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General Information

The Journal

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Aims and Scope

Pacific Journal of Medical and Health Sciences is a peer reviewed journal with multidisciplinary approach. The goal of the journal is to publish new, challenging and radical ideas, dedicated to promote innovative and high quality research work in the field of medical and health sciences. The journal provides a platform for advances in basic and advanced clinical medical research for all branches of health-sciences. The journal provides cutting edge updates, developments in the medical arena and helps to synchronise and share knowledge.

The key aims of the Journal are to provide interpretations of growing points in medical knowledge by trusted experts in the field, and to assist practitioners in incorporating not just evidence but new conceptual ways of thinking into their practice.

We focus on the clinical aspects of diseases with basic science contributions in areas of clinical interest.

The journal invites articles related to different aspects of Medical and allied Health Sciences including Dental Sciences. The journal publishes original research articles, reviews, case reports and commentaries. The journal is an important and reliable source of current information on developments in the field of medical and health sciences. The emphasis is always on publishing high quality articles with fast review process.

Please note that Call for Papers, Peer-Review Policy, Reviewers' Guidelines, Publication Ethics and Publication Malpractice Statement and Disclaimer have been provided at the end of the issue.

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April to June 2026 Issue (Volume 2, Issue 2)

PJMHS
PACIFIC JOURNAL OF MEDICAL AND HEALTH SCIENCES

INDEX

Editorial

Minds, Mapped: A Season of the Brain Charting the New Frontiers of Neurology and Neuropsychiatry **01**

Research Paper

Targeting Neuroinflammation and Apoptosis in Cypermethrin-Induced Neurotoxicity: An *In Silico* Exploration of *Nigella sativa* Phytochemicals **08**
Aisha Abdulrauf, Tooba Noor ul Ieman, Wahab Kehinde Idris and Aminu Imam

Neuroprotective Effects of *Nigella sativa* Oil Against Prenatal Di-Butyl Phthalate-Induced Cerebellar Neurotoxicity in Wistar Rat Offspring **20**
Aminat Temitayo Atoyebi, Abdulmuiz Oluwatobi Adebiyi, Aisha Abdulrauf, Abdullah Muslimat, Kafilat Alasirin, Ismail Adetayo Lawal, Fatima Omowumi Hamzat, Solihu Olashile Ibrahim, Sulaiman Muhammad Eze and Babatunde Joseph Dare

Ameliorative Effect of Vitamin C on *Cannabis sativa*-induced Nephrotoxicity in Wistar rats **37**
A. Oluwasola

***Tetrapleura tetraptera* Extract Ameliorates Cognitive Decline and Neurodegeneration on the Pre-Frontal Cortex in an Aluminium Chloride-Induced Rat Model of Alzheimer's Disease** **46**
S.M Eze, O.S Ibrahim, Y.O Ibrahim, A.O Yusuf, A.O Kaylaniy, SO Tokunbo, A.T Atoyeb, F.O Hamzat, I.A Lawal, S.O Adeleke, D.A Adekomi, T.A Abayomi and B.J. Dare

Program / Curriculum Innovation

Biomedical Engineering Development: Contributing to Quantitative Physiology, Precision Medicine, and Quality Healthcare Delivery **64**
Dhanjoo Ghista

Review

Revisiting Expressed Emotion in Psychiatric Disorders **76**
Omityah Grigo, Suresh Mehta and Bhawna Yadav

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PJMHS
PACIFIC JOURNAL OF MEDICAL AND HEALTH SCIENCES

INDEX

Anthropometric, Microscopic and Neuroimaging Markers of Somatization in Psychogenic Non-Epileptic Seizures: A Narrative Review 80
Aisha Abdulrauf, Abdulmuiz Oluwatobi Adebiyi, Ajayi Praise-God, Tooba Noor ul Ieman and Wahab Kehinde Idris

Harnessing the Gut-Brain Axis for Neuroprotection: Synergistic Role of Natural Bioactive Products and Microbiota 84
Abosede M. Ayoola, Babatunde Joseph Dare, Samson Opeyemi Adeleke, David T. Ovioke and Eniola A. Adesanya

Air Pollution, The Nrf2-Ferroptosis Axis, and Neonatal Seizure Susceptibility 96
Aisha Abdulrauf, Bolaji Ojo, Ajayi Praise-God, Adejumo Mercy Adebanke, Abdulmumeen Omotosho Abdulkareem, Grace Moyinoluwa Famuwagun and Temitope Jolayemi

The Bear Fable: A Narrative Psychoeducation Tool for Dissociative and Conversion Disorders 103
Omityah Madhurendra Grigo and Suresh Kumar Mehta

Editor's Picks

New Drug Approvals 107

Recent Medical Advances 112

Call for Papers 220

Peer-Review Policy 230

Reviewers' Guidelines 233

Publication Ethics and Publication Malpractice Statement 237

Disclaimer 242

Minds, Mapped: A Season of the Brain

Charting the New Frontiers of Neurology and Neuropsychiatry

"Every man can, if he so desires, become the sculptor of his own brain."
— Santiago Ramón y Cajal, Father of Modern Neuroscience

We did not set out to publish a 'Brain' issue. There was no call for papers on Neurology, no theme announced to authors, no quiet nudge from the editorial desk in that direction. And yet, when we sat down a few weeks ago to take stock of what had arrived for this issue, nine of the ten manuscripts on our desk turned out, in one way or another, to be about the brain. A cerebellum bruised by an insecticide. A prefrontal cortex studied for the scars left by a common industrial chemical. A narrative review tracing the invisible thread between gut and mind. A fable, of all things, used to explain to frightened families why a seizure need not be a lie. A quiet reconsideration of what we mean when we say a family's emotions can heal or harm.

It felt less like coincidence and more like a signal, and perhaps it should not have surprised us as much as it did. This journal entered Volume 11 having already declared its direction. The Golden Heart that carried us through four issues of cardiovascular and metabolic medicine in 2025 gave way, on the cover of our January-March 2026 issue, to the Golden Brain, *Aurum Cerebri*, a translucent anatomical form with its cranial vault opened to reveal the cerebral cortex, the limbic circuit, the thalamus, and the cerebellum rendered in luminous gold against black. That transition was announced as an intention, an expansion of this journal's gaze from the organ that sustains survival to the organ that defines the person surviving. What arrived on our desk this quarter was not, then, an accident colliding with that intention. It was the intention beginning to fulfil itself, submissions finding their way to a journal that had already told the world, quite deliberately, where its attention now lay.

Something in the wider scientific conversation, and perhaps in the clinical instincts of the researchers who write for this journal, has turned unmistakably toward the brain. This issue's Recent Medical Advances section, curated separately from these submitted papers, tells the same story: twenty summaries this quarter, and every one of them touches neurology, neuropsychiatry, or brain health in some form. An issue that was never conceived as themed has become one anyway, gathered under a cover that had already named its subject before a single manuscript arrived. We hope you will forgive the immodesty of calling it a 'season', but between the gold on our cover and the nine papers in these pages, it plainly is one.

As we read through these manuscripts one after another, we found ourselves struck by how differently each author had chosen to approach the same underlying organ. One team reached for molecular pathways and oxidative stress markers. Another reached for a 16-segment cardiac-style model borrowed and adapted for the cerebellum. A third reached, almost disarmingly, for a folk story about a bear in a forest. That range is, we think, exactly what a healthy field looks like at a given moment: not a single dominant method sweeping all before it, but many honest attempts converging on the same target from different directions, each willing to be tested against the others. Editing this issue felt less like assembling a themed collection and more like watching a shared conversation take shape without anyone having planned it.

Brain Neuroplasticity

It is worth beginning with the idea that made much of what follows possible: that the adult brain is not a finished structure but a living, rearranging one. For most of the twentieth century, neurology operated on the quiet assumption that the brain you had at twenty-five was, more or less, the brain you would keep. Neurons died; they did not regenerate. Circuits were laid down in childhood and adolescence and then largely fixed. That assumption has not merely been revised. It has been overturned.

We now understand plasticity as a feature of the brain across the entire lifespan, not a privilege of early development. It shows itself in unexpected corners of ordinary life. One of the summaries in this issue's Recent Medical Advances section looks at new fathers, tracking measurable changes in brain structure across the first six months of fatherhood, changes that plausibly underlie the shift in attention, vigilance, and emotional responsiveness that new parents describe. Another looks at bilingualism, and the possibility that the lifelong cognitive exercise of operating in two languages builds a kind of structural reserve against Alzheimer's disease in men. Neither of these findings would have been considered plausible research questions a generation ago, because neither would have assumed the brain capable of that kind of change in response to ordinary life experience.

Plasticity is not always benign, of course, and one of the more sobering entries in this issue's advances section makes that point clearly: a study linking night shift work to measurable shrinkage in key brain regions. The same property that allows the brain to grow new connections in response to love, language, or fatherhood also allows it to be worn down by circadian disruption, occupational stress, and chronic sleep debt. Plasticity, in other words, is not a one-way street toward improvement. It is simply the brain's capacity to change, and whether that change helps or harms depends heavily on what we ask of it and how we protect it.

This dual nature of plasticity runs through several of the full research papers in this issue as well. The *Tetrapleura tetraptera* study, testing a West African plant extract against aluminium-chloride-induced cognitive decline in a rat model of Alzheimer's disease, is fundamentally a plasticity story, an attempt to determine whether a natural compound can support the prefrontal cortex's capacity to resist and recover from neurodegenerative injury. So too is the gut-brain axis review in this issue, which surveys the growing evidence that the microbial populations in our intestines can influence neuroinflammation and, through it, the brain's own resilience. Once you begin looking for plasticity, it turns up almost everywhere in contemporary neuroscience, quietly underwriting both the damage we now understand and the recovery we now believe is possible.

There is also a quieter, more clinical dimension to plasticity that deserves mention: rehabilitation medicine has, in many ways, been built almost entirely on the premise that damaged neural circuits can be coaxed into reorganising around an injury rather than simply accepting the deficit it leaves behind. Constraint-induced movement therapy after stroke, intensive early intervention in paediatric brain injury, and the graded exposure protocols used in post-traumatic stress work all rest on the same underlying wager, that repeated, structured demand on a circuit can change its function over time. What has shifted in recent years is not the wager itself but our confidence in it. Where plasticity-based rehabilitation was once offered somewhat apologetically, as a supportive measure alongside the "real" pharmacological treatment, it is increasingly understood as a primary intervention in its own right, with a measurable biological mechanism behind it rather than a vague appeal to hope and effort.

Brain Research Breakthroughs: From Lab Discoveries to Real-World Patient Impact

If plasticity supplies the underlying premise, the last few years have supplied an extraordinary volume of discovery built on top of it, and the pathway from laboratory bench to patient bedside has never moved faster. Consider biomarkers first, because biomarkers are what allow a disease to be caught before it introduces itself through symptoms. This issue's advances section includes a study on blood mitochondrial DNA changes associated with midlife cognitive decline, work that points toward a blood test capable of flagging risk decades before memory loss becomes clinically obvious. Alongside it sits a paper on a blood test ratio that improves detection of Alzheimer's amyloid pathology, part of a broader movement away from expensive PET imaging and invasive lumbar punctures and toward diagnostics a general practitioner could plausibly order during a routine visit.

Imaging itself continues to mature in parallel. One of this issue's summaries describes brain scans that reveal how depression appears to trap the mind in rigid, difficult-to-escape mental states, a finding that reframes depression not simply as low mood but as a kind of computational stuckness in the brain's own dynamics. This sits comfortably alongside our own submitted narrative review on psychogenic non-epileptic seizures, which surveys what anthropometric, microscopic, and neuroimaging markers can and cannot tell us about a condition long dismissed as purely psychological. The honest message of that review, that structural and functional imaging increasingly reveal genuine, measurable correlates of a condition still too often treated as imaginary, is precisely the kind of finding that changes how a clinician speaks to a frightened patient in clinic.

Gene and cell therapy remain the frontier furthest from routine practice, but the direction of travel is unmistakable. Basic science continues to refine our understanding of exactly which circuits govern attention and arousal. This issue's advances section highlights work identifying an ancient brainstem circuit, our built-in attention switch, that helps explain why focus can be so fragile and so trainable at once. Elsewhere, a study on infection and dementia risk from Finnish national registry data adds weight to the growing suspicion that some proportion of what we call neurodegeneration may have an immune or infectious component rather than a purely proteinopathic one, a suspicion echoed in another summary proposing that Alzheimer's disease may begin in the body's immune system rather than in the brain itself. These are not small revisions. They are the kind of findings that, if they hold up, will eventually reshape prevention strategy as much as treatment.

Gene and cell therapy, more specifically, is edging closer to neurology's oldest ambition: not merely slowing a degenerative process but reversing or replacing what has already been lost. Viral vector delivery systems are steadily improving their ability to cross the blood-brain barrier with useful genetic cargo rather than being trapped at its edge. Stem-cell-derived approaches to Parkinson's disease, still experimental, are inching toward the kind of controlled trials that could eventually make cell replacement a genuine clinical option rather than a laboratory curiosity. None of this is close to routine practice yet, and we would caution any clinician reading this editorial against overpromising these therapies to a hopeful patient. But the trajectory is real, and it is worth watching closely over the coming decade rather than dismissing as perpetually five years away, a phrase gene therapy researchers have heard, not unfairly, for far too long.

Clinical research, meanwhile, is delivering results that matter immediately rather than eventually. A trial of Factor XIa inhibition for secondary stroke prevention represents a genuinely new pharmacological approach to one of neurology's oldest and most stubborn problems, the prevention of a second stroke in a patient who has already survived a first. And in psychiatry, a trial of high-dose psilocybin for treatment-resistant depression missed its primary endpoint but still eased symptoms meaningfully, a result that is

scientifically more interesting than a clean win would have been, because it forces a more careful conversation about who psilocybin actually helps and why. A companion case report in this same issue, describing temporary cognitive gains in a patient with advanced Alzheimer's disease after high-dose psilocybin, adds a provocative, still-anecdotal thread to that same conversation. None of this is settled science. All of it is real movement.

It is worth pausing here to note how differently these two trials illustrate what a null or partial result can still teach us. A stroke-prevention trial that clearly beats its comparator gives clinicians a straightforward new tool to reach for. A depression trial that misses its primary endpoint while still easing symptoms in a meaningful subset of patients gives something arguably more valuable to a field as heterogeneous as psychiatry: a reason to ask which patients responded, and why, rather than treating the entire trial population as a single undifferentiated group. Some of the most useful clinical science of the next decade will likely come not from bigger trials but from smarter, more honest interrogation of the trials we already have.

Neurotechnology Advancements in Clinics: Smarter Tools for Safer, Wider Access

Discovery is only half the story. The other half is whether a discovery ever reaches a patient who needs it, and here neurotechnology has quietly become one of the most consequential areas in all of medicine. Real-time brain monitoring, once confined to intensive care units and epilepsy monitoring wards, is steadily becoming lighter, cheaper, and more continuous, allowing clinicians to observe brain activity as it unfolds rather than reconstructing it after the fact from an occasional scan.

Brain-computer interfaces have moved from science fiction demonstration to genuine, if still narrow, clinical tool. Their most mature clinical cousin, deep brain stimulation, continues to expand well beyond its original home in Parkinson's disease, now reaching into treatment-resistant depression, obsessive-compulsive disorder, and a widening circle of movement disorders, as electrode targeting and stimulation algorithms grow more precise. What excites us most, though, is the way neurotechnology is beginning to escape the neurology ward altogether. This issue's advances section includes a randomised trial combining virtual reality with electrical nerve stimulation to help stroke survivors regain hand and arm function, and a separate trial of magnetic brain stimulation that improved social communication in autistic children. Neither of these interventions requires an operating theatre. Both point toward a future in which meaningful neurotechnology sits in an outpatient rehabilitation clinic, or eventually a patient's own home, rather than a specialist neurosurgical suite.

Remote patient monitoring completes this picture. Wearable sensors that track tremor, gait, sleep architecture, and seizure risk are turning the interval between clinic visits, once a black box to the treating physician, into a continuous, reviewable stream of data. For a specialty that has long depended on a patient's imperfect memory of symptoms between appointments, this is not a minor convenience. It is a genuine shift in what a neurologist can know about a patient's day-to-day reality, and it matters enormously for patients in rural or under-resourced settings who may see a specialist only once or twice a year.

There is a quiet but important engineering story running underneath all of this, one that rarely makes it into clinical summaries. Every advance described above depends on batteries lasting longer, sensors drawing less power, and wireless transmission protocols becoming more reliable in precisely the low-connectivity settings where remote monitoring would matter most. A brain-computer interface that needs to be recharged every ninety minutes is a laboratory demonstration. One that lasts a week between charges is a device a patient could plausibly live with. The clinical literature tends to celebrate the neuroscience of these tools

while treating the underlying hardware as a solved problem, but for many of the physicians and educators reading this journal, particularly those practising in settings where reliable electricity and connectivity cannot be assumed, the hardware is very much still the story.

AI in Neurology: Transforming Diagnostics, Prediction, and Everyday Care

Artificial intelligence deserves its own section here, not because it is fashionable to include one, but because it is genuinely reshaping how neurological disease is caught, predicted, and managed at every stage. Diagnostic imaging is the most visible example. Algorithms trained on thousands of scans can now flag subtle white matter changes, early amyloid deposition, or the faint asymmetries of an evolving stroke faster and, in some well-validated settings, more consistently than a fatigued clinician at the end of a long shift.

Prediction is where the technology becomes genuinely transformative rather than merely efficient. One of the more striking findings in this issue's advances section, that handwriting speed during dictation may help detect early cognitive decline, is a small but telling illustration of what AI-era diagnostics increasingly look like: not a dramatic new scanner, but a pattern buried in ordinary behaviour, extracted with tools sensitive enough to notice a decline no human observer would catch. The same logic underlies efforts to combine genetic, metabolic, and clinical data to flag which patients are likeliest to progress from mild cognitive impairment to dementia, or which stroke patients are likeliest to benefit from aggressive early intervention.

Everyday care is where these advances will ultimately be judged, and the honest picture is mixed but encouraging. AI-assisted triage tools are beginning to help emergency departments prioritise suspected stroke patients within the narrow treatment window where intervention matters most. Natural language processing is being used to scan clinical notes for early warning signs of delirium or depression that might otherwise go undocumented amid a busy ward round. None of this replaces clinical judgement, and it should not. But used well, it narrows the gap between a subtle early sign and the moment a clinician acts on it, which in neurology is very often the gap between a good outcome and a permanent one.

We would be doing this section a disservice, however, if we did not also name the honest limitations. Algorithms trained predominantly on data from wealthier, whiter, and more thoroughly documented populations do not automatically generalise to the patients most of this journal's readership actually treats. A stroke-detection model validated in a well-resourced Western emergency department may perform very differently on a scan acquired on older equipment, from a patient population with a different burden of untreated hypertension and diabetes, in a hospital where the algorithm's training data has never been meaningfully represented. This is not a reason to reject the technology. It is a reason to insist, as a matter of basic scientific and ethical practice, that validation studies be conducted in the populations where these tools will actually be deployed before we trust them with a patient's diagnosis. A journal like this one, publishing from and for clinicians across Africa, South Asia, and beyond, has a genuine role to play in demanding exactly that kind of validation rather than simply importing tools built elsewhere and assuming they translate.

Neurology Innovations for Patients: Faster, Personalized, and More Accessible Care

For all this technological momentum, we want to return the conversation to where it ultimately belongs, which is the patient in front of the clinician. Speed matters enormously in neurology because so much of the specialty's damage is time-dependent. Faster diagnosis of stroke, faster recognition of status epilepticus,

faster identification of a treatable cause behind an otherwise unexplained cognitive decline: these are not incremental gains. They are, quite literally, the difference between a preserved life and a diminished one.

Personalisation is the second thread, and it runs through much of what this issue has to offer. This issue's advances section carries a piece asking why Alzheimer's risk hits women harder than men, and a companion piece on how ADHD manifests differently across the sexes, both pointing toward a future clinical practice that treats sex and gender as genuine variables in diagnosis and treatment rather than an afterthought buried in a subgroup analysis. Our own submitted review on expressed emotion within families makes a similar case from a different angle, arguing that how families themselves respond to a relative's psychiatric illness, criticism, warmth, over-involvement, is not background noise but a measurable clinical variable that shapes relapse and recovery, and one that deserves to be assessed and addressed as deliberately as any medication.

Accessibility, finally, is where we think the field still has the most honest work to do. A gene therapy or an implanted brain-computer interface means very little to a patient who will never see the tertiary centre that offers it. This is precisely why the more modest, low-resource interventions in this issue matter as much as the high-technology ones. Our submitted paper on the Bear Fable, a simple narrative device used to help families understand dissociative and conversion symptoms without accusing the patient of fabrication, requires no equipment, no specialist training beyond a compassionate clinician, and no funding beyond the time it takes to tell a short story well. It is, in its own quiet way, exactly the kind of innovation this section is meant to celebrate: unglamorous, inexpensive, and genuinely transformative for the family sitting across the desk from a confused and disbelieving relative.

This journal receives a considerable proportion of its submissions from clinician-researchers working in precisely the resource-constrained settings we described in the previous section, and we think that vantage point produces a particular kind of innovation that deserves more recognition than it typically receives in the wider literature. It is easy, from a well-funded academic centre, to propose a solution that assumes a functioning cold chain, a stable electricity supply, and a specialist pharmacist available for consultation. It is a different and, in some ways, more demanding kind of ingenuity to design an intervention that works without any of those assumptions holding. The two toxicology papers in this issue, examining how a natural extract might counter the neurological and renal harms of a common insecticide and an industrial chemical respectively, sit squarely in that tradition: practical, low-cost, locally relevant science aimed at exposures that disproportionately affect exactly the populations least equipped to seek specialist treatment after the damage is already done.

The Future of Neuroscience: Trends That Will Transform the Health Journey of People

Where does this leave us as we look ahead? We would resist the temptation to predict a single dramatic breakthrough, because the pattern across every section of this editorial has been convergence rather than a single decisive discovery. Biomarkers are becoming more accessible, imaging more interpretable, neurotechnology more portable, and artificial intelligence more woven into the ordinary rhythm of clinical decision-making. None of these trends alone would transform neurological care. Together, layered onto one another the way this issue's papers layer onto one another almost by accident, they plausibly will.

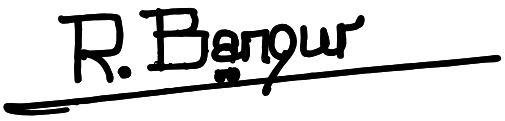
We would also note, gently but firmly, the two submitted papers in this issue that examine environmental threats to the brain, the cerebellar effects of a common insecticide, and the nephrotoxic and neurotoxic burden of another widely used agent, alongside this issue's advances piece on air pollution and neonatal seizure susceptibility through the Nrf2-ferroptosis axis. Brain health in the coming decade will not be

determined solely in hospitals and research laboratories. It will be determined just as much by air quality, occupational chemical exposure, and the countless environmental variables that most neurology curricula still treat as peripheral. A field that has spent a century mapping the brain's internal architecture is now being asked, urgently, to map its external vulnerabilities as well.

And we would end on the human note that Cajal's epigraph opens this piece with, because it feels like the right closing thought as much as the right opening one. For most of medicine's history, the brain was the one organ we treated with a kind of respectful helplessness, examined, described, mapped in exquisite anatomical detail, but rarely touched with real therapeutic confidence. That helplessness is ending. Not everywhere, not evenly, and not without the setbacks that every genuine frontier produces along the way, but ending nonetheless. The nine papers that arrived on our desk this quarter did not know they were part of anything larger. They simply did what good science does: asked a narrow question honestly, and answered it as far as the evidence allowed.

A cerebellum can be protected. A frightened family can be spoken to differently. A fable can do work that a lecture cannot. None of these is a cure. All of them are progress, the unglamorous, cumulative kind that rarely makes a headline but slowly changes what is possible in a clinic. That is how a golden brain earns the metal on its cover: not through a single discovery bright enough to justify it, but through issue after issue of researchers, most of them working in the settings this journal has always served best, refusing to accept that the mind's fragility is beyond medicine's reach.

The heart taught this journal, and this profession, how to intervene. The brain is now teaching us how to protect, restore, and, where we can, prevent the need for intervention altogether. That is the real story of this issue, and we suspect it will be the real story of several more to come.



(Ravindra Bangar)
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Research Paper

Targeting Neuroinflammation and Apoptosis in Cypermethrin-Induced Neurotoxicity: An *In Silico* Exploration of *Nigella sativa* Phytochemicals

Aisha Abdulrauf[1,2]*, Tooba Noor ul Ieman[2], Wahab Kehinde Idris[2] and **Aminu Imam[1]**

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ABSTRACT

Background:

Cypermethrin, a widely used type II pyrethroid insecticide, has been increasingly implicated in neurotoxicity through the activation of neuroinflammatory and apoptotic pathways, particularly involving nuclear factor-kappa B (NF-κB) and caspase-3. Nigella sativa possesses several bioactive phytochemicals with established antioxidant and neuroprotective properties, yet their target-specific interactions in cypermethrin-induced neurotoxicity remain poorly understood.

Objective:

This study investigated the molecular interactions of selected Nigella sativa phytochemicals with NF-κB and caspase-3 to identify potential neuroprotective candidates against cypermethrin-induced neuroinflammation and apoptosis.

Methods:

An in silico molecular docking approach was employed using PyRx. Thymoquinone, thymol, carvacrol, and p-cymene were docked against human caspase-3 (PDB: 1GFW) and NF-κB p65 (PDB: 1VKX), with cypermethrin included as the reference toxicant. Drug-likeness and ADMET properties were evaluated using Swiss ADME.

Results:

Cypermethrin exhibited the strongest binding affinities to caspase-3 (-6.2 kcal/mol) and NF-κB (-7.7 kcal/mol), supporting its direct interaction with proteins implicated in neuronal injury. Among the phytochemicals, carvacrol demonstrated the highest affinity for NF-κB (-6.3 kcal/mol), while p-cymene showed the strongest interaction with caspase-3 (-4.8 kcal/mol). All phytochemicals demonstrated favorable pharmacokinetic properties, including blood-brain barrier permeability and zero Lipinski violations, except p-cymene, which showed one violation.

Discussion:

These findings suggest that Nigella sativa phytochemicals may exert neuroprotective effects by modulating the inflammatory–apoptotic axis central to cypermethrin neurotoxicity. Carvacrol, in particular, emerged as a promising anti-inflammatory candidate, while thymoquinone's established multi-target activity supports its continued development for mitigating pesticide-induced neuronal damage.

KEYWORDS: *Nigella sativa;* Cypermethrin; Neuroinflammation; Caspase-3; NF-κB.

INTRODUCTION

Cypermethrin is one of the most extensively used type II synthetic pyrethroid insecticides globally, owing to its effectiveness in agricultural pest control, public health interventions, and domestic applications. Despite its perceived safety profile, increasing evidence indicates that chronic and repeated exposure to cypermethrin poses substantial risks to the central nervous system. Experimental studies have demonstrated that cypermethrin induces oxidative stress, neuroinflammation, synaptic dysfunction, and neuronal loss in several brain regions, including the hippocampus, cerebral cortex, and corpus callosum[1,2,3,4].

The neurotoxic effects of cypermethrin are mediated through a complex interplay of inflammatory and apoptotic pathways. Among these, nuclear factor-kappa B (NF-κB) serves as a master regulator of neuroinflammation by promoting the transcription of pro-inflammatory cytokines such as interleukin-1β, interleukin-6, and tumor necrosis factor-α. Concurrently, activation of caspase-3, a key executioner caspase, drives programmed neuronal cell death. Persistent activation of this inflammatory–apoptotic axis has been implicated in the progression of numerous neurodegenerative conditions and represents a critical mechanism underlying pesticide-induced neuronal injury[1,5].

Natural products continue to attract considerable attention as sources of multi-target therapeutic agents for neurological disorders. *Nigella sativa* (black seed) is a medicinal plant with a long history of ethnopharmacological use and is rich in bioactive constituents including thymoquinone, thymol, carvacrol, and p-cymene. These phytochemicals possess antioxidant, anti-inflammatory, and anti-apoptotic properties and have demonstrated protective effects in both experimental and computational models of neurological disease[2,6]. Notably, thymoquinone has been reported to ameliorate cypermethrin-induced oxidative stress, preserve GABAergic neuronal integrity, and improve cognitive outcomes in animal models, highlighting the therapeutic promise of *Nigella sativa* against pesticide-induced neurotoxicity.

Although the neuroprotective effects of *Nigella sativa* have been increasingly recognized, the molecular interactions between its phytochemicals and key mediators of cypermethrin-induced neuroinflammation and apoptosis remain insufficiently characterized. Molecular docking provides a rapid and cost-effective approach for elucidating these interactions and prioritizing compounds for subsequent experimental validation.

Therefore, this study employed an in silico molecular docking strategy to investigate the binding interactions of selected *Nigella sativa* phytochemicals with NF-κB p65 and caspase-3, using cypermethrin as a reference toxicant. By integrating docking and pharmacokinetic analyses, this work aims to provide mechanistic insights into the potential of *Nigella sativa*-derived compounds as modulators of the inflammatory –apoptotic axis in cypermethrin-induced neurotoxicity.

METHODS

Study Design

This study employed a structure-based computational (*in silico*) design in which four *Nigella sativa* phytochemicals were docked individually against two apoptosis- and inflammation-related protein targets implicated in cypermethrin neurotoxicity, with cypermethrin itself docked in parallel as an index/reference ligand at both targets to allow direct comparison of binding behaviour between the toxicant and the candidate phytochemicals.

Target Protein Retrieval and Rationale

Two protein targets were selected based on their established mechanistic role in cypermethrin-associated neurotoxicity, namely the executioner phase of apoptosis and the transcriptional control of neuroinflammation, both of which are up-regulated following cypermethrin exposure[1]. Structural coordinates for caspase-3 (PDB: 1GFW) and NF-κB p65 (PDB: 1VKX) were retrieved from the RCSB Protein Data Bank[7,8].

Ligand Library Retrieval

Four *Nigella sativa* phytochemicals, selected on the basis of documented antioxidant, anti-inflammatory, and anti-apoptotic bioactivity, were retrieved as reference standards, alongside cypermethrin itself, which was additionally docked at both targets as the index toxicant against which phytochemical performance was benchmarked. Canonical SMILES and three-dimensional structure-data files (SDF) for all six ligands were retrieved from the PubChem Compound database using their respective Compound Identifiers (CID), as summarised in Table 2[9-13].

Table 1: Two protein targets used in this study

Target	PDB ID	Structural Description
Caspase-3 (executioner caspase)	1GFW	Human recombinant caspase-3 (apopain/CPP32) resolved at 2.8 Å in complex with an isatin sulfonamide inhibitor bound at the S2 subsite; a widely used template for structure-based caspase-3 inhibitor discovery.
NF-κB p65 (RelA)	1VKX	NF-κB p50/p65 (RelA) heterodimer bound to κB DNA, resolved at 2.9 Å; the standard, literature-precedented docking template for p65-targeted anti-inflammatory phytochemical screening

Table 2: Ligand library retrieved from PubChem, with molecular identity and Canonical SMILES

Ligand	PubChem CID	Molecular Formula	Molecular Weight (g/mol)	SMILES
Thymoquinone	10281	C10H12O2	164.20	CC1=CC(=O)C(=CC1=O)C(C)C
Thymol	6989	C10H14O	150.22	CC1=CC(=C(C=C1)C(C)C)O
Carvacrol	10364	C10H14O	150.22	CC1=C(C=C(C=C1)C(C)C)O
p-Cymene	7463	C10H14	134.22	CC1=CC=C(C=C1)C(C)C
Cypermethrin (Toxic Agent)	2912	C22H19Cl2NO3	416.30	CC1(C(C1C(=O)OC(C#N)C2=CC(=CC=C2)OC3=CC=CC=C3)C=C(Cl)Cl)C

Ligand and Protein Preparation

Ligand structures downloaded from PubChem were energy-minimised using the MMFF94 force field to relax bond lengths, angles, and torsions prior to docking, and were converted to the docking-engine input format (PDBQT), with rotatable bonds assigned and Gasteiger partial charges computed for each atom. For protein preparation, co-crystallised water molecules, native ligands/inhibitors, and, where present, the DNA duplex were removed from each retrieved structure; missing side chains and hydrogen atoms were added, and Kollman united-atom charges were assigned. Each protein was then converted to the PDBQT format required for docking. The docking search space (grid box) for each target was centred on the native ligand-binding pocket identified from the co-crystallised inhibitor coordinates (caspase-3) or the previously reported p65 ligand-binding/DNA-proximal interface (NF-κB p65), with dimensions set generously to encompass the full binding cavity and immediately adjacent surface residues.

Molecular Docking Protocol

Docking of each of the five ligands (four phytochemicals with cypermethrin) against each of the two prepared targets was performed using pyRx, with an exhaustiveness setting sufficient to sample multiple ligand poses and orientations per run. Docking protocol validity was first confirmed by redocking the native co-crystallised ligand of each target (the isatin sulfonamide inhibitor for caspase-3) into its original binding site and confirming acceptable superposition with the experimentally observed pose, in line with standard practice for caspase-3 docking studies[14]. For each ligand-target pair, the pose with the most favourable (most negative) predicted binding free energy (kcal/mol) was retained for subsequent analysis.

Post-Docking Interaction Analysis

The best-ranked pose for each ligand-target complex was visualised and analysed for non-covalent interactions, including hydrogen bonds, hydrophobic contacts, and π-stacking, using a molecular visualisation and interaction-mapping tool (Discovery Studio Visualizer/ PyMOL). Residues contacted by each phytochemical were compared against those contacted by cypermethrin at the same target to identify shared or divergent binding-site engagement, and against residues previously reported as functionally important for ligand binding at each target.

Drug-Likeness and Pharmacokinetic Screening

Each phytochemical was additionally evaluated for oral drug-likeness using Lipinski's rule of five (molecular weight ≤ 500 g/mol, hydrogen bond donors ≤ 5, hydrogen bond acceptors ≤ 10, calculated log P ≤ 5) and for predicted absorption, distribution, metabolism, excretion, and toxicity (ADMET) profile, including blood-brain barrier permeability, given the neurological target of interest.

Data Analysis

Binding affinities (kcal/mol) obtained for the four phytochemicals and cypermethrin at each of the two targets were ranked in ascending order using GraphPad Prism 8.0.3 to identify the phytochemical(s) with the strongest predicted affinity relative to cypermethrin at each target. Interaction fingerprints were compared qualitatively across ligands to identify recurring binding-site residues that may underlie shared or differential activity.

RESULTS

Molecular Docking of Cypermethrin and *Nigella sativa* Phytochemicals

Molecular docking analysis revealed that the reference toxicant, cypermethrin, exhibited the strongest binding affinities toward both caspase-3 (-6.2 kcal/mol) and NF-κB (-7.7 kcal/mol), highlighting its capacity to directly engage proteins associated with apoptotic and neuroinflammatory signaling.

Among the *Nigella sativa* phytochemicals, carvacrol demonstrated the highest affinity for NF-κB (-6.3 kcal/mol), followed by thymol (-6.1 kcal/mol) and thymoquinone (-6.0 kcal/mol). Conversely, p-cymene exhibited the most favorable interaction with caspase-3 (-4.8 kcal/mol), marginally exceeding thymoquinone (-4.7 kcal/mol), thymol (-4.6 kcal/mol), and carvacrol (-4.6 kcal/mol).

Although the phytochemicals displayed lower binding energies than cypermethrin, their ability to interact with the same molecular targets suggests a potential role in modulating pathways implicated in cypermethrin-induced neurotoxicity.

Table 3: Molecular docking scores of *Cypermethrin* (Toxic agent) and *Nigella sativa* Phytochemicals against Caspase-3 and NF-kB

S. No.	Ligands	Caspase-3 Binding Affinity (kcal/mol)	NF-kB Binding Affinity (kcal/mol)
1.	Cypermethrin (Toxic)	-6.2	-7.7
2.	Thymoquinone	-4.7	-6.0
3.	Thymol	-4.6	-6.1
4.	Carvacrol	-4.6	-6.3
5.	p-Cymene	-4.8	-5.8

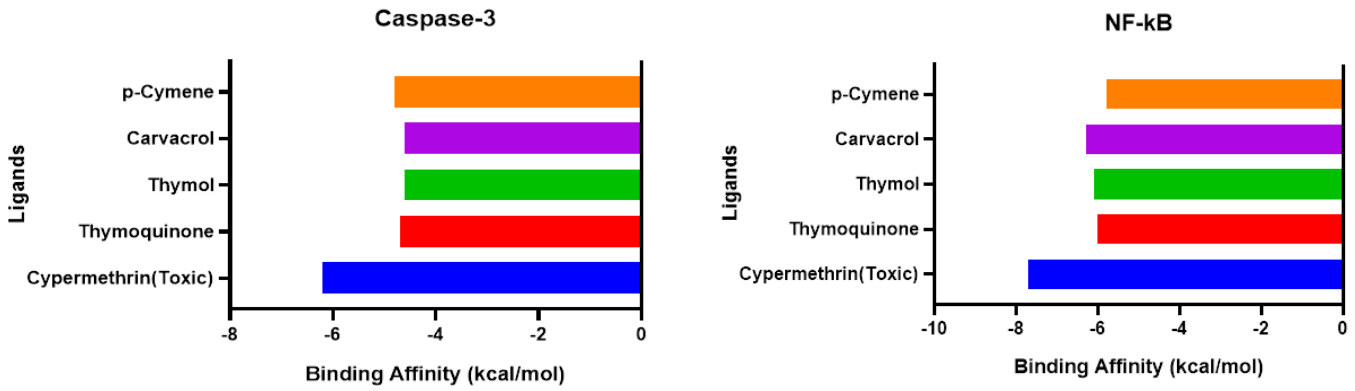


Figure 1: Ranking of Docking Scores for Cypermethrin (Toxic) and *Nigella sativa* Phytochemicals against Caspase-3 and NF-kB

Protein–Ligand Interaction Profiles

Protein–ligand interaction analysis demonstrated that cypermethrin established extensive hydrophobic and stabilizing interactions within the active sites of both proteins, consistent with its strong docking performance.

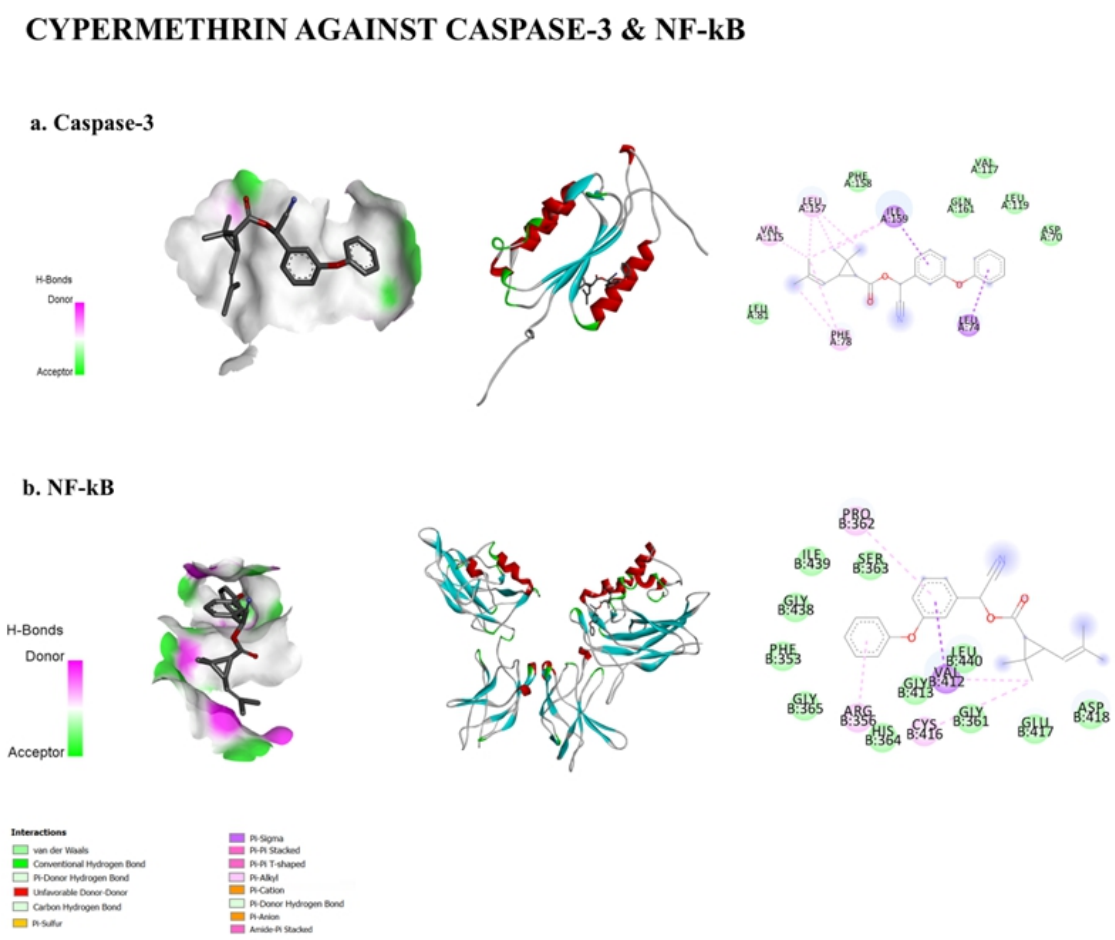


Figure 2: Protein–ligand Interaction Maps of the Cypermethrin Docked against CASPASE-3 & NF-kB [**a. Caspase-3**, **b. NF-kB**]

Similarly, all four *Nigella sativa* phytochemicals occupied the target binding pockets and formed favorable non-covalent interactions. Thymoquinone exhibited additional polar contacts attributable to its quinone moiety, whereas thymol and carvacrol displayed highly comparable interaction patterns owing to their structural resemblance. The predominance of hydrophobic interactions across the monoterpenes suggests that lipophilicity contributes substantially to target engagement.

Importantly, the observed interactions indicate that the phytochemicals possess the structural capability to engage proteins central to the inflammatory–apoptotic axis, supporting their potential as neuroprotective modulators.

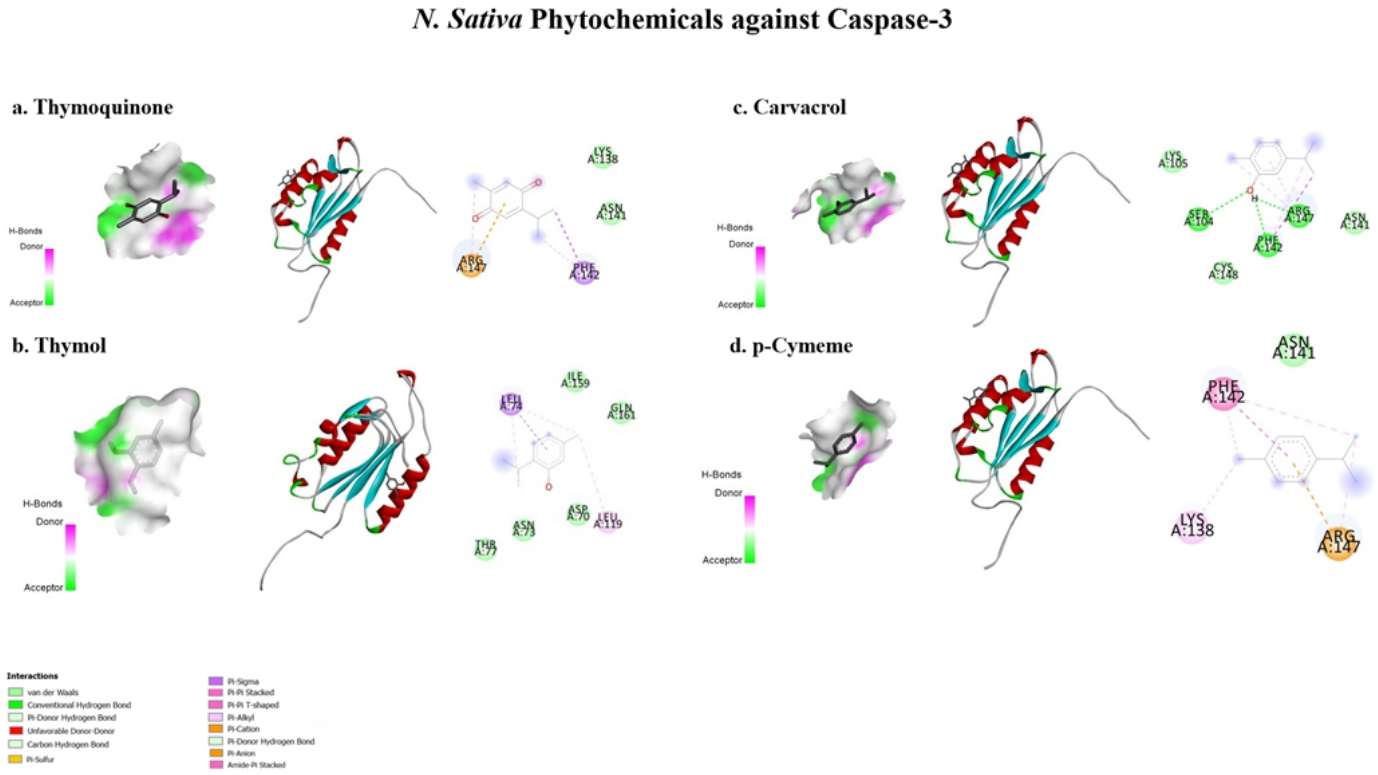


Figure 3: Protein–ligand Interaction Maps of the *Nigella Sativa* Phytochemicals Docked against CASPASE-3 [**a. Thymoquinone**, **b. Thymol**, **c. Carvacol**, **d. P-Cymene**]

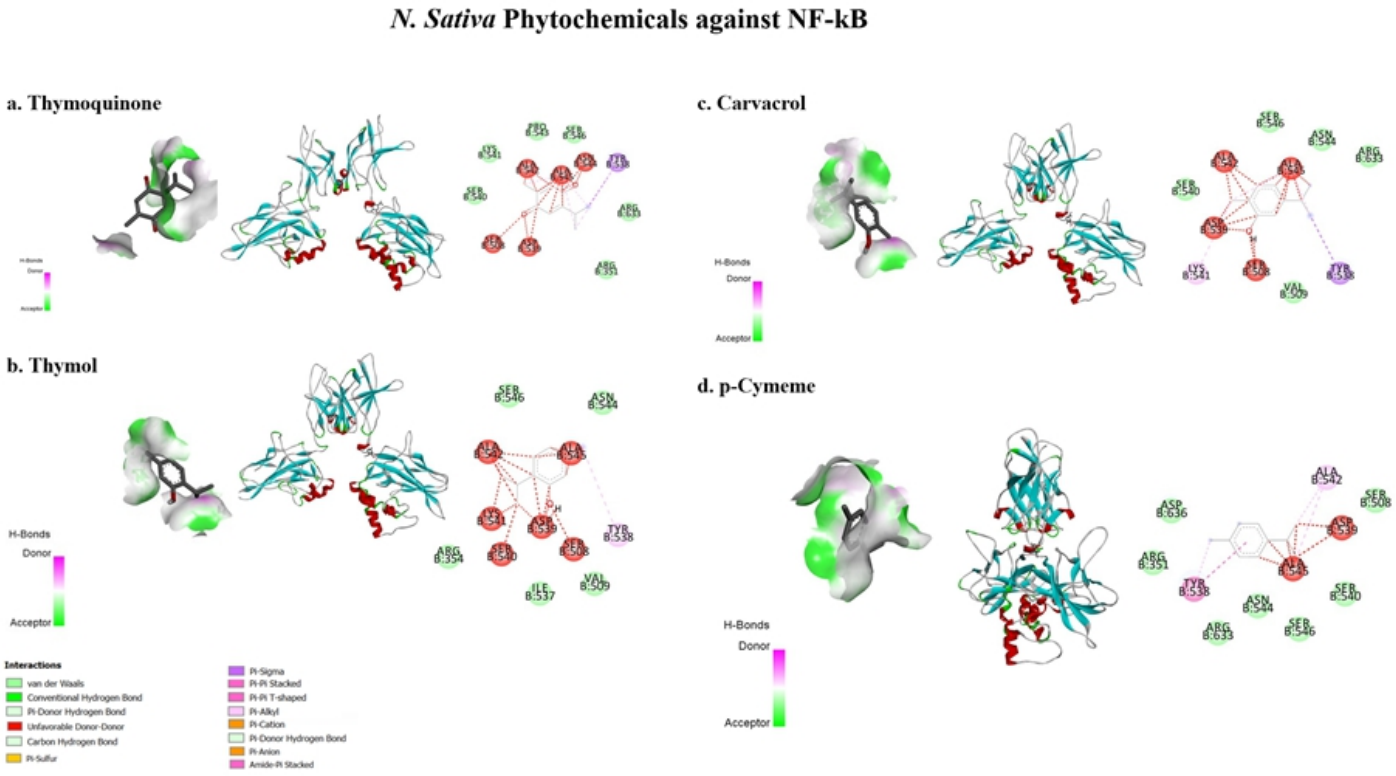


Figure 4: Protein–ligand Interaction Maps of the *Nigella Sativa* Phytochemicals Docked against NF-kB [**a. Thymoquinone**, **b. Thymol**, **c. Carvacol**, **d. P-Cymene**]

Drug-Likeness and ADMET Properties

SwissADME analysis demonstrated favorable pharmacokinetic characteristics for the *Nigella sativa* phytochemicals. Thymoquinone, thymol, and carvacrol exhibited high gastrointestinal absorption, predicted blood–brain barrier permeability, and no Lipinski violations, with all compounds achieving a bioavailability score of 0.55.

Table 4: Predicted ADMET and Drug-Likeness Properties of Selected *Nigella sativa* Phytochemicals and Cypermethrin Using Swiss ADME

Ligand	Molecular Weight (g/mol)	TPSA (Å²)	Consensus LogP	GI Absorption	BBB Permeability	P-gp Substrate	Lipinski Violations	Bio-availability Score
Thymoquinone	164.20	34.14	1.81	High	Yes	No	0	0.55
Thymol	150.22	20.23	2.92	High	Yes	No	0	0.55
Carvacrol	150.22	20.23	2.96	High	Yes	No	0	0.55
p-Cymene	134.22	0.00	3.74	Low	Yes	No	1	0.55
Cypermethrin (Reference Toxicant)	416.30	59.32	5.24	High	No	No	0	0.55

Abbreviations: TPSA, Topological Polar Surface Area; LogP, octanol/water partition coefficient; GI, gastrointestinal; BBB, blood–brain barrier; P-gp, P-glycoprotein.

Thymoquinone demonstrated the lowest consensus LogP (1.81), indicating an advantageous balance between lipophilicity and solubility. Carvacrol (LogP = 2.96) and thymol (LogP = 2.92) similarly displayed desirable pharmacokinetic profiles. Although p-cymene exhibited blood–brain barrier permeability, it recorded one Lipinski violation and low gastrointestinal absorption.

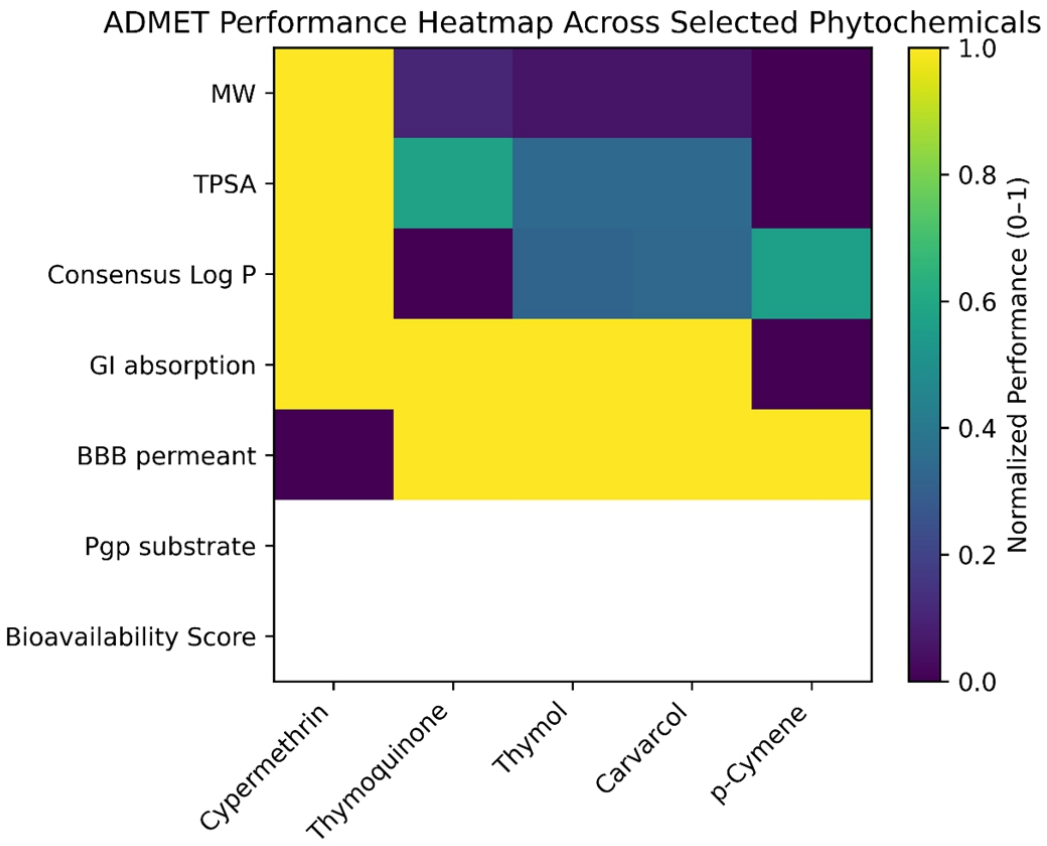


Figure 5: ADMET Performance Heatmap Across Cypermethrin and *Nigella sativa* Phytochemicals

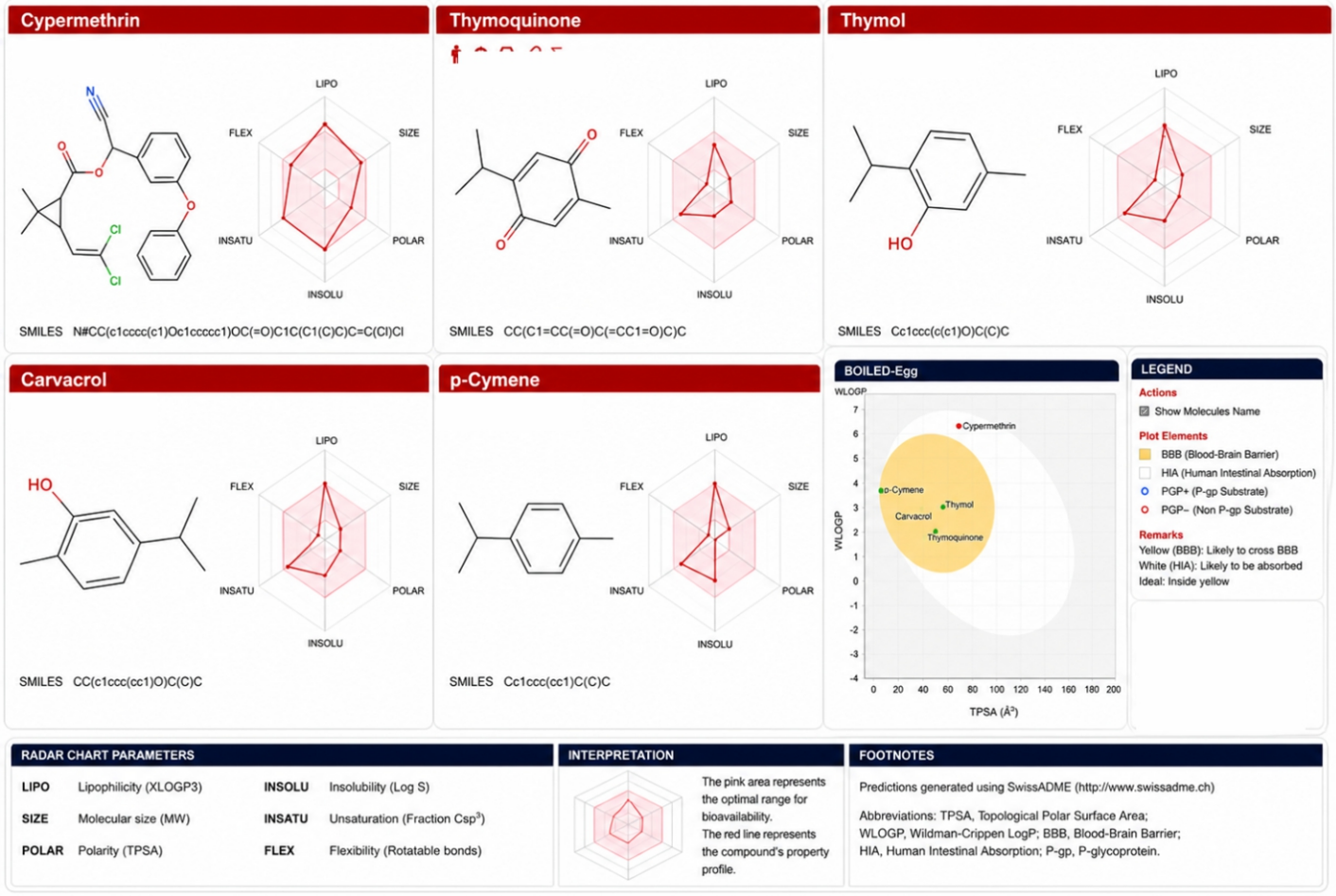


Figure 6: Radar Chart and Boiled Egg Predictions Across Cypermethrin and *Nigella sativa* Phytochemicals

In contrast, cypermethrin exhibited the highest molecular weight (416.30 g/mol) and consensus LogP (5.24), with no predicted blood–brain barrier permeability despite its established neurotoxic effects.

Summary of the Key Findings

Collectively, the findings demonstrate that the selected *Nigella sativa* phytochemicals possess favorable molecular and pharmacokinetic characteristics relevant to neuroprotection. Carvacrol emerged as the strongest NF-κB-interacting phytochemical, while p-cymene exhibited the greatest affinity toward caspase-3 among the plant-derived compounds.

Notably, thymoquinone demonstrated a balanced profile characterized by acceptable target engagement, favorable ADMET properties, and previously documented neuroprotective activity against cypermethrin-induced neuronal injury. These findings support the prioritization of *Nigella sativa* phytochemicals for future molecular dynamics simulations and experimental validation as potential modulators of cypermethrin-associated neuroinflammation and apoptosis.

DISCUSSION

The present study employed a structure-based computational approach to investigate the ability of selected *Nigella sativa* phytochemicals to interact with two principal mediators of cypermethrin-induced neurotoxicity, namely NF-κB and caspase-3. Cypermethrin demonstrated the strongest binding affinity toward both targets, exhibiting docking scores of -7.7 kcal/mol against NF-κB and -6.2 kcal/mol against caspase-3. Given that cypermethrin is a well-established neurotoxicant, these findings provide further mechanistic support for its direct involvement in activating the inflammatory and apoptotic pathways implicated in neuronal injury.

Accumulating evidence suggests that cypermethrin exposure initiates oxidative stress, resulting in excessive reactive oxygen species (ROS) generation, mitochondrial dysfunction, and activation of NF-κB signaling. Activated NF-κB subsequently promotes the transcription of pro-inflammatory mediators, including IL-1β, IL-6, TNF-α, inducible nitric oxide synthase (iNOS), and cyclooxygenase-2 (COX-2), thereby amplifying neuroinflammation. Persistent inflammatory signaling further converges on mitochondrial apoptotic pathways, culminating in caspase-3 activation and neuronal cell death[1,5].

Importantly, the objective of the present study was not to identify compounds exhibiting greater affinity than cypermethrin, but rather to determine whether *Nigella sativa* phytochemicals possess the capacity to engage molecular targets central to cypermethrin-induced neurotoxicity. The ability of thymoquinone, thymol, carvacrol, and p-cymene to occupy the binding pockets of both NF-κB and caspase-3 suggests that these compounds may modulate the inflammatory–apoptotic axis that underlies pesticide-mediated neuronal damage.

Among the phytochemicals, carvacrol demonstrated the greatest affinity toward NF-κB (-6.3 kcal/mol), indicating a potential role as an anti-inflammatory modulator. Previous investigations have shown that carvacrol suppresses NF-κB nuclear translocation and attenuates the expression of IL-1β, IL-6, and TNF-α across several inflammatory models, findings that are consistent with its interaction profile observed in the present study[15,16]. Likewise, thymol exhibited comparable binding characteristics, reinforcing reports describing its antioxidant and anti-inflammatory activities in neurological disorders[6].

Although thymoquinone did not exhibit the strongest docking score, it arguably represents the most biologically relevant phytochemical identified in this study. Numerous experimental studies have demonstrated that thymoquinone exerts neuroprotective effects through simultaneous regulation of multiple signaling pathways, including NF-κB, Nrf2/ARE, PI3K/Akt, AMPK, and SIRT1. Furthermore, thymoquinone has been shown to inhibit the activation of caspases-3, -8, and -9, reduce microglial activation, preserve mitochondrial membrane integrity, and suppress ROS-mediated neuronal injury[2,17,18].

Interestingly, p-cymene demonstrated the highest affinity toward caspase-3 (-4.8 kcal/mol) among the *Nigella sativa* phytochemicals. Although comparatively less studied than thymoquinone, p-cymene has been reported to exhibit antioxidant and anti-inflammatory activities, suggesting that it may contribute synergistically to the overall neuroprotective effects of *Nigella sativa*. This observation further supports the concept of phytochemical polypharmacology, whereby multiple constituents collectively modulate interconnected signaling pathways rather than acting through a single molecular target.

The ADMET analysis provides additional support for the translational potential of the investigated phytochemicals. Thymoquinone, thymol, and carvacrol exhibited favorable gastrointestinal absorption, predicted blood–brain barrier permeability, and no violations of Lipinski's Rule of Five. These properties are particularly relevant considering that effective neuroprotective agents must achieve adequate central nervous system bioavailability. In contrast, cypermethrin exhibited poor predicted blood–brain barrier permeability despite its known neurotoxicity, highlighting the limitations of computational pharmacokinetic models when applied to environmental toxicants.

Collectively, the findings support a mechanistic model in which cypermethrin induces neuronal injury through NF-κB-mediated neuroinflammation and caspase-3-dependent apoptosis, while *Nigella sativa* phytochemicals may mitigate these effects through target engagement and modulation of the inflammatory–apoptotic axis. Notably, thymoquinone appears to function as a multi-target neuroprotective agent, whereas carvacrol emerges as a promising NF-κB-directed phytochemical. The observed molecular interactions provide a plausible explanation for the previously reported neuroprotective effects of *Nigella sativa* in experimental models of pesticide-induced neurotoxicity.

Nevertheless, this study is limited by the inherent constraints of molecular docking, which provides a static representation of protein–ligand interactions and does not account for protein flexibility, metabolic transformation, or intracellular signaling complexity. Consequently, future studies incorporating molecular dynamics simulations, transcriptomic analyses, and in vivo validation are warranted to confirm the therapeutic relevance of these findings.

In conclusion, the present study demonstrates that *Nigella sativa* phytochemicals possess the molecular capability to interact with critical mediators of cypermethrin-induced neurotoxicity. By targeting NF-κB and caspase-3, these compounds may represent promising candidates for the development of novel interventions aimed at attenuating pesticide-associated neuroinflammation and apoptosis.

DECLARATIONS

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Research Paper

Neuroprotective Effects of *Nigella sativa* Oil Against Prenatal Di-Butyl Phthalate-Induced Cerebellar Neurotoxicity in Wistar Rat Offspring

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ABSTRACT

Background:

Di-butyl phthalate (DBP) is a widely used plasticizer and environmental endocrine disruptor known to induce oxidative stress and neurodevelopmental toxicity. The developing brain, particularly regions involved in motor coordination and behavior, is highly vulnerable to prenatal toxicant exposure. Natural antioxidants such as Nigella sativa oil (NSO) have shown promise in mitigating chemically induced neural damage.

Aim:

This study investigated the neurobehavioral, biochemical, and histological effects of prenatal DBP exposure and evaluated the protective potential of Nigella sativa oil in Wistar rat offspring.

Materials and Methods:

Twenty pregnant Wistar rats were randomly assigned to four groups: control, NSO (1 mL/kg b.w.), DBP (500 mg/kg b.w.), and DBP + NSO. Treatments were administered orally from gestational day 4 to 21. Offspring were assessed for neurobehavioral performance using the open field test on postnatal day 35. Cerebellar tissues were analyzed for oxidative stress markers including malondialdehyde (MDA), catalase (CAT), and glutathione peroxidase (GPx), and processed for histological evaluation using hematoxylin and eosin and cresyl fast violet staining.

Results:

Prenatal DBP exposure resulted in reduced locomotor activity, elevated MDA levels, and decreased CAT and GPx activities, indicating oxidative stress and impaired antioxidant defense. Histological analysis revealed neuronal degeneration, vacuolation, disrupted cortical layering, and loss of Nissl substance in the cerebellum. Co-administration of NSO significantly improved behavioral performance, reduced lipid peroxidation, restored antioxidant enzyme activity, and preserved cerebellar cytoarchitecture.

Conclusion:

Prenatal DBP exposure induces significant neurobehavioral deficits, oxidative stress, and cerebellar neurodegeneration in rat offspring. Nigella sativa oil confers substantial neuroprotection, likely through its

antioxidant and cytoprotective properties, highlighting its potential as a natural intervention against environmental neurotoxins.

KEYWORDS: Di-butyl phthalate; *Nigella sativa* oil; Neurotoxicity; Oxidative stress; Cerebellum; Neurobehavior.

INTRODUCTION

Phthalates are synthetic esters of phthalic acid widely used as plasticizers in numerous consumer and industrial products, including plastics, food packaging, toys, cosmetics, medical devices, and pharmaceuticals[1]. Their widespread application has resulted in continuous human exposure through ingestion, inhalation, and dermal absorption, raising serious concerns regarding their long-term health effects[1,2]. Accumulating evidence indicates that phthalates function as endocrine-disrupting chemicals, capable of interfering with hormonal regulation and contributing to reproductive, developmental, and neurological disorders[2,3]. Among these compounds, Di-butyl phthalate (DBP), a low-molecular-weight phthalate commonly encountered in daily environments, has drawn particular attention due to its environmental prevalence and documented toxicity affecting multiple organs, including the nervous system[3,4].

Experimental and animal studies have demonstrated that DBP exposure disrupts neural development and brain function through mechanisms involving oxidative stress, endocrine imbalance, altered gene expression, and mitochondrial dysfunction[5,6]. DBP-induced neurotoxicity has been associated with neuronal apoptosis, synaptic dysfunction, impaired neurogenesis, and behavioral abnormalities[6]. Prenatal exposure is of particular concern, as DBP and its metabolites can cross the placental barrier and interfere with hormone-dependent neuro-developmental processes[3,5]. Histopathological studies have revealed DBP-induced neuronal loss and structural alterations in developing brain regions, with the cerebellum being especially vulnerable due to its critical role in motor coordination, balance, and cognitive processing[3,5].

In parallel, increasing attention has been directed toward natural antioxidants as potential protective agents against toxicant-induced neural injury. *Nigella sativa* oil (NSO) has gained prominence due to its bioactive constituents, particularly thymoquinone and thymohydroquinone, which exhibit potent antioxidant, anti-inflammatory, and neuroprotective properties[7-9]. Thymoquinone has been shown to attenuate oxidative stress by reducing lipid peroxidation and enhancing endogenous antioxidant enzyme activity, including catalase and glutathione peroxidase[9]. These properties are especially relevant for counteracting DBP-induced oxidative damage and neuronal apoptosis within the developing cerebellum[10]. Experimental evidence further supports the efficacy of NSO in preserving neural architecture and function against chemically induced neurotoxicity[8,10].

Despite regulatory efforts, DBP remains widely present in plastics, cosmetics, and other consumer products, resulting in persistent exposure throughout life, including during critical periods of prenatal development[4,5]. Although DBP is rapidly metabolized to mono-butyl phthalate and excreted following glucuronidation, both DBP and its metabolites have been detected in various biological samples, including urine, serum, breast milk, and amniotic fluid[3,5]. While the neurotoxic effects of DBP on brain development are increasingly recognized, limited data exist regarding protective strategies against DBP-induced cerebellar damage during gestation. Therefore, the present study aims to investigate the neuroprotective role of *Nigella sativa* oil in preventing DBP-induced cerebellar injury during prenatal exposure, with the goal of reducing developmental impairments in the offspring of exposed Wistar rats.

METHODOLOGY

Ethical Approval

All experimental procedures were conducted in strict compliance with the National Institutes of Health (NIH) Guide for the Care and Use of Laboratory Animals and in accordance with the guidelines of the Institutional Animal Care and Use Committee (IACUC). Ethical approval for the study was obtained from the Ethical Review Committee of Al-Hikmah University, Ilorin, Nigeria (approval number: HUI-FHS-ERC-25-0041). The principles of the 3Rs (Replacement, Reduction, and Refinement) were strictly adhered to in the handling, housing, and care of the experimental animals to ensure animal welfare and scientific validity.

Chemicals and Reagents

Di--butyl phthalate (DBP) was obtained from Central Drug House (P) Ltd., New Delhi, India (Batch No: 171019) and purchased through Laotech Scientific Nigeria Company. *Nigella sativa* oil (NSO) was procured from Hemani Herbals Trading and purchased from Al-Alameen Store, Ilorin, Nigeria. Normal saline solution was manufactured by Fidson Healthcare Plc (Nigeria) and purchased from One Step Pharmacy. All other reagents, including sucrose,

formalin, ethanol, methylated spirit, cresyl fast violet, and ELISA kits, were of analytical grade and used as supplied.

Experimental Animals

The experimental animals used in this study were Wistar rats bred and housed at the Animal Holding Facility of the Department of Human Anatomy, Faculty of Basic Medical Sciences, College of Health Sciences, Ilorin, Kwara State, Nigeria. The rats were originally procured from Fulcrum Innovation Limited, Ilorin, Kwara State. A total of twenty unmated female Wistar rats and twelve adult male albino rats, weighing between 220 g and 280 g, were utilized.

Animals were maintained under standard laboratory conditions of temperature (20–22 °C), adequate ventilation, and a 12-hour light/dark cycle. They were fed pelleted rat feed and provided with clean drinking water ad libitum. All animals were allowed to acclimatize for two weeks prior to the commencement of the experiment and were housed in plastic cages with sawdust bedding that was replaced regularly.

Experimental Design and Grouping

Mating was carried out during the third week of acclimatization using a 2:1 female-to-male ratio. Pregnancy was confirmed by vaginal smear analysis and progressive weight gain. Confirmed pregnant rats were randomly assigned into four groups (n = 5 per group):

- **Group A (Control):** Normal saline (10 ml/kg body weight, orally)
- **Group B (NSO):** *Nigella sativa* oil (1 ml/kg body weight, orally)
- **Group C (DBP):** Di-butyl phthalate (500 mg/kg body weight, orally)
- **Group D (DBP + NSO):** Di-butyl phthalate (500 mg/kg body weight) + *Nigella sativa* oil (1 ml/kg body weight, orally)

Treatments were administered once daily from gestational day 4 to gestational day 21 using an appropriately sized oral cannula. The dose of DBP was selected based on previous studies demonstrating consistent induction of neurotoxic effects[11], while the dose of NSO was chosen based on reports of antioxidant and neuroprotective efficacy without toxicity[12].

Neurobehavioral Assessment

Neurobehavioral assessment was conducted on postnatal day 35 (PND35) prior to sacrifice. Eight pups were randomly selected from each group for behavioral testing. Locomotor activity and anxiety-like behavior were evaluated using the open field test (OFT). Each rat was placed individually in the center of a 100 × 100 cm square arena divided into 16 equal squares, and exploratory behavior was recorded for 5 minutes. Parameters assessed included total locomotion, number of center square entries, and time spent in the central square. The apparatus was cleaned with ethanol after each trial to eliminate olfactory cues.

Termination of Experiment and Tissue Collection

At the end of the experimental period, animals were humanely euthanized by cervical dislocation. Brains were immediately excised, and the cerebellum was carefully dissected and divided for histological and biochemical analyses.

Histological Analysis

Cerebellar tissues from all experimental groups were harvested and fixed immediately in 10% neutral buffered formalin at room temperature for at least 48 hours. The tissues were then trimmed into coronal sections, dehydrated through ascending grades of ethanol, cleared in xylene, and embedded in molten paraffin wax at approximately 55 °C. Serial sections of 5 µm thickness were obtained using a rotary microtome and mounted on clean glass slides for histological staining.

Sections were stained with Hematoxylin and Eosin (H&E) to evaluate general cerebellar histoarchitecture and Cresyl Fast Violet (CFV) to demonstrate Nissl substance integrity. Staining procedures involved deparaffinization, rehydration, and staining using standard protocols, followed by dehydration, clearing, and mounting with DPX. Slides were examined under a compound light microscope using 4× and 10× objectives to assess neuronal integrity, Purkinje cell distribution, and overall cortical organization. Photomicrographs were captured using a calibrated digital imaging system, and all evaluations were performed in a blinded manner by independent observers to minimize bias and assess treatment-related morphological changes and neuroprotective effects.

Biochemical Analysis

Following sacrifice, cerebellar tissues were excised, rinsed, and homogenized in ice-cold 0.25 M sucrose. Homogenates were centrifuged at 10,000 × g for 15 minutes at 4 °C, and the supernatant was used for oxidative stress and antioxidant enzyme analyses. Catalase (CAT) activity was measured spectrophotometrically at 410 nm based on hydrogen peroxide decomposition. Lipid peroxidation was assessed by malondialdehyde (MDA) levels using the TBARS assay at 532 nm, while glutathione peroxidase (GPx) activity was determined via reduced glutathione-dependent hydroperoxide reduction at 460 nm. These assays collectively evaluated oxidative stress status, antioxidant defense, and neuroprotective effects in cerebellar tissue.

Statistical Analysis

Data were expressed as mean ± standard error of the mean (SEM). Statistical analysis was performed using GraphPad Prism software. Comparisons among groups were made using one-way analysis of variance (ANOVA), followed by Tukey's post-hoc test. Statistical significance was set at $p \leq 0.05$.

RESULTS

1. **Physical Observations during Gestation (Maternal)**

A. Maternal Weight Changes

Maternal weight changes during gestation varied across the experimental groups [Figure 1]. Dams in the control and *Nigella sativa* oil–treated groups maintained a progressive and physiologically appropriate pattern of weight gain throughout gestation. In contrast, exposure to Di-butyl phthalate was associated with disrupted gestational weight progression, suggestive of maternal stress and metabolic alteration. Notably, concurrent administration of *Nigella sativa* oil moderated these adverse effects with a gradual improvement in maternal weight trajectory.

B. Duration of Gestation

Gestational duration varied across the experimental groups [Figure 2]. Dams in the control and *Nigella sativa* oil–treated groups showed gestation lengths within the expected physiological range. In contrast, Di-butyl phthalate exposure was associated with a prolongation of gestation, indicating disruption of normal parturition timing. Co-administration of *Nigella sativa* oil moderated this effect, suggesting a protective influence against DBP-induced gestational delay.

C. Litter Size

Litter size varied across the experimental groups [Figure 3]. Control and *Nigella sativa* oil–treated dams exhibited litter outcomes consistent with normal gestational performance. In contrast, prenatal exposure to Di-butyl phthalate was associated with a reduction in litter size, suggesting adverse effects on gestational outcome. Co-administration of *Nigella sativa* oil moderated this effect, indicating partial preservation of normal pregnancy outcome despite DBP exposure.

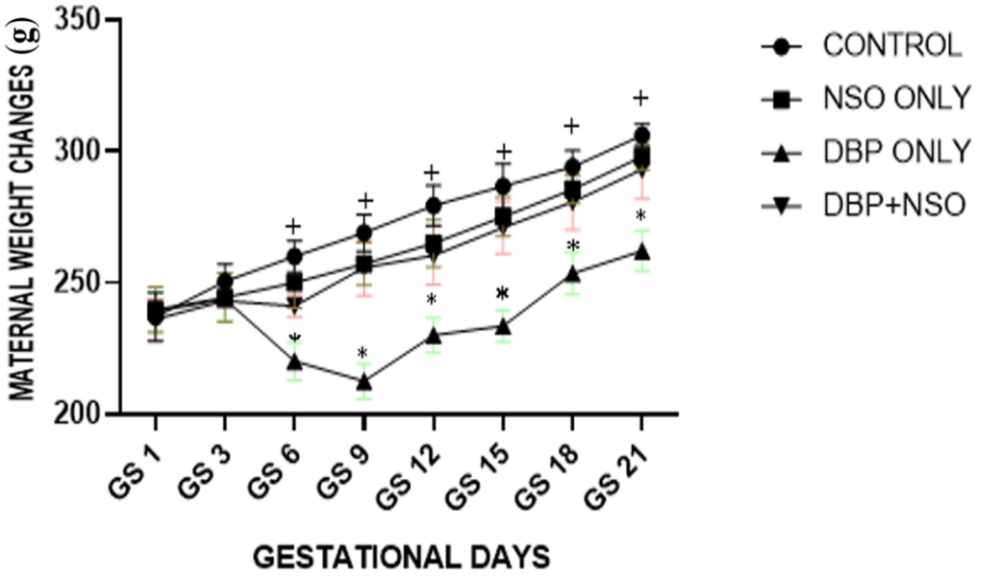


Figure 1: Graph showing the effect of DBP and NSO administration on maternal body weight changes of experimental animals. Asterisk (*) indicates statistical significance compared to the control group, (+) indicates statistical significance compared to the NSO group, **CONTROL** = Control (normal saline), **NSO** = *Nigella sativa* oil (1 ml/kg b.w.), **DBP** = Di-butyl phthalate (500 mg/kg b.w.), and **DBP+NSO** = Di-butyl phthalate (500 mg/kg b.w.) + *Nigella sativa* oil (1 ml/kg b.w.)

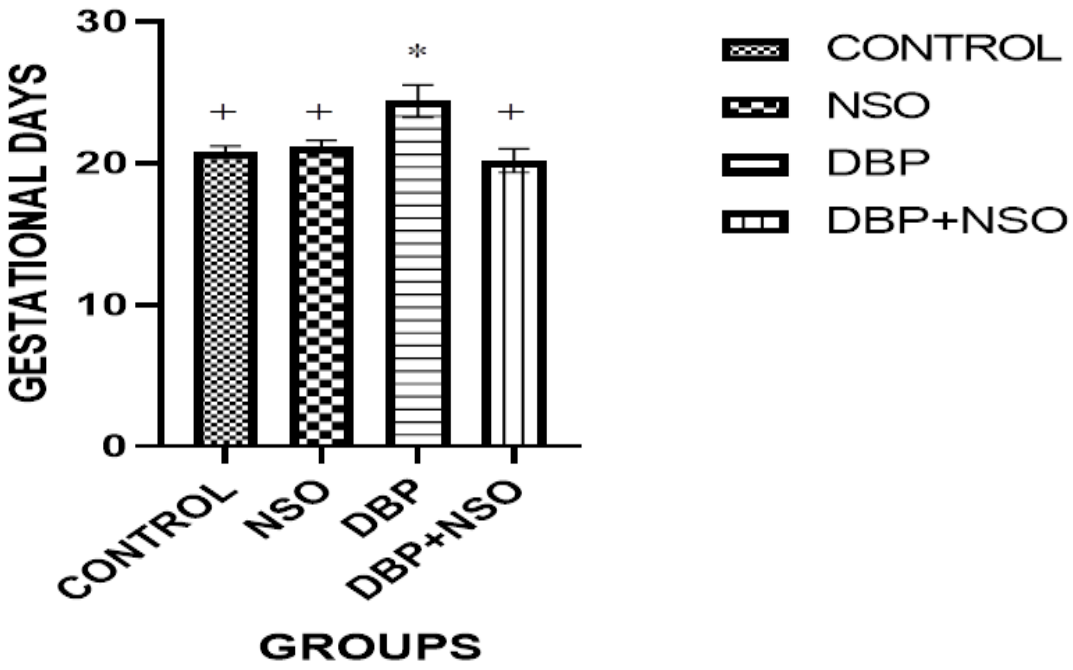


Figure 2: Graph showing the effect of DBP and NSO administration on the duration of gestation across experimental groups. Asterisk (*) indicates statistical significance compared to the control group, (+) indicates statistical significance compared to the NSO group, while **CONTROL** = Control (normal saline), **NSO** = *Nigella sativa* oil (1 ml/kg b.w.), **DBP** = Di-butyl phthalate (500 mg/kg b.w.), and **DBP+NSO** = Di-butyl phthalate (500 mg/kg b.w.) + *Nigella sativa* oil (1 ml/kg b.w.)

