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INDOOR ENVIRONMENTAL QUALITY IN HEALTHCARE FACILITIES: BIOLOGICAL PATHWAYS AND MOLECULAR BIOMARKERS ASSOCIATED WITH PATIENT RECOVERY—A SYSTEMATIC REVIEW

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ABSTRACT
Indoor Environmental Quality (IEQ), including indoor air quality, thermal conditions, lighting, acoustics, and the visual environment, may influence physiological processes relevant to recovery. However, evidence linking architectural exposures to molecular and epigenetic outcomes in healthcare settings is dispersed across clinical, environmental-health, and controlled indoor studies, and the directness of this evidence varies considerably. This systematic review synthesizes and critically evaluates evidence on associations between IEQ exposures and molecular, neuroendocrine, inflammatory, oxidative-stress, circadian, and autonomic biomarkers relevant to patient recovery. A secondary objective is to distinguish direct healthcare evidence from mechanistic or indirect evidence derived from controlled indoor and non-hospital settings. The review was structured in accordance with PRISMA 2020 guidelines. A comprehensive search was conducted across PubMed/MEDLINE, Embase, Web of Science, Scopus, and the Cochrane Library for studies published from January 2000 to February 2026. Eligibility was defined using a PICO/PECO framework. Due to substantial heterogeneity in populations and biomarker outcomes, findings were synthesized narratively. Risk of bias was evaluated using design-appropriate JBI critical appraisal instruments. Forty-eight studies were included. The most consistent biomarker evidence concerned indoor air quality, where particulate exposure and filtration studies reported changes in inflammatory and oxidative-stress markers (e.g., IL-6, CRP, 8-OHdG). Lighting interventions, particularly circadian-relevant exposures, were associated with altered expression of clock genes (*BMAL1*, *PER1*) and melatonin timing. Noise studies supported associations with cortisol and autonomic dysregulation (heart rate variability). Evidence linking thermal conditions to heat-shock pathways (HSP70/90) was predominantly mechanistic. Biophilic studies supported neuroendocrine stress reduction, while evidence for DNA methylation effects (e.g., *BDNF*, *SLC25A10*) was largely indirect and derived from green-space or prenatal exposure studies. The findings indicate that IEQ represents a potentially modifiable aspect of healthcare environments that may influence biological pathways associated with patient recovery. The available evidence is most consistent for inflammatory responses associated with air-quality exposures and circadian and neuroendocrine responses to lighting and noise. However, direct evidence that architectural or environmental interventions in healthcare settings induce changes in gene expression or epigenetic profiles remains limited. This evidence gap underscores the need for longitudinal, hospital-based studies integrating standardized IEQ measurements with transcriptomic and epigenomic analyses and clinically relevant recovery outcomes.

KEYWORDS: Indoor Environmental Quality; Molecular Biomarkers; Circadian Rhythm; DNA Methylation; Hospital Architecture; Gene Regulation; Patient Recovery.

1. INTRODUCTION

The built environment of healthcare facilities continuously shapes environmental exposures experienced by patients, staff, and visitors. Hospital design has traditionally emphasized clinical efficiency, operational flow, infection prevention, and patient safety. More recent salutogenic and evidence-based design approaches additionally consider whether environmental conditions can support stress reduction, physiological stability, and recovery (Du et al., 2024). Indoor Environmental Quality (IEQ) integrates indoor air quality (IAQ), thermal conditions, acoustic exposure, lighting, and visual characteristics such as access to nature and biophilic elements. These domains may interact with human physiology through inflammatory, oxidative, neuroendocrine, autonomic, and circadian pathways (Rad, 2026); however, the strength and directness of evidence differ across IEQ domains and populations.

Hospitalization is frequently accompanied by illness-related stress, pain, pharmacological treatment, disrupted sleep, and repeated exposure to unfamiliar environmental stimuli. In intensive care units (ICUs) and general wards, noise, nocturnal light exposure, altered day–night cues, and air-quality problems may add to this physiological burden (Jiménez-Pastor et al., 2025). Activation of the sympathetic nervous system (SNS) and hypothalamic–pituitary–adrenal (HPA) pathways provides a biologically plausible link between environmental stress and changes in cortisol, autonomic regulation, immune activity, and inflammation. Nevertheless, adverse clinical outcomes in hospitalized patients are multifactorial, and environmental exposures should therefore be interpreted as potentially modifiable contributors rather than isolated causes of delayed recovery.

Advances in molecular and environmental health research have expanded the range of objective indicators available to characterize biological responses to indoor exposures. Inflammatory cytokines such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α), acute-phase reactants such as C-reactive protein (CRP), neuroendocrine hormones including cortisol and melatonin, oxidative-stress markers such as 8-hydroxy-2′-deoxyguanosine (8-OHdG), and autonomic indices such as heart rate variability (HRV) can provide complementary measures of exposure-related physiological response (Fawzy et al., 2024; Ren et al., 2024). Circadian gene expression (e.g., *CLOCK*, *BMAL1*) and epigenetic markers (e.g., DNA methylation, microRNA) are also increasingly studied in environmental research, although their application to architectural interventions in operational healthcare facilities remains comparatively limited.

