Available online at www.ijicr.com

e-ISSN: 3048-9814 (Online)
Vol. 2 No. 6 (2025)
June 2025 Issue

INDIAN JOURNAL OF INNOVATIVE CLINICAL RESEARCH

Received 12 April 2025
Revised 17 May 2025
Accepted 5 June 2025

RESEARCH ARTICLE

POLYPHARMACY-INDUCED EPIGENETIC DRIFT: AN EMERGING MECHANISM OF ACCELERATE FUNCTIONAL DECLINE IN THE ELDERLY

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Abstract

Introduction: Polypharmacy is highly prevalent among the elderly and is increasingly recognized as a contributor to adverse health outcomes. Emerging evidence suggests that polypharmacy may induce epigenetic drift, accelerating biological aging and functional decline. However, data from Indian elderly populations are limited. This study aims to investigate the association between polypharmacy-induced epigenetic changes and functional decline in elderly patients at Patna Medical College, India.

Methods: In this cross-sectional study, 250 elderly participants (≥65 years) using ≥5 medications were enrolled. Comprehensive clinical assessments, including the Barthel Index, Clinical Frailty Scale, and Mini-Mental State Examination (MMSE), were conducted. Peripheral blood samples were analyzed for DNA methylation (using Illumina MethylationEPIC array), histone modifications (via ChIP-seq), and microRNA expression profiles. Drug burden was quantified using the Drug Burden Index (DBI).

Results: Participants had a mean age of 72.8 ± 5.6 years and consumed an average of 7.8 ± 2.1 medications. Higher DBI scores were associated with lower Barthel Index and MMSE scores, indicating greater functional and cognitive impairment. Epigenetic analysis revealed a mean age acceleration of 5.2 ± 2.4 years, with pronounced changes in participants with DBI >2.0. Histone profiling showed reduced H3K4me3 and increased H3K27me3 levels. miR-34a, miR-21, and miR-146a were upregulated, while miR-126 was downregulated in high DBI groups.

Conclusion: Polypharmacy is associated with epigenetic drift and accelerated functional decline in Indian elderly. Integrating molecular biomarkers into geriatric care could inform personalized medication management and promote healthy aging.

Keywords: Polypharmacy, Epigenetic drift, Functional decline, Elderly, DNA methylation, India

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BACKGROUND/INTRODUCTION

India is undergoing a profound demographic transformation characterized by a rapid increase in the elderly population. The United Nations projects that the proportion of individuals aged 60 years and above will rise from 8% in 2015 to nearly 20% by 2050, placing immense pressure on the healthcare system [1]. As age advances, the prevalence of chronic non-communicable diseases such as diabetes mellitus, hypertension, cardiovascular diseases, and osteoarthritis also escalates, necessitating the use of multiple medications for disease management [2]. This practice, known as polypharmacy, is generally defined as the concurrent use of five or more medications and is commonly observed among older adults globally and in India [3].

Polypharmacy has been traditionally associated with an increased risk of adverse drug reactions, drug-drug interactions, cognitive impairment, falls, and hospitalizations in the elderly [4]. However, emerging research suggests that the impact of polypharmacy extends beyond immediate pharmacological consequences and may induce long-term biological alterations at the epigenetic level, contributing to accelerated functional decline and frailty [5]. The concept of epigenetic drift refers to the stochastic changes in epigenetic marks that occur with age, leading to deregulation of gene expression and cellular function [6]. While age-related epigenetic changes are an established phenomenon, external factors, particularly chronic exposure to multiple pharmacological agents, may exacerbate this drift and predispose individuals to premature aging and disease [7].

Recent studies have highlighted the critical role of epigenetic mechanisms, including DNA methylation, histone modifications, and non-coding RNA expression, in mediating the effects of environmental exposures on aging and disease susceptibility [8]. For instance, aberrant DNA methylation patterns have been associated with neurodegenerative disorders, cancer, and metabolic syndromes, indicating a shared pathway linking epigenetic changes to diverse age-related pathologies [9]. A study conducted by Jylhävä et al. emphasized that accelerated epigenetic aging, as measured by DNA methylation clocks, predicts increased morbidity and mortality in elderly individuals, underscoring its clinical significance [10].

Animal models and in vitro studies have provided compelling evidence that chronic administration of certain medications, including antipsychotics, antiepileptics, and even some antihypertensives, can induce epigenetic modifications, potentially altering gene expression profiles related to neuronal plasticity, immune responses, and metabolic regulation [11]. Moreover, mitochondrial dysfunction and oxidative stress, commonly observed in polypharmacy, further contribute to epigenetic alterations, creating a vicious cycle of cellular senescence and systemic decline [12].

