

AWARENESS

Newer Horizons in Human Excellence



About the Journal

The journal Awareness is dedicated to promoting and disseminating knowledge derived from innovative research that serves humanity, all forms of life, and their environments. It aims to foster deeper understanding by integrating empirical, experimental, experiential, and spiritual dimensions of knowledge across diverse disciplines. At its core, the journal seeks to expand the horizons of collaborative and empirical research, motivated by a love for humanity, child-like curiosity, and an unwavering commitment to truth. Awareness aims to be a publicly accessible platform for fresh, creative knowledge and shared scholarly exchange, thus embracing the principle that knowledge, like light, must be shared freely and openly to dispel ignorance and inspire the pursuit of human excellence. Only through such open exchange can the journal fulfill its commitment to the ideals of the University for Human Excellence. The journal also provides a forum for exploring critical issues related to the advancement of human excellence, welcoming a wide range of perspectives across multiple fields. It publishes original research articles, reviews, perspectives, editorials, commentaries, and book reviews, all of which reflect the personal views of the authors. These contributions do not represent the official stance of the University or the institutions affiliated with the authors, editors, or reviewers, preserving the journal's commitment to intellectual independence and diversity of thought.

JOURNAL PARTICULARS

Title	AWARENESS – Newer Horizons in Human Excellence
Frequency	Bi – Annual
ISSN	3107-9881
Publisher	Sri Sathya Sai University for Human Excellence
Chief Editor	Prof. Kanwaljeet J. S. Anand
Starting Year	2024
Subject	Multidisciplinary
Language	English
Publication format	Online
E-mail ID	awareness.journals@sssuhe.ac.in
Website	https://awarenessjournals.com/
Author Guidelines	https://awarenessjournals.com/author-instructions
Privacy Policy	https://www.awarenessjournals.com/public/img/pdf/privacy-policy.pdf
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Editorial

The Political Economy of Geographic Healthcare Inequity

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Keywords: healthcare; health workforce distribution; rural health; telemedicine

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Introduction

The geographical maldistribution of the medical workforce is a structural failure of modern society, driven by unchecked market forces in the healthcare industry, accentuated by regulatory bottlenecks, and a systemic underinvestment in the rural infrastructure required for healthcare delivery.¹⁻³ After synthesizing recent reports on the shortage of doctors and nurses in rural United States, this editorial summarizes critical evidence on market consolidation,^{4,5} pediatric^{6,7} and maternity care unit closures,^{8,9} systemic limitations of Graduate Medical Education (GME) allocation,¹⁰ and the role of telemedicine in rural physician retention.^{11,12}

Citation: K.J.S. Anand;
Awareness, 3 (2): 1-9



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Health Workforce Maldistribution

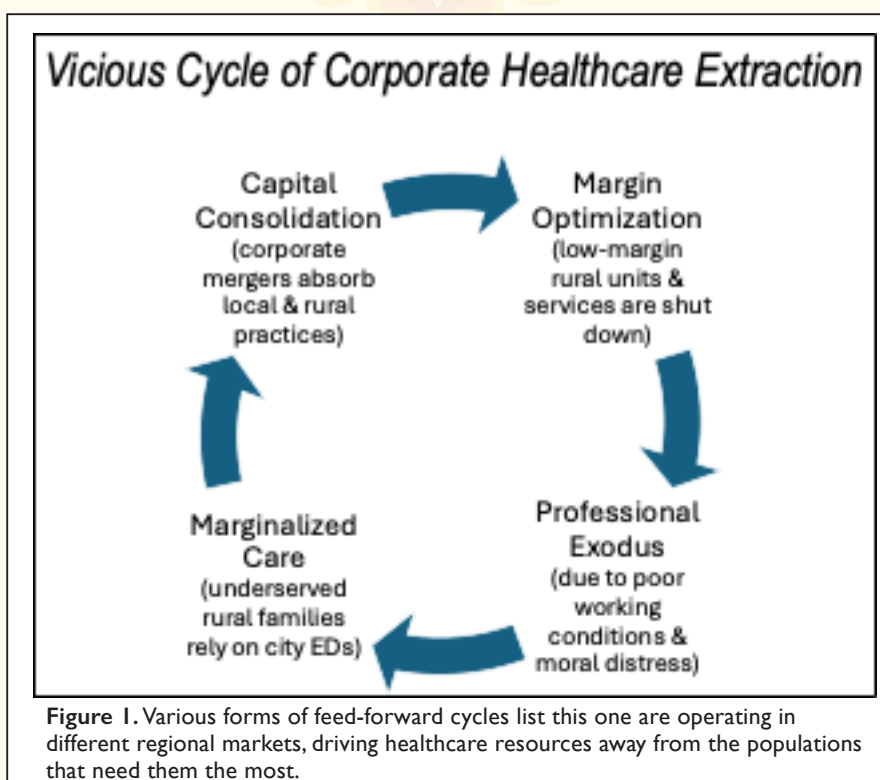
Only 9-11% of US physicians practice in rural areas, completely inadequate for the lives covered in rural communities.¹³ The persistent deficit of physicians in rural communities is not an accident of geography, it stems from the direct consequence of structural economic failures and political choices.¹⁴ In profit-hungry, market-driven healthcare systems, capital allocation inevitably flows toward paths that maximize financial returns, creating a severe chasm between thriving urban centers and neglected rural geographies.^{15,16}

While medical schools have graduated record numbers of clinicians globally, the lack of strong regulatory frameworks ensures that these professionals remain concentrated not only in the most affluent metropolitan locations but also gravitate to financially lucrative specialties. Let us examine how commercial and institutional factors have interacted to create a crisis of rural medical access, highlighting structural flaws, and exploring potential solutions.

1. The Profit-Driven Neglect of Underserved Communities

In the United States, healthcare delivery operates under the constraints of late-stage capitalism, where shareholder value and corporate returns take priority over equitable public health distribution and patient outcomes. Market dynamics have undermined the viability of rural clinics and community hospitals through several distinct mechanisms.

Large-scale hospital consolidations have proceeded unchecked across many regional markets, directed towards limiting competition and raising prices. These market forces have driven the total assets held by US hospitals from \$750 billion in 2000 to \$1.6 trillion in 2019.¹⁷ The systematic acquisition of physician practices by for-profit entities and private equity firms has accelerated in the last decade, now estimated at almost two-thirds of all physician practices. These strategies had left only 18% of US doctors practicing in physician-owned clinics by the start of 2026, consequently eroding both physician autonomy and patient-centered care.^{18,19} Economic analyses show that corporate mergers predictably drive up baseline healthcare costs rather than generating efficiencies, partly because of the huge power differential between individual customers and their corporate providers. Capital allocations have consistently shifted away from unprofitable services (like maternal and pediatric care) and out of low-margin rural sectors to fund highly profitable urban facilities and services (Figure 1).



Financial extraction from healthcare markets directly and indirectly triggers a cascade of detrimental effects at multiple levels, in overt or insidious ways, often leading to systemic societal harm over time. Multi-hospital conglomerates, owning numerous physician practices continue to build massive balance sheets while cutting costs and essential local services. As market share access and referral patterns shift, nonprofit hospitals and academic institutions are forced to close down their medical services in low-income zip codes and open lucrative sites in wealthy suburbs. Excessive executive compensation and high administrative overheads pull vital resources out of frontline clinical delivery.^{20,21} Aggressive collection agencies and predatory pricing practices have locked up over 40% of American adults into deep medical debt, causing moral injury to local clinicians.^{22,23}

2. GME Allocation Failures and Pipeline Bottlenecks

The structural foundation of the U.S. physician shortage is rooted in statutory restrictions on graduate training pipelines. Medical student enrollment in the US has increased by 60% over the past two decades, with a sustained majority of women (57%) entering medical school,²⁴ while the representation of minorities and rural students has lagged behind.²⁵ This gap widens further in residency and fellowship training because of the lack of investment in postgraduate training infrastructure and jobs, creating the strongest bottleneck in the physician supply pipeline. Two main factors sustaining this bottleneck include statutory constraints and regulatory inequities in job distribution.

Legislation such as the Balanced Budget Act of 1997 imposed a rigid cap on Medicare-funded residency positions, restraining the annual growth in GME training pathways below 3%, despite a growing and aging population as well as a larger pool of medical graduates. Hospitals and academic institutions were forced to absorb the direct costs of residency slots onto their own bottom lines, directly impacting their profit margins. Several corporate hospitals have eliminated or significantly reduced their financial support for GME training. Climbing average medical educational debt (\$200,000 to \$250,000) also drives medical graduates away from the lower-paying rural primary care into urban sub-specialties.²⁶

Regulatory inequities in slot distribution have further worsened the rural healthcare crisis. In 2020, Medicare dedicated \$16.2 billion to GME funding, yet a mere 2% of that was allocated to rural areas. The Consolidated Appropriations Act of 2021 authorized 1,000 new residency slots, but its rollout failed to bridge the urban-rural gap.²⁷ Despite the fact that trainees who spend at least 50% of their residency in a rural setting have five-fold higher odds of practicing there, the gap in residency slots between urban and rural areas continues to widen. Only 5% of training programs receiving these new slots trained residents in rural Health Professional Shortage Areas for 50% of their residency, completely underrepresenting 32.1% of the US population living in underserved rural communities.

3. The Collapse of Rural Inpatient Care

The ongoing physician shortage creates a dangerous loop of health infrastructure decay. As doctors leave rural practices, the local clinics and small hospitals become unsafe or financially non-viable, leading to closures that prevent any future physician recruitment. High fixed baseline operating costs due to regulatory requirements make maintaining standalone, low-volume units unsustainable. Extreme difficulties in retaining nursing and multidisciplinary ancillary teams makes it even harder to keep these rural units open.

Consequently, rural families are forced to navigate complex, long-distance interfacility transfers for common medical issues like asthma, croup, and seizures.²⁸ The risk of poor clinical outcomes rises significantly for the most vulnerable patients, include rural children, mothers with high-risk pregnancies, and elderly patients with complex, chronic diseases. Low-income families are forced to bear substantial indirect financial burdens, including unpaid time away from work and high travel and parking costs in urban centers for routine medical care. Instead, they may compromise by accepting a lower health-related quality of life or disease-induced limitations in their daily living activities. A 2021 survey reported that millions of people in the US forgo prescribed medicines to reduce costs.²⁹ When inpatient services close, pediatric and adult specialists often shut down their outpatient clinics in the community, leaving entire regions without access to local specialty care.

4. Telemedicine as a Structural Mitigant

Digital health technology and telemedicine were considered as potential solutions, particularly after the COVID-19 pandemic, to fill the geographic gaps created by rural physician shortages.^{30,31} Despite these predictions, the academic literature highlights that virtual care models may function as a double-edged sword for retaining physicians in rural areas,¹² or for sustaining access to primary or secondary healthcare for rural families and communities. Emerging advantages and disadvantages are summarized in Table I below.

Table I. Opposing Effects of Rural Telemedicine	
BENEFITS:	CHALLENGES:
• Lower local admission and ED utilization rates by 10-25% • Extends overbooked primary care capacity to patients in isolated areas • Connects rural clinics directly with urban specialists	• Increases daily charting and administrative workloads • Demands major upfront capital investment for digital tools and broadband access • Fails to replace hands-on diagnostic and surgical capabilities • Delays care for acute emergencies well beyond the 'golden hour'

Many people living in rural communities are less comfortable with technology, and they particularly feel the lack of physician warmth, gentle touch, and genuine concern during telehealth consultations. Rural folks may lack the appropriate equipment (computer, camera, smartphone, broadband service) and the motivation to access healthcare remotely, leading to significant differences in the use of telemedicine between urban and rural patients across younger and older age groups.^{32,33} Rural families are also reluctant to allow healthcare providers to view their homes and living conditions because of privacy needs. Though telemedicine may provide a reasonable solution to access urban specialty care for rural communities, but it cannot adequately replace the loss of local primary care or emergency services.³⁴

Albeit limited, telemedicine does have an important role in rural healthcare delivery. Virtual consult networks do expand the reach of rural doctors, allowing them to care for isolated populations with limited mobility. For example, a telemedicine consultation network in rural California successfully

lowered local hospital admissions and emergency department utilization.³⁴ Remote support options can also ease the clinical burden on overbooked primary care physicians by triaging non-acute cases. Telemedicine integration can also help rural community emergency departments to maintain pediatric readiness without requiring permanent on-site specialists.

However, virtual tools cannot replace on-the-ground diagnostic infrastructure, hands-on clinical intuition, or local surgical capabilities. Small rural hospitals frequently face severe funding and reimbursement challenges when trying to set up and maintain advanced telehealth systems. Relying heavily on digital care can also worsen administrative burnout if it adds to data entry burdens rather than reducing paperwork. In summary, telemedicine works best as a retention tool when it connects rural doctors to urban specialist networks, making them feel less professionally isolated.

5. International Parallels: Rural healthcare in India

The structural challenges seen in the United States match the inequity in healthcare workforce distribution in India, though the economic contexts differ. India produces a large volume of medical graduates every year, yet it faces a deep urban-rural chasm driven by the demographics of medical graduates and their training design.

Approximately 80% of India's MBBS graduates settle in urban cities, while only 20% practice in rural areas. This maldistribution leaves a massive 65% of the population medically underserved in rural districts. Rural public health postings are widely viewed by medical interns as a form of "punishment" because of their distance from urban amenities and social networks. Staffing vacancies persist in rural Primary Health Centres (PHCs), which often lack reliable electricity, clean water, safe housing, or good local schools for physician families. The traditional medical curriculum focuses heavily on high-tech tertiary care, preparing students more for careers in developed countries rather than for practicing in rural settings.

The National Eligibility cum Entrance Test (NEET) is India's sole national-level entrance examination for undergraduate medical education. It is mandatory for securing a seat in MBBS, BDS, AYUSH, and Veterinary courses across all government and private institutions. The NEET exam poses as a major educational barrier, because less than 5% of top scorers come from rural backgrounds.³⁵ Illegal capitation practices and exorbitant tuition fees at private medical colleges force graduates to seek high-paying urban corporate positions to pay off their educational debts.³⁶ Furthermore, exclusive use of the English-language in medical school training further blocks qualified rural youth receiving instruction in regional languages from rural government schools, before applying for the NEET exam.

For the MBBS graduates of government medical colleges, mandatory rural service for 1-2 years was traditionally enforced by some States, through compulsory rural service bonds. These coercive mandates often did not work as intended because medical graduates from middle-class or wealthy families could simply paid off the financial penalty to avoid rural service postings. Some states, including Maharashtra, Kerala, and Andhra Pradesh have scrapped these service bonds, whereas other states like Karnataka have relaxed the enforcement of their mandatory one-year social responsibility service bond. National institutions like AIIMS and JIPMER and private medical colleges did not implement mandatory post-MBBS service bonds.

Similar factors apply to residency training or postgraduate medical education in India. Most seats are available only in urban centres and these programs charge even higher fees for admission and tuition than the MBBS courses. The pipeline of MBBS graduates from rural areas is already restricted, but it faces further drastic reductions in their entry into the highly competitive postgraduate programs.³⁷ Innovative and effective approaches must be explored to address these glaring inequities, and to bridge the widening gaps in rural healthcare workforce distribution.

6. Pathways of Promise

Conceived and built during the COVID-19 pandemic and inaugurated in March 2023, the *Sri Madhusudan Sai Institute of Medical Sciences and Research (SMSIMSR)* has introduced a radically new alternative, creating free-of-charge training pipelines for both under-graduate and postgraduate medical students. This unique and innovative program provides completely free tuition, boarding, books, materials, clothing, toiletries, and other amenities to rural youth in exchange for a binding commitment to serve in rural healthcare facilities for a duration equal to their years of subsidized study. All teaching and training courses are conducted in state-of-the-art, advanced facilities within a values-based, residential and holistic educational system, and endowed with deep spiritual understandings. This unprecedented approach seeks to build a community-specific healthcare workforce by training medical professionals within a rural milieu, eliminating student debt, and bypassing the well-beaten paths to urban migration. In addition to nurturing clinical talent, imparting knowledge and skills, this unique institute is building character and integrity among medical professionals, creating an inspired healthcare workforce dedicated to building their careers in rural medical practices.

Generating a sustainable rural healthcare workforce, however, will require much greater investment than the efforts of one institution. International healthcare systems must shift from short-term recruitment bonuses to systemic structural reforms. All countries dealing with the rural healthcare crisis must adopt models like SMSIMSR that actively recruit, support, and train rural youth within rural clinical environments to foster a long-term commitment to community service. The US must first overhaul GME funding models by uncapping residency slots and legally mandating that a significant percentage of funding be allocated to rural underserved areas and regional primary care programs. Legislators and administrators at all levels must also work hard to protect the smaller regional and rural hospitals from corporate exploitation, stabilize Medicaid and public health insurance reimbursements, upgrade clinical utilities in underserved areas, and provide full student loan forgiveness that is annually tied to physicians, nurses, or other healthcare providers remaining and exclusively practicing in rural geographies. Policy reform, political will, and innovative models like the SMSIMSR have the potential to bridge rural-urban disparities in healthcare delivery, edging the world closer towards achieving the UN Sustainable Development Goals (SDGs), namely, SDG#3 and SDG#10.³⁸

Supplementary Materials: None.

Author Contributions: N/A.

Funding: None.

Institutional Review Board Statement: N/A.

Informed Consent Statement: N/A.

Data Availability Statement: N/A.

Acknowledgments: The author is deeply grateful to Sadguru Sri Madhusudan Sai for his tireless efforts to uplift the downtrodden masses and to serve the poorest of the poor, inspiring millions to follow his example of selfless love and service. His One World One Family Global Humanitarian Mission promises to provide completely free-of-charge nutrition, education, and healthcare to each and every human being on this planet, regardless of caste, color, creed, religion, national origin, and any other identifying features.

Conflicts of Interest: None.

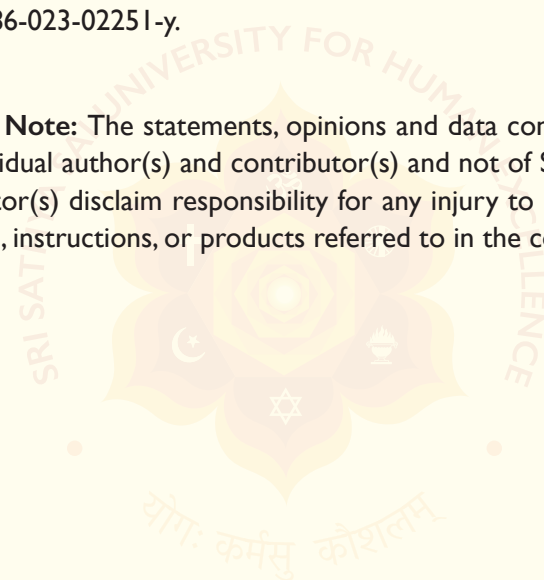
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Poetry

Colour the Mind

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Keywords: mind, mother earth, serenity

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Colour the mind

Is there a language for thought,
And, is there a colour to mind
Like the notes on my violin
Are they pleasant for all-in
Chirped the little Robin in my garden.
Colours are plenty and jargon aplenty too,
As the colours in the rainbow
Are they enduring too?
Black, brown and blue,
My friends are of varied hue
Blooms in my garden, varied in view
Who hang together and cradle together
In deep roots too
No clash, no friction
Devour from the Mother Earth platter too.
Aren't we all the blooms of the same Mother Earth,
In varied glow and varied minds
As life folds and unfolds
Why do the colours change?

Citation: Rajeshwari N.:
Awareness, 3 (2): 11-12



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Change like the spinning wheel,
To crush when it's time to blush
A single note can't be a symphony
Single colour can't be a palette.
Feel the fragrance and smell the floret,
Crack the code and celebrate the essence
Yay,
It's silence the language of thought
And, serenity that colours the mind
To make the strokes bold and the strings in sync.
Time is an illusion,
The mind is delusive
Rhythm of change all over
Celebrate the essence
IT is all one.

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Article

Potential Harm of Hyperoxia in Children: A Narrative Review

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Abstract:

Background: Hyperoxia is common in pediatric critical care, yet its harmful effects remain underappreciated. This review combines clinical, physiologic, and molecular evidence showing that excessive oxygen exposure causes a range of lung and systemic injuries.

Methods: A structured literature search was performed in PubMed, Scopus, and Embase. Articles were selected to represent mechanistic, translational, and clinical evidence across relevant pediatric populations. The initial search strategy yielded 252 articles; 194 studies were excluded after initial screening. The remaining studies underwent independent full-text review and data extraction.

Pathophysiology: High FiO₂ leads to oxidative stress, damage to alveolar epithelial and endothelial cells, increased reactive oxygen species, release of inflammatory cytokines, changes in gene expression, and disruption of the alveolar-capillary barrier. Hyperoxia contributes to atelectasis, reduced lung compliance, decreases in vital capacity and diffusing capacity, and, with prolonged exposure, diffuse pneumonitis. Beyond the lungs, hyperoxia impairs immune regulation, gastrointestinal integrity, and nervous system development.

Results: Clinical research shows mixed results across different populations, but severe or sustained hyperoxemia is consistently linked to higher morbidity and mortality in critically ill children, those on ECMO, and certain neonatal and trauma groups. Studies in pediatric cardiac arrest and traumatic brain injury highlight the complex relationship between oxygen levels and neurologic outcomes, with hypoxia showing the strongest link to death. Advances like automated, closed-loop FiO₂ controllers show promise for optimizing oxygen delivery and reducing exposure to harmful extremes. Emerging molecular therapies, including growth factor modulation, antioxidants, and stem-cell-based treatments, may further reduce oxygen-related injury.

Conclusion: Overall, the evidence underscores the importance of carefully managing oxygen, a powerful drug with both lifesaving benefits and significant risks.

Keywords: Hyperoxia, hypoxia, critical care, pediatrics, oxygen toxicity

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Citation: Vidit B., Jeffrey C., Azadeh F.; Awareness, 3 (2): 13-32



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Introduction

Oxygen is a common therapy to treat hypoxia in patients. Although vital to cell function, excessive exposure to oxygen can be detrimental.¹ While hyperbaric oxygen has specific clinical indications, excessive oxygen administration in most other conditions is unwarranted and often under-recognized.² While exposure to high levels of oxygen has been well-studied in animals, the clinical relevance of these findings may not be fully applicable to humans, as different species respond differently to high oxygen exposure.³ In this review, we discuss results from human clinical and in vitro studies regarding the pulmonary effects of excessive oxygen administration.

Materials and Methods

A structured literature search was performed in PubMed, Scopus, and Embase using combinations of the terms: *hyperoxia, oxygen toxicity, pediatric, PICU, ECMO, traumatic brain injury, cardiac arrest, perioperative oxygen, COVID-19, automated FiO₂ control*. Articles were selected to represent mechanistic, translational, and clinical evidence across relevant pediatric populations. Because of marked heterogeneity in patient groups, exposures, and outcomes, formal systematic review methodology (PRISMA/PROSPERO) was not appropriate, and no meta-analysis was attempted. The initial search strategy yielded 252 articles, which were downloaded to Covidence for further screening by two reviewers (VB, JC). 194 studies were found irrelevant based on the inclusion and exclusion criteria. The remaining studies underwent independent full-text review and data extraction by the two reviewers (VB, JC) based on the inclusion and exclusion criteria listed here.

Inclusion Criteria: Case series, case control, cohort, Clinical trial: randomized or non-randomized, Meta-analysis with or without review. Population: Pediatric, neonate, Lab studies focused on hyperoxia. Intervention/exposure: Exposure to oxygen via mechanical or non-mechanical routes, Lab model of hyperoxia. Outcomes: Measures of cell, tissue, or organ dysfunction

Exclusion Criteria: Case report, Review without meta-analysis, Protocols. Population: Adults. Intervention/exposure: If no exposure to oxygen. Outcomes: If no outcome measures are studied

Definitions

The term hyperoxia is used interchangeably to describe both excessive oxygen administration as well as elevated partial pressure of oxygen (PaO₂) in the body. Excessive oxygen delivery and hyperoxemia can occur independently. In the setting of severe lung disease and limited diffusion, the PaO₂ may remain low or normal. Therefore, while pulmonary oxygen toxicity may occur with high oxygen delivery, hyperoxemia may not. On the other hand, any FiO₂ >21% has the potential to cause hyperoxemia and toxicity in organs exposed to elevated PaO₂.

Better terminology is necessary to characterize the appropriateness of oxygen therapy. *Excessive oxygen delivery* is the amount of administered oxygen that causes oxygen toxicity. *Hyperoxemia* refers to the presence of a supraphysiologic amount of oxygen in the blood, commonly defined by a PaO₂ threshold. The specific threshold of the fraction of inspired oxygen (FiO₂) above which toxicity occurs depends on the cell tolerance of the concentration and duration of oxygen to which it is exposed. Different cell types have different thresholds and variable responses.⁴ Pulmonary oxygen toxicity is most common during normobaric oxygen therapy as airway and alveolar epithelial cells have the most exposure. A definitive threshold concentration or duration of oxygen therapy has not been found in humans. The commonly cited FiO₂ limit of 50-60% is largely based on animal and

in vitro studies.^{5,6} A clear threshold PaO_2 that leads to end-organ injury has also not been identified. Many studies use PaO_2 thresholds beyond (e.g., 300 mm Hg) the upper limit of normal (approximately 100 mm Hg). Further studies are necessary to define the limits of oxygen therapy and toxicity in humans. Until more is known, setting FiO_2 with target oxygen saturation and PaO_2 ranges (with upper limits) is most appropriate, with the acknowledgment that pulmonary toxicity can occur at high FiO_2 settings. Recently published pediatric guidelines in the management of patients with acute respiratory distress syndrome (ARDS) recommend maintaining a goal SpO_2 88% – 97% and < 92% in patients with severe ARDS with central venous oxygen saturation monitoring.⁷

Pathophysiology

Pathological changes occur with excessive oxygen delivery. In the 70s, multiple post-mortem case series attributed hyaline membrane formation and capillary proliferation in the child and adult population to high oxygen concentrations. Across both pediatric and adult patients—many without preexisting lung disease—post-mortem and clinical observations revealed diffuse alveolar damage after sustained oxygen therapy, regardless of delivery method or duration. Many patients in studies showing hyaline membrane disease had primary or secondary lung disease, required mechanical ventilation with high or unknown volumes or pressures, and received variable durations of oxygen supplementation. Collectively, these reports established an association between excessive FiO_2 and structural lung injury, though confounding factors such as infection and ventilation parameters make it difficult to attribute causality solely to oxygen toxicity.

In mechanically ventilated patients with acute lung injury (ALI), excessive oxygen delivery—e.g., $\text{FiO}_2 > 50\%$ with $\text{SpO}_2 > 92\%$ —is common and linked to adverse changes.⁸ For example, FiO_2 1.0 increases intrapulmonary shunting due to derecruitment resulting from resorption atelectasis.⁹ Pathological changes due to hyperoxia in mechanically ventilated patients are similar to those in patients who died with acute respiratory distress syndrome. Diffuse alveolar damage can occur after 48 hours of exposure to elevated oxygen levels.¹⁰ During the exudative phase of ARDS, alveolar epithelial and endothelial cells show increased ROS-generating enzymes and apoptosis signaling (including NOX-linked pathways), consistent with concurrent oxidative stress and programmed cell death.¹¹ Even though oxygen toxicity cannot be identified as a cause of ALI, it can certainly contribute to similar clinical findings and exacerbate the disease process.

While many of the negative effects of excessive oxygen exposure on the lungs are well-documented, it is still unclear just how long it takes before this exposure causes significant risks. According to published reports, 6 hours of elevated oxygen increases reactive oxygen species and the elevation of inflammatory markers, a decrease in vital capacity occurs between ~24–77 hours on FiO_2 0.75–1.0, and tracheobronchitis occurs after ~6 hours on FiO_2 1.0 or ~12 hours on FiO_2 0.75.^{12,13} Although the duration of hyperoxia in these studies is arbitrary, we can estimate that injury begins within hours of exposure and progresses over days, with a likely cumulative effect on lung architecture and mechanics.

Molecular Pathophysiology

Oxygen toxicity results from interference of reactive oxygen species (ROS) with normal cell structure and function and can occur with excessive oxygen exposure. ROS include superoxide ($\text{O}_2^{\cdot-}$), hydrogen peroxide (H_2O_2), and hydroxyl ($\cdot\text{OH}$). They can form without excessive oxygen delivery and under physiologic conditions (e.g., infection). Normally, enzymes such as superoxide

dismutase and glutathione peroxidase inactivate reactive oxygen species. However, when antioxidant mechanisms are overwhelmed, such as in critical illness, oxygen toxicity can occur. ROS are produced by various cells through enzymes such as NADPH oxidase and xanthine oxidase.¹¹ Phagocytic cells (e.g., neutrophils, macrophages), pulmonary vascular endothelial cells, and alveolar epithelial cells have all been implicated in the production of ROS.^{11,14} NADPH oxidase is an important source of ROS in pulmonary endothelial cells and alveolar epithelial cells.^{11,14} The SphK1/SIP/Spns2 axis also drives hyperoxia-induced endothelial NOX2 activation and ROS generation.¹⁵

ROS cause cellular injury by altering gene expression, signaling pathways, and/or damaging DNA, protein, and lipids.¹⁶ Cell signaling is altered to initiate protective mechanisms, such as maintaining mitochondrial integrity or triggering programmed cell death, during oxidative stress.¹⁷ Increase in ATP production in human pulmonary endothelial cells and release into the extracellular environment leads to activation of receptors that signal changes in protein synthesis and glucose metabolism during periods of oxidative stress.¹⁸ Enzymes involved with apoptosis increased in airway epithelial cells exposed to >95% oxygen in vitro for up to 72 hours. These enzymes induced cell death by affecting apoptotic signaling pathways.¹⁹ Alveolar epithelial function is also affected by changes to signaling pathways that lead to cell death, evidenced by apoptotic and necrotic changes. Other signaling mechanisms can enhance the ROS response, possibly activating protective mechanisms. Activation of mitogen-activated protein kinases (MAPK) in human pulmonary endothelial cells occurred when exposed to 95% oxygen.¹⁴ MAPKs, which are important signaling proteins, in turn alter signaling pathways that increased ROS production.

Altered gene expression in the lungs results in the synthesis of proteins that regulate detoxification, inflammation, cell proliferation, and cell death. Although these changes are initially adaptive—aimed at protecting cells from oxidative injury—they can paradoxically contribute to local damage through inflammation and cell loss, ultimately impairing lung function. In vitro studies have shown that exposing human pulmonary artery endothelial cells to 90% oxygen for 48–72 hours increases the expression of intercellular adhesion molecule-1 (ICAM-1), thereby enhancing neutrophil adherence.²⁰ Similarly, exposure to hyperoxia modulates the expression of pro-inflammatory cytokines, including TNF- α , IL-1 β , IL-6, and IL-8, with IL-8 demonstrating the most consistent and pronounced increase. In alveolar macrophages isolated from bronchoalveolar lavage (BAL) fluid of children and exposed to 95% oxygen for 48 hours, IL-8 levels were significantly elevated. A comparable increase in IL-8 was also associated with enhanced polymorphonuclear leukocyte chemotaxis in adult cell models. Inflammatory activation also extends to TNF- α ; its concentration rises under both LPS-stimulated and high-oxygen conditions, reaching statistically significant levels in macrophages exposed to 60–95% oxygen compared with normoxic (21%) conditions.²¹ Additional genes implicated in oxygen-induced injury include *gasdermin D (GSDMD)*, which mediates pyroptotic cell death, and *connective tissue growth factor (CTGF)*, which promotes fibrotic and inflammatory pathways.^{22,23}

Excessive oxygen leads to short and long-term damage. Alveolar macrophages release fibronectin and alveolar-macrophage-derived growth factors, which attract fibroblasts, causing chronic lung changes. Human lung fibroblasts exposed to 95% oxygen ROS increased RhoA activation.²⁴ RhoA is a small GTPase that regulates various cell functions, including the mediation of collagen-I synthesis and lung fibrosis in the setting of high oxygen.

While most studies investigating the molecular pathophysiology of hyperoxia have focused on cell signaling in the lungs (and, in the neonatal population, retinal tissues), there is also evidence of damage to various other organs including the brain, immune system, and gastrointestinal tract. Yis et al found that exposure of rat pups to 80% oxygen from birth to five days of life was associated with increased cell death in the developing brain as compared to 21% oxygen.²⁵ Additional studies

have shown impaired FoxP3⁺- regulated T cell generation and T cell autoreactivity in mice, increased secretory IgA (SIgA) from intestinal epithelial cells, and gut inflammation/dysbiosis via TLR-4, TNF, NF- κ B, and Nrf2 pathway activation.^{22,25,26}

Alveolar Cell Death & Damage to Alveolar-Capillary Barrier

ROS-induced changes in gene expression, signaling pathways, and damage to DNA, proteins, and lipid membranes can lead to cell death by apoptosis and/or necrosis. Many studies support apoptotic processes in cells exposed to high levels of oxygen. Apoptosis was attenuated in the presence of vitamin E, an antioxidant. Evidence of necrosis was observed in alveolar epithelial cells, specifically in human lung adenocarcinoma cells A549, upon exposure to 95% oxygen. The term “necroptosis” has been proposed to encompass a dual mechanism of cell death. Simultaneous occurrence in different cells and/or sequential processes has been suggested. Injury to alveolar epithelial and endothelial cells compromises the alveolar-capillary barrier. This occurs independent of cellular inflammation when exposed to excessive oxygen.

Clinical Studies

Early studies dating back to the 1940s showed the effects of the delivery of high concentrations of oxygen to the lungs. A few studies isolated excessive oxygen exposure by including only healthy adults with no history of lung pathology and administering oxygen by noninvasive methods, thereby excluding any effects of positive-pressure ventilation. Later studies included mechanically ventilated lungs. Many of these studies did not provide details on ventilator management or explain the possible roles of barotrauma or volutrauma. Accurate conclusions cannot be made about the isolated effects of oxygen therapy, but the results indicate that caution is warranted when determining the level of FiO₂ to administer.

Hyperoxia Clinical Trials

Elevated oxygen levels, when employed clinically, can induce various pulmonary damages, ranging from tracheobronchitis to widespread alveolar injury. Tracheobronchitis, often attributable to diminished ciliary activity, represents among the earliest indicators of pulmonary oxygen toxicity. Patients may present with chest pain, cough, and dyspnea.¹³ For instance, in one study, the exposure to 95% oxygen via a non-rebreather mask for 15.5-18 hours resulted in chest pain in 9 of 14 patients.²⁷ Although the discomfort subsided following cessation of oxygen therapy, bronchoscopy revealed erythema in 6 patients, indicative of inflammation.

Further symptoms of pulmonary oxygen toxicity include alveolar atelectasis (both absorptive and obstructive), decreased lung compliance, reduced vital capacity, and diminished diffusing capacity.²⁸ A study involving eight aircrew subjected to high oxygen delivery and hypergravity associated oxygen exposure with atelectasis, with ultrasound indicating greater atelectasis following breathing 100% oxygen compared to 44.5% and 21% oxygen.²⁹ A decline in vital capacity was noted between 24 and 77 hours at FiO₂ 0.75-1.0. Although limited, these studies suggest that oxygen levels of 50% or higher can provoke adverse clinical effects, with cellular damage likely initiating within hours, even if clinical signs manifest subsequently.

Extensive research has examined hyperoxia's impact on mortality across various populations. These are summarized below in Table I.

Hyperoxia and Critically Ill Pediatric Patients

Hyperoxia is common in critically ill children at admission to a PICU and is associated with increased risk-adjusted mortality. The effect of hyperoxia on critically ill pediatric patients appears dose-dependent. Like the studies on cardiac arrest, it is consistently observed that hypoxia results in worse outcomes compared to hyperoxia. However, several studies have identified a link between hyperoxia and increased morbidity and mortality in critically ill children. Most pediatric research indicates that severe hyperoxia or hyperoxemia is associated with poorer outcomes, especially with longer or more frequent exposures to these conditions effects.³⁰⁻³⁶ The level of hyperoxia differs across studies, with Numa et al identifying a risk minimum around a PaO_2 of 100-200 mmHg, whereas Pelletier et al reported that harmful hyperoxia occurs over 450 mmHg in one study and between 250-400 mmHg in another.³⁷⁻³⁹ (Table 1)

Table 1: Characteristics and Outcomes of Studies Assessing Hyperoxia in Critically Ill ICU Populations

AUTHOR, YEAR OF PUBLICATION	TARGET POPULATION	STUDY DESIGN, SAMPLE SIZE. (N)	OXYGENATION PARAMETER	STUDY FINDINGS
KAPADIA, 2013 ⁴⁰	Neonates (24-34 Weeks Gestational Age); delivery room resuscitation	Prospective, RCT N = 88 (44 per group)	Limited oxygen strategy (LOX): incremental increase in FiO_2 from 21% to achieve the target SpO_2 . High oxygen strategy (HOX): 100% FiO_2 initiated and adjusted every 30 seconds to meet the target SpO_2 of 85% to 94%.	LOX effectively resuscitated preterm neonates, decreased oxygen load by 50% (401 ± 151 vs 662 ± 249 ; $P < .01$), lowered ventilator days (3 [0-64] vs 8 [0-96]; $P < .05$), rescue HFOV, and BPD (7% vs 25%; $P < .05$). LOX group spent less time with $\text{SpO}_2 > 94\%$ and developed less oxidative stress by 1 hour of life.
LILIEN, 2022 ⁴¹	Pediatric patient	Systematic review N = 27,555 11 studies pooled for meta-analysis (N = 23,204)	Variable definitions of hyperoxia, with studies determining hyperoxia as PaO_2 values $> 120\text{mm Hg}$ to $> 300\text{mm Hg}$.	Variability in mortality associated with hyperoxia across studies. Hyperoxia increased the odds of mortality (OR 1.59, 95% CI, 1.00-2.51).
RAMGOPAL, 2019 ³²	Patients admitted to the pediatric ICU (age ranges < 30 days to ≤ 18 years) with PaO_2 values collected at any point during admission	Retrospective cohort study N = 6,250	Severe hyperoxemia: $\text{PaO}_2 \geq 300\text{mm Hg}$.	Severe hyperoxemia (dose-response relationship) is independently associated with in-hospital mortality. ([aOR], 1.78; 95% CI, 1.36-2.33; $P < .001$).
RAMGOPAL, 2020 ³³	Pediatric patients admitted to the PICU with PaO_2 values obtained in the 6 hours prior to or after admission to the ICU	Single-center observational study N = 4,093	Hyperoxemia: $\text{PaO}_2 \geq 300\text{mm Hg}$; Hypoxia: $\text{PaO}_2 < 60\text{mm Hg}$.	Hypoxemia was associated with increased in-hospital mortality. Hyperoxemia overall is not associated with in-hospital mortality (aOR, 1.38; 95% CI, 0.98-1.93), except at extremes ($\text{PaO}_2 \geq 550$ torr)

RAMAN, 2016³⁴	Patients < 18 years admitted to ICU	Retrospective cohort study N = 7,410 patients	Hyperoxia: PaO ₂ > 300 torr; Hypoxia: PaO ₂ < 60 torr OR SpO ₂ < 90%.	U-shaped association between admission PaO ₂ and mortality. Hypoxia increased risk of death. OR 3.13 (95% CI, 1.79-5.48; p < 0.001) No increase in mortality with hyperoxia (OR, 1.15; 95% CI, 0.42-3.17; p = 0.77).
NUMA, 2018³⁷	Pediatric patients ages 0 to 18 years admitted to ICU	Single-center retrospective analysis N = 1,447	Oxygenation values broken down by 50mm Hg increments for analysis. Hyperoxia defined as PaO ₂ > 250mm Hg.	U-shaped relationship between mortality and admission PaO ₂ . Lowest mortality observed in PaO ₂ of 101-150mm Hg and 151-200mm Hg. Highest mortality in the PaO ₂ > 350mm Hg and PaO ₂ < 50mm Hg. Odds ratio for hyperoxia predicting death was 2.66 (p = 0.047).
VAN DER WAL, 2023⁴²	Patients > 18 years with mechanical ventilation duration of at least 24 hours	Randomized multicenter trial N = 664 Stopped prematurely due to COVID-19 pandemic (only 664 of the planned 1,512 patients recruited)	Low oxygenation group: PaO ₂ 55-80mm Hg OR SpO ₂ 91-94%. High oxygenation group: PaO ₂ 110-150mm Hg OR SpO ₂ 96-100%.	No reduction in 28-day mortality with low oxygenation strategy compared to high oxygenation strategy.
BALCARCEL, 2022³¹	Patients < 18 years requiring mechanical ventilation within 3 days of admission	Retrospective, observational cohort study N = 5,406	Hypoxemia: SpO ₂ < 90% at any point in the first 24 hours of mechanical ventilation. Cumulative Excess Oxygen Exposure (CEOE): mean hourly FiO ₂ provided above 0.21 when the SpO ₂ was ≥ 95% during the first 24 hours of mechanical ventilation.	Higher CEOE increased odds of in-hospital mortality (aOR, 1.7; 95% CI, 1.1-2.9), and MODS on day 7 (aOR, 3.9; 95% CI, 2.7-5.9). Hypoxemia-associated mortality and MODS were comparable to the highest CEOE group.
GEVA, 2023³⁶	Patients aged 7 months to < 16 years admitted to the PICU and mechanically ventilated via endotracheal tube for at least 24 hours	Retrospective cross-sectional study N = 3,354	Hypoxia: SpO ₂ reading < 90% at any point during the 24 hours of mechanical ventilation. Hyperoxia: Cumulative Excess Oxygen Exposure (CEOE): mean hourly FiO ₂ provided above 0.21 when the SpO ₂ was ≥ 95% during the first 24 hours of mechanical ventilation.	Higher CEOE quartiles were associated with greater mortality, but this finding was primarily in the highest quartile.