Despite a growing literature on IEQ and health, the evidence is fragmented across building science, environmental epidemiology, clinical research, and molecular biology. In particular, direct hospital-based evidence should be distinguished from mechanistic evidence obtained in controlled indoor environments and from indirect evidence involving broader environmental exposures. This review therefore evaluates five IEQ domains: indoor air quality, thermal conditions, lighting, noise, and the visual environment, and maps the reported biomarkers and biological pathways while explicitly considering the setting and directness of the evidence. Tailored for researchers in genetics and molecular biology, the proposed framework is intended as an evidence map and hypothesis-generating model rather than proof of a single, definitive causal pathway from architecture to gene regulation and patient recovery.

2. METHODOLOGY

2.1. Research Question and Protocol

The primary research question was: In healthcare facilities and clinically relevant controlled indoor environments, how are specific IEQ exposures—air quality, thermal conditions, lighting, noise, and visual environmental characteristics—associated with molecular, epigenetic, neuroendocrine, inflammatory, oxidative stress, circadian, or autonomic biomarkers relevant to patient recovery? This systematic review was structured and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2020) statement (Page et al., 2021) (Figure 1).

2.2. Eligibility Criteria (PICO/PECO Framework)

Evidence was classified by setting as: (i) direct healthcare evidence from operational clinical facilities; (ii) clinically relevant controlled indoor evidence; or (iii) indirect mechanistic evidence. The third category was retained only when it informed a prespecified biological pathway and was interpreted separately from direct hospital evidence.

- **Population:** Hospitalized or clinically managed human participants in ICUs, inpatient wards, maternity, rehabilitation, or orthopedic settings. Healthy participants in controlled indoor studies were considered only as indirect mechanistic evidence.
- **Intervention/Exposure:** Prespecified IEQ exposures included indoor particulate matter (PM2.5, UFPs), VOCs, CO_2, particle filtration (HEPA); ambient thermal exposure; spectral and circadian-relevant lighting; environmental noise (>45 dB) and noise-control interventions; and visual or biophilic environmental exposure. Outdoor green-space exposure was eligible only as indirect epigenetic evidence.
- **Comparison:** Standard or usual-care indoor conditions, lower- or higher-exposure conditions, pre-intervention periods, sham filtration, or conventional lighting.
- **Outcomes:** Primary outcomes were objective molecular, biochemical, or genetic biomarkers, including inflammatory mediators (e.g., IL-6, IL-1β, TNF-α, CRP), oxidative-stress markers (e.g., 8-OHdG), neuroendocrine markers (cortisol, melatonin), circadian gene-expression markers (*BMAL1*, *CLOCK*, *PER*, *CRY*), heat-shock pathway markers (HSP70, HSP90), and epigenetic outcomes (DNA methylation, miRNA). Secondary outcomes included physiological measures (HRV) and clinical recovery outcomes (sleep architecture, delirium, length of stay).

