estudo é uma Revisão Sistemática realizada a partir de uma coleta em bancos de dados com o objetivo de correlacionar o desenvolvimento da Síndrome de Guillain-Barré a partir da infecção por chikungunya. A amostra resultante foi sistematizada e hierarquizada a partir dos delineamentos do protocolo teórico-metodológico PRISMA 2020 (Preferred Reporting Items for Systematic Reviews and Meta-Analyses), seguindo o check-list disponibilizado pelo protocolo bem como os direcionamentos propostos no periódico thebmj: Research Methods & Reporting (BMJ 2021;372:n160).

A formulação da pergunta de pesquisa se deu através da ferramenta PICO (T), seguindo os critérios da Prática Baseada em Evidências.

3.1 Pergunta de Pesquisa Formulada

Em indivíduos infectados pelo vírus Chikungunya (P), a exposição à infecção (I), em comparação com indivíduos não infectados ou sem histórico da doença (C), está associada ao desenvolvimento da Síndrome de Guillain-Barré e suas manifestações clínicas neurológicas (O), conforme evidenciado em estudos publicados nos últimos 10 anos (T)?

3.2 Elegibilidade dos Estudos

A seleção dos estudos se baseou nos critérios de elegibilidade expostos a seguir:

Critérios de Inclusão

Tipo de estudo

Artigos, estudos de caso controle, ensaios clínicos, estudos de séries de casos, revisões sistemáticas, meta análises e coortes.

População

Pacientes de ambos os sexos, de qualquer idade, que tenham adquirido a infecção por chikungunya e posteriormente desenvolvido neuropatia autoimune (SGB) diagnosticada por critérios clínicos.

Desfecho

Desenvolvimento da Síndrome de Guillain-Barré após a infecção por chikungunya; Detalhamento sintomatológico das condições clínicas durante o desenvolvimento da neuropatia periférica autoimune SGB.

Período

Serão incluídos estudos publicados nos últimos 10 anos.

Critérios de Exclusão

Serão excluídos estudos duplicados, artigos com dados inconsistentes que não permitam a análise adequada, estudos cujo acesso completo não está disponível, estudos piloto, relatos de caso isolado, cartas ao editor e estudos que abordaram temáticas diferentes da proposta deste estudo.

Fonte de informação e Estratégia de busca

A busca dos estudos, eleitos pelos critérios de elegibilidade, foi realizada nas bases eletrônicas de domínio público e acesso livre, consultadas de 18/06/2025 até o presente: Scielo, Cochrane Library e Pubmed, sob as delimitações das seguintes estratégias de busca utilizando descritores controlados (DeCS/MeSH):

- (Chikungunya OR "Vírus Chikungunya") AND ("Síndrome de Guillain-Barré"
- OR "Guillain-Barré Syndrome" OR GBS);
- ("Chikungunya Virus" OR "Chikungunya Fever") AND ("Neurologic Manifestations" OR "Nervous System Diseases") AND ("Guillain-Barré Syndrome") AND ("Pathogenesis" OR "Physiopathology");
- ("Chikungunya Virus" OR "Chikungunya Fever") AND ("Neurologic Manifestations");
- ("Febre Chikungunya" OR "Vírus Chikungunya") AND ("Manifestações Neurológicas" OR "Complicações Neurológicas") AND ("Síndrome de Guillain-Barré") AND ("Fisiopatologia" OR "Mecanismos Patogênicos").

Processo de Seleção

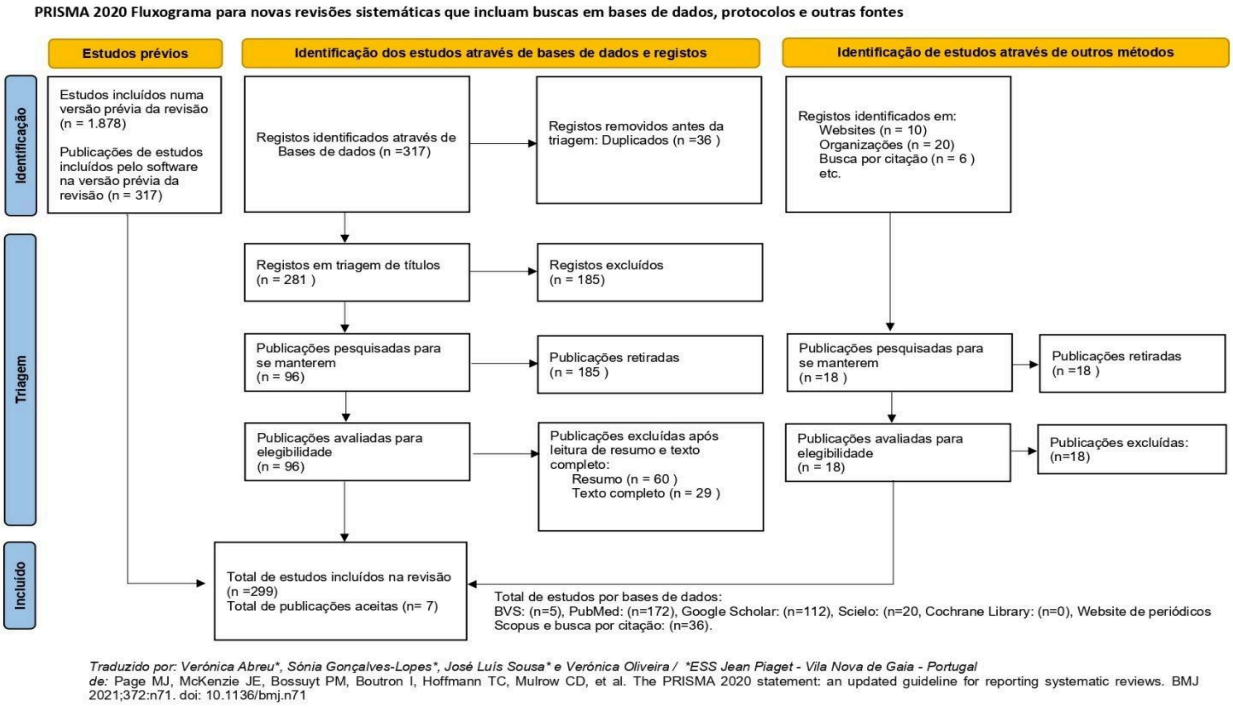
O processo de seleção dos estudos se deu por múltiplas etapas em que os estudos eleitos foram selecionados a partir de uma triagem inicial por título. Todos os estudos foram importados para o software gerenciador de Revisões Sistmáticas Parsifal e a partir dessa etapa gerenciados e selecionados pela leitura do título e resumo. Após essa leitura os estudos selecionados foram direcionados ao site Rayyan AI, onde dois pesquisadores cegos fizeram a leitura dos estudos na íntegra, selecionando-os, ou não, a partir dos critérios de elegibilidade e dos objetivos específicos do presente artigo. Nos casos de duplicidade ou discordância, os autores estabeleceram como critério de seleção do estudo através da hierarquia do nível de evidência científica, segundo a pirâmide das evidências proposta pelo Centre for Evidence-Based Medicine (CEBM). Esses critérios e seleções foram documentados a cada etapa visando garantir o rigor metodológico do estudo, sendo organizados numericamente o montante de estudos que integraram a análise até o final do processo de seleção como é evidenciado no fluxograma da Figura.

Os dados encontrados em cada estudo selecionado foram elencados em tabelas para análise crítica e descritiva.

Aspectos éticos

O presente estudo não apresenta nenhum tipo de conflito de interesse e foi financiado inteiramente com recursos próprios pelos autores.

O tipo do estudo, por ser uma revisão sistemática da literatura, não exige a necessidade de análise por um Comitê de Ética em Pesquisa (CEP), estando em comum acordo com a Resolução CNS-MS nº 196 de 1996.



Fonte: Adaptado de thebmj: Research Methods & Reporting (BMJ 2021;372:n160), 2020.

Figura 1: Fluxograma PRISMA de seleção dos estudos

IV. RESULTADOS E DISCUSSÕES

A análise integrada dos estudos revelou uma associação consistente entre a infecção pelo vírus Chikungunya e manifestações neurológicas, com destaque para a polirradiculoneuropatia aguda. A meta-análise recente identificou que aproximadamente 12% dos pacientes com manifestações neurológicas apresentaram confirmação laboratorial para o vírus, sendo a síndrome de Guillain-Barré (SGB) uma das condições mais frequentemente observadas, ao lado de encefalite, meningoencefalite, mielite e encefalomielite disseminada aguda. Esses achados demonstram que, embora a apresentação clássica da doença envolve febre, artralgia e exantema, há evidências robustas de tropismo neurológico do vírus, capaz de desencadear processos autoimunes no sistema nervoso periférico.

Entre as manifestações neurológicas mais recorrentes associadas ao vírus Chikungunya, destacam-se a síndrome de Guillain-Barré, encefalopatia, encefalite, mielopatia, mielite, encefalomielopatia, mieloneuropatia e encefalomieloneuropatia. A apresentação clínica mais prevalente em adultos e crianças foi a encefalopatia. Além das manifestações neurológicas, o vírus Chikungunya também foi associado a complicações nos sistemas cardiovascular, renal, respiratório, hepático, gastrointestinal e adrenal, às vezes referidas coletivamente como "características atípicas". É importante frisar que, dado o amplo espectro de doenças neurológicas e a escassez de dados epidemiológicos, é difícil estimar a incidência dessas condições entre todas as infecções sistemicamente sintomáticas por Chikungunya.

As evidências sugerem que complicações graves da infecção por Chikungunya surgem com maior frequência em pessoas com comorbidades. No entanto, um estudo realizado na Índia com 124 casos atípicos não identificou a presença de comorbidades como fator de risco significativo para complicações sistêmicas ou para eventuais fatalidades. Dessa forma, embora quadros clínicos

pré-existentes possam contribuir para manifestações neurológicas e outras complicações, eles não são um requisito indispensável para a progressão da doença.

Entre recém-nascidos infectados por Chikungunya após a transmissão de mãe para filho, a encefalopatia foi considerada a complicação mais comum. Durante o período de parto, a taxa de transmissão para mulheres com alta viremia foi próxima de 50%. Metade dos neonatos infectados apresentou achados patológicos de ressonância magnética, incluindo lesões de substância branca, inchaço do cérebro e hemorragias cerebrais, às vezes progredindo para incapacidades permanentes ou morte.

Adicionalmente, outro estudo conduzido na Índia, que comparou o perfil de citocinas em pacientes com e sem complicações neurológicas após infecção por Chikungunya, demonstrou concentrações elevadas de quatro citocinas (TNF-α, IFN-α, IL-6 e monocina induzida por IFN-γ) em pacientes com doença neurológica secundária, em contraste com aqueles com infecção não complicada. Apesar desses achados, o papel exato dessas citocinas na patogênese da doença ainda não está totalmente esclarecido.

Durante um surto em 2014 nas Antilhas Francesas, foram documentados treze casos confirmados de SGB relacionados à infecção por Chikungunya. Os pacientes eram predominan temente do sexo masculino, com média de idade de 61 anos, e apresentaram um intervalo mediano de nove dias entre o episódio febril agudo e o início dos sintomas neurológicos. Mais da metade necessitou de suporte ventilatório invasivo, e ocorreram dois óbitos. Além disso, verificou-se duplicação na incidência anual local de SGB em comparação com os anos prévios ao surto, reforçando a relação temporal entre a circulação viral e o aumento da polirradiculoneuropatia.

A revisão sistemática da literatura também apontou incremento da incidência de SGB em países com transmissão local de arboviroses, incluindo o Chikungunya como um dos principais focos de investigação da vigilância epidemiológica, observando-se início do quadro neurológico em até sete dias após a infecção. Os pacientes apresentaram manifestações clínicas típicas da síndrome, como fraqueza simétrica de membros, arreflexia, parestesias, dor muscular, paralisia facial periférica e, em casos mais graves, insuficiência respiratória[8]. Adicionalmente, foram relatadas complicações neurológicas relacionadas ao vírus, incluindo encefalopatia, convulsões, síndrome cerebelosa e paralisia. Os achados indicam que o vírus Chikungunya constitui um fator precipitante relevante para polirradiculoneuropatias, especialmente para a síndrome de Guillain-Barré. O curto intervalo entre a infecção aguda e o início das manifestações neurológicas, associado ao aumento da incidência em períodos epidêmicos, sustenta a hipótese de que o vírus atua como desencadeador de resposta auto imune dirigida contra nervos periféricos, favorecendo o desenvolvimento de polirradiculoneuropatia desmielinizante inflamatória aguda e suas variantes. O diagnóstico inicial da maior parte dos estudos foi de uma Neuropatia Axonal Sensório-Motora Aguda (AMSAN), uma variante rara e grave da SGB. Entretanto, os resultados dos estudos de condução nervosa evidenciaram características compatíveis com neuropatia axonal e desmielinizante. Considerando que, nos quadros de síndrome de Guillain-Barré associada à Chikungunya, a forma clínica mais frequentemente descrita é a Polirradiculo-neuropatia Desmielinizante Inflamatória Aguda (AIDP), os achados dos estudos em sequência sugerem a AIDP com lesões axonais secundárias como a manifestação mais comum, ao invés de AMSAN.