Abbreviations: Randomized control trial (RCT), fraction of inspired oxygen (FiO_2), arterial partial pressure of oxygen (PaO_2), oxygen peripheral saturation (SpO_2), odds ratio (OR), intensive care unit (ICU), adjusted odds ratio (aOR), pediatric intensive care unit (PICU), high frequency oscillatory ventilation (HFOV), bronchopulmonary dysplasia (BPD), cumulative excess oxygen exposure (CEOE), multiorgan dysfunction syndrome (MODS)

Hyperoxia and Traumatic Brain Injury (TBI)

Numerous studies involving both adult and pediatric TBI patients suggest that hyperoxia might be neuroprotective. While some studies suggest improvement in biomarkers and reduced intracranial pressure across adult and pediatric patients. None of the studies demonstrated an association between hyperoxia and improvement in neurological outcomes. (Table 2)

Table 2: Characteristics and Outcomes of Studies Assessing Hyperoxia in Critically Ill patients after trauma or a traumatic brain injury

AUTHOR, YEAR OF PUBLICATION	TARGET POPULATION	STUDY DESIGN, SAMPLE SIZE. (N)	OXYGENATION PARAMETER	STUDY FINDINGS
BAEKGAARD, 2020 ⁴³	Trauma patients > 17 years	Observational study using a multicenter, prospective trauma registry. N = 5,912	Hyperoxia: $\text{PaO}_2 \geq 150$ mmHg on admission	Univariate analysis showed higher in-hospital mortality for hyperoxemic patients compared to normoxemic patients. After propensity matching, significantly lower in-hospital mortality for hyperoxemic patients compared to normoxemic patients.
JEONG, 2018 ⁴⁴	Patients > 16 years, who survived for at least 5 days after ED arrival	Observational cohort study N = 10,141 Exclusion: < 2 ABGs, maximum $\text{PaO}_2 < 60$ mm Hg, Died, transferred to ICU, or had complications within 5 days of ED arrival, hospital LOS > 90 days, unable to calculate AUC, acute MI	Area under the curve over 72 hours (AUC72) calculations using highest PaO_2 , average PaO_2 , and median PaO_2 . Hyperoxemia: max $\text{PaO}_2 > 137$ mm Hg, average $\text{PaO}_2 > 105$ mm Hg, median $\text{PaO}_2 > 103$, and AUC72 > 174 mm Hg.	Significant correlations between all hyperoxemia variables with 90-day in-hospital mortality. After adjustment, only AUC ₇₂ was significantly associated with 90-day in-hospital mortality. (aOR 1.53 (95% CI 1.25 to 1.88; $p < 0.0001$). AUC ₇₂ also associated with ICU transfer, end organ failure.
TOLIAS, 2004 ⁴⁵	Patients > 16 years with severe TBI treated with normobaric hyperoxia (FiO_2 1.0) for 24 hours, starting within 6 hours of admission	Prospective clinical trial N = 52 in treatment and N = 112 in matched control cohort	Hyperoxia: FiO_2 1.0 administration for 24 hours, started within 6 hours of admission.	Hyperoxia group: Improved biomarker profile and lower intracranial pressure.

NORTJE, 2008⁴⁶	Patients > 15 years with TBI	Prospective clinical trial N = 11 patients	Cerebral microdialysis, brain tissue oximetry (PbO ₂), and oxygen-15 positron emission tomography (15O-PET) normoxia (FiO ₂ : 0.35 to 0.5) and repeated at hyperoxia (FiO ₂ : 0.6 to 0.8). PaO ₂ at baseline: 99 +/-23; Hyperoxia PaO ₂ : 226 +/- 68	Hyperoxia increased the mean PbO ₂ and reduced the lactate: pyruvate ratio.
FIGAJI, 2010⁴⁷	Patients < 15 years with severe TBI	Prospective observational study 48 tests performed in 28 patients who underwent PbO ₂ monitoring and an oxygen challenge test (temporary increase in FiO ₂ for 15 minutes)	Pre- and post-test values (PbO ₂ , ICP, CPP, PaO ₂ , arterial saturation (SaO ₂), arterial partial pressure of carbon dioxide (PaCO ₂)) measured	Linear increase in PbO ₂ with normobaric hyperoxia. A greater PbO ₂ response to PaO ₂ change is associated with a worse outcome.
KETHARANATHAN, 2020⁴⁸	Patients < 18 years with accidental severe TBI (GCS 8 or less)	Retrospective explorative study N = 71	Hyperoxia cutoffs: PaO ₂ > 200mm Hg, > 250mm Hg, > 300mm Hg. Highest PaO ₂ value for each individual patient in the first 24 hours of PICU admission used PaO ₂ cumulative area under the curve (AUC); AUC value cutoffs: <2000 (physiological oxygen exposure), 2000-4000 (intermediate oxygen exposure), >4000 (high oxygen exposure)	Hyperoxia classification differed depending on PaO ₂ cutoff vs AUC analysis. AUC better approximates physiological circumstances due to time and dose-dependent approach
TANG, 2024⁴⁹	Patients < 18 years with severe accidental TBI (GCS 3-8)	Prospective institutional registry N = 98	First, highest, and area under the curve (AUC) PaO ₂ in the first 24 hours of admission to the ICU were evaluated Hyperoxia: PaO ₂ > 300mm Hg.	Hyperoxia incidence 33% Hyperoxia not associated with unfavorable outcome after 6 months.

Abbreviations: Arterial partial pressure of oxygen (PaO₂), emergency department (ED), arterial blood gas (ABG), emergency department (ED), length of stay (LOS), area under the curve (AUC), myocardial infarction (MI), area under the curve over 72 hours (AUC72), adjusted odds ratio (aOR), confidence interval (CI), traumatic brain injury (TBI), fraction of inspired oxygen (FiO₂), brain tissue oximetry (PbO₂), intracranial pressure (ICP), cerebral perfusion pressure (CPP) arterial oxygen saturation (SaO₂), arterial partial pressure of carbon dioxide (PaCO₂), Glasgow coma score (GCS)

Hyperoxia and Pediatric Cardiac Arrest

Multiple studies have examined the link between hyperoxia and outcomes following pediatric cardiac arrest. These are summarized below in Table 3. The smaller studies demonstrated no difference in outcomes in patients with hyperoxia ($\text{PaO}_2 > 200 \text{ mmHg}$) in the first six hours⁵⁰. The larger studies revealed worse outcomes associated with hypoxia and extremes of hyperoxia ($\text{PaO}_2 > 600 \text{ mmHg}$), which the studies concluded were rarely observed.⁵¹ These studies concluded that in the post cardiac arrest phase hypoxia is more critical than hyperoxia and associated with worse outcomes.

Table 3: Characteristics and Outcomes of Studies Assessing Hyperoxia in Critically Ill patients after cardiac arrest or requiring extracorporeal membrane oxygenation (ECMO)

AUTHOR, YEAR OF PUBLICATION	TARGET POPULATION	STUDY DESIGN, SAMPLE SIZE. (N)	OXYGENATION PARAMETER	STUDY FINDINGS
SZNYCER-TAUB, 2016 ⁵²	Patients < 1 year undergoing cardiac surgery requiring postoperative VA ECMO	Retrospective chart review; N = 93	Hyperoxia: mean $\text{PaO}_2 > 193 \text{ mm Hg}$ in the first 48 hours of ECMO.	Total mortality~ 38%. Hyperoxia an independent risk factor for 30-day mortality. ($p = 0.001$) Hyperoxia is associated with the need for dialysis ($p = 0.02$).
BENNETT, 2013 ⁵⁰	Pediatric patients aged 24 hours to 18 years who experienced cardiac arrest with return of circulation for ≥ 20 minutes	Retrospective cohort study; N = 195 cardiac arrest events were included in the study	Hyperoxia: defined as $\text{PaO}_2 > 200 \text{ mm Hg}$ in the first 6 hours post-cardiac arrest. Hypoxia: $\text{PaO}_2 < 50 \text{ mm Hg}$.	13% of patients maintained both normoxia and normoventilation. 10% of patients with both hyperoxia and hypoxia. No difference in outcomes (survival with good outcome 34% for hyperoxia compared to 42% with normoxia ($p = 0.23$)).
FERGUSON, 2012 ⁵¹	Patients < 16 years with cardiac arrest and ABG taken within 1 hour of PICU admission	Retrospective cohort study N = 1875 patients included in analysis	Hypoxia: $\text{PaO}_2 < 60 \text{ mm Hg}$; Hyperoxia: $\text{PaO}_2 \geq 300 \text{ mm Hg}$.	Mortality 39%. Incidence (hypoxia 24%, hyperoxia 11%, normoxia 65%). Severe hypoxia increased the probability of death (OR 1.92; 95% CI, 1.80-2.21). Hyperoxia also increased risk of ICU mortality (OR 1.2; 95% CI 1.0-1.5). Increased risk with higher degrees of hyperoxia (mortality OR 1.12 per 100 mm Hg increase in PaO_2). Optimal PaO_2 after cardiac arrest: 60-75 mm Hg.
CASHEN, 2018 ³⁵	Pediatric patients < 19 years treated with ECMO	Retrospective, secondary analysis N = 484	Hyperoxia: highest $\text{PaO}_2 > 200 \text{ Torr}$ during the first 48 hours on ECMO.	Hyperoxia associated with higher mortality and shorter durations of ECMO and ICU stays (167 [50.5%] vs 48 [31.4%]; $p < 0.001$. No functional status differences at discharge.
FRAZIER, 2024 ⁵³	Patients ≤ 18 years receiving chest compressions during ICU stay	Embedded prospective observational study N = 284 Exposures: hypoxemia, hyperoxemia, or normoxemia based on the lowest PaO_2 within the first 24 hours post-arrest	Hypoxemia: $\text{PaO}_2 < 60 \text{ mm Hg}$; Hyperoxemia: $\text{PaO}_2 \geq 300 \text{ mm Hg}$; Normoxemia: PaO_2 between 60 mm Hg and 300 mm Hg	Hypoxemia group less likely to survive to hospital discharge (aRR 0.71; 95% CI 0.58-0.87).

Abbreviations: Veno-arterial extracorporeal membrane oxygenation (VA ECMO), arterial partial pressure of oxygen (PaO₂), arterial blood gas (ABG), pediatric intensive care unit (PICU), intensive care unit (ICU), odds ratio (OR), adjusted risk ratio (aRR)

Hyperoxia in COVID-19

Hyperoxemia was common during the COVID-19 pandemic, especially among mechanically ventilated patients receiving prolonged high FiO₂.⁵⁴ Prospective and observational cohorts consistently showed a high prevalence of hyperoxemia and “excessive oxygen use” in COVID-19 ARDS populations. Outcome associations, however, have been inconsistent. In a single-center cohort of invasively ventilated patients, time spent in hyperoxemia (PaO₂ >100 mmHg) and combined hyperoxia–hyperoxemia (FiO₂ >0.60 with PaO₂ >100 mmHg) were independently linked to higher ICU mortality and increased ventilator-associated pneumonia.⁵⁵ Conversely, analysis of the multicenter PROVENT-COVID study found no difference in 28-day, 90-day, or out of hospital mortality between hyperoxemic and normoxemic patients after matching, despite frequent early PaO₂ >90 mmHg.⁵⁴ Interventional evidence from the HOT-COVID randomized trial showed that targeting a lower PaO₂ (~60 mmHg) was associated with more days alive without life support than targeting a higher PaO₂ (~90 mmHg), supporting conservative oxygen strategies, even without a difference in mortality.⁵⁶ Overall, these data suggest that while hypoxemia remains the primary concern, sustained hyperoxemia offers no benefit and may cause harm, emphasizing the importance of early FiO₂ reduction in COVID-19 ARDS. There is currently a lack of specific pediatric data on hyperoxemia (e.g., elevated PaO₂ levels) and its effect on clinical outcomes in children with COVID-19. Current pediatric COVID-19 research mainly concentrates on respiratory support methods, predictors of severe disease, and managing hypoxemia, rather than the effects of prolonged high PaO₂ exposure.

Management Targets

Contemporary pediatric guidance emphasizes that oxygen should be titrated to avoid both hypoxemia and sustained hyperoxemia. The PALICC-2 recommendations for pediatric ARDS support targeting oxygenation ranges that achieve adequate delivery while minimizing FiO₂ exposure, using SpO₂ goals generally in the 92–97% range and prioritizing early FiO₂ reduction once targets are met.⁷ In pediatric cardiac arrest care, international consensus recommends FiO₂ 1.0 during active resuscitation, followed by prompt titration after return of spontaneous circulation to avoid extremes of oxygenation (goal SpO₂ 94 - 99%); post-ROSC management aims for near-normal oxygenation, avoiding hyperoxemia when arterial blood gases are available.⁵⁷ Across these settings, guidance consistently highlights frequent reassessment, use of arterial blood gas (ABG) confirmation when feasible, and avoidance of prolonged high FiO₂ in the absence of refractory hypoxemia, reflecting the principle that oxygen is a drug with both lifesaving benefits and potential toxicity.

Oxygen administration is similar to other drugs and must be titrated to achieve the desired effect. However, achieving the exact blood oxygen level is challenging. Adjusting FiO₂ during maintenance and weaning can be challenging, as even small changes in inspired oxygen can lead to unintended fluctuations in oxygen saturation. Proper titration is essential, but it's often hindered by factors such as staff experience and staffing levels, leading to significant variability in SpO₂ levels. Automated oxygen controllers can help reduce the risks associated with weaning from oxygen therapy. Automated oxygen controllers have successfully maintained oxygen saturation in target ranges in neonatal patients⁵⁸⁻⁶⁵ and shown to be feasible for titration in adults with chronic obstructive pulmonary

disease (COPD). Neonatal studies compared manual FiO_2 adjustment with automated open and closed-loop FiO_2 control systems in neonates receiving both invasive and non-invasive oxygen support. The automated systems consistently demonstrated greater effectiveness in keeping oxygen levels within the target range. While neonatal studies did not consistently prove the prevention of acute hypoxia, they did show a decrease in the duration of prolonged hypoxemic and hyperoxemic episodes.⁶⁴ Neonatal patients using automated oxygen controllers were found to have much better compliance with normoxic target ranges with less time spent severely hyperoxic.⁶⁶ Additionally, these patients tended to have a shorter duration of mechanical ventilation compared to those not on automated oxygen controllers.⁶⁷ These studies are summarized in table 4.

Table 4: Table summarizing open and closed loop automated controllers in the neonatal and pediatric population.

AUTHOR, YEAR OF PUBLICATION	TARGET POPULATION	STUDY DESIGN, SAMPLE SIZE. (N)	STUDY FINDINGS
IR, 1979	Preterm neonates in the first week of life	Prospective clinical trial N=12 Automated control of FiO_2 to meet PaO_2 goals between 55mm Hg and 80mm Hg using an indwelling arterial electrode sensor connected to the ventilator.	PaO_2 outside target range 12.2% of the time during the automatic servo-control period compared to 27.6% in the manual-control period.
DUGDALE, 1988	Neonates with RDS	Prospective clinical trial N=7 A microcomputer-based closed-loop control system using the PaO_2 value from an indwelling umbilical artery electrode as input. Titration of oxygen. Duration 48 hours	Percentage of time for which the PaO_2 was within ± 1 kPa of the chosen target value using a closed-loop PaO_2 regulator was 74.9 $\pm$ 10.2% compared to 45.2 $\pm$ 16.0% when using comparable manual control intervals
BHUTANI, 1992	Infants with BPD	Prospective clinical trial N=14 Adaptive adjustment of inspired oxygen (FIO_2), based on a desired percent arterial hemoglobin saturation.	SpO_2 values within target range: 54% with standard protocol, 69% ($P < 0.01$) with bedside manual control and 81% ($P < 0.01$) with adaptive control. Fluctuations in SpO_2 values and overshoots were less common with adaptive control.
SUN, 1997	Newborn infants requiring mechanical ventilation	Prospective clinical trial N=16 Open-loop computer control of inspired oxygen concentration.	More time spent at the target SaO_2 ($p < 0.025$), $\text{SaO}_2 < 90\%$ less frequent ($p < 0.01$) and less overall variations during the experimental period than during either control period.
CLAURE, 2001	Mechanically ventilated very low birthweight infants	Prospective clinical trial N=14 Closed-loop FiO_2 control (cFiO_2) to maintain SpO_2 within a target range was compared with continuous manual FiO_2 (mFiO_2) adjustments by a nurse.	cFiO_2 is noninferior to a fully dedicated nurse in maintaining SpO_2 within the target range. Mean SpO_2 and FiO_2 levels were similar in both modes. Significant increase in the duration of normoxemia during cFiO_2 (75 $\pm$ 13 vs 66 $\pm$ 14%).

CLAURE, 2011	Mechanically ventilated preterm infants	Crossover study N=32 Automated versus manual adjustment of the fraction of inspired oxygen (FiO ₂).	Time with SpO ₂ in goal range increased significantly during the automated period compared to the manual period (40 +/- 14% versus 32 +/- 13%), less time spent hyperoxic in the automated period. Statistically significant increase in the time spent hypoxic in the automated period (32% ± 12% vs 23% ± 9%).
HALLENBERGER, 2014	Preterm infants receiving mechanical ventilation or nasal continuous positive airway pressure and supplemental oxygen	Multicenter, randomized controlled, crossover clinical trial N=34 Routine manual control of FIO ₂ versus a closed-loop automatic control (CLAC).	Median percentage of time with SaO ₂ levels within target range was 61.4% (31.5-99.5) for routine manual control and 71.2% (44.0-95.4) for CLAC (p<0.001).
DIJLMAN, 2025	Extremely preterm infants who survived to NICU discharge and	Prospective cohort study; patients matched 1:1 with a control cohort who received routine manual FiO ₂ control N=25 Comparison of FiO ₂ control by the PRICO-automated FiO ₂ controller versus routine manual care (RMC).	When requiring supplemental oxygen during the first 2 weeks of life, time within the SpO ₂ target range significantly increased with FiO ₂ -c, while time in hyperoxia decreased.
DIJLMAN, 2023	Preterm infants on different modes of invasive and noninvasive respiratory support	Feasibility study N=32 Observation of infants receiving FiO ₂ control by the PRICO automated controller.	The time percentage within the SpO ₂ target range was increased with PRICO (74.4% [IQR 67.8-78.5]) compared to RMC1 (65.8% [IQR 51.1-77.8]; p = 0.011) and RMC2 (60.6% [IQR 56.2-66.6]; p < 0.001).
DIJLMAN, 2021	Preterm patients on high flow nasal cannula support receiving FiO ₂ > 0.25	Single-center randomized two-period crossover study N=27 Comparison of FiO ₂ control by the PRICO-automated FiO ₂ controller versus routine manual care (RMC).	The mean time within the target range increased with PRICO: 10.8% (95% CI 7.6 to 13.9). No difference in time spent in severe hyperoxia. There was a decrease in time below target range: 7.6% (95% CI 4.2 to 11.0), above target range: 3.1% (95% CI 2.9 to 6.2) and in severe hypoxia: 0.9% (95% CI 1.5 to 0.2). Mean FiO ₂ was higher during PRICO: 0.019 (95% CI 0.006 to 0.030).
WILINSKA, 2024	Mechanically ventilated infants in neonatal intensive care	Multicenter randomized crossover study N=39 Evaluate the performance of the PRICO system for automated control of FiO ₂ .	During automated control, subjects spent more time in normoxemia (74%±22% vs 51%±22%, p<0.001) Patients spent less time in severe hyperoxemia (1% (0%-3.5%) vs 5% (1%-10%), p < 0.001).
SALVERDA, 2021	Infants of 24-29 weeks gestational age receiving respiratory support	Retrospective pre-post implementation cohort study N=588 (293 pre-implementation, 295 post-implementation) Comparison of routine care versus AOC.	Length of stay in NICU was not different, but duration of invasive ventilation was shorter in infants who received AOC (6.4 ± 10.1 vs 4.7 ± 8.3, p = 0.029).

Abbreviations: Fraction of inspired oxygen (FiO_2), arterial partial pressure of oxygen (PaO_2), respiratory distress syndrome (RDS), bronchopulmonary dysplasia (BPD), peripheral oxygen saturation (SpO_2), arterial oxygen saturation (SaO_2), closed-loop FiO_2 control (cFiO_2 or $\text{FiO}_2\text{-c}$), closed-loop automatic oxygen control (CLAC), chronic obstructive pulmonary disease (COPD), confidence interval (CI), interquartile range (IQR), routine manual control (RMC), Predictive Intelligent Control of Oxygenation (PRICO), automated oxygen control (AOC), neonatal intensive care unit (NICU)

Oxygen-related injury results from the combined effect of FiO_2 levels and exposure time, without a single threshold. Short exposure to very high FiO_2 , such as during pre-oxygenation for intubation or brief surgeries, mainly causes reversible absorption atelectasis and is usually tolerated. Conversely, prolonged exposure to even moderate FiO_2 levels (0.40–0.60) can induce sustained production of reactive oxygen species, cytokine activation, and epithelial cell damage. Human studies show increased inflammatory markers within about 6 hours of high oxygen, decreased vital capacity after 24–48 hours at $\text{FiO}_2 \geq 0.75$, and signs of diffuse pneumonitis after exposures longer than 48 hours.

Along with clinical measures like implementation of automated oxygen controllers, there are a number of potential molecular targets that have the potential to reduce tissue injury secondary to exposure to excess oxygen. Examples include connective tissue growth factor antibodies to improve alveolarization and vascularization²³, administration of mesenchymal stromal cell extracellular vesicles to improve thymic medullary architecture⁶⁸, and N-acetylcysteine (NAC) to mitigate hyperoxia-induced gut injury by reducing ROS production.²² However, clinical trials evaluating their role in patient management are currently not available.

Conclusion

While oxygen therapy remains a cornerstone in the management of hypoxemia, excessive oxygen delivery poses underappreciated risks across patient populations. The pulmonary system is particularly vulnerable, as prolonged exposure to high FiO_2 and hyperoxemia initiates a cascade of oxidative, inflammatory, and structural injuries mediated by reactive oxygen species and altered cellular signaling. Despite decades of research, a definitive threshold for safe oxygen administration in humans remains elusive, as both cellular tolerance and systemic responses vary by context, duration, and disease state. The challenge lies in achieving adequate oxygenation without crossing into toxicity—a balance that can be difficult to maintain during dynamic clinical conditions. Recent advances, such as automated and closed-loop FiO_2 controllers, show promise in minimizing episodes of hyperoxia and hypoxia, thereby reducing preventable injury and improving ventilation outcomes. Parallel progress in molecular therapeutics—including antioxidants, targeted growth factor modulation, and stem cell-derived interventions—suggests a future in which oxygen toxicity may be mitigated at both the system and cellular level. Continued integration of physiologic monitoring, precision automation, and translational molecular research will be essential to redefine safe oxygen delivery and optimize outcomes for critically ill patients.

Author Contributions: All authors have made substantial contributions to the conception or design of the work; and have drafted the work or substantively revised it. All authors have approved the submitted version (and version substantially edited by journal staff that involves the author's contribution to the study); AND agrees to be personally accountable for the author's own contributions and for ensuring that questions related to the accuracy or integrity of any part of the

work, even ones in which the author was not personally involved, are appropriately investigated, resolved, and documented in the literature.

Funding: This research received no external funding.

Institutional Review Board Statement: Not applicable

Informed Consent Statement: Not applicable

Conflicts of Interest: The authors do not have any conflicts of interest pertinent to this work.

Acknowledgments: We would like to thank Emma O'Hagan from the UAB Lister Hill Library of the Health Sciences for her assistance in developing and running the search strategy for this review.

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Narrative Review

Artificial Intelligence in Congenital Heart Disease: A Review of Computational Approaches Across Multiple Data Modalities

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Abstract: Congenital heart disease (CHD) is the major cause of infant morbidity and death worldwide. In developing countries, the disease often goes undetected due to limited access to diagnostic resources. The current research using machine learning and deep learning methods is promising for accurate disease diagnosis, but most of these studies treat data modalities in isolation.

This study suggests that electronic health records (EHR)-based models provide early risk assessment capabilities but lack the ability to identify specific structural elements; echocardiographic models achieve diagnostic performance close to expert standards, but they depend on the image quality, and genomic methods can identify causal information but lack the ability to establish direct connections between genetic factors and observable traits. The research approach requires EHR, echocardiography, and genomics to be examined in unison, as CHD has multi-factorial and temporally evolving characteristics. This review elaborates on the literature available from individual modalities and points to CHD prediction as a temporally evolving multimodal learning problem rather than a static classification task.

The analysis reveals major gaps, including the need for CHD-specific multimodal datasets, better temporal modelling, and prospective validation studies. This research presents a conceptual framework that enables multimodal CHD prediction by combining EHR, echocardiographic imaging, and genomic information. The findings suggest that multimodal AI systems that leverage temporal data as the next frontier for developing CHD prediction technologies for clinical use. Unlike prior works, this study reframes CHD prediction as a temporally evolving multimodal learning problem, establishing a clear direction for next-generation clinically deployable AI systems.

Keywords: Congenital heart disease; Multimodal fusion; Temporal modelling; Echocardiography; Electronic health records; Genomics; Clinical prediction.

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Citation: Shruthi S., Hanumanth R. N.; *Awareness*, 3 (2): 33-62



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1. Introduction

Congenital heart disease (CHD) is a structural malformation of the heart present at birth. The defects vary in severity from minor septal openings that self-correct to extreme cases that require immediate surgical treatment within the first hours after birth. However, CHD does not include conditions arising strictly from broader syndromic disorders affecting extracardiac or neurodevelopmental.¹⁻³ Cardiac defects develop through multiple genetic and environmental risk factors, which combine with chromosomal abnormalities, maternal infections and teratogenic exposures that happen during heart development.^{4,5}

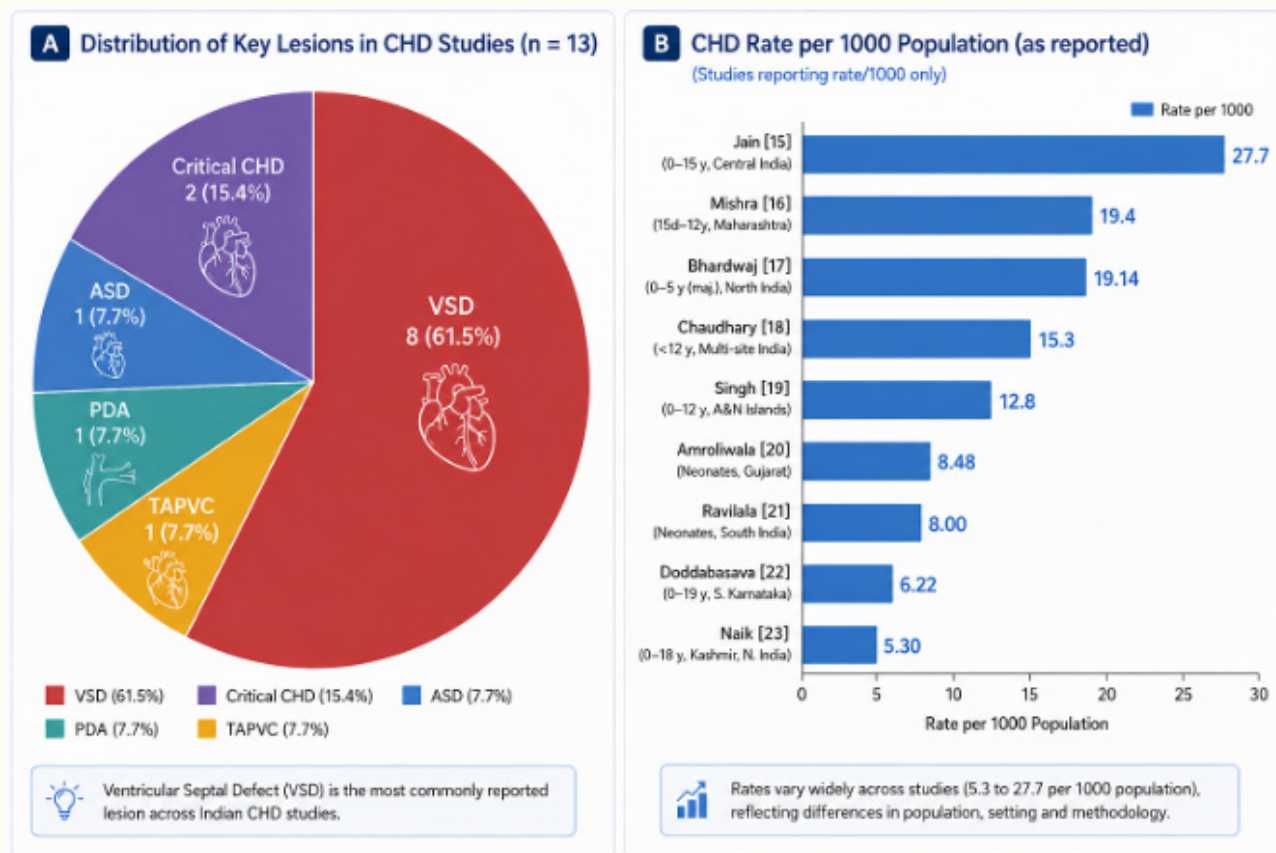
CHD is the leading non-communicable cause of infant mortality worldwide and among the most frequently diagnosed birth defects, affecting approximately 0.8–1.0% of live births.⁶⁻⁸ An estimated 1.35 million children are born with CHD each year, and around 250,000 deaths are ascribed to the condition annually.^{1,9} The development of echocardiographic imaging, cardiac surgical techniques, and neonatal intensive care has improved survival rates but has major access disparities between socioeconomic groups across low- and middle-income countries.^{6,10}

1.1 Classification of CHD

Two main haemodynamic categories define CHD. Acyanotic forms that show left-to-right shunting keep their systemic oxygen saturation but their pulmonary blood flow increases. The cyanotic form of CHD permits deoxygenated blood to flow throughout the body, leading to a marked decrease in arterial oxygen saturation. Major acyanotic lesions, including ventricular septal defect (VSD), atrial septal defect (ASD), patent ductus arteriosus (PDA), pulmonary stenosis (PS), aortic stenosis (AS), coarctation of the aorta (COA), and atrioventricular septal defect (AVSD), make up approximately 85% of all CHD cases.^{4,11} A minority (15%) comprises rarer, more complex types. Prevalence varies by subtype: VSD is the single most common CHD globally, followed by ASD. For cyanotic defects, Tetralogy of Fallot (TOF) represents 60 per cent of cases and is the predominant cyanotic heart disease seen in Indian hospitals.¹² The severe conditions that require treatment through multiple surgical procedures include Transposition of the Great Arteries, Total Anomalous Pulmonary Venous Connection, Hypoplastic Left Heart Syndrome, Double Outlet Right Ventricle, and Ebstein Anomaly. The worldwide patterns of disease occurrence observed in the study¹³ show strong similarities to those detected in India. This distribution of CHD subtypes indicates that VSD and ASD are the leading acyanotic lesions, while TOF is the most common occurring cyanotic type.

CHD is a major health problem in India. Every year, about 24.2 million babies are born, and 9 out of every 1,000 have CHD. This means around 240,000 children are born with CHD each year, and 43,000 to 48,000 of them need treatment in their first year. Hospital-based echocardiographic studies estimate CHD rates ranging from 3.9 to 74.4 per 1,000 live births across different regions. The geographic region shows significant differences because South Indian children with critical CHD face a 70% chance of accessing cardiac care, while only 12% of children in Uttar Pradesh, Bihar, Jharkhand, and Madhya Pradesh receive similar treatment.¹⁴ Around 40,000 to 50,000 CHD surgeries happen each year, yet this remains insufficient relative to the actual requirement, which ranges from 35,000 to 80,000 necessary procedures for infants.⁷ Surgery costs range from Indian rupees 75,000 to 5,60,000, depending on hospital category, and are affordable when compared to global standards, but still unaffordable for most of the Indian families, especially given the direct payment for private hospital care.

Figure 1. Prevalence of CHD in India and Distribution of Major Lesions



The Figure 1 consolidates all the prevalence studies, including the in-between references of¹⁴⁻²⁷ and shows differences in reported rates of CHD across several studies in India, along with the relative frequency of the main types of the disease. Panel A shows VSD is the most common lesion, followed by ASD and PDA. Panel B compares CHD rates (per 1,000 people) from different studies. The reported prevalence range spans 5.3 per 1,000²³ to 27.7 per 1,000.¹⁵ Studies using hospital data reported higher rates of the CHD as they can be the referred cases who needed care. Community screenings, as indicated by studies,^{22,23} typically reflect actual prevalence registry data.

Prevalence studies indicate that CHD rates vary considerably across studies due to geographic and population differences. VSD and other septal defects consistently predominate within the CHD spectrum in India. These results show the need for regular screening and wider community testing to get more accurate counts of CHD cases.

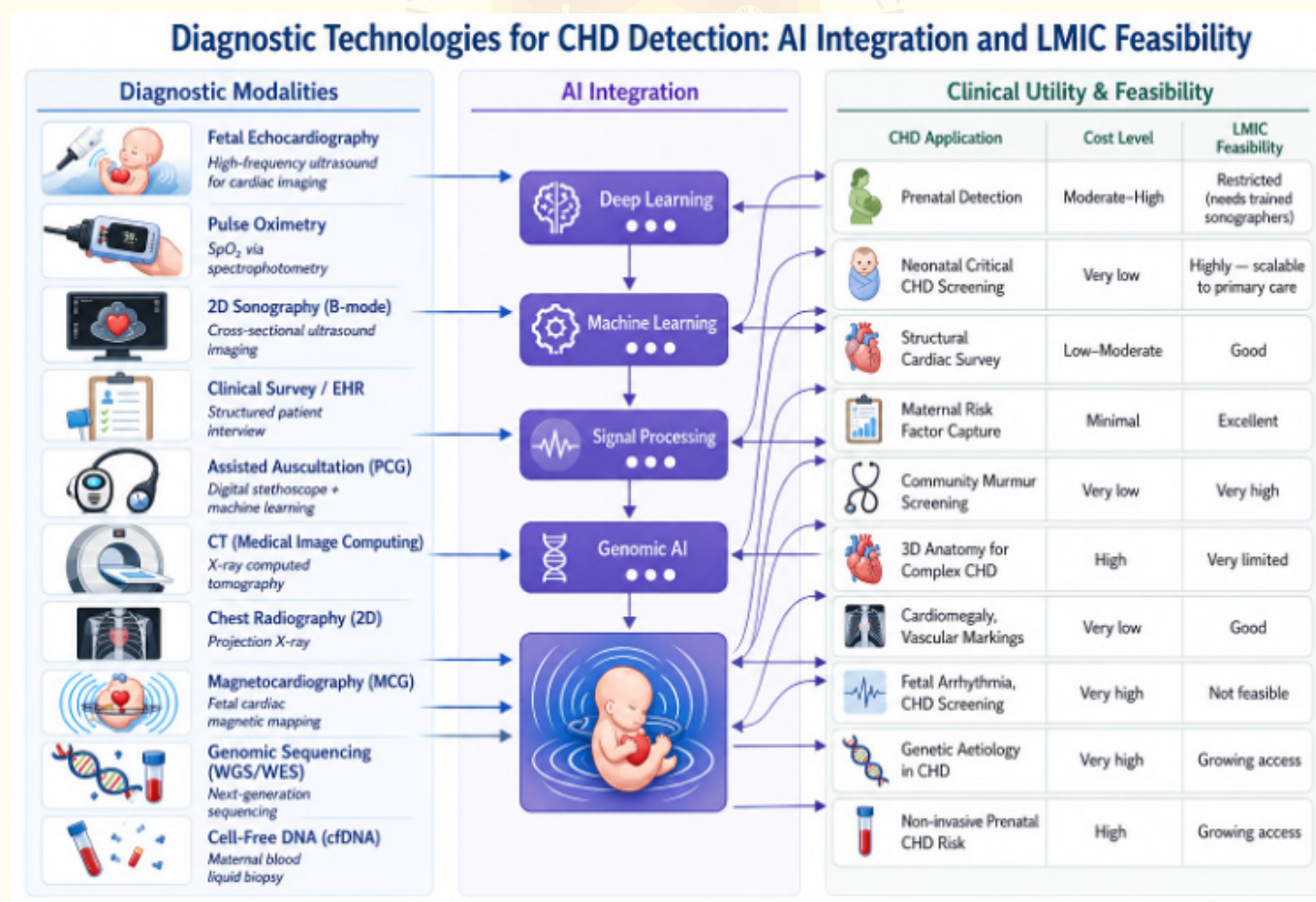
The government has initiated programs such as Ayushman Bharat (AB-PMJAY), Rashtriya Bal Swasthya Karyakram (RBSK), and Janani-Shishu Suraksha Karyakram (JSSK), but these programs fall short because their coverage gaps leave many families unprotected. The Sri Sathya Sai Sanjeevani hospitals <https://srisathyasaisanjeevani.org/> serve as philanthropic centres that provide comprehensive financial support for surgical procedures while providing essential assistance to families in need.⁴

1.2 Diagnostic technologies used for CHD detection

CHD detection and monitoring employ different diagnostic methods, yielding varying detection success rates and incurring different operational costs.