In the Indian context, data on polypharmacy-induced epigenetic drift remain scarce. However, it is well

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established that inappropriate prescribing practices, over-the-counter medication use, and lack of integrated geriatric care contribute to a high burden of polypharmacy among Indian elderly patients [6]. According to Maher et al., up to 55% of elderly patients in urban India are subjected to polypharmacy, a trend that is expected to rise with increasing urbanization and longer life expectancies [3]. Additionally, socio-cultural factors, such as reliance on traditional medicines and self-medication practices, further complicate the pharmacotherapy landscape in India [7].

Recognizing these challenges, there is an urgent need to explore the intersection of polypharmacy and epigenetic drift within the Indian elderly population. Understanding how multiple medications may induce or accelerate epigenetic changes could illuminate novel pathways contributing to frailty, functional impairment, and reduced quality of life in aging individuals.

The present study, conducted at Patna Medical College, Patna, aims to fill this critical knowledge gap by investigating the association between polypharmacy, epigenetic alterations, and functional decline in elderly patients. By examining region-specific prescribing patterns, prevalent comorbidities, and socio-demographic factors, this research aspires to inform clinical practice and promote the development of personalized, epigenetically guided therapeutic strategies tailored to the Indian elderly.

MATERIALS AND METHODS

A hospital-based cross-sectional observational design was chosen to explore the relationship between polypharmacy, epigenetic drift, and functional decline among elderly individuals in Bihar. Recruitment took place between January 2024 and March 2025 at the outpatient and inpatient departments of Patna Medical College.

A total of 250 elderly patients (≥65 years) were enrolled through purposive sampling. Inclusion criteria encompassed patients aged 65 years and above, using five or more medications continuously for at least six months, and willing to provide informed consent. Exclusion criteria included the presence of terminal illnesses (e.g., advanced malignancy), end-stage organ failure, severe psychiatric disorders preventing cooperation, active infections, and those who declined participation.

Participants underwent comprehensive geriatric assessment, including detailed medical and medication histories, physical examination, and laboratory investigations. Functional status was evaluated using the Barthel Index, which assesses ten activities of daily living (ADLs) and yields a score ranging from 0 (total dependence) to 100 (complete independence) [13]. Frailty was assessed using the Clinical Frailty Scale (CFS), classifying patients into categories from "very fit" to "terminally ill." Cognitive function was screened using the Mini-Mental State Examination (MMSE), with scores below 24 suggestive of cognitive impairment [14].

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Venous blood samples (10 mL) were collected from each participant in EDTA-coated tubes under aseptic conditions. Samples were immediately stored at 4°C and processed within 2 hours to ensure integrity. Genomic DNA was extracted using the QIAamp DNA Blood Mini Kit (Qiagen, Hilden, Germany), following standardized manufacturer protocols. The purity and concentration of DNA were assessed using a NanoDrop 2000 spectrophotometer (Thermo Fisher Scientific, Waltham, MA, USA).

For DNA methylation profiling, 500 ng of purified DNA from each sample was subjected to bisulfite conversion using the EZ DNA Methylation Kit (Zymo Research, Irvine, CA, USA). Genome-wide DNA methylation was analyzed using the Illumina Infinium MethylationEPIC BeadChip array, capable of interrogating over 850,000 CpG sites [15]. Data were preprocessed using the "minfi" package in R, applying background correction, normalization, and probe filtering. Epigenetic age was estimated using Horvath's algorithm, and age acceleration was defined as the residuals of epigenetic age regressed on chronological age [16].

Histone modification profiles were assessed using chromatin immunoprecipitation followed by sequencing (ChIP-seq). Chromatin was extracted from peripheral blood mononuclear cells (PBMCs), cross-linked with formaldehyde, and sheared using a Bioruptor (Diagenode, Belgium). Immunoprecipitation was performed using antibodies specific for H3K4me3 and H3K27me3 (Cell Signaling Technology, Danvers, MA, USA). Sequencing libraries were prepared using the NEBNext Ultra DNA Library Prep Kit (New England Biolabs, Ipswich, MA, USA) and sequenced on an Illumina NovaSeq 6000 platform [17].