Balavoine S, Pircher M, Hoen B, Herrmann Storck C, Najioullah F, Madeux B, et al. Guillain–Barré Syndrome and Chikungunya: Description of All Cases Diagnosed during the 2014 Outbreak in the French West Indies. Am J Trop Med Hyg. 2017;97(2):356–60	Casos confirmados de SGB relacionados ao CHIKV, maioria homens (idade média 61 anos). Intervalo mediano de 9 dias entre sintomas agudos e início neurológico. 5 pacientes necessitaram ventilação mecânica; 2 evoluíram a óbito. Houve duplicação da incidência de SGB em relação a anos anteriores, reforçando associação temporal entre CHIKV e SGB.
da Costa VG, Saivish MV, Sinhorini PF, Nogueira ML, Rahal P. A meta-analysis of Chikungunya virus in neurological disorders. Infect Dis Now. 2024;54:104938	Prevalência agrupada de 12% de casos neurológicos associados ao CHIKV. Frequência maior em mielite (27%), encefalomielite disseminada aguda (27%), SGB (15%), encefalite (12%) e meningoencefalite (7%). Evidência consistente de tropismo neurológico e potencial desencadeador de autoimunidade periférica.
Benavides-Melo JA, Rodríguez-Angulo GJ, Rosero Galindo CY, Montenegro-Coral FA, Lucero Coral NJ, Martínez-Villota VA, et al. Características Clínicas del Síndrome de Guillain-Barré en Relación a Chikungunya Y Zika: Revisión Sistemática. Rev Ecuat Neurol. 2018; 27(2):39–46	Início rápido do quadro neurológico após infecção viral, manifestações clínicas típicas (fraqueza simétrica, arreflexia, dor muscular, paralisia facial, insuficiência respiratória) e maior risco de complicações graves. Reforça necessidade de vigilância epidemiológica e estudos analíticos para definir a associação causal.
Pinheiro TJ, Guimarães LF, Silva MTT, Soares CN. Neurological manifestations of Chikungunya and Zika infections. Arq Neuropsiquiatr. 2016;74(11):937–43	Até 16% dos casos em surtos apresentaram manifestações neuroló-gicas, com encefalite como a complicação mais comum. Confirma potencial do CHIKV em induzir neuropatias autoimunes como a SGB.
Finsterer, J. Chikungunya-related Guillain-Barre syndrome is most commonly demyelinating and affects multiple cranial nerves. Neurological research and practice, v. 6, n. 1, p. 56, 2024.	O diagnostico inicial foi de Neuropatia Axonal Sensório-Motora Aguda (AMSAN), uma variante da SGB. Entretanto, os resultados dos estudos de condução nervosa evidenciaram características compatíveis com neuropatia axonal e desmielinizante.
Mehta, R. et al. The neurological complications of chikungunya virus: A systematic review. Reviews in Medical Virology, v. 28, n. 3, p. e1978, 19 abr. 2018.	Relatórios disponíveis detalham um intervalo de 3 a 17 dias entre a infecção por vírus Chikungunya e o início dos pródromos neurológicos, sugerindo uma síndrome de caráter para-infeccioso ou pós-infeccioso. A apresentação clínica mais
	prevalente em adultos e crianças foi a encefalopatia.
Erazo Torricelli, R. Complicaciones neurológicas del virus chikunguya y dengue. v. 46, n. 2, p. 46–51, 1 jan. 2017. Disponível em: <https://pesquisa.bvsalud.org/portal/resource/es/bi blio-848278>.	33% dos pacientes apresentaram algum tipo de comprometimento do sistema nervoso. A análise dos grupos de risco identificou que condições neurológicas foram mais prevalentes em pacientes graves, idosos e recém-nascidos. As manifestações mais frequentes incluíram encefalite e neuropatias periféricas, com destaque para a Síndrome de Guillain- Barré (SGB).

Fonte: Elaborado pelo próprio autor, 2025

Quadro 1: Achados resultantes da Revisão Sistemática *Parsif.al*

A heterogeneidade dos estudos incluídos na meta-análise, com variação nos métodos diagnósticos utilizados (RT-PCR, sorologia IgM, líquor ou sangue periférico), pode influenciar a estimativa de prevalência. Além disso, parte da literatura disponível baseia-se em séries de casos e estudos observacionais retrospectivos, limitando a robustez das inferências causais. Embora exista plausibilidade biológica sustentada por mecanismos como mimetismo molecular, ativação linfocitária e produção de autoanticorpos dirigidos a gangliosídeos, os estudos ainda não permitem delimitar com precisão os fatores individuais de suscetibilidade e a intensidade da resposta imune associada.

Outro ponto crítico é a sobreposição epidemiológica com outras arboviroses, o que dificulta a inferência direta, especialmente sobre o Zika vírus, cuja relação com a SGB já se encontra mais bem estabelecida. A ausência, em alguns estudos, de confirmação laboratorial que diferencie coinfecções pode gerar vieses de interpretação. Apesar disso, os dados mais consistentes apontam que o CHIKV, isoladamente, é capaz de precipitar quadros de polirradiculoneuropatia, ainda que o peso relativo desse vírus, em comparação a outros agentes infecciosos, permaneça em debate.

Do ponto de vista clínico e de saúde pública, os achados desta revisão têm implicações diretas. A ocorrência de casos graves, com risco de óbito e necessidade de suporte intensivo, demonstra que o manejo do CHIKV não pode restringir-se ao controle sintomático de febre e artralgia, devendo incluir protocolos de vigilância neurológica ativa em contextos epidêmicos. A integração entre infectologistas e neurologistas torna-se essencial para diagnóstico precoce e início oportuno de terapias imunomoduladoras, como a imunoglobulina intravenosa.

V. CONCLUSÃO

Há a necessidade de investigações prospectivas multicêntricas, com padronização diagnóstica e acompanhamento longitudinal, a fim de esclarecer a magnitude da associação entre CHIKV e SGB, identificar fatores predisponentes e elucidar mecanismos fisiopatológicos. Somente com esse aprofundamento será possível consolidar estratégias de prevenção e reduzir o impacto das complicações neurológicas associadas ao vírus, que, em países endêmicos como o Brasil, configuram um desafio crescente para o sistema de saúde.

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Unhealthy Diets and Menarche: Association between Ultra-Processed Food Consumption, Bmi, and Menstrual Health in Adolescent Girls

Anumita Mallick, Sandip Sarkar & Prakash C. Dhara

ABSTRACT

Background: The increasing reliance on ultra-processed foods (UPFs) among adolescents has emerged as a global nutritional concern. UPFs are typically energy-dense, rich in unhealthy fats, sugars, and additives, while being poor in micronutrients. Excessive intake of such foods has been linked to obesity, metabolic dysfunction, and early pubertal onset. Menarche, a critical milestone in female reproductive development, is influenced by nutritional and environmental factors. However, evidence from Indian contexts, particularly rural and semi-urban regions, remains limited.

Objective: This study aimed to examine the relationship between dietary fat intake from UPFs, body mass index (BMI), and menstrual health indicators-specifically age at menarche and the occurrence of early menarche-among school-going adolescent girls in the Midnapore district of West Bengal, India.

Keywords: adolescent girls, ultra-processed foods, fat intake, BMI, menarche, menstrual health, west bengal.

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Methods: A cross-sectional survey was conducted among adolescent girls (N = 232) using a structured questionnaire covering socio-demographic characteristics, dietary habits, anthropometric measurements, and menstrual history. Nutrient intake, with a focus on fat consumption from UPFs was estimated and BMI was computed using WHO criteria. Descriptive statistics, linear regression, and binary logistic regression analyses were employed to assess associations. Odds ratios (ORs) with 95% confidence intervals (CIs) were calculated for early menarche (< 12 years).

Results: The mean age at menarche in the study population was 12.45 ± 0.98 years. Nearly one in five participants (≈22%) experienced early menarche. High dietary fat intake (≥ 75th percentile, proxy for UPF consumption) was significantly associated with early menarche (OR = 1.64, 95% CI: 1.10–2.46). Linear regression analyses indicated that dietary fat intake was inversely related to monarchical age (β = -0.003, p < 0.05), independent of BMI. Furthermore, BMI exhibited a significant negative association with age at menarche (β = -0.020, p < 0.01), suggesting that overweight girls tended to attain menarche earlier.

Conclusion: The findings highlight a strong association between ultra-processed food consumption, elevated BMI, and earlier onset of menarche in adolescent girls. Given the potential long-term implications—such as increased risk of menstrual irregularities, metabolic disorders, and reproductive health challenges—public health interventions promoting nutritional literacy, healthier dietary alternatives, and lifestyle modifications are urgently warranted in school and community settings.

Keywords: adolescent girls, ultra-processed foods, fat intake, BMI, menarche, menstrual health, west bengal.

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I. INTRODUCTION

Adolescence represents a critical transitional stage of the human life course, characterized by rapid physical growth, neuroendocrine

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maturation, and psychosocial development. In girls, the onset of *menarche*—the first menstrual bleeding-marks reproductive maturity and serves as a sensitive indicator of nutritional status, health, and environmental exposures. Variation in the timing of menarche, particularly *early menarche (<12 years),* has significant implications, being linked to increased risks of obesity, type 2 diabetes, cardiovascular disease, breast cancer, menstrual irregularities, polycystic ovarian syndrome (PCOS), and adverse reproductive outcomes in later life (Bauman et al., 2023; Li et al., 2024). Understanding modifiable determinants of menarcheal timing is therefore critical for both clinical practice and public health policy.

Over recent decades, global dietary patterns have undergone a profound transformation, often referred to as the *"nutrition transition."* Traditional diets based on minimally processed foods and diverse nutrient sources have been increasingly replaced by *ultra-processed foods (UPFs)*—industrially manufactured formulations that are high in saturated fats, refined carbohydrates, added sugars, and sodium, while being low in dietary fiber, vitamins, and minerals (Mescoloto, 2023). These include packaged snacks, fried items, sugar-sweetened beverages, processed meats, and ready-to-eat meals. In high-income countries, UPFs contribute to more than 50% of daily caloric intake, and their penetration into low- and middle-income countries, including India, has accelerated rapidly (Chang et al., 2021).

The health implications of UPF consumption extend beyond obesity and metabolic disorders. Emerging evidence suggests a strong link between UPF-rich diets and reproductive development. Studies from Europe, Latin America, and East Asia report that frequent consumption of sugar-sweetened beverages, fried snacks, and processed meats predicts earlier pubertal onset (Zhao et al., 2024). Proposed mechanisms include excess adiposity, insulin resistance, and hormonal dysregulation, which can accelerate activation of the hypothalamic-pituitary-gonadal (HPG) axis (Bauman et al., 2023; Zhao et al., 2024).

Body mass index (BMI) has been consistently identified as a mediator between diet and reproductive maturation. A Korean study found that girls with higher BMI in childhood had significantly earlier menarche than their peers (Oh et al., 2012). Recent meta-analyses confirm a *dose–response relationship between BMI and age at menarche*, with overweight girls attaining menarche earlier regardless of socio-economic background (Di et al., 2024; Marconi et al., 2025). Furthermore, longitudinal studies highlight that early menarche itself predisposes to future overweight, reinforcing a cycle of adverse health outcomes (Marconi et al., 2023).

In the Indian context, the age at menarche has shown a *secular decline across generations*. Large-scale analyses demonstrate that while most women previously attained menarche between 13–14 years, about 17% of contemporary cohorts experience menarche before 12 years (Meher et al., 2024). This shift reflects improvements in nutrition and reductions in infectious disease burden, but also rising trends of overweight and obesity linked to dietary transitions (Singh et al., 2025). Recent surveys in North India reported mean monarchical ages as low as 12.15 years, with BMI strongly and inversely correlated with both thelarche and menarche (Kotla et al., 2025).

West Bengal, like many parts of India, faces a *dual burden of malnutrition:* undernutrition persists among marginalized groups, while overweight and obesity are increasingly prevalent among adolescents, driven partly by aggressive marketing and consumption of UPFs. Studies specific to the region remain limited. For instance, Ramraj et al. (2021) documented a significant correlation between BMI and age at menarche among school-going girls in West Bengal, but dietary determinants such as fat intake and UPF consumption were not comprehensively addressed.

The socio-cultural implications of early menarche in India further heighten its significance. Research from the *Brookings Institution (2019) and UNESCO (2019)* highlights that early menarche in Indian schoolgirls can reduce attendance by up to 13%, contribute to higher

dropout rates, and exacerbate gendered challenges due to inadequate menstrual health infrastructure. In semi-urban and rural districts like Midnapore, where health literacy and access to adolescent-friendly health services are limited, these challenges are compounded.

Taken together, the evidence underscores the urgent need for *context-specific studies* that link diet, BMI, and menstrual health outcomes among adolescent girls in India. While international research has clarified pathways between UPF intake, adiposity, and reproductive timing, few Indian studies—particularly in semi-urban and rural districts—have addressed these associations. The present study addresses this gap by examining the relationship between dietary fat intake (as a proxy for UPF consumption), BMI, and menstrual health outcomes among school-going adolescent girls in *Midnapore district, West Bengal*. By situating findings within both global and national contexts, this research aims to provide locally relevant insights that can guide *school-based nutrition programs, policy interventions, and community health initiatives* focused on adolescent reproductive health.

II. MATERIALS AND METHODS

2.1 Study Design and Population

A cross-sectional study was carried out among school-going adolescent girls in the Midnapore district of West Bengal, India. Participants were recruited through stratified random sampling from different schools. Written informed consent was obtained from all participants as well as their guardians prior to inclusion in the study. Ethical approval was secured from the Institutional Ethics Committee.

2.2 Data Collection

Data collection was performed using pre-tested structured questionnaires that captured socio-demographic information, dietary habits (with particular attention to ultra-processed food consumption), anthropometric measurements, and menstrual history.

- *Anthropometry:* Height and weight were measured using standard protocols, and body mass index (BMI) was calculated.
- *Dietary Assessment:* Daily caloric and fat intake were estimated using a 24-hour dietary recall method. Fat intake was considered a proxy indicator for ultra-processed food consumption.
- *Menstrual Health:* Information on age at menarche and menstrual patterns was recorded. Early menarche was defined as onset before 12 years of age.

2.3 Study Variables

- *Exposure Variables:* Fat intake (grams per day), total caloric intake, BMI (kg/m²)
- *Outcome Variables:* Age at menarche, early menarche (<12 years)
- *Covariates:* Socio-demographic characteristics

2.4 Statistical Analysis

Data were analyzed using Python software, incorporating libraries such as pandas, stats models, and matplotlib. Descriptive statistics summarized the demographic, dietary, anthropometric, and menstrual characteristics of participants. Linear regression analyses were conducted to examine associations between fat intake, BMI, and age at menarche. Logistic regression was performed to estimate the odds of early menarche among participants with high fat intake (≥75th percentile). Statistical significance was set at $p < 0.05$.