Figure 2 summarises a unified pipeline for CHD detection, linking diverse diagnostic modalities as pointed out in the above literature section, including imaging, physiological signals, clinical/EHR data, and genomics, corresponding AI techniques such as signal processing, machine learning, deep learning, and genomic AI, which transform raw data into predictive insights. Each method is useful in its own way, depending on the level of information the modality gives, cost incurred, and accessibility. Methods such as echocardiography and genomics provide precise information about structure or aetiology but require specialised resources and are costlier. Cheaper tools, such as pulse oximetry and clinical screening, can be used widely to screen large numbers of people and are widely recommended given their acceptable false-positive rate when established protocols are followed.²⁸ By linking these methods to specific medical uses and to their practicality in low- and middle-income countries, the figure highlights an important balance between accuracy and ease of use.

Figure 2. The hierarchical mapping between diagnostic modalities and AI techniques, highlighting the trade-off between accessibility and diagnostic precision, particularly in LMIC settings



Echocardiography is the gold standard technique for both pre- and post-natal detection of CHD, providing real-time visualisation of cardiac structures and blood flow patterns. Deep learning systems for fetal CHD classification primarily utilise this modality.²⁹ The medical field uses structured clinical surveys, together with EHR data, to identify maternal demographic information, behavioural patterns, and environmental risk factors, which serve as the basis for ML model development. Digital stethoscopes equipped with ML algorithms analyse phonocardiogram (PCG) signals to detect murmurs, achieving a pooled sensitivity of 90.9% in meta-analyses analyses.^{30,31} The use of CT imaging for CHD assessment provides complete 3D anatomical information, but it entails both financial costs and radiation exposure.³² Chest radiography provides essential cardiac information due to its widespread availability, despite its lower imaging accuracy. The development of magnetocardiography technology enables fetal cardiac magnetic field mapping, yet most LMICs cannot use it because it requires specialised magnetically protected environments. Genetic testing now uses whole-genome and whole-exome sequencing to achieve accurate diagnosis, and has become the primary method for testing these conditions according to a study.³³ Meanwhile, non-invasive prenatal screening through cell-free DNA analysis of maternal blood achieves high detection accuracy, which is analysed using artificial intelligence, with an area under the curve score of 0.97 according to studies.^{34,35}

Although clinical diagnostics have improved, CHD detection remains limited by the strengths and weaknesses of each method. Most computational tools focus on a single type of data, such as predicting risk from structured EHR data, detecting abnormalities in echocardiographic images, or identifying genetic risks from sequencing data. CHD is a complex condition that is caused by genetic and environmental factors, including maternal risks and structural heart issues, that can appear anytime during heart development. The lack of systems that integrate these disparate data sources is a major gap in current research. Additionally, the CHD detection process suffers from another limitation that occurs from the fragmented nature of clinical workflows and data modalities. The prenatal screening process evaluates risk levels based on the EHR information, while to examine structural characteristics, imaging modalities are used. The two stages operate as independent systems because they lack computational connections, which leads to separate predictive models that do not track disease progression. The existing system for early-stage risk prediction, which operates independently of diagnostic tests, poses a significant obstacle to both healthcare professionals and artificial intelligence research.

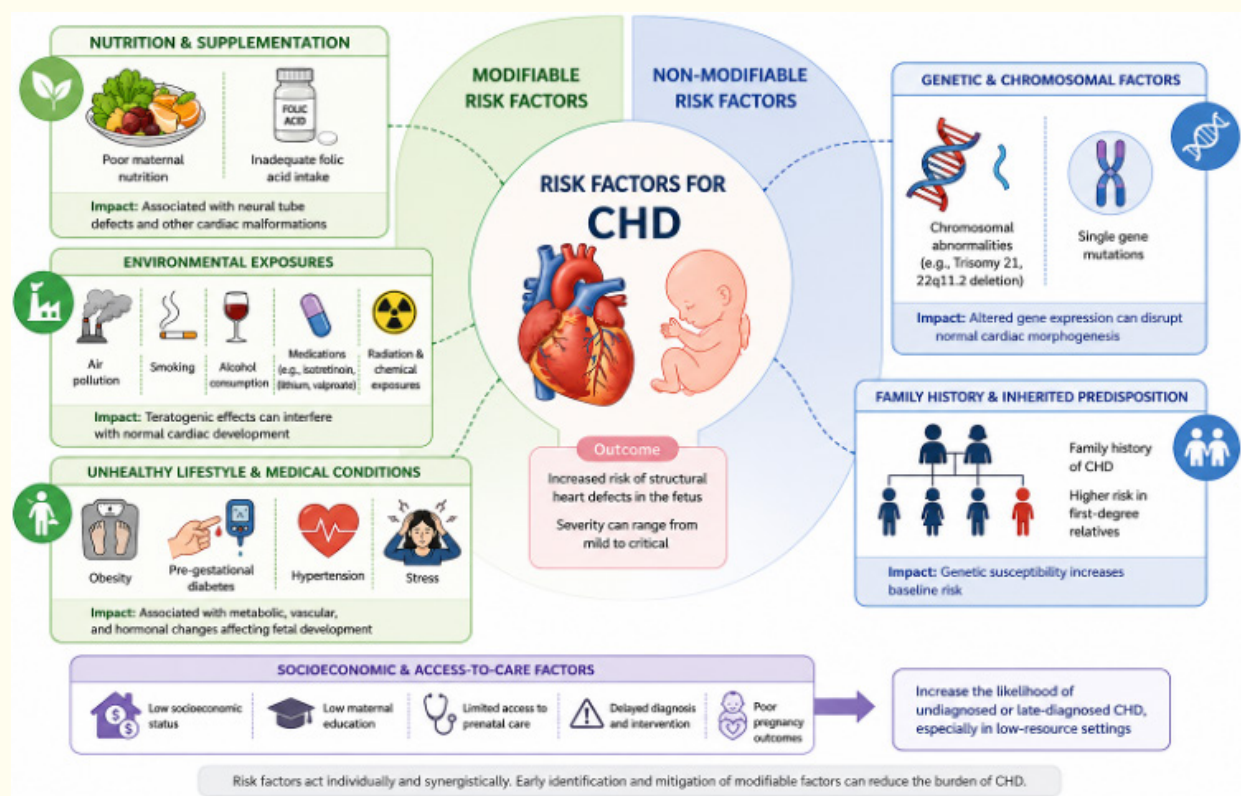
A key observation across these modalities is the trade-off between accessibility and diagnostic precision. While low-cost screening approaches such as pulse oximetry and clinical assessment enable large-scale population testing, advanced techniques such as echocardiography and genomic sequencing provide richer and more precise diagnostic information but remain expensive and less accessible in low- and middle-income countries. The existing trade-off between the two systems necessitates the development of hybrid AI systems that integrate multiple diagnostic methods to achieve better results.

1.3 Risk Factors for Congenital Heart Disease

Around 25% of CHD's are classified as critical lesions that may become clinically apparent before the first scheduled neonatal examination.^{36,37} Its causes are multifactorial, arising from interacting genetic, maternal, environmental, and socioeconomic determinants. Identifying and quantifying these risk factors is important for both designing preventive strategies and building feature sets for ML prediction models. The Risk factors affecting CHD can be grouped into modifiable and non-modifiable categories as shown in Figure 3. Non-genetic modifiable risk factors are attributes that,

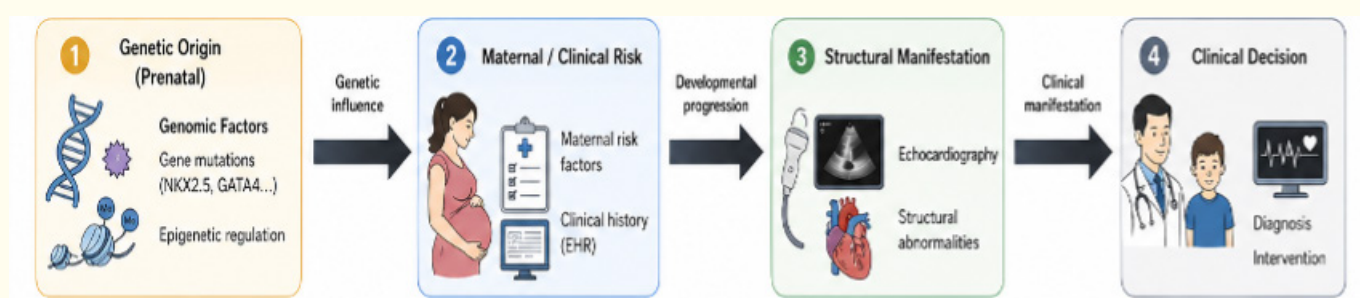
when controlled, can reduce CHD risk and are therefore considered of prime importance. The modifiable risk factors include nutrition and folic acid supplementation, environmental exposures, and an unhealthy lifestyle. The attributes contributing to CHD are called Risk factors, and related risk factors are grouped under an indicator variable. Non-modifiable risk factors are characteristics that cannot be changed or controlled, but they increase the likelihood of CHD. These are mainly genetic and inherent factors, such as family history and genetic composition.

Figure 3. Maternal Risk Factors for CHD



CHD develops through a sequential and interconnected process spanning genetic predisposition, maternal risk exposure, and structural manifestation, as illustrated in the Figure 4. This multiscale progression underscores the limitations of isolated data modalities and indicates that CHD prediction should be viewed as a temporally evolving multimodal learning problem.

Figure 4. CHD Disease Detection pipeline



While diagnostic modalities enable the detection of structural abnormalities, they do not fully capture the upstream determinants of CHD risk. This necessitates a complementary understanding of underlying risk factors.

Family History: A positive family history,³⁸⁻⁴⁰ which includes consanguinity and affected relatives, suggests that genetic factors contribute to the condition. The risk of CHD recurrence among children who have affected parents or parents with past congenital anomalies in their family history shows a significant increase.

Sociodemographic and Maternal Demographic Factors: Low maternal educational attainment has been identified as an independent CHD risk factor.⁴¹ A meta-analysis of 64 observational studies, which included 182290 CHD cases, found no significant association with maternal age.^{38,42} The analysis showed that women who reached advanced maternal age (35 years or older) had a slightly increased risk, which was only detected in the adjusted estimates.

The income level of a family determines their socioeconomic status,⁴³ which subsequently affects their access to proper nutrition and medical services, their exposure to different environmental factors, and their use of prenatal screening services.

Nutrition and Supplementation: Research shows that mothers-to-be who lack essential micronutrients, especially folic acid and iron, have a higher chance of CHD occurrence.^{38,44,45}

Environmental Exposure: The body can lose its ability to process environmental toxins from pollutants, radiation, or contaminated water during the first three months of pregnancy, which disrupts the normal process of organ development.^{38,46}

Unhealthy Lifestyle: Research has categorised alcohol use, tobacco use, areca nut consumption, drug use, and passive smoking as modifiable behaviours that impact fetal oxygen supply and organ.^{38,47-49}

Maternal Medical Conditions: The maternal health conditions present before pregnancy,^{38,50-52} which include hypertension, thyroid disorders, anaemia, tuberculosis, psychiatric illness, cancer, prior miscarriages, and assisted conception, disrupt blood flow, metabolism, and immune function, create potential risks for fetal heart development. The strongest modifiable risk factor for CHD from the literature is pre-gestational diabetes mellitus, resulting in a fourfold risk. Maternal clotting disorders confer approximately ninefold excess CHD risk, with enoxaparin prescription in the first trimester also associated with elevated risk. Maternal obesity with BMI ≥ 30 is associated with a 29% excess CHD risk across 23 pooled studies, mediated by hyperinsulinaemia, hyperglycaemia, reduced folate status, and elevated systemic cytokines.

Medications Used during pregnancy: Fertility drugs, psychoactive medications, anaesthesia exposure, and insulin-dependent diabetes treatment were grouped due to their potential pharmacological and teratogenic effects.³⁸

Complications in Pregnancy: Psychological stress, accidents, and other pregnancy complications were grouped as acute systemic stressors that may indirectly influence fetal development through inflammatory or hemodynamic pathways.

2 Prediction of CHD Using EHR Data

This section presents the studies that applied machine learning to predict CHD using structured clinical tabular data. Various studies have shown that EHR-based machine learning methods can predict CHD, but their accuracy depends on the models used, how they handle data imbalance, and the size of their datasets. The study⁵³ evaluated a three-layer backpropagation neural network (BPNN) on maternal clinical data and found that nonlinear systems outperformed logistic regression by capturing complex interactions among risk factors. The subsequent studies raised awareness of extreme class imbalance, and a study⁵⁴ used cost-sensitive weighted SVM (WSVM) to achieve an AUC of 0.819 by penalising minority-class misclassifications. In the work⁵⁵ the authors developed new cluster-then-classify methods that employed Balanced Random Forest and Easy-ensemble to improve recall by leveraging resampling and ensemble learning techniques. The researchers employed gradient boosting decision trees (GBDT) on Quebec claims and hospitalisation databases to conduct their research at a larger scale,⁵⁶ which enabled tree-based ensembles to use high-dimensional ICD-coded data for automatic CHD detection. Optimisation was incorporated into the study⁵⁷ by combining particle swarm optimisation (PSO) with a Support Vector Machine (SVM) to enhance hyperparameter tuning; however, the limitations were that the data used were from a single centre only. The meta-analysis³⁰ on neural network ensembles showed that these systems deliver excellent performance across studies, yet there is insufficient validation specific to low- and middle-income countries. The clinical scoring system²⁶ uses simple rules to produce results that researchers validated against echocardiography.

From a computational perspective, the risk factors used in the above studies form the foundational feature space for EHR-based predictive models. However, not all risk factors contribute equally to model performance. Strong predictors such as nutrition taken during pregnancy, pre-gestational diabetes, and genetic predisposition demonstrate high discriminative power. The results obtained from these models are difficult to generalise because the datasets contain an extremely low percentage of CHD cases. Risk-factor-based models cannot function as complete diagnostic systems because they only identify probabilistic associations between variables.

The predictive accuracy of machine learning models that use EHR data has high discriminative ability for CHD classification, with AUROC scores ranging between 0.82 and 0.99. EHR-based analyses identify statistical patterns rather than causal relationships. These approaches can support initial risk assessment but cannot directly identify structural heart defects that doctors need for diagnosing CHD. The EHR-based models aid in screening and triage processes, but they do not provide sufficient information for diagnosis.

The literature reviewed suggests the need to combine risk-based features with imaging and genomic data to improve predictive model performance. The next section details studies that used echocardiography modality. The Table I summarises the experimental details of the CHD prediction studies using EHR data.

Table 1. Machine learning models for CHD prediction using structured clinical and EHR data

Study	Data Source	n (CHD: Non-CHD)	Models	Best Algo	Metrics	Validation	Main Finding
Luo (2017) ⁵⁴	Shanxi survey, China	78:33,753	WSVM, WRF, LR	WSVM	AUC 0.819; TPR 0.692	1000× resampling	Cost-weighted SVM handles extreme class imbalance
Salehi (2024) ⁵⁵	Shanxi dataset, China	78:33,753	Bal. RF, EasyEns., RUSBoost	Balanced RF	Recall 0.886; Acc 0.830	Internal CV	Cluster-then-classify enables personalised risk scoring
Li (2017) ⁵³	Hunan hospitals, China	119:239	BPNN, LR, Risk score	BPNN	Acc 0.86; AUC 0.87	Train/test split	NN outperforms regression for maternal risk prediction
Marelli (2024) ⁵⁶	Quebec claims	3,784:15,403	GBDT, SVM, DT, LASSO	GBDT	AUPRC 0.993; Spec 0.997	External (68k)	Automated CHD identification using ICD-coded data
Dehghan (2023) ⁵⁷	Isfahan CV Centre	1,389 total	PSO-SVM, SVM, RF	PSO-SVM	Acc 81.57%	Internal	PSO improves SVM hyperparameter tuning

3 Prediction of CHD Using Echocardiographic Data

Echocardiography has emerged as one of the most widely adopted modalities for CHD diagnosis, owing to its real-time imaging capability and high diagnostic value in identifying structural cardiac abnormalities.

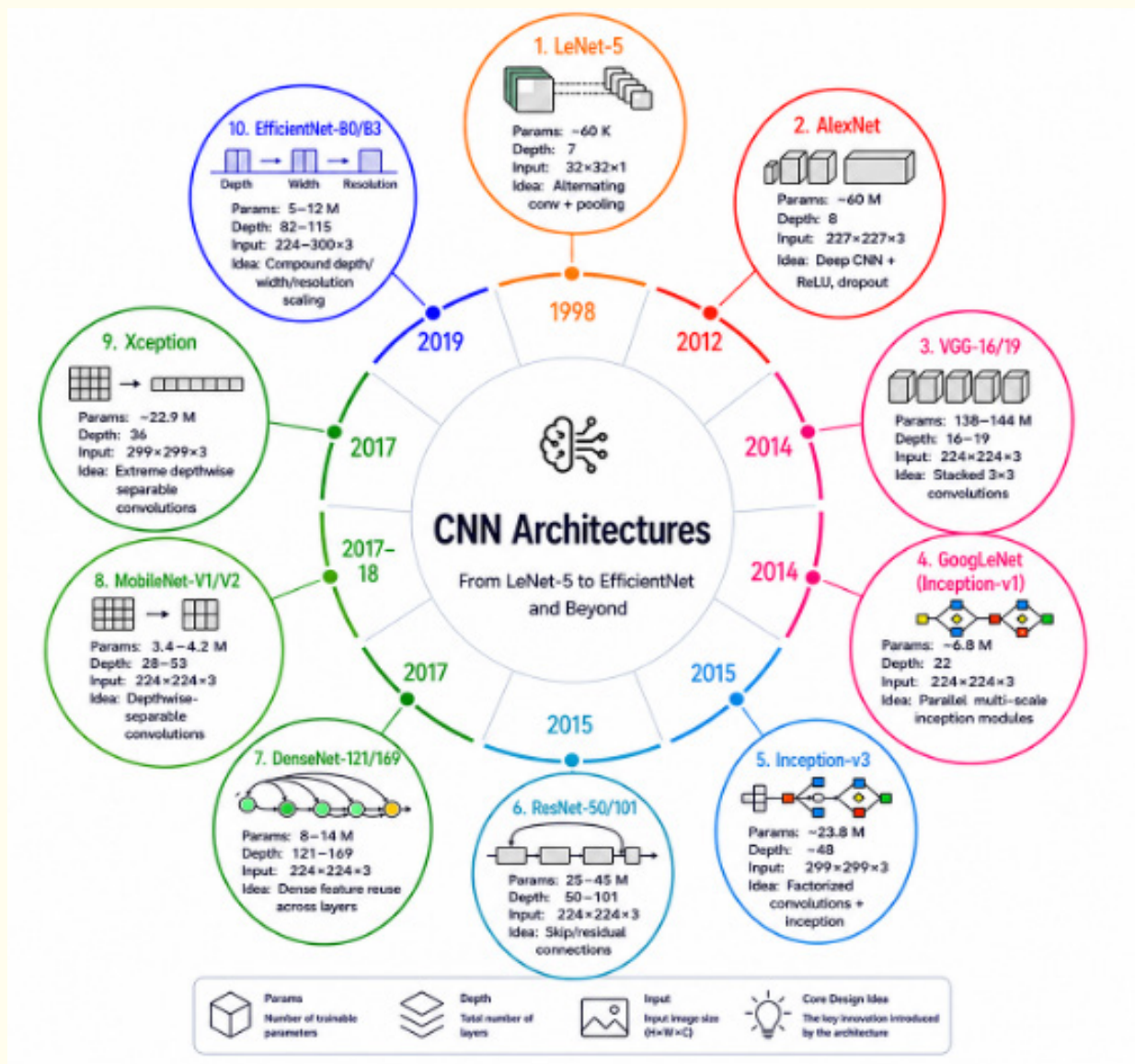
3.1 Classic Machine Learning Approaches

Early automated approaches to CHD detection using echocardiography data relied on conventional machine learning with handcrafted features. The study⁵⁸ applied a Random Forest (RF) classifier to 3,910 patients from a tertiary unit in Vietnam, one of the very few prenatal CHD AI studies conducted in a low-to-middle-income country setting, performing binary classification of fetal hearts using manually extracted cardiac biometric parameters. Similarly, SVM was used to extract textural features from 2D-echo videos to classify mitral regurgitation severity as normal, mild, moderate, or severe.⁵⁹ These methods rely on manual feature engineering, which limits their ability to identify fine anatomical structures and subtle morphological differences in ultrasound images, particularly when the images are unclear. Because of these problems, researchers started using Deep Learning (DL) systems that can automatically find important features during the process.

3.2 Convolutional Neural Network (CNN)-Based Feature Extraction and Transfer Learning

Transfer learning (TL) has been used to apply deep CNNs pretrained on extensive natural image datasets to cardiac imaging tasks. It has become a leading method in echocardiographic analysis, using pretrained CNNs⁶⁰ to capture overall visual features from ultrasound images. Figure 5 shows the comparison between essential CNN models that researchers employ in echocardiographic AI, showing their respective parameter counts and system depths and their ability to process ultrasound data. Recent studies indicate a shift from traditional transfer-learning approaches toward methods that support domain-specific representation learning.

Figure 5. CNN-Architectures studied in the past literature



TL models are used for view classification,⁶¹ and the EchoNet-Dynamic system⁶² show that pretrained models can reach high diagnostic accuracy, with AUC scores between about 0.90 and 0.97. These methods save training time and work better, especially when there is limited labelled medical data.

CNNs have made echocardiographic analysis more effective by learning spatial patterns from raw data. Transfer learning, which leverages CNN weights trained on large datasets such as ImageNet, has been widely adopted in medical imaging because labelled echocardiographic datasets are often limited.^{63,64} AIEchoDx⁶⁵ framework predicts heart disease subtypes from apical 4-chamber videos. The study⁶⁶ used a multi-view CNN model on 1,308 patients to automatically diagnose ventricular septal defect (VSD) and atrial septal defect (ASD), reaching an accuracy of 93.9% by applying TL. A multi-view DL model trained on 1,128 case data and tested on 141, achieved 91% accuracy and an AUC of 0.92 for VSD and ASD diagnosis, also used TL.⁶⁷ A multi-view multi-modal fusion framework⁶⁸ was validated for 1,932 children, training 10 sub-models across five standard transthoracic echocardiography views and two imaging modalities, achieving a cross-centre AUC of 0.990 and the accuracy of clinicians with under three years' experience improved from 0.707 to 0.953 with AI assistance. CHDNet,⁶⁹ a Bayesian echo video classifier demonstrated promising predictive probability distributions.

In a different heart problem,⁷⁰ applied a deep learning model to ultrasound data from 473 training and 277 test cases to detect coarctation of the aorta (CoA) in newborns, achieving a CoA error rate of 7.7% across 840 patients. In a study⁷¹ authors made use of CNN for identifying patent ductus arteriosus (80% accuracy) and in the study⁷² CNN was used for detecting ASD using colour doppler (AUC 0.92) and in⁷³ CNN was used for 3D ultrasound segmentation in hypoplastic left heart syndrome (HLHS).

Some of the studies below used self-supervised learning harnessing CNNs. In the research,⁷⁴ a self-supervised segmentation pipeline was developed that used watershed segmentation, Hough circle detection, and clinical shape priors to create weak labels, which were then improved through U-Net training on more than 18000 echocardiograms. The label-free pipeline achieved LV (Left Ventricle) Dice of 0.89 and r2 of 0.55–0.84 for chamber parameter estimation, with correlations with cardiac MRI comparable to those of supervised clinical echocardiography. The study by^{75,76} used an ensemble model modified U-Net to segment thoracic and cardiac structures from A4C images, while an ensemble classifier computed cardiothoracic ratio, cardiac axis, and fractional area change as transparent medical diagnostic intermediates. The first segmentation and EF estimation model specifically designed for pediatric use, EchoNet-Peds⁷⁷, achieved an MAE of 3.66% and an AUROC of 0.954 across the age range of 0 to 18 years, which surpassed the performance of the adult-trained EchoNet-Dynamic model on pediatric data ($p < 10^{-100}$), thereby demonstrating that age-specific training data needs to be used for effective performance.

Direct classification methods provide quick results while needing fewer labels, but lack an understanding of anatomical structure. The supervised segmentation approach requires extensive annotations because it yields precise anatomical information across all body parts. SKGC (Semantic-Level Knowledge Guided Classification)⁷⁶ framework was developed to address the limited availability of annotations using a two-stage framework that requires only a small number of segmentation masks.

Most existing DL methods for echocardiography focus on classifying individual frames,⁵⁹ but this does not align with how doctors make diagnoses. In practice, diagnosis is made at the patient-level by looking at information from the whole video sequence. Therefore, there is a clear need for advanced temporal modelling techniques that can capture long-range dependencies and contextual relationships across echocardiographic sequences to better align with real-world clinical diagnosis.

3.3 Transformer-Based Modelling in Medical Imaging

Temporal modelling is important in echocardiography because heart function changes over time. AIEchoDx⁶⁵ uses a CNN to combine information over time; CHDNet⁶⁹ uses Bayesian methods to estimate uncertainty; EchoCLR⁷⁸ applies contrastive learning to keep spatial and temporal information consistent. However, all these methods focus on short or limited time periods. Sequential data are handled by Recurrent Neural Networks (RNNs), which may also fail to capture complex long-term dynamics due to vanishing gradients and limited context retention.

Transformer architectures can mitigate these limitations by enabling global temporal attention across entire sequences, making them well-suited for modelling the full cardiac cycle, including correlations between spatially and temporally distant systolic and diastolic events. The self-attention mechanism used by the transformer enables a model to determine the importance of different elements in a sequence by dynamically assigning attention weights based on their contextual relevance.

Vaswani et al. presented architecture of transformers,⁷⁹ which works by enabling full-sequence global attention to overcome the limitations of RNNs and is increasingly recognised as the preferred architecture for long-range temporal modelling in biomedical sequences, motivating their application to the full-sequence temporal aggregation task in the proposed study. Self-attention allows transformer models to overcome the constraints that restrict CNN performance. This method enables a sequence element to access all other elements simultaneously, which results in complete contextual understanding without losing distant information.

Recent hybrid CNN-Transformer frameworks, including CTransCNN,⁸⁰ demonstrate the potential to combine local feature extraction with global temporal modelling by using the chest X-ray dataset.

The EchoCLR⁷⁸ research study introduced the first self-supervised learning framework designed to capture both spatial and temporal information from echocardiography videos using SimCLR-based contrastive learning for the classification of CHD, such as ASD and AS. Using different videos from the same datapoint, by rearranging video frames, even with a small dataset. The system reached an AUROC of 0.818 for identifying severe aortic stenosis after training on only 1% of labelled data, much better than the 0.612 AUROC from usual transfer learning.

The recently proposed EchoFocus-CHD81, extends the PanEcho architecture⁸² by incorporating a study-level transformer encoder to aggregate temporal and cross-view information, enabling prediction of 12 critical and 8 non-critical CHD lesions. PanEcho is a multi-view echocardiography framework designed to integrate information from multiple cardiac ultrasound views for CHD analysis. The training data consisted of 3.6 million videos from 58000 echocardiograms collected from various testing sites around the world. The system recorded an AUC score of 94%, but it struggled with external referral groups, achieving an AUC score of 77%. However, the observed performance degradation across external cohorts highlights the limitations of current multi-task architectures in handling domain variability and temporal inconsistency in echocardiographic data. Addressing these challenges requires more robust temporal representation learning and domain-invariant feature extraction, which motivates the approach proposed in this study. Other types of transformers proposed in the literature are vision transformers⁸³ and Swin transformer.⁸⁴ Table 2 provides a summary of experimental details of echocardiographic AI studies reviewed.

Table 2. Comprehensive Summary of Echo-Based Deep Learning Studies for CHD. EF: Ejection Fraction; LV: Left Ventricle; ASD: Atrial Septal Defect; VSD: Ventricular Septal Defect; HLHS: Hypoplastic Left Heart Syndrome; SSL: Self-Supervised Learning; A4C: Apical four-chamber; MAE: Mean Absolute Error; AUC: Area Under ROC curve; Acc: Accuracy

Study	Focus	Country	n	Architecture	Performance	Limitation
Ouyang (2019) ⁶²	EchoNet-Dynamic (EF)	USA	10,036	R2+1D CNN (A4C)	MAE 4.1%, AUC 0.97	Adult-only cohort
Reddy (2023) ⁷⁷	EchoNet-Peds	USA	4,467	Video DL (seg + EF)	MAE 3.66%, AUROC 0.954	Limited views
Tan (2023) ⁶⁹	Bayesian CHDNet	China	5,880	Bayesian MC-dropout	Robust to noise	External shift issue
Liu (2023) ⁶⁵	AIEchoDx	China	1,807	Inception-V3 + 1D CNN	AUC 98.5–99.6%	Single-centre
Cheng (2024) ⁶⁸	Multi-view CHD	China	1,932	Multi-view multimodal	AUC 0.990	Limited subtypes
Holste (2024) ⁷⁸	EchoCLR SSL	USA	23,448	Contrastive SSL	AUROC 0.818 (1%)	Adult disease only
Truong (2022) ⁵⁸	RF fetal echo	Vietnam	3,910	Random Forest	Sen 0.85, AUC 0.94	Single-centre
Ferreira (2025) ⁷⁴	LV segmentation SSL	Europe	18,000+	Unsupervised U-Net	Dice 0.89	No CHD labels
Arnaut (2020) ⁷⁵	Fetal CHD detection	USA	4,108	Ensemble + U-Net	AUC 0.99	Preprint, limited subtypes
Lu (2024) ⁷⁶	SKGC	China	1,575	SKEM + MFM	Acc 99.68%	Needs masks

4 Prediction of CHD Using Genomic Data

Unlike imaging and EHR data, genomic information provides causal insight rather than observable phenotype, positioning it as a complementary modality rather than a standalone predictive tool.

Genetic factors are estimated to explain 34–40% of CHD cases, encompassing chromosomal aneuploidies, copy number variants (CNVs), single-gene Mendelian disorders, and polygenic contributions.⁸⁵⁻⁸⁷ Sequencing technologies are getting widely used for accurate diagnosis for detecting genetic causes of CHD, the emerging role of AI in variant interpretation, non-invasive prenatal screening via cfDNA, and epigenomic methylation as a disease biomarker.

The diagnostic toolkit for genetic CHD spans multiple technologies. Karyotyping and fluorescence in situ hybridisation (FISH) identify chromosomal aneuploidies and major structural rearrangements; chromosomal microarray analysis (CMA) provides genome-wide CNV resolution; whole-exome sequencing (WES) targets protein-coding regions; and whole-genome sequencing (WGS) covers non-coding regulatory variants in addition to coding sequences.^{85,88}

Chromosomal aneuploidies principally trisomies 21 and 18 and monosomy X account for 8-10% of CHD cases; CNVs contribute a further 3-15%; and de novo variants (DNVs) identified from trio WES/WGS account for up to 20% of CHD cases associated with neurodevelopmental disorders.^{86,89} Approximately 400 genes have been linked to CHD, with cardiac transcription factors NKX2.5, GATA4, TBX1, and TBX5 occupying central positions in cardiogenic regulatory.^{86,90,91} iPSC-based patient-specific modelling combined with NGS, CRISPR editing, and ML offers a pathway to elucidating these race-related genetic contributors.^{92,93} Fotiou et al.⁹⁴ demonstrated through meta-analysis of 4,634 nonsyndromic CHD cases 27,000+ controls that genes retained from ancestral whole-genome duplications known as *ohnologs*, are disproportionately represented among CHD candidate loci.

The process of cardiac embryogenesis (heart development in the fetus) depends on DNA methylation, which functions as a vital epigenetic control mechanism for gene expression. Disruption of methylation leads to the development of abnormal cardiac structures.^{95,96}

Zhou et al. assembled CHDbase,⁹⁷ a curated knowledge base integrating 1,114 publications and linking 1,124 CHD-associated genes and 3,591 variants to over 300 CHD subtypes. Gene network analysis identified a core subnetwork of 163 highly connected genes, with GATA4, NKX2-5, and TBX5 having the highest centrality scores.

AI is reshaping genomic data interpretation. Deep learning models particularly CNNs and RNNs have demonstrated utility in variant calling, non-coding variant annotation, and phenotype-to-genotype mapping.^{98,99} CNN frameworks, such as DeepVariant, are used to detect SNVs and indels in sequencing reads, whereas SpliceAI identifies cryptic splice-site variants that account for at least 10% of rare pathogenic variation and are disproportionately relevant to CHD cases with unexplained aetiology.^{99,100} Phenotype-to-genotype mapping tools that integrate facial image analysis, NLP of clinical records, and deep-learning variant prioritization, exemplified by the PEDIA system, have been used to support automated diagnosis across hundreds of monogenic disorders simultaneously.^{99,101}

Circulating cfDNA in maternal blood, derived largely from the placenta, enables non-invasive access to fetal chromosomal and epigenomic information from early gestation. The study³⁴ combined genome-wide epigenomic cfDNA analysis with a support vector machine (SVM) classifier for non-invasive fetal congenital heart disease (CHD) detection. The model achieved an AUC of 0.97, sensitivity of 98%, and specificity of 94%. The research³⁴ also indicate that AI-powered cfDNA epigenomics as an innovative prenatal screening method that enables accurate assessment of CHD risk in the first trimester. Table 3 summarises the described genomic studies.

Table 3: Summary of genomic, epigenetic, and artificial intelligence-based approaches for CHD detection. NGS: next-generation sequencing; WES: whole-exome sequencing; WGS: whole-genome sequencing; CMA: chromosomal microarray analysis; cfDNA: cell-free DNA; CNV: copy number variant; SVM: support vector machine; DL: deep learning; iPSC: induced pluripotent stem cell.

Study	Focus	n	Methods	Key Findings	AI Used
Rachamadugu (2022) ⁸⁵	Genetic CHD detection (review)	Review	Karyotyping, FISH, CMA, WES, WGS, cfDNA	NGS improves diagnostic yield; cfDNA enables early non-invasive screening	No
Yue & Wang (2018) ⁹⁸	Deep learning in genomics (overview)	Review	CNN, RNN, autoencoders	DL extracts high-dimensional genomic features	Yes (theory)
Fotiou (2019) ⁹⁴	Novel CHD loci discovery	4,634 + 27k ctrl	CNV meta-analysis + WES	54 new CHD genes; SLIT2/SLIT3 implicated	Partial
Dias & Torkamani (2019) ⁹⁹	AI in genomic diagnostics	Review	ML/DL for variant analysis	DeepVariant, SpliceAI outperform traditional methods	Yes
Chhatwal (2023) ⁸⁶	Genetic basis of CHD	Review	Monogenic + CNV + WES/WGS	~34% CHD genetically explained; personalised genomics emerging	Partial
Zhou (2023) ⁹⁷	CHDbase knowledgebase	1,114 studies	Manual curation + network analysis	163 core genes; GATA4, NKX2-5, TBX5 central	Partial
Joshi (2022) ⁹⁵	DNA methylation in CHD	48 + 47 ctrl	Expression analysis (DNMT3A/3B/MBD2)	DNMT3B downregulated in cyanotic CHD	No
Mullen (2021) ⁹²	Genetics, race, iPSC	Review	iPSC + omics + ML	Higher CHD incidence in Black infants; ML maps gene–environment links	Yes
Bahado-Singh (2022) ³⁴	cfDNA + AI prenatal CHD	Clinical cohort	cfDNA sequencing + SVM	AUC 0.97; high sensitivity and specificity; epigenetics outperform clinical predictors	Yes (SVM)

5 Multimodal Integration

Multimodal data refers to the integration of information from multiple data sources or modalities, such as clinical records, medical imaging, genomic data, and physiological signals, to provide a more comprehensive understanding of disease. The absence of CHD-specific multimodal fusion studies represents the most significant gap in the field. Just as clinicians combine imaging findings, laboratory results, patient history, and clinical narratives to reach a diagnostic decision, computational models integrating complementary data sources may improve the robustness and generalisability of model predictions than their unimodal counterparts.^{102,103}

5.1 Fusion Strategies and Evidence

In a systematic review of 17 studies (2012–2020),¹⁰² a taxonomy of three multimodal fusion approaches was formalised. Early fusion (feature-level) concatenates extracted features from all modalities prior to model training, simple to implement but prone to dimensionality-related overfitting when high-dimensional imaging features are combined with sparse clinical data.¹⁰⁴ Joint fusion (intermediate) trains modality-specific encoders simultaneously, which can promote complementary representation learning, at the cost of greater architectural complexity. Late fusion (decision-level) trains separate models per modality and aggregates their outputs, offering flexibility and robustness to missing data. Across all reviewed studies, multimodal models consistently outperformed unimodal baselines in accuracy by 1.2–27.7% and in AUROC by 0.02–0.16, with no single fusion strategy universally dominant.^{106,109}

The study¹⁰⁶ operationalised multimodal fusion on the MIMIC-III critical care database using two architectures, Fusion-CNN and Fusion-LSTM, that combined static demographic variables, temporal vital signs and laboratory results. Similarly, the study¹⁰⁷ added unstructured clinical notes that improved AUROC by 0.043 for Fusion-CNN and 0.034 for Fusion-LSTM on the in-hospital mortality task, confirming that clinical narratives encode prognostic information not represented in structured features alone.^{106,108}

The research⁶⁶ extended the multimodal fusion to three modalities, including chest X-ray (CXR) images, structured EHR data, and radiology notes, on the MIMIC-IV-MM dataset. SHAP analysis (an explainable AI technique that interprets ML predictions by quantifying the contribution of each feature to the model's output) attributed approximately 40–45% of predictive contribution to structured EHR variables, with CXR contributing least for readmission prediction (where longitudinal clinical context dominates) and radiology notes providing intermediate value. Susetzky et al. introduced TAMME (Time-Aware MultiModal Transformer Encoder).¹⁰⁹ Liang et al. introduced a unified architecture that treats the complete longitudinal EHR, including numerical, categorical, textual, and image data, as a single temporally ordered token sequence processed by a standard transformer encoder.¹¹⁰ BioLORD-2023¹¹¹ integrated semantic text representation with a knowledge graph. Table 4 summarises the experimental details of reviewed multimodal studies.

