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Edited by Prof. Darko Nozic

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He was working more than 30 years In Clinic of infectious and tropical disease of Military Medical Academy in Belgrade and treated more than ten thousand patients with different infectious diseases. He is an expert for viral hepatitis and antimicrobial therapy. He has educated many generation of students of University of Military Medical Academy and Higher Medical School in Belgrade in the field of infectious disease. Now, he is the head of hospital part of Acibadem Belmedic hospital in Belgrade. His medical work consists of clinical management of infectious diseases, mainly focusing viral hepatitis especially hepatitis C and hepatitis B research, and antiviral and antimicrobial therapy. His specialization includes Hepatitis B , hepatitis C ,immunology, infectious disease, antibiotics.

PREFACE

This book covers key areas of disease and health. The contributions by the authors include functional neurological disorders, psychogenic nonepileptic seizures, psychogenic symptom, severe acute respiratory syndrome, cardiovascular disease, type-2 diabetes, pandemic's stress, medical staff members, essential micronutrients, fortification, micronutrient stability, rice consumption profile, gastroesophageal reflux disease, proton pump inhibitors, nutrient malabsorption, Nissen fundoplication, metal ceramic restorations, anterior maxillary teeth, fixed partial denture, zirconia-based materials, autosomal recessive spastic paraplegia-51, mutations, hereditary spastic paraplegia, genetic testing, respiratory allergy, allergic rhinitis, asthma, pollen allergies, sickle cell disease, homozygous state, Arab-Indian haplotype, beta-globin gene, antenatal care, rural-urban disparities, maternal health service, health care-seeking behaviour. This book contains various materials suitable for students, researchers, and academicians in the fields of disease and health.

Chapter 1
Print ISBN: 978-93-49970-25-0, eBook ISBN: 978-93-49970-85-4

A Critical Review on Functional Neurological Disorders and Psychogenic Nonepileptic Seizures: Neurologic Disease NOT a 'Functional Aetiology'

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ABSTRACT

Neurologic symptoms deemed inconsistent, incongruent, or incompatible with recognised neurologic disease will likely garner a functional (formerly psychogenic) diagnosis, or Conversion Disorder in modern nomenclature. Functional neurological disorders (FND) embody a broad phenomenological spectrum, encompassing psychogenic nonepileptic seizures (PNES), abnormal movements, gait abnormalities, and sensorimotor deficits. The theory underlying the functional diagnosis presumes that in the absence of organic findings, the neurologic symptom must have a psychological aetiology and thus, symptom remission rests on psychological intervention. In fact, it is the absence of organic (neurologic) findings that *distinguishes a functional disorder from ordinary neurologic disease*. This paper explored the history that underlies the FND diagnosis and the modern clinical findings to assess whether the data supports or refutes the FND diagnosis. To generate and support the analysis, a wide sampling of articles on the relevant populations (FND patients and those with symptoms labelled ordinary neurologic disease) was reviewed. The results show that every premise of the psychogenic theory has been debunked by the empirical data. Studies show pervasive organic (neurologic) disease in FND and PNES patient populations; that in many FND and PNES patients, there is no discernible psychological factor that could be responsible for the 'psychogenic' symptom.; that physical therapies, not psychotherapy, have emerged as highly effective treatments for movement disorders labelled functional; that, like a substantial proportion of untreated epilepsy patients, many PNES patients show spontaneous remission of symptoms without any psychotherapy at all. The

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findings starkly expose the inherent flaws of the diagnostic practice promoted in the FND and PNES literature. The diagnosis of PNES relies on the scalp vEEG, a 'gold standard' that fails to capture a substantial proportion of epileptiform discharges, particularly those of a frontal lobe origin. The 'positive signs' underlying the diagnosis of functional movement disorders are fallible, have been observed in neurologic conditions, and label *atypical* presentations, and *likely early-stage disease*, as inconsistent with *classic* neurologic disorders. Despite compelling evidence that these patients indeed suffer from ordinary neurologic disease and epilepsy, FND and PNES investigators remain highly invested in the 'functional' aetiology and show confirmation bias in their interpretation of the empirical data. The ongoing misdiagnosis of neurologic disease and epilepsy as FND and PNES is the *real crisis in neurology.*

Keywords: Neurological disorders; psychogenic nonepileptic seizures; neurologic disease; functional aetiology; atypical; FND and PNES.

1. INTRODUCTION

Functional Neurological Disorders (FND), or Conversion Disorder in modern nomenclature [1], embody a broad phenomenological spectrum encompassing psychogenic nonepileptic seizures (PNES), abnormal movements, gait abnormalities, and sensorimotor deficits [2]. Functional symptoms (aka hysterical, non-organic, psychogenic, and medically unexplained) [3] are common [4], and not only mimic organic disease such as epilepsy [5] and movement disorders [6], but are *just as disabling* as neurologic disease [7-10]. Functional neurological disorders are associated with a poor outcome [11,12], occupy a grey area between neurology and psychiatry [13], and have been deemed a crisis in neurology [14,193].

Functional Neurological Disorders are a legacy of the clinical sensation known as hysteria, and since the beginning of the 19th century, have been conceived as primarily psychiatric illnesses arising from the *conversion* of psychological distress into physical symptoms [196]. The latter has an enduring history [15] but that does not equate with a uniform or proven entity. In the early 20th century, both the definition and nature of hysteria were subject to animated debates among neurologists and psychiatrists [16]. Jean-Martin Charcot is regarded as a preeminent neurologist who made substantial contributions to the field of neurology, achieving celebrity status in large part due to his demonstrations of hysterical symptoms during his 'Tuesday Lessons' at the Salpêtrière Hospital in the late 19th century [17]. He utilised hypnosis to both create and suppress hysterical symptoms, which he concluded were triggered by psychological factors [17,193]. He is often heralded by FND investigators as an original authority on hysteria [18], but he was ridiculed by his contemporaries who thought he was being duped by his patients, and later in life, he regretted his work on hysteria and wanted to rewrite his basic tenets on the subject [17].

Arguably, the most famous case of 'hysteria' was that of Anna O. In the early 1880s, she was treated by Dr. Josef Breuer, who discovered the 'talking cure', further developed by his protégé, Sigmund Freud [18-20]. During the course of her treatment, in addition to inexplicable physical symptoms, Anna O demonstrated the following psychiatric symptoms and markers: hallucinations; disorganized and incoherent speech; paranoia (accused others of persecuting her, telling her nothing but lies); extended periods of mutism and continuous trance (read catatonia); non-responsive when spoken to (interpreted as hysterical deafness); irritability; periods of high excitement and agitation that involved aggression towards others; decreased need for sleep (went days without sleep); and rapid mood swings wherein she oscillated between exaggerated high spirits and anxious melancholy [19]. Anna O told Dr. Breuer she thought she was going mad, and while he did refer to her as *psychotic* at one point, he attributed all her symptoms to 'hysteria,' a serious psychical disturbance [19,39]. He hypothesised that a two-week period of muteness was caused by an unidentifiable event wherein Anna felt acutely offended and had determined not to speak about it [19]. He suggested the origins of her intermittent 'deafness' included: "Her father had asked her in vain for wine" and "Her young brother shook her angrily when he caught her listening at the door of the sickroom [20,193]." Anna O was not cured by hypnosis or talk therapy, and in her early to late 20s, she was in and out of sanitariums [19]. *In modern psychiatry, Anna O's presentation would likely garner a diagnosis other than Conversion Disorder,* especially if her 'hysterical' symptoms remitted on antipsychotic and mood stabilising medication.

In 1975, in preparation for an International Symposium on Dystonia, Stanley Fahn and Roswell Eldridge apologised to the "many victims" of dystonia who had been *misdiagnosed with a psychogenic disorder* [20]*.* They told attendees that psychologically based dystonia was a rare or *non-existent condition* and pointed out how past attempts to manage generalised dystonia along psychiatric lines had *ignored strong evidence for organic causation* [22,39]. Three years later, Lesser and Fahn [23] reported the "first case of psychogenic dystonia" in a teenager who subsequently admitted to feigning her dystonic symptoms, which then disappeared. In 1988, Fahn and Williams [24] published a classification for psychogenic dystonia that included intentional feigning as a variant. The conflation of intentional feigning with unconsciously generated psychogenic symptoms has been a longstanding conceptual problem [25], but Conversion Disorders should be distinguished from malingering and factitious conditions [26], and most FND and PNES investigators make this discrimination [25,27-30].

In 2006, William G. Ondo, M.D., reviewed the book *Psychogenic Movement Disorders* for the New England Journal of Medicine [18]. Dr. Ondo found that Jean-Martin Charcot and other 19th-century researchers were cited throughout the book as frequently as current investigators and that this reliance on the past, "attests to the uncertainty of the subject matter [18]." He described the content as "highly theoretical" with much of it "based on the opinions of experts" and concluded that "the evidence-oriented physician might be appalled by the lack of good data [18]."

A great deal of literature on functional disorders has been amassed in recent decades, but with very few exceptions [31,32], it *presumes* that the 'psychogenic' or 'functional' diagnostic entity does in fact exist and proceeds from that position. The terms 'psychogenic' and 'functional' are used interchangeably in the clinical literature and refer to neurologic symptoms that most investigators *presume* are primarily psychological in origin, though 'biopsychosocial' models are increasingly popular [33-35].

2. METHODS AND TERMINOLOGY

To generate and support the analysis, a wide sampling of articles on FND and PNES was reviewed. The term 'non-neurologic' refers to neurologic symptoms that have been labelled as having a 'psychogenic' or 'functional' aetiology.

3. LITERATURE REVIEW AND ANALYSIS OF FINDINGS

Functional (psychogenic) Neurological Disorders are common [36-38], challenging to diagnose given the resemblance of symptoms to recognised neurologic disease [5,36,40], and just as disabling as neurologic disorders like epilepsy [8] and Parkinson's Disease [41].

Functional Neurological Disorders (Conversion Disorder in modern nomenclature) have long been attributed to a psychogenic aetiology [42]. *In the absence of organic findings*, investigators *presumed* the neurologic symptom had a psychological origin [29,43-50], and that thorough neurologic and psychiatric histories would confirm the psychogenic source [51]. Patients with functional disorders purportedly have a mysterious capacity to unconsciously transform unspecified psychic distress into often disabling symptoms resembling organic disease [5]. By exposing and examining the psychological source, the patient can develop the necessary insight, resulting in the abandonment of the functional (psychogenic) symptom [5]. The Freudian influence on FND and PNES investigators is unmistakable [5,28,29,50,52-54], and *the validity of the functional diagnostic entity is never questioned*.

Modern neurology is immensely intrigued by functional neurological disorders [55], which is evident by the rapid rate of publications on these conditions [35,37]. Functional Neurological Disorders are now a 'rule in' diagnosis based on validated neurological signs [40] with examinations "aimed at excluding" neurologic disease [56]. While the aetiology of these 'non-neurologic' symptoms remains a mystery [57-60], and the diagnostic challenges in neurology are well known [29,40,61,62], investigators express confidence in the ability to accurately and *rapidly* diagnose functional disorders [4,40,58,63-65].

Functional symptoms are generally attributed to "psychodynamic causes" [28], and the cornerstone of treatment is psychotherapy [6,66-71]. Without treating and resolving the underlying psychological issues, the "curing" of functional symptoms is considered unlikely [70]. Treatment for Conversion Disorder may require years of intensive counselling to get to the point where patients can safely approach the inner conflicts causing the psychogenic symptom [70].

Investigators have emphasised the importance of identifying psychological factors relevant to the aetiology and maintenance of functional symptoms [72]. A problem list with predisposing, precipitating, and perpetuating factors, or "the 3 Ps," is a key component of the clinical formulation [73]. These factors may be remote, occurring during development and early adulthood, and can include psychiatric co-morbidities, maladaptive personality traits, insecure attachment, adverse life events, alexithymia, family dysfunction, intellectual disability, or comorbid medical/ neurological conditions, among other factors [74]. In PNES patients, one common scenario presented is being raised in an alcoholic home, leading to a people-pleasing and perfectionistic personality style (predisposing), with a recent motor vehicle accident leading to job loss (precipitating), and ongoing family stressors (perpetuating) [72]. Of course, these psychological factors are also found in people who do not have functional disorders [75], and psychiatric comorbidity is *common* in patients with neurologic disease [76].

Investigators *presumed* that the psychological origin of functional symptoms would be discernible in FND and PNES patients [51], *but epidemiological studies did not support this presumption* [77,78]. The contribution of psychiatric and traumatic contributions has been inconsistent and mixed [75]. The conversion hypothesis, that intrapsychic distress is unconsciously converted into somatic symptoms, is unproven [34]. "Childhood trauma, recent negative life events, depression, and anxiety are all more common in patients with functional neurological symptoms than in the healthy population, but many, even the majority, have none of these [80]."

The epidemiological data led to a controversial change in terminology. Some investigators thought replacing 'psychogenic' with 'functional' was obfuscating and motivated by the desire to increase patient acceptance of the diagnosis [81], which is famously poor [30,82,83]. Other investigators considered the term 'psychogenic' and its proposed aetiology "poorly defined" and not supported by current evidence [34]. The term 'functional recommended because, like other psychiatric disorders, "the cause of Conversion Disorder is unknown and it is desirable that it remain an atheoretical category in which primacy is given to the symptoms without making assumptions about their aetiology [84]." While the empirical evidence may have led to a change in terminology, it has not disabused most FND and PNES investigators of their *conviction* that the origin of functional symptoms is primarily psychological [37,53,54,57,75,81,85-87]. Thus, the search continues for the mysterious aetiology producing these 'non-neurologic' symptoms with seasoned investigators acknowledging, "we really do not know the cause [57]" and welcoming alternative explanations of functional symptoms which "should be given due consideration [88]."

Studies show that *physical therapy*, not psychotherapy, has emerged as a "surprisingly effective [89]" treatment for functional motor and gait disturbances [46,90-93]. These studies led to the development of an expert consensus recommending the use of physical therapy in functional movement disorders [74]. The question has been posed, "Why offer a physical treatment for a mental problem? [70]" and the short answer is because it works. The more salient question is, why does it work so well? Occam's razor, the law of parsimony, concludes that the abnormal movements labelled 'functional' respond surprisingly well to targeted physical interventions because these patients have ordinary neurologic disease, *not a disorder with a psychogenic or otherwise 'non-neurologic' aetiology.*

Patients diagnosed with PNES have demonstrated improvements with psychotherapy [8], but the same response to psychotherapy has been reported in patients with drug-resistant epilepsy [94]. Both populations have shown a reduction in seizure frequency and improvements in clinical co-morbidities [8,94,95]. A positive response to psychotherapy *does not differentiate* patients with PNES from patients with epilepsy.

The absence of neurologic (organic) findings is what *distinguishes* functional conditions from genuine neurologic disorders. The literature is *unequivocal* on this point. For decades, the terms 'hysterical' and 'psychogenic' were synonymous with a 'non-organic' aetiology [15,96]. Conversion Disorder (FND) is a diagnosis of exclusion requiring that any neuropathological explanation of symptoms has been ruled out [29,70,97]. Psychogenic Movement Disorders are to be distinguished from organic diseases [24]. Functional neurological symptoms are somatic symptoms superficially resembling organic disorders of the nervous system, but for which no physical explanation can be found [98]. The brains of patients diagnosed with FND are structurally normal [86]. Functional neurological symptoms are not explained by organic pathology [48,49,82,99,100]. Functional symptoms are not caused by organic damage [101]. Patients with FND have no neurological disease [102]. Functional neurological disorders are not due to irreversible brain damage [103,104]. Functional symptoms refer to weakness or movement disorders that are genuine but do not relate to an underlying neurologic disease [13,105]. The potential for *mistaking a neurologic condition* for a functional disorder has *decreased considerably with advances in neuroimaging* [67]. Patients were told that their 'functional' symptoms involved a "software problem with the brain rather than a hardware problem [104]."

The sole distinguishing characteristic- that patients with symptoms deemed 'functional' do not have neurologic disease- has been *debunked by empirical studies* showing pervasive brain pathology in the FND and PNES populations [37,106]. In a review of the literature, Szaflarski and LaFrance [106] found both structural imaging and sub-macroscopic abnormalities in patients with FND and PNES to the extent that both are now considered network disorders, *just like epilepsy* [107] *and dystonia* [108]. Seasoned investigators acknowledged that these findings were unexpected: The structural imaging in patients with functional disorders "should be" normal [106] and "the identification of such neurobiological correlates does not sit well with the understanding of PNES as a purely 'psychological' or 'psychogenic' disorder without any discernible 'physical correlates' [88]." It 'does not sit well' because for decades PNES and FND investigators asserted *unequivocally* that the *exclusion of neurologic disease was the basis* for a 'psychogenic' or 'functional' diagnosis. Now that the 'absence of neurologic disease' in the FND and PNES populations has been disproven, all that remains are 'neurologic symptoms' and 'evidence of pervasive neurologic disease.' The unanticipated data must then be plugged into the original hypothesis; In the *absence of organic findings*, investigators *presumed* that the neurologic symptom had a psychological origin [29,43-50]. The new equation reveals that when the 'absence of neurologic disease' is replaced with 'presence of neurologic disease,' there is *no longer any basis to presume a psychological or otherwise 'non-neurologic' aetiology*. The law of parsimony concludes that evidence of neurologic disease is simply evidence of a neurologic disorder.

Rather than revisiting the original hypothesis to examine the validity of the 'functional aetiology,' FND and PNES investigators *readily incorporated* the 'evidence of neurologic disease' into their 'functional' frameworks. Functional neurological disorders are now a "software" and a "hardware" problem [55]. "Neuroimaging research is at the forefront of establishing neurobiological models" for functional disorders [60] and will "provide a foundation for postulating the neurobiological underpinnings of PNES [106]." The neurobiology of FNDs is not well understood, but neural network dysfunction may underlie the symptomatic manifestation in FNDs [53]. It remains unclear whether structural alterations relate to predisposing vulnerabilities or are consequences of the functional disorder [55]. Functional neuroimaging has elucidated dysfunction in FNDs at the level of brain network activity, connectivity, and specific anatomic areas of altered metabolic demand during tasks [4]. Brain imaging techniques provide unprecedented opportunities to study the neural mechanisms underlying FND, which have long remained a mystery and clinical challenge for physicians, as they arise with no apparent underlying organic disease [109]. Neuroimaging is employed to exclude co-morbid organic disease in the diagnostic phase *and* explore the brain abnormalities in functional populations [37]. So, the 'evidence of neurologic disease' in patients diagnosed with 'non-neurologic' (functional) symptoms is being interpreted by investigators as 'neurologic evidence' of the 'non-neurologic' (functional) disorder. This amalgam of incoherence is born of *confirmation bias*.

While 'evidence of neurologic disease' has been absorbed into the theoretical framework, at the individual level, a functional diagnosis still rests on the 'absence of neurologic findings' (i.e. symptoms that cannot be explained by a neurologic disorder) [1]. But why is it that patients with symptoms deemed 'functional' (non-neurologic) show pervasive neurologic abnormalities when studied in-depth and en masse? The answer lies in the phenomenology of neurologic disease and the faulty diagnostic practice promoted in the FND and PNES literature.

Manifestations of neurologic disease are known for their kaleidoscopic and sometimes bizarre presentations. The clinical features of movement disorders can be various and heterogeneous, and the correct clinical diagnosis is often a challenge, even for expert neurologists [61]. The dyskinesias encountered in neurology clinics entail a "hotch potch of miscellaneous and largely unclassified phenomena" which are "strikingly situation specific and variable in severity [110]." The symptoms of dystonia are *unusual, inconsistent* (e.g. can run but not walk, sing but not talk, have spasms of the eyelids that occur while reading but not while watching TV), fluctuate over time, worsen with anxiety, lessen while the patient is under hypnosis, and remit during sleep [23]. The clinical features of idiopathic torsion dystonia are *highly variable,* and severity is largely determined by age of onset [111]. Because there are so many different clinical manifestations and causes, there are *no simple algorithms* for diagnosis addressing all dystonias [112]. The clinical presentation of movement disorders is complex, often variable, and sometimes bizarre [113]. The clinical signs of neurologic disease are often varied and confusing [114]. Medical teaching programs typically take *classic clinical presentations as the starting point* and present students with a representative constellation of features; however, patients *rarely present in this way* to a physician in clinical practice, *particularly in the early stages of a disease* [115]. Renowned neurologist David Marsden (who was instrumental in establishing dystonia as a neurologic disease rather than a psychogenic condition) [15] concluded that the bizarre and inconsistent presentation of dystonias, and their relief by certain inexplicable trick manoeuvres, *were erroneously considered signs of a psychogenic aetiology* [116].

Studies indicate that during the neurologic examination, clinical signs viewed as *atypical* or non-prototypical will likely garner a functional diagnosis. Functional Neurological Disorders; comprise neurologic symptoms unexplained by a *classical* neurologic disease [2]; have positive signs and symptoms that are *not typically seen* in other movement disorders [34]; may appear bizarre and should be inconsistent or incongruent with *classic* organic syndromes [117]; demonstrate *atypical* neurologic symptoms that do not conform to any neurologic disorder [58]; are positively identified as not being due to *recognized neurologic disease* [84]; show signs that are inconsistent and incongruent with the *normal rules* of pathology [118]; are characterized by inconsistent character with *unusual* presentations in amplitude, frequency, and distribution [83]; show internal inconsistency or incongruity with *known patterns* of neurologic disease [119].

The demand for a 'classic presentation' is a *wholly ill-suited* bar for a phenomenon that is strikingly variable, confusing, largely unclassified, and sometimes bizarre. Eminent neurologist Jean-Martin Charcot stressed that classic signs (e.g. absent reflexes in patients with tabes dorsalis) are not always present and that it would be a "grave error" to rule out a condition based on the absence of a prototypical sign [17]. Manifestations of neurologic disease *do not lend themselves to rigid classification,* and the scientific literature is replete with studies showing that non-prototypical presentations are not that atypical [97,114,119-127]. A diagnostic standard that demands a *prototypical* presentation produces, as an artefact, a not insubstantial subgroup of patients whose neurologic symptoms will be considered 'incongruent,' 'inconsistent' or 'incompatible' with *classic* neurologic disease (i.e. the FND population *during the diagnostic phase*).

The diagnosis of FND is based on 'positive signs' deemed inconsistent with neurologic disease [62]. The Hoover sign, for example, is hailed as a reliable test for functional leg weakness [64], but this sign has *well-documented limitations*.

Pain may affect the sign in several ways [64], and many clinicians have pointed out that the test can yield variable or equivocal results [128-133]. Entrainment, distractibility, and variability are all considered 'positive' evidence of FNDs [134,135] but these clinical signs are also found in patients with recognised neurologic disease [116,135,136]. Inexplicably, spontaneous remission is promoted as 'positive' evidence of a functional disorder [83,134]. Why would a symptom with a 'psychogenic' or otherwise 'non-neurologic' aetiology simply remit without any intervention? The *incongruence* with the 'functional theory' aside, spontaneous remission has been observed in many neurologic disorders, including Tourette's Syndrome [136], dystonia [137] and *a substantial proportion of untreated epilepsy patients* [138-140]. A placebo response is considered evidence of a functional disorder [24,75], but studies show these effects are ubiquitous across diseases, patient populations, and experimental paradigms, making them a key consideration in the design of clinical trials [141]. While these 'positive signs' are fallible and have been observed in neurologic disorders, they are presented in the literature as pathognomonic for a 'functional' disorder.

In functional gaits, walking is often *bizarre* and does not conform to any of the *usual patterns* observed with neurologic gait disorders [142]. In a recent case study, a 28-year-old woman developed transient weakness in her limbs and a gait disturbance that was deemed "bizarre" and functional by several neurologists [58]. Her neurologic examination was considered normal, and no brain imaging had been completed because of the "obviously atypical nature of her symptoms [58]." During her fourth work-up, the patient finally got a CT scan, which showed a large left frontal meningioma with considerable oedema and midline shift. After the tumour was removed, her neurologic symptoms resolved, including the 'functional' gait. The author defended the FND diagnosis, pathologised the patients' sense of vindication, and emphasised that every medical professional involved was confident "the odd gait was functional" and "less certainty was expressed on the role of such a large brain tumour in her presentation [58]." The law of parsimony concludes that the patient's neurologic symptoms, including her atypical gait, were caused by the tumour and the 'positive sign' that convinced the neurologists that her gait was 'functional' was *erroneous and invalid.*

'Medically unexplained' symptoms are often equated with a functional aetiology [3,143], but the logic is faulty [144] and constitutes a diagnostic approach not universally accepted in medicine. "Many patients with chronic diseases remain without a diagnosis despite extensive medical evaluation [145]." The Undiagnosed Diseases Program (UDP) was established at the National Institutes of Health (NIH) to meet the needs of patients with undiagnosed diseases and investigate the biologic characteristics of the diseases [123]. This program has defined "entirely new syndromes, rare diseases, and unusual presentations of common diseases [123]." A diagnostic approach inferring a 'functional' aetiology from 'medically unexplained' symptoms has the *obvious potential to increase the incidence of 'functional' disorders*.

Psychogenic nonepileptic seizures have been *eliminated and induced by epilepsy surgery* [146-148]. In one study, nine of thirteen patients with PNES and co-morbid epilepsy stopped having PNES, and of those, seven also became free of epileptic seizures [146]. The PNES investigators' conclusion: "That 7 of our patients became free of both seizure types does not necessarily mean that psychogenic seizures were also caused by focal, organic disease, which was cured by resection of the ictogenic part of the brain. Epilepsy surgery, whether successful or not, represents a significant life event, and the reasons for an improvement of psychogenic seizures could well be psychological [146]." In another study, five of nine patients with PNES and co-morbid epilepsy became seizure-free, and eight subsequently developed PNES [147]. Why would 'psychogenic' or 'functional' seizures disappear or emerge following epilepsy surgery? The interpretation that the impact of neurosurgery "could well be psychological" [148] *shows confirmation bias*. The law of parsimony concludes that PNES and epileptic seizures are significantly affected by epilepsy surgery because *both are epileptic events*.

The ictal scalp vEEG test result determines whether a seizure is designated epileptic or PNES [63,149-151]. While studies confirm that a substantial proportion of epileptic seizures can only be detected by intracranial electrodes [149-155], the fallible surface electrode of the vEEG is *still employed as a litmus test* and hailed worldwide as the diagnostic 'gold standard' [5]. Though investigators assert PNES are "not associated with ictal electrical discharges in the brain [28]", this is merely a *presumption* and one unsupported by the objective evidence. Patients diagnosed with PNES and patients with epilepsy are *identical populations* separated only by an assessment tool with known limitations [32]. The condition known as PNES is just as disabling as epilepsy [8] because it is epilepsy [32]. The high incidence of PNES diagnoses [157,158] speaks to how frequently epileptic seizures are not captured by scalp EEG electrodes.

There is no condition precluding a functional diagnosis. People with intellectual disabilities make up a subgroup of PNES patients [159]. In a 2-year-old with a transient dystonic sign deemed 'functional,' poor frustration tolerance and emphasis on toilet training were identified as the probable origin of the 'functional' sign [160]. In one study, a 2-month-old infant was diagnosed with PNES [161]. Apparently, PNES are "quite commonly" encountered in infants and young children and in most cases, "a careful history and examination will elucidate their nature [161]." The authors did not speculate as to what psychological factors could possibly be the origin of PNES in a newborn. Do these patients suffer from neurologic disease and epilepsy or a 'non-neurologic' disorder with a mysterious aetiology? The law of parsimony concludes the former.

'Functional overlay' refers to the co-morbidity of neurologic disease and functional symptoms, and apparently it is common [162]. Epilepsy and PNES are a well-documented variant of 'functional overlay' which may co-occur more frequently than previously thought [163]. Patients with Parkinson's Disease (PD) are also prone to functional symptoms [57,164], *especially 'functional' tremors that are located on the most (PD) affected side* [165]. Investigators of FND and PNES submit that while patients with PD and epilepsy suffer from recognised neurologic disorders with global neurologic impact, many of them have comorbid 'functional' symptoms distinct from the neurologic disease [55] and that stem from a mysterious condition with a 'psychogenic' or otherwise 'non-neurologic' etiology. The position for 'functional overlay' in these patients is insupportable. The law of parsimony concludes that *all tremors* observed in patients with PD are a manifestation of *the neurodegenerative disease (PD)*, and that *all seizures* observed in patients with epilepsy are *epileptic*.

Objective data is the arbitrator, not highly theoretical expert opinion, and it points *unwaveringly* to epilepsy and neurologic disease. Traumatic brain injury is a significant risk factor for *both* epileptic seizures [166,167] and seizures labelled PNES [168,169]. After a woman was kicked in the head by a horse, she started having seizures that were labelled PNES [170]. Epilepsy and PNES populations demonstrate pervasive brain abnormalities, and *both* are considered network disorders [106,107]. No single biomarker successfully differentiates PNES from epileptic seizures [151]. The semiology of PNES and epileptic seizures is so similar [5,45,171], there is *no clinical sign that has diagnostic value* [156]. Seizure-trained dogs, who *recently demonstrated the existence of an epileptic odour* in humans [172], have reliably *alerted to both epileptic seizures* [172-175] and *seizures labelled* PNES [170,176,177]. The mortality rate of patients diagnosed with PNES is 2.5 times that of the general population and *similar to most patients with epilepsy* [178]. Patients 'mistakenly' treated for epilepsy, and later diagnosed with PNES, had their seizures *remit, or experienced a substantial reduction in seizure frequency* after they started antiepileptic medication [179]. Patients with seizures labelled PNES have shown mesial temporal lobe sclerosis on MRIs [180]. In two adolescents with drug-resistant epilepsy, the semiology of their 'psychogenic' seizures showed a *striking resemblance* to their epileptic seizures [181]. Patients diagnosed with FND show pervasive brain abnormalities [37,106] to the extent that FND is considered a network disorder [106] *just like dystonia* [108]. Patients with cervical dystonia and patients diagnosed with FND *both* show structural brain abnormalities [37,106,182]. Functional neurological disorders are *just as disabling* as neurologic disorders [9,10]. *Physical injuries* are frequently associated with the *onset* of movement disorders labelled 'functional [183,184]. A patient with a family history of Huntington's Disease received a diagnosis of *psychogenic chorea* [185]. Physiotherapies are a highly effective treatment for patients with organic movement disorders [186,187] and patients with abnormal movements labelled 'functional' [74]. Transcranial magnetic stimulation (TMS) studies have shown that psychogenic and organic dystonia exhibit *similar neurophysiological abnormalities*, as compared to controls [188,189]. A patient diagnosed with 'functional' weakness showed significant improvement following repetitive transcranial magnetic stimulation (rTMS) [190]. A randomised, double-blind controlled study concluded that repetitive transcranial magnetic stimulation could represent a valuable intervention for patients with tremors labelled 'functional' [191]. Patients with dystonic tremor and patients diagnosed with FND have demonstrated significant improvement following administration of transcutaneous electrical stimulation (TENS) [192,48]. The objective evidence is compelling, and the law of parsimony concludes that patients diagnosed with FND and PNES *suffer from ordinary neurologic disease and epilepsy*.

4. CONCLUSION

Empirical evidence debunks the psychogenic presumption underlying the functional diagnostic entity. Patients diagnosed with 'non-neurologic' (psychogenic or functional) symptoms show pervasive brain abnormalities. When this data is plugged into the originating hypothesis, and the 'absence of organic findings' is replaced with the 'presence of neurologic disease,' *there is no longer any basis to presume an aetiology other than neurologic disease*. Evidence of neurologic disease is simply evidence of a neurologic disorder.

The diagnostic practice as promoted in the PNES and FND literature is fatally flawed, and the proof of this *lies in the data*. Conditions labelled FND and PNES are *just as disabling* as neurologic disorders and epilepsy for a reason. The vEEG test result and the 'positive signs' employed to identify functional or 'non-neurologic' disorders have *isolated* patient populations with pervasive brain disease. In other words, *the 'functional' diagnostic markers identify patients with serious neurologic disorders*. While the theory underlying the 'functional' diagnosis has been dismantled by the data, modern investigators, like the neurologists who were called out by Eldridge and Fahn years ago [21], *are ignoring strong evidence of neurologic causation*. The prevalent misdiagnosis of patients with neurologic disease and epilepsy is the *real crisis in neurology*.

DISCLAIMER (ARTIFICIAL INTELLIGENCE)

The author hereby declares that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc) and text-to-image generators have been used during writing or editing of this manuscript.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Author has declared that no competing interests exist.