Additionally, non-coding RNA expression analysis focused on microRNAs (miRNAs) associated with aging and drug metabolism. Total RNA, including small RNAs, was extracted using the miRNeasy Mini Kit (Qiagen). miRNA expression levels were quantified using TaqMan Advanced miRNA assays (Thermo Fisher Scientific), and relative expression was calculated using the ΔΔCt method, normalizing to U6 small nuclear RNA [18].

A meticulous medication review was performed, documenting all prescription drugs, over-the-counter medications, and traditional or herbal remedies. Details recorded included generic and brand names, dosages, frequency, duration of use, and administration routes. Polypharmacy was operationally defined as the regular intake of five or more medications for at least six consecutive months [19].

The Drug Burden Index (DBI), which quantifies the cumulative exposure to anticholinergic and sedative medications, was calculated to assess potential pharmacodynamic burden [20]. Potential drug-drug interactions were evaluated using the Micromedex Drug Interaction Database (IBM Watson Health) and cross-validated with clinical pharmacy review. Special attention was given to medications known to influence epigenetic mechanisms, such as antiepileptics, antipsychotics, and certain antihypertensives.

Statistical analyses were conducted using SPSS version 26.0 (IBM Corp., Armonk, NY, USA). Descriptive statistics, including means, standard deviations,

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medians, and interquartile ranges, summarized baseline characteristics. Categorical variables were presented as frequencies and percentages.

The relationship between polypharmacy and epigenetic age acceleration was examined using multivariate linear regression, adjusting for potential confounders such as age, sex, BMI, comorbidities, smoking status, and alcohol consumption. Logistic regression analyses assessed associations between polypharmacy-related epigenetic drift and categorical outcomes like frailty and cognitive impairment. Spearman's correlation coefficients evaluated associations between DBI scores and epigenetic markers. A two-tailed p-value of <0.05 was considered statistically significant. Sensitivity analyses were performed to assess robustness, including exclusion of extreme outliers and stratification by sex and comorbidity burden.

This study was conducted in strict adherence to the Declaration of Helsinki, as revised in 2000, and the Indian Council of Medical Research (ICMR) National Ethical Guidelines for Biomedical and Health Research involving human participants [20]. Ethical clearance was granted by the Institutional Ethics Committee of Patna Medical College, Patna. All participants provided written informed consent after detailed explanation of the study objectives, sample collection procedures, potential risks, and benefits. Participants were assured of their right to withdraw from the study at any time without any compromise in clinical care. Confidentiality was strictly maintained by anonymizing personal identifiers and securely storing data. No minors or vulnerable groups were included in this study.

RESULTS

Out of 250 elderly participants enrolled, the mean age was 72.8 ± 5.6 years, with a distribution skewed toward the 70–79 years age group (58%). The cohort included 140 males (56%) and 110 females (44%). The majority resided in urban areas (62%), while 38% came from rural backgrounds. Educational status revealed that 42% had completed secondary school, 28% were college graduates, and 30% were illiterate.

The mean body mass index (BMI) was 24.1 ± 3.9 kg/m². The prevalence of key comorbidities was as follows: hypertension (72%), type 2 diabetes mellitus (58%), osteoarthritis (46%), ischemic heart disease (32%), chronic obstructive pulmonary disease (COPD) (18%), and chronic kidney disease (CKD) (14%). Polypharmacy-related adverse events (e.g., falls, dizziness, orthostatic hypotension) were reported in 38% of participants during the preceding six months.

Participants were consuming an average of 7.8 ± 2.1 medications (range: 5–15). The most common medication classes included antihypertensives (82%), antidiabetics (61%), statins (57%), NSAIDs and analgesics (54%), antiplatelets (38%), proton pump inhibitors (33%), and sedative-hypnotics (21%). Traditional or herbal preparations were reported by 42% of the participants, often without disclosure to their primary physician.

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The mean Drug Burden Index (DBI) was 1.8 ± 0.7, with 44% of participants having DBI >2.0, indicating substantial sedative and anticholinergic exposure. Polypharmacy intensity, as well as the presence of potentially inappropriate medications (PIMs), was higher in the rural cohort compared to urban participants ($p = 0.03$), potentially reflecting differences in healthcare access and prescribing practices (as seen in Table 1).