Table 4: Overview of multimodal artificial intelligence studies combining imaging, electronic health records, and clinical text for healthcare prediction tasks. Although none of the studies were conducted specifically for congenital heart disease (CHD), they demonstrate the potential of multimodal fusion strategies for improving predictive performance and provide a foundation for future CHD-specific multimodal diagnostic frameworks. EHR: electronic health record; CXR: chest X-ray; AUROC: area under the receiver operating characteristic curve; AUPRC: area under the precision-recall curve; LOS: length of stay.

Study	Dataset	Fusion	Modalities	Task	Gain	Limitation	CHD Relevance
Huang (2020) ¹⁰²	17 studies (2012–2020)	Early / Joint / Late	Imaging + EHR	Multiple	+0.02–0.16	Heterogeneous reporting; no genomics	Facilitate fusion taxonomy
Zhang (2020) ¹⁰⁶	MIMIC-III (39k admissions)	Early	Clinical notes + EHR	Mortality, LOS, readmission	+0.034–0.043	24 h window; no imaging/genomics	Text adds independent signal
Wang (2023) ¹¹²	MIMIC-IV-MM	Early / Joint / Late	CXR + EHR + notes	Mortality, LOS, readmission	Late fusion best; EHR 40–45%	No genomics; adult data	Modality contribution quantified
Susetzky (2024) ¹⁰⁹	MIMIC-IV (431k stays)	Joint (temporal transformer)	Imaging + text + structured data	6 tasks	AUROC 0.87–0.95	Adult ICU only; no paediatric genomics	Temporal modelling improves outcomes

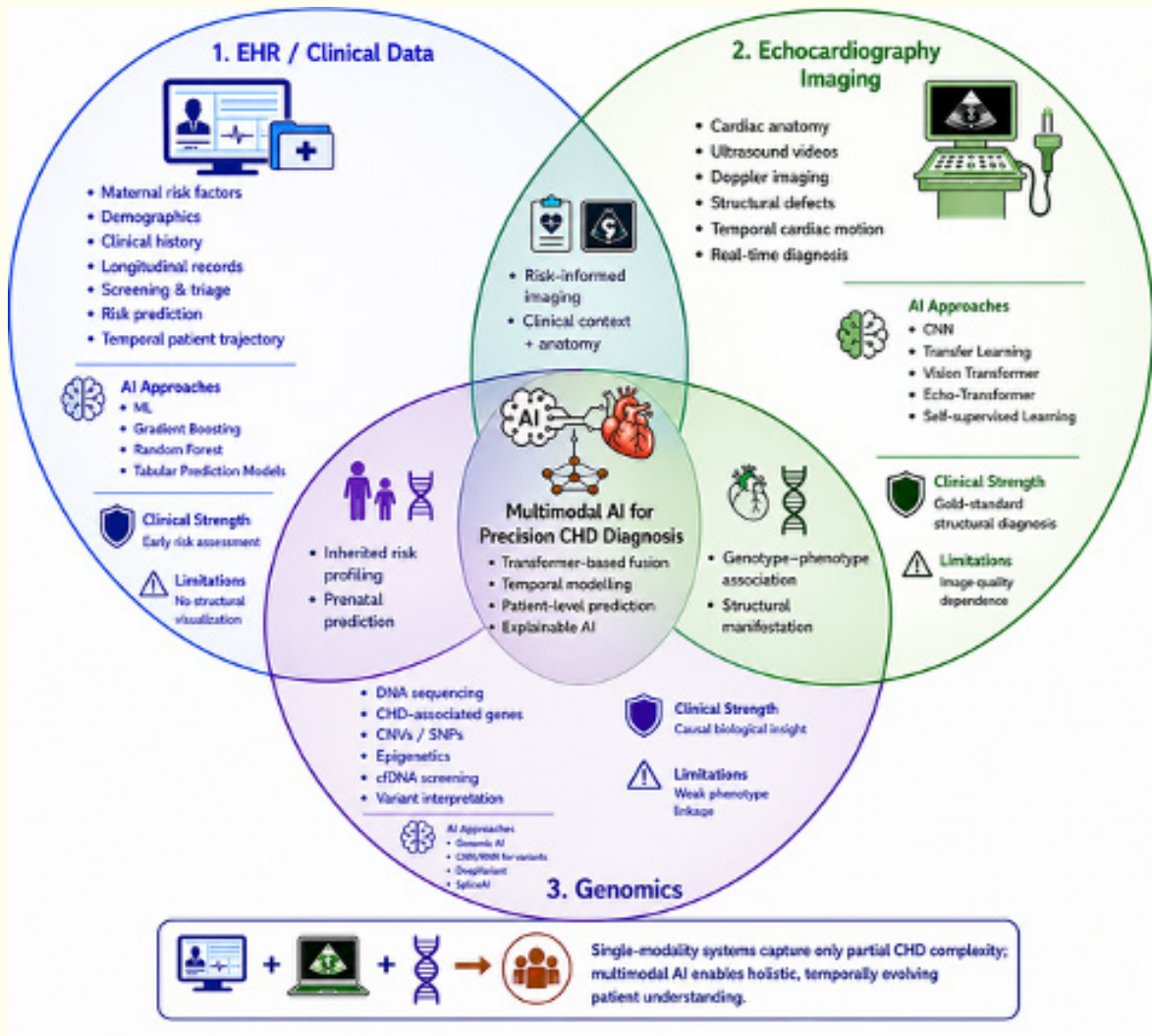
5.2 Relevance to CHD and Research Gaps

Multimodal integration is necessary because individual modalities have distinct limitations when considered in isolation for CHD prediction. The multi-factorial nature of CHD develops in three stages, which begin with genetic factors that impact heart development and continue through maternal and environmental influences on pregnancy risk and the final stage presentation of structural abnormalities through imaging. This complete trajectory is associated with multiple modalities to achieve full understanding. Multimodal approaches attempt to address this limitation by integrating heterogeneous data, enabling users to predict risks early and make precise assessments of structural problems. Many existing fusion methods have limited ability to capture temporal dependencies but it is essential for studying disease progression from prenatal to postnatal development.

Multimodal fusion studies targeted at CHD in paediatric populations are sparse. The current state of research shows that predictive systems based on AI can accurately predict CHD, but still have critical research gaps. Firstly, most studies analyse unimodal data, which limits their ability to understand how multiple factors contribute to coronary heart disease. Secondly, need to develop models that use time-dependent data to track patient progress from the prenatal period through postnatal development. Thirdly, paediatric-specific datasets, particularly from LMICs, are scarce, limiting the ability to apply research findings across diverse populations. Fourthly, there are few validation studies that reveal discrepancies between reported system performance and its actual use in real-world settings. The current state of explainability research limits its use in clinical settings due to its underdevelopment.

Addressing these gaps will likely require integrated multimodal systems that can process heterogeneous data types while still producing explainable and reliable results. CHD prediction inherently requires integrating precisely the modalities these architectures address: maternal demographic and social history (structured EHR), echocardiographic imaging, clinical documentation, and genomic variant data as compiled in the Figure 6.

Figure 6: Multimodal AI integration for CHD diagnosis

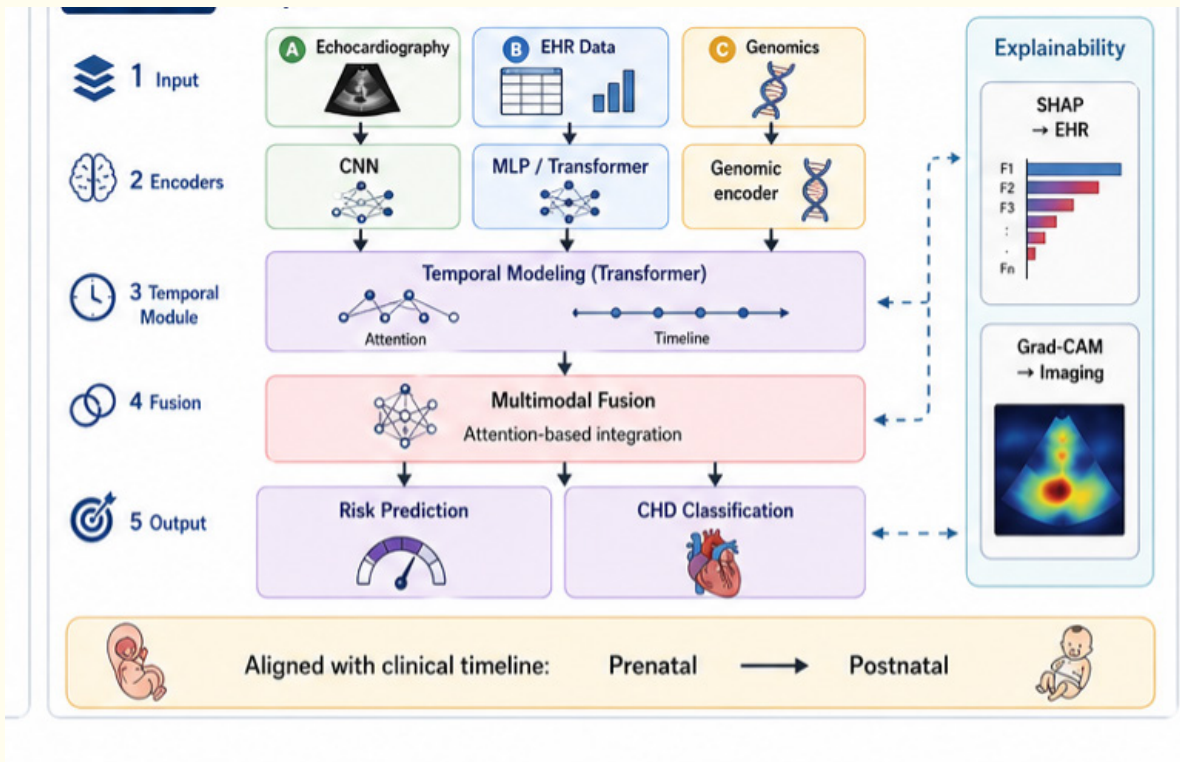


6 Proposed Framework

The gaps analysed lead to an approach to include a hierarchical multimodal framework, as shown in Figure 7, which uses multiple data sources from different time periods to improve CHD prediction accuracy. The model comprises three parts that process different types of data: CNN-based architectures handle echocardiographic imaging, neural networks process structured EHR data, and deep learning models analyse genomic features. The system uses sequence-based architectures, such as recurrent neural networks and transformers, to model temporal dependencies among patient data points. The proposed fusion module would use attention-based mechanisms to merge different representations, potentially allowing greater emphasis on clinically relevant features. The system

combines risk prediction and disease classification in its final output layer, while SHAP and Grad-CAM provide tools for developing understandable explanations. The framework integrates with existing clinical workflows to develop CHD prediction systems that deploy precision-based methods.

Figure 7: Proposed Fusion Model framework



7 Conclusions

The reviewed literature indicates that AI-based approaches have made substantial advances in CHD prediction, but the available methods still exhibit fragmented development and lack clinical effectiveness. EHR-based models detect initial health risks, echocardiographic tools provide precise assessments of structural defects through their diagnostic capabilities, and genomic techniques identify the genetic origins of diseases. However, no single approach captures the intricate tapestry of CHD.

The evidence suggests that predicting CHD is a layered, evolving challenge, with each data type offering unique insights at different moments in a patient's journey. Future systems must go beyond their current technical criteria to incorporate integrated systems that reflect actual medical practice. The transition to multimodal AI is more than a system upgrade because it could facilitate machines to make intelligent decisions and adapt to diverse contexts. The vision requires three essential actions: creating extensive multimodal databases for children, developing methods for ongoing assessment, and conducting thorough clinical testing of new technologies.

Moving from single-focus models to integrated, multimodal systems represent a pivotal step toward addressing the true complexity of CHD. The next wave of research should champion models that are not only explainable and validated in real-world clinical settings but also time-sensitive and

tailored to children and underserved regions. By closing the gap between technical breakthroughs and bedside care, multimodal AI could shift CHD detection from a game of catch-up to one of anticipation and prevention. The future of CHD prediction lies in weaving together diverse data sources into intelligent, time-aware systems that serve clinicians and patients alike.

Supplementary Materials: None.

Author Contributions: Shruthi S: Conceptualisation; Methodology; Investigation; Paper curation; Formal analysis; Writing -- original draft, Visualisation, Validation, Project administration.

D Hanumanth Rao Naidu: Conceptualisation; Supervision; Writing -- review and editing, Visualisation, Validation, Project administration.

Funding: This research received no external funding.

Institutional Review Board Statement: Not Applicable.

Informed Consent Statement: Not Applicable.

Data Availability Statement: Not Applicable.

Acknowledgements: Our heartfelt gratitude to Sadguru Sri Madhusudan Sai for this invaluable opportunity to contribute to this healthcare initiative, and to Sri Sathya Sai University for Human Excellence, Muddenahalli, Karnataka, for providing all essential resources required to conduct this research.

Conflicts of Interest: The author declares no conflicts of interest to report regarding the present study.

Declaration of Generative AI use: During the preparation of this work, the authors used ChatGPT (OpenAI, San Francisco, CA, USA) to assist in the preparation of the graphical abstract, figure layout design, and LaTeX table code generation. All AI-generated outputs were carefully reviewed, verified, edited, and validated by the authors to ensure scientific accuracy, completeness, and consistency with the study findings. The authors take full responsibility for the content of the published article.

Abbreviations

Abbreviation	Full Form
ANN	Artificial Neural Network
AUC	Area Under the Receiver Operating Characteristic Curve
AUROC	Area Under the Receiver Operating Characteristic Curve
AUPRC	Area Under the Precision–Recall Curve
BPNN	Back-Propagation Neural Network
CHD	Congenital Heart Disease
CNN	Convolutional Neural Network
CMA	Chromosomal Microarray Analysis
CNV	Copy Number Variant
CXR	Chest X-ray
DL	Deep Learning
DT	Decision Tree
EF	Ejection Fraction
EHR	Electronic Health Record
FISH	Fluorescence In Situ Hybridisation
GBDT	Gradient Boosting Decision Tree
HLHS	Hypoplastic Left Heart Syndrome
ICU	Intensive Care Unit
LASSO	Least Absolute Shrinkage and Selection Operator
LR	Logistic Regression
MAE	Mean Absolute Error
ML	Machine Learning
PCG	Phonocardiogram
PDA	Patent Ductus Arteriosus
PSO	Particle Swarm Optimisation
RF	Random Forest
SHAP	SHapley Additive exPlanations
SNP	Single Nucleotide Polymorphism
SVM	Support Vector Machine
TPR	True Positive Rate (Sensitivity/Recall)
VSD	Ventricular Septal Defect
WES	Whole-Exome Sequencing
WGS	Whole-Genome Sequencing
WRF	Weighted Random Forest
WSVM	Weighted Support Vector Machine
XGBoost	Extreme Gradient Boosting

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Article

Sustainable Dietary Strategies to Improve Iron Bioavailability in Adolescent Health

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Abstract:

Background: Anaemia remains a major prevalent public health concern among adolescent girls globally, driven by increased physiological needs during growth and menstruation, inadequate intake of iron, folate, and vitamin B12, and socio-economic constraints. These micronutrients are key components in oxygen transport, immune regulation, and cell proliferation and their deficiency during adolescence can compromise immune function, impair growth, and increase long-term reproductive risks. Addressing adolescent micronutrient deficits ensures long-term health. This narrative review synthesises current evidence on sustainable, locally sourced dietary approaches to enhance the iron status in adolescents, with a specific focus on enhancing the bioavailability of non-haem iron from plant-based foods.

Methods: We searched PubMed, Scopus, Web of Science, and Google Scholar for peer-reviewed literature (January 2000 – December 2025) regarding adolescent iron deficiency, non-haem bioavailability, and food system nutrition interventions.

Results: Vitamin C and carotenoids are potent enhancers of non-haem iron absorption. To optimise a plant-based diet, consuming three to four iron-rich meals or snacks daily alongside concurrent vitamin C enhancers is recommended. Sustaining this dietary pattern for three to six months is typically required to observe measurable increases in haemoglobin and iron stores. Given the global rise of plant-based diets and the prevalence of lacto-vegetarianism in India, vitamin B12 deficiency is highlighted as a frequently underdiagnosed contributor to anaemia, with dairy foods and fortified products recommended as accessible dietary sources.

Conclusions: Overall, locally grounded, sustainable, bioavailability-focused dietary interventions represent a practical and environmentally responsible strategy to enhance adolescent health and reduce the burden of anaemia.

Keywords: adolescent health; iron-deficiency anaemia; dietary intervention; food-based approaches; iron bioavailability; micronutrient deficiency.

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Citation: Wathsala S. K., Rajeshwari U; *Awareness*, 3 (2): 63-77



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Main Message

Preventing adolescent anaemia requires more than increasing iron intake. Sustainable dietary practices that enhance iron bioavailability through locally available foods, appropriate meal combinations, and traditional food preparation methods provide a realistic, long-term solution that complements supplementation while supporting both human and environmental health.

Introduction

Anaemia remains a major global public health challenge despite decades of intervention efforts demonstrating positive outcomes in controlled settings, particularly through iron supplementation, food fortification and nutrition education.¹ However, population-level success has been limited by barriers such as poor adherence, gastrointestinal side effects, resource constraints, economic disparities and inequities in access. As a result, anaemia prevalence continues to rise alongside population growth, contributing to increased morbidity and mortality in women and children, reduced productivity in adults, and impaired cognitive and behavioural development in young children.² Adolescent girls are especially vulnerable due to rapid growth, menstrual onset and common dietary inadequacies, placing them at heightened risk of iron-deficiency anaemia, which affects cognitive function, work capacity, immunity and future pregnancy outcomes. Thus, the growing burden of anaemia, particularly amongst reproductive-aged women (15 to 49 years), has underscored the necessity to develop complementary and sustainable solutions that can be easily incorporated into everyday food habits over a long duration (Figure 1).^{1,3}

Figure 1. Sustainable nutrition cycle for adolescent well-being¹



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These persistent challenges in conventional strategies have led to a growing interest in long-term, food-based solutions. Sustainable dietary approaches prioritise nutritional adequacy, affordability, cultural relevance and environmental responsibility, aiming to improve individual health while supporting ecosystem integrity. Within this context, plant-based foods represent a promising source of dietary iron, particularly when aligned with local food systems that enhance micronutrient intake and build food system resilience. However, the bioavailability of non-haem iron from plant sources is often low due to dietary inhibitors, reinforcing the need for strategies to enhance iron absorption, such as including vitamin C-rich foods, carotenoids, traditional food preparation methods, and appropriate meal combinations.

This narrative review explores sustainable dietary patterns as a complementary approach to reducing anaemia, with a focus on enhancing non-haem iron bioavailability in adolescents. The review examines evidence on local, plant-based foods, traditional food processing and dietary diversification, considering their potential to improve iron status, support long-term health outcomes, and contribute to sustainable nutrition frameworks.

Materials and Methods

This narrative review was based on a thorough literature search for relevant studies published between January 2000 and December 2025. Computerized searches of primary electronic databases (PubMed, Scopus, Web of Science and Google Scholar) were performed for peer reviewed literature on adolescent anaemia, iron deficiency, iron bioavailability, sustainable diets and local food system-based nutrition strategies. The search strategy used various keyword combinations and Boolean operators, including “adolescent anaemia,” “iron deficiency,” “iron bioavailability,” “non-haem iron,” “plant-based diets,” “sustainable nutrition,” “local food systems,” “dietary diversification,” and “nutrition education.”

Database filters were used to limit results by publication type, language, and relevance to human nutrition and public health. Eligible studies included original research articles, systematic reviews, meta-analyses, and authoritative reports from international health agencies on dietary approaches, food-based interventions, traditional food processing strategies, or sustainability-oriented practices focused on improving iron status among adolescents. Emphasis was given to evidence on factors affecting non-haem iron absorption, dietary enhancers and inhibitors, nutritionally favourable traditional eating patterns and environmentally sustainable models of nutrition.

Exclusion criteria were conference abstracts, case reports, opinion papers, non-peer-reviewed articles and articles published in a language other than English. Studies in animals and research not directly pertinent to adolescent nutrition or iron were also excluded. Reference lists of included articles were manually searched to identify potential additional studies. The included literature was qualitatively synthesised to generate a holistic understanding of sustainable, locally produced dietary strategies that can be utilised to increase the bioavailability of dietary iron among adolescents. This systematic methodological approach adds to the rigour and credibility of the review by reducing selection bias and provides a sound basis for assessing sustainable diets with respect to adolescent health and anaemia prevention.

Anaemia

One-quarter of the global population is affected by anaemia.³ Anaemia is a serious global public health ailment affecting both developed and developing countries, with young children (0-5 years), women of childbearing age and pregnant women a greater risk.⁴ In 2021, anaemia affected over 1.9 billion people worldwide, an increase of 420 million cases over the past three decades.³ The Global Burden of Diseases, Injuries and Risk Factors Study (GBD) estimated that anaemia accounts for 52 million years lived with disability in 2021.³

Despite multiple global health efforts, little progress has been observed in some population groups. For example, anaemia prevalence among women of reproductive age remains high at 30%, with rates showing minimal changes over the last two decades.⁵ Consequently, the WHO has extended its target to reduce the prevalence of anaemia by half in women of reproductive age by 2030.⁵

Iron deficiency anaemia (IDA) is the most common form of anaemia, accounting for approximately half of all anaemia cases globally,⁴ and it is the leading cause of morbidity in women.⁶ In adults, IDA can lead to adverse outcomes such as reduced physical capacity, impaired thermoregulation, immune dysfunction, gastrointestinal disturbances and cognitive impairment.⁷ The second most common cause of anaemia is anaemia of chronic diseases associated with conditions such as cancer, chronic kidney disease, congestive heart failure, human immunodeficiency virus and rheumatoid arthritis, leading to diminished quality of life and increased mortality.⁸

In pregnancy, anaemia is associated with serious maternal and foetal complications, including preterm labour, intrauterine growth restriction, stillbirth, infections, and maternal and neonatal mortality.^{3,9} Nutritional deficiencies of folate and vitamins B12 also contribute to anaemia, most commonly due to inadequate dietary intake. Less frequently, deficiencies in vitamins A and E, thiamine, pyridoxine, and copper have also been identified as causes of anaemia.¹⁰

Anaemia in Adolescence

Anaemia can significantly affect adolescents' growth and development. It is associated with developmental delay, learning difficulties, reduced concentration, diminished physical fitness and decreased productivity¹¹ (Figure 2). Causes of anaemia in adolescence include poor diet, poverty, increased iron requirements due to physiological changes of rapid growth, intestinal worm infection, blood loss (particularly from heavy menstrual bleeding) and early conception.¹²

Adolescent females are particularly vulnerable due to increased physiological demands and the onset of menstruation.¹³ Other contributing factors include rural residence, low socioeconomic status, underweight status, and early menarche.¹⁴ Social influences (such as marketing, sponsorship, advertising and peer-pressure) also shape dietary behaviours, often promoting higher intake of convenient, processed, and fast foods.¹⁵

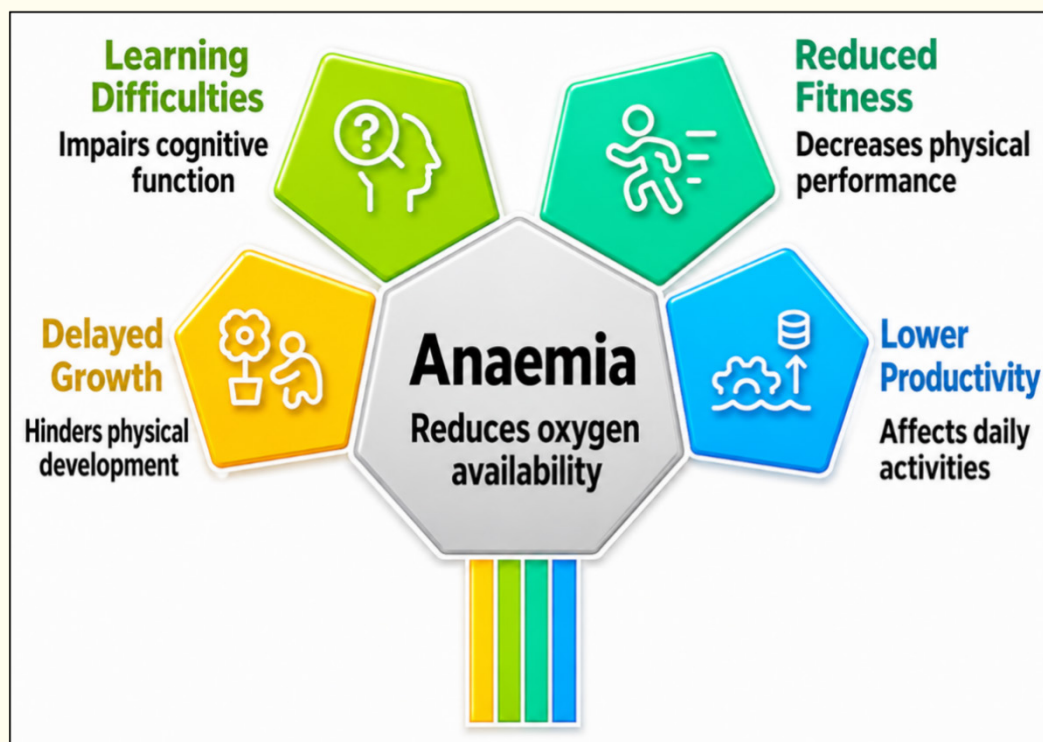
Figure 2. Physiological and functional consequences of anaemia¹¹

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Role of Nutrition in Anaemia and Haem Synthesis

Nutrition plays a central role in haemoglobin formation and red blood cell maturation, both of which are essential for effective oxygen transport.¹⁶ Haemoglobin is the oxygen-carrying protein within red blood cells, supporting energy delivery throughout the body; when production is compromised, individuals may experience fatigue, weakness and shortness of breath.¹⁷

Iron, vitamin B12 and folate are integral to haem synthesis and erythropoiesis, contributing to processes such as DNA replication, cell proliferation, and haemoglobin assembly. Other micronutrients, including zinc, copper, and vitamin A, also support red blood cell development, immune function and overall cell function.¹⁸ Iron, in particular, plays a critical role in DNA synthesis, energy production, and immune function.¹⁹

While iron deficiency is the most common form of nutrition-related anaemia, insufficient intake of vitamin B12 and folate gives rise to megaloblastic anaemia, characterized by the production of abnormally large, immature red blood cells that are structurally defective, prone to premature destruction, and unable to carry oxygen effectively.¹⁰ In megaloblastic anaemia, impaired DNA synthesis interrupts the normal cell division during erythropoiesis, which results in red blood cells with reduced oxygen-carrying capacity despite their enlarged size.¹⁸ Consequences include fatigue, impaired cognition, and other neurological symptoms, overlapping considerably with those of iron deficiency anaemia, which underscores the importance of a holistic, multi-nutrient approach to anaemia prevention.

Adolescents on vegetarian or vegan diets are at a higher risk of vitamin B12 deficiency, as it is found almost exclusively in animal-sourced foods such as meat, fish, eggs, and dairy products. In India, where lacto-vegetarianism is embedded across diverse cultural and socioeconomic demographics, B12 deficiency represents a clinically significant and often underdiagnosed contributor to anaemia in adolescents.²⁰ The concern of B12 deficiency extends beyond South Asia, with increasing frequency documented among adolescents adopting plant-based diets globally.²¹ For these adolescents, dairy foods such as milk, curd and paneer remain the most accessible and culturally appropriate dietary B12 sources; two to three servings of dairy per day can help adolescents achieve the recommended intake of 2.2 µg/day.²² If dairy consumption is limited or absent, either B12-fortified foods or low-dose supplementation should be considered as part of a comprehensive anaemia prevention strategy.

Folate is found in dark leafy greens, legumes, and whole grains and is equally essential for red blood cell maturation, particularly important during periods of rapid growth, such as adolescence.²³ The risk of megaloblastic anaemia is compounded by inadequate folate intake, which is further aggravated by poor dietary diversity and the growing global trend of processed food dependency among adolescents.¹⁵ Promisingly, numerous indigenous plant-derived foods highlighted in this review, such as moringa, amaranth leaves, spinach, lentils and chickpeas, are rich in folate and iron, addressing multiple micronutrient deficiencies simultaneously through dietary diversification.

Thus, these nutritional interdependencies highlight that effective anaemia prevention in adolescents requires attention to the full spectrum of haematopoietic nutrients (iron, vitamin B12 and folate, and supporting micronutrients), rather than focusing on iron alone.

Bioavailability and Factors Affecting Iron Absorption

Two forms of dietary iron exist: haem and non-haem iron. Haem iron, found in animal products such as meat, poultry and fish, is absorbed more efficiently than non-haem iron from plant sources such as leafy greens, legumes, grains, nuts, seeds and fortified foods. Bioavailability refers to the proportion of a nutrient that is absorbed and utilised by the body from the digested food. Improving intestinal iron bioavailability ensures that the maximum amount of iron is absorbed by the body, preventing iron deficiency anaemia.²⁴

Non-haem iron absorption rates are typically <10%, compared with 25-30% for haem iron, due to greater sensitivity of non-haem iron to dietary modifiers and the individual's iron status.²⁴ Ascorbic acid (vitamin C), found in citrus fruits, bell peppers and tomatoes and animal proteins enhance non-haem iron absorption, while phytic acid, polyphenols, calcium and oxalic acid act as inhibitors (Figure 3).²⁴ Consequently, tea and coffee should be avoided with meals, and large amounts of calcium-rich dairy should be limited during iron-rich meals to protect non-haem iron absorption.

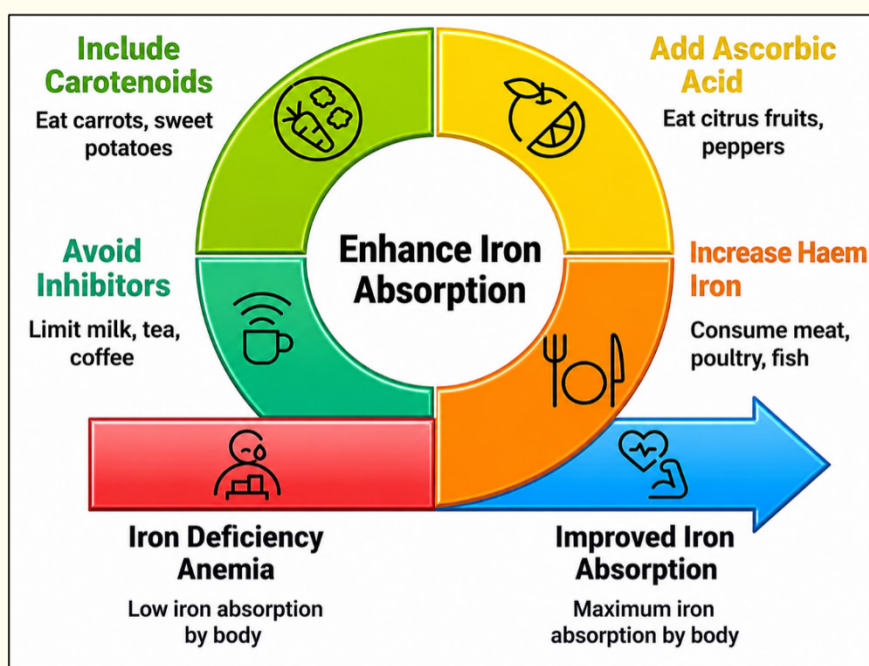
Figure 3. Nutritional factors influencing iron absorption²⁴

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Carotenoids (provitamin A), known for their antioxidant and anti-cancer properties, have also been demonstrated to improve iron absorption, tripling absorption from cereals such as rice-based meals and nearly doubling absorption from wheat- and corn-based meals.^{25,26} Carotenoid-rich foods include carrots, sweet potatoes, squash, spinach, kale and broccoli.

Common Treatment Options

Oral iron supplementation is the first-line treatment for iron deficiency anaemia and is effective at replenishing iron stores and relieving symptoms. However, it frequently causes gastrointestinal side effects, leading to poor compliance.

A recent systemic meta-analysis concluded that iron fortification can improve haemoglobin levels in adolescent girls.²⁷ The greatest improvement was observed in a study using iron-fortified soy sauce, while the smallest effect was reported with iron-fortified rice; however, most interventions were short-term (12-24 weeks), providing insufficient time to determine sustainability. Nutrition education has also been highlighted as crucial in preventing micronutrient deficiencies in adolescents.²⁸ Education empowers adolescents with the knowledge and skills needed to make informed food choices, able to prioritise nutrient-rich foods and understand the importance of adequate nutrition for growth and wellbeing. Nutrition education can also address misconceptions and cultural beliefs, reduce reliance on processed and convenience foods, and promote healthier eating behaviours that establish positive dietary patterns into adulthood.

Alternative Dietary Approaches Through Sustainable Eating

Despite extensive public health strategies, progress in reducing anaemia prevalence, particularly among women of reproductive age, remains limited. Sustainable diets promote health and wellbeing with low environmental impact and prioritise affordability, cultural acceptability, and the utilise local, natural resources.

To address anaemia, dietary patterns emphasising nutrient-dense foods and strategies to maximise iron absorption should be considered as sustainable alternatives to supplementation and food fortification. Sustainable diets also align with multiple Sustainable Development Goals (SDGs), including:

- SDG 2 (Zero Hunger): improving food security and nutrition
- SDG 3 (Good Health): reducing malnutrition and disease
- SDG 12 (Responsible Consumption): reducing food waste and promoting efficient use of local resources
- SDG 13 (Climate Action): lowering carbon footprint and greenhouse gas emissions through the consumption of locally sourced food

Achieving these goals requires strong nutrition education to build sustainable food systems and reduce food waste.²⁹ The World Health Organisation and Food and Agriculture Organization recommend addressing micronutrient deficiencies through nutrition education, food fortification, supplementation and dietary diversification. Sustainable eating also supports long-term dietary patterns based on health, economic and socio-cultural considerations.³⁰

A healthy vegetarian dietary pattern rich in nutrient-dense whole plant foods such as fruit, vegetables, grains, legumes, nuts and seeds provides essential fibre, vitamins, minerals and antioxidants, which can reduce the burden of non-communicable diseases such as cardiovascular disease, cancer and diabetes. Such diets are also socially desirable, environmentally beneficial, supporting sustainable and resilient food systems.

Nutrient Enhancement Through Recipe Adaptation

To support dietary diversification through sustainable eating, recipe adaptation should reflect local dietary patterns and culinary traditions to align with the cultural diet. Kaur et al.³¹ reported that iron-rich, plant-based foods that are inexpensive, traditional and locally available are increasingly underutilised due to the rising trend towards consumption of processed and convenient foods. The authors also emphasised that these plant-based foods, once part of a traditional diet, are highly nutritious and offer health benefits beyond reducing anaemia.

Examples of iron-rich plant-based foods include cereals and millets (such as ragi or finger and bajra or pearl millet and buckwheat), pulses (such as chickpeas, lentils and soybeans), dark leafy greens (such as beet greens, broccoli, kale, moringa and amaranth leaves and spinach), dried fruits (such as apricots, dates, figs and raisins), and various nuts and oilseeds (such as almonds, cashews, hemp, flaxseed, Niger seeds, pine nuts, pistachios, pumpkin seeds, and sesame seeds). Table 1 presents a selection of adolescent-friendly dishes using locally available ingredients with estimated iron content per serving and percentage contribution to the recommended daily allowance (RDA) for girls. Examples of adolescent-friendly dishes include millet-based breakfast porridge and pancakes such as ragi or spinach and lentil pancakes, stuffed roti, pulses (beans and lentils) added to soups, leafy greens such as spinach and kale added to curries, parathas, salads, and fruit smoothies, and nut- and dried fruit-based energy balls or laddus.

Table 1. Estimated iron content of adolescent-friendly dishes per common serving

Dish	Key iron-rich ingredients	Serving size	Estimated Iron (mg)	%RDA (adolescent girls 30mg/day*)
<i>Ragi / finger</i>	millet porridge	Finger millet, fortified milk	1 cup (240ml)	3.8 – 4.2
<i>Moringa dal (lentil soup)</i>	Masoor dal, moringa leaves	1 bowl (200g)	5.5 – 6.0	~19%
<i>Spinach chickpea curry</i>	Chickpeas, spinach	1 cup (150g)	4.0 – 5.0	~15%
<i>Rajma (kidney bean) rice</i>	Kidney beans, rice	1 plate (200g)	3.5 – 4.5	~13%
<i>Sesame jaggery energy balls</i>	Sesame seeds, jaggery	2 balls (~40g)	3.0 – 3.5	~11%
<i>Garden cress seed (Halim) laddu</i>	Garden cress seeds, jaggery	1 piece (~40g)	5.0 – 7.0	~20%
<i>Amaranth leaf paratha</i>	Amaranth leaves, whole wheat	2 parathas (~100g)	4.2 – 5.0	~15%
<i>Bajra (pearl millet) pancakes</i>	Pearl millet flour	2 pancakes (~80g)	2.5 – 3.0	~9%

*RDA: Recommended Dietary Allowance; Average RDA value used; age-specific values are 28mg/day for 10 – 12 yr girls, 30mg/day for 13 – 15 yr girls, and 32mg/day for 16 – 18 year girls²²; Iron content estimated from Indian Food Composition Tables³²; Actual content may vary with preparation methods, ingredient quality and regional variations.

Achieving measurable improvements in haemoglobin levels and iron stores necessitates consistent, long-term adherence to dietary modifications. The recommended intake of 28-32 mg/day for adolescent girls²² is nutritionally demanding and cannot be achieved without deliberate and consistent meal planning. Every meal must be strategically planned to maximise both iron content and bioavailability. Consuming at least three to four iron-rich meals and snacks is therefore necessary but not sufficient. Each meal must also incorporate enhancers such as vitamin C-rich accompaniments, including fruit juice, sliced tomato or a squeeze of lemon juice, which can increase non-haem iron absorption by two to threefold.²⁴

Concurrently, known absorption inhibitors such as tea, coffee and excessive calcium intake should be avoided during and immediately following iron-rich meals. Every meal is therefore critical, as systematically maximizing bioavailability across all daily eating occasions yields a cumulative effect that ensures the long-term efficacy needed to achieve recommended nutrient benchmarks. Whilst iron supplementation can produce measurable haemoglobin responses within two to three months, food-based interventions typically require a minimum of three to six months of consistent adherence to observe meaningful haemoglobin improvements, with serum ferritin stores requiring six to twelve months to rebuild adequately.^{1,27} To accurately monitor the efficacy of these interventions, a combination of haemoglobin and serum ferritin should be used, as this dual approach provides the highest sensitivity for tracking the recovery of functional iron and

underlying cellular stores.^{5,6} Ultimately, sustaining these dietary habits into long-term lifestyle patterns beyond 12 months is essential to maintain iron balance and prevent regression of iron stores over time.