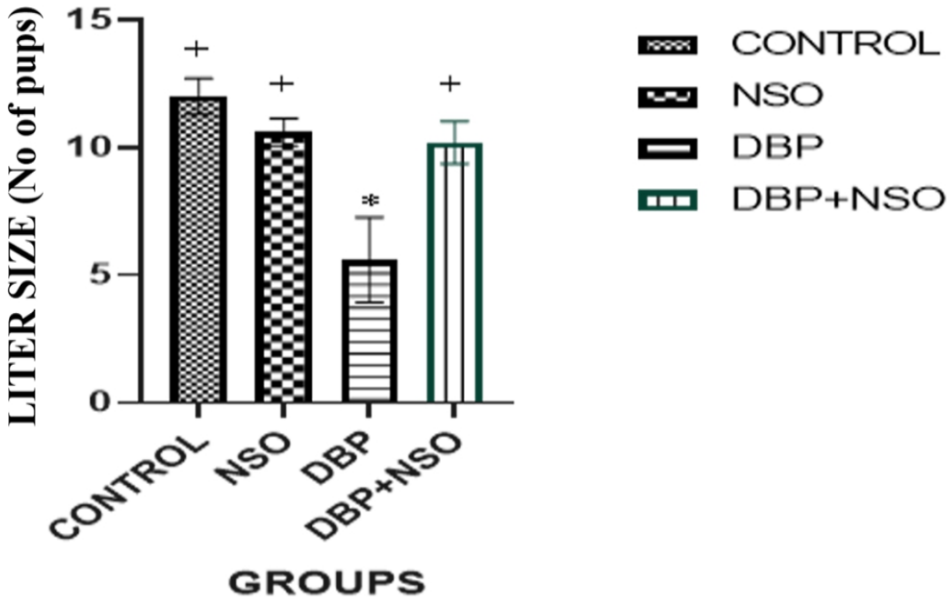


Figure 3: Graph showing the effect of DBP and NSO administration on litter size across experimental groups. Asterisk (*) indicates statistical significance compared to the control group, (+) indicates statistical significance compared to the NSO group, while **CONTROL** = Control (normal saline), **NSO** = *Nigella sativa* oil (1 ml/kg b.w.), **DBP** = Di-butyl phthalate (500 mg/kg b.w.), and **DBP+NSO** = Di-butyl phthalate (500 mg/kg b.w.) + *Nigella sativa* oil (1 ml/kg b.w.)

1. **Physical Observations during Gestation (Offspring)**

A. Offspring Body Weight Changes

Postnatal body weight progression of offspring differed across the experimental groups [Figure 4]. Pups from the control and *Nigella sativa* oil–treated groups exhibited growth patterns consistent with normal postnatal development. In contrast, prenatal exposure to Di-butyl phthalate was associated with altered weight gain, reflecting impaired early growth. Co-administration of *Nigella sativa* oil attenuated these effects, suggesting a modulatory influence on DBP-induced growth alterations.

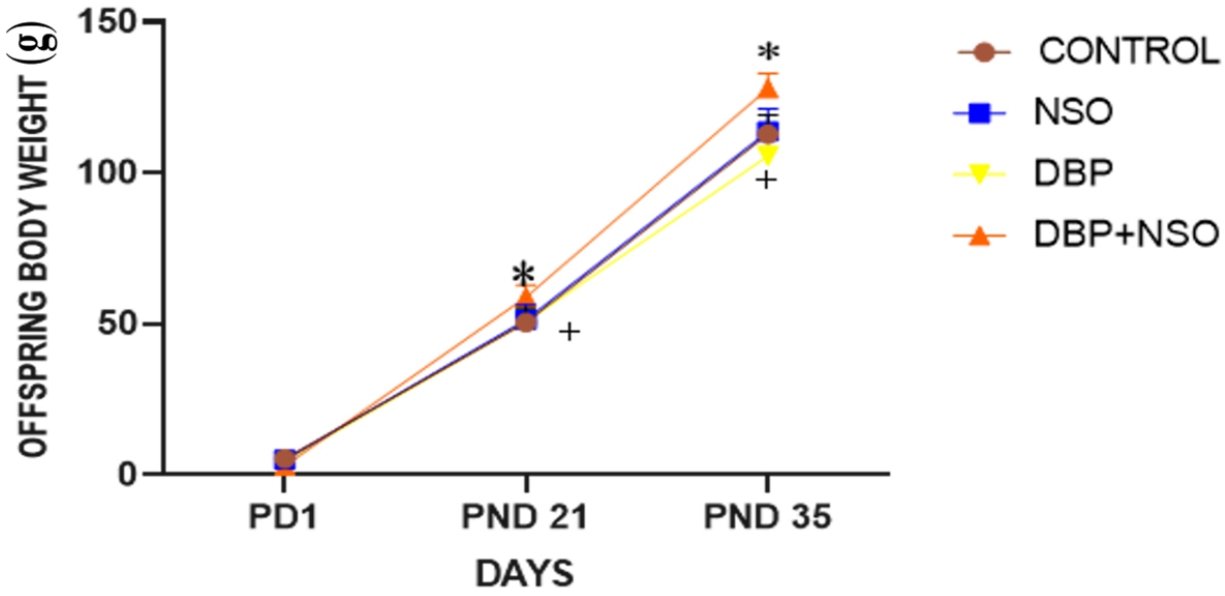


Figure 4: Graph showing the effect of DBP and NSO administration on offspring body weight changes across experimental groups. Asterisk (*) indicates statistical significance compared to the control group, (+) indicates statistical significance compared to the NSO group, while **CONTROL** = Control (normal saline), **NSO** = *Nigella sativa* oil (1 ml/kg b.w.), **DBP** = Di-butyl phthalate (500 mg/kg b.w.), and **DBP+NSO** = Di-butyl phthalate (500 mg/kg b.w.) + *Nigella sativa* oil (1 ml/kg b.w.)

B. Fur Appearance

Assessment of fur appearance revealed no marked differences across the experimental groups [Figure 5]. Fur development followed a similar timeline in all groups; however, offspring in the *Nigella sativa* oil–treated group and Control group exhibited visibly increased fur density. Prenatal exposure to Di-butyl phthalate did not produce overt alterations in fur appearance, and co-administration of *Nigella sativa* oil did not markedly deviate from the general pattern observed**.**

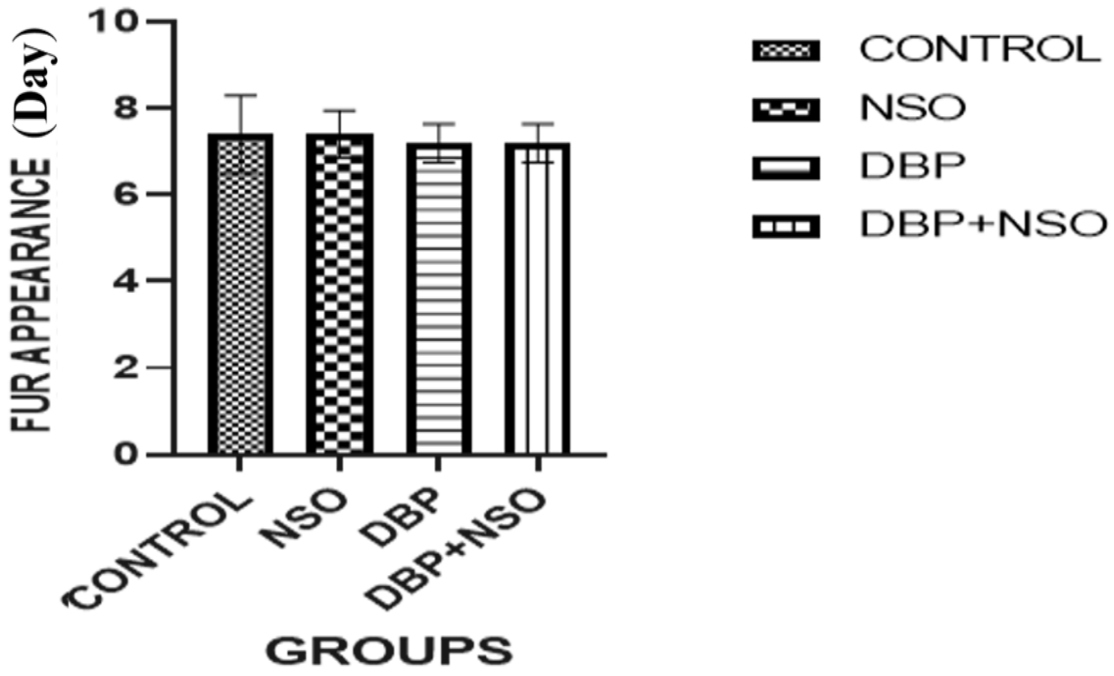


Figure 5: Graph showing fur appearance day across experimental groups. **CONTROL** = Control (normal saline), **NSO** = *Nigella sativa* oil (1 ml/kg b.w.), **DBP** = Di-butyl phthalate (500 mg/kg b.w.), and **DBP+NSO** = Di-butyl phthalate (500 mg/kg b.w.) + *Nigella sativa* oil (1 ml/kg b.w.)
No statistically significant difference was observed across the groups.

C. Eye Opening Assessment

Assessment of eye opening revealed no marked differences across the experimental groups [Figure 5]. Eye Opening followed a similar timeline in all groups. Prenatal exposure to Di-butyl phthalate did not produce overt alterations in eye opening of the offspring, and co-administration of *Nigella sativa* oil did not markedly deviate from the general pattern observed in control and *Nigella sativa* oil treated groups**.**

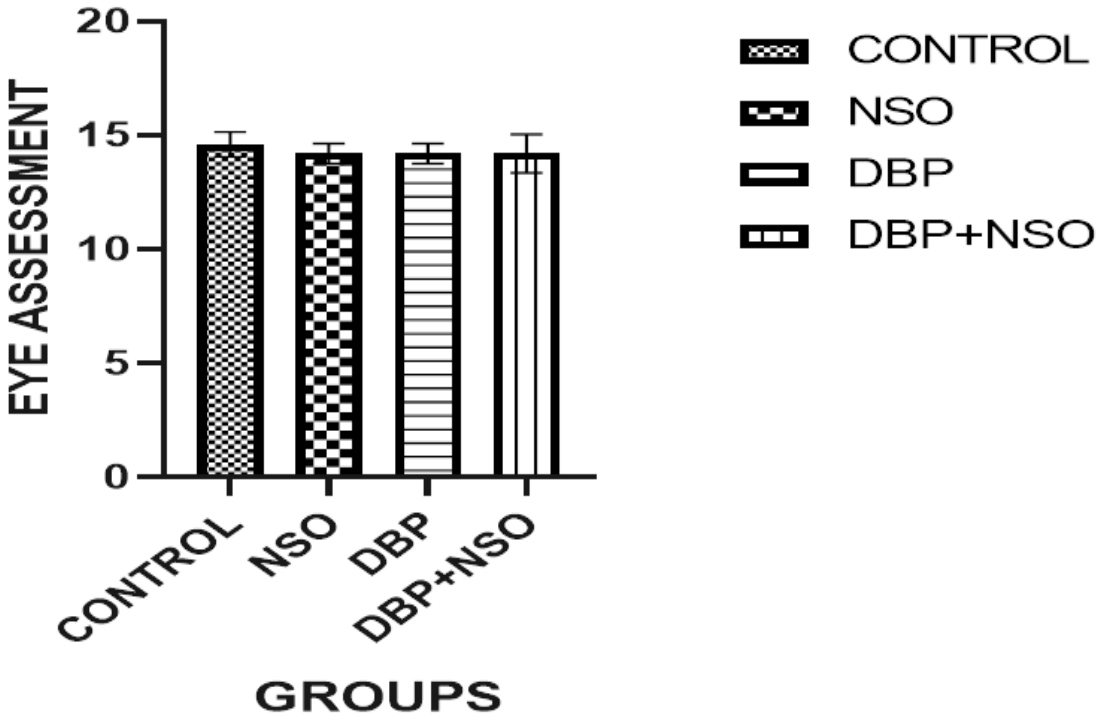


Figure 6: Graph showing eye opening assessment across experimental groups. **CONTROL** = Control (normal saline), **NSO** = *Nigella sativa* oil (1 ml/kg b.w.), **DBP** = Di-butyl phthalate (500 mg/kg b.w.), and **DBP+NSO** = Di-butyl phthalate (500 mg/kg b.w.) + *Nigella sativa* oil (1 ml/kg b.w.)

No statistically significant difference was observed across the groups.

3. **Neurobehavioral Test (Open Field test)**

Neurobehavioral performance assessed using the open field test differed across the experimental groups [Figure 7]. Offspring in the control and *Nigella sativa* oil–treated groups displayed normal locomotor and exploratory activity, as evidenced by a higher number of line crossings. In contrast, offspring prenatally exposed to Di-butyl phthalate showed a significant reduction in line crossings, indicating impaired locomotor activity and reduced exploratory behavior. Co-administration of *Nigella sativa* oil significantly ameliorated this deficit, with the DBP + NSO group demonstrating improved locomotor performance compared to the DBP-only group, suggesting a protective effect of NSO against DBP-induced neurobehavioral impairment.

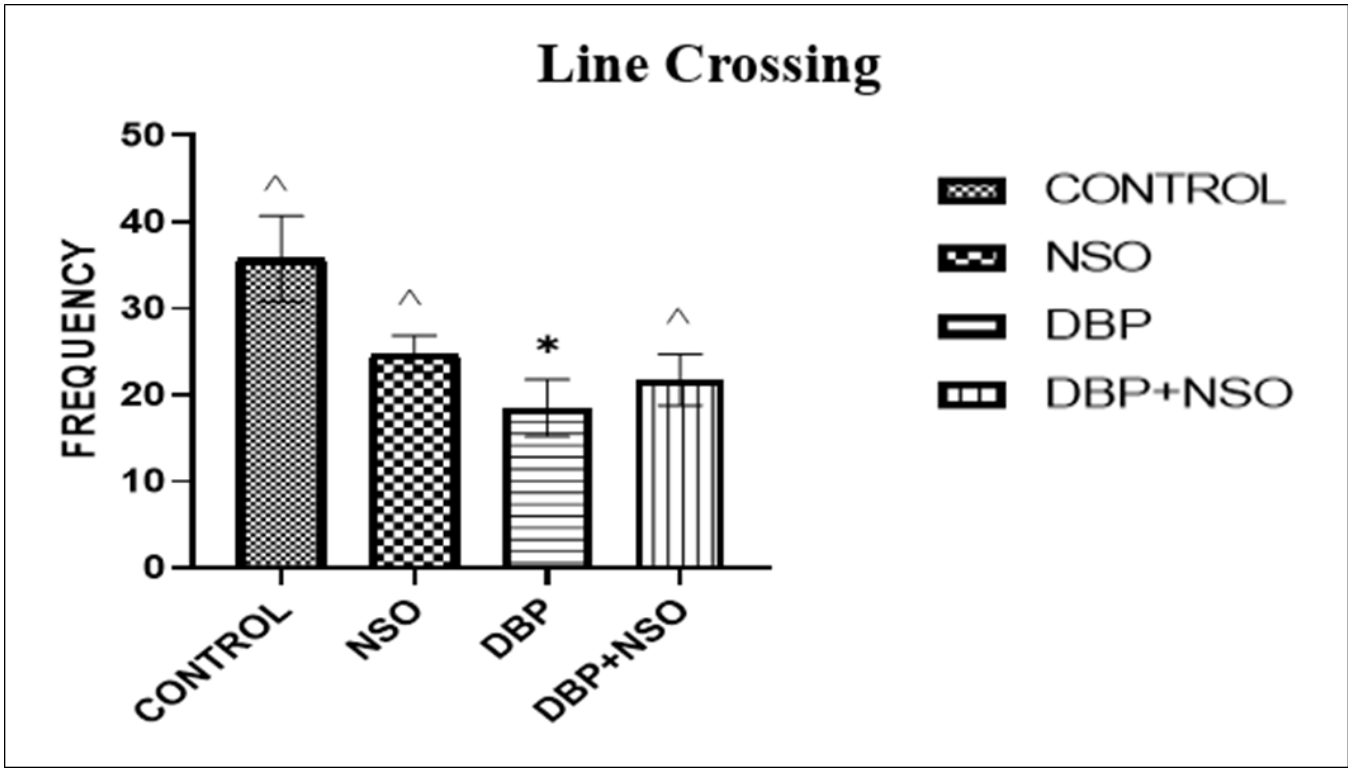


Figure 7: Graph showing the number of line crossings in the open field test across experimental groups. Asterisk (*) indicates statistical significance compared to the control group, (^) indicates statistical significance compared to the DBP-only group, while **CONTROL** = Control (normal saline), **NSO** = *Nigella sativa* oil (1 ml/kg b.w.), **DBP** = Di-butyl phthalate (500 mg/kg b.w.), and **DBP+NSO** = Di-butyl phthalate (500 mg/kg b.w.) + *Nigella sativa* oil (1 ml/kg b.w.)

4. **Biochemical Analysis**

A. Levels of Malondialdehyde (MDA)

Lipid peroxidation, assessed by malondialdehyde levels, differed significantly among the groups [Figure 8]. Offspring from the Di-butyl phthalate group exhibited a significant elevation in MDA levels compared to control, indicating increased oxidative damage. In contrast, control and *Nigella sativa* oil–treated groups showed lower MDA levels consistent with normal oxidative status. Co-administration of *Nigella sativa* oil significantly reduced MDA levels compared to the DBP-only group, demonstrating attenuation of DBP-induced lipid peroxidation.

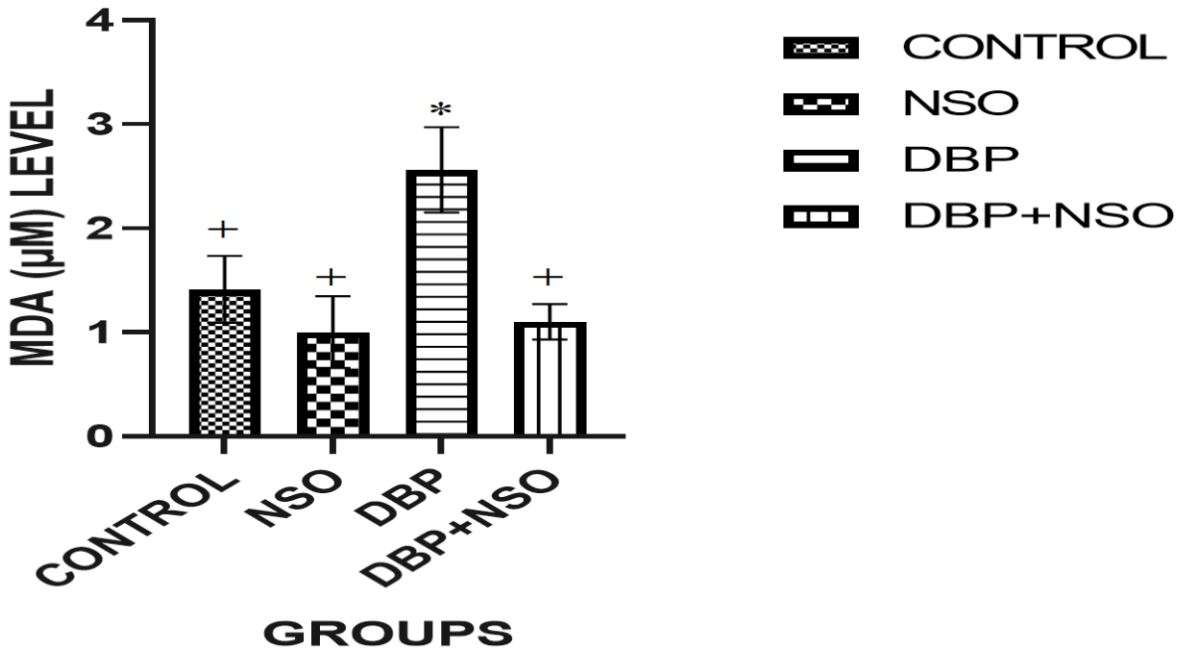


Figure 8: Graph showing malondialdehyde (MDA) levels in the cerebellum of experimental animals. Asterisk (*) indicates statistical significance compared to the control group, (+) indicates statistical significance compared to the DBP-only group, while **CONTROL** = Control (normal saline), **NSO** = *Nigella sativa* oil (1 ml/kg b.w.), **DBP** = Di-butyl phthalate (500 mg/kg b.w.), and **DBP+NSO** = Di-butyl phthalate (500 mg/kg b.w.) + *Nigella sativa* oil (1 ml/kg b.w.)

A. Activities of Catalase

Catalase activity in the cerebellum varied significantly among the experimental groups [Figure 9]. Control and *Nigella sativa* oil–treated groups exhibited normal catalase activity levels. In contrast, Di-butyl phthalate exposure resulted in a significant reduction in catalase activity, reflecting compromised antioxidant defense. Co-administration of *Nigella sativa* oil significantly restored catalase activity compared to the DBP-only group, indicating attenuation of DBP-induced oxidative stress.

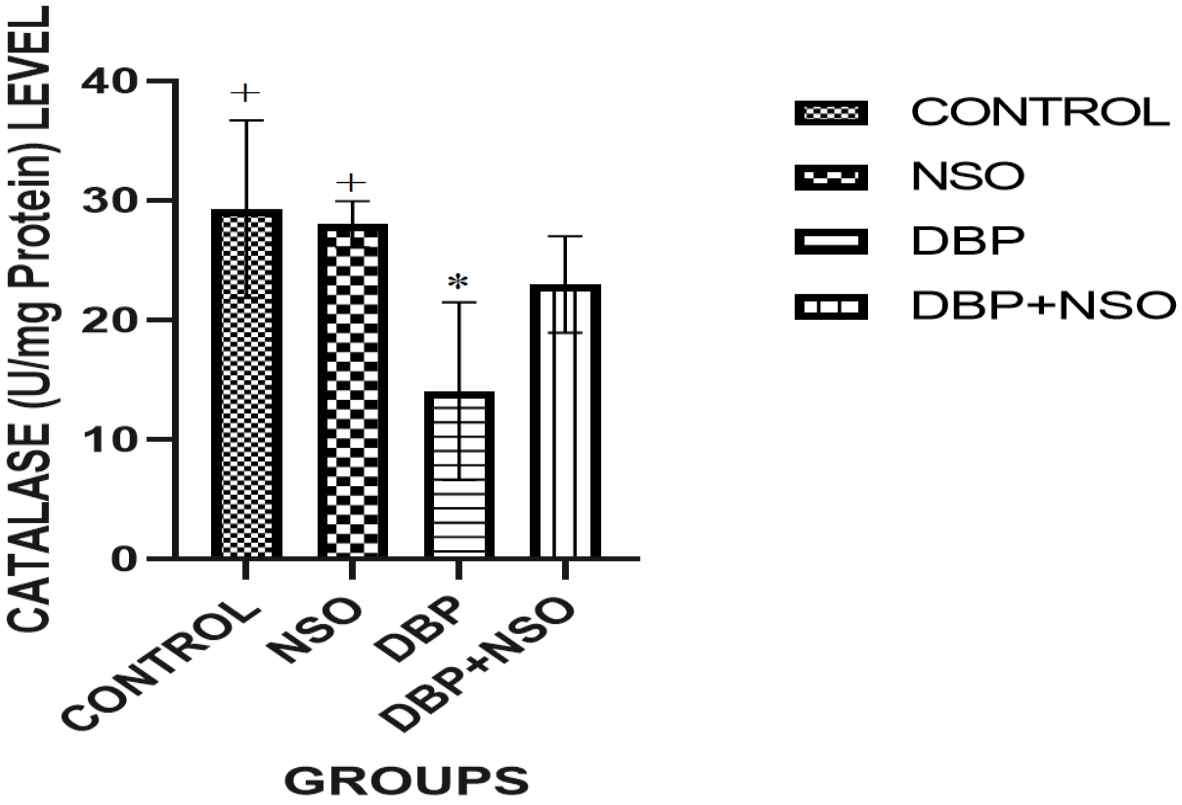


Figure 9: Graph showing catalase levels in the cerebellum of experimental animals. Asterisk (*) indicates statistical significance compared to the control group, (+) indicates statistical significance compared to the DBP-only group, while **CONTROL** = Control (normal saline), **NSO** = *Nigella sativa* oil (1 ml/kg b.w.), **DBP** = Di-butyl phthalate (500 mg/kg b.w.), and **DBP+NSO** = Di-butyl phthalate (500 mg/kg b.w.) + *Nigella sativa* oil (1 ml/kg b.w.).

C. Glutathione Peroxidase (GPx) Activity

Glutathione peroxidase activity showed marked differences across the experimental groups [Figure 10]. The control and *Nigella sativa* oil groups-maintained baseline GPx activity. However, a significant decrease in GPx activity was observed in the Di-butyl phthalate–exposed group, indicating impaired antioxidant capacity. Co-treatment with *Nigella sativa* oil significantly increased GPx activity relative to the DBP-only group, suggesting restoration of endogenous antioxidant defense mechanisms.

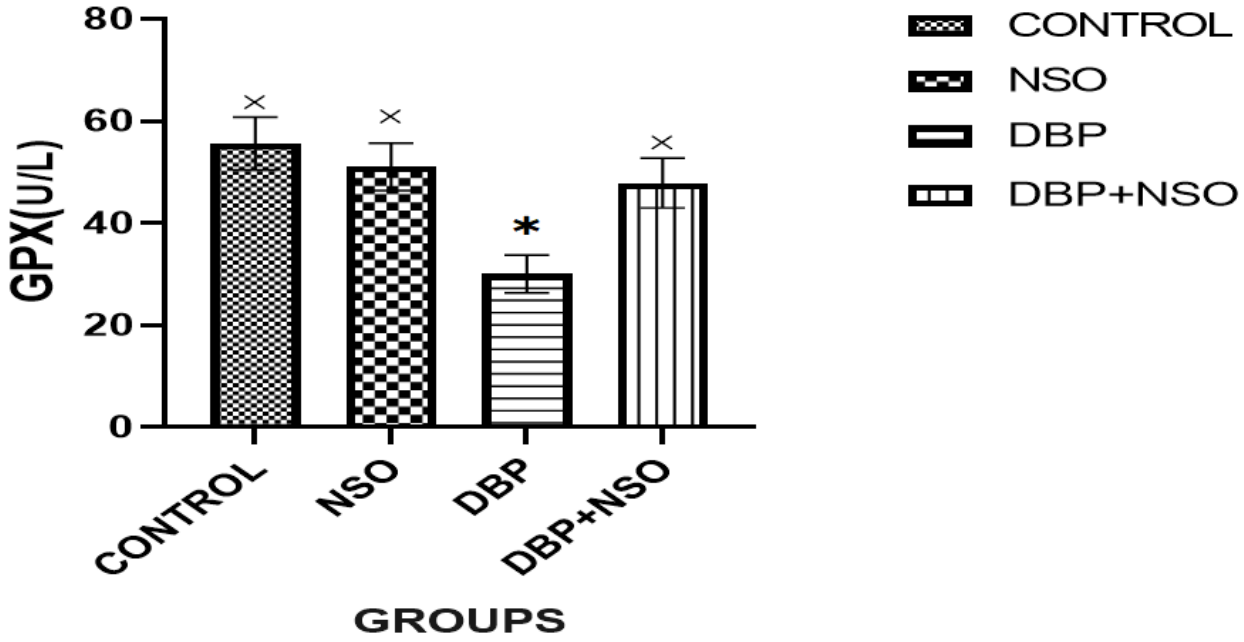


Figure 10: Chart showing glutathione peroxidase (GPx) levels in the cerebellum of experimental animals. Asterisk (*) indicates statistical significance compared to the control group, (×) indicates statistical significance compared to the DBP-only group, while **CONTROL** = Control (normal saline), **NSO** = *Nigella sativa* oil (1 ml/kg b.w.), **DBP** = Di-butyl phthalate (500 mg/kg b.w.), and **DBP+NSO** = Di-butyl phthalate (500 mg/kg b.w.) + *Nigella sativa* oil (1 ml/kg b.w.)

1. **Histological Findings**

A. Hematoxylin and Eosin Stain

Hematoxylin and eosin–stained cerebellar sections showed well-preserved cortical organization with intact molecular, Purkinje, and granular layers in the control and *Nigella sativa* oil–treated groups [Figure 11]. In contrast, the Di-butyl phthalate group exhibited marked histopathological alterations, including neuronal degeneration, shrinkage of cell bodies, vacuolation, pyknotic nuclei, and disrupted layering. Co-administration of *Nigella sativa* oil attenuated these changes, with the DBP + NSO group showing improved cellular morphology and relative preservation of cerebellar architecture compared to the DBP-only group.

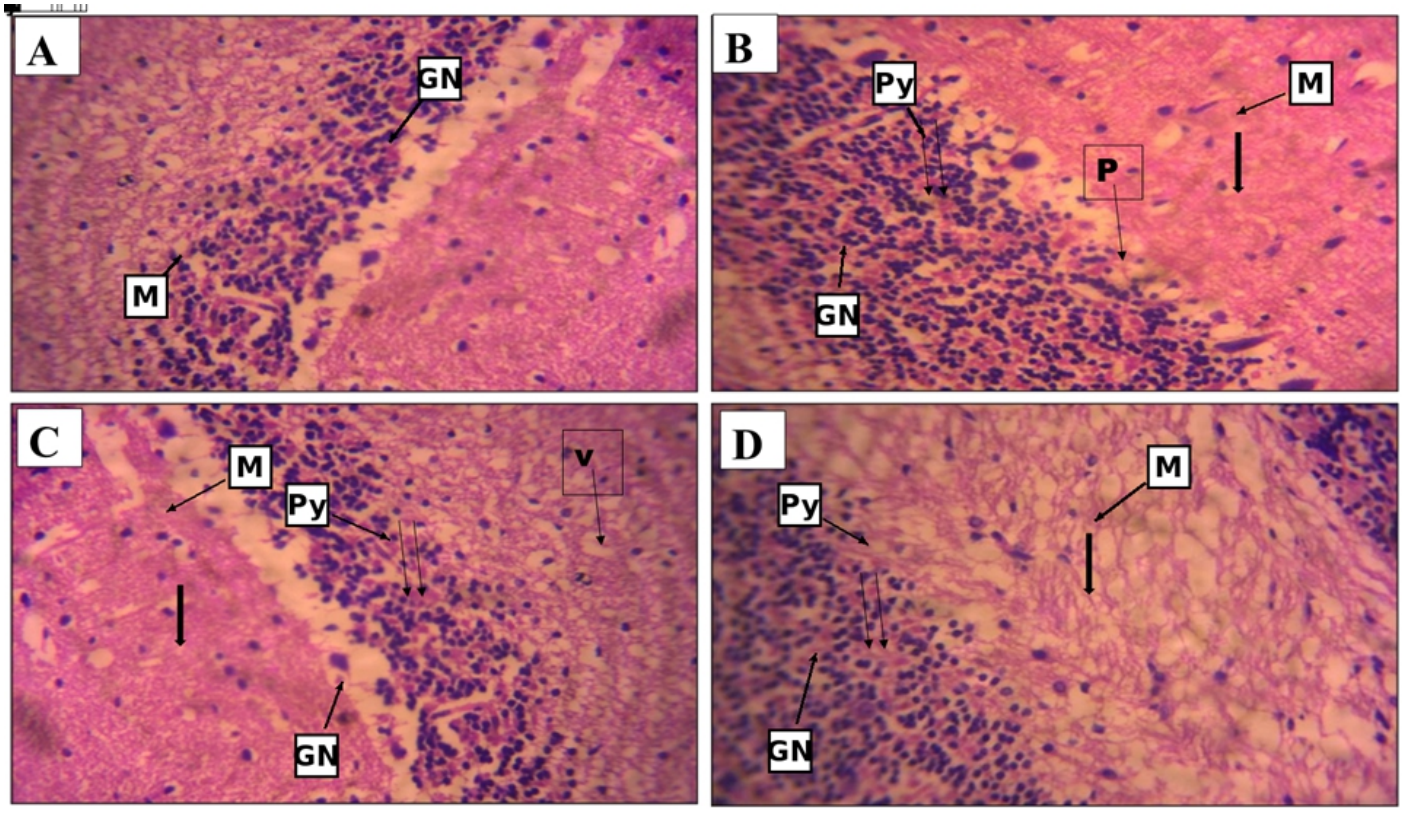


Figure 11: Photomicrograph showing cerebellar histoarchitecture stained with H&E (×400). **CONTROL (A)** and **NSO (B)** groups show normal layering and intact neurons, **DBP group (C)** shows neuronal degeneration and structural disruption, while **DBP+NSO group (D)** shows reduced histological alterations.

GN = Granular layer, **P** = Purkinje layer, **M** = Molecular layer, **Py** = Pyknotic nuclei, **V** = Vacuolation

B. Cresyl Fast Violet (Nissl Profile) Stain

Cresyl fast violet staining revealed dense and uniform Nissl substance distribution in the control and *Nigella sativa* oil–treated groups, indicating preserved neuronal integrity [Figure 12]. In contrast, cerebellar sections from the Di-butyl phthalate group showed reduced staining intensity, chromatolysis, dispersion of Nissl bodies, vacuolation, and pyknotic nuclei, suggestive of impaired neuronal metabolism. Co-treatment with *Nigella sativa* oil resulted in restoration of Nissl staining intensity and improved neuronal appearance relative to the DBP-only group.

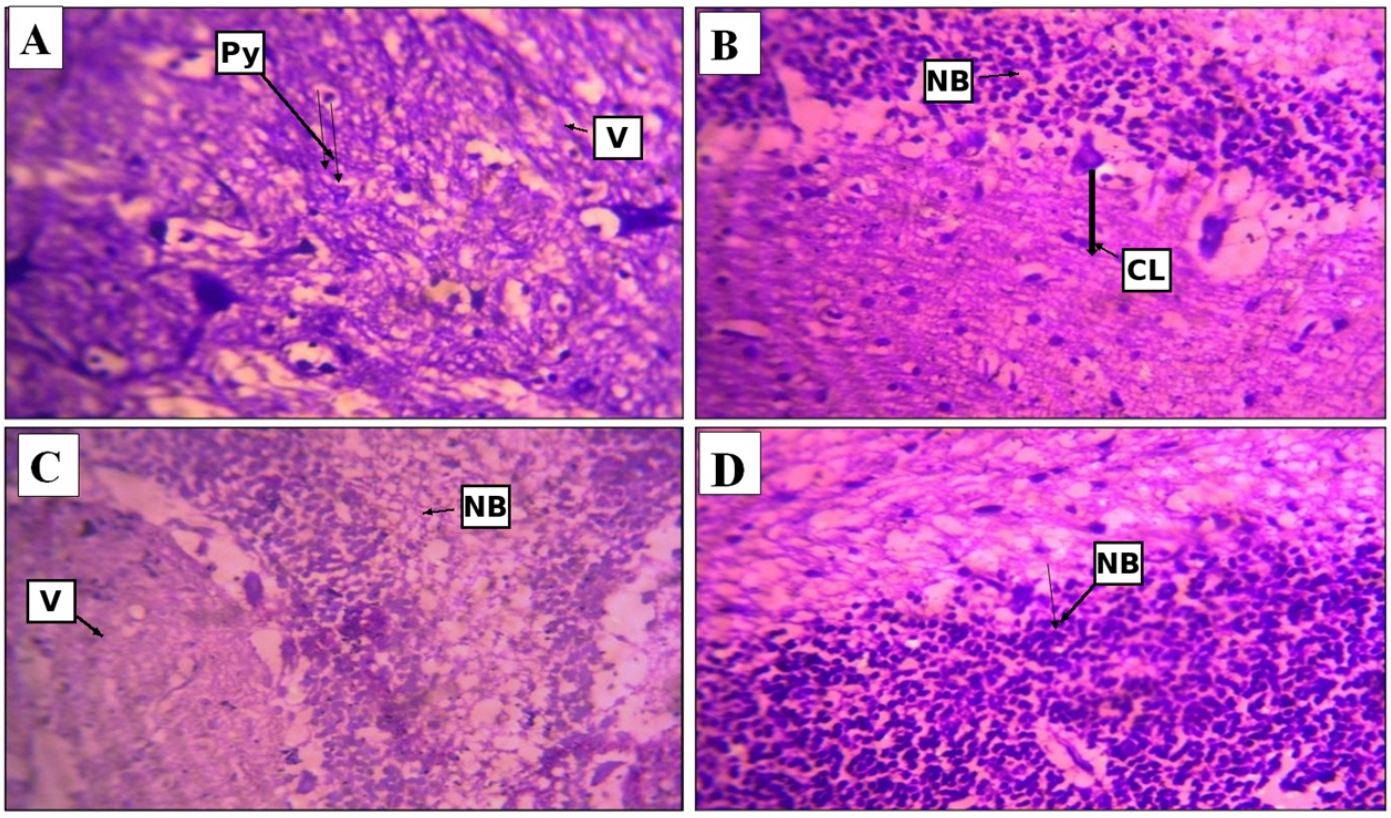


Figure 12: Photomicrograph showing Nissl substance distribution in cerebellar sections stained with CFV (×400). **CONTROL (A) and NSO groups (B)** show intense Nissl staining, **DBP group (C)** shows reduced staining and chromatolysis, while **DBP+NSO group (D)** shows restored Nissl bodies.

NB = Nissl bodies, **CL** = Chromatolysis, **Py** = Pyknotic nuclei, **V** = Vacuolation

DISCUSSION

Prenatal exposure to Di-butyl phthalate (DBP) in the present study produced pronounced adverse effects on maternal gestational indices, offspring development, neurobehavioral performance, oxidative status, and cerebellar histoarchitecture. DBP-exposed dams showed evidence of gestational stress, including altered weight gain patterns and prolonged gestation [Figures 1 and 2], which were accompanied by reduced litter size and impaired postnatal growth in offspring [Figures 3 and 4]. These observations align with earlier reports demonstrating that phthalates disrupt endocrine homeostasis, placental steroidogenesis, and nutrient transfer, resulting in intrauterine growth restriction and altered pregnancy outcomes[13]. Similar developmental impairments following prenatal phthalate exposure have been linked to long-term vulnerability to neurobehavioral and cognitive dysfunction, supporting the relevance of the present findings[14].

Neurobehavioral assessment using the open field test revealed that offspring prenatally exposed to DBP exhibited significantly reduced locomotor activity and exploratory behavior [Figure 7]. Such hypoactivity and anxiety-like responses are indicative of dysfunction in brain regions governing motor coordination, emotional regulation, and executive control, particularly the cerebellum[15,16]. These results are consistent with previous experimental studies reporting diminished exploratory behavior and increased anxiety following DBP exposure, effects attributed to disrupted neurotransmitter signaling, oxidative stress, and altered synaptic plasticity[6,11]. Notably, co-administration of *Nigella sativa* oil (NSO) markedly improved locomotor performance and exploratory behavior [Figure 7], corroborating earlier studies that demonstrated the behavioral ameliorative effects of antioxidant-rich natural products in models of developmental neurotoxicity.

Biochemical analyses further substantiated the neurotoxic impact of prenatal DBP exposure. Cerebellar tissues from DBP-exposed offspring showed significantly elevated malondialdehyde (MDA) levels alongside reduced catalase (CAT) and glutathione peroxidase (GPx) activities [Figures 8–10], confirming the induction of oxidative stress. These findings are in agreement with prior reports identifying lipid peroxidation and impaired antioxidant defenses as central mechanisms in phthalate-induced neurotoxicity[17]. The heightened susceptibility of the developing brain to oxidative injury, owing to its high lipid content, rapid oxygen consumption, and immature antioxidant systems, has been well documented and provides a plausible explanation for the pronounced oxidative imbalance observed in this study[16].

Conversely, NSO co-administration significantly attenuated DBP-induced oxidative stress, as evidenced by reduced MDA levels and restoration of CAT and GPx activities toward control values [Figures 8–10]. This protective effect is consistent with previous studies attributing the antioxidant and neuroprotective properties of NSO primarily to thymoquinone, its major bioactive constituent, which enhances endogenous antioxidant enzyme activity and scavenges reactive oxygen species[18]. Earlier experimental models have similarly shown that *Nigella sativa* and thymoquinone mitigate oxidative damage, preserve mitochondrial integrity, and suppress neuroinflammatory pathways in chemically induced neurotoxicity and neurodegeneration[19]. The biochemical normalization observed in the DBP + NSO group therefore reinforces existing evidence supporting NSO as a potent modulator of redox homeostasis in neural tissues.

Histological findings provided structural confirmation of the biochemical and behavioral outcomes. Hematoxylin and eosin-stained cerebellar sections from DBP-exposed offspring revealed marked cytoarchitectural disruption, including Purkinje cell degeneration, neuronal vacuolation, pyknotic nuclei, and loss of normal cortical layering [Figure 11]. Cresyl fast violet staining further demonstrated chromatolysis, dispersion of Nissl substance, and reduced staining intensity, indicative of impaired protein synthesis and neuronal degeneration [Figure 12]. These alterations are consistent with earlier reports of DBP-induced developmental neurotoxicity characterized by neuronal loss and cerebellar dysfunction[20]. In contrast, co-administration of NSO preserved cerebellar cortical organization, improved Purkinje cell integrity, and restored Nissl substance distribution [Figures 11 and 12]. These histological improvements are in agreement with previous studies demonstrating the ability of *Nigella sativa* oil and thymoquinone to protect neuronal structure and maintain synaptic integrity in experimental models of neurodegeneration[8].

CONCLUSION

This study shows that chronic prenatal exposure to Di-butyl phthalate (DBP) induces significant neurodevelopmental toxicity in the cerebellum of Wistar rat offspring. DBP caused Purkinje cell degeneration, disrupted cortical layering, vacuolations, and neuronal chromatolysis in the cerebellum, accompanied by anxiety-like behavior and reduced exploratory activity. These impairments were associated with elevated oxidative stress, reflecting DBP's neurotoxic and endocrine-disrupting effects. Importantly, co-administration of *Nigella sativa* oil (NSO) mitigated these adverse outcomes by preserving neuronal integrity, restoring cortical architecture, reducing oxidative stress, and partially improving behavior, likely via its antioxidant, anti-inflammatory, and cytoprotective actions attributed to thymoquinone. These findings highlight that DBP exposure during critical developmental periods can cause significant cerebellar deficits, while NSO offers significant neuroprotection, supporting its potential as a natural intervention against environmental neurotoxins.

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Research Paper

Ameliorative Effect of Vitamin C on *Cannabis sativa*-induced Nephrotoxicity in Wistar rats

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ABSTRACT

Background:

The kidneys play a critical role in removing waste products and excess water from the blood, as well as maintaining chemical balance. Damage to the kidneys can pose serious health risks. Cannabis sativa (CS) is one of the commonly abused substances and has been associated with various adverse health effects.

Objective:

This study investigated the ameliorative effects of Vitamin C (Vit C) on CS-induced nephrotoxicity in male and female rats.

Method:

Different doses of CS (2, 4, and 6 mg/kg) and Vit C (4 mg/kg) were administered orally, both individually and in combination, for a period of three weeks. Kidney function parameters, including urea, creatinine, induced protein, albumin, sodium (Na), and potassium (K), were measured using standard methods.

Results:

CS administration significantly increased urea and creatinine levels in the high dose groups (4 and 6 mg/kg) compared with the control and low dose (2 mg/kg) groups in both sexes. Conversely, induced protein, albumin, Na, and K levels were significantly decreased in the high dose groups. However, these adverse effects were significantly ameliorated at the 4 mg/kg CS dose when co-administered with Vit C.

Conclusion:

The effects of CS on kidney function were dose dependent and sex-specific, while Vit C exhibited a protective effect, particularly at the 4 mg/kg dose. These findings suggest that further studies are needed to evaluate whether higher doses of Vit C could mitigate the nephrotoxicity observed at the 6 mg/kg CS dose, since the same dose of Vit C was administered across all treatment groups.

KEYWORDS: *Cannabis sativa*; Vitamin C; Nephrotoxicity; Renal function; Oxidative stress; Wistar rats.

INTRODUCTION

Cannabis(*C.*) is a genus of flowering plants belonging to the family *Cannabaceae*. It is generally classified into three species: *Cannabis sativa*, *Cannabis indica*, and *Cannabis ruderalis*. However, Simiyu DC, Jang JH, Lee OR. Understanding *Cannabis sativa* L.: current status of propagation, use, legalization, and haploid-inducer-mediated genetic engineering. Plants. 2022 May 2;11(9):1236[1]. Globally, cannabis remains one of the most commonly used illicit substances[2], and its consumption has been linked to a range of adverse health outcomes in both humans and animals. Several studies have reported the detrimental effects of *C. sativa* use, whether through ingestion or inhalation, on multiple physiological systems[2–15].

Vitamin C (Vit C), also referred to as ascorbic acid, is well known for its potent antioxidant activity[16]. It exerts its effects primarily by neutralizing free radicals and preventing oxidative damage to critical biomolecules, including DNA, proteins, and lipids[17–18]. Furthermore, Vit C contributes to the regeneration of other antioxidants, particularly Vitamin E, thereby strengthening the body's overall antioxidant defense system[19]. In plant systems, including cannabis, Vit C also plays a role in mitigating oxidative stress by scavenging reactive oxygen species and maintaining cellular stability[20]. A deeper understanding of the role of Vit C in oxidative stress regulation may aid in developing strategies to enhance antioxidant capacity and improve resilience to both environmental and physiological stressors[21].

The kidneys are paired organs situated along the posterior abdominal wall. They perform essential functions, including the excretion of metabolic waste products and toxic substances from the bloodstream, as well as the regulation of fluid and electrolyte homeostasis[22]. Previous studies have reported both protective and harmful effects of *Cannabis sativa* (CS) on renal function in humans and experimental animals[23–25]. However, to the best of our knowledge, no study has investigated the use of Vit C in mitigating CS-induced nephrotoxicity.

Therefore, this study was designed to fill this gap by evaluating the protective effects of Vit C against CS-induced impairment of kidney function in both male and female Wistar rats, with particular emphasis on sex-related differences and dose-dependent responses. Key renal biomarkers, including urea, creatinine, total protein, albumin, sodium, and potassium, were assessed, as they serve as important indicators of kidney function.

The objectives of this study were to: (i) evaluate the effects of *Cannabis sativa* (CS) on kidney toxicity in male and female Wistar rats; (ii) compare the extent of CS-induced kidney toxicity between sexes; (iii) examine sex-specific variations in renal toxicity in relation to dose-dependent exposure; and (iv) assess the protective effects of Vit C against CS-induced kidney toxicity in both male and female Wistar rats.

The study was guided by the following hypotheses:

Null hypothesis (H_0): Vit C has no protective effect against CS-induced kidney toxicity in male and female Wistar rats.

Alternative hypothesis (H_1): Vit C exerts a protective effect against CS-induced kidney toxicity in male and female Wistar rats.

Methods

Sample Collection

The leaves of CS used in this experiment were obtained from the Nigerian National Drug Law Enforcement Agency (NDLEA), solely for research study.

Extraction of *Cannabis sativa* Leaves

The extraction was done using Soxhlet apparatus after 450 grams of CS was soaked in 98% ethanol for two days. Filtration method was used to separate the filtrate, which was poured into a round bottom conical flask mounted on a rotary evaporator. It was then allowed to cool after evaporation. Approximately, 32g of the yield was obtained after drying.

Experimental Animals

The principle of ARRIVE 2.0 guideline was used throughout the experiment. Forty male (165±12 g) and forty female Wistar rats (140±9 g) were supplied by Temilade Animal Venture, Nigeria. The animas have access to food and water without restriction to day/light period. They were taken care of in line with the Principles of laboratory animal care (NIH publication No. 85-23, revised 1985). The Ethical Committee of University of Ilesa, Ilesa, Osun State, Nigeria approved the experimental protocol (UNILESA/ERC/2026/033).

Experimental Protocol

After two weeks of acclimatization, the animals (male and female) were randomly assigned into experimental groups, with five rats per group for each sex. The rats in groups IM & 1F, IIM & IIF, IIIM & IIIF, and IVM & IVF received the following treatments, respectively: 1 mL of distilled water (control), CS at 2 mg/kg body weight (bw), CS at 4 mg/kg bw, CS at 6 mg/kg bw, Vitamin C (Vit C) at 4 mg/kg bw, CS (2 mg/kg bw) + Vit C (4 mg/kg bw), CS (4 mg/kg bw) + Vit C (4 mg/kg bw), and CS (6 mg/kg bw) + Vit C (4 mg/kg bw). All treatments were administered orally once daily via gavage between 08:00 and 10:00 h for 21 consecutive days. At the end of the treatment period, the animals were sacrificed after the final dose, with free access to food and water maintained until sacrifice.

Preparation of Serum

ketamine (80mg/kg bw) was used to induce sleep in the animal through intraperitoneal injection, after which, sample plain bottles were used for blood collection. After 30 min, the blood

clotted and centrifuged at 625×*g* for 10 min with the help of a Uniscope Laboratory Centrifuge (Model SM800B, Surgifield Medicals, Essex, England). With the aid of a Pasteur pipette, the serum was collected into plain bottles. Sera were used within 12 hours of preparation after being stored in a freezer maintained at -5 °C.

Determination of Albumin and IP

Albumin, induced protein (IP), and total protein levels were determined spectrophotometrically using a SpectraMax Plus spectrophotometer (Molecular Devices, Sunnyvale, CA, USA), according to the manufacturer's instructions (Product Code: BXC0243; Fortress Diagnostics, UK).

Determination of Urea

Urea was determined by Urease method[26] shown below:

Urea is hydrolyzed by the enzyme urease to produce ammonia and carbon(iv)oxide. The ammonia released reacted with a phenol-hypochlorite reagent in an alkaline medium to form blue-coloured indophenols dye. The intensity of the blue colour was measured spectrophotometrically and this was directly proportional to the urea concentration in the sample.

Determination of Creatinine

In an alkaline medium, creatinine reacts with **Picric acid** to form an orange-red colored complex (creatinine-picrate complex). The intensity of the color produced is directly proportional to the creatinine concentration in the sample[27].

Determination of Sodium

Sodium reacts with sodium tetraphenylborate in a specially prepared buffer to form a colloidal suspension. The degree of turbidity produced is directly proportional to the sodium concentration in the sample.

Determination of Potassium

Potassium reacts with potassium tetraphenylborate in a specially prepared buffer to form a colloidal suspension. The resulting turbidity is directly proportional to the potassium concentration in the sample.

Statistical Analysis

Mean ± standard error of mean was used to express the data obtained from the results. Students Package for Social Science, version 20.0 (SPSS Inc., Chicago, USA) and Graph Pad Prism (version 9.0) were used to interpret the data. Two-way analysis of variance was used to analyze the data with the significant differences determined by the least significance difference (LSD) post-hoc test for all the parameters. Shapiro-Wilk and Bartlett's Tests were used to test for normality and homogeneity among groups. The statistically significant was $P < 0.05$ for all values.

Results

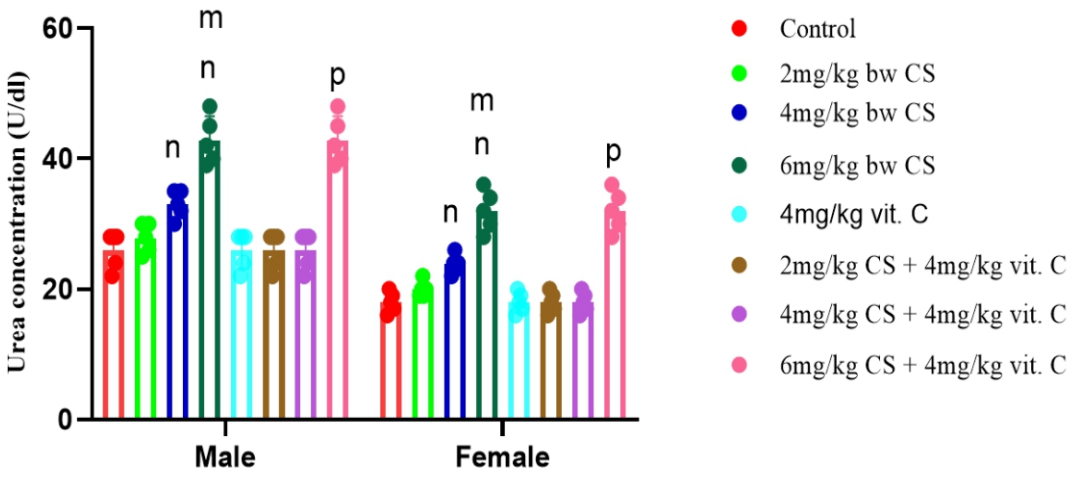


Figure 1: Urea Concentration for Control, 2 mg/kgbw CS, 4 mg/kgbw CS, 6 mg/kgbw CS, 4 mg/kgbw Vit. C, 2 mg/kgbw CS + 4 mg/kgbw Vit. C, 4 mg/kgbw CS + 4 mg/kgbw Vit. C, and 6 mg/kgbw CS + 4mg/kgbw Vit. C respectively. Values are expressed as mean ± SEM; Number of experiments (n=80, 40 males and 40 females)

Where:

n: P<0.05 vs control, 2 mg/kgbw CS, and Vit C groups (male and female)

m: P <0.05 vs CS (4 mg/kgbw) (male and female)

p: P <0.05 vs control, Vit C, and 4 mg/kgbw CS + 4mg/kgbw Vit C (male and female) groups

Vit C: Vitamin C

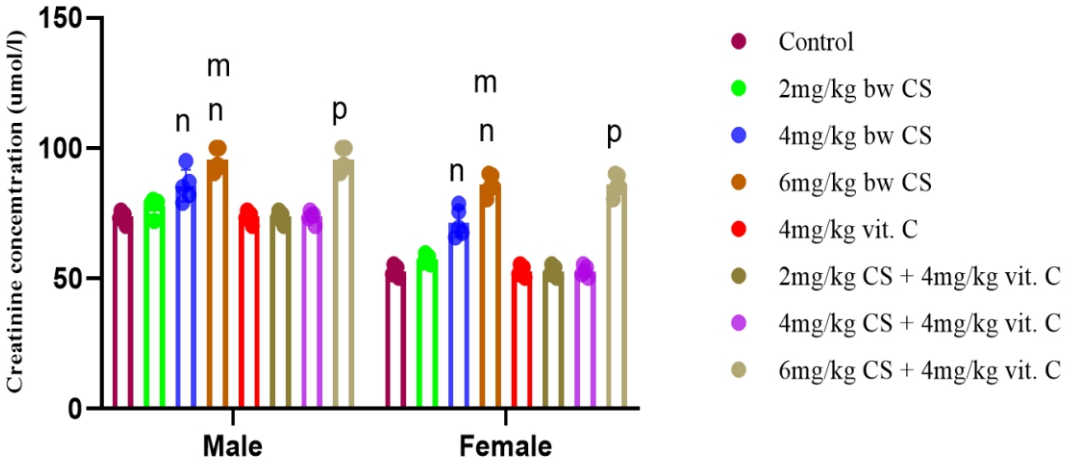


Figure 2: Creatinine Concentration for Control, 2mg/kgbw CS, 4mg/kgbw CS, 6mg/kgbw CS, 4mg/kgbw Vit. C, 2mg/kgbw CS+4mg/kgbw Vit. C, 4mg/kgbw CS+4mg/kgbw Vit. C, and 6mg/kgbw CS+4mg/kgbw Vit. C respectively. Values are expressed as mean ± SEM; Number of experiments (n=80, 40 males and 40 females)

Where:

n: P<0.05 vs control, 2 mg/kgbw CS, and Vit C groups (male and female)

m: P <0.05 vs CS (4 mg/kgbw) (male and female)

p: P <0.05 vs control, Vit C, and 4 mg/kgbw CS + 4mg/kgbw Vit C (male and female) groups

Vit C: Vitamin C

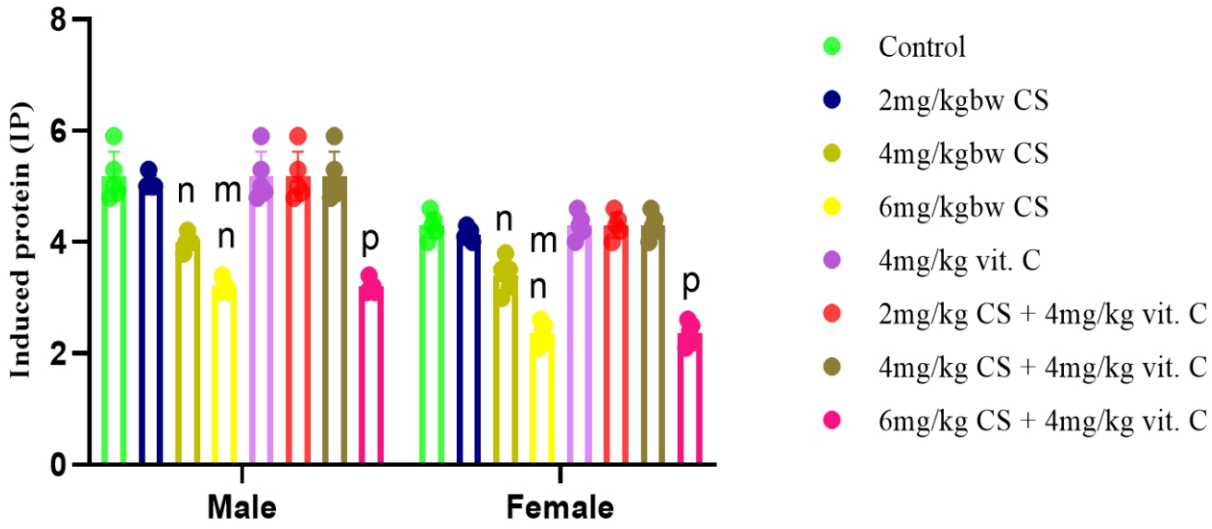


Figure 3: IP for Control, 2 mg/kgbw CS, 4 mg/kgbw CS, 6 mg/kgbw CS, 4 mg/kgbw Vit. C, 2 mg/kgbw CS + 4 mg/kgbw Vit. C, 4 mg/kgbw CS + 4 mg/kgbw Vit. C, and 6 mg/kgbw CS + 4mg/kgbw Vit. C respectively. Values are expressed as mean ± SEM; Number of experiments (n=80, 40 males and 40 females)

Where:

n: P<0.05 vs control, 2 mg/kgbw CS, and Vit C groups (male and female)

m: P <0.05 vs CS (4 mg/kgbw) (male and female)

p: P <0.05 vs control, Vit C, and 4 mg/kgbw CS + 4mg/kgbw Vit C (male and female) groups

Vit C: Vitamin C

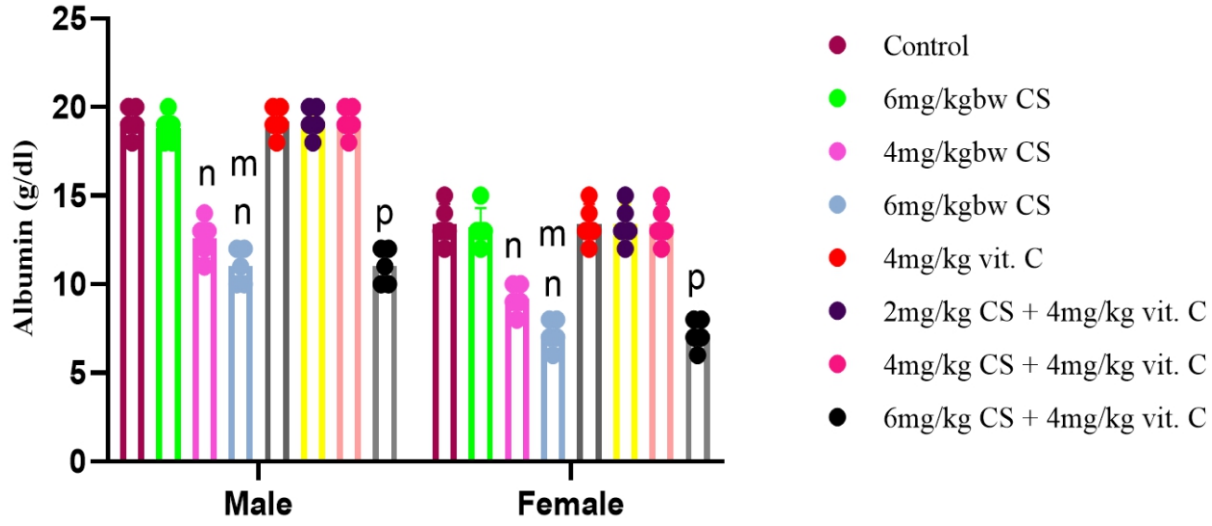


Figure 4: Albumin for Control, 2 mg/kgbw CS, 4 mg/kgbw CS, 6 mg/kgbw CS, 4 mg/kgbw Vit. C, 2 mg/kgbw CS + 4 mg/kgbw Vit. C, 4 mg/kgbw CS + 4 mg/kgbw Vit. C, and 6 mg/kgbw CS + 4mg/kgbw Vit. C respectively. Values are expressed as mean ± SEM; Number of experiments (n=80, 40 males and 40 females)

Where:

n: P<0.05 vs control, 2 mg/kgbw CS, and Vit C groups (male and female)

m: P <0.05 vs CS (4 mg/kgbw) (male and female)

p: P <0.05 vs control, Vit C, and 4 mg/kgbw CS + 4mg/kgbw Vit C (male and female) groups

Vit C: Vitamin C

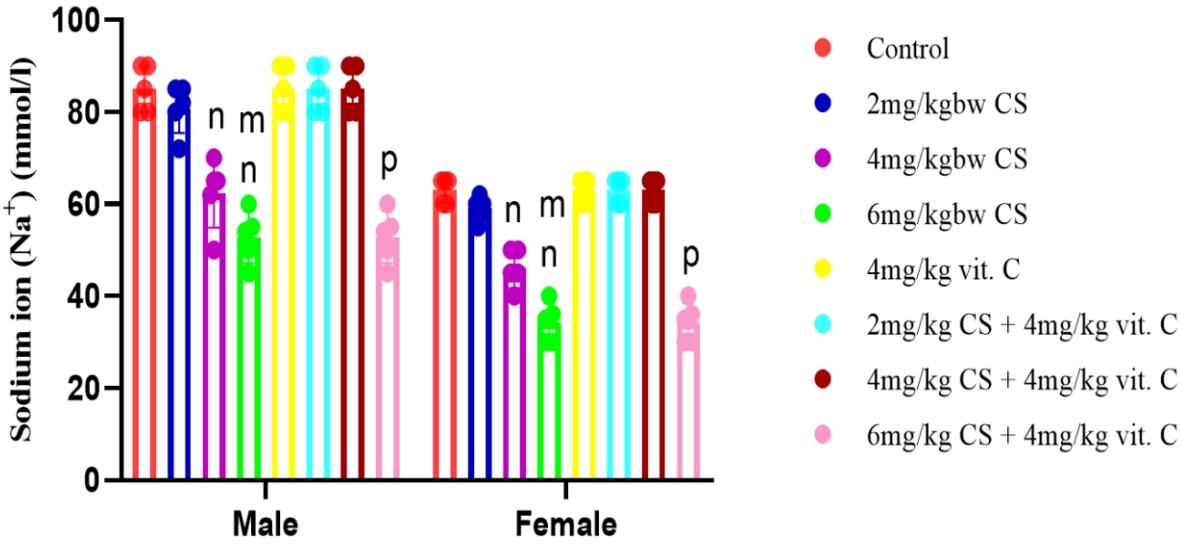


Figure 5: Na+ for Control, 2 mg/kgbw CS, 4 mg/kgbw CS, 6 mg/kgbw CS, 4 mg/kgbw Vit. C, 2 mg/kgbw CS + 4 mg/kgbw Vit. C, 4 mg/kgbw CS + 4 mg/kgbw Vit. C, and 6 mg/kgbw CS + 4mg/kgbw Vit. C respectively. Values are expressed as mean ± standard error of mean. Values are expressed as mean ± SEM; Number of experiments (n=80, 40 males and 40 females)

Where:

n: P<0.05 vs control, 2 mg/kgbw CS, and Vit C groups (male and female)

m: P <0.05 vs CS (4 mg/kgbw) (male and female)

p: P <0.05 vs control, Vit C, and 4 mg/kgbw CS + 4mg/kgbw Vit C (male and female) groups

Vit C: Vitamin C

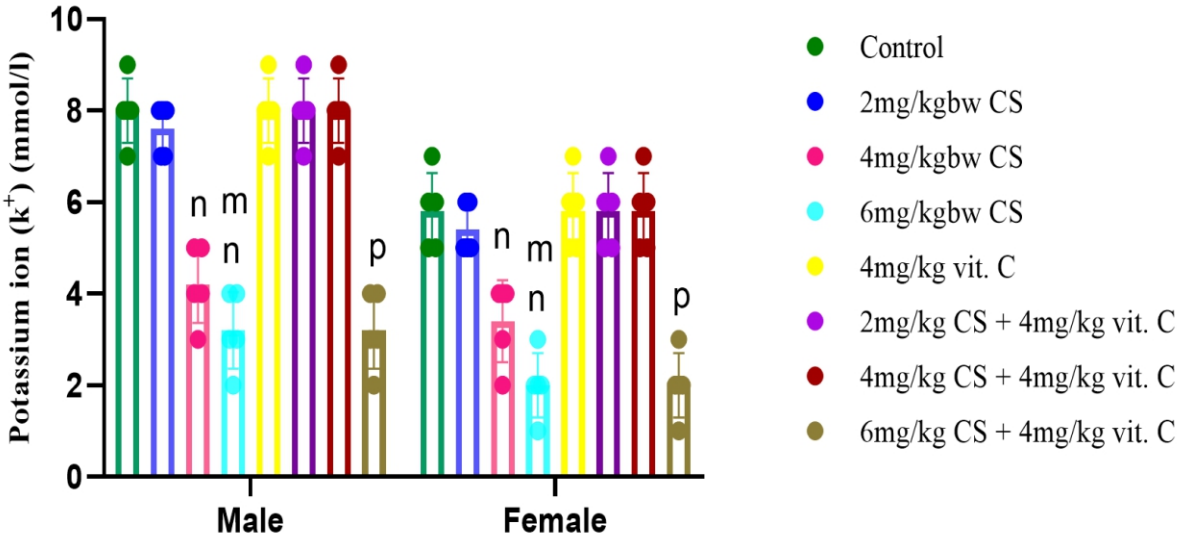


Figure 6: K^+ for Control, 2 mg/kgbw CS, 4 mg/kgbw CS, 6 mg/kgbw CS, 4 mg/kgbw Vit. C, 2 mg/kgbw CS + 4 mg/kgbw Vit. C, 4 mg/kgbw CS + 4 mg/kgbw Vit. C, and 6 mg/kgbw CS + 4mg/kgbw Vit. C respectively. Values are expressed as mean ± standard error of mean. Values are expressed as mean ± SEM; Number of experiments (n=80, 40 males and 40 females)

Where:

n: P<0.05 vs control, 2 mg/kgbw CS, and Vit C groups (male and female)

m: P <0.05 vs CS (4 mg/kgbw) (male and female)

p: P<0.05 vs control, Vit C, and 4 mg/kgbw CS + 4mg/kgbw Vit C (male and female) groups

Vit C: Vitamin C

CS administration significantly increased urea and creatinine levels in the high-dose groups (4 and 6 mg/kg) compared with the control and low-dose (2 mg/kg) groups in both sexes [Figures 1 and 2]. In contrast, IP, albumin, Na^+, and K^+ levels were significantly reduced in the high-dose groups [Figures 3–6]. However, these alterations were significantly attenuated in animals co-administered Vitamin C at the 4 mg/kg CS dose [Figures 1–6]. Furthermore, significant sex-related differences ($p< 0.05$) were observed across all measured parameters, with males exhibiting more pronounced changes than females in the high-dose groups.

DISCUSSION

This study demonstrated that low-dose CS exposure does not pose a significant risk to renal physiological function over a short duration, whereas high-dose exposure exerts detrimental effects on kidney function irrespective of exposure period.

The use of cannabis may have important implications for renal health. Evidence suggests that heavy cannabis consumption is associated with an increased risk of chronic kidney disease (CKD)[28], a condition characterized by a progressive decline in kidney function over time[28–30]. Cannabis may also influence renal hemodynamics, potentially altering kidney function[30]. Δ9-tetrahydrocannabinol (THC), the primary psychoactive constituent of cannabis, affects vascular tone by modulating vasodilation and vasoconstriction, thereby influencing renal blood flow and glomerular filtration[30]. In addition, cannabis use has been associated with alterations in urinary parameters, including increased urine output and frequency, which may reflect its effects on hydration status and the regulation of renal function[31].

In the kidney, cannabinoid receptors 1 (CB_1) and 2 (CB_2) play important roles in regulating renal blood flow, glomerular filtration rate (GFR), glomerular permeability, interstitial collagen deposition, and tubular function[32]. The observed increase in urea and creatinine levels at high doses in this study is consistent with the findings of Rein[33] and Nedumaran et al.[34],who reported elevated urea and creatinine levels following CS administration in rats. This effect may be attributed to alterations in glomerular filtration rate and renal blood flow[33], which impair the kidney's ability to effectively eliminate creatinine and urea, both end products of protein and muscle metabolism[35].

However, these findings contradict those of Mobisson et al.[36], who reported decreased creatinine and urea levels following CS administration in rats. These discrepancies may be due to differences in sample types used for analysis; whereas their study utilized bile samples, the present study analyzed blood serum.

Moreover, the observed decrease in induced protein (IP), albumin, sodium, potassium, and total protein in the high-dose groups suggests abnormal loss of these substances through urine rather than their retention in the bloodstream. This may be due to activation of cannabinoid receptors in the renal vasculature and kidney, leading to altered renal handling and increased excretion of these biomolecules[37]. However, Vitamin C ameliorated CS-induced renal toxicity at the 4 mg/kg dose, likely due to its potent antioxidant properties and ability to reduce oxidative stress[4,18–21].

Furthermore, this study reveals sex-specific differences in renal responses to CS, with males exhibiting more pronounced toxicity than females. One of the contributing factors may involve differences in the expression of cannabinoid receptor associated with signaling pathways. It has been reported that males possess more cannabinoid receptors than females[33]. Also, CS may induce epigenetic alterations by modifying global DNA methylation patterns, which could be due to cannabis-associated immunosuppression[39].

This study has some limitations. First, it remains unclear whether prolonged administration of low-dose CS (2 mg/kg body weight) beyond the three-week period used in this study would produce effects similar to those observed at higher doses (4 and 6 mg/kg body weight). Second, it is not known whether administration at different times of the day (e.g., afternoon or night) would yield outcomes comparable to those observed with morning administration in this study. Third, it is uncertain whether increasing the dose of Vitamin C would provide protection against CS-induced renal toxicity at the highest dose (6 mg/kg), as observed at 4 mg/kg.

A major strength of this study is that Vitamin C demonstrated potential as a mitigating agent against CS-induced kidney toxicity at moderate doses specifically when CS is being used for recreational and medicinal purposes.

This suggests that further studies are needed to determine whether higher doses of Vitamin C could also attenuate the renal toxicity observed in the 6 mg/kg group, given that the same dose of Vitamin C was administered in both the 4 mg/kg and 6 mg/kg treatment groups.

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Research Paper

Tetrapleura tetraptera Extract Ameliorates Cognitive Decline and Neurodegeneration on the Pre-Frontal Cortex in an Aluminium Chloride-Induced Rat Model of Alzheimer's Disease

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ABSTRACT

Introduction:

Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterized by cognitive impairment, neuronal degeneration, oxidative stress, and neuroinflammation.

Aim:

To investigate the effects of Tetrapleura tetraptera extract (TTE) on the prefrontal cortex following aluminum chloride ($AlCl_3$)-induced Alzheimer's-like disease in adult male Wistar rats.

Methodology:

Fifty (50) adult male Wistar rats were randomly assigned into five groups (n = 10). Group I (control) received 2 mL/kg body weight (bw) distilled water. Group II received 200 mg/kg bw $AlCl_3$, while Groups III and IV received 200 mg/kg bw $AlCl_3$ plus 250 and 500 mg/kg bw TTE, respectively. Group V received 10 mg/kg bw Donepezil. All treatments were administered orally for 42 days. Following treatment, rats were sacrificed, and the prefrontal cortex was harvested for histological, biochemical, and protein analyses.

Results:

TT significantly improved behavioral alterations in the elevated plus maze and Morris water maze tests ($P<0.05$), while reducing tissue amyloid-beta (AB), Glia Fibrillary Acidic protein (GFAP) and phosphorylated tau (p-tau) levels ($P<0.05$). TT significantly decreased malondialdehyde (MDA) and increased Catalase (CAT), superoxide dismutase (SOD), and glutathione peroxidase (GPx) levels ($P<0.05$). Neuronal and cortical restoration was observed in TT-

treated groups compared with the $AlCl_3$ group, with greater effects at the high dose. Donepezil similarly restored antioxidant enzyme activities, reduced protein deposits, and improved neuronal and cyto-architectural organization, comparable to high-dose TT.

Conclusion:

TT exhibited neuroprotective effects against $AlCl_3$-induced Alzheimer's-like disease by mitigating oxidative stress and preserving prefrontal cortical integrity.

KEYWORDS: *Tetrapleura tetraptera;* Oxidative stress; Prefrontal cortex; Alzheimer's Disease; Neurodegeneration.

INTRODUCTION

Alzheimer's disease (AD) is the most common form of dementia and a progressive neurodegenerative disorder characterized by a gradual decline in memory, cognition, learning ability, and executive function[1]. It accounts for approximately 60–70% of all dementia cases worldwide and constitutes a major public health challenge due to increasing life expectancy and population aging[2]. The pathological hallmarks of Alzheimer's disease include extracellular deposition of amyloid-β (Aβ) plaques, intracellular accumulation of hyper phosphorylated tau protein in the form of neurofibrillary tangles, synaptic dysfunction, neuronal loss, neuroinflammation, oxidative stress, and progressive cerebral atrophy[3].

Oxidative stress is recognized as one of the central mechanisms underlying aluminum-induced neurodegeneration[4]. Excessive generation of free radicals overwhelms endogenous antioxidant defense systems, resulting in lipid peroxidation, protein oxidation, DNA damage, and ultimately neuronal death[5,6]. In addition to oxidative injury, aluminum exposure activates inflammatory pathways involving microglial activation and astrocytes proliferation, leading to increased production of pro-inflammatory cytokines that exacerbate neuronal damage[6]. Consequently, therapeutic strategies possessing antioxidant, anti-inflammatory, anti-apoptotic, and neuroprotective properties are increasingly being explored as potential interventions against Alzheimer's disease[7].

Tetrapleura tetraptera, commonly known as Aidan fruit, is a medicinal plant indigenous to West and Central Africa and has been widely utilized in traditional medicine for the management of numerous ailments[8]. The fruit contains a rich array of bioactive phytochemicals, including phenolic compounds, flavonoids, tannins, alkaloids, saponins, and essential oils[9]. Several experimental studies have demonstrated that extracts of *Tetrapleura tetraptera* effectively scavenge reactive oxygen species, enhance endogenous antioxidant enzyme activities, suppress inflammatory mediators, and reduce oxidative tissue damage in various experimental models[10-12].

Despite the growing body of literature describing the pharmacological properties of *Tetrapleura tetraptera*, limited information exists regarding its protective effects on the prefrontal cortex following aluminum chloride-induced Alzheimer's-like neurodegeneration. Most previous investigations have focused primarily on general antioxidant activity or hippocampal protection, while relatively few studies have comprehensively evaluated the structural preservation of the prefrontal cortex. Given the crucial role of the prefrontal cortex in cognition and executive function, investigating the effects of *Tetrapleura tetraptera* on this brain region is of considerable scientific and therapeutic importance. Therefore, this study aims to evaluate the effects of *Tetrapleura tetraptera* on the prefrontal cortex following aluminum chloride-induced Alzheimer's-like disease in adult male Wistar rats.

MATERIALS AND METHODS

Materials

Experimental Chemicals

Aluminum Chloride ($AlCl_3$): 20 g $AlCl_3$ produced by Span Chemie, India and was gotten from Dennis and Dennis Store Ilorin, Kwara State and authenticated in the Department of Chemistry, Faculty of Natural and Applied Sciences, Al-Hikmah University, Ilorin.

Donepezil: 10 gm Donepezil: was bought from One-Step Pharmacy Ilorin, Kwara State.

Experimental Plant: 1000 g of *Tetrapleura tetraptera* was obtained from Oja Oba market Osogbo, Osun State where it was powdered and the seed were removed and was taken to the Department of Industrial Chemistry, Faculty of Physical Science, University of Ilorin, and Kwara State for extraction.

Experimental Animals: Fifty (50) apparently healthy Wistar rats were purchased from the animal facility of Department of Human Anatomy, Faculty of Basic Medical Science, College of Health Science, Osun State University, Osogbo, Osun State, Nigeria. To replicate their natural habitat, the Wistar rats were housed at ambient temperature with a typical light-dark cycle (12:12). To suit their nutritional needs, the Wistar rats were

given purified water and grower pellet diet during the trial. Two weeks prior to the start of the experiment, the Wistar rats were acclimated.

Other Materials: Syringes, gloves, sample bottles, distilled water and dissecting kits were of analytical grades.

METHODS

Ethical Approval

All experimental procedures were carried out in accordance with the regulation stipulated by the Health Research Ethics Committee of College of Health Sciences, Osun State University Osogbo, Osun State, Nigeria, in conformity with the Guidelines of the National Institutes of Health for the care and use of laboratory Animals.

Experimental Protocol

Fifty (50) adult male Wistar rats were randomly assigned into five groups (n = 10). Group I (control) received 2 mL/kg body weight (bw) distilled water. Group II received 200 mg/kg bw $AlCl_3$, while Groups III and IV received 200 mg/kg bw $AlCl_3$ plus 250 and 500 mg/kg bw TTE, respectively. Group V received 10 mg/kg bw Donepezil. All treatments were administered orally for 42 days. The rats were kept under standard condition of 12 hours dark and day cycle and were fed with rat feed and water *Ad libitum*. All administrations were done orally. Neurobehavioral tests (Morris Water Maze and Standard elevated plus maze) were carried out a day before sacrifice. After the last day of administration, the rats were fasted overnight and their final body weights were taken. The rats were humanely euthanized through cervical dislocation and the brains were harvested through mid-sagittal incision. The rats' brains were divided into two. Five rats' brains were homogenized in (5x W/V) of sucrose solution for biochemical and protein analysis and the others fixed in 10% formalin for histological and histochemical assays.

NEUROBEHAVIOURAL TEST

Morris Water Maze

The Morris water test (spatial memory and learning) was used to assess spatial learning and memory in the rats. The test was conducted in a circular pool (diameter 150 cm) filled with opaque water, with a hidden platform submerged just below the surface. Each rat was given three trials per day for 12 days to locate the platform. The time taken each rat to find the platform (escape latency) was recorded as a measure of spatial learning ability[13].

Standard Elevated plus Maze

The maze consisted of four arms arranged in a 'plus' shape, with two enclosed arms and two open arms, elevated 50 cm above the ground. The open arms are 45 cm × 10cm x30 cm length and width respectively. The two closed arms are 45 cm ×10 cm × 30 cm, long, width and height respectively. The central platform is 10 cm × 10 cm. The rats were placed in the center of the maze, and their behavior (grooming and rearing behavior) was observed for 5 minutes. The primary outcome measure was the percentage of time spent in the open arms, with more time spent in the open arms indicating lower anxiety levels[14].

Oxidative Stress Markers

Malondialdehyde (MDA)

MDA was determined using the thiobarbituric acid reactive substances (TBARS) method originally described by Ohkawa *et al*[15]. 0.2 mL of the supernatant was mixed with 0.2 mL of 8.1% sodium dodecyl sulfate (SDS), 1.5 mL of 20% acetic acid (pH 3.5), and 1.5 mL of 0.8% thiobarbituric acid (TBA). The reaction mixture was heated in a boiling water bath (95–100°C) for 60 minutes and then cooled to room temperature. Distilled water (1.0 mL) and 5.0 mL of n-butanol:pyridine (15:1, v/v) were added, followed by vigorous mixing and centrifugation at 4,000 rpm for 10 minutes. The organic layer was carefully collected, and its absorbance was measured spectrophotometrically at **532 nm** against a reagent blank. MDA concentration was calculated using a standard curve prepared from 1,1,3,3-tetraethoxypropane[16].