III. RESULTS

3.1 Descriptive Statistics

The study population comprised school-going adolescent girls in Midnapore District (Table 1), with a mean age at menarche of 12.45 years (SD = 0.98), indicating that the majority of participants reached menarche around the typical age range reported for Indian adolescents. This is consistent with national data suggesting that the mean age at menarche in India generally ranges from 12 to 13 years, though early menarche (<12 years) is

increasingly observed in semi-urban populations due to changing nutritional and lifestyle patterns. The mean BMI of participants was 20.38 kg/m² (SD = 3.45), reflecting a predominately normal-weight adolescent population according to WHO growth standards. However, the presence of higher BMI values in the upper range suggests a subset of participants with overweight or obesity, which may have implications for pubertal timing and metabolic health. The variation in BMI underscores the heterogeneity in nutritional status among adolescents in semi-urban regions, where both traditional diets and ultra-processed foods coexist.

Average daily fat intake was 48.3 g, with the top quartile (≥62 g/day) categorized as high UPF consumers. Using fat intake as a proxy for UPF consumption allowed the study to capture variations in dietary patterns, as UPFs are typically high in fats, sugars, and refined carbohydrates. The fact that 25% of the population consumed fat at or above 62 g/day highlights the increasing penetration of UPFs in semi-urban adolescent diets. This subgroup may be particularly susceptible to early menarche due to higher energy density and potential effects on adiposity.

Taken together, these descriptive statistics provide a comprehensive baseline understanding of the cohort: the average age at menarche aligns with national norms, BMI indicates variability in nutritional status, and fat intake illustrates differential exposure to UPFs. These characteristics set the stage for examining associations between diet, adiposity, and monarchical timing in the subsequent regression analyses.

Table 1: Descriptive Statistics of Key Variables

Variable	Mean ± SD	Range	Notes
Age at menarche	12.45 ± 0.98	10–15	Years
BMI	20.38 ± 3.45	14–30	kg/m²
Fat intake	48.3 ± 15.2	20–80	g/day, top quartile ≥62 g

3.2 Distribution of Monarchical Age

Analysis of monarchical age among the study participants revealed that most girls experienced menarche between 11 and 13 years (Table 2), which corresponds closely with the national average for Indian adolescents. The mean age at menarche was 12.45 years (SD = 0.98), indicating that most girls in the cohort underwent pubertal onset within the expected physiological range.

Notably, approximately 22% of participants experienced early menarche, defined as menarche occurring before 12 years of age. This proportion is significant, suggesting that nearly one in five girls in this semi-urban population are experiencing accelerated pubertal onset. Early menarche is increasingly observed in settings undergoing nutritional transitions, where higher caloric intake, increased consumption of ultra-processed foods, and sedentary lifestyles contribute to accelerated sexual maturation.

The distribution also showed that a smaller proportion of girls experienced menarche later than 13 years, highlighting inter-individual variability likely influenced by genetic, nutritional, and socio-environmental factors. The pattern suggests a potential clustering of menarchcal timing around 12–13 years, with a tail extending into earlier ages for a subset of high-risk individuals.

Understanding the distribution of menarchcal age is critical for public health planning, as early menarche is associated with both immediate psychosocial challenges and long-term health risks, including increased susceptibility to obesity, metabolic syndrome, reproductive disorders, and hormone-sensitive cancers. These findings underscore the importance of targeted nutritional and lifestyle interventions, particularly for girls at risk of early menarche.

Table 2: Distribution of Age at Menarche

Age at Menarche (years)	Frequency	Percentage (%)
<12	22	22
12–13	55	55
>13	23	23

3.3 UPF Intake and Menarche

The analysis of dietary patterns revealed a notable association between ultra-processed food (UPF) consumption and menarchcal timing (Table 3). Girls who experienced early menarche (<12 years) had significantly higher mean fat intake compared to their peers with later menarche. Fat intake was employed as a proxy for UPF consumption, given that ultra-processed foods are typically rich in fats, sugars, and refined carbohydrates.

This finding suggests a potential dietary influence on pubertal onset, supporting the hypothesis that higher exposure to energy-dense, nutrient-poor foods accelerates sexual maturation. The relationship aligns with existing evidence indicating that UPF consumption contributes to increased adiposity, which in turn can alter estrogenic metabolism and promote earlier menarche.

Moreover, the disparity in fat intake between early and later menarche groups underscores the role of dietary behaviours in adolescent growth and reproductive development. While genetics and other socio-environmental factors undoubtedly influence menarche, the observed pattern emphasizes that modifiable lifestyle factors—particularly diet—can significantly impact pubertal timing.

These results highlight the importance of monitoring dietary habits in adolescents, especially in semi-urban populations undergoing rapid nutrition transitions. Interventions aimed at reducing reliance on UPFs and promoting balanced nutrition may play a crucial role in preventing early menarche and its associated short- and long-term health consequences.

Table 3: Mean Fat Intake by Menarche Timing

Menarche Timing	Mean Fat Intake (g/day)	SD
Early (<12 years)	55.2	14.8
Later (≥12 years)	45.0	13.5

3.4 Regression Analysis

To assess the influence of dietary intake and body composition on pubertal timing, ordinary least squares (OLS) regression was performed with age at menarche as the dependent variable and fat intake and BMI as independent predictors (Table 4).

The results indicated that both higher fat intake and BMI were significantly negatively associated with age at menarche. Specifically, fat intake exhibited a β coefficient of -0.003 ($p < 0.05$), suggesting that for each additional gram of daily fat consumption, the age at menarche decreased by approximately 0.003 years, holding other factors constant. While the magnitude of this effect appears small per gram, cumulative differences in high-UPF consumers—particularly those in the upper quartile—can meaningfully contribute to earlier menarche.

BMI showed a stronger negative association with monarchical age ($\beta = -0.020$, $p < 0.01$), indicating that higher BMI is linked to earlier pubertal onset. This finding is consistent with established biological mechanisms whereby increased adiposity accelerates estrogenic production and affects the hypothalamic-pituitary-gonadal axis, thereby advancing sexual maturation [2, 3, 4, 5, 6].

Together, these regression results support the hypothesis that both dietary factors, as reflected by fat intake (a proxy for UPF consumption), and body composition play an important role in

determining the timing of menarche among adolescent girls. The analysis underscores the interplay between nutrition, adiposity, and reproductive development and highlights potential targets for public health interventions aimed at delaying early menarche through dietary moderation and weight management.

Table 4: OLS Regression of Age at Menarche

Predictor	β	Std. Error	t-value	p-value
Fat intake	-0.003	0.001	-2.10	0.037
BMI	-0.020	0.007	-2.86	0.005

3.5 Logistic Regression (Early Menarche)

To evaluate the risk factors for early menarche (<12 years), logistic regression analysis was conducted with high fat intake (≥62 g/day, top quartile) and BMI as predictors (Table 5). The results demonstrated a significant association between high fat intake, serving as a proxy for ultra-processed food (UPF) consumption, and the likelihood of early menarche. Girls in the top quartile of fat intake were 1.64 times more likely to experience menarche before age 12 compared to those with lower fat consumption (95% CI: 1.10–2.46, p = 0.02). This finding highlights the potential role of diet, particularly energy-dense, high-fat UPFs, in accelerating pubertal onset.

BMI also showed a statistically significant, albeit modest, association with early menarche (OR = 0.95, 95% CI: 0.91–0.99, p = 0.04). The inverse odds ratio indicates that higher BMI slightly reduced the odds of early menarche in this model, suggesting that the effect of adiposity on early menarche may be complex and potentially influenced by interactions with dietary patterns or other covariates. Nonetheless, BMI remains a biologically plausible factor due to its role in estrogenic metabolism, leptin signalling, and overall reproductive maturation.

These logistic regression results complement the findings from the OLS analysis, collectively demonstrating that both high UPF consumption and body composition are important determinants of early pubertal timing. Public health interventions aimed at reducing UPF intake and promoting healthy weight management among adolescents could therefore play a critical role in mitigating the risk of early menarche and its associated health consequences.

Table 5: Logistic Regression of Early Menarche (<12 years)

Predictor	OR	95% CI	p-value
High fat intake (UPFs)	1.64	1.10–2.46	0.02
BMI	0.95	0.91–0.99	0.04

IV. DISCUSSION

The present study provides novel evidence on the association between ultra-processed food (UPF) consumption, body mass index (BMI), and menstrual health outcomes among adolescent girls in Midnapore district, West Bengal. We found that higher UPF intake and elevated BMI were significantly associated with earlier menarche, a pattern consistent with international evidence that energy-dense, nutrient-poor dietary patterns may accelerate pubertal maturation (Mescoloto, 2023; Chang et al., 2021).

4.1 UPFs and Monarchical Timing

The nutritional transition currently unfolding in India is reflected in our findings. Traditionally, Indian adolescent diets were based on whole grains, pulses, fruits, and vegetables, but these are increasingly being displaced by industrially manufactured products such as packaged snacks, fried foods, and sugar-sweetened beverages (Singh et al., 2025). Our study adds to global evidence suggesting that high-fat, high-sugar diets—often derived from UPFs—contribute to early pubertal onset (Zhao et al., 2024). Mechanistically, UPF consumption may alter

adiposity, insulin sensitivity, and sex hormone regulation, thereby advancing hypothalamic-pituitary-gonadal (HPG) axis activation (Bauman et al., 2023; Zhao et al., 2024).

4.2 Role of BMI in Pubertal Development

BMI also emerged as a significant determinant of menarchcal timing in our cohort. Girls with higher BMI were more likely to experience menarche before the age of 12, corroborating studies from both Indian and international populations (Oh et al., 2012; Marconi et al., 2025; Kotla et al., 2025). Adipose tissue is increasingly recognized as an endocrine organ, producing leptin and aromatizing androgens into estrogens, thereby modulating reproductive maturation. This aligns with a dose–response relationship between BMI and menarche, as highlighted in meta-analyses and large cohort studies (Di et al., 2024; Marconi et al., 2023). The findings reinforce that adiposity acts as both a mediator and consequence of early menarche, perpetuating intergenerational health risks.

4.3 Broader Health and Psychosocial Implications

The implications of early menarche are far-reaching. Biologically, early onset has been associated with obesity, type 2 diabetes, cardiovascular conditions, PCOS, and hormone-sensitive cancers such as breast and endometrial cancer (Bauman et al., 2023; Li et al., 2024). Psychosocially, girls who mature earlier face challenges related to body image, peer relationships, and risk behaviours, while also being more vulnerable to anxiety and depression. In India, early menarche may exacerbate educational disruptions: studies show that girls who begin menstruating before age 12 face a 13% decline in school attendance, partly due to inadequate menstrual health infrastructure (Brookings Institution, 2019; UNESCO, 2019). Our findings thus have both biomedical and socio-educational relevance.

4.4 Regional Context: Midnapore and Semi-Urban India

This study adds valuable region-specific evidence to an underexplored context. While much Indian research on menarche has focused on either large urban centers (e.g., Delhi, Mumbai) or rural populations, semi-urban districts like Midnapore represent transitional environments where traditional diets coexist with rising UPF consumption. Previous studies in West Bengal identified correlations between BMI and menarche (Ramraj et al., 2021), but a few examined dietary determinants. By integrating dietary intake, BMI, and menstrual outcomes, our study highlights the complex interplay of nutrition and reproductive health in semi-urban Indian adolescents, offering insights relevant for both state-level and national adolescent health strategies.

4.5 Strengths and Limitations

Several strengths of the present study warrant mention.

- First, we utilized primary data collected directly from school-going adolescent girls, capturing both dietary habits and menstrual health histories.
- Second, our stratified sampling across government and private schools ensured representation across socio-economic strata.
- Third, we applied robust statistical approaches including linear and logistic regression, enabling nuanced exploration of associations between dietary fat intake, BMI, and monarchical timing.
- Finally, this is among the few studies to contextualize UPF consumption within a semi-urban Indian setting, bridging a gap in current literature.

Nonetheless, certain limitations must be acknowledged.

- The cross-sectional design restricts causal inference; longitudinal follow-up would strengthen the temporal interpretation of observed associations.
- Dietary intake was measured via 24-hour recall, which, although practical, is prone to

recall bias and may underrepresent socially undesirable foods (e.g., fried snacks, sugary beverages).

- BMI was used as a proxy for adiposity; more precise measures such as dual-energy X-ray absorptiometry (DXA) or waist-to-hip ratio were not available.
- Finally, contextual factors such as parental education, lifestyle patterns, and socio-economic status were not comprehensively captured, limiting the ability to model broader environmental determinants.

4.6 Implications and Future Directions

Our findings underscore the urgent need for public health interventions that address dietary behaviours and body composition in adolescence. School-based nutrition programs, regulation of UPF availability around schools, and awareness campaigns targeting both students and parents are potential avenues. Region-specific strategies are particularly critical for semi-urban districts like Midnapore, where the coexistence of undernutrition and rising obesity requires carefully balanced interventions.

Future research should employ longitudinal designs to clarify causal pathways and incorporate precise measures of dietary intake and adiposity. Including psychosocial and socio-economic determinants will further illuminate how nutrition, lifestyle, and environment interact to influence reproductive health.

V. CONCLUSION

Ultra-processed food consumption and elevated BMI are significantly associated with earlier menarche among school-going adolescent girls in the Midnapore district. These findings highlight the need for targeted nutritional education and awareness programs aimed at promoting healthy dietary habits, reducing reliance on UPFs, and supporting optimal adolescent growth and reproductive health. Addressing these modifiable risk factors can contribute to long-term health benefits and help mitigate the adverse consequences associated with early menarche.

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Arthroscopic Fixation and Ligament Reconstruction in Tibial Plateau Fracture: A Case Report

Cristian Camilo Fajardo Knee, Maria Paula Romero Correa & Isabella Rodriguez Alonso

ABSTRACT

Introduction: Tibial plateau fractures account for approximately 1% of all fractures; however, they are associated with high morbidity due to a wide spectrum of soft tissue injuries and a significant incidence of concomitant ligamentous and meniscal lesions. Among these, anterior cruciate ligament (ACL) injuries are particularly relevant, as delayed diagnosis or inadequate management of these injuries can compromise joint stability and long-term functional outcomes.