Vitamin C enhances non-haem iron absorption by converting iron from ferric (Fe^{3+}) to ferrous (Fe^{2+}) iron, forming a soluble chelate in the duodenum that counteracts inhibitors such as tea and calcium.³³ This enhancing effect is dose-dependent and is most effective when vitamin C is consumed simultaneously with iron-rich foods (Figure 4).²⁴ Therefore, incorporating vitamin C-rich foods such as citrus fruits (lemons and oranges), tomatoes, and bell peppers into iron-containing meals can significantly improve dietary iron bioavailability. Practical recipe adaptations to enhance iron absorption include adding fresh lemon juice to curries and serving iron-rich meals with salads containing leafy greens and tomatoes, complemented by a squeeze of lemon juice, a citrus-based dressing, or vitamin C-rich chutneys. Additionally, fresh fruits or freshly prepared fruit juices, such as papaya, mango, and oranges, can be consumed alongside meals to enhance non-haem iron absorption. Likewise, incorporating vitamin A-rich foods such as carrots and sweet potatoes into everyday recipes may further improve iron bioavailability. These nutrient-dense foods also serve as convenient and healthy snack options for adolescents.

Traditional food preparation methods such as soaking, sprouting, germination, fermentation and cooking can reduce antinutrients (such as phytate), increasing mineral bioavailability.³⁴ For example, soaking and germinating garden cress, wheat and finger millets significantly reduces phytic acid content.³⁵ Cooking with iron cookware, such as cast iron and ingots, can also increase iron content by leaching iron into food, increasing the iron content of foods by at least 16%.^{36,37}

Figure 4. Strategies for enhancing iron absorption²⁴

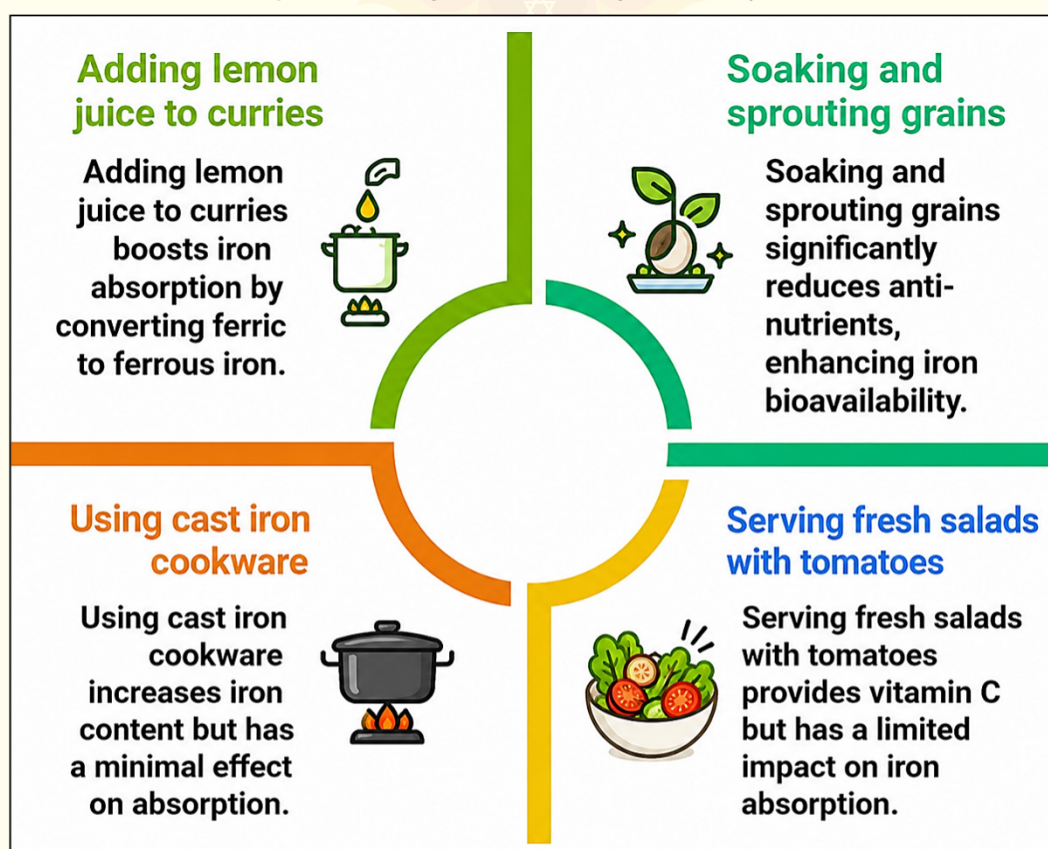


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Although improving dietary diversity and quality is essential for anaemia prevention, cost and limited access to iron-rich foods such as animal protein, fruit, and vegetables remain major barriers. While dietary diversification offers a sustainable long-term solution, the behavioural changes required may take time. In contrast, supplementation and food fortification can have a more immediate impact on iron status. However, adherence to iron supplementation is often low among adolescent girls due to factors such as personal attitudes and social factors, including a lack of family and peer support.³⁸

Conclusion

Anaemia continues to pose significant public health implications due to its complex and multifactorial nature. Adolescents, particularly females, are at increased risk due to dietary limitations, physiological iron requirements, and the onset of menarche. Previous strategies have provided some benefits; however, they have not adequately addressed the wider determinants of dietary behaviour and nutrient intake to prevent anaemia. Beyond iron, this review highlights vitamin B12 and folate deficiency as clinically significant contributors to anaemia, particularly among vegetarian adolescents. Dairy foods, B12-fortified products, and folate-rich plant foods should be incorporated into dietary strategies to ensure a holistic micronutrient approach to preventing anaemia.

A sustainable dietary approach complements existing interventions by focusing on recipe adaptation, which uses traditional preparation techniques to enhance nutrient absorption, and by prioritising nutrient-rich plant foods that are readily available and affordable. Achieving measurable improvements in iron status requires consuming at least three to four iron-rich meals daily, along with vitamin C enhancers, with consistent adherence for a minimum of three to six months and sustained beyond 12 months to prevent regression of iron stores. Sustainable food practices also align with global developmental priorities, including environmental sustainability and food security.

This study introduces a novel perspective by shifting the focus from traditional clinical interventions (such as supplementation and food fortification, where adherence is poor) to sustainable dietary strategies to prevent and manage iron deficiency anaemia among adolescents. The study highlights the potential to increase iron intake through culturally relevant recipe adaptation, traditional food processing techniques and increased use of locally available, nutrient-dense plant foods. It offers a long-term, food-based solution that supports environmental goals and sustainability principles while addressing anaemia by integrating nutrition science to enhance iron bioavailability. Therefore, the study bridges a significant research gap by combining public health nutrition with sustainable food systems to improve adolescent health and well-being.

Future research and policy initiatives should consider how sustainable eating models could contribute to improved health outcomes, especially for adolescents who represent the future adult population and workforce. The findings highlight the need to encourage dietary diversity, enhance nutrient bioavailability and recognise determinants of food choices as key elements in managing and preventing anaemia. Specific implications include nutrition programmes that incorporate dietary diversification and bioavailability-enhancing practices for anaemia prevention; policies that prioritise nutrition education for adolescents and caregivers, particularly on recipe adaptation, preparation, and the roles of enhancers and inhibitors in iron absorption; and the importance of vitamin B12 and folate sufficiency for comprehensive anaemia prevention. Schools should serve

as key platforms for implementing nutrition programmes and education. Government sectors of health, agriculture, education and environment should collaborate to link nutrition outcomes with sustainability goals (SDGs 2, 3, 12 and 13).

Author Contributions: The authors' contributions were as follows: conceptualisation, R.U.; original draft preparation, R.U. and W.S.K.; review & editing, R.U. and W.S.K.

Funding: This research received no external funding.

Institutional Review Board Statement: The study did not require ethical approval.

Acknowledgements: The authors extend their sincere gratitude to Sadguru Sri Madhusudan Sai, Chancellor of Sri Sathya Sai University for Human Excellence (SSSUHE), and Bhagavan Sri Sathya Sai Baba for the guidance and inspiration. W.S.K. wishes to express heartfelt gratitude to Dr Rajeshwari Ullagaddi, co-author and guide, whose tireless encouragement, scholarly guidance and unwavering support were instrumental in the conception, development and completion of this manuscript. W.S.K. also wishes to express sincere appreciation to the community at Jethavanarama Buddhist Monastery in Sri Lanka for their blessings and support throughout this work.

Conflicts of Interest: None.

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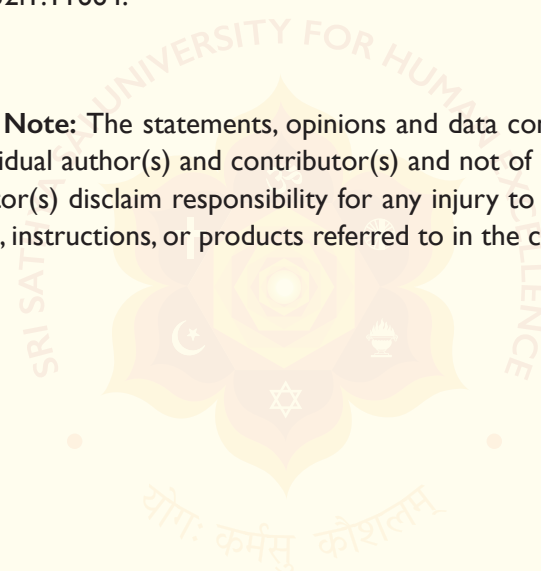
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Article

In Vitro Propagation Strategy for *Croton bonplandianus* through Internodal Segments

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Abstract: *Croton bonplandianus* is an important medicinal herb and has been used to prepare herbal formulations to cure many diseases. Its potential to heal wounds can be exploited as an effective formulation in medicines. In vitro-raised plantlets provide a suitable alternative to mass multiplication and cell culture-based metabolite production. It is an effective strategy for the conservation of plants in their natural and native habitats. An efficient protocol for in vitro shoot multiplication of *Croton bonplandianus* has been developed using internodal segments as explants. It was observed that shoot multiplication could be induced on a slightly modified Murashige and Skoog's (MS) medium supplemented with 6-benzylaminopurine, Naphthalene Acetic Acid, Indole 3-Acetic Acid, in various combinations. Shoot proliferation and root induction were induced with an enhanced number of plantlets, and optimization was successfully done to obtain viable and healthy plantlets with a success rate of more than 82%. The optimized protocol can be used to optimize cell suspension cultures.

Keywords: Internodal segments, Conservation, Micropropagation, Plant Growth regulators, Shoot proliferation, Root induction, *in vitro* raised Plantlets.

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Citation: Jeevan S., Santosh K. S., Ramya R.; *Awareness*, 3 (2): 79-88

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Introduction

Medicinal plants are known to possess active ingredients that are significantly used in different medicinal formulations. Such formulations have been used from ancient times as mentioned in Ayurveda and Yunani literature. The significance of medicinal properties of plants have been reported in the literature and writings of Charaka, Shushruta, and many other sages. The extracts of plants, decoction, or tincture have been used to treat different disorders and diseases. India is rich in biodiversity hotspots for medicinal plants. Karnataka is one of those

hotspots of biodiversity. The Panchagiri hills are known for many endemic and valuable flora, but extensive studies are needed to record and document the diversity. Panchagiri is a collective name for a place surrounded by five hills named Nandi Giri, Skanda Giri, Chandra Giri, Brahma Giri, and Hema Giri.

Croton bonplandianus is a large flowering shrub that grows along the hilly and plains areas of the Panchagiri hills. It belongs to the family Euphorbiaceae. The plant is an annual/perennial herbaceous plant with a height of 80-100 cm with a multiple-branched system. Stem is erect (covered with fine hairs); leaves are simple and in an alternate arrangement, ovate to lanceolate with serrated margins; flowers: small, unisexual, and arranged in terminal/axillary racemes. Fruits are three-lobed capsules with flattened and oval seeds. The plants are mostly observed in the disturbed and dry regions with less fertile soils. It is known for its anticancer, antioxidant, and antimicrobial properties.^{7, 13, 14, 15} The previous studies show that this can also act as an anaesthetic agent in relieving stomach and oesophagus-related issues,³ and it can also help reduce the over-secretion of the stomach. The plant is also found to have wound-healing active ingredients in it.³ To conserve this plant and to propagate it with ease, a few techniques are used, and *in vitro* propagation is one of them.

In vitro propagation is growing genetically identical copies by asexual reproduction. It involves the aseptic culture of explants of tissues and organs using a defined culture medium in a sterile and controlled environment. *In vitro* propagation of *Croton bonplandianus* plant is significant because a large number of plants can be grown in a lab under controlled conditions. In recent times, the technique has been widely used to study plants and their significance. Since the *Croton* plant is proven to possess a wide range of pharmaceutical properties, to study them larger number of plants are required at the lab. This technique can aid in supplying the plants for the study. The objective of the study was to establish the optimised protocol for the micropropagation of this plant with various combinations of plant growth regulators.

Materials and Methods

Plant collection and identification

Young and healthy plants of *Croton bonplandianus* were collected from Panchagiri hills, Muddenahalli, Karnataka, India. The plant species was identified with the help of available literature and the Botanical Survey of India, Coimbatore Circle, Tamil Nadu (Certificate no. BSI/SRC/5/23/2024-25/Tech/6/2).

Sterilization & Culture inoculation

Internodal segments from young & healthy plants were selected as explants for the initiation of cultures *in vitro*. The whole procedure was conducted in a laminar hood under strict aseptic conditions. The laminar hood's floor was sanitized with 70% alcohol. The explants were washed 5-6 times thoroughly under running tap water to remove all the dirt, then exposed to 90% ethyl alcohol for 10 seconds for surface sterilization and rinsed with sterile double-distilled water. Afterwards, the explants were placed in a beaker containing water and 3-4 drops of Tween 20 (detergent). Stirred the beaker gently for 7 minutes and washed under running tap water (6 times), followed by double-distilled water ($\times 5$). After removal of all traces of detergent, surface disinfection was carried out with 0.01-0.1% HgCl₂ (w/v), followed by washing several times (10 times) with sterilized distilled water. The plant material was allowed to dry in a laminar hood on a tissue paper towel (soaked in

Alcohol and dried) for 20 minutes to evaporate any excess water present on the surface of the explant^{8,5,9,14}. Since the cells in the stem that retain totipotency are mainly the parenchymatous cells of the cortex and pith, along with some vascular parenchyma associated with xylem and phloem, the internodal segments were used as explants. The internodal segments were infused onto Murashige and Skoog's (MS) medium under aseptic conditions. The medium was supplemented with usual salts and vitamins and 3% sucrose (w/v; Hi-Media), 100 mg/litre myo-inositol (E. Merck) and 0.8% agar (w/v; Hi-Media).

MS media were used for *in vitro* mass propagation of *Croton bonplandianus*. The media included all the macronutrients as well as micronutrients, along with the organic supplements as vitamins and organic acids. Different plant growth regulators were standardized for their optimum concentrations for organogenesis. All media components were purchased from HiMedia and were of molecular biology grade. Growing calli were subcultured on media supplemented with BAP and IAA for organogenesis, especially for further shoot multiplication. Shoot Proliferation rate was measured by counting the total number of shoots produced per explant across replicates ($n=3$), and the values were presented as mean $\pm$ SE. The bud induction rate (%) was measured after 6 weeks by counting the percentage of explants showing bud induction with respect to total explants cultured. Roots were then induced in MS medium supplemented with different combinations of IAA and NAA. 5-week-old plantlets were transferred to pots containing a sterilized soil and sand mix (1:1), covered with polythene bags with perforations, for 10 days and the pots were kept below $25 \pm 2^\circ\text{C}$ for acclimatization and hardening.

Acclimatization

Plantlets with viable and thick roots were safely taken out of the culture medium. The roots were carefully washed to get rid of the media components and agar. Then they were grown in Knop's mineral solution for 48 hours, and later they were transplanted to fresh plastic pots containing sterilized soil mixed (garden soil and sand simultaneously) with peat moss in a 1:1 ratio. The plantlets were kept in a culture room at $25 \pm 2^\circ\text{C}$ for 5-7 days, and the plantlets were transferred to earthen pots (10 cm in diameter with natural soil), and maintained under shade for 2 more weeks. Then the pots were slowly exposed to the sun outdoors. Viability % was counted to analyze the efficacy of optimization experiments.

Statistical Analysis of the Data

The data were statistically analysed using SPSS software tool (version 11.5; SPSS, Chicago, IL, USA). A one-way ANOVA, followed by Bonferroni's post hoc analysis, was conducted to determine the statistical significance. A two-sample t-test was performed to determine the statistically significant difference in the total protein, proline, flavonoid, ascorbate and thiol content between the wild and *in vitro*-propagated plants. Differences were considered significant at $P < 0.05$.

Results

Croton bonplandianus plants were observed to be herbaceous in nature with an average height of 80-100 cm. Stems were observed to be erect (covered with fine hairs), multi-branched; leaves as simple and in alternate arrangement. It was identified that the leaves had serrated edges and were ovate to lanceolate in shape. The flowers were small, unisexual, and arranged in terminal/axillary racemes. Fruits were three-lobed capsules with flattened and oval seeds (Figure 1).



Figure 1. Morphological features of *Croton bonplandianus*.

Shoot Proliferation and Bud Induction

The effect of varying concentrations of BAP and NAA on shoot proliferation and bud induction in *Croton* explants was evaluated (Figure 2). The control treatment (0 mg/L BAP and NAA) yielded a mean shoot proliferation coefficient of 1.87 and an induction rate of 7%. Supplementation with 0.4 mg/L BAP and 0.02 mg/L NAA significantly increased shoot proliferation (mean: 2.4) and induction rate (40%). Further enhancement was observed with 0.6 mg/L BAP and 0.04 mg/L NAA, resulting in a mean proliferation of 4.07 and 60% induction. The highest shoot proliferation (mean: 7.57) and induction rate (84%) were recorded at 0.8 mg/L BAP and 0.06 mg/L NAA (Table 1).

Table 1 Effect of optimum PGR composition/s on shoot proliferation and induction rate of bud proliferation- *Croton bonplandianus*

BAP (mg/L)	NAA (mg/L)	Shoot Proliferation (Mean $\pm$ SE)	% Induction Rate
Control	0.00	1.87 $\pm$ 0.29 a	7
0.4	0.02	2.40 $\pm$ 0.49 a	40
0.4	0.04	3.40 $\pm$ 0.42 ab	35
0.6	0.04	4.40 $\pm$ 0.61 bc	60
0.6	0.06	5.43 $\pm$ 0.35 cd	58
0.8	0.04	4.47 $\pm$ 0.72 bc	70
0.8	0.06	7.57 $\pm$ 0.46 d	84

Values are presented as Mean $\pm$ SE ($n = 3$). Superscript letters (a-d) denote statistical groupings based on Tukey's HSD test ($p < 0.05$). Treatments sharing the same letter are not significantly different.

Among the tested combinations, 0.8 mg/L BAP with 0.06 mg/L NAA yielded the highest mean shoot proliferation coefficient (7.57 ± 0.80), significantly outperforming the control (1.87 ± 0.50) and other treatments ($p < 0.001$, Tukey HSD). These findings align with previous reports in *Croton* species and other Euphorbiaceae members, where BAP has been shown to stimulate axillary bud break and shoot multiplication.^{10, 16} The observed increase in shoot proliferation may be attributed to BAP's role in promoting cell division and meristematic activity, while NAA modulates tissue polarity and vascular differentiation.²

Levene's test confirmed homogeneity of variances ($F = 0.538$, $p = 0.771$), validating the assumptions for ANOVA and post hoc comparisons. The significant mean differences between control and high-performing treatments (e.g., I vs. Control: mean diff = 5.7, $p < 0.001$) reinforced the biological relevance of the statistical findings. These results are consistent with studies in *Jatropha curcas* and *Ricinus communis*, where similar hormonal regimes yielded optimal shoot regeneration.²

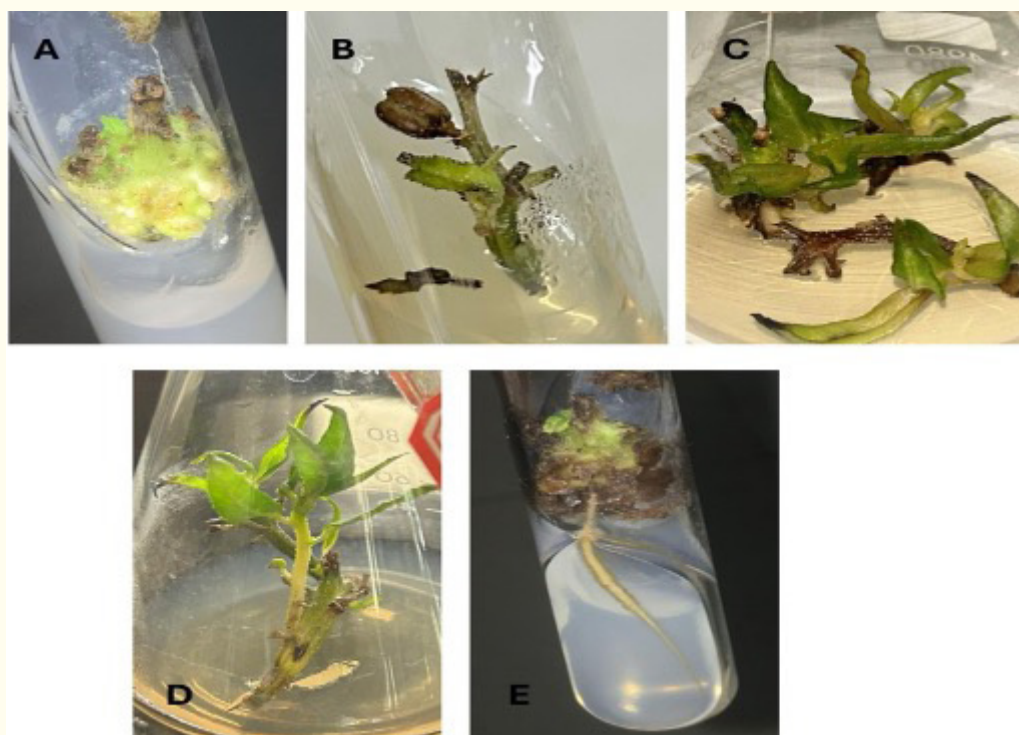


Figure 2 Plant *Croton bonplandianus* - Fig A: swelling of tissues and growth of callus, Fig B: initiation of shoot growth. Fig C & Fig D: Elongation of Shoots, Fig E: Development of Roots.

Root Initiation and Induction Rate

Rooting responses varied significantly across treatments with different concentrations of IBA and NAA. The control group (0 mg/L IBA and NAA) showed no root formation. Introduction of 0.02 mg/L NAA alone resulted in 20% induction with 2–3 roots per plant-let. Combined treatments of 0.02 mg/L NAA and 0.06 mg/L IBA yielded the highest root induction rate of 82%, with an average of 8–9 roots per plantlet (Table 2).

Table 2: Effect of different compositions and concentrations of IBA and NAA on root initiation

Treatment	NAA (mg/L)	IBA (mg/L)	% Root Induction	Number of Roots/Plantlet (Mean $\pm$ SE)
Control	0.00	0.00	0	0.00 $\pm$ 0.00 a
2	0.02	0.00	20	2.67 $\pm$ 0.33 b
3	0.00	0.02	25	3.33 $\pm$ 0.33 bc
4	0.06	0.00	40	4.67 $\pm$ 0.33 cd
5	0.00	0.06	48	4.67 $\pm$ 0.67 cd
6	0.02	0.02	50	5.33 $\pm$ 0.88 de
7	0.02	0.04	65	7.00 $\pm$ 0.58 fg
8	0.02	0.06	70	7.67 $\pm$ 0.33 gh
9	0.02	0.08	78	7.33 $\pm$ 0.33 fg
10	0.06	0.02	35	6.00 $\pm$ 0.58 ef
11	0.06	0.04	65	7.33 $\pm$ 0.33 fg
12	0.06	0.06	82	8.67 $\pm$ 0.33 h
13	0.06	0.08	70	8.67 $\pm$ 0.33 h

Values are presented as Mean $\pm$ SE ($n = 3$). Superscript letters (a-h) denote statistical groupings based on Tukey's HSD test ($p < 0.05$). Treatments sharing the same letter are not significantly different.

Treatments with 0.06 mg/L NAA and 0.08 mg/L IBA also showed strong rooting (70% induction, 8–9 roots), confirming the efficacy of auxin combinations in promoting rhizogenesis (Figure 2). The present study elucidated the significant impact of auxin combinations specifically IBA and NAA on root initiation in *Croton bonplandianus*, supported by rigorous statistical validation. The ANOVA results revealed a highly significant treatment effect ($F = 30.46$, $p < 0.001$), with a large effect size ($\eta^2 = 0.934$; $\omega^2 = 0.901$), indicating that over 90% of the variance in root number was attributable to the treatment conditions. This underscored the potent influence of auxin concentration and composition on rhizogenic response. These findings are consistent with previous reports where IBA was shown to enhance root primordia formation and elongation in woody and medicinal plants.^{6, 10} Post hoc comparisons revealed statistically significant differences between the control and all auxin-supplemented treatments with large Cohen's d values indicating strong practical significance. The synergistic effect of NAA and IBA likely stems from their complementary roles- NAA promoting cell division and IBA facilitating root elongation and vascular differentiation.⁴ Similar synergism has been reported in *Azadirachta indica* and *Jatropha curcas*, where combined auxin treatments yielded superior rooting outcomes. These results provided a reproducible framework for optimizing root induction protocols in *C. bonplandianus*, a species of ecological and pharmacological interest due to its allelopathic and antimicrobial properties.

Substrate Effects on Survival and Plant Height

After 60 days of acclimatization, substrate composition significantly influenced both survival percentage and plant height. The mixed substrate of sand: vermicompost: garden soil (50:25:25) resulted in the highest survival rates (mean: 82%) and tallest plantlets (mean height: 5.5–6.8 cm). Garden soil alone supported moderate survival (mean: 41.7%) and plant height (2.3–3.2 cm), while pure sand yielded the lowest survival (mean: 34.3%) and shortest plantlets (1.6–2.4 cm) (Table 3). These results underscore the importance of substrate composition in post-micropropagation acclimatization.

Table 3. Effect of different substrates on survival (%) and plant height of in vitro raised plantlets (after 60 days)

Substrate(s)	% Survival	Plant Height (cm)
Sand (100%)	34.33 ± 3.48 a	1.96 ± 0.23 a
Garden soil (100%)	41.67 ± 6.01 a	2.67 ± 0.27 a
Sand:Vermicompost: Garden soil (50:25:25)	82.00 ± 5.29 b	5.50 ± 0.75 b

Values are expressed as Mean ± SE (n = 3). Superscript letters (a, b) indicate statistical groupings based on Tukey's HSD test ($p < 0.05$). Treatments sharing the same letter are not significantly different.

The acclimatization phase is critical in micropropagation, and the present study demonstrates that substrate composition significantly influences survival rates and plantlet vigor in *Croton bonplandianus*. ANOVA results revealed a highly significant effect of substrate type on survival percentage ($F = 25.93$, $p = 0.001$), with a large effect size ($\eta^2 = 0.896$; $\omega^2 = 0.847$), indicating that nearly 90% of the variance in survival was attributable to substrate differences.

Among the tested substrates, the mixture of sand, vermicompost, and garden soil (50:25:25) yielded the highest mean survival rate ($82 \pm 9.16\%$), significantly outperforming garden soil ($41.67 \pm 10.41\%$) and sand ($34.33 \pm 6.03\%$) ($p < 0.01$, Tukey HSD). The low coefficient of variation ($CV = 0.112$) in the mixed substrate group underscores its consistency and reliability. These findings are consistent with previous reports where organic amendments such as vermicompost enhanced moisture retention, microbial activity, and nutrient availability, thereby improving plantlet establishment.¹⁶

Post hoc comparisons confirmed significant mean differences between vermicompost-based substrate and both garden soil (mean diff = 40.33, $p = 0.003$) and sand (mean diff = 47.67, $p = 0.001$), with large Cohen's d values (>4.6), indicating strong practical relevance. The improved survival in the mixed substrate may be attributed to its balanced texture and nutrient profile, which supports root aeration and microbial symbiosis factors known to enhance post-transfer acclimatization.¹² These results aligned with studies in *Withania somnifera* and *Azadirachta indica*, where substrate optimization was pivotal for successful hardening and field establishment. The statistical evidence strongly supported the use of a sand: vermicompost: garden soil mixture for enhancing the survival and growth of *Croton bonplandianus* plantlets during acclimatization. This substrate combination offers a reproducible and scalable solution for conservation and commercial propagation efforts. Future work may explore microbial inoculants and nutrient dynamics within this substrate system to further optimize post-micropropagation success.

The integrated statistical analyses across shoot proliferation, root initiation, and acclimatization parameters in *Croton bonplandianus* revealed a coherent and reproducible micropropagation strategy. Optimized concentrations of BAP (0.8 mg/L) and NAA (0.06 mg/L) significantly enhanced shoot multiplication, aligning with prior findings in Euphorbiaceae. The current work provides preliminary information and methodology for the rapid propagation of this valuable plant from internodal explants that might help in the improvement of conservation methods. It is a high-value medicinal plant, and its mass propagation strategy can be used further in suspension cultures to obtain suitable secondary metabolites for commercial uses in antioxidant, antimicrobial, anticancer, and other activities. The researchers may focus on methodological improvements in cell culture-based metabolite production. The use of elicitors in cell suspension cultures might be suitable to activate metabolite production in cultures and increase the significance of plant tissue culture technology. It will help to establish a scalable strategy for using different stages of callus for obtaining medicinal compounds from culture media. This approach has been successfully demonstrated previously.^{17,18}

Conclusion

The current study effectively optimized an efficient *in vitro* propagation technique for *Croton bonplandianus* using internodal explants. It indicated the capacity of this valuable medicinal plant for rapid clonal multiplication under controlled conditions. The optimized cultures not only promoted regular shoot formation and elongation with higher multiplication rate but it also provided a dependable pathway for generating viable and healthy roots for better acclimation. The sterilized soil mix compositions ensured the recovery of healthy plantlets with very high percentage rate. This technique shows promise for large-scale propagation, conservation, and possible use of *Croton bonplandianus* in phytochemical and pharmaceutical research, as well as contributing to sustainable management of its wild populations. The callus can be used to generate and establish cell suspension cultures for selective metabolite production. Future research may concentrate on improving secondary metabolite production using suspension cultures using elicitors, expanding the scope of this species in both scientific and commercial sectors.

Author Contributions: Conceptualization – J.S.; SKS; Methodology – J.S.; writing- original draft preparation – J.S. and S.K.S; Formal analysis (Application of statistical techniques to analyze the studied data)- RR

Acknowledgments: The authors wish to thank Sri Sathya Sai University for Human Excellence, Kalaburagi, Karnataka, for supporting the current piece of research work through the Seed Money Grant.

Declaration of conflicts of Interest: The authors declare no conflict of interest.

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Poetry

Boundaries via Distance: Topologically Speaking

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Key words: Topology; boundary; distance; philosophy

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Boundaries via Distance: Topologically Speaking

A probing mind with queries,
Conditions and consequences,
Nets of thoughts converging
Seeking the solutions fitting.
Mathematical thinking- an idea
Solid and precise, yet so intangible.

Math-a fearsome field to ever so many,
A way of thinking with precision;
A language of mind in focus,
Where logic forms bricks to bolster
To build the structures for giants to stand.

Each mind has a language
To be nurtured, cajoled and pampered,
To lay foundations strong to withstand
The tempests of things to come;
This language is part of mind, so abstract,
Who will dare to keep it there?

Citation: Bhamini M. P. N.;
Awareness, 3 (2): 89-92



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Or

Is it beyond a language of mind?

Is this a form of thought endowed
With a philosophy of its own mold?
Does that create a path for mind
To follow what we want to find?
Isn't one's thought abstract by nature?
Can anyone see one's own thought?

So

Being abstract is part of nature.

Why do we fear what we can't see?
Freedom and beauty of abstractness,
A combo of such rare class!
Encompassing depths of sea.
Epsilon, delta all so clear,
Neighborhoods of countless many,
Bringing all beyond and together,
With different sense of, oh, so near.

Topologists, they say, don't see a difference,
'Coffee cups from doughnuts'
Why so, how absurd, are they blind!
Doughnut and coffee cups, how so different!

How close a point is from another
In the structure-the topology- which is created;
Bend it, mold it in a shape so well,
Be careful not to break and leave some.
There is no difference in the substance
Of the new incarnation to the one before!
I have heard of this philosophy
As the essence of nature, the core.

As a child is taught to count
 A sense of distance forms with it:
 How far apart is one from another?
 Numbers give this sense as such.
 Distance notion builds Calculus,
 Analysis and so on,
 Structures of limit, continuity, and beyond.
 Creating possibilities of countless
 Applications, problems' solutions
 Could never have been possible
 But for these wings of abstractness!

As we move from number sets
 To sets of any, arbitrarily conceived,
 Can we have this distance concept?
 Yes, we can, here comes the notion,
 The space with a metric so defined,
 An abstract form of distance,
 A set with distance, call it a Metric Space.

The nearness concept in a metric space
 Guided by the 'metric'-
 Subtle connection to a numerical notion.
 Yet with freedom of structure of sets
 And keeping Calculus, Analysis intact,
 But rich enough to build on more.

Taking cue from this structure of sets
 Topology, created by great minds
 Able to see in abstract and beyond.
 Topological space- a set with a structure
 Defined on the collection of its subsets.
 The structure-the Topology-
 Tells the nearness of a point from another
 Epsilon, delta, so abstract
 Pave the way for more fluid
 Treatment of continuity, convergence and such
 Keeping foundations learned before
 Safe and giving room for more.

Beauty of this abstract distance,
Nearness notion so thought of
Without numerical value claiming it,
Free to fly high, yet knows the distance,
Shines so well, all encompassing,
Calculus, Analysis, Metric Spaces and all!
Topology-the abstract distance,
Makes it possible for sets of points
Come together or stay apart.

Boundaries formed, distance comes in,
Positions are taken with choices in,
Philosophies of minds blend in,
A tool with an eye on the goal.
Collectively civilizations fostered,
Wonder the all-embracing nature,
Philosophical key- a notion to nurture?
Topology-a mathematical philosophy raised.

Author's Note: When work is done in a specific field, within the boundary of a field, the effect of the work does not stay within that boundary. The effect of the research is universal. Topology is one such field within the universe of mathematics that blurs most boundaries., and therefore, its ripple effects can be noted across all scientific fields.

Supplementary Materials: None.

Author Contributions: N/A

Funding: None.

Acknowledgments: None.

Conflicts of Interest: None.

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Article

Biocompatibility of Medical Devices

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Abstract: All objects used in the diagnosis and treatment of disease must elicit an appropriate host response. This property, referred to as biocompatibility, is governed by requirements codified in international medical device standards, which define rigorous evaluation methods to ensure that only devices showing superior biocompatibility are placed into clinical use.

This article, the first in a series on the biocompatibility of medical devices, introduces the framework used to categorise devices according to the nature and duration of their contact with the patient, and outlines the corresponding risk-based testing strategies required to ensure that no unacceptable biological effects occur during clinical use.

Subsequent articles in the series will expand on these foundations by addressing chemical characterisation methodologies, tests for cytotoxicity, irritation and sensitisation, systemic toxicity, genotoxicity and carcinogenicity, implantation-related effects, and the application of the 3Rs principle in the context of animal welfare. Together, this series will provide a structured overview of contemporary biocompatibility evaluation and its role in ensuring medical device safety.

Keywords: Medical device; Biocompatibility; Risk-based assessment; Chemical characterisation; ISO 10993-1:2025

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Citation: Mohit K.; Awareness, 3 (2): 93-101



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Medical Devices

The statutory definition of a *medical device* in the United States, as laid down in the *Food, Drug, and Cosmetic Act*, is notably broad. It includes instruments, apparatuses, machines, implants, in vitro reagents, and other articles intended for use in the diagnosis, treatment, or prevention of disease, or to affect the structure or function of the body without relying on chemical action.¹ Similar definitions, albeit with jurisdiction-specific differences, exist in other regulatory regimes worldwide. For example, in the European Union, the *Medical Device Regulation* (EU MDR) also defines medical devices in broad terms, covering a wide range of products, from simple tools like bandages and tongue depressors to complex technologies such as implanted pacemakers and software used for medical purposes.² These broad

statutory definitions bring a highly diverse range of products within the scope of medical device regulations and necessitate regulatory frameworks that are sufficiently flexible and adaptable to accommodate this diversity.

Importantly, not all medical devices are designed to come into physical contact with patients or users. Software that supports clinical decision-making or imaging algorithms used for diagnostics, for instance, operate entirely through electronic interfaces and do not directly interact with the body. In contrast, other medical devices, such as catheters, surgical implants, and diagnostic swabs, are specifically designed to make physical contact with the patient, sometimes penetrating tissue or remaining in situ for extended periods. The interaction of such devices with the human body introduces a distinct set of safety considerations, particularly regarding host responses to the presence and materials of the device.