Superoxide dismutase (SOD)

SOD activity was determined according to the method of Kakkar *et al*[17]. 0.1 mL of tissue homogenate was added to a reaction mixture containing sodium pyrophosphate buffer (0.052 M, pH 8.3), phenazine methosulfate (PMS), nitroblue tetrazolium (NBT), and nicotinamide adenine dinucleotide (NADH). The reaction was initiated by the addition of NADH and allowed to proceed for 90 seconds at room temperature before termination with glacial acetic acid. The chromogen was extracted using n-butanol, and absorbance was measured at **560 nm** using a UV-visible spectrophotometer

Catalase (CAT)

Catalase activity was determined using the method described by Aebi[18]. Brain tissue homogenates were prepared in ice-cold phosphate buffer (50 mM, pH 7.0) and centrifuged at 10,000 × g for 15 minutes at 4°C. The reaction mixture consisted of phosphate buffer, freshly prepared hydrogen peroxide (30 mM), and tissue supernatant. Catalase activity was determined by monitoring the decomposition of hydrogen peroxide spectrophotometrically at **240 nm** for 3 minutes. The decrease in absorbance per minute was recorded, and enzyme activity was calculated using the molar extinction coefficient of hydrogen peroxide (43.6 M^{-1} cm).

Glutathione peroxidase (GPx)

GPx activity was estimated using the method of Rotruck et al.[19] Briefly, tissue homogenate was incubated with phosphate buffer (0.4 M, pH 7.0), sodium azide, reduced glutathione (GSH), hydrogen peroxide, and ethylenediaminetetraacetic acid (EDTA). The reaction mixture was incubated at 37°C for 10 minutes to allow enzymatic reduction of hydrogen peroxide by GPx. The reaction was terminated with trichloroacetic acid (TCA), followed by centrifugation. The remaining reduced glutathione in the supernatant was reacted with 5,5′-dithiobis-(2-nitrobenzoic acid) (DTNB), producing a yellow-colored complex. Absorbance was measured at **412 nm** using a spectrophotometer.

Apoptotic and Neurodegenerative Markers

Determination of Bcl-2

The concentration of B-cell lymphoma-2 (Bcl-2) was carried out using ELISA kit. 100 µL tissue were added into microplate wells pre-coated with monoclonal antibodies specific for rat Bcl-2 and incubated at 37°C for 90 minutes. Following washing to remove unbound proteins, biotin-conjugated anti-Bcl-2 detection antibody was added and incubated for 60 minutes. After additional washing, horseradish peroxidase (HRP)-streptavidin conjugate was added and incubated for 30 minutes. Tetramethylbenzidine (TMB) substrate solution was subsequently added and allowed to react in the dark for 15–20 minutes before the reaction was terminated using stop solution. Optical density was measured at 450 nm using a microplate reader. Bcl-2 concentrations were calculated from a standard calibration curve[20].

Determination of Bax

Bax protein concentration was determined using a rat-specific sandwich ELISA kit according to the manufacturer's protocol. Brain tissues were homogenized in ice-cold PBS containing protease inhibitors and centrifuged at 10,000 × g for 15 minutes at 4°C. The resulting supernatant was collected for assay.100 µL of tissue homogenates were pipetted into antibody-coated wells and incubated for 90 minutes at 37°C. Following washing, biotin-labelled anti-Bax antibody was added, followed by HRP-conjugated streptavidin. The antigen-antibody complex was visualized using TMB substrate and the enzymatic reaction was terminated with acidic stop solution. Absorbance was read at 450 nm, and Bax concentrations were calculated from the standard curve[21,22].

Determination of Caspase-3

Caspase-3 levels were quantified using ELISA kit. One hundred microliters added to antibody-coated wells and incubated at 37°C for 90 minutes. Wells were washed thoroughly before incubation with biotinylated anti-caspase-3 antibody, followed by HRP-labelled streptavidin. After washing, TMB substrate solution was added, and colour development was allowed to proceed for approximately 15 minutes in the dark. The reaction was terminated using stop solution, and absorbance was measured at 450 nm using a microplate reader. Caspase-3 concentrations were obtained from the standard curve[23,24].

Determination of Glial Fibrillary Acidic Protein (GFAP)

GFAP concentration was determined using a ELISA kit. Tissue homogenates were transferred into microplate wells coated with anti-GFAP capture antibody and incubated for 90 minutes at 37°C. Following washing, biotin-labelled detection antibody and HRP-streptavidin conjugate were sequentially added with incubation and washing steps between each stage. Colour was developed using TMB substrate and stopped with acidic stop solution. Optical density was measured at 450 nm using a microplate spectrophotometer. GFAP concentrations were determined from the standard curve[25].

Determination of Phosphorylated Tau (p-Tau)

Phosphorylated tau protein (p-Tau) was quantified using ELISA kit Tissue homogenates were added into antibody-coated wells and incubated at 37°C for 90 minutes. Following washing, biotinylated anti-p-Tau detection antibody was added, followed by HRP-streptavidin conjugate. TMB substrate solution was added for colour development, and the reaction was stopped using sulfuric acid stop solution. Absorbance was measured at 450 nm. Protein concentrations were calculated using a standard curve[26].

Determination of Amyloid-β

Amyloid-β (Aβ), quantified using ELISA kit 100 µL were added to wells coated with anti-Aβ capture antibody and incubated for 90 minutes at 37°C. Following washing, biotinylated anti-Aβ detection antibody and HRP-conjugated streptavidin were added sequentially. Colour development was achieved using TMB substrate, and the reaction was terminated with stop solution. Absorbance was measured at 450 nm, and Aβ concentrations were calculated from a standard curve[27].

RESULTS

Physical Observation

Induction Phase

The rats in the control group remained healthy and active throughout the experimental period. Normal grooming, rearing, feeding behavior, and locomotors activities. No visible signs of toxicity, inflammation, paralysis, or mortality were recorded throughout the study period.

However, the rats in the $AlCl_3$), treated groups exhibited behavioral and neurological abnormalities including reduced activity, calmness, weakness, and excessive grooming. By Day 24, one rat became temporarily unconscious and later developed difficulty in movement.

Between Days 24 and 28, some rats showed obvious neurological signs such as sideways walking, imbalance, rapid breathing (tachycardia), and partial paralysis of the limbs. Progressive enlargement of the scrotum was observed in several rats across the groups, while swelling of the nose, face, and tail became more pronounced in this week.

Treatment Phase

From Days 29 to 42, the rats in $AlCl_3$ only Group revealed worsened inflammatory and or toxicity signs including swollen nose, face, tail, scrotal bleeding and scleritis. One rat also developed a cut on its tail. Body weight reduction and poor feeding behavior became noticeable during this period. More so, loss of normal movement, paralysis, reduced feed intake, scrotal swelling, weakness, and decreased locomotors activity.

Following administration of low-dose TT, gradual improvement in feeding pattern, grooming behavior, and movement was observed. Some animals regained normal rearing activity and became more active toward the later stage of treatment, although mild weakness and swelling persisted in a few rats.

More so, upon treatment with high-dose TT group, improvement in locomotors activities, grooming behaviors, and feeding response became more evident with recovery from neurological symptoms and inflammatory changes appeared faster and more pronounced in this group when compared to the low-dose TT treated group. Meanwhile, Donepezil administration, improved movement, grooming, and feeding behavior. Although mild inflammatory signs such as scrotal swelling persisted in some rats toward the end of the experimental period.

Organ and Body Weight

There were no significant differences in initial body weight among experimental groups ($P = 0.07$), confirming homogeneity before treatment. However, following the experimental period, final body weight differed significantly ($P < 0.05$). Rats exposed to $AlCl_3$ exhibited the smallest weight gain, suggesting impaired growth and systemic toxicity. In contrast, both TT-treated groups demonstrated greater weight gain, particularly the high-dose group, indicating improved physiological status after treatment.

Brain weight (organ weight) did not differ significantly among groups, Although TT-treated rats tended to have slightly greater brain weights than the $AlCl_3$ group. This suggests that while $AlCl_3$ primarily affected brain function rather than gross morphology, TT may have exerted a mild protective effect against tissue loss [Table 1].

Table 1: Initial, Final Body and Brain Weights of Rats across the Groups

GROUPS & TREATMENT	INITIAL BW (g)	FINAL BW (g)	BRAIN WEIGHT (g)
A (Control)	213.857 ± 5.353	239.286 ± 4.934	1.53 ± 0.12
B ($AlCl_3$)	212.286 ± 6.149	218.286 ± 5.017*	1.554 ± 0.23
C ($AlCl_3$ + Low Dose TT)	210.857 ± 5.075	229.571 ± 4.256	1.768 ± 0.14
D ($AlCl_3$ + High Dose TT)	215.429 ± 5.103	235.429 ± 15.784	1.654 ± 0.34
E ($AlCl_3$ + Donepezil)	213.143 ± 6.092	227.143 ± 4.647	1.7945 ± 0.13

Data expressed as Mean±SEM.BW (Body Weight)
Asterisk (*) indicates statistically significant differences.

Morris Water Maze Test (Spatial Learning and Memory)

The findings demonstrated no statistically significant differences among the experimental groups during the training phase (P = 0.077), indicating that all rats possessed comparable learning capacity before disease induction. However, following aluminum chloride ($AlCl_3$) administration, escape latency during the induction phase increased markedly from 8.37 ± 1.74 s in the control group to 18.43 ± 0.78 s in the $AlCl_3$-treated group (P = 0.037), demonstrating significant impairment of spatial learning. Meanwhile, rats that received $AlCl_3$ alone exhibited significant increase in escape latency (28.57 ± 4.36 s), indicating persistent cognitive dysfunction. Conversely, treatment with TT significantly reduced escape latency to 8.00 ± 0.44 s in the low-dose group and 7.00 ± 0.31 s in the high-dose group. Similarly, donepezil-treated animals showed improved performance (8.14 ± 0.91 s). These improvements were statistically significant (P = 0.005) [Table 2].

Standard Elevated Plus Maze Test

The results revealed significant alterations in anxiety-related behavior following $AlCl_3$ administration. Rats treated with $AlCl_3$ spent only 2.86% of the testing period in the open arms compared with 66.57% in control animals (P = 0.05), while occupancy of the closed arms increased dramatically to 97.14%. These findings indicate severe anxiety-like behavior induced by aluminum toxicity. Treatment with TT significantly increased open-arm exploration to 41.43% (low dose) and 45.71% (high dose), while reducing time spent in the closed arms. Donepezil produced similar anxiolytic effects. Although Head-dipping behavior was not significantly altered among groups, rearing activity differed significantly (P < 0.05), with the high-dosed group exhibiting the highest frequency, indicating restoration of exploratory locomotors behavior. More so, Aluminum-treated rats exhibited excessive grooming, a behavioral indicator of stress and anxiety, whereas TT treatment reduced grooming frequency toward normal control values [Table 3].

Table 2: T, IPEL and TPEL in Morris Water Maze Test

S.No.	GROUPS & TREATMENT	T (sec)	IPEL (Sec)	TPEL (Sec)
1.	**A (Control)**	7.714 ± 0.474	8.37 ± 1.74*	5.857 ± 0.340
2.	**B ($AlCl_3$)**	7.429 ± 0.481	18.429 ± 0.781	28.571 ± 4.358*
3.	**C ($AlCl_3$ + Low Dose TTE)**	7.286 ± 0.421	15.286 ± 0.121	8.000 ± 0.436
4.	**D ($AlCl_3$ + High Dose TTE)**	9.419 ± 0.520	12.419 ± 0.320	7.000 ± 0.309
5.	**E ($AlCl_3$ + Donepezil)**	6.714 ± 0.993	16.714 ± 0.295	8.143 ± 0.911

Data expressed as Mean ± SEM
T (Training), IPEL (Induction Escape Latency), TPEL (Treatment Phase Escape Latency)
Asterisk (*) indicates statistically significant differences.

Table 3: PPOA, PPCA, HD, RF and GF in Standard Elevated Plus Maze Test

GROUPS & TREATMENT	PPOA(%)	PPCA(%)	HD	RF	GF
A (Control)	66.571 ± 4.041	33.429 ± 4.041	2.143 ± 0.911	5.286 ± 1.017	5.430 ± 1.020
B ($AlCl_3$)	2.857 ± 2.857*	97.143 ± 2.857*	1.429 ± 1.152	3.000 ± 0.976*	12.000 ± 0.816*
C ($AlCl_3$ + Low Dose TT)	41.429 ± 4.041	58.571 ± 4.041	4.286 ± 0.565	6.000 ± 0.976	3.857 ± 0.340
D ($AlCl_3$ + High Dose TT)	45.714 ± 8.411	54.286 ± 8.411	3.429 ± 0.369	8.143 ± 0.634*	5.571 ± 0.481
E ($AlCl_3$ + Donepezil)	43.0 ± 10.690	56 ± 10.690	3.571 ± 0.751	7.857 ± 0.884	3.429 ± 0.649

Data expressed as Mean ± SEM
PPOA (Percentage permanency in the open arm), PPCA (Percentage Permanency in the Close Arm, HD (Head Dip), RF (Rearing Frequency), GF (Grooming Frequency)
Asterisk (*) indicates statistically significant differences.

BIOCHEMICAL STUDIES

Oxidative Stress Markers

The $AlCl_3$-treated group showed a significant increase in malondialdehyde (MDA) compared with the control ($p < 0.05$), indicating enhanced lipid peroxidation and oxidative stress. Conversely, the activities of the endogenous antioxidant enzymes superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx) were significantly decreased ($p < 0.05$), demonstrating impairment of the antioxidant defense system. However, treatment with low-dose TT significantly reduced MDA while significantly increasing SOD, CAT, and GPx activities compared with the $AlCl_3$ group ($p < 0.05$). Although antioxidant activities improved, they remained below control values, suggesting partial restoration of oxidative balance Administration of high-dose TT produced greater reductions in MDA and more pronounced increases in SOD, CAT, and GPx activities than the low-dose treatment ($p < 0.05$), indicating a dose-dependent antioxidant effect. The Donepezil-treated group also demonstrated significant antioxidant effects comparable to those of high-dose TT group [Figure 1].

Apoptotic/ Neurodegenerative Markers

The $AlCl_3$-treated group exhibited a significant increase ($p < 0.05$) in amyloid-β (Aβ), phosphorylated tau (pTau), GFAP, Bax, and Caspase-3 compared with the control group, while Bcl-2 expression was significantly reduced. These findings indicate that aluminum chloride successfully induced Alzheimer's-like neuropathology characterized by amyloid deposition, tau hyper phosphorylation, astrocyte activation, and increased neuronal apoptosis.

Furthermore, administration of low-dose TT significantly reduced Aβ, pTau, GFAP, Bax, and Caspase-3 levels compared with the $AlCl_3$ group ($p < 0.05$). However, these values remained significantly different from those of the control group, suggesting partial neuroprotection.

Similarly, the high-dose TT group demonstrated significant reductions in the neurodegenerative and apoptotic markers relative to the $AlCl_3$-treated animals ($p < 0.05$). The reductions were generally greater than those observed with the low dose, indicating a dose-dependent protective effect. Bcl-2 levels were significantly increased in both TT-treated groups compared with the $AlCl_3$ group ($p < 0.05$), suggesting enhanced neuronal survival and inhibition of apoptosis [Figure 2].

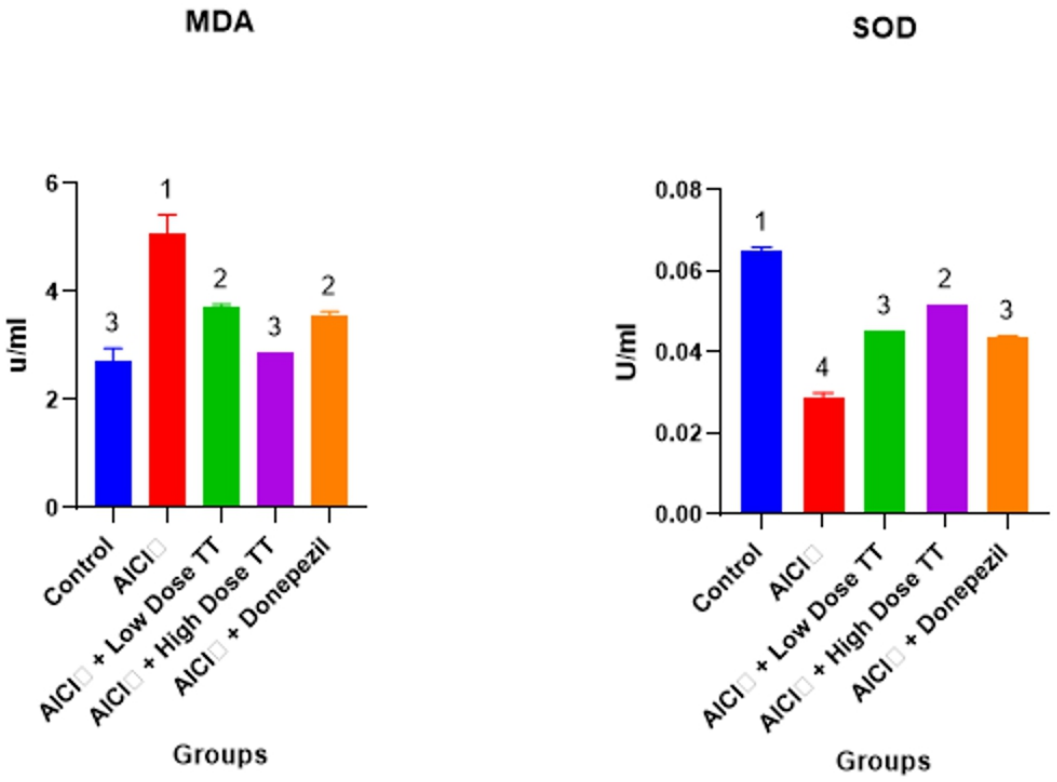


Figure 1: Bar charts showing Mean ± Standard Error of Mean (SEM) of MDA, SOD, CAT and Gpx in Experimental Rats across the Groups.
(Groups bearing diffrent superscript differ at P<0.05)

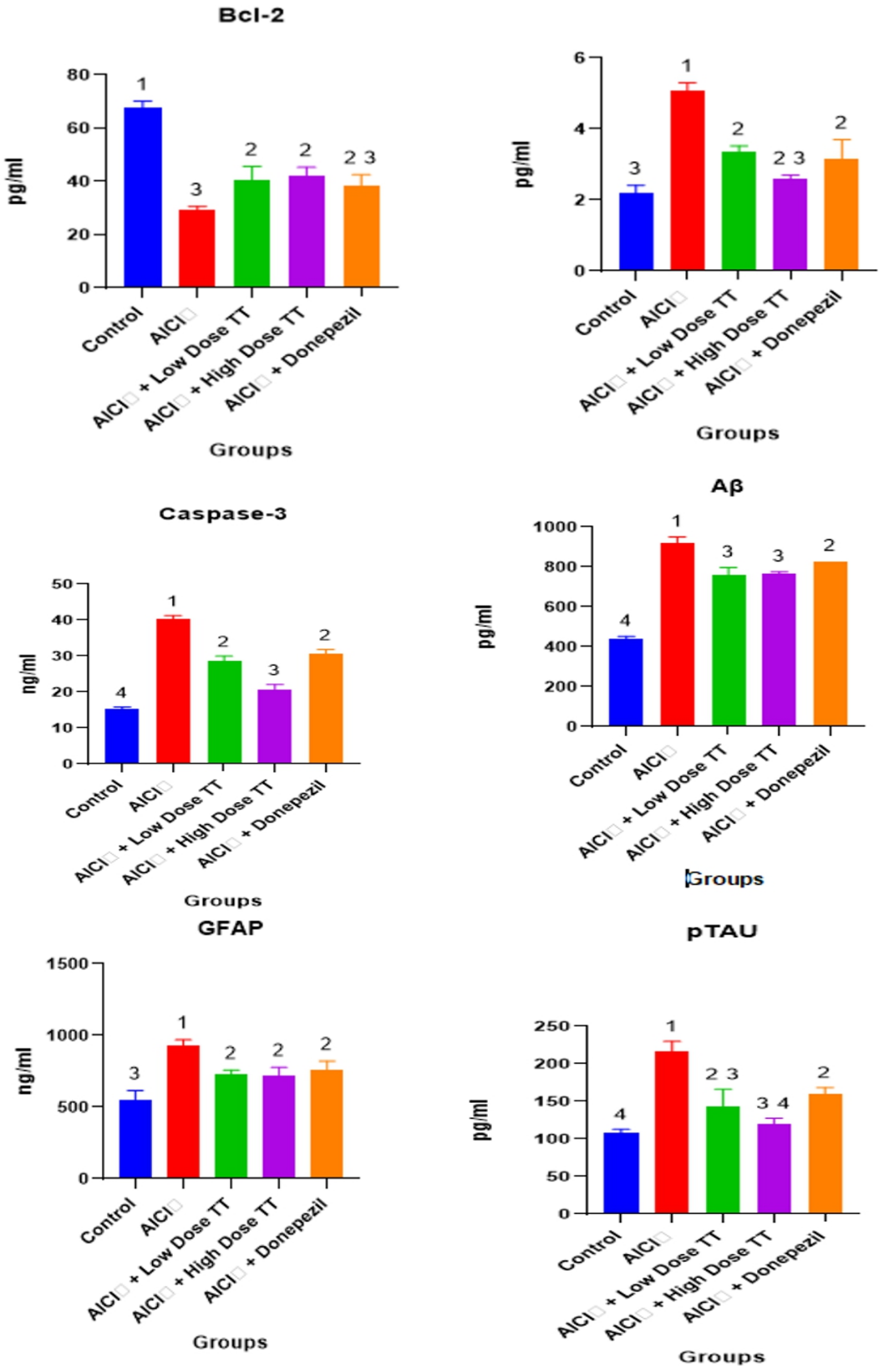
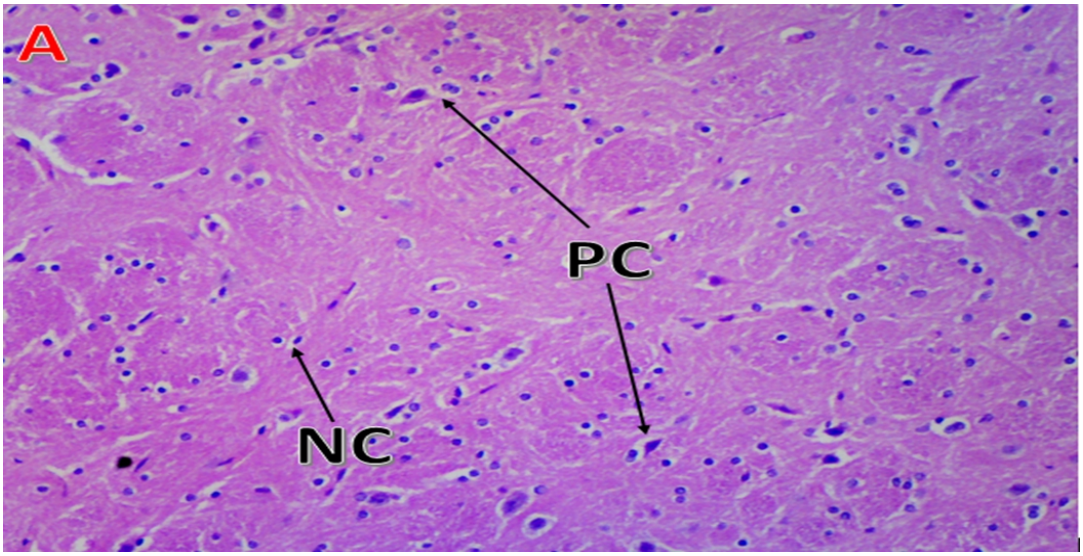


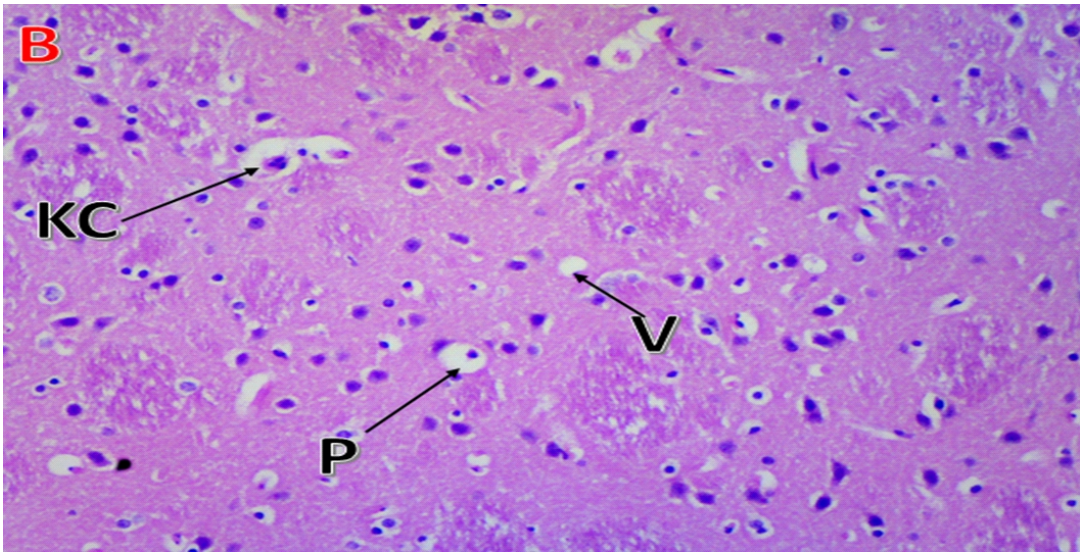
Figure 2: Bar charts showing Mean ± Standard Error of Mean (SEM) of B cell Lymphoma 2 (Bcl-2), B cell Associated X Protein (Bax), and Caspase-3, A/β, GFAP and pTAU in Experimental Rats across the Groups. (Groups bearing diffrent superscript differ at P<0.05)

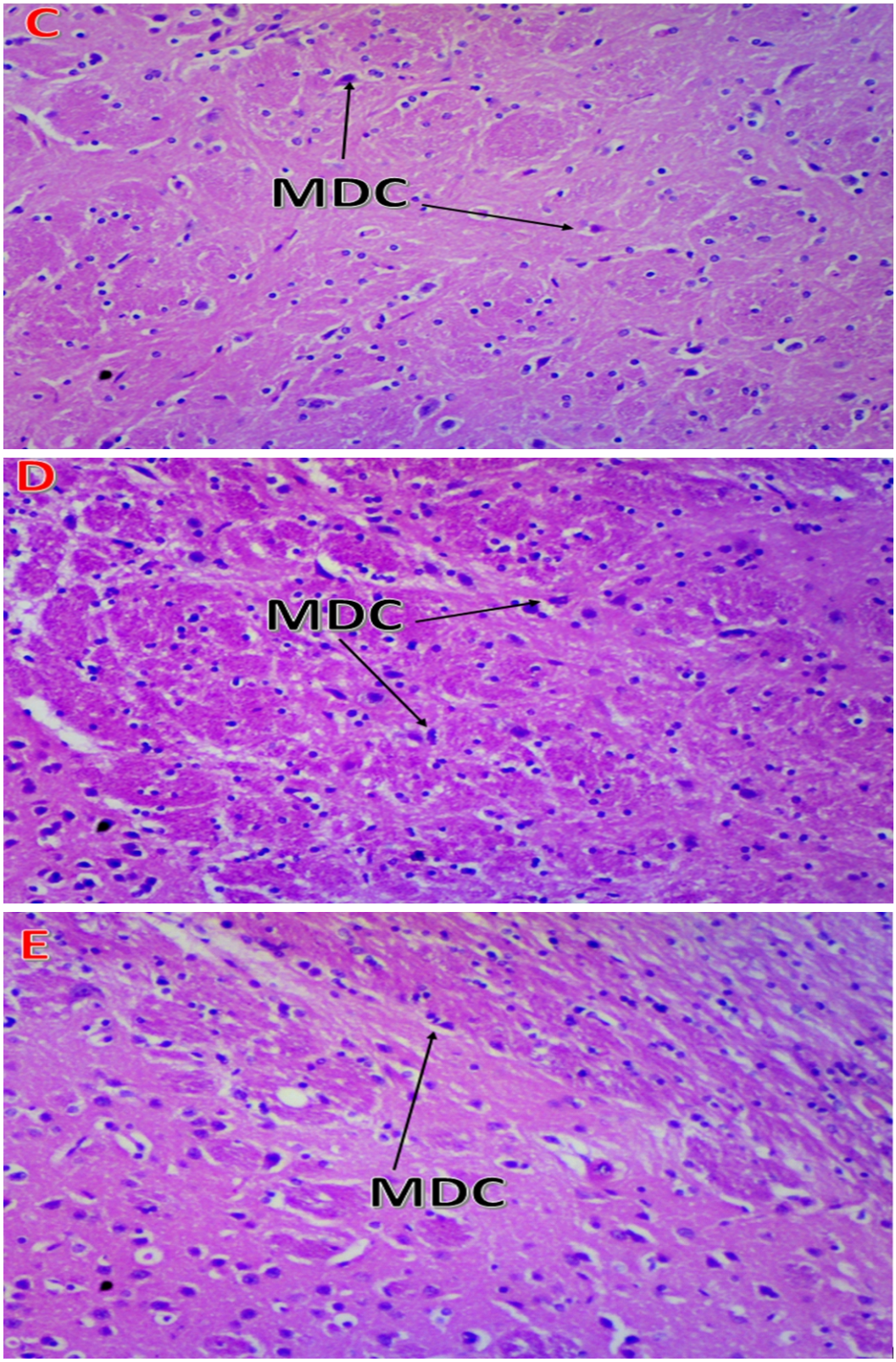
HISTOLOGICAL FINDINGS

Aluminum chloride produced profound neurodegenerative changes in the prefrontal cortex, characterized by neuronal loss, nuclear degeneration, and cytoplasmic vacuolation, impaired Nissl substance integrity (Plates B & F) and Alzheimer's disease-like pathological lesions including senile plaques (Plate L) TT substantially ameliorated these alterations, preserving neuronal architecture, reducing neuronal degeneration (Plates C & D), maintaining Nissl substance integrity (Plates H & I) and decreasing the extent of amyloid plaque deposition (Plates M & N). The histological improvements observed in TT-treated groups were comparable to those produced by donepezil, suggesting that the TT extract possesses significant neuroprotective properties, likely mediated through its antioxidant, anti-inflammatory, and anti-apoptotic activities.

HEMATOXYLIN AND EOSIN (H&E) STAIN RESULTS







Plates A - E:
A, Showing Photomicrograph of rats in the Control group showing normal cytoarchitecture of the layer V of the prefrontal cortex with normal Pyramidal cells (PC) and normal Neuronal cells (NC). **B**, $AlCl_3$ only group showing several degrees of neurodegenerations: Karyorrhectic Cells (KC), Vacuolations (V) and Pyknosis (P). **C & D**: $AlCl_3$ + Low and High Dose TT group showing Moderate and Mild degenerations of Cells (MDC) respectively. **E**, $AlCl_3$ + Donepezil group showing areas Mild degenerations of Cells (MDC) (H&E X 100).

CRISYLE FAST VIOLET STAIN RESULTS

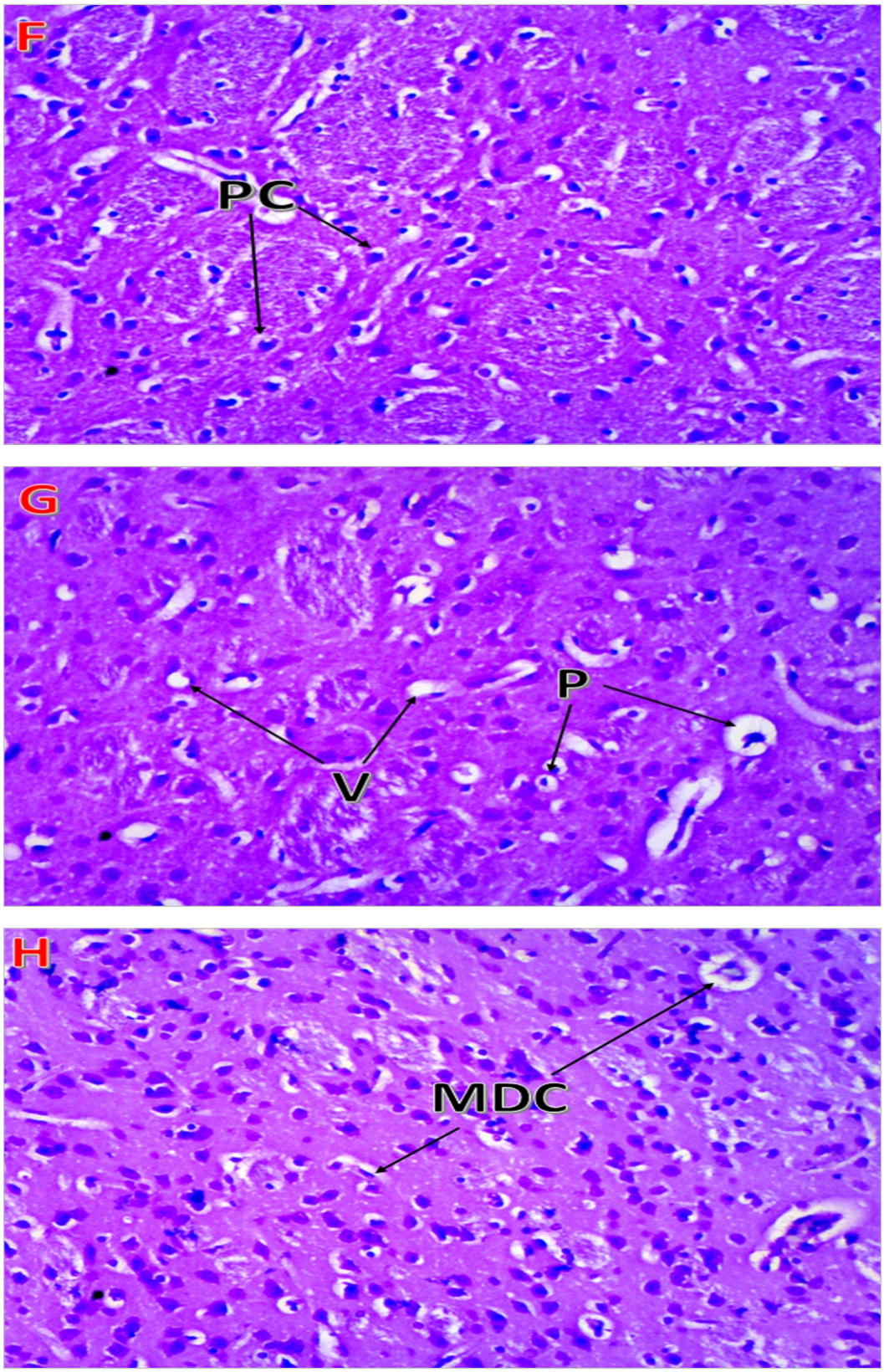
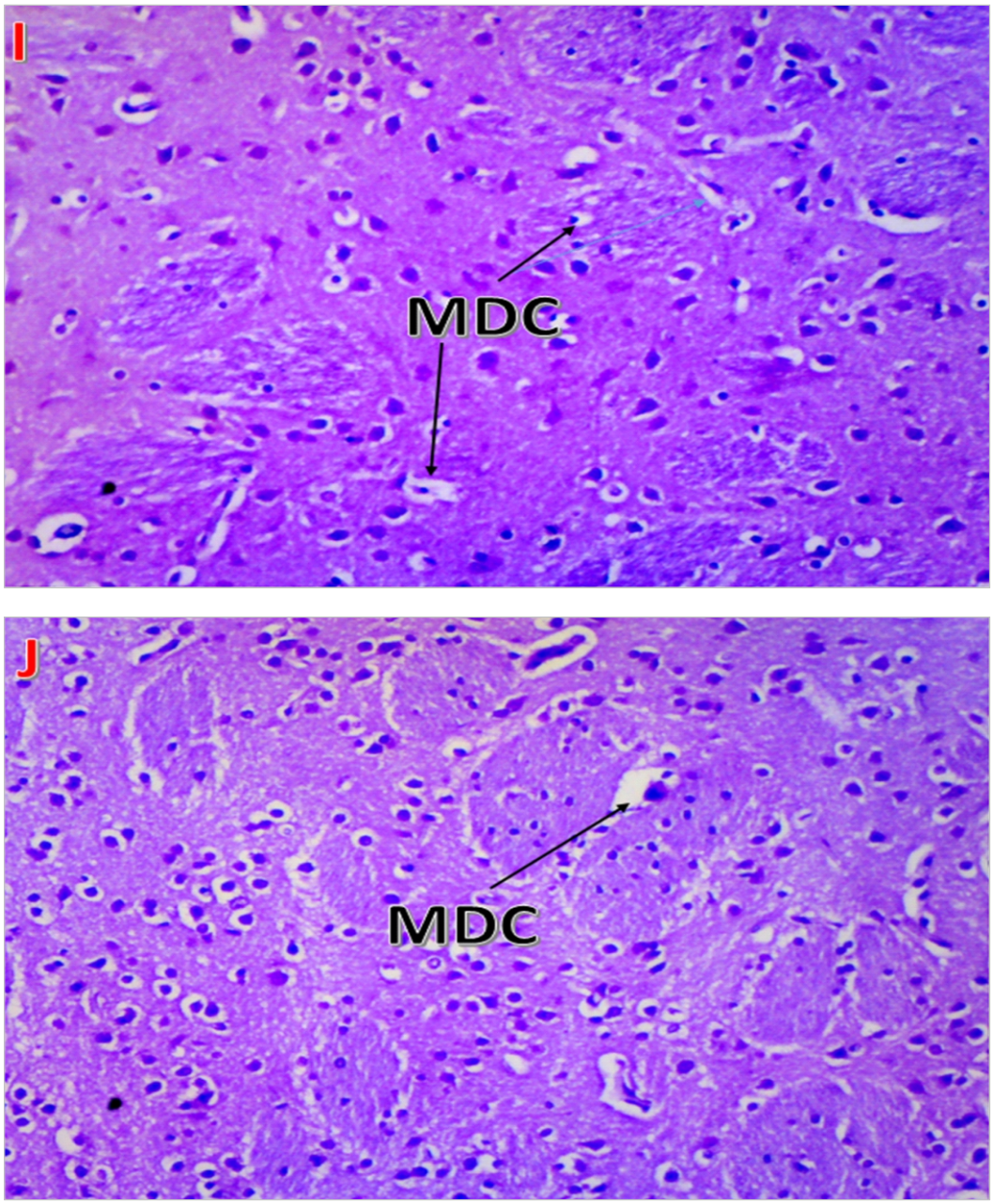


Figure 5: Algorithm for Fluid Management in Severe Dengue

Flowchart for Stepwise IV Fluid Therapy in Shock/ Plasma Leakage with Reassessment Points



Plates F - J:

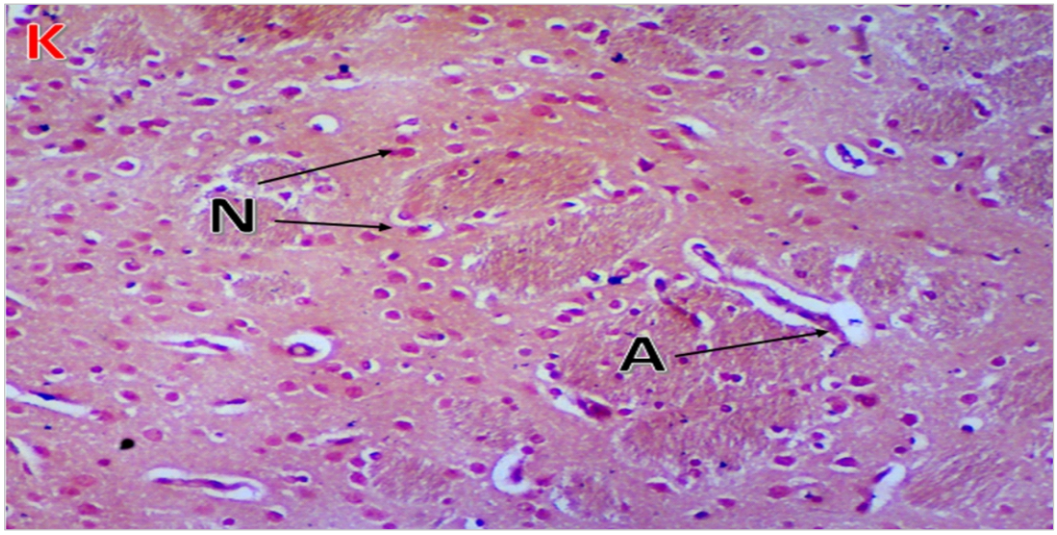
F, Photomicrograph of rats in the Control group showing normal cytoarchitecture of the layer V of the prefrontal cortex showing densely stained normal Pyramidal cells (PC) and normal Neuronal cells (NC).

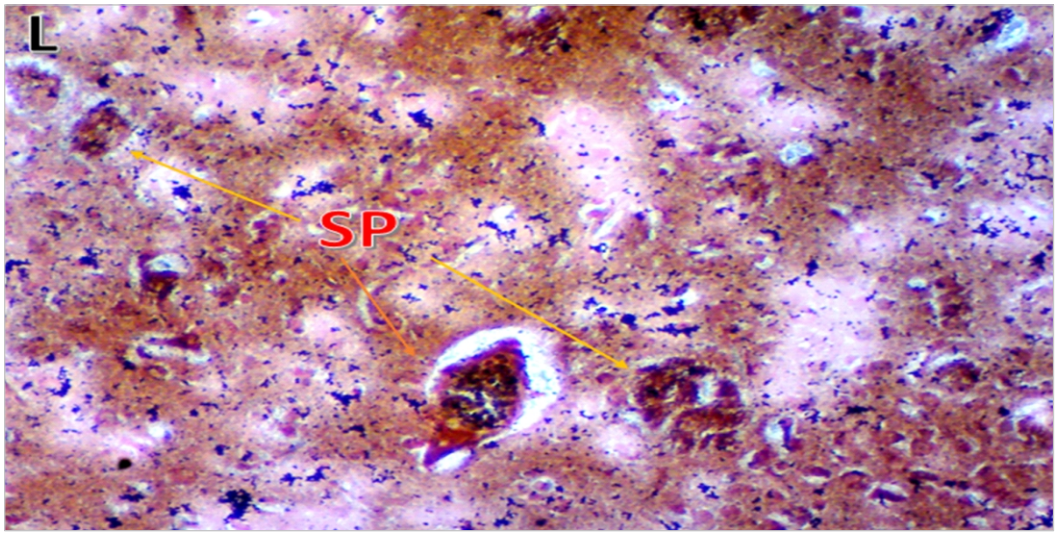
G, $AlCl_3$ only group showing several degrees of neurodegenerations: Vacuolations (V) and Pyknosis (P),

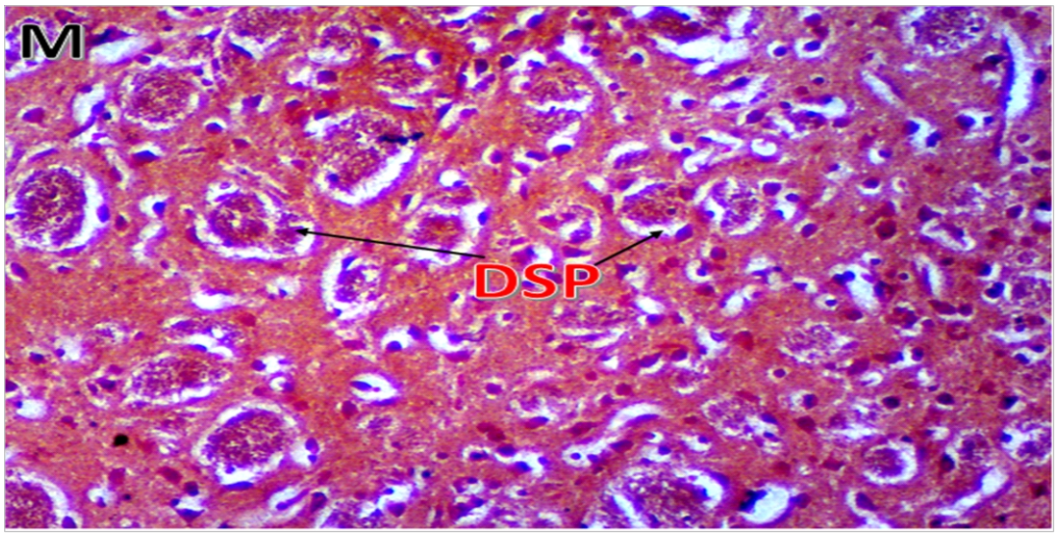
H & I: $AlCl_3$ + Low and High Dose TT groups showing areas moderate degenerations of Cells (MDC).

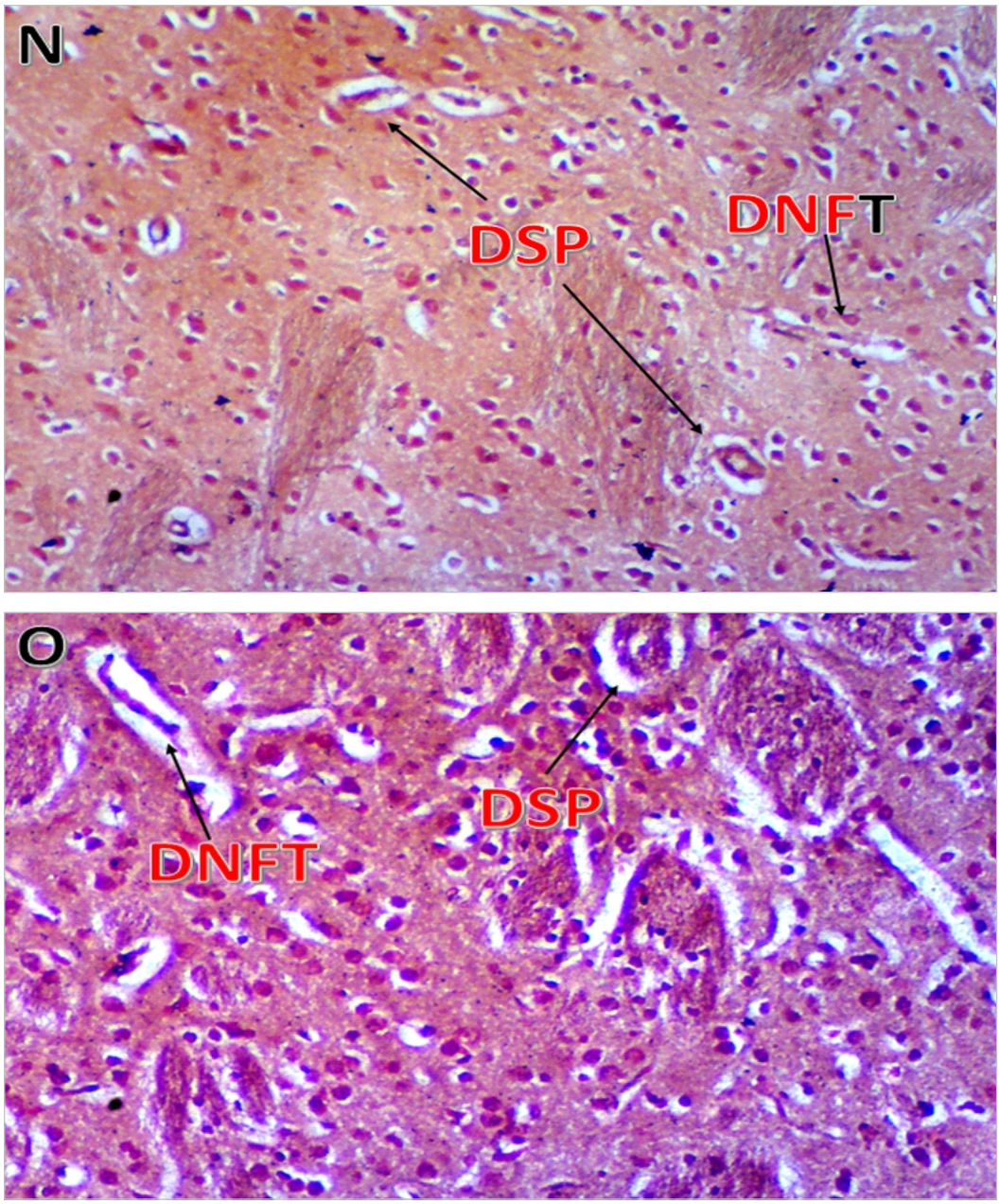
J, $AlCl_3$ + Donepezil group showing areas Mild degenerations of Cells (MDC) (CFV X 100).

BIELSCHOWSKY STAIN RESULTS









Plates K - O:
K, Photomicrograph of layer V of prefrontal cortex of rats in the Control group showing brown stained normal Neurons (N) and normal cell Axons with no Senile Plaques nor Neurofibrillary Tangles (A). **L**, $AlCl_3$ only group showing deep brown-stained Senile Plaques (SP). **M & N**, $AlCl_3$ + Low & High Dose TT groups showing moderate Diffusing Senile Plaques (DSP) and Neurofibrillary Tangles (DNFT). **O**, $AlCl_3$ + Donepezil group showing mild Diffusing Senile Plaques (DSP) and Neurofibrillary Tangles (DNFT) (BWK X 100).

DISCUSSION

Oxidative stress is widely recognized as one of the earliest and most important mechanisms involved in Alzheimer's disease pathogenesis[28]. In the present study, $AlCl_3$ administration significantly increased malondialdehyde (MDA) while significantly decreasing the antioxidant enzymes superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx) ($p < 0.05$). These findings indicate excessive generation of reactive oxygen species (ROS), resulting in membrane lipid peroxidation and exhaustion of endogenous antioxidant defense systems. The observed biochemical alterations are consistent with numerous experimental studies demonstrating that chronic aluminum exposure promotes oxidative injury by disrupting mitochondrial function, increasing free radical production, and impairing antioxidant enzyme activities[4,29,30]. Elevated MDA reflects severe lipid peroxidation of neuronal membranes, which compromises membrane integrity, synaptic transmission, and neuronal survival, whereas depletion of SOD, CAT, and GPx further exposes neurons to oxidative damage.

Treatment with TT significantly reversed these oxidative changes in a dose-dependent manner. Both doses significantly reduced MDA while restoring SOD, CAT, and GPx activities ($p < 0.05$), with the high-dose TT producing effects comparable to donepezil. These observations suggest that the neuroprotective effect of TT is largely attributable to its potent antioxidant properties[8,9].

$AlCl_3$ markedly increased amyloid-β (Aβ), phosphorylated tau (pTau), glial fibrillary acidic protein (GFAP), Bax, and Caspase-3 while significantly reducing Bcl-2 expression ($p < 0.05$). These molecular alterations collectively indicate successful induction of Alzheimer's disease-like neuropathology. Increased Aβ accumulation and tau hyperphosphorylation are the principal pathological hallmarks of Alzheimer's disease and are closely associated with synaptic dysfunction, neuronal degeneration, and progressive cognitive decline[32]. Similarly, increased GFAP expression reflects astrocyte activation, an important indicator of neuroinflammation and reactive gliosis. The simultaneous increase in Bax and Caspase-3 together with suppression of the anti-apoptotic protein Bcl-2 demonstrates activation of the intrinsic mitochondrial apoptotic pathway, leading to accelerated neuronal death[33].

However, TT significantly attenuated these pathological changes. Both treatment doses significantly reduced Aβ, pTau, GFAP, Bax, and Caspase-3 while increasing Bcl-2 expression ($p < 0.05$), with greater improvement observed following high-dose treatment. These findings suggest that TT not only suppresses oxidative stress but also interrupts downstream molecular pathways responsible for neuronal degeneration. The increase in Bcl-2 accompanied by reductions in Bax and Caspase-3 indicates inhibition of mitochondrial-mediated apoptosis, thereby promoting neuronal survival. Likewise, suppression of GFAP suggests attenuation of astrocytic activation and neuroinflammatory responses. The reduction in Aβ and pTau further implies that TT may interfere with amyloidogenic processing and abnormal tau phosphorylation, thereby limiting progression of Alzheimer's-like pathology.

More so, the behavioral findings strongly support the biochemical evidence. Rats exposed to $AlCl_3$ exhibited prolonged escape latency in the Morris Water Maze together with marked anxiety-like behavior in the Elevated Plus Maze, evidenced by reduced open-arm exploration, increased closed-arm occupancy, excessive grooming, and impaired rearing activity. These behavioral abnormalities are characteristic manifestations of prefrontal cortical dysfunction[34]. TT treatment significantly improved spatial learning, memory performance, exploratory behavior, and anxiety indices ($p < 0.05$), with high-dose TT producing improvements comparable to donepezil. These behavioral improvements likely reflect preservation of neuronal integrity within cognitive brain regions following attenuation of oxidative stress and apoptosis. The observed improvements in body weight following TT administration provide additional evidence of its systemic protective effects. Although initial body weights were comparable among groups, $AlCl_3$-treated rats exhibited significantly reduced final body weight ($p = 0.037$), suggesting generalized toxicity and impaired physiological function. TT-treated rats demonstrated greater weight gain, particularly at the higher dose, indicating improved overall health status. Interestingly, brain weights were not significantly different among groups, suggesting that functional impairment preceded overt anatomical atrophy, which is consistent with the early stages of experimental Alzheimer's disease[35].

The histological findings corroborate the biochemical and behavioral results. $AlCl_3$ exposure produced severe neuronal degeneration characterized by neuronal loss, cytoplasmic vacuolation, pyknotic nuclei, karyorrhexis, disruption of Nissl substance, and abundant senile plaque formation within the prefrontal cortex. These histopathological abnormalities are classical features of Alzheimer's disease and reflect irreversible neuronal injury resulting from oxidative stress, neuroinflammation, and apoptosis[35,36]. TT treatment markedly preserved neuronal cytoarchitecture, reduced neuronal degeneration, maintained Nissl substance integrity, and decreased amyloid plaque deposition. The preservation of neuronal morphology observed in both H&E and Cresyl Fast Violet staining together with reduced Bielschowsky-positive senile plaques provides compelling morphological evidence supporting the biochemical demonstration of reduced Aβ accumulation and apoptotic activity.

CONCLUSION

Tetrapleura tetraptera effectively ameliorated $AlCl_3$-induced Alzheimer's disease-like pathology through multiple interconnected mechanisms involving suppression of oxidative stress, inhibition of neuronal apoptosis, attenuation of neuroinflammation, reduction of amyloid and tau pathology, preservation of neuronal architecture, and restoration of cognitive function. The convergence of behavioral, biochemical, and histological evidence substantially strengthens the validity of these findings and supports the growing evidence that *Tetrapleura tetraptera* may represent a promising phyto-therapeutic candidate in a dose dependent regimen for the prevention or management of Alzheimer's disease.

DECLARATIONS

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Conflict of Interests Disclosure: The author(s) have declared that no competing interests exist.

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Program/ Curriculum Innovation

Biomedical Engineering Development: Contributing to Quantitative Physiology, Precision Medicine, and Quality Healthcare Delivery

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ABSTRACT

This article comprises the following Items:

Item 1. Biomedical Engineering (BE, ME & PhD) Programs

Biomedical Engineering is the application of engineering disciplines' formulations (of theories and designs) to biology, physiology and medicine, to improve medical monitoring, diagnosis, and therapy.

Item 2. Quantitative Physiology Program, jointly with College of Medicine

Quantitative Physiology Program can help to develop more precise medical diagnostics. This program involves formulation of Human Physiology courses from physics and engineering perspectives. It comprises two parts: Part I. Fundamental Physiological Processes: Physics and Engineering Modelling, and Part II. Physiological Systems Functions: Physics and Engineering Modelling.

Item 3. Precision Quantitative Medicine Program, jointly with College of Medicine

The Precision Quantitative Medicine Program is based on my Biomedical Engineering developments in (i) Physiology, Medicine, Orthopaedics and Surgery, (ii) Sports Biomechanics and Medicine, and (iii) Mind-Body Medicine in Psychiatry. This Program can be offered as an MD-PhD (Biomedical Engineering) Program, jointly between the Biomedical Engineering Department and the College of Medicine.

Item 4. MD-PhD (Biomedical Engineering) Program, jointly with College of Medicine

This Program is intended for medical students interested in combining medical practice with competency in biomedical engineering, to implement BME technologies in clinical research and applications in clinical care in hospitals. The program emphasizes computational medicine and computational surgery.

Item 5. Hospital and Healthcare Management (MBA and MD-MBA) Program, jointly with College of Business and College of Medicine

The Hospital and Healthcare (HOHM) Program is designed to provide the relevant multidisciplinary knowledgebase in business administration, clinical and hospital engineering, economic and financial management, related to cost-effective operation of hospitals and healthcare delivery (as represented by the three pillars of HOHM depicted below), to healthcare and hospital administrators.

Together, these developments constitute a novel model of Biomedical Engineering, contributing to Quantitative Physiology, Precision Quantitative Medicine, and Quality Healthcare Delivery.

Item 6. In Conclusion

Biomedical Engineering drives modern healthcare through its integration with medicine. By enabling advanced measurement, targeted therapies, and data-driven treatments, the field has fundamentally transformed how we understand human physiology and deliver quality patient care.

KEYWORDS: Biomedical engineering; Curriculum development; Quantitative physiology; Precision medicine; MD-PhD program; Healthcare management.

Item I. Biomedical Engineering (BE, ME & PhD) Programs

Biomedical Engineering is the application of engineering disciplines' formulations (of theories and designs) to biology, physiology and medicine, to improve medical monitoring, diagnosis, and therapy.

Biomedical engineering bridges engineering and medical disciplines to provide an overall enhancement of health care. Today, Biomedical Engineering has advanced incredibly, and is poised to provide new insights in medicine and healthcare, through: 1. Quantitative analysis of mechanisms and functions of Physiological systems (such as cardiovascular and musculoskeletal systems), 2. Cellular and Molecular Engineering, 3. Computerized processing and diagnostic pattern recognition of medical signals and images, 4. Design of prosthetic devices and implanted systems, 5. Regenerative Tissue engineering, 6. Pharmaceutical Engineering, 7. Rehabilitation systems, prosthetic and orthotic devices.

Biomedical Engineering Courses:

1. Quantitative Physiology I (Cells and Molecules), Quantitative Physiology II (Organ Systems).
2. Biomaterials, Cellular and Tissue Biomechanics, Biofluid Mechanics, Biotransport processes, Musculoskeletal Biomechanics.
3. Cellular and Molecular Engineering, Pharmaceutical Engineering: Drug designing, producing and delivery Systems.
4. Bioelectrical Processes, Physiological Control Systems, Tissue Engineering and Regenerative Medicine.
5. Physiological Signals and Processing, Medical Image Processing and Pattern Recognition, Medical Instrumentation.
6. Orthopaedic Biomechanics, Cardiovascular System Engineering, Pulmonary System Engineering, Renal System Engineering, Neurological System Engineering.

Clinical Internship

We can catalogue these courses into the following five domains:

1. Quantitative Human Physiology: Physics and Engineering formulations of Physiological Systems functions and dysfunctions, enable us to clearly understand the physiological system functional mechanisms, monitoring systems, and diagnostics. For example, in Neurophysiology, the physics formulation of the concepts of electrical potential, current, resistance and capacitance can be applied to neurobiology phenomenon of nerve conduction, by enabling us to analyse the resting potential of axon membrane, the action potential from stimulus, and propagation of the action potential in a nerve axon. In Cardiovascular Physiology, we can develop a novel cardiac contractility index, in terms of the maximum rate of change of LV systolic wall stress normalized to intra-LV pressure, which can be determined noninvasively in terms of myocardium volume and maximum outflow rate[1,2].
2. Organ Systems Function: Biomedical Engineering formulation of Organ Systems, such as the Heart, Lungs and Kidneys, involving (i) analyses of their function, (ii) detection of abnormal function by formulation of indices (such as left ventricle contractility index to assess heart dysfunction due to cardiomyopathy), and (iii) design of systems and devices to compensate for dysfunction (as for example, ventricular assist device to assist the weakened-contractile left ventricle in providing adequate cardiac output).
3. Medical Diagnostic Apps: Over the years, there has been significant number of works and publications on medical signal and image processing methods and techniques for making medical diagnosis. We now need to convert them into devices that can automate accurate medical diagnostics. Medical Diagnostic

Apps combine these signal and image processing software into smart apps by using machine learning computer-generated artificial intelligence technique, for automatically classifying patterns in data to crowdsource and build on the best medical knowledge from thousands of physicians across many countries. Our goal is to provide timely and affordable specialist advice to general practitioners serving millions of people worldwide, in the "safety net" hospitals and clinics. Learning of these Medical Apps as part of medical education can help improve the training and performance of primary care physicians.

4. Customized Surgical Systems and Procedures: This category includes (i) Presurgical Patient-specific Surgical Design, and (ii) Creating 3D Surgical Models from Patient Scans.

   For obtaining more reliable surgical outcomes, it is necessary to pre-surgically design patient-specific procedures. For example, in order to obtain the best outcome from coronary bypass surgery on a patient, we need to determine the optimal configuration of distal anastomosis of graft and occluded artery, to obtain the ideal blood flow distribution in this anastomotic space which will promote long-term patency of the surgical procedure.

   Then for Surgical Precision, surgeons can learn how to (i) guide surgical instruments to the exact place, and (ii) move organs out of the way without causing damage.

5. Customized Precision 3-d printed Limb Prostheses, Human tissues and Organ Replacements: The medical industry is now utilizing the rapidly advancing 3D printing technology for human health benefit in a big way. We can now print anything from 3d printed customized prosthetic limbs to heart valves and dentures, to human organs and human tissues with blood vessels. For a 3D printer to work, we have to feed it instructions in the form of a 3D model, which is a 2-d computer-aided design file designed by using special 3D production software, to create an accurate 3D representation of an object's surface area. The 3D medical printers for artificial tissue use biodegradable materials along with hydrogels comprising of real human cells, which gives the tissue both strength and structure.

This program can be supported by my Textbooks:

1. Cardiac Perfusion and Pumping (World Scientific, 2006): Physiomics of Coronary Perfusion and Cardiac Pumping; Quantification of Cardiac Perfusion and Function Using Nuclear Cardiac Imaging; Perfusion Depiction by SPECT Imaging, Computation of Blood Flow Pressure and Velocity Patterns Within Myocardial Regions; Left Ventricular (LV) Pressure Increase Mechanism During Isovolumic Contraction, and Determination of the Equivalent LV Myocardial Fibers Orientation; New Clinically Relevant Left Ventricular Contractility Index (based on Normalized Wall Stress); Augmented Myocardial Perfusion by Coronary Bypass Surgical Procedure: Emphasizing Flow and Shear Stress Analysis at Proximal and Distal Anastomotic sites.

2. Applied Biomedical Engineering (CRC Press, Taylor and Francis, 2009): Uses a problem-based approach to quantify physiological processes, formulate diagnostic and interventional procedures, develop orthopaedic surgical procedures; Features: Incorporates material from solid mechanics, fluid mechanics, dynamics and vibrations, control systems, and mathematical Modelling; Provides biomechanical guidelines for internal fixation of bone and spinal fractures as well as the treatment of herniated discs; Presents the mechanics of heart function, heart structures, non-invasive determination of aortic pressure, and characterization of left-ventricular afterload; Discusses detection of infarcted myocardial segments; Assesses the constitutive properties and degeneration of heart valves; Covers the modelling of lung ventilation, its application to lung disease diagnosis, lung gas-transfer mechanism, and indices to assess its performance; Examines how human anatomical structures and physiological processes are designed for optimal functionality.

3. Biomedical Science, Engineering and Technology (InTech Publishers, 2012): Cohesively integrates biomedical science (disease pathways, models and treatment mechanisms), biomaterials and implants, biomedical engineering, biotechnology, physiological engineering, and hospital management science and technology. Together, these topics are providing a pathway for incorporation of STEM into medical knowhow, procedures and devices, towards a higher order of translational medicine applied in tertiary patient care.

4. Cardiology Science and Technology (CRC Press, Taylor and Francis, 2016):

   Book Contents

   Section 1: Left Ventricular Wall Stress, Contractility and Vector Cardiogram, with Applications in Cardiology: Left ventricular Wall Stress Compendium; Assessment of Cardiac Function in Filling and Systolic Ejection Phases; Novel Cardiac Contractility Index $d\sigma^*/dt$ (max); Cardiomyopathy effect on Left ventricle (Shape, Wall stress and Contractility) and Improvement after Surgical

Ventricular Restoration; Cardiac Contractility Measures for Left Ventricular Systolic Functional Assessment in Normal and Diseased Hearts; Analysis for Left Ventricular Pressure Increase during LV Isovolumic Contraction Phase, due to Activation of the Myocardial Fibers: Computation of LV Myocardial Wall Stresses, Myocardial Fiber Stresses and Orientation; Myocardial Infarct Induced Left Ventricular Shape Remodelling, and Surgical Ventricular Restoration to restore LV Shape and Cardiac Contractility; Vector Cardiogram Theory and Clinical Application.

Section II: ECG Signal Analysis and Cardiac Pumping (Intra-Ventricular, Aortic and Coronary Flow), with Applications in Cardiology and Cardiac Surgery: ECG and Heart Rate Variability Signal Processing and Analysis to detect Cardiac Arrhythmias; Left Ventricular Blood Pump Analysis and Outcome: Intra-LV Flow and Pressure Distributions to determine Candidacy for Coronary Bypass Surgery; Cardiac Perfusion Analysis and Quantification by Nuclear Cardiac Imaging and Computation of Intra-Myocardial Blood Flow Velocity and Pressure Patterns; Determination of Arterial Pulse Wave Propagation Velocity and Arterial Properties; Blood Flow in Patient-Specific Coronary Arteries: Causes of Atheromas at Arterial Curvatures and Bifurcations based on Hemodynamic Parameters; Intra-Left Ventricular Diastolic and Systolic Flow Distributions, based on Colour Doppler Echo Velocity Flow Mapping of Normal subjects and Heart Failure Patients; Coronary Blood Flow Analysis and Coronary Artery Bypass Graft Flow and Design; Coupled Sequential Anastomotic Bypass Graft (SABG) Design.

5. Computational and Mathematical Methods in Cardiovascular Physiology (World Scientific, 2018): This book has literally transformed Cardiovascular Physiology into a STEM discipline, involving (i) quantitative formulations of heart anatomy and physiology, (ii) technologies for imaging the heart and blood vessels, (iii) fluid mechanics and computational analysis of blood flow in the heart, aorta and coronary arteries, (iv) design of heart valves, percutaneous valve stents, and ventricular assist devices.

   So how is this mathematically and computationally configured landscape going to impact cardiology and even cardiac surgery? We are now entering a new era of mathematical formulations of anatomy and physiology, leading to technological formulations of medical and surgical procedures towards more precision medicine and surgery. This will even entail reformatting of (i) the medical MD curriculum and courses, so as to educate and train a new generation of physicians who are conversant with medical technologies for applying into clinical care, as well as (ii) structuring of MD-PhD (Computational Medicine and Surgery) Program, to train competent medical and surgical specialists in precision medical care and patient-specific surgical care.

   This book is providing a gateway for this new emerging scenario of (i) science and engineering based medical educational curriculum, and (ii) technologically oriented medical and surgical procedures. As such, this book can be usefully employed as a textbook for courses in (i) cardiovascular physiology in both the schools of engineering and medicine of universities, as well as (ii) cardiovascular engineering in biomedical engineering departments world-wide.

6. Biomedical Engineering of Pancreatic, Pulmonary, and Renal Regulatory Systems, and Applications to Medicine (Elsevier Publisher, 2023).

Book Contents

Section I. Pancreatic and Glucose-Insulin Regulatory System Engineering and Medical Assessment

- Chapter 1. Pancreatic Regulatory Physiology and Medical Assessment
- Chapter 2. Glucose-Insulin Regulatory Kinetics
- Chapter 3. Automated Insulin Infusion Regulatory System
- Chapter 4. Using Diabetes Technology to Maximize Diabetes Management

Section II. Respiratory and Pulmonary System Engineering and Medical Assessment

- Chapter 5. Physiologic and Medical Assessments of Respiratory Mechanics and Ventilation
- Chapter 6. Lung Ventilation Modelling and Medical Assessment
- Chapter 7. Respiratory Control Mechanism-Modelling
- Chapter 8. Lung Alveoli and Pulmonary Capillary Gas Transfer Analysis

Section III. Renal System Engineering and Medical Assessment

- Chapter 9. Renal Physiology Theory and Functional Assessment
- Chapter 10. Determining Kidney Obstructions by Renogram Data Modelling
- Chapter 11. Artificial Kidney Function and Dialysis

Physiology: Mechanisms and Analysis of Haemodialysis and Peritoneal Dialysis

- Chapter 12. Renal Physiology Modelling, Part 1: Acid Base Balance, Part 2: Body Fluid Balance

This book addresses the need for biomedical engineering to provide physiological analysis of organ systems and their medical applications to help enable quantitative formulation of physiological systems and defining their functions and dysfunctions, leading to precision diagnostics of diabetes, lung diseases, and kidney failure, often in the form of non-dimensional indices. The book chapters also deal with treatment systems, namely automated insulin infusion systems, haemodialysis, and peritoneal dialysis. The book is formulated to solve many physiological, bioengineering, and medical problems.

Item 2. Quantitative Physiology Program (Jointly with the College of Medicine)

This Quantitative Physiology Program can help to develop more precise medical diagnostics. This program involves formulation of Human Physiology courses from physics and engineering perspectives. It comprises two parts: Part I. Fundamental Physiological Processes: Physics and Engineering Modelling, and Part II. Physiological Systems Functions: Physics and Engineering Modelling.

In the College of Medicine, this Program can be offered as a Physiology course in the Biomedical Engineering Department, as well as contribute to Master's and PhD program in Physiology.

I can also help to set up a new STEM College of Medicine, in which there would be a Biomedical Engineering Foundation course in semester 1 of Year 1. Then in semester 2 of Year 1, this Program can be offered as a Quantitative Physiology course.

Curriculum

Part 1: Fundamental Physiological Processes: Physics and Engineering Modelling

- Unit 1: Cell Structure and Biochemical Reactions: Cell Structure, Cell Chemicals, Reaction Equations
- Unit 2: Cellular Homeostasis and Membrane Potential: Membrane: composition, Equilibrium Potential, Cell Model and Membrane potential.
- Unit 3: Action Potential: Na+/K+ Action Potential, Ca2+ Contribution, Hodgkin-Huxley Model.
- Unit 4: Cellular Transport and Communication: Passive and Active Transport, Cellular Communications, Electrical and Chemical Synapses, Action Potential Propagation.
- Unit 5: Tissue Mechanics: Stress-Strain relationships and Constitutive properties; Coupled Cell-Tissue, Fluid-Tissue and Blood Vessel-Tissue Models.

Part II: Physiological Systems Functions: Physics and Engineering Modelling

Unit 1: Cardiovascular System:

1. Bioelectrical Process in the Heart: Electrical activity is initiated in the SA node, and the impulse spreads via specialized pathways to myocardial contractile cells in the ventricles, causing ventricular contractility; this bioelectrical activity is characterized by ECG, and its signal processing enables cardiac diagnostics.
2. Contraction Process of the Heart Myocardium: Development of stress in the left ventricular wall contractility index, by which the intra-ventricular pressure rises adequately to be able to promote LV ejection[3].
3. Intra-Ventricular Blood Flow Analysis: Governing equations of fluid flow, and analysis of blood flow patterns in the LV, to show how adequate pressure is generated to open the aortic valve. Doppler echo images.
4. Blood Flow into the Aorta and Pulse Wave Propagation: Determine pulse wave propagation velocity in terms of the aortic constitutive property to characterize arteriosclerosis; carry out analysis of blood flow into the aorta to yield the differential equation for aortic pressure in terms of the aortic inflow by Doppler Echocardiography; solve the differential equation to obtain aortic pressure-time profile[4].
5. Blood Flow in the Coronary Vasculature: CFD modelling of the Navier-Stokes equations to determine flow patterns, wall shear stress and wall pressure gradient in imaging-based coronary arterial models.
6. Cardiac Perfusion Analysis: Compute intra-myocardial blood flow velocity and pressure patterns, by carrying out myocardial perfusion SPECT imaging; to quantify decreased blood flow in ischemic areas of the myocardium[5].

Unit 2: Pulmonary System:

1. Lung Ventilation modelling (with application to lung disease determination): Differential equation of lung volume (V) response to lung driving pressure (PN) (in an intubated patient), in terms of

lung compliance (C) and resistance-to-airflow (R); these R and C parameters are then combined into non-dimensional ventilatory performance indices, for detection of lung fibrotic lung disease, obstructive lung disease, and emphysema[6].

2. Lung Gas-transfer performance analysis: Analysis of inspired and expired air composition analysis, based on mass balances; derive expressions for O2 and CO2 diffusion coefficients in terms of O2 consumption-rate and CO2 production-rate (from the inspired-expired air composition analysis), alveolar air O2 and CO2 partial pressures, and O2 and CO2 concentrations in the venous blood; formulation of non-dimensional Gas-transfer Index (NDGTI) in terms of DO2, DCO2, O2 consumption-rate and CO2 production-rate; this NDGTI can be employed to assess the gas-transfer capacity of the lung-capillary bed system[7].

Unit 3: Nervous System

1. Central Nervous System: Neurons, Autonomic Nervous System: Autonomic Control of the Heart, Cardiac Efferents and Afferents.
2. Somatic Nervous System: Temporal and Spatial Summation of Synaptic Potentials; Excitatory and Inhibitory Synapses; the Brain, Bioelectrical processes leading to generation of EEG; signal processing of EEG for neurological disease detection.
3. Propagation of Axon Potential: In an axon that has been excited at one end, the action potential is positive; positive ions move towards this end on the outside and away from it inside; this decreases the charges on the adjacent portion of the membrane, so that the axoplasm potential rises to the action potential threshold; this triggers increased Na permeability, leading to Na influx and an action potential at the adjacent portion of the membrane; this is how the axon potential propagates.

Unit 4: Glucose-Insulin Regulatory System, and Diabetes detection by oral glucose tolerance test

1. Glucose-Insulin Regulatory System: Derivation of governing second-order differential equations (DEQs) of glucose and insulin concentration responses to glucose ingestion represented by an impulse function, in oral glucose tolerance test (OGTT)[8].
2. Determining the system response: The model parameters are determined by making the solution (for underdamped, overdamped and critically damped) for glucose and insulin responses match the OGTT clinical data[9].
3. Diabetes non-dimensional index (DNDI): is then developed in terms of the model parameters; this DNDI has distinct ranges underdamped response of normal subjects, overdamped response of diabetic subjects, and critically damped response of at-risk subjects; this enables more precise diagnosis of diabetic subjects[10].

Unit 5: Renal System

1. Analysis of the operating characteristics of the Renal system: Examine the optimal features of several aspects of renal physiological engineering mechanisms, particularly, the counter current multiplier mechanism for urine concentration and how optimal renal function in terms of renal clearance is maintained.
2. Analytical model of the loop of Henle and Renal handling of metabolic substrates: This modelling is carried out to show how the renal system is optimized for filtration and regulation of urine concentration by the counter current mechanism in the loop of Henle and its medullary environment, which is largely physiologically engineered to increase and maintain at steady-state the high osmolality of the urine fluid to as high as 4 times normal blood osmolality. The renal clearance of substrates is modelled as a single-compartment kinetic model, with continuous input of metabolic substrates. The analytical solution obtained from the continuous input of creatinine predicts the plasma creatinine concentration to be an inverse hyperbolic function of the renal clearance. The formula predicts reasonable estimates of the actual serum creatinine levels in the body based on renal clearance and substrate input parameters.

Item 3. Precision Quantitative Medicine Program (Jointly with the College of Medicine)

This Precision Medicine Program is based on my Biomedical Engineering developments in (i) Physiology, Medicine, Orthopaedics and Surgery, (ii) Sports Biomechanics and Medicine, and (iii) Mind-Body Medicine in Psychiatry.

This Precision Quantitative Medicine Program can be offered as an MD-PhD (Biomedical Engineering) Program, jointly

between the Biomedical Engineering Department and the College of Medicine.

I can also help to set up a new format of STEM College of Medicine, in which there would be a Biomedical Engineering Foundation course in semester 1 of Year 1. Then in semester 2 of Year 1, the above-described Quantitative Physiology course can be offered. Thereafter the below-described Quantitative Medicine and Surgery courses could be offered in Year 3.

Quantitative Medicine and Surgery Courses:

1. Cardiovascular Medicine: Left Ventricular Wall Stress and Contractility Index[3], Vector Cardiogram and ECG Signal Processing, Coronary Blood flow and Myocardial Perfusion, Myocardial Infarct detection and Heart Failure, Intra-Ventricular Blood Flow and Candidacy for bypass surgery, Pulse wave velocity and Detection of Arteriosclerosis[11], Aortic Pressure Profile and Aortic stiffness determination[12], Coronary Bypass surgery design for maximal patency[13,14], Prosthetic Aortic and Mitral Valve designs.

2. Pulmonary Medicine: Lung Ventilation modelling for lung disease detection, Lung Ventilatory Index, Lung Gas Transfer performance analysis, Determination of O2 and CO2 Diffusion coefficients, Non-dimensional Gas-transfer index, Indicators for Extubation of Mechanically ventilated COPD patients[6,7].

3. Diabetic Medicine: Glucose-Insulin Regulatory Control systems, Oral Glucose Tolerance Test modelling and model parameters determination, Non-dimensional indices for glucose and insulin responses, Non-dimensional Diabetic Index for Diabetes detection[8-10].

4. Nephrology: Kidney Functional analysis, Counter current mechanisms and modelling of urine concentration, Osmolality in the descending and ascending limbs of the Loop of Henle, compartmental model of renal clearance kinetics, Physiological measurement of the Glomerular Filtration Rate (GFR), Relationship between blood creatinine levels and the renal clearance rate, Renal clearance convolution analysis; Renography modelling and determination of normalized urine flow rate index to differentiate between obstructed and normal kidneys[15].

5. Orthopaedic Biomechanics and Surgery: Osteoporosis Index for osteoporosis detection; Structural analysis of plate-reinforced fractured bone and Optimal design of fixation plate; Osteosynthesis using hemihelical plates for fixation of oblique bone fractures, Finite Element analysis and design of Bone-Plate assemblies and Helical Fixation plate[16,17].

6. Spinal Biomechanics and Surgery: Biomechanical Simulation of Scoliotic Spinal deformity and Correction, Presurgical Finite-element Simulation of Scoliosis Correction[18,19]; Structural analysis of the Spinal Vertebral body as an intrinsically optimal lightweight and high-strength structure, Fractured Vertebral body fixation techniques and design of a vertebral body cage, Clinical Biomechanics of Spinal Fixation: Anterior, Posterior Fixations[20]; Structural analysis of Intervertebral Disc as an intrinsically optimal minimally deformed structure under spinal loading, Nucleotomized Disc model analysis and solution for disc herniation[21].

7. Sports Science, Biomechanics and Medicine: Optimal Walking Modality based on modelling the leg as a Simple-compound pendulum, Optimal Jogging Mode based on Double-compound model of the lower limb[22]; Analysis of Spinning Ball Trajectories of Soccer kicks and Basketball throws[23], Analysis of high jump and pole vault, Analysis of tennis serves and cricket bowling, Analysis of Ice Hockey Slap shots and Field Hockey Drag flick; Cardiac Fitness Index based on Treadmill test[24], Evaluation of Hip Joint based on Differential equation model of the Swinging Leg motion, to determine the hip joint damping and stiffness parameters.

8. Mind-Body Psychosomatic Medicine, Therapy for Psychiatric Disorders, Regenerative Medicine: Mind-body rejuvenation, by boosting cognitive function, increasing Gray matter density in the hippocampus, lowering blood pressure and boosting the immune system, reducing depression and easing stress; Triggering of neurohormonal mechanisms that bring about health benefits, as evidenced by increased parasympathetic and reduced sympathetic nerve activity and increased overall HRV, reducing stress and anxiety; Enhanced release of melatonin, which has anti-inflammatory, immune-stimulating, anti-oxidant and regeneration-enhancing properties; Development of non-volitional EEG Biofeedback System Therapy for treating neurological disorders[25].