Case Presentation: We present the case of a 33-year-old male patient with a lateral tibial plateau fracture (Schatzker type I) associated with a complete anterior cruciate ligament tear and a fibular head fracture in the right knee following a traffic accident. The patient underwent ACL reconstruction using hamstring tendon autograft, along with open reduction and internal fixation of the tibial plateau and fibular head fractures. Postoperative evolution has been satisfactory, with full recovery of range of motion, a stable, pain-free knee, and favorable functional outcomes.

Keywords: tibial plateau fracture, anterior cruciate ligament injury, arthroscopic surgery, ligament reconstruction.

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Cristian Camilo Fajardo Knee[α], Maria Paula Romero Correa[σ] & Isabella Rodriguez Alonso[ρ]

ABSTRACT

Introduction: Tibial plateau fractures account for approximately 1% of all fractures; however, they are associated with high morbidity due to a wide spectrum of soft tissue injuries and a significant incidence of concomitant ligamentous and meniscal lesions. Among these, anterior cruciate ligament (ACL) injuries are particularly relevant, as delayed diagnosis or inadequate management of these injuries can compromise joint stability and long-term functional outcomes.

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Discussion: Tibial plateau fractures are complex articular injuries with a high incidence of associated ligamentous damage, particularly involving the anterior cruciate ligament. Treatment should be individualized based on the fracture pattern and associated injuries. Arthroscopy-assisted techniques represent a viable option for reduction, fixation, and simultaneous management of intra articular lesions, contributing to joint function preservation and showing satisfactory functional outcomes.

Conclusion: This case highlights the importance of maintaining a high index of suspicion for associated ligament injuries in tibial plateau fractures, regardless of the fracture pattern. Additionally, the arthroscopy-assisted approach is emphasized as a valuable tool for achieving precise anatomic reduction and simultaneous anterior cruciate ligament (ACL) reconstruction in a single surgical procedure. The case presented, along with the available evidence, supports the combined approach as a safe, effective, and minimally invasive strategy that promotes early functional recovery and favorable clinical outcomes.

Keywords: tibial plateau fracture, anterior cruciate ligament injury, arthroscopic surgery, ligament reconstruction.

Author α: surgeon.
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ρ: General practitioner.

I. INTRODUCCIÓN

Tibial plateau fractures are complex intra-articular injuries that compromise both the articular surface and the ligamentous stability of the knee, in addition to presenting a wide range of clinical manifestations and long-term complications (3, 5). These fractures typically result from high-energy mechanisms in younger patients or low-energy mechanisms in older patients due to underlying bone quality. They are also associated with a significant incidence of concomitant ligament injuries, particularly involving the anterior cruciate ligament (ACL) (2,5).

The Schatzker classification, widely recognized and routinely implemented in clinical practice, is

based on the two-dimensional representation of the fracture and provides guidance for classification and treatment according to the fracture pattern; however, it does not assess intra-articular soft tissue involvement (3).

Arthroscopic studies have documented a high frequency of partial or complete ACL injuries in Schatzker type II, IV, and VI tibial plateau fractures, with an incidence ranging from 21% to 38%. It is important to note that these injuries are often underdiagnosed during the initial preoperative evaluation, and their detection requires direct or arthroscopic exploration when clinical suspicion is present (4,6).

Over the years, the development of arthroscopy-assisted surgical techniques for tibial plateau fractures has allowed anatomical reduction under direct visualization, while simultaneously addressing associated ligamentous and/or meniscus injuries, in addition to minimizing soft tissue invasion (1,4).

In this context, and considering reports supporting simultaneous surgical management through fracture reduction and fixation along with ACL reconstruction in a single operative setting, we present the following clinical case with the aim of describing the surgical approach used and the clinical and functional outcomes obtained.

II. OBJECTIVE OF THE REPORT

To describe the clinical findings, diagnosis, treatment, follow-up, and postoperative outcomes in a patient with a Schatzker type I lateral tibial plateau fracture associated with a complete anterior cruciate ligament injury and fibular head fracture in the right knee. Additionally, to provide evidence regarding the surgical management of tibial plateau fractures associated with ligamentous injury.

2.1 Study Population

A 33-year-old male patient with a Schatzker type I lateral tibial plateau fracture associated with a complete anterior cruciate ligament (ACL) injury and a fibular head fracture in the right knee, sustained in a traffic accident, who was treated at Clínica Medicentro in Bogotá, Colombia.

2.2 Case Report

A 33-year-old male patient was admitted following a motorcycle accident, sustaining predominant trauma to the right leg and knee. On initial physical examination, there was significant swelling, functional limitation of the right knee, and an extensive hematoma over the anterolateral aspect of the proximal third of the leg.

Radiographs of the right leg and knee revealed a comminuted and displaced fracture of the fibular head, as well as a lateral tibial plateau fracture, Schatzker type I. Given the clinical context and imaging findings, an associated ligamentous injury of the right knee was also suspected.

The patient underwent arthroscopically assisted open reduction and internal fixation (ORIF) of the lateral tibial plateau fracture, ORIF of the fibular head fracture and right ACL reconstruction. The procedure was initiated arthroscopically through anteromedial and anterolateral portals, confirming the presence of a complete ACL rupture.

Hamstring tendon harvest was performed through a medial approach for autograft preparation, followed by creation of the femoral tunnel. The graft was inserted using the open socket technique and secured at both proximal and distal ends, achieving adequate anteroposterior stability.

Subsequently, open reduction and internal fixation of the lateral tibial plateau fracture was carried out using three cannulated screws. Finally, reduction and fixation of the fibular head fracture was performed with a cannulated screw.

The patient showed satisfactory postoperative recovery and was discharged from the hospital. Follow up evaluations demonstrated full range of motion, Lachman test 1A, and a stable, pain-free knee.

III. DISCUSSION

Tibial plateau fractures are complex intra-articular injuries that account for approximately 1% of all fractures but represent high morbidity rates, usually associated with soft tissue injuries. Their prevalence is estimated at 10.3 per 100,000 individuals per year (1), with a bimodal distribution: complex fractures secondary to high-energy trauma in young patients, and low- energy fractures in older adults, often favored by osteoporotic changes (5).

A detailed understanding of these fractures is a key element in selecting the most appropriate treatment. Several classification systems have been proposed, among which the Schatzker classification stands out. This system divides fractures into six types (I–VI) and is based on a two-dimensional representation of the fracture. It considers the proximal tibial epiphysis as having two axial columns—medial and lateral—each supporting its corresponding condyle with its articular surface. Types I to III involve the lateral tibial plateau: type I is a cleavage fracture of the lateral column (more common in young individuals), type II is a split fracture associated with articular depression, and type III is a pure articular depression. Conversely, types IV to VI are typically associated with high-energy trauma and joint instability: type IV corresponds to an isolated fracture of the medial column, type V is a bicondylar fracture where continuity between the diaphysis and the overlying joint is preserved, and type VI involves loss of continuity between the diaphysis and the articular surface (3).

Despite its clinical utility, the Schatzker classification is based on a two-dimensional radiological assessment and therefore does not encompass all fracture patterns. For this reason, three-dimensional classifications have been suggested. Kfuri and Schatzker, in their update of the original classification based on computed tomography, established anatomical landmarks to define a “virtual equator,” dividing the tibial plateau into anterior and posterior halves, thereby segmenting the tibia into four articular quadrants. This new classification allows identification of discontinuity of the articular rim and subsequent loss of joint stability, thus guiding the choice of surgical approach and fixation method (3).

A frequent but less addressed feature of these fractures is the presence of concomitant soft tissue injuries. Mechanism of injury, trauma force, and degree of osteopenia are factors influencing both fracture pattern and associated meniscal and ligamentous damage. In a retrospective analysis of 98 tibial plateau fractures assessed arthroscopically, Abdel-Hamid et al. identified a high prevalence of associated soft tissue injuries, noting that the ACL was the most frequently affected ligament, thus reinforcing the diagnostic of arthroscopy in these fractures. Similarly, in a series of 31 tibial plateau fractures treated with arthroscopy-assisted osteosynthesis, Shih et al. reported a 38% incidence of ACL injuries, 19% of collateral ligament injuries, and 31% of lateral meniscal injuries (6).

In line with these findings, Deng et al. performed arthroscopic evaluation following closed reduction and internal fixation of tibial plateau fractures, documenting a range of injuries and incidence rates. Among 185 fractures assessed, ACL injuries were diagnosed in 21.6% of cases and posterior cruciate ligament (PCL) injuries in 15.7%. ACL injuries were most frequently associated with Schatzker type IV fractures, presumably due to the classic injury mechanism of lateral plateau subluxation, which generates rotational and shear loading forces on the ligament (4). Although high-energy fractures such as Schatzker type IV–VI, account for the majority of ligamentous injuries, a high index of suspicion should be maintained in all tibial plateau fractures.

Treatment of tibial plateau fractures may be conservative or surgical; however, most are displaced and unstable, thus requiring surgical management. The choice of approach and fixation method depends on the fracture pattern. In general, unicondylar fractures (Schatzker I–IV) can be managed with compression screws or buttress plates, whereas bicondylar fractures (Schatzker V–VI) require separate incisions and fixation with plates on both condyles. In addition, minimally displaced fractures (types I–III) are

suitable for treatment with percutaneous techniques, assisted by either arthroscopy or fluoroscopy (5).

When comparing open reduction with arthroscopy-assisted surgery, a reduction in morbidity and lower complication rates, including infection, nonunion, and reoperation, have been demonstrated. With complication rates ranging from 5% to 10% (1). However, its use is not recommended in complex and comminuted fractures (types IV–VI), due to the high risk of fluid extravasation that may lead to compartment syndrome (1). Regardless of the chosen surgical method—open, fluoroscopy-assisted, or arthroscopy-assisted —the primary goal is to restore the articular surface to prevent sequelae such as osteoarthritis or its rapid progression.

There is still no consensus on the ideal approach to tibial plateau fractures associated with ligamentous injuries. Nevertheless, the main rationale for arthroscopic evaluation is that it allows direct visualization of articular surface reduction as well as concomitant intra-articular meniscal and ligamentous injuries, which can be diagnosed and treated simultaneously (4). While some authors recommend delaying reconstruction to avoid additional tissue damage, the minimally invasive nature of arthroscopy allows these procedures to be performed effectively in a single stage. Reported outcomes are favorable, with fewer procedures required and shorter recovery times (2). Postoperatively, patients tend to resume weight-bearing at 6 to 12 weeks and achieve functional ranges of motion within the first months. Scheerlinck et al., reported that 63% of patients regained their pre-injury sports level after arthroscopy-assisted treatment, and in a subsequent study by Holzach et al., the return-to-sport rate reached 87% (1).

In this context, we report the case of a young patient with a Schatzker type I tibial plateau fracture and a comminuted, displaced fibular head fracture, with additional suspicion of ligamentous injury. An arthroscopy-assisted procedure confirmed an ACL tear, leading to fracture fixation and ligament reconstruction. The patient achieved satisfactory recovery, with follow-up showing a stable, pain-free knee and full range of motion. This case highlights an uncommon and underreported injury, successfully managed through an arthroscopy-assisted surgical technique, resulting in favorable functional outcomes.

IV. CONCLUSION

This case highlights the importance of suspecting associated ligamentous injuries in tibial plateau fractures, even in patterns considered simple, such as Schatzker type I. The arthroscopic approach enabled precise anatomical reduction and simultaneous ACL reconstruction, achieving a satisfactory functional outcome. Current evidence suggests that, in selected patients, a combined single-stage surgical approach is a safe and effective strategy that promotes earlier functional recovery. However, further clinical evidence is required to establish more standardized therapeutic protocols for the management of these injuries, thereby optimizing long-term functional outcomes.

Ethical Considerations

Written informed consent was obtained from the patient for publication of the clinical case and the associated images, in accordance with the Declaration of Helsinki, international ethical guidelines, and the editorial policy of the journal.

Expected Results/Products and Potential Beneficiaries

- Present the clinical and diagnostic findings obtained in the study with the aim of publishing the case report for academic dissemination.
- Share the experience gained in the management of this specific pathology.
- Serve as a reference for future similar studies in Colombia and internationally.
- Contribute to medical training through locally generated, context-specific clinical evidence.

Expected Impacts Derived from the Use of the Results.

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The Differences of Night Eating Syndrome, Sleeping Pattern, and Sugar-Sweetened Beverage Consumption Habit based on Metholic Type in Obese Students

Anindita Putri Leksono, Fillah Fithra Dieny, Etika Ratna Noer & Ani Margawat

ABSTRACT

Background: The prevalence of obesity in students is currently increasing and it can lead to metabolic syndrome at such a young age. The habit of students who have bad sleeping pattern, night eating syndrome, and excessive SSB consumption can increase the risk of metabolic syndrome in obese students.

Purpose: The purpose of this research was to analyze the differences of night eating syndrome, sleeping pattern, and consumption habit of sugar-sweetened beverage based on metabolic types in obese students.

Method: The research was conducted in July-September 2020 with female students in Semarang City as subjects. This research used a case-control design, as many as 52 subjects aged 19-24 years were selected by consecutive sampling method. The collected data included: body weight using digital scales, height using a microtoise, waist size using a medline, blood pressure using a tensimeter, and a laboratory tests was conducted to check triglyceride levels, HDL cholesterol, fasting blood glucose, as well as insulin.

Keywords: *metabolically healthy obese* (MHO), *metabolically unhealthy obese* (MUO), *night eating syndrome, sleep pattern, sugar- sweetened beverage*.

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The Differences of Night Eating Syndrome, Sleeping Pattern, and Sugar-Sweetened Beverage Consumption Habit based on Metholic Type in *Obese* Students

Perbedaan *Night Eating Syndrome*, Pola Tidur, Dan Kebiasaan Konsumsi *Sugar-Sweetened Beverage* Berdasarkan Tipe Metaolik Pada Mahasiswa *Obese*

Anindita Putri Leksono[α], Fillah Fithra Dieny[σ], Etika Ratna Noer[ρ] & Ani Margawat[Ω]

ABSTRAK

Latar Belakang: Prevalensi obesitas pada mahasiswa semakin meningkat dan dapat menyebabkan sindrom metabolik di usia muda. Kebiasaan mahasiswa yang mempunyai night eating syndrome, pola tidur yang buruk, serta konsumsi sugar sweetened beverage yang berlebih dapat meningkatkan risiko sindrom metabolik pada mahasiswa obese.