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Chapter 2
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Impact of Emerging Pandemics on Cardiovascular Health and Psychological Stress: A Systematic Review

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ABSTRACT

Introduction: Every epidemic that breaks out could cause confusion and fear in society. Little is known regarding behavioural changes and health condition responses, despite the dramatic warning in the media. There is an extremely strong correlation between the onset of cardiovascular disease and the pandemic.
Aim: The goal of the study was to find out how the pandemic's stress affected the heart's regular physiological processes.
Methodology: Information about the potential effects of psychological stress brought on by the pandemic on cardiac physiological function was gathered from several databases. Using the various databases, studies that examined the relationship between stress on CVDs or the emergence of the pandemic and the cardiovascular system were found. A total of 37 studies were chosen for full assessment out of the more than 200 abstracts that were screened to ascertain whether all inclusion requirements were satisfied. Among these studies, one focused on evaluating the stress levels of front-line medical staff in China, particularly those working at a provincial hospital during the coronavirus outbreak and severe acute respiratory syndrome (SARS).
Discussion: As a result, a study revealed that medical staff members experienced significantly higher levels of moderate and severe anxiety than their administrative counterparts. Prior research on severe acute respiratory syndrome emphasised the importance of increasing awareness of mitigating strategies. Because a larger perceived danger of infection was more likely to result in an increase in cautionary events in contrast to contamination, this strategy was taken into consideration with

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the underlying insights of risk and anxiety. The implementation of control measures raises the stress level, which may cause CVD to develop.
Conclusion: There is adequate evidence that illustrates the physiological manifestation of the respiratory system and obstruction of the blood flow that might lead to the development of CVD. If not properly controlled might lead to death due to a heart attack.

Keywords: Pandemic; stress; emotion; cardiovascular disease; central nervous system; cardiac muscles; pulses; influenza; COVID-19; swine flu; Spanish flu.

1. INTRODUCTION

“Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection is the cause of the development of coronavirus 19 (COVID-19), which has affected more than 670 million people worldwide as of January 2023” (Baloch et al., 2020; Moorthy et al., 2020; Zhao et al., 2020). “The fact that COVID-19 has been blamed for over 7 million fatalities is significant. Further evidence supports the existence of Long COVID-19, which presents clinically as persistent symptoms and/or delayed or long-term problems that appear weeks after the onset of COVID-19 symptoms” (Nalbandian et al., 2021; Sadeghi Dousari et al., 2020). “It was discovered shortly after the pandemic began that the severity of the illness is correlated with coexisting cardiovascular risk factors and disease. Multiple studies consistently demonstrate that the prevalence of certain common cardiometabolic conditions, such as obesity, type-2 diabetes (T2D), cardiovascular disease (CVD), and hypertension, significantly heightens the risk and severity of COVID-19, including in-hospital mortality” (Laddu et al., 2023). “Additionally, 20–30% of hospitalised COVID-19 patients have elevated troponin levels triggered by the infection” (Cheng et al., 2021; Hageman, 2020). “Doshi argued clearly that the description of influenza contagion in 2009 was indeterminate but does not conform to the conventional epidemiological definition of a pandemic.” (Doshi, 2011). Therefore, the term pandemic is distinct as “an epidemic that is occurring worldwide, or over a very wide area, crossing international boundaries and usually affecting a large number of people.” (Last, 2001). The conventional explanation of a pandemic also takes into account virology, population immunity mechanisms, or the evolution of disease severity over time. In the northern and southern hemispheres of the temperate zone, the pandemic can happen once a year. A seasonal epidemic that spreads over international borders and has the potential to impact a significant number of people can be called a pandemic. Seasonal epidemics, however, are not regarded as pandemics due to several environmental factors (Liu et al., 2021; Nalbandian et al., 2021).

Therefore, the occurrence of a pandemic in a country may lead to the development of a variety of health conditions. The following infectious disease outbreak like human immune virus (HIV), different strains of Influenza (H1N1, H5N1) and Severe Acute Respiratory symptoms (SARS) epidemics and pandemics to put strain on country economic status and regional instability of the country (Duma et al., 2022; Hadian & Rezayatmand, 2022). These deteriorating conditions are visible in the country over a very short period. The presence of the pandemic can be beyond the debilitating, sometimes fatal, consequences for those directly affected by the pandemic. As a result, the occurrence of a pandemic in a country has a range of negative socio-economic and political consequences. Therefore, the negative effect of the occurrence of pandemic in most cases affect which can be experienced by both developing and developed countries (Duma et al., 2022; Sawicka et al., 2022). In 2019 wide variety of economic indicators showed that H1 was not just on mortality, but also on health-care systems, animal health, agriculture, education, transport, tourism, and the financial sector. In short, a pandemic event threatens all aspects of the economic and social fabric" (Clemente-Suárez et al., 2021; Panneer et al., 2022).

The prevalence of pandemics in a country can infect and affect millions of people within a short period of time. In large populations, the widespread occurrence of serious illness is a common outcome. If the pandemic is not properly controlled, it might lead to thousands of deaths due to the 'Black Death' plague (Banaś, 2021; Jedwab et al., 2022), Spanish flu (Berche, 2022; Tambolkar et al., 2022), and Hong Kong flu (Bonnet et al., 2022; Zhang et al., 2021) over a period. Therefore, the prevalence of pandemics may lead to infectious disease disasters, including emerging infectious disease outbreaks. If these conditions are not properly controlled, they have the potential to cause high morbidity and mortality in the country and the world. In most cases, the occurrence of the pandemic may account for a quarter to a third of global mortality over a period (Msemburi et al., 2023). "In some other developing countries, both pandemics and infectious diseases have the potential to cost lots of lives in a short period of time. In which the potential of the death rate to increase within the range of 5 to 10 per cent over time. In 2003, due to the outbreak of SARS, there were more than 8000 infected individuals, with over 700 deaths (almost 9%) worldwide in just 6 months" (Coccia 2021; Anderson et al., 2020).

Mental stress is a common term signifying a progression that is supposed to underwrite a wide variety of mental and physical conditions experienced by individuals. Regardless of prevalent attention on the hypothesis and significance for negative health and well-being, there is little agreement on descriptions for psychological stress (Paschke et al. 2021; Yang et al. 2021) The three perspectives on psychological stress, i.e. acute stress, episodic acute stress, and chronic stress, vary in terms of the relative prominence of each according to places on the environment, the organism, and the interaction between the organism and the environment over a period (Paschke et al. 2021; Yang et al. 2021). The presentation of the stress generally refers to two things: the psychological perception of how the body responds to pressure, and the involvement of multiple body systems, from biochemistry of the body, morphology and capability to keep things in memory. With respect to the negative effects of mental stress, some stress is necessary for all living systems. It is how individuals encounter and respond to the challenges, experiences, and uncertainties of life.

"Cardiovascular diseases (CVDs) include a variety of heart and blood vessel abnormalities that affect physiological functioning. Consequently, a vast range of heart diseases exist that impact many different bodily systems if they are not controlled. High blood pressure, high cholesterol, smoking, poor diet, inactivity, and obesity can all raise the risk of some cardiovascular illnesses. Chest pain, heart attacks, and stroke can result from coronary artery disease, which is the most prevalent cardiovascular condition" (Duggan et al., 2022). Congenital heart disease (heart illness at birth), congestive heart failure (Roger 2021), heart rhythm issues (Roger 2021), and endocarditis (inflamed inner layer of the heart) are other cardiovascular diseases (Miao et al., 2024).

A range of heart and blood vessel disorders that impact physiological functioning are referred to as cardiovascular diseases (CVDs). As a result, there are numerous heart conditions that, if left untreated, affect numerous body systems. Obesity, smoking, poor diet, high blood pressure, high cholesterol, and inactivity can all increase the chance of developing certain cardiovascular diseases. The most common cardiovascular disease, coronary artery disease, can cause heart attacks, stroke, and chest pain (Duggan et al., 2022). Other cardiovascular disorders include endocarditis (inflamed inner layer of the heart), congenital heart disease (heart illness at birth), congestive heart failure (Roger 2021), and heart rhythm problems (Roger 2021; Miao et al., 2024).

During virus outbreaks, these limitations will have a significant impact on lifestyle choices, increasing the burden of cardiovascular disease and its psychosocial effects on individuals, communities, and the global community (Mattioli and Ballerini Puviani 2020; Wang et al., 2020). Prior studies have uncovered a significant and diverse range. One significant adverse consequence of quarantine is psychological anguish (Brooks, Webster, & Smith, 2020). Depression, rage, and long-term stress are linked to mass quarantine, self-quarantine, and isolation. Longer quarantine periods, frustration, boredom, a lack of supplies, a lack of information, financial loss, and stigma were among the stressors that were proposed. Additionally, during an outbreak, people are afraid of getting sick or dying.

According to Mattioli and Ballerini Puviani (2020), these unpleasant emotions are linked to endothelial dysfunction, systemic inflammation, and a propensity to lead an unhealthy lifestyle. According to Mattioli et al. (2023) and Morales et al. (2023), both acute and subacute stress trigger the adrenergic system, which in turn increases the inflammatory response and endothelial dysfunction, ultimately increasing atherosclerotic plaques. A significant proportion of myocardial infarctions were preceded by some form of stress.

1.1 Aim

To study the effect of the stress caused by the pandemic on the normal physiological functioning of the heart and psychological stress.

1.2 Objectives

Using the body of available scientific literature that focused on the possible health hazards that could result from the development of COVID-19 disease on the physiological functioning of the heart.

2. METHODOLOGY

This study was based on a non-meta-analytic systematic approach to review the existing literature on menarche and hereditary pattern.

2.1 Registration and Protocol

The review was not registered.

2.2 Study Selection

The abstract was initially analysed using the keywords. if the abstract passes the first test of selection. The article was downloaded if the keywords appeared in the content, especially in the results sections. The article will undergo another screening to ensure it addresses the targeted issues. the impact of COVID-19 disease progression on the heart's physiological processes. The approach, results, analysis, limitations, and recommendations were examined and documented. The article's central argument will be supported by the results, discussion, and conclusion of the body of current scientific literature (Appendix Fig. 1).

2.3 Eligibility Criteria (Inclusion and Exclusion Criteria)

A total of 37 studies were chosen for full assessment out of the more than 200 abstracts that were screened to ascertain whether all inclusion requirements were satisfied. Due to their failure to satisfy all of the inclusion criteria listed below, sixteen studies were finally disqualified. Twenty-one papers were included in this review because they satisfied all inclusion requirements. The review was carried out by five researchers. To minimise inter-rater selection bias, a data extraction form was created to gather information from every research.

The study will include nearly all of the full-text publications that have been made since the inspection. Additionally, the research needs to fulfil the requirements given in Table 1. Articles that satisfied the requirements in Table 2 were excluded. The publications were published in English and only appeared in peer-reviewed journals. Using comparable keyword sets, studies were taken out of each database. To complete the manuscript compilation, a last search was carried out from 1985 to 2025. Additional articles were discovered by applying a snowball method to those that met one or both of the requirements listed in Table 3.

2.4 Criteria of Inclusion

The non-systematic review and identification of eligible studies were performed using different keywords. The titles and abstracts were screened to determine their relevance to the objective of the study. The full text of potentially relevant studies was then examined, and applied the eligibility criteria study (Table 1). Articles that were utilised for this review were strictly studies investigating the genetic determinants of menarche amongst young adults.

Table 1. Inclusion criteria for research articles to be used in compiling this non-meta-analysis research

Number	Criterion
1	The participants must experience both psychological stress, respiratory complications, and CVDs
2	Evidence of substance use confirmed by self-reported questionnaires or hospital reports
3	Original research describing cohort, cross-sectional, or prospective studies, or other reviews
4	English written papers only

Table 2. The following exclusion guidelines were used to remove from the study

No.	Criteria
i.	People with comorbidity diseases.
ii.	People in mental institutions
iii.	People suffering from substance use disorder
iv.	Participants who use alcohol

2.5 Information Source

The following search engines: Google Scholar, PubMed, Semantic Scholar, Science.gov, and Ref Seek were the first computer-based searches used to find the studies that would form part of this review. Abstracts from EBSCO and Science Direct were also looked up. To fill in the gaps in the information, we made an effort to contact the authors of any papers with ambiguous or unreported parameters, such as the kind of adulterated drug with an unidentified name. The time frame covered was 2004-2025; medical meeting abstracts were excluded.

2.6 Search Strategies

Studies that investigated the hereditary pattern and the onset of menarche amongst young adults were identified using the following databases: Google Scholar, PubMed, Science Direct, and EBSCO search engines. A preliminary total of 150 related published research articles up to 2004 were found using a combination of various keywords such as shown in Table 3, with no restrictions on publication types and dates (Appendix I). Hence, the reference list of relevant publications identified was checked for additional studies and recent articles in relevant journals that can be used to compile adequate information for discussion. The whole search was limited to studies published in English and peer-reviewed journals only.

At least two or three keyword combinations were tried to find the pertinent articles (Table 3). As part of the articles that employed original research data, only eleven (11) were found to be eligible for the study. Thus, to locate any publications that are pertinent to the current manuscripts. For the current manuscripts, we also used forward and backwards citation searches. As mentioned earlier, we also use authors to search many databases for forward and backwards citations.

In order to filter the found articles, we modified the results section by utilising the records' titles, abstracts, and subject indexing. We then use those search phrases along with additional search terms we discovered during the inquiry to make a plan to find more articles. Furthermore, many search engines were used to locate and validate the search terms. The study was restricted to English-language publications and was designed to examine the relation between respiratory complications, cardiovascular disease and psychological stress (Table 1).

2.7 Selection Process

Various databases were searched for relevant literature using a general appraisal form for systematic review papers. A variety of subheadings were also utilised for the appraisal worksheet, such as the study's limitations, the year it was published, sample size, outcomes, and the goals, aims, and objectives of the study. Using Mendeley and the Micro Software reference manager, duplicate entries were removed.

2.8 Data Collection

A structural form was made with the following details to make sure that pertinent data for this systematic review was gathered, as indicated in Table 3.

2.9 Data Items

The current project's components were not categorised as originating from different regions. The findings of the study will illustrate how the development of COVID-19 disease might affect the physiological functioning of the heart. If the stress caused by COVID-19 symptoms is not detected early, a patient might die due to the development of cardiovascular disease within a very short period.

2.10 Study Risk of Bias

The Downs and Black instrument (Appendix II) was used to assess bias. To find reporting bias, the tool's multiple domains were used.

2.11 Results of Individual Synthesis

The outcomes of the manuscripts will be to inform the readers about the high mortality rate that prevails during COVID 19 might be due to the development of CVDS due to the manifestation of COVID-19 disease.

Table 3. The following headings are used to search for articles to be included or excluded from the study

No	Group 1 Cardiovascular diseases	*Group 2* Respiratory disease	*Group 3* Physiological stressors	*Combining results
1	Heart attacks	Covid	Depression	Group 1 and Group 2 and Group 3
2	Congestive heart failure	'Black Death' plague	Anxiety	
3	Heart rhythm problems	Spanish flu	Acute stress	
4	Congenital heart disease	Hong Kong flu	Chronic stress:	
5	Endocarditis		Episodic acute stress	
6	Heart disease at birth		Routine stress	

**The combination of groups will be done per item in each group, e.g., 1 and/or 7 and/or 11 and/or 13*

2.12 Biases in Reporting

The possibility of bias among the studies that could affect the total quantity of evidence was assessed by looking at the recommendations made by the research. All included papers that complied with the same guidelines were included in the preparation of this review.

2.13 Features of the Study

This will cover the kinds of studies that are carried out using either human or animal models.

2.14 Bias Risk in Research

The Downs and Black tool for evaluating bias risk was used for this (Appendix III).

2.15 Findings from Individual Research

Refer to Table 4 below.

2.16 Synthesis Outcomes

Discussion compelled the results to be synthesised.

3. RESULTS

In Table 4, the study by Matsuishi et al. (2012) whereby the structure of the questionnaires was designed into four (4) factors, whereby factors were categorised as: 1: anxiety about infection; 2: exhaustion; 3: Workload; 4: feeling of being protected. Whereby, the standardised partial regression coefficients relationship between the independent variable on the dependent variable is illustrated, with the influence of all the remaining variables held constant. Each coefficient is the slope between the dependent variable and each of the independent variables. Hence, the independent variables with bigger standard partial regression coefficients have a stronger relationship with the dependent variable. In the study by, (Matsuishi, et al., 2012) the independent variables were the variables, and the dependent variable was the Factor. Also, the impact of event scales (IES) was calculated, which can measure the amount of distress that you associate with a specific event. The IES was also calculated between the Factor and variable SPSS 17.0 J: SPSS, Tokyo, Japan) With the p-value ranging from 0.05 to 0.001. The type of job for nurses and others, hospital (Z) and work environment significantly differ with the values 0.14*, 0.13**, -0.06* and 0.09** respectively. In Table 4, for factor 1, "anxiety about infection, workers in their 20s were less anxious compared to the older group. For factor 2, exhausted workers in their 50s felt more exhausted compared to 20s (Table 4). In Table 4, (Wong, et al., 2010) whereby a 270 /401 distributed questionnaires were completed for the study conducted among community nurses in Hong Kong. The suspected H1N1 cases were mainly those which the participants were unwilling or not sure about the care of patients reported a high level of psychological stress in various areas of their work environment. Including the contraction risk of their own and family members due to their psychological stress and emotional status (Table 4).

Table 4. The presentation of data from the different literature

Part 1: Psychological stress and pandemic

No	Authors	Country	Sample size	Types of disease	Statistical analysis	
1	(Hawryluck, et al., 2004)	Toronto	129/ 15,000	Severe Acute Respiratory Syndrome	Impact of Event Scale—Revised (IES-R) (9) and the Centre for Epidemiologic Studies—Depression Scale (CES-D)	Income CES-D (mean; SD) - < \$40,000 (18.3; 15.4) - \$40,000–\$75,000 (15.5; 13.2) - > \$75,000 (10.9; 9.2) - Income IES-R (Mean; SD) - < \$40,000 (24.2;20.6) - \$40,000–\$75,000 (19.9; 24.4) - > \$75,000 (11.8; 11.6) Duration of quarantine IES-R (Days; mean; SD) - < 10; 11.7; 10.7 - >10 ;23.7; 27.2
2	(Goodwin, Haque, Neto, & Myers, 2009)	Malaysia	328	H1N1		Public transport and cancellation of flights X^2 = 21.91, 49.20, both $p < .001$). Risk group: (pig industry, LGBT and Sexual workers (χ^2) = 68.03, 11.44, 31.82, and 12.10, $p < 0.001$, respectively The elderly and immunocompromised (χ^2= 8.27, 3.49, $p < .05$).

No	Authors	Country	Sample size	Types of disease		Statistical analysis	
						↑ Anxiety 71% (127/178) $\chi^2 = 91.67$, $p < 0.001$).	
3	(Wong, et al., 2010)	Hong Kong	401(270)			Depression (> 2 Weeks) (mean: SD) - No or Not sure = 30.33: 25.97 - Yes =. 17.18: 20.27 Emotionally stressful (> 2 weeks) (mean: SD) - No or not sure (mean: SD) – 33.16: 26.29	p-value < 0.001
4	(Matsuishi, et al., 2012)	Kobe city	2000	H1N1	Factor 1	$\beta_{(\text{Age group: 40 -49 \& 50 -59 years}} = -0.13 - 0.14$*** $\beta_{(\text{Age group: 60 -70 years})} = 0.05$ * $\beta_{(\text{Job: nurses \& Others})} = 0.27$*** $\beta_{(\text{Work environment high risk})} = 0.13$***	
					Factor 2	$\beta_{(\text{Age group: 50 -59 years})} = 0.008$** $\beta_{(\text{Jobs: Nurse})} = 0.14$** $\beta_{(\text{Hospital}}$ X & Y) = - 0.12*** to - 0.06**	
					Factor 3	$\beta_{(\text{Gender: Female})} = -0.06$* $\beta_{(\text{Job: Nurses})} = 0.14$*** $\beta_{(\text{Hospital:}}$ Y) = -0.09*** $\beta_{(\text{Work Environment: High risk})} = 0.36$***	
					Factor 4	$\beta_{(\text{Age group: 40-49 years})} = 0.10$*** $\beta_{(\text{Age group: 50 -59 years}) =} 0.14$*** $\beta_{(\text{Age group: 60-70 years})} = 0.06$*	

No	**Authors**	**Country**	**Sample size**	**Types of disease**	**Statistical analysis**		
						$\beta_{(Job:\ Nurses)} = 0.10^{*}$ $\beta_{(Job:\ Others)} = 0.13^{**}$ $\beta_{(Hospital:\ Y)} = -0.06^{*}$	
5	(Bakare, Yusuf, Habib, & Obembe, 2015)	Nigeria	111	Leprosy		Prevalence of different disorders by duration of illness Complete treatment versus still on treatment $X^2 = 14.27$ df = 1OR = 0.35 95% CI = (0.19 – 0.63 Association between treatment status and psychiatric disorder Duration of illness: t = 6. 893	p-value <0.001
6	(Lu, Wang, Lin, & Li, 2020)	China	Medical staff = 2042, Administrative staff 257	COVID 19	Level (Medical & Administrative) ○ Fear scale Severity (Medical & Administrative) ○ Fear scale ○ Working in isolation wards ○ Days of working in isolation wards ○ Frustrated with unsatisfactory results at work	p-value < 0.001	

No	**Authors**	**Country**	**Sample size**	**Types of disease**	**Statistical analysis**	
7	(Mazza, et al., 2020)	Italy	2766	COVID 19	DASS21: Depression Education level - Estimate = - 0239 - EXP(B) = 0.787 - 95% CI = - 0.355 to – 0.123 Gender ref male * - Estimate = 0.638 - EXP(B) = 1.893 - 95% CI = 0.445 to 0.830 Working position ref Unemployed ○ Employee - Estimate = - 0.330 - EPX(B) = 0.719 - 95% CI = -0.648 TO - O. O11 ○ Having a child, ref. Yes - Estimate = 0.393 - EXP(B) = 1.481 - 95% CI = 0.031 TO 0.755 Acquaintance infected by COVID-19, Ref. No - Estimate = 0.293 - EXP(B) = 1.340 - 95%CI = 0.084 to 0.502 DASS21: Anxiety Age - Estimate = - 0.026 - EXP(B) = 0.974	 p-value < 0.001

No	Authors	Country	Sample size	Types of disease	Statistical analysis
					- 95% CI = -0.42 to – 0.011 Gender ref. Male - Estimate = 1.179 - EXP(B) = 3.251 - 95% CI = 0.899 to 1.459 DASS 21 Stress Age - Estimate = - 0.024 - EXP(B) = 0.976 - 95% CI = -0.037 to – 0.011 Gender ref. Male - Estimate = 0.918 - EXP(B) = 2.504 95% CI = 0.699 to 1.1364

Part II: Pandemic and Cardiovascular Disease

No.	Authors	Countries	Sample size	Type of study	Type of disease	Statistical analysis
1	(Hanson, et al., 2015)		160		Malaria	Plasma Ang-2 (malaria vs healthy): median (IQR) 19.1[10.8-29.1]:1.6 [1.4-2.3]; p = 0.0001 Plasma Ang–2 (deceased vs survivors): median (IQR) 21.9 [13.4-29.4]: 14.9[9.8-29.3]; p = 0.035 High plasma lactate p = 0.0001 Plasma ADAM (patients vs healthy): median (IQR):0.75[0.59 – 1.03]: 0.55 [0.49 – 0.59]; P=0.0001 ANG-2: rs = 0.41, p < 0.0001
2	(Nguyen, et al., 2016)	New York	69 271 (157 648)		H1N1	Ischemic heart disease (ILI) (Years): - 65 (r=0.75; p=0.05) - 65 (r= 0.82; p=0.02 IQR - CVD (↑3.1% (95% CI: 0.5 to 5.7% - ILI: ↑ 4.0% (95% CI: 1.1 TO 6.9%) MI: ↑9.4% (95% CI: 1.2 TO 17.6%)
3	(Huaman, et al., 2018)	Lima			Tuberculosis	Acute myocardial infarction: Cases vs Controls (46% vs 49%; p-value =0.03; OR = 1.86; 95% CI 1.08 – 3.22) Median number of coronary vessels: 2 (IQR 2-3)
4	(Guo, et al., 2020)	Wahun City	52/211		COVID 19	MI: ↑ TnT levels ↑ Creatine Kinase- myocardial ↑ Myoglobin :(median N-terminal pro–brain natriuretic peptide (NT-proBNP)

**p-value < 0.05; **p-value < 0.01; ***p-value < 0.001*

A study by Goodwin, Haque, Neto, & Myers (2009) aimed to gather a brief understanding of the attitudinal and behavioural responses during the early stages of the development of the H1N1 pandemic. The epistemology about the changes amid seasonal and pandemic flu, and those groups seen as most at risk' from contamination. Whereby, 'Common intelligence', unintended principles about those most likely to be at jeopardy, and the suitable behaviours to circumvent infection, were often not taken into account by medical practitioners. Hence, those myths have been shown to inspire obedience and self-care behaviours changes (De Vet, Nooijer, A, K, & Brug, 2008). As a result, the elderly, immunocompromised individuals and people with comorbidity diseases were hit hard by the emerging pandemic within a very short period of time (Table 4).

In China, with the intention of realising the psychological status of the medical workforce from Fujian Provincial Hospital fighting against severe acute respiratory syndrome-coronavirus (SARS-CoV-19). Therefore, a study that was conducted by Lu et al. (2020) showed that reasonable and severe anxiety prevailed extremely in higher levels amongst medical staff members as compared to administrative counterparts. Moreover, 22.6% of medical staff showed mild to moderate anxiety, and 2.9% were severe; the corresponding proportions of administrative staff were 17.1% and 2.9%, respectively, over time. The different severity of fear was significantly different at $p < 0.001$, and anxiety $p = 0.049$ between the two groups. In addition, 11.8% of the medical staff presented with mild to moderate depression, and 0.3% with severe depression (Table 4) as compared to the administrative staff group. This relationship showed no significant difference between the severity of depression in the medical ($p = 0.191$) and administrative staff groups. Whereby, further analysis of the factors that facilitate them feeling worried, pressured, or frustrated was also analysed and showed were significantly different between the two groups. As expected, several factors contributed to the expansion of psychological pressure including working in the isolation wards, worrying about being infected, shortage of the protective equipment, the epidemic would never be controlled, frustrated with unsatisfactory results on work, and feeling lonely with being isolated from loved ($p = 0.005$) were significantly different at p-value < 0.001 between medical and administrative staff (Table 4).

The factors associated with depression and anxiety disorder among the people of Nigeria due to leprosy, with the Composite International Diagnostic Interview (CIDI) generated among female respondents were 62.4% and 18.3% among males in a sample size of 235 (Bakare, Yusuf, Habib, & Obembe, 2015). Furthermore, Table 4 showed that longer duration of illness was significantly associated with moderate depression ($X^2 = 23.65$, $p < 0.001$ and depressive disorder ($X^2 = 11.30$, $p < 0.001$). Also, there was a significant association between treatment status and having a diagnosis of psychiatric disorder.

3.1 Pandemic and Cardiovascular Disease

A study by Nguyen et al. (2016) demonstrated that periodical addition of daily average CVD death between 65-year-old adults and, 65 and older generation was strongly correlated with daily average total influenza-like illness (ILI), with r = 0.75, 0.082 and the p-value <0.05 (Table 4). In contrast, the correlation amongst candidates younger than 65 years was not significant for total ILI (r = 0.59, P = 0.16) or total ILI+ (r = 0.44, P = 0.32). The outcomes of this study suggested that periodic influenza outbreaks principally affected CVD mortality amongst older people. Each IQR increase of total ILI+ was associated with 3.1% (95% CI, 0.5%–5.7%), 4.0% (95% CI, 1.1%–6.9%), and 9.4% (95% CI, 1.2%–17.6%) increased in mortality rate from CVD, IHD, and myocardial infarction, respectively over a period.

Most candidates on the first day of admission, none showed no signs of acute myocardial infarction, chronic liver disease, thromboembolic diseases, or rheumatism. Over a period of time candidates starts to show elevated cardiac troponin (TnT) levels at a significantly higher levels of other cardiac injury biomarkers, specifically creatine kinase–myocardial band test as compared to the healthy patients (median [IQR], 3.34 [2.11-5.80] vs 0.81 [0.54-1.38], ng/mL and myoglobin (median [IQR], 128.7 [65.8-206.9] vs 27.2 [21.0-49.8] μg/L (P < .001, for all) and also had higher levels of N-terminal pro–brain natriuretic peptide (NT-proBNP) (median [IQR], 817.4 (336.0-1944.0] vs 141.4 [39.3-303.6] pg/mL respectively over time (Guo, et al., 2020).

4. DISCUSSION

Globally, it is known that the emergence of a pandemic is causing people to experience moderate to severe psychological stress. Also, the mitigation strategies that are implemented to reduce the spread of the pandemic add more health issues to the affected and infected family members. One of the most severe psychological stresses emanates from the collapse of the country's economy, which will affect the livelihood of source of income for individuals and business people. If the pandemic becomes worldwide, the highly affected community members are those from previously disadvantaged backgrounds and developing countries.

“Previous studies of severe acute respiratory syndrome (SARS) highlighted the need for the promotion of preventive measures to take into account background perceptions of risk and anxiety, because higher perceived risk of infection was more likely to lead to an increase of precautionary measures against infection” (GM, Ho, & Chan, 2005) (Bish & Michie, 2010). The front runners in most countries also experience psychological stress due to the new cases that are admitted to hospitals. A study was conducted in Japan with the purpose of investigating the psychological impact of the H1N1 influenza pandemic on hospital workers in 2009 in Kobe city. Whereby, the age group of 40 to 59 years were more anxious about the infection compared to youth (Table 4) (Matsuishi, et al., 2012). Also, the people at high risk of the hospitals were anxious about the infection compared with a low-risk work environment (Table 3). Also, older people had a problem of physical exhaustion, which was common amongst the nurses as compared to medical doctors. This was due to the workload.

A similar study was done in Portugal in which the community members were the study focus. In which behavioural change, people at risk were the indicator used to assess the physiological stress. Whereby most community members had reported using less public communal transportation or had anticipated withdrawing or postponing flights, 124/312 were significantly different at p-value <0.001 (Table 4) (Goodwin, Haque, Neto, & Myers, 2009). The elderly and immunocompromised people were more at risk. The emergence of a pandemic in a country sends a wave of fear towards the constituents of that world. In some cases, it sends a wave of fear to the whole world. This wave of fear leads to a wide variety of health conditions that will affect a wide range of events. Therefore, the psychosocial aspects of individuals are important predictors of behavioural responses to the pandemic. A study by Goodwin, Haque, Neto, & Myers (2009) concluded that there were unacceptable echelons of anxiety about swine flu in Malaysia as related to Europe and the superior level of behavioural change over time.

In Mexico, during the study period, 36 patients were hospitalised and admitted to the ICU, and all were subsequently confirmed as having A/H1N1. (Elizarrarás-Rivas, et al., 2010). We note that most family members reported sub-threshold levels of stress and depression, and reported levels of depression above the established cut-off score for higher risk of clinical depression. This was higher than levels recorded for caregivers of patients who had been mechanically ventilated for > 48 hours in the ICU (30% at 2 months) ((Van Pelt, Schulz, Chelluri, & Pinsky, 2010) but much lower than caregivers of chronically critically ill patients when in ICU (75% at ICU enrolment) and similar to levels at 2 months post-discharge (43%) (Douglas, Daly, O'Toole, & Hickman, 2009). In their review of ICU studies, McAdam and Puntillo (McAdam & Puntillo, 2009) conclude that depression affected 15%-35% of patient family members; however, they are comparing studies with inconsistent time.