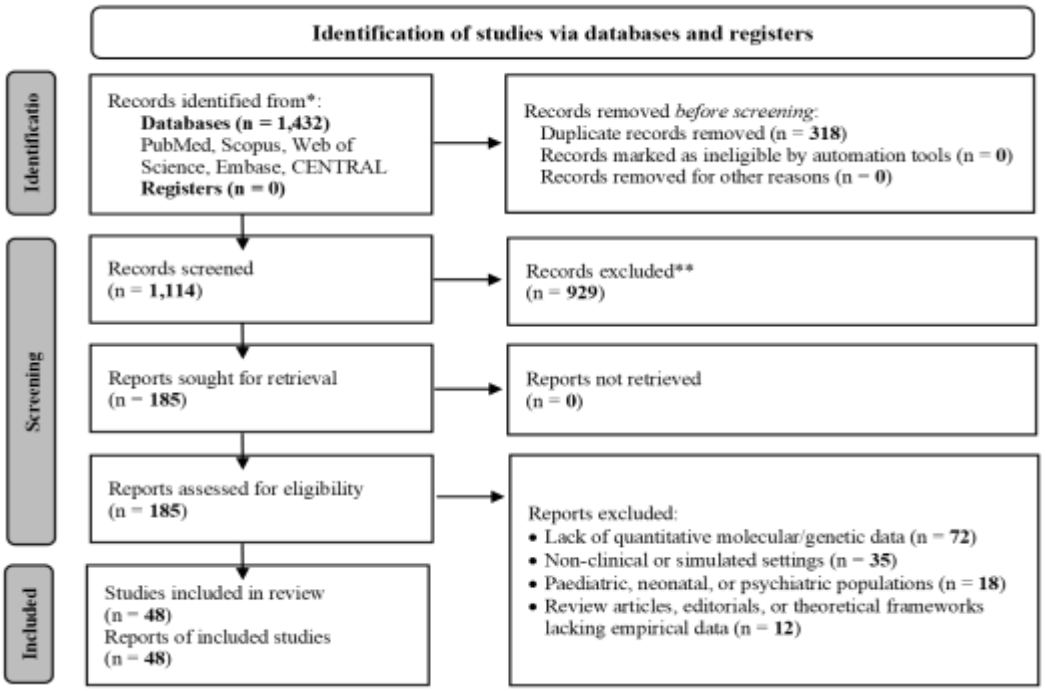

Figure 1: PRISMA flow diagram. The researchers based on Page et al. (2021).

2.3. Search Strategy and Study Selection

A comprehensive, computerized literature search was conducted across PubMed/MEDLINE, Embase, Web of Science, Scopus, and the Cochrane Library for articles published from January 1, 2000, to February 2026. The search strategy utilized combinations of MeSH and free-text terms. The core Boolean search string used across databases was: ("Indoor Environmental Quality" OR "hospital architecture" OR "built environment" OR "indoor air quality" OR "HEPA" OR "noise pollution" OR "circadian lighting" OR "thermal comfort" OR "biophilic design") AND ("biomarker*" OR "IL-6" OR "CRP" OR "cortisol" OR "melatonin" OR "DNA methylation" OR "epigenetics" OR "gene expression" OR "CLOCK" OR "BMAL1" OR "HSP") AND ("patient recovery" OR "hospital*" OR "intensive care unit" OR "ward").

Two independent reviewers screened titles and abstracts using Rayyan software to ensure independent blinding during the selection process. Full-text articles were subsequently evaluated against the eligibility criteria. Disagreements were resolved through consensus or consultation with a third independent reviewer. Data extraction was performed using standardized forms and double-checked for accuracy. Animal studies, editorials, and studies relying exclusively on subjective questionnaires without objective biomarker data were excluded.

2.4. Risk of Bias and Quality Assessment

Risk of bias was evaluated independently by two reviewers using design-appropriate Joanna Briggs Institute (JBI) critical appraisal tools for randomized controlled trials (RCTs), quasi-experimental studies, cohort studies, and analytical cross-sectional studies (Barker et al., 2023). Appraisal focused on allocation, blinding, exposure and outcome measurement, confounding, follow-up, and statistical analysis. Study-level judgments are reported to inform the interpretation of the synthesis, particularly where evidence was indirect or observational.

Due to substantial heterogeneity in IEQ exposure definitions, study populations, biomarker assays, and study designs, a meta-analysis was deemed inappropriate. A structured narrative synthesis was organized by the five prespecified IEQ domains in line with Synthesis Without Meta-analysis (SWiM) reporting guidelines (Campbell et al., 2020).

3. RESULTS

The study-selection process yielded 48 included records for the broader evidence synthesis. Because the evidence base was heterogeneous, results are presented as a structured narrative synthesis. Direct healthcare evidence is distinguished from controlled indoor and indirect mechanistic evidence throughout the synthesis.

Theme 1: Indoor Air Quality (IAQ)

Fine (PM2.5) and ultrafine particles (UFPs) can reach the distal respiratory tract and are biologically capable of promoting oxidative and inflammatory signaling. Across indoor exposure and filtration studies, higher particle

exposure was associated with changes in inflammatory or oxidative-stress biomarkers.

PM2.5, VOCs, and Systemic Inflammation: Inhalation of PM2.5 and UFPs is associated with the systemic release of pro-inflammatory cytokines (IL-6, IL-8, IL-1β) and acute-phase reactants (CRP/hsCRP). These findings are compatible with oxidative stress and NF-κB-related inflammatory pathways, though pathway activation was not directly measured in every included study. For instance, Cui et al. (2025) measured CRP levels in patients with acute COPD exacerbations, finding that PM2.5 elevation during hospitalization significantly increased systemic CRP and altered coagulation (prothrombin time).

Filtration Interventions: HEPA-based filtration and combined filtration systems (e.g., electrostatic precipitators) can reduce indoor particle concentrations. Controlled intervention evidence indicates that filtration may modify selected inflammatory and oxidative-stress biomarkers, but effects vary by baseline exposure and biomarker type (Day et al., 2018). A recent meta-analysis of RCTs demonstrated that indoor air filtration significantly reduced IL-6 and 8-OHdG levels, acting as a direct modifier of systemic oxidative stress (Ren et al., 2024). Fawzy et al. (2024) further reported strong associations between indoor particulate concentrations (specifically UFPs) and elevated IL-8, IL-1β, and interferon-γ among former smokers with COPD. Collectively, these studies support a modifiable exposure–biomarker relationship; however, they do not definitively establish that filtration alone shortens hospital length of stay.