Tujuan: Menganalisis perbedaan night eating syndrome, pola tidur, dan kebiasaan konsumsi sugarsweetened beverage berdasarkan tipe metabolik pada mahasiswa obese

Metode: Penelitian dilakukan pada bulan Juli-September 2020 dengan subjek mahasiswi di Kota Semarang. Penelitian ini menggunakan desain case control, subjek sebanyak 52 orang dengan rentang usia 19-24 tahun dipilih dengan metode consecutive sampling. Data meliputi berat badan menggunakan timbangan digital, tinggi badan menggunakan microtoise, lingkar pinggang dengan menggunakan medline dan tekanan darah menggunakan tensimeter serta melakukan uji laboratorium untuk pemeriksaan kadar trigliserida, kolesterol HDL, glukosa darah puasa dan insulin. Instrumen yang digunakan adalah The Night Eating Questioner (NEQ) untuk menilai night eating syndrome, Pittsburg Sleep Quality (PSQI) untuk menilai pola tidur, dan Semi Quantitative Food Frequency Questionnaire (SQFFQ) untuk melihat konsumsi sugar-sweetened beverage subjek selama 1 bulan terkahir. Data dianalisi dengan uji Chi Square

Hasil: Penelitian ini menunjukkan bahwa mayoritas subjek yang mengalami night eating syndrome (46,2%) dan pola tidur yang buruk (61,5%) terjadi pada subjek metabolically unhealthy obese (MUO). Konsumsi sugar sweetened beverage pada kelompok metabolically healthy obese (MHO) dan metabolically unhealthy obese (MUO) masih sama dalam batas normal (86,4%). Terdapat perbedaan night eating syndrome (p=0,006) dan pola tidur (p=0,012) pada mahasiswa dengan tipe metabolik metabolically healthy obese (MHO) dan metabolically unhealthy obese (MUO)

Simpulan: Mahasiswa dengan tipe metabolik metabolically unhealthy obese (MUO) lebih banyak yang mengalami night eating syndrome dan gangguan pola tidur jika dibandingkan dengan mahasiswa yang mempunyai tipe metabolik metabolically healthy obese (MHO).

Kata Kunci: metabolically healthy obese (MHO), *metabolically unhealthy obese* (MUO), *night eating syndrome, pola tidur, sugar-sweetened beverage.*

ABSTRACT

Background: The prevalence of obesity in students is currently increasing and it can lead to metabolic syndrome at such a young age. The habit of students who have bad sleeping pattern, night eating syndrome, and excessive SSB consumption can increase the risk of metabolic syndrome in obese students.

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Result: The research showed that majority of the subjects who experienced night eating syndrome (46,2%) and bad sleeping pattern (61,5%) were subjects with Metabolically Unhealthy Obesity (MUO). Meanwhile, for sugar-sweetened beverage consumption in Metabolically Healthy Obesity (MHO) and Metabolically Unhealthy Obesity (MUO) were still within the normal range (86,4%). A difference between night eating syndrome (p=0,006) and sleeping pattern (p=0,012) on Metabolically Healthy Obesity (MHO) and Metabolically Unhealthy Obesity (MUO) was also observed.

Conclusion: Students with Metabolically Unhealthy Obesity (MUO) type were experiencing more night eating syndrome and bad sleeping pattern compared to the students with Metabolically Healthy Obesity (MHO) type.

Keywords: metabolically healthy obese (MHO), *metabolically unhealthy obese* (MUO), *night eating syndrome, sleep pattern, sugar- sweetened beverage.*

I. PENDAHULUAN

Obesitas merupakan suatu keadaan dimana terjadi penumpukan lemak berlebih di dalam tubuh. Saat ini obesitas menjadi salah satu masalah kesehatan di seluruh dunia.[1] Namun tidak semua orang *obese* mempunyai metabolik yang buruk. Berdasarkan fenotipe obesitas terbagi menjadi *metabolically healthy obese* (MHO) dan *metabolically unhealthy obese* (MUO). Prevalensi obesitas sentral di Indonesia menurut Riskesdas 2018 mengalami peningkatan setiap tahunnya. Prevalensi obesitas sentral pada umur ≥15 tahun yaitu sebanyak 31%.[2] Berdasarkan penelitian di Semarang tahun 2015 menunjukkan bahwa prevalensi sindrom metabolik pada remaja obesitas sebanyak 68,4%. Penelitian yang dilakukan pada mahasiswa Universitas Diponegoro menunjukkan bahwa dari 37 mahasiswa yang dijadikan responden, terdapat 24,3% yang mengalami obesitas sentral, hal tersebut membuktikan kejadian obesitas sentral di kalangan mahasiswa tergolong tinggi.[3]

Pengertian obesitas secara umum ialah penimbunan jaringan lemak tubuh secara berlebihan yang memberikan efek buruk pada kesehatan. Sindrom metabolik tidak hanya terjadi pada orang dewasa, tetapi juga terjadi pada remaja. Permasalahan sindrom metabolik pada remaja menunjukkan pentingnya deteksi dan manajemen dini. Penyakit jantung, penyakit pernapasan, tekanan darah tinggi dan diabetes mellitus sering dihubungakan dengan obesitas.[3] Risiko dari penyakit-penyakit tersebut tergantung pada subjek memiliki obesitas dengan metabolik sehat - MHO atau obesitas dengan metabolik tidak sehat - MUO.[4] Orang dengan MHO berisiko lebih rendah untuk terkena DM tipe 2 dan penyakit kardiovaskular dibandingkan orang dengan MUO.[5] Komponen sindrom metabolik antara lain seperti tekanan darah sistolik dan diastolik yang tinggi, trigliserid tinggi, HDL rendah, GDS tinggi dan lingkar pinggang yang besar. Kriteria MHO yaitu memiliki IMT ≥25 kg/m², tetapi tidak mengalami dislipidemia dan hipertensi, sedangkan MUO memiliki IMT ≥25 kg/m² dan memiliki 3 dari 5 kriteria komponen sindrom metabolik.[6]

Beberapa penelitian menemukan bahwa pola tidur memiliki kontribusi terhadap meningkatnya obesitas terutama tidur yang kurang. Tidur yang kurang diduga akan menyebabkan gangguan regulasi hormonal terutama pengeluaran hormon leptin dan ghrelin yang berdampak pada pengaturan nafsu makan dan jumlah asupan makan. Suatu penelitian menyebutkan, bahwa tidur kurang dari 6 jam perhari dikaitkan dengan peningkatan lingkar pinggang, dan tidur lebih dari 10 jam dapat terjadi peingkatan trigliserida dan peningkatan gula darah puasa (GDP) pada wanita.[7] Menurut *National Sleep Foundation* (NSF) pada tahun 2012 di Amerika, sekitar seperempat populasi orang dewasa mengalami masalah tidur, dan sekitar 6-10% memiliki gangguan insomnia. Survei selanjutnya yang diadakan oleh *Behavioral Risk Factor Surveillance System* (BRFSS) pada tahun 2008 dan 2009 melaporkan bahwa 35,3% dari 74.571 orang dewasa di 12 negara bagian Amerika Serikat tidur kurang dari 7 jam dalam sehari. Kebutuhan durasi tidur pada orang dewasa kurang lebih 8 jam perhari. Sebanyak 70,6% mahasiswa di Indonesia rata-rata mempunyai durasi tidur kurang dari 8 jam dalam sehari.[8]

Mahasiswa pada umumnya memiliki aktivitas yang padat baik dalam bidang akademik maupun non akademik, sehingga seringkali menyebabkan tidur larut malam. Hal ini dapat meningkatkan risiko mengonsumsi makanan lebih banyak pada malam hari karena waktu sebelum tertidur yang lebih panjang. Kebiasaan makan di malam hari dapat memungkinkan terjadinya *Night Eating Syndrome* (NES) yang diartikan sebagai sindrom yang berpotensi menjadi salah satu jenis perilaku makan menyimpang baru. *Night Eating Syndrome* ditandai dengan tidak sarapan pagi, makan banyak pda malam hari yaitu mengkonsumsi 50% atau lebih dari asupan makan setelah jam 7 malam, dan insomnia.[9] Penelitian di Swedia menyebutkan prevalensi orang yang mengalami NES pada orang obesitas sebanyak 8,4% pria dan 7,5% pada wanita. Makan malam dinilai lebih berperan menyebabkan kegemukan dibandingkan sarapan dan makan siang.[10]

Saat ini sedang tren konsumsi minuman manis kekinian yang mewabah di kalangan mahasiswa atau dikenal sebagai *sugar-sweetened beverage* (SSB) yang merupakan minuman ringan dalam kemasan yang menambahkan pemanis berkalori tinggi sebagai salah satu bahan dalam minuman. Asupan dari SSB yang tinggi (>50 g/hari) diketahui berhubungan postif dengan peningkatan lingkar pinggang, trigliserida dan GDS.[11] Ada beberapa studi menyatakan bahwa ada perbedaan konsumsi jenis makanan tertentu pada kelompok MHO dan MUO. Orang dengan MHO memiliki tingkat asupan gula yang lebih rendah dan minuman dengan penambahkan gula yang rendah dibandingkan orang dengan MUO.[12] Pada salah satu penelitian *cross-sectional* pada 59 remaja berusia 15-18 tahun, ditemukan 72,9% subjek memiliki asupan tinggi SSB, 62,7% subjek memliki trigliserida yang tinggi, dan 44,11% subjek memiliki lingkar pinggang yang besar.[11]

Kebiasaan mahasiswa yang mempunyai pola tidur yang buruk, *night eating syndrome* serta konsumsi SSB yang berlebih dapat meningkatkan risiko sindrom metabolik pada mahasiswa *obese*. Namun sayangnya penelitiaan yang fokus meneliti tipe metabolik yang kaitannya dengan *night eating syndrome*, pola tidur, dan kebiasaan konsumsi *sugar-sweetened beverage* masih jarang di Indonesia. Berdasarkan latar belakang tersebut maka peneliti tertarik untuk meneliti perbedaan *night eating syndrome*, pola tidur, dan kebiasaan konsumsi *sugar-sweetened beverage* berdasarkan tipe metabolik pada mahasiswa *obese*.

II. METODE

Penelitian ini merupakan penelitian dalam lingkup gizi masyarakat yang menggunakan metode *observasional* dengan rancangan penelitian *case control*. Pengumpulan data dilakukan dalam rentang waktu Juli 2020 hingga September 2020. Pengambilan data dilakukan di Laboratorium Klinik CITO Setiabudi, Semarang. Penelitian ini telah memperoleh *ethical clearance* dari Komisi Bioetika Penelitian Kedokteran/ Kesehatan Fakultas Kedokteran Universitas Islam Sultan Agung Semarang dengan No. 242/VII/2020/Komisi Bioetik.

Pengambilan data penelitian ini berlangsung saat masa pandemi, oleh sebab itu jaringan komunikasi untuk mencari subjek dilakukan melalui *social media*. Skrining subjek pada penelitian ini sebanyak 58 mahasiswa, kemudian dipilih 52 mahasiswa yang memenuhi kriteria inklusi pada kelompok kontrol dan kelompok kasus. Terdapat 6 subjek *drop out* dikarenakan perbandingan jumlah subjek antara kelompok kasus dan kelompok kontrol harus sama, 6 subjek tersebut merupakan subjek dengan tipe metabolik MHO. Populasi target adalah seluruh mahasiswa di Jawa Tengah. Populasi terjangkau pada penelitian ini adalah mahasiswa di Kota Semarang. Penentuan besar subjek minimal berdasarkan rumus untuk penelitian *case control* yaitu dengan jumlah subjek minimal 22 mahasiswa dengan perkiraan *drop out* 10 menjadi 25 subjek. Pengambilan sampel dengan teknik *consecutive sampling,* yaitu dengan menetapkan subjek yang memenuhi kriteria penelitian dimasukkan dalam penelitian hingga kurun waktu tertentu hingga jumlah responden terpenuhi. Sampel dipilih berdasarkan kriteria inklusi yaitu bersedia menjadi subjek penelitian, berusia 19-24 tahun, tidak mengonsumsi alkohol, tidak merokok, memiliki Indeks Massa Tubuh ≥25 kg/m² yang memiliki tiga atau lebih gejala kelainan metabolik seperti lingkar pinggang >80 cm, kadar trigliserida ≥150 mg/dl, kadar kolesterol HDL <50 mg/dl, tekanan darah ≥130/85 mmHg, dan kadar glukosa darah puasa ≥110 mg/dl serta resistensi insulin sebagai kelompok kasus dan kelompok kontrol dengan Indeks Massa Tubuh ≥25 kg/m² memiliki kurang dari 2 atau tanpa memiliki gejala kelaianan metabolik. Kriteria eksklusi yaitu mengundurkan diri selama penelitian dan sakit selama penelitian. Berdasarkan kriteria eksklusi yang disebutkan tidak ada subjek yang masuk dalam kriteria eksklusi tersebut.

Prosedur penelitian diawali dengan mengumpulkan mahasiswa di Kota Semarang dengan menyebarkan *google form* kemudian melakukan skrining awal untuk mencari subjek penelitian yang memenuhi kriteria yaitu mahasiswa di Kota Semarang dengan Indeks Massa Tubuh (IMT) ≥25 kg/m². Jika dari hasil skrining awal terdapat subjek yang memenuhi kriteria penelitian maka subjek tersebut akan diberikan sosialisasi penelitian, pengisian *informed consent* sebagai bentuk kesediaan untuk menjadi responden dalam penelitian yang dilakukan dan mengisi kuesioner identitas diri. Lalu, melakukan pengukuran antropometri berat badan menggunakan timbangan digital, lingkar pinggang dengan menggunakan *medline* dan tekanan darah menggunakan tensimeter serta melakukan uji laboratorium untuk pemeriksaan kadar trigliserida, kolesterol HDL, glukosa darah puasa dan insulin untuk melihat adanya kelainan metabolik. Selanjutnya mengelompokkan subjek dengan kelompok IMT *obese* tanpa kelainan metabolik dan IMT *obese* dengan tiga atau lebih kelainan metabolik. Setelah mengelompokkkan subjek kemudian memberikan *The Night Eating Questioner* (NEQ) untuk menilai *night eating syndrome*,[13] *Pittsburg Sleep Quality* (PSQI) untuk menilai pola tidur,[14] dan *Semi Quantitative Food Frequency Questionnaire* (SQFFQ) untuk melihat konsumsi *sugar sweetened beverage* subjek selama 1 bulan terkahir.