The uncontrollable dispersion of coronavirus disease 2019 (COVID-19) has called for unprecedented regulatory measures by individual governments worldwide. Most countries promote quarantine for suspected individuals for a particular period. Whereby, Public health measures to achieve these goals may include quarantine, which involves the restriction of movement, or separation from the rest of the population, of healthy persons who may have been exposed to the virus, with the objective of monitoring their symptoms and ensuring early detection of cases (WHO, 2019). Many countries have the legal authority to impose quarantine. Quarantine should be implemented only as part of a comprehensive package of public health response and containment measures and, in accordance with Article 3 of the International Health Regulations (IHR) 2005, be fully respectful of the dignity, human rights and fundamental freedoms of persons (IHR, 2020). A study by the (Hawryluck, et al., 2004) had shown the manifestation of psychological stress between quarantine and non-quarantine (Table 4). The indicators used were the source of income and duration of the quarantine. People who stayed longer showed signs of stress as compared with people at home (Table 4). Similar quantitative studies Twu, et al. (2003); Centres for Disease Control and Prevention, (2003; Mandavilli, (2003) had underlined those quarantined persons with high psychological symptomatology, including post-traumatic and depressive symptoms, stress and anxiety. The emergence of COVID-19 differs from the previously existing pandemics. Whereby, (Barbera, et al., 2001) (Markel, 1995) have shown that during the emergence of COVID-19, people showed severe to moderate levels of psychological stress and anxiety. In other cases, the gender effect plays a significant role. In Italy, the female gender was associated with increased anxiety, depression and stress (Table 4 (Mazza, et al., 2020)). The good indices of internalising psychological stress amongst females were more vulnerable to experiencing stress and developing post-traumatic symptoms. This study also found that young age participants were associated with increasing depression and stress, which was different from other studies (Mazza, et al., 2020). They concluded that having an acquaintance infected with COVID-19 increases both depression and stress. This psychological effect can be exacerbated by the history of stressful situations and medical problems that can raise depression and anxiety levels.

A study that was conducted in Sekoto, North-western Nigeria, showed that the prevalence of psychiatric disorders was generated by the Composite International Diagnostic Interview (CIDI). Whereby, the duration of the leprosy was significantly associated with moderate depression (Table 4) (Bakare, Yusuf, Habib, & Obembe, 2015). "Leprosy patients living in isolated camps are at greater risk of depression because they have been displaced from their place of abode because of their desire to stay away from people/kingship because of the embarrassment they experience or due to outright rejection by those they normally live with because of the perceived infectivity of the illness. In some societies in Nigeria, leprosy patients are completely banished from the community. A typical example is the Igbo community. The finding of higher prevalence of psychiatric morbidity in women compared to men is consistent with previous studies" (Horwath & Weissman, 1995; Picardi, Damiano, Cristina, & Braga, 2001).

4.1 Pandemic and Cardiovascular Disease

Lung and respiratory system complications like infections, allergies, asthma and bronchitis can all lead to difficulties breathing, but sometimes breathlessness could be an indication that there's a problem with your heart. Death from cardiovascular diseases, particularly acute myocardial infarction (AMI), is common in winter than in summer (Danesh, Collins, & Peto, 1997). Although many factors could contribute to this association, the greater number of respiratory infections in winter months is a possible causal link (Danesh, Collins, & Peto, 1997; Curwen, 1990/9). Death rates from cardiovascular diseases increase during epidemics of influenza,3 and anecdotal reports as well as a few small studies suggest that acute respiratory-tract infections shortly before AMI could be a risk factor (Pesonen & Siitonen, 1981; Spodick, Flessas, & Johnson, 1984; Mattila, 1989). In the first, the adjusted odds ratio (OR) for MI within 10 days of a respiratory infection was 3.0 (95% confidence interval (CI) 2.1 to 4.4, $p < 0.0001$) and was nearly 4.0 within five days of infection. In the second study, incidence ratios for MI were 4.95, 3.20, 2.81, and 1.95 at days 1–3, 4–7, 8–14, and 15–28 after infection, respectively (Smeeth, Thomas, & Hall, 2004).

A study that was conducted in India of 72.5% of 200 lepromatous leprosy patients showed the symptoms pertaining to the cardiovascular system. One hundred and ten (55%) of lepromatous had abnormal electrocardiographic findings (Katoch & Ramu, 1983). Our study shows definite evidence of involvement of cardiac autonomic control in three patients having leprosy (Khattri, Radhakrishnan, Kaur, Kumar, & Wahi, 1978). According to (Gupta, Koranne, & Kaul, 2002) the study of lipid metabolism in leprosy is important since lipid plays a central role in the pathology of the disease, and cholesterol dynamics in macrophages may influence the occurrence of cardiovascular diseases. (Kumar, Saraswai, & Shanker, 1988) suggested that lipids might also play an important role as an etiological agent of the vascular abnormalities observed in leprosy. “In the present work, we demonstrate a consistent procoagulant profile in 40 reactional and non-reactional multibacillary leprosy patients. A retrospective analysis in search of signs of coagulation abnormalities among 638 leprosy patients identified 35 leprosy patients (5.48%) which displayed a characteristic lipid-like clot formed between blood clot and serum during serum harvesting, herein named ‘leprosum clot’. Most of these patients (n = 16, 45.7%) belonged to the lepromatous leprosy pole of the disease” (Silva, et al., 2018).

4.2 Psychological Stress and Cardiovascular Disease

Stress, which may exist in many forms, is an unavoidable element of human existence that often leads to a maladaptive physiological response (Steptoe & Kivimaki, 2012). Although acute emotional stress has long been linked to acute cardiovascular events (Kloner, Leor, Poole, & Perritt, 1997), the long-term effects of chronic stress on physical well-being, and specifically cardiovascular disease (CVD), have only recently been recognised (Stewart, et al., 2017;). Nevertheless, clinical guidelines continue to lag behind this evidence. There is an enormous amount of literature on psychological stress and cardiovascular disease. It is clear that psychosocial stress, assessed by a variety of measures, directly correlates with a higher prevalence and clustering of traditional cardiovascular risk factors (Williams, Barefoot, & Haney, 1988) (Siegler, Peterson, & Barefoot, 1992). “An organism’s response to stress is triggered by its nervous system. The hypothalamus receives afferents from several neural structures involved in the response to stress. The hypothalamus, in turn, activates the sympathetic nervous system (SNS) and (through the anterior pituitary gland) the hypothalamic pituitary-adrenal (HPA) axis, leading to increased cortisol levels in humans. Increased cortisol has many somatic effects, including increased insulin resistance, central redistribution of adiposity, increased blood pressure, and impaired immune response” (Girod & Brotman, 2004). “The SNS activates the adrenal medulla and the peripheral sympathetic nerves, leading to increased circulating levels of catecholamines (mainly epinephrine and norepinephrine, respectively), which increase insulin resistance, blood pressure, and heart rate as well as drive systemic inflammation by increasing interleukin-6 and C-reactive protein] (Goebel, Mills, Irwin, & Ziegler, 2000). Sympathetic nervous system and HPA axis activity can both lead to endothelial dysfunction” (Mangos, et al., 2000).

“Cardiovascular responses to stress are exquisitely coordinated and functional up to a point. When the stressor continues or when the patient continues imposing the stressor through brooding, there are adverse effects on the heart. From all of these studies there are extensive data concerning stressors’ contributions to diverse pathophysiological changes including sudden death, myocardial infarction, myocardial ischemia, and wall motion abnormalities, as well as to alterations in cardiac regulation as indexed by changes in sympathetic nervous system activity and haemostasis" (Deanfield et al. 1984, von Känel et al. 2001). "Several studies have shown that laboratory modelled mental stress is an effective trigger of myocardial ischaemia in patients with coronary artery disease" (Jennings and Follansbee 1985; Specchia et al. 1984). "There is compelling evidence that mental stress provokes myocardial ischaemia, with concordance of perfusion defects and wall motion abnormality during mental stress and exercise" (Deanfield, Shea, & Kensett, 1984).

The uncontrolled spread of coronavirus disease (COVID-19) has called for unprecedented measures, to the extent that most countries have imposed several measures to curb the blowout of the virus. Those measures include placing people in an isolation place, minimising the movement and social distancing. The implementation of the measures had a huge impact and caused considerable psychological stress. "The prevalence of both stress-related psychological conditions and cardiovascular disease (CVD) is high in many countries. In addition to traditional risk factors, there is evidence that elements of the modern city lifestyle may confer risk for CVD. Although these lifestyle factors are not well-defined and may also be related to healthcare provision, there is evidence for synergy between stress-related psychological conditions and the development of vascular disease, suggesting that stress is an independent risk factor" (Scott, de Jonge, & Alonso, 2013). "Mental stress–induced myocardial ischemia has strong clinical and prognostic similarities to exercise- or pharmacology-induced myocardial ischemia during standard cardiac testing" (Peix, Trapaga, & Asen, 2006).

5. CONCLUSION

The relationship between the way in which the pandemic may lead to stress, which can trigger the development of cardiovascular disease. Also, the ways in which the pandemic itself can affect the normal functioning of the heart are of paramount importance. The existing literature has shown that the previously encountered different forms of pandemic have led to the massive development of new cases of cardiovascular disease. It is also known that different forms of psychological stress can lead to the abnormal physiological functioning of the human heart. Therefore, though a good portion of these patients already had underlying health issues involving the heart, like heart disease or high blood pressure, many otherwise healthy patients have also developed heart problems, including blood vessel injuries, blood clots, arrhythmia, strokes, and heart attacks. Whereby lung injury and acute respiratory distress syndrome must also take centre stage as the most dreaded complications of a respiratory pandemic. Yet, a number of those infected develop heart-related problems either out of the blue or as a complication of pre-existing cardiac disease. First, people with pre-existing heart disease are at a greater risk for severe cardiovascular and respiratory complications from severe respiratory disease. Second, people with previously undiagnosed heart disease may be presenting with previously silent cardiac symptoms unmasked by the viral infection. In people with existing heart-vessel blockages, infection, fever, and inflammation can destabilise previously asymptomatic fatty plaques inside the heart vessels. Fever and inflammation also render the blood more prone to clotting, while also interfering with the body's ability to dissolve clots. At the moment, people with heart problems are ignored during the fight against the coronavirus.

6. IMPLICATIONS OF THE RESULTS

Therefore, further research needs to be conducted to be able to identify the potential sick people with heart problems.

DISCLAIMER (ARTIFICIAL INTELLIGENCE)

Authors Matome M. Sekhotha, Tlou R Senosha and Maropeng R Ntsoane, we hereby declare that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc) and text-to-image generators have been used during writing or editing of this manuscript.

ETHICAL APPROVAL

The study did not require any ethical approval.

CONSENT

It is not applicable.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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APPENDIX I

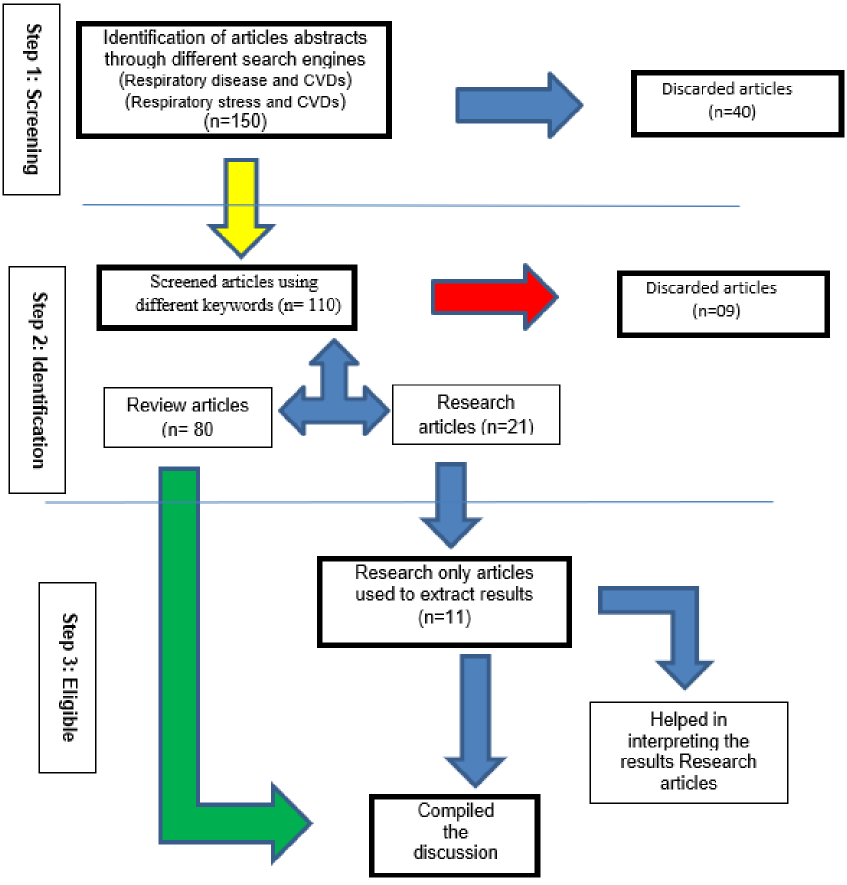

Fig. 1. Flow diagram to illustrate the searching strategy

APPENDIX II

Table 5. Completed Downs and Black

Item	Criteria	Answers
	Reporting	
1	Is the aim/objective of the study clearly described?	Yes = 1
2	Are the main outcomes to be measured clearly described in the Introduction or Methods section? If the main outcomes are first mentioned in the Results section, the question should be answered “no”.	Yes = 1
3	Are the characteristics of the patients included in the study clearly described? In cohort studies and trials, inclusion and/or exclusion criteria should be given. In case-control studies, a case definition and the source for controls should be given.	Yes = 1
4	Are the interventions of interest clearly described? Treatments and placebo (where relevant) that are to be compared should be clearly described.	No = 0
5	Are the distributions of principal confounders in each group of subjects to be compared clearly described? A list of principal confounders is provided [a].	Partially = 1
6	Are the main findings of the study clearly described? Simple outcome data (including denominators and numerators) should be reported for all major findings so that the reader can check the major analyses and conclusions. (This question does not cover statistical tests, which are considered below.)	Yes = 1
	Reporting	
7	*Does the study provide estimates of the random variability in the data for the main outcomes?* In non-normally distributed data, the interquartile range of results should be reported. In normally distributed data, the standard error, standard deviation or confidence intervals should be reported. If the distribution of the data is not described, it must be assumed that the estimates used were appropriate and the question should be answered yes[b].	No = 0
8	*Have all important adverse events that may be a consequence of the intervention been reported?* This should be answered yes if the study demonstrates that there was a comprehensive attempt to measure adverse events. (A list of possible adverse events is provided).	No = 0
	Have the characteristics of patients lost to follow-up been described?	No = 0

Item	Criteria	Answers
9	This should be answered "yes" where there were no losses to follow-up or where losses to follow-up were so small that findings would be unaffected by their inclusion. This should be answered 'no' where a study does not report the number of patients lost to follow-up.	No = 0
10	*Have actual probability values been reported (e.g., 0.035 rather than <0.05) for the main outcomes except where the probability value is less than 0.001*[c]	No = 0
	External validity	
11	*Were the subjects asked to participate in the study representative of the entire population from which they were recruited?* The study must identify the source population for patients and describe how the patients were selected. Patients would be representative if they comprised the entire source population, an unselected sample of consecutive patients, or a random sample. Random sampling is only feasible where a list of all members of the relevant population exists. Where a study does not report the proportion of the source population from which the patients are derived, the question should be answered as unable to determine.	Unable to determine = 0
12	*Were those subjects who were prepared to participate representative of the entire population from which they were recruited?* The proportion of those asked who agreed should be stated. Validation that the sample was representative would include demonstrating that the distribution of the main confounding factors was the same in the study sample and the source population.	No = 0
13	*Were the staff, places, and facilities where the patients were treated, representative of the treatment the majority of patients receive?* For the question to be answered yes, the study should demonstrate that the intervention was representative of that in use in the source population. The question should be answered no if, for example, the intervention was undertaken in a specialist centre unrepresentative of the hospitals that most of the source population would attend.	No = 0
	Internal validity – bias	
14	*Was an attempt made to blind study subjects to the intervention they have received?* For studies where the patients would have no way of knowing which intervention they received, this should be answered "yes" [d].	Unable to determine = 0
15	*Was an attempt made to blind those measuring the main outcomes of the intervention?*	Unable to determine = 0

Item	Criteria	Answers
16	*If any of the results of the study were based on "data dredging", was this made clear?* Any analyses that had not been planned at the outset of the study should be clearly indicated. If no retrospective unplanned subgroup analyses were reported, then answer "yes".	Unable to determine = 0
17	*In trials and cohort studies, do the analyses adjust for different lengths of follow-up of patients, or in case-control studies, is the time period between the intervention and outcome the same for cases and controls?* Where follow-up was the same for all study patients, the answer should be "yes". If different lengths of follow-up were adjusted for by, for example, survival analysis, the answer should be yes. Studies where differences in follow-up are ignored should be answered "no".	Unable to determine = 0
18	*Were the statistical tests used to assess the main outcomes appropriate?* The statistical techniques used must be appropriate to the data. For example, nonparametric methods should be used for small sample sizes. Where little statistical analysis has been undertaken but where there is no evidence of bias, the question should be answered yes. If the distribution of the data (normal or not) is not described, it must be assumed that the estimates used were appropriate, and the question should be answered "yes".	Unable to determine = 0
19	*Was compliance with the intervention/s reliable?* Where there was noncompliance with the allocated treatment or where there was contamination of one group, the question should be answered no. For studies where the effect of any misclassification was likely to bias any association to the null, the question should be answered "yes".	Unable to determine = 0
20	*Were the main outcome measures used accurate (valid and reliable)?* For studies where the outcome measures are clearly described, the question should be answered yes. For studies which refer to other work or that demonstrates the outcome measures are accurate, the question should be answered as "yes".	Unable to determine = 0
	Internal validity – confounding (selection bias)	
21	*Were the patients in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited from the same population?* For example, patients for all comparison groups should be selected from the same hospital. The question should be answered, unable to determine for cohort and case-control studies where there is no information concerning the source of patients included in the study[d].	Unable to determine = 0

Item	Criteria	Answers
22	*Were study subjects in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited over the same period of time?* For a study which does not specify the time period over which patients were recruited, the question should be answered as unable to determine[d].	Unable to determine = 0
23	*Were study subjects randomised to intervention groups?* Studies which state that subjects were randomised should be answered yes, except where the method of randomisation would not ensure random allocation. For example, alternate allocation would score no because it is predictable[d].	Unable to determine = 0
24	*Was the randomised intervention assignment concealed from both patients and health care staff until recruitment was complete and irrevocable?[d]* All nonrandomized studies should be answered no. If the assignment was concealed from patients but not from staff, it should be answered "no".	Unable to determine = 0
25	*Was there adequate adjustment for confounding in the analyses from which the main findings were drawn?* This question should be answered no for trials if: the main conclusions of the study were based on analyses of treatment rather than intention to treat; the distribution of known confounders in the different treatment groups was not described; or the distribution of known confounders differed between the treatment groups but was not taken into account in the analyses. In non-randomised studies, if the effect of the main confounders was not investigated or confounding was demonstrated but no adjustment was made in the final analyses, the question should be answered as no.[d]	Unable to determine = 0
26	*Were losses of patients to follow-up taken into account?* If the numbers of patients lost to follow-up are not reported, the question should be answered as unable to determine. If the proportion lost to follow-up was too small to affect the main findings, the question should be answered yes.	No = 0
	Power	
27*	*Was a power analysis performed?[d]*	No = 0

[*]Modified from the original form published by Downs and Black

[a] Sex, age, hypertrophic lesions, Fitzpatrick skin phototype, and previous treatments were considered principal confounders that should be reported in both controlled and uncontrolled studies

[b] Studies wherein all individual outcome scores have been reported but not variability parameters the item was answered yes (because variability parameters can be derived retrospectively)

[C] Item was answered 'yes' when no statistical tests were performed

[d] Item number 14, 15, 21-25, and 27

APPENDIX III

Table 6. PRISMA guideline

Section and Topic	Item #	Checklist item	Location where item is reported
		Title	
Title	1	Identify the report as a systematic review.	Pg1
		Abstract	
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	Pg 1
		Introduction	
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	Pg 1- 2
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	Pg 2
		Methods	
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	Pg2
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	Pg 3
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Pg 4
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	Pg 4
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	Pg 4

Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	Pg 4
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	Pg 4
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	Pg 4
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	N/A
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	N/A
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	N/A
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	Pg 5
	13d	Describe any methods used to synthesise results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	N/A
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	N/A
	13f	Describe any sensitivity analyses conducted to assess the robustness of the synthesised results.	N/A
Reporting bias assessment	14	Describe any methods used to assess the risk of bias due to missing results in a synthesis (arising from reporting biases).	Pg 5
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	N/A

		Results	
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	Pg 4
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	N/A
Study characteristics	17	Cite each included study and present its characteristics.	N/A
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	N/A
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	Pg 6- 9
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	N/A
	20b	Present the results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	Pg 6 - 9
	20c	Present the results of all investigations of possible causes of heterogeneity among study results.	N/A
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesised results.	N/A
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	N/A
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	N/A
		Discussion	
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	Pg -10-13
	23b	Discuss any limitations of the evidence included in the review.	
	23c	Discuss any limitations of the review processes used.	
	23d	Discuss implications of the results for practice, policy, and future research.	

		Other Information	
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	N/A
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	N/A
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	N/A
NSupport	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	None
Competing interests	26	Declare any competing interests of review authors.	None
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	N/A

Peer-Review History:
This chapter was reviewed by following the Advanced Open Peer Review policy. This chapter was thoroughly checked to prevent plagiarism. As per editorial policy, a minimum of two peer-reviewers reviewed the manuscript. After review and revision of the manuscript, the Book Editor approved the manuscript for final publication. Peer review comments, comments of the editor(s), etc. are available here: https://peerreviewarchive.com/review-history/5511

Chapter 3

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A Review of Key Considerations for Rice (*Oryza sativa*) Fortification with Essential Micronutrients in Public Health Intervention

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ABSTRACT

Rice (*Oryza sativa* L.) is the most popular staple food grain and an important source of fibre, energy, minerals, vitamins, and other biomolecules. Fortification of staple foods and commonly used condiments with vitamins and minerals has been considered one of the most cost-effective interventions to prevent and control micronutrient deficiencies. Because of its wide local consumption, acceptability, reach, and quantum of consumption, rice (*Oryza sativa*) far exceeds the requirements of a staple food vehicle that can be considered for fortification purposes at a population-level intervention. The World Health Organisation (WHO) has the mandate to develop evidence-informed guidelines for the fortification of staple foods as a public health intervention, including rice fortification with micronutrients. The WHO, in collaboration with the Global

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Alliance for Improved Nutrition (GAIN), convened a consultation on “Technical Considerations for Rice Fortification in Public Health” in Geneva, Switzerland, in 2012 to provide technical inputs to the guideline development process, particularly concerning feasibility and implementability. The objective of this study is to review the industrial and regulatory technical considerations in rice fortification, as well as the considerations for implementing it as a public health strategy and assuring equitable access and universal coverage. Key challenges, including micronutrient stability, regional cooking preferences, economic feasibility, and policy integration, are discussed, along with research priorities to support effective scale-up. Overall, rice fortification is a promising strategy for countries in which rice is a food staple. Decisions regarding which nutrients to add and in which amounts must be guided by the nutritional needs of the population, the rice consumption profile of the target groups, existing nutrition programs and their coverage (supplementation, fortification, and others), and available delivery platforms.

Keywords: Fortification; micronutrients; behaviour change communication; quality control; quality assurance.

1. INTRODUCTION

Background and Rationale: Fortification is the practice of deliberately increasing the content of essential micronutrients, such as vitamins and minerals, in food, seasonings, or condiments, so as to improve their nutritional quality (Giasuddin et al., 2020). This is a proven, safe and cost-effective strategy for improving diets and for the prevention and control of micronutrient deficiencies (Olson et al., 2021; Das et al., 2013). Because of its wide local consumption, acceptability, reach, and quantum of consumption, rice (*Oryza sativa*) far exceeds the requirements for adoption as a staple food vehicle for food fortification for the purposes of a population-level intervention (Allen et al., 2006; Moench-Pfanner et al., 2012). In fact, five countries currently have legislation to fortify this cereal, and many more are interested in doing so. Fortifying rice with micronutrients is an effective strategy for addressing nutritional imbalances in post-harvest rice (Liu et al., 2025). Nutrient-fortified rice was first developed in the Philippines in 1948 and has since proven effective in preventing deficiencies of B vitamins, niacin, and iron (Fe). Over time, its adoption expanded across Asia (e.g., Japan, Sri Lanka), Latin America (e.g., Cuba, Colombia), and even certain U.S. states (Kumari & Roy, 2025). As rice differs from other fortified food staples, such as maize or wheat, in that the grain is fortified directly rather than the subproducts. (e.g., flour or porridge), Meeting such a mandate still entails overcoming some technological and technical barriers (Giasuddin et al., 2020). Three main methods to fortify rice have been described to date: dusting, coating, and extrusion, which could be cold, warm, or hot (Food Fortification Initiative, 2019; Steiger et al., 2014).

Rice (*Oryza sativa*) is the most staple cereal component that sustains two-thirds of the world population. The chief livelihood of human beings abundantly relies on rice due to their sovereignty nutritive properties and energy value (Sen et al., 2020). Rice is a highly culturally sensitive commodity. Growing, selecting, and cooking rice grains are subject to regional, national, and even local preferences, which in turn affect, to different degrees, the micronutrient retention and the final amount of vitamins and minerals that will be consumed (Giasuddin et al., 2020). A pending assignment in this area is to generate more data on the efficacy of this intervention in different contexts and for different nutrients, and, furthermore, on its cost-effectiveness as a public health intervention implemented at sub-national or national scale (Steiger et al., 2014; Peña-Rosas et al., 2012).

The World Health Organisation (WHO) is updating several evidence-informed guidelines for the fortification of staple foods as a public health intervention, including the fortification of rice with iron and other micronutrients. The WHO, in collaboration with the Global Alliance for Improved Nutrition (GAIN), convened a consultation on Technical Considerations for Rice Fortification in Public Health in Geneva, Switzerland, on October 9-10, 2012, to provide additional technical inputs to the guideline-development process, particularly in terms of feasibility and implementability (Giasuddin et al., 2020). The objective of this consultation was to review the industrial and regulatory technical considerations in rice fortification, as well as the considerations for implementing it as a public health strategy and assuring equitable access and universal coverage (Peña-Rosas et al., 2012).

2. RICE PRODUCTION AND CONSUMPTION

Rice is the staple food for an estimated 3.5 billion people, making it the world’s most consumed cereal after wheat. Rice milling removes B vitamins and minerals found in the outer germ and bran layers (Giasuddin et al., 2020). Twelve countries in Asia account for 90% of the world’s total production. Rice is mostly eaten in the same country where it is produced; therefore, the amount of rice that is traded internationally is small (Peña-Rosas et al., 2012).

2.1 Industrial Processing Worldwide and Fortification Technologies for Rice

Type, production, nutrient losses and contents, industrial processes, extraction rate, and the implications for fortification were considered. Various processing methods are used in the food industry to manufacture rice products with desirable sensory quality on the basis of cultural and cooking preferences and nutritional considerations (Giasuddin et al., 2020). The processes result in changes in the nutrient contents, stabilities, and retentions depending on the rice variety and the original nutritional quality (Atungulu & Pan, 2014). Currently used technologies include coating, dusting, and the various extrusion technologies. The main focus is on cold, warm, and hot extrusion technologies, including process flow, required facilities and sizes of operation. The advantages and disadvantages of the various processing methods, including micronutrients, with respect to their technical feasibility during processing, storage, washing, and various cooking methods and their physiological importance must be kept in mind (Steiger et al., 2014).

2.2 Stability and Retention of Micronutrients in Fortified Rice

Some investigators described some of their original work in assessing micronutrient retention in rice with different cooking processes (Giasuddin et al., 2020). Differences in the production of rice premix affect the final amount of micronutrients consumed. Their study investigated the retention of vitamin A, iron, zinc, vitamin B12, and folic acid in six different rice premixes, used to prepare fortified rice cooked in five different ways. Considering retention and losses in cooking methods is important when planning a program and setting expectations on the nutritional impact on the target populations (Giasuddin et al., 2020). Rice used in different regions in the world seems not to lead to a loss of most micronutrients with the exception of vitamin A. Factors involved in protecting vitamin A against losses during the cooking of the rice need to be identified (Wieringa et al., 2014).

2.3 Models for Estimating Nutrient Fortification Levels in Rice

While different approaches can be used to estimate safe and efficacious amounts of key fortificants in rice and considerations in relation to stability, bioavailability, cost and diet given, the proposed use of WHO/FAO food fortification guidelines to decide which micronutrients to add and at what level (Giasuddin et al., 2020). For rice fortification in public health, some investigators' rationale was to use iron, folic acid, vitamin B12, vitamin A, and zinc, at the same levels recommended for flours, but adding thiamin, vitamin B6 and niacin in order to cover the estimated average requirement for adults. It was argued that economic sustainability must be built into the entire supply chain and distribution network and suggested to adopt the experiences and lessons learned from rice fortification experiences of Costa Rica and the Philippines (de Pee, 2014; Van et al., 2014; World Health Organisation, 2019).

2.4 Economic Feasibility of Industrially Fortified Rice in Different Contexts

The financial issues related to the implementation of rice-fortification programmes must be considered based on existing facilities, production, and considerations for the implementation of fortified rice in countries with different levels of market development (Giasuddin et al., 2020). Using the World Food Programme's pilot countries as sample cases, core cost elements included in the production of fortified rice kernels, transportation to the point of blending, blending of fortified with non-fortified rice, and quality control (QC) and quality assurance (QA), among other issues, were described. In the early stages of implementation, implementers of the rice-fortification programme may face unforeseen additional costs related to the initiation of rice fortification (World Health Organisation, 2019; Forsman et al., 2014; Roks, 2014).

3. CONSIDERATIONS FOR RICE FORTIFICATION IN PUBLIC HEALTH

3.1 Legislation and Policies

It is essential to explain the compatibility between the World Trade Organisation (WTO) trade regulation and fortification legislation to national policymakers, so as not to delay the process of potential development of technical standards and mandatory legislation. The principles of the WTO can be found in the General Agreement on Tariffs and Trade (GATT). According to them, there should not be any discrimination between trading partners, nor between imported and locally produced goods. Have countries to prove that the health measure is necessary and effective and that it does not represent an arbitrary discrimination (Giasuddin et al., 2020). In order to comply with such regulations, it may be required to build on the data from different food and nutrition national surveys conducted in a representative sample of the population to identify the groups at risk of micronutrient deficiencies and their dietary intake, the availability of other fortified products and nutrition interventions aimed at improving the micronutrient intake and the use of rice for derivative products such as rice flour (The General Agreement on Tariffs and Trade [GATT], 1947).

A deep understanding of the regulatory environment and possible barriers to trade, such as having a set of requirements not aligned to international standards, is critical when deciding on rice fortification Programs as a public health intervention. Standards need to list technical considerations, have broad stakeholder engagement, and keep in mind other fortification programs and nutrition interventions occurring simultaneously in the country. Countries implementing a fortification program may need support to capacitate technical staff of the regulatory agencies on this novel intervention to assure a high-quality, safe, and effective product that is acceptable to the consumer. Other staple foods, such as wheat flour, vegetable oil, sugar, salt, and condiments, are also increasingly being fortified with various micronutrients (The General Agreement on Tariffs and Trade [GATT], 1947; WK Kellogg Foundation, 2004; De-Regil et al., 2014).

Before legislating a desirable premix composition, it is therefore essential to have a holistic picture of every current or potential fortification and supplementation programme to avoid any micronutrient intake above the upper level tolerable limit for each vulnerable group consuming the fortified foods, particularly children (Giasuddin et al., 2020). An additional consideration in this area is that the financial burden of fortification (mainly the fortificant) could and is usually divided among multiple food vehicles (The General Agreement on Tariffs and Trade [GATT], 1947; WK Kellogg Foundation, 2004).

3.2 Quality Control (QC) and Quality Assurance (QA) of Fortified Rice

The enactment of national standards and/or mandatory legislation on its own is not sufficient and requires a well-designed monitoring system for quality control and assurance. Enforcement is the most critical, and this is not only for rice but also for all fortification programs of staple foods in public health. QA refers to the implementation of planned and systematic activities necessary to ensure that products or services meet quality standards. In the case of fortified rice produced locally, these activities may require assessment of kernels, premix, and final product. Separate requirements for the different technologies may be needed, as the operational procedures for one method may not be applicable to others. QC refers to the techniques and assessments used to document compliance of the product with established technical standards through the use of objective and measurable indicators (Giasuddin et al., 2020). This may include the development of semi-quantitative or quantitative rapid test kits for the premix, as well as some fortified rice and the cooked rice (as it has already been developed for other fortification strategies). Once developed, support to countries implementing the fortification program will be needed to ensure that technical staff of the regulatory agencies is able to perform those tests and hence assure a high-quality, safe, and effective product that is acceptable to the consumer (Allen et al., 2006; Moench-Pfanner et al., 2012; World Health Organization, 2019).