9. Non-dimensional Physiological Indices in Medical Assessment: New Concept of Non-dimensional Physiological Indices (NDPIs) or Physiological Numbers (PHYNs) for analysing Physiological Systems and Medical Tests' Data, Sports Fitness index, Cardiac contractility index, Lung ventilation Index to detect lung disorders, Diabetes diagnosis index from oral-glucose-tolerance test, Arterial stiffness or arteriosclerosis index, Mitral Valve Elasticity Index from heart sound and echocardiography data, Bone osteoporosis index, Hospital Departments' performance-cost indices, and optimizing budget allocation for maximizing patient care with cost-effective hospital operation[26].

Item 4. MD-PhD (Biomedical Engineering) Program (Jointly with the College of Medicine)

This Program is intended for medical students interested in combining medical practice with competency in biomedical engineering, to implement BME technologies in clinical research and applications in clinical care in hospitals. The program emphasizes computational medicine and computational surgery.

The PhD component of the Program can consist of Courses in:

i. Quantitative Physiology, Medical Signal and Image Processing;

ii. Cardiological and Cardiac Surgical Engineering, Renal Engineering, Neurological engineering;

iii. Orthopaedic and Spinal Surgical Biomechanics, Rehabilitation Engineering.

These courses lead to teaching and application of computational medicine and computational surgery.

Computational Medicine involves biomedical engineering models of physiological systems and medical procedures, using computationally based solution methods and algorithms, to develop precision medical diagnostic, treatment and rehabilitative procedures and systems. Examples of Computational Medicine are (i) Development of cardiac contractility formula index in terms of the maximum rate of change of LV systolic wall stress normalized to intra-LV pressure, $d(\sigma/P)/dtmax$ or $d\sigma^*/dtmax$, where $\sigma^* = \sigma/P$, and its application to diagnose heart failure, and (ii) ECG waveform signal analysis for detection of cardiac arrhythmias[27,28].

Computational Surgery involves the use of medical imaging, robotics, patient-specific surgical simulation and information technology to analyse and plan patient-specific surgical procedures for obtaining optimal outcomes. Examples of computational surgery are (i) Cardiac Surgical Engineering, such as in computational planning of coronary bypass surgery[13,14], and (ii) Orthopaedic & Spinal Surgical Engineering, such as design of helical bone plates for oblique bone fractures[16,17], and design of hyperboloid shaped spinal vertebral body cage for vertebral body fractures[20].

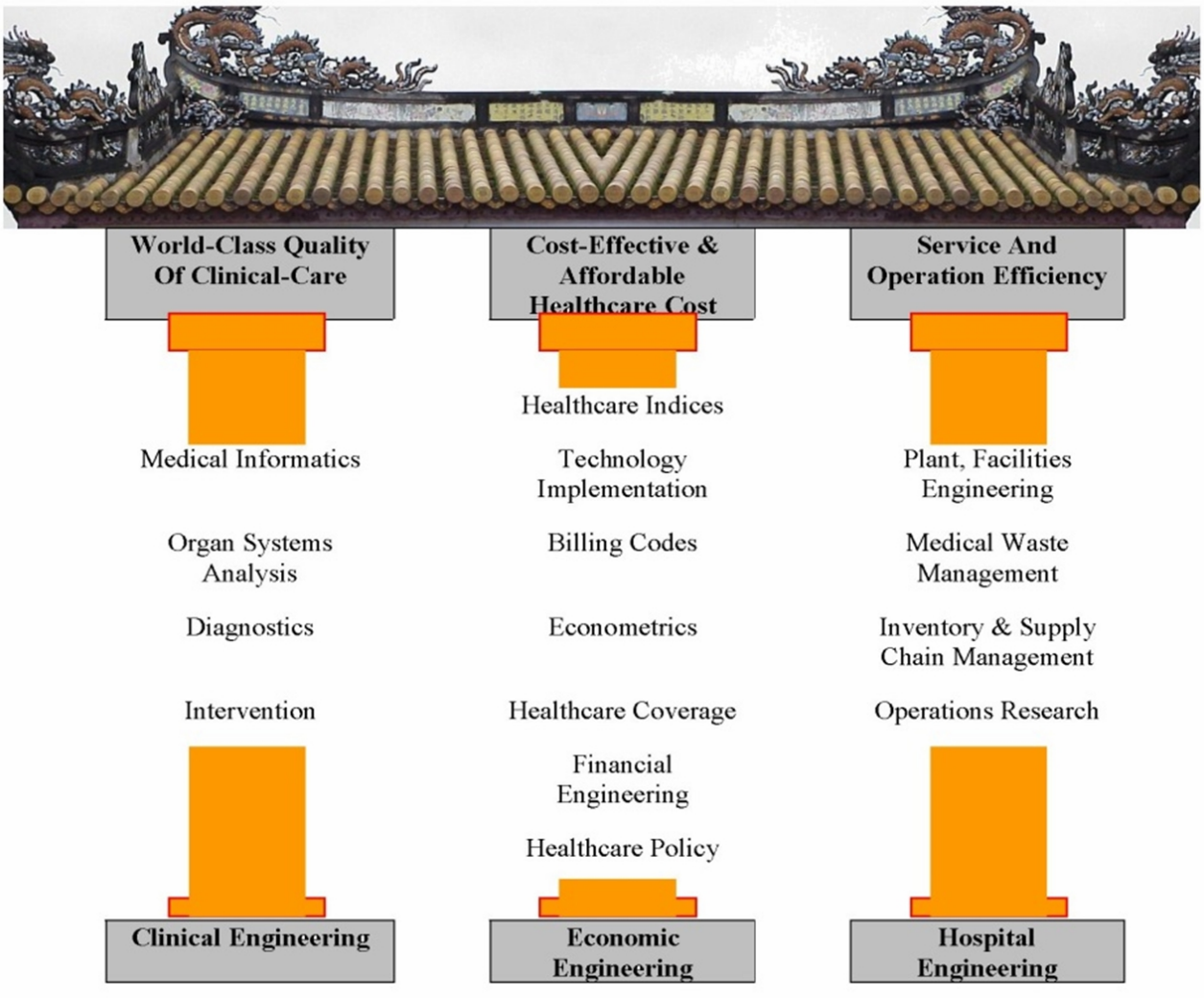
This novel program can provide a quantitative approach to disease processes, medical diagnosis and treatment, surgical simulation and techniques. This Program can be offered to educate medical doctors (for academic medicine career) who want to learn about biomedical engineering formulations of medical systems and surgical procedures, and implement them in clinical care.

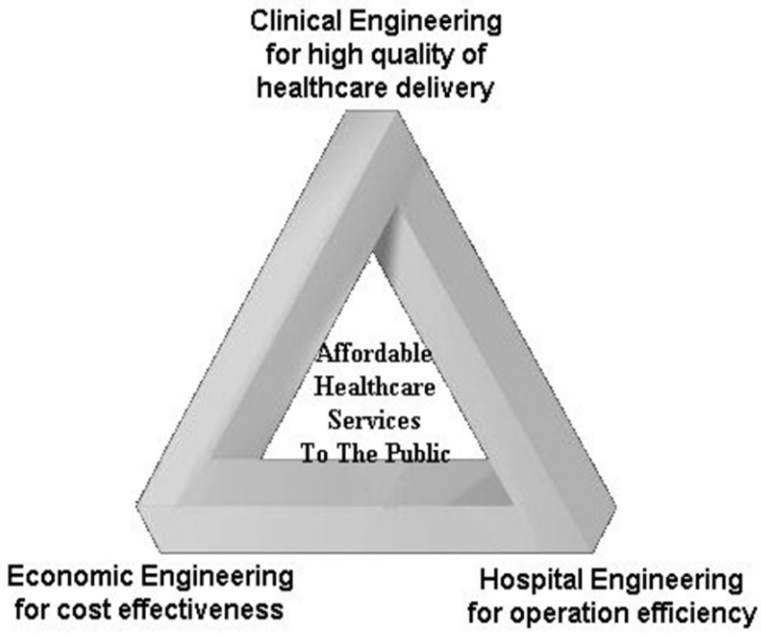
Item 5. Hospital and Healthcare Management (MBA and MD-MBA) Program (Jointly with College of Business and College of Medicine)

The Hospital and Healthcare (HOHM) Program is designed to provide the relevant multidisciplinary knowledgebase in business administration, clinical and hospital engineering, economic and financial management, related to cost-effective operation of hospitals and healthcare delivery (as represented by the three pillars of HOHM depicted below), to healthcare and hospital administrators.

This program is designed to offer MBA (HOHM) and PhD degrees in the School of Business. It can also be offered as MD-MBA (HOHM) in the College of Medicine.

The HOHM program is designed to prepare graduates for careers as administrators in hospitals (in hospital operations management) and healthcare organizations, in providing cost-effective healthcare delivery. The figure below represents a balanced approach to an affordable healthcare delivery system.


World-Class Quality Of Clinical-Care
Cost-Effective & Affordable Healthcare Cost
Service And Operation Efficiency
Medical Informatics
Organ Systems Analysis
Diagnostics
Intervention
Healthcare Indices
Technology Implementation
Billing Codes
Econometrics
Healthcare Coverage
Financial Engineering
Healthcare Policy
Plant, Facilities Engineering
Medical Waste Management
Inventory & Supply Chain Management
Operations Research
Clinical Engineering
Economic Engineering
Hospital Engineering


Clinical Engineering for high quality of healthcare delivery
Affordable Healthcare Services To The Public
Economic Engineering for cost effectiveness
Hospital Engineering for operation efficiency

The HOHM professional MBA program in the School of Business would be a heavily subscribed program. We could even offer an exciting MD-MBA (HOHM) program to those students in the MD program who are interested in a career in hospital administration or in setting up and managing a community healthcare system[29-31].

The HOHM program can comprise the following courses:

- Health Care Organization, Policy, and Administration
- Healthcare Economics
- Principles of Biostatistics
- Healthcare and Hospital Operations and Logistics Management
- Principles of Cost-effective Management of Hospitals and Healthcare Delivery System
- Healthcare Informatics Technology for Better Patient Care
- Billing Codes for Biomedical Engineering Operations in a Tertiary-care Hospital
- Maximizing Hospital's Bed-occupancy and Patient Flow
- Integrated Cost-Performance Indices of Hospital Departments
- Hospital Budget Management: to determine the Resource index for all the hospital departments to obtain acceptable values of their Cost-Performance indices.

Item 6. In Conclusion

Biomedical Engineering drives modern healthcare through its integration with medicine. By enabling advanced measurement, targeted therapies, and data-driven treatments, the field has fundamentally transformed how we understand human physiology and deliver patient care.

1. Quantitative Physiology

   Modern biomedical engineering transforms qualitative biological observations into actionable data and predictive mathematical models.

   - Computational Modelling: Biomedical Engineers can develop models to simulate cardiovascular hemodynamics, respiratory mechanics, and neurological pathways.
   - Advanced Biosensors: Wearable and implantable sensors provide real-time, longitudinal data on physiological parameters, allowing for continuous monitoring and diagnostic insights.

2. Precision Medicine

   Biomedical engineers can tailor medical treatments and interventions to the specific molecular and genetic characteristics of each individual patient.

   - Genomics and Diagnostics: High-throughput sequencing technologies and microfluidics enable rapid, cost-effective genetic profiling.
   - Targeted Drug Delivery: Nanotechnology utilizes engineered nanoparticles to transport chemotherapeutics directly to tumour cells, sparing healthy tissue and minimizing side effects.

3. Quality Healthcare Delivery

   Biomedical innovations can increase access to care, improve surgical precision, and enhance patient outcomes across diverse clinical settings.

   - Medical Imaging and Robotics: Innovations in MRI, PET, and robot-assisted surgical systems allow for minimally invasive procedures and pinpoint anatomical accuracy.
   - Telehealth and mHealth: Interoperable connected health platforms and remote patient monitoring tools expand care beyond traditional hospital walls, reducing readmission rates.

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Review

Revisiting Expressed Emotion in Psychiatric Disorders

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ABSTRACT

Background:

Expressed emotion (EE) refers to the emotional climate within a family, encompassing critical comments, hostility, and emotional over-involvement, as well as warmth and positive remarks. First identified in 1958 through relapse patterns among psychiatric patients discharged to different living arrangements, EE was formalised as a measurable construct with Michael Rutter in 1966.

Objective:

To revisit the construct of EE and examine its relevance to the course, relapse risk, and management of psychiatric disorders.

Methods:

This narrative review draws on existing literature on EE across psychiatric conditions, with particular focus on schizophrenia, and examines proposed mechanisms, caregiver burden, and intervention strategies.

Discussion:

EE has been studied most extensively in schizophrenia, but growing evidence links it to outcomes in depression, bipolar disorder, eating disorders, alcohol use disorder, and dementia. The stress-vulnerability model offers a mechanistic explanation, describing how EE interacts with biological vulnerability and life events to influence relapse. The review also considers the paradox of positive over-involvement, the burden EE places on caregivers amid deinstitutionalisation, and the modifiability of EE through psychoeducation, family therapy, and counselling, supported by validated instruments such as the Level of Expressed Emotion Scale and the Family Attitude Scale.

Conclusion:

Involving families in psychiatric management, while attending to caregivers' own well-being, remains central to improving long-term outcomes. Further research into strength-based family interventions is warranted.

KEYWORDS: Expressed emotion; Psychiatric disorders; Relapse; Family intervention; Caregiver burden; Schizophrenia.

INTRODUCTION

In 1958, Brown and colleagues observed that psychiatric patients discharged from hospital to live with parents or spouses relapsed at significantly higher rates than those who returned to siblings or independent living arrangements[1]. This finding, drawn from a series of family-environment studies, gave rise to the concept of "expressed emotion," which was formalised as a measurable index in collaboration with Michael Rutter in 1966[2].

As psychiatric research has advanced, Expressed Emotion (EE) has attracted growing attention for its role in the course and outcome of psychiatric illness[3]. EE refers to the emotional atmosphere within a family i.e. the relational climate that provides (or fails to provide) basic emotional support, comfort, and space for the patient's expression. Cultural and societal norms shape both the expression of these emotions and the impact they have on the patient[2].

The core dimensions of EE include critical comments, hostility, and emotional over-involvement, which together define a high-EE environment. In addition, warmth and positive remarks are assessed during EE evaluation and are generally considered protective factors associated with better clinical outcomes. High levels of criticism, hostility, and emotional over-involvement have consistently been associated with an increased risk of relapse, whereas warmth and positive remarks are associated with improved treatment adherence and recovery[4].

The specific verbal and non-verbal traits caregivers display form the basis for assessing EE using various validated scales[4].

Clinical Significance Across Disorders

EE has been studied most extensively in schizophrenia, but its relevance to major depression, mood disorders, eating disorders, alcoholism, dementia, and other chronic illnesses is now well supported by a growing evidence base[4]. The emotional valence of a patient's environment significantly affects outcomes across these conditions[5]. Among patients with bipolar disorder, EE also predicts symptom severity during both pharmacological and psychosocial treatment[6]. In alcohol use disorder, O'Farrell and colleagues found that relapse was more likely among patients whose family members displayed high EE compared with those in low EE households[7].

Mechanism: The Stress-Vulnerability Model

EE is thought to influence relapse largely through its effect on the patient's emotional state and, in turn, on symptom control. The stress vulnerability model captures this process, incorporating biological vulnerability alongside a cycle of mutual influence between symptomatic behaviour, life events, and EE[8].

The Role of the Family

The family plays a central role in the management of psychiatric illness. Among the many functions a family serves, communication, emotional support, and understanding of the patient's behaviour have the greatest bearing on outcome and relapse risk. Long term prognosis and recovery correlate closely with the quality and intensity of expressed emotion, which is why numerous family intervention programmes have been designed specifically to reduce EE and support full recovery while minimising relapse[9].

A substantial body of evidence links the development, maintenance, and treatment response of many psychiatric illnesses to the quality of family relationships. Negative emotions expressed by family members often stems not from hostility toward the patient but from frustration, the prolonged course of treatment, caregiver burnout, and limited understanding of the illness. In this context, blame for a poor outcome is frequently placed on the patient, framed as wilful avoidance of responsibility rather than as part of the illness itself[8].

The Paradox of Positive Over-Involvement

Excessive positive emotional involvement carries its own risks. It can manifest as over-protectiveness or self-sacrifice, disproportionate praise, and excuse-making that shields the patient from the consequences of their behaviour. Whether this pattern genuinely benefits long-term recovery or, like hostility and criticism, ultimately worsens relapse risk remains an open question. Patients may retreat back into illness as a way of coping with the pressure of being pitied, unable to sustain the disproportionate expectations or protectiveness directed at them. Conversely, recognising a patient's progress and treatment adherence can motivate continued engagement with maintenance treatment and active participation in non-pharmacological care. Unconditional acceptance strengthens the patient's self-respect and confidence[8].

Deinstitutionalisation and Caregiver Burden

As psychiatric care has shifted from institutional settings toward home-based care, families have taken on far greater responsibility for relatives with mental illness. This added burden, compounded by poor cooperation from patients, produces a negative caregiving experience that fuels irritability and frustration and, in turn, heightens EE[10].

Modifiability and Intervention

The most encouraging feature of EE is that it is modifiable. Because it involves environmental and personal factors, it responds well to psychoeducation, family therapy, and

counselling. Key targets for intervention include the stress of caregiving, faulty communication styles, and the development of constructive, healthy coping mechanisms. These interventions have been refined through extensive evaluation of caregivers using instruments such as the Level of Expressed Emotion Scale and the Family Attitude Scale[11-13].

Advances in EE research across diverse psychiatric populations and settings have shaped psychosocial intervention strategies for family caregivers. The various interventions which can be really helpful are psychoeducation for patients and caregivers, crisis management, skills training to tackle various issues, awareness and education about various myths and misconceptions, emotional support, and communication-skills training[9].

Barrowclough and colleagues proposed two competing models of this education:

1. **THE DEFICIT MODEL**, which holds that inadequate knowledge of the illness drives negative behaviour and that disseminating information will foster more positive attitudes and behaviours.
2. **THE INTERACTION MODEL**, which holds that people construct their own explanations of illness, so that professionally provided information will be filtered and possibly rejected according to the person's existing beliefs and perceptions[14].

Key Elements of Family Intervention

Ongoing research on EE has informed family-intervention strategies built around the following priorities:

a) Reducing harsh, wounding communication and frequent critical comments;

b) Avoiding over-involvement, possessiveness, and excessive control over the patient's activities;

c) Setting progressive, realistic goals moving from simple to more demanding targets while maintaining steady, achievable expectations for the patient's recovery, employment, and finances alongside gradual gains in day-to-day functioning and

d) Encouraging caregivers to maintain their own routines, physical and mental health, and social support networks, to guard against burnout and frustration.

CONCLUSION

Family expressed emotion has repeatedly been shown to predict outcome across a range of psychiatric disorders and cultural settings, making it one of the most thoroughly investigated psychosocial constructs in psychiatry. This underscores the importance of involving the family in overall management: educating them about the disease process and non-pharmacological treatment options, and the aspect most often neglected viz. attending to the caregivers' own well-being. Future research should focus on the feasibility and efficacy of strength-based interventions, delivered alongside ongoing psychosocial support at the individual and group level, to help patients and families across psychiatric disorders address the negative emotional climate within the family.

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Review

Anthropometric, Microscopic and Neuroimaging Markers of Somatization in Psychogenic Non-Epileptic Seizures: A Narrative Review

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ABSTRACT

Paroxysmal episodes similar to epileptic seizures are called psychogenic non-epileptic seizures (PNES) however, they do not have a corresponding epileptiform correlate on video electroencephalography (vEEG) which is unarguably the current diagnostic gold standard. PNES are well known to be characterized by psychological distress regarding somatic expression but the biological somatization of PNES remains incompletely defined. This narrative review probes evidences on anthropometric (body mass index and waist circumference), structural/volumetric ("microscopic"), and neuroimaging correlates of somatization in PNES. PubMed, Google Scholar, ScienceDirect and ResearchGate were used to generate literature using series of key terms "psychogenic non-epileptic seizures", "somatization", "anthropometric markers", "microscopic markers" and "neuroimaging markers". Various evidences show that patients with PNES carry more than psychological dysfunction but a disproportionately high burden of obesity similar to epileptic cases. Also, volumetric imaging revealed reduced volume of amygdala, hippocampus and altered uncinate fasciculus microstructure. Although, some findings across structural and functional neuroimaging studies are inconsistent but they converge on the limbic-prefrontal emotion-regulation networks dysfunction rather than a single discrete lesion. vEEG therefore remains indispensable, while anthropometric and neuroimaging findings offer adjunctive, biologically informative but not diagnostic, insight into the somatization construct that underlies PNES.

KEYWORDS: Psychogenic non-epileptic seizures; Somatization; Anthropometry; Amygdala; Neuroimaging; Conversion disorder.

INTRODUCTION

Many conditions similar seizure are very common in emergency departments leading to admission to intensive care units for a neurological complaint[1]. Psychogenic non-epileptic seizures (PNES) are encountered frequently by clinicians as they strongly mimic epileptic seizures due to their sudden, dramatic presentation posing a recurring challenge in diagnosis for emergency physicians, neurologists and psychiatrists in-charge. It is now classified as one of the most common manifestations of functional neurological symptom disorder (FND), popularly known as conversion disorder[2]. However, with the adoption of video electroencephalography (vEEG), clinicians' confidence in diagnosing PNES has improved substantially which allows clinicians to critically differentiate epileptic seizures (ES) from PNES[3].

PNES are neurobehavioral conditions that rely on the convergence between neurology and psychiatry; the DSM-5 classifies them within the conversion (functional neurological symptom) disorders, while the ICD-10 places them among the dissociative disorders. Epidemiologically, the incidence and prevalence of PNES are 1.4 - 4.9 per 100,000 per year and 2 - 33 per 100,000, with a significant proportion of patients carrying a dual diagnosis of epilepsy and PNES[4]. Usually, the onset of PNES occurs during adolescence and early adulthood which disproportionately affects females. This pattern is characterized by the combination of neurobiological, psychosocial and trauma-related vulnerability factors[5].

Jafari et al. (2020) characterized the neurobiological parameters of PNES similar to other literatures, however, less attention has been paid to other classes of biological markers, such as anthropometric indices, structural or volumetric brain correlates, that might further establish the somatization process underlying the PNES disorder[6,7]. This narrative review explores current evidence on anthropometric, structural/volumetric, and neuroimaging correlates of somatization in PNES to collectively examine and consider what the findings further imply about the biology of the disorder.

METHODS

Literature was identified through scientific search engines such as PubMed, Google Scholar, ScienceDirect and ResearchGate. Key terms including "psychogenic non-epileptic seizures" or "PNES", "somatization", "anthropometric markers", "body mass index", "waist circumference", "histopathology", "amygdala", "hippocampus", "magnetic resonance imaging", "diffusion tensor imaging", "functional MRI" and "video electroencephalography" were used to extract literatures. Studies were restricted to English-language publications involving adult patients with PNES diagnosed by clinical assessment or vEEG, with case reports and single-author commentaries excluded; key systematic reviews and meta-analyses were also retained.

RESULTS

Anthropometric Markers of Somatization

One of the most accessible and low-cost indices that might reflect the somatic burden of PNES is body habitus. The study conducted by Marquez et al. compared body mass index (BMI) in 46 patients with PNES and 46 age- and sex-matched patients with epilepsy. This study found significantly higher BMI in the PNES group (30.5 vs 26.1 kg/m², $p = 0.006$) with a difference that persisted after accounting for the weight-promoting effects of antiepileptic drugs[8]. Abubakr and Wambacq's study further supported this finding by reporting that 69.3% of a PNES cohort were overweight or obese, this rate is statistically comparable to the 55.2 - 72% range reported in epilepsy populations and higher than general-population estimates[9]. Because anti-seizure medication and reduced physical activity can significantly contribute to obesity in epilepsy, and because a comparable rate is observed in PNES, these findings corroborate the interpretation that excess adiposity in PNES reflects a more generalized pattern of psychosocial and behavioral dysregulation, comorbid depression, reduced physical activity secondary to disability, psychotropic medication use, and possible hypothalamic-pituitary-adrenal axis dysregulation rather than a direct neurophysiological consequence of seizure activity itself despite the absence of true ictal cortical discharge[8,9].

Studies regarding other anthropometric indices such as waist circumference (WC), waist-hip ratio (WHR), Body mass index (BMI) and skinfold measures in relation to PNES are significantly limited, and existing reports rarely apply standardized anthropometric protocols or population-specific reference ranges. This heterogeneity limits comparison across studies and represents a clear gap for future prospective work.

Structural and Microscopic Correlates

Epileptogenic structural lesions and brain biopsy are usually neither indicated nor ethically justified in these PNES patients. This is why true histopathological data on brain tissue in PNES are essentially very limited. Consequently, "microscopic" evidence in PNES is usually derived indirectly and chiefly by depending on high-resolution volumetric MRI morphometry rather than from basic tissue histology. However, for epilepsy, studies have documented its histological characterization by hippocampal sclerosis, neuronal loss and astrogliosis[6]. Nonetheless, morphometric correlates are obtained from volumetric studies of PNES provided that they plausibly reflect the same limbic circuitry implicated in somatization.

Using a semi-automated segmentation approach, the study by Tatekawa et al. revealed significantly smaller left amygdala and right hippocampus in patients with dissociative seizures than in healthy patients (controls), this is independent of psychiatric comorbidity; however, this difference was not statistically significant. With the ipsilateral structure volume obtained, it is suggestive of atrophy which may reflect broader

network-level change rather than a focal lesion[10]. This finding is consistent with a wider cross-sectional MRI study reporting a significantly higher-than-expected prevalence of structural brain abnormalities in patients with PNES[14]. The study by Hernando et al. using diffusion tensor imaging (DTI) demonstrated a marked rightward asymmetry in uncinate fasciculus connectivity which is the principal white-matter tract linking the amygdalohippocampal complex to the medial prefrontal cortex at the white-matter level in patients with PNES compared with healthy patients (controls)[11]. The study by Lee et al., via complementary tract-based spatial statistics, found increased fractional anisotropy in the left corona radiata, internal and external capsules, superior temporal gyrus and uncinate fasciculus of patients with PNES[12], while more recent neurite-orientation imaging has confirmed that white-matter and neurite microstructure differ between patients with PNES and healthy patients (controls)[13]. These structural findings implicate the amygdala-hippocampal-prefrontal emotion-regulation network as a recurring, if inconsistent, correlate of PNES, rather than pointing to a single discrete or histologically defined lesion.

Neuroimaging Markers

Although individual findings are heterogeneous, neuroimaging studies in PNES have shown structural and functional brain abnormalities affecting sensorimotor, emotion-regulation and executive-control networks in patients with PNES[15]. Altered connectivity between regions implicated in dissociation and emotional dysregulation has been revealed variably by functional MRI studies, including the amygdala, orbitofrontal cortex, anterior cingulate cortex and default-mode network nodes, again supporting a network-based rather than localizationist model of the disorder[6,7]. Despite these advances, there are yet to be structural or functional neuroimaging indices that possess sufficient sensitivity or specificity to be used diagnostically at the individual-patient level; vEEG remains the only tool that directly demonstrates the absence of epileptiform activity during a typical event in PNES[3].

Basal hyper-cortisolism, blunted post-ictal prolactin rise, and altered post-ictal ghrelin and nesfatin levels are non-neuroimaging biomarkers that have also been proposed as adjuncts to differentiate PNES from ES, further illustrating the broader biopsychosocial character of somatization in this disorder rather than a single unifying biological signature[6].

DISCUSSION

This review narrates available evidence that establishes a distributed pattern of dysfunction in PNES. This includes a psychosocial disability plausibly defined by a body habitus skewed toward overweight and obesity and reduced activity rather than a direct neurophysiological effect of seizures[8,9]. Furthermore, the subtle, inconsistent reductions in amygdala and hippocampal volume together with altered uncinate fasciculus and broader white-matter microstructure[10-13] corroborate these findings structurally; while functional connectivity changes within limbic-prefrontal networks governing emotion regulation, interoception and executive control further support this pattern[15]. This pattern is compatible with contemporary biopsychosocial and network-based models of functional neurological disorder, in which symptoms arise from altered communication between limbic, salience and motor-control networks rather than from a discrete structural lesion[2,6]. However, these parameters do not converge on any single reliable biomarker of PNES or of the somatization construct that underlies it.

Due to the limited rate of PNES presentations, there are several limitations recurring across PNES studies which include typically small sample sizes (often fewer than 30 patients per group). Additionally, comparator groups (healthy controls versus patients with epilepsy versus psychiatric controls) vary considerably, while few studies adequately control for psychotropic medication use, comorbid depression, anxiety or post-traumatic stress disorder, or illness duration, all of which can independently influence body composition and brain structure. Most neuroimaging studies involved are predominantly cross-sectional, precluding any causal inference as to whether the observed anthropometric and structural changes precede, accompany, or result from the onset of PNES.

From a clinical standpoint, these findings strongly reinforce rather than displace the central role of vEEG and structured psychiatric assessment in diagnosis. However, anthropometric screening and neuroimaging findings should be regarded as adjunctive contextual information used to potentially characterize the somatic burden of illness and guide multidisciplinary management rather than as stand-alone diagnostic tools.

CONCLUSION

This narrative review confirms that video electro-encephalography remains the gold standard for diagnosis, and comprehensive psychological and behavioral evaluation continues to be the most valuable tool for understanding and managing somatization in PNES. Anthropometric data is critical as a major highlight of disproportionate burden of overweight and obesity among patients with PNES; structural and diffusion imaging point toward subtle limbic and white-matter alterations rather than a discrete lesion; and functional neuroimaging implicates disrupted emotion-regulation networks. No single anthropometric, structural, or neuroimaging marker currently provides definitive diagnostic evidence for psychogenic non-epileptic seizures. Larger, prospective, multicenter studies with standardized anthropometric protocols and harmonized imaging methodology are needed to clarify whether these biological

correlates can ultimately be translated into clinically useful markers.

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Review

Harnessing the Gut-Brain Axis for Neuroprotection: Synergistic Role of Natural Bioactive Products and Microbiota

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ABSTRACT

Diseases causing neurodegeneration, including Alzheimer's disease and Parkinson's disease, encompass several pathological processes such as progressive neuronal damage and increased neuronal loss. Currently, there are limited available therapeutic options capable of halting progression of the disease. The Gut microbiota has emerged as a significant pathway in modulating neuroinflammation, oxidative stress, protein aggregation, neurotransmitter disruption and mitochondrial dysfunction.

Simultaneously, natural products including isoflavones, flavonoids, curcumin, alkaloids and turmeric, alongside gut metabolites, have demonstrated great neuroprotective effects through antioxidative and anti-inflammatory mechanisms. This review examines the synergistic interactions between gut microbiota and bioactive compounds in modulating pathways associated with neurodegeneration. Synergy between gut metabolites and bioactives collectively enhances intestinal barrier integrity, regulates immune responses, reduces oxidative damage, and preserves mitochondrial function and influences neurotransmitter synthesis and neuronal signaling. Integrating the gut microbiota with bioactive supplementation of provides a multifaceted intervention for neurodegenerative diseases.

KEYWORDS: Neurodegenerative diseases; Gut microbiota; Bioactive; Neuroprotection.

Overview of Neurodegenerative Diseases

Neurodegenerative diseases, including Alzheimer's disease (AD), Parkinson's disease (PD), Amyotrophic Lateral Sclerosis (ALS) and Multiple Sclerosis (MS), are characterized by the irreversible loss of cholinergic neurons, abnormal protein folding, and synaptic impairment leading to progressive cognitive or memory loss[1,2]. Several studies have investigated neurodegenerative diseases at the molecular level; however, the cellular basis underlying disease progression is yet to be fully understood. This has been a major concern in the development of effective therapeutics for these diseases. Neurodegenerative diseases share common threads that underpin their pathophysiology, including protein misfolding and aggregation, chronic neuroinflammation

and mitochondrial dysfunction, indicating common underlying vulnerabilities[3,4].

The societal impact of neurodegenerative diseases is staggering and rapidly growing, with an estimated 55 million individuals currently affected, which will almost triple by 2050 due to demographic changes[5]. According to statistics, the average prevalence of Parkinson's disease was projected to be 275 cases per 100 000 individuals in 2050; this suggests a marked increase of 56% to 120% from 2021[6].

The economic burden is commensurate with this figure, and the cost of dementia exceeds $1.3 trillion, with a burden predominantly borne by informal carers[7]. This is reflected in the Disability-Adjusted Life Years (DALYs), thus requiring a radical shift that will provide a solution[8]. Management of neurodegenerative diseases poses challenges in the global health and research sectors due to the symptomatic effects of the currently available therapeutic agents rather than the pathogenic effects and adverse effects in the body[9].

The Gut-Brain Axis

In recent times, neuroscience research has identified the gut–brain axis as a bidirectional communication providing key mechanistic pathways into neurodegenerative diseases[10]. It integrates enteric nervous system signaling, vagal signals, immune pathways, and microbial metabolites[11,12]. Germ-free models underscore the importance of the gut microbiota on brain development and function, revolutionizing understanding of this complex crosstalk. The intriguing aspect is that the convergence of protein misfolding, neuro-inflammation, and oxidative stress in neurodegenerative diseases could be modulated by signals originating within the gastrointestinal tract. This paradigm shift reveals the profound influence of the gut–brain axis on neurological health. Dietary interventions, primarily natural bioactive compounds and their interactions with gut microbiota, promise as an exciting new paradigm for multifaceted neuroprotection[13].

Major Neural Pathways involved in Gut-Brain Axis

The gut-brain axis orchestrates a complex bidirectional interaction between the gastrointestinal tract and the central nervous system. The intricate dialogue hinges on several major pathways, each contributing to the brain's evaluation of gut condition[14]. This 'information superhighway' conveys information on microbial composition, metabolite concentrations, immune status and mechanical stimuli, and this information acts upon critical regions in the brain responsible for mood, emotion and cognition[15]. Vagus nerve stimulation (VNS) exemplifies its mechanism as modulating neuroplasticity and mitigating neuroinflammation[16]. The enteric nervous system (ENS) is a vast, semi-autonomous network of neurons embedded within the gut wall that intricately communicates with the brain via the vagus nerve, thereby facilitating bidirectional link and translating microbial signals into neurological impacts[17]. This supports the idea that gut dysbiosis can hinder neurodevelopment, thus precipitating neurological disorders[18].

Intestinal Barrier Integrity

Integrity of the intestinal barrier is essential as it separates luminal microbes from the host's internal milieu. An interrupted gut barrier disrupts the gut-brain axis, thereby causing systemic neuroinflammation. The single-layer epithelium of the gut, supported by tight junctions, forms an important barrier of protein complexes (occludin, claudin-1 and Z0-1) close to the paracellular space, which prevents uncontrolled migration of microbial antigens and toxins into circulation[19,20]. Short-chain fatty acids (SCFAs) like butyrate and valerate play a key role in upholding TJ integrity; depletion of them as a result of dysbiosis precipitates a 'leaky gut'[21]. Gut dysbiosis compromises BBB integrity, facilitating infiltration of peripheral inflammatory mediators and microbial products into the CNS (Beltran-Velasco and Clemente-Suárez). This failure is compounded by activation of HPA axis, especially under stress, creating a vicious cycle between inflammation and barrier failure[22]. On the other hand, SCFAs, notably butyrate, strengthen BBB integrity by controlling endothelial tight junctions and components of neurovascular units.

The bacteria within the gut release gut metabolites and communicate them to the brain via the vagus nerve to facilitate a bidirectional interaction and translate microbial signals into neurological effects.

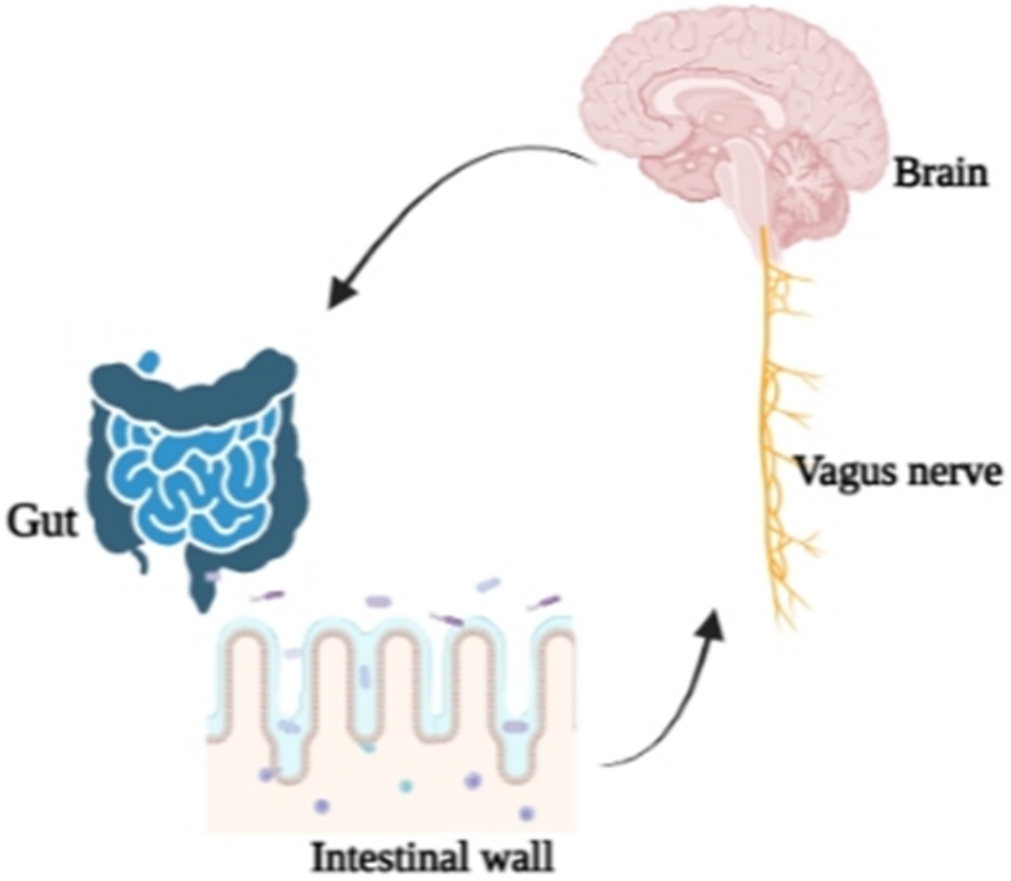


Figure 1: The Gut-Brain Axis

Microbial Metabolites

Metabolic processes of the gut microbiota have profound influence on the host physiology and brain function. Short-chain fatty acids (SCFAs), including butyrate, propionate and acetic acids from bacterial fermentation of dietary fiber, support the integrity of the intestinal barrier. They exert anti-inflammatory effects, cross the blood-brain barrier (BBB) and help in the development of microglia and neurons[11]. Enteroendocrine cells, stimulated by microbial presence, release neuroactive molecules like GLP-1, PYY and 5-HT (serotonin); the latter are mostly produced in the gut and impact mood and cognition[23].

Table 1: Major Microbial Metabolites relevant to Bioactive Products

Class of Metabolite	Metabolites	Key Producing Bacteria	Dietary Precursors	Biological Effects
Short-chain fatty acids (SCFAs)[24]	Acetate, propionate, butyrate	*Faecalibacterium prausnitzii, Roseburia spp., Eubacterium rectale, Bacteroides spp., Akkermansia muciniphila*	Dietary fiber, resistant starch, non-digestible oligosaccharides	Source of energy for colonocyte (butyrate); HDAC inhibition; GPR41/43 signaling; anti-inflammatory; gut barrier reinforcement; satiety hormone (GLP-1, PYY) induction
Secondary bile acids[25]	Deoxycholic acid (DCA), lithocholic acid (LCA)	*Clostridium scindens, Eggerthella lenta, Bacteroides spp.*	Primary bile acids (cholic acid, chenodeoxycholic acid) from liver	FXR/TGR5 receptor activation; glucose/ lipid metabolism regulation; antimicrobial activity; implicated in colorectal carcinogenesis at high levels
Tryptophan-derived metabolites[26]	Indole, indole-3-acetic acid (IAA), indole-3-propionic acid (IPA), skatole	*Lactobacillus spp., Clostridium sporogenes, E. coli, Bacteroides spp.*	Dietary tryptophan	Aryl hydrocarbon receptor (AhR) agonism; gut barrier integrity; antioxidant activity; neuroprotection (IPA); immune modulation
Trimethylamine (TMA)/TMAO Pathway[26]	Trimethylamine (TMA), trimethylamine -N-oxide (TMAO, host-derived)	*Clostridium spp., Anaerococcus spp., Escherichia spp.*	Choline, carnitine, betaine (from red meat, eggs, fish)	TMA oxidized in liver to TMAO; associated with atherosclerosis, cardiovascular risk, platelet hyperreactivity
Polyamines[24]	Putrescine, spermidine, spermine	*Bacteroides spp., Fusobacterium spp., Campylobacter spp.*	Arginine, ornithine	Cell proliferation; mucosal growth/repair; autophagy induction (spermidine); longevity-associated pathways
Vitamins (microbial synthesis)[27]	Vitamin K2 (menaquinone), B12, folate, biotin	*Bacteroides fragilis, E. coli, Lactobacillus spp., Bifidobacterium spp.*	Endogenous synthesis (not diet-dependent)	Coagulation cofactor (K2); one-carbon metabolism; energy metabolism; host micronutrient supplementation

Continued ...

Polyphenol-derived metabolites[28]	Urolithins (A, B), equol, enterolactone, enterodiol	*Gordonibacter spp., Eggerthella lenta, Slackia spp.*	Ellagitannins (pomegranate, berries), lignans, isoflavones (soy)	Antioxidant; anti-inflammatory; mitophagy induction (urolithin A); estrogen-receptor modulation (equol); cardioprotective
Branched-chain fatty acids (BCFAs)[29]	Isobutyrate, isovalerate, 2-methylbutyrate	*Bacteroides spp., Clostridium spp.*	Branched-chain amino acids (valine, leucine, isoleucine)	Minor energy source; gut barrier modulation; biomarkers of proteolytic fermentation
Hydrogen sulfide (H2S)[24]	H2S	*Sulfate-reducing bacteria (Desulfovibrio spp.), Bilophila wadsworthia*	Sulfated amino acids (cysteine, taurine), dietary sulfate	Dual role: signaling molecule at low levels (vasodilation, anti-inflammatory); genotoxic/ pro-inflammatory at high levels
Lipopolysaccharide (LPS)[27]	Endotoxin	*Gram-negative bacteria (Bacteroides, Enterobacteriaceae)*	Bacterial cell wall component	TLR4 activation; low-grade metabolic endotoxemia; linked to insulin resistance and systemic inflammation

Role of Microbial Regulation in Activation of Microglia

The gut microbiota influences the CNS immune cells, notably microglia. Germ-free model studies show that microbial signals are vital for microglial development and maintaining their homeostatic protective neural function[11]. In Alzheimer's disease, gut dysbiosis is implicated in triggering chronic neuroinflammation through microglial dysfunction, thus exacerbating pathology[16]. Likewise, in Parkinson's disease, gut-derived inflammatory signals contribute to microglial activation and neuroinflammation that may trigger or accelerate alpha-synuclein pathology[30].

Microbiota Alterations across Neurodegenerative Diseases

Gut alterations or dysbiosis have been linked to the progression of Neurodegenerative diseases. These diseases have specific gut dysbiosis signatures. Parkinson's disease consistently showed reduced SCFA-producing Faecalibacterium and Roseburia, as well as increased Akkermansia, Ruminococcus and Lactobacillus. Alzheimer's disease has been linked to heterogeneous and increased levels of Erysipelato-clostridiaceae, Erysipelotrichales and Saccharimonadales, which are associated with the APOE gene carrier expressed in the disease, thereby causing more deteriorative dementia management[31].

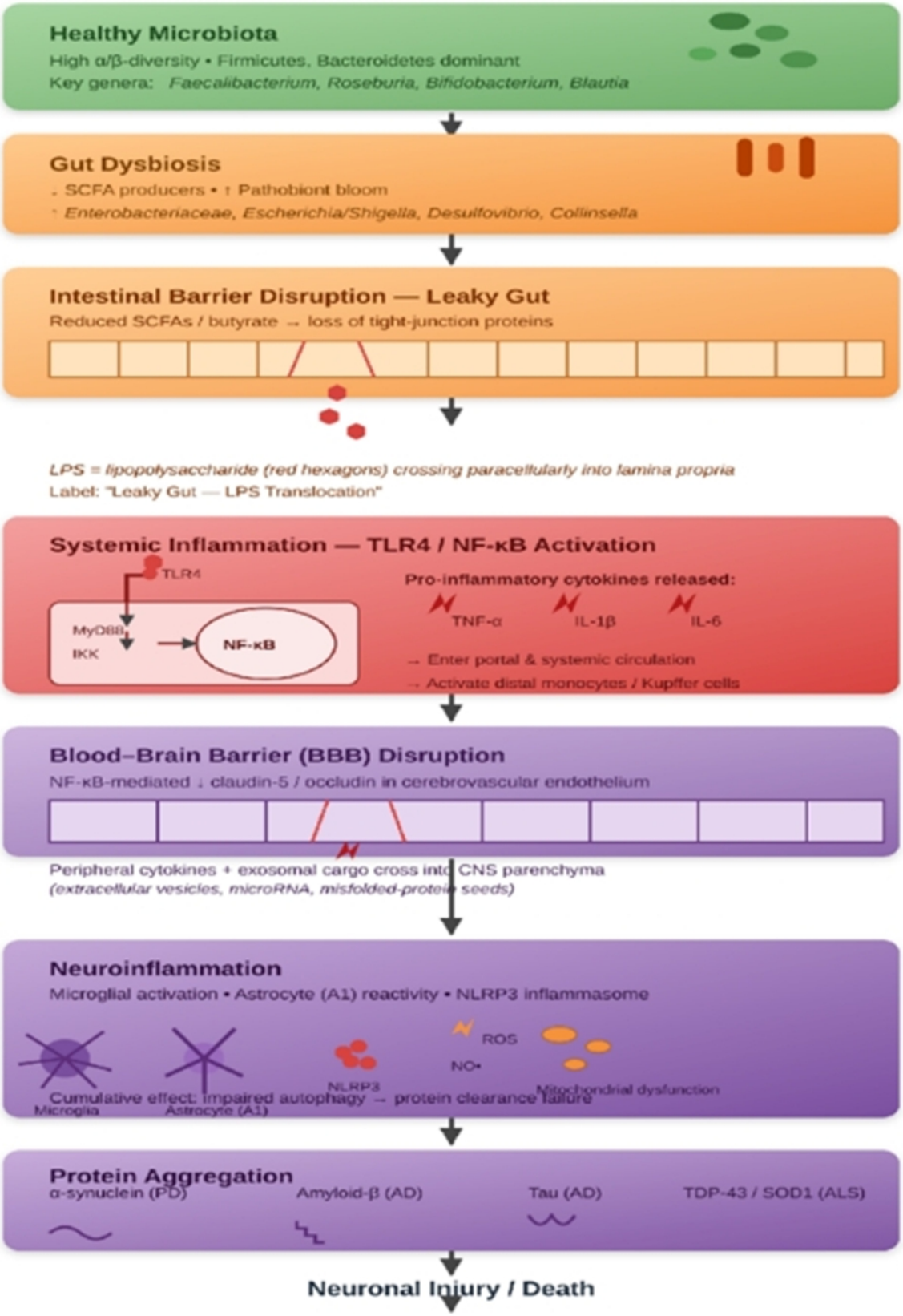


Figure 2: Schematic illustration of Microbiota Alterations in Neurodegenerative Diseases

Natural Bioactive Compounds: Promising Intervention for Neuroprotection

Natural bioactive compounds are emerging in the management of neurodegenerative diseases and are documented for their connections to neuroprotective mechanisms. These act through oxidative stress mitigation, mitochondrial guarding, neurotrophin support, anti-inflammatory tuning, blood-brain barrier reinforcement, and gut microbial biotransformation[32]. Key representatives include isoflavones from soyabeans and red-clover, polyphenols from grapes, teas and berries, Curcuminoids from turmeric, omega-3s (DHA, EPA) from fatty fish and algae, alkaloids like berberine and piperine, terpenoids such as ginkgolides and ursolic acid, SCFA precursors (inulin, resistant starch) from chicory and oats, carotenoids (astaxanthin, luteins); glucosinolate-derived isothiocyanates from broccoli, and lignans from flaxseed[32-34].

Isoflavones

The gut microbiota metabolizes Isoflavones (genistein, daidzein, puerarin) to form bioactive derivatives that can more efficiently cross the BBB than parent compounds. A study demonstrates that an isoflavone-enriched diet ameliorates Parkinson's disease in mice by inhibiting ferroptosis via gut microbiota mediating serotonin production. Daidzein and Puerarin were reported to exhibit neuroprotective effects against MPTP-induced Parkinson's pathology and microglial activation[35].

Polyphenols

Bidirectional communication between the gut and microbiota is enhanced by polyphenols; their bioavailability results from bacterial metabolism and concurrently augments important benefits and stifles pathogens. According to reports, polyphenols improved the composition of gut microbes and reduced neuroinflammation across animal models of Alzheimer's, Parkinson's and multiple sclerosis by reducing amyloid deposition and tau hyperphosphorylation in the brain. They exert their effect through antioxidative, anti-inflammatory and MAPK-pathway modulation[36].

Flavonoids

Flavonoids such as quercetin, EGCG, kaempferol and naringenin modify the gut-brain axis by promoting SCFA- and GABA-producing bacteria as well as correcting dysbiosis associated with neurodegeneration. Quercetin and kaempferol collectively restored the balance of gut microbiota and attenuated multi-pathogenic mechanisms in Parkinson's disease models. Quercetin particularly reconfigured gut microbiota composition and adjusted brain metabolic profiles to curtail depression-like behavior. Flavonoids act through bitter-taste receptor (TAS2R) activation, thereby linking the gut hormone to reducing Alzheimer's incidence[37].

Curcuminoids

Curcumin, and related curcuminoids (demethoxycurcumin, bisdemethoxycurcumin) from turmeric modulate gut microbiota bidirectionally. Bacteria biotransform curcumin into more bioavailable metabolites, while curcumin in turn adjusts microbiota taxa. Curcumin restored short-chain fatty acid profiles in a study of 1-methyl- 4-phenyl- 1,2,3,6-tetrahydropyridine (MPTP) induced Parkinson's mice, mitigated dopaminergic neuron losses, and repaired intestinal barrier dysfunction[38]. In APP/PS1 Alzheimer's mice, curcumin also altered Bacteroidaceae, Prevotellaceae, and Lactobacillaceae abundance, ameliorated spatial memory and curtailed hippocampal amyloid plaques[39].

Alkaloids

Despite the low absorption of alkaloids such as berberine in the gut, they possess significant effects in the GBA. In Parkinson's models, orally ingested berberine improved brain dopa/dopamine levels by modulating gut microbiota[40]. It also inhibited α-synuclein aggregation, thus preventing Lewy body formation. In Alzheimer's models, berberine reduced tau hyperphosphorylation and amyloid-β deposition while restoring gut barrier integrity and microglial M1/M2 polarization balance[41].

Bioavailability Challenges of Natural Products and Gut-Mediated Bioactivation

The bioavailability challenges of natural products are linked to poor solubility, rapid metabolism and excretion, incomplete gut retention and poor stability, thus resulting in limited systemic exposure. The gut microbiota drive reactions such as hydrolysis, reduction, demethylation, and ring fission of parent compounds to form more absorbable bioactive compounds, thus greatly influencing the availability of natural products[42]. These challenges pose significant individual variability depending on initial microbiota composition, diet, medications, and dysbiosis[43].

Microbiota-Bioactive Synergy in Neuroprotection

Despite the pharmacological properties of bioactive products, their modulation against neurodegeneration depends strongly on interaction with the gut microbiota. This two-way dialogue orchestrates metabolite generation, barrier function, neuroimmune signaling and microglial behavior, ultimately modulating the trajectory of neurodegenerative and cerebrovascular diseases[44,45]. Actively sculpting microbial ecosystems favors beneficial microbes such as Bifidobacterium, Lactobacillus, Akkermansia, and Faecalibacterium, while suppressing pro-inflammatory invasion. These bioactives enhance production of SCFAs, reduce lipopolysaccharide (LPS)-producing pathogens, lower

endotoxemia, and dampen gut-brain-inflammatory signaling[45,46]. SFAs, including acetate, propionate and butyrate that are generated during fermentation of fiber, and polyphenol-rich substrates also function as primary regulators of bioactives and microbiota synergy. They mature microglia, reinforce BBB, and suppress excessive inflammation. Polyphenol consumption amplifies SCFA output, linking dietary patterns to neurological resilience[47].

Challenges, Future Directions and Therapeutic Opportunities

Persistent problems, including poor bioavailability, short durations, heterogeneity, mismatched endpoints and failure to measure microbiota interaction, pose major challenges to the efficacy of synergy between bioactive products and microbiota[48,49]. Most research continues to approach bioactives or microbes separately; individual gut microbiota composition represents a major hurdle in the management of Alzheimer's disease. Rather than uniform doses, there is a shift toward precision approaches that see the individual microbiota as a therapeutic variable. Preclinical efforts show that responses to polyphenols vary significantly depending on host genetics, such as APOE status[50]. The bench-to-bed gap still poses challenges to the feasibility of exploring natural products and gut microbes in the management of neurodegenerative diseases. Solving the research-to-translation gap is one of the most persistent research challenges of neuroscience concerning neurodegeneration. Promising compounds with strong preclinical profiles often have disappointing applications in translation research, as translation requires significant precision in dosing, timing, formulation, and patient stratification[51].

Microbiota-Sequencing and Precision Medicine

Advances in multi-omics and deep sequencing allow microbiota profiling in routine clinical practice. Integration of metagenomics, metabolomics, dietary and clinical data provides predictions of a microbiota signature linked to amyloid pathology, microglial activation and SCFA/LPS dynamics. It allows for targeted selection of polyphenols based on an individual's metabolic capacity to generate neuroprotective metabolites[52-54]. Also, the exploration of machine learning models is accelerating and considerably reducing the challenges of bioactive-gut interaction. Neural networks have achieved AUCs of 0.89 in predicting cognitive impairment from microbiome patterns, paving the way for early and mechanism-based dosing of bioactives. AI-driven multi-omics integration is moving the science from associations to causation and actionable insights, while standardized analytical pipelines remain required to ensure reproducibility[53,55,56].

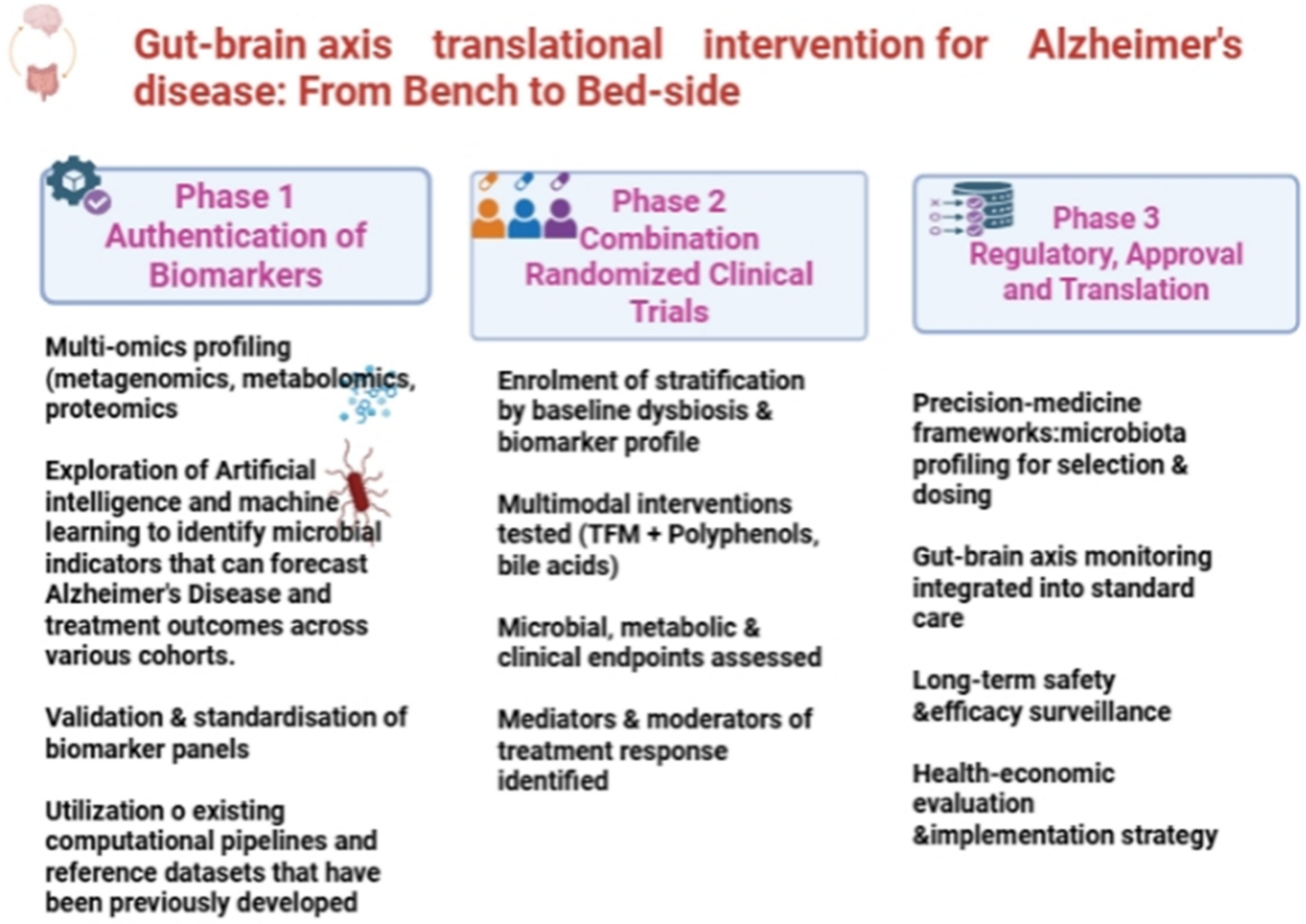


Figure 3: Road-map of Gut-brain Axis to Translational Medicine

CONCLUSION

The microbiota-bioactive axis opens a promising area of research for next-generation neuroprotective therapeutic agents, and future clinical trials must prioritize early-stage, biomarker-stratified trials with advanced formulations, extended durations, and multi-omic biomarkers to close this long-standing gap. Future strategies must consider multi-omics (metagenomics, metabolomics) and address individual microbiota variability to permit personalized approaches.

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Review

Air Pollution, The Nrf2-Ferroptosis Axis, and Neonatal Seizure Susceptibility

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ABSTRACT

Neonatal seizures remain a leading cause of acute neurological morbidity in the newborn period, yet a substantial proportion of cases have no identified structural, infective, or metabolic cause. Air pollution, particularly fine particulate matter of 2.5 micrometers or less in diameter (PM2.5), has recently been implicated as a modifiable environmental contributor to seizure risk across the lifespan, with proposed mechanisms centered on oxidative stress, disrupted iron handling, and regulated cell death. Two convergent bodies of evidence are reviewed here: first, epidemiological and mechanistic work linking PM2.5 exposure to seizure exacerbation through impaired nuclear factor erythroid 2-related factor 2 (Nrf2) signaling; and second, the emerging role of ferroptosis, an iron-dependent form of lipid peroxidation-driven cell death, as a downstream effector of this impairment in hippocampal neurons. Because the fetal and neonatal antioxidant system is developmentally immature and iron handling in the perinatal brain is already in flux, this axis may confer disproportionate vulnerability during gestation and the immediate postnatal period, a population in which direct mechanistic data are still lacking. This review synthesises the current evidence, outlines a plausible developmental extension of the Nrf2-ferroptosis hypothesis to neonatal epileptogenesis, and proposes a research agenda to close the gap between adult mechanistic data and perinatal clinical relevance.

KEYWORDS: Neonatal Seizures, Nrf2, Ferroptosis, PM2.5, Air Pollution.

INTRODUCTION

Seizures occurring in the first 28 days of life are a distinct clinical entity from later-onset epilepsy, both electroclinically and mechanistically, and they carry a disproportionate burden of long-term neurodevelopmental sequelae[1]. Established causes include hypoxic-ischaemic encephalopathy, intracranial haemorrhage, infection, and inborn errors of metabolism, but a meaningful fraction of neonatal seizures still occurs without a clearly identified precipitant. Over the past several years, environmental epidemiology has begun to reframe air pollution, and fine particulate matter (PM2.5) in particular, as a plausible and modifiable contributor to seizure risk, largely on the basis of adult and paediatric cohort data[2,3].

What has been missing until quite recently is a coherent cellular mechanism connecting inhaled particulate exposure to an altered seizure threshold. Two strands of laboratory work, one on the transcription factor Nrf2 and its role as the master regulator of the cellular antioxidant response, and the other on ferroptosis as an iron-dependent mode of neuronal death, have now been drawn together into a single explanatory framework[1,4]. This review outlines that framework, then asks a question the existing literature has not yet addressed directly: whether the same pathway operating in the mature or aging brain might also operate, and plausibly with greater consequence, in the developing brain during gestation and the neonatal period.

PM2.5 and the Seizure Threshold: What the Epidemiological Evidence Shows

A scoping review of thirty-four epidemiological studies found consistent, if heterogeneous, associations between short-term increases in ambient air pollution and both new-onset seizures and acute exacerbations in people with established epilepsy, alongside a smaller but growing literature on ambient temperature as an independent trigger[2]. A separate narrative review has argued that epilepsy has received comparatively little attention within the air pollution and brain health literature relative to stroke and neurodegenerative disease, despite biologically plausible pathways through inflammation, oxidative stress, and disrupted neurodevelopment, and despite evidence that prenatal exposure to diesel particulates, carbon black nanoparticles, methylmercury, and dioxin-like compounds interferes with the normal maturation of fast-spiking parvalbumin-positive interneurons, a cell population whose loss is mechanistically tied to network hyperexcitability[3]. A time-series analysis of hospital seizure presentations against local pollutant and meteorological data reached similar conclusions, reporting associations between particulate and gaseous pollutant levels and short-term fluctuations in seizure-related admissions[5].

Nrf2: The Cell's Oxidative Stress Sensor

Nrf2 is a transcription factor that, under basal conditions, is held in the cytoplasm by its repressor Keap1 and targeted for degradation. Oxidative or electrophilic stress disrupts this interaction, allowing Nrf2 to translocate to the nucleus and drive transcription of antioxidant and cytoprotective genes through the antioxidant response element, including glutathione peroxidase 4 (GPX4), the cystine-glutamate antiporter subunit SLC7A11, and heme oxygenase-1 (HO-1)[1,4]. In the context of epilepsy, reduced expression of components of the Nrf2 pathway has been documented in temporal lobe epilepsy and after traumatic brain injury, while pharmacological activation of Nrf2 has been shown to reduce seizure severity, limit microglial activation, and preserve learning and memory in animal models[1].

The relevance to air pollution is that Nrf2 activation is itself triggered by PM2.5 exposure, positioning the pathway as a point of convergence between an external environmental insult and an endogenous disease process. Transcriptomic comparisons between individuals exposed to high ambient PM2.5 and those with newly diagnosed epilepsy have shown overlapping changes in Nrf2 pathway components, suggesting the two conditions may perturb a shared molecular substrate rather than acting through entirely separate mechanisms[1]. Critically, the direction of that perturbation appears to matter: acute or adaptive Nrf2 activation is protective, but chronic or overwhelming particulate exposure has instead been associated with suppression of Nrf2 pathway proteins, tipping the balance toward injury rather than defence[1].

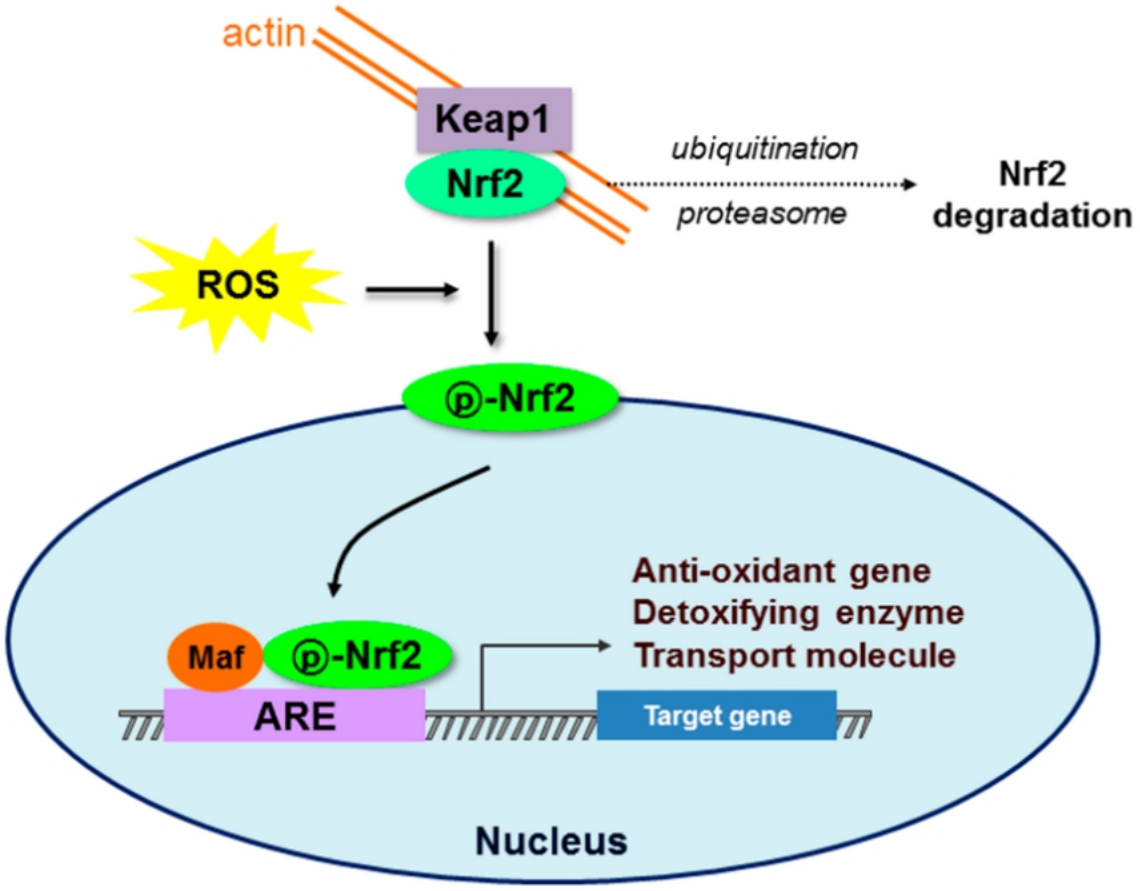


Figure 1: The Nrf2-Keap1-ARE Antioxidant Signaling Pathway under Normal Conditions

Under normal conditions, nuclear erythroid-2 like factor-2 (Nrf2) is constantly ubiquitinated through Kelch-like ECH-associated protein1 (Keap1) and degraded in the proteasome. After exposure to oxidative stress (ROS), Keap1 is inactivated and Nrf2 becomes phosphorylated. Phosphorylated Nrf2 (p-Nrf2) accumulates in the nucleus and binds to antioxidant response element (ARE) sites, subsequently activating many genes including antioxidants, detoxifying enzymes, and transport molecules.

[Adapted from Oh and Jun[10]]

Ferroptosis as the Downstream Effector

Ferroptosis is a form of regulated cell death driven by iron-catalysed lipid peroxidation, distinct from apoptosis or necrosis, and dependent on the balance between pro-oxidant iron flux and the antioxidant capacity of the GPX4-glutathione system[4]. Because Nrf2 transcriptionally regulates several nodes of this system, including GPX4, SLC7A11, and proteins governing cellular iron storage and export, loss of Nrf2 activity removes a key brake on ferroptotic vulnerability[4].

Direct evidence that PM2.5 induces ferroptosis in neural tissue has accumulated rapidly. In murine hippocampal HT22 cells, PM2.5 exposure increased intracellular iron content and lipid peroxidation while disturbing the expression of iron-handling genes, with the resulting neurotoxicity partially reversible by ferroptosis inhibitors[6]. In a combined clinical and animal study, patients with seizures living in areas of high ambient PM2.5 showed greater disturbance of iron homeostasis and the Nrf2-dependent ferroptosis pathway than those in less polluted areas, and PM2.5-exposed epileptic mice showed worsened seizure severity and cognitive performance on the Morris water maze alongside electroencephalographic and histological evidence of hippocampal ferroptosis[7]. A broader review of pollutant-induced ferroptosis situates these hippocampal findings within a wider pattern in which PM2.5 drives ferroptotic injury across multiple organ systems through convergent disruption of the Nrf2-SLC7A11-GPX4 axis[4].

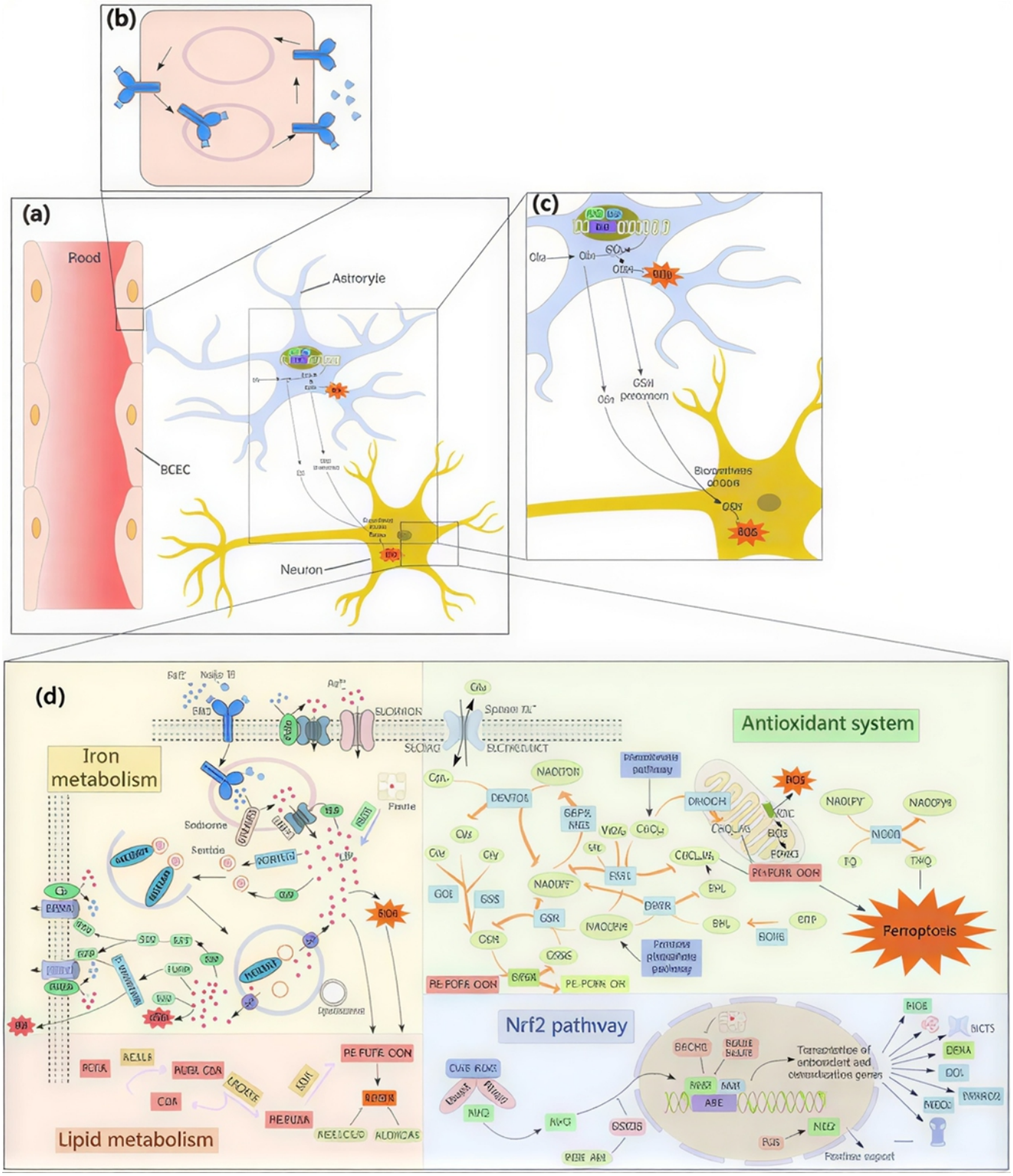


Figure 2: Regulation of Iron Homeostasis and Ferroptosis by Nrf2 in the Context of Neurodegenerative Diseases

(a) Neurogliovascular unit (BMECs, astrocytes and neurons) are the main players of iron transport across the BBB. The brain parenchyma iron homeostasis is maintained through astrocyte-mediated uptake and neuronal delivery, and the limiting of the harmful effects of the excess iron by astrocytes.

(b) Iron in the circulation is bound by Tfs and reaches BMECs via Tf/TfR1. Iron is delivered to parenchyma by endocytosis.

(c) Through the generation of antioxidant molecules, mainly the supply of glutathione (GSH) precursors, activation of antioxidant defenses by Nrf2 in astrocytes leads to neuronal protection against oxidative stress.

(d) The iron uptake through Tf-TfR1 system and the consequent reduction of Fe^{3+} to Fe^{2+} in neurons contributes to the formation of the labile pool of iron. This pool is mainly under the control of ferritin, NCOA4-ferritinophagy, and FPN1-export of iron. Increased ROS and PUFA peroxidation by an excessive Fe^{2+} lead to ferroptosis. ACSL4, LPCAT3 and the lipoxygenases are among the lipid peroxidation enhancers responsible for driving ferroptosis while GSH, GPX4, FSP1, CoQ10, DHODH, CoQ10H and GCH1, BH4 pathways counteract ferroptosis. Nrf2 dependent antioxidant and cytoprotective genes are triggered by the Keap1, Nrf2, ARE pathway under oxidative stress conditions, thereby limiting the iron-induced oxidative damage and ferroptosis.

[Adapted from Xiang et al.[11]]

Extending the Model to the Perinatal and Neonatal Period

None of the mechanistic studies cited above were conducted in neonatal or fetal tissue, and this is the central gap this review seeks to make explicit rather than to paper over. Several lines of indirect evidence nonetheless make a perinatal extension of the Nrf2-ferroptosis hypothesis plausible, and arguably urgent. First, PM2.5 and its carbon-based components are able to cross the placental barrier and have been detected directly on the fetal side of the human placenta, establishing a physical route of exposure during gestation rather than a purely maternal one[8]. Second, gestational PM2.5 exposure in rodent models produces hippocampal neurodevelopmental impairment in offspring, including reduced neurogenesis, increased apoptotic markers, and elevated neuroinflammatory signaling, changes that overlap substantially with the injury pattern described in ferroptosis-mediated models[9]. Third, the fetal and neonatal antioxidant system, including glutathione synthesis capacity and Nrf2-responsive gene expression, is developmentally immature relative to the adult system, which would be expected to lower the exposure threshold at which pro-oxidant insults overwhelm cytoprotective capacity.

Iron handling in the perinatal brain adds a further layer of plausibility. The third trimester and early postnatal period are characterised by active iron accretion to support myelination and oxidative metabolism, meaning that regional iron availability in the neonatal brain is, if anything, higher relative to antioxidant buffering capacity than in the mature brain. A pathway whose central toxic mechanism is iron-catalysed lipid peroxidation would be expected to find fertile ground under these conditions. Several of the exposures already linked to disrupted interneuron development and network hyperexcitability, including diesel particulates and other combustion-derived pollutants, are also established inducers of the Nrf2-ferroptosis cascade in non-neural tissue, raising the possibility that interneuronopathy and ferroptotic injury are not competing explanations for pollutant-associated seizure risk but two visible faces of the same underlying redox failure[3].

Sex-dependent susceptibility is a further recurring theme worth carrying into any neonatal-focused review. Male fetuses tend to accumulate higher body burdens of several persistent pollutant classes, and gestational PM2.5 exposure produces sex-divergent glial and cognitive outcomes in animal models, with male offspring more often showing microglial dysfunction and female offspring showing transient astroglial reactivity[9]. Whether this pattern holds for ferroptotic markers specifically in the neonatal hippocampus has not, to our knowledge, been tested.

Gaps in the Evidence and a Proposed Research Agenda

Three gaps stand out as priorities for future work. The first is direct mechanistic confirmation: no published study has yet measured Nrf2 pathway activity or ferroptotic markers, such as tissue GPX4, SLC7A11, malondialdehyde, or labile iron, in fetal or neonatal brain tissue following gestational or early postnatal PM2.5 exposure, in either animal models or archived human material. The second is temporal specificity: because Nrf2 activation is protective at physiological levels of stress and only becomes pathological under sustained or high-dose exposure, dose-response and timing studies are needed to establish whether typical ambient exposure in high-pollution settings, as opposed to experimentally concentrated PM2.5, is sufficient to tip the balance toward ferroptotic injury in the developing brain. The third is translational relevance to regions with the highest ambient PM2.5 burden and the least epidemiological surveillance of neonatal seizure outcomes, where household and ambient particulate exposure, heavy-metal co-exposure, and limited access to continuous EEG monitoring may combine to produce a population at particularly high and currently invisible risk.

CONCLUSION

The Nrf2-ferroptosis axis offers one of the more mechanistically coherent explanations to have emerged for how an entirely modifiable environmental exposure, fine particulate air pollution, might lower the seizure threshold in the brain. The evidence base for this pathway is currently strongest in adult and juvenile animal models and in epidemiological data drawn from established epilepsy populations. Extending it to the neonatal period rests, for now, on developmental plausibility rather than direct proof: an immature antioxidant system, an active perinatal iron pool, a documented ability of particulate matter to cross the placenta, and overlapping injury patterns in gestationally exposed rodent hippocampus. Testing this extension directly, in fetal and neonatal tissue and in populations with high ambient exposure, is a tractable and clinically important next step for research into the environmental contributors to neonatal seizures.

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Review

The Bear Fable: A Narrative Psychoeducation Tool for Dissociative and Conversion Disorders

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ABSTRACT

Dissociative and conversion disorders are frequently complicated by skepticism from families and caregivers, which can impede treatment engagement. Conventional psychoeducation often fails by inadvertently suggesting volitional control or fabrication. This paper describes a simple, narrative-based psychoeducational tool, the "Bear Fable" used in outpatient psychiatric practice to reframe such symptoms as involuntary, survival-oriented responses. By combining metaphor, humour, and non-confrontational reframing, this approach reduces defensiveness, validates patient experience, and facilitates therapeutic alliance. Its low resource, culturally adaptable nature makes it particularly suitable for primary care and resource limited settings. Preliminary clinical observations suggest improved family acceptance and earlier disclosure of psychosocial stressors. Formal evaluation is warranted.

KEYWORDS: Conversion Disorder; Dissociative Disorders; Functional Neurological Disorder; Psychoeducation; Narrative Therapy; Tonic Immobility.

INTRODUCTION

Dissociative and conversion disorders (functional neurological symptom disorders) remain among the most clinically challenging presentations in psychiatry, not because of diagnostic complexity alone, but because of the profound disbelief and frustration they routinely generate among families, caregivers, and wider social networks[1]. Understanding and management of dissociative disorders have long been hindered by polarized conceptualizations: either symptoms reflect genuine, involuntary neurobiological phenomena, or they represent socially constructed, malingered, or hysterical performances[2]. This rigid either/or framing fails clinician and patient alike at the bedside, where what is critically needed is psychoeducation that validates the patient's subjective distress while simultaneously opening a viable therapeutic pathway[2,3].

Standard clinical approaches that emphasize the "functional," "psychogenic," or "unconscious" nature of symptoms frequently misfire[3,4]. To families unfamiliar with somatic manifestations of psychological distress, such terminology often implies volitional deception or secondary gain, inadvertently reinforcing suspicions that the patient is exaggerating or manufacturing their disability[3]. Clinicians are widely advised not to confront or challenge the patient on the reality of the symptom; while investigations reveal no structural organic lesion, the

functional impairment and distress are entirely genuine. When families interpret normal diagnostic workups as evidence of fabrication, the resulting invalidation exacerbates the patient's baseline distress, often worsening somatic symptoms in a vicious feedback loop[1,5]. A practical framework is needed that communicates the somatic reality of the experience without foreclosing psychological exploration or triggering defensive alienation[3].