Data yang telah terkumpul dilakukan uji *Chi Square*. untuk mengetahui perbedaan *night eating syndrome*, pola tidur, dan konsumsi *sugar sweetened beverage* pada individu MHO dan MUO dilakukan uji *Chi Square*. Tingkat ketelitian dalam analisis data yaitu sebesar 95% atau p value 0,05.

III. HASIL PENELITIAN

3.1 Karakteristik Subjek

Jumlah mahasiswa yang melakukan skrining pada penelitian ini berjumlah 58 subjek. Sampel yang didapatkan sesuai kriteria inklusi sebesar 52 orang dengan setiap kelompok sebesar 26 orang. Pada kelompok kontrol didapatkan sebanyak 26 mahasiswa dengan Indeks Massa Tubuh *obese* (≥25 kg/m$^{2)}$ dengan memiliki kelainan metabolik kurang dari 2 atau tanpa adanya kelainan metabolik sedangkan kelompok kasus didapatkan sebanyak 26 mahasiswa dengan Indeks Massa Tubuh *obese* (≥25 kg/m$^{2)}$ dengan setidaknya memiliki 3 atau lebih kelainan metabolik. Pada penelitian ini seluruh subjek berjenis kelamin perempuan.

Diagram 1: Jumlah Subjek Berdasarkan Kategori MHO

Berdasarkan diagram 1. subjek obesitas dengan tipe metabolik MHO tidak ada yang memiliki 0 resiko, sebagian besar subjek mempunyai 2 kelainan komponen sindrom metabolik yaitu sebanyak 52% (13 subjek). Kelainan metaboliknya yaitu lingkar pinggang >80 cm dan resistensi insulin.

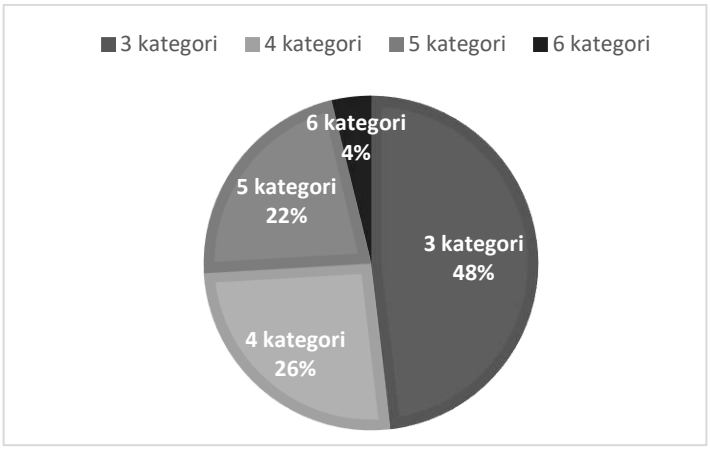

Diagram 2: Jumlah Subjek Berdarkan Kategori MUO

Berdasarkan diagram 2. Subjek dengan tipe metabolik MUO sebagian besar mempunyai 3 kelainan metabolik yaitu sebanyak 48% (13 subjek), kelaian metabolik paling sering dialami yaitu lingkar pinggang >80 cm, tekanan darah tinggi, resistensi insulin, dan profil HDL yang rendah.

Tabel 1: Rerata, Std.deviasi, median, dan p value Indeks Massa Tubuh (IMT), dan komponen sindrom metabolik

Variable	Rerata ± SD		Median		p *value*
	MHO	MUO	MHO	MUO	
IMT (kg/m$^{2)}$	26,8± 1,5	31,2±4,4	26,7	30,9	*0,000
Lingkar pinggang (cm)	86,7± 4,6	92,8±9,5	85,0	91,0	*0,004
TD sistolik (mmHg)	114,7± 7,9	126,5±8,7	115,0	130,0	*0,000
TD diastolik (mmHg)	78,2±7,6	86,7±9,1	77,0	84,5	*0,001
Gula darah puasa (mg/dL)	89,9±6,8	97,7±6,7	89,0	97,0	*0,000
HDL (mg/dL)	63,2±9,1	49,9±9,3	60,5	48,5	*0,000
Trigliderida (mg/dL)	85,1±20,2	126,7±69,9	81,0	107,0	*0,005
HOMA-IR (uU/ml)	2,8±1,2	4,2±1,8	2,7	4,1	*0,002

** signifikan (p<0,05; uji t-test)*

Berdasarkan tabel 1. Seluruh subjek baik MHO dan MUO mempunyai lingkar pinggang >80 cm, rata-rata subjek dengan tipe MUO mempunyai IMT lebih besar, mempunyai tekanan darah diastolik 86,7 mmHg yang mana melewati ambang batas risiko sindrom metabolik yaitu 85 mmHg, selain itu juga mempunyai HDL buruk dibawah 50 mg/dL dan resistensi insulin.

Tabel 2: Karakteristik Subjek Berdasarkan Komponen Sindrom Metabolik

Variabel	n (%)	
	MHO (n=26)	MUO (n=26)
Lingkar Pinggang		
Normal (< 80 cm)	0 (0%)	0 (0%)
Obesitas Sentral	26 (100%)	26 (100%)
Tekanan Darah Sistolik		
Normal (< 130 mmHg)	25 (96,2%)	11 (42,3%)
Tinggi	1 (3,8%)	15 (57,7)
Tekanan Darah Diastolik		
Normal (< 85 mmHg)	21 (80,8%)	13 (50%)
Tinggi	5 (19,2%)	13 (50%)
Gula Darah Puasa		
Normal (60 -110 mg/dL)	26 (100%)	25 (96,2%)
Hiperglikemia	0 (0%)	1 (3,8%)
HDL		
Normal (50 – 59 mg/dL)	26 (100%)	12 (46,2%)
Rendah	0 (0%)	14 (53,8%)
Trigliserida		
Normal (< 150 mg/dL)	26 (100%)	18 (69,2%)
Hipertrigliseridemia	0 (0%)	8 (30,8%)
Resistensi Insulin		
Normal (< 3,16 uU/mL)	18 (69,2%)	7 (26,9%)
Resisten	8 (30,8%)	19 (73,1%)

Berdasarkan tabel 2. Semua subjek mengalami obesitas sentral dan lebih dari 50% subjek dengan tipe metabolik MUO mempunyai tekanan darah sistolik dan diastolik tinggi, HDL rendah, serta mengalami resistensi insulin.

Tabel 3: Perbedaan Night Eating Syndrome, Pola Tidur, dan Konsumsi Sugar Sweetened Beverage

Variabel	n(%)		p value
	MHO (n 26)	MUO (n 26)	
Night Eating Syndrome			
Normal (skor: ≥11)	23 (88,5)	14 (53,8)	*0,006
NES	3 (11,5)	12 (46,2)	
Pola tidur			
Baik (skor: ≥4)	19(73,1)	10(38,5)	*0,012
Buruk	7(26,9)	16(61,5)	
Konsumsi SSB			
Normal (<50 gram/hr)	21(80,8)	22(84,6)	0,714
Berlebih	5(19,2)	4(15,4)	

**signifikan (p<0,05; uji Chi Square)*

Berdasarkan Tabel 2. Sebagian besar subjek dengan tipe metabolik MUO lebih banyak mengalami *night eating syndrome* dan pola tidur yang buruk. Terdapat perbedaan *night eating syndrome* yang signifikan pada kedua kelompok subjek (p=0,006). Terdapat perbedaan pola tidur yang signifikan pada kedua subjek (p=0,012). Sedangkan konsumsi SSB pada kedua kelompok subjek tidak ditemukan adanya pebedaan yang signifikan.

Subjek MUO banyak mengalami *night eating syndrome* dikarenakan subjek tidak sarapan pagi dan lebih banyak asupan makan setelah jam 7 malam. Mahasiswa *obese* dengan tipe metabolik MUO juga lebih banyak yang mengalami pola tidur yang buruk dikarenakan jadwal tidur yang tidak menentu, subjek lebih banyak menghabiskan waktu di malam hari untuk mengerjakan tugas hingga larut malam. Berbeda dengan konsumsi SSB pada kedua subjek, mereka sudah ada pemahaman untuk mengurangi penggunaan pemanis di dalam minuman.

IV. PEMBAHASAN

4.1 Karakteristik Subjek

Subjek dalam penelitian ini merupakan mahasiswi putri dengan rentang usia 19-24 tahun yang memiliki IMT ≥25 kg/m^2 dengan mengelompokkan subjek berdasarkan komponen kelainan metabolik yang dimiliki, yaitu obesitas dengan tipe MHO dan MUO. Terdapat perbedaan yang signifikan pada komponen sindrom metabolik antara kedua kelompok. Berdasarkan hasil penelitian, subjek dengan tipe MUO memunyai IMT yang lebih besar, hal tersebut sejalan dengan penelitian Sugondo, bahwa IMT sangat berkaitan dengan sindrom metabolik dikarenakan persebaran lemak tubuh. Besarnya persebaran lemak sangat berkaitan dengan tingkat morbiditas dan mortalitas di berbagai populasi.[27] Diketahui juga semua subjek memiliki lingkar pinggang >80 cm yang berarti semua subjek mengalami obesitas sentral, dimana obesitas sentral merupakan faktor utama yang mendasari sindrom metabolik. Lingkar pinggang berhubungan dengan jaringan lemak subkutan dan jaringan intraabdomen Selain lingkar pinggang yang besar, cukup banyak juga subjek yang mengalami resistensi insulin dan profil HDL rendah yang berhubungan erat dengan diabetes mellitus tipe 2 dan penyakit kardiovaskuler.[15] Lebih dari setengah subjek dengan tipe metabolik MHO (52%) mempunyai 2 kelainan metabolik, yang mana subjek tersebut mendekati ambang batas kriteria tipe metabolik MHO.

4.2 Perbedaan Night Eating Syndrome, Pola Tidur, dan Konsumsi Sugar Sweetened Beverage

Pada analisis bivariat menunjukkan menunjukkan terdapat perbedaan *night eating syndrome* antara mahasiswa tipe MHO dan MUO (*p value 0,006)*. Hal ini sejalan dengan penelitian yang dilakukan oleh Junko Yoshida, dimana perempuan dengan kebiasaan makan malam memiliki kemungkinan sindrom metabolik lebih tinggi dibandingkan dengan mereka yang tidak memiliki kebiasaan tersebut.[16] Rata-rata asupan energi subjek dengan MUO 1894 kkal lebih tinggi daripada subjek MHO yaitu 1675 kkal. Kebanyakan subjek dengan tipe MUO mengasup makanan diantara jam 811 malam, contohnya berupa makan besar, cemilan seperti martabak, roti bakar, seblak, dll. Rata-rata subjek membeli makanan jadi baik langsung atau lewat aplikasi pesan antar dikarenakan hampir semua subjek tinggal di rumah kost. Mereka lebih aktif makan di malam hari dikarenakan sibuknya jadwal perkuliahan yang membuat mereka tidak sarapan pagi, dan tidur sampai larut malam untuk mengerjakan tugas. Makan larut malam dapat menyebabkan pengurangan pengeluaran energi (penurunan kadar leptin) peningkatan sensasi nafsu makan, dan penambahan berat badan.[17] Orang yang mengalami *night eating syndrome* juga memiliki durasi tidur yang lebih pendek, dan sering menunda waktu sarapan dan makan malam.[18] Saat seseorang mengkonsumsi makanan di malam hari kadar glukosa, insulin, dan trigliserid meningkat secara signifikan, yang mengakibatkan berkurangnya sensitivitas insulin.[19] Oleh karena itu, direkomendasikan makan tidak lebih dari jam 7 malam dan merencakan jadwal makan sebagai rutinitas keseharian untuk memutus siklus perilaku tidak sehat guna mencegah sindrom metabolik dan komponenya.[20]

Terdapat perbedaan pola tidur antara mahasiswa tipe MHO dan MUO *(p-value 0,012)*. Berdasarkan hasil pengukuran menunjukkan ratarata pada kedua kelompok memiliki pola tidur yang buruk dilihat dari jumlah skor >5, namun ditemukan kelompok mahasiswa tipe *metabolically unhealthy obese* memiliki skor >5 lebih banyak jumlahnya yaitu sebanyak 16 mahasiswa, dibandingkan dengan mahasiswa tipe

metabolically healthy obese yaitu sebanyak 7 mahasiswa. Pola tidur yang buruk pada kelompok mahasiswa tipe *metabolically unhealthy obese* disebabkan karena pada mahasiswa secara tidak sengaja terbentuk kebiasaan pola tidur dan pola makan kurang tepat yang menjadi sebuah kebiasaan. Mahasiswa sering tidur larut malam, bermain *game,* menonton serta kebiasaan tidur larut dan kemudian harus bangun pagi hari untuk kuliah, namun proporsi yang paling mengganggu jam tidur mahasiswa yaitu begadang mengerjakan tugas kuliah. Hal ini sejalan dengan penelitian yang dilakukan oleh Thirumagal, dkk pola tidur yang buruk menghasilkan konsekuensi metabolik, salah satunya yaitu penggunaan glukosa di malam hari yang dapat meningkatkan resistensi insulin dan meningkatkan risiko diabetes. Penelitian lain juga menyebutkan bahwa pola tidur yang buruk berhubungan dengan obesitas, tekanan darah dan diregulasi glukosa.[21,22] Orang dengan tipe *metabolically unhealthy obese* secara teratur terbangun pada malam hari (yaitu 16-20 kali sebulan), merasa tidak tenang di siang hari, merasa mengantuk di siang hari, dan kesulitan tidur.[23] Pola tidur yang buruk dapat memengaruhi irama sirkadian. Irama sirkadian dalam keadaan normal berfungsi mengatur siklus biologi irama tidur sampai bangun, sepertiga waktu untuk tidur dan dua pertiga untuk aktifitas, siklus irama sirkadian dapat mengalami gangguan apabila irama tersebut mengalami pergeseran. Jika siklus tidur sampai bangun sesuai dengan irama sirkadian akan menghasilkan kualitas tidur yang baik, begitu pula sebaliknya.[24,25] *National Sleep Foundation* pada usia dewasa muda dianjurkan untuk tidur dengan waktu 7-9 jam/hari pukul 10 malam, dikarenakan pola tidur yang buruk berdampak pada penurunan leptip sebesar 18% dan peningkatan ghrelin 28% yang mengakibatkan meningkatnya rasa lapar, selanjutnya jika nafsu makan meningkat juga akan membuat glukosa, insulin dan trigliserid meningkat. Bila hal tersebut terjadi terus-menerus akan mengakibatkan berkurangnya sensitivitas insulin.[30]