Theme 2: Thermal Comfort

Thermal conditions may influence sleep, cardiovascular strain, autonomic regulation, and cellular stress responses. However, compared with IAQ and lighting, direct evidence linking room-temperature interventions in operational healthcare facilities to molecular biomarkers of recovery is limited.

Cortisol and the HPA Axis: Ambient temperature directly influences sleep architecture and autonomic tone. Extreme or poorly tolerated heat exposure may increase cardiovascular strain, elevate cortisol secretion, and prompt autonomic dysregulation. Nevertheless, the current evidence base does not support a universal "moderately cool" hospital temperature as a targeted molecular intervention to lower cortisol. Patient age, illness, medication, and clinical requirements heavily modify thermal responses.

Heat-Shock Pathways: At the cellular level, thermal stress induces the unfolding of proteins, triggering the heat shock response mediated by the transcription factor HSF-1. This upregulates heat shock proteins, notably HSP70 and HSP90, which act as molecular chaperones preventing apoptosis. While physiological adaptation to thermal variations can upregulate HSP70 and enhance cellular cytoprotection, evidence demonstrating that routine hospital room-temperature modification alters HSP70/HSP90 expression in recovering patients is insufficient. The heat-shock pathway is therefore included in the conceptual framework as a candidate molecular mechanism requiring direct clinical validation.

Theme 3: Lighting

Light is a major environmental time cue for the human circadian system. In healthcare settings, reduced daytime light and nocturnal light exposure contribute to circadian disruption, particularly among patients in ICUs.

Circadian Genes (*CLOCK*, *PER*, *CRY*, *BMAL1*): Light detected by intrinsically photosensitive retinal ganglion cells (ipRGCs) contributes to signaling to the suprachiasmatic nucleus (SCN), which coordinates circadian timing. *CLOCK–BMAL1* and *PER–CRY* transcriptional-translational feedback loops are central components of molecular circadian regulation. Direct measurement of clock-gene expression in ICU populations has shown that ICU stays exceeding 7 days disrupt *BMAL1* and *PER1* expression, correlating with adverse cardiovascular events (Jiménez-Pastor et al., 2025).

Melatonin and Clinical Relevance: Altered melatonin profiles have been reported in critically ill populations, correlating directly with fragmented sleep and acute brain dysfunction (delirium). Human controlled-light studies support the ability of dynamic spectral lighting to alter circadian phase. For example, dynamic lighting systems delivering blue-enriched light during the day (high melanopic equivalent daylight illuminance) and blue-depleted light at night successfully advanced the circadian phase, restored normal melatonin rhythms, and significantly increased nocturnal sleep duration (Rahman et al., 2022; Vethe et al., 2021).

Theme 4: Noise

Hospital noise is a persistent environmental exposure generated by alarms, equipment, and staff activity, frequently exceeding recommended nighttime values (Pan et al., 2025).

Cortisol, HPA Axis, and Stress Biomarkers: Noise acts as an acute stressor, activating sympathetic (SAM) and HPA-axis responses. This results in the release of catecholamines and sustained elevations in serum and salivary cortisol. Chronic noise exposure in patient wards causes profound dysregulation of this axis, promoting systemic inflammation and delaying functional recovery (Pan et al., 2025). Clinical interventions, such as noise management combined with skin-to-skin contact in maternity wards, have successfully buffered noise-induced cortisol spikes in neonates and mothers, stabilizing cardiorespiratory function (Li et al., 2025).

Heart Rate Variability (HRV) and Recovery: The autonomic imbalance caused by hospital noise is highly

quantifiable through HRV. In a retrospective cohort of patients with coronary artery disease (CAD), treatment in noise-controlled wards (sub-45 dB) significantly improved HRV parameters (increased SDNN, lowered LF/HF ratios), lowered salivary cortisol, reduced the incidence of recurrent angina, and accelerated hospital discharge compared to standard noisy wards (Wang et al., 2025).

Theme 5: Visual Environment and Colours

The intentional integration of natural visual elements into the built environment—termed biophilic design—exerts restorative effects on patient physiology.

Neuroendocrine and Autonomic Responses: Guided by Stress Recovery Theory (SRT), visual exposure to natural stimuli actively promotes autonomic nervous system recovery. Biophilic hospital spaces have been shown to rapidly decrease stress-induced cortisol, lower blood pressure, and increase parasympathetic activity (Yin et al., 2018). However, reductions in cortisol should be interpreted cautiously due to multiple clinical confounders.