Biocompatibility

The concept of biocompatibility emerged with the development of implantable medical devices and was initially understood to mean that an ideal implant would be compatible with the biological host and would not provoke adverse reactions. During the early development of implantable devices (1940s – 1980s), materials used in the construction of medical devices were chosen for their minimal chemical reactivity, emphasizing the principle of “biological inertness”.³ During this period, material selection increasingly focused on minimizing undesirable biological responses. Early metallic implants, constructed from plain carbon and vanadium steels, were prone to corrosion and were progressively replaced by more chemically stable alternatives such as stainless steels, passivated cobalt–chromium alloys, titanium and its alloys, and the platinum-group metals. Similarly, polymeric materials such as nylon and polyester, initially valued for their availability and versatility, were supplanted by alternatives that offered greater chemical resistance and durability, including polytetrafluoroethylene (PTFE), polymethyl methacrylate (PMMA), polyethylene, and silicone elastomers.³ Implanted materials were chosen to minimize the risks associated with corrosion or degradation products, residual additives, or contaminants that could provoke local or systemic effects. Accordingly, biocompatibility criteria gradually came to be defined through a catalogue of “nons”: suitable materials were expected to be non-toxic, non-immunogenic, non-thrombogenic, non-carcinogenic, non-irritant, and so on. This catalogue became, *de facto*, the defining feature of biocompatibility for early implantable medical devices.³

Three factors eventually prompted a re-evaluation of this understanding of biocompatibility. First, it became clear that the biological response to a given material could vary depending on the site of implantation. Consequently, biocompatibility could not be determined solely by the intrinsic properties of a material but had to be considered in the context of its specific application. Second, an increasing number of medical applications required materials to actively interact with host tissues, rather than remain entirely inert. Third, certain applications necessitated that materials degrade over time within the body instead of remaining there indefinitely. Defining biocompatibility solely as the avoidance of harm was thus no longer appropriate.³ The current edition of ISO 10993-1 defines biocompatibility as *the ability of a medical device or material to perform with an appropriate host response in a specific application*.⁴

This definition positions biocompatibility as a performance-based conceptual framework rather than an intrinsic property of the material used in the construction of the medical device. It is founded on three key principles: a material must actively perform rather than merely exist in the tissues; the host

response it elicits must be appropriate for the intended application; and the nature and suitability of this response may vary with context.³

Although the conceptual definition of biocompatibility remains widely accepted, its practical interpretation continues to evolve. Contemporary biomaterials are increasingly designed not merely to avoid adverse reactions, but to actively modulate biological processes, such as tissue integration, immune signalling, angiogenesis, or controlled biodegradation. Consequently, modern biocompatibility assessments increasingly require consideration of dynamic host-material interactions rather than a simple absence of toxicity.^{3,5,6}

Key considerations for assessing biocompatibility

The biological response to a medical device is influenced by multiple factors, but the two most critical determinants are the invasiveness of contact between the device and the patient and the duration of that contact. These parameters form the foundation for categorizing medical devices for risk assessment and biocompatibility evaluation.

Invasiveness of contact refers to the extent to which a device penetrates or interacts with the body. The potential for adverse biological responses varies according to the tissue type involved, the device's intended function, and the local physiological environment. For example, devices that contact skin may primarily present risks of skin irritation or sensitization, whereas devices that contact circulating blood present additional risks, such as thrombosis or hemolysis. In the latest revision of the ISO 10993-1:2025 standard, several categories of contact have been defined to ensure selection of appropriate testing strategies. These categories include⁴:

- Non-contacting medical devices (for which no biocompatibility evaluation is required),
- Devices in contact with intact skin,
- Devices in contact with intact mucosal membranes,
- Devices in contact with either breached or compromised surfaces (skin or mucosal membranes) or internal tissues other than circulating blood, and
- Devices in contact with circulating blood.

The *duration of contact* is equally important, since the time a device interacts with the body significantly affects the host response. The ISO 10993-1:2025 classifies device contact as limited (≤ 24 hours), prolonged (> 24 hours to 30 days), or long-term (> 30 days).⁴ Devices intended for short-term use generally pose a lower risk of adverse biological effects, whereas devices intended for long-term use require a more comprehensive evaluation.

By integrating these two variables (invasiveness and duration of contact), medical device manufacturers can establish a risk-based biocompatibility testing programme. This systematic approach ensures that each device undergoes a level of biological evaluation commensurate with the potential severity of any adverse effects.

This framework is also reflected in US FDA guidance on the biological evaluation of medical devices.⁷ Table I presents a selected excerpt comparing the recommended biological effects for surface-contacting devices (intact skin, mucosal membranes, and breached or compromised surfaces) and implant devices (in contact with circulating blood). The information in Table I should not be

interpreted as a checklist of tests to be performed for each device category. Rather, it provides a framework for consideration, and additional testing guided by scientific judgment should be undertaken where justified. Readers are referred to the full FDA guidance for further detail.⁷

Table I. Excerpt of biological effects recommended for consideration⁷

Contact Category	Contact type	Contact Duration	Cytotoxicity	Sensitization	Irritation / Intracutaneous reactivity	Acute systemic toxicity	Material-mediated pyrogenicity	Subacute / Subchronic toxicity	Genotoxicity	Implantation	Hemocompatibility	Chronic toxicity	Carcinogenicity	Reproductive / developmental toxicity	Degradation
Surface device	Intact skin	<24 h	X	X	X										
		>24 h –30 d	X	X	X										
		>30 d	X	X	X										
	Mucosal membrane	<24 h	X	X	X										
		>24 h –30 d	X	X	X	X	X	X		X					
		>30 d	X	X	X	X	X	X	X	X		X			
	Breached / compromised surface	<24 h	X	X	X	X									
		>24 h –30 d	X	X	X	X	X	X		X					
		>30 d	X	X	X	X	X	X	X	X		X	X		
Implant	Circulating blood	<24 h	X	X	X	X	X		X	X	X				
		>24 h –30 d	X	X	X	X	X	X	X	X	X				
		>30 d	X	X	X	X	X	X	X	X	X	X	X		

X = biological effects for which testing should be considered. All relevant effects should be addressed in the biological evaluation using existing data, additional testing, or a scientific rationale for omission.

It is important to recognize that while this categorisation provides a practical framework for biological evaluation, it necessarily simplifies highly complex biological interactions. Devices with similar invasiveness or duration of contact may evoke substantially different biological responses depending on material chemistry, surface characteristics, degradation, mechanical stress, or patient-specific factors. Therefore, biological evaluation requires scientific judgment that goes beyond categorical classification.

Biocompatibility testing: chemical characterisation and biological endpoint tests

The evaluation of medical device biocompatibility begins with an understanding of its chemical composition. A *chemical characterisation programme* provides the foundation for identifying substances that may be released from the device during clinical use. This is supplemented by testing for specific biological effects, which assess the physiological or toxicological effects that could arise either from exposure to released substances or from the presence of the device itself. Taken together, these activities enable manufacturers to establish a comprehensive, risk-based biocompatibility evaluation.

Chemical characterisation aims to identify and quantify the extractable and leachable substances present in a medical device under conditions that simulate clinical exposure. These substances may originate from the raw materials of the device, manufacturing additives, processing aids, residues from sterilisation, or degradation products. Techniques such as gas chromatography-mass spectrometry (GC-MS), liquid chromatography-mass spectrometry (LC-MS), and inductively coupled plasma-mass spectrometry (ICP-MS) are commonly employed for the detection and quantification of organic and inorganic compounds. The chemical profile obtained from these experiments enables toxicologists to evaluate potential risks by comparing exposure estimates with known toxicological thresholds. If chemical data demonstrate that all extractables are below relevant toxicological thresholds, further evaluation is often limited to targeted biological testing. Conversely, where data gaps or substances of concern are identified, additional testing may be required to fully characterise the biological response. Consequently, a meaningful biological evaluation requires careful integration of analytical chemistry, exposure assessment, and toxicological risk assessment.^{8,9}

The emphasis on chemical characterisation reflects a broader regulatory transition towards toxicological risk assessment and reduction of unnecessary animal testing. Modern analytical techniques can detect extremely small quantities of chemical constituents, but the toxicological significance of many of these compounds cannot always be readily determined because interpretation is often complicated by unidentified compounds, complex mixtures, ultra-trace extractables, and degradation products formed during clinical use.

In the frameworks prescribed in ISO 10993-1:2025, biological evaluation requires consideration of various biological effects based on the invasiveness and duration of contact. Common tests for relevant biological effects include:

- **Cytotoxicity:** Cytotoxicity is an initial in vitro screen for potential adverse biological effects associated with a medical device. This endpoint applies to devices with direct or indirect contact with the body, irrespective of contact duration, and is therefore broadly assessed across all device categories.⁴
- **Sensitization and irritation:** Devices that make contact with the body are evaluated for their potential to induce sensitization through exposure to allergenic constituents, as well as irritation arising from chemical or physical interactions such as surface contact or particulate release. This assessment generally applies to all devices regardless of contact duration.⁴
- **Systemic toxicity:** Devices capable of introducing constituents or particulates into the systemic circulation, lymphatic system, or cerebrospinal fluid may require evaluation for systemic toxicity, to assess potential effects on organs and tissues throughout the body. The depth of evaluation is linked to exposure duration, with more extensive testing typically required for prolonged or long-term contact (acute, sub-acute, sub-chronic, or chronic exposure scenarios).⁴

- **Local effects after tissue contact:** Devices that come into direct contact with specific tissues or organs are assessed for potential local tissue responses, including effects arising from particulate release. The extent of evaluation depends on contact duration, with more comprehensive assessment required for prolonged or long-term use. In general, such testing is not required for devices contacting only intact skin or those with limited-duration exposure, unless additional risk factors are present. Where appropriate, implantation studies may be used to characterise local tissue responses and support related assessments such as systemic toxicity or hemocompatibility⁴
- **Genotoxicity:** Genotoxicity assessment is used to determine whether device constituents may induce genetic damage. The need for this test depends on both nature and duration of contact. In general, testing is not required for devices contacting only intact skin or for limited-duration exposure to tissues, with exceptions for implantable or extracorporeal blood-contacting devices. However, where materials of concern are present or other risk factors apply, additional assessment is warranted. Devices with prolonged or long-term tissue or blood contact typically require genotoxicity evaluation to ensure that exposure does not result in genetic damage or downstream adverse outcomes.⁴
- **Carcinogenicity:** Carcinogenicity assessment is considered where there is concern for either genotoxic mechanisms (e.g., DNA-reactive substances) or non-genotoxic pathways such as chronic inflammation or sustained proliferative responses. Routine carcinogenicity testing is generally not required for devices contacting only intact skin but may be indicated for long-term tissue or blood-contacting devices. Given the limited predictive value and resource intensity of traditional in vivo studies, evaluation is usually based on chemical characterisation and toxicological risk assessment. Identified carcinogens are addressed within the overall biological risk assessment regardless of contact type or duration.⁴
- **Hemocompatibility:** Devices in contact with circulating blood, whether directly or indirectly, require evaluation for hemocompatibility due to the potential for effects such as haemolysis or thrombosis. This assessment considers both chemical composition and surface properties that may influence blood–material interactions and flow behaviour. Integration of chemical and physical characteristics is therefore essential within the overall biological risk evaluation for blood-contacting devices.⁴

Not all biological effects are relevant for every device. The selection of appropriate tests must be supported by a clear scientific rationale grounded in the intended use of the device, anatomical location, exposure duration, and chemical profile. For instance, a surface-contacting device making limited-duration contact with intact skin will only require evaluation of cytotoxicity, irritation, and sensitization, whereas a long-term intravascular implant would necessitate a comprehensive assessment of systemic toxicity, hemocompatibility, and implantation effects (Table 1).

The integration of chemical characterisation and biological testing allows for a rational and risk-proportionate approach to biocompatibility evaluation. This ensures that testing is driven by scientific evidence and biological plausibility, rather than prescriptive or redundant requirements. Together, these steps form a bridge between material chemistry, biological safety, and clinical performance.

Risk-based biocompatibility assessment

Biocompatibility testing is undertaken to ensure that a device performs its intended function without causing unacceptable biological effects. Modern regulatory frameworks, particularly those defined by ISO 10993-1:2025 and the complementary guidance documents separately issued by other regulatory agencies, emphasize that the biocompatibility evaluation must be conducted using a risk-based approach rooted in scientific rationale and risk assessment principles.^{4,7}

A risk-based approach begins with the creation of a *biological evaluation plan*, which identifies the relevant biological risks associated with a device based on its invasiveness of contact and duration of exposure, as outlined above. The evaluation must consider the material composition of the device/packaging, its manufacturing processes, sterilization methods, and potential for chemical release or degradation under conditions of use. The chemical characterisation of the device provides the foundation for assessing toxicological risk. Only where the available data are insufficient to characterise the risk should additional *in vivo* testing be undertaken. In practice, this means that testing is not performed by default but rather justified based on evidence and scientific reasoning. For example, if extractables and leachables studies demonstrate that all potential chemical constituents of a device are below toxicologically relevant thresholds, additional long-term systemic toxicity tests may not be necessary. Conversely, if the chemical data reveal substances of concern or information gaps, further biological testing becomes warranted.

The risk-based framework integrates biocompatibility assessment within the broader context of risk management for medical devices.^{4,7} Biological evaluation is not a stand-alone exercise but part of an iterative process that identifies hazards, estimates and evaluates associated risks, and implements control measures throughout the lifecycle of the medical device. The outcome of this process is documented in a *biological evaluation report*, which provides the rationale for all testing decisions and conclusions on the overall biological safety of the device.

Ultimately, the risk-based paradigm promotes scientific efficiency and animal welfare, aligning with the 3R principles of replacement, reduction, and refinement in animal testing. By focusing on material characterisation and data integration, modern biocompatibility evaluations move away from a prescriptive testing paradigm and instead focus on a predictive assessment of biological safety.

Concluding remarks, challenges, and trends

Biocompatibility evaluation remains a central component of medical device safety assessment. Over the past several decades, the concept has evolved from a relatively simple focus on biological inertness toward a comprehensive, context-dependent evaluation of the interactions between medical devices and the host environment. It should not be understood as a fixed property of a material, but rather as the outcome of a dynamic interaction between the medical device and the biological system in which it is used.

In the assessment of biocompatibility, contemporary regulatory frameworks emphasize risk-based testing strategies that integrate chemical characterisation, toxicological evaluation, testing for biological effects, and scientific justification within an overall risk management process. As medical technologies continue to evolve, biological evaluation frameworks will likewise require continuous refinement to ensure that innovation proceeds alongside strong assurance of patient safety. Scientific judgment will always remain essential in this process, particularly since biological responses are influenced by complex interactions among material composition, device design, tissue environment,

and the duration of exposure.

A cornerstone of biocompatibility assessment is chemical characterisation, alongside computational toxicology and integrated risk assessment strategies. However, the increasing complexity of innovative medical devices presents new challenges for a comprehensive evaluation. Emerging technologies such as bioresorbable materials, nanostructured surfaces, and patient-specific implants may exhibit biological behaviours that are not always fully captured by existing testing paradigms. In parallel, advances in mass spectrometry have significantly improved the sensitivity of analytical detection, enabling the identification of increasingly small quantities of extractable and leachable substances. However, this enhanced sensitivity is not always matched by toxicological interpretability. Chemical profiles frequently include unidentified compounds, mixtures of poorly characterised constituents, or substances for which toxicological data are limited, absent, or derived from non-comparable exposure contexts. As a result, the toxicological significance of such findings cannot always be reliably established, which may reduce the overall confidence in exposure-based risk assessments and, in some cases, limit the ability of the chemical characterisation programme to fully support biological safety evaluation.

Despite these challenges, the evolution of biocompatibility assessment reflects a clear transition toward more rational, predictive, and evidence-based evaluation strategies. The integration of chemical, biological, and computational approaches within a risk management framework has significantly improved the scientific robustness of medical device safety assessment. Continued methodological development, combined with informed scientific judgment, will remain essential to ensure that biocompatibility evaluation keeps pace with technological innovation while maintaining a high level of patient safety assurance.

Next in this series: chemical characterisation and toxicology

The biological response to a medical device is strongly influenced by its chemical composition. Chemical substances, including residual monomers, additives, processing aids used during manufacture, and degradation products, represent the primary contributors to adverse biological effects. Consequently, chemical characterisation of extractable and leachable substances forms a cornerstone of biocompatibility assessment, requiring potentially hazardous compounds to be identified, quantified, and evaluated prior to, or in parallel with, biological endpoint testing.

In the next article of this series, we will discuss methodologies used to characterise chemical substances that are extracted from, or leach from, medical devices. This will include solvent extraction, mass spectrometry techniques, and the subsequent toxicological evaluation used to contextualise these findings within a risk-based framework. Understanding the chemical composition of a device is essential for anticipating host responses, guiding in vitro and in vivo testing strategies, and ensuring that medical devices perform safely in their intended clinical applications.

Supplementary Materials: None.

Author Contributions: Sole author.

Funding: None.

Acknowledgments: None.

Conflicts of Interest: The author declares no conflicts of interest.

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Article

Ink to Infrastructure: Uncovering Newspaper Sentiments on India's PMGSY Rural Road Infrastructure Program

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Abstract: The Pradhan Mantri Gram Sadak Yojana (PMGSY), launched in 2000, represents one of India's most ambitious rural infrastructure efforts, aiming to connect eligible villages with durable, all-weather roads. Drawing on 14 Factiva export files from the same search/download sequence of English-language newspaper coverage, this study analyzes 968 outlet-attributed articles after text extraction, de-duplication, and source classification. VADER sentiment analysis is used to quantify media framing over time, across outlets, across state-linked city editions, and around a 2015 reform period. The results indicate generally positive English-language press sentiment toward PMGSY, substantial outlet-level and state-linked variations, weak spatial clustering, and no robust evidence that national ruling-party affiliation or BJP-governed state status systematically shifted coverage tone. The analysis therefore contributes to the framing of governmental infrastructure programs while also emphasizing that the English-language print media capture elite media discourse, not the full range of rural or regional-language public opinions.

Keywords: Sentiment Analysis; Media Framing; Infrastructure; India; Spatial Autocorrelation; Political Economy; Public Policy.

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Citation: Armen B.;
Awareness, 3 (2): 103-120



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Introduction

The Pradhan Mantri Gram Sadak Yojana (PMGSY) emerged in December 2000 as a landmark central government initiative to address India's pervasive rural road deficit. Prior to PMGSY's rollout, nearly half of India's 600,000 villages lacked reliable all-weather connectivity, particularly during monsoon seasons when unpaved roads became impassable. Policymakers allocated nearly ₹60,000 crores (~US \$20 billion) across central and state budgets to construct more than 180,000 kilometers of rural roads by 2020. This required extensive coordination among the Ministry of Rural Development, state public works departments, district authorities, and local Gram Panchayats,

which are India's local village governments, leading to an extremely complex delivery of new infrastructure.

Existing research generally finds substantial benefits from rural road construction, ranging from poverty alleviation to improved health outcomes^{1,5,16}. While infrastructure projects often navigate complex political realities and corruption¹⁷, Asher and Novosad³ offer one of the most rigorous causal evaluations of PMGSY's economic impact, employing a difference-in-differences strategy on matched habitations. They report that within three years of road completion, connected villages exhibit meaningful improvements in agricultural outcomes, primarily driven by lower transport costs and reduced travel times. Datta⁹ extends the impact narrative by analyzing PMGSY's effect on nonfarm employment and informal enterprise performance, showing that rural road density can reduce transport costs, elevate non-farm employment, and increase rural wages. Binswanger, Khandker, and Rosenzweig⁶ provide a theoretical foundation by conceptualizing rural roads as public goods that reduce transaction costs, enhance information flows, and catalyze private investment. Government sources, including the Ministry of Rural Development's Basic Road Statistics of India¹¹ and the PMGSY Annual Progress Report²⁰, document road length, quality, maintenance cycles, and implementation milestones. Yet these sources largely examine delivery and socioeconomic effects rather than the public narratives through which PMGSY is presented. This creates an important gap: media coverage can frame infrastructure as technical achievement, political credit-claiming, local development, corruption risk, or administrative delay. A systematic analysis of press sentiment therefore complements the existing impact-evaluation literature by showing how PMGSY is represented in elite public discourse.

Entman's framing theory¹⁰ delineates four core frame elements—problem definition, causal interpretation, moral evaluation, and treatment recommendation—through which media narratives shape audience perceptions. In social-policy domains, human-interest and conflict frames often outcompete technical frames in audience salience^{8,23}, a dynamic particularly evident in India's highly competitive, multilingual press environment^{19,25}. No prior study applies framing theory to PMGSY coverage, leaving questions unanswered about how narratives emphasizing developmental benefits versus bureaucratic challenges have evolved. As a result, three gaps become evident. *First*, rigorous impact evaluations confirm PMGSY's economic and social returns but do not examine how media narratives may influence program legitimacy and public buy-in. *Second*, institutional reviews highlight administrative lessons but omit systematic press analysis. *Third*, theoretical framing models remain largely untested on PMGSY's national and city-edition coverage.

This study addresses those gaps through three research questions: (RQ1) How has English-language media sentiment toward PMGSY changed since the program's inception? (RQ2) How do Times of India city editions compare with national newspapers in coverage tone? (RQ3) Is sentiment associated with national ruling-party control or with a post-2015 reform-period shift in BJP-governed states? By answering these questions, the study provides an empirical examination of PMGSY's media portrayal while clarifying the limits of English-language print media as evidence of broader public sentiment.

Materials and Methods

The empirical foundation of this study is a reproducible text-analysis pipeline, consistent with text-as-data research practices, that transforms Factiva PDF export files into an analyzable corpus of PMGSY news articles¹². The analysis begins with 14 Factiva PDF export files from the same underlying search/download sequence, containing English-language newspaper coverage. Because Factiva search-summary fields record search hits rather than the final analyzable corpus, the article count is reported through an explicit attrition funnel: 1,539 raw article segments were extracted, 18 duplicates were removed, and 968 articles remained after unmatched outlets were dropped (Figure 1).

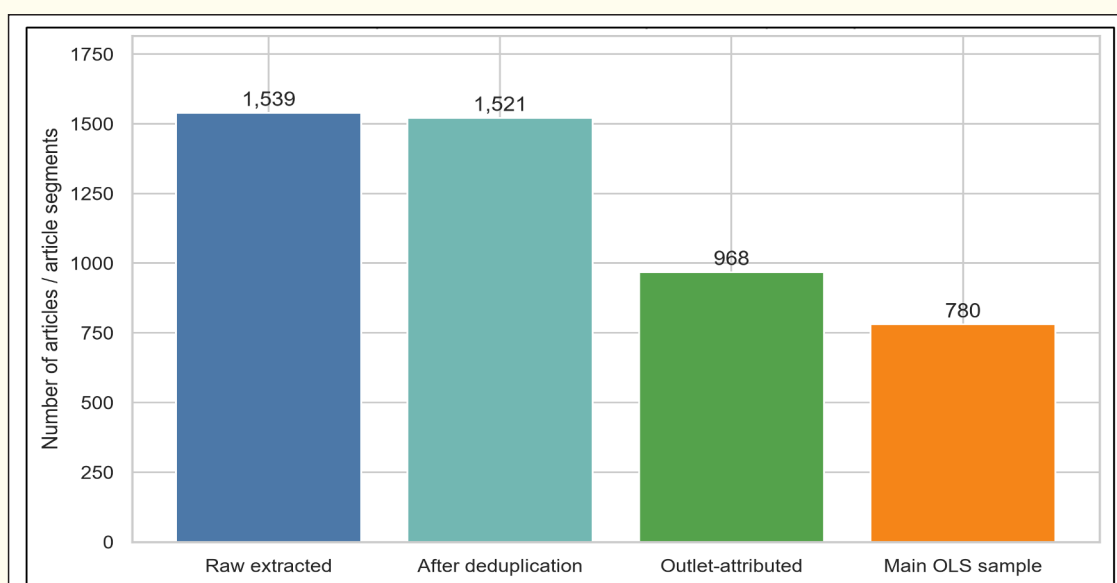


Figure 1: Corpus Attrition from Factiva Exports to Analysis Samples.

Note: The analyzed corpus is the outlet-attributed sample after extraction, deduplication, and source classification.

This distinction is important because search hits, downloaded PDFs, extractable article segments, deduplicated records, and outlet-attributed articles are not the same quantity. The text extraction process reads PDF text, segments article-length passages using Factiva-style boundaries, assigns outlet labels from source identifiers, parses article dates, and retains a short excerpt of article text for auditability, using standard text-processing and tabular-data tools^{7,18}. Articles whose outlet could not be identified are excluded from outlet-level and regression analyses. This approach preserves the substantive logic of the original data collection while making the final analyzed number of articles (N) transparent and reproducible.

Sentiment analysis serves as the baseline for all subsequent analysis and uses VADER (Valence Aware Dictionary and sEntiment Reasoner), a rule-based lexicon model designed to score text along positive, negative, neutral, and composite sentiment dimensions^{4,14,24}. The composite score is a normalized weighted measure that ranges from -1 (most negative) to +1 (most positive), and it is the primary dependent variable in this study. VADER is useful for this project because it provides a transparent, replicable measure of polarity across a large text corpus. At the same time, its limitations are important: lexicon-based models can miss sarcasm, context-specific political meanings, regional idioms, and issue-specific frames in Indian media. For that reason, the results are

interpreted as measured tone in English-language newspaper text rather than as direct evidence of public opinion. The article-level dataset includes the article date, identified newspaper outlet or city edition, sentiment scores, state mapping where available, national ruling-party period, and a short article excerpt used for verification. For visual displays, sparse TOI city editions are treated consistently: TOI-Ahmedabad ($n=1$), TOI-Bangalore ($n=3$), and other very low-count editions are retained in article-count summaries but excluded from distribution or trend figures that require minimum support.

Statistical Analysis

The statistical analysis combines descriptive visualization, spatial analysis, and regression models. State-level averages are calculated from mapped TOI city editions and visualized alongside a Moran's I statistic to assess whether neighboring states show similar average sentiment^{2,13,15,21}. The core regression is estimated using OLS with cluster-robust standard errors grouped by newspaper outlet²²; the dependent variable is the VADER compound sentiment score, and the model includes newspaper edition and year fixed effects alongside ruling-party period. OLS is used as a descriptive linear summary, not as a claim that sentiment scores are normally distributed. Because the VADER compound score is bounded and skewed, the analysis reports distributional diagnostics and an asinh-transformed robustness check. Multicollinearity is assessed using variance inflation factors and condition-number diagnostics. These diagnostics are central to the interpretation: the fully saturated model contains substantial collinearity between ruling-party period and year fixed effects, so parsimonious no-party and no-year specifications serve as robustness checks. Coverage-intensity analyses test whether state-year article counts predict mean sentiment. A difference-in-differences analysis around the March 2015 reform date compares post-reform changes in BJP-governed states with other mapped states. Since treatment status is time-invariant within state, and TOI city editions map one-to-one onto states in this corpus, the stand-alone treatment indicator is omitted when state or newspaper fixed effects are included; only post-reform timing and the post-by-treatment interaction are identified. Event-study diagnostics assess pre-period support and parallel-trends limitations.

The corpus provenance deserves particular emphasis because it affects the interpretation of every empirical result. Factiva's search interface reports search-hit metadata, but those hits are not the same as articles that can be extracted, segmented, deduplicated, attributed to an outlet, and linked to a valid date. Treating search hits as the analyzed corpus would overstate the empirical base and make the regression sample appear larger than it is. The revised manuscript therefore distinguishes between raw search/export metadata and the final analytic sample. This distinction is not merely technical; it clarifies the scope of inference. The study can speak to the tone of articles that were successfully extracted and attributed to English-language outlets, but it cannot claim to represent all PMGSY-related search hits, all Indian media coverage, or all public discourse around rural roads.

The decision to retain OLS as the main modeling strategy is also interpretive rather than mechanical. The VADER compound score is bounded between -1 and $+1$ and is not normally distributed, so the model should not be read as a perfect data-generating process for sentiment. Instead, it is used as a transparent summary of conditional mean differences across party periods, outlets, and years. In a sample of this size, non-normality of the dependent variable is less damaging for estimating average linear associations than it would be for small-sample inference, especially when the manuscript is careful not to overclaim causality; this follows standard large-sample treatments of OLS inference²⁶. The distributional diagnostics and asinh robustness check are reported so readers can evaluate how much weight to place on the linear specification.

The difference-in-differences design is included because the 2015 reform period provides a useful temporal benchmark, but the design is deliberately framed as a diagnostic comparison rather than a standalone causal proof. Treatment is defined at the state level as BJP governance at the reform date, while the observable media units are state-linked TOI city editions. That structure creates two important constraints. First, the standalone treatment indicator is collinear with state fixed effects and also with city-edition fixed effects in this sample. Second, the number of treated state-year cells is limited. The revised analysis therefore drops the collinear treatment main effect, reports the full post-by-treatment estimate, and uses event-study support tables to show where the identifying variation is thin.

Results

Guided by the research questions introduced above, the results first describe broad patterns in PMGSY coverage across outlets and city editions. Across the 968 outlet-attributed articles, coverage is generally positive, although the degree of positivity varies substantially by outlet and state-linked edition (Figures 2, 4, and 5). Among mapped states, Delhi has the highest mean sentiment (0.768,

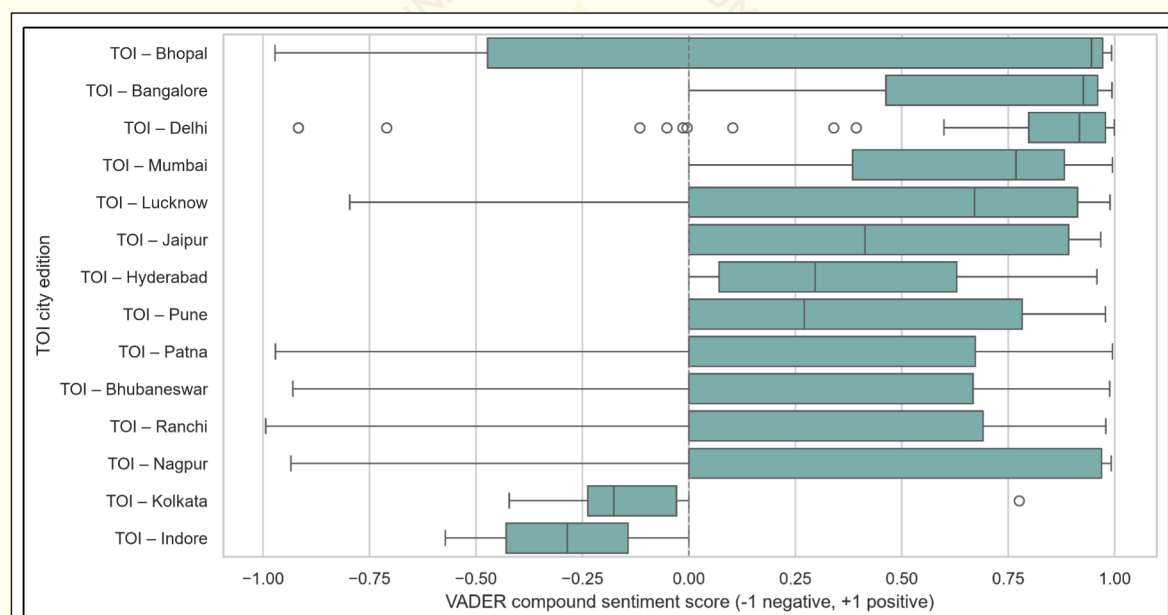


Figure 2: Sentiment Distribution by Times of India City Edition

Note: The x-axis reports the VADER compound sentiment score, ranging from -1 (negative) to +1 (positive).

$n = 83$), followed by Karnataka-linked Bangalore coverage (0.640, $n = 3$), Rajasthan (0.443, $n = 14$), and Uttar Pradesh (0.387, $n = 48$). These rankings reconcile the earlier inconsistency between the text and choropleth: Delhi is the clearest high-sentiment case, while Karnataka is high but based on very few articles and therefore should not be overinterpreted. The revised figures label the y-axis as the VADER compound sentiment score rather than the internal variable name. The TOI time-series display is also revised as annual small multiples to reduce visual clutter and make edition-specific patterns easier to compare (Figure 3).

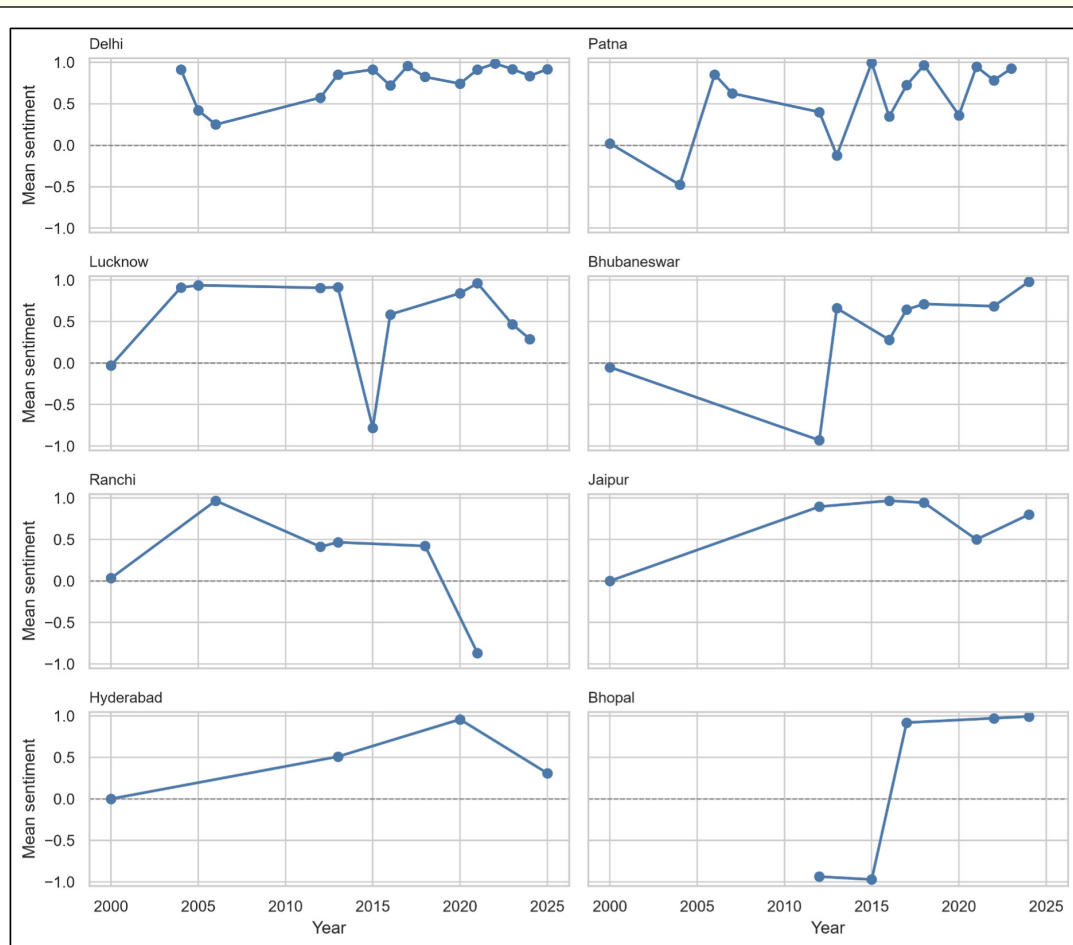


Figure 3. Annual Mean PMGSY Sentiment by TOI City Edition

Note: Small multiples replace the original cluttered multi-line display.

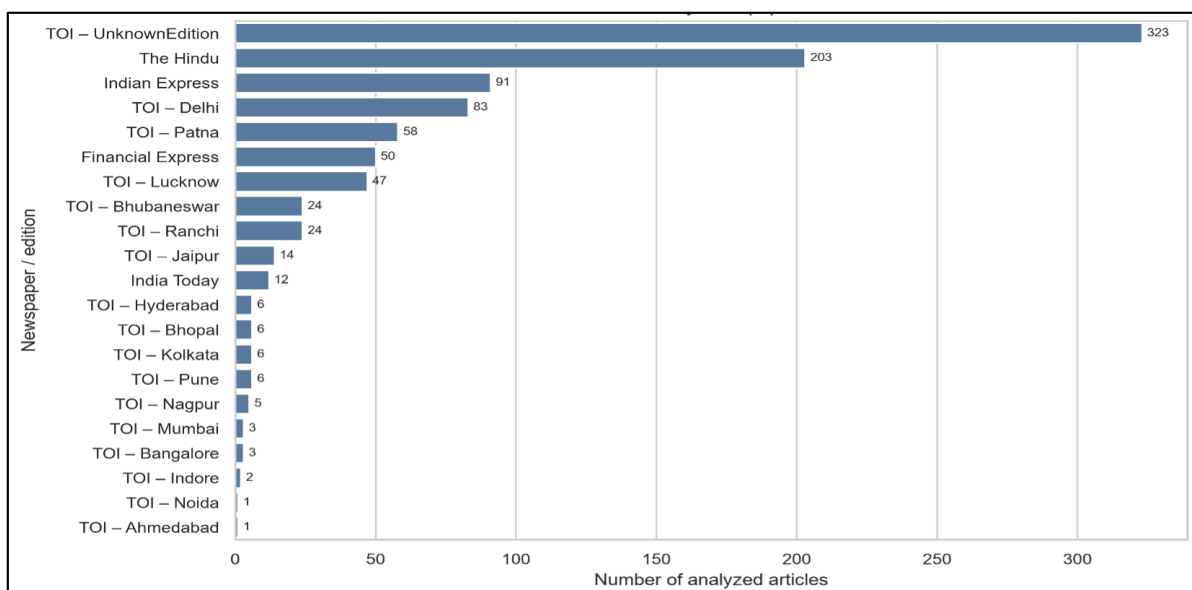


Figure 4. Article Counts by Newspaper / Edition

Note: Counts reflect outlet-attributed articles in the analyzed corpus.

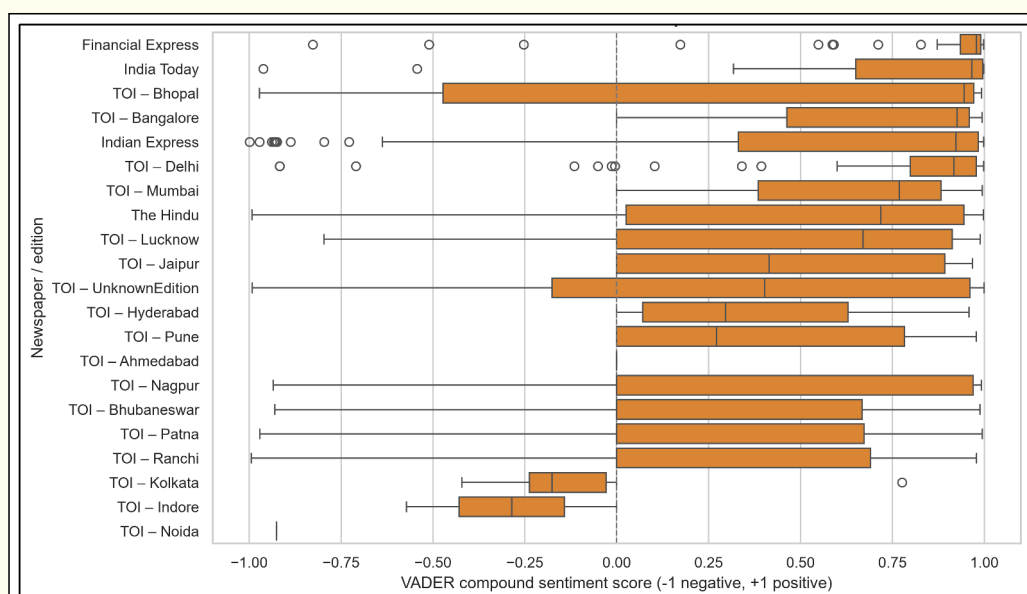


Figure 5. Sentiment Distribution by Outlet

Note: Outlet comparisons are descriptive and should be interpreted with sparse-cell cautions.