3.3 Behaviour-Change Communication

Strategies for behavior change communication can help to (1) understand knowledge of and attitudes toward fortification of this staple food from different quarters involved in the fortification program, not only from consumers; (2) identify crucial success factors and opportunities for the program; (3) choose best appropriate delivery channels according to target groups; (4) generate demand from different sectors; and (5) communicate other nutritional aspects related to rice fortification, e.g. household storing and use of rice. The establishment of a behaviour-change intervention requires proper planning and budgeting to ensure there is an effect in a sustained manner (De-Regil et al., 2014).

3.4 Programme Monitoring and Evaluation

Assuring effective monitoring of the implementation of the programme in its early stages and as it scales up is essential to assess whether good coverage and adherence to the intervention are achieved. The decision of whether to implement an evaluation, either an impact evaluation or another type, depends upon many factors and is context-specific (Giasuddin et al., 2020). It needs to be complemented with a logical framework and an indicators matrix. Monitoring indicators for measuring the potential of rice fortification to prevent micronutrient deficiencies and therefore increase the intake of nutrients should include (1) ongoing internal and external QC of the fortified rice available on the market, (2) coverage of the fortified rice, and (3) estimation of the daily consumption by target groups. There are several resources developed for other micronutrient interventions that can be adapted in a rice-fortification program (WK Kellogg Foundation, 2004).

3.5 Research Priorities on Rice Fortification

The key areas of research priorities for implementation to scaling up of rice fortification as a public health strategy were identified as the following: (i) stability of different micronutrients and compounds in different cooking processes that are context specific; (ii) relative bioavailability among different chemical forms of various micronutrients that can be used in rice fortification, including nutrient-nutrient interactions; (iii) acceptability of changes, if any, in organoleptic characteristics with different micronutrient combinations on different fortified rice preparations and cooking methods; (iv) effects of different phytate contents on the absorption of iron from the premix formulation; (v) most appropriate delivery platforms for reaching the intended target population; and (vi) effectiveness of different methods of fortification for rice in different contexts (World Health Organization, 2019; WK Kellogg Foundation, 2004; Tsang et al., 2016).

4. CONCLUSIONS

There is no single best model appropriate to increase the micronutrient intakes for all population segments, and strategies should not be mutually exclusive (Giasuddin et al., 2020). It is imperative to combine different approaches to be able to penetrate most segments, if not all, of the population, especially in countries where large sections of the population have relatively limited access to a nutritious and diverse diet. Rice fortification is a promising strategy for countries in which rice is a food staple. Decisions about which nutrients to add and in which amounts must be guided by the nutritional needs of the population, the rice consumption profile of the target groups, other programs already in place and their coverage (supplementation, fortification, and others) and the existence of proper delivery platforms. Behaviour communication campaigns to generate demand and drive the development of appropriate policies are also needed. The governments or any agencies may make decisions on whether the use of locally or imported fortified rice is a feasible option to improve the diet and nutritional status of populations where vitamin and mineral deficiencies are still prevalent (Giasuddin et al., 2020).

DISCLAIMER (ARTIFICIAL INTELLIGENCE)

Author(s) hereby declare that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc) and text-to-image generators have been used during writing or editing of this manuscript.

CONSENT AND ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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An Overview of Therapeutic Options between Proton Pump Inhibitors (PPI) and Fundoplication in Gastroesophageal Reflux Disease (GERD) Management

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ABSTRACT

Introduction: Gastroesophageal reflux disease (GERD) is a prevalent, chronic condition characterised by the retrograde flow of gastric contents into the oesophagus, resulting in symptoms such as heartburn, regurgitation, and chest discomfort. The disease imposes a substantial burden on healthcare systems and significantly affects patients' quality of life. First-line therapy for GERD typically includes lifestyle modifications and acid suppression with proton pump inhibitors (PPIs). While PPIs are effective in the majority of patients, a significant proportion report persistent symptoms or develop concerns about long-term use, including risks of nutrient malabsorption, renal complications, and infections. Surgical options, particularly laparoscopic Nissen fundoplication, provide symptomatic relief but carry the potential for adverse outcomes such as dysphagia, gas bloat, and surgical failure over time.
Aim: This review aimed to clarify the role of Stretta, transoral incisionless fundoplication (TIF), endoscopic full-thickness plication (EFTP), LINX® magnetic sphincter augmentation system, laparoscopic electrical stimulation (EndoStim®), and the RefluxStop™ implant in modern GERD management and define their potential in bridging the gap between conservative and surgical therapies.

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Methods: This review evaluated current data on the emerging therapies, as well as techniques such as endoscopic mucosal resection and ablation seek to augment the anti-reflux barrier through mucosal remodelling.
Results: Evidence from multiple clinical studies and meta-analyses supports Stretta's role in improving GERD-related quality of life, reducing oesophageal acid exposure, and, in many cases, lowering dependence on proton pump inhibitors. Moreover, both TIF and EFTP offer significant benefits as less invasive alternatives to traditional GERD surgery, with the potential for improved patient outcomes and quicker recovery times. While TIF is less invasive and focuses on reshaping the gastroesophageal junction to restore LES function, EFTP offers a more robust structural intervention, which may be preferable in patients with more severe GERD. As these therapies continue to evolve, understanding their efficacy, safety, and appropriate indications is critical. Minimally invasive and endoscopic therapies represent a significant advancement in the treatment of GERD, offering alternatives to conventional pharmacologic and surgical strategies. While data supporting these interventions are promising, particularly in terms of symptom relief and reduced acid exposure, most studies to date are limited by short follow-up periods, heterogeneity in study design, and variability in patient selection. Stretta, TIF, and EFTP show utility in enhancing lower oesophagal sphincter function with a favourable safety profile, particularly in patients with mild to moderate disease. Similarly, device-based interventions such as LINX® and EndoStim® offer innovative mechanisms of action with growing clinical support. More recently, anatomical solutions like the RefluxStop™ implant and endoscopic mucosal remodelling have opened new avenues for intervention, though they remain in earlier stages of evaluation.
Conclusion: In conclusion, while emerging GERD therapies do not yet replace conventional treatment, they significantly expand the therapeutic toolkit. Collaboration between gastroenterologists, surgeons, and patients is essential to select the most appropriate treatment strategy, balancing innovation with evidence-based care. With ongoing refinement and validation, these approaches have the potential to address unmet needs and reshape the standard of care for GERD. Future directions should focus on long-term outcomes, head-to-head comparative trials, and defining patient subgroups most likely to benefit from each therapy. Importantly, successful GERD management increasingly depends on a multidisciplinary approach that incorporates patient-specific factors such as motility patterns, anatomical features, symptom phenotype, and treatment preferences.

Keywords: Gastroesophageal reflux; endoscopy; laparoscopy; transoral procedures.

1. INTRODUCTION

Gastroesophageal reflux disease (GERD) is a chronic and highly prevalent condition affecting millions worldwide. At some point, about half of all individuals will report reflux symptoms (Chhabra & Ingole, 2022). It is characterised by the retrograde movement of gastric contents into the oesophagus, leading to symptoms such as heartburn, regurgitation, chest discomfort, and, in some cases, extra-oesophagal manifestations like chronic cough or laryngitis. These symptoms can significantly impair patients' quality of life and, when inadequately treated, may progress to complications such as erosive esophagitis, Barrett's oesophagus, and oesophagal adenocarcinoma (Vakil et al., 2006). The incidence of GERD is high in the general population; it is estimated to affect up to 20% of the population worldwide. Nowadays, GERD is found to be the most common diagnosis made in a gastroenterology practice (Boulton & Dettmar, 2022; Hoerter et al., 2023). Many individuals with GERD are asymptomatic, including those with Barrett's oesophagus. Furthermore, assessing GERD based on objective testing such as endoscopy and pH testing in population-based studies is impractical (Loganathan et al., 2024).

The cornerstone of GERD management has traditionally been pharmacologic therapy, particularly proton pump inhibitors (PPIs), which effectively reduce gastric acid secretion and provide symptomatic relief for the majority of patients (Lee & Chang, 2022; Noar & Lotfi-Emran, 2007). However, concerns have been raised regarding long-term PPI use, including risks of nutrient deficiencies, renal disease, infections, and rebound acid hypersecretion upon discontinuation. Treatment with PPIs is less effective in approximately 30%–40 % of patients, and minimally invasive anti-reflux therapy may be a better option for these patients (Sui et al., 2024). As such, clinicians and researchers have increasingly sought alternatives that reduce reliance on chronic medication use (Reymunde & Santiago, 2007).

Surgical intervention, most commonly laparoscopic Nissen fundoplication, has demonstrated long-term efficacy in symptom control and oesophagal acid normalisation. However, this procedure is typically reserved for patients with severe or refractory GERD due to its invasive nature and the risk of postoperative side effects such as dysphagia, gas-bloat syndrome, and inability to belch or vomit (Lee et al., 2023; Schwameis et al., 2017). These limitations have prompted the development of a range of minimally invasive therapeutic strategies that aim to offer symptom relief and acid control without the need for lifelong medication or the risks of traditional surgery.

This review examines the evolving landscape of GERD treatment, focusing on therapeutic modalities that occupy the middle ground between medical therapy and surgical fundoplication (Rosen et al.,2025). Specifically, we explore emerging minimally invasive procedures—including both endoscopic and laparoscopic techniques—that aim to restore or enhance the function of the lower oesophagal sphincter (LES), reduce reflux, and improve patient outcomes with a more favourable safety profile.

Across the studies referenced in this review, diagnostic work-up typically included upper gastrointestinal endoscopy and oesophagal high-resolution manometry as essential components of pre-treatment assessment (Rosen et al.,2025). These investigations were instrumental in determining patient suitability for the various interventions and in identifying anatomical and functional abnormalities of the gastroesophageal junction (Katz et al.,2022).

The new interventional strategies discussed in this paper can be broadly categorised into endoscopic and laparoscopic approaches. These include modalities such as transoral incisionless fundoplication (TIF), endoscopic full-thickness plication (EFTP), radiofrequency ablation (Stretta), magnetic sphincter augmentation (LINX®), laparoscopic electrical stimulation (EndoStim®), and the more recent RefluxStop™ implant. By examining the clinical evidence supporting these interventions, this review aims to clarify their role in modern GERD management and define their potential in bridging the gap between conservative and surgical therapies (Table 1).

Table 1. Approaches for new strategies

Endoscopic methods	**Radiofrequency (STRETTA)**
	Transoral (incisionless) fundoplication
	Endoscopic full-thickness plication
	Transoral antegrade suturing
	Mucosal resection/ablation
Laparoscopic methods	Magnetic ring (LINXX)
	Endostim
Combined endoscopic/ laparoscopic method	Transoral fundoplication + laparoscopic hiatoplasty

2. STRETTA THERAPY: RADIOFREQUENCY ABLATION FOR THE LOWER ESOPHAGEAL SPHINCTER (LES)

The Stretta procedure has emerged as a noteworthy innovation in the treatment of GERD, particularly for patients who are inadequately controlled on pharmacotherapy or prefer to avoid surgical intervention (Arts et al., 2012).

Corley et al. 2003; Dughera et al. (2011, 2014). Evidence from multiple clinical studies and meta-analyses supports Stretta's role in improving GERD-related quality of life, reducing oesophagal acid exposure, and in many cases, lowering dependence on proton pump inhibitors. Longitudinal data further reinforce the durability of these benefits, with follow-up studies documenting sustained symptom relief and medication reduction for up to eight years post-procedure (Triadafilopoulos et.al, 2002, 2003).

Mechanistically, Stretta appears to exert multifactorial effects—ranging from subtle tissue remodelling to modulation of LES neuromuscular function—that collectively contribute to improved antireflux barrier integrity (Coron et al. 2008, Liu et al, 2011). Findings from animal models have also supported its influence on TLESRs and LES pressure, providing a plausible physiological basis for the observed clinical improvements (Kim et al.,2003; Utley et al., 2000). Nonetheless, scepticism remains. Some systematic reviews have challenged the robustness of Stretta's therapeutic impact, particularly when compared to sham treatments (Perry et al., 2012). Concerns centre around the lack of consistent changes in objective physiological parameters such as LES pressure or acid exposure time, as well as variability in patient-reported outcomes (Wolfsen et al., 2002). Furthermore, major gastroenterology societies, including the American College of Gastroenterology, have expressed caution regarding the routine use of Stretta, citing insufficient evidence for its widespread recommendation (Lipka et al. 2015).

In conclusion, while Stretta may not yet represent a universal solution for all GERD patients, it serves as a valuable option in selected cases, especially for those with persistent symptoms despite medication, or those seeking a less invasive alternative to surgery. Future studies focusing on better patient selection, standardised protocols, and long-term comparative effectiveness will be essential to more clearly define Stretta's role within the broader GERD treatment algorithm.

3. TRANSCORAL INCISIONLESS FUNDOPLICATION (TIF) AND ENDOSCOPIC FULL-THICKNESS PLICATION (EFTP)

Transoral incisionless fundoplication (TIF) and endoscopic full-thickness plication (EFTP) are innovative endoscopic procedures designed to treat gastroesophageal reflux disease (GERD) (Rosen et al.,2025). While both techniques aim to address the underlying issues associated with GERD, such as dysfunction of the lower oesophagal sphincter (LES) and gastroesophageal junction (GEJ) abnormalities, they differ significantly in terms of procedural approaches, techniques, target anatomy, and goals of treatment.

3.1 Procedure Technique

- **Transoral Incisionless Fundoplication (TIF):** TIF is a minimally invasive endoscopic procedure typically performed using the EsophyX device (Endogastric Solutions, Merit Medical, UT, USA). The device employs a series of fasteners to create folds in the stomach wall at the gastroesophageal junction (GEJ) (Rosen et al.,2025). This process aims to reconstruct the valve-like function of the LES, thus strengthening the anti-reflux barrier. The goal of TIF is to restore proper LES function by creating a 270–300° wrap, also known as a partial fundoplication. The procedure is less invasive than traditional laparoscopic fundoplication surgery, as it avoids external incisions and significantly reduces recovery time. TIF is particularly appealing to patients who seek a less invasive option with minimal disruption to the anatomy.
- **Endoscopic Full-Thickness Plication (EFTP):** EFTP, by contrast, uses a technique involving transmural sutures that pass through the entire thickness of the stomach wall. This method creates a more robust structural alteration compared to TIF, as it secures the applications deeper into the tissue layers, effectively enhancing the function of the LES and reinforcing the gastroesophageal junction. The procedure is typically performed using the GERDx™ system (G-SURG GmbH, Seeon-Seebruck, Germany), which is a next-generation, single-use device that succeeded the Plicator technology after its discontinuation. EFTP aims to create a more durable and stable anti-reflux barrier by placing sutures at strategic points along the gastroesophageal junction, making it a

potentially more effective solution for patients with more severe LES dysfunction.

3.2 Key Differences in Techniques and Goals

- **TIF** focuses on creating a valve-like structure at the gastroesophageal junction using tissue folds and fasteners. This approach is designed to mimic the natural function of the LES while being less invasive than traditional surgery.
- **EFTP** involves a more invasive technique, with sutures that penetrate the full thickness of the stomach wall (Rosen et al.,2025). This offers a more significant structural modification at the GEJ, potentially providing a more durable solution to GERD for patients with substantial reflux or significant LES dysfunction.

In conclusion, both TIF and EFTP offer significant benefits as less invasive alternatives to traditional GERD surgery, with the potential for improved patient outcomes and quicker recovery times. While TIF is less invasive and focuses on reshaping the gastroesophageal junction to restore LES function, EFTP offers a more robust structural intervention, which may be preferable in patients with more severe GERD. Both techniques, however, require further investigation to better understand their long-term efficacy, optimal patient selection, and potential complications. Nonetheless, these procedures represent promising options for individuals seeking effective treatment for GERD with fewer risks and faster recovery compared to conventional surgical interventions (Ihde et al., 2019).

4. EFFICACY AND SYMPTOM RELIEF

4.1 Transoral Incisionless Fundoplication (TIF)

The efficacy of transoral incisionless fundoplication (TIF) in treating gastroesophageal reflux disease (GERD) has been supported by multiple clinical studies, showcasing significant benefits in symptom relief, quality of life improvement, and reduction in dependence on proton pump inhibitors (PPIs). Numerous trials and studies have demonstrated TIF’s effectiveness in addressing GERD symptoms, with many patients experiencing lasting relief.

- **TEMPO Trial:** In the TEMPO trial, one of the most significant studies evaluating TIF, approximately 88% of patients were able to either eliminate or greatly reduce their PPI use one year following the procedure. This finding highlights the potential for TIF to reduce long-term medication dependency, a common challenge for GERD patients who rely on PPIs for symptom management (Trad et al., 2015; Trad et al., 2018).
- **Meta-analysis by Gerson et al. (2018):** A meta-analysis by Gerson et al. analysed multiple randomised trials and confirmed the efficacy of TIF in improving GERD symptoms. The study found that 70–80% of patients experienced a significant reduction in heartburn and regurgitation compared

to those on medical therapy alone (Rosen et al.,2025). This reinforces the argument that TIF can be more effective than traditional medical treatments, particularly in managing these key symptoms of GERD (Gerson et al., 2018).

- **Hunter et al. Study:** Research by Hunter et al. showed that TIF led to a significant reduction in distal oesophagal acid exposure, with 85% of patients achieving normalised pH levels compared to only 12% in the PPI-treated group. Additionally, patients in the TIF group reported a substantial improvement in quality of life, indicating the broader benefits of the procedure beyond just symptom relief (Hunter et al., 2015).
- **Rinsma et al. Findings:** Rinsma et al. documented that TIF effectively increased lower oesophagal sphincter (LES) resting pressure, a critical factor in reducing reflux events (Rosen et al.,2025). Their findings demonstrated that TIF resulted in enhanced LES function and a significant decrease in reflux episodes, as evidenced by impedance-pH monitoring. This underscores TIF's potential to address the underlying mechanisms of GERD and provide lasting symptom relief (Rinsma et al., 2014).
- **Barnes et al. Satisfaction Rates:** Barnes et al. reported high patient satisfaction rates following TIF, with over 80% of participants indicating improvement in symptoms and quality of life. Furthermore, 67% of patients expressed satisfaction with their ability to stop or reduce their medication use after undergoing TIF, further supporting the long-term benefits of the procedure in managing GERD symptoms and reducing the reliance on pharmacological treatments (Barnes et al., 2011).
- **Bell et al. Study:** Another study by Bell et al. found that 76% of patients experienced clinically significant improvements in GERD symptoms following TIF. Patients also reported a marked improvement in their quality of life, highlighting the broader impact of the procedure beyond just symptom control (Bell et al., 2014).

4.2 Long-Term Efficacy

Long-term follow-up data from several studies have further demonstrated the durability and sustained effectiveness of TIF in managing GERD symptoms, offering patients lasting relief even years after the procedure.

- **Chimukangara et al. (2019) Cohort Study:** A longitudinal cohort study by Chimukangara et al. revealed that 74% of patients continued to experience symptom relief up to eight years after undergoing TIF. This finding suggests that TIF provides durable long-term benefits, offering continued relief and improved quality of life long after the initial procedure (Chimukangara et al., 2019).
- **Testoni et al. (2015) Study:** Testoni et al. documented sustained symptomatic relief and a decrease in PPI dependency in 65–75% of patients between three and ten years post-TIF. This underscores the procedure’s long-term effectiveness in managing GERD and reducing the

need for ongoing medication, even years after the intervention (Testoni et al., 2015).

- **TEMPO Trial (Five-Year Follow-up):** The TEMPO trial also provided valuable long-term data, showing a 72% reduction in regurgitation symptoms and a 67% reduction in extraesophageal symptoms at the five-year follow-up (Rosen et al.,2025). These findings highlight the lasting impact of TIF in improving both oesophagal and extraesophageal manifestations of GERD, such as chronic cough or asthma-like symptoms, which are often harder to treat with traditional therapies (Trad et al., 2018).

5. SAFETY

Transoral incisionless fundoplication (TIF) is generally regarded as a safe and minimally invasive procedure for the treatment of gastroesophageal reflux disease (GERD). However, as with any medical intervention, there are potential risks and complications that need to be considered. The literature provides detailed information on the types of complications that may occur, their frequency, and how they are typically managed.

- **Postoperative Pain:** Mild to moderate pain, including a sore throat, is a common side effect following TIF, particularly due to the use of the endoscopic device and the manipulation of the gastroesophageal junction. According to the TEMPO trial by Trad et al., around 40% of patients reported experiencing transient sore throat and abdominal discomfort after the procedure. These symptoms generally resolve within days to weeks without the need for further intervention (Trad et al., 2015).
- **Dysphagia (Difficulty Swallowing):** Dysphagia is one of the more commonly reported complications of TIF, with an incidence ranging from 3% to 8% of patients. A study by Bell et al. found that 4% of patients experienced post-procedure dysphagia, which typically resolved within a few weeks. However, in rare instances, dysphagia may persist, requiring additional treatment or even intervention to alleviate symptoms (Bell et al., 2014). This suggests that while dysphagia is usually transient, it can be a significant concern for some patients, particularly those with more sensitive oesophagal motility.
- **Postoperative Bloating and Flatulence:** Postoperative bloating and flatulence are common complaints after TIF, affecting approximately 15–20% of patients (Rosen et al.,2025). These symptoms are often linked to temporary alterations in gastric emptying or changes in the gastroesophageal junction’s anatomy following the procedure. Gerson et al. reported that around 17% of patients experienced bloating, which typically improved over time as the body adjusted to the changes made during the procedure (Gerson et al., 2018). While these symptoms can be uncomfortable, they are usually self-limiting and resolve with time.
- **Perforation:** Although rare, perforation remains a serious potential complication of TIF. The rate of oesophagal or gastric perforation is reported to be less than 0.5%, making it an infrequent but concerning event. In cases of perforation, patients typically require surgical intervention to repair the

damage. Fortunately, due to the precision of the TIF procedure and the use of advanced technology, perforations are uncommon (Gerson et al., 2018; Nguyen et al., 2021).

- **Minor Bleeding:** Minor bleeding is another complication that can occur in about 1–2% of TIF patients. In most cases, bleeding is self-limited and can be managed conservatively without the need for further surgical procedures. The TEMPO trial reported that 1.3% of patients experienced bleeding, which generally did not require additional interventions (Trad et al., 2015). This suggests that while minor bleeding can occur, it is typically manageable and does not often lead to more serious issues.

In conclusion, while TIF is generally safe, like all medical procedures, it carries some risk of complications. The most common issues include transient postoperative pain, dysphagia, bloating, and mild bleeding. These complications are typically short-lived and resolve with minimal intervention. Serious complications, such as perforation, are rare, but they can require more intensive treatment. Overall, the safety profile of TIF is favourable, especially when compared to traditional surgical options, and these risks should be discussed with patients as part of the decision-making process.

6. ENDOSCOPIC FULL-THICKNESS PLACEMENT (EFTP)

Endoscopic full-thickness plication (EFTP) has emerged as a promising alternative for the treatment of gastroesophageal reflux disease (GERD). Multiple studies have demonstrated its potential in providing significant symptom relief, improving quality of life, and reducing dependence on medications, positioning it as a viable option for patients who seek a less invasive treatment for GERD (Kaindlstorfer et al. 2013).

- **Efficacy and Symptom Relief:** A meta-analysis conducted by Gerson et al. reported that 60–70% of GERD patients experienced substantial symptom relief following EFTP. The study highlighted significant reductions in heartburn, regurgitation, and overall GERD-related symptoms within the first year of follow-up. These findings suggest that EFTP can effectively address the core symptoms of GERD, particularly in patients for whom medical therapy has proven inadequate or undesirable (Gerson et al., 2018).
- **Pleskow et al. (2007) Study:** Pleskow et al. observed that nearly 80% of patients showed a reduction in GERD symptoms six months following EFTP. This study further reinforces the effectiveness of the procedure in providing relief from both typical GERD symptoms, such as heartburn and regurgitation, and atypical symptoms, such as chest pain and extraesophageal manifestations (e.g., asthma-like symptoms or chronic cough). This broad spectrum of symptom improvement underscores EFTP's potential as a comprehensive treatment for GERD that can address a wide variety of clinical presentations (Pleskow et al., 2007).
- **Quality of Life Improvements:** In addition to symptom relief, patients who undergo EFTP often experience significant improvements in quality of life.

Reductions in the frequency and severity of GERD-related symptoms lead to better overall patient well-being, less reliance on medication, and improvements in daily functioning (Niu et al., 2024). These quality of life improvements are particularly important for patients who experience debilitating symptoms and seek a long-term solution to manage their condition (von Renteln et al., 2009, 2010).

- **Mechanism and Effectiveness:** The underlying mechanism of EFTP involves the placement of transmural sutures through the full thickness of the stomach wall, which strengthens the gastroesophageal junction and improves the function of the lower oesophagal sphincter (LES). By directly altering the anatomy of the gastroesophageal junction, EFTP provides a more durable and potentially more effective solution for GERD compared to less invasive procedures like transoral incisionless fundoplication (TIF).

In conclusion, EFTP has demonstrated promising efficacy in the treatment of GERD, with a significant proportion of patients experiencing symptom relief, a reduction in medication dependence, and improved quality of life (Kalapala et al. 2022). While further research is necessary to assess its long-term outcomes and refine patient selection criteria, current evidence supports EFTP as a viable option for patients seeking an effective, minimally invasive alternative to traditional GERD treatments. The ability of EFTP to address both typical and atypical GERD symptoms makes it a comprehensive approach to managing this complex and often challenging condition.

7. COMBINED TRANSORAL AND LAPAROSCOPIC APPROACH (c-TIF)

The combined transoral incisionless fundoplication (TIF) and laparoscopic hiatal hernia (HH) repair (c-TIF) has emerged as a highly effective interdisciplinary strategy for managing gastroesophageal reflux disease (GERD), particularly in patients with larger hiatal hernias (Rosen et al.,2025). This combined approach aims to address both the anatomical defect at the hiatus, which contributes to GERD, and the weakened anti-reflux barrier at the gastroesophageal junction (GEJ). By addressing both factors simultaneously, c-TIF offers a more comprehensive solution for patients with complex GERD presentations.

- **Choi et al. Study:** A study by Choi et al. demonstrated the success of the c-TIF approach, with 85% of patients experiencing significant reduction or complete resolution of their GERD symptoms after undergoing the combined procedure. Additionally, there was a 71% decrease in daily proton pump inhibitor (PPI) use, highlighting the procedure’s effectiveness in reducing medication dependency. Quality of life improved markedly, with significant reductions in heartburn and regurgitation scores, which remained stable at the one-year follow-up. Objective measures, such as oesophagal pH monitoring, also revealed substantial reductions in acid exposure following the combined procedure, further confirming its efficacy in controlling GERD symptoms (Choi et al., 2021).

- **Ihde's Findings:** Supporting these results, Ihde reported similar findings in his study, noting that patients who underwent combined hiatal hernia repair and TIF experienced a 50–60% reduction in acid exposure time (AET). Additionally, 76% of patients achieved normalised AET, which reflects a substantial improvement in acid control. These objective measures align with the self-reported outcomes of patients, as over 80% reported symptom relief and expressed high satisfaction with the procedure. This data underscores the importance of combining both techniques to achieve enhanced acid control and greater patient satisfaction (Ihde et al., 2011).
- **Bazerbachi et al. Review:** A review by Bazerbachi et al. further supported the value of the combined approach, demonstrating that it provides greater durability in symptom control compared to TIF alone, particularly in patients with larger hiatal hernias. The combined procedure not only strengthens the gastroesophageal junction (GEJ) but also reduces the risk of hiatal hernia recurrence. In fact, less than 10% of patients in their study experienced symptomatic recurrence of GERD within the first year post-procedure, emphasising the long-term effectiveness of c-TIF in providing sustained symptom relief (Bazerbachi et al., 2019).
- **Janu et al. Study in Community Hospitals:** A study by Janu et al. conducted across two community hospitals demonstrated that the combined procedure is not only effective in specialised centres but also highly practical in more generalised settings. The study reported a 60% reduction in symptom severity scores and a 75% reduction in daily PPI use. Furthermore, approximately 85% of patients expressed satisfaction with their GERD symptom management after undergoing the combined procedure. These findings suggest that c-TIF is a versatile and effective treatment option for a broad range of patients, including those treated in non-specialised clinical settings (Janu et al., 2019).

In conclusion, the combined transoral incisionless fundoplication (TIF) and laparoscopic hiatal hernia (HH) repair approach has shown significant and sustained efficacy in managing GERD, particularly for patients with larger hiatal hernias. By addressing both the structural defect at the hiatus and the weak anti-reflux barrier at the gastroesophageal junction, this combined technique offers enhanced symptom relief, better acid control, and a substantial reduction in medication dependency. Studies have consistently shown that c-TIF results in high patient satisfaction and durable symptom control, with benefits extending up to one year or more post-procedure. Given its demonstrated success, c-TIF represents a promising strategy for improving GERD management in patients with complex presentations, providing a comprehensive and long-term solution to GERD symptoms.

8. TRANORAL ANTEROGRADE SUTURING DEVICES

The OverStitch device (Apollo Endosurgery, Austin, TX, USA) is an advanced full-thickness endoscopic suturing system that allows endoscopists to perform suturing in various areas of the gastrointestinal tract. It has gained significant recognition for its role in the management of gastroesophageal reflux disease (GERD), particularly in reinforcing the gastroesophageal junction (GEJ) to improve the anti-reflux barrier. Beyond GERD management, the OverStitch device has also been utilised in closing fistulas, managing perforations, and reducing stomach volume in weight-loss procedures (Ge & Thompson, 2020; Zorron et al., 2018).

- **Precision and Versatility in Suturing:** The OverStitch system is designed to offer precision and control when placing sutures, which is crucial for procedures that require full-thickness tissue apposition (Rosen et al.,2025). Banerjee et al. reviewed various endoscopic closure devices, including the OverStitch, and highlighted its ability to create either continuous or interrupted sutures. This flexibility allows endoscopists to tailor the suturing technique to the specific clinical scenario, whether for therapeutic or surgical purposes (Banerjee et al., 2012). The device's versatility has made it a valuable tool not only for **gastrointestinal closure and reconstruction** but also for **bariatric interventions**, further cementing its role as an essential tool in endoscopic surgery.
- **Efficacy in GERD Treatment:** Han et al. explored the use of the OverStitch device specifically for GERD patients and demonstrated that it effectively creates full-thickness plications at the gastroesophageal junction. These applications enhance the anti-reflux barrier, improving reflux control and providing significant symptomatic relief. In their study, GERD patients who underwent the procedure showed notable improvements in GERD-related symptoms, such as heartburn and regurgitation, and experienced a reduction in their reliance on proton pump inhibitors (PPIs) (Han et al., 2018). The ability to create robust, durable sutures provides a distinct advantage over other endoscopic devices, as these sutures are more stable and may reduce the likelihood of recurrence compared to superficial plications.
- **Advantages Over Other Devices:** One of the key strengths of the OverStitch device is its ability to provide durable, full-thickness sutures, which not only reinforce the gastroesophageal junction more effectively but also offer long-term stability. This advantage is particularly important in the management of GERD, where a long-lasting anti-reflux barrier is crucial to prevent symptom recurrence. The OverStitch's design helps minimise the need for repeat interventions, offering a more permanent solution compared to less stable, superficial plications used by other devices.
- **Broad Range of Applications:** Beyond GERD, the OverStitch device has proven to be a versatile tool in a variety of therapeutic and surgical endoscopy applications. It has been used in procedures involving gastrointestinal closure, such as the closure of perforations and fistulas, and plays an important role in bariatric surgery, including procedures like endoscopic sleeve gastroplasty. Additionally, the OverStitch has applications in mucosal resection procedures, as it can secure the tissue after resection and help promote proper healing.

In conclusion, the OverStitch device is a highly effective and versatile tool in the endoscopic management of GERD. It allows for the creation of full-thickness plications at the gastroesophageal junction, enhancing the anti-reflux barrier and improving symptom control. Studies support its efficacy in reducing GERD symptoms and decreasing medication dependence, with a distinct advantage in providing durable, stable sutures that reduce the risk of recurrence. Furthermore, the OverStitch's flexibility in endoscopic interventions makes it a valuable asset not only in GERD treatment but also in a range of other gastrointestinal procedures, including bariatric and mucosal resection procedures. As endoscopic technologies continue to evolve, the OverStitch device represents a key advancement in minimally invasive treatment options for GERD and other gastrointestinal conditions.