Indirect Epigenetic Evidence (DNA Methylation): Epigenome-wide association studies (EWAS) demonstrate that prolonged exposure to green space directly influences DNA methylation (DNAm). For example, maternal exposure to urban green space has been shown to biologically buffer the impact of stress by modulating the methylation of the Brain-Derived Neurotrophic Factor (*BDNF*) gene in neonates, highlighting a neuroprotective epigenetic mechanism (Nazzari et al., 2023). Furthermore, green space access is associated with differentially methylated regions in genes regulating metabolism (*SLC25A10*) and extracellular matrix organization (*ADAMTS2*) (Alfano et al., 2023; Lacasaña et al., 2024). However, these findings are treated here as *indirect, hypothesis-generating evidence*, as they derive from prenatal/urban cohorts and do not directly prove that hospital colours or window views induce equivalent epigenetic changes in hospitalized patients.

Key Evidence Synthesis

To systematically map the evidence linking health care facilities' IEQ factors to molecular pathways and patient outcomes, the findings from selected landmark empirical studies and meta-analyses are aggregated in Table 1. Biological Mapping of Molecular Biomarkers to IEQ Factors is illustrated in Table 2. Study-level risk-of-bias considerations are reported in Table 3.

Table 1: Key Original Studies on IEQ, Molecular Biomarkers, and Patient Recovery

Study/ Author	Country	Healthcare/ Indoor Setting	IEQ Factor	Molecular/ Physiological Biomarker	Main Finding	Evidence Role & Design
Ren et al. (2024)	China	Simulated Indoor	IAQ (HEPA)	IL-6, CRP, 8-OHdG	HEPA filtration significantly reduced systemic inflammation (IL-6) and oxidative stress (8-OHdG).	Indirect mechanistic (Meta-analysis of RCTs)
Fawzy et al. (2024)	USA	Clinical (COPD)	IAQ (Air Cleaner)	IL-8, IL-1β, IFN-γ	UFPs and PM2.5 strongly associated with elevated IL-8, inflammation, and platelet activation.	Direct healthcare (RCT)
Day et al. (2018)	China	Office / Residential	IAQ (ESP + HEPA)	O3, P-selectin, BP	Combined filtration reduced PM2.5; ESP ozone production associated with platelet activation.	Indirect mechanistic (Crossover RCT)
Cui et al. (2025)	China	Hospital Admissions	IAQ (PM2.5)	CRP, Prothrombin Time	PM2.5 elevation during COPD exacerbations significantly increased systemic CRP.	Direct healthcare (Cross-sectional)
Lin et al. (2013)	Taiwan	Simulated Indoor	IAQ (AC/Filtration)	hs-CRP, 8-OHdG, HRV	Reducing indoor PM/VOCs via AC reduced oxidative stress, inflammation, and autonomic dysfunction.	Indirect mechanistic (Crossover Panel)
Wang et al., (2025)	China	Cardiology Ward	Noise Control	HRV (SDNN), Salivary Cortisol	Noise reduction significantly improved HRV, lowered cortisol, and shortened hospital stay in CAD patients.	Direct healthcare (Retrospective Cohort)
Li et al.	China	Maternity	Noise Control &	Serum Cortisol,	Noise control buffered HPA axis	Direct

Study/ Author	Country	Healthcare/ Indoor Setting	IEQ Factor	Molecular/ Physiological Biomarker	Main Finding	Evidence Role & Design
(2025)		Ward	Biophilia	HR, SpO2	stress, lowering maternal/neonatal cortisol and improving recovery.	healthcare (Retrospective Cohort)
Pan et al., (2025)	Switzer-land	Orthopedic Ward	Noise (>55 dB)	Salivary Cortisol, PSQI, HADS	High noise elevated cortisol, increased anxiety/depression, and delayed functional fracture recovery.	Direct healthcare (Retrospective Cohort)
Vethe et al. (2021)	Norway	Psychiatric Hospital	Lighting (Blue-depleted)	Melatonin, Sleep architecture	Blue-depleted evening lighting targeted ipRGCs, reducing melatonin suppression and improving sleep.	Direct healthcare (RCT)
Rahman et al. (2022)	USA	Space Analog / Indoor	Dynamic Circadian Lighting	Melatonin phase, Circadian clock	Dynamic lighting (blue-enriched day/depleted night) advanced circadian phase and aligned sleep.	Indirect mechanistic (Experimental)
Jiménez -Pastor et al. (2025)	Spain	Intensive Care Unit	General IEQ / Chrono disruption	Melatonin, *BMAL1*, *PER1*	ICU stays >7 days disrupted *BMAL1*/*PER1* expression and melatonin, correlating with adverse CV events.	Direct healthcare (Prospective Cohort)
Nazzari et al. (2023)	Italy	Maternity / Neonatal	Visual (Green Space)	*BDNF* DNA methylation	Green space buffered the impact of maternal anxiety on neonatal *BDNF* epigenetic methylation.	Indirect epigenetic (Cohort)
Lacasañ a et al. (2024)	Spain	Prenatal / Clinical	Visual (Green Space)	Placental DNAm (*SLC25A10*)	High green space exposure inversely associated with DNA methylation of metabolic genes in the placenta.	Indirect epigenetic (EWAS)
Alfano et al. (2023)	Europe	Birth Cohorts	Visual (Green Space)	Cord Blood DNAm (*ADAMTS2*)	Greenness associated with specific Differentially Methylated Regions (DMRs) in cord blood.	Indirect epigenetic (Meta-EWAS)
Du, et al. (2024)	Italy	Hospital Environment	Biophilic Design / Colours	Cortisol, HR, Pain Medication	Biophilic interventions enhanced stress recovery, reduced pain medication use, and improved mood.	Direct healthcare (Rapid Review)
Yin et al. (2018)	USA	Virtual Reality Hospital	Biophilic Design	Physiological Restoration	Virtual nature views in hospital rooms maximized restorative utility and physiological relaxation.	Indirect mechanistic (VR Experiment)