Turning to party-period patterns, descriptive statistics show that sentiment remains positive under both INC and BJP national governments (Figure 6). The main OLS regression, estimated with cluster-robust standard errors by newspaper, has $N = 780$, $R^2 = 0.090$, and adjusted $R^2 = 0.050$. The coefficient for INC rule relative to BJP rule is positive but not statistically significant (coefficient = 0.066, $p = 0.691$). These results do not support a strong partisan interpretation. The low explanatory power is also not presented as evidence that outlet and temporal factors dominate sentiment; instead, it suggests that much of the article-level variation likely lies in unobserved characteristics such as topic, journalist identity, geographic specificity, local implementation context, or whether a story emphasizes benefits, delays, corruption, funding, or human-interest narratives. Diagnostics reinforce this caution. The fully saturated model has a very high condition number because ruling-party period is highly collinear with year fixed effects. The VIF diagnostics identify the INC period indicator as the largest source of collinearity ($VIF = 17.34$), while no-party and no-year robustness specifications are much better conditioned. Thus, the political-period results are best understood as descriptive evidence against a large partisan shift, not as definitive proof that party context is irrelevant.

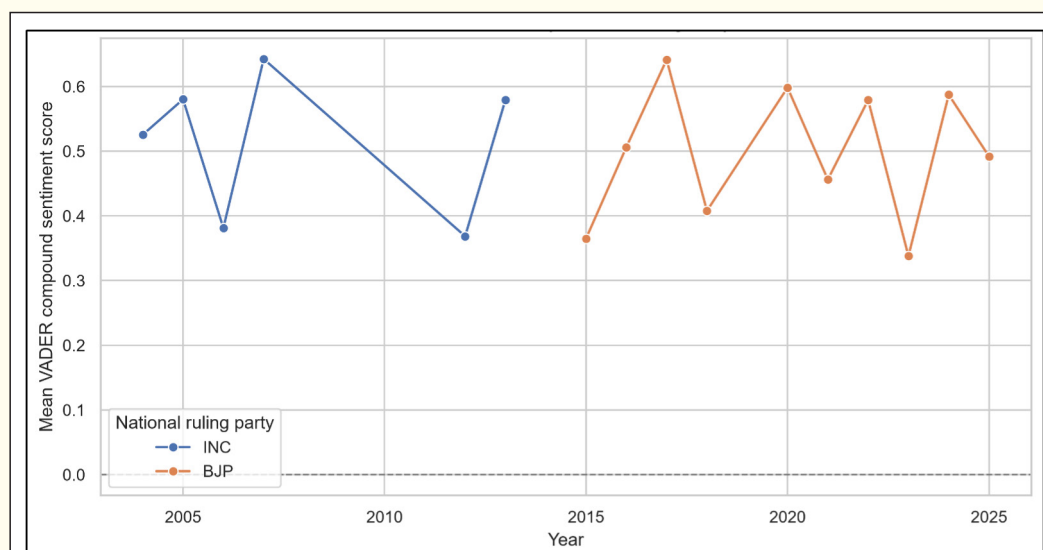


Figure 6. Annual Sentiment by National Ruling-Party Period

Note: The trend is descriptive; the regression model does not identify a reliable party effect.

Geography adds further nuance to PMGSY coverage, but the spatial findings are modest. The revised state sentiment figure identifies Delhi, Karnataka, Rajasthan, and Uttar Pradesh as the highest observed state-linked averages, with explicit small-*n* caution for Karnataka and Gujarat (Figure 7). Moran's *I* is positive (0.112 across 11 shapefile-matched states), suggesting weak spatial similarity in neighboring state sentiment, but the finding is substantively limited. The state sentiment table contains 12 states; Telangana is excluded from Moran's *I* because it does not match the state-boundary shapefile used to construct spatial weights. The spatial weights matrix is sparse because the corpus maps only a limited set of TOI city editions to states, and the analysis does not include regional-language coverage that would better represent rural audiences.

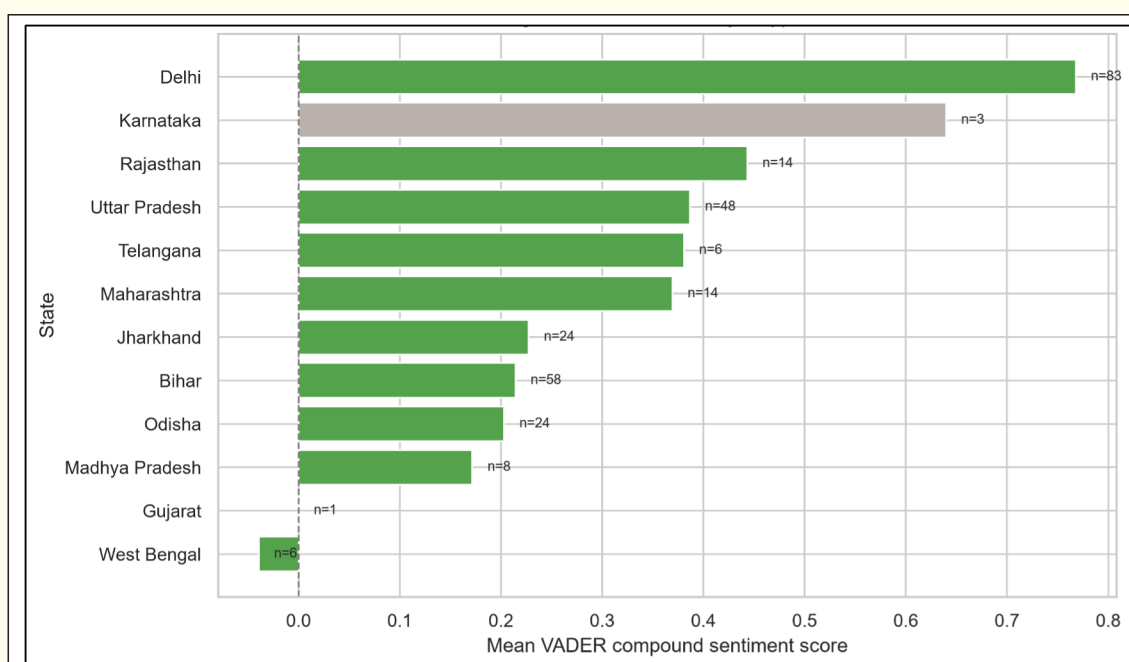


Figure 7. Average PMGSY Sentiment by Mapped State

Note: Small-*n* states are marked in the figure and interpreted cautiously.

The difference-in-differences analysis around the March 2015 reform date also counsels caution (Figures 8 and 9). The treatment group is defined as mapped TOI state editions located in BJP-governed states at the reform date, with other mapped states serving as controls. In the primary state-fixed-effects model, the post-reform coefficient is positive, but the post-by-treatment interaction is near zero and not statistically significant (coefficient = 0.008, $p = 0.977$; $N = 289$). The model's condition number is 19.94 after dropping the collinear standalone treatment term. The newspaper fixed-effects sensitivity specification applies the same logic because city editions map to states and therefore also absorb the state-level treatment indicator. The event-study check is estimated on state-year collapsed data because sparse cells make a saturated state-fixed-effects event study unreliable at this sample size. After filtering sparse relative years, the event-study model is well-conditioned (condition number = 6.41), and no pre-treatment interaction is statistically significant at $p < 0.05$. Nevertheless, the limited number of treated observations means that the DiD should be interpreted as a descriptive reform-period comparison rather than as strong causal evidence of partisan influence.

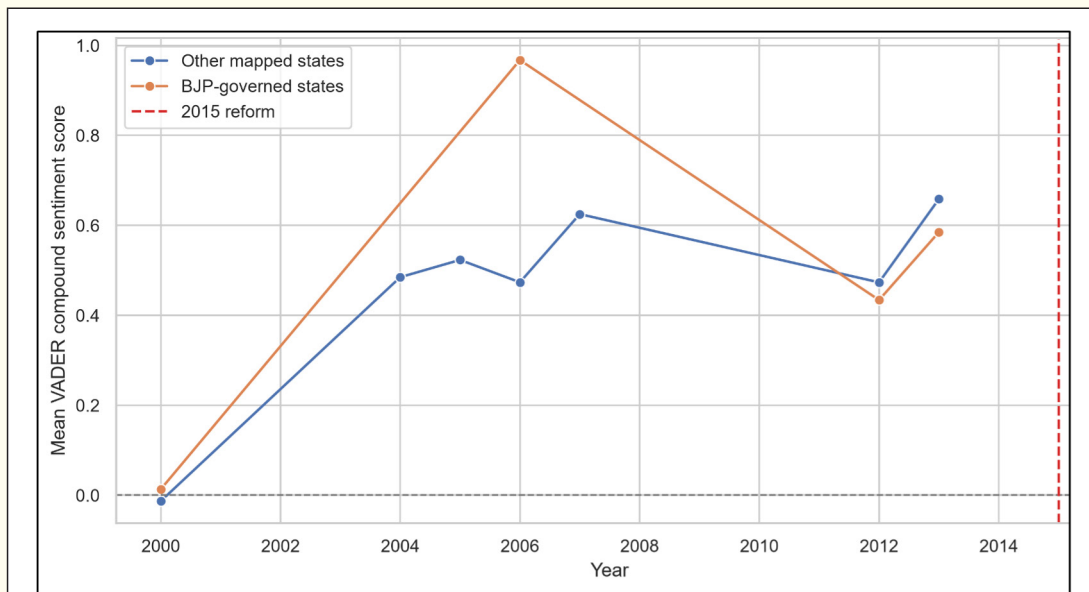


Figure 8. Pre-Reform Parallel Trends Check

Note: Treatment is BJP-governed state in March 2015; sparse cells limit causal claims.

The substantive implication of the DiD results is therefore modest but still useful. The absence of a significant post-by-treatment interaction suggests that the 2015 reform period did not produce a clear differential shift in English-language PMGSY sentiment for BJP-governed states relative to the available controls. This does not mean that party politics played no role in program publicity, credit-claiming, or implementation. Rather, it means that the available English-language newspaper corpus does not provide strong evidence of a differential sentiment shift at the state-edition level. That distinction is important because it narrows the claim from ‘partisanship does not matter’ to the more defensible conclusion that broad sentiment in this corpus is not well explained by the party-period variables tested here.

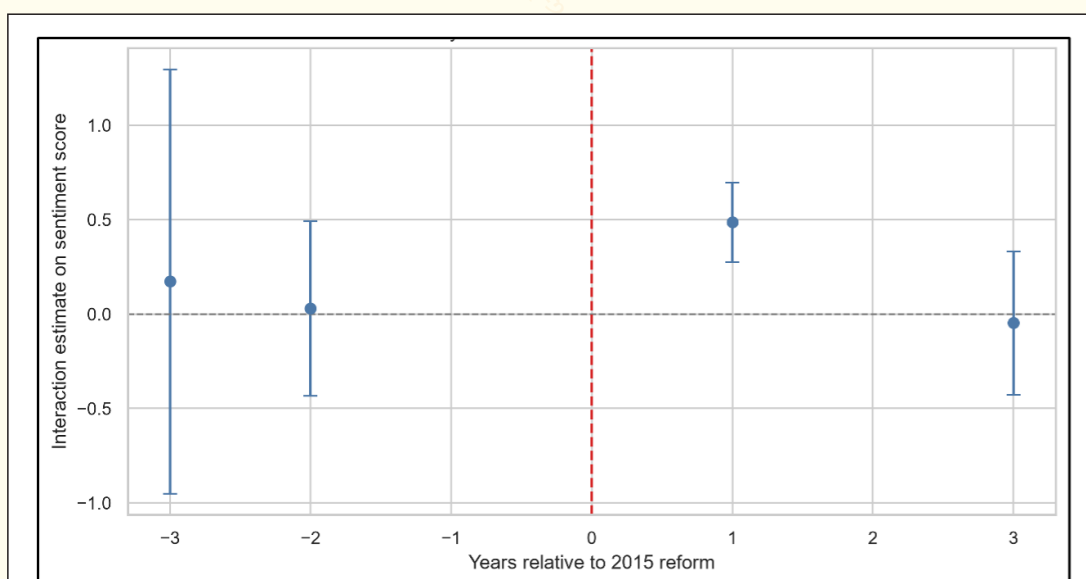
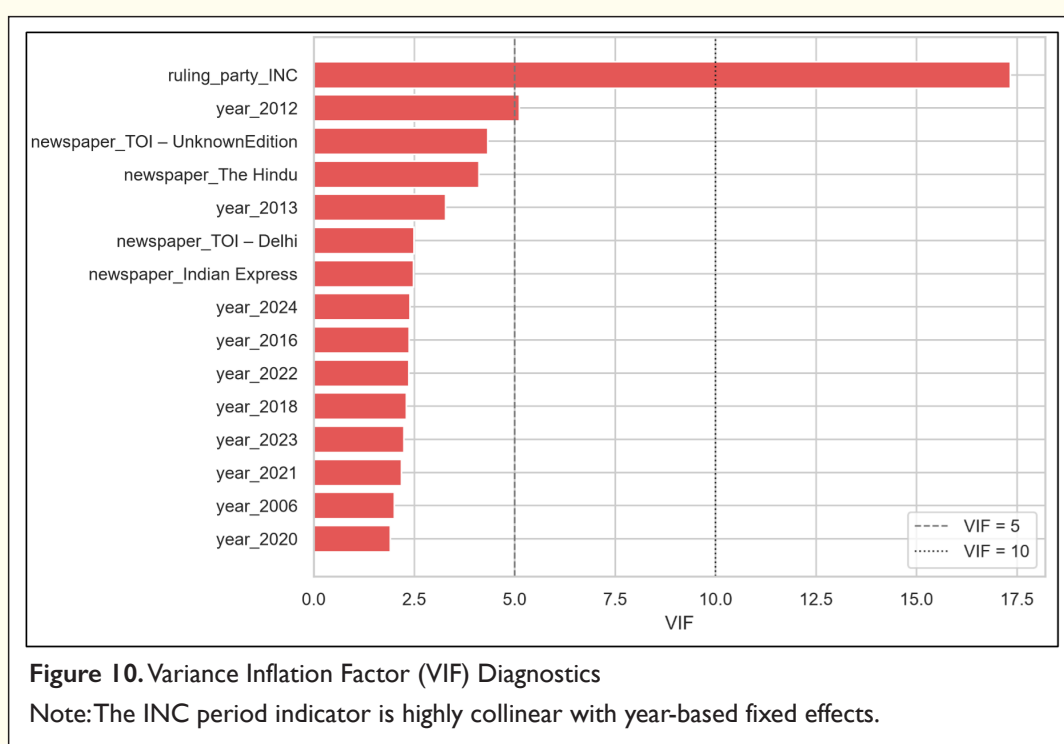


Figure 9. Event-Study Coefficients

Note: Estimates use state-year collapsed data after sparse-cell filtering.

Figure 7 shows why Karnataka should not be described as a major high-sentiment case without mentioning its small article count. The revised exhibits are designed to make those constraints visible. Figures 8 and 9 show that the DiD design has limited support in some relative years. These visual changes are not cosmetic; they align the empirical presentation with the scope of the data. Figure 10 shows why the fully saturated ruling-party model must be interpreted cautiously. A reviewer should now be able to see not only the substantive patterns, but also the diagnostic evidence that qualifies those patterns. The coverage-intensity analysis also offers no support for a volume-drives-tone interpretation (Figure 11). A regression of state-year mean sentiment on log article count is statistically insignificant ($p = 0.742$, $R^2 = 0.002$), so the negative coefficient carries no substantive interpretive weight. In short, neither geography nor article volume overturns the broader finding of generally positive but heterogeneous English-language coverage.



At the same time, the absence of strong partisan effects should not be mistaken for the absence of politics in infrastructure communication. PMGSY is a centrally sponsored pro-gram implemented through state and local institutions, so political incentives may operate through funding announcements, project selection, ribbon-cutting events, and local credit-claiming rather than through a simple shift in article sentiment after one national reform date. The present data are better suited to detecting broad tonal patterns than to identifying those micro-level mechanisms. For this reason, the revised discussion treats partisanship as one possible source of framing variation but not as the only one or even the dominant one.

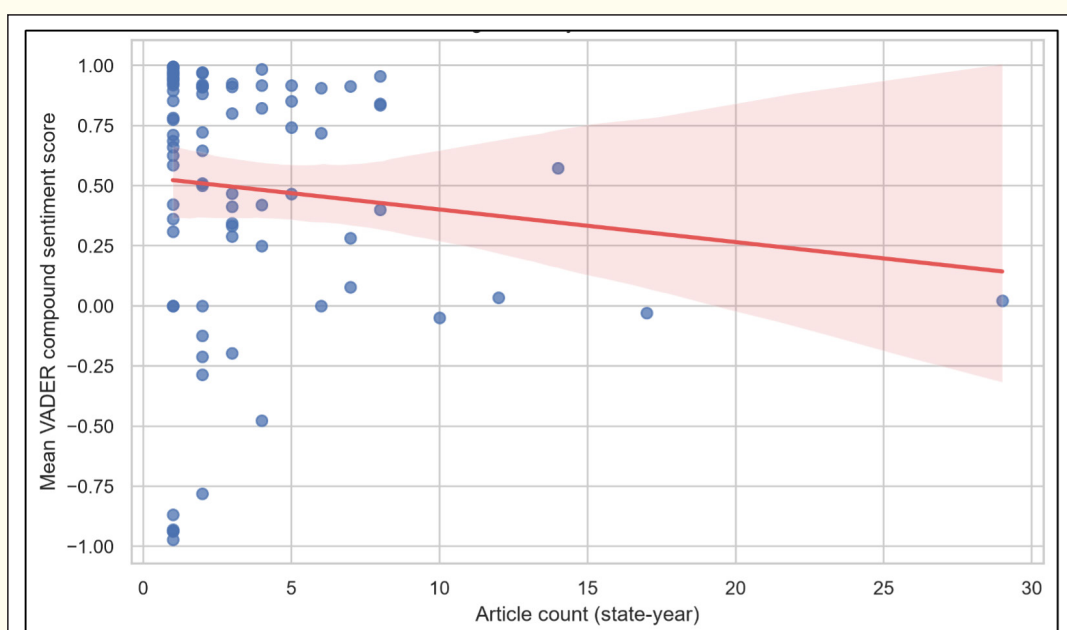


Figure 11. Coverage Intensity and Mean Sentiment

Note: The article-count coefficient is not statistically significant, so the sign is not interpreted.

Discussion

This is the first analysis to demonstrate that the English-language print coverage of PMGSY has generally been favorable, but the revised evidence supports a more cautious interpretation. Positive sentiment is visible across outlets, city editions, and time, yet the regression models explain only a modest share of article-level variation and do not show a robust partisan effect. This suggests that PMGSY was often framed as a development and implementation story rather than as a straightforward party-political story. That finding is substantively important because it shows how large infrastructure programs can receive favorable elite-media coverage even when their delivery depends on complex intergovernmental coordination. At the same time, the models indicate that article-level content—such as whether a story emphasizes beneficiaries, delays, corruption, funding, road access, or local economic outcomes—likely matters more than the broad political variables available in this dataset. The broader implication is not that infrastructure coverage is apolitical, but that party labels alone do not explain how PMGSY is narrated in English-language print media.

This study has several limitations that should be foregrounded. First, the exclusive focus on English-language print media omits vernacular newspapers, regional-language television, radio, and digital platforms that reach much larger shares of rural India. Because PMGSY's beneficiaries are overwhelmingly rural and often Hindi- or regional-language-speaking, the positive sentiment identified here may reflect elite urban media framing rather than broader public sentiment. Second, the final analyzed corpus contains 968 outlet-attributed articles, not the larger raw search-hit figure sometimes reported by Factiva exports. This distinction matters because search hits, downloads, PDF extraction, deduplication, and outlet attribution all reduce the analyzable corpus. Third, VADER is transparent and replicable but cannot fully capture sarcasm, regional idioms, or issue-specific frames in Indian media. Fourth, the regression models are descriptive and limited by omitted article-level predictors. Fifth, the DiD and event-study analyses are constrained by sparse state-year cells and should be treated as diagnostic reform-period comparisons rather than strong causal estimates.

Future research should extend the corpus to regional-language and digital outlets, incorporate topic modeling or supervised frame classification, and link media framing to implementation data such as road completion, maintenance, budget releases, or local economic outcomes. As India continues to invest in large-scale rural development, these extensions would help explain not only whether infrastructure is covered positively, but which stories, communities, and political actors shape that coverage.

These limitations also point to a broader theoretical implication. Infrastructure programs such as PMGSY are often evaluated through kilometers built, villages connected, budgets allocated, or economic outcomes produced. Media framing adds a different layer: it shows how policy achievements are translated into narratives of development, access, political competence, or administrative failure. A favorable English-language press environment may help normalize a flagship program as a nonpartisan development success, but it may also obscure local grievances, maintenance failures, or regional inequalities that are more visible in vernacular media. The value of this study is therefore not that it provides a final measure of public approval, but that it documents one influential media layer in the politics of interpreting rural infrastructure.

Future work should build a more multilingual and content-rich corpus. A stronger next-stage design would collect Hindi, regional-language, and digital coverage; classify articles by topic or frame; and link sentiment to district-level project outcomes such as completion dates, cost overruns, road quality, or maintenance records. Such a design would allow researchers to distinguish positivity driven by beneficiary stories from positivity driven by government announcements, and to test whether negative coverage clusters around delays, corruption allegations, or regions with weaker implementation. It would also make the causal claims more credible by moving beyond broad party-period indicators toward more precise article-level and project-level mechanisms.

Supplementary Materials: The following supplementary tables are available: Table S1. Corpus Attrition; Table S2. Per-PDF Extraction Results; Table S3. Main OLS Regression Summary; Table S4. Top VIF Diagnostics; Table S5. Difference-in-Differences Regression; Table S6. Event-Study Diagnostics; Table S7. State Sentiment Summary; Table S8. Coverage Intensity Regression; and Table S9. Robustness Specifications for Main OLS.

Author Contributions: Conceptualization, A.B.; methodology, A.B.; software, A.B.; validation, A.B.; formal analysis, A.B.; investigation, A.B.; resources, A.B.; data curation, A.B.; writing—original draft preparation, A.B.; writing—review and editing, A.B.; visualization, A.B.; project administration, A.B. The author has read and agreed to the published version of the manuscript.

Funding: This research received no external funding. The APC was not externally funded.

Institutional Review Board Statement: Not applicable. This study analyzes publicly available newspaper text and does not involve human participants or animals.

Informed Consent Statement: Not applicable. This study does not involve human participants.

Data Availability Statement: The article-level data were derived from Factiva export files and are subject to database access restrictions. Derived aggregate tables and figures supporting the reported results are included in the manuscript and supplementary tables.

Acknowledgments: The author thanks Dr. Holli Semetko for her continued support, and thanks the reviewers and Review Editor for constructive comments that improved the manuscript.

Conflicts of Interest: The author declares no conflicts of interest. There were no funders involved in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript; or in the decision to publish the results.

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Supplementary Tables

Nine supplementary tables report corpus provenance, regression outputs, diagnostics, robustness checks, spatial summaries, and coverage-intensity results.

Table S1. Corpus Attrition

Stage	N	Notes
Source PDFs	14	
Raw extracted article segments	1539	After segmentation + min 40 words
Duplicates removed	18	Across PDF exports
After deduplication	1521	
Final outlet-attributed corpus	968	Excludes fully unidentified outlets; TOI - UnknownEdition is retained when TOI is identified but city edition is not.
Main OLS sample	780	Main OLS regression sample (INC/BJP ruling-party periods).

Note: Main OLS regression sample excludes articles without ruling-party period or required covariates. TOI - UnknownEdition is retained when TOI is identified but city edition is not.

Table S2. Per-PDF Extraction Results

Source PDF	Results Found	Articles Extracted
Factiva-20250409-1148.pdf	1739	145
Factiva-20250409-1149.pdf	1739	118
Factiva-20250409-1150 (1).pdf	1739	128
Factiva-20250409-1150.pdf	1739	119
Factiva-20250409-1151.pdf	1739	186
Factiva-20250409-1152.pdf		80
Factiva-20250409-1153 (1).pdf	1739	108
Factiva-20250409-1153 (2).pdf	1739	117
Factiva-20250409-1153.pdf		80
Factiva-20250409-1154 (1).pdf		102
Factiva-20250409-1154 (2).pdf		82
Factiva-20250409-1154.pdf		108
Factiva-20250409-1155.pdf	1739	119
Factiva-20250409-1156.pdf		47

Note: Results Found is per-export metadata from the same underlying Factiva search/download sequence; blank cells indicate that the search-summary text was absent or not machine-readable in that export file.

Table S3. Main OLS Regression Summary

Term	Coef.	SE	p	Sig.
INC period	0.066	0.165	0.691	
N	780			
R-squared	0.09			
Adjusted R-squared	0.05			
Covariance				cluster

Table S4. Top VIF Diagnostics

Variable	VIF
ruling_party_INC	17.34
year_2012	5.12
newspaper_TOI – UnknownEdition	4.33
newspaper_The Hindu	4.11
year_2013	3.28
newspaper_TOI – Delhi	2.49
newspaper_Indian Express	2.48
year_2024	2.39
year_2016	2.38
year_2022	2.37
year_2018	2.3
year_2023	2.24

Table S5. Difference-in-Differences Regression

Term	Coef.	SE	p	Sig.
Post-reform	0.331	0.101	0.001	***
Post x treatment	0.008	0.293	0.977	
N	289			
R-squared	0.258			
Adjusted R-squared	0.223			
Covariance				cluster

Table S6. Event-Study Diagnostics

Rel. Year	Period	Estimate	SE	p	Reliable
-3	pre	0.172	0.573	0.764	Yes
-2	pre	0.029	0.236	0.902	Yes
1	post	0.486	0.107	5.47e-06	Yes
3	post	-0.047	0.193	0.806	Yes

Table S7. State Sentiment Summary

State	Mean Sentiment	Articles
Delhi	0.768	83
Karnataka	0.64	3
Rajasthan	0.443	14
Uttar Pradesh	0.387	48
Telangana	0.381	6
Maharashtra	0.369	14
Jharkhand	0.227	24
Bihar	0.214	58
Odisha	0.203	24
Madhya Pradesh	0.172	8
Gujarat	0	1
West Bengal	-0.039	6

Note: Moran's $I = 0.112$ across 11 shapefile-matched states. Telangana appears in this table but is excluded from Moran's I because it does not match the shapefile used for spatial weights.

Table S8. Coverage Intensity Regression

Term	Coef.	SE	p	Sig.
Log article count	-0.031	0.095	0.742	
N	83			
R-squared	0.002			
Adjusted R-squared	-0.01			
Covariance				cluster

Table S9. Robustness Specifications for Main OLS

Specification	N	R ²	Adj. R ²	Condition #	Party coef. (p)
Main OLS	780	0.09	0.05	3.69e+15	0 . 0 6 6 (p=0.691)
No-party OLS	780	0.09	0.05	32.66	—
No-year OLS	780	0.075	0.052	33.04	- 0 . 0 7 5 (p=0.273)
Asinh OLS	780	0.09	0.05	3.69e+15	0 . 0 5 6 (p=0.705)

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Article

Holistic Education: Philosophical Roots and Contemporary Relevance in Independent India

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Abstract: Holistic education is an educational philosophy and practice that aims to nurture learners' intellectual, emotional, social, physical, ethical and spiritual development. It seeks to form persons rather than merely train performers, and therefore challenges narrow educational models that reduce learning to examination success, employability, or the mechanical acquisition of information. This paper examines the philosophical roots and contemporary relevance of holistic education in independent India. It traces the idea from Vedic and Upanishadic reflections on knowledge, the Gurukula tradition, and major Indian educational thinkers such as Mahatma Gandhi, Swami Vivekananda, Rabindranath Tagore, Sri Aurobindo, J. Krishnamurti and Sri Sathya Sai Baba. It also places these Indian traditions in dialogue with Western educational thinkers such as Plato, Rousseau, Pestalozzi, Montessori, Dewey, Steiner and Smuts. This paper further analyses the post-Independence education commissions and policy frameworks, culminating in the National Education Policy 2020. The central argument of this paper is that holistic education in India should not be merely understood as a contemporary policy slogan or a nostalgic return to the past; rather, a historically rooted, philosophically rich and socially relevant educational framework that should be critically recovered for the present. This paper also argues that the crisis of the present-day educational system is not only curricular or administrative but also cultural in nature: education has increasingly become capable of producing skilled individuals without necessarily forming the morally grounded, emotionally stable, socially responsible and spiritually sensitive human beings. In this context, holistic education becomes not an optional supplement but a necessary reorientation of educational purpose. At the same time, this paper maintains that the recovery of holistic education must be critical and inclusive. Ancient and modern traditions must be examined in relation to caste, gender, access, social equity, institutional practice and implementation. This paper therefore moves beyond a descriptive survey and presents holistic education as a living framework for addressing youth mental health, value erosion, social fragmentation, examination pressure and the gap between policy vision and classroom reality in contemporary India. 5313

Citation: Sai Preetham V.;
Awareness, 3 (2): 121-132



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Main Message: Holistic education, rooted in India's Vedic, Upanishadic and modern philosophical traditions, addresses a deepening crisis in contemporary education: the production of technically skilled but humanly fragmented persons. Drawing on Gandhi, Vivekananda, Tagore, Aurobindo, Krishnamurti and Sri Sathya Sai Baba, and placing these in dialogue with Western thinkers and Indian education policy from the Ra-dhakrishnan Commission to NEP 2020, this paper argues that holistic education must be recovered as a critical, inclusive and practically applicable framework for Indian education today — one that forms the whole person while remaining responsive to questions of equity, access, and social justice.

Keywords: Holistic Education; Education Commissions; Gurukulam; NEP 2020; Value Education; Integral Education

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Introduction

The modern education system in India and across the world stands at difficult crossroads. On the one hand, education has expanded access to knowledge, produced professional competence, supported technological progress and enabled social mobility. On the other hand, it has also become increasingly dominated by examinations, rankings, employability, institutional competition and measurable outputs. Students are expected to acquire information quickly, compete continuously and adapt to a fast-changing world. Yet this pressure has not always been accompanied by equal attention to emotional maturity, ethical judgement, social responsibility, creativity, physical well-being or spiritual depth.

The problem, therefore, is not that modern education teaches too much. The problem is that it often forms too little. It may sharpen memory without deepening wisdom; it may train intelligence without cultivating character; it may prepare students for employment without preparing them for life. This imbalance has created a serious educational and social concern. A learner may become technically competent and still remain emotionally fragile, ethically uncertain, socially indifferent or spiritually empty. The question that must be asked, therefore, is not only what students know, but what kind of human beings they are becoming through the educational process.

An increasing number of adolescents and young adults are showing signs of distress, anxiety, depression, suicidal tendencies, substance misuse, social alienation and behavioral instability¹⁻⁵. These concerns point to the limits of an education system that treats academic performance as the primary measure of success. Contemporary India needs an educational framework that can help learners develop resilience, self-understanding, ethical clarity, emotional balance, social responsibility and a sense of meaningful belonging. Holistic education responds to this need by insisting that the learner is not merely an intellect to be trained but a whole person to be formed.

This paper argues that holistic education in India has to be understood in three interconnected ways. First, it is a civilisational idea with deep roots in Indian philosophical and educational traditions. Second, it is a modern pedagogical necessity because the pressures faced by young people today cannot be answered by academic instruction alone. Third, it is a policy challenge because the ideals of holistic education, especially as articulated in NEP 2020⁶, will remain incomplete unless they are translated into classroom practice, teacher formation, assessment reform, institutional culture and inclusive access.

The term “holistic” became widely known in the twentieth century through Jan Smuts’s idea of holism⁷, but the educational intuition behind it is much older. In the Indian context, learning was traditionally connected with self-knowledge, discipline, truth, righteousness, service and liberation. Indian philosophy, particularly the Upanishadic tradition, did not treat knowledge as mere information. It linked knowledge with transformation. Similarly, many modern Indian thinkers such as Gandhi, Vivekananda, Tagore, Aurobindo, Krishnamurti and Sri Sathya Sai Baba placed character, freedom, self-realisation, creativity, service and values at the centre of education⁸⁻¹⁵.

At the same time, a serious study of holistic education must not romanticise the past. The recovery of tradition must be accompanied by critical examination. Questions of caste, gender, social access, institutional power and marginalised voices must be included. A holistic education that speaks of the whole person but ignores social exclusion cannot be truly holistic. Therefore, this paper attempts to combine philosophical recovery with critical analysis.

This paper proceeds by examining Indian philosophical foundations, modern Indian educational thinkers, Western educational traditions, post-Independence education commissions, NEP 2020 and the contemporary challenges of implementation and inclusion.

The Indian Philosophical Foundations of Holistic Education

Understandings from the Vedic and Upanishadic Traditions

The roots of holistic education in India can be traced to the Vedic and Upanishadic understanding of knowledge. In these traditions, learning was not merely a preparation for livelihood. It was connected with the formation of the person and the search for truth. The Sanskrit term *vidyā* carries a meaning deeper than literacy or instruction. It suggests illumination, discernment and the awakening of the learner to a larger order of life.

The Upanishadic distinction between *apara vidyā* and *para vidyā* is central to this understanding¹⁶. *Apara vidyā* refers to worldly, textual and intellectual knowledge, while *para vidyā* refers to the higher knowledge through which ultimate reality is known. This distinction does not reject worldly knowledge. Rather, it places it within a larger ethical and spiritual horizon. In educational terms, it means that knowledge must serve both practical life and inner growth.

The Gurukula system is often remembered as an important example of integrated education¹⁷. It brought together study, discipline, service, physical work, moral training, spiritual practice and close teacher-student relationship. Learning was not separated from living. The student was expected to cultivate humility, self-control, attention, memory, reverence and responsibility. This model reminds modern education that curriculum alone does not educate; atmosphere, relationship, discipline and example also educate.

However, the Gurukula tradition must be recovered critically rather than romantically. Historically, access to formal and advanced learning was not equally available to all sections of society¹⁸. Women, lower caste communities and many marginalised groups were often excluded from institutional learning, even though the historical picture varied across regions and periods. Therefore, the Gurukula cannot be presented as a perfect model to be reproduced. Its value lies in its integrated vision of life and learning, but its limitations remind us that contemporary holistic education must be consciously inclusive. It must preserve the concern for character, discipline, service, teacher-student relationship and inner growth, while rejecting exclusion and affirming equality, constitutional values, gender justice and social dignity.

Mahatma Gandhi: Nai Talim and the Unity of Head, Heart and Hand

Mahatma Gandhi's concept of Nai Talim or Basic Education is one of the most important modern Indian contributions to holistic education⁸. Gandhi understood education as the drawing out of the best in the child and the human being in body, mind and spirit⁸. His emphasis on the head, heart and hand expressed a powerful educational philosophy. The head represented intellectual clarity, the heart represented moral and emotional refinement and the hand represented productive work, service and dignity of labour.

Gandhi criticised colonial education because it separated learners from their communities, languages, manual work and moral responsibilities. He believed that education should be rooted in life and should prepare students for self-reliance, social responsibility and service. Craft was not merely vocational training in his scheme. It was a method of learning through which the child could develop concentration, discipline, cooperation, creativity and respect for labour⁸.

Gandhi's Nai Talim remains powerful because it challenges one of the deepest hierarchies of modern education: the separation between intellectual work and manual work. However, it must also be examined critically. Scholars have questioned whether craft-centred education, if poorly implemented, could restrict opportunities for learners in a modern scientific and technological society. There is also the danger that Nai Talim may be reduced to manual activity without its ethical, social, and philosophical depth. Therefore, Gandhi's educational vision must be reinterpreted today, not mechanically repeated. Its contemporary relevance lies in combining dignity of labour, community engagement, moral formation, ecological responsibility, scientific learning and critical thinking.

Swami Vivekananda: Man-Making Education

Swami Vivekananda offered one of the most forceful definitions of education in modern India when he described it as the manifestation of the perfection already within the human being⁹. For Vivekananda, education was not the mere transfer of information from teacher to student. It was the awakening of inner strength, character, fearlessness, self-reliance and spiritual awareness.

His idea of man-making education placed character at the centre of national and individual regeneration. He wanted education that would build character, strengthen the mind, expand the intellect and enable the learner to stand on his or her own feet. This was not a narrow moralism. It was a complete vision of human development in which physical strength, intellectual clarity, moral courage and spiritual awareness supported one another⁹.

Vivekananda's educational thought is especially relevant in the present context because many young people are trained to compete but not always trained to become inwardly strong. They are prepared for careers but not always prepared for crisis, service, sacrifice or ethical decision-making. His man-making education therefore speaks directly to the contemporary need for confidence, resilience, courage, compassion and purpose.

Rabindranath Tagore: Education for Harmony, Beauty and Freedom

Rabindranath Tagore approached education through the language of freedom, creativity, nature, beauty and harmony^{10,19,20}. His educational experiment at Santiniketan was a response to rigid, mechanical and examination-centred schooling. He believed that children should learn in contact with nature, art, music, literature, community and the wider world.

Tagore's vision was holistic because it integrated intellectual, emotional, aesthetic, ecological and social dimensions of learning. He understood that imagination and beauty are not luxuries in education. They are essential to the formation of a sensitive and complete human being¹⁰.

Tagore's approach to education is very important in today's context because modern education often separates knowledge from wonder. Students may learn environmental science without developing reverence for nature. They may study literature without developing empathy. They may learn language without learning sensitive communication. Tagore's educational philosophy reminds us that education must not become a factory of information. It must remain a space where freedom, beauty, creativity and human relationship are cultivated.

Sri Aurobindo: Integral Education

Sri Aurobindo developed one of the most systematic frameworks of integral education in modern India¹¹. His understanding of the human being included the physical, vital, mental, psychic and spiritual dimensions. Education, therefore, had to address all these levels. It could not be limited to intellectual instruction.

Integral education is significant because it offers a developmental view of the whole person. The body requires discipline and strength. The vital nature requires purification and direction. The mind requires clarity and concentration. The psychic being requires awakening. The spiritual dimension requires openness to higher consciousness. This framework makes education a process of inner and outer growth¹¹.

In present-day terms, Sri Aurobindo's thought can contribute to discussions on topics such as emotional intelligence, mindfulness, physical education, creativity, value education and spiritual development. Yet its deeper significance lies in its insistence that education is incomplete unless it addresses the inner life of the learner.

J. Krishnamurti: Freedom, Awareness and Self-Knowledge

J. Krishnamurti rejected mechanical conformity and insisted that education should free the mind from fear, imitation and unthinking obedience¹². For him, education should help the learner understand the movement of thought, the nature of fear, the burden of conditioning and the importance of self-knowledge.