The Bear Narrative Reframe Method

Clinical Procedure

The author has utilized the following narrative approach across years of outpatient psychiatric practice in a resource-limited setting. When faced with diagnostic impasse and familial skepticism, families are told a classic folk fable: two friends encounter an apex predator, a bear, while walking through a dense forest. One companion quickly climbs a high tree to safety; the other, unable to escape or climb, drops to the ground and lies completely still. The bear approaches, sniffs the motionless traveller closely, and eventually wanders away. When asked afterward what the beast whispered in his ear, the prostrate traveller quips: never trust a companion who abandons you in moments of acute danger.

In clinical practice, this punchline reliably introduces levity into a tense consultation room, shifting the emotional dynamic between the patient, family, and clinician from adversarial tension to shared amusement. The clinician then capitalizes on this open moment by posing a reflective question to the room: was the bear deceived by an intentional theatrical performance, or did something far deeper take place?

The Therapeutic Reframe offered is that the man's physiological system shut down entirely viz., behaving as if dead and without his conscious volition. In the evolutionary defense cascade, when active fight or flight mechanisms fail or escape is impossible, the autonomic nervous system defaults to tonic immobility or profound dissociation as an involuntary, survival-oriented adaptation[1,5]. The functional symptom, whether motor paralysis, non-epileptic seizures, or sensory loss, is thus reframed not as an act of deceit, but as a biological enactment of an organism's only perceived survival response to an overwhelming, inescapable threat.

The clinician addresses the patient directly in the presence of their family: what you are experiencing is not imagined, made up, or false. The “bear” representing the unbearable psychological, emotional, or environmental stressor, was entirely real. The nervous system's somatic shutdown was the only protective response it could muster under acute duress.

The consultation concludes with a single, unpressured premise: gradually, collaboratively, and safely, we will work together to understand what your bear was.

Proposed Mechanisms of Action

The clinical utility of this narrative psychoeducational approach rests on four specific therapeutic mechanisms:

1. Narrative Distance and Externalization:

   Grounding the discussion in a third-person folk tale creates a safe conceptual buffer. Patient and relatives process the mechanics of threat-induced paralysis in a neutral story before mapping those insights onto their own domestic dynamics, significantly lowering defensive barriers.

2. Affective Reset via Humour:

   The sudden shift from clinical solemnity to shared laughter breaks the adversarial atmosphere, temporarily neutralizing defensiveness and preparing the family to absorb a non-punitive reframe.

3. Absolution of Volitional Guilt:

   Explicitly stating that the body acted "without him choosing it" dismantles the accusations of malingering held by caregivers and relieves the debilitating shame internalized by the patient. Psychoeducation facilitates active patient participation only when welcomed rather than rejected; affective containment of the family system is therefore a mandatory clinical prerequisite[6].

4. Trauma-Informed Pacing:

   Framing therapy around "understanding" rather than directly "facing" or "confronting" the stressor prevents premature exposure and re-traumatization. It replaces clinical interrogation with mutual exploration. Consequently, patients frequently disclose their core developmental or interpersonal stressors by the second or third session without direct clinical interrogation.

Clinical Observations

In routine outpatient practice, this approach has been associated with:

- Improved family acceptance of the diagnosis;
- Reduction in confrontational dynamics during consultations;
- Earlier spontaneous disclosure of psychosocial stressors (typically by the second or third visit) and
- Increased patient engagement in follow-up

These observations are anecdotal and require systematic evaluation.

Scope and Limitations

This model is most applicable to presentations where dissociative or conversion symptoms arise in the context of perceived inescapability or overwhelming stress. However, not all such disorders can be fully explained by acute threat responses alone. Chronic somatization, personality-related factors, and secondary gain may also contribute and require additional formulations.

There is also a risk of oversimplification if the metaphor is interpreted narrowly as "fear-based" rather than as a complex interaction of neurobiological and psychological processes.

The reported clinical benefits are based on practitioner observation and have not yet been formally studied. Variability in patient response, particularly in cases of severe or complex trauma, should be expected.

Implications for Practice

The Bear Narrative Reframe Method offers a pragmatic, scalable tool for psychoeducation because:

- It requires no materials or specialized training;
- It is adaptable across literacy levels and cultural contexts;
- It can be implemented in primary care and low-resource settings.
- Its simplicity makes it particularly valuable in environments where access to formal psychotherapy is limited.

Future Directions

Formal evaluation of this approach is warranted. Potential study designs might include:

- Prospective cohort studies assessing family acceptance and treatment adherence;
- Qualitative analyses of patient and caregiver responses;
- Comparative studies with standard psychoeducation approaches;
- Operationalizing outcome measures such as therapeutic alliance, stigma reduction, and time to stressor disclosure would further strengthen the evidence base.

CONCLUSION

The Bear Fable provides a simple yet effective narrative framework for communicating the nature of dissociative and conversion symptoms. By shifting the focus from questions of authenticity to understanding adaptive response, it preserves patient dignity while enabling therapeutic engagement. Narrative-based psychoeducation may represent a valuable adjunct in the management of functional psychiatric disorders, particularly in resource-constrained settings.

DECLARATIONS

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New Drug Approvals

S. No.	Treatment Indication	Drug's Name	Company	Description	Date of FDA Approval
1.	Weight Loss	Foundayo (Orforglipron) Tablets	Eli Lilly and Company	Foundayo (Orforglipron) is an oral glucagon-like peptide-1 (GLP-1) receptor agonist for use in adults with obesity, or overweight with weight-related medical problems.	April 1, 2026
2.	HIV-1 Infection	Idvynso (Doravirine and Islatravir) Tablets	Merck	Idvynso (Doravirine and Islatravir) is a HIV-1 non-nucleoside reverse transcriptase inhibitor (NNRTI) and a nucleoside analogue reverse transcriptase inhibitor (NRTI) combination for the treatment of HIV-1 infection in adults.	April 20, 2026
3.	Hearing Loss	Otarmeni (Lunsotogene parvec-cwha) Suspension for Intracochlear Infusion	Regeneron Pharma-ceuticals, Inc.	Otarmeni (Lunsotogene parvec-cwha) is an adeno-associated virus vector-based gene therapy for genetic *OTOF*-related hearing loss.	April 23, 2026
4.	Diabetes, Type 1, Type 2 Diabetes	Langlara (Insulin Glargine-aldy) Injection	Lannett Company, Inc.	Langlara (Insulin Glargine-aldy) is a long-acting human insulin analogue interchangeable biosimilar to Lantus for the treatment of diabetes mellitus.	April 23, 2026
5.	Breast Cancer	Veppanu (Vepdegestrant) Tablets	Arvinas, Inc.	Veppanu (Vepdegestrant) is a heterobifunctional protein degrader for the treatment of oestrogen receptor (ER)-positive, human epidermal growth factor receptor 2 (HER2) - negative, oestrogen receptor 1 (*ESR1*)-mutated advanced or metastatic breast cancer.	May 1, 2026

Continued ...

S. No.	Treatment Indication	Drug's Name	Company	Description	Date of FDA Approval
6.	Neutropenia Associated with Chemotherapy, Hematopoietic Syndrome of Acute Radiation Syndrome	Ennumo (Pegfilgrastim -pccg) Injection	Accord BioPharma Inc.	Ennumo (Pegfilgrastim-pccg) is a leukocyte growth factor biosimilar to Neulasta (Pegfilgrastim) used to reduce the incidence of febrile neutropenia in patients treated with chemotherapy and to increase survival in patients acutely exposed to myelosuppressive doses of radiation.	May 7, 2026
7.	Mantle Cell Lymphoma	Beqalzi (Sonrotoclax) Tablets	BeOne Medicines Ltd.	Beqalzi (Sonrotoclax) is a BCL-2 inhibitor for use in the treatment of adult patients with relapsed or refractory mantle cell lymphoma.	May 13, 2026
8.	Asthma, Maintenance	Trimbow (Beclomethasone dipropionate, Formoterol fumarate and Glycopyrrolate) Inhalation Aerosol	Johnson & Johnson	Trimbow (Beclomethasone dipropionate, Formoterol fumarate and Glycopyrrolate) is an inhaled corticosteroid, a long-acting beta$_2$-adrenergic agonist, and an anticholinergic combination for the treatment of asthma.	May 14, 2026
9.	Rheumatoid Arthritis, Ulcerative Colitis	Immgolis (Golimumab -sldi) Injection	Accord BioPharma, Inc.	Immgolis (Golimumab-sldi) is a tumour necrosis factor (TNF) blocker interchangeable biosimilar to Simponi for the treatment of rheumatoid arthritis and ulcerative colitis.	May 15, 2026
10.	Rheumatoid Arthritis	Immgolis Intri (Golimumab -sldi) Injection	Accord BioPharma, Inc.	Immgolis Intri (Golimumab-sldi) is a tumour necrosis factor (TNF) blocker interchangeable biosimilar to Simponi Aria for the treatment of rheumatoid arthritis.	May 15, 2026

Continued ...

S. No.	Treatment Indication	Drug's Name	Company	Description	Date of FDA Approval
11.	High Blood Pressure	Baxfendy (Baxdrostat) Tablets	AstraZeneca	Baxfendy (Baxdrostat) is a first-in-class, highly selective aldosterone synthase inhibitor (ASI) for use in the treatment of hypertension.	May 15, 2026
12.	Acne	Differin Epiduo Acne Gel (Adapalene and Benzoyl peroxide) Topical Gel	Galderma	Differin Epiduo Acne Gel (adapalene and benzoyl peroxide) is a retinoid and oxidizing agent combination for the topical treatment of acne.	May 22, 2026
13.	Hepatitis Delta	Hepcludex (Bulevirtide -gmod) Lyophilized Powder for Injection	Gilead Sciences, Inc.	Hepcludex (Bulevirtide-gmod) is a novel virion entry inhibitor for the treatment of adults with chronic hepatitis delta virus (HDV) infection.	May 22, 2026
14.	Blastic Plasmacytoid Dendritic Cell Neoplasm	Decnupaz (Pivekimab sunirine-pvzy) Lyophilized Cake for Injection	AbbVie	Decnupaz (Pivekimab sunirine-pvzy) is a CD123-directed antibody and alkylating agent conjugate indicated for the treatment of adult patients with blastic plasmacytoid dendritic cell neoplasm.	May 27, 2026
15.	Urinary Tract Infection	Zaynich (Cefepime and Zidebactam) Powder for Injection	Wockhardt	Zaynich (Cefepime and Zidebactam) is a cephalosporin antibacterial and a beta-lactamase inhibitor and non-beta-lactam antibacterial combination indicated for the treatment of complicated urinary tract infections.	May 29, 2026

Continued ...

S. No.	Treatment Indication	Drug's Name	Company	Description	Date of FDA Approval
16.	Anaesthesia	Cypsedo (Cipepofol) Injection	Haisco Pharma-ceutical Group	Cypsedo (Cipepofol) is a general anaesthetic drug indicated for induction of general anaesthesia in adults undergoing surgery.	May 29, 2026
17.	Post-Exposure Prophylaxis of COVID-19	Xocova (Ensitrelvir) Tablets	Shionogi & Co., Ltd.	Xocova (Ensitrelvir) is a 3CL protease inhibitor for post-exposure prophylaxis of COVID-19.	May 29, 2026
18.	Philadelphia Chromosome Positive Chronic Myeloid Leukaemia	Cavhanza (Nilotinib) Orally Disintegrating Tablets	Cycle Pharma-ceuticals	Cavhanza (Nilotinib) is a kinase inhibitor for use in the treatment of Philadelphia chromosome positive chronic myeloid leukaemia.	May 29, 2026
19.	Macular Degeneration, Diabetic Macular Oedema, Macular Oedema, Diabetic Retinopathy, Myopic Choroidal Neovascularization	Ranluspec (Ranibizumab -hkdz) Intravitreal Injection	Lupin Limited	Ranluspec (Ranibizumab-hkdz) is an interchangeable biosimilar to Lucentis for the treatment of patients with neovascular (wet) age-related macular degeneration (AMD), macular oedema following retinal vein occlusion (RVO), diabetic macular oedema (DME), diabetic retinopathy (DR), and myopic choroidal neovascularization (mCNV).	June 2, 2026
20.	Diagnosis and Investigation	Ambelvist (Gadoquatrane) Injection	Bayer	Ambelvist (Gadoquatrane) is a gadolinium-based contrast agent for contrast-enhanced magnetic resonance imaging (MRI) to detect and visualize lesions with abnormal vascularity in the central nervous system and non-CNS body regions.	June 12, 2026

Continued ...

S. No.	Treatment Indication	Drug's Name	Company	Description	Date of FDA Approval
21.	Urinary Tract Infection	Utebzi (Tebipenem pivoxil) Tablets	GSK	Utebzi (Tebipenem pivoxil) is an oral carbapenem antibiotic used for the treatment of complicated urinary tract infections.	June 17, 2026
22.	Thyroid Eye Disease	Lumvoa (Veligrotug -vvze) Injection	Viridian Thera-peutics, Inc.	Lumvoa (Veligrotug-vvze) is an insulin-like growth factor-1 receptor inhibitor for use in the treatment of thyroid eye disease.	June 26, 2026
23.	Graft Versus Host Disease - Prophylaxis	Tregzi (Allogeneic regulatory T cell Immunotherapy with HSPC and T cells-vldq) - formerly Orca-T	Orca Bio	Tregrzi (Orca-T) is a cell therapy for allogeneic transplant in adults with haematological malignancies used in a stem cell transplant to improve survival free of chronic graft versus host disease (GVHD) in adults.	June 30, 2026

- Editor

Recent Medical Advances
From the Journals - Edited Highlights

When the Boundaries of Medicine Redraw Themselves

Medicine has always advanced along disciplinary lines drawn by convention rather than by nature. A cardiologist studies the heart, a neurologist the brain, a nutritionist the diet, and rarely do their findings appear to speak to one another. This issue of Recent Medical Advances offers a quiet but persistent challenge to that convention. Across the 101 research papers presented here, one pattern stands out again and again: some of the most useful discoveries did not come from within a single specialty, but from the space between two specialties.

Consider what a daily habit of listening to music can do for a brain recovering from stroke, or protecting itself against dementia. Consider how a molecule in coffee, or a compound found in beans, can reshape the bacteria living in the gut, and through them, influence mood, metabolism, and even the strength of the gut's own lining. Consider that the biological age of the retina may predict how strong or fragile a person's bones are, that simple daily patterns of activity and rest can reveal how fast someone is ageing at a cellular level, and that mitochondrial DNA, once seen as mere cellular housekeeping, may hold early clues to cognitive decline in midlife. These are not isolated curiosities. They show that medicine's old boundaries are starting to blur, and that many of today's most important answers are being found exactly where two fields meet.

This issue presents a carefully assembled collection of 101 cutting-edge research papers published globally, predominantly in 2026, spanning the breadth of contemporary medicine, from cellular mechanism through clinical trial to population-level pattern. These papers were not selected at random. Each was chosen for its scientific significance, its clinical relevance, and its ability to genuinely inform the thinking of a practising clinician, an inquiring student, or a researcher deciding what question to study next.

To help readers navigate this range of material, the collection has been organised into eleven thematic categories: Oncology and Precision Immunotherapy; Neurology, Neuropsychiatry and Brain Health; The Music-Brain Axis; Cardio-Metabolic Medicine, Diabetes and Endocrinology; Immunology and Infectious Disease; Maternal, Neonatal and Paediatric Health; Reproductive and Fertility Health; Surgery, Transplantation and Regenerative Medicine; Biological Ageing and Longevity; Nutrition, Diet and Gut Health; and Fundamental Science, Technology and Public Health. Each category offers its own point of entry, yet none stands entirely apart from the others, and a reader who lingers long enough will find the same threads, inflammation, ageing, the gut, the nervous system, running quietly beneath more than one heading.

The collection deliberately includes many kinds of studies, including randomised controlled trials, systematic reviews, cohort studies, case reports, and basic science investigations. Different clinical questions call for different kinds of studies, and no single study design, however well conducted, tells the whole story on its own. Confidence in a finding grows when several different kinds of evidence point in the same direction.

Every research paper included here underwent independent verification to confirm its scientific accuracy. Misinformation can spread quickly, even through summaries written with good intentions, and a journal has a duty to its readers, and through them to their patients, to check what it publishes rather than simply repeat it. Complete Digital Object Identifiers accompany every entry, and wherever a paper is indexed in PubMed, its PMID and PMCID are provided as well, allowing readers to consult the original publication directly and reach their own conclusions.

Every paper in this collection speaks twice, once in words and once in image. Each has been distilled into a short summary written in Vancouver citation style, and paired with a custom-designed infographic built to carry the same finding at a glance: its key result, its likely mechanism, its clinical relevance, and its defining statistic, rendered in colour and shape as much as in text. Together, the two are meant to travel easily, into a ward round, a conversation with a patient, a conference slide, or a classroom lecture, wherever a moment of understanding is needed quickly.

This feature will be of particular value to practising physicians and general practitioners looking for evidence-based updates to guide their clinical decisions, and to researchers looking for open questions worth pursuing. Medical educators will find reliable, up-to-date teaching material ready to use in class or at conferences. Nutritionists, dietitians, and public health professionals will find findings directly relevant to their work, often from unexpected corners of medicine, while students at every stage of training will find the foundational knowledge that will shape how they practise in years to come.

The body does not read a table of contents. It does not know that the heart belongs to one chapter and the gut to another, that ageing sits apart from cancer, or that a night's sleep and a morning's mood are filed under different headings. Only medicine draws those lines, and only medicine can choose to look past them. This issue is offered as an invitation to do exactly that: to read a little beyond one's own specialty, to notice where two fields quietly touch, and to carry that wider view back into the clinic, the classroom, and the conversation with the next patient. That, in the end, is where these boundaries are truly redrawn.

- The Editor

Table of Contents

Category I: Oncology & Precision Immunotherapy		Page No.
1.	Nearly Four in Ten Cancer Cases Worldwide Linked to Preventable Risk Factors, Global Study Finds (2026)	**119**
2.	HPV Vaccination Linked to Zero Cervical Cancer Deaths in Young Vaccinated Women in England (2026)	**120**
3.	A Stretchable Skin Patch That Uses Copper and Light to Fight Melanoma Without Surgery (2026)	**121**
4.	How a New Compound Tricks Drug-Resistant Cancer Cells into Destroying Their Own Repair Machinery (2026)	**122**
5.	A Bioengineered Chewing Gum That Targets the Microbes Linked to Mouth Cancer (2026)	**123**
6.	Could a Simple Amino Acid Found in Meat, Fish and Eggs Help Cancer Immunotherapy Work Better (2026)	**124**
7.	GLP-1 Weight-Loss Drugs Linked to Lower Breast Cancer Risk in Overweight Women (2026)	**125**
8.	Low Testosterone in Men Linked to Higher Risk of Dying from Cancer (2026)	**126**
9.	Some Contraceptive Hormones Linked to Slightly Higher Risk of a Common Brain Tumour (2026)	**127**
10.	Younger Generations May Be Ageing Faster Inside, Raising Their Cancer Risk (2026)	**128**
Category II: Neurology, Neuropsychiatry & Brain Health		
11.	Omega-3 Supplements Linked to Faster Cognitive Decline in Older Adults (2026)	**129**
12.	Blood Mitochondrial DNA Changes Linked to Midlife Cognitive Decline (2026)	**130**
13.	Magnetic Brain Stimulation Improves Social Communication in Autistic Children in Randomised Trial (2026)	**131**
14.	Factor XIa Inhibition: A New Paradigm in Secondary Stroke Prevention (2026)	**132**
15.	Could Mixing Virtual Reality with Electrical Nerve Stimulation Help Stroke Survivors Regain Hand and Arm Function (2026)	**133**
16.	Becoming a Father Reshapes the Brain: Neuroplasticity in New Fathers Across the First Six Months (2026)	**134**
17.	The Brain's Built-In "Attention Switch": An Ancient Brainstem Circuit That Keeps Us Focused (2026)	**135**
18.	Could 'Hyperonirism' Be a New Sleep Disorder? French Case Series Proposes Diagnostic Criteria (2026)	**136**
19.	Brain Scans Reveal How Depression Traps the Mind Between Rigid Mental States (2026)	**137**
20.	High-Dose Psilocybin Misses Primary Goal but Eases Symptoms in Resistant Depression Trial (2026)	**138**

21.	Severe Infections Independently Increase Dementia Risk, Finnish Registry Study Shows (2026)	**139**
22.	Bilingual Men May Have Extra Brain Protection Against Alzheimer's, Study Finds (2026)	**140**
23.	Handwriting Speed During Dictation May Help Detect Early Cognitive Decline (2026)	**141**
24.	Case Report Describes Temporary Gains in Advanced Alzheimer's After High-Dose Psilocybin Mushrooms (2026)	**142**
25.	Why Alzheimer's Risk Hits Women Harder: A Closer Look at Modifiable Risk Factors (2026)	**143**
26.	Alzheimer's Disease May Begin in the Body's Immune System, Not the Brain (2026)	**144**
27.	Blood Test Ratio Improves Detection of Alzheimer's Amyloid Pathology (2026)	**145**
28.	Vitamin B12 Levels Within the "Normal" Range May Still Affect Brain Health in Older Adults (2025)	**146**
29.	Night Shift Work Linked to Shrinkage in Key Brain Regions, Study Finds (2025)	**147**
30.	Women, Men and ADHD: Same Disorder, Different Struggles (2025)	**148**
	Category III: The Music-Brain Axis	
31.	Music Therapy Shows Promise as an Adjunct Treatment for Stroke, Parkinson's Disease, and Cerebral Palsy (2026)	**149**
32.	Music Therapy Linked to Improved Cognitive Scores in Older Adults with Mild Cognitive Impairment (2026)	**150**
33.	How Music Therapy Supports Physical and Psychological Healing Across Clinical Populations (2026)	**151**
34.	Testing Whether Group Music Sessions Can Help School Children with Emotional or Behavioural Difficulties (2026)	**152**
35.	Listening to Music Daily May Lower Dementia Risk in Older Adults (2025)	**153**
36.	Music Therapy Delivered by Trained Therapists Meaningfully Reduces Anxiety Symptoms (2025)	**154**
	Category IV: Cardio-Metabolic Medicine, Diabetes & Endocrinology	
37.	Oral Semaglutide Redefines Heart Failure Management in Type 2 Diabetes (2026)	**155**
38.	Oral Pill Aleniglipron Shows Meaningful Weight Loss in Obesity Trial (2026)	**156**
39.	Ketogenic Diet Eases Pancreatic Stress in People with Type 2 Diabetes (2026)	**157**
40.	Multidisciplinary Diabetes Care Achieves Remission in Nearly One in Three Patients (2026)	**158**
41.	A Clinical Guideline Brings More Consistency to Ayurvedic Diabetes Care (2026)	**159**
42.	Prolonged Water Fasting Combined with a GLP-1 Drug Enabled Bariatric Surgery in a Man with Severe Obesity (2026)	**160**

43.	Common Second-Line Blood Pressure Drug Linked to Faster Kidney Decline in People with Type 2 Diabetes on Modern Kidney-Protective Therapy (2026)	**161**
44.	A Diabetes-Specific Model to Better Predict Heart Disease Risk (2026)	**162**
45.	How Are People with Diabetes Searching for Health Information Online (2026)	**163**
46.	Can Your Glucose Monitor Predict a Heart Attack? What the Evidence Really Shows (2026)	**164**
47.	Wearable Tech and the Future of Heart Health (2026)	**165**
48.	Heart Disease Costs Are Rising Even as Treatment Keeps Improving (2026)	**166**
49.	Charting the Future of Type 2 Diabetes Treatment: From Metformin to Gene Editing (2025)	**167**
	Category V: Immunology & Infectious Disease	
50.	Moderna's Experimental mRNA Vaccine Outperforms the Standard Flu Shot in Older Adults (2026)	**168**
51.	Dutch Study Pinpoints How Long It Took COVID to Become Endemic (2026)	**169**
52.	Ultrasound at Medical-Imaging Frequencies Disrupts Flu and COVID-19 Viruses in Lab Tests (2026)	**170**
53.	One Amino Acid Shift: How Coronaviruses Jump from Bats to Humans (2026)	**171**
54.	A Popular Skincare Ingredient Shows Promise Against Drug-Resistant Bacteria, With a Twist (2026)	**172**
55.	A Compound in Turmeric and Ginger Weakens Drug-Resistant Staphylococcus aureus (2026)	**173**
56.	Better Oral Hygiene Cuts Hospital-Acquired Pneumonia Risk in Half, Australian Trial Finds (2026)	**174**
57.	Suspected Brain Cancer, Actually Tapeworm Cysts: A Rare Case from Spain (2026)	**175**
58.	Sea Anemones Teach Us That Immune Suppression Can Fight Viruses (2026)	**176**
	Category VI: Maternal, Neonatal & Paediatric Health	
59.	Discovery of a Mystery Cell Type That Exists Only During Early Pregnancy (2026)	**177**
60.	Do Foetuses Copy Their Mother's Yawns (2026)	**178**
61.	Foetal Exposure to Vegetable Flavours May Still Shape Children's Smell Reactions Years Later (2026)	**179**
62.	High-Dose Vitamin D3 in Pregnancy Linked to Better Memory in 10-Year-Olds (2026)	**180**
63.	Vitamin K Shot Refusal in Newborns: A Growing Threat to Infant Brain Health (2026)	**181**
	Category VII: Reproductive & Fertility Health	
64.	PCOS Renamed to PMOS: Why Scientists Changed the Name of a Condition Affecting 170 million Women (2026)	**182**

65.	Women with PCOS Experience Menopause Later and With Fewer Symptoms (2026)	**183**
66.	How Ageing Ovaries Quietly Turn into Sites of Chronic Inflammation (2026)	**184**
67.	Genetic Variation in Meiosis Genes Shapes Miscarriage Risk (2026)	**185**
68.	Why Storing Sperm for Longer May Backfire (2026)	**186**
Category VIII: Surgery, Transplantation & Regenerative Medicine		
69.	A Better-Timed Stem Cell Protocol Yields Purer, More Reliable Insulin-Producing Islets (2026)	**187**
70.	Stem Cell Transplant Achieves 15+ Years of Disease-Free Remission in Neuromyelitis Optica (2026)	**188**
71.	Menstrual Blood Could Hold a Natural Repair Kit for Damaged Joint Cartilage (2026)	**189**
72.	New Hydrogel Could Deliver Biologic Drugs Directly to the Oesophagus, MIT Study Shows (2026)	**190**
Category IX: Biological Ageing & Longevity		
73.	Semaglutide Slows Biological Ageing in Adults with HIV-Associated Fat Gain (2026)	**191**
74.	Arts and Cultural Engagement Linked to Slower Biological Ageing, Comparable to Exercise (2026)	**192**
75.	Steadier Daily Activity and Rest Patterns Linked to Slower Biological Ageing in Older Adults (2026)	**193**
76.	Moderate Long-Term Strength Training Linked to Lower Risk of Death from All Causes (2026)	**194**
77.	Retinal Biological Age Could Signal Weakening Bones and Fracture Risk (2026)	**195**
78.	Scientists Pinpoint the 'Goldilocks Zone' of Sleep for Slower Body-Wide Ageing (2026)	**196**
Category X: Nutrition, Diet & Gut Health		
79.	Two Days of Intensive Oats Cut Cholesterol via Gut Bacteria (2026)	**197**
80.	Coffee Reshapes Gut Bacteria and Mood, Not Just via Caffeine (2026)	**198**
81.	Phytic Acid in Beans, Rice, and Nuts Acts as a Cellular Switch, Not Just a Nutrient, to Seal the Gut Barrier (2026)	**199**
82.	Does Wanting to Change Your Diet Affect Your Gut Bacteria and Memory (2026)	**200**
83.	Ultra processed Food Consumption Linked to Worse Health and Earlier Death (2026)	**201**
84.	Do Shoppers Know Which Foods Count as "Ultra-Processed" (2026)	**202**
85.	Common Food Preservatives Linked to Higher Risk of High Blood Pressure and Heart Disease (2026)	**203**
86.	Alcohol Intake and Mortality: Even Moderate Weekly Drinking Raises Risk of Death, US Study Finds (2026)	**204**

87.	Trans Fats Naturally Found in Dairy Foods Do Not Raise Heart Disease or Diabetes Risk (2026)	**205**
88.	One Avocado a Day May Meaningfully Lower Blood Sugar Impact of the Diet (2026)	**206**
89.	Following Standard "Five-a-Day" Advice May Not Give You Enough Heart-Protective Plant Compounds Called Flavanols (2026)	**207**
90.	The Vitamin D Paradox: Why Pills Don't Seem to Help the Lungs (2026)	**208**
91.	Higher Vitamin C Levels Linked to Healthier Brain Structure in Older Adults (2026)	**209**
92.	Vegetarian Diets and Cancer: A Mixed Picture from 1.8 million People Worldwide (2026)	**210**
93.	Grape Consumption Alters Skin Gene Activity Linked to UV Defence (2026)	**211**
94.	CDC's 24-Year Nutrition Biomarker Database Now Covers 131 Indicators (2026)	**212**
Category XI: Fundamental Science, Technology & Public Health		
95.	AI Foundation Model Turns One Night's Sleep Study into a Disease Risk Forecast (2026)	**213**
96.	How Cells Keep Their Mitochondrial DNA Evenly Spaced (2026)	**214**
97.	The Pathway to Genome Doubling Shapes the Cell Fate (2026)	**215**
98.	Tendons, Cartilage and Bone Renew Far More Slowly Than Muscle, and Two Weeks of Extra Protein Doesn't Speed This Up (2026)	**216**
99.	Wild Orangutans Pair Up Medicinal Plants in Their Diet (2026)	**217**
100.	When Modern Living Clashes with Ancient Biology: An Evolutionary Lens on Disease (2026)	**218**
101.	How Leucine Keeps Mitochondria Running Strong (2025)	**219**

Nearly Four in Ten Cancer Cases Worldwide Linked to Preventable Risk Factors, Global Study Finds (2026)

If tobacco, infections, and excess weight could be eliminated tomorrow, how many of the world's cancer diagnoses would simply not happen?

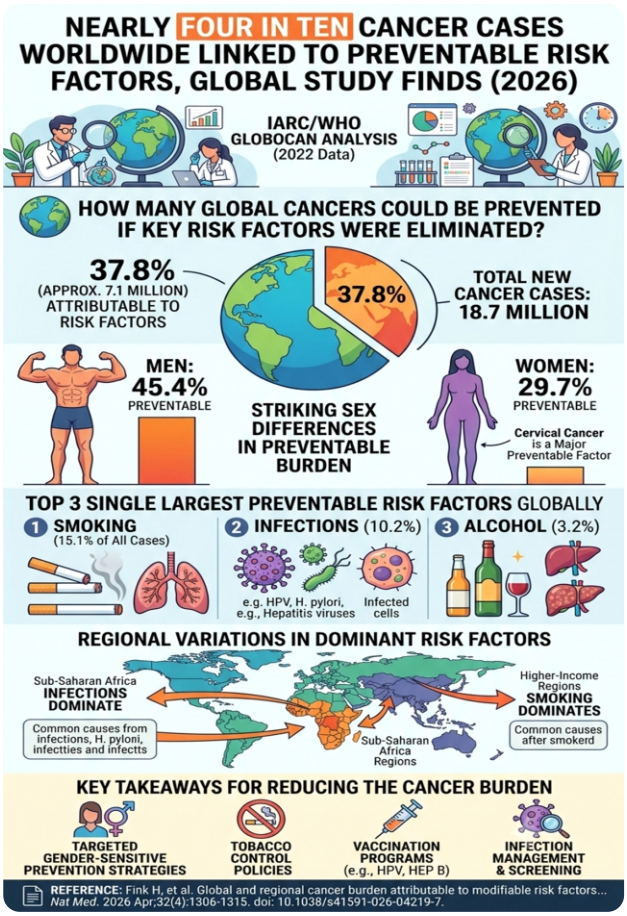
Researchers from the International Agency for Research on Cancer (IARC/WHO) and the World Health Organization analysed 2022 cancer incidence data across 185 countries to estimate the global burden attributable to thirty modifiable risk factors, including tobacco smoking, alcohol consumption, high body mass index, insufficient physical activity, air pollution, ultraviolet radiation, nine infectious agents, and thirteen occupational exposures. Using population-attributable fractions derived from GLOBOCAN data and established relative risk estimates, the study found that of 18.7 million new cancer cases worldwide, around 7.1 million (37.8 percent) were attributable to these factors, with a striking sex difference: 45.4 percent of cases in men versus 29.7 percent in women. Smoking was the single largest contributor globally (15.1 percent of all cases), followed by infections (10.2 percent) and alcohol (3.2 percent). Lung, stomach, and cervical cancers carried the greatest preventable burden. Regional patterns varied widely, with infections dominating in sub-Saharan Africa and smoking dominating in higher-income regions. The authors conclude that targeted, gender-sensitive prevention strategies, including tobacco control, vaccination, and infection management, could meaningfully reduce the future global cancer burden.

Source:

RESEARCH PAPER

Fink H, Langselius O, Vignat J, Rumgay H, Rehm J, Martinez RX, et al. Global and regional cancer burden attributable to modifiable risk factors to inform prevention. Nat Med. 2026 Apr;32(4):1306-1315. doi: 10.1038/s41591-026-04219-7. Epub 2026 Feb 3. PMID: 41634393.





HPV Vaccination Linked to Zero Cervical Cancer Deaths in Young Vaccinated Women in England (2026)

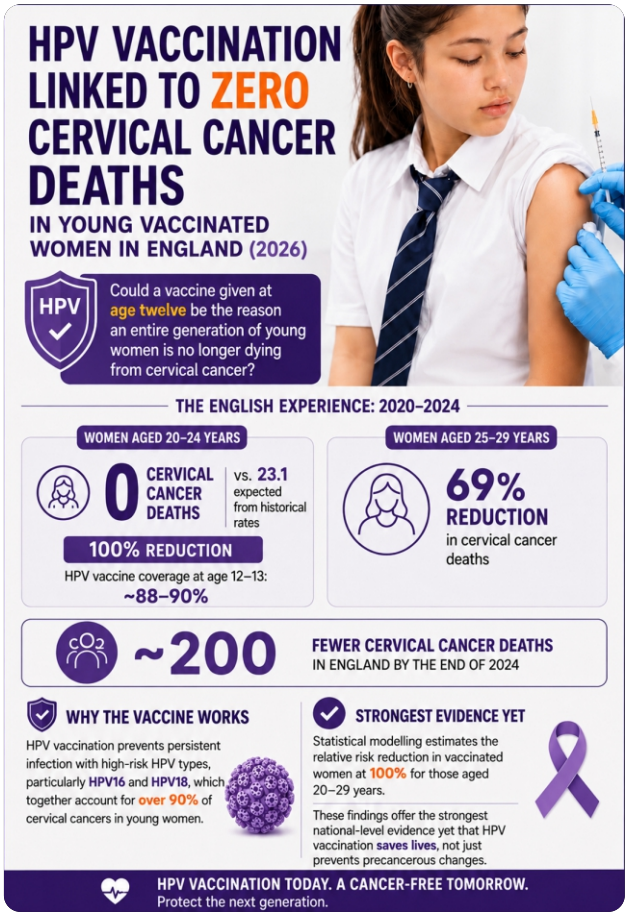
Could a vaccine given at age twelve be the reason an entire generation of young women is no longer dying from cervical cancer?

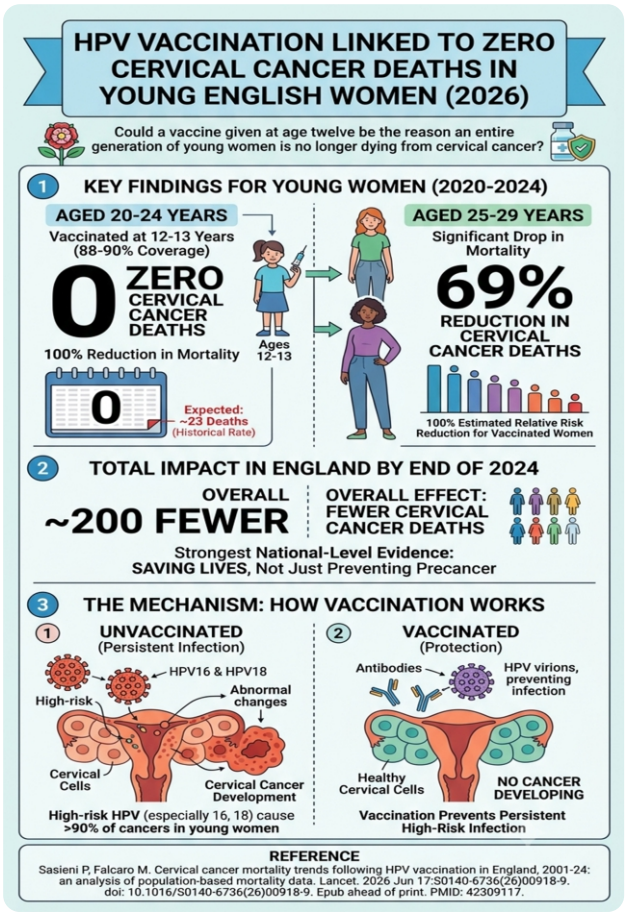
A national study from Queen Mary University of London analysed population-based cervical cancer mortality data for England between 2001 and 2024, using official vaccination coverage records linked to mortality statistics for women aged 20 to 34 years. Among women aged 20 to 24 years, who had received HPV vaccination at age 12 to 13 years with coverage of around 88 to 90 percent, there were zero cervical cancer deaths between 2020 and 2024, compared with 23.1 deaths expected from historical rates, a 100 percent reduction. Women aged 25 to 29 years showed a 69 percent reduction over the same period. Statistical modelling estimated the relative risk reduction in vaccinated women at 100 percent for those aged 20 to 29 years. Overall, HPV vaccination was associated with around 200 fewer cervical cancer deaths in England by the end of 2024. The likely mechanism is that vaccination prevents persistent infection with high-risk HPV types, particularly HPV16 and HPV18, which together account for over 90 percent of cervical cancers in young women. These findings offer the strongest national-level evidence yet that HPV vaccination saves lives, not just prevents precancerous changes.

Source:

RESEARCH PAPER

Sasieni P, Falcaro M. Cervical cancer mortality trends following HPV vaccination in England, 2001-24: an analysis of population-based mortality data. Lancet. 2026 Jun 17: S0140-6736(26)00918-9. doi: 10.1016/S0140-6736(26)00918-9. Epub ahead of print. PMID: 42309117.





A Stretchable Skin Patch That Uses Copper and Light to Fight Melanoma Without Surgery (2026)

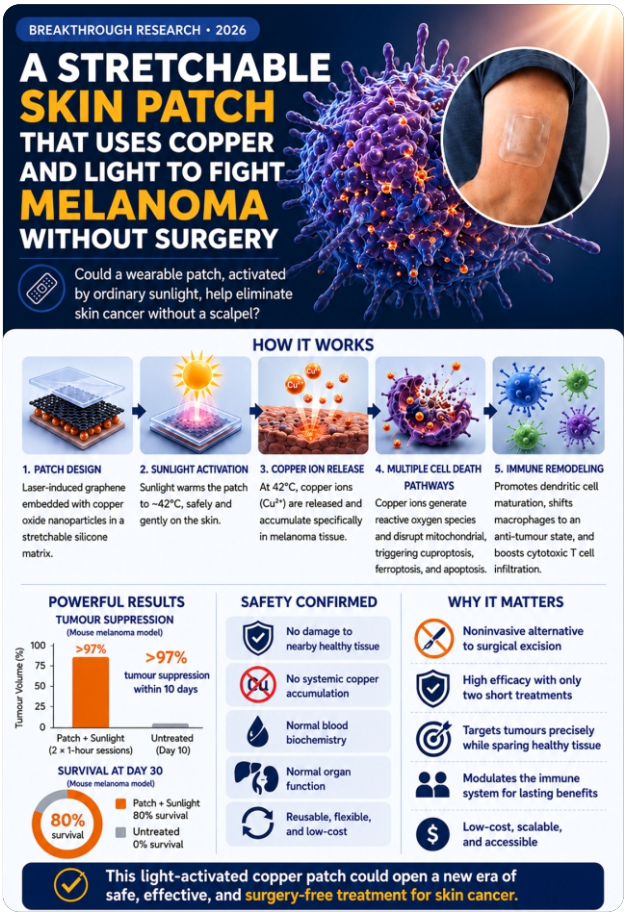
Could a wearable patch, activated by ordinary sunlight, help eliminate skin cancer without a scalpel?

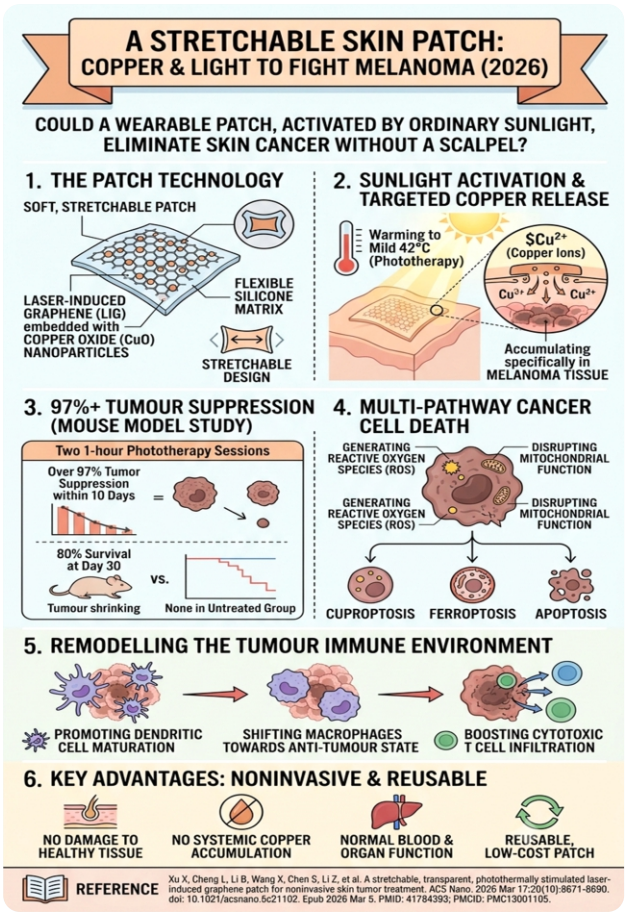
Researchers from Wuhan University and the City University of Hong Kong developed a soft, stretchable patch made of laser-induced graphene embedded with copper oxide nanoparticles, set within a flexible silicone matrix. When warmed by sunlight to a mild 42°C, the patch releases copper ions that accumulate specifically in melanoma tissue. In a mouse model of subcutaneous melanoma, just two one-hour phototherapy sessions achieved over 97 per cent tumour suppression within ten days, and 80 per cent of treated mice survived to day 30, compared with none in the untreated group. Mechanistically, the copper ions triggered a combination of cell death pathways, including cuproptosis, ferroptosis, and apoptosis, by generating reactive oxygen species and disrupting mitochondrial function within cancer cells. The treatment also remodelled the tumour immune environment, promoting dendritic cell maturation, shifting macrophages towards an anti-tumour state, and boosting cytotoxic T cell infiltration. Importantly, extensive safety testing showed no damage to nearby healthy tissue, no systemic copper accumulation, and normal blood and organ function in treated mice. These findings suggest this reusable, low-cost patch could offer a promising, non-invasive alternative to surgical excision for skin tumours.

Source:

RESEARCH PAPER

Xu X, Cheng L, Li B, Wang X, Chen S, Li Z, et al. A stretchable, transparent, photothermally stimulated laser-induced graphene patch for non-invasive skin tumour treatment. ACS Nano. 2026 Mar 17;20(10):8671-8690. doi: 10.1021/acsnano.5c21102. Epub 2026 Mar 5. PMID: 41784393; PMCID: PMC13001105.





How a New Compound Tricks Drug-Resistant Cancer Cells into Destroying Their Own Repair Machinery? (2026)

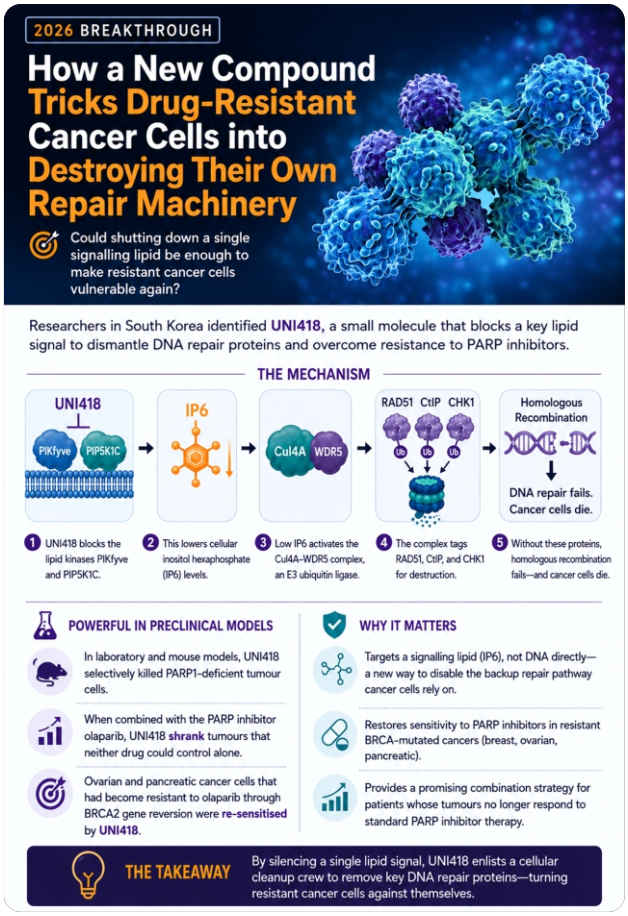
🎯 ***Could shutting down a single signalling lipid be enough to make resistant cancer cells vulnerable again?***

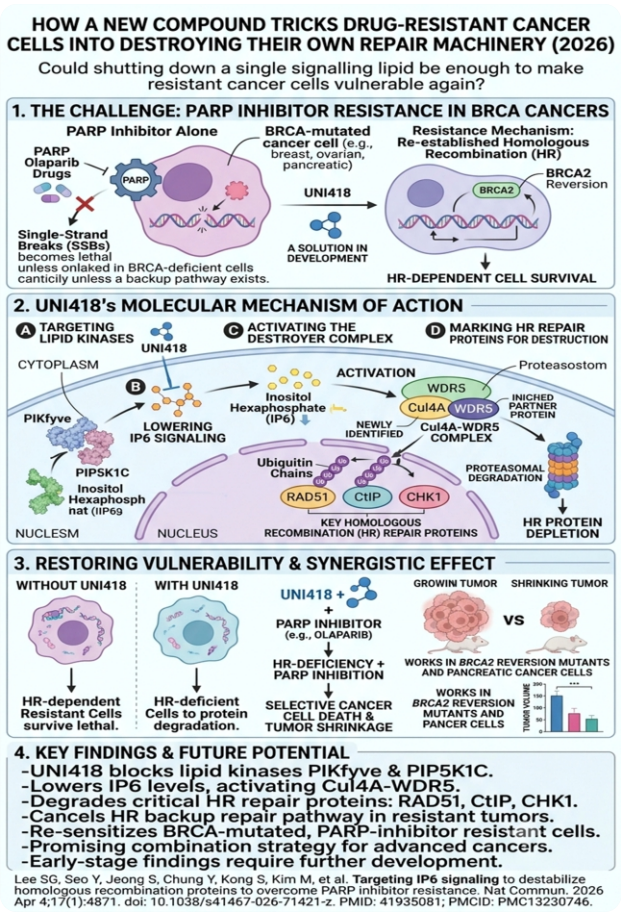
Researchers at the Institute for Basic Science and Ulsan National Institute of Science and Technology in South Korea identified a small molecule, UNI418, that overcomes resistance to PARP inhibitors, a class of cancer drugs used in BRCA-mutated breast, ovarian, and pancreatic cancers. Through high-throughput screening, the team found that UNI418 blocks two lipid kinases, PIKfyve and PIP5K1C, lowering cellular levels of a signalling molecule called inositol hexaphosphate (IP6). This activates an enzyme complex, Cul4A, working alongside a newly identified partner protein, WDR5, that marks three key DNA repair proteins, RAD51, CtIP, and CHK1, for destruction. Without these proteins, cancer cells lose their ability to repair DNA breaks through homologous recombination, a backup repair route that resistant tumours rely on once PARP itself is blocked. In laboratory and mouse models, UNI418 selectively killed PARP1-deficient tumour cells and, when combined with the PARP inhibitor olaparib, shrank tumours that neither drug could control alone. Notably, ovarian and pancreatic cancer cells that had become resistant to olaparib through BRCA2 gene reversion were re-sensitised by UNI418. While still early-stage and requiring further pharmacological development, these findings point to a promising combination strategy for tumours that have stopped responding to standard PARP inhibitor therapy.

Source:

RESEARCH PAPER

Lee SG, Seo Y, Jeong S, Chung Y, Kong S, Kim M, et al. Targeting IP6 signalling to destabilize homologous recombination proteins to overcome PARP inhibitor resistance. Nat Commun. 2026 Apr 4;17(1):4871. doi: 10.1038/s41467-026-71421-z. PMID: 41935081; PMCID: PMC13230746.





A Bioengineered Chewing Gum That Targets the Microbes Linked to Mouth Cancer (2026)

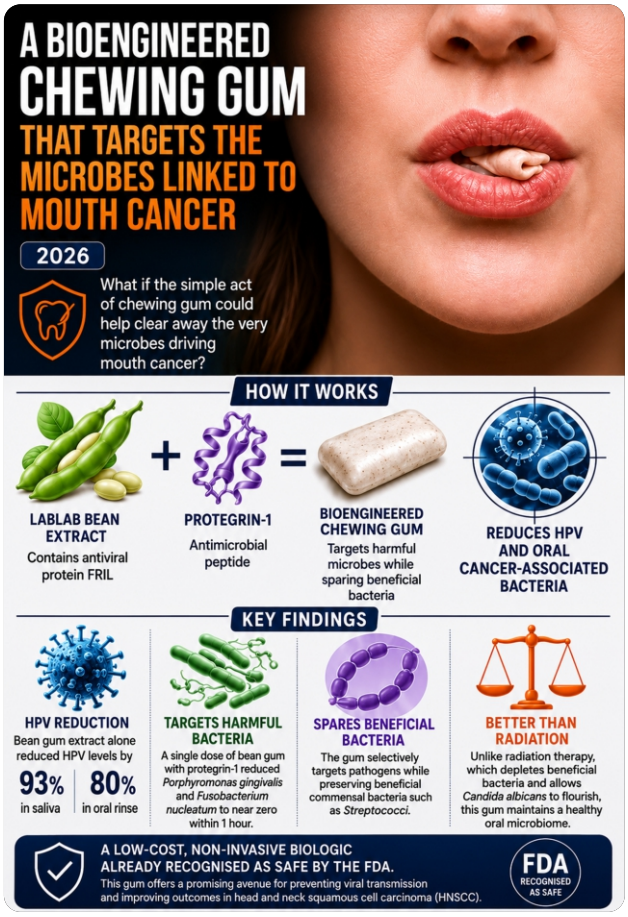
😬 ***What if the simple act of chewing gum could help clear away the very microbes driving mouth cancer?***

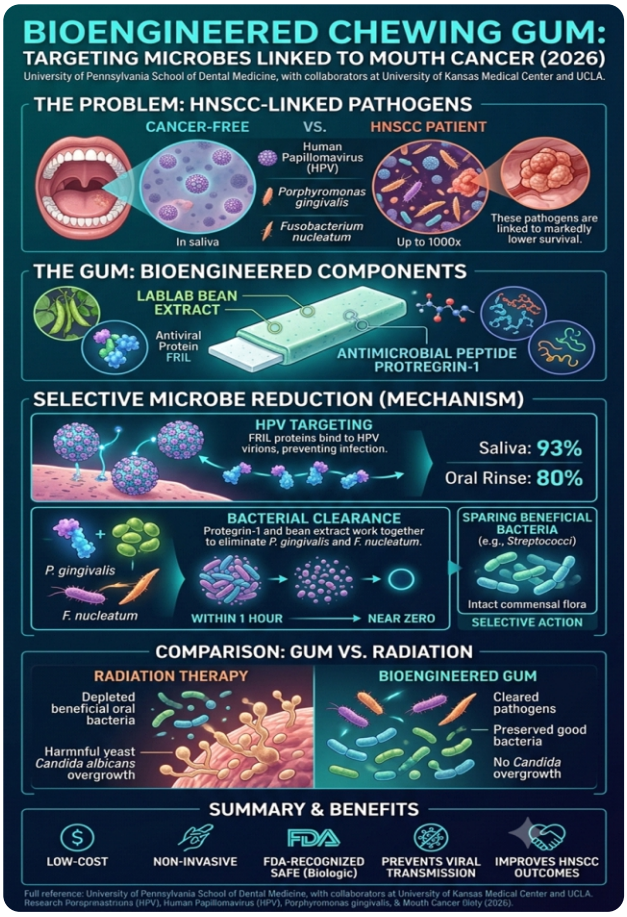
Researchers at the University of Pennsylvania's School of Dental Medicine, working with collaborators at the University of Kansas Medical Centre and the University of California, Los Angeles, tested a chewing gum made from lablab bean extract, containing the antiviral protein FRIL, alongside the antimicrobial peptide protegrin-1, against pathogens linked to head and neck squamous cell carcinoma (HNSCC). Using saliva and oral-rinse samples from HNSCC patients, the team detected human papillomavirus (HPV) in all saliva samples and three-quarters of oral-rinse samples, alongside markedly higher levels of the bacteria Porphyromonas gingivalis and Fusobacterium nucleatum compared with cancer-free participants, up to a thousandfold higher in saliva. Bean gum extract alone reduced HPV levels in saliva by 93 per cent and in oral rinse by 80 per cent. A single dose of bean gum combined with protegrin-1 reduced Porphyromonas gingivalis and Fusobacterium nucleatum, both linked to markedly lower survival in oral cancer patients, to near zero within an hour, while sparing beneficial commensal bacteria such as Streptococci. This selectivity stands in contrast to radiation therapy, which depletes beneficial oral bacteria while allowing disease-causing yeast such as Candida albicans to flourish. As a low-cost, non-invasive biologic already recognised as safe by the FDA, this gum offers a promising avenue for preventing viral transmission and improving outcomes in HNSCC.

Source:

📄 RESEARCH PAPER

📌 Daniell H, Wakade G, Singh R, Nair S, Basak SK, Srivatsan ES, et al. Ex vivo HNSCC clinical studies using saliva and antiviral or antibacterial chewing gums reveal reduction in carcinogenic microbes. Sci Rep. 2026 Feb 9;16(1):7886. doi: 10.1038/s41598-026-39062-w. PMID: 41656354; PMCID: PMC12953606.





Could a simple amino acid found in meat, fish and eggs help cancer immunotherapy work better? (2026)

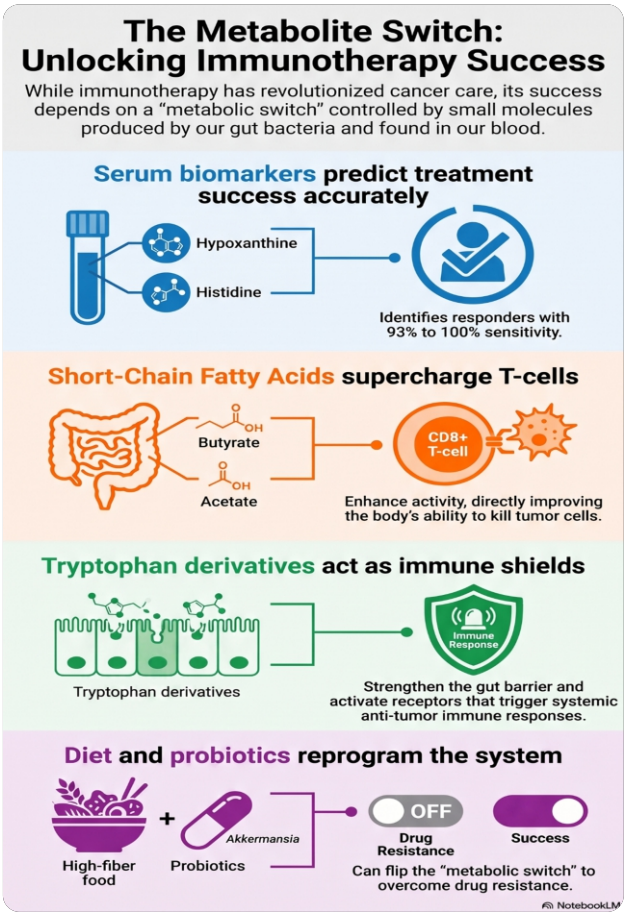
Could blood histidine levels predict who responds to cancer immunotherapy?

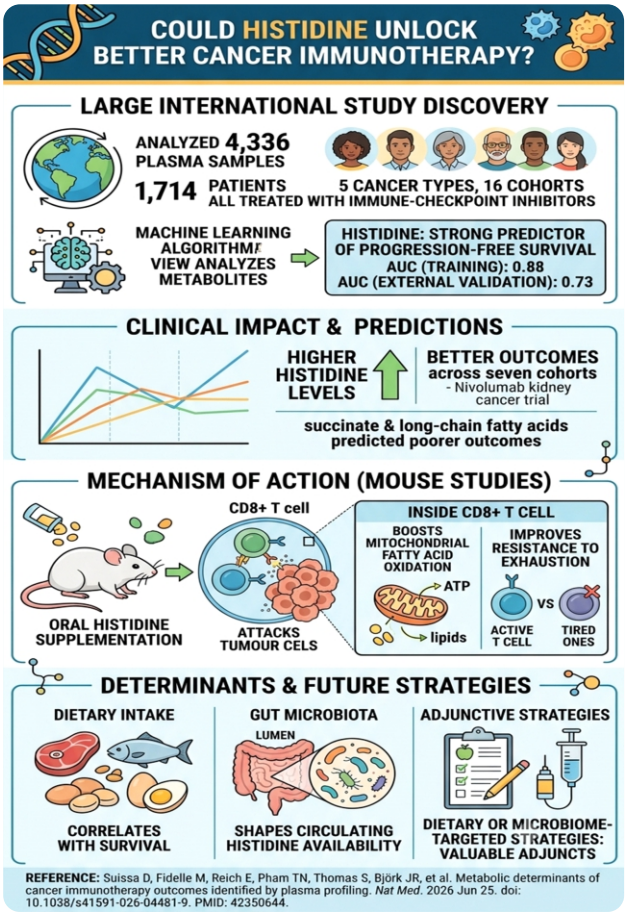
A large international study led by researchers at Gustave Roussy and the ONCOBIOME consortium analysed 4,336 plasma samples from 1,714 patients across five cancer types and 16 cohorts in Europe and North America, all treated with immune-checkpoint inhibitors. Using machine learning on 154 metabolites alongside clinical variables, the team identified histidine, alongside age, body mass index and renal function, as a strong predictor of progression-free survival, achieving an area under the curve of 0.88 in training and 0.73 in external validation. Higher histidine levels were consistently linked to better outcomes across seven independent cohorts, including a large nivolumab trial in kidney cancer, whereas succinate and long-chain fatty acids predicted poorer outcomes. In mice, oral histidine supplementation enhanced antitumour immunity by boosting mitochondrial fatty acid oxidation in CD8+ T cells, improving their resistance to exhaustion. Dietary histidine intake, rather than blood levels alone, also correlated with survival, with gut microbiota composition shaping how much circulating histidine was available. These findings suggest dietary or microbiome-targeted strategies could become valuable adjuncts to immunotherapy.

Source:

COHORT STUDY

Suissa D, Fidelle M, Reich E, Pham TN, Thomas S, Björk JR, et al. Metabolic determinants of cancer immunotherapy outcomes identified by plasma profiling. Nat Med. 2026 Jun 25. doi: 10.1038/s41591-026-04481-9. Epub ahead of print. PMID: 42350644.





GLP-1 Weight-Loss Drugs Linked to Lower Breast Cancer Risk in Overweight Women (2026)

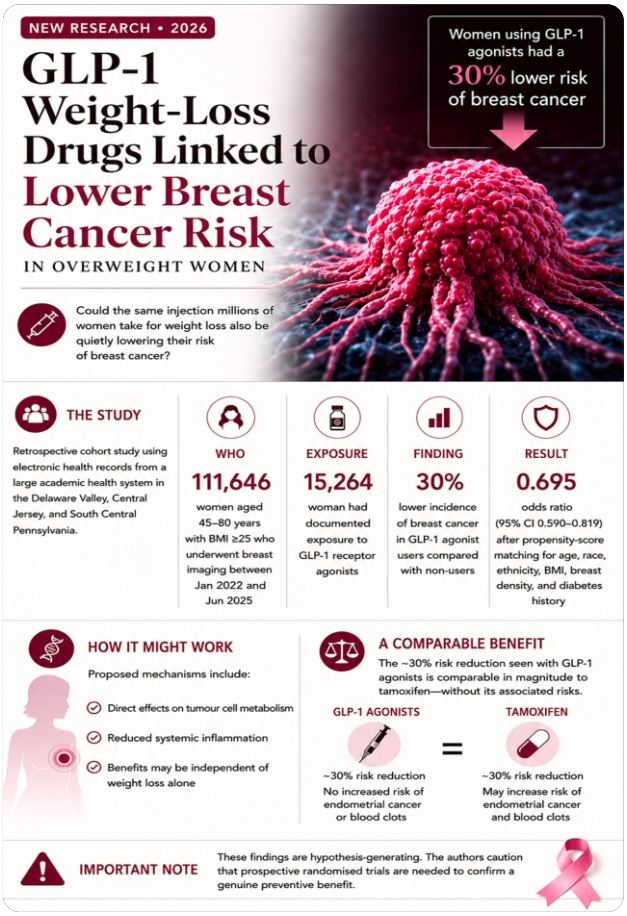
💊 ***Could the same injection millions of women take for weight loss also be quietly lowering their risk of breast cancer?***

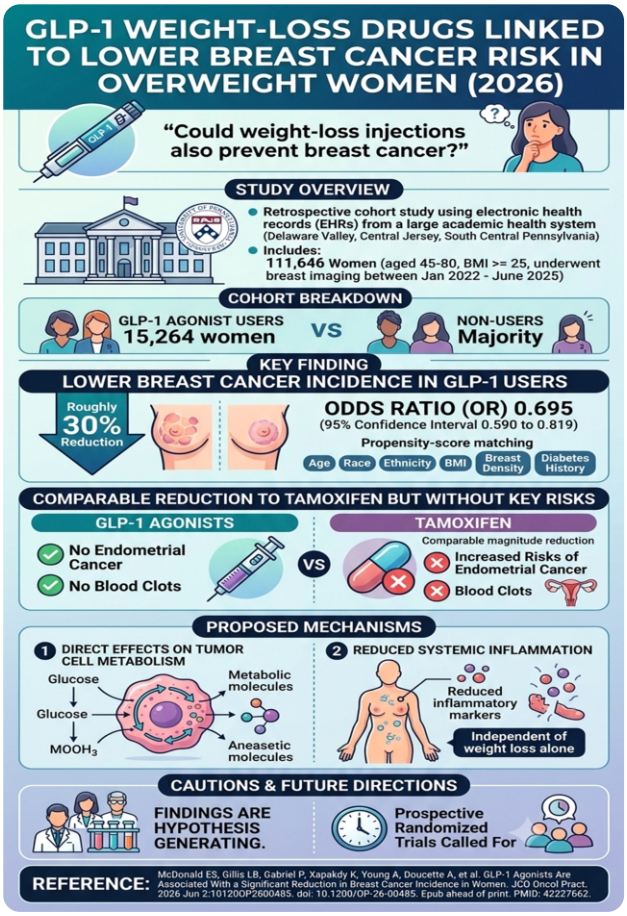
Researchers at the University of Pennsylvania conducted a retrospective cohort study using electronic health records from a large academic health system in the Delaware Valley, Central Jersey, and South-Central Pennsylvania, examining 111,646 women aged 45 to 80 years with a body mass index of 25 or higher who underwent breast imaging between January 2022 and June 2025. Of these, 15,264 women had documented exposure to GLP-1 receptor agonists, commonly prescribed for diabetes and weight management. Women who had taken a GLP-1 agonist were found to have a lower incidence of breast cancer compared with non-users, an association that held even after propensity-score matching for age, race, ethnicity, BMI, breast density, and diabetes history (odds ratio 0.695, 95 percent confidence interval 0.590 to 0.819). The roughly thirty percent reduction was comparable in magnitude to that seen with tamoxifen, though without its associated risks of endometrial cancer and blood clots. Proposed mechanisms include direct effects on tumour cell metabolism and reduced systemic inflammation, independent of weight loss alone. The authors caution that these findings are hypothesis generating and call for prospective randomised trials to confirm a genuine preventive benefit.

Source:

RESEARCH PAPER

McDonald ES, Gillis LB, Gabriel P, Xapakdy K, Young A, Doucette A, et al. GLP-1 Agonists Are Associated with a Significant Reduction in Breast Cancer Incidence in Women. JCO Oncol Pract. 2026 Jun 2:101200OP2600485. doi: 10.1200/OP-26-00485. Epub ahead of print. PMID: 42227662.





Low Testosterone in Men Linked to Higher Risk of Dying from Cancer (2026)

🧪 ***Could a man's testosterone level today hint at his cancer risk decades from now?***

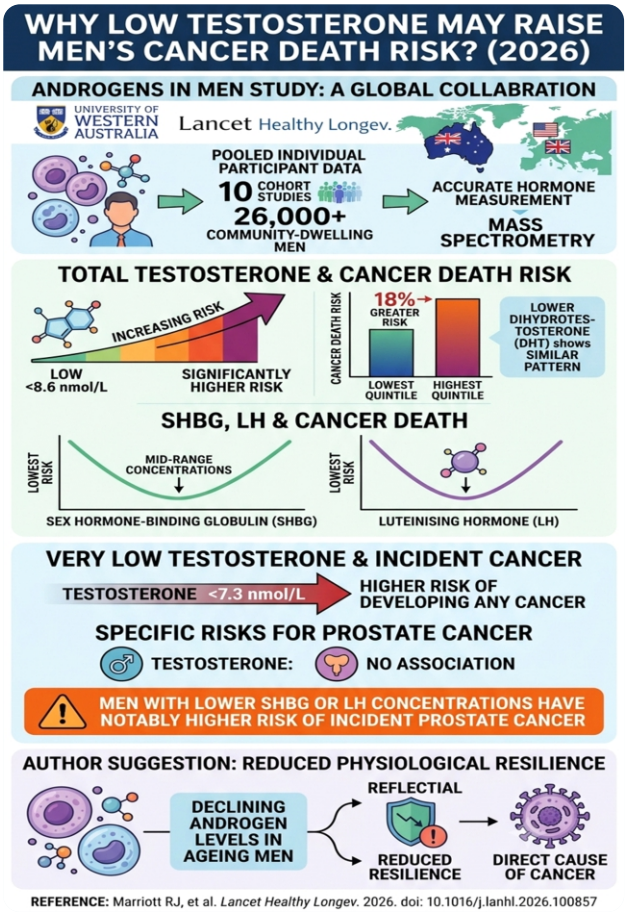
The study was led by researchers at the University of Western Australia (Perth, Australia), with collaborators including Johns Hopkins University (Baltimore, USA) and Harvard Medical School (Boston, USA). The team pooled individual participant data from eleven cohort studies covering more than 26,000 community-dwelling men, with testosterone measured using mass spectrometry. Men with the lowest testosterone concentrations had a higher risk of dying from cancer. This risk rose below a threshold of 8.6 nmol/L. Very low testosterone was also linked to a higher risk of any cancer, but not prostate cancer. SHBG and luteinising hormone showed a different pattern. Men with mid-range levels of either hormone had the lowest risk of cancer death. Lower SHBG or luteinising hormone levels were linked to a higher risk of incident prostate cancer. SHBG carries testosterone in the blood, shaping how much reaches body tissues. Lower luteinising hormone may reflect suppressed hormonal signalling linked to underlying illness. As an observational study, reverse causation cannot be ruled out. Low testosterone may signal frailty or ill health rather than directly cause cancer. These sex hormones may prove useful as biomarkers of cancer risk in ageing men.

Source:

📄 RESEARCH PAPER

📌 Marriott RJ, Murray K, Antonio L, Adams RJ, Ballantyne CM, Bauer DC, et al. Associations of testosterone, sex hormone-binding globulin, and related hormones with risks of cancer death, incident cancer, and incident prostate cancer in men: individual participant data meta-analyses. Lancet Healthy Longev. 2026 Jun;7(6):100857. doi: 10.1016/j.lanhl.2026.100857. Epub 2026 Jun 19. PMID: 42320510.





Some Contraceptive Hormones Linked to Slightly Higher Risk of a Common Brain Tumour (2026)

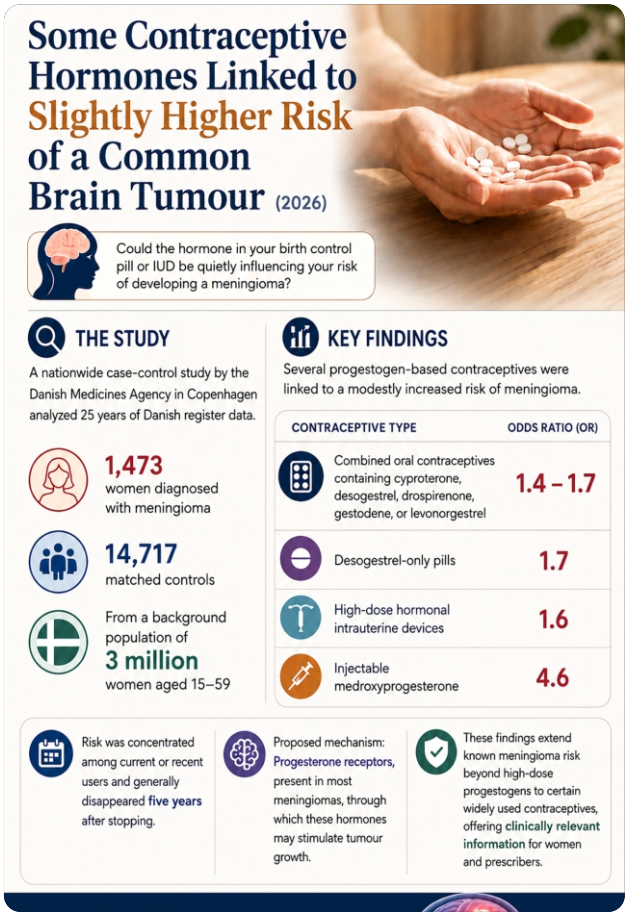
Could the hormone in your birth control pill or IUD be quietly influencing your risk of developing a meningioma?

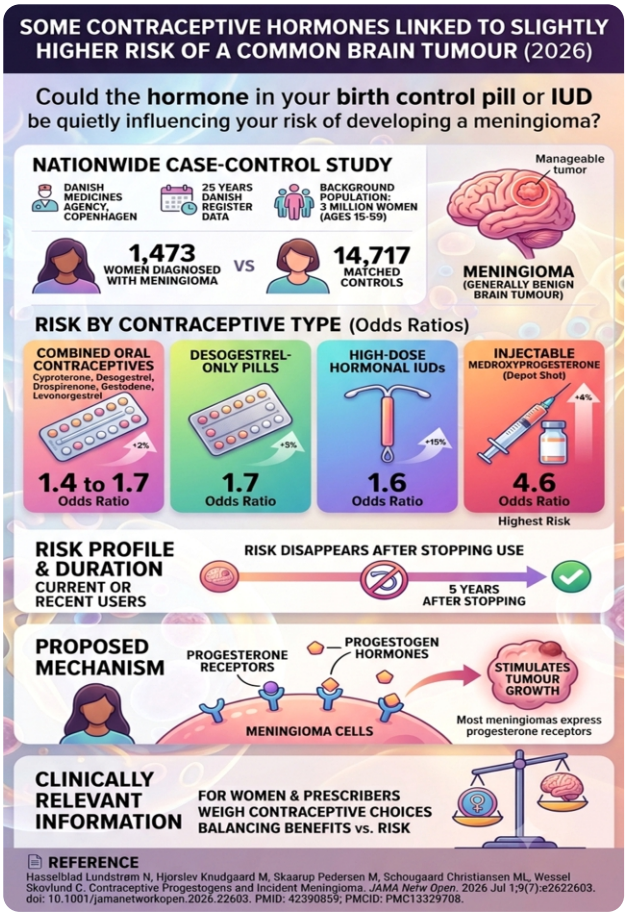
This nationwide case-control study by the Danish Medicines Agency in Copenhagen examined 25 years of Danish register data, comparing 1,473 women diagnosed with meningioma against 14,717 matched controls, drawn from a background population of three million women aged 15 to 59. Several progestogen-based contraceptives were linked to a modestly increased risk of this generally benign brain tumour, with odds ratios ranging from 1.4 to 1.7 for combined oral contraceptives containing cyproterone, desogestrel, drospirenone, gestodene, or levonorgestrel, 1.7 for desogestrel-only pills, and 1.6 for high-dose hormonal intrauterine devices. Injectable medroxyprogesterone carried the highest risk, with an odds ratio of 4.6. Risk was concentrated among current or recent users and generally disappeared five years after stopping. The proposed mechanism involves progesterone receptors, present in most meningiomas, through which these hormones may stimulate tumour growth. These findings extend known meningioma risk beyond high-dose progestogens to certain widely used contraceptives, offering clinically relevant information for women and prescribers weighing contraceptive choices.

Source:

CASE-CONTROL STUDY

Hasselblad Lundstrøm N, Hjorslev Knudgaard M, Skaarup Pedersen M, Schougaard Christiansen ML, Wessel Skovlund C. Contraceptive Progestogens and Incident Meningioma. JAMA Netw Open. 2026 Jul 1;9(7): e2622603. doi: 10.1001/jamanetworkopen.2026.22603. PMID: 42390859; PMCID: PMC13329708.





Younger Generations May Be Aging Faster Inside, Raising Their Cancer Risk (2026)

⏳ ***What if the number on your birth certificate isn't the age your body is actually living?***

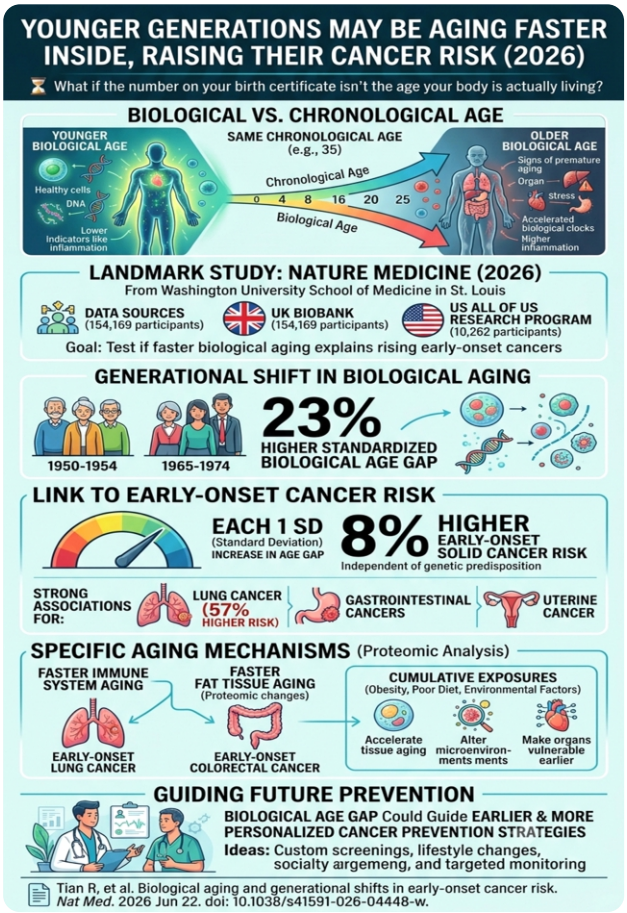
A study published in Nature Medicine in 2026 by researchers at Washington University School of Medicine in St. Louis analysed 154,169 UK Biobank participants and validated findings in 10,262 US All of Us Research Program participants to test whether faster biological aging explains rising early-onset cancer rates. People born between 1965 and 1974 showed a 23% higher standardized biological age gap than those born between 1950 and 1954. Each standard deviation increase in this age gap raised early-onset solid cancer risk by 8%, with stronger associations for lung cancer (57% higher risk), gastrointestinal cancers, and uterine cancer, independent of genetic predisposition for aging or cancer. Proteomic analysis linked faster immune system aging to early-onset lung cancer and faster fat tissue aging to early-onset colorectal cancer, suggesting organ-specific biological changes contribute independently to cancer risk. The authors propose that cumulative exposures, including obesity, poor diet, and environmental factors, accelerate tissue aging and alter tissue microenvironments, increasing vulnerability to tumour formation earlier in life. These findings suggest biological age gap could guide earlier, more personalized cancer prevention strategies.

Source:

📄 COHORT STUDY

📌 Tian R, Zong X, Ren D, Tica S, Hong D, Oduyale O, et al. Biological aging and generational shifts in early-onset cancer risk. Nat Med. 2026 Jun 22. doi: 10.1038/s41591-026-04448-w. PMID: 42332142.





Omega-3 Supplements Linked to Faster Cognitive Decline in Older Adults (2026)

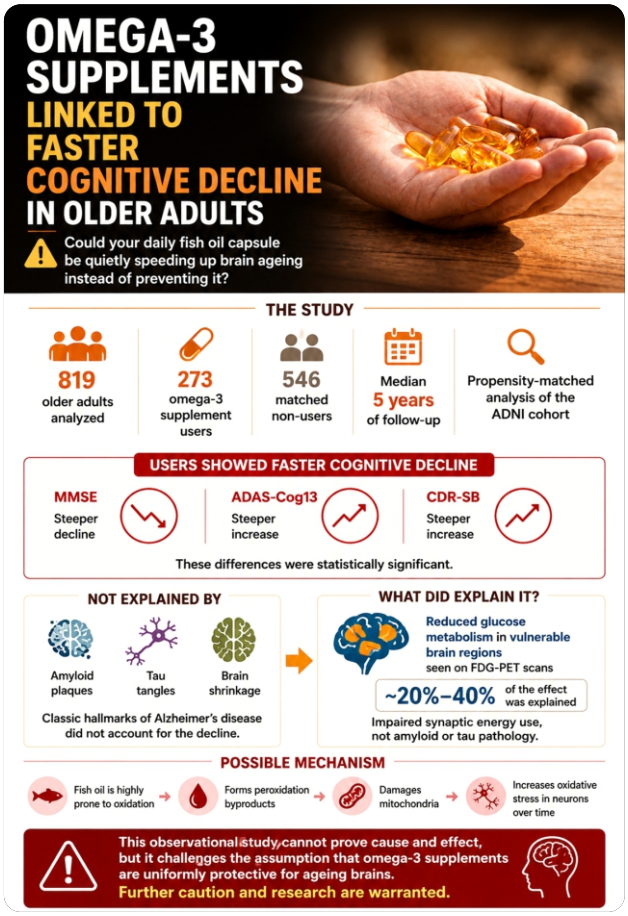
🐟 ***Could your daily fish oil capsule be quietly speeding up brain ageing instead of preventing it?***

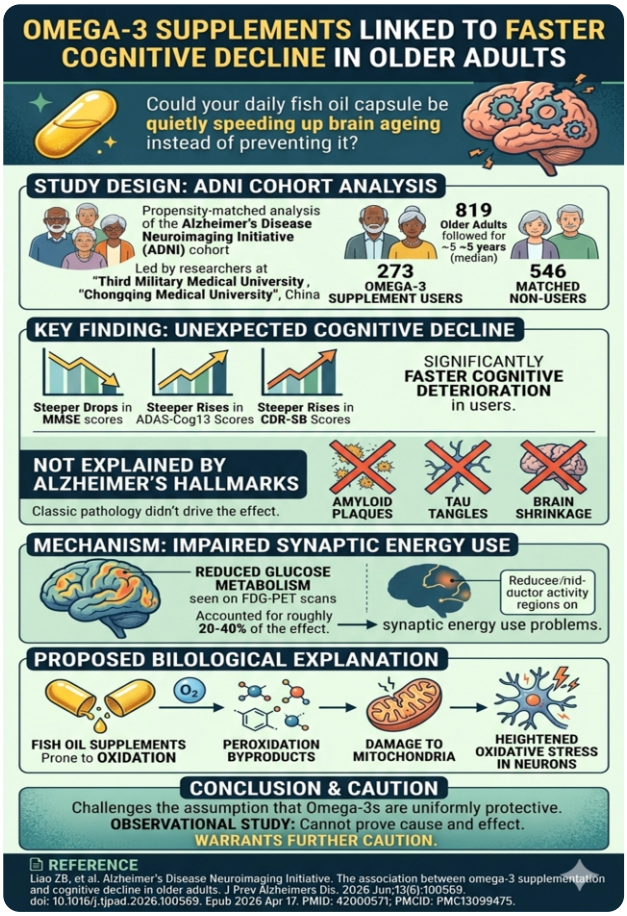
A propensity-matched analysis of the Alzheimer's Disease Neuroimaging Initiative (ADNI) cohort, led by researchers at Third Military Medical University and Chongqing Medical University in China, studied 819 older adults, comprising 273 omega-3 supplement users and 546 matched non-users, followed for a median of five years. Supplement users showed significantly faster cognitive deterioration, with steeper drops in MMSE scores and steeper rises in ADAS-Cog13 and CDR-SB scores. This decline was not explained by amyloid plaques, tau tangles, or brain shrinkage, the classic hallmarks of Alzheimer's disease. Instead, reduced glucose metabolism in vulnerable brain regions, seen on FDG-PET scans, accounted for roughly one-fifth to two-fifths of the effect, pointing to impaired synaptic energy use rather than amyloid or tau pathology. The authors suggest that fish oil, the main supplement used, is particularly prone to oxidation, and resulting peroxidation byproducts may damage mitochondria and heighten oxidative stress in neurons over time. As an observational study, it cannot prove cause and effect, but it challenges the assumption that omega-3 supplements are uniformly protective for ageing brains, warranting further caution.