Table 2: Biological Mapping of Molecular Biomarkers to IEQ Factors

Biomarker	Biological Process	Clinical Significance in Patient Recovery	Primary Modulating IEQ Factor(s)
IL-6 / TNF-α	Systemic Inflammation	Markers of systemic inflammatory activity; potential relevance to tissue repair and disease burden.	IAQ (PM2.5, UFPs, Pathogens, VOCs)
CRP (hsCRP)	Systemic Inflammation	Acute-phase marker of systemic inflammation; clinically relevant but non-specific.	IAQ (PM2.5, VOCs)
8-OHdG / ROS	Oxidative Stress	Markers of oxidative damage/stress indicate lipid peroxidation and cellular aging.	IAQ (PM2.5, Gases), Thermal stress
Cortisol	HPA Axis Stress Response	Index of HPA-axis activity; prolonged dysregulation may be relevant to	Noise, Thermal Comfort, Lack of Biophilia

Biomarker	Biological Process	Clinical Significance in Patient Recovery	Primary Modulating IEQ Factor(s)
		metabolic/immune stress.	
Melatonin	Circadian Rhythm Regulation	Circadian hormone associated with sleep timing and antioxidant pathways; prevents ICU delirium.	Lighting (m-EDI spectra, daylight)
CLOCK / BMAL1	Gene Regulation (TTFL)	Core circadian transcriptional regulators with potential relevance to metabolic and immune timing.	Lighting (Light-dark cycles)
HSP70 / HSP90	Protein Chaperoning	Molecular chaperones involved in proteostasis and cellular stress responses.	Thermal Comfort (Temperature extremes)
DNA Methylation	Epigenetic Gene Silencing	Epigenetic regulation at specific loci (e.g., *BDNF*); healthcare-design relevance remains indirect.	Visual Environment (Green space exposure)
microRNA (miRNA)	Post-transcriptional Regulation	Post-transcriptional regulation; candidate pathway requiring direct healthcare evidence.	Emerging evidence (IAQ, Visual Environment)
HRV (SDNN / LF:HF)	Autonomic Nervous System	The autonomic index is influenced by vagal modulation and multiple clinical and measurement factors.	Noise, Visual Environment (Nature views)

Table 3: Study-Level Risk-of-Bias Assessment Using Design-Appropriate JBI Critical Appraisal Tools

Study	Design	JBI tool	Indicative appraisal	Key risk-of-bias considerations	Overall judgment
Ren et al. (2024)	Systematic review/meta-analysis of RCTs	JBI Systematic Reviews	9/11	Review-level evidence, not an original RCT. Publication-bias reporting requires caution.	Moderate
Fawzy et al. (2024)	Secondary exposure–biomarker analysis within RCT	JBI Analytical Cross-sectional	7/8	Objective PM and biomarker measures. Secondary association analysis and residual confounding limit causal attribution.	Low–moderate
Day et al. (2018)	Randomized double-blind crossover	JBI RCT	10/13	Objective measures. Small healthy-adult sample; short exposure; intervention-personnel blinding difficult.	Low
Cui et al. (2025)	Retrospective hospital exposure study	JBI Cohort	7/11	Large sample (1,284 hospitalizations). Retrospective exposure assignment and residual confounding.	Moderate
Wang et al., (2025)	Retrospective cohort	JBI Cohort	7/11	Defined CAD cohort. Non-random noise exposure, retrospective design, and residual care/environment confounding.	Moderate
Li et al. (2025)	Comparative clinical intervention	JBI Quasi-experimental	7/9	Objective neonatal cortisol. Skin-to-skin contact and noise management are bundled, limiting the isolation of the acoustic effect.	Moderate
Pan et al., (2025)	Retrospective exposure cohort	JBI Cohort	7/11	Standardized noise threshold. Non-random groups and residual confounding.	Moderate
Vethe et al. (2021)	Randomized crossover trial	JBI RCT	10/13	Quantified melanopic exposure. Very small sample	Low