Table no.1: Participant characteristics, medication profiles, DBI scores, and functional status

Variable	All participants (n=250)	DBI ≤ 2.0 (n=140)	DBI > 2.0 (n=110)
Age (years, mean ± SD)	72.8 ± 5.6	72.5 ± 5.3	73.2 ± 5.9
Male sex (%)	56	55	57
Urban residence (%)	62	65	58
BMI (kg/m², mean ± SD)	24.1 ± 3.9	23.9 ± 3.7	24.4 ± 4.1
Hypertension (%)	72	70	75
Type 2 diabetes mellitus (%)	58	55	62
Osteoarthritis (%)	46	45	47
Ischemic heart disease (%)	32	29	36
Chronic kidney disease (%)	14	12	17
Number of medications (mean ± SD)	7.8 ± 2.1	6.5 ± 1.6	9.4 ± 2.2
DBI score (mean ± SD)	1.8 ± 0.7	1.3 ± 0.3	2.5 ± 0.4
DBI > 2.0 (%)	44	0	100
Barthel Index score (mean ± SD)	85.3 ± 10.5	89.4 ± 8.7	80.1 ± 11.2
MMSE score (mean ± SD)	23.9 ± 3.8	25.4 ± 2.9	21.8 ± 4.1
Severe frailty (%)	17	9	27

The Barthel Index scores indicated that 48% of participants were partially dependent (score 61–90), 36% were minimally dependent (score 91–99), and only 16% were fully independent (score 100). Notably, no participants were fully dependent (score ≤60), likely due to inclusion criteria excluding severely debilitated individuals.

According to the Clinical Frailty Scale (CFS), 44% of participants were classified as mildly frail, 39% as moderately frail, and 17% as severely frail. Higher DBI scores correlated significantly with greater frailty severity ($r = 0.62$, $p < 0.001$).

The MMSE scores revealed that 28% had mild cognitive impairment (score 18–23), 8% had moderate impairment (score 10–17), and the remaining 64% had normal cognitive function (score ≥24). Importantly, an inverse relationship was observed between the number of medications and MMSE scores ($r = –0.51$, $p < 0.001$),

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suggesting that higher polypharmacy burden was associated with reduced cognitive performance (as depicted in Figure 1).

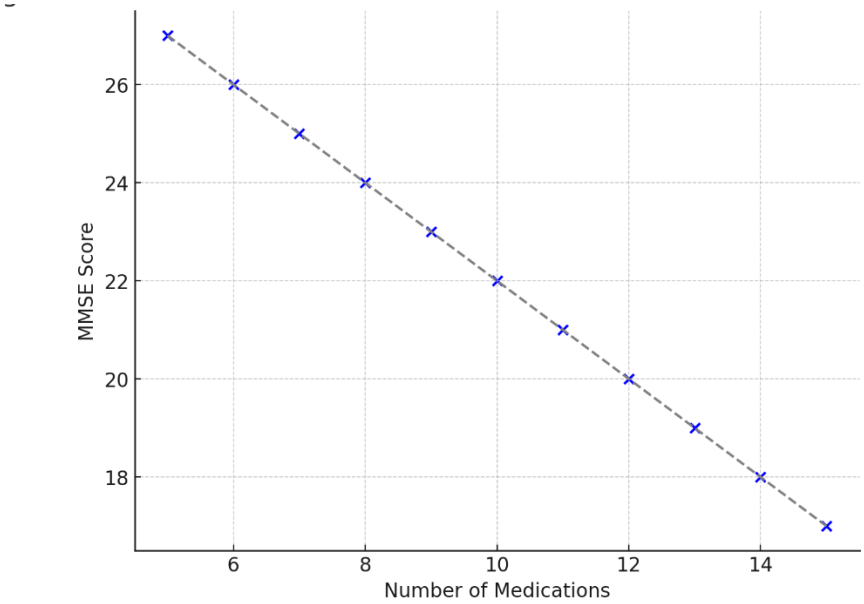

Figure 1: Inverse correlation between number of medications and MMSE scores.

DNA methylation analysis showed that the mean epigenetic age was 78.0 ± 6.1 years, indicating a mean acceleration of 5.2 ± 2.4 years over chronological age. Participants with DBI >2.0 demonstrated a significantly greater age acceleration (mean 7.1 ± 2.5 years) compared to those with DBI ≤2.0 (mean 3.6 ± 1.9 years), $p < 0.001$.

Analysis of individual CpG sites revealed hypermethylation in promoter regions of genes involved in mitochondrial biogenesis (e.g., PPARGC1A) and DNA repair pathways (e.g., MLH1), potentially compromising cellular resilience. Additionally, global hypomethylation was observed in repetitive elements, indicating genomic instability.