9. ENDOSCOPIC RESECTION/ABLATION TECHNIQUES (TABLE 2)

Endoscopic resection and ablation techniques offer innovative options for patients with gastroesophageal reflux disease (GERD), especially those who do not respond to proton pump inhibitors (PPIs) or seek non-surgical interventions. These approaches, which include anti-reflux mucosectomy (ARMS), mucosal ablation and suturing (MASE), and resection and plication (RAP), focus on modifying the gastroesophageal junction to reduce acid reflux effectively (Rosen et al.,2025).

Table 2. Endoscopic resection/ablation techniques

ARMS	Anti-Reflux Mucosectomy
MASE	Mucosal Ablation and Suturing
ARMS with Band Ligation	Banded Anti-Reflux Mucosectomy
RAP	Resection and Plication

10. ANTI-REFLUX MUCOSECTOMY (ARMS)

Anti-Reflux Mucosectomy (ARMS) is an innovative endoscopic procedure designed to address gastroesophageal reflux disease (GERD) by resecting mucosal tissue at the gastroesophageal junction (GEJ). The goal of ARMS is to induce localised fibrosis, which strengthens the anti-reflux barrier and improves the function of the lower oesophagal sphincter (LES), ultimately reducing acid exposure and alleviating GERD symptoms. This technique is particularly beneficial for patients who do not respond to proton pump inhibitors (PPIs) or for those seeking a non-surgical option.

Procedure Overview:

- ARMS involves the targeted removal of mucosal tissue from around the gastroesophageal junction. The resection stimulates the formation of fibrous tissue, which tightens the junction and helps to reinforce the anti-reflux barrier. By modifying the GEJ, ARMS aims to improve LES function, thus preventing acid reflux from the stomach into the oesophagus.

Clinical Outcomes:

Several studies have demonstrated the efficacy of ARMS in reducing GERD symptoms, improving quality of life, and allowing patients to decrease or discontinue their PPI use.

1. **Pilot Study by Inoue et al. (2014):**
   - A pilot study by Inoue et al. demonstrated that 68% of GERD patients without a hiatal hernia showed a significant reduction in acid exposure and symptom scores following ARMS (Inoue et al., 2014). This finding highlighted the procedure's potential in patients with typical GERD without additional anatomical complications like hiatal hernia.
2. **Indian Cohort Study by Patil et al. (2020):**
   - In Patil et al.'s study of the first Indian cohort, 70% of patients achieved sustained symptom relief and were able to discontinue PPIs six months after ARMS (Patil et al., 2020). This study suggests that ARMS may provide a viable option for GERD patients in diverse populations, particularly in resource-limited settings.
3. **Follow-up by Ota et al. (2024):**
   - In a more recent study, Ota et al. found that up to 85% of patients who underwent ARMS remained symptom-free and off PPIs at two-year follow-up. This outcome demonstrates the potential long-term durability of the procedure and its ability to maintain symptom control over an extended period (Ota et al., 2024).
4. **Innovations in ARMS**:
   - Recent innovations in ARMS include cap-assisted endoscopic mucosal resection, which enhances the precision and safety of the procedure (Lee et al., 2024). Lee et al. explored this method in a cohort of refractory GERD patients and reported that 74% of patients experienced significant symptom improvement, with effects lasting up to two years (Lee et al., 2024). The addition of cap-assisted resection improves the accuracy of tissue removal and reduces the risk of complications during the procedure.
5. **Stable Reduction in Symptoms**:
   - In a study by Zhu and Shen, it was emphasised that ARMS could yield a stable reduction in GERD symptoms and acid exposure, indicating its potential for durable outcomes in PPI-dependent GERD cases (Zhu & Shen, 2024). This makes ARMS a promising alternative for patients with chronic GERD who have not responded well to medical management.

Key Advantages of ARMS:

- **Symptom Relief and PPI Discontinuation:** Many patients experience significant improvements in GERD symptoms and can reduce or completely stop their use of PPIs after undergoing ARMS.
- **Long-Term Efficacy:** Long-term follow-up data suggest that ARMS provides durable symptom relief, with a substantial proportion of patients maintaining symptom control and acid exposure reduction for up to two years.
- **Non-Surgical Nature:** As a minimally invasive procedure, ARMS offers a less invasive alternative to traditional surgery, with faster recovery times and fewer complications.

- **Adaptability:** Innovations, such as cap-assisted mucosal resection, continue to improve the procedure's safety and effectiveness, making it a valuable option in GERD management.

In conclusion, Anti-Reflux Mucosectomy (ARMS) has shown promising results in the treatment of GERD, particularly for patients who struggle with PPI dependence or those seeking a non-surgical intervention. Studies have demonstrated both short-term efficacy and long-term durability, with many patients experiencing significant symptom improvement and a reduction in acid exposure. The procedure's ability to provide sustained relief, even in refractory cases of GERD, makes it an appealing alternative to traditional treatments. As the technique continues to evolve, ARMS may become an increasingly important tool in the multidisciplinary approach to GERD management.

11. MUCOSAL ABLATION AND SUTURING (MASE)

Mucosal Ablation and Suturing (MASE) is a hybrid endoscopic technique designed to reinforce the gastroesophageal junction (GEJ) by combining mucosal ablation with endoscopic suturing (Rosen et al.,2025). The goal is to promote fibrosis and mechanically tighten the lower oesophagal sphincter (LES), thereby reducing gastroesophageal reflux and alleviating symptoms in GERD patients, particularly those who remain symptomatic despite PPI therapy.

Clinical Efficacy:

In a study conducted by Han et al. (2018), patients undergoing MASE demonstrated:

- An 80% improvement in GERD symptoms, as measured by GERD-HRQL scores (Rosen et al.,2025).
- A significant reduction in oesophagal acid exposure at one-year follow-up.
- 85% of patients were able to reduce or discontinue PPI therapy.
- Overall, patient satisfaction with the procedure was notably high.

These findings suggest that MASE is not only effective in symptom control but also enhances patient quality of life and reduces medication dependence.

Mechanism of Action:

- **Mucosal ablation**: Induces fibrosis around the GEJ, promoting a stiffer and more reflux-resistant tissue barrier.
- **Suturing**: Mechanically narrows the GEJ and augments the LES, further strengthening the anti-reflux barrier.

Advantages of MASE:

- Combines two therapeutic strategies (ablation + mechanical reinforcement) for a synergistic effect.

- Minimally invasive, with a lower complication rate compared to surgical interventions.
- Promising results even in PPI-refractory GERD.

12. BANDED ANTI-REFLUX MUCOSECTOMY (ARMS WITH BAND LIGATION)

Banded Anti-Reflux Mucosectomy (ARMS with Band Ligation) is an evolution of the ARMS technique that incorporates band ligation to enhance the precision and safety of mucosal resection. The banding creates controlled zones of resection, minimising trauma while optimising the fibrotic remodelling of the gastroesophageal junction.

12.1 Clinical Studies and Outcomes

1. **Hedberg et al. (2019):**
    - Introduced the banded ARMS technique.
    - Reported a 75% reduction in heartburn symptoms in GERD patients.
    - Noted minimal adverse events, demonstrating the safety profile of this method.

2. **Monino et al. (2019):**
    - Confirmed that band-assisted ARMS offers:
        - High patient satisfaction.
        - Effective symptom control, particularly in refractory GERD.
        - Lower risk of complications due to controlled, targeted mucosal resection.

12.2 Clinical Significance

- Band ligation provides a standardised, reproducible technique that can limit mucosal injury and bleeding.
- Improves the accuracy and safety of ARMS, particularly in difficult anatomical locations.

12.3 Ideal Patient Population

- GERD patients who have not responded to medication and are unsuitable for traditional surgical interventions.
- Especially useful in PPI-refractory cases or patients with high procedural risk.

In conclusion, both MASE and Banded ARMS represent important advancements in endoscopic GERD management. MASE offers a dual-action therapeutic benefit through ablation and suturing, while Banded ARMS enhances the safety and efficacy of mucosal resection. These approaches provide effective, minimally invasive options for GERD patients who need alternatives to medical or surgical therapy, with strong outcomes in symptom relief, medication reduction, and patient satisfaction.

13. RESECTION AND PLACEMENT (RAP)

The resection and plication (RAP) technique combines mucosal resection with plication to create a tighter gastroesophageal junction, preventing acid backflow. In a study by Benias et al. (2018), RAP led to a 70% reduction in GERD symptoms among patients, with 67% showing marked improvement in quality-of-life scores related to reflux. Importantly, this method allows for more comprehensive remodelling of the gastroesophageal junction (Rosen et al.,2025).

14. SAFETY OF RESECTION/ABLATION TECHNIQUES

Endoscopic interventions like Anti-Reflux Mucosectomy (ARMS), Mucosal Ablation and Suturing (MASE), and Resection and Plication (RAP) have expanded the therapeutic landscape for GERD by providing minimally invasive alternatives to long-term pharmacologic therapy or surgical fundoplication. While these approaches demonstrate promising efficacy, their safety profiles, though generally favourable, must be closely considered due to certain procedure-specific risks.

1. Bleeding

- Incidence: ~5–10%
- Typical Onset: Immediate to early post-procedure
- Severity: Generally minor to moderate
- Management: Mostly endoscopic, without need for surgery
- Supporting Studies:
  - Monino et al. (2019) and Lee et al. (2024) both documented manageable bleeding following ARMS.
  - Bleeding is more likely with larger or deeper mucosal resections.

2. Esophageal Stricture

- Incidence: 1–5% (up to 10% in some series)
- Mechanism: Fibrotic healing after mucosal resection causes oesophagal narrowing
- Symptoms: Dysphagia (difficulty swallowing)
- Management: Typically resolved with endoscopic dilation
- Supporting Data:
  - Zhu and Shen (2024) and Lee et al. (2024): 5–10% required dilation.
  - Ota et al., (2014): ~5% stricture rate post-cap-assisted ARMS.
  - Patil et al. (2020): Larger resections correlated with higher stricture risk.
- **Outcomes**: Most patients respond well after 1–2 dilation sessions

3. Dysphagia

- Incidence: 10–15% in the early post-procedural phase
- Cause: Transient oedema or fibrosis at the GEJ
- Duration: Typically resolves spontaneously within weeks
- Supporting Study:
  - Hedberg et al. (2019): ~12% of patients had dysphagia after banded ARMS, resolving without intervention

4. Perforation

- Incidence: <1%
- Severity: Serious complication requiring urgent surgical intervention
- Supporting Evidence:
  - Han et al. (2018) and Ota et al. (2014): Very low rates, emphasising rarity but seriousness

In conclusion, while ARMS, MASE, and RAP are effective and relatively safe for select GERD patients, they do carry procedure-specific risks:

- Most complications are mild and manageable, particularly in experienced centres.
- Close post-procedural monitoring and timely follow-up are essential to manage and minimise complications.
- As these techniques become more widespread, especially in tertiary or quaternary care centres, long-term safety and efficacy data will help refine patient selection and procedural protocols.

15. LAPAROSCOPIC TECHNIQUES

Magnetic Sphincter Augmentation the LINX magnetic sphincter augmentation (MSA) device is a ring of magnetic beads placed around the lower oesophageal sphincter (LES) designed to reinforce the LES, reducing acid reflux by preventing gastric contents from moving back into the oesophagus while still allowing normal swallowing and burping (Fig. 1).

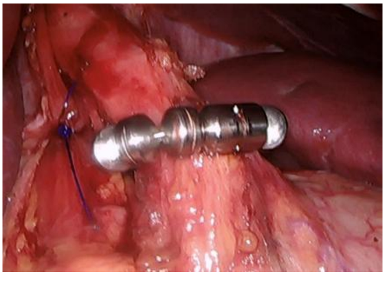

Fig. 1. LINX ring implanted at the distal oesophagus

The LINX ring shares some conceptual similarities with earlier surgical innovations, such as the Angelchik prosthesis, developed by Angelchik and Cohen in 1979. The Angelchik device, a C-shaped silicone ring positioned around the lower oesophagal sphincter (LES), was intended to reinforce the LES and reduce acid reflux, much like the LINX device (Rosen et al.,2025). However, this device has encountered challenges, particularly with device erosion and migration, which have affected its long-term success and safety profiles (Aiolfi et al., 2024). The LINX magnetic sphincter augmentation (MSA) device has emerged as a promising intervention for managing gastroesophageal reflux disease (GERD), providing a less invasive alternative to traditional fundoplication surgeries. The data from numerous studies illustrate both the effectiveness and complications associated with LINX (Ferrari et al., 2020; Ganz et al., 2016; Guidozzi et al., Bell et al., 2020; Froiio et al., 2023).

16. EFFICACY IN GERD MANAGEMENT – THE LINX® SYSTEM

The LINX Reflux Management System, a magnetic sphincter augmentation device, has been extensively studied and is increasingly recognised as a minimally invasive yet effective option for treating GERD, especially in patients seeking an alternative to both lifelong medication and traditional fundoplication surgery.

16.1 Long-Term Symptom Control

- **Ferrari et al. (2020):**
  - 88% of patients reported sustained symptom relief.
  - Notable reduction in PPI use over 6–12 years post-implantation.
- **Ganz et al.** (**2016):**
  - 85% of patients either reduced or discontinued PPIs.
  - Significant improvement in GERD-related quality-of-life scores.

These findings support the durability of LINX in managing GERD long-term.

16.2 Comparative Efficacy: LINX vs. Fundoplication & PPIs

- **Guidozzi et al. (2019) (Systematic Review & Meta-analysis):**
  - LINX offers comparable symptom control to Nissen fundoplication.
  - May be superior in preserving physiological functions like belching and vomiting.
- **Bell et al. (2019; 2020) (RCTs):**
  - Compared LINX with double-dose PPIs.
  - LINX showed superior control of regurgitation, especially in moderate-to-severe cases.

These comparisons highlight LINX's potential to offer surgical-level efficacy with fewer drawbacks.

16.3 Patient Satisfaction & Safety

- **Froiio et al. (2023):**
  - ~90% of patients would recommend LINX to others.
  - Overall positive safety profile.
- **Bonavina et al. (2008) (multicenter trial):**
  - Demonstrated early safety and feasibility.
  - Low rate of intraoperative complications.
- **Bell et al. (2019):**
  - Emphasised LINX's preservation of natural GI function, unlike fundoplication.

The high patient satisfaction, low adverse event rate, and preserved physiology make LINX especially appealing for active individuals or those hesitant about traditional surgery.

17. MORBIDITY AND COMPLICATIONS

17.1 Dysphagia

While the LINX® device is effective in managing GERD, postoperative dysphagia is a commonly reported complication. In the study by Dominguez-Profeta et al. (2021), approximately 68% of patients experienced dysphagia immediately after surgery. Encouragingly, this rate decreased to around 13% within one year, as most cases resolved spontaneously without further intervention (Rosen et al.,2025).

Several factors influence the likelihood and severity of dysphagia, including:

- The tightness of the magnetic ring.
- The patient's oesophagal peristaltic reserve.
- The number of beads in the ring, with more beads often reducing constriction and improving swallowing function.

However, persistent dysphagia remains a challenge for some. A community-based study by Czosnyka et al. (2017) reported that 17% of patients required endoscopic dilation or device removal due to severe and ongoing swallowing difficulties. These findings highlight the importance of postoperative monitoring and early intervention for those who do not improve over time.

According to Froiio et al. (2023), patients with poor oesophagal motility are particularly at risk for adverse outcomes. Because LINX augments the lower oesophagal sphincter (LES), adequate peristaltic strength is needed to propel food past the magnetic ring. For this reason, preoperative oesophagal motility testing is essential. Improper ring sizing—especially using a ring that is too tight—can further exacerbate dysphagia and may necessitate dilation or, in rare cases, removal.

17.2 Risk of Erosion and Migration

Although rare, device erosion and migration are serious complications that warrant attention. These issues are far less common than those seen with older devices like the Angelchik prosthesis, but remain a concern for long-term outcomes.

- Salvador et al. (2017) and Alicuben et al. (2018) documented cases where the LINX device eroded into the oesophagal wall. While the incidence of erosion is typically reported as less than 1%, these cases underscore the need for careful patient selection, accurate device sizing, and routine follow-up.
- Alicuben et al. (2018) also noted that erosion occurred more frequently in patients with anatomical challenges, such as larger hiatal hernias.
- In a focused study on patients with hiatal hernias ≥3 cm, Buckley et al. (2018) found that while GERD control remained favourable, the risk of erosion and migration increased. As a result, patients with larger anatomical defects may be better suited for traditional fundoplication or other tailored surgical options.

Valinoti et al. (2024) highlighted that device erosion can occur months to years postoperatively, emphasising the need for long-term monitoring. They identified early warning signs, including:

- Persistent or new-onset dysphagia
- Worsening GERD symptoms
- Localised chest pain

In some instances, erosion may be asymptomatic until it becomes severe, necessitating device explantation. Valinoti also observed that the risk of erosion increases over time, with a calculated 1.4-fold increase in risk per year of follow-up. This trend reflects the gradual nature of tissue breakdown around the implanted device.

18. ELECTRICAL STIMULATION (EST)

EndoStim® (EndoStim BV, Nijmegen, The Netherlands) represents an innovative, less invasive therapeutic option for gastroesophageal reflux disease (GERD). This technology employs electrical stimulation therapy (EST) to enhance the function of the lower oesophagal sphincter (LES) without altering gastrointestinal anatomy.

Unlike traditional surgical treatments such as fundoplication or device implantation (e.g., LINX), EndoStim® relies on a small, implantable pulse generator connected to two laparoscopically placed electrodes positioned in the distal oesophagus, close to the vagal nerves. These electrodes deliver low-energy electrical impulses designed to strengthen the LES and reduce reflux episodes, while preserving normal anatomical and physiological functions.

Development and Mechanism of Action: The concept of using electrical impulses to control reflux emerged from early experimental research into neuromodulation and oesophagal physiology. Foundational studies, including those by Ellis, Berne, & Settevig (1968), demonstrated that electrical stimulation applied to the distal oesophagus significantly reduced reflux events in experimental models. This research provided critical insights into how neuromodulatory signals could alter LES tone and function.

These findings laid the foundation for the development of EndoStim®, with the goal of:

- Enhancing LES pressure without anatomical manipulation.
- Reducing reflux episodes and symptom severity.
- Minimising side effects such as dysphagia or gas bloat, commonly seen with surgical procedures.

As a minimally invasive and reversible treatment, EST offers a promising alternative for patients who are:

- Inadequately managed on proton pump inhibitors (PPIs),
- Seeking a non-destructive solution to reflux,
- Unsuitable for or unwilling to undergo traditional anti-reflux surgery.

Fig. 2. Endostim system with electrodes positioned around the distal oesophagus

Decades later, Sanmiguel et al. (2008) advanced this research by studying the effects of electrical stimulation on LES pressure in a canine model. Their findings showed that electrical stimulation could reliably increase LES pressure without causing significant side effects, a critical factor for both efficacy and safety. This research confirmed that controlled, targeted stimulation could enhance LES function, suggesting a pathway for clinical applications in humans (Sanmiguel et al., 2008).

Rodríguez et al. (2013) conducted a short-term study on electrical stimulation of the LES in GERD patients (Rodríguez et al., 2013). The study revealed that electrical stimulation could successfully increase LES pressure, confirming the findings from animal models. Importantly, this study showed that even brief sessions of stimulation could have a measurable impact on LES tone and pressure in human patients, reinforcing the potential of EndoStim® for treating GERD. Similarly, Banerjee et al. (2014) further investigated EST's effects in GERD patients, observing that electrical stimulation consistently increased LES pressure over time. This study provided some evidence that EST not only strengthens the LES but also maintains enhanced sphincter pressure over extended periods, offering a promising alternative to surgical interventions like fundoplication or device implants (Rosen et al.,2025).

Results from two studies by Rodríguez et al. demonstrated that this therapy provides substantial symptom relief and sustained improvements in LES function (Rodríguez et al., 2013; Rodríguez et al., 2016).

In an open-label prospective trial, 25 GERD patients received EndoStim® therapy. The study found a significant reduction in acid exposure time, with the average percentage of time the oesophagus was exposed to acid decreasing from 10.3% at baseline to 5.1% after one year. Symptom relief was significant, with 90% of patients reporting a reduction in GERD symptoms, and 64% of patients were able to discontinue or reduce their use of proton pump inhibitors (PPIs) (Rosen et al.,2025). The LES resting pressure also improved, increasing from an average of 7.4 mmHg to 10.2 mmHg, indicating enhanced LES function (Rodríguez et al., 2013).

A three-year follow-up study by the same working group included 22 patients from the original group (Rodríguez et al., 2016). It confirmed sustained improvement, with the average acid exposure time remaining at 5.2%, demonstrating long-term effectiveness in reducing reflux. Overall, 72% of patients continued to experience symptom relief without needing PPIs or only requiring minimal doses. LES resting pressures were maintained, supporting the therapy's effectiveness in strengthening the LES over the long term (Rodríguez et al., 2016). Paireder et al. (2021) conducted a study in 17 patients with GERD in whom Endostim® was applied. In contrast to the findings mentioned above, no significant changes could be observed between the baseline and 12-month follow-up for the percentage of pH < 4 as well as the LES pressure, as measured by impedance pH measurement and manometry (Rosen et al.,2025). However, patients reported significant improvement in quality of life evaluation by standardised questionnaires at 12-month follow-up (Paireder et al., 2021). According to the authors, it is difficult to understand how this controversy can be explained, and the possibility of a placebo effect must be taken into account (Paireder et al., 2021). It must also be mentioned that there is a lack of randomised, sham-controlled trials that seek to evaluate the scientific evidence for this approach, as well as the multiple restrictions (e.g., cardiac arrhythmia) for its use as pointed out by the manufacturer (EndoStim, 2018).

Furthermore, it is noteworthy that the product is presently not commercially available anymore.

19. RefluxStop™

RefluxStop™ (Implantica, Vaduz, Liechtenstein) is a novel, laparoscopically implanted device designed to treat gastroesophageal reflux disease (GERD) by preventing the displacement of the lower oesophagal sphincter (LES) into the thorax. Unlike traditional anti-reflux procedures, which compress or reconstruct the gastroesophageal junction, RefluxStop™ works by mechanically supporting the LES in its anatomically correct position, thereby preserving the natural passage of food and reducing acid reflux (Fig. 3).

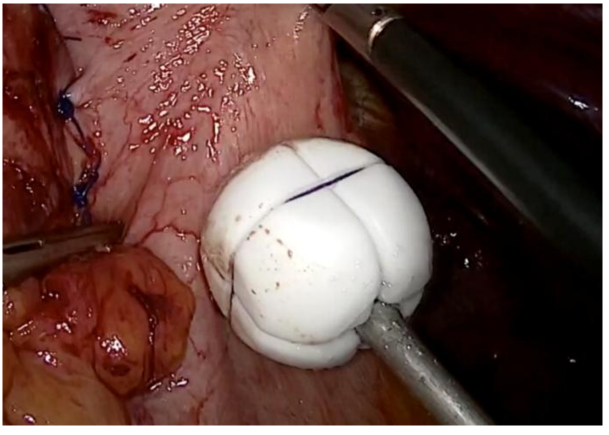

Fig. 3. RefluxStop™ applied at the fundus

Mechanism and Clinical Evaluation: The device restores normal anatomy without compressing the oesophagus or altering peristalsis. In a prospective multicenter study, Bjelovic et al., (2020) assessed the safety and efficacy of RefluxStop™ in 50 patients with chronic GERD. Key findings included:

- No serious adverse events linked to the device.
- A mean GERD-HRQL score improvement of 86% at one year ($p < 0.001$).
- 24-h pH monitoring revealed a dramatic reduction in total acid exposure time, with mean pH < 4 time decreasing from 16.35% to 0.80% at six months ($p < 0.001$).

- 98% of patients achieved normal 24-h pH profiles.
- PPI dependency dropped significantly, with only one patient requiring daily PPIs due to suboptimal device positioning.
- Regurgitation was minimal or absent in 97.8% of subjects.
- Gas bloating resolved in 30 patients and improved in 7 others.

19.1 Long-Term Outcomes

In a four-year follow-up of the same cohort, Bjelovic et al., (2020) reported that:

- The median GERD-HRQL score remained 90% improved from baseline (Rosen et al.,2025).
- Only 2 of 44 patients continued to use daily PPIs, despite normal pH results on therapy.
- Importantly, no device-related adverse events, migrations, oesophagal dilations, or explants were recorded throughout the study duration (Harsányi et al., 2024).

Current Considerations: Although RefluxStop™ shows encouraging short- and long-term outcomes, these findings come from a limited patient population and a single research group. Broader validation through controlled, multi-institutional trials is necessary to confirm safety, efficacy, and generalizability before widespread clinical adoption.

20. CONCLUSIONS

Gastroesophageal reflux disease (GERD) continues to pose a significant global health burden due to its chronic course, increasing prevalence, and the inherent limitations of traditional treatment strategies. Standard long-term use of proton pump inhibitors (PPIs), while effective in many cases, remains controversial due to potential side effects and incomplete symptom resolution in a subset of patients. Likewise, conventional surgical options such as Nissen fundoplication, although effective, may compromise physiological functions and are not suitable for all patients.

This review has explored the emerging landscape of GERD therapies, emphasising minimally invasive endoscopic and laparoscopic innovations that aim to bridge the therapeutic gap between pharmacologic management and classical surgical intervention. Procedures such as Stretta, transoral incisionless fundoplication (TIF), anti-reflux mucosectomy (ARMS), LINX® magnetic sphincter augmentation, EndoStim® electrical stimulation, and RefluxStop™ illustrate the dynamic shift toward preserving natural anatomy and function while achieving symptom control.

While these techniques offer exciting potential—demonstrating improvements in GERD-related quality of life, reduced oesophagal acid exposure, and lower dependence on medication—the evidence base remains in evolution. Key limitations persist, including:

- Limited long-term data to confirm the durability of symptom relief.
- Risks of late complications, such as device erosion, dysphagia, or anatomical alterations.
- Variability in outcomes, due in part to patient heterogeneity and procedural technique.

Thus, broad adoption of these therapies should be approached with careful consideration. Longitudinal studies, randomised controlled trials, and post-market surveillance will be critical to fully define the role of each modality within the GERD treatment algorithm.

Ultimately, the management of GERD is moving toward a personalised, multidisciplinary approach, wherein the choice of therapy is tailored to the patient's clinical characteristics, anatomical considerations, and personal preferences. Collaboration between gastroenterologists, surgeons, and patients is essential to select the most appropriate treatment strategy, balancing innovation with evidence-based care.

DISCLAIMER (ARTIFICIAL INTELLIGENCE)

Author(s) hereby declare that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc.) and text-to-image generators have been used during the writing or editing of this manuscript.

CONSENT AND ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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Chapter 5

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Esthetic and Functional Outcomes of Zirconia and Metal-Ceramic Fixed Partial Dentures in the Maxillary Anterior Region: A Clinical Perspective

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ABSTRACT

Metal ceramic restorations were long-time considered as gold standard for fixed dental prostheses. The evolution in material science and patients' aesthetic requests led to the introduction of new materials for frameworks, which are ceramics. The absence of anterior maxillary teeth as a result of congenital anomalies, or their loss due to extensive carious lesions, or trauma, may lead to serious esthetic and functional problems. Therefore, the anterior esthetic and functional rehabilitation is a common practice in fixed prosthodontics. This paper presents the case of a 55-year-old male patient. In this case report, the intraoral examination showed a favourable occlusion. The edentulous ridge seemed to be satisfactory. The coronal height of teeth to be supporting the FPD was also examined, which was judged as favourable. After decision-making, teeth preparations were made. The intraoral examination showed an extrusion in tooth #21 with a slight deviation of the midline. A gingival recession was also clearly revealed in all anterior teeth. Thus, the whole patient's smile was remade while replacing the missing teeth using a Fixed Partial Denture (FPD). Intraoral examination showed a favourable occlusion, which is necessary for the ceramic FPD integration. The study concluded that the zirconia-based FPD is a suitable

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solution to replace anterior teeth, restore esthetics, and respect the biological and mechanical context of the restoration.

Keywords: Fixed partial denture; zirconia-based FPD; maxillary anterior region; metal ceramic restorations.

1. INTRODUCTION

In the realm of dental prosthodontics, which focuses on esthetics, functionality, and the physiological aspects of dental prostheses, lasers provide promising outcomes. Among the prosthetic options, fixed partial dentures stand out for their ability to mimic natural teeth, offering both esthetic and functional features, leading to satisfactory long-term outcomes if managed properly (Kwaśna et al., 2024). The fabrication of Fixed Partial Denture **(**FPDs) is one of the most common procedures for replacing missing teeth, which is still highly considered. Tooth loss may occur because of caries, periodontal disease, or trauma. Missing teeth can be replaced with different treatment options, fixed or removable, to restore oral function and aesthetics (Hawthan et al., 2023). For most cases, the choice we are offered is either metal ceramic FPD or all ceramic FPD. Several parameters should be studied and checked to indicate one of the two options. As is known, metal ceramic restorations were long-time considered as gold standard for fixed dental prostheses. The evolution in material science and patients' aesthetic requests led to the introduction of new materials for frameworks, which are ceramics. Regarding their vast applicability in the dental field, one of the main applications of metal–ceramic systems in dentistry is in the manufacture of dental crowns and bridges. The combination of metal and ceramic allows precise control over the hue, translucency, and texture of the restoration surface, allowing the restoration result to blend seamlessly with the patient's natural dentition (Dawod et al., 2023). Nowadays, many commercially available ceramic systems use a ceramic core replacing the metal framework. The In-Ceram Alumina system uses high-temperature sintered alumina glass-infiltrated copings for ceramic crowns. It was introduced for the fabrication of 3-unit anterior FPDs, and has demonstrated functional and esthetic results in the anterior area. The Empress II system uses a lithium-disilicate glass framework that is veneered with fluorapatite-based veneering porcelain. The system is limited to the fabrication of 3-unit FPDs that replace a missing tooth up to the first premolar. Zirconia-based materials are now becoming a reliable option for anterior FPDs. Aside from clinical reports, no clinical data are available yet. In-Ceram Zirconia system uses a framework that is fabricated from glass-infiltrated, high-temperature sintered alumina with 35% partially stabilised zirconia and then veneered with porcelain. The framework can be fabricated by the ceramist with the use of the slip-cast technique or milled from zirconia-based blocks with CAD/CAM technology; the latter promotes consistency of the quality and control of the framework material and thus reduces the probability of defects caused by human error (Daou, 2014; Monleau, 2015).

Transformation-toughened zirconia is prone to be a successful alternative in different clinical situations compared to other all-ceramic systems. Their mechanical and optical properties allowed them to be used as a framework material.

2. CASE REPORT

2.1 First Case Report (Riahi et al., 2018)

A 55-year-old male patient was referred to our department. His chief complaint concerned teeth # 11 and #12. Both teeth were root-treated and restored with amalgam restorations. The two incisors were also severely discoloured and extruded with a degree 2 mobility (Riahi et al., 2018). The teeth extraction was indicated. After that, an immediate Partial Removable Denture was placed.

Fig. 1. Pre-op view of discoloured teeth

Fig. 2. Periapical radiograph of teeth #11 and #12

3 months later, when the bone healing was obtained, a 6-unit zirconia-based FPD was indicated to replace the extracted teeth and to correct the anterior teeth tipping and extrusion. Why a ceramic FPD?

The first and primary advantage of ceramic FPDs is the aesthetic result they can provide. In fact, it increases in depth the translucency as well as the light transmission throughout the whole restoration. This allows the practitioner to provide the patient with a natural-looking restoration.

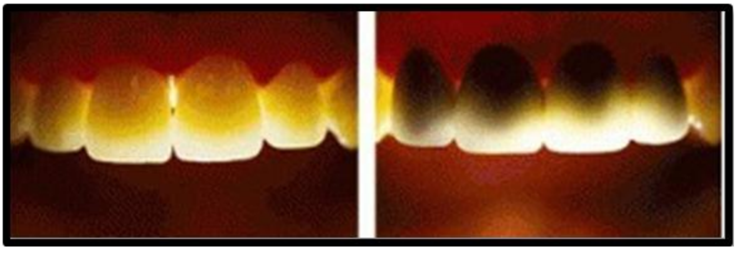

Fig. 3. All ceramic FPD versus metal ceramic FPD

Second, the ceramic core used with all ceramic prostheses, such as a Zirconia core, has a high masking ability, allowing the ceramist to get rid of the opaque layer, usually used to mask the colour of the metal framework. Third, the elimination of the metal framework allows the practitioner to place the finish line of the preparation either at the free gingival margin or slightly below, without compromising the esthetic outcome of the restoration. This prevents the biologic width from being violated and facilitates the fabrication of an accurate definitive impression. Fourth, the ceramic seems to be a material with high biocompatibility compared to metal. It has a reduced thermal conductivity, resulting in less thermal sensitivity and potential pulpal irritation. It is also worth noting that a ceramic core is extraordinarily well tolerated by marginal tissues in comparison with metal. Sixth, ceramic restorations require less reduction than metal ceramic ones. Only 1 to 1.5 of facial reduction is necessary to achieve an esthetic result with ceramic restorations, while 1.5 to 1.7 of reduction is required for metal ceramic restorations. Finally, a large portion of the population can be sensitive to metal alloys. Metal-free ceramic systems can solve this problem (Ariel & Gerard, 2011; Motta & Pereira, 2007).