Berdasarkan hasil penelitian menunjukkan tidak terdapat perbedaan bermakna konsumsi *sugar sweetened beverage* (SSB) antara mahasiswa tipe MHO dan MUO (*p-value 0,714*). Hal tersebut mungkin terjadi dikarenakan pengambilan data asupan SSB dilakukan saat pandemi *covid19* yang mengakibatkan mahasiswa jarang mengunjungi *cafe* atau tempat untuk nongkrong, dimana biasanya mereka memesan kopi, *milk boba,* minuman bersoda dll. Baik tipe metabolik MUO maupun MHO rata-rata mengkonsumsi SSB 40 gram/hari. Responden berjenis kelamin perempuan semua dimana mereka juga sudah ada pemahaman untuk mengurangi penggunaan pemanis di dalam minuman. *Menurut* Won O.Song lemak merupakan kontribusi utama tinginya asupan energi total, namun untuk kontribusi energi dari SSB memiliki kecenderungan tidak berhubungan dengan tingginya asupan energi total yang melebihi angka kecukupan asupan energi yang dianjurkan. Energi dari asupan SSB termasuk tinggi jika ≥10% dari asupan energi total atau > 50 gram/hari dan normal jika <10% dari asupan energi total.[26] Asupan SSB secara independen mempengaruhi lingkar pinggang dengan cara meningkatkan massa lemak tubuh. Energi yang berasal dari SSB yang diketahui berbentuk cairan tidak memberi rasa kenyang dibandingkan energi dari makan padat, sehingga banyak orang yang tetap mengkonsumsi banyak makanan walaupun sudah mengkonsumsi banyak minuman manis yang akan menyebabkan makan secara berlebihan. Pada saat itulah energi meningkatkan sintesis lemak tubuh. Meningkatnya lemak dalam tubuh dapat mempengaruhi terjadinya peningkatan lingkar pinggang. Asupan SSB meningkatkan konsentrasi insulin di sirkulasi.

Kadar insulin yang tinggi serta rendahnya glukagon plasma merangsang *uptake* glukosa ke sel dan asam lemak menurunkan oksidasi lemak di dalam otot, sel adiposa, dan sel hati. SSB mengandung 150 kkal/porsi yang jika dikonsumsi berlebihan akan memperngaruhi keseimbangan energi dan dapat meningkatkan berat badan.[27] Konsumsi SSB sebelum makan akan menyebabkan konsumsi energi yang lebih besar. Diet tinggi fruktosa tidak menstimulasi leptin, sehingga orang yang konsumsi tinggi fruktosa akan mengeluh akan makan lebih banyak energi yang akan meningkatkan berat badan secara

cepat. Hasil penelitian menyatakan bahwa pemberian fruktosa menyebakan resistensi leptin, peningkatan akumulasi lemak intra abdominal, dan kelebihan berat badan. Hormon leptin berfungsi mengatur keseimbangan energi dan berat badan melalui interaksi dengan nukleus hipotalamus sehingga terjadi penurunan asupan makanan dan pengeluaran kelebihan energi.[28]

V. KESIMPULAN

Pada kelompok MUO lebih banyak yang mengalami pola tidur yang buruk dan *night eating syndrome*. Sedangkan konsumsi *sugar sweetened beverage* pada kelompok MHO dan MUO masih tergolong normal. Salah satu upaya protektif pada remaja dalam menjaga metabolisme tubuh yaitu mengatur jadwal makan supaya tidak makan diatas jam 7 malam, merencakan jadwal makan sebagai rutinitas keseharian dan tidur 7-9 jam/hari pukul 10 malam serta membatasi konsumsi asupan gula dari minuman < 50 gram/hari.

Ucapan Terima Kasih

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Lampiran

Lampiran 1: Ethical Clearance

KOMISI BIOETIKA PENELITIAN KEDOKTERAN/KESEHATAN
FAKULTAS KEDOKTERAN
UNIVERSITAS ISLAM SULTAN AGUNG SEMARANG

Sekretariat : Gedung C Lantai I Fakultas Kedokteran Unissula
Jl. Raya Kaligawe Km 4 Semarang, Telp. 024-6583584, Fax 024-6594366

Ethical Clearance

No. 242/VII/2020/Komisi Bioetik

Komisi Bioetika Penelitian Kedokteran/Kesehatan Fakultas Kedokteran Universitas Islam Sultan Agung Semarang, setelah melakukan pengkajian atas usulan penelitian yang berjudul :

PERBEDAAN NIGHT EATING SYNDROME, POLA TIDUR, DAN KEBIASAAN KONSUMSI SUGAR-SWEETENED BEVERAGE BERDASARKAN TIPE METABOLIK PADA MAHASISWA OBESE

Peneliti Utama : Anindita Putri Leksono
Pembimbing : Fillah Fithra Dieny, S.Gz, M.Si
Dr. Etika Ratna Noer, S.Gz, M.Si
Tempat Penelitian : Universitas Diponegoro

dengan ini menyatakan bahwa usulan penelitian diatas telah memenuhi prasyarat etik penelitian. Oleh karena itu Komisi Bioetika merekomendasikan agar penelitian ini dapat dilaksanakan dengan mempertimbangkan prinsip-prinsip yang dinyatakan dalam Deklarasi Helsinki dan panduan yang tertuang dalam Pedoman Nasional Etik Penelitian Kesehatan (PNEPK) Departemen Kesehatan RI tahun 2004.

Semarang, 30 Juli 2020
Komisi Bioetika Penelitian Kedokteran/Kesehatan
Fakultas Kedokteran Unissula
Ketua,

(dr. Sofwan Dahlan, Sp.F(K))

Lampiran 2: Inform Consent

PERNYATAAN KESEDIAAN MENJADI SUBJEK PENELITIAN (INFORMED CONSENT)

Yang bertanda tangan di bawah ini, saya:

Nama : ANGGARDHA AYU P

Umur/TTL : 22 / Wonogiri 3 Januari 1998

Alamat : Jl Tembalang Selatan V

No Telepon/HP : 089 5800 246560

Bersedia berpartisipasi menjadi responden/subjek penelitian terkait "Asupan makan, aktifitas fisik, dan pola tidur pada mahasiswa dengan bebagai tipe metabolik" yang akan dilakukan oleh :

Nama : 1. Permata Laila Kurniastuti
2. Junita Devianty Naibaho
3. Anindita Putri Leksono

Alamat : Tembalang

Instansi : Program Studi Ilmu Gizi Fakultas Kedokteran Universitas Diponegoro Semarang

No. HP : 089671982166

Demikian pernyataan ini saya buat dengan sesungguhnya tanpa ada paksaan siapapun.

Mengetahui,

Peneliti	Peneliti	Peneliti
Permata Laila Kurniastuti	Junita Devianty Nainaho	Anindita Putri Leksono

Semarang, 1 Agustus 2020

(ANGGARDHA AYU P)

Lampiran 3: Master Data

No	Nama	BB	TB	IMT	Ling Ping g ang	Tekanan Darah	GDP	HDL	LDL	Trigliserida	Insulin	HOMA-IR	Pola Tidur	Energi SSB	NES
1.	DK	64,9	160,85	25,08	80	111/81	78	66	102	76	10,67	2,05	normal	144,2	normal
2.	AMA	66,2	162,05	25,21	87	129/90	88	60	105	80	7,27	1,58	normal	234,6	normal
3.	SKD	64,5	158,8	25,58	84	124/73	93	58	86	50	4,59	1,05	normal	101,7	normal
4.	RS	64	159	25,3	85	114/77	87	85	101	93	9,23	1,98	sleep disorder	132,7	NES
5.	AAS	73	167,5	26,02	85	117/69	88	71	128	71	6,03	1,31	normal	366,3	normal
6.	ES	58,2	146,55	27,1	85	117/82	93	71	123	57	5,7	1,31	normal	25,5	normal
7.	AAED	77,8	168,5	27,38	92	119/82	81	59	118	125	7,83	1,56	normal	110	normal
8.	SSA	58,6	145,5	27,68	85	109/74	89	58	109	120	10,29	2,26	sleep disorder	97,3	normal
9.	SY	65,5	151,55	28,52	94	111/72	99	51	131	74	8,65	2,11	normal	175,5	NES
10.	AE	64,4	150,4	28,4	89,2	120/71	97	53	87	106	8,58	2,05	sleep disorder	103	normal
11.	MR	66,2	160,1	25,8	94,1	107/81	99	66	94	81	8,92	2,18	normal	257,5	normal
12.	KB	59,4	153	25,4	85	116/76	98	58	121	85	9,17	2,22	normal	110	normal
13.	HR	54,8	148	25	81	106/76	84	83	125	73	14,06	2,91	normal	170	normal
14.	RIS	62,8	158,5	25	82	120/87	99	63	114	80	15,98	3,9	normal	130	normal
15.	APW	70,1	166,55	25,2 7	81	123/77	99	77	140	58	20,93	5,11	normal	173	NES
16.	SSW	61,5	154,5	25,76	80	103/63	91	53	140	79	22,05	4,95	normal	98	normal
17.	J	64,5	157	26,17	85	100/69	97	76	130	90	13,58	3,25	normal	256,2	normal
18.	NAR	65,2	155	27,14	90	103/73	76	67	51	99	15,91	2,98	sleep disorder	162,4	normal
19.	URK	64,7	154,5	27,08	85	113/74	88	59	120	106	20,06	4,35	sleep disorder	207	normal
20.	KM	70,3	159,5	27,61	91	116/82	86	73	77	81	18,88	4,01	sleep disorder	97	normal
21.	FA	71,3	158,5	28,38	92	112/81	82	61	134	92	14,5	2,93	normal	121	normal
22.	NLAR	76,3	163,45	28,5 6	95	119/69	89	51	101	55	11,96	2,63	sleep disorder	109	normal
23.	ANR	77,4	162	29,49	90	122/78	85	66	133	93	16,62	3,48	normal	130	normal
24.	VMI	69,4	153,25	29,55	89	111/85	97	55	136	117	11,55	2,76	normal	129	normal
25.	AN	67	153,5	28,4	86,1	107/73	97	57	126	93	12,3	2,94	normal	101	normal
26.	IDP	55,6	146,95	25,75	81	132/89	86	63	113	104	16,69	3,54	normal	108	normal
27.	PI	60,5	153	25,82	85	131/98	90	59	87	65	22,24	4,94	normal	225,4	NES
28.	MMA	97,5	160	38,09	109	138/94	96	52	101	106	18,75	4,44	sleep disorder	122	normal
29.	JA	78,9	162,65	29,9	93	142/79	94	69	98	77	14,76	3,42	normal	109	normal
30.	RSO	97,5	157,5	39,3	92	130/98	104	54	136	108	19,78	5,07	sleep disorder	105	NES
31.	CZL	77,1	162,5	29,2	95	116/81	101	67	168	79	11,95	2,98	sleep disorder	122	normal
32.	AZ	92,5	164	34,39	101	115/76	105	41	150	135	22,41	5,8	normal	120	NES
33.	EP	57,5	148,05	26,23	81	116/82	95	48	175	91	9,73	2,28	sleep disorder	123	NES
34.	R	65,7	160,5	25,5	82	108/72	96	44	119	34	0,93	2,2	normal	85	normal
35.	SD	91,3	154,5	38,23	104	130/100	101	64	147	80	18,45	4,6	sleep disorder	140,4	NES
36.	AMLA	69,7	149,75	31,08	91	131/80	101	56	157	29	11,11	2,77	sleep disorder	80	normal

37.	ETA	77,8	157	31,6	91,9	137/85	97	56	170	89	10,03	2,4	sleep disorder	101	normal
38.	ESR	73,6	151,2	32,1	83,8	111/81	97	48	88	135	34,86	8,34	sleep disorder	103	NES
39.	P	66	153,45	28,03	83	130/90	95	37	129	97	14,8	3,47	sleep disorder	169	NES
40.	CFR	89,5	158	35,9	112,1	130/106	100	60	155	90	17,71	4,37	normal	152,7	NES
41.	SR	92,8	155	38,6	108,8	130/84	90	53	135	115	18,48	4,1	normal	142.1	normal
42.	FR	62,3	140	31,8	85,7	130/80	110	62	97	60	18,45	5,01	sleep disorder	92	NES
43.	VS	82,3	164	30,6	90	126/77	83	40	172	79	12,5	2,56	normal	21,1	normal
44.	YTA	64,25	154,5	26,9	88	131/85	91	50	137	211	12,91	2,9	sleep disorder	138,2	normal
45.	SM	65,8	144	31,73	91	130/81	94	49	81	58	17,91	4,15	sleep disorder	119	normal
46.	NJ	71,6	159,1	28,3	86,6	112/90	92	38	114	193	28,32	6,43	normal	153	normal
47.	RK	70,25	158	28,14	89	123/92	84	48	120	286	25,95	5,38	normal	201,3	normal
48.	GGAW	58,4	152,3	25,18	82	124/89	95	40	174	117	12,78	2,99	normal	102	NES
49.	DP	65,5	159	25,9	81,6	135/108	107	46	101	154	15,89	4,19	sleep disorder	204	NES
50.	K	74,5	155,4	30,8	102,2	131/83	106	56	141	177	25,04	6,55	sleep disorder	197	normal
51.	KC	90	163,4	33,7	104,1	126/79	107	39	157	299	28,71	7,58	sleep disorder	180	NES
52.	AMK	91,5	163	34,4	100	126/91	100	41	190	197	14,61	3,6	sleep disorder	178	normal

Lampiran 4: Kuisioner Data Diri Subjek

Kuisioner Identitas Subjek Penelitian

Kode Subjek :
Tanggal Pengukuran :

A. Identitas Subjek Penilitian
Nama :
Jenis Kelamin :
Tanggal Lahir :
Usia :
Alamat :
No HP :
Fakultas/Jurusan :

B. Data Antropometri
Tinggi Badan (TB) : cm
Berat Badan (BB) : kg
Lingkar Pinggang : cm
Tekanan Darah : mm/Hg

Lampiran 5: Kuisioner Pola Tidur

Pittsburg Sleep Quality Index (Psqi)
Kuesioner Pola Tidur
PETUNJUK

Pertanyaan berikut ini berkaitan dengan kebiasaan tidur yang biasa Anda lakukan selama seminggu lalu. Dimohon Anda menjawab semua pertanyaan

A. JAWABLAH PERTANYAAN BERIKUT INI PADA TITIK-TITIK YANG DISEDIAKAN!

1. Selama sebulan terakhir, kapan (jam berapa) biasanya Anda tidur pada malam hari?

.....