Source:

📄 PROPENSITY-MATCHED ANALYSIS

📌 Liao ZB, Hu ZC, Zeng GH, Chen J, Li XP, Liu YH, et al. Alzheimer's Disease Neuroimaging Initiative. The association between omega-3 supplementation and cognitive decline in older adults. J Prev Alzheimer's Dis. 2026 Jun;13(6):100569. doi: 10.1016/j.tjpad.2026.100569. Epub 2026 Apr 17. PMID: 42000571; PMCID: PMC13099475.





Blood Mitochondrial DNA Changes Linked to Midlife Cognitive Decline (2026)

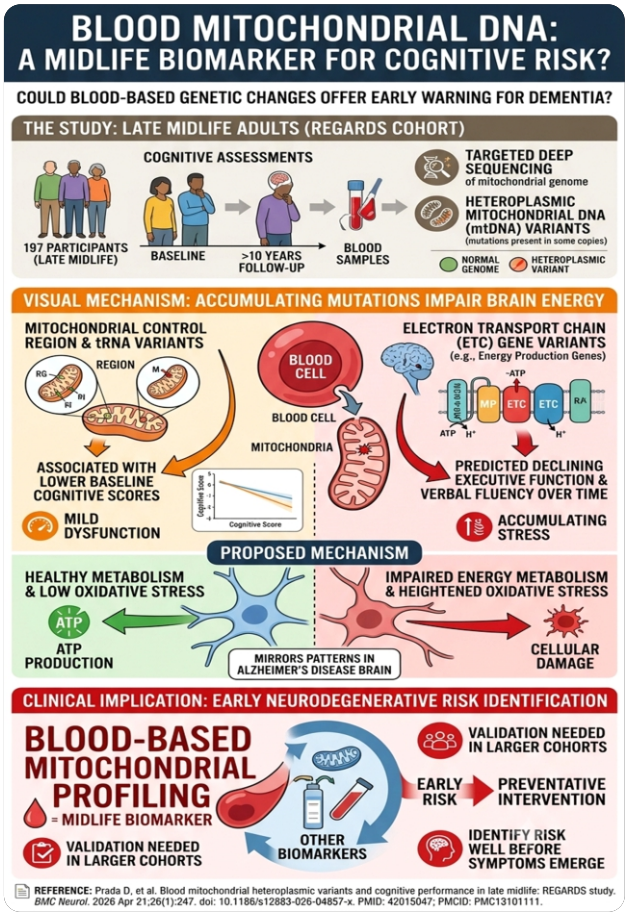
Could tiny genetic changes in the mitochondria circulating in your blood offer an early warning sign for dementia?

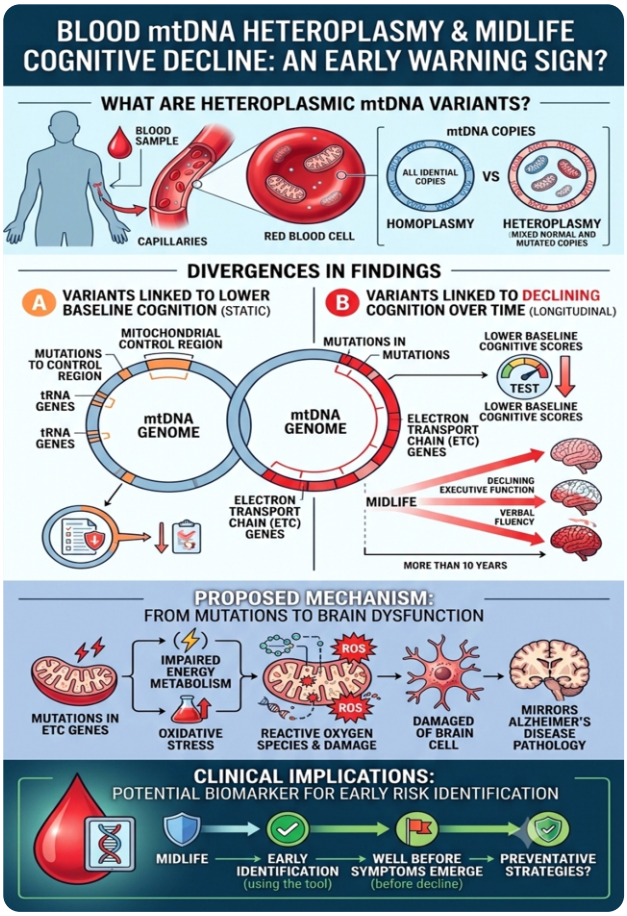
Researchers from the Icahn School of Medicine at Mount Sinai, Columbia University, and the University of Vermont examined whether heteroplasmic mitochondrial DNA variants, meaning mutations present in only a portion of a person's mitochondrial genome copies, relate to cognitive performance in 197 late midlife adults from the REGARDS cohort. Using targeted deep sequencing of blood samples, the team measured variant burden across functional mitochondrial regions and individual genes, then linked these to cognitive scores collected over more than a decade of follow-up. Heteroplasmic variants in the mitochondrial control region and transfer RNA genes were associated with lower baseline cognitive scores, while variants in genes belonging to the electron transport chain, including those governing cellular energy production, showed links to declining executive function and verbal fluency over time. Mechanistically, the authors propose that accumulating mitochondrial mutations impair energy metabolism and heighten oxidative stress in the brain, mirroring patterns previously observed in postmortem Alzheimer's disease brain tissue. While the findings are preliminary and require validation in larger cohorts, they suggest that blood-based mitochondrial profiling could eventually complement other biomarkers in identifying early neurodegenerative risk during midlife, well before symptoms emerge.

Source:

COHORT STUDY

Prada D, Morava-Kozicz E, Rajendrakumar AL, Kupsco A, et al. Blood mitochondrial heteroplasmic variants and cognitive performance in late midlife: REGARDS study. BMC Neurol. 2026 Apr 21;26(1):247. doi: 10.1186/s12883-026-04857-x. PMID: 42015047; PMCID: PMC13101111.





Magnetic Brain Stimulation Improves Social Communication in Autistic Children in Randomised Trial (2026)

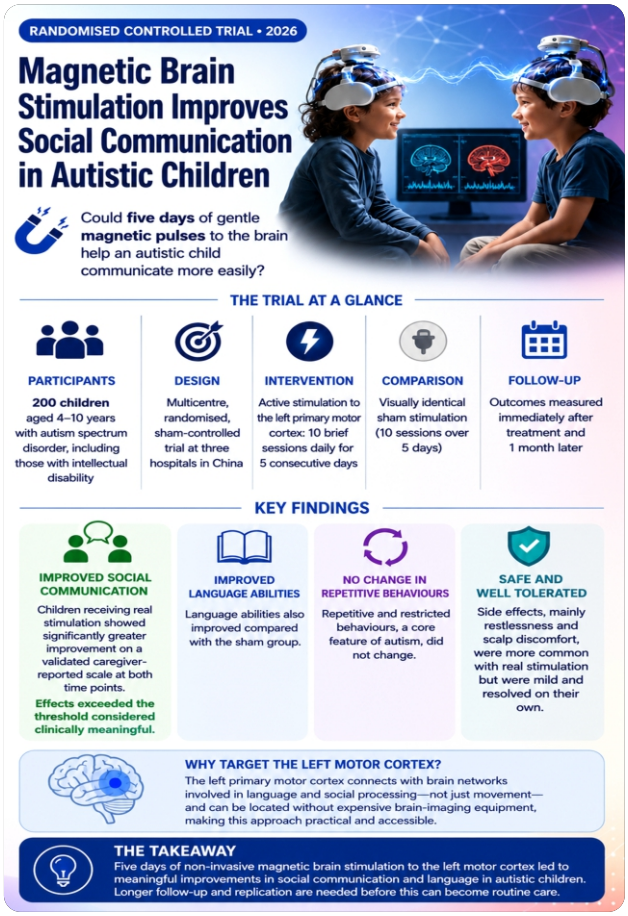
Could five days of gentle magnetic pulses to the brain help an autistic child communicate more easily?

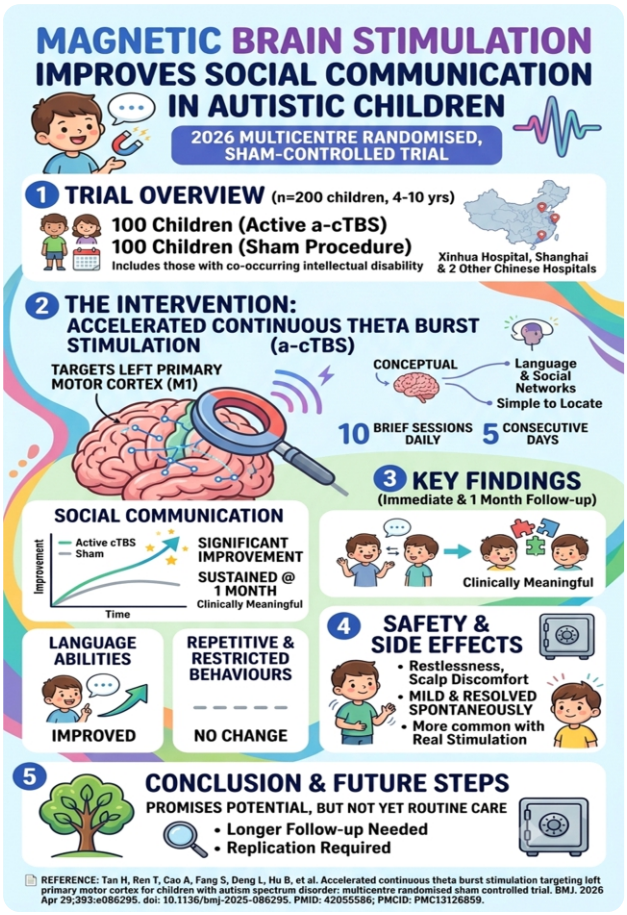
This multicentre, randomised, sham-controlled trial, led by researchers at Xinhua Hospital in Shanghai and two other academic hospitals in China, enrolled 200 children aged 4 to 10 with autism spectrum disorder, including those with co-occurring intellectual disability, a group often excluded from similar research. Half received active magnetic stimulation targeting the left primary motor cortex, delivered across ten brief sessions daily for five consecutive days, while the rest received a visually identical sham procedure. Children receiving real stimulation showed significantly greater improvement in social communication, measured on a validated caregiver-reported scale, both immediately after treatment and one month later, with effects exceeding the threshold considered clinically meaningful. Language abilities also improved, though repetitive and restricted behaviours, a separate core feature of autism, did not change. The left motor cortex was chosen partly because it connects to brain networks involved in language and social processing, not only movement, and can be located without expensive brain-imaging equipment. Side effects, mainly restlessness and scalp discomfort, were more common with real stimulation but were mild and resolved on their own. The authors caution that longer follow-up and replication are needed before this becomes routine care.

Source:

RESEARCH PAPER

Tan H, Ren T, Cao A, Fang S, Deng L, Hu B, et al. Accelerated continuous theta burst stimulation targeting left primary motor cortex for children with autism spectrum disorder: multicentre randomised sham-controlled trial. BMJ. 2026 Apr 29;393: e086295. doi: 10.1136/bmj-2025-086295. PMID: 42055586; PMCID: PMC13126859.





Factor XIa Inhibition: A New Paradigm in Secondary Stroke Prevention (2026)

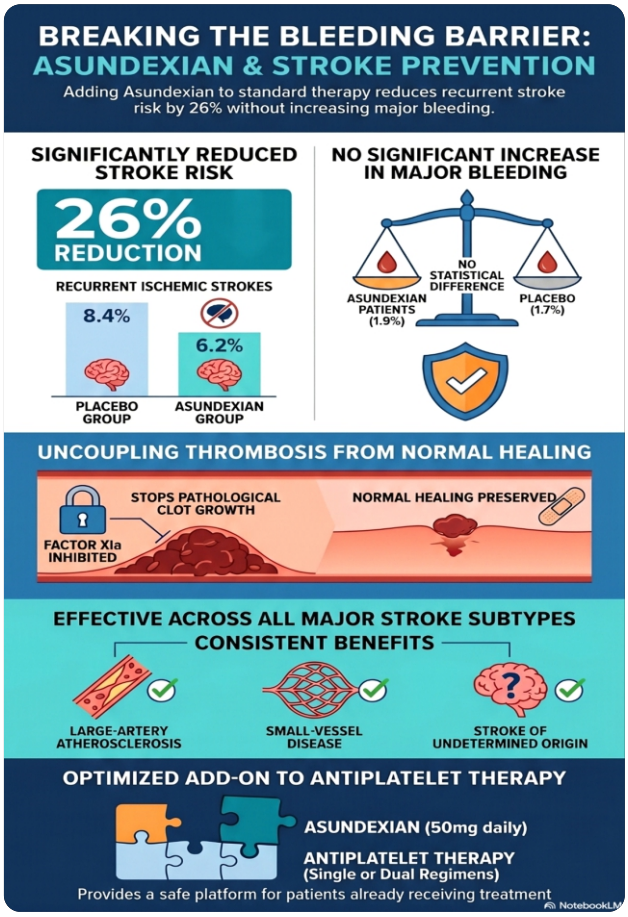
Could a new class of anticoagulants prevent secondary strokes without the dangerous trade-off of increased bleeding?

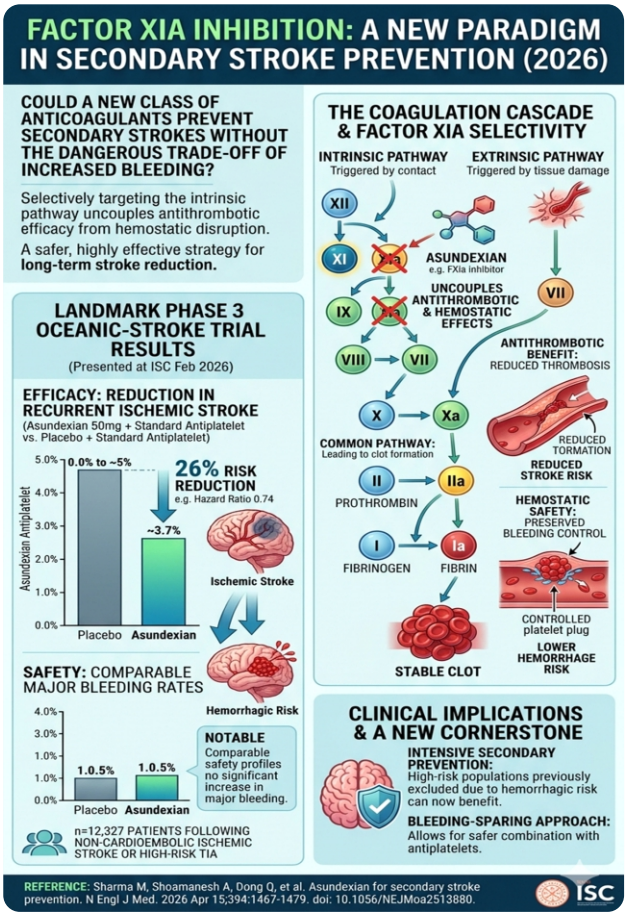
The landmark results of the Phase 3 OCEANIC-STROKE trial, presented at the International Stroke Conference in February 2026 and published in The New England Journal of Medicine, mark a significant milestone in vascular neurology. The study evaluated Asundexian, a potent oral Factor XIa inhibitor, in 12,327 patients following a non-cardioembolic ischemic stroke or high-risk transient ischemic attack. Data demonstrated that Asundexian 50 mg daily reduced the risk of recurrent ischemic stroke by twenty-six percent compared to placebo when added to standard antiplatelet therapy. Most notably, there was no significant increase in major bleeding rates, with safety profiles remaining comparable to placebo. By selectively targeting the intrinsic pathway of the coagulation cascade, Asundexian successfully uncouples antithrombotic efficacy from hemostatic disruption. This "bleeding-sparing" approach allows for intensive secondary prevention in high-risk populations who were previously excluded from anticoagulation due to haemorrhagic risk. These findings establish Factor XIa inhibition as a cornerstone for the next generation of antithrombotic management, offering a safer, highly effective strategy for long-term stroke reduction.

Source:

RESEARCH PAPER

Sharma M, Shoamanesh A, Dong Q, et al. OCEANIC-STROKE Investigators. Asundexian for Secondary Stroke Prevention. N Engl J Med. 2026 Apr 16;394(15):1467-1479. doi: 10.1056/NEJMoa2513880. PMID: 41985132.





Could mixing virtual reality with electrical nerve stimulation help stroke survivors regain hand and arm function (2026)

🥽 ***Could a video-game headset paired with gentle electrical pulses retrain the brain after stroke?***

A randomised feasibility trial conducted at the Clinic for Rehabilitation Dr Miroslav Zotović in Belgrade tested MultiSensy, a platform combining immersive virtual reality with synchronous transcutaneous electrical nerve stimulation of the median nerve, in patients with chronic stroke. Following an initial nine-patient pilot confirming usability and embodiment, 25 patients with persistent upper-limb impairment were randomised to three weeks of MultiSensy therapy or dose-matched conventional rehabilitation, twelve sessions in total. Patients using MultiSensy showed significantly greater gains in arm function, with Fugl-Meyer Assessment scores improving by over 13 points compared to under eight in the conventional group, and Action Research Arm Test scores improving by more than nine points compared to roughly three. All twelve MultiSensy patients reached a clinically meaningful motor improvement, compared with eight of thirteen on conventional therapy. The platform also restored a more accurate sense of limb size and improved tactile sensitivity, both commonly distorted after stroke. Built-in motion tracking allowed continuous, objective monitoring of recovery without relying solely on therapist assessment. No adverse events occurred. The findings support larger trials of immersive, minimally supervised rehabilitation, potentially extending therapy into patients' homes.

Source:

📄 RESEARCH PAPER

📌 Aurucci GV, Djordjevic O, Cimolato A, Secerovic N, Dimkic Tomic T, Ardura Carnicero MD, et al. Immersive virtual reality with synchronous neurostimulation for upper-limb recovery after stroke: a randomized feasibility trial. Nat Med. 2026 Jun 26. doi: 10.1038/s41591-026-04486-4. Epub ahead of print.





Becoming a Father Reshapes the Brain: Neuroplasticity in New Fathers Across the First Six Months (2026)

👶 ***Does the brain of a new father physically restructure itself to prepare him for caregiving and bonding?***

The paternal brain undergoes significant structural and functional reorganisation following childbirth, according to a longitudinal neuroimaging study from RWTH Aachen University and Research Center Jülich, Germany. Using MRI across six time points over 24 weeks, 25 new fathers were assessed for gray matter volume (GMV) and resting-state functional connectivity. GMV reductions peaked within the first six weeks, affecting bilateral occipital, frontal, temporal and parietal cortices, the temporo-parietal junction, insula, and hippocampal regions. From 12 weeks onward, localised increases emerged in frontal and cerebellar regions. Connectivity analysis revealed significant reorganisation within the Salience, Default Mode, and Frontoparietal Networks, peaking during the first nine weeks, reflecting a shift from sensory to higher-order cognitive and emotional processing. Crucially, increased amygdala-cingulate and amygdala-hippocampal connectivity was significantly associated with paternal attachment scores during the first 12 weeks, implicating the amygdala as a central driver of early bonding. Unlike maternal neuroplasticity driven by hormonal shifts, paternal brain changes reflect experience-dependent adaptation to caregiving demands. These findings collectively outline a clear trajectory of paternal neuroplasticity with key implications for understanding paternal neurobiology.

Source:

📄 RESEARCH PAPER

📌 Daneshnia N, Losse EM, Kurz A, Chechko N, Nehls S. The paternal brain: longitudinal insights into structural and functional plasticity and attachment over 24 weeks postpartum. Transl Psychiatry. 2026 May 14;16(1):247. doi: 10.1038/s41398-026-04082-7. PMID: 42135294; PMCID: PMC13176344.





The Brain's Built-In "Attention Switch": An Ancient Brainstem Circuit That Keeps Us Focused (2026)

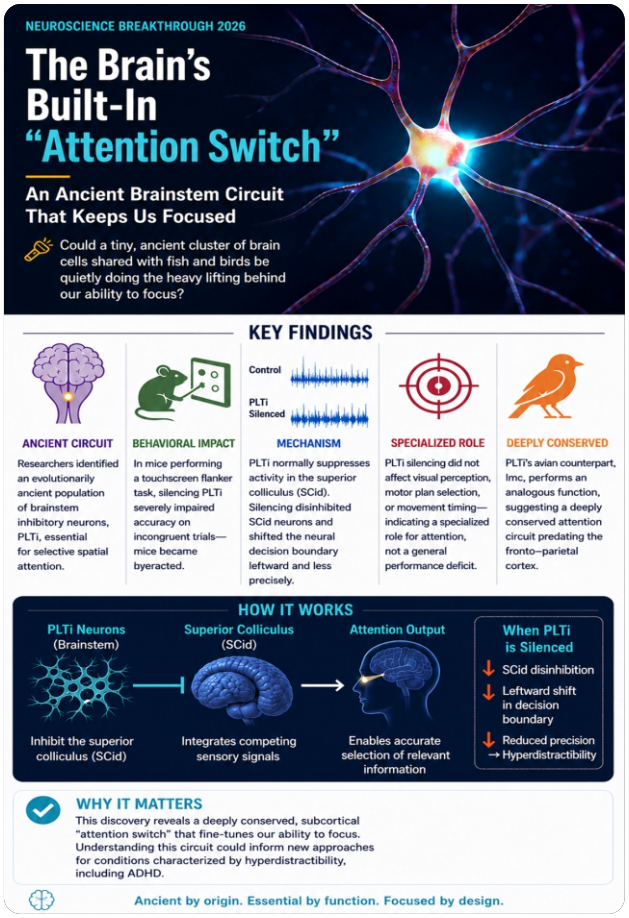
Could a tiny, ancient cluster of brain cells shared with fish and birds be quietly doing the heavy lifting behind our ability to focus?

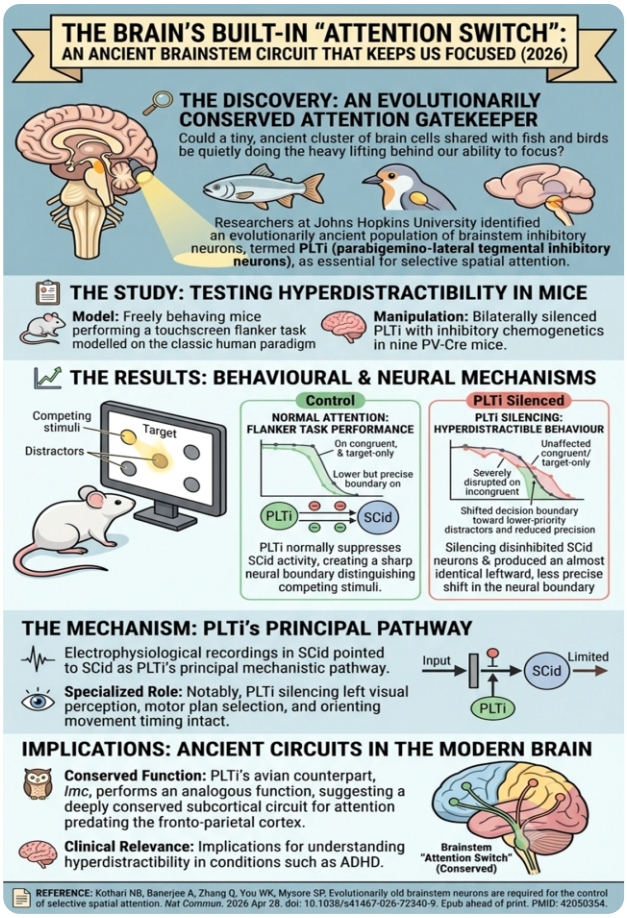
Researchers at Johns Hopkins University identified an evolutionarily ancient population of brainstem inhibitory neurons, termed PLTi (parabigemino-lateral tegmental inhibitory neurons), as essential for selective spatial attention. Using freely behaving mice performing a touchscreen flanker task modelled on the classic human paradigm, the team bilaterally silenced PLTi with inhibitory chemogenetics in nine PV-Cre mice. Silencing left performance on congruent and target-only trials unaffected but severely disrupted accuracy on incongruent trials, shifting the behavioural decision boundary toward lower-priority distractors and reducing its categorical precision, effectively rendering mice hyperdistractible. Electrophysiological recordings in the superior colliculus (SCid) revealed that PLTi normally suppresses SCid activity; silencing disinhibited SCid neurons and produced an almost identical leftward, less precise shift in the neural boundary distinguishing competing stimuli, pointing to SCid as PLTi's principal mechanistic pathway. Notably, PLTi silencing left visual perception, motor plan selection and orienting movement timing intact, indicating a specialised rather than distributed role. Because PLTi's avian counterpart, Imc, performs an analogous function, the findings suggest a deeply conserved subcortical circuit for attention predating the fronto-parietal cortex, with implications for understanding hyperdistractibility in conditions such as ADHD.

Source:

RESEARCH PAPER

Kothari NB, Banerjee A, Zhang Q, You WK, Mysore SP. Evolutionarily old brainstem neurons are required for the control of selective spatial attention. Nat Commun. 2026 Apr 28. doi: 10.1038/s41467-026-72340-9. Epub ahead of print. PMID: 42050354.





Could 'Hyperonirism' Be a New Sleep Disorder? French Case Series Proposes Diagnostic Criteria (2026)

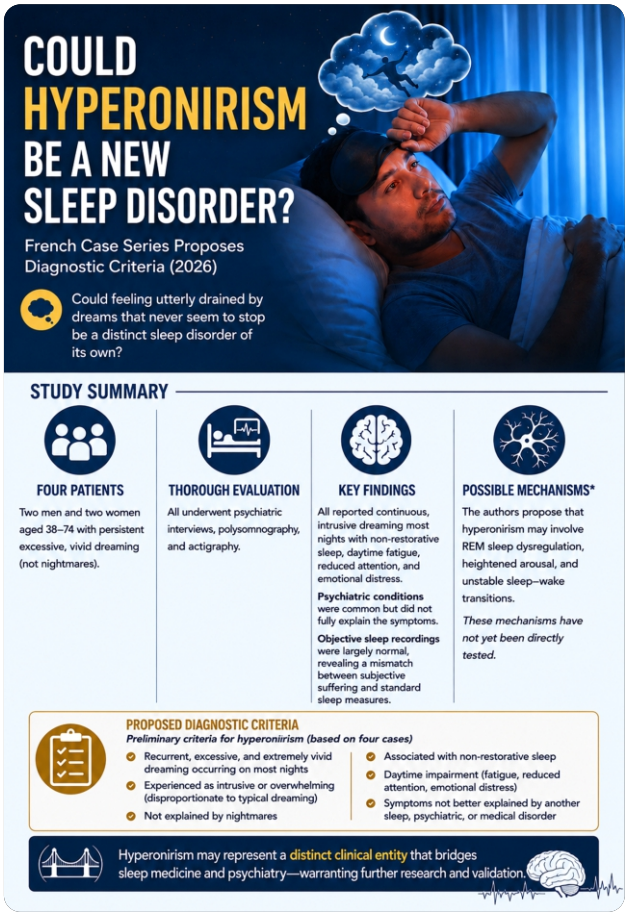
Could feeling utterly drained by dreams that never seem to stop be a distinct sleep disorder of its own?

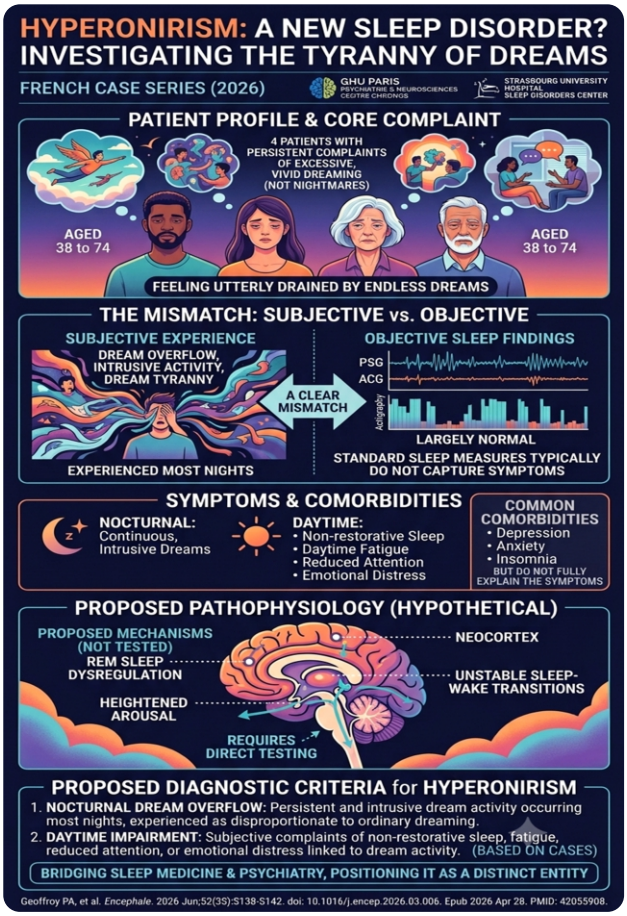
Researchers from the Centre ChronoS at GHU Paris Psychiatrie & Neurosciences and the Sleep Disorders Centre at Strasbourg University Hospital, France, describe four patients, two men and two women aged 38 to 74, with persistent complaints of excessive, vivid dreaming unrelated to nightmares. Each underwent detailed psychiatric and sleep assessment, including polysomnography and actigraphy. All four described continuous, intrusive dream activity occurring most nights, experienced as disproportionate to ordinary dreaming and accompanied by non-restorative sleep, daytime fatigue, reduced attention, and emotional distress. Psychiatric conditions such as depression, anxiety, or insomnia were common but did not fully explain the symptoms, and objective sleep recordings were largely normal, highlighting a mismatch between subjective experience and standard sleep measures. The authors propose that the condition, termed hyperonirism, may involve REM sleep dysregulation, heightened arousal, and unstable sleep-wake transitions, though this has not yet been directly tested. Based on these cases, they put forward preliminary diagnostic criteria covering nocturnal dream overflow and daytime impairment, positioning hyperonirism as a distinct entity bridging sleep medicine and psychiatry that warrants further study.

Source:

CASE REPORT

Geoffroy PA, Saadi S, Mauries S, Clerici E, Lejoyeux M, Maruani J, et al. Dream tyranny: Hyperonirism diagnostic criteria. Encephale. 2026 Jun;52(3S): S138-S142. doi: 10.1016/j.encep.2026.03.006. Epub 2026 Apr 28. PMID: 42055908.





Brain Scans Reveal How Depression Traps the Mind Between Rigid Mental States (2026)

🧠 ***Could depression be less about damaged brain regions and more about getting stuck cycling through the wrong mental gears?***

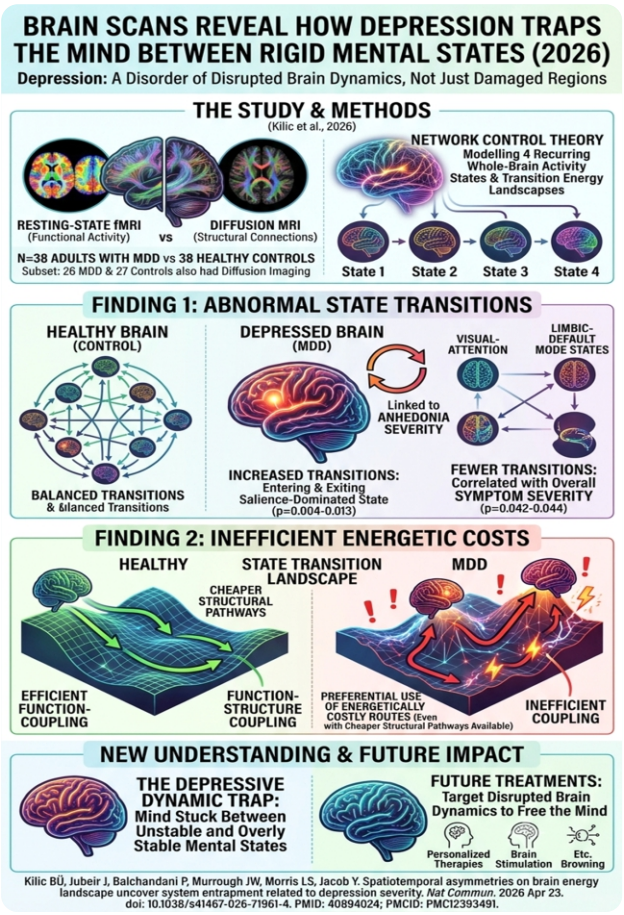
Researchers at the Icahn School of Medicine at Mount Sinai, New York, combined resting-state and diffusion MRI to study how brain activity patterns shift over time in depression. The study compared 38 adults with major depressive disorder (MDD) to 38 healthy controls, with a subset of 26 MDD patients and 27 controls also undergoing diffusion imaging to map structural brain connections. Using network control theory, the team modelled four recurring whole-brain activity states and the 'energy' required to move between them. People with MDD entered and exited a salience-dominated state significantly more often (p=0.004-0.013), and this pattern correlated with anhedonia severity. They also showed fewer transitions between visual-attention and limbic-default mode states (p=0.042-0.044), correlating with greater overall symptom severity. Crucially, MDD participants preferentially used energetically costly transition routes even when cheaper structural pathways existed, pointing to inefficient coupling between brain structure and function. These findings reframe depression as a disorder of disrupted brain dynamics, in which the mind becomes trapped between unstable and overly stable mental states, offering a new mechanistic target for future treatments.

Source:

📄 RESEARCH PAPER

📌 Kilic BÜ, Jubeir J, Balchandani P, Murrough JW, Morris LS, Jacob Y. Spatiotemporal asymmetries on brain energy landscape uncover system entrapment related to depression severity. Nat Commun. 2026 Apr 23. doi: 10.1038/s41467-026-71961-4. Online ahead of print. PMID: 40894024; PMCID: PMC12393491.





High-Dose Psilocybin Misses Primary Goal but Eases Symptoms in Resistant Depression Trial (2026)

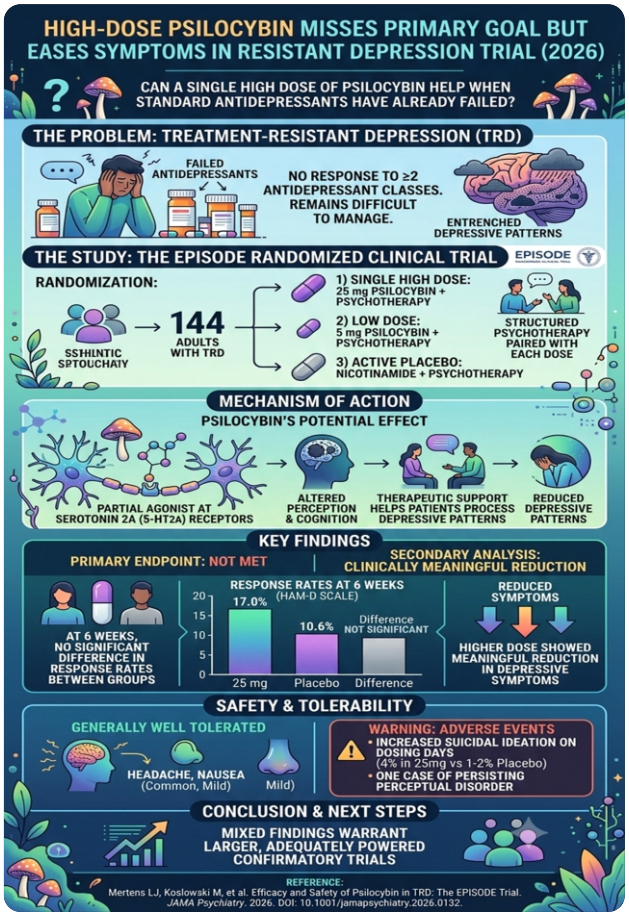
Can a single high dose of psilocybin help when standard antidepressants have already failed?

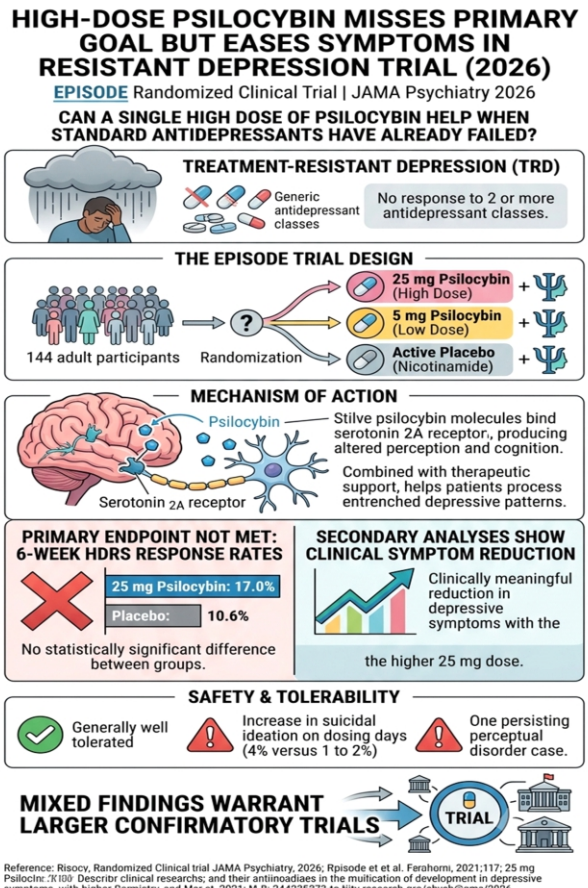
Treatment-resistant depression, defined as no response to two or more antidepressant classes, remains difficult to manage. The EPISODE trial, conducted at the Central Institute of Mental Health in Mannheim and Charité Berlin, randomised 144 adults with treatment-resistant depression to a single 25 mg dose of psilocybin, a low 5 mg dose, or an active placebo (nicotinamide), each paired with structured psychotherapy. Psilocybin acts as a partial agonist at serotonin 2A receptors, producing altered perception and cognition that, combined with therapeutic support, is thought to help patients process entrenched depressive patterns. At six weeks, response rates on the Hamilton Depression Rating Scale did not differ significantly between groups (17.0% for 25 mg versus 10.6% for placebo), so the primary endpoint was not met. However, secondary analyses showed a clinically meaningful reduction in depressive symptoms with the higher dose. Psilocybin was generally well tolerated, though suicidal ideation on dosing days was more frequent (4% versus 1 to 2%), and one participant developed a persisting perceptual disorder. The authors concluded these mixed findings warrant larger, adequately powered confirmatory trials.

Source:

RESEARCH PAPER

Mertens LJ, Koslowski M, Betzler F, Brand M, Evens R, Kärtner L, et al. Efficacy and Safety of Psilocybin in Treatment-Resistant Major Depression: The EPISODE Randomized Clinical Trial. JAMA Psychiatry. 2026 May 1;83(5):448-460. doi: 10.1001/jamapsychiatry.2026.0132. PMID: 41848690; PMCID: PMC13000742.





Severe Infections Independently Increase Dementia Risk, Finnish Registry Study Shows (2026)

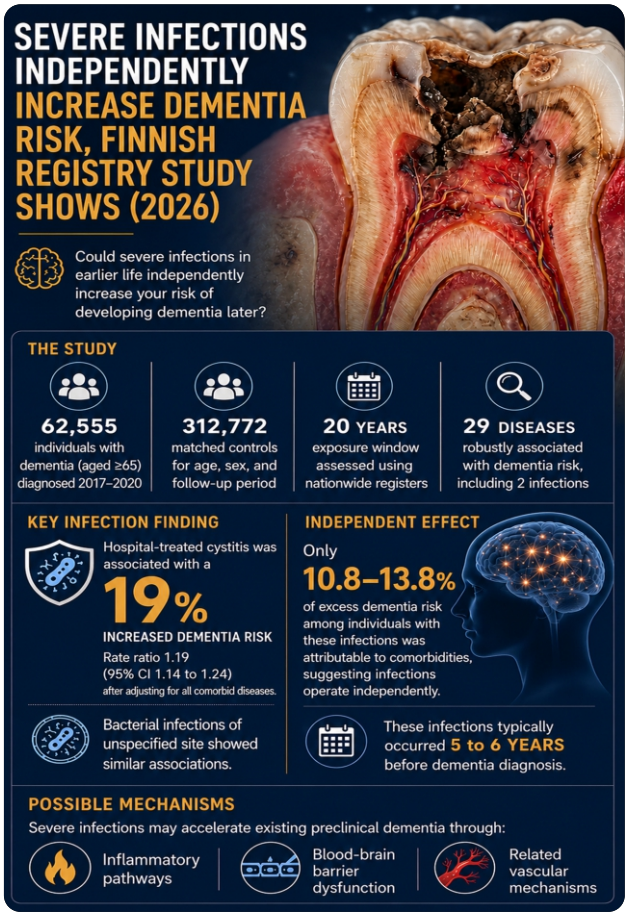
Could severe infections in earlier life independently increase your risk of developing dementia later?

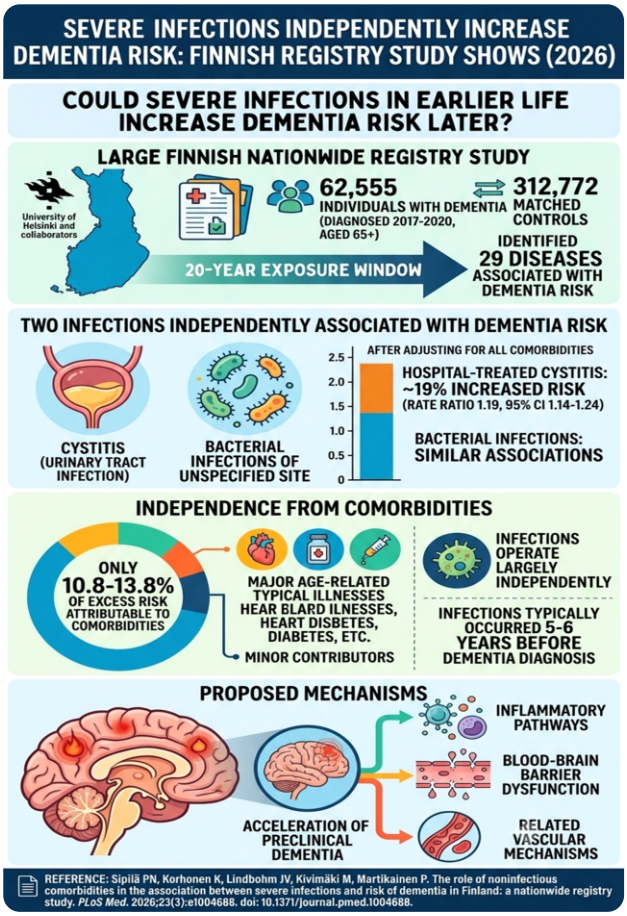
Researchers from the University of Helsinki and collaborating institutions analysed nationwide Finnish health registers to examine whether severe hospital-treated infections independently increase dementia risk beyond other age-related illnesses. They studied 62,555 individuals aged 65 or older diagnosed with dementia between 2017 and 2020, matched with 312,772 controls for age, sex, and follow-up period. Over a 20-year exposure window, the team identified 29 diseases robustly associated with dementia risk, including two infections: cystitis and bacterial infections of unspecified site. Hospital-treated cystitis was associated with a 19 per cent increased dementia risk (rate ratio 1.19, 95 per cent confidence interval 1.14 to 1.24) after adjusting for all comorbid diseases. Bacterial infections showed similar associations. Notably, only 10.8 to 13.8 per cent of excess dementia risk among individuals with these infections was attributable to comorbidities, suggesting infections operate independently. These infections typically occurred 5 to 6 years before dementia diagnosis. The authors propose that severe infections may accelerate existing preclinical dementia through inflammatory pathways, blood-brain barrier dysfunction, and related vascular mechanisms.

Source:

COHORT STUDY

Sipilä PN, Korhonen K, Lindbohm JV, Kivimäki M, Martikainen P. The role of non-infectious comorbidities in the association between severe infections and risk of dementia in Finland: A nationwide registry study. PLoS Med. 2026 Mar 24;23(3): e1004688. doi: 10.1371/journal.pmed.1004688. PMID: 41875076; PMCID: PMC13012496.





Bilingual Men May Have Extra Brain Protection Against Alzheimer's, Study Finds (2026)

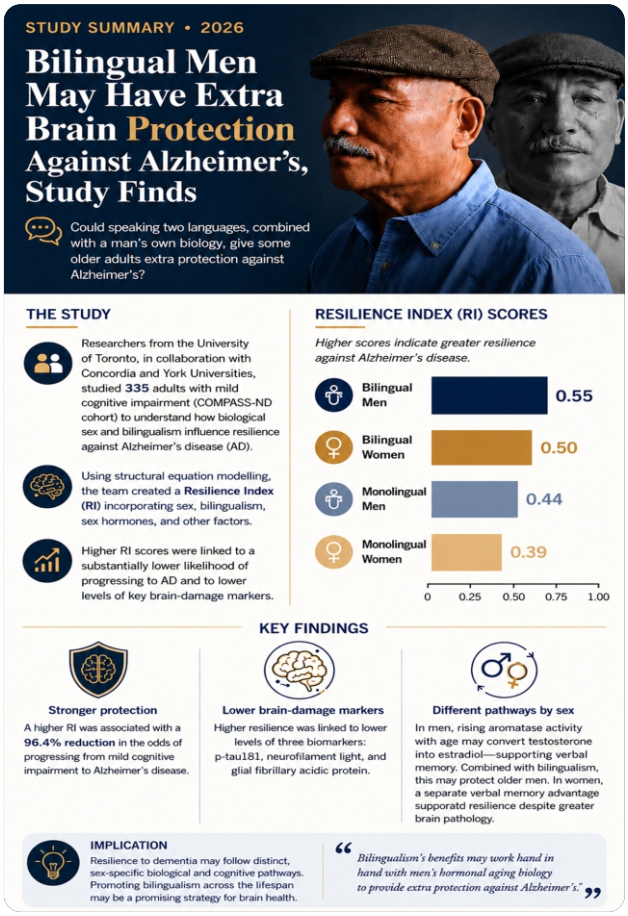
Could speaking two languages, combined with a man's own biology, give some older adults extra protection against Alzheimer's?

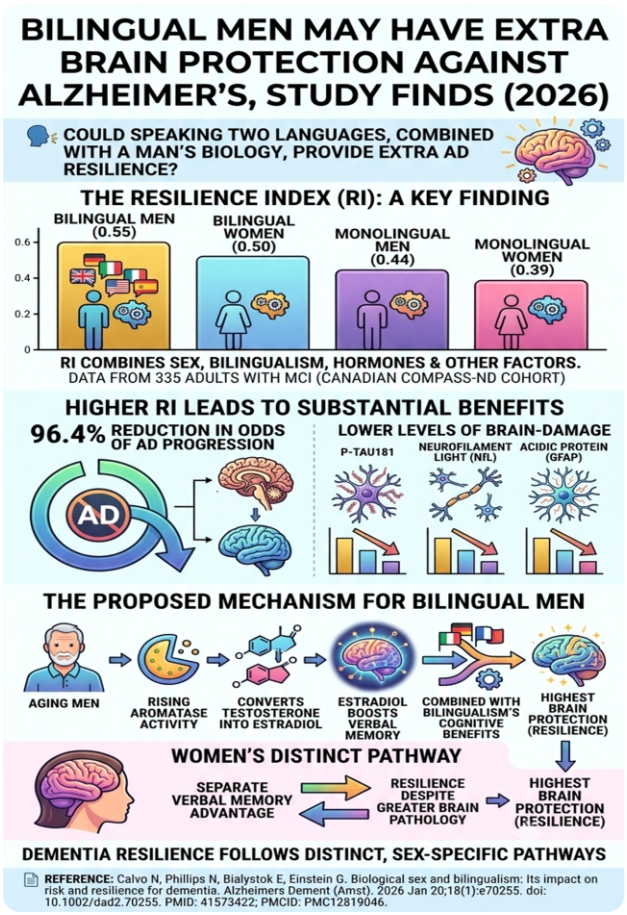
Researchers at the University of Toronto, working with colleagues at Concordia and York Universities, examined how biological sex and bilingualism together shape resilience against Alzheimer's disease (AD) in 335 adults with mild cognitive impairment from the Canadian COMPASS-ND cohort. Using structural equation modelling, the team created a resilience index (RI) combining sex, bilingualism, sex hormones, and other factors. Bilingual men had the highest RI (0.55), followed by bilingual women (0.50), monolingual men (0.44), and monolingual women (0.39). A higher RI was linked to a substantially lower likelihood of progressing to AD (a 96.4% reduction in the odds) and to lower levels of three brain-damage markers: p-tau181, neurofilament light, and glial fibrillary acidic protein. The authors propose that as men age, rising aromatase activity converts testosterone into estradiol, a hormone important for verbal memory, and that this shift may combine with bilingualism's known cognitive benefits to protect older bilingual men. In women, a separate verbal memory advantage appeared to support resilience despite greater brain pathology. These findings suggest resilience to dementia may follow distinct, sex-specific pathways.

Source:

RESEARCH PAPER

Calvo N, Phillips N, Bialystok E, Einstein G. Biological sex and bilingualism: Its impact on risk and resilience for dementia. Alzheimers Dement (Amst). 2026 Jan 20;18(1): e70255. doi: 10.1002/dad2.70255. PMID: 41573422; PMCID: PMC12819046.





Handwriting Speed During Dictation May Help Detect Early Cognitive Decline (2026)

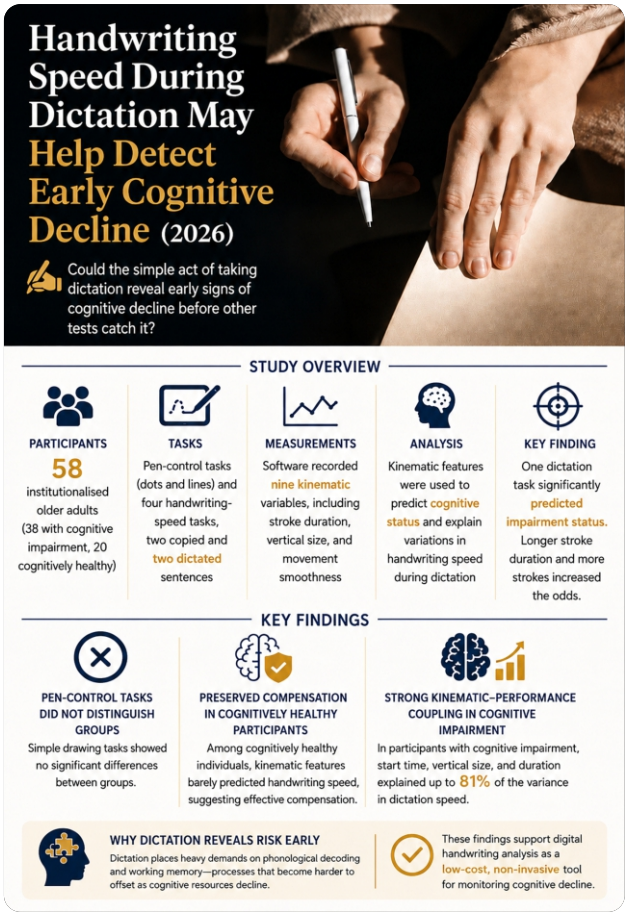
✍️ ***Could the simple act of taking dictation reveal early signs of cognitive decline before other tests catch it?***

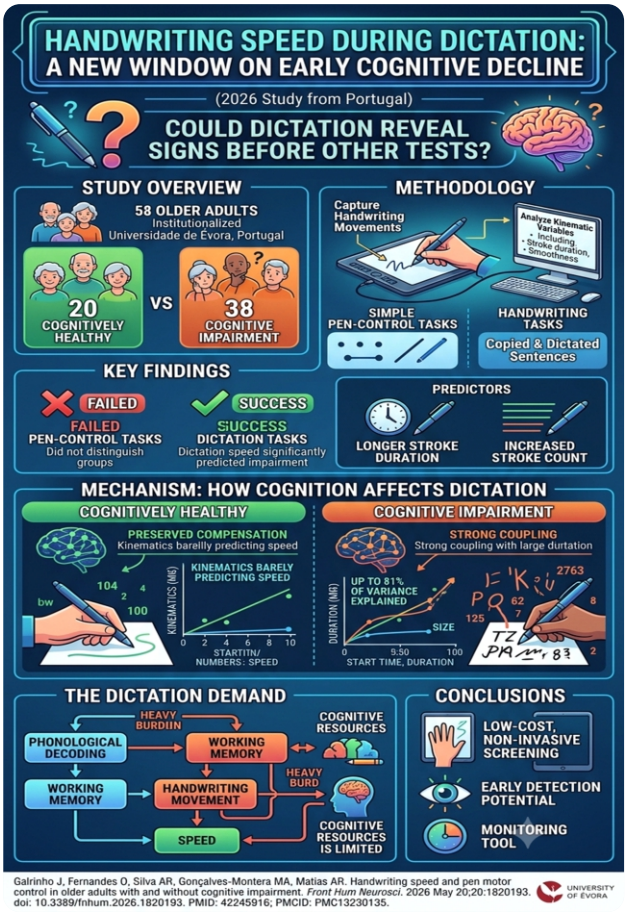
Researchers at the Universidade de Évora, Portugal, examined whether handwriting movements captured on a digitizing tablet could distinguish cognitive status in 58 institutionalised older adults, 38 with cognitive impairment and 20 cognitively healthy. Participants completed simple pen-control tasks (drawing dots and lines) and four handwriting-speed tasks, two copied and two dictated sentences, while software recorded nine kinematic variables, including stroke duration, vertical size, and movement smoothness. Pen-control tasks failed to distinguish the groups, but one dictation task significantly predicted impairment status, with longer stroke duration and more strokes increasing the odds of impairment. Among cognitively healthy participants, kinematics barely predicted handwriting speed, suggesting preserved compensation. In contrast, participants with cognitive impairment showed strong coupling between kinematic features and performance, with start time, vertical size, and duration explaining up to 81 percent of the variance in dictation speed. The authors attribute this to dictation's heavy demands on phonological decoding and working memory, which grow harder to offset as cognitive resources decline. These findings support digital handwriting analysis as a low-cost, non-invasive tool for monitoring cognitive decline.

Source:

RESEARCH PAPER

Galrinho J, Fernandes O, Silva AR, Gonçalves-Montera MA, Matias AR. Handwriting speed and pen motor control in older adults with and without cognitive impairment. Front Hum Neurosci. 2026 May 20; 20:1820193. doi: 10.3389/fnhum.2026.1820193. PMID: 42245916; PMCID: PMC13230135.





Case Report Describes Temporary Gains in Advanced Alzheimer's After High-Dose Psilocybin Mushrooms (2026)

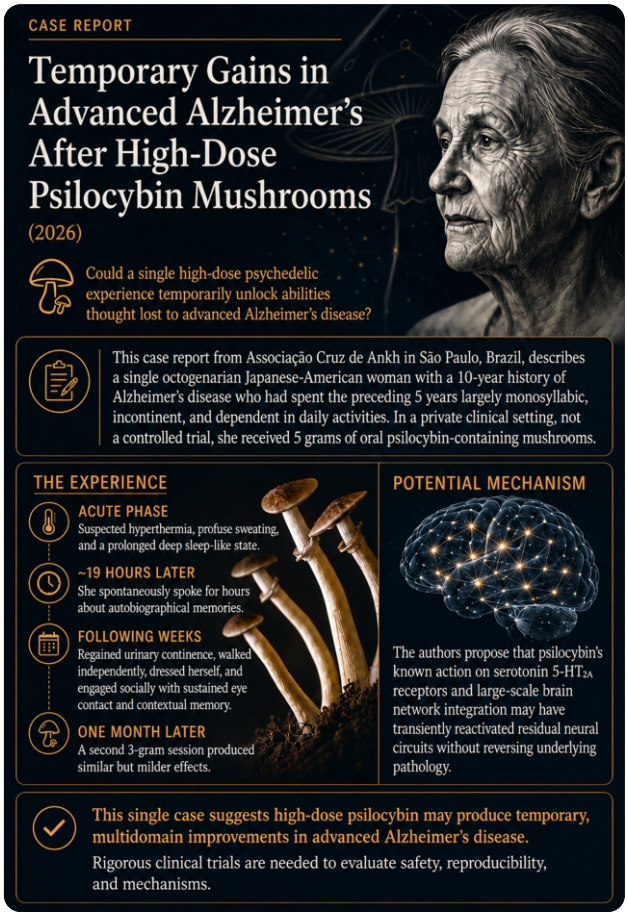
🍄 ***Could a single high-dose psychedelic experience temporarily unlock abilities thought lost to advanced Alzheimer's disease?***

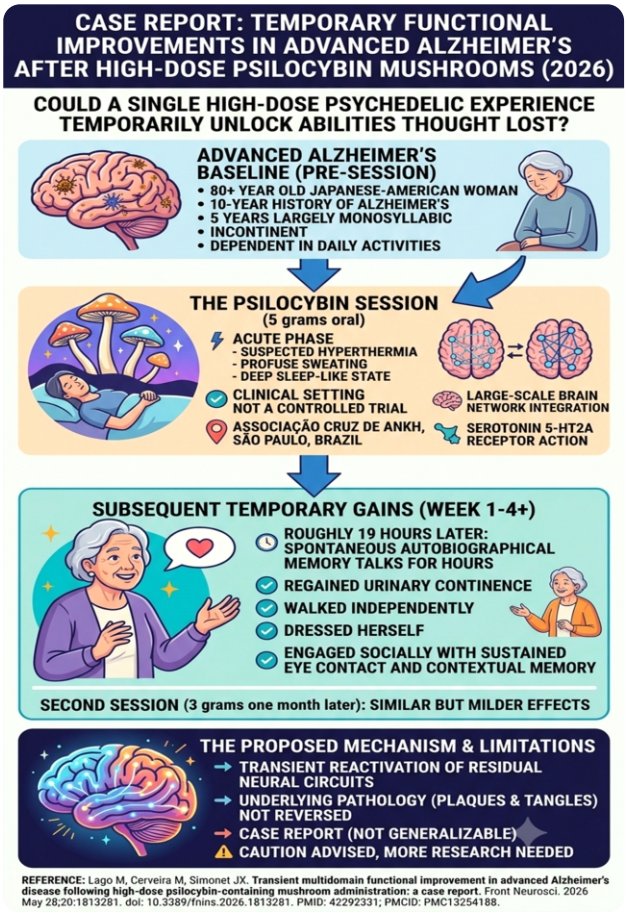
This case report from Associação Cruz de Ankh in São Paulo, Brazil, describes a single octogenarian Japanese-American woman with a 10-year history of Alzheimer's disease who had spent the preceding 5 years largely monosyllabic, incontinent, and dependent in daily activities. In a private clinical setting, not a controlled trial, she received 5 grams of oral psilocybin-containing mushrooms. The acute phase involved suspected hyperthermia, profuse sweating, and a prolonged deep sleep-like state. Roughly 19 hours later, she spontaneously spoke for hours about autobiographical memories. Over the following weeks, she regained urinary continence, walked independently, dressed herself, and engaged socially with sustained eye contact and contextual memory. A second 3-gram session one month later produced similar but milder effects. The authors propose that psilocybin's known action on serotonin 5-HT2A receptors and large-scale brain network integration may have transiently reactivated residual neural circuits without reversing underlying pathology.

Source:

📄 CASE REPORT

📌 Lago M, Cerveira M, Simonet JX. Transient multidomain functional improvement in advanced Alzheimer's disease following high-dose psilocybin-containing mushroom administration: a case report. Front Neurosci. 2026 May 28; 20:1813281. doi: 10.3389/fnins.2026.1813281. PMID: 42292331; PMCID: PMC13254188.





Why Alzheimer's Risk Hits Women Harder: A Closer Look at Modifiable Risk Factors (2026)

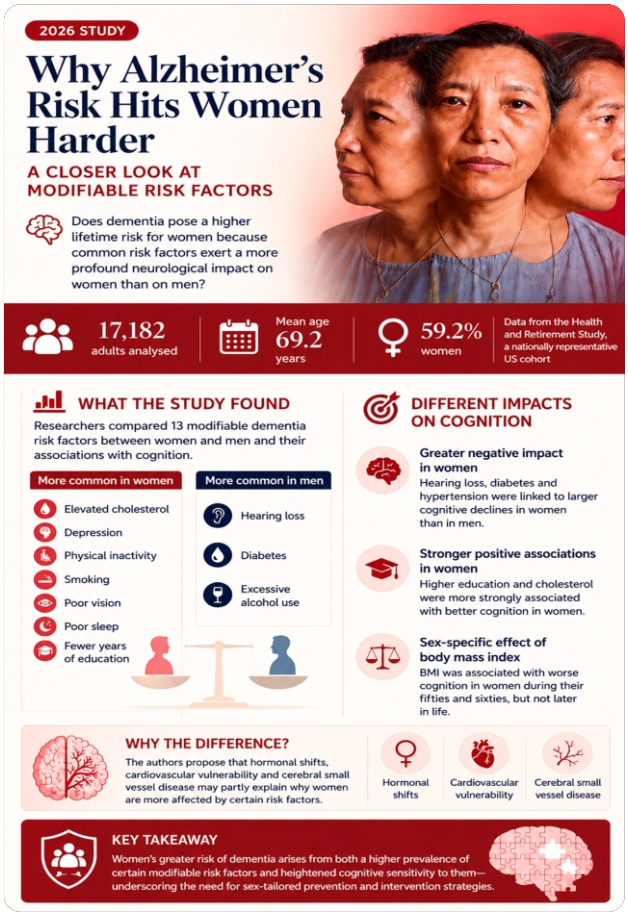
Does dementia pose a higher lifetime risk for women because common risk factors exert a more profound neurological impact on women than on men?

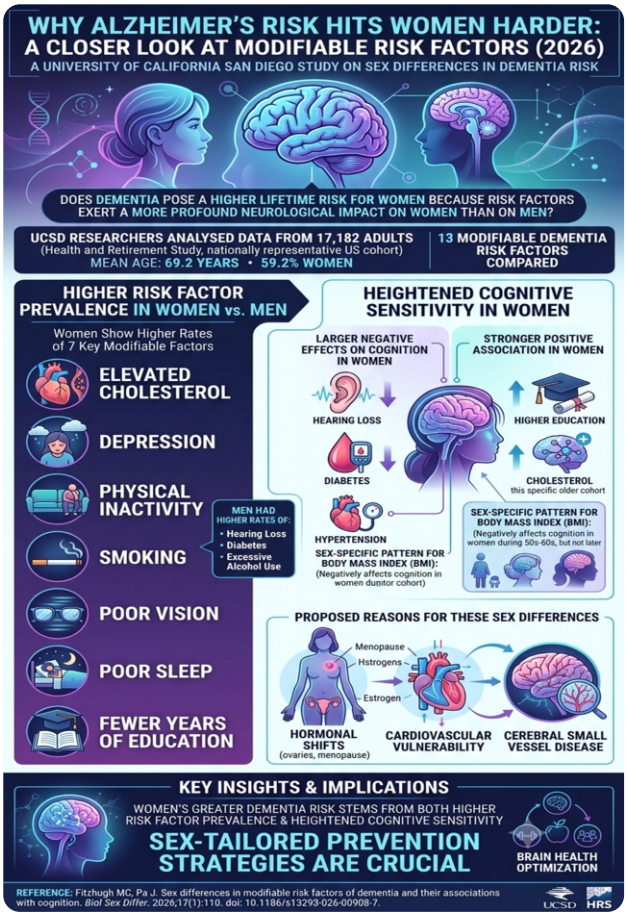
Researchers at the University of California San Diego analysed data from 17,182 adults (mean age 69.2 years, 59.2% women) in the Health and Retirement Study, a nationally representative US cohort, to compare 13 modifiable dementia risk factors between the sexes and their associations with cognition. Women showed higher prevalence of seven risk factors, including elevated cholesterol, depression, physical inactivity, smoking, poor vision and poor sleep, alongside fewer years of education, while men had higher rates of hearing loss, diabetes and excessive alcohol use. Hearing loss, diabetes and hypertension were linked to larger negative effects on cognitive performance in women than men, while higher education and cholesterol were more strongly, positively associated with cognition in women. Body mass index showed a sex specific pattern, negatively affecting cognition in women during their fifties and sixties but not later in life. The authors propose that hormonal shifts, cardiovascular vulnerability and cerebral small vessel disease may partly explain these differences. Findings suggest women's greater dementia risk stems from both higher risk factor prevalence and heightened cognitive sensitivity, supporting sex-tailored prevention strategies.

Source:

COHORT STUDY

Fitzhugh MC, Pa J. Sex differences in modifiable risk factors of dementia and their associations with cognition. Biol Sex Differ. 2026;17(1):110. doi: 10.1186/s13293-026-00908-7.





Alzheimer's Disease May Begin in the Body's Immune System, Not the Brain (2026)

What if Alzheimer's disease doesn't start in the brain, but in the immune system?

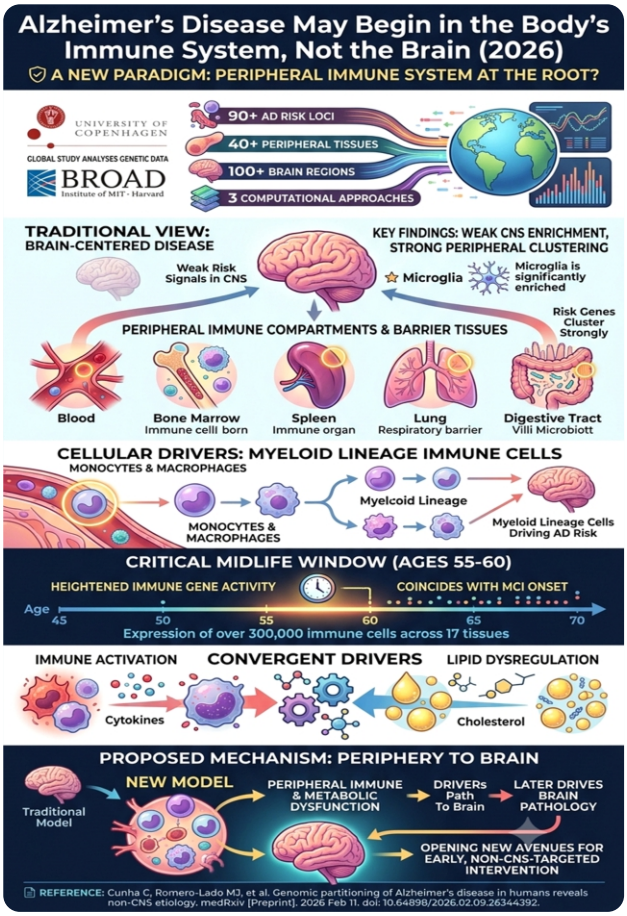
Researchers at the University of Copenhagen and the Broad Institute of MIT and Harvard analysed genetic data linked to more than 90 Alzheimer's disease (AD) risk loci across up to 40 peripheral tissues and 100 brain regions using three independent computational approaches. Contrary to the long-standing view of AD as a brain-centred disease, genetic risk signals were only weakly enriched in the central nervous system, with microglia the sole brain cell type showing significant enrichment. Instead, risk genes clustered strongly in peripheral immune compartments and barrier tissues, including blood, bone marrow, spleen, lung, and the digestive tract, particularly within myeloid lineage cells such as monocytes and macrophages. Leveraging gene expression profiles from more than 300,000 immune cells across 17 tissues, the authors identified ages 55 to 60 as a critical midlife window of heightened immune gene activity linked to AD risk, coinciding with the typical onset of mild cognitive impairment. Pathway analysis further implicated immune activation and lipid dysregulation as convergent drivers. The authors propose that Alzheimer's disease may originate from peripheral immune and metabolic dysfunction that later drives brain pathology, rather than beginning within the brain itself, opening new avenues for early, non-CNS-targeted intervention.

Source:

RESEARCH PAPER

Cunha C, Romero-Lado MJ, Pielies Avelli M, Sanz Martínez R, Belanich JR, Jones TR, et al. Genomic partitioning of Alzheimer's disease in humans reveals non-CNS etiology. medRxiv [Preprint]. 2026 Feb 11 [cited 2026 Jul 2]. doi: 10.64898/2026.02.09.26344392.





Blood Test Ratio Improves Detection of Alzheimer's Amyloid Pathology (2026)

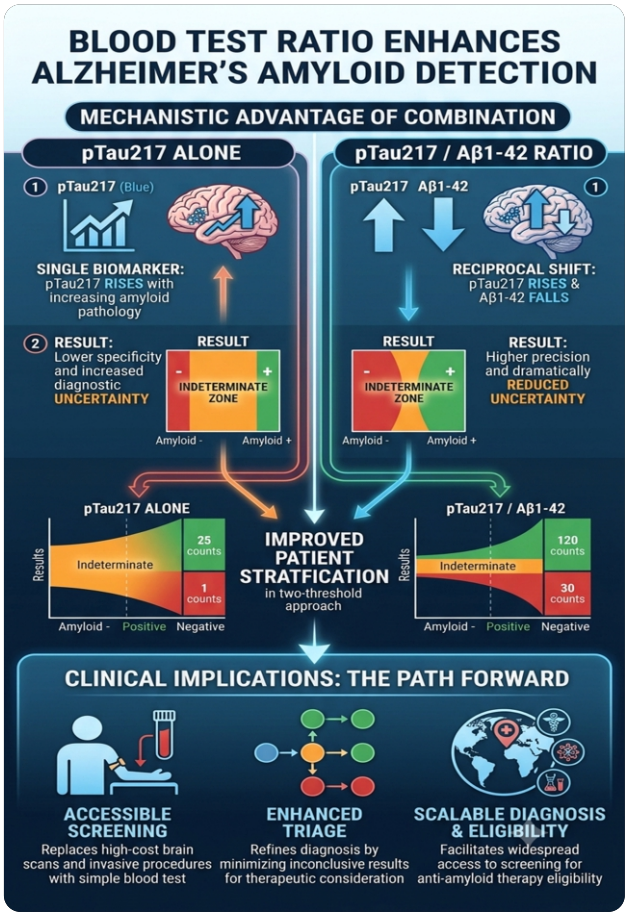
Could a simple blood test replace costly brain scans and invasive spinal taps in diagnosing Alzheimer's disease?

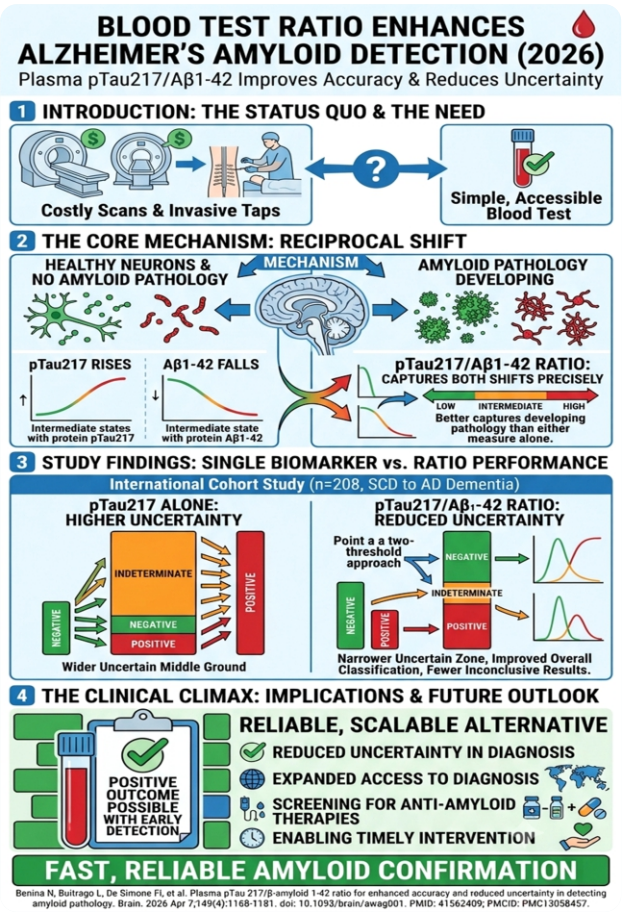
Researchers at Fujirebio Diagnostics, Johns Hopkins School of Medicine, and Lund University analysed plasma samples from 208 participants across three international cohorts, spanning subjective cognitive decline, mild cognitive impairment, and Alzheimer's disease dementia. The team compared how well individual biomarkers and their combination predicted amyloid pathology confirmed by PET imaging and/or cerebrospinal fluid testing. While plasma pTau217 alone showed strong discriminative power, combining it with Aβ1-42 into a single ratio produced better overall classification and notably fewer inconclusive test results. Using a two-threshold approach that sorts results into positive, negative, and indeterminate categories, the ratio maintained high predictive accuracy while narrowing the uncertain middle ground compared with pTau217 alone. Mechanistically, pTau217 rises while Aβ1-42 falls as amyloid pathology develops, so combining both markers into one ratio captures this reciprocal shift more precisely than either measure alone. These findings suggest the plasma ratio could offer a more reliable, scalable, and less invasive alternative for confirming amyloid pathology, potentially expanding access to diagnosis and treatment eligibility screening for emerging anti-amyloid therapies.

Source:

RESEARCH PAPER

Benina N, Buitrago L, De Simone FI, et al. Plasma pTau 217/β-amyloid 1-42 ratio for enhanced accuracy and reduced uncertainty in detecting amyloid pathology. Brain. 2026 Apr 7;149(4):1168-1181. doi: 10.1093/brain/awag001. PMID: 41562409; PMCID: PMC13058457.





Vitamin B12 Levels Within the "Normal" Range May Still Affect Brain Health in Older Adults (2025)

Could your B12 blood test read "normal" while your brain is already feeling the strain?

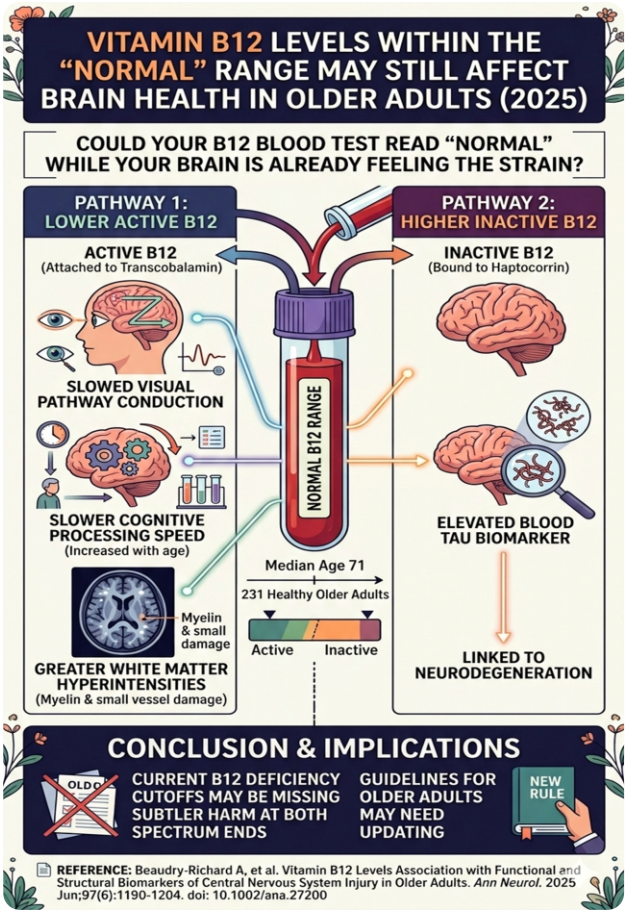
This cross-sectional study from the University of California, San Francisco, drew on 231 healthy older adults (median age 71) enrolled through the university's Brain Aging Network for Cognitive Health. Researchers measured not just total blood B12, but its two carrier-bound fractions, the biologically active form attached to transcobalamin and the inactive form bound to haptocorrin. Even though every participant's B12 fell within the standard normal range, those with lower active B12 showed slower conduction along the visual pathway on evoked potential testing, slower cognitive processing speed that became more pronounced with age, and a greater volume of white matter hyperintensities on brain MRI, a marker of myelin and small vessel damage. Curiously, the opposite extreme carried its own risk: participants with higher levels of the inactive, haptocorrin-bound fraction had elevated blood Tau, a biomarker linked to neurodegeneration. The authors propose that current B12 "deficiency" cutoffs, set decades ago using population statistics rather than clinical outcomes, may be missing subtler but meaningful harm at both ends of the spectrum. This raises questions about whether B12 adequacy guidelines for older adults need updating.

Source:

RESEARCH PAPER

Beaudry-Richard A, Abdelhak A, Saloner R, Sacco S, Montes SC, Oertel FC, et al. Vitamin B12 Levels Association with Functional and Structural Biomarkers of Central Nervous System Injury in Older Adults. Ann Neurol. 2025 Jun;97(6):1190-1204. doi: 10.1002/ana.27200. Epub 2025 Feb 10. PMID: 39927551; PMCID: PMC12082028.





Night Shift Work Linked to Shrinkage in Key Brain Regions, Study Finds (2025)

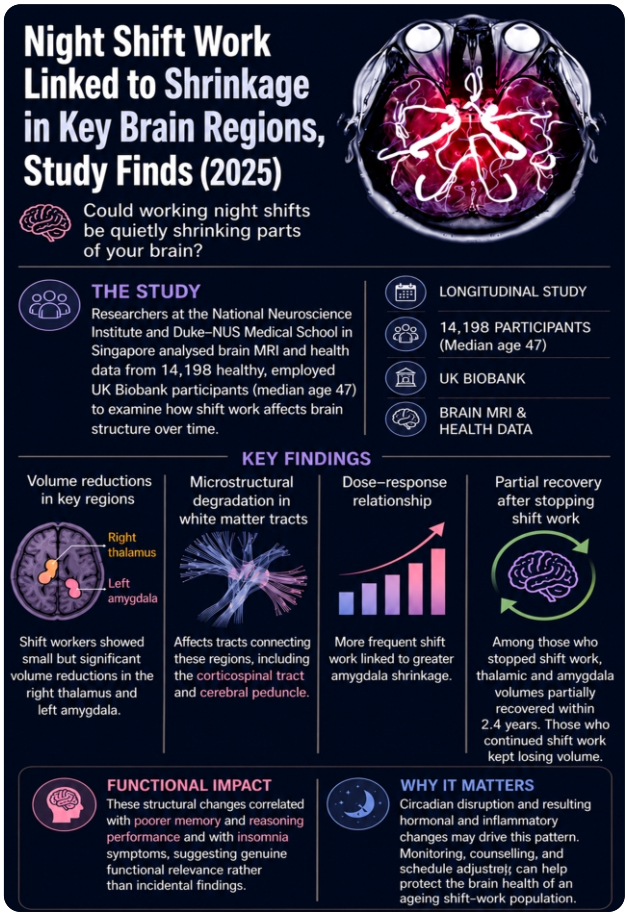
Could working night shifts be quietly shrinking parts of your brain?