As is known, the indication of a ceramic FPD should not be hazardous. Before indicating a ceramic system for anterior FPDs, a good case study must be established, considering the whole clinical context (Riahi et al., 2018).

In this case report, the intraoral examination showed a favourable occlusion, which is necessary for the ceramic FPD integration. The edentulous span seemed to be satisfactory, allowing the placement of 2 pontics replacing both lateral and central right incisors, without exceeding 12 mm in mesio-distal measurement. We also examined the coronal height of teeth to support the FPD, which was judged as favourable to achieve the required connectors' dimensions.

After decision making, teeth preparations were made. To do so, several steps should be followed:

- A deep chamfer bur is used to make a wide finish line, allowing the reduction of stress by more than 50% at the ceramic. Cervical margins of the preparation should be smooth and uniform for better precision while scanning the model, and a well-fitting of the zirconia core (Riahi et al., 2018). This also prevents ceramic chipping and cracking in the margin area.

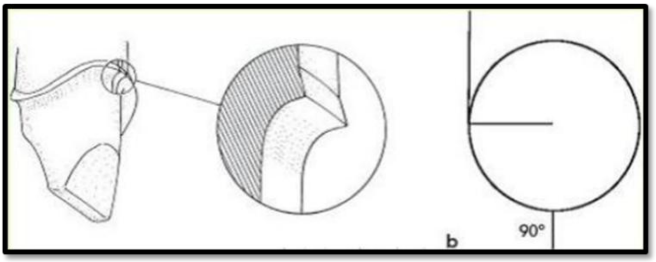

Fig. 4. Deep chamfer finish line

- On top of the preparation, a taper of 7 to 10° is required, and it can go up to 15°. All the tooth preparation edges should be rounded, with no sharp angles, to prevent internal stresses in the crown.
- **Reduction values: -** Incisal edge: axial reduction of 2 mm,
  - **Proximal surfaces:** 6 to 8/10th of a mm,
  - **Labial surface:** 12 to 15/10th mm matching to 8/10th to 1 mm cosmetic ceramic + 4 to 5/10th for the framework,
  - **Palatal surface:** 8/10th to 1 mm (Adli, 2014).

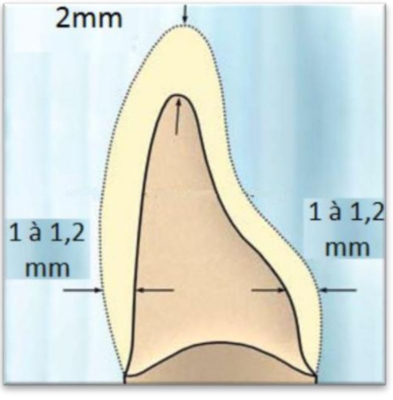

Fig. 5. Reduction values

- In the final step, the preparation is finished to a smoother surface with the same size tapered diamond but with medium diamond grit.

Fig. 6. Intraoral view of teeth abutments after preparation

After that, the chair-side temporary prosthesis was fabricated. We made the master impression using a commercial tray with high and light viscosity silicone. A master cast was then made to be scanned for the computer-assisted design of the Zirconia framework (Riahi et al., 2018).

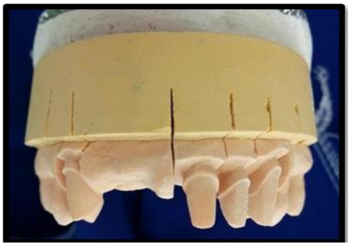

Fig. 7. Master cast Design of Zirconia-based FPDs

Both in vitro and in vivo studies demonstrated that fracture of the connectors was the exclusive mode of failure in all-ceramic FPDs. Therefore, Connectors are the most important parameters to be considered while planning a zirconia-based FPD. The fracture is initiated at the gingival embrasure. An occlusogingival height of 2.5 mm and a buccolingual width of 2.5 mm of the connectors (a connector surface area of 6.25 mm^2) are sufficient to ensure the long-term success of metal-ceramic FPDs. These dimensions are achievable both in the anterior and in the posterior segments.

Fig. 8. Connectors' height of the zirconia core of the anterior FPD

The connector section must have a “T” shape to be more resistant to fracture. The vertical part offers resistance to flexion stresses, while the horizontal one resists flexion (Nouira et al., 2013).

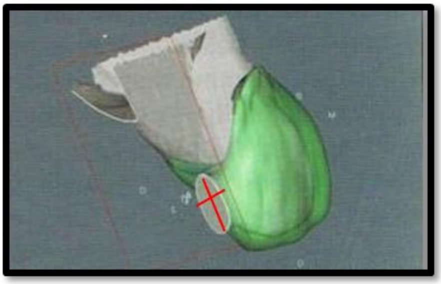

Fig. 9. The connector shape in anterior all ceramic FPD (Nouira et al., 2013)

Zirconia-based FPDs are composed of anchorages on the abutment teeth and pontics replacing missing teeth. To guarantee the long-term survival of the restoration, some rules according to its design should be respected. As far as pontics are concerned, these pieces seem to be a fragile spot, tightly influenced by flexion stresses. Therefore, an anterior ceramic FPD must not exceed 3 pontics in maxillary restorations. The length of the edentulous crest must be 9 to 12mm (Ariel & Gerard, 2011).

Shade mapping: There is no single base shade to provide an adequate shade match. Different shades are needed in the gingival, body and incisal third of the tooth. VITA 3D Master shade guide should be preferred to other shade guides since it is based on the selection of luminosity (Adli, 2014).

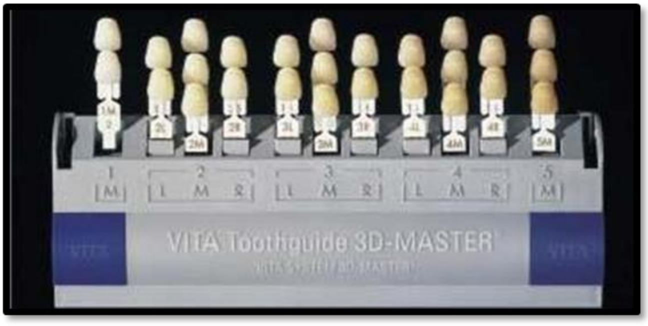

Fig. 10. VITA 3D Master shade guide

Clinical trials: When the Zirconia framework was delivered from the laboratory, several try-ins were performed. We started with the zirconia-core try-in to verify the margin limits fitting.

Fig. 11. Intraoral view of the Zirconia framework try-in

When this step is checked, we move to the second try-in after the cosmetic ceramic has been carried out. This allows the verification of teeth morphology, colour, embrasures, and occlusion. Then, staining and glazing are made before the definitive cementation.

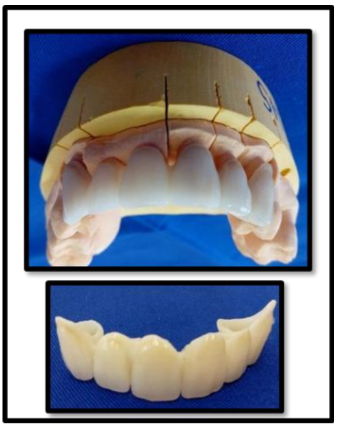

Fig. 12. Definitive 6-unit Zirconia based FPD

Fig. 13. Intraoral definitive Zirconia-based FPD cemented

3. SECOND CASE PRESENTATION

A 38-year-old male patient in good health consulted our department for the replacement of lost maxillary and mandibular incisors. The patient was a victim of a road accident that caused the loss of his three maxillary incisors (11,12, and 21) and his four mandibular incisors (31,32,41, and 42).

Fig. 14. Extraoral examination of the patient showed nothing unusual but a scar caused by the injury

An intraoral examination was conducted, revealing:

- A non-satisfactory oral hygiene
- A satisfactory attached gingiva
- High and large edentulous crest
- The absence of teeth #11, #12 and #21 in the maxillary arch, teeth #31, #32, #41, #42, #45 and #46 in the mandibular arch.

Fig. 15. Intraoral views

In order to establish the treatment plan and the prosthetic decision, diagnostic casts were waxed.

Even though ceramic FPD is more known to be esthetic enough in the anterior area, in this case, the edentulous crest mesiodistal measurement cannot be in favour of this option. So, our decision was to fabricate a 7-unit metal ceramic FPD to replace the 3 lost maxillary teeth. Metal ceramic bridges may have limits, but they also have several pros. First, metal alloys are known to be highly resistant to fracture and flexion stresses. Second, a major advantage of metal frameworks is their flexibility in favour of their indication in complex clinical cases. Third, to indicate a metal ceramic restoration, there is no limitation on the number of pontics. Fourth, porcelain fused to metal restorations can be designed with underdimensioned connectors compared to zirconia-based restorations, which offer a better esthetic result with appropriate gingival embrasures. Finally, in some clinical cases, we may be faced with compromise situations where a lack of preparedness retention is observed. That requires particular measures as adding secondary retention means within the abutment teeth. In this case, only a metal framework could be able to fit in (Ariel & Gerard, 2011; Motta & Pereira, 2007).

Fig. 16. Waxed diagnostic casts up

The next appointment was fixed to do teeth preparations. Diamond large chamfer burs were used. To prepare teeth # 13, #14, #22 and #23. The finish line was placed below the gingival margin to hide the metal framework. Proximal walls were prepared with a relief angle on the top of 3°. Reduction values are: 2mm for the incisal edge, 1.5 mm for the labial surface, and 0.8 mm for the proximal walls.

Fig. 17. Intraoral view of teeth abutment preparations.

The next step was the fabrication of the provisional prosthesis.

Fig. 18. Intraoral view of the provisional prosthesis

After that, the master impression was taken using a commercial tray, a high and a low viscosity silicone in a double mixing technique. Then the master cast was used for the anterior guide rehabilitation after mounting casts with a facebow and diagnostic bite record.

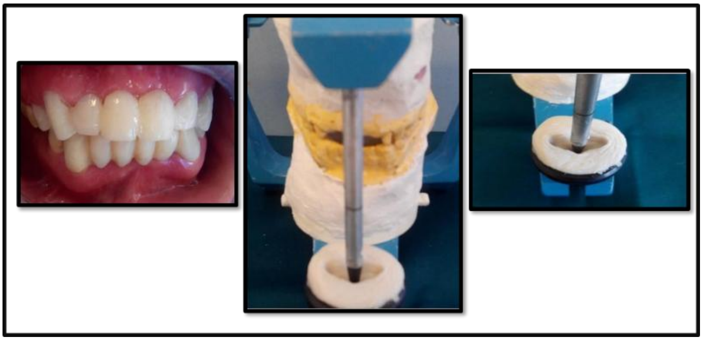

Fig. 19. Anterior guide restoration using provisional prosthesis and articulated casts

Fig. 20. Definitive metal ceramic FPD try-in

Fig. 21. Definitive metal ceramic FPD cemented

Clinical data on the long-term efficacy of metal ceramic FPDs are in favour of a large indication of this type of restoration. Several studies have been conducted on the survival of metal ceramic restorations for more than 40 years. Thus, those restorations were long considered as a gold standard, allowing for successful solution of most clinical cases and offering a satisfactory esthetic and functional result (Agustín-Panadero & Román-Rodríguez, 2014).

4. DISCUSSION

To be able to indicate the most suitable option for the right clinical case, a deep knowledge of the pros and cons of every option is necessary. The practitioner must be able to analyse the whole clinical context and choose the right type of FPD to fit in.

Zirconium oxide has been in use since 1960. From the start, its promising *in vitro* properties attracted the attention of dental researchers, and in the last decade, it has acquired increasing prominence. The properties that are in favour of its use in dentistry are biocompatibility, low thermal conductivity, resistance to corrosion and high tenacity, due to its totally crystalline microstructure (Crispa & Cowanb, 2012).

According to studies, some metal alloys produce allergic reactions, and their degree of cytotoxicity is highly dependent on the dental alloy used in the metal-cored FPD. But recent studies revealed that zirconia has the same amount of cytotoxicity as Alumina, but it is less cytotoxic than Titanium. Moreover, the plaque accumulation is highly related to surface roughness and irregularities. Studies showed that zirconia-based FPDs are made with highly polished surfaces, so they prevent plaque buildup (confirmed with the SEM analysis).

Although zirconia cores are now considered reliable materials for FPD frameworks, these restorations are not problem-free. The first disadvantage is the absence of data on the long-term efficacy of ceramic restorations. Second, the creation of heavy stresses in the connector area increases the risk of catastrophic fracture. Finally, open embrasures for facilitating plaque control and oral hygiene and for maintaining healthy papillae are mandatory. If the patient has a reduced interocclusal distance, it may be difficult to achieve the required connector dimensions without compromising these biologic demands. Caution is advisable if the patient is a heavy bruxer and the parafunctional activity cannot be controlled (Riahi et al., 2018). Restoration with a traditional metal-ceramic FPD is the safer alternative in this situation.

Table 1. Metal versus Zirconia

Metal	Zirconia
subject to corrosion and galvanic reactions (cellular and meridian disturbance) Contains Ni, Al, Cr… Not really an allergen, but triggers intolerances in some patients. Higher surface free energy: • Hydrophobic • Significant plaque accumulation • Acceptable soft tissue health Undesirable aesthetics: • Thinning of gum tissue around implants • Grey shadow effect showing through gum • Does not resemble real tooth structure. Observed bone erosion over the long term, and good bone osseointegration.	Electrochemically inert, causing no galvanising or electrocurrent disturbance effects at the inter- or intra-cellular level. Contains only ceramic, metal-free ceramics. No known allergies or intolerances. The most bio-inert and biocompatible material on the market. Lower surface free energy: • Hydrophilic • Reduced plaque accumulation • Resembles real tooth esthetics Highly desirable aesthetics: • Healthy pink tissue around the implant • No gum shows through, like natural teeth • Resembles real tooth esthetics. Stimulates bone growth long term with ultimate osseointegration for both bone and gum.

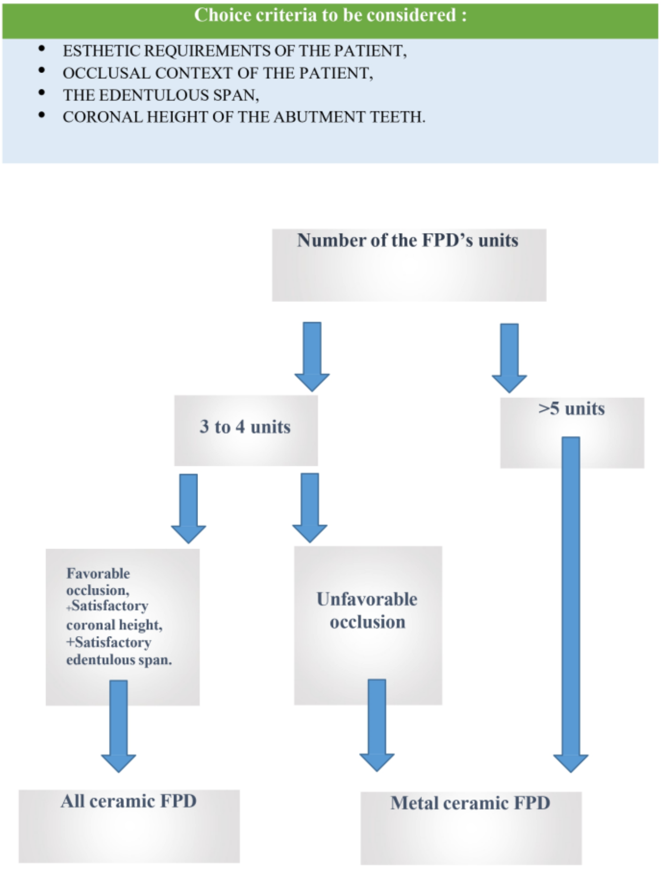

Fig. 22. Diagram of choice (Nouira, et al., 2013)

When the function of restorations, both all-ceramic and metal-ceramic, is evaluated over time, there are two concepts that are often regarded as synonymous: success and survival. The survival of a restoration means that it fulfils its function in the mouth even though it may have suffered some additional deterioration. Success can be defined as a restoration that survives intact, maintaining surface qualities, anatomical shape and function, as well as optimum esthetics (Miyazaki & Nakamura, 2013).

In zirconia-based fixed dental prostheses, in spite of the material's high fracture resistance, the porcelain veneer can chip during mastication, and this is a frequent problem. This complication generates some uncertainty as to the long-term performance of the material's use in dental restorations (Motta & Pereira, 2007).

Clinical studies have revealed a high rate of fracture for porcelain-veneered zirconia-based restorations that varies between 6% and 15% over a 3- to 5-year period (Riahi et al., 2018). These are high values compared to the 4% fracture rate shown by conventional metal-ceramic restorations over 10 years. The cause of these fractures is unknown but might be associated with bond failure between the porcelain-veneered and the zirconia structure (Motta & Pereira, 2007).

For metal-ceramic FDPs, 15 studies provided data on 1796 FDPs after a mean follow-up time of 7.0 years. Out of these, 145 FDPs were reported to be lost. The annual failure rate was estimated at 1.15%, translating into a 5-year survival rate for metal-ceramic FDPs of 94.4% (Motta & Pereira, 2007).

In spite of the increase in the use of all-ceramic fixed partial dentures (FPDs), metal-ceramic systems continue to be used due to their clinical longevity and biocompatibility. This kind of prosthesis is used mainly when a large number of teeth should be replaced. Advantages of metal-ceramic FPDs lie in their predictable structural performance, versatility and cost (Agustín-Panadero & Román-Rodríguez, 2014).

5. CONCLUSION

Metal-ceramic FPDs had lower failure rates than all-ceramic FPDs after a mean observation period. Framework fractures were frequently reported for reinforced glass ceramic and glass-infiltrated alumina FDPs. Densely sintered zirconia was significantly more stable as a framework material, but misfit led to complications such as discolourations, secondary caries and loss of retention. Moreover, ceramic fractures and chipping of ceramics were frequent. In the future, further refinements in the production of all-ceramic reconstructions must be indicated (Agustín-Panadero & Román-Rodríguez, 2014).

There is no perfect solution that may, at the same time, enhance aesthetics and respond to all the clinical cases. Zirconia-based FPDs or metal ceramic FPDs, the choice must be made after a good study of the clinical context.

Technical progress and the evolution of dental materials, added to high aesthetic requirements within patients, lead us to choose all-ceramic restorations as the best option nowadays. But we have to keep in mind the limited indications, the high rate of chipping and fracture of these restorations, which makes the metal framework still an important option in our current practice.

CONSENT

As per international standards or university standards, patient(s) written consent has been collected and preserved by the author(s).

ETHICAL APPROVAL

It is not applicable.

DISCLAIMER (ARTIFICIAL INTELLIGENCE)

Author(s) hereby declare that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc) and text-to-image generators have been used during writing or editing of this manuscript.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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Chapter 6
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Homozygous Mutation of the AP4E1 Gene as a Cause of Autosomal Recessive Spastic Paraplegia Type 51 (SPG51) in a 17-Years-Old Boy

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ABSTRACT

Autosomal recessive spastic paraplegia-51 (SPG51) is a rare neurodevelopmental disorder caused by a homozygous mutation in the AP4E1 gene, located on chromosome 15q21. SPG51 is characterized by neonatal hypotonia that progresses to hypertonia and spasticity. This is an often underdiagnosed condition in childhood, frequently presenting with clinical inconsistencies that can lead to misdiagnosis. Due to clinical overlap with conditions like cerebral palsy and other hereditary spastic paraplegias (e.g., SPG47, SPG50, SPG52), SPG51 is frequently underdiagnosed. Mutations in the AP-4E1 gene on chromosome 15q21.2 can lead to SPG51. Different mutations in this gene have been identified in affected individuals, leading to disruption of the AP4 complex and vesicular trafficking processes. The specific characteristics of SPG51 are, due to only a few cases, not well understood, due to limited reports of affected families. Affected individuals also have global developmental delay with impaired intellectual development and poor or absent speech. They typically present with hypotonia in the neonatal period, which progresses to muscular hypertonia, especially in the lower limbs. They may also exhibit contractures, talipes equinovarus, decreased muscle mass, short stature, and microcephaly. Severe mental retardation, absent speech, and dysmorphic facial features are common. Some patients may experience seizures. Neurological examination often reveals spastic paraplegia of the lower limbs, and brain imaging may show atrophy of the cerebellar vermis and cortical atrophy.

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This study presents an extremely rare case of a 17 years-old boy with autosomal recessive spastic paraplegia type 51. A compound heterozygous mutation in the AP4E1 gene was found in genetic analysis. The most disruptive symptoms were severe episodes of restlessness and aggression, particularly triggered by unfamiliar people and environments, including within the home. This case highlights the phenotypic variability of SPG51 and the importance of genetic testing and careful clinical evaluation in suspected cases of hereditary spastic paraplegia for accurate diagnosis.

Keywords: Autosomal recessive; SPG51; mutation; hypotonia; hypertonia.

1. INTRODUCTION

Hereditary spastic paraplegia (HSP) is a myriad of monogenic neurological defects aiding corticospinal and dorsal spinal cord axonal atrophy with a prevalence of 0.1–9.6 instances in every 100,000 around the world (Damiani et al., 2024). More than 90 SPG (for "SPastic parapleGia") loci/genes have been identified, and the number will continue to grow as long as new sequence technologies are used in clinical laboratory practice (Meyyazhagan & Orlacchio, 2022).

HSP is a group of genetically and clinically heterogeneous neurodegenerative disorders characterized primarily by spasticity and weakness in the lower limbs (Bittmann, 2024). It includes four genetic inheritance forms: autosomal dominant inheritance (AD), autosomal recessive inheritance (AR), X-linked inheritance, and mitochondrial inheritance. HSP patients may have either pure or complicated HSP, differing based on symptoms. Patients with pure HSP simply develop spasticity and weakness of the lower limbs, while patients with complicated HSP are often accompanied by other symptoms, such as early cognitive impairment, ataxia, visual disturbance, macular degeneration, dysarthria, and callosal agenesis" (Lai et al., 2023). Autosomal recessive mutations in the AP-4 (adaptor protein complex 4) complex subunit $\epsilon - 1$ (AP4E1) gene on chromosome 15q21.2 are known to cause spastic paraplegia 51 (SPG51), a recessive form of HSP (Niyoyita et al., 2025).

2. CASE REPORT

We present a case of a 17-years-old German boy with an autosomal recessive spastic paraplegia type 51 (SPG51), undefined variant. A compound heterozygous mutation in the AP4E1 gene was found in genetic exome sequencing (Bittmann, 2024). An unclassifiable epilepsy, most likely with complex focal seizures, is mostly present in SPG51. Perampanel was initiated as an anticonvulsant therapy after previous treatments with Sultiam, Lacosamide, Lamotrigine, Oxcarbazepine, Levetiracetam, and Zonisamide. SPG51 is a combined developmental disorder and a severe expressive language development disorder. Past medical history showed an epileptological situation quite stable, but general developmental delay. Head circumference was normal. No major seizure events were observed anymore; occasionally, episodes of smacking occur, which were interpreted differently. These episodes were hardly noticeable and very brief with a duration of less than a minute. The current medication consisted of Baclofen 10-0-20 mg and Perampanel 3.5 mg. The main problem affecting both school and especially the home environment was extreme episodes of restlessness and aggression, provoked by unfamiliar people and environments. They also occur in the home environment. Examination findings included the patient in a fairly good general condition, quite communicative, but mostly with non-verbal communication (Bittmann, 2024). Muscle tone increasingly spastic distally and leg- dominant, there were no side differences, no clearly recognizable cranial nerve abnormalities. The EEG showed a polymorphic mixed wave rhythm, emphasized in the upper theta frequency spectrum. The amplitudes barely exceeded 70 volts. An on/off effect was hardly discernible. Plenty of muscle activity overlayed, but no specific pathological patterns, especially no seizure predisposition, were found. The assessment and recommendations included that the epileptological situation was not the main focus; rather, the behavioral disorder was hardly bearable.

3. DISCUSSION

“Most of all hereditary spastic paraplegias (HSP) are classified due to the genetic loci that are classified by numbers according to their discovery (Abou Jamra et al., 2011; Kong et al., 2013; Moreno-De-Luca et al., 2011; Manoochehri et al., 2022). Four types are described in HSP and have been related to disturbances of different adaptor protein complex subunits” (Manoochehri et al., 2022). “The functional loss of the AP-4 protein complex is the molecular mechanism in all AP-4 HSP disorders (Manoochehri et al., 2022; Ebrahimi-Fakhari et al., 2020). AP-4-associated hereditary spastic paraplegia (HSP) is a group of progressive neurodegenerative disorders that typically present in infancy or early childhood. Spastic paraplegia type 51 is a genetic disorder characterized by the degeneration and dysfunction of certain nerve tracts (Abou Jamra et al., 2011; Kong et al., 2013; Moreno-De-Luca et al., 2011; Manoochehri et al., 2022; Abdollahpour et al., 2015; Chowet al., 2021). The AP-4E1 subunit is involved in recognizing and binding sorting signals within cells, which is crucial for proper protein localization in neurons (Bittmann, 2024). It is involved in sorting proteins to specific cell membranes and establishing protein localization in neurons” (Manoochehri et al., 2022; Sager et al., 2022). The AP4E1 gene encodes a member of the adaptor complex large subunit protein family, which are essential components of adaptor protein complexes involved in vesicle formation and sorting of integral membrane proteins in the secretory and endocytic pathways (Chow et al., 2021; Winkler et al., 2021; Sager et al., 2022; Rudenskaya et al., 2021; Ebrahimi-Fakhari et al., 2020; Ebrahimi-Fakhari et al., 2018; Hatsugai et al., 2018). The encoded protein is a large subunit of adaptor protein complex-4, associated with both clathrin- and nonclathrin-coated vesicles. Mutations in this gene may be linked to cerebral palsy. Multiple isoforms of this gene have been identified due to alternative splicing. This gene is expressed ubiquitously, including in lymph nodes (Tüysüz et al., 2014; Wang et al., 2013; Kong et al., 2013; Castro et al., 2024; İpek et al., 2024; Ebrahimi-Fakhari et al., 2020; Ortega Suero et al., 2021; Damiani et al., 2024). AP4 complex-mediated trafficking is essential for brain development, with the AP4E1 gene encoding the AP-4 adaptor protein complex subunit ϵ−1 (Bittmann, 2024). Knock-out mice with mutations in this gene exhibit abnormal white blood counts, enlarged lateral ventricles, a smaller corpus callosum, and hypoferremia. The clinical phenotype observed in this study aligns with previous reports of SPG51. Further mutational analysis and evaluation of AP4E1 in individuals with spastic paraplegia and their families are warranted to assess the disorder's frequency (Winkler et al., 2021; Sager et al., 2022; Rudenskaya et al., 2021; Ebrahimi-Fakhari et al., 2020).

This condition is often mistaken for cerebral palsy, but differs in its association with parental age and birth order (Abdollahpour et al., 2015; Rudenskaya et al., 2021; Wang et al., 2013). Symptoms include hypotonia progressing to spasticity, leading to difficulty walking or standing (Bittmann, 2024). Upper extremities may also be affected, resulting in spastic tetraplegia (Ebrahimi-Fakhari et al., 2018; Hatsugai et al., 2018; Tüysüz et al., 2014; Wang et al., 2013; Kong et al., 2013; Castro et al., 2024; İpek et al., 2024). “Other complications include bladder and bowel dysfunction, dysphagia, foot deformities, and contractures” (Moreno-De-Luca et al., 2011; Rudenskaya et al., 2021; Hatsugai et al., 2018; Wang et al., 2013). “Seizures occur in about half of patients, and the condition is associated with microcephaly and developmental delays. Speech development is delayed or absent, and stuttering could be rarely found” (Chow et al., 2021). One case report describes the genetic defect with a mycobacterial disease (Kong et al., 2013; Bittmann, 2024).

4. CONCLUSION

SPG51 is a rare and often underdiagnosed condition in childhood, frequently presenting with clinical inconsistencies that can lead to misdiagnosis. This case highlights the importance of genetic testing and careful clinical evaluation in suspected cases of HSP (Bittmann, 2024).

CONSENT

As per international standards, parental written consent has been collected and preserved by the author(s).

ETHICAL APPROVAL

It is not applicable.

DISCLAIMER (ARTIFICIAL INTELLIGENCE)

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COMPETING INTERESTS

Author has declared that no competing interests exist.

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Chapter 7
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Prevalence of Intermittent Allergic Rhinitis to Pollen among Students of the Polydisciplinary Faculty of Beni Mellal, Morocco

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ABSTRACT

Background: The frequency of respiratory allergy, including asthma and allergic rhinitis due to pollen, is increasing in the young and urban dwellers in developed countries. Allergic rhinitis negatively affects academic performance and quality of life. A better understanding of the prevalence and characteristics of allergy can help guide to strategy of management against the development of allergic rhinitis, asthma and anaphylaxis within and outside academic institutions in order to reduce the risk of morbidity and mortality.
Objective: This study was carried out to characterise pollen allergy and its relation with the environment at a university institution in order to propose a strategy of management against this disease.
Methods: The study was conducted at the Polydiscipline Faculty of Beni Mellal. For this study, 529 students (female 316 and male 213) were selected randomly from a set of about 7000 students from the institution. To support the descriptive analysis, a survey was administered to collect relevant data.
Results: The percentage of students allergic to pollen surveyed in the FPBM was 39%. This percentage was within the confidence interval of all students in the allergic FPBM [35%; 44%], estimated 5% error risk. The results proved that the selected sample was representative. The most common symptoms of pollen allergy among the students were the nasal symptoms (sneezing and nasal itching). These symptoms characterise allergic rhinitis. This study also revealed that the olive tree was the main allergen causing pollen allergy in the region. Moreover, most students experienced allergic reactions during the spring season; this could be explained by the pollination of the olive tree in this period.

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The majority of surveyed students were allergic to one or two types of plants, and the cross-reactivity between pollen and food was the most dominant.
Conclusion: This study is particularly significant, as no prior studies have documented a high prevalence of pollen allergy in the Beni Mellal-Khenifra region. The olive tree was the main allergen; this can be explained by the richness of the region of Beni-Mellal-Khénifra with this plant. These results are unexpected; normally, these youngsters must present a resistance to the pollen present in the region because they are native and have an adaptation to the environment. However, nearly a quarter of the young people surveyed in the area present an allergy. These findings highlight the need for further investigation into environmental factors and their role in the growing prevalence of pollen allergies.

Keywords: Pollen allergy; symptoms; allergen; cross-reactivity; students.

1. INTRODUCTION

Allergic rhinitis (AR) is a prevalent chronic respiratory condition characterised by nasal inflammation, sneezing, congestion, and itching, significantly impacting quality of life (Tidke et al., 2024). AR is caused by immunoglobulin E (IgE)-mediated reactions to inhaled allergens (Bousquet et al., 2020). It impacts a large segment of the global population, with prevalence rates ranging from 10% to 30% in different areas, underscoring its significant public health implications (Ellis et al., 2024; Szigeti et al., 2018).

The World Health Organisation (WHO) classifies allergic diseases fourth in the world of afflictions and considers that these diseases are a major public health problem in terms of quality of life, loss of work days or treatment of drug and even mortality. According to a WHO estimate, it could reach 50% of the world population in less than ten years (Shahali et al., 2013). For over 40 years, the frequency of respiratory allergies, including asthma and allergic rhinitis, has been increasing in the young and urban dwellers in developed countries (Abou Chakra et al., 2009; 2011) (Sabour Alaoui & Barje, 2017).

Several studies have revealed a high prevalence of AR among university students. The majority of affected students perceive a negative impact; it impacts their wakefulness and sleeping patterns of AR on their academic performance. These studies highlight the importance of greater awareness and increased screening for AR among students to minimise its detrimental effects on health and academic success (Almalki et al., 2023).