2. Selama sebulan terakhir, berapa lama (dalam menit) Anda perlukan untuk dapat tertidur tiap malam?

.....

3. Selama sebulan terakhir, kapan (jam berapa) biasanya Anda bangun di pagi hari?

.....

4. Selama sebulan terakhir, berapa jam lama tidur Anda yang sebenarnya tiap malam? (hal ini erbeda dengan jumlah jam yang Anda habiskan di tempat tidur)

.....

B. BERIKAN TANDA (V) PADA SALAH SATU JAWABAN YANG ANDA ANGGAP SESUAI!

No	Pertanyaan	Tidak Pernah	1x seminggu	2x seminggu	≥3x seminggu
5a.	Selama seminggu yang lalu, seberapa sering Anda mengalami tidak dapat tidur di malam hari dalam waktu 30 menit				
5b.	Selama seminggu yang lalu, seberapa sering Anda mengalami bangun tengah malam atau dini hari				
5c.	Selama seminggu yang lalu, seberapa sering Anda mengalami harus bangun di malam hari untuk ke kamar mandi				
5d.	Selama seminggu yang lalu, seberapa sering Anda mengalami tidak dapat bernapas dengan nyaman saat tidur di malam hari				
5e.	Selama seminggu yang lalu, seberapa sering Anda mengalami batuk atau mendengkur keras saat tidur di malam hari				
5f.	Selama seminggu yang lalu, seberapa sering Anda merasa kedinginan atau menggigil demam saat tidur di malam hari				
5g.	Selama seminggu yang lalu, seberapa sering Anda merasa terlalu kepanasan saat tidur di malam hari				

5h.	Selama seminggu yang lalu, seberapa sering Anda mengalami mimpi buruk saat tidur di malam hari				
5i.	Selama seminggu yang lalu, seberapa sering Anda merasa kesakitan saat tidur di malam hari (misal: kram, pegal, nyeri)				
5j.	Selama seminggu yang lalu, seberapa sering Anda mengalami hal lain yang membuat Anda terganggu di malam hari, tolong jelaskan: .... Berapa sering Anda mengalami kesulitan tidur karena alasan tersebut?				
6.	Selama seminggu yang lalu, seberapa sering Anda mengonsumsi obat yang bisa menyebabkan rasa kantuk? (diresepkan oleh dokter atau obat bebas)				
7.	Selama seminggu yang lalu, seberapa sering Anda mengalami kesulitan untuk tetap terjaga/segar/tidak merasa ngantuk ketika makan atau melakukan aktivitas lain?				

No.	Pertanyaan	Tidak Antusias	Kecil	Sedang	Besar
8.	Seberapa antusias Anda ingin menyelesaikan masalah yang Anda hadapi				

No.	Pertanyaan	Sangat Baik	Baik	Kurang	Sangat Kurang
9.	Bagaimana kualitas tidur Anda selama 1 minggu yang lalu				

Lampiran 6: Kuisioner Night Eating Syndrome

Night Eating Diagnostic Questionnaire (Nedq) Kuesioner Night Eating Syndrome Silakan Anda menjawab dengan angka atau memberi contreng pada pilihan yang tersedia atau coret yang tidak perlu pada pertanyaan dengan tanda (*)

No.	Pertanyaan	Jawaban
1.	Jam berapa biasanya Anda tidur (mematikan lampu untuk tidur)?	
2.	Jam berapa biasanya Anda bangun pada pagi hari?	
3.	Apakah Anda sering kehilangan nafsy makan pada pagi hari?	Ya / Tidak*

4.	Seberapa sering Anda sarpan pagi? (setelah bangun tidur)	_____kali/minggu
5.	Pukul berapa biasanya Anda makan pertama kali?	
6.	Berapa banyak makanan yang Anda konsumsi setelah jam 7 malam? Nyatakan dalam persen dari 0 sampai 100 (diminta spesifik, misal 15%)	_____%
7.	Jam berapa biasanya Anda makan malam?	
8.	Berapa banyak makanan yang Anda konsumsi setelah makan malam? Nyatakan dalam persen dari 0 sampai 100? (diminta spesifik, misal 15%) a. Sudah berapa lama Anda mengkonsumsi makanan seperti yang disebutkan di atas setelah makan malam?	_____% _____tahun _____bulan
9.	Apakah Anda sering merasakan keinginan unuk makan pada waktu setelah makan malam dan sebelum tidur atau selama malam hari?	Ya / Tidak*
10.	Apakah Anda mempunyai masalah tidur? a. Jika Ya, berapa kali dalam seminggu?	Ya / Tidak* _____kali/minggu
11.	Apakah Anda mempunyai masalah dalam mempertahankan tidur? a. Jika Ya, berapa kali seminggu? b. Jika Ya, berapa kali dalam seminggu Anda bangun dari tempat tidur Anda setelah bangun?	Ya / Tidak* _____kali/minggu _____kali/minggu
12.	Berapa kali dalam seminggu Anda bangun dari tidur untuk menggunakan kamar mandi?	_____kali/minggu
13.	Apakah Anda terbangun dari tidur malam dan setelahnya Anda makan malam? Jika Tidak, lanjut ke pertanyaan nomor 14 a. Jika Ya, berapa kali dalam seminggu? b. Sudah berapa lama Anda terbangun dari tidur malam untuk makan? c. Apakah Anda percaya bahwa Anda harus makan agar dapat tidur kembali setelah terbangun pada malam hari? d. Seberapa sadarkah Anda akan kebiasaan makan pada malam hari? e. Seberapa sering Anda mengingat apa yang Anda makan selama malam hari pada keesokan harinya?	Ya / Tidak* _____kali/minggu _____tahun _____bulan Ya / Tidak*
		Tidak sama sekali / Sedikit / Sangat* Tidak sama sekali / Sedikit / Sangat*

14.	Apakah Anda menganggap diri Anda sebagai *night eater?* Jika Tidak, lanjut ke pertayaan nomor 15 a. Jika Ya, seberapa kecewanya Anda tentang kebiasaan tesebut? b. Jika Ya, seberapa menggangunya kebiasaan tersebut terhdapa diri Anda atau kehidupan keseharian Anda? c. Sudah berapa lama Anda mengalami kebiasaan makan pada malam hari ini?	Ya / Tidak* Tidak sama sekali / Sedikit / Sangat* Tidak sama sekali / Sedikit / Sangat* __Kurang dari 3 bulan __3-6 bulan --6-12 bulan __lebih dari 1 tahun
15.	Apakah Ada mempunyai riwayat henti nafas saat tidur?	Ya / Tidak*
16.	Apakah Anda pernah merasa depresi atau murung dikebanyakan hari?	Ya / Tidak*
17.	Secara umum, kapan Anda merasa depresi atau murung yang paling parah dalam sehari?	____saat pagi hari ____saat siang hari ____saat malam hari ____tidak dapat dijelaskan
18.	Apakah sekarang Anda sedang menjalani diet untuk menurunkan berat badan?	Ya / Tidak *
	a. Jika Ya, berapa banyak berat badan yang berhasil Anda turunkan dalam waktu 3 bulan?	_____kg
19.	Berapa berat badan dan tinggi Anda sekarang?	_____cm _____kg

Lampiran 7: Kuesioner Konsumsi Sugar Sweetened Beverage

Semi-Quantitative Food Frequencu 1 Bulan Terakhir
Kuesioner Konsumsi *Sugar Sweetened Beverage*
Isilah kolom di bawah ini sesuai dengan frekuensi komsumsi Anda

Jenis Minuman	Ukura n	Frekuensi				Jumlah yg dikosumsi		Rata -rata x/H	Bera t (g/H)	Total kalori (Kkal)
		x/ H	x/ M	x/ B	Tidak Perna h	Ukura n	m L			
Minuman rasa buah										
ABC	250 mL									
	1000 mL									
Ale-ale	200 mL									
Buavita	125 mL									
	250 mL									
	1000 mL									
Country choice	250 mL									
	200 mL									
	1000 mL									
Floridina	360 mL									
Frutang	200 mL									
Happy juice	200 mL									
	300 mL									
Jasjus	250 mL									
Marimas	8 g									
Minute maid pulpy	240 mL									
	350 mL									
Nutrisari	29 g									
	200 mL									
	300 mL									
Pop ice	25 g									
Tebs	330 mL									
	500 mL									

Jenis Minuman	Ukuran	Frekuensi				Jumlah yg dikosumsi		Rata-rata x/H	Berat (g/H)	Total kalori (Kkal)
		x/H	x/M	x/B	Tidak Pernah	Ukuran	mL			
MINUMAN RASA BUAH										
Oki jeli drink	150 mL									
	220 mL									
UC 100	140 mL									
	600 mL									
Sari kacang hijau	150 mL									
	250 mL									
Sari kelengkeng	200 mL									
TEH										
Frestea	350 mL									
	500 mL									
Fruit tea	200 mL									
	300 mL									
	500 mL									
Futami 17	485 mL									
Joytea	500 mL									
Mirai ocha	450 mL									
Mountea	200 mL									
NU green tea	500 mL									
Pucuk harum	480 mL									
	350 mL									
Teh kotak	300 mL									
Teh sosro	200 mL									
	450 mL									
Teh gelas	250 mL									
	350 mL									
	500 mL									
Thai tea	400 mL									
	500 mL									
Jenis Minuman	Ukuran	Frekuensi				Jumlah yg dikosumsi		Rata-rata x/H	Berat (g/H)	Total kalori (Kkal)
		x/H	x/M	x/B	Tidak Pernah	Ukuran	mL			
KOPI										
ABC white coffee	27 g									
Good day	20 g									
	200 mL									

	250 mL									
Indocafe coffemix	20 g									
Kapal api	7 g									
Kopiko 78C	250 mL									
Luwak white coffee	20 g									
Nescafe	200 mL									
Torabika	28 g									
Top coffee	31 g									
	240 mL									
SOFT DRINK										
A&W	355 mL									
Big cola	535 mL									
	3100 mL									
Calpico soda	320 mL									
Coca-cola	250 mL									
	330 mL									
	425 mL									
	1500 mL									
Fanta	250 mL									
	330 mL									
	425 mL									
	1500 mL									
Sprite	250 mL									
	330 mL									
	425 mL									
Jenis Minuman	Ukura n	Frekuensi				Jumlah yg dikosumsi		Rata -rata x/H	Bera t (g/H)	Total kalori (Kkal)
		x/ H	x/ M	x/ B	Tidak Perna h	Ukura n	m L			
MINUMAN ISOTONIK / ENERGY DRINK										
Iso plus	350 mL									
Coolant	350 mL									
Mizone	250 mL									
Pocari	330 mL									
	350 mL									
	500 mL									
	2000 mL									

Lampiran 8: Output Analisis Statistik Crosstab NES

		Tipe Metabolik		Total
		MHO	MUO	
nes	normal nes	23	14	37
		3	12	15
Total		26	26	52

Chi-Square Tests NES

	Value	df	Asymp. Sig. (2sided)	Exact Sig. (2sided)	Exact Sig. (1sided)
Pearson Chi-Square	7,589[a]	1	,006		
Continuity Correction[b]	5,996	1	,014		
Likelihood Ratio	7,994	1	,005		
Fisher's Exact Test				,013	,006
Linear-by-Linear Association	7,443	1	,006		
N of Valid Cases	52				

Crosstab Pola Tidur

		Tipe Metabolik		Total
		MHO	MUO	
Pola Tidur	baik buruk	19	10	29
		7	16	23
Total		26	26	52

Chi-Square Tests Pola Tidur

	Value	df	Asymp. Sig. (2 sided)	Exact Sig. (2 sided)	Exact Sig. (1 sided)
Pearson Chi-Square	6,315[a]	1	,012		
Continuity Correction[b]	4,990	1	,026		
Likelihood Ratio	6,457	1	,011		
Fisher's Exact Test				,025	,012
Linear-by-Linear Association	6,193	1	,013		
N of Valid Cases	52				

Crosstab SSB

		Tipe Metabolik		Total
		MHO	MUO	
ssb	normal berlebih	21	22	43
		5	4	9
Total		26	26	52

Chi-Square Tests SSB

	Value	df	Asymp. Sig. (2 sided)	Exact Sig. (2 sided)	Exact Sig. (1 sided)
Pearson Chi-Square	,134[a]	1	,714		
Continuity Correction[b]	,000	1	1,000		
Likelihood Ratio	,135	1	,714		
Fisher's Exact Test				1,000	,500
Linear-by-Linear Association	,132	1	,717		
N of Valid Cases	52				

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