Krishnamurti's contribution to holistic education lies in his insistence that academic success without self-understanding is incomplete. A student may be highly successful in examinations and still remain inwardly confused, fearful, ambitious or violent. Education must therefore create an atmosphere where questioning, observation, sensitivity and freedom from fear are possible¹².

This remains highly relevant in today's context because many students experience education as pressure rather than awakening. Krishnamurti reminds us that fear may produce obedience, but it cannot produce intelligence.

Sri Sathya Sai Baba: Education as Educare

Sri Sathya Sai Baba offered a distinctive formulation of holistic education through the concept of Educare¹³⁻¹⁵. He distinguished between education as the acquisition of external knowledge and Educare as the drawing out of inherent human values. The five human values of truth, righteousness, peace, love and non-violence form the core of this educational philosophy^{14,15}.

His statement that the end of education is character captures the central thrust of this vision. Education is not rejected as worldly knowledge, but it is considered incomplete if it does not lead to character formation. The integration of head, heart and hand is central. The head represents knowledge, the heart represents love and compassion, and the hand represents action and service¹³⁻¹⁵.

The Sri Sathya Sai Institute of Higher Learning and the Sri Sathya Sai Loka Seva Gurukulam represent institutional attempts to bring this philosophy into educational practice by combining academic learning with values, discipline, service, and spiritual culture²¹.

Since the authors write from an institutional context shaped by Sri Sathya Sai educational ideals, this positionality must be acknowledged. The discussion of Educare is not merely external; it emerges from a lived educational environment in which value-based education, service, discipline and spiritual culture are practised as part of institutional life. This can be a scholarly strength if presented reflectively rather than devotionally. It allows this paper to contribute a situated understanding of how a value-based educational philosophy may shape institutional culture. At the same time, the discussion must remain open to wider academic dialogue so that Educare is placed in conversation with broader debates on value education, character formation, service learning and holistic pedagogy.

Western Philosophical Foundations of Holistic Education

Western educational thought also contains important strands of holistic thinking. Although the cultural and philosophical foundations differ from Indian traditions, many Western thinkers also resisted narrow intellectualism and argued for the development of the whole person.

Plato viewed education as the ordering of the soul and the formation of just individuals²². His model integrated physical training, music, mathematics, dialectic and moral formation. Rousseau challenged rigid and artificial education and argued that learning should follow the natural development of the child²³. Pestalozzi gave the influential formulation of educating the head, heart and hand²⁴. Montessori developed a method based on independence, sensory learning, observation and prepared environments²⁵. Dewey emphasised experience, democracy, reflection and social relevance²⁶. Steiner's Waldorf model integrated imagination, art, rhythm, moral development and spiritual anthropology²⁷. Smuts gave the philosophical language of holism, describing the tendency of nature to form wholes greater than the sum of parts⁷.

These Western thinkers should not be treated as simply repeating Indian ideas, nor should Indian traditions be valued only when they resemble Western theories. The relationship between Indian and Western traditions is better understood as a dialogue between different civilisational approaches to the same educational problem: the fragmentation of the human person. Indian traditions often begin from self-realisation, dharma, spiritual anthropology and the relation between worldly and higher knowledge. Western progressive traditions often begin from the child, nature, experience, democracy, freedom or social reform^{28,29}. Their union shows that the need for whole-person education is universal, while their differences remind us that educational philosophy is always shaped by culture and history. In a postcolonial context, this comparison must be handled carefully. Indian

educational thought should not be subordinated to Western validation and Western educational thought should not be rejected merely because it is Western¹⁸. A mature Indian theory of holistic education can learn from both while remaining rooted in its own historical and social realities.

Indian Education Commissions and Holistic Vision

After Independence, India had to build an education system that could support democracy, national development, scientific progress, cultural continuity and social justice. The major education commissions and policy frameworks repeatedly returned to questions central to holistic education: What kind of citizen should education produce? How should values be integrated into learning? How can education serve both individual development and national reconstruction?

The Radhakrishnan Commission (1948–49)

The University Education Commission, chaired by Dr. S. Radhakrishnan, emphasised that higher education should not be reduced to professional training³⁰. It should cultivate wisdom, citizenship, moral responsibility and cultural understanding. The Commission recognised that universities must serve the nation not merely by producing degree-holders but by forming thoughtful and responsible human beings³¹.

The Commission's concern for moral and spiritual education shows that holistic education was present at the very beginning of post-Independence educational planning. It encouraged moral and religious reflection in a broad and non-sectarian manner, along with arts, culture, community life, national service and citizenship training. Its importance lies in its insistence that higher education must contribute to the ethical and cultural life of the nation.

The Mudaliar Commission (1952–53)

The Secondary Education Commission, chaired by Dr. A. Lakshmanaswami Mudaliar, focused on adolescence as a crucial stage of development³². It recognised that secondary education should not merely prepare students for examinations or higher studies but should support the formation of personality. The Commission recommended a varied curriculum which included arts, humanities, sciences, crafts and vocational subjects. It also emphasised health, physical education, character formation³³, cultural expression, citizenship and social service. Its importance lies in recognising that adolescence is a formative stage in which intellectual growth must be supported by emotional, physical, moral and social development.

The Kothari Commission (1964–66)

The Kothari Commission remains one of the most comprehensive statements on Indian education³⁴. Its famous declaration that the destiny of India is being shaped in her classrooms continues to express the moral seriousness of education.

The Commission connected education with national development, democracy, social justice, science and technology, work experience, moral values and national integration. Its vision was holistic because it did not separate individual development from social transformation. It recognised that education must produce not only knowledgeable individuals but also responsible citizens capable of contributing to a democratic and just society³⁴.

National Policy on Education, Yashpal Committee and NCF 2005

The National Policy on Education 1968³⁵, the National Policy on Education 1986³⁶ and the Programme of Action 1992³⁷ carried forward many of these concerns by emphasising equality, women's education, value education, work experience, environmental awareness and national integration.

The Yashpal Committee's report *Learning Without Burden*³⁸ added a crucial pedagogical dimension by criticising excessive content load, rote learning and examination pressure. It argued that learning should be joyful, meaningful, creative and child-centred. The National Curriculum Framework 2005³⁹ further developed these ideas by emphasising constructivist learning, peace education, gender sensitivity, environmental concern, arts, health, and work.

Taken together, these commissions and frameworks show that holistic education has never been absent from Indian policy imagination. The difficulty has been implementation. Policy documents have repeatedly affirmed broad and humane educational ideals, but classrooms have often remained dominated by marks, textbooks, examinations, and administrative pressure. This gap between the vision and the practice is one of the central challenges of the holistic education in present-day India.

NEP 2020 and the Renewal of Holistic Education

The National Education Policy 2020⁶ represents the most explicit contemporary policy articulation of holistic education in India. It calls for multidisciplinary learning, flexibility, critical thinking, creativity, ethical reasoning, constitutional values, experiential learning, vocational education, arts, sports and the integration of Indian knowledge systems. It seeks to move away from rigid separations between curricular and extracurricular, arts and sciences, vocational and academic, knowledge and values.

NEP 2020 echoes many earlier traditions. Its emphasis on multidisciplinary learning recalls the Indian idea that knowledge should not be fragmented. Its concern for values and ethics resonates with Gandhi, Vivekananda, Aurobindo and Sri Sathya Sai Baba^{8,9,11,13}. Its stress on experiential learning connects with Dewey, Montessori, Tagore and the Yashpal Committee^{10,25,26,38}. Its inclusion of arts, sports, yoga and vocational education carries forward the idea that the body, mind, emotion and practical skill must all be developed.

Yet NEP 2020 should not be treated as the completion of the holistic education project. It is better understood as an opportunity and a challenge. The policy carries a powerful vision, but the translation of that vision into practice is difficult. Many institutions continue to face shortages of trained teachers, uneven infrastructure, large class sizes, examination pressures, language challenges and social inequalities. This multidisciplinary education may remain a slogan if the institutions lack the academic flexibility and at the same time the value of education may become moral instruction if the teachers are not trained to facilitate this reflection and lived practice. Even here the catch is that vocational education may reproduce hierarchy if manual and practical work are not treated with genuine dignity. Indian knowledge systems may become superficial if they are not approached with scholarly rigour and openness.

Equity is central to the success of the holistic education. It must be available not only in the elite institutions but also in the public schools, government schools, rural schools, first-generation learner contexts and institutions serving economically weaker communities. It must also include girls, Dalit students, Adivasi students, linguistic minorities, and children with disabilities, and learners from marginalised backgrounds. If holistic education becomes a privilege of well-resourced schools alone, it will contradict its own ethical foundation.

Expanding the Sources of Holistic Educational Wisdom

A stronger theory of holistic education must expand whose voices are recognised as sources of educational wisdom. Canonical Indian and Western thinkers are important, but they do not exhaust the field. If holistic education means the development of the whole person and the whole society, then the experiences of historically marginalised communities must be included.

Dalit educational thought adds a crucial dimension to holistic education. Dr. B. R. Ambedkar's emphasis on education as a means of dignity, self-respect, and liberation shows that education is not merely a path to personal development but also a means of social emancipation⁴⁰. In this regard, Paulo Freire's concept of education as a practice of freedom is particularly relevant⁴¹. Freire argued that education enables oppressed communities to develop critical consciousness and challenge structures of domination. Together, Ambedkar and Freire remind us that holistic education must address not only the development of the individual but also the transformation of unjust social conditions. For communities which were historically denied access to knowledge, education becomes a path to human dignity and democratic participation. A holistic education that ignores caste would remain incomplete because it would speak of wholeness while ignoring structures that have denied wholeness to many.

Feminist pedagogy also deepens the meaning of holistic education. It asks whether education enables girls and women to develop voice, confidence, safety, agency and intellectual freedom. It challenges patriarchal assumptions in curriculum, classroom culture and institutional life. bell hooks⁴² similarly argues that education should be a practice of freedom, where learners develop voice, agency, critical awareness and the capacity to challenge structures of domination. Her work reinforces the holistic educational goal of nurturing intellectual, emotional and social transformation. Similarly, adivasi and indigenous knowledge traditions remind us that learning can be connected to land, ecology, oral memory, community and collective life. These traditions are especially important in an age of ecological crisis because they challenge the modern separation between knowledge and nature. Including dalit, feminist, adivasi and other marginalised perspectives does not dilute the philosophical discussion of holistic education. It makes it more truthful. Holistic education cannot be only about the inner development of privileged learners. It must also address the social conditions that prevent many learners from becoming whole.

Practical Relevance of Holistic Education Today

Holistic education becomes meaningful only when it enters classroom and institutional practice. It cannot remain a philosophical ideal or a policy phrase. In a classroom, it may take the form of reflective dialogue, arts integration, community service, environmental projects, yoga and physical education, counselling support, ethical case studies, interdisciplinary learning and opportunities for student self-expression.

For example, environmental education should not merely teach definitions of pollution. It should connect science with local observation, ethics with consumption and community service with ecological responsibility. History education should not just ask students to memorise events rather it should help them understand human choices, cultural memory, moral complexity and the relationship between past and present. Science education should also cultivate curiosity and responsibility, not only technical skill. Language education should develop empathy, imagination and communication, not merely grammar and examination writing.

This holistic education also requires transformation of the institutional culture. A school cannot teach compassion through fear and in the same way it cannot teach dignity through humiliation. It cannot teach freedom through silence, nor can it teach service through competition alone. Teachers must therefore be prepared not only as subject experts but also as mentors, facilitators and ethical examples. Institutions must create environments where students experience belonging, discipline, creativity, dialogue and moral responsibility.

Conclusion

The development of holistic education reveals a deep continuity between ancient philosophy, modern educational reform and contemporary policy. From the Vedic and Upanishadic traditions to Gandhi and Vivekananda^{8,9}, from Tagore and Aurobindo to Krishnamurti and Sri Sathya Sai Baba¹⁰⁻¹³, from Plato and Rousseau to Dewey and Montessori^{22,23,25,26} and from the Radhakrishnan Commission to NEP 2020^{6,30}, the need to educate the whole person has remained a recurring concern.

However, this paper has argued that holistic education should not be treated merely as a historical idea or a pleasant educational ideal. It must be understood as a serious response to the crisis of contemporary education. The present age requires learners who are intellectually capable, emotionally stable, ethically grounded, socially responsible, physically healthy, spiritually sensitive and ecologically aware.

The central contribution of this paper is to argue that holistic education in India must be recovered as a critical, inclusive and practical framework. It must draw strength from Indian philosophical traditions without romanticising them. It must adapt Western educational thoughts without becoming dependent on Western validation. It must embrace NEP 2020 without ignoring the difficulties of implementation. It must speak of values without becoming authoritarian and of spirituality without becoming sectarian. Above all, it must include those voices and communities that have historically been denied equal access to education⁴⁰⁻⁴².

Holistic education is therefore not a luxury for ideal institutions. It is a necessity for the future of Indian education. The question before educators today is not only how to make students more successful, but how to help them become more fully human. To educate holistically is to recognise that the learner is not merely a mind to be trained, but a person to be awakened, strengthened, refined and guided towards meaningful participation in the world.

Author Contributions: Conceptualization, V.S.P. and M.B.; Methodology, V.S.P.; Formal Analysis, V.S.P. and M.B.; Investigation, V.S.P.; Writing—Original Draft Preparation, V.S.P.; Writing—Review & Editing, M.B.; Supervision, M.B.. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: No new data were created or analyzed in this study. Data sharing is not applicable to this article.

Conflicts of Interest: The authors declare no conflicts of interest.

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Article

Designing a Circadian-Aligned Educational Timetable for Residential University Education: Integrating Modern Chronobiology and Ayurvedic Dinacharya

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Abstract: Educational timetables are usually organized according to academic and administrative requirements, with limited attention to students' biological rhythms. However, chronobiology shows that health, performance, and well-being are closely influenced by the time of day. This paper presents the design of a circadian-aligned annual timetable at Sri Sathya Sai University for Human Excellence, India. The framework also draws upon the Ayurvedic principle of *Dinacharya*, or daily routine. A descriptive research design was adopted based on the educational practices followed at the institution. The university's daily timetables and annual calendar were analyzed. These schedules had evolved through nearly three years of planning, implementation, review, and revision. Scientific literature and classical Ayurvedic texts were also examined to identify principles related to sleep, nutrition, physical activity, intellectual learning, experiential engagement, spiritual practice, and rest. The resulting framework includes coordinated timetables for working days, examinations, holidays, vacations, sports, internships, conferences, and other institutional activities. These schedules follow a consistent daily rhythm throughout the academic year. The framework is based on a residential educational model covering five interrelated domains: Spiritual, Intellectual, Personal, Experiential, and Regenerational development. Together, these domains support academic learning, physical health, practical skills, personal growth, spiritual awareness, nutrition, sleep, and recovery. Although the study does not quantitatively measure the effect of the timetable on students' performance or well-being, it shows how chronobiology and Ayurvedic principles can be integrated into educational planning. The study offers a useful framework for residential institutions seeking to organize learning in harmony with biological rhythms and holistic development.

Citation: Roopa C., Thothathri V.; *Awareness*, 3 (2): 133-143



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Keywords: Circadian rhythm; Chronobiology; Educational timetable; Residential education; Dinacharya; Ayurveda; Holistic education; Educational planning; Student well-being

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1. Introduction

The organization of one's activities plays a vital role in a person's health, performance, and wellbeing. Though educational establishments care about the syllabus, teaching methods, and evaluation strategies, they rarely consider whether the time schedule fits human biology. The field of chronobiology has explored the relevance of the timing of our sleep, nutrition, sport, and hard work^{3,4}. Thus, the very organization of our time emerges as a significant concept.

Chronobiology focuses on the chronology of bodily functions³. More specifically, the circadian (daily) rhythms of sleep-wake cycles, hormonal response, body temperature, alertness, and other vital signs, regulate physiological processes^{4,6}.

A circadian rhythm is a process that follows the daily cycle; thus, it depends on the time of the day^{3,6}. The pattern occurs due to the body's internal clock, which is programmed by external factors⁷. For instance, light and exercise can affect the clock, thereby aligning a specific physiological process with certain hours^{4,7}.

Disruptions of the circadian rhythms cause health issues including learning and concentration problems, increased risks of metabolic syndrome, and psychological dysfunction^{1,8,9}. Therefore, chronological health has become a topic of interest among scientists, and the study has broad implications, including education.

The chronological organization of bodily processes was acknowledged in the ancient world. For example, the traditional system of medicine and science called Ayurveda recommends following the circadian rhythms to optimize health and wellbeing. The ancient wisdom has been systematized in the concept of Dinacharya, a guide for arranging sleep, nutrition, sport, work, relaxation, and other activities in accordance with the circadian rhythms¹⁰.

Ayurveda and chronobiology are different systems, but they share broad similarities, regarding the basics of daily life^{5,11}. The similarities are crucial, as chronological health can become an integral part of education.

A residential educational organization represents an ideal model for incorporating chronological health into the daily life of students. Indeed, the students of residential universities do not have much freedom, as their daily activities are determined by the staff. Simultaneously, the university setting allows making global changes to the organization of students' activities.

This study is centered at Sri Sathya Sai University for Human Excellence, Karnataka, India. This university gives equal importance to Para Vidya and Aparā Vidya. The entire years routine is based on this undertone.

The entire day is organized chronologically by the institution as though it were a single academic entity. To put it another way, the staff views daily practices that promote health as an essential component of education. As a result, the university has incorporated Ayurvedic Dinacharya's teachings on athletics, diet, health, and sleep into the everyday schedules of its students.

Despite the lack of research on the subject, chronological health can be a crucial component of schooling^{1,12}. Researchers have rarely systematized the chronobiology-based recommendations for educational institutions, despite the fact that chronological science has received a lot of attention^{1,3}.

The applicability of traditional Indian medicine in the setting of higher education has also received little attention from academics. Consequently, a chrono-review that investigates the use of chronological health in the residential university education paradigm can add significantly to the body of current knowledge. The results will, in fact, demonstrate the possible use of chronological health in education, which will improve both the quality of education and the wellbeing of students.

However, this study's scope is restricted to a particular educational organization's historical examination. Furthermore, the study did not assess students' wellbeing, despite showing the possible advantages of a daily plan that is organized chronologically.

Because of its possible ramifications, chronobiology is an emerging topic of study that has garnered significant attention. This research shows how students at residential institutions might incorporate the concepts of chronological health into their everyday routines. As a result, adhering to chronobiology's suggestions will help the kids in many ways.

However, the study just provides an overview of Sathya Sai University's chronologically organized curriculum. The results are intended to improve the general well-being of residential university students. However, the study's conclusions are restricted to outlining the advantages of chronological health. As a result, the study urges educational institutions to view the subject as an essential component of education.

2. Background and Literature Review

2.1 Circadian Rhythms and Human Performance

In order to enable the synchronization of physiological and behavioral processes, organisms experience biological rhythms, which are cyclical patterns lasting around twenty-four hours^{3,7}. The bulk of physiological processes, including hormone synthesis, metabolism, body temperature, immunological response, and sleep-wake cycles, are regulated by these rhythms, which start in the hypothalamic structure known as the suprachiasmatic nucleus. Physical activity, eating, and social interactions can temporally gate certain physiological processes, but the light-dark cycle is the most common way that these rhythms are entrained^{4,7}.

Deviations from natural cycles have an impact on human performance, learning, health, and emotion, according to chronobiology, the science of biological rhythms. Research over the past 20 years has shown that temporal structure can enhance both psychological stability and physiological well-being in sleep/wake, light exposure, eating routines, and physical exercise^{12,13}. Research has demonstrated that interventions that consider the human body's circadian structure can enhance mood, sleep, cognition, metabolism, and cardiovascular health^{1,6}.

It can be argued that, given the extensive scientific literature on the health benefits of temporal organization, the principles of biological timing should be used in clinical as well as educational settings in order to benefit human health.

2.2 Chronobiology in Education

Numerous educational research have demonstrated that how sleep, classes, meals, and physical exercise are arranged can all have an impact on learning^{12,14}. Lack of sleep has been demonstrated to impair motivation, focus, and memory consolidation in the classroom. Mood, alertness, and general performance have all been linked to the timing of sleep, wakefulness, classes, and meals. Regular meals and exercise have also been demonstrated to improve academic performance¹⁵.

Furthermore, it has been suggested that the measurement of students' sleep cycles can be used to determine how university lessons should be structured. However, rather than examining the temporal organization of a full day, the majority of studies that have examined circadian preference in relation to learning have concentrated on specific elements of the daily schedule, such as the relationship between sleep and cognition^{1,3}.

The majority of students at residential universities are unable to choose where and when to sleep, eat, or exercise because classes, meals, and recreational spaces are overseen by the staff. This is significant when weighing organizational aspects of education against individual choice.

In order to provide students with the best possible living conditions in terms of education, nutrition, wellbeing, and spiritual enrichment, living in an educational institution allows for the investigation of a fully structured daily schedule where the staff designs the educational, feeding, and spiritual aspects of the student's life. The advantages of biological timing can be integrated into the creation of a completely planned daily routine in these kinds of establishments.

2.3 Ayurvedic View on Daily Living

It has been suggested that various levels of education have been organized using Ayurvedic principles. The ancient medical system hypothesized the presence of daily schedules that account for both individual and seasonal variation prior to the emergence of chronobiology as a distinct field.

According to the circadian fluctuations in physiology and mental activity, Ayurveda suggests scheduling cleanliness, meals, exercise, study, social interactions, meditation, and sleep^{8,9}. It may be inferred that the daily timetable follows the transitions between daylight and nighttime activities, despite minor variations between sources. When it comes to the best times to eat, sleep, meditate, exercise, and interact with others, Ayurvedic recommendations and chronobiology findings are quite consistent^{2,5}.

In terms of planning daily activities around the diurnal change of hormone concentrations, it can be argued that the ancient medical system adheres to the principles of contemporary endocrinology. However, Ayurveda proposes that daily activities should be planned around changes in Pitta, Kapha, and Vata dominance, whereas chronobiology links physiological fluctuation to the action of the endocrine system. One may claim that the principles of chronobiology and Ayurveda are similar, and that the variances between the two can be explained by the diverse chronological structures proposed by various sources.

2.4 Chronobiology and Educational Timetable Design

Although research has demonstrated that temporal organizing principles can improve performance and health, chronobiology has not yet been used to construct institutional schedules^{1,3}. It is crucial to remember that the majority of colleges create their schedules based on the infrastructure and teacher availability on campus. Because SSSUHE is residential, it is possible to experiment with an ideal schedule that would align students' daily activities with their circadian rhythms.

While academics have historically been the focal point of education, it is crucial to remember that holistic student development necessitates the inclusion of spiritual, physical, character-building, and experiential aspects of development in addition to physiological maintenance. To improve student wellness, Sri Sathya Sai University for Human Excellence has implemented holistic development principles at the individual level. It became feasible to coordinate the planning of food, entertainment, and education in line with the tenets of chronobiology and Ayurveda when the new educational system was created across departments.

Over the last three years, the management of SSSUHE has worked on the design of a student-friendly schedule which would synchronize multiple aspects of student life while following a consistent timeline without disrupting the academic syllabus.

2.5 Research Gap

Numerous studies have been conducted on the impact of circadian variation on health and education, as well as the applicability of Ayurvedic texts as temporal organizing guides, according to the literature examined for this work. It has been demonstrated that whereas the majority of chronobiology research concentrates on specific facets of physiology, Ayurvedic principles recommend the best times to complete everyday activities. There is little data on the effects of applying comparable organizational strategies at a communal level, despite a wealth of research demonstrating that strict adherence to a schedule of meals, recreation, education, and sleep can improve individual health^{1,3,12}.

The organizational features of student life at a residential institution are a research gap that this paper aims to fill. In order to arrange meals, entertainment, and education in line with the principles of biological and Ayurvedic temporal structure, SSSUHE management has proposed a fully-integrated educational timetable, which is the subject of this study. This research aims to review the literature on the principles of daily schedule organization and assess the viability of establishing a comparable system at SSSUHE, rather than evaluating the impact of such a timetable on student health.

3. Materials and Methods

3.1 Study Design

An institutional design-based descriptive study was conducted to explore the development of a chronological educational timetable at Sri Sathya Sai University for Human Excellence (SSSUHE), Karnataka, India. The emphasis was on designing the university timetable as opposed to examining physiological or educational outcomes. Hence, the study concentrated on the content of the timetable according to contemporary chronobiological and Ayurvedic literature³.

3.2 Institutional Setting

SSSUHE is a residential educational institution offering quality education and value-based lifestyle, hostel management, sports activities, and spiritual development. Given that the students live within the campus all year round, the University has the opportunity to manage not only their education but also their health and wellbeing. The academic year consists of distinct types of days, which include working days, exam days, vacation days, shibhira, dasara, sports days, and sundays, among others. Each type of days was given separate consideration

3.3 Development of the Timetable

The present timetable under study was developed over the course of three years through an iterative process. Thereafter, the timetables were discussed with the university administration and faculty to further hone the design. Particular consideration was devoted to temporal organization of the academic, spiritual, and physical development activities in order to achieve an appropriate balance between education, rest, and sport.

3.4 Data Sources

There were three categories of data sources used in this study. First, the actual timetable and the annual schedules for the SSSUHE, which had been designed by the University administration. The timetables specify the sequence of activities, which have to be undertaken on a given type of day. Second, a review of the literature on modern chronobiology with a specific focus on sleep physiology, chrono-nutrition, and educational health was undertaken. Ayurvedic texts and reviews on contemporary understandings of Dinacharya, Nidra, and Aahara were also consulted^{3,4,14}. Finally, the analysis of the timetable was performed.

3.5 Analytical Framework

The analytical framework consisted of four key aspects of the described timetable analysis. First, the chronological organization of the timetable was determined. Next, the activities were related to the principles of modern chronobiology. Third, a similar comparative analysis was made in the context of the Ayurvedic principles of Dinacharya^{3,11}. Finally, a conclusion regarding the concordance of the timetable with the underlying principles was drawn.

3.6 Limitations

Since the current study aimed at describing and analysing the features of the institutional timetable, as opposed to studying its physiological or educational outcomes, the focus of the current research was narrowed down to the design of the timetable. Physiological measurements were not taken, and the results should not be over-interpreted as proof of efficacy but rather understood as descriptions of concordance. Similarly, no psychological measures were undertaken.

3.7 Study Design

Since the study did not involve any human subjects or interventions, no approval from the ethics committee was needed.

4. Results

4.1 Development of the Institutional Timetable

The educational timetable that was eventually developed at Sri Sathya Sai University for Human Excellence was the result of an extended period of planning that lasted for approximately three years. It was not developed in a vacuum, but rather it was gradually adjusted to best suit the needs of the University, taking into account both institutional goals and the needs of the students in terms of physical, intellectual, emotional, and spiritual development.

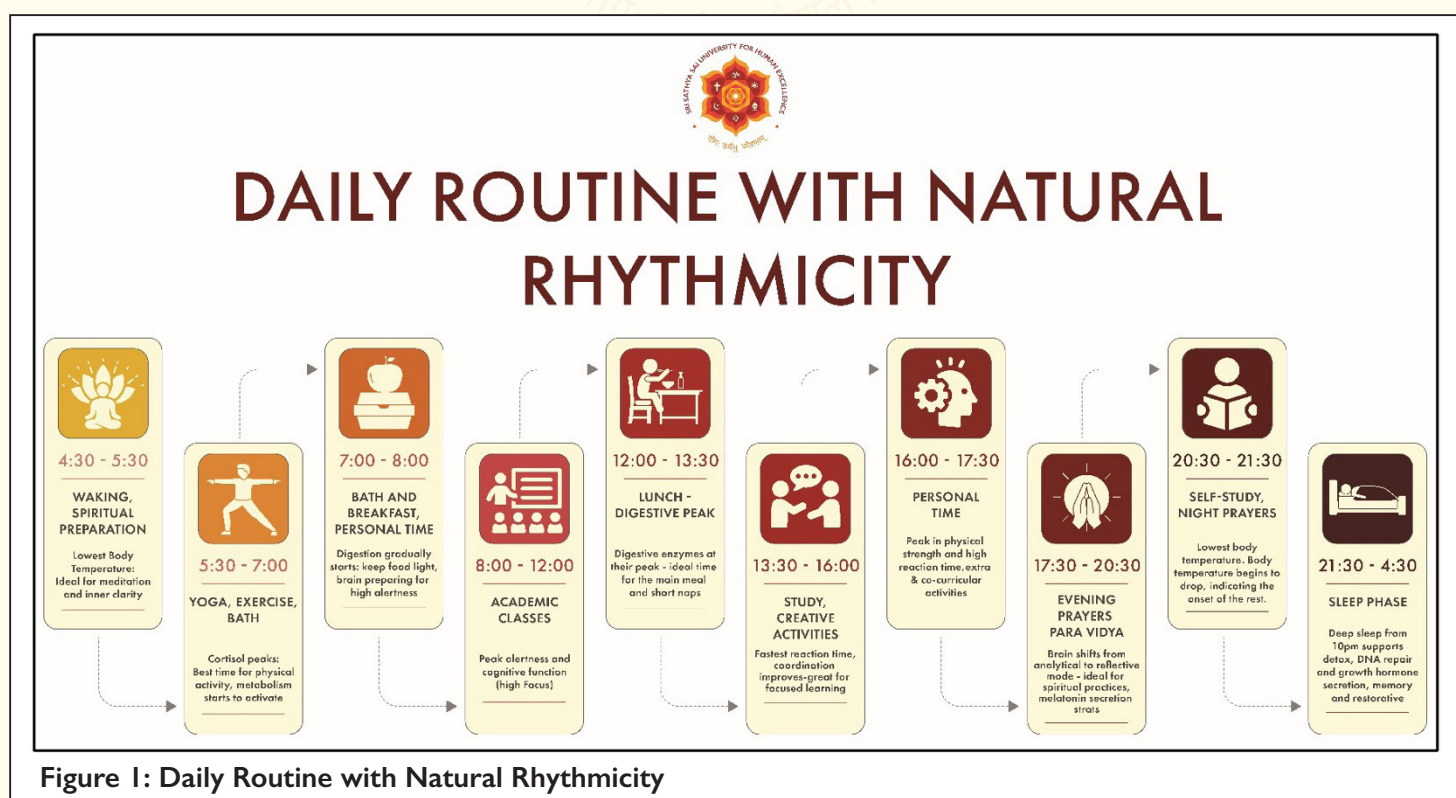


Figure 1: Daily Routine with Natural Rhythmicity

The primary emphasis was placed on establishing a consistent daily rhythm that would allow for both the needs of a residential university to be met, as well as the students' well-being. Subsequent iterations of the project then focused on the allocation of time to specific activities, as well as the division of the day into segments that would allow for a balanced mix of sleep, meals, and other activities. The final product was a set of timetables that were developed in a coordinated manner that fit the goals of the University.

4.2 Structure of the Annual Timetable

In order to best fit the needs of the institution and its students, separate timetables were created for each category of days that fell within the annual academic calendar. They included days of work, examinations, vacations, Shibhira, Dasara, sports, Sundays, holidays, conferences, and internships.

Although the amount of time dedicated to specific activities varied from one timetable to the other, they were all coordinated in terms of the overall daily schedule. The primary physiological needs of the students, including the time dedicated to eating and sleeping, were consistent across all timetables, with variations in the amount of time dedicated to academic, experiential, and co-curricular activities depending on the purpose of the day ³.

4.3 Organization of Daily Activities

The working-day schedule was the primary reference point for all other timetables that were developed by the University. It can be seen that it follows a logical progression, starting with activities that would help students prepare themselves for the day ahead. Instructional time was then scheduled during daylight hours, with experiential, personal, and recreational activities being scheduled during the afternoon. Evening activities were then organized in a way that would allow for a smooth transition into the night ^{4,6}. It should also be noted that the timetable was not focused on academic instruction exclusively, but rather it attempted to organize a full set of activities that would need to be completed throughout the day.

4.4 Distribution Across the Five Educational Domains

One of the most fascinating features of the working-day schedule is how the five major domains of human development - Spiritual, Intellectual, Personal, Experiential, and Regenerational - were incorporated into the schedule. This development is as follows:

As can be noticed, depending on the type of day, different domains were given preference in the number of hours allocated to them, in some cases, working days saw a strong emphasis on intellectual development, and hours for the remaining domains were allocated. In contrast, the days designated to devote time to the examination had a larger number of hours devoted to intellectual development.

Days that were devoted to internships had a strong emphasis on learning through experience, while the days assigned to sports had, as one might expect, a strong emphasis on physical development. Lastly, as it is clear from the spirit of the University, the spiritual development of the students was catered for in all the menus.

4.5 Alignment with Circadian Principles

The university timetables demonstrate the inclusion of various circadian principles as the schedules for the various types of days had a lot in common. Irrespective of the type of day, students' wake up and sleep times, as well as meal-times, were kept the same, helping to promote the consistency of their sleep cycles. The same can be said of times of the day for which the schedules incorporated the least physically strenuous, and relatively lighter, instructional activities, evening activities included for the students in preparation for sleep were also, less strenuous in nature.

It is clear from the employment of various circadian principles that significant thought has been applied to the institutional timetables from the perspective of the students' circadian activities rather than the inverse ¹⁶.

4.6 Key Observations

An analysis of the institutional timetables that were developed by Sri Sathya Sai University for Human Excellence allows for several key observations to be made. First of all, it can be noted that regardless of the category of day, the daily schedule remained largely consistent throughout the academic year.

Table 1: Demographic Profile of Students at SSSUHE

Total Students	897	Percentage
Below Poverty	719	80.156076
Boys	448	49.944259
Girls	449	50.055741
First Generation Graduate	553	61.649944
First Generation Literate Count	257	28.651059
Rural	588	65.551839

The demographic profile of the students shows that the university has learners from different states, age groups, socio-economic backgrounds, and educational backgrounds.

Second, it can be seen that the focus of the timetables was not on academic instruction exclusively, as they also took into account the spiritual, physical, and experiential development of the students, as well as the need for rest and recovery. Third, it can be seen that the activities were organized in a logical progression throughout the day, with more intensive activities being scheduled during daylight hours and evening activities being focused on lighter activities. Fourth, it can be noted that the timetables allowed for a high degree of institutional flexibility while still following the general circadian principles.

Finally, the five-domain approach used by the University is a good example of how a single educational timetable can be used to balance the needs of multiple areas of development. All in all, it can be concluded that the institutional timetables developed by Sri Sathya Sai University for Human Excellence represent a truly integrated approach to education.

5. Discussion and Conclusion

By using chronobiology in the creation of institutional educational frameworks, the current study expands on earlier applications of chronobiology in personalized lifestyle solutions. Although earlier research has examined the effects of circadian rhythms on sleep, metabolism, and cognitive development as well as their relationship to health, there hasn't been as much published on how these discoveries relate to university scheduling ^{1,3,4}. The SSSUHE Experience demonstrates how educational schedules can be created using the idea of biological time while taking into account all institutional and academic issues.

The uniformity of academic and institutional days across major categories is an illustration of the new schedule's flexibility. The arrangement of waking, eating, physical activity, and sleep is maintained to the greatest extent possible, even though workdays, tests, internships, athletic schedules, and vacations need significantly changing time divisions. This is consistent with modern theories of circadian control of behavior, which demonstrate how regular behavioral control maintains the body's biological clock ^{3,6}.

Additionally, the study acknowledges the intriguing convergence between contemporary chronobiology and the Dinacharya Ayurvedic tradition ¹³. The two approaches agree on strict daily schedules, punctual completion of daily tasks, daylight physical exercise, and sufficient sleep, even though they concentrate on distinct fields of study and employ different ideas ⁵.

This study demonstrates the differences between these two fields of study and the combined models they provide, which can be very helpful in the construction of educational models, rather than arguing that they are the same. In the field of health, this design would be especially useful for integrating contemporary scientific ideas and evidence with conventional methods.

The SSSUHE framework's recognition that education is more than merely what takes place in the classroom is a key component. By incorporating the Spiritual, Intellectual, Personal, Experiential, and Regenerational domains into its schedule, the SSSUHE framework clearly sets itself apart from other schedules that prioritize academic instruction over personal growth, wellbeing, and recuperation. The domain-based framework provides educational planners with a strong tool to assess how well the institution's objectives are applied to the many areas of student life.

Additionally, the results go beyond residential universities. A number of the framework's fundamental concepts, such as the scheduling of learning interventions using biological time, the balance of learning interventions, and the integration of both recovery and movement, could be applied in schools, colleges, and professional education systems, even though it is unlikely that the entire framework could be directly relevant to other institutions ^{9,12}. The design of timetables as part of the learning environment has to be a targeted topic as more and more higher education addresses the issues of student mental health, stress, and lifestyle-related diseases ⁹.

This study has certain limitations. The creation of a schedule was the main topic of discussion rather than how it actually affects pupils. Because of this, the results are highly consistent with some of the fundamental principles of chronobiology and Ayurveda; however, no connections to improvements in academic achievement, psychological well-being, or physical health were found. Another problem is that this framework was created for totally residential universities, which have a single educational philosophy. As a result, it will probably need to be adjusted to be applicable in various settings.

Future studies on the subject should concentrate on the educational and health results of students' lives controlled by biologically optimized timetables rather than just analyzing the schedule. To offer strong evidence for the efficacy of this strategy, longitudinal studies evaluating the effectiveness of such educational settings with control groups of students attending residential and non-residential educational institutions are necessary ¹.

This study emphasizes how chronobiology and the Ayurvedic idea of Dinacharya can be used to structure instructional procedures at residential universities. Over the course of three years, it was carried out using the iterative feedback loop method, which aided in optimizing the first iteration of the schedule. The study demonstrates how the residential education idea can incorporate biological rhythms into the planning of extracurricular, recreational, and instructional activities.

This study uses the example of SSSUHE to show how the ideas of contemporary chronobiology and traditional Indian Ayurveda might be used in practice, but it makes no claims about providing a general solution for optimizing the time schedule of students at residential educational institutions. According to the study, students' health can be enhanced and the educational process can be optimized by scheduling their time according to their biological rhythms and Ayurvedic principles. Time management will be a crucial component of the entire experience as residential education continues to gain popularity among parents and students worldwide owing to its distinctive educational results.

Supplementary Materials: Not Applicable

Author Contributions: Conceptualization of the research work by Dr. Thoathathri Venugopal. Analysis, flow of the paper and coordination with infographic design by Roopa C.

Both the authors have read and agreed to the published version of the manuscript. The tables were sent for reference of reviewers and need not be included for publication of the paper.

Funding: None

Institutional Review Board Statement: Not Applicable

Informed Consent Statement: Not Applicable

Data Availability Statement: Not Applicable

Acknowledgements: We thank Sri Sathya Sai Premamruta Prakashana for designing infographic pictures of distribution of Nutrients in the menu pattern of Sri Sathya Sai University for Human Excellence.

Conflict of interest declaration: We have no financial, personal, professional, or institutional conflicts of interest that could have influenced the conduct, findings, or interpretation of this research.

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