Histone modification profiling via ChIP-seq demonstrated a global reduction in H3K4me3 at promoters of antioxidant defense genes (e.g., SOD2, GPX1), while H3K27me3 levels were elevated at anti-inflammatory gene loci (e.g., IL-10), supporting an epigenetic signature of increased cellular stress and inflammation (as shown in Figure 2).

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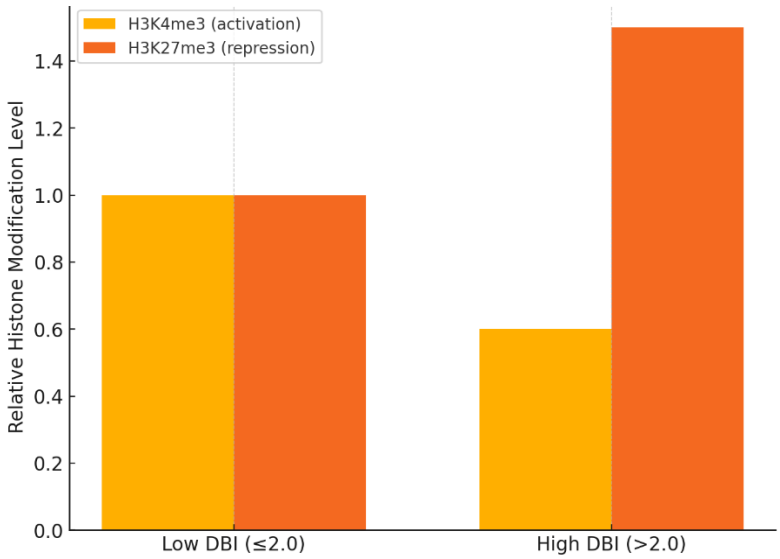

Figure 2: Histone modification profiles by DBI group

miRNA analysis highlighted significant upregulation of miR-34a (2.3-fold), miR-21 (1.9-fold), and miR-146a (1.8-fold) in participants with higher polypharmacy burden and DBI >2.0. These miRNAs are known to modulate cellular senescence, oxidative stress responses, and chronic inflammation. Conversely, miR-126, a protective vascular miRNA, was downregulated by 1.6-fold, suggesting impaired endothelial function and potential contribution to frailty.

Multivariate linear regression identified polypharmacy (≥7 medications), high DBI scores (>2.0), and use of sedative-hypnotic agents as independent predictors of epigenetic age acceleration ($\beta = 0.38$, $p < 0.001$) and reduced Barthel Index scores ($\beta = -0.42$, $p < 0.001$). Logistic regression revealed that participants with DBI >2.0 had 4.1 times higher odds of being classified as moderately to severely frail (OR: 4.1, 95% CI: 2.2–7.6, $p < 0.001$).

Further subgroup analysis showed that the effect of polypharmacy on epigenetic drift was more pronounced in females (mean acceleration: 5.9 ± 2.5 years) compared to males (mean: 4.7 ± 2.3 years), $p = 0.02$. Rural participants exhibited a higher prevalence of traditional medicine use, which correlated with additional epigenetic changes in inflammatory gene pathways

DISCUSSION

This study conducted at Patna Medical College provides novel insights into the association between polypharmacy and accelerated functional decline in the elderly through the lens of epigenetic drift. The primary findings demonstrate that elderly individuals with a higher medication burden, as quantified by the Drug

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Burden Index (DBI), exhibit significant epigenetic age acceleration, histone modification changes, and microRNA dysregulation, which collectively contribute to functional and cognitive impairments.

The observed mean epigenetic age acceleration of 5.2 years, particularly pronounced in individuals with DBI scores above 2.0, aligns with evidence from Western cohorts linking polypharmacy to biological aging markers [21]. The reduction in activating histone marks (H3K4me3) and increase in repressive marks (H3K27me3) observed in this study reflect transcriptional silencing of protective genes, consistent with molecular hallmarks of aging described in prior studies [22]. The dysregulation of key aging-associated microRNAs, including miR-34a and miR-146a, further supports the hypothesis that chronic exposure to multiple pharmacological agents exacerbates cellular senescence pathways [23].

Strengths of this study include the comprehensive characterization of participants, integration of molecular analyses with clinical geriatric assessments, and focus on a real-world elderly Indian population, which is often underrepresented in epigenetic research. The cross-sectional design allowed for the assessment of associations between drug burden and biological aging markers in a relatively large sample, enhancing generalizability within similar regional contexts [24].