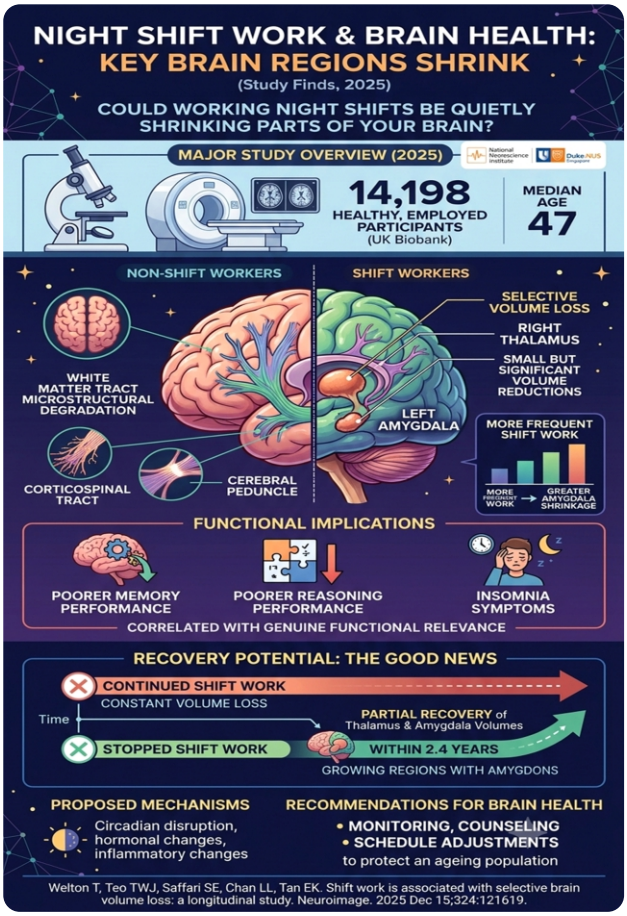
Researchers at the National Neuroscience Institute and Duke-NUS Medical School in Singapore analysed brain MRI and health data from 14,198 healthy, employed UK Biobank participants (median age 47) to examine how shift work affects brain structure over time. Compared to non-shift workers, shift workers showed small but significant volume reductions in the right thalamus and left amygdala, along with microstructural degradation in white matter tracts connecting these regions, including the corticospinal tract and cerebral peduncle. A dose-response relationship was observed, with more frequent shift work linked to greater amygdala shrinkage. Encouragingly, among participants who stopped shift work, thalamic and amygdala volumes partially recovered within 2.4 years, while those who continued working shifts kept losing volume. These structural changes correlated with poorer memory and reasoning performance and with insomnia symptoms, suggesting genuine functional relevance rather than incidental findings. The authors propose that circadian disruption and resulting hormonal and inflammatory changes may drive this pattern, and recommend monitoring, counselling, and schedule adjustments to help protect the brain health of an ageing shift-work population.

Source:

COHORT STUDY

Welton T, Teo TWJ, Saffari SE, Chan LL, Tan EK. Shift work is associated with selective brain volume loss: a longitudinal study. Neuroimage. 2025 Dec 15; 324:121619. doi: 10.1016/j.neuroimage.2025.121619. Epub 2025 Nov 25. PMID: 41308939.





Women, Men and ADHD: Same Disorder, Different Struggles (2025)

Why do so many women only discover their ADHD well into adulthood, often after years of misattributed anxiety or depression?

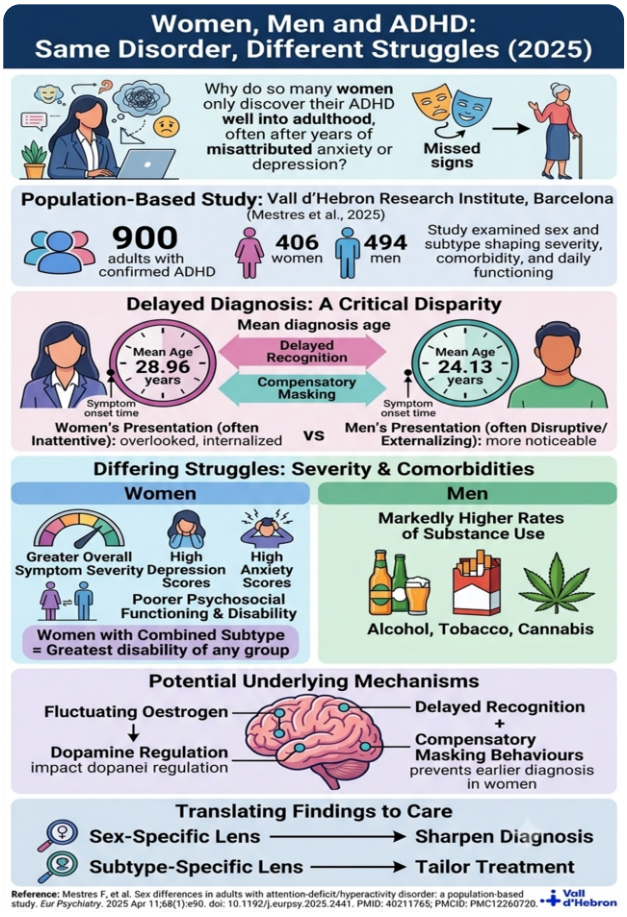
A population-based study from the Adult ADHD Programme at Hospital Universitari Vall d'Hebron in Barcelona, involving the Vall d'Hebron Research Institute and Universitat Autònoma de Barcelona, analysed 900 adults with confirmed ADHD (406 women, 494 men) to examine how sex and ADHD subtype shape severity, comorbidity and daily functioning. Women received their diagnosis significantly later than men (mean age 28.96 versus 24.13 years) despite no difference in when symptoms first appeared, reflecting how inattentive presentations are more easily overlooked than disruptive, externalising behaviour. Women also showed greater overall symptom severity, higher depression and anxiety scores, and poorer psychosocial functioning and disability, while men reported markedly higher rates of alcohol, tobacco and cannabis use. Notably, women with the combined subtype experienced the greatest disability of any group. The authors propose that fluctuating oestrogen affecting dopamine regulation, combined with delayed recognition and compensatory masking behaviours in women, may underlie these disparities. The findings support evaluating ADHD through both a sex-specific and subtype-specific lens to sharpen diagnosis and tailor treatment.

Source:

COHORT STUDY

Mestres F, Richarte V, Crespín JJ, Torrent C, Biel S, Ramos C, et al. Sex differences in adults with attention-deficit/hyperactivity disorder: a population-based study. Eur Psychiatry. 2025 Apr 11;68(1): e90. doi: 10.1192/j.eurpsy.2025.2441. PMID: 40211765; PMCID: PMC12260720.





Music Therapy Shows Promise as an Adjunct Treatment for Stroke, Parkinson's Disease, and Cerebral Palsy (2026)

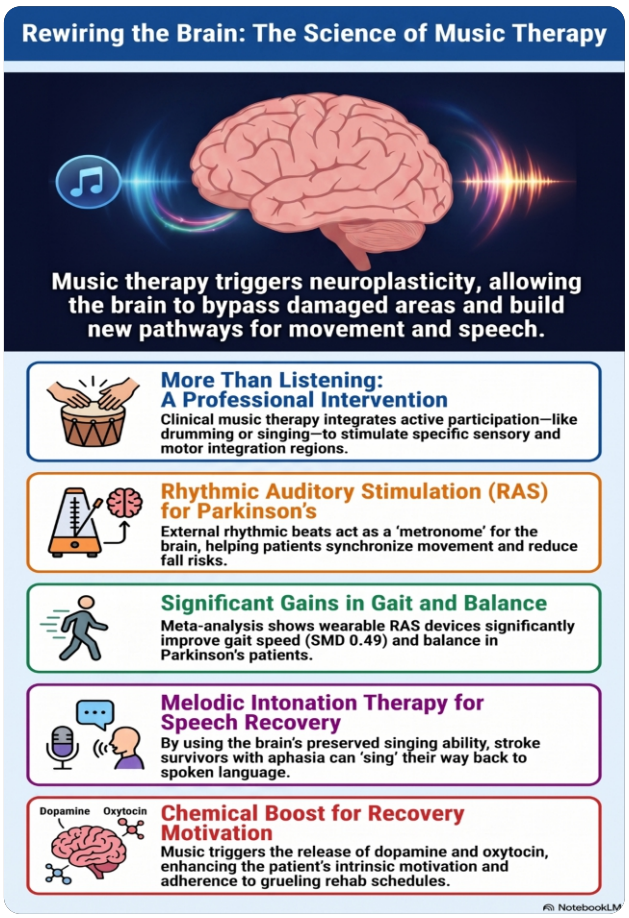
Could rhythm and melody genuinely help rewire the brain after conditions like stroke or Parkinson's disease?

This review, published in Frontiers in Neurology by researchers from Changchun University, Tianjin Medical University, Beijing Union University, and the First Hospital of Jilin University, synthesises current evidence on music therapy in neurorehabilitation. The review outlines four main technical approaches, receptive listening, active participation, improvisation, and vibroacoustic therapy using low-frequency vibrations, and traces their mechanisms through auditory-motor integration, dopaminergic and cholinergic pathways, and neuroplasticity. Cited clinical studies report meaningful gains: 14 stroke patients showed improved hand dexterity after six weeks of percussion-based training, 60 stroke patients had better gait and balance following rhythmic auditory stimulation, and 288 dementia patients experienced fewer neuropsychiatric symptoms after three months of singing or music listening. In Parkinson's disease, rhythmic auditory cues improved walking velocity and reduced fall risk in 60 patients. The proposed mechanism centres on rhythmic entrainment, where external musical cues synchronise with motor timing, alongside neurotransmitter release and structural brain changes from repeated musical engagement. The authors note that most underlying trials remain small and heterogeneous, calling for larger, standardised studies to establish optimal dosing and confirm long-term benefit.

Source:

REVIEW

Yu M, Song Y, Song H, Duan H, Zhang G. Advances in music therapy for neurological rehabilitation. Front Neurol. 2026 Apr 22; 17:1821915. doi: 10.3389/fneur.2026.1821915. PMID: 42099975; PMCID: PMC13143721.





Music Therapy Linked to Improved Cognitive Scores in Older Adults with Mild Cognitive Impairment (2026)

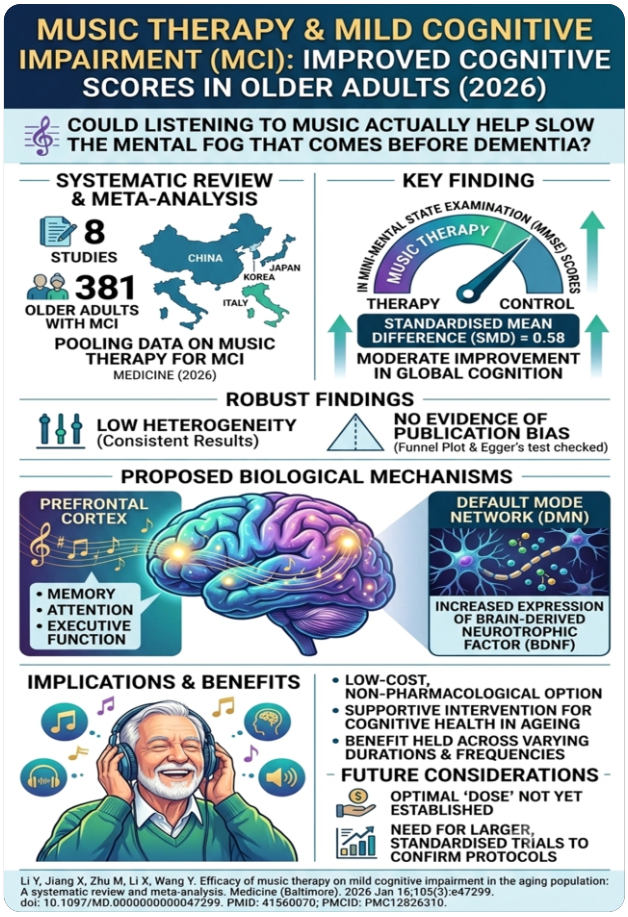
Could listening to music actually help slow the mental fog that comes before dementia?

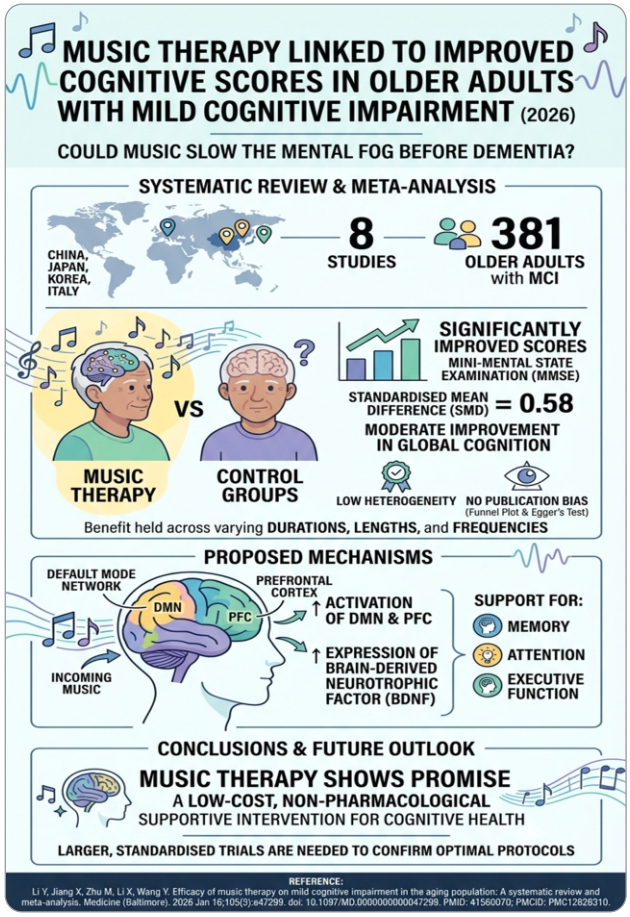
Researchers from Jinjiang Municipal Hospital in China conducted a systematic review and meta-analysis, published in Medicine, pooling data from eight studies covering 381 older adults with mild cognitive impairment across China, Japan, Korea, and Italy. Using a fixed-effect model, the analysis found that music therapy significantly improved scores on the mini-mental state examination compared with control groups, with a standardised mean difference of 0.58, indicating a moderate improvement in global cognition. Heterogeneity between studies was low, and no evidence of publication bias was detected through funnel plot inspection and Egger's test. The benefit held across varying treatment durations, session lengths, and intervention frequencies, though an optimal "dose" could not be established. Proposed mechanisms include music-induced activation of the default mode network and prefrontal cortex, alongside increased expression of brain-derived neurotrophic factor, which together may support memory, attention, and executive function. As a low-cost, non-pharmacological option, music therapy shows promise as a supportive intervention for cognitive health in ageing populations, though larger, standardised trials are needed to confirm optimal delivery protocols.

Source:

REVIEW

Li Y, Jiang X, Zhu M, Li X, Wang Y. Efficacy of music therapy on mild cognitive impairment in the aging population: A systematic review and meta-analysis. Medicine (Baltimore). 2026 Jan 16;105(3): e47299. doi: 10.1097/MD.0000000000047299. PMID: 41560070; PMCID: PMC12826310.





How Music Therapy Supports Physical and Psychological Healing Across Clinical Populations (2026)

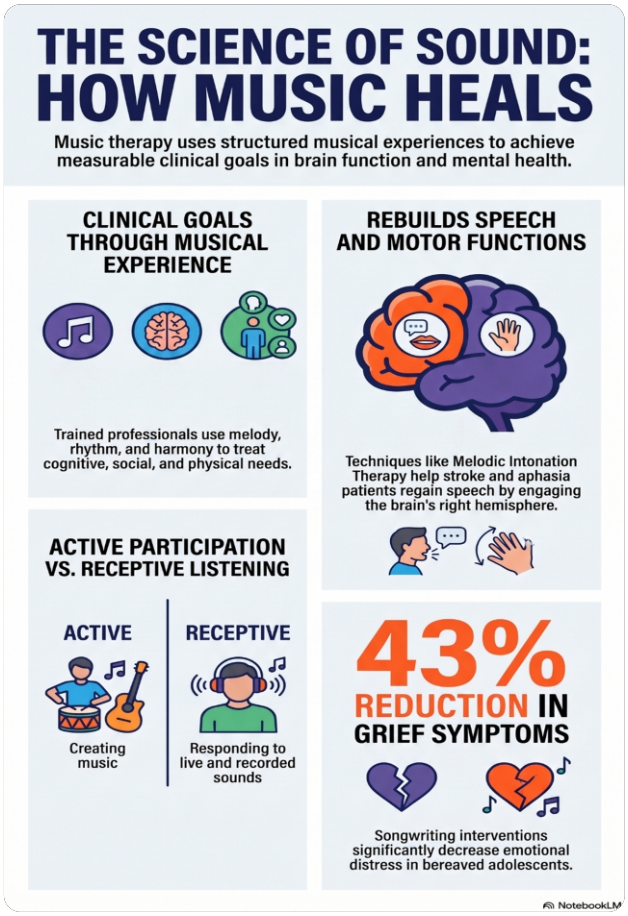
Could music, guided by a trained therapist rather than simply played in the background, genuinely help people manage everything from schizophrenia to stroke recovery?

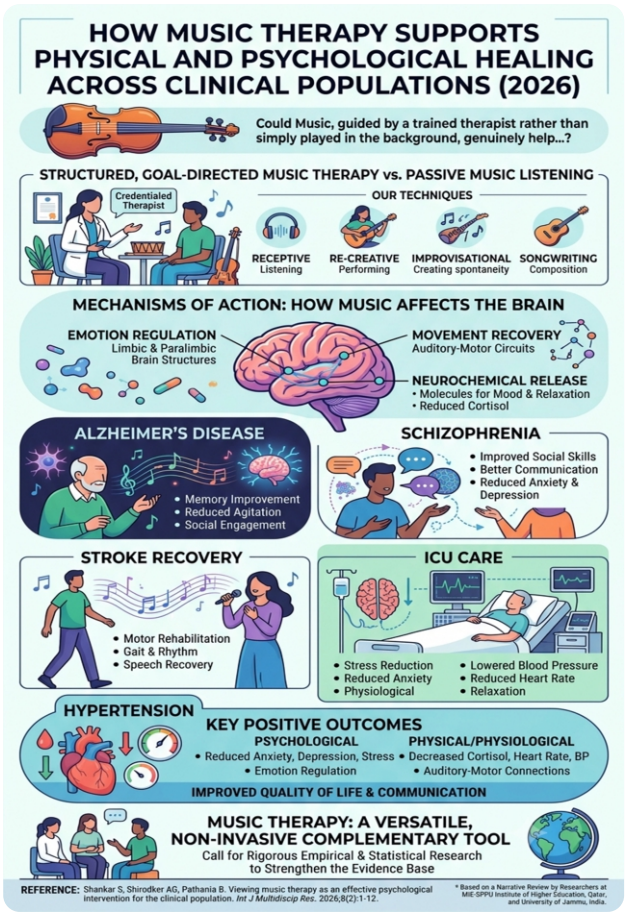
This narrative review, conducted by researchers at MIE-SPPU Institute of Higher Education in Doha, Qatar, and the University of Jammu, India, synthesises findings from a broad literature search across databases including ResearchGate, ScienceDirect, and the National Library of Medicine to examine music therapy's effects on the clinical population. The review distinguishes structured, goal-directed music therapy, delivered by credentialed therapists using receptive, re-creative, improvisational, or songwriting techniques, from passive music listening. Drawing on findings from Alzheimer's disease, schizophrenia, stroke, ICU care, and hypertension research, the review describes consistent reductions in anxiety, depression, stress hormones such as cortisol, and physiological markers like heart rate and blood pressure, alongside improvements in social skills, communication, and quality of life. Proposed mechanisms include activation of limbic and paralimbic brain structures involved in emotion regulation, stimulation of auditory-motor circuits supporting movement recovery, and the release of neurochemicals linked to mood and relaxation. The authors conclude that music therapy offers a versatile, non-invasive complementary tool across diverse clinical settings, though they call for more rigorous empirical and statistical research to strengthen this evidence base.

Source:

REVIEW

Shankar S, Shirodker AG, Pathania B. Viewing music therapy as an effective psychological intervention for the clinical population. Int J Multidiscip Res. 2026;8(2):1-12. doi: 10.36948/ijfmr. 2026.v08i02





Testing Whether Group Music Sessions Can Help School Children with Emotional or Behavioural Difficulties (2026)

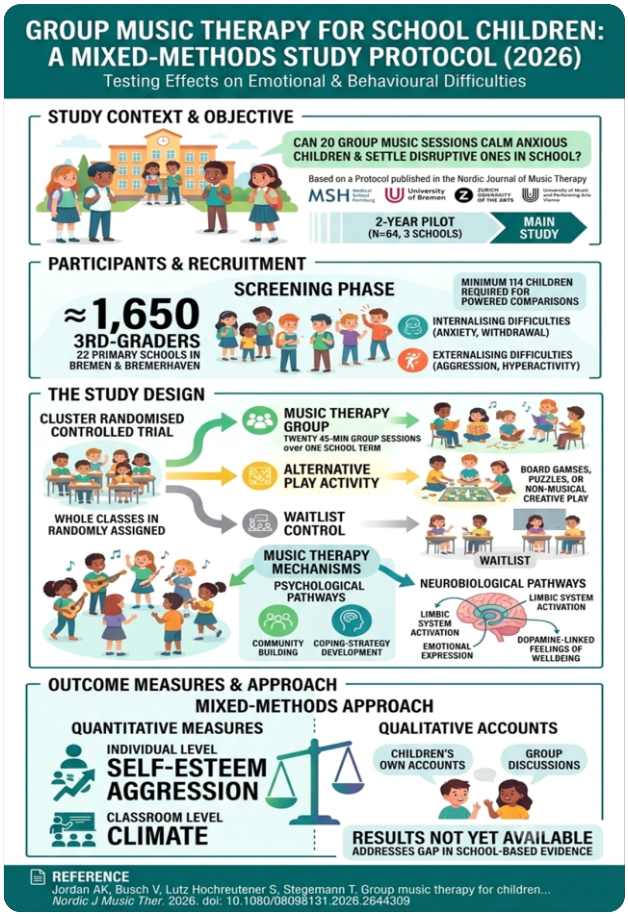
Could twenty sessions of group music-making genuinely calm anxious children and settle disruptive ones, all within the school day?

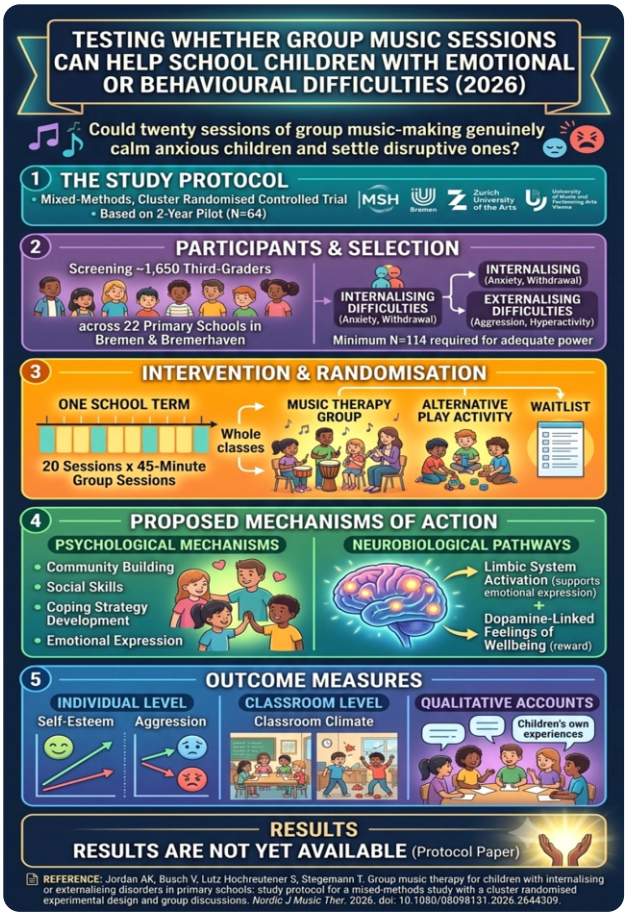
Published in the Nordic Journal of Music Therapy, this protocol paper from MSH Medical School Hamburg, the University of Bremen, Zurich University of the Arts, and the University of Music and Performing Arts Vienna outlines a mixed-methods, cluster randomised controlled trial building on a two-year pilot (N = 64) across three primary schools. The main study will screen roughly 1,650 third-graders across 22 primary schools in Bremen and Bremerhaven, randomising whole classes to music therapy, an alternative play activity, or a waitlist, with a minimum of 114 children required for adequately powered comparisons. Children with internalising (anxiety, withdrawal) or externalising (aggression, hyperactivity) difficulties will attend twenty 45-minute group sessions over one school term. Music therapy is proposed to work through both psychological mechanisms, such as community building and coping-strategy development, and neurobiological pathways, including limbic system activation that supports emotional expression and dopamine-linked feelings of wellbeing. Outcomes will be tracked at individual level (self-esteem, aggression) and classroom level (climate), combining quantitative measures with children's own qualitative accounts. Results are not yet available, but the design addresses a genuine gap in school-based evidence for music therapy.

Source:

PROTOCOL PAPER

Jordan AK, Busch V, Lutz Hochreutener S, Stegemann T. Group music therapy for children with internalising or externalising disorders in primary schools: study protocol for a mixed-methods study with a cluster randomised experimental design and group discussions. Nordic J Music Ther. 2026. doi: 10.1080/08098131.2026.2644309.





Listening to Music Daily May Lower Dementia Risk in Older Adults (2025)

Could simply turning on the radio or playing music each day help protect your brain as you age?

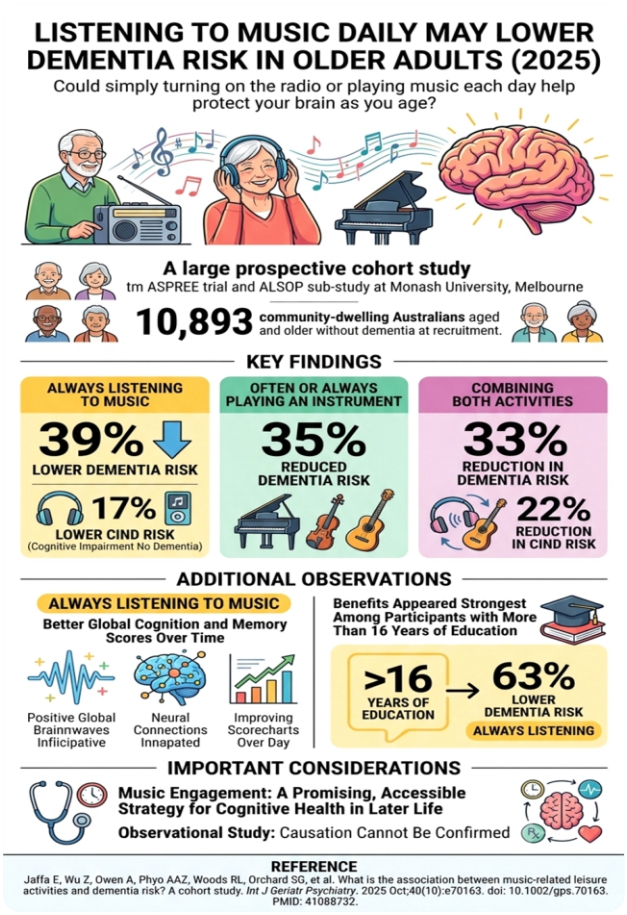
A large prospective cohort study, drawn from the ASPREE trial and ALSOP sub-study at Monash University, Melbourne, followed 10,893 community-dwelling Australians aged 70 and older without dementia at recruitment. Researchers examined whether listening to music or playing an instrument was linked to dementia risk, cognitive impairment no dementia (CIND), and cognitive wellbeing. Participants who always listened to music had a 39% lower dementia risk and a 17% lower CIND risk than those who rarely or never listened. Often or always playing an instrument was associated with a 35% reduced dementia risk, though not with CIND. Combining both activities produced a 33% reduction in dementia risk and a 22% reduction in CIND risk. Always listening to music also corresponded with better global cognition and memory scores over time. Benefits appeared strongest among participants with more than 16 years of education, where always listening was linked to a 63% lower dementia risk. As an observational study, causation cannot be confirmed, but the findings position music engagement as a promising, accessible strategy for cognitive health in later life.

Source:

COHORT STUDY

Jaffa E, Wu Z, Owen A, Phyo AAZ, Woods RL, Orchard SG, et al. What is the association between music-related leisure activities and dementia risk? A cohort study. Int J Geriatr Psychiatry. 2025 Oct;40(10): e70163. doi: 10.1002/gps.70163. PMID: 41088732.





Music Therapy Delivered by Trained Therapists Meaningfully Reduces Anxiety Symptoms (2025)

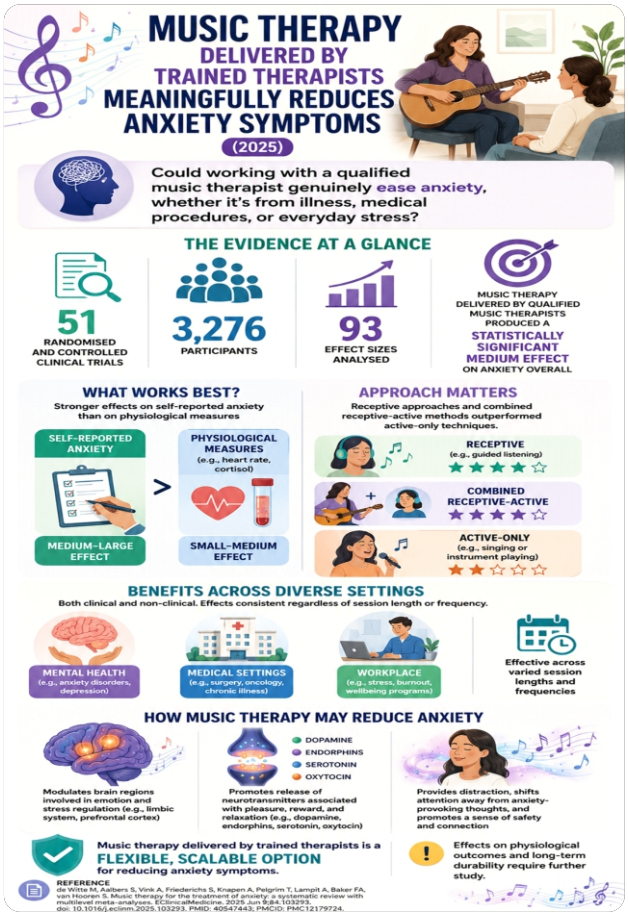
Could working with a qualified music therapist genuinely ease anxiety, whether it's from illness, medical procedures, or everyday stress?

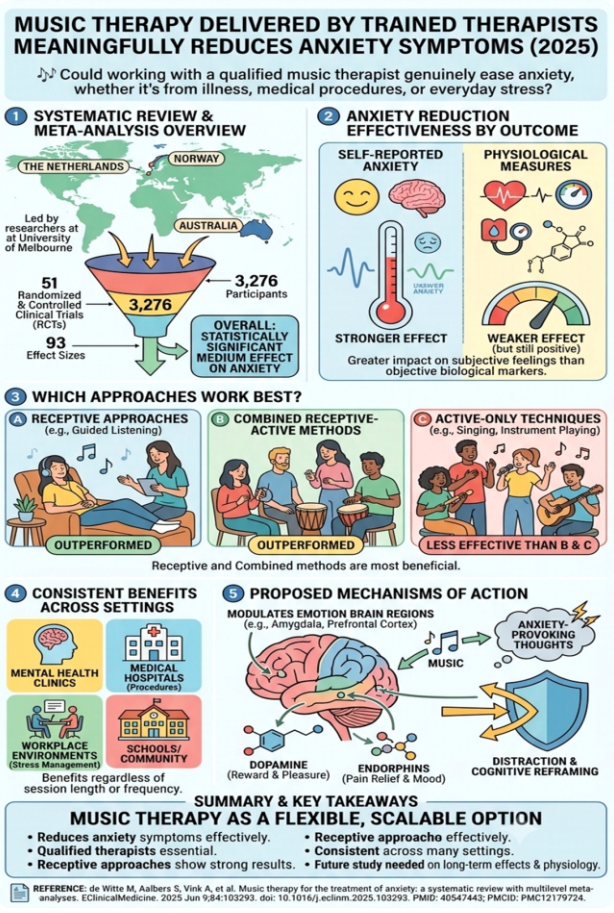
This systematic review and multilevel meta-analysis, led by researchers at the University of Melbourne alongside institutions across the Netherlands, Australia, and Norway, pooled data from 51 randomised and controlled clinical trials involving 3,276 participants to evaluate music therapy delivered specifically by qualified music therapists. Across 93 effect sizes, music therapy produced a statistically significant medium effect on anxiety overall, with a stronger effect on self-reported anxiety than on physiological measures such as heart rate or cortisol. Receptive approaches, such as guided listening, and combined receptive-active methods outperformed active-only techniques like singing or instrument playing, and benefits were consistent across mental health, medical, and workplace settings regardless of session length or frequency. The proposed mechanism involves music's capacity to modulate brain regions governing emotion, alongside the release of neurotransmitters such as dopamine and endorphins, and its role in distracting from anxiety-provoking thoughts. These findings position music therapy as a flexible, scalable option for reducing anxiety symptoms, though its effects on physiological outcomes and long-term durability require further study.

Source:

REVIEW

de Witte M, Aalbers S, Vink A, Friederichs S, Knapen A, Pelgrim T, Lampit A, Baker FA, van Hooren S. Music therapy for the treatment of anxiety: a systematic review with multilevel meta-analyses. EClinicalMedicine. 2025 Jun 9; 84:103293. doi: 10.1016/j.eclinm.2025.103293. PMID: 40547443; PMCID: PMC12179724.





Oral Semaglutide Redefines Heart Failure Management in Type 2 Diabetes (2026)

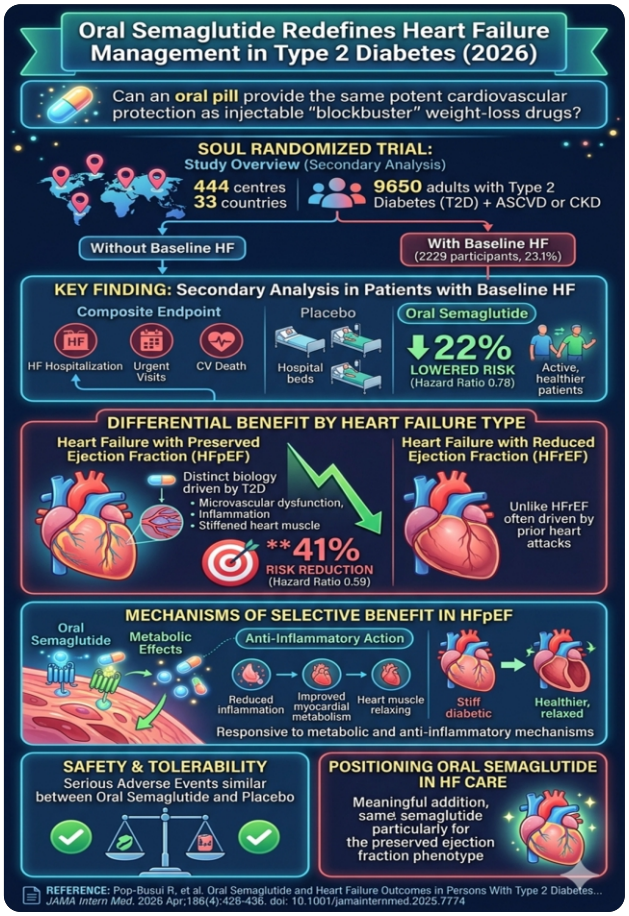
💊 ***Can an oral pill provide the same potent cardiovascular protection as injectable "blockbuster" weight-loss drugs?***

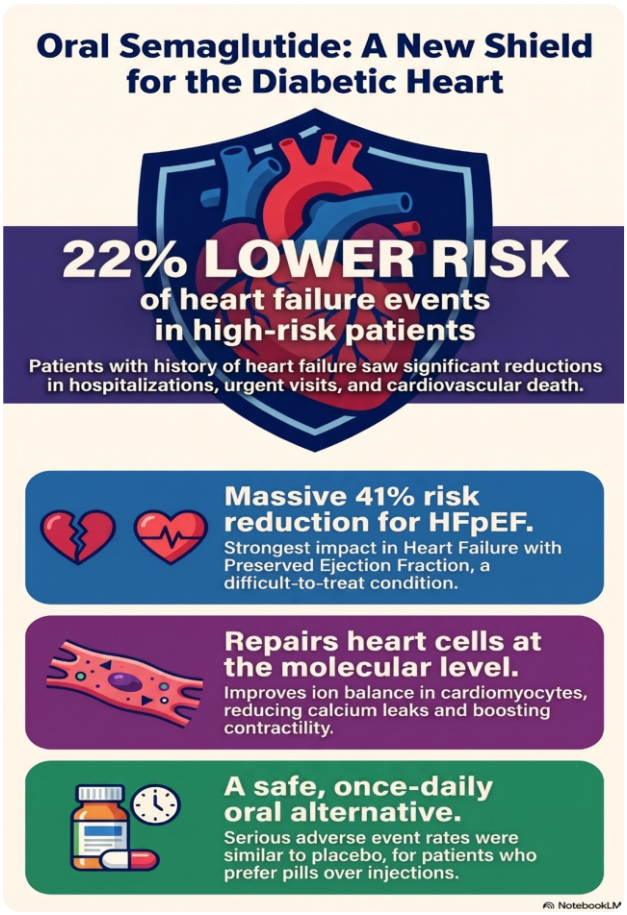
This secondary analysis of the SOUL randomised trial, led by researchers from Oregon Health & Science University and the University of Michigan, examined 9650 adults with Type 2 Diabetes and atherosclerotic cardiovascular disease or chronic kidney disease across 444 centres in 33 countries. Among the 2229 participants (23.1%) with pre-existing heart failure, oral semaglutide lowered the risk of heart failure hospitalisation, urgent visits, or cardiovascular death by 22% (hazard ratio 0.78), with no benefit in those without baseline heart failure. The protection was concentrated in heart failure with preserved ejection fraction, where risk fell by 41% (hazard ratio 0.59). Researchers attribute this selective benefit to the distinct biology of preserved ejection fraction heart failure, driven in diabetes by microvascular dysfunction, inflammation, and stiffened heart muscle, rather than the prior heart attacks underlying reduced ejection fraction, mechanisms more responsive to semaglutide's metabolic and anti-inflammatory effects. Serious adverse events were similar between groups. These findings position oral semaglutide as a meaningful addition to heart failure care in Type 2 Diabetes, particularly for the preserved ejection fraction phenotype.

Source:

RESEARCH PAPER

Pop-Busui R, Rasmussen S, Deanfield JE, Buse JB, Marx N, Mulvagh SL, et al.; SOUL Study Group. Oral Semaglutide and Heart Failure Outcomes in Persons with Type 2 Diabetes: A Secondary Analysis of the SOUL Randomized Clinical Trial. JAMA Intern Med. 2026 Apr;186(4):426-436. doi: 10.1001/jamainternmed.2025.7774. Epub 2026 Feb 2. PMID: 41627802; PMCID: PMC12865694.





Oral Pill Aleniglipron Shows Meaningful Weight Loss in Obesity Trial (2026)

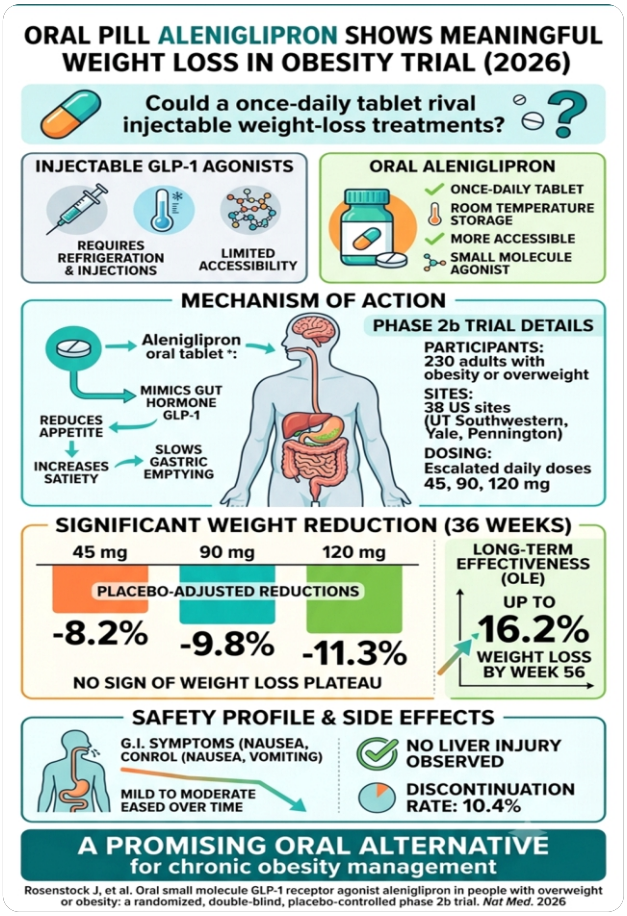
💊 ***Could a once-daily tablet rival injectable weight-loss treatments?***

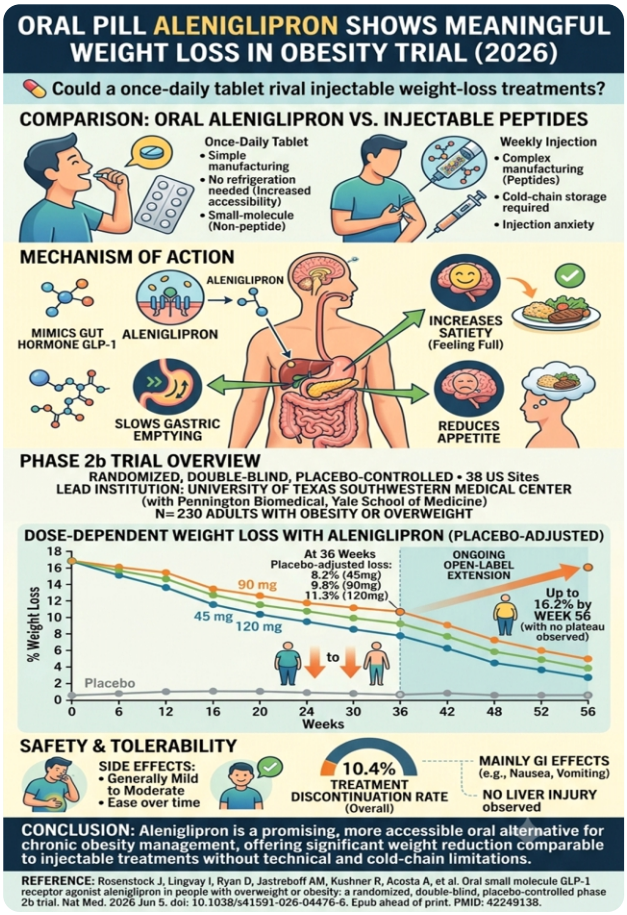
Injectable GLP-1 receptor agonists have transformed obesity treatment, but their need for refrigeration and injection limits accessibility. A phase 2b trial led by the University of Texas Southwestern Medical Center, with sites including Pennington Biomedical Research Foundation and Yale School of Medicine, randomised 230 adults with obesity or overweight across 38 US sites to receive Aleniglipron, an oral small-molecule GLP-1 receptor agonist, or placebo. Aleniglipron works by mimicking the gut hormone GLP-1, reducing appetite, increasing satiety and slowing gastric emptying, without requiring the complex manufacturing or cold-chain storage that peptide-based injectables demand. After 36 weeks of once-daily dosing escalated to 45, 90 or 120 mg, participants achieved placebo-adjusted weight reductions of 8.2%, 9.8% and 11.3% respectively, with no sign of a weight-loss plateau. An ongoing open-label extension recorded further loss, up to 16.2% by week 56. Gastrointestinal side effects, mainly nausea and vomiting, were generally mild to moderate and eased over time, with an overall treatment discontinuation rate of 10.4% and no liver injury observed. These findings position Aleniglipron as a promising, more accessible oral alternative for chronic obesity management.

Source:

RESEARCH PAPER

Rosenstock J, Lingvay I, Ryan D, Jastreboff AM, Kushner R, Acosta A, et al. Oral small molecule GLP-1 receptor agonist Aleniglipron in people with overweight or obesity: a randomized, double-blind, placebo-controlled phase 2b trial. Nat Med. 2026 Jun 5. doi: 10.1038/s41591-026-04476-6. Epub ahead of print. PMID: 42249138.





Ketogenic Diet Eases Pancreatic Stress in People with Type 2 Diabetes (2026)

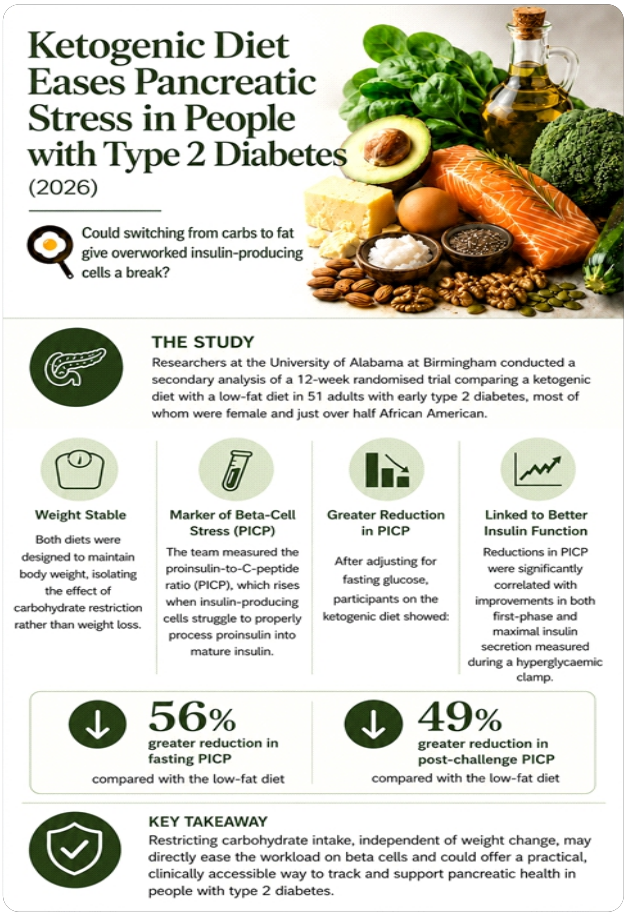
Could switching from carbs to fat give overworked insulin-producing cells a break?

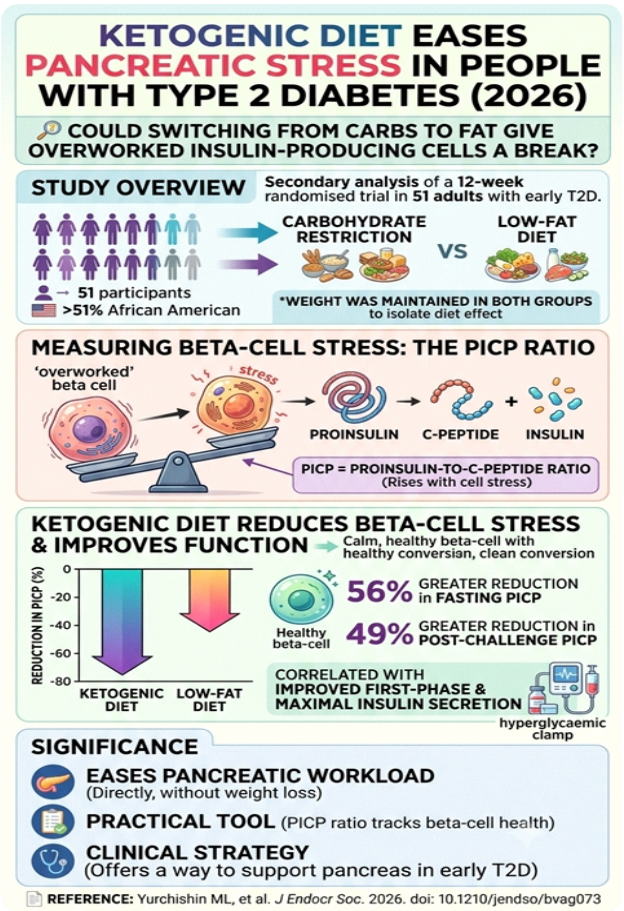
Researchers at the University of Alabama at Birmingham conducted a secondary analysis of a 12-week randomised trial comparing a ketogenic diet with a low-fat diet in 51 adults with early Type 2 Diabetes, most of whom were female and just over half African-American. Both diets were designed to maintain body weight, isolating the effect of carbohydrate restriction itself rather than weight loss. The team measured the proinsulin-to-C-peptide ratio (PICP), a marker of beta-cell stress that rises when insulin-producing cells struggle to properly process proinsulin into mature insulin. After adjusting for fasting glucose, participants on the ketogenic diet showed a 56% greater reduction in fasting PICP and a 49% greater reduction in post-challenge PICP compared with the low-fat group. Crucially, these reductions in PICP were significantly correlated with improvements in both first-phase and maximal insulin secretion measured during a hyperglycaemic clamp. The findings suggest that restricting carbohydrate intake, independent of weight change, may directly ease the workload on beta cells and could offer a practical, clinically accessible way to track and support pancreatic health in people with Type 2 Diabetes.

Source:

RESEARCH PAPER

Yurchishin ML, Finn AR, Fowler LA, Vere-Whiting SL, Gower BA. Greater reduction in the proinsulin-C-peptide ratio with a ketogenic vs control diet in patients with Type 2 Diabetes. J Endocr Soc. 2026 Apr 21;10(5): bvag073. doi: 10.1210/jendso/bvag073. PMID: 42022842; PMCID: PMC13097434.





Multidisciplinary Diabetes Care Achieves Remission in Nearly One in Three Patients (2026)

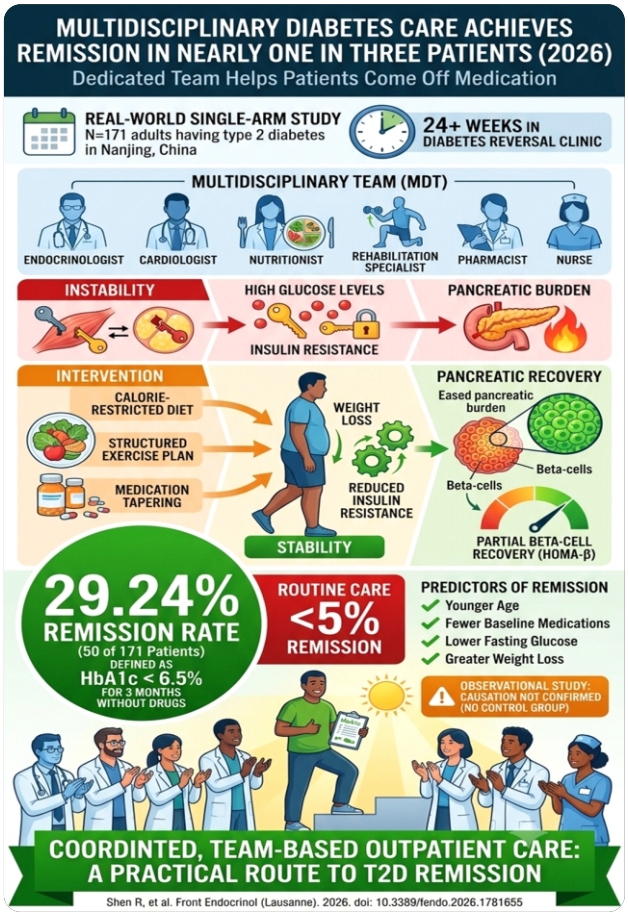
Can a dedicated diabetes team help nearly a third of patients come off their medication altogether?

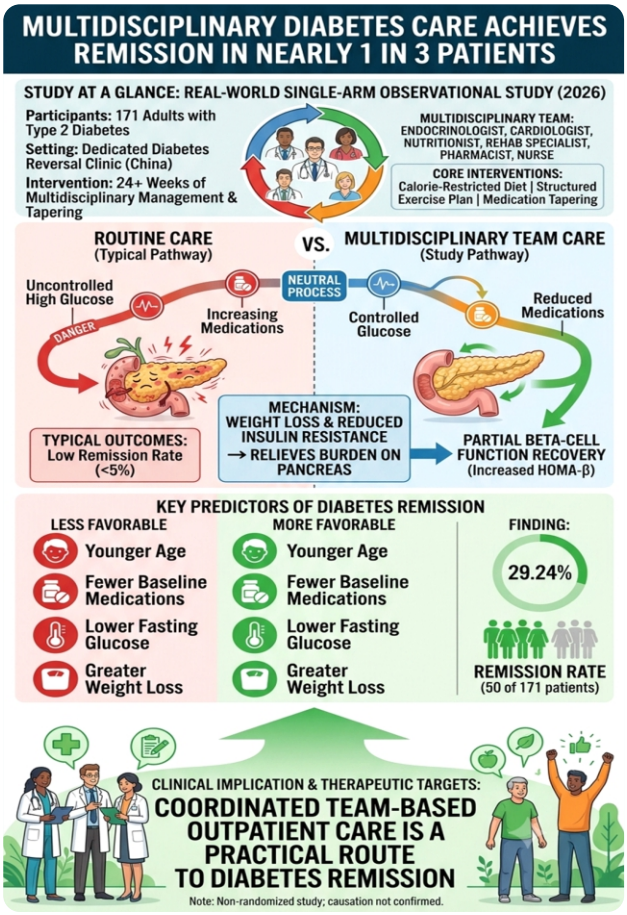
Researchers at the Affiliated Hospital of Integrated Traditional Chinese and Western Medicine, Nanjing University of Chinese Medicine, China, studied 171 adults with Type 2 Diabetes. All attended a dedicated Diabetes Reversal Clinic for at least 24 weeks. This real-world, single-arm study tested a multidisciplinary care model. It combined an endocrinologist, cardiologist, nutritionist, rehabilitation specialist, pharmacist, and nurse. Patients followed a calorie-restricted diet and a structured exercise plan. Medications were tapered as glycaemic control improved. Remission, defined as HbA1c below 6.5% for three months without drugs, occurred in 29.24% of patients (50 of 171). This is markedly higher than the under-5% rate typically seen with routine care. Younger age, fewer baseline medications, lower fasting glucose, and greater weight loss independently predicted remission. Mechanistically, weight loss and reduced insulin resistance appear to ease the burden on the pancreas. This allows beta-cell function, measured by HOMA-β, to partially recover. As an observational study without a control group, causation cannot be confirmed. Even so, the findings suggest coordinated, team-based outpatient care could offer a practical route to diabetes remission outside strict clinical trials.

Source:

RESEARCH PAPER

Shen R, Zhang Z, Sun H, Li D, Cheng Q, Zhou J, et al. Remission rate of Type 2 *Diabetes mellitus* following multidisciplinary management in the diabetes reversal clinic and its predictive factors: a real-world study. Front Endocrinol (Lausanne). 2026 Apr 14; 17:1781655. doi: 10.3389/fendo.2026.1781655. PMID: 42058782; PMCID: PMC13120954.





Clinical Guideline Brings More Consistency to Ayurvedic Diabetes Care in Nepal (2026)

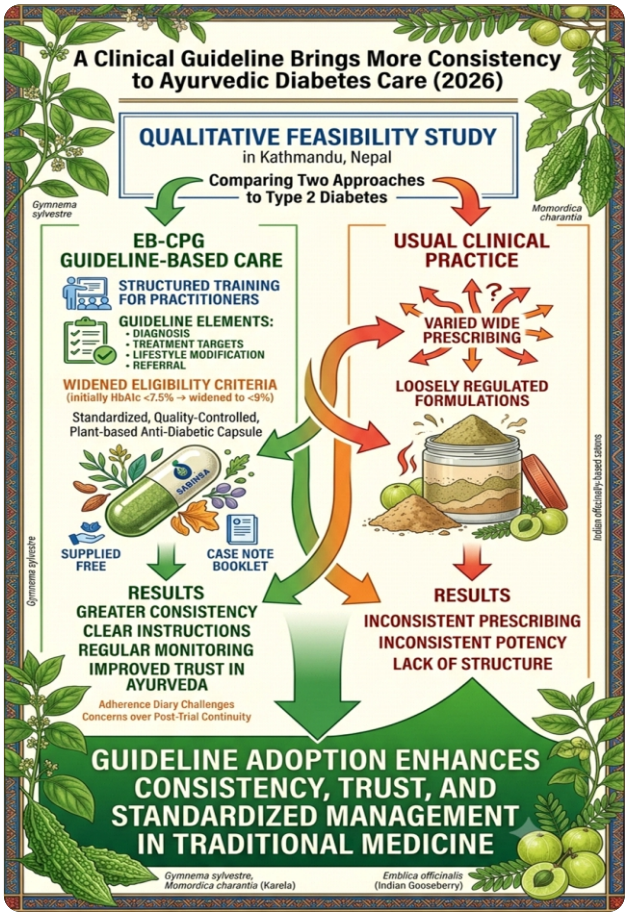
Could a simple clinical guideline help Ayurvedic doctors manage diabetes more consistently?

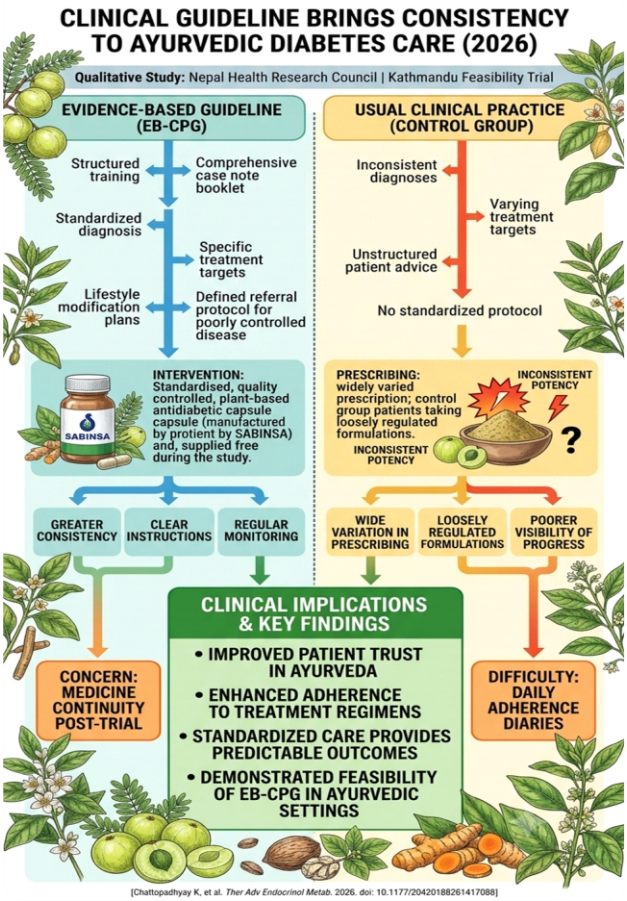
This qualitative study, led by the University of Nottingham and the Nepal Health Research Council, explored how Ayurvedic practitioners and patients experienced two approaches to managing Type 2 *Diabetes mellitus* in a Kathmandu-based feasibility trial: care guided by a newly developed evidence-based clinical practice guideline (EB-CPG) versus usual clinical practice. Researchers interviewed 41 participants, including seven practitioners and ten patients from each group, plus several who declined or withdrew, with data analysed thematically from semi-structured interviews. EB-CPG-based care, supported by structured practitioner training, a standardised case-note booklet, and a quality-controlled plant-based antidiabetic capsule, was viewed as markedly more consistent and trustworthy than usual practice, which was marked by variable prescribing, unclear lifestyle advice, and inconsistently regulated formulations. Patients reported improved adherence and greater confidence in Ayurveda, whilst practitioners valued the reduced ambiguity in decision-making. Challenges included maintaining daily adherence diaries, particularly among illiterate or busy patients, and concern over medicine continuity once the trial ended. Practitioners proposed widening the glycated haemoglobin eligibility threshold beyond the trial's cautious limit. Overall, the guideline appeared to meaningfully improve consistency and perceived quality in Ayurvedic diabetes care, offering lessons for a future definitive trial.

Source:

RESEARCH PAPER

Chattopadhyay K, Rana N, Karki S, Regmi P, Gyanwali P, Upadhyay V, Bista B, Tandon N, Kinra S, Biswas TK, Leonardi-Bee J, Heinrich M, Panniyammakal J, Lewis SA, Greenfield SM, Dhimal M. Diabetes management using a clinical guideline versus usual practice: a feasibility trial-based qualitative study among Ayurvedic practitioners and patients in Nepal. Ther Adv Endocrinol Metab. 2026; 17:20420188261417088. doi:10.1177/20420188261417088. PMID: 41694292.





Prolonged Water Fasting Combined with a GLP-1 Drug Enabled Bariatric Surgery in a Man with Severe Obesity (2026)

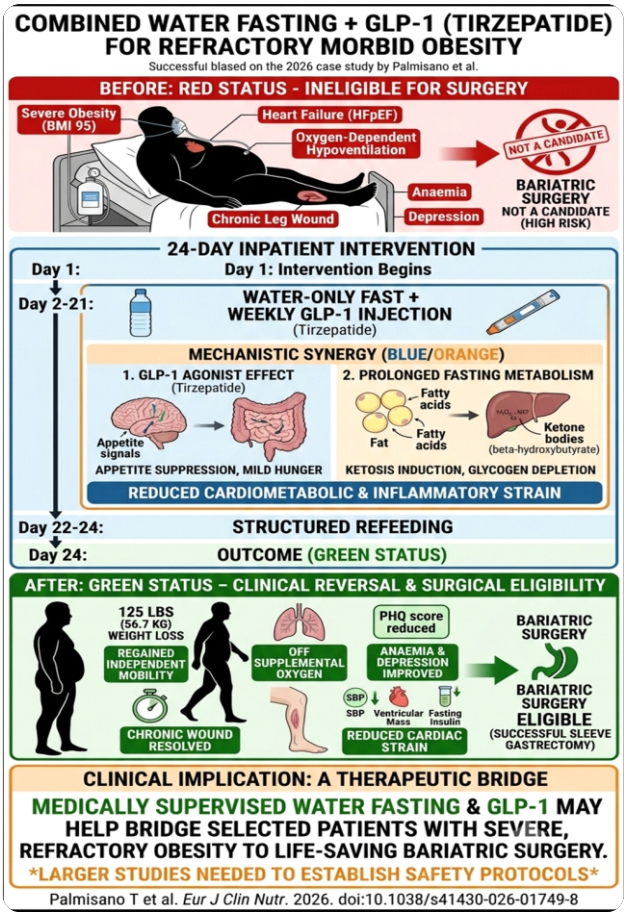
💧 ***Could a three-week water fast, paired with a weekly GLP-1 injection, turn a bed-bound patient into a surgical candidate?***

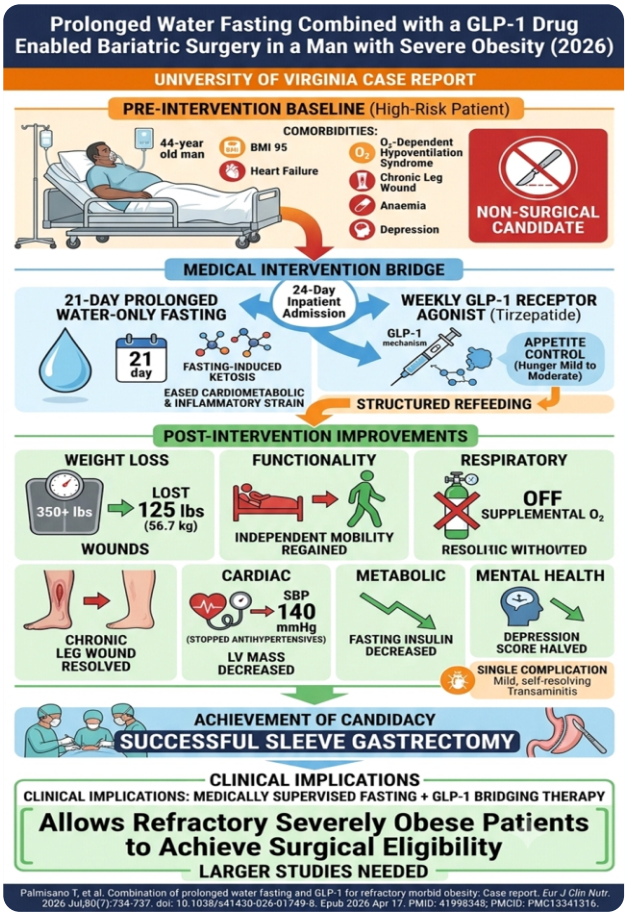
Clinicians at the University of Virginia in Charlottesville describe a single case of a 44-year-old man with a body mass index of 95, heart failure, oxygen-dependent hypoventilation syndrome, anaemia and depression, whose severe obesity had previously ruled him out as a surgical candidate. Over a 24-day inpatient admission, he completed a 21-day water-only fast alongside weekly tirzepatide, a GLP-1 receptor agonist, followed by structured refeeding before sleeve gastrectomy. He lost 125 pounds (56.7 kilograms), regained independent mobility, came off supplemental oxygen, and his chronic leg wound and anaemia resolved without treatment. Systolic blood pressure fell from around 170 to 140 mmHg despite stopping antihypertensives, left ventricular mass and fasting insulin both decreased, and his depression score nearly halved. Hunger stayed mild to moderate throughout, which the authors credit partly to tirzepatide's appetite-suppressing effect. The only complication was mild, self-resolving transaminitis. The authors suggest that fasting-induced ketosis, combined with GLP-1-assisted appetite control, eased the cardiometabolic and inflammatory strain underlying his condition. This case indicates that medically supervised fasting paired with GLP-1 therapy may help bridge carefully selected patients with severe obesity to bariatric surgery, though larger studies are needed.

Source:

📄 CASE REPORT

📌 Palmisano T, Roeschenthaler P, Passerini H, Shin T, Guarraia D. Combination of prolonged water fasting and GLP-1 for refractory morbid obesity: Case report. Eur J Clin Nutr. 2026 Jul;80(7):734-737. doi: 10.1038/s41430-026-01749-8. Epub 2026 Apr 17. PMID: 41998348; PMCID: PMC13341316.





Common Second-Line Blood Pressure Drug Linked to Faster Kidney Decline in People with Type 2 Diabetes on Modern Kidney-Protective Therapy (2026)

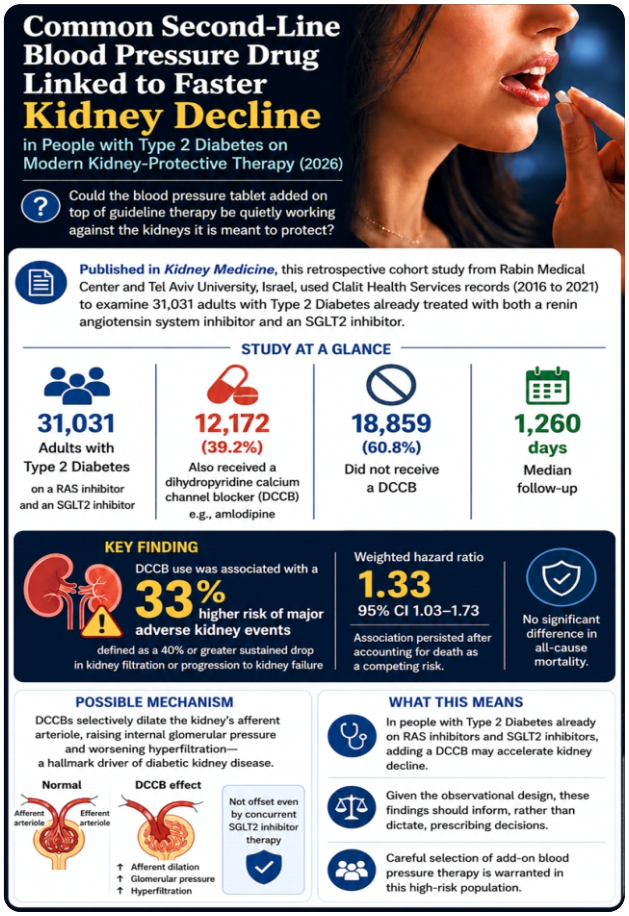
💊 ***Could the blood pressure tablet added on top of guideline therapy be quietly working against the kidneys it is meant to protect?***

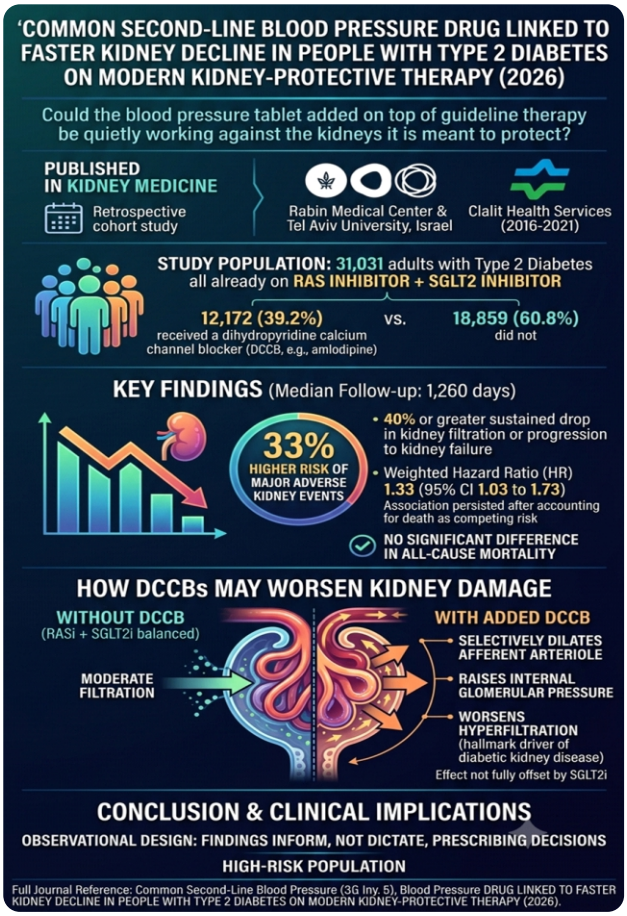
Published in Kidney Medicine, this retrospective cohort study from Rabin Medical Centre and Tel Aviv University, Israel, used Clalit Health Services records (2016 to 2021) to examine 31,031 adults with Type 2 Diabetes already treated with both a renin angiotensin system inhibitor and an SGLT2 inhibitor. Of these, 12,172 (39.2%) additionally received a dihydropyridine calcium channel blocker (DCCB, such as amlodipine), while 18,859 (60.8%) did not. Over a median follow-up of 1,260 days, DCCB use was associated with a 33% higher risk of major adverse kidney events, defined as a 40% or greater sustained drop in kidney filtration or progression to kidney failure (weighted hazard ratio 1.33, 95% CI 1.03 to 1.73), an association that persisted after accounting for death as a competing risk. No significant difference emerged in all-cause mortality. Mechanistically, DCCBs selectively dilate the kidney's afferent arteriole, raising internal glomerular pressure and worsening hyperfiltration, a hallmark driver of diabetic kidney disease, an effect seemingly not offset even by concurrent SGLT2 inhibitor therapy. Given the observational design, findings should inform, rather than dictate, prescribing decisions for this high-risk population.

Source:

RESEARCH PAPER

Agur T, Steinmetz T, Goldman S, Zingerman B, Bielopolski D, Nesher E, et al. Dihydropyridine calcium channel blocker therapy and risk of CKD progression in Type 2 Diabetes treated with renin angiotensin system inhibitors and SGLT2 inhibitors: a real-world retrospective cohort study. Kidney Med. 2026;8(7):101394. doi: 10.1016/j.jrkme.2026.101394.





A Diabetes-Specific Model to Better Predict Heart Disease Risk (2026)

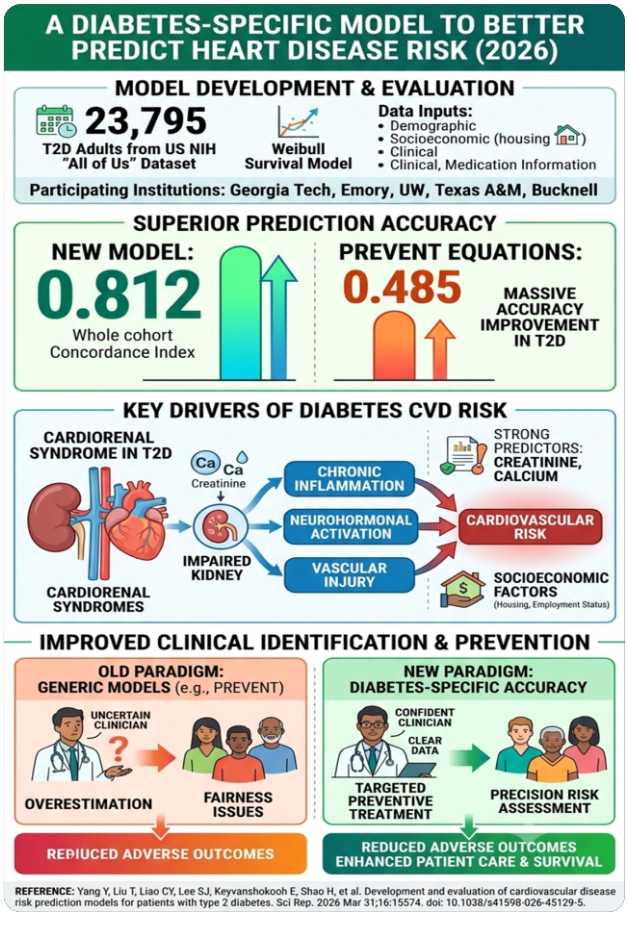
Could a new prediction tool spot heart disease risk in diabetes patients better than current guidelines?

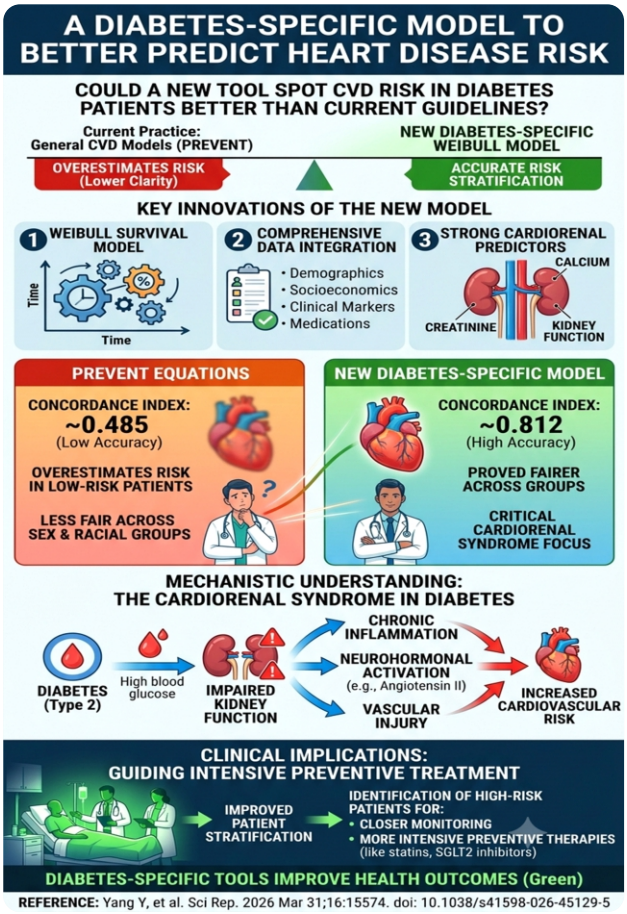
Researchers from Georgia Institute of Technology, Emory University, University of Washington, Texas A&M University, and Bucknell University developed a new statistical model to predict cardiovascular disease risk specifically in people with Type 2 Diabetes. Using data from 23,795 adults with Type 2 Diabetes in the United States National Institutes of Health All of Us dataset, they built a Weibull survival model incorporating demographic, socioeconomic, clinical, and medication information. When tested, this model achieved a concordance index of 0.812 for the whole cohort, considerably outperforming the widely used PREVENT equations, which scored just 0.485. The new model also proved fairer across sex and racial groups, whereas PREVENT tended to overestimate cardiovascular risk, particularly in lower-risk patients. Notably, markers of kidney function, including creatinine and calcium levels, emerged among the strongest predictors specifically in this diabetic population. This reflects cardiorenal syndrome, wherein impaired kidney function drives cardiovascular risk through chronic inflammation, neurohormonal activation, and vascular injury, effects less pronounced in people without diabetes. Socioeconomic factors such as housing and employment status also contributed meaningfully to predictions. These findings support developing diabetes-specific cardiovascular risk tools rather than relying on generic equations, potentially improving how doctors identify patients needing closer monitoring or more intensive preventive treatment.

Source:

RESEARCH PAPER

Yang Y, Liu T, Liao CY, Lee SJ, Keyvanshokooh E, Shao H, et al. Development and evaluation of cardiovascular disease risk prediction models for patients with Type 2 Diabetes. Sci Rep. 2026 Mar 31; 16:15574. doi: 10.1038/s41598-026-45129-5.





How Are People with Diabetes Searching for Health Information Online (2026)

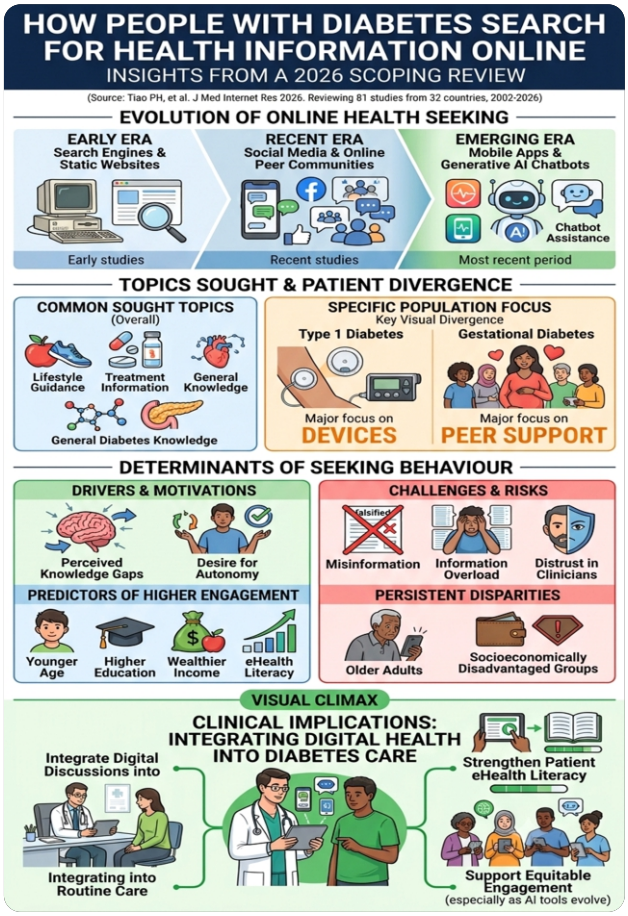
📱 ***Has your patient's next question already been answered by a Facebook group instead of you?***

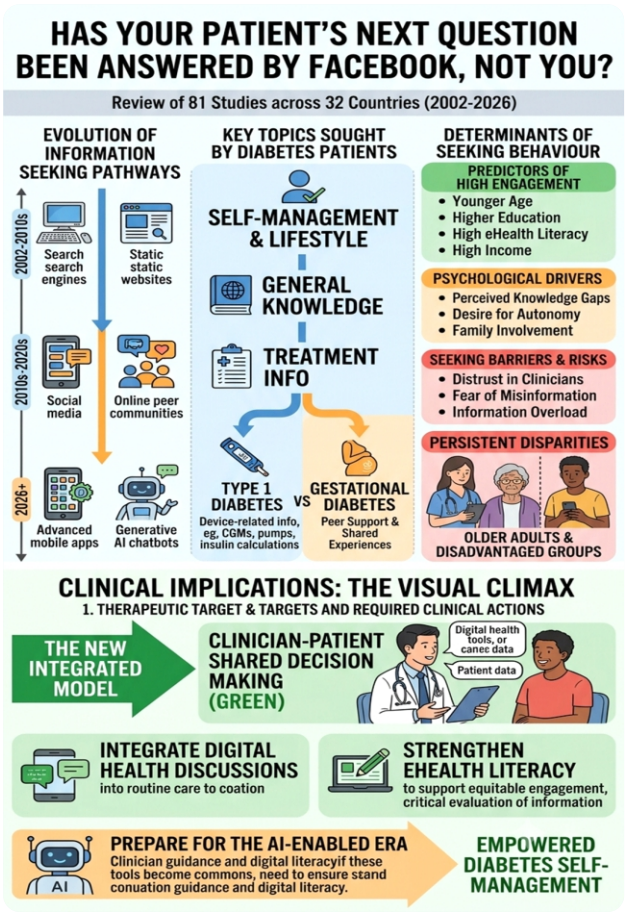
Researchers at National Taiwan University and National Taiwan Normal University conducted a scoping review mapping how people with diabetes seek health information online, drawing on 81 studies from 32 countries published between 2002 and 2026. The review traced a clear shift over time: early studies relied mainly on search engines and static websites, while more recent ones increasingly described social media and online peer communities, with mobile apps and generative AI chatbots emerging only in the most recent period. Across the whole dataset, self-management and lifestyle guidance, general diabetes knowledge, and treatment information were the topics most frequently sought, though people with Type 1 Diabetes more often looked into device-related information, while those with Gestational Diabetes leaned toward peer support. Determinants of information seeking operated at several levels: younger age, higher education, income, and eHealth literacy predicted greater engagement, while psychological drivers included perceived knowledge gaps and a desire for autonomy. Peer communities and family involvement shaped seeking behaviour, as did trust (or distrust) in clinicians and concerns about misinformation and information overload online. Persistent disparities appeared among older adults and socioeconomically disadvantaged groups. The authors conclude that online health information seeking has become an integral, evolving part of diabetes self-management, and argue for integrating digital health discussions into routine care and strengthening eHealth literacy to support equitable engagement as AI-enabled tools become more common.