Other studies have shown that childhood Rhinoconjunctivitis (AR/C) can have a major impact on a child's life. Therefore, proper diagnosis and management are important to minimise the negative consequences of AR/C. The diagnosis of seasonal and perennial AR/C can be made through a thorough history, paying particular attention to the timing and severity of symptoms, a physical examination, and, if necessary, confirmation by allergen sensitisation testing. Management of AR/C symptoms can be achieved through allergen avoidance (Rance et al., 2025).

Today, the number of allergies is increasing in industrialised countries. Allergies due to pollens affect 10 to 15% of the overall population (Ravault et al., 200). Pollen allergy, pollinosis, is a disease linked to the presence in the air, the seasons, more or less quantity of pollen grains from a variety of plants (Abou Chakra et al., 2009). Pollinosis causes reactions at the contact areas, such as the respiratory and ocular mucosa, and occasionally, they may be responsible for skin reactions such as eczema or hives (Sabour Alaoui & Barje, 2017). She is responsible for various symptoms, including rhinitis, conjunctivitis, dry cough, skin disorders and allergic asthma. Nasal and ocular manifestations are central to the clinical symptoms (Kirmaz et al., 2005; Wagner et al., 2016). In allergic cases, the encounter with the allergen in a particular context (sensitisation phase) is determinant (Sabour Alaoui & Barje, 2017). This con- text is defined by the nature of the allergen, quantity, its modes, time and frequency in the body penetration and also by the history of immune (infection, inflammation...) of the individual (Sahali et al., 2013).

The allergic reactions are less serious, whereas they can develop into a serious form of asthma and anaphylaxis that can endanger life and require immediate medical care (Sabour Alaoui & Barje, 2017).

Anaphylaxis is a severe, potentially fatal, systemic allergic reaction that occurs suddenly after contact with an allergen, causing symptoms (pollen, food, drugs, stinging insects) (Ramón et al., 2017). It is characterised by compromise of airways, breathing circulatory problems and is usually associated with changes in the skin and mucosa (Ramón et al., 2017).

The environment (pollution, lifestyles) and climate change have been proven to play an important role in the increased prevalence of allergic diseases (D'Amato et al., 2016).

The awareness phase is defined as the exposure to the allergen, but it never enters the body as pure protein; but is often accompanied by other compounds or non-allergenic proteins, molecules or organic or inorganic particles, bacteria, viruses, or mushrooms (Sahali et al., 2013) (Sabour Alaoui & Barje, 2017). The adjuvant role of the environment associated with climate change playing on the length of exposure, the dispersion of pollen and on the distribution of species of trees and plants (rise in latitude) is involved in the increase in cases of allergy observed in recent years (Bonofiglio, et al., 2013; D'Amato, et al., 2016).

The impact of climate change on the occurrence of allergic diseases can be evaluated on the basis of changes in the time of appearance of specific phenological phases, the intensity of pollination, or the number of days when concentrations result in allergic symptoms (Sabour Alaoui & Barje, 2017). One of the most important analyses is the evaluation of how these changes can be reflected in reference to the start of the pollen season for some allergenic plant taxa (Perveen et al., 2015).

The health effects of climate change are causing an increase in the prevalence of allergic respiratory diseases, exacerbations of chronic obstructive pulmonary disease, and premature mortality (Katotomichelakis M., et al., 2016). Climate change associated with the greenhouse effect is causing adverse health effects among the most vulnerable populations, such as the elderly, children and those in socioeconomic strata in distress (D'Amato et al., 2015; D'Amato et al., 2016).

In Morocco, allergic diseases are becoming more frequent (Mallol J., et al., 2013). However, no official data are available on the prevalence of asthma and allergic rhinitis (Kettani SE., et al., 2009). This lack of epidemiological data prompted us to carry out a study to determine the prevalence of allergy amongst young people in the Béni Mellal region (Sabour Alaoui & Barje, 2017) (Sabour Alaoui & Barje, 2017).

2. MATERIALS AND METHODS

Study area: The region of Beni Mellal-khénifra is one of the twelve Moroccan regions created by the territorial division of 2015; it includes the region of Tadla-Azilal and the provinces of khénifra and Khouribga, located in the centre of the country. It encompasses the plain of Tadla, between the High Atlas and the Middle Atlas. Its centre is Béni Mellal (Sabour Alaoui & Barje, 2017). The region is characterised by a very continental climate, and the precipitation slope varies between 300 and 750 mm depending on the year. Agriculture represents the dominant activity at the level of the region, both by the jobs offered and by the effects induced on the regional economy (Sabour Alaoui & Barje, 2017).

We chose the Polydiscipline Faculty of Beni Mellal (PFBM) as a place for the study of pollen allergy; it is a public institution of higher education, which receives each year thousands of young students from different places in this region, which is characterised by its rich vegetation (Sabour Alaoui & Barje, 2017).

Study Participants: The project consists of studying the prevalence of pollen allergy in a sample size of 529 students (female 316, male 213), chosen randomly from a set of about 7000 students from PFBM (Sabour Alaoui & Barje, 2017). A questionnaire (see annexe) was prepared for this study.

Questionnaire: We conducted a questionnaire at PFBM on 529 students as a sample. These students were asked to study the prevalence of pollen allergy.

Several categories of questions were used in our questionnaire: personal data (sex, age, habitat), dichotomous question (the existence of pollen allergy), multiple choice questions to know plants that cause pollen allergy, allergic symptoms (ocular, nasal and asthmatic symptoms), onset of symptoms (summer, spring, fall and winter), the study of the existence of another disease, the existence of cross-allergy and the type of treatment used (Sabour Alaoui & Barje, 2017).

2.1 Statistical Analysis

Confidence interval: The study of the proportion of allergy in the PFBM students is an important feature in our study, but its exact value cannot be given since it is impossible to have comprehensive information about the population (Sabour Alaoui & Barje, 2017). We estimate its exact value by the confidence interval with an error risk of 5%.

The method: At the risk of error 5%, the unknown proportion of a population, which can be deduced from a random sample, is within the confidence interval of the form:

$$[p - Z_{1-\frac{\alpha}{2}} \times \sqrt{\frac{p(1-p)}{n}}, p + Z_{1-\frac{\alpha}{2}} \times \sqrt{\frac{p(1-p)}{n}}]$$

With:

p = proportion of the sample
α = risk of error equal to 5%
n = sample size
$Z_{(1-(\alpha)/2)}$ = A normal centered reduced variable for the case of $n > 30$

Statistical analysis of the data was performed using Excel and handled by the software of statistical processing (SPSS), version 22. Variables were considered statistically significant at p values of less than 0.05.

The information about the number of young people affected by pollen allergy in the FPBM was statistically evaluated by measuring the prevalence P.

$P = p * 100$

Chi-Square Test of Independence: The chi-squared test of independence is used to determine if there is a significant relationship between gender (male *vs.* female) and allergy. The chi-square statistic was calculated by using the STATISTICA 7 Software.

3. RESULTS

Pollen allergy in PFBM: The proportion of pollen allergy students in the PFBM was estimated by a confidence interval test. From the table of the law N (0, 1): $Z_{(1-(\alpha/2))} \cong 2$

The proportion of allergic students in the random sample within the poly-disciplinary faculty, number n = 529, is:

Table 1. Number of allergic students

Sex	Female	Man
Number of allergic students	128	78

$p = (128 + 78)/529 \cong 0,39$
$p = 0,39 * 100 = 39\%$

That is, in our sample, we have almost 39% of the students who are allergic to pollen according to the following table of data: [0.35; 0.44]. That is, in all students, between 35% and 44% are allergic to pollen (Sabour Alaoui & Barje, 2017).

According to the analysis of the survey results conducted at the PFBM, the prevalence of allergic students to pollen is 39% and 61% for students not allergic to pollen (Fig. 1). It means that the pollen allergy is present in almost a quarter of the students of PFBM. The 39% of allergic students fall within the confidence interval (35%; 44%) calculated for all students of the faculty at the risk of error 5%. These results show that our sampling of 529 students is representative of all students of PFBM (Sabour Alaoui & Barje, 2017).

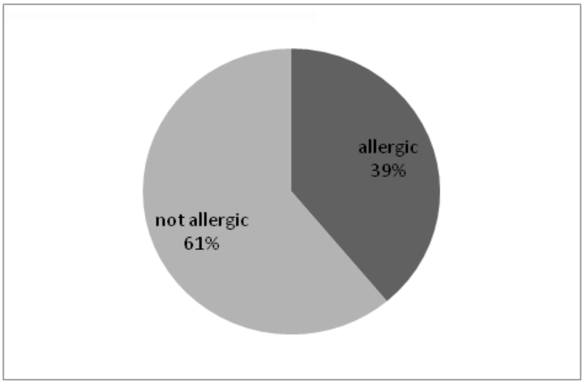


Fig. 1. Distribution of students surveyed as allergic and non-allergic to the pollen of PFBM

Pollen allergy and sex: Fig. 2 and Table 2 show that 40.5% of female students are allergic to pollen compared to all female students, while 36.6% of male students are pollen compared to all male students surveyed (Sabour Alaoui & Barje, 2017). We concluded that this difference between females and males is not significant.

Table 2. Distribution of allergic and non-allergic students according to the sex of the FPBM

Allergy			Total
Number of allergic students		**Number of non-allergic students**	
Female	128	188	316
Male	78	135	213
Total	206	323	529

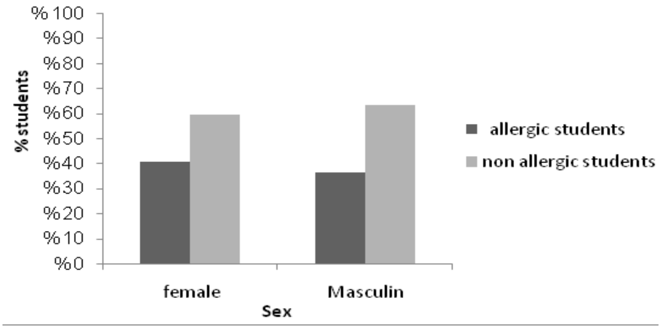


Fig. 2. Distribution of allergic and non-allergic surveyed students to the pollen of PFBM according to the category of sex

At the risk of error 5%, the unknown proportion of a population, which can be deduced from a simple random sample, is within the confidence interval of the form:

$$[p - Z_{1-\frac{\alpha}{2}} \times \sqrt{\frac{p(1-p)}{n}}, p + Z_{1-\frac{\alpha}{2}} \times \sqrt{\frac{p(1-p)}{n}}]$$

As a result, at the risk of error 5%, the proportion of allergy students in the PFBM is given by a confidence interval:

From the STATISTICA 7 Software and the table of Chi-Square,
we have the following results: Khi^2 (the observed value) = 0.81
Khi^2 (the critic value) = 3.48
DF = (2-1)(2-1)
p-value = 0,3686

Thus, we can conclude that there is independence between the two factories' sex and the presence of allergy, at the risk level of 5%.

Allergens responsible for pollen allergy: The main allergens responsible for pollen allergy in students PFBM are shown in Fig. 3 (Sabour Alaoui & Barje, 2017). We observed that the plants that promote allergy to pollen in students surveyed are olive (38%), orange (16%), almonds (12%), peach (11%) and pomegranate (10%). It is concluded that the olive tree is the main allergen causing pollen allergy. We can explain these results by the richness of the region of Beni Mellal-Khénifra by these trees, and mainly the olive tree.

Relationship between seasonal variation and pollen allergy: It is observed in Fig. 4 that the percentage of pollen allergy of allergic students, depending on the season, is as follows: 10% in autumn, 20% in winter, 64% in spring and 5% in the summer (Sabour Alaoui & Barje, 2017). From these results, it is found that the pollen allergy is frequent in the spring compared to other seasons.

Since it was found that the olive tree is the main allergen responsible for the allergy to pollen, and also we know that the olive tree pollination season is spring, this explains the increasing number of students allergic to pollen during this season (Sabour Alaoui & Barje, 2017).

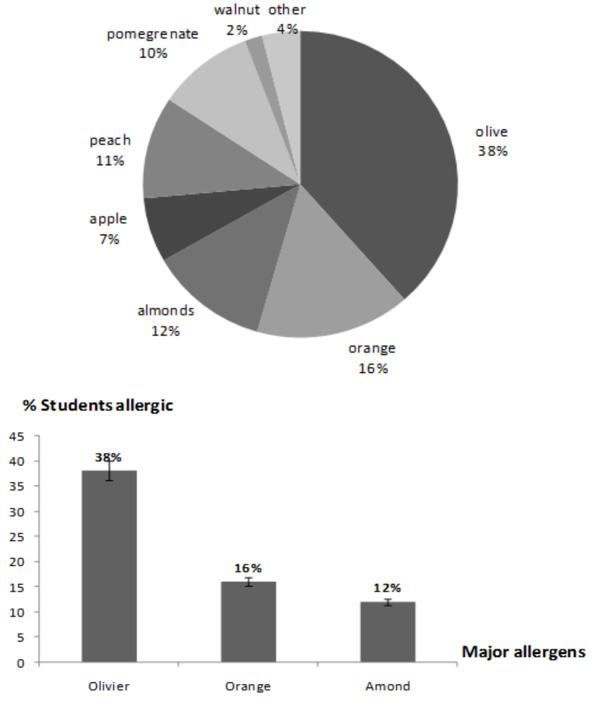


Fig. 3. Distribution of allergens responsible for pollen allergy in the allergic students PFBM

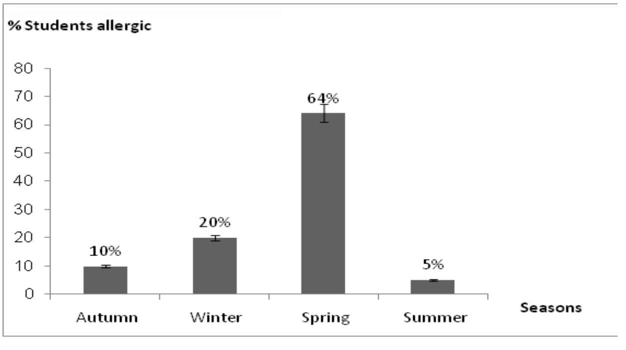
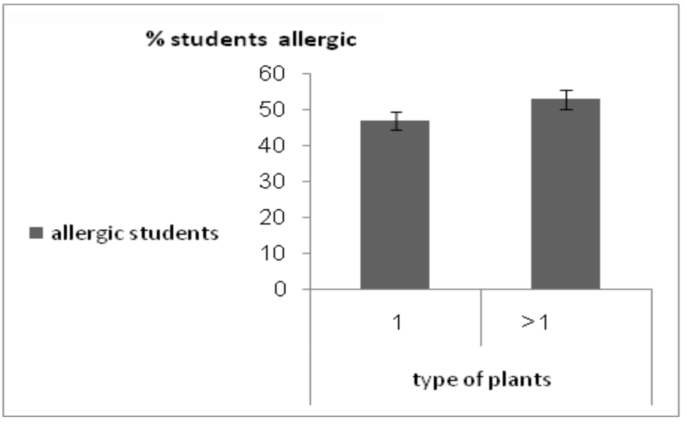


Fig. 4. Distribution of pollen allergy in allergic students depending on the seasons

Relationship between the number of types of plants and pollen allergy: The results show that 52% of young people are allergic to more than one plant, while 47% are allergic to a single plant. Analysis of the results (Fig. 5) shows that the percentage of allergic students to one plant is 47%, two plants 31%, three plants 17%, four plants 4% and more than four 1% (Sabour Alaoui & Barje, 2017). We find that the majority of surveyed students are allergic to more than one type of plant.



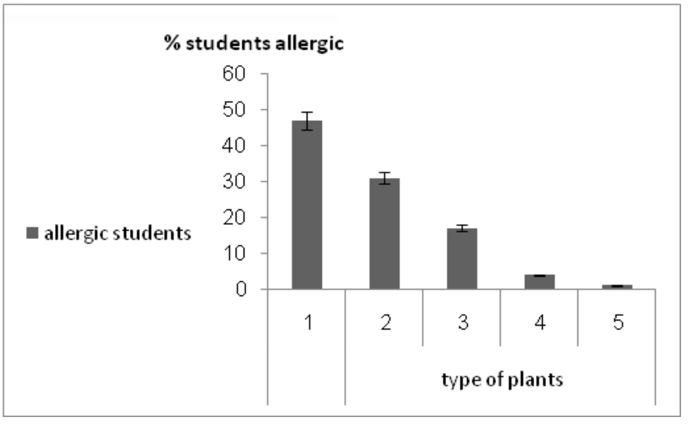


Fig. 5. Distribution of students surveyed at PFBM depending on the number of types of plants responsible for pollen allergy

Symptoms due to pollen allergy among students allergic: The most common symptoms responsible of the allergy to pollen among students in the PFBM are: sneezing (70%) and eyes watering (59%) and nasal itching (51%) (Fig. 6) (Sabour Alaoui & Barje, 2017). These results show that the nasal symptoms and ocular symptoms are the most dominant.

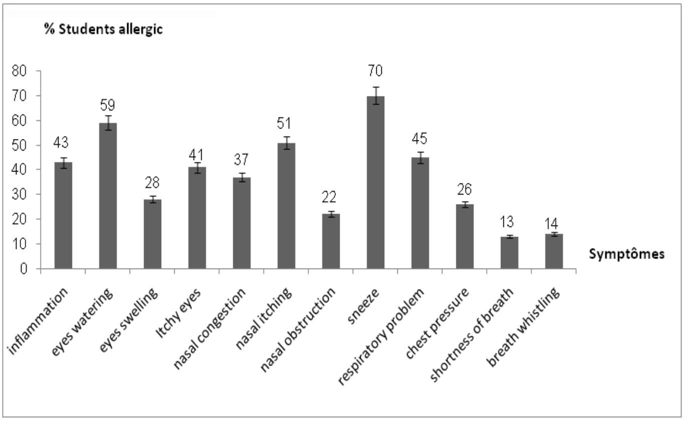


Fig. 6. Distribution of symptoms due to pollen allergy among students surveyed by the PFBM

Cross-reactivity between pollen and other allergens: Questionnaire data carried out show that the cross-reactivity in the allergic students in PFBM between pollen allergen and food is the most dominant (27%). While cross-reactivity pollen allergy-dust is 16%, and pollen allergy-animals is less common, 5% (Fig. 7) (Sabour Alaoui & Barje, 2017).

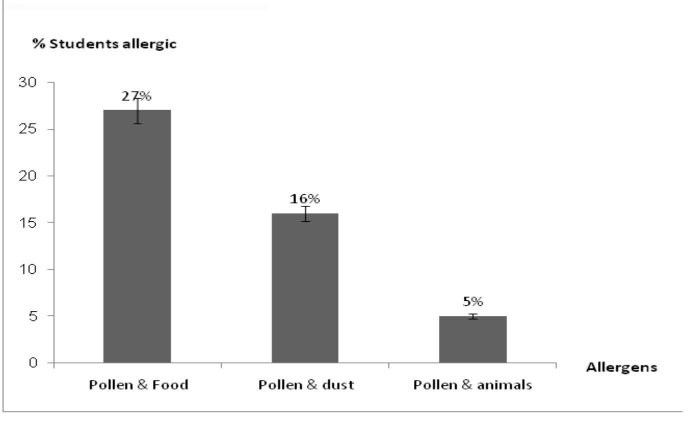


Fig. 7. Distribution of cross-reactivity between pollen and other allergens in the surveyed students, PFBM

4. DISCUSSION

Allergy diseases are currently a global public health problem. The scarcity of epidemiological studies in Morocco prompted us to carry out this study which the objective is to determine the prevalence of pollen allergy in the Beni Mellal region (Sabour Alaoui & Barje, 2017).

The percentage of students allergic to pollen surveyed in PFBM is 39%, this percentage might be explained by the wealth of the region in vegetation. This percentage falls into the confidence interval [35%; 44%] estimated at a 5% error risk of all allergic students in PFBM, which proves that our sample is representative (Sabour Alaoui & Barje, 2017). We show for the first time that almost a quarter of students had hypersensitivity to pollens.

All students surveyed are from the region of Beni Mellal. These results are unexpected; normally, these youngsters must show resistance to pollen present in the region, but we find the opposite (Sabour Alaoui & Barje, 2017). However, constraints such as climate change have affected the region over the past few years, notably, global warming is exacerbating the problem of increasing pollination.

We suggest that climate and environmental factors have the ability to influence local botany and aerobiology by increasing the number of tree pollen.

We also found that the female and male allergic percentages are not significant. We concluded that there is independence between the two factories' sex and the presence of allergy (Sabour Alaoui & Barje, 2017).

Our study shows that the olive tree is the main allergen causing pollen allergy because the region Beni Mellal-Khénifra is rich in this plant. Olive pollen is an important cause of pollinosis and is considered one of the most important causes of respiratory allergic disease in the Mediterranean region.

The results show that 52% of young people are allergic to more than one plant, while 47% are allergic to a single plant (Sabour Alaoui & Barje, 2017). These results suggest the possibility that pollen allergy over time weakens the immune system and makes it susceptible to aggression with other pollen, or suggests the possibility of aggression with pollen that presents molecular resemblances or proteins that share common epitopes.

The most common symptoms of pollen allergy among students are nasal (sneezing and nasal itching) and ocular symptoms (Sabour Alaoui & Barje, 2017). These manifestations are central to the clinical symptoms of allergic rhinitis.

This study shows that most students, 64%, have allergies in the spring season; this could be explained by the pollination of olive trees in this period (from April to June). Our study also shows that pollen allergy is present in the other seasons, autumn 10 %, winter 20% and summer 5% (Sabour Alaoui & Barje, 2017). These results can be explained by the climate change that influences the duration and intensity of pollen seasons, which can be in line with the air pollution contributing to the increase in respiratory allergies and asthma (D'Amato et al., 2015; D'Amato et al., 2016) in this region.

Our study also shows that cross-reactivity between pollen and food is the most dominant, and then that pollen allergy cross-dust (Sabour Alaoui & Barje, 2017). Our results confirm other recent research on the evidence of this reactivity between pollen and food, and which tries to understand the mechanism (Popescu, 2015). Research shows that pollinosis patients often display adverse reactions upon ingestion of plant-derived foods as a result of IgE cross-reactive epitopes shared by pollen and food allergen sources (Bousquet et al., 2008; Popescu, 2015).

5. CONCLUSIONS

Using the questionnaire as a screening tool for diagnosing the presence of pollen allergy in students of PFBM, we confirmed the high rates of pollen allergic students and found that the prevalence of allergy in students varies across seasons. We suggest that the seasonal variation associated with climate change influences the duration and intensity of pollen seasons in the region (Sabour Alaoui & Barje, 2017).

Our results allow us to ask several questions about the causes of allergy and to look for strategies to control the epidemic of this disease in these universities.

CONSENT

As per international standards or university standards, Participants' written consent has been collected and preserved by the author(s).

ETHICAL APPROVAL

It is not applicable.

DISCLAIMER (ARTIFICIAL INTELLIGENCE)

Author(s) hereby declare that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc) and text-to-image generators have been used during writing or editing of this manuscript.

COMPETING INTERESTS

Author has declared that no competing interests exist.

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Chapter 8
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Influence of Homozygous Sickle Cell Disease on the Outcome of *P. falciparum* Malaria Infections in Indian Patients

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ABSTRACT

Sickle cell disease includes a variety of conditions, including the homozygous state of the disease, which is commonly known as sickle cell anaemia. India has a high frequency of the sickle haemoglobin allele, like many other countries. The common geographical distribution of sickle cell haemoglobin (HbS) and *P. falciparum* malaria in Africa has led to the hypothesis that HbS provides partial protection against *P. falciparum* malaria. While the heterozygous state of the disease (HbAS) is known to provide protection against *P. falciparum* malaria, less is known about the role of the homozygous state (HbSS). *P. falciparum* infection possibly worsens the clinical condition of HbSS subjects because of their lower baseline haemoglobin level and with a hypofunctional spleen. India has the second largest population of sickle cell disease births after Nigeria. The disease is found predominantly in the malaria-endemic areas of central India. However, the clinical presentation of HbSS subjects seems far more benign in India than in Africa, with fewer complications in childhood and a higher longevity. The clinical consequence of *P. falciparum* infection in Indian HbSS subjects is not clearly known. It is also not known whether the homozygous (HbSS) state in India provides similar protection as that of the heterozygous (HbAS) state against *P. falciparum* malaria, considering their benign clinical presentation, particularly in childhood. A cohort study recruiting HbS infants from *P. falciparum* malaria endemic areas in India will help in understanding the interaction of disease-modifying factors as well as the impact of *P. falciparum* infection on the severity of the disease, and whether antimalarial prophylaxis is indicated.

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1. INTRODUCTION

Sickle cell disease (SCD) is a global disorder, with the highest number of births in Nigeria and the Democratic Republic of the Congo, followed by India, with the third-highest number of births with sickle cell anaemia (Gupta et al., 2024; Uyoga et al., 2022). SCD is a genetic haematological disorder resulting from a mutation in the beta-globin gene, which leads to the production of abnormal haemoglobin S (HbS) (West and Aitafo, 2023). India exhibits a high prevalence of the sickle haemoglobin (HbS) allele (Almarghalani et al., 2024).

JBS Haldane was the first to speculate that the risk of dying due to a parasitic disease is partly dependent on the genetic makeup of the individual and that the thalassemia heterozygote condition could provide protection against malaria infection (Haldane, 1949). The hypothesis was taken forward by Allison AC in 1954 (Allison, 1954), who showed that the HbS gene distribution was more frequent in areas of high malaria transmission, and the heterozygotes for HbS (HbAS) appeared to have less susceptibility to malaria infection. Allison's observations were subsequently confirmed by others (Williams, 2006). Haemoglobin is a tetramer protein composed of two alpha (α)-like and two beta (β)-like globin polypeptides, each polypeptide containing a haem ring. Unequal synthesis of either of the globin gene polypeptides leads to thalassemia; reduced α-chain synthesis to α thalassemia and reduced β-chain synthesis to β-thalassemia. Structural disorder of the globin chain leads to haemoglobinopathies. Sickle haemoglobin is a structural disorder of the beta globin chain, where a glutamic acid in the sixth position is replaced by a valine (Steinberg et al., 2010). The term sickle cell disease (SCD) includes a variety of conditions, the homozygous (HbSS) state of the disease, commonly known as sickle cell anaemia (SCA), and the compound heterozygous states, such as HbS-β-thalassemia, HbSD, HbSE, HbSC, HbSO-Arab disease, etc (Serjeant and Serjeant, 2001). SCA is the commonest life-threatening genetic disorder worldwide (Uyoga et al., 2022). Although SCA is the most common genetic variant of SCD, the term SCD is used for any condition in which pathological consequences result from HbS production.

HbS undergoes polymerisation at lower oxygen availability, commonly encountered in post-capillary venules, and is responsible for the pathophysiology of the disease. Since humans are diploid, the abnormality can be homozygous, involving both alleles (HbSS), or heterozygous, involving only one allele (HbAS). While the heterozygous state is fairly benign, the homozygous state manifests with severe complications such as severe anaemia and vaso-occlusive disorders (Serjeant and Serjeant, 2001). The relative fitness (i.e., survival to reproductive age) of the African homozygous SCD subjects is close to zero, and the selective agent is considered as *P. falciparum* malaria (Modell and Darlison, 2008). The homozygous HbSS disease is considered a health hazard because of its inherent complications, but the heterozygous HbAS subjects, who are otherwise normal, are protected from malaria (Pasvol, 2009). This is called balanced polymorphism because the disadvantage of homozygotes coexists with the advantage of heterozygotes.

2. *P. Falciparum* INFECTION WORSENS SCD COMPLICATIONS

The heterozygous state (HbAS) of the disease is known to provide protection against *P. falciparum* malaria (Luzzatto, 2012), while the protective effect of the homozygous state (HbSS) on malaria infection is less studied and less understood. Protection against *P. falciparum* is considered proportionate to the HbS content in the RBCs (Williams and Obaro, 2011). Thus, it is expected that the homozygous state with higher HbS content should provide better protection than either heterozygotes (HbAS) or individuals with normal haemoglobin (HbAA) against *P. falciparum* malaria. Evidence from *in vitro* studies indicated that HbSS-containing RBCs prevent both invasion and development of *P. falciparum* parasites under conditions of low oxygen tensions, even more than in HbAS-containing RBCs (Pasvol et al., 1978). However, these observations cannot be extrapolated to *in vivo conditions* because of the influences of the microcirculatory and immunological status of the host.

One of the earlier clinical studies had shown higher resistance to *P. falciparum* infection in patients with HbSS than those with HbAS or HbAA (Aluoch, 1997). In this study, malaria parasites were present in 44.1% of HbAA, 36.2% of HbAS, and 20% of HbSS RBCs. Another study from Kenya also observed that the prevalence of parasite density was lower among patients with HbSS than they were among patients with HbAA (Komba et al., 2009). But because of the increased haemolysis and impaired splenic function, the complications were more in the homozygous SCD patients, in spite of low parasitaemia (Mwaiswelo et al., 2020). Most of the published studies are hospital-based and do not reflect the situation at the community level, where most African children with SCD die early, before they can reach any health care facility. Indian studies on the malaria infection in SCD patients are also hospital-based. A study from Odisha state of India observed that the consequence of malaria infection was more severe in SCA patients than those with normal haemoglobin (HbAA) subjects, because of more haemolysis in the SCA group (Purohit et al., 2018).

The RBC lifespan in SCD patients is far less due to persistent haemolysis, which worsens on infection with *P. falciparum* parasites, and the resulting anaemia may be life-threatening (Luzzatto, 2012). Similarly, like any other acute infection, malaria can trigger vaso-occlusive pain crisis in HbSS individuals. In addition, functional asplenia seen in HbSS disease prevents filtering and removing parasitised RBCs. Therefore, the malaria-related mortality in SCD children could be as high as 10 times higher than the non-SCD (HbAA) children (McAuley et al., 2010). Thus, malaria is considered to contribute substantially to the early mortality of SCD children in Africa. In sub-Saharan Africa, malaria claims the life of a child every two minutes (Eleonore et al., 2020). Although HbSS erythrocytes, like HbAS erythrocytes, can provide some protection against *P. falciparum* parasites, the protective advantage is overwhelmed by the disadvantages of homozygous SCD complications. Malaria is considered an important cause of morbidity and mortality in African children with SCA; therefore, malaria chemoprophylaxis is often recommended (Aneni et al., 2013).

2.1 Distribution of HbS in India

India had the second largest predicted SCA births in 2010, after Nigeria, based on the global burden of disease (GBD) modelling data (Piel et al., 2013). A later epidemiological map with an enlarged number of data points showed considerable geographical overlap with the previous map (Hockham et al., 2018). The new map included population composition of SCD and claimed that the socioeconomically disadvantaged classes of the population suffer most from the disease. It showed the highest frequencies of HbS alleles across a central belt, an area of high allele frequency in southern India, and a heterogeneous distribution of the HbS allele across the whole country (Hockham et al., 2018). SCD forms a major public health problem in states of Madhya Pradesh, Odisha, Chhattisgarh, Jharkhand, parts of Gujarat, Maharashtra, Andhra Pradesh and Tamil Nadu (Fig. 1a). The spatial distribution map of SCD almost overlaps with the *P. falciparum* malaria endemic areas (Fig. 1b).