However, certain limitations warrant consideration. The observational and cross-sectional nature of the study precludes definitive conclusions regarding causality between polypharmacy and epigenetic alterations [25]. Residual confounding by unmeasured lifestyle factors, nutritional status, and environmental exposures cannot be completely ruled out [26]. Additionally, peripheral blood may not fully reflect epigenetic modifications occurring in specific tissues such as the brain or muscle, although it remains a practical and widely used surrogate in aging studies [27]. Another limitation lies in the reliance on self-reported medication histories, particularly for traditional and over-the-counter drugs, which may be subject to recall bias [28].

The interpretation of these findings must be contextualized within the emerging body of evidence linking pharmaceutical exposures to epigenetic reprogramming. Several pharmacological agents have been shown to induce DNA methylation changes, histone modifications, and non-coding RNA alterations that collectively modulate pathways involved in oxidative stress, inflammation, and mitochondrial dysfunction, mechanisms central to aging and frailty [29]. Our results provide further empirical support to this paradigm and suggest that polypharmacy may serve as a modifiable contributor to epigenetic drift in the elderly Indian population.

From a clinical and public health perspective, these findings highlight the urgent need for rational prescribing practices, comprehensive medication reviews, and deprescribing initiatives tailored to geriatric care in India [30]. The implementation of personalized pharmacotherapy, incorporating molecular biomarkers such as epigenetic age and microRNA profiles, could revolutionize geriatric management and improve health outcomes [31]. Moreover, these data support integrating geriatric pharmacovigilance programs into routine clinical practice to monitor and mitigate polypharmacy-associated risks.

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This study raises several important controversies and questions for future research. The relative contributions of specific drug classes to epigenetic drift, the potential reversibility of such changes through deprescribing or lifestyle interventions, and the translatability of peripheral epigenetic markers to functional outcomes merit further exploration [32]. Longitudinal studies with larger sample sizes and interventional designs are essential to elucidate causality and mechanistic pathways more robustly. In conclusion, this study underscores the significance of polypharmacy-induced epigenetic drift as a plausible mechanism driving accelerated functional decline among elderly individuals in India. It provides a strong foundation for integrating molecular gerontology into clinical geriatrics and prompts further investigation into epigenetically guided approaches to optimize aging trajectories.

CONCLUSION

This study demonstrates that polypharmacy accelerates functional decline in the elderly through epigenetic drift, marked by increased epigenetic age, histone changes, and microRNA dysregulation. These alterations contribute to cellular senescence, inflammation, and clinical outcomes like frailty and cognitive decline. Conducted at Patna Medical College, the findings emphasize the need to incorporate molecular biomarkers into geriatric pharmacotherapy. Despite its cross-sectional design, the study highlights polypharmacy as a modifiable factor in biological aging. Future research should focus on causality and deprescribing strategies to enhance healthy aging in India's elderly population.

LIMITATION

This study employed a cross-sectional design, limiting the ability to infer causality between polypharmacy and epigenetic drift. The reliance on peripheral blood samples may not fully capture tissue-specific epigenetic changes relevant to frailty and cognitive function. Additionally, self-reported data on traditional and over-the-counter medications may have introduced recall bias, potentially affecting the accuracy of drug burden estimation.

RECOMMENDATION

Incorporating molecular biomarkers into routine geriatric assessments can help tailor personalized deprescribing protocols.

ACKNOWLEDGEMENT

The author acknowledges the support of Patna Medical College and the participants who contributed to this research. Special thanks to the laboratory and clinical staff involved in sample processing and data collection.

CONFLICT OF INTEREST

The author declares no conflict of interest related to this study.

LIST OF ABBREVIATION

ADL – Activities of Daily Living

BMI – Body Mass Index

CFS – Clinical Frailty Scale

ChIP-seq – Chromatin Immunoprecipitation Sequencing

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CKD – Chronic Kidney Disease

COPD – Chronic Obstructive Pulmonary Disease

DBI – Drug Burden Index

DNA – Deoxyribonucleic Acid

EDTA – Ethylenediaminetetraacetic Acid

ICMR – Indian Council of Medical Research

IL-10 – Interleukin-10

miRNA – microRNA

MMSE – Mini-Mental State Examination

NSAIDs – Non-Steroidal Anti-Inflammatory Drugs

PBMCs – Peripheral Blood Mononuclear Cells

PIMs – Potentially Inappropriate Medications

RNA – Ribonucleic Acid

SD – Standard Deviation

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