Study	Design	JBI tool	Indicative appraisal	Key risk-of-bias considerations	Overall judgment
				(n=12) and healthy volunteers.	
Jiménez-Pastor et al. (2025)	Prospective observational ICU study	JBI Cohort	8/11	Direct ICU population, molecular measures. ICU chronodisruption is not a randomized IEQ intervention; confounding remains.	Moderate
Nazzari et al. (2023)	Mother–infant observational cohort	JBI Cohort	8/11	Objective *BDNF* methylation. Small sample, residential exposure proxy, and indirect relevance to hospital design.	Moderate
Alfano et al. (2023)	Prospective birth cohort / meta-EWAS	JBI Cohort	9/11	Objective methylation arrays. Observational greenness exposure and indirect healthcare relevance.	Low–moderate

4. DISCUSSION

The architectural design of healthcare facilities serves as the interface between a patient's vulnerable physiological state and continuous external environmental stimuli. The evidence synthesized in this review supports a biologically plausible relationship between healthcare IEQ exposures and molecular pathways relevant to recovery, but it does not demonstrate a uniform causal continuum across all domains. A more defensible interpretation is a graded evidence model in which environmental exposures may modify intermediate biological responses, while clinical recovery is simultaneously shaped by disease severity, treatment, and medication.

4.1 The Conceptual Framework of IEQ and Biological Responses

Based on empirical evidence, we propose the following comprehensive conceptual framework, mapping the trajectory from building engineering to molecular biology:

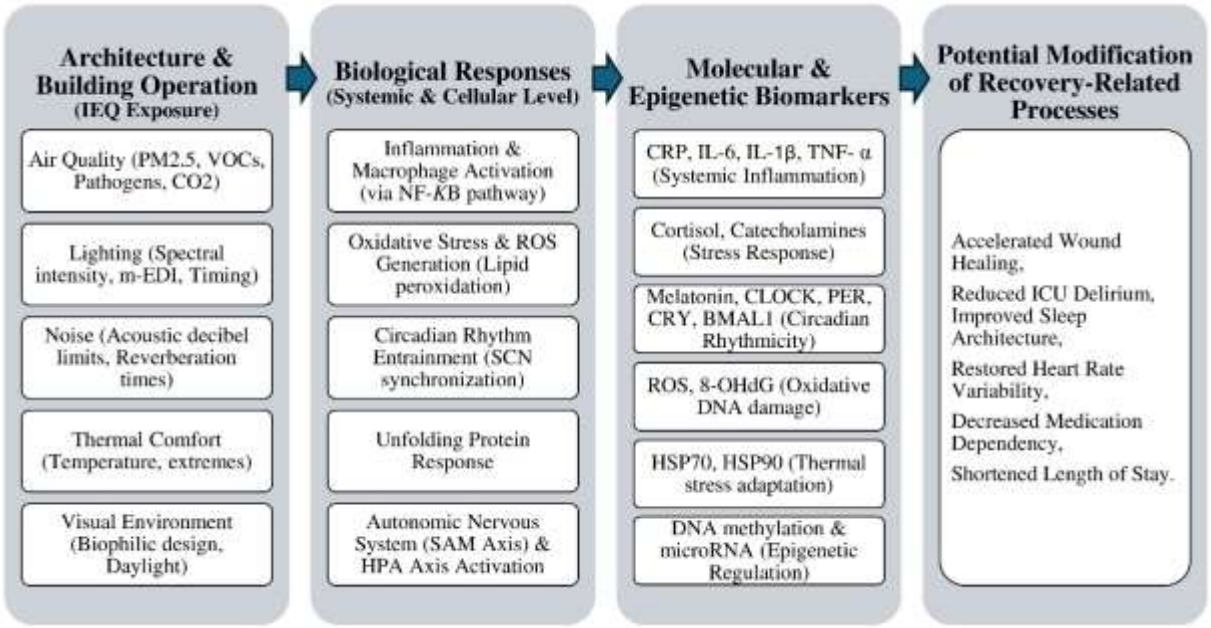

Figure 1: Comprehensive conceptual framework (The researchers).

This framework explicitly bridges the historical gap between facilities management and clinical medicine. It integrates environmental exposure with gene expression, identifying where direct healthcare evidence is available (e.g., noise and HRV) and where the relationship remains mechanistic or hypothesis-generating (e.g., thermal HSP pathways and visual-environment epigenetics).