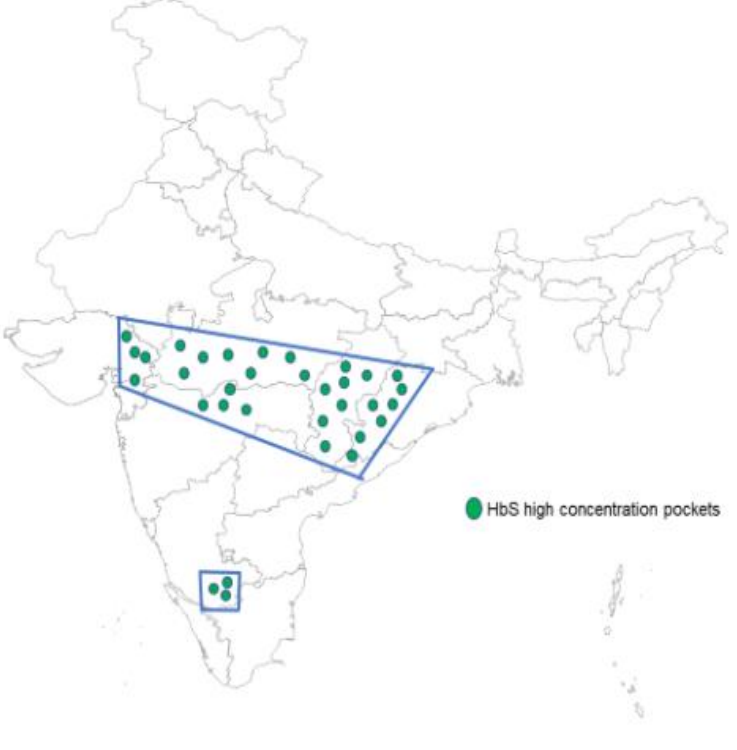

Fig. 1a. Map of Sickle Cell Disease in India

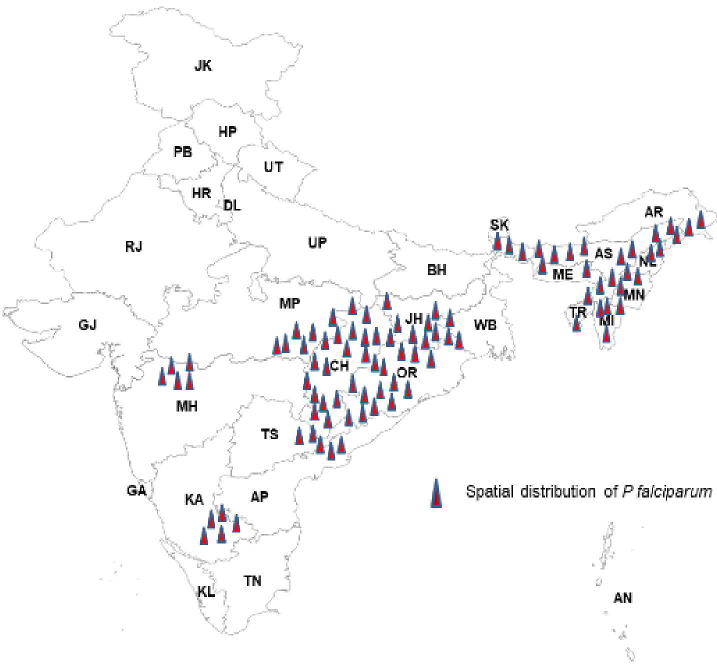

Fig. 1b. Map of *Plasmodium falciparum* distribution in India

3. CLINICAL MANIFESTATIONS OF SCD IN INDIA ARE DIFFERENT FROM AFRICA

Although SCD is caused by a single mutation in the β globin gene, the clinical manifestation of the disease is heterogeneous. The predominant phenotypic expression of SCD can either be the vaso-occlusive type or the haemolytic type. The vaso-occlusive events are triggered by adherent sickle erythrocytes, and the most important manifestation is the repeated attacks of acute pain crisis. In the hemolytic phenotype, intravascular hemolysis occurs due to injured sickle RBCs leading to anaemia (Kato et al., 2017). Observations from India on the clinical manifestation of homozygous sickle cell disease appear different from the African pattern (Serjeant, 2016). The disease manifestation is less severe in Indian children than in African children. While African children often develop SCD symptoms at 3-4 months of age and the majority of them rapidly deteriorate to die between 6-12 months of age, most Indian children with HbSS are asymptomatic and develop complications later in life (Serjeant and Serjeant, 2001). The baseline haemoglobin levels in Indian children are much higher than African children (Serjeant, 2016). While functional asplenia is more common in African children, splenic hypertrophy is common in Indian HbSS patients

(Table 1). Some Indian SCD patients may continue to remain asymptomatic even in adulthood (Serjeant, 2016). What contributes to this difference in clinical severity between African and Indian SCD patients, though not clear, differences in several genetic, physical, and environmental factors have been noticed in these populations. Association of α-thalassemia, mutations in the β-globin gene cluster, foetal haemoglobin concentration (HbF, $\alpha 2\gamma 2$), and splenic function have been proposed to play a major role in the differences (Serjeant, 2016). In addition, environmental factors such as infections, dehydration, physical and psychological stress, extreme temperatures, etc, also influence sickling episodes (Tewari et al., 2015).

Table 1. Clinical course difference between African and Indian sickle cell disease subjects

	African	**Indian**
Onset of disease	Early onset	Late onset
Death	Early childhood death (70% below five years)	More in adults
Spleen function in children	Hypofunction, Asplenia	Splenomegaly
Infections	Pneumococcal sepsis	Not known
Frequency of severe anemia (Hb < 6.0 g/dl)	More	Less

HbF presumably interferes with HbS polymerisation and provides protection against frequent episodes of painful crisis (Steinberg et al., 2014). Watson first reported that the absence of clinical symptoms of SCD in newborns may have been due to a higher concentration of HbF, and the occurrence of clinical symptoms starts with a decline in HbF levels (Watson, 1948). Higher HbF levels were associated with lower frequency of SCD complications such as acute painful crisis, leg ulcers, osteonecrosis and acute chest syndromes (Brousse et al., 2018). Recent studies from India as well as from Africa have shown that higher HbF concentrations in SCD patients protect against severe complications and death (Uyoga et al., 2019, Jit et al., 2019). Several therapeutic agents targeted at increasing the levels of HbF concentration have been explored; the most widely used is the cytotoxic agent hydroxyurea (Charache et al., 1995; Thakur et al., 2019).

Concurrent association of α-thalassemia with SCD decreases the deleterious effects of SCD. Reduced synthesis of one type of globin polypeptide compensates for reduced synthesis or premature destruction of the complementary globin polypeptide. Co-inheritance of one copy of the $-\alpha 3.7$ deletion in the α-globin gene decreases the severity of many clinical complications in SCD patients (Raffield et al., 2018). While α-thalassemia occurs in 35-40 per cent of African HbSS patients, it may reach the level of 50 per cent in Asian haplotypes (Higgs et al., 1982; Kar et al., 1986). A later study from Maharashtra State found that the simultaneous presence of α-thalassaemia in SCA patients was less common, but a high proportion of them were compound heterozygotes with HbS/β thalassaemia (Jain et al., 2016). This raises a query about the existence of multiple clinical phenotypes in India, depending on their geographical distribution.

The β globin gene haplotype in SCD is different in India from that of African subjects. There are five known β globin gene haplotypes, i.e Benin, Bantu, Cameroon, Senegal and Arab-Indian (AI) (Steinberg, 2020). Sickle cell mutations in Africa occurred independently at different sites in the beta globin gene locus. These were named according to the area from which they were first identified (Nagel et al., 1985). These haplotypes are also commonly found in African migrants to Europe and the Americas. Indian SCD is of Arab-Indian (AI) or Asian haplotype, which occurred independently of African haplotypes (Kulozik et al., 1986). HbSS subjects with AI haplotype show a milder form of the disease during childhood, while adults develop more complications resembling African patients(Habara et al., 2017).

In African SCD patients, the spleen is central to the early pathology. The spleen in SCD is morphologically and functionally normal at birth, but early development of intravascular sickling rapidly deteriorates splenic function in the first year of life (Pearson et al., 1969). These children develop symptoms at the age of 3-4 months, and the greatest chance of dying is between 6-12 months of age (Serjeant and Serjeant, 2001). By the age of 5 years, most children develop functional autosplenectomy due to repeated splenic vaso-occlusion and infarction leading to fibrosis and progressive atrophy of the organ (Brousse et al., 2014). Sometimes, however, splenomegaly may be the predominant manifestation, which may persist into adulthood. In Indian SCD patients, the spleen is often larger and the splenomegaly may persist longer, occasionally requiring splenectomy (Kar, 1999). The spleen has an important immune defence function against senescent and altered red cells and against malaria infection (Engwerda et al., 2005). Spleen is responsible for clearing parasite-infected erythrocytes, and parasite clearance is prolonged in persons with impaired splenic function. Several studies have shown significantly more malaria parasitaemia in those who have undergone surgical splenectomy in comparison to those with functioning spleens (Kar, 1999; Boone and Watters, 1995; Bach et al., 2005).

In summary, Indian SCD patients have comparatively higher frequencies of alpha thalassemia, higher HbF levels, higher total haemoglobin and red cell counts, and lower mean RBC volume and haemoglobin concentration, and reticulocyte counts, thus with less SCD-related complications than the African SCD patients (Serjeant, 2016). But other studies have questioned the benign nature of Indian SCD. One study from Odisha state, India, observed frequent episodes of pain crisis in adult SCD patients, in despite having higher HbF levels and association of α-thalassemia (Mashon et al., 2009). Similarly, another study from Maharashtra State, India, noticed a higher frequency of complications in spite of higher HbF levels, but found that α-thalassaemia was less common than in previous studies, and more patients were compound heterozygotes with HbS/β-thalassaemia (Serjeant, 2016). These observations raise a suspicion that Indian SCD phenotypes may not be homogenous.

4. NEGATIVE EPISTASIS OF A-THALASSEMIA AND HBF WITH HBS IN *P. falciparum MALARIA*

If the association of higher HbF level and α-thalassemia reduces the severity of complications in SCD, what effect would it have on the protection against malaria? HbAS and α-thalassemia, when inherited alone, each is protective against severe P. falciparum malaria, but the protection afforded is lost when the two conditions are inherited together (Williams et al., 2005). Negative epistasis can limit the frequency of α-thalassaemia in a population in which sickle cell is present. Thus, in sub-Saharan Africa, the frequency of α-thalassaemia does not exceed 50%. The relationship between α-thalassaemia and SCD in South Asian populations is more complex, showing very high levels of α-thalassaemia combined with varying levels of HbS in different geographic regions. Malaria selection can explain why sickle cell has penetrated certain South Asian populations but not others (Penman et al., 2011). Similarly, higher levels of HbF in SCD are reported to attenuate the protective efficacy of HbS (Oxendine Harp et al., 2023). A study from Tanzania showed a higher prevalence of malaria in HbAA compared to HbAS and HbSS, confirming the protective effect of HbS. Lower prevalence of malaria in HbAA with high HbF supports a protective effect of HbF. However, higher prevalence of malaria in HbSS subjects with high levels of HbF suggests loss of malaria protection, a negative epistasis between HbF and HbS on malaria (Mmbando et al., 2015).

5. CONCLUSION

While the life expectancy of SCD patients of African origin in Europe and the Americas has substantially increased, in sub-Saharan Africa, less than half of those born with SCD live beyond the age of five years. Very little is known about the natural history of SCD in India and the estimated life expectancy of those with SCD. Information about the life-course sequence of SCD complications, the rate of decline of HbF level, the effect of wide variation in HbF concentrations, deterioration in the splenic function, which infections are important, and the role of antibiotic and antimalarial prophylaxis, etc, is not available from India. Recognising the magnitude of the problem, the Government of India has framed a policy on the prevention and control of haemoglobinopathies in India. The policy concentrates more on setting up “centres of excellence for haemoglobinopathies” with the primary purpose of case management and prevention. However, the interventions will be successful only when we clearly know the epidemiology of the disease in India.

The other important issue to be addressed is regarding the negative epistasis on protection against malaria. Whether the association of α-thalassemia and higher levels of HbF in Indian SCD patients contributes to negative epistasis on falciparum malaria is also not known. It is not clear whether homozygous HbSS disease in India provides protection against falciparum malaria because of its milder form, especially in children, or if the protective potential is completely lost due to negative epistasis leading to aggravation of the complications. In addition, Indian SCD patients are frequently associated with the β-thalassemia gene.

Though distinguishing SCA from SCA-β-thalassemia is of little clinical consequence, they are important for genetic counselling and prenatal diagnosis.

This lack of information limits the possibility and development of evidence-based locally appropriate models of clinical care and prophylaxis for Indian children and adults. Though the SCD-related mortality in Europe and the Americas has declined among children of African origin, SCD mortality in adults has not decreased in the last 30 years because of acute and chronic end-organ damage. The fundamental gaps in knowledge persist in relation to the identification of disease modifiers and the control mechanisms of switching of fetal to adult haemoglobin. To answer some of these questions, large longitudinal cohort studies can be conducted in malaria-endemic areas. The studies can be designed to address the contribution of environmental, social, and genetic risk factors and health and disease outcomes, to address the public health policies.

DISCLAIMER (ARTIFICIAL INTELLIGENCE)

We haven’t used generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc) and text-to-image generators have been used during writing or editing of this manuscript.

CONSENT AND ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Author has declared that no competing interests exist.

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Chapter 9
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Health Care Seeking Behaviour Among Pregnant Women in Rural Western India: A Qualitative Study

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ABSTRACT

Background: One of the most important aspects of maternal health services is antenatal care (ANC).
Aim of the Study: The perceptions and care-seeking behaviour of pregnant women living in rural Western India are examined in this study, as is their knowledge of pregnancy-related complications.
Methods: A qualitative descriptive study was carried out in 2022 with 74 pregnant women who were randomly selected from the ANC register and were in their third trimester. Using a pretested guide that covered eight thematic areas, data were collected through in-depth interviews. Thematic coding was used to analyse the transcriptions of the interviews.
Results: The majority of women understood the value of regular ANC visits. However, little was known about specific complications like pre-eclampsia or gestational diabetes. Although transportation obstacles and reliance on spouses for decision-making were observed, government health services were favoured because they were accessible and reasonably priced. Families provided support, and there was little dependence on traditional healers. A few participants voiced concerns about the results of deliveries, especially caesarean sections.
Conclusions: The study draws attention to the disparity in general ANC awareness and specialised knowledge regarding pregnancy complications.

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Maternal outcomes can be improved in rural Western India with sustained community involvement and education provided by primary healthcare systems.

Keywords: Antenatal care; pregnancy; qualitative study; rural health; Western India.

1. INTRODUCTION

Because of its vital role in lowering maternal and neonatal morbidity and mortality, maternal health remains a key priority in both national and international health agendas. The current sustainable development goal is to reduce the maternal mortality ratio (MMR) to 70 per 100,000 live births by 2030 (Madhusoodanan et al., 2025). In order to achieve favourable maternal and child health outcomes, antenatal care (ANC) acts as a preventive platform that makes it possible to promptly identify pregnancy-related complications, provide health education, and encourage institutional delivery. It gives a chance for the pregnant mothers and health care providers to discuss adequate nutrition, identify obstetrics danger signs, and a childbirth plan, and protective care, such as the supply of ferrous sulfate or folic acid pills and tetanus toxoid immunization (Yoseph et al., 2025; Nihal & Shekhar, 2024; Nargus et al., 2022). In order to guarantee thorough monitoring and intervention for the health of both the mother and the foetus, the World Health Organisation advises having at least eight ANC contacts during pregnancy (World Health Organisation, 2016).

Significant regional and rural-urban disparities in maternal health service utilisation and access still exist in India, despite significant progress made through initiatives like the Pradhan Mantri Surakshit Matritva Abhiyan (PMSMA), the Janani Suraksha Yojana (JSY), and the larger RMNCH+A strategy (Ministry of Health and Family Welfare, 2013; Ministry of Health and Family Welfare, 2016). Only 51.2% of pregnant women nationwide received four or more ANC visits, according to the fourth round of the National Family Health Survey (NFHS-4), with lower percentages recorded in a number of rural Western Indian districts (International Institute for Population Sciences & ICF, 2017). Even though coverage has increased, issues with care quality, timeliness, and comprehensiveness still exist.

Western India, comprising states such as Maharashtra, Gujarat, and parts of Rajasthan, presents a unique socio-cultural and economic milieu. Rural areas within this region are often characterised by patriarchal family structures, limited female autonomy, seasonal employment, and under-resourced healthcare infrastructure, all of which affect healthcare-seeking behaviour during pregnancy (Sharma et al., 2014; Gaikwad et al., 2018). In such contexts, pregnancy is often perceived as a routine physiological process rather than a potentially risky period requiring medical surveillance, contributing to delays in seeking antenatal care unless complications become evident (Chandhiok et al., 2006; Finlayson & Downe, 2013).

Apart from these social and cultural factors, structural barriers such as transport problems, costs of care, and the lack of involvement of health professionals also contribute to the underuse of ANC services. This is exacerbated by a lack of awareness of the warning signs of pregnancy, reliance on male decision-makers in the household and concern about the quality of public health services (Qureshi et al., 2016; Singh et al., 2012). While the national surveys provide important quantitative data on the indicators of midwifery, they are insufficient to explain the behavioural and perceptual dimensions that underlie rural women's health-seeking patterns.

Quality research provides an opportunity to explore these dimensions in greater depth. Studies in South and North India have shown similar barriers, but despite its sizeable rural population and diverse socio-economic profile, rural West India is still under-represented in the literature (Salve et al., 2017; Mohanty et al., 2019). It is crucial to understand how pregnant women in these regions perceive the ANC, what informs their health choices and what obstacles they face in order to design tailor-made interventions that are in tune with local realities.

With an emphasis on their awareness of pregnancy complications, knowledge of prenatal care, and the factors influencing their decision-making, this study intends to investigate the health care-seeking behaviour and perceptions of pregnant women in rural Western India. The study aims to highlight the importance of maternal health in reducing maternal and neonatal morbidity and mortality, which remains a top priority in both national and international health agendas.

This study seeks to generate insights that can guide more context-sensitive maternal health policies and community-level interventions by using qualitative methods to document their lived experiences.

2. MATERIALS AND METHODS

Study Design and Setting: In 2022, a qualitative descriptive study was carried out in a Western Indian rural area. The study area served a population mostly involved in daily wage labour and agriculture, and was situated within the service jurisdiction of a Rural Health Training Centre (RHTC) connected to a medical college. In order to reflect the sociocultural diversity and maternal health-seeking behaviours characteristic of rural Western India, this area was specifically chosen. The purpose of the study was to investigate the use of prenatal care, knowledge of pregnancy-related issues, and obstacles to seeking care among third-trimester pregnant women. In order to obtain a deeper comprehension of individual experiences, convictions, and contextual factors that quantitative approaches might not fully capture, the qualitative design was selected.

Participant Selection: Women who were registered with the ANC register at RHTC and were older than 27 weeks of gestation were eligible to be included. From the eligible list, 74 participants were chosen using a straightforward random sampling technique.

Pregnant women who were 18 years of age or older, were currently living in the chosen village for at least six months, and were willing to give informed consent were the requirements for inclusion. Women who had language barriers or known cognitive impairments that hindered effective communication were not included.

Data Collection Procedure: In-depth, in-person interviews in the local tongue (Gujarati or Hindi, depending on the region) were used to collect data. Before the study began, a semi-structured interview guide was created and pretested. Eight predetermined thematic areas comprised the open-ended questions in the guide: (1) prenatal care knowledge and perception; (2) pregnancy complications understanding; (3) provider preferences; (4) financial burdens and care costs; (5) the impact of family and social support; (6) perceived barriers to healthcare access; (7) the role of traditional/spiritual beliefs; and (8) emotional concerns and fears regarding pregnancy.

Medical interns and certified medical social workers who had completed a two-day training program on qualitative interviewing methods, ethical issues, and data recording procedures were among the interviewers. Depending on the comfort and privacy of the participants, interviews were held at either their homes or nearby health sub-centres. With prior consent, each interview was audio recorded and lasted roughly thirty to forty-five minutes.

Data Management and Analysis: Where required, audio recordings were translated into English and transcribed. Bilingual researchers checked translations for accuracy and cultural context. Following Braun and Clarke's six-phase methodology—becoming familiar with the data, initial coding, finding themes, evaluating themes, defining themes, and creating the final report—manual coding was done using thematic analysis.

Three trained interns, a medical social worker, and an assistant professor of community medicine made up the multidisciplinary analysis team that examined the transcripts and coded them on their own. Discussion and agreement were used to settle disagreements over interpretation. Microsoft Word and Excel were used to analyse the data.

3. RESULTS

The study included 74 pregnant women who were in the third trimester of their pregnancy. A summary of the demographic traits is provided below, followed by an in-depth thematic analysis.

3.1 Sociodemographic Profile

Participants were 22 years old on average (SD ±1.8), and their households had an average of 3.6 people (SD ±1.3). In terms of education, 8–11% of the participants lacked literacy. While 41.89 per cent of participants worked in the informal sector or in agriculture, the majority (58.11 per cent) were homemakers.

Table 1. Socio-demographic details of participants

Variables	
Age mean (SD)	22 (1.8)
Family Members mean (SD)	3.6 (1.3)
Education n (%)	
Illiterate	6 (8.11)
Literate	68 (91.89)
Occupation n (%)	
Home maker	43 (58.11)
Agricultural/Others	31 (41.89)

3.2 Knowledge, Perception, and Beliefs About Antenatal Care

Every participant acknowledged how important regular prenatal checkups are. Community health workers' counselling and prior experiences played a major role in the acceptance of the concept of monthly visits to health centres. The majority of participants thought that getting supplements, checking blood pressure, and tracking foetal growth were all advantages of prenatal visits.

"If I miss a check-up, the doctor and nurse ask about it next time. They take it seriously," – Participant R10

Positive experiences at primary health centres were also recalled by the women, including regular health education sessions, iron and calcium tablet distribution, and courteous treatment. Although they did not fully incorporate it into their conception of prenatal care, they did perceive ANC as a preventive measure.

3.3 Perceptions and Awareness of Pregnancy Complications

Women were aware of common pregnancy-related discomforts like nausea, fatigue, and swelling, but they were not as aware of serious complications like hypertensive disorders, gestational diabetes, or anaemia. While some participants acknowledged that serious problems might necessitate hospital-based care, they were unable to identify specific warning signs or their consequences.

"I don't know the names of problems, but if there is too much weakness, it's not good," – Participant R17

However, it was widely acknowledged that frequent visits and early diagnosis could help avert negative consequences.

3.4 Healthcare Preferences: Government vs. Private Facilities

Because government facilities are affordable, offer free medications, and are conveniently located, most participants reported using them for ANC. Trust in community-known government healthcare providers was another factor mentioned by many. However, when questioned about emergencies or childbirth, several women said that they might choose private hospitals or transportation because they were worried about the public system's insufficient facilities or lengthy wait times.

"For check-ups, I go to the government clinic. But for delivery, if needed, we may go to a private hospital," – Participant R28

3.5 Financial Considerations and Perceived Burden of Care

Participants showed a mixed awareness of the expected delivery costs. Some estimated that the cost of a secure delivery would be between 5000 and 10000 rupees, while others were confident that government schemes would cover their costs. Many of them were prepared by saving up or by planning informal loans from family members or local self-help groups.

"We are poor, but I know the government gives something back if we deliver in the hospital," – Participant R6

3.6 Influence of Family and Community in Care-Seeking

Family members, particularly husbands and mothers-in-law, were crucial in determining the use of healthcare services and prenatal visits. Most women disclosed that their husbands provided transportation or accompanied them to medical facilities. Family members' and neighbours' practical and emotional support was often cited as a major contributing factor to their health-seeking behaviour.

"My husband takes leave to come with me. Also, my sister helps with household work," – Participant R25

However, some women alluded to limited autonomy by saying that they couldn't get checkups unless their families approved of it.

3.7 Barriers to Health-Seeking During Pregnancy

Inadequate or unreliable transportation was the most frequently mentioned obstacle, particularly during emergencies. Women voiced concerns about government ambulance services being unavailable or delayed, as well as the lack of buses during the night. They favoured private vehicles during labour because they felt more in control and in a sense of urgency.

"We will use a private car during labour if possible. The ambulance takes too long," – Participant R32

Other barriers. According to 41% of respondents, access to ANC is hampered by transportation issues, especially in underserved or rural areas. 54 per cent of participants stated that their spouses influenced or made the majority of decisions pertaining to their health, indicating that gender dynamics play a significant role in ANC utilisation, including household responsibilities, fear of overcrowded facilities, and occasional verbal mistreatment by healthcare staff.

3.8 Role of Traditional and Spiritual Beliefs

It is interesting to note that none of the participants reported having visited traditional healers or using native remedies in pregnancy care. Trust in biomedical medicine was high, especially among younger women. Others recognised the role of the traditional attendants in previous generations, but considered doctors to be more competent and reliable.

"My mother delivered with help from dai, but now doctors know better," – Participant R19

3.9 Fears and Emotional Responses to Pregnancy

Many women seemed at ease and self-assured, but some were worried about potential problems, particularly caesarean sections or miscarriages. These anxieties were frequently influenced by firsthand accounts or tales from other women in the community.

"I lost two babies before. This time I am scared, but I trust the doctor," – Participant R34

"They may cut me open—what if something happens?" – Participant R27

Such fears sometimes influenced care-seeking urgency or preference for delivery in a better-equipped facility.

4. DISCUSSION

This qualitative study on the behaviour of pregnant women in rural West India in relation to antenatal care (ANC) reveals the complex interaction of awareness, structural access, socio-cultural factors and emotional responses that shape the use of maternal health services.

The study's most promising finding is the high level of general awareness regarding the significance of routine ANC visits. This trend contrasts with previous research that found inconsistent ANC uptake in rural India as a result of fatalistic attitudes and ignorance (World Health Organisation, 2016; Ministry of Health and Family Welfare, 2013). This change might be a result of the growing popularity of national programs that prioritise institutional care and regular checkups, such as Pradhan Mantri Surakshit Matritva Abhiyan (PMSMA) and Janani Suraksha Yojana (JSY) (Ministry of Health and Family Welfare, 2016; International Institute for Population Sciences & ICF, 2017). Improved outreach by ASHAs and ANMs has been linked to an increase in public trust in public health services, according to earlier studies done in Gujarat and Maharashtra (Sharma et al., 2014; Gaikwad et al., 2018).

Nevertheless, a deeper comprehension of pregnancy-related complications is not entirely a result of this awareness. While potentially fatal conditions like gestational diabetes or pre-eclampsia were not well known, the majority of study participants linked pregnancy to minor discomforts like nausea and fatigue. The results of national-level studies that link inadequate knowledge of warning signs to improper or delayed care-seeking are in line with this cursory comprehension (Gaikwad et al., 2018). Chandhiok and associates. additionally discovered that timely ANC attendance and delivery in medical facilities were significantly impacted by increased awareness of complications (Chandhiok et al., 2006).

Due to cost and accessibility benefits, government health services are strongly preferred for prenatal checkups. This is another important finding. This is consistent with research conducted in rural North and Western India, where women reported that JSY cash incentives, free medication, and proximity influenced their choice (Gaikwad et al., 2018; Salve et al., 2017). However, during labour or emergencies, this preference frequently shifts in the opposite direction, with many women choosing private transportation or facilities because of perceived shortcomings in public health infrastructure and delays in ambulance services. Similar results were noted in Madhya Pradesh, where women expressed concern about crowding or the lack of qualified personnel at night (Mohanty et al., 2019).

An important factor in facilitating the use of ANC was family support, particularly from mothers-in-law and husbands. It is important to include men in maternal health programs because husbands frequently organised transportation and accompanied women to health facilities. This supports other South Asian research that highlights the benefits of social support and male involvement in maternal care-seeking (Elsenbruch et al., 2006; Mullany et al., 2007). However, other participants also expressed a lack of autonomy, especially in joint family situations, suggesting that patriarchal norms still have an impact on decision-making (Dhakal et al., 2007).

The most frequently mentioned obstacle was the availability of transportation, which supports previous research that found that inadequate rural connectivity is a significant barrier to timely health access (Paul et al., 2011). Government ambulance services (e.g. G. 108) exist, but participants reported being unavailable or delayed in emergency situations, necessitating the use of private vehicles, which raises out-of-pocket costs even more. In tribal and semi-urban areas of India, transportation problems have consistently impeded institutional delivery and ANC attendance (Banerjee & Kapur, 2020).

Remarkably, our research revealed little dependence on spiritual therapies or traditional healers, which is indicative of the increasing medicalisation of pregnancy in rural regions. Participants, particularly younger women, clearly preferred allopathic care over the dais and folk remedies used by earlier generations. This represents a positive change and is consistent with research by Finlayson and Downe, who found that community-level health system engagement boosts trust in trained birth attendants (Finlayson & Downe, 2013).

Participants frequently had delivery-related fears, especially those related to cesarean sections, which were frequently based on anecdotal stories or unpleasant experiences from the past. According to other qualitative studies conducted in South Asia, where fear of surgical intervention was a significant deterrent to institutional care, these emotional reactions can affect the location and timing of delivery (Bohren et al., 2014).

Overall, the results indicate that although the basis for ANC use is growing, attention now needs to be directed toward enhancing health literacy, developing respectful maternity care, and improving transportation infrastructure. In addition to encouraging more visits, health communication should stress the importance of identifying warning signs like severe anaemia, hypertension, and bleeding. Incorporating family members, particularly men, into educational sessions may also improve timely care-seeking and group decision-making.

Leveraging the existing trust in public health services offers a solid foundation for scaling up interventions from a policy perspective. ASHA-led counselling, village health and nutrition days, and group education are examples of targeted outreach that can close the knowledge gap and increase awareness. To lower maternal and perinatal complications, programs must also address antenatal risk assessment and emergency transport responsiveness, especially for high-risk pregnancies.

5. CONCLUSION

Important new information about pregnant women's prenatal health-seeking behaviour in rural Western India is provided by this study. The results show that most women now understand the benefits of regular prenatal checkups, indicating a positive shift in public awareness regarding the significance of antenatal care (ANC). This suggests that community-level maternal health behaviours are starting to be positively impacted by government initiatives like the Pradhan Mantri Surakshit Matritva Abhiyan and the Janani Suraksha Yojana.

But there is still a big disconnect between a general understanding of certain pregnancy-related issues and a more thorough comprehension of them. In high-risk pregnancies in particular, ignorance of warning signs like pre-eclampsia, anaemia, or gestational diabetes can lead to delayed or inappropriate care-seeking. This emphasises how urgently targeted prenatal counselling and risk communication must be strengthened, especially by frontline health workers like ASHAs and ANMs.

The importance of family, particularly husbands, in influencing healthcare choices is also highlighted by the study. Despite the generally positive family support, the results also imply that some women still do not have the freedom to make their own health decisions. Maternal outcomes may improve if these gender dynamics are addressed through community sensitisation and male-inclusive health initiatives.

Lack of transportation has been identified as a persistent obstacle to timely care access. Emergency situations, especially around delivery, frequently resulted in reliance on private transport, which many found financially burdensome, even though women preferred public facilities for prenatal visits because they were more affordable and easily accessible. This highlights the necessity of responsive ambulance services and better referral transport systems in rural areas.

It is encouraging to note that participants almost never used traditional or untrained birth attendants, indicating a growing preference for institutional and biomedical care. This offers a solid platform on which health systems can expand by guaranteeing considerate, superior maternity care that strengthens satisfaction and trust.

In conclusion, even though there has been a lot of progress in encouraging the attendance of prenatal care, a comprehensive strategy is now required to improve the quality, scope, and responsiveness of care. This strategy must go beyond service coverage. Important next steps include enhancing health literacy, removing systemic obstacles, involving families in maternal health, and guaranteeing continuity of care from the prenatal to the postnatal stages. Rural Western India can get closer to attaining universal access to effective and equitable maternal health care with focused interventions and community involvement.

6. RECOMMENDATIONS

Create and carry out organised community-based health literacy initiatives to raise awareness of pregnancy danger signs (e.g. severe anaemia, high blood pressure, and gestational diabetes. Include interactive and visual communication resources for populations with low or no literacy, such as flip charts, brief films, and community plays. Through frequent retraining on interpersonal communication and counselling techniques, ASHAs and ANMs can expand their role as educators rather than just service providers. 108 ambulance services should be made more accessible and timely, especially in isolated or difficult-to-reach villages. To promote male awareness and collaborative decision-making, start husband-inclusive maternal health sessions during village health and nutrition days. To emphasise the value of routine ANC and institutional delivery, support household-level counselling involving mothers-in-law and other influential people. For high-risk women who live far from medical facilities, establish or improve maternity waiting homes close to CHCs or FRUs.

7. LIMITATIONS

Because the study was limited to a single rural block in Western India, it might not be applicable to other sociocultural contexts, such as tribal areas or urban slums. Additionally, the cross-sectional design restricts how behaviour change is interpreted over time. Nevertheless, the knowledge has important ramifications for developing maternal health interventions that are equity-focused and sensitive to context.

ETHICAL APPROVAL AND CONSENT

The study received ethical approval from the parent medical college's Institutional Ethics Committee. All participants gave their written informed consent after being fully informed about the study's objectives, the voluntary nature of participation, data confidentiality, and their freedom to discontinue participation at any time without facing any repercussions. During transcription and analysis, codes were used in place of names to preserve anonymity.

DISCLAIMER (ARTIFICIAL INTELLIGENCE)

Author(s) hereby declare that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc) and text-to-image generators have been used during writing or editing of this manuscript.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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