4.2 Linking Built Environment to Gene Expression and Recovery

Lighting provides one of the clearest examples of a mechanistically defined IEQ pathway manipulating genetic transcription. Temporal and spectral light exposure influences ipRGC signaling and circadian timing (Bass et al., 2026). Standard hospital lighting, typically composed of static fluorescent tubes, critically lacks the short-wavelength intensity required during the day, while providing excessive blue light at night. This temporal dysregulation flattens the amplitude of the *CLOCK* and *BMAL1* feedback loops in the SCN, halting the natural suppression of melatonin and fundamentally breaking the patient's biological sleep-wake cycle (Jiménez-Pastor et al., 2025). Chronodisruption directly drives acute brain dysfunction and ICU delirium. Implementing dynamic circadian lighting actively upregulates *BMAL1* transcription, restoring the cellular rhythms necessary for immune function and neurological recovery (Rahman et al., 2022; Vethe et al., 2021).

Simultaneously, acoustic engineering profoundly dictates autonomic and neuroendocrine stability. The persistent background noise of a clinical ward maintains the HPA and SAM axes in a state of chronic hyperactivation. The resulting relentless secretion of cortisol induces a catabolic state, suppressing localized immune responses required for tissue healing (Pan et al., 2025). Upgrading architectural acoustic materials to absorb sound can directly lower salivary cortisol (Sui et al., 2026) and restore the Heart Rate Variability (HRV) necessary for cardiovascular recovery (Li et al., 2025; Wang et al., 2025).

Furthermore, mitigation of indoor air pollution via HEPA filtration reduces particulate exposure and has been associated with improved respiratory outcomes, with emerging evidence that it may blunt downstream inflammatory signaling (Li et al., 2026; Hernandez-Garcia et al., 2026). Inhalation of PM2.5 indoors continuously stimulates the NF-κB pathway in alveolar macrophages, sustaining high levels of IL-6 and CRP (Cui et al., 2025). This systemic inflammation diverts metabolic energy away from tissue repair and toward managing oxidative stress (elevated 8-OHdG). Strict IAQ control neutralizes this inflammatory trigger (Ren et al., 2024).

The visual-environment evidence requires the greatest caution. Biophilic indoor exposure supports neuroendocrine pathways and short-term stress restoration (Du et al., 2024; Yin et al., 2018). However, the most novel epigenetic findings—epigenome-wide association studies (EWAS) confirming that visual and physical exposure to green space drives differential DNA methylation at specific CpG sites, buffering stress-induced methylation of the *BDNF* gene—arise from prenatal or neighborhood green-space cohorts (Lacasaña et al., 2024; Alfano et al., 2023; Nazzari et al., 2023). They cannot currently validate hospital biophilia or colour palettes as direct "epigenetic therapeutics." Their value in this review is to identify candidate environmental-epigenetic pathways (*SLC25A10*, *ADAMTS2*) that could be tested prospectively in healthcare facilities using transcriptomic measurements.

4.3 Limitations and Future Directions

This review has several limitations. First, substantial methodological heterogeneity in measuring volatile IEQ factors (e.g., ambient PM2.5 monitoring vs. UFP dosimetry) precluded a pooled meta-analysis. Second, the evidence base combines direct healthcare studies with controlled indoor and indirect mechanistic studies, which reduces clinical directness. Third, many biomarkers (cortisol, CRP, HRV) are highly non-specific and strongly influenced by disease severity, medication, sleep, and care procedures; residual confounding is therefore likely in observational studies. Fourth, evidence for thermal regulation of HSP70/HSP90 in operational hospitals and biophilic design effects on DNA methylation or miRNA is particularly limited. Fifth, a narrative synthesis carries a risk of selective emphasis and publication bias. Finally, clinical recovery outcomes were not consistently measured alongside molecular biomarkers, preventing firm conclusions that biomarker changes mediate shorter lengths of stay.

Future research must leverage advanced wearable biosensors, continuous biomarker monitoring, and high-throughput transcriptomics to map real-time gene expression changes as patients move through differently designed hospital zones. Longitudinal, randomized hospital-based trials integrating quantitative IEQ monitoring with repeated epigenetic profiling are essential.

5. CONCLUSION

This systematic review indicates that Indoor Environmental Quality is a potentially modifiable component of healthcare environments with measurable associations with biological pathways relevant to patient recovery. Evidence is most consistent for inflammatory and oxidative-stress responses related to indoor particulate exposure and filtration, and for circadian and neuroendocrine responses related to light and noise. Thermal stress pathways involving heat-shock proteins are biologically plausible but insufficiently validated through room-level interventions in hospitalized patients. Similarly, while biophilic visual exposures support short-term stress restoration, current epigenetic evidence (DNA methylation) is largely indirect and should not be interpreted as definitive proof that hospital visual design modifies genetic expression. The proposed framework identifies a set of testable exposure–biomarker pathways rather than a definitive causal chain. Progress in this field requires rigorously designed, hospital-based molecular trials integrating quantitative IEQ monitoring with transcriptomic profiling to support a biologically informed approach to healthcare architectural design.

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