Source:

REVIEW

Tiao PH, Chan HY, Huang YM. Navigating diabetes management in the digital era: scoping review of online health information-seeking behaviour. J Med Internet Res. 2026;28: e82081. doi:10.2196/82081. PMID: 42304771.





Can Your Glucose Monitor Predict a Heart Attack? What the Evidence Really Shows (2026)

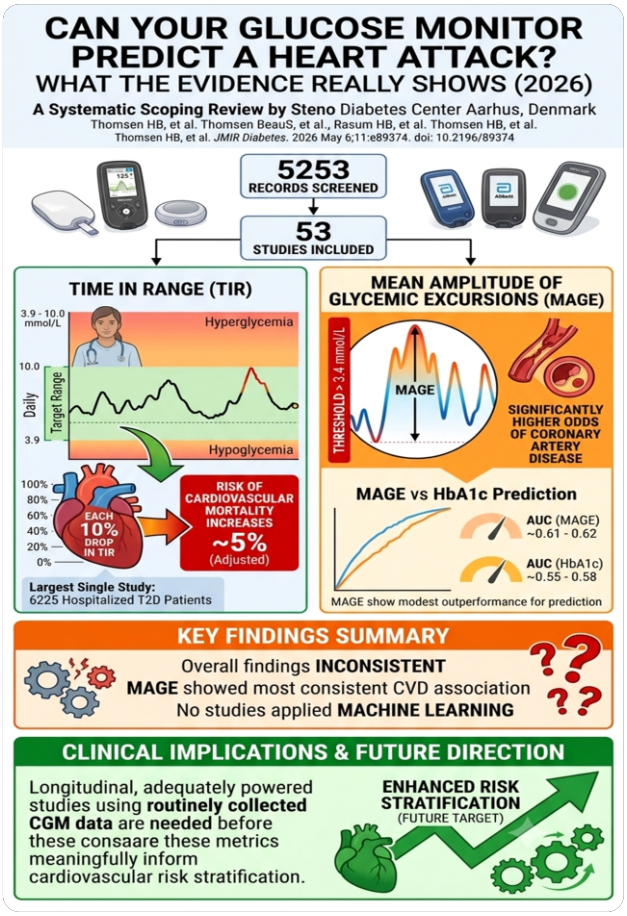
Could your glucose monitor reveal hidden heart disease risk in diabetes?

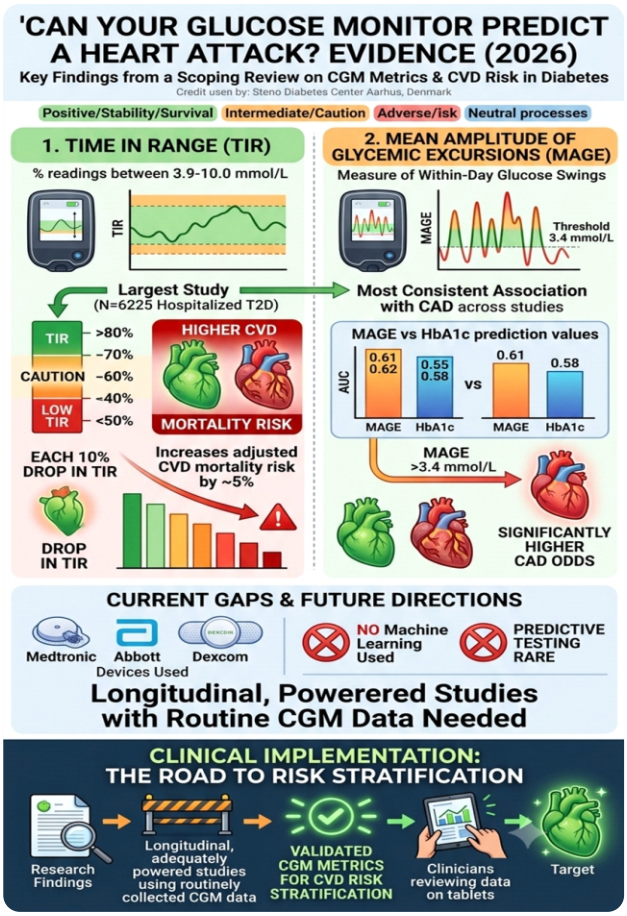
Researchers at Steno Diabetes Centre Aarhus in Denmark conducted a systematic scoping review of 53 studies, drawn from 5253 records, examining whether continuous glucose monitoring (CGM) metrics predict cardiovascular disease in people with diabetes. Findings were inconsistent overall, but two metrics stood out clinically. Time in range (TIR), the percentage of readings between 3.9 and 10.0 mmol/L, was linked to cardiovascular mortality in the largest single study, involving 6225 hospitalised patients with Type 2 Diabetes, where each 10 per cent drop in TIR raised adjusted mortality risk by about 5 per cent. Mean amplitude of glycaemic excursions (MAGE), a measure of within-day glucose swings, showed the most consistent association with coronary artery disease across studies, with a threshold of 3.4 mmol/L linked to significantly higher odds of disease. However, MAGE only modestly outperformed HbA1c for prediction, with area-under-curve values around 0.61 to 0.62 versus 0.55 to 0.58. Devices used included Medtronic, Abbott and Dexcom sensors. No study applied machine learning methods, and predictive testing remained rare. The authors concluded that longitudinal, adequately powered studies using routinely collected CGM data are needed before these metrics can meaningfully inform cardiovascular risk stratification.

Source:

REVIEW

Thomsen HB, Lebiecka-Johansen B, Nørgaard O, Helms Andersen T, Andersen ST, Fagherazzi G, et al. Continuous Glucose Monitoring-Derived Metrics and Cardiovascular Risk Among People with Diabetes: Systematic Scoping Review. JMIR Diabetes. 2026 May 6;11: e89374. doi: 10.2196/89374. PMID: 42090337; PMCID: PMC13148326.





Wearable Tech and the Future of Heart Health (2026)

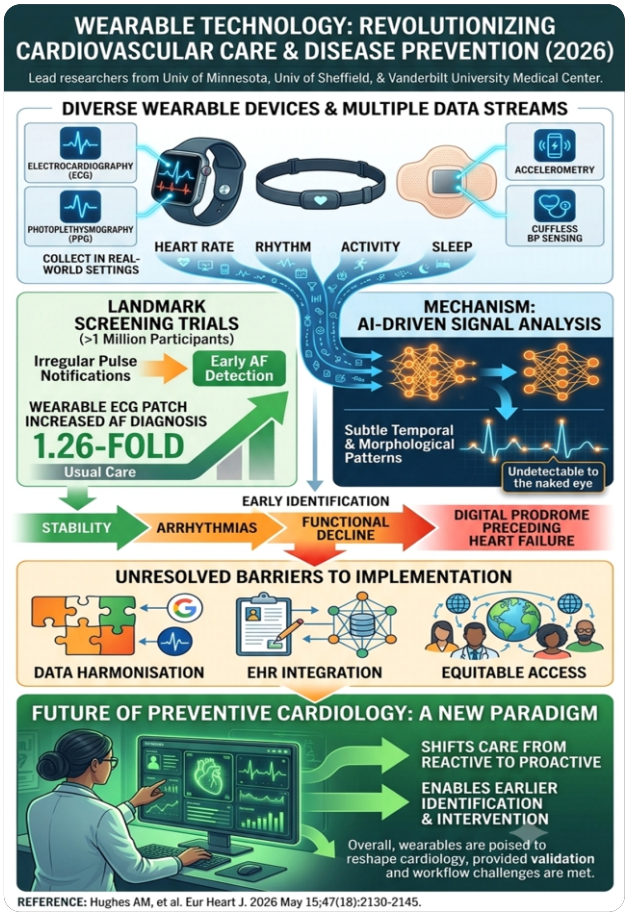
Could the watch on your wrist one day flag a heart problem before you even notice symptoms?

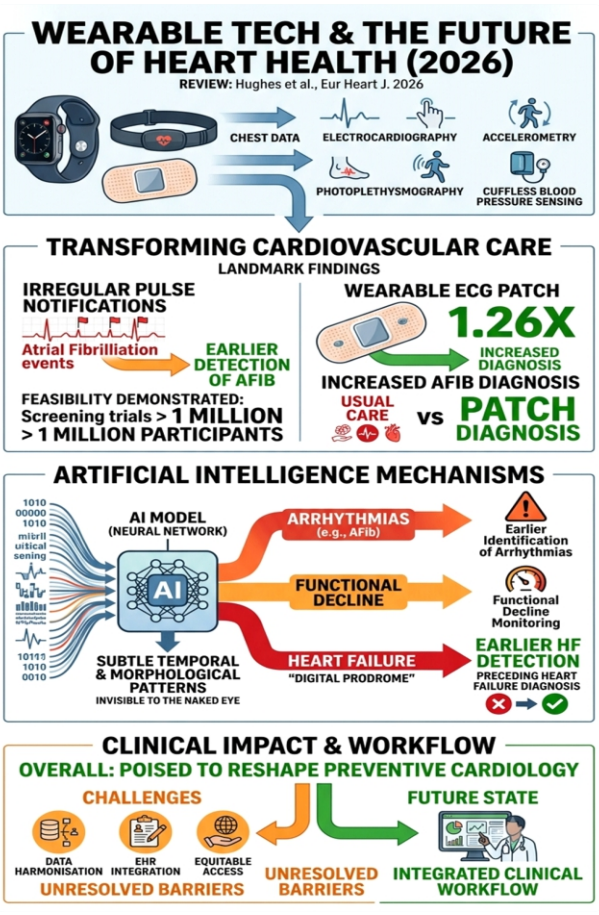
This state-of-the-art review, led by researchers from the University of Minnesota, the University of Sheffield, and Vanderbilt University Medical Centre, examines how wearable devices such as smartwatches, chest straps, and skin patches are transforming cardiovascular care. These devices use technologies including electrocardiography, photoplethysmography, accelerometry, and cuffless blood pressure sensing to capture heart rate, rhythm, activity, and sleep data in real-world settings. The authors highlight landmark screening trials enrolling over one million participants that demonstrated the feasibility of using irregular pulse notifications to detect atrial fibrillation, alongside evidence that a wearable electrocardiogram patch increased atrial fibrillation diagnosis 1.26-fold compared with usual care. Mechanistically, artificial intelligence models trained on wearable-derived signals can extract subtle temporal and morphological patterns undetectable to the naked eye, enabling earlier identification of arrhythmias, functional decline, and even a "digital prodrome" preceding heart failure diagnosis. Despite this promise, the review stresses that data harmonisation, electronic health record integration, and equitable access remain unresolved barriers. Overall, wearables are poised to reshape preventive cardiology, provided validation and clinical workflow challenges are addressed.

Source:

REVIEW

Hughes AM, Taylor DJ, Morris PD, Brittain EL. Wearable devices and cardiovascular health: revolutionizing remote monitoring and disease prevention. Eur Heart J. 2026 May 15;47(18):2130-2145. doi: 10.1093/eurheartj/ehag189. PMID: 41879156; PMCID: PMC13178683.





Heart Disease Costs Are Rising Even as Treatment Keeps Improving (2026)

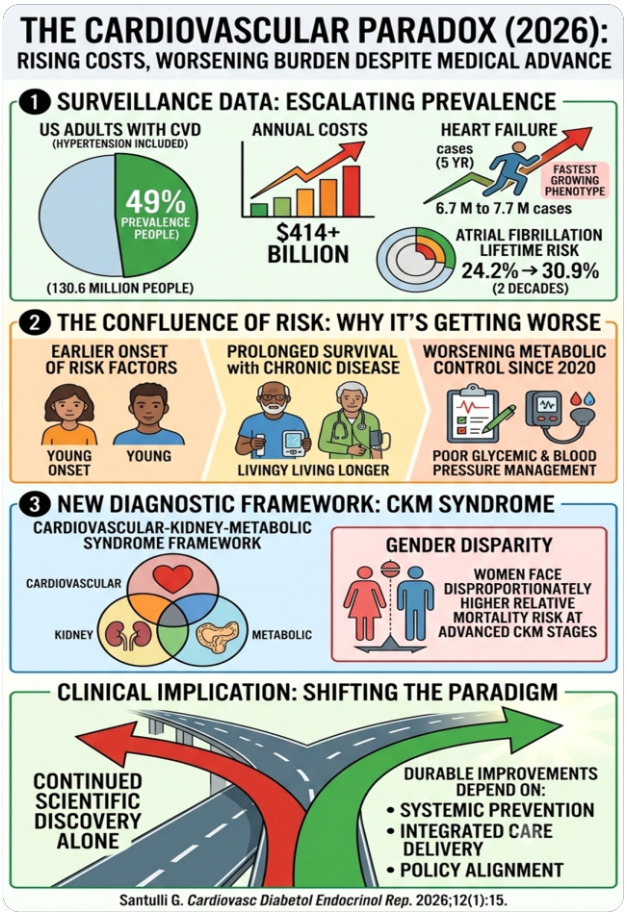
Why is cardiovascular disease costing more than ever, even as medicine keeps getting better at treating it?

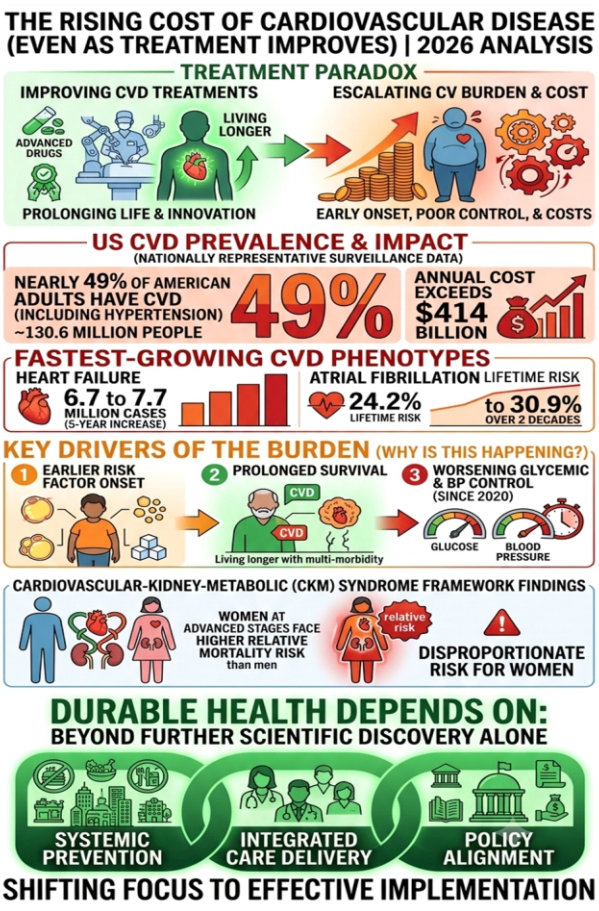
This commentary from the Department of Molecular, Cellular and Biomedical Sciences at the City University of New York School of Medicine examines the 2026 American Heart Association Heart Disease and Stroke Statistics Update, published in Cardiovascular Diabetology - Endocrinology Reports. Drawing on nationally representative US surveillance data, the analysis finds that nearly 49% of American adults, around 130.6 million people, now meet criteria for cardiovascular disease when hypertension is included, with annual costs exceeding 414 billion dollars. Heart failure has become the fastest-growing cardiovascular phenotype, rising from 6.7 to 7.7 million cases within five years, while atrial fibrillation's lifetime risk has climbed from 24.2% to 30.9% over two decades. The author argues these trends reflect earlier onset of risk factors, prolonged survival, and worsening glycaemic and blood pressure control since 2020, rather than any shortfall in pharmacological innovation. The newly incorporated cardiovascular-kidney-metabolic syndrome framework reveals that women face disproportionately higher relative mortality risk at advanced disease stages than men. The commentary concludes that durable improvements in population cardiovascular health now depend on systemic prevention, integrated care delivery, and policy alignment rather than further scientific discovery alone.

Source:

COMMENTARY

Santulli G. Epidemiology of cardiovascular disease and diabetes in 2026: expanding prevalence, escalating costs, and the limits of contemporary prevention. Cardiovasc Diabetol Endocrinol Rep. 2026 Apr 1;12(1):15. doi: 10.1186/s40842-026-00283-7. Erratum in: Cardiovasc Diabetol Endocrinol Rep. 2026 Apr 21;12(1):29. doi: 10.1186/s40842-026-00297-1. PMID: 41918034; PMCID: PMC13041046.





Charting the Future of Type 2 Diabetes Treatment: From Metformin to Gene Editing (2025)

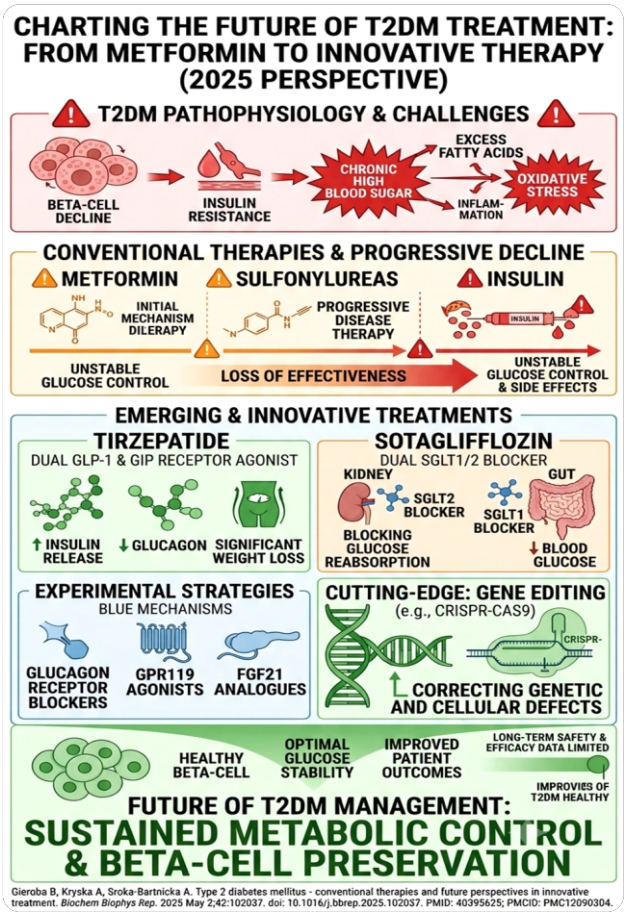
💊 ***What comes after Metformin and Insulin in treating Type 2 Diabetes?***

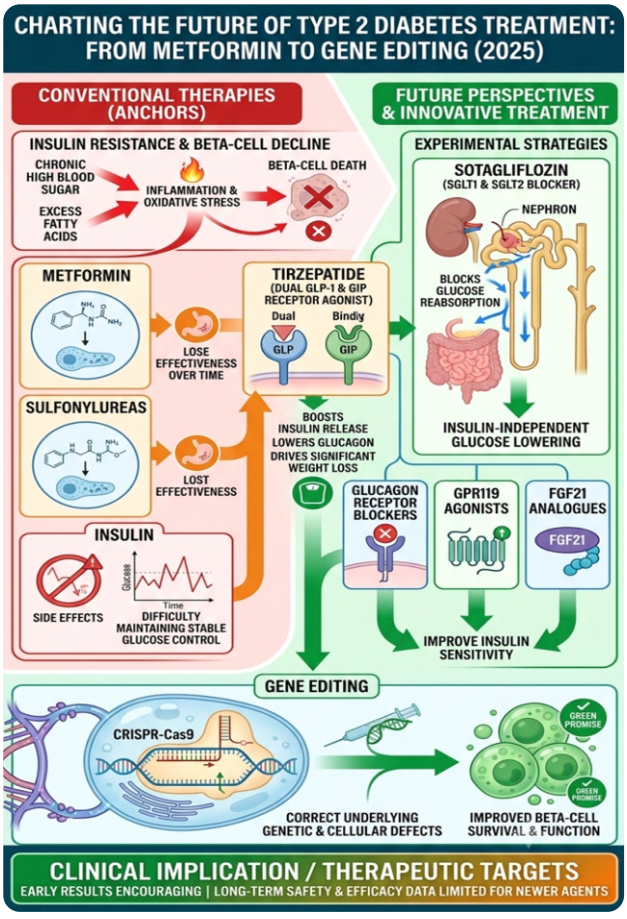
Researchers at the Medical University of Lublin, Poland, reviewed the current and emerging treatment landscape for Type 2 *Diabetes mellitus* (T2DM). T2DM stems from insulin resistance and declining beta-cell function. Chronic high blood sugar and excess fatty acids drive this decline through inflammation and oxidative stress. Conventional therapies still anchor treatment. These include Metformin, Sulfonylureas, and Insulin. However, they often lose effectiveness over time. Side effects and difficulty maintaining stable glucose control are common. The review highlights promising newer approaches. Tirzepatide, a dual GLP-1 and GIP receptor agonist, boosts insulin release, lowers glucagon, and drives significant weight loss. Sotagliflozin blocks glucose reabsorption in both the gut and kidneys. This lowers blood sugar through an insulin-independent route. Other experimental strategies target different mechanisms. These include glucagon receptor blockers, GPR119 agonists, and FGF21 analogues, which aim to improve insulin sensitivity. Gene-editing tools such as CRISPR-Cas9 are also being explored to correct the underlying genetic and cellular defects. While early results are encouraging, the authors note that long-term safety and efficacy data for most of these newer agents remain limited.

Source:

📄 REVIEW

📌 Gieroba B, Kryska A, Sroka-Bartnicka A. Type 2 *Diabetes mellitus* - conventional therapies and future perspectives in innovative treatment. Biochem Biophys Rep. 2025 May 2; 42:102037. doi: 10.1016/j.bbrep.2025.102037. PMID: 40395625; PMCID: PMC12090304.





Moderna's Experimental mRNA Vaccine Outperforms the Standard Flu Shot in Older Adults (2026)

Could the same mRNA technology behind COVID vaccines finally give older adults better protection against the Flu?

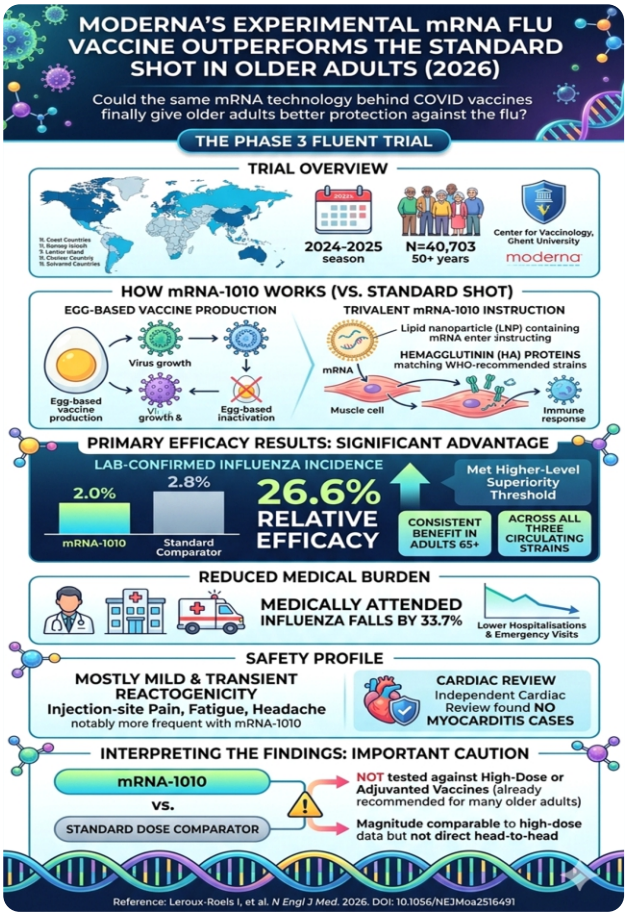
This phase 3 FLUENT trial, led by the Centre for Vaccinology at Ghent University and funded by Moderna, enrolled 40,703 adults aged 50 and older across 11 countries during the 2024-2025 influenza season. Participants received trivalent mRNA-1010, which instructs cells to produce hemagglutinin proteins matching World Health Organization-recommended strains without egg-based manufacturing, or a licensed standard-dose comparator vaccine. Laboratory-confirmed influenza occurred in 2.0% of mRNA recipients versus 2.8% of comparator recipients, a 26.6% relative efficacy that met the trial's higher-level superiority threshold. Benefit held up among adults 65 and older and across all three circulating strains, and medically attended influenza fell by 33.7%, with hospitalisations and emergency visits also lower. Injection-site pain, fatigue, and headache were notably more frequent with mRNA-1010, though mostly mild and transient, and independent cardiac review found no myocarditis cases. Researchers note the comparator was a standard-dose vaccine rather than the high-dose or adjuvanted vaccines many countries already recommend for older adults, so the magnitude of benefit, while comparable to high-dose data, has not been tested head-to-head against these enhanced alternatives.

Source:

RESEARCH PAPER

Leroux-Roels I, Huang G, Ferguson M, Kohli A, Clark R, Bickel M, Soens M, Du E, Pucci A, Hicks B, Eschen C, Das R, Wilson E; Fluent Trial Investigators. Efficacy and Safety of an mRNA Seasonal Influenza Vaccine in Adults. N Engl J Med. 2026 May 7;394(18):1803-1813. doi: 10.1056/NEJMoa2516491. PMID: 42090792.





Dutch Study Pinpoints How Long It Took COVID to Become Endemic

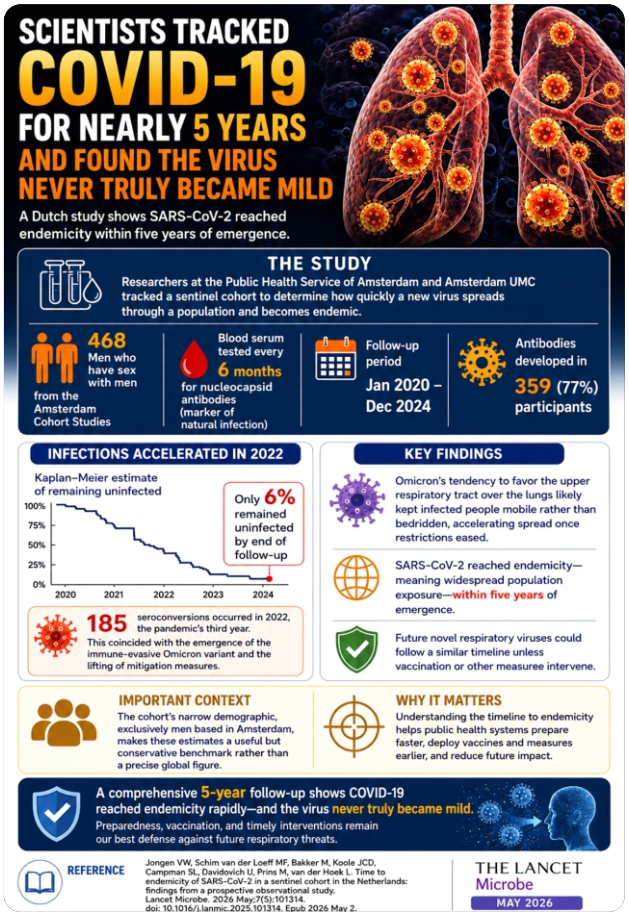
How long does it actually take for a brand-new virus to spread through almost everyone?

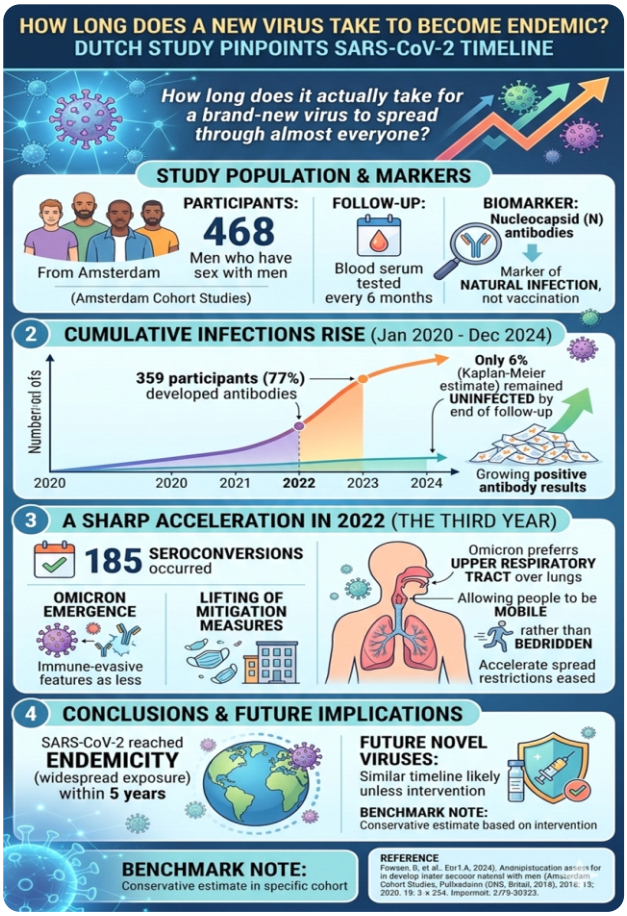
Researchers at the Public Health Service of Amsterdam and Amsterdam UMC tracked 468 men who have sex with men from the Amsterdam Cohort Studies, testing blood serum every six months for nucleocapsid antibodies, a marker of natural infection rather than vaccination. Between January 2020 and December 2024, 359 participants (77%) developed these antibodies, with a Kaplan-Meier estimate suggesting only 6% remained uninfected by the end of follow-up. Infections accelerated sharply in 2022, the pandemic's third year, when 185 seroconversions occurred, coinciding with the emergence of the immune-evasive Omicron variant and the lifting of mitigation measures. Omicron's tendency to favour the upper respiratory tract over the lungs likely kept infected people mobile rather than bedridden, accelerating spread once restrictions eased. The researchers conclude that SARS-CoV-2 reached endemicity, meaning widespread population exposure, within five years of emergence, and suggest future novel respiratory viruses could follow a similar timeline unless vaccination or other measures intervene. The cohort's narrow demographic, exclusively men based in Amsterdam, makes these estimates a useful but conservative benchmark rather than a precise global figure.

Source:

COHORT STUDY

Jongen VW, Schim van der Loeff MF, Bakker M, Koole JCD, Campman SL, Davidovich U, Prins M, van der Hoek L. Time to endemicity of SARS-CoV-2 in a sentinel cohort in the Netherlands: findings from a prospective observational study. Lancet Microbe. 2026 May;7(5):101314. doi: 10.1016/j.lanmic.2025.101314. Epub 2026 May 2.





Ultrasound at Medical-Imaging Frequencies Disrupts Flu and COVID-19 Viruses in Lab Tests (2026)

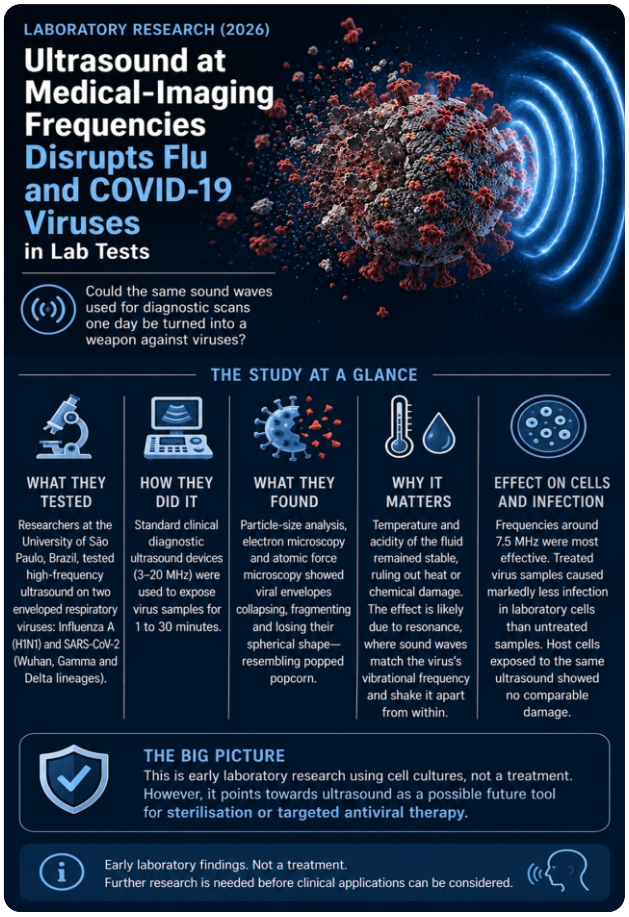
Could the same sound waves used for diagnostic scans one day be turned into a weapon against viruses?

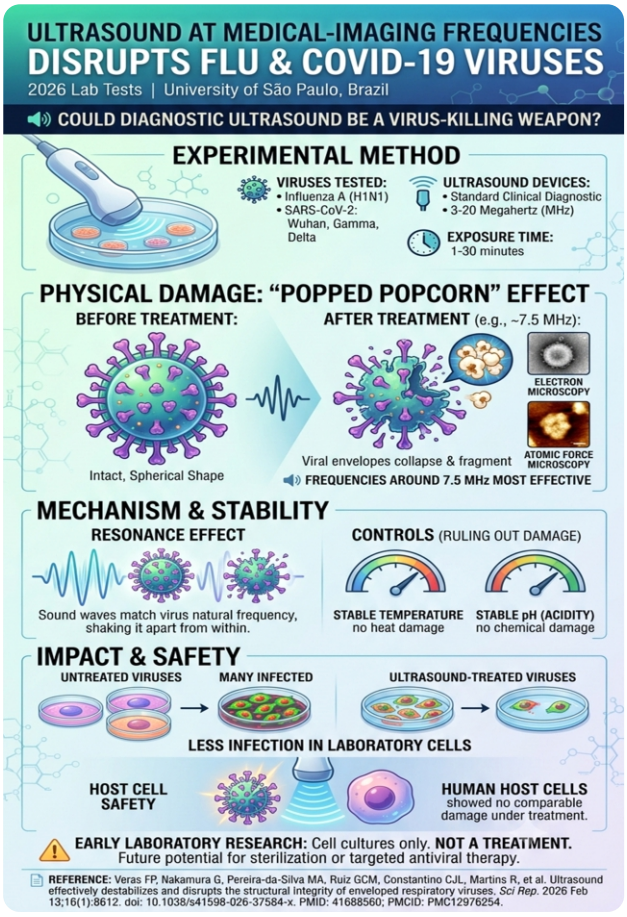
Researchers at the University of São Paulo in Brazil tested whether high-frequency ultrasound, similar to that used in medical imaging, could physically damage two enveloped respiratory viruses: Influenza A (H1N1) and SARS-CoV-2, including its Wuhan, Gamma and Delta lineages. Using standard clinical diagnostic ultrasound devices operating between 3 and 20 megahertz, they exposed virus samples for one to thirty minutes. Particle-size analysis, electron microscopy and atomic force microscopy all showed the viral envelopes collapsing, fragmenting and losing their normal spherical shape after treatment, with imagery resembling popped popcorn. Crucially, the surrounding fluid's temperature and acidity stayed stable throughout, ruling out heat or chemical damage and pointing instead to resonance, where sound waves match the virus's own vibrational frequency and shake it apart from within. Frequencies around 7.5 megahertz were most effective, and treated virus samples caused markedly less infection in laboratory cells than untreated samples. Host cells exposed to the same ultrasound showed no comparable damage. The authors stress this is early laboratory work using cell cultures, not a treatment, but it points towards ultrasound as a possible future tool for sterilisation or targeted antiviral therapy.

Source:

RESEARCH PAPER

Veras FP, Nakamura G, Pereira-da-Silva MA, Ruiz GCM, Constantino CJL, Martins R, et al. Ultrasound effectively destabilizes and disrupts the structural integrity of enveloped respiratory viruses. Sci Rep. 2026 Feb 13;16(1):8612. doi: 10.1038/s41598-026-37584-x. PMID: 41688560; PMCID: PMC12976254.





One Amino Acid Shift: How Coronaviruses Jump from Bats to Humans (2026)

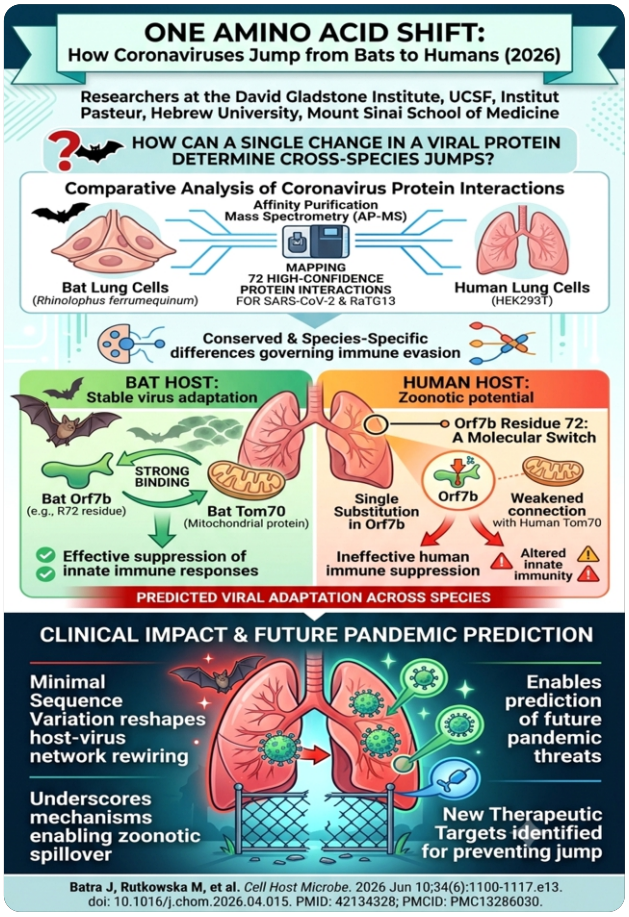
How can a single change in a viral protein determine whether a coronavirus can cross species barriers and trigger human pandemics?

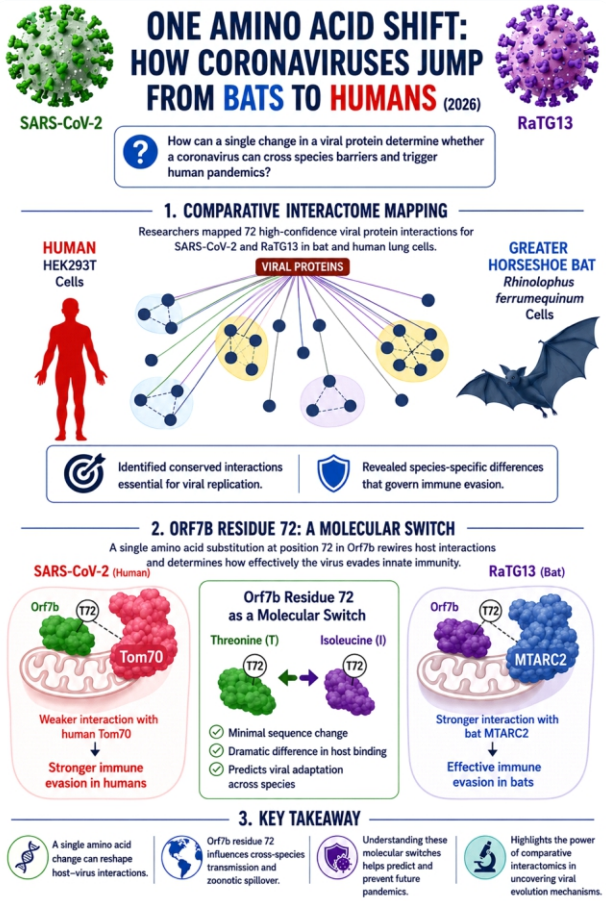
Researchers at the David Gladstone Institute, University of California San Francisco, and collaborating institutions including Institut Pasteur, Hebrew University and Mount Sinai School of Medicine conducted a comparative analysis of coronavirus protein interactions in human and bat lung cells. Using affinity purification mass spectrometry, they mapped 72 high-confidence protein interactions for SARS-CoV-2 and its bat-origin relative RaTG13 in both *Rhinolophus ferrumequinum* (horseshoe bat) and human HEK293T cells. The study identified conserved interactions essential for viral replication alongside species-specific differences that govern immune evasion. A single amino acid substitution at residue 72 in the viral protein Orf7b functioned as a molecular switch, weakening interaction with the human mitochondrial protein Tom70 whilst enhancing binding in bat cells. This difference altered how effectively each virus suppressed innate immune responses and predicted viral adaptation across species. The findings reveal that minimal sequence variation can reshape host-virus interactions and underscore mechanisms enabling zoonotic spillover, with implications for understanding viral evolution and predicting future pandemic threats.

Source:

RESEARCH PAPER

Batra J, Rutkowska M, Zhou Y, Ye C, Adavikolanu R, Young JM, Anand D, Verma S, Gordon M, Malpotra S, et al. Coronavirus protein interaction mapping in bat and human cells reveals network rewiring governing immune evasion and zoonotic potential. Cell Host Microbe. 2026 Jun 10;34(6):1100-1117.e13. doi: 10.1016/j.chom.2026.04.015. Epub 2026 May 13. PMID: 42134328; PMCID: PMC13286030.





A Popular Skincare Ingredient Shows Promise Against Drug-Resistant Bacteria, With a Twist (2026)

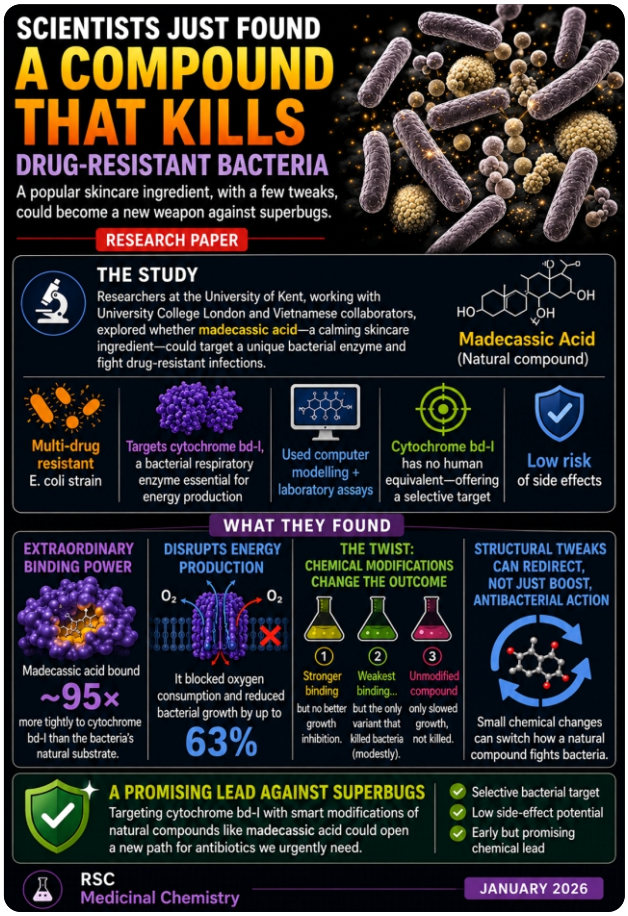
Could a calming skincare ingredient also help fight superbugs that are running out of treatment options?

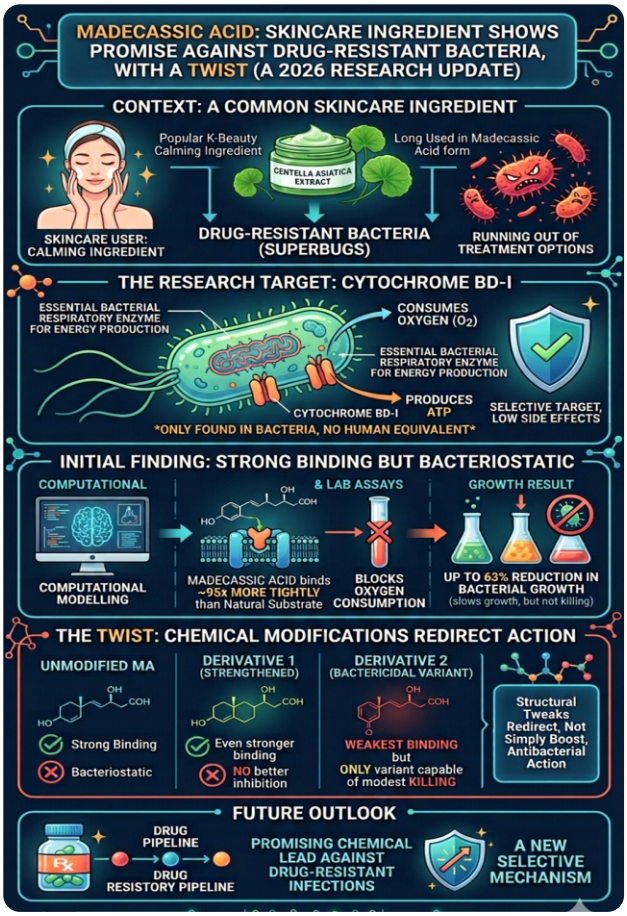
Researchers at the University of Kent, working with University College London and Vietnamese collaborators, investigated whether madecassic acid, a calming ingredient long used in Korean skincare, could inhibit cytochrome bd-I, a respiratory enzyme found only in bacteria and essential for their energy production. Using computer modelling and laboratory assays on a multidrug-resistant E. coli strain, the team found madecassic acid bound roughly 95 times more tightly to this enzyme than the bacteria's natural substrate, blocking oxygen consumption and reducing bacterial growth by up to 63%. However, the unmodified compound only slowed growth without killing the bacteria. Three chemically modified versions revealed a more complex picture: one bound the enzyme more strongly without improving growth inhibition, while another, despite binding most weakly, became the only variant capable of killing the bacteria, albeit modestly. This suggests structural tweaks can redirect, rather than simply boost, a natural compound's antibacterial action. Because cytochrome bd-I has no human equivalent, this approach offers a selective target with low risk of side effects, an early but promising chemical lead against drug-resistant infections.

Source:

RESEARCH PAPER

Henry SA, Sansom GN, Tran TTP, Boughton RA, Joiner G, Webster CM, et al. Investigating the role of cytochrome bd oxidases in the antibacterial activity of madecassic acid and derivatives thereof. RSC Med Chem. 2026 Jan 13;17(3):1513-1520. doi: 10.1039/d5md01116g. PMCID: PMC12822377. PMID: 41574235.





A Compound in Turmeric and Ginger Weakens Drug-Resistant Staphylococcus aureus (2026)

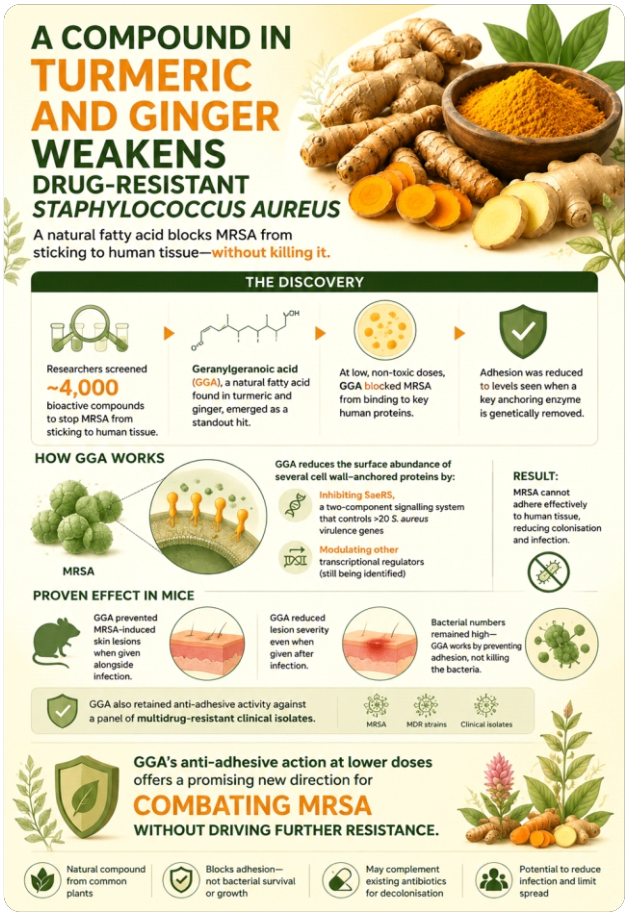
Could a natural fatty acid block one of the most dangerous antibiotic-resistant bacteria from attaching to the human body, without killing it at all?

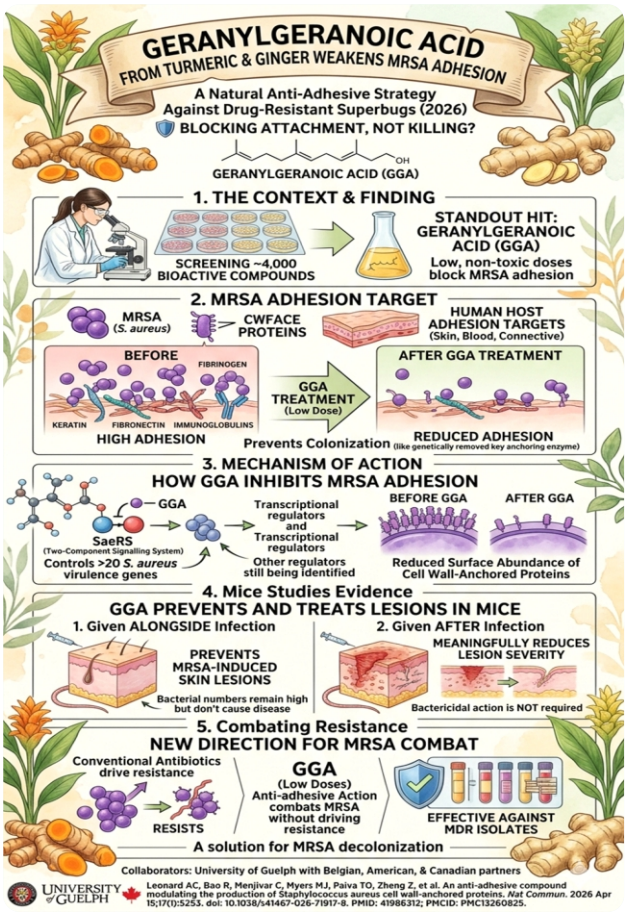
Researchers at the University of Guelph, with collaborators in Belgium, the US, and Canada, screened nearly 4,000 bioactive compounds in search of ways to stop methicillin-resistant Staphylococcus aureus (MRSA) from sticking to human tissue, a critical first step in colonisation and infection. One compound, geranylgeranoic acid (GGA), a polyunsaturated fatty acid naturally found in plants such as turmeric and ginger, emerged as a standout hit. At low, non-toxic doses, GGA blocked MRSA's ability to bind keratin, fibronectin, fibrinogen and immunoglobulins, reducing adhesion to levels seen when a key anchoring enzyme is genetically removed. The team found that GGA works by lowering the surface abundance of several cell wall-anchored proteins, partly by inhibiting SaeRS, a two-component signalling system controlling more than twenty S. aureus virulence genes, alongside other transcriptional regulators still being identified. In mice, GGA prevented MRSA-induced skin lesions when given alongside infection, and meaningfully reduced lesion severity even when administered afterwards, despite bacterial numbers remaining high. GGA also retained its anti-adhesive activity against a panel of multidrug-resistant clinical isolates. With existing decolonisation antibiotics losing effectiveness to resistance, GGA's anti-adhesive action at lower doses offers a promising new direction for combating MRSA without driving further resistance.

Source:

RESEARCH PAPER

Leonard AC, Bao R, Menjivar C, Myers MJ, Paiva TO, Zheng Z, et al. An anti-adhesive compound modulating the production of Staphylococcus aureus cell wall-anchored proteins. Nat Commun. 2026 Apr 15;17(1):5253. doi: 10.1038/s41467-026-71917-8. PMID: 41986312; PMCID: PMC13260825.





Better Oral Hygiene Cuts Hospital-Acquired Pneumonia Risk in Half, Australian Trial Finds (2026)

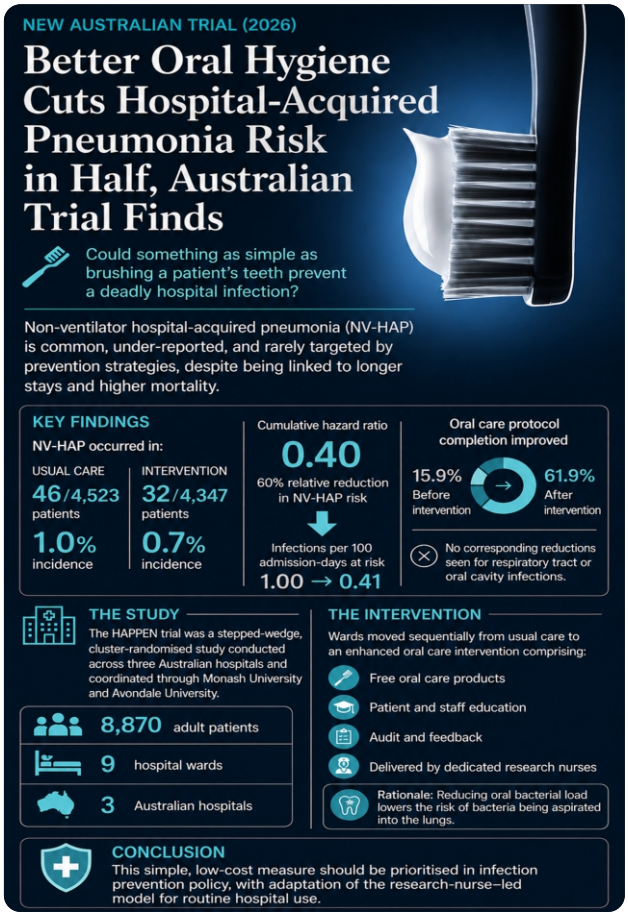
Could something as simple as brushing a patient's teeth prevent a deadly hospital infection?

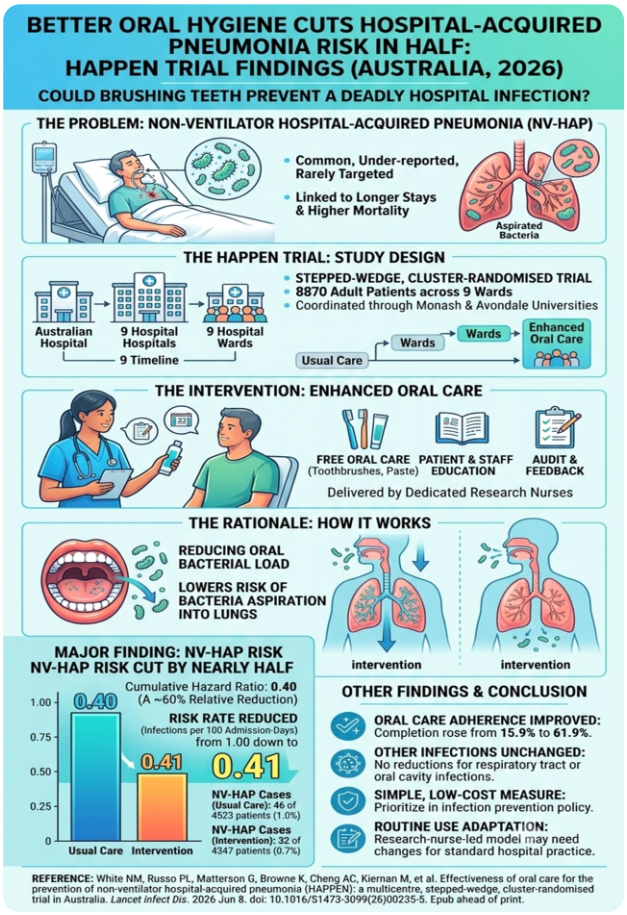
Non-ventilator hospital-acquired pneumonia (NV-HAP) is common, under-reported, and rarely targeted by prevention strategies, despite being linked to longer stays and higher mortality. The HAPPEN trial, a stepped-wedge, cluster-randomised study conducted across three Australian hospitals and coordinated through Monash University and Avondale University, enrolled 8870 adult patients across nine hospital wards. Wards moved sequentially from usual care to an enhanced oral care intervention comprising free oral care products, patient and staff education, and audit and feedback, delivered by dedicated research nurses. The rationale is that reducing oral bacterial load lowers the risk of bacteria being aspirated into the lungs. NV-HAP occurred in 46 of 4523 patients (1.0%) under usual care compared with 32 of 4347 patients (0.7%) under the intervention, a cumulative hazard ratio of 0.40, equivalent to a reduction from 1.00 to 0.41 infections per 100 admission-days at risk. Completion of the oral care protocol rose from 15.9% to 61.9% following the intervention. No corresponding reductions were seen for respiratory tract or oral cavity infections. The authors concluded that this simple, low-cost measure should be prioritised in infection prevention policy, while noting that a research-nurse-led model may need adaptation for routine hospital use.

Source:

RESEARCH PAPER

White NM, Russo PL, Matterson G, Browne K, Cheng AC, Kiernan M, et al. Effectiveness of oral care for the prevention of non-ventilator hospital-acquired pneumonia (HAPPEN): a multicentre, stepped-wedge, cluster-randomised trial in Australia. Lancet Infect Dis. 2026 Jun 8. doi: 10.1016/S1473-3099(26)00235-5. Epub ahead of print.





Suspected Brain Cancer, Actually Tapeworm Cysts: A Rare Case from Spain (2026)

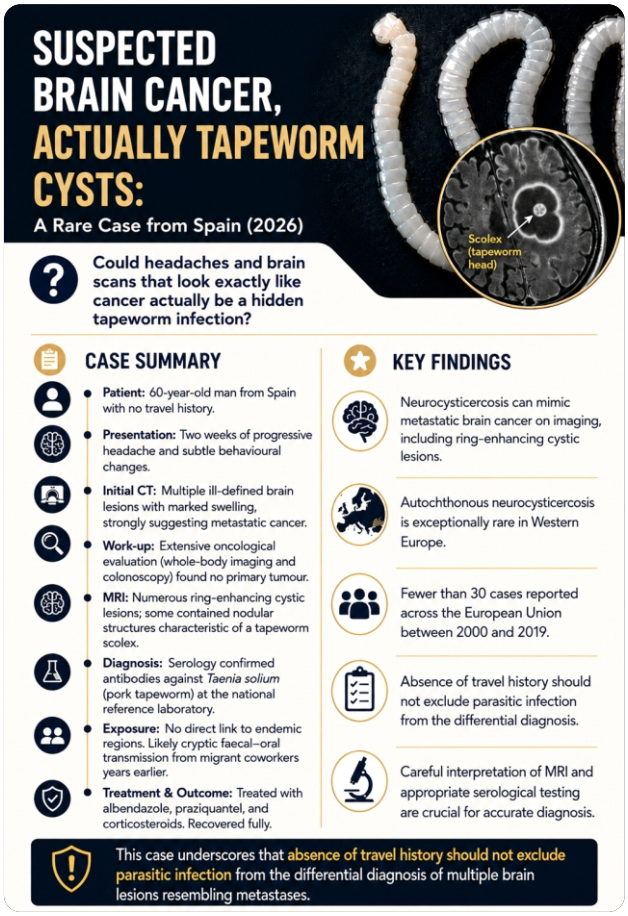
Could headaches and brain scans that look exactly like cancer actually be a hidden tapeworm infection?

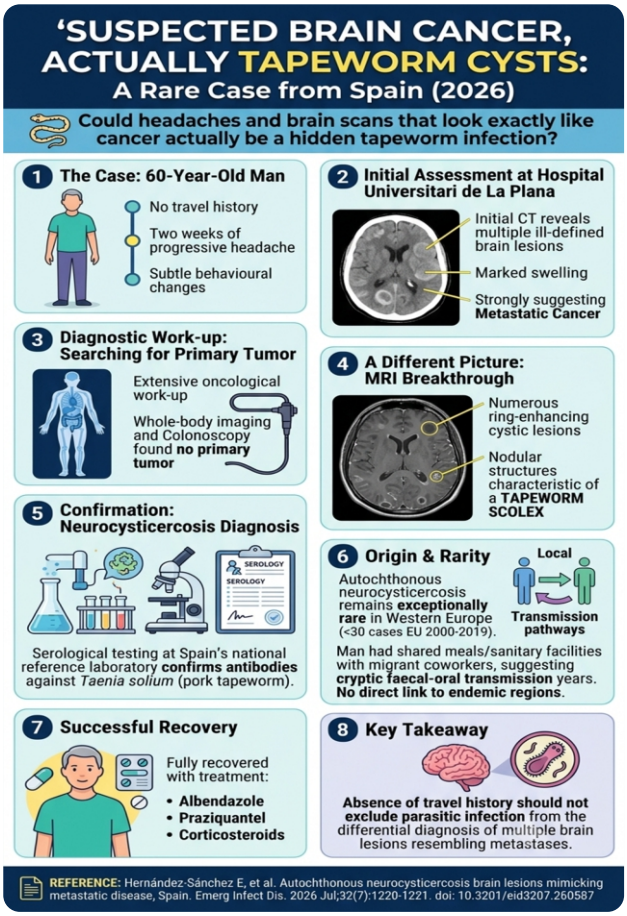
Physicians at Hospital Universitari de La Plana, Vila-real, Spain, report the case of a 60-year-old man with no travel history who presented with two weeks of progressive headache and subtle behavioural changes. Initial computed tomography revealed multiple ill-defined brain lesions with marked swelling, strongly suggesting metastatic cancer. An extensive oncological work-up, including whole-body imaging and colonoscopy, found no primary tumour. Magnetic resonance imaging instead showed numerous ring-enhancing cystic lesions, some containing nodular structures characteristic of a tapeworm scolex. Serological testing at Spain's national reference laboratory confirmed antibodies against *Taenia solium*, the pork tapeworm, establishing a diagnosis of neurocysticercosis. The man had no direct link to endemic regions but had previously shared meals and sanitary facilities with migrant coworkers, suggesting cryptic faecal-oral transmission years earlier. He recovered fully with albendazole, praziquantel, and corticosteroids. Autochthonous neurocysticercosis remains exceptionally rare in Western Europe, with fewer than thirty cases reported across the European Union between 2000 and 2019. This case underscores that absence of travel history should not exclude parasitic infection from the differential diagnosis of multiple brain lesions resembling metastases.

Source:

CASE REPORT

Hernández-Sánchez E, Monllor P, Gil-Fortuño M, Guillamón E. Autochthonous Neurocysticercosis Brain Lesions Mimicking Metastatic Disease, Spain. Emerg Infect Dis. 2026 Jul;32(7):1220-1221. doi: 10.3201/eid3207.260587. PMID: 42365978; PMCID: PMC13322418.





Sea Anemones Teach Us That Immune Suppression Can Fight Viruses (2026)

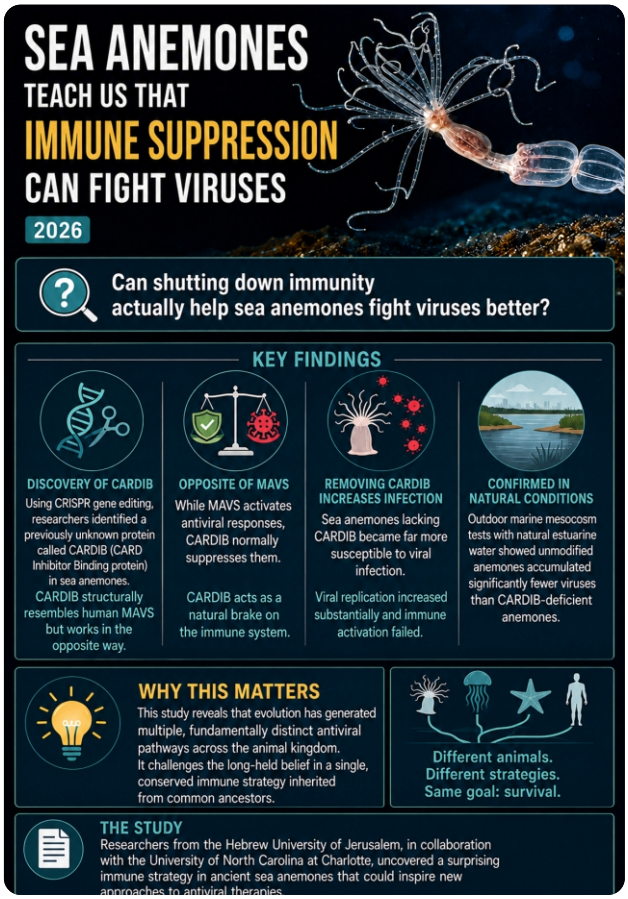
Can shutting down immunity actually help sea anemones fight viruses better?

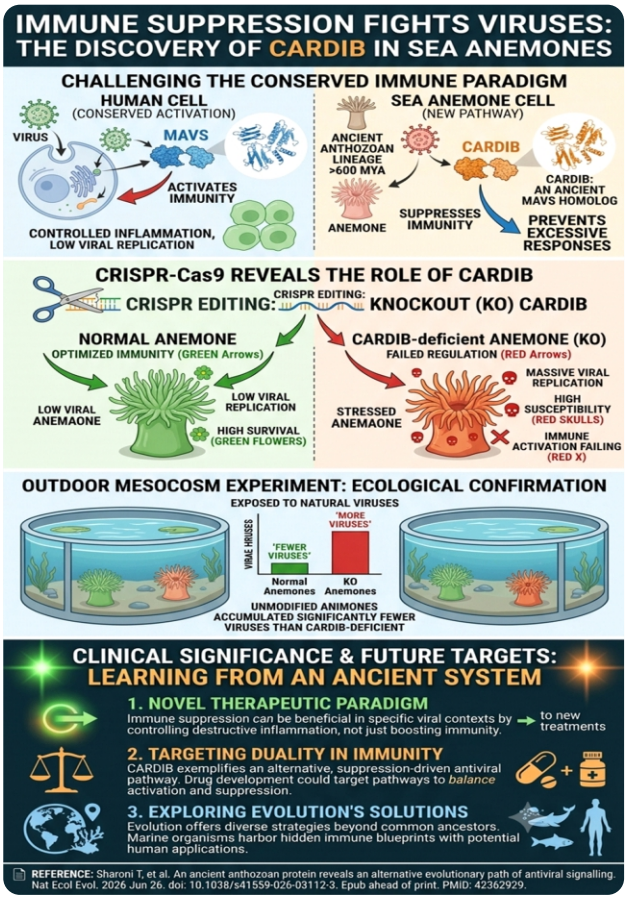
Researchers at the Hebrew University of Jerusalem, working with collaborators from the University of North Carolina at Charlotte, investigated antiviral defences in sea anemones, ancient marine animals that diverged from the human lineage over 600 million years ago. Using CRISPR gene editing, the team discovered a previously unknown protein called CARDIB (CARD Inhibitor Binding protein) that resembles the human antiviral protein MAVS structurally yet functions opposite to it. Whilst MAVS activates antiviral responses, CARDIB normally suppresses them. Remarkably, sea anemones lacking CARDIB became far more susceptible to viral infection, with viral replication increasing substantially and immune activation failing. Testing in outdoor marine mesocosms exposed to natural estuarine water confirmed the finding's ecological relevance: unmodified anemones accumulated significantly fewer viruses than CARDIB-deficient animals. The research reveals that evolution has generated multiple, fundamentally distinct antiviral pathways across the animal kingdom, challenging the longstanding assumption of a single, conserved universal immune strategy inherited from common ancestors.

Source:

RESEARCH PAPER

Sharoni T, Jaimes-Becerra A, Birch S, Kwak HJ, Aleshkina D, Lewandowska M, Surm JM, Justin H, Aharoni R, Reitzel AM, Moran Y. An ancient anthozoan protein reveals an alternative evolutionary path of antiviral signalling. Nat Ecol Evol. 2026 Jun 26. doi: 10.1038/s41559-026-03112-3. Epub ahead of print. PMID: 42362929.





Discovery of a Mystery Cell Type That Exists Only During Early Pregnancy (2026)

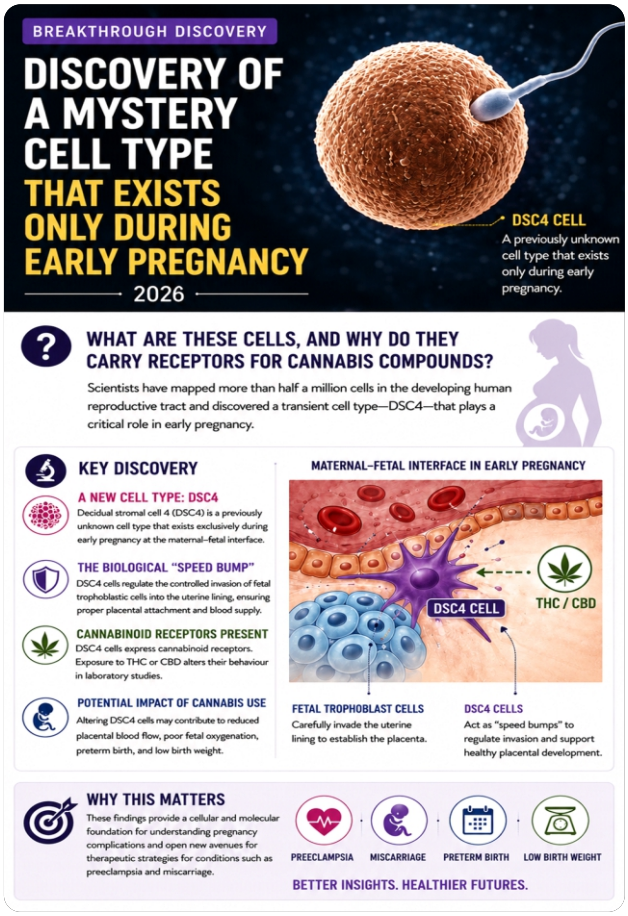
What are the unusual cells that suddenly appear at the junction between mother and foetus, and why do they carry receptors for cannabis compounds?

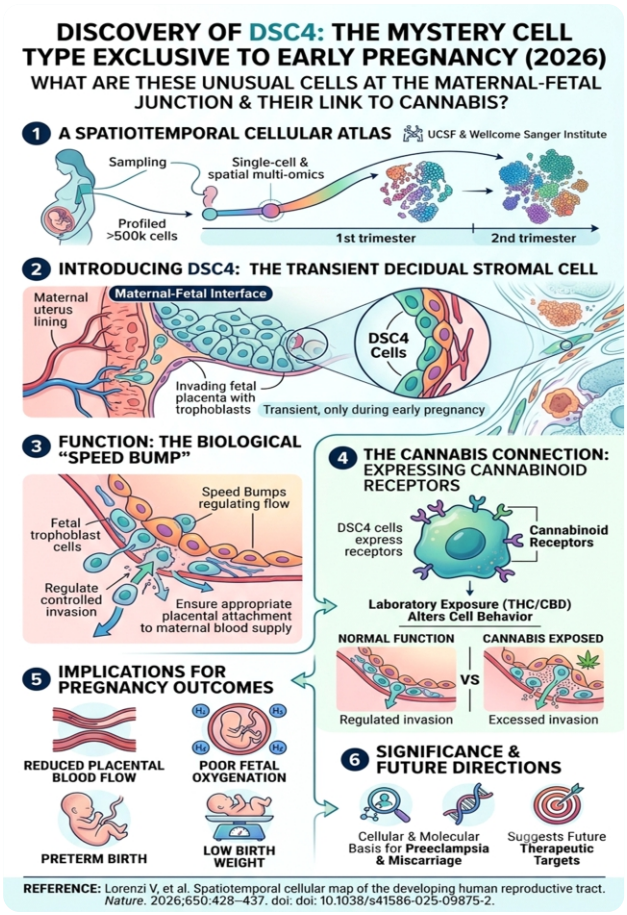
Researchers at the University of California, San Francisco, and collaborating institutions from the Wellcome Sanger Institute created a detailed spatiotemporal cellular atlas of the developing human reproductive tract during prenatal development, profiling more than half a million cells across the first and second trimesters. In this comprehensive single-cell and spatial multi-omic study, scientists identified a previously unknown cell type designated DSC4 (decidual stromal cell 4) that exists exclusively during early pregnancy at the maternal-foetal interface. These transient cells function as biological "speed bumps" that regulate the controlled invasion of foetal trophoblastic cells into the uterine lining, ensuring appropriate placental attachment to maternal blood supply. Remarkably, DSC4 cells express cannabinoid receptors; laboratory exposure to THC or CBD altered their behaviour, potentially explaining why cannabis use during pregnancy is associated with reduced placental blood flow, poor foetal oxygenation, preterm birth, and low birth weight. The findings provide a cellular and molecular foundation for understanding pregnancy complications and suggest future therapeutic targets for conditions including preeclampsia and miscarriage.

Source:

RESEARCH PAPER

Lorenzi V, Icoresi-Mazzeo C, Cassie C, et al. Spatiotemporal cellular map of the developing human reproductive tract. Nature. 2026; 650:428–437. doi: 10.1038/s41586-025-09875-2.





Do Foetuses Copy Their Mother's Yawns (2026)

Can a baby in the womb respond to behaviour from its mother?

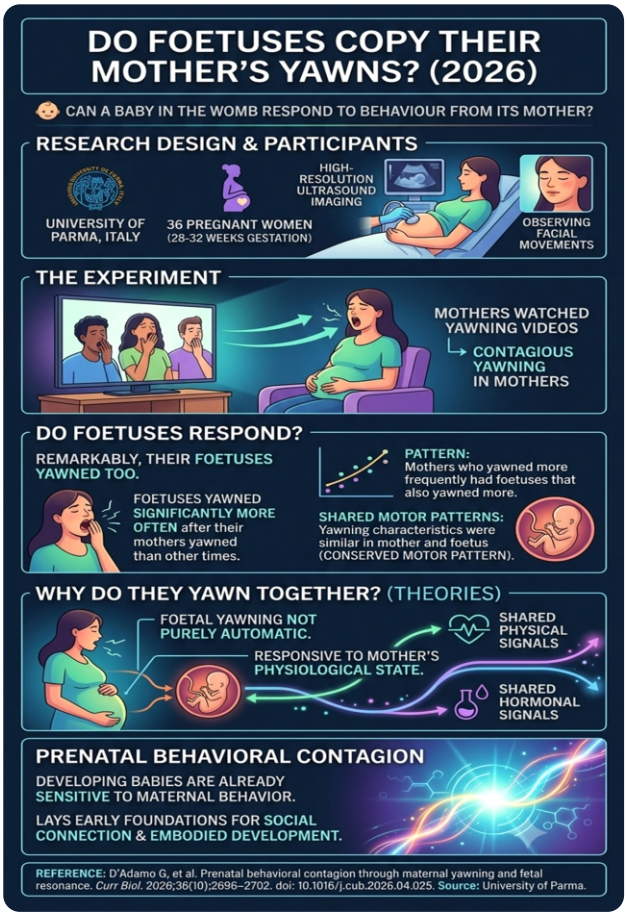
Researchers at the University of Parma used ultrasound imaging to observe facial movements in 36 pregnant women at 28–32 weeks gestation. When mothers watched videos of people yawning, they yawned contagiously, and remarkably, their foetuses yawned too. Foetuses yawned significantly more often after their mothers yawned than at other times, and there was a clear pattern: mothers who yawned more frequently had foetuses that also yawned more. The study found that yawning movements in mothers and foetuses shared similar characteristics, suggesting a conserved motor pattern across different life stages. The researchers propose that foetal yawning may not be purely automatic but rather responsive to the mother's physiological state through mechanisms involving shared physical and hormonal signals between mother and foetus. This prenatal response suggests that developing babies are already sensitive to maternal behaviour, laying early foundations for social connection and embodied development.

Source:

RESEARCH PAPER

D'Adamo G, Dall'Asta A, Ardizzi M, Sorrentino S, Mora V, Arenare G, et al. Prenatal behavioural contagion through maternal yawning and foetal resonance. Curr Biol. 2026;36(10):2696–2702. doi: 10.1016/j.cub.2026.04.025.





Foetal Exposure to Vegetable Flavours May Still Shape Children's Smell Reactions Years Later (2026)

Could the carrot or kale your baby tasted in the womb still shape how they react to its smell three years later?

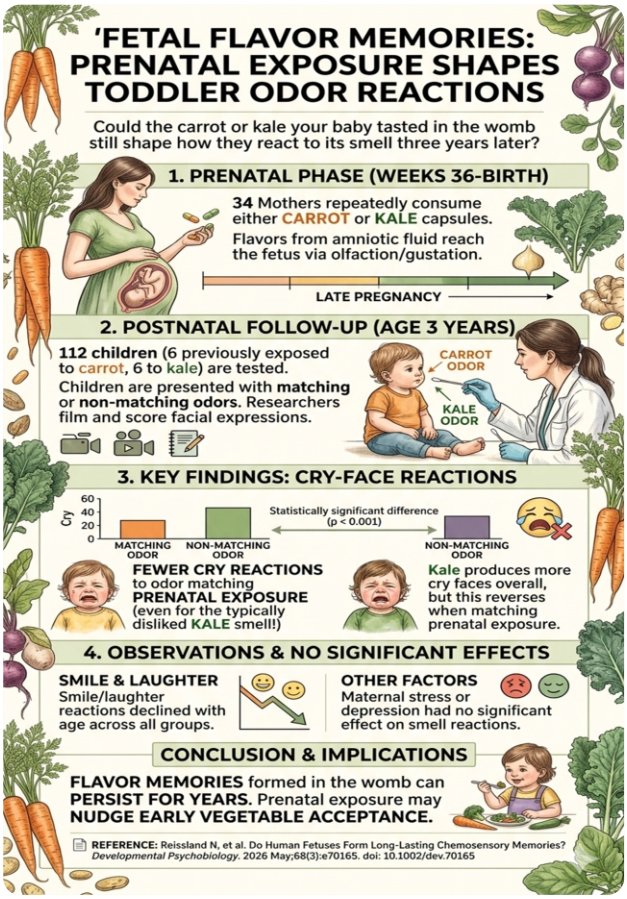
Researchers at Durham University, with collaborators at Aston University and the Centre for Taste, Smell, and Feeding Behaviour Science in Dijon, tracked 34 foetuses whose mothers consumed carrot or kale capsules repeatedly from 36 weeks of pregnancy until birth. Twelve of these children, six exposed to Carrot and six to Kale, were retested at age three using cotton swabs scented with Carrot or Kale held under the nose, while researchers filmed and scored facial reactions as smile/ laughter or cry expressions. Children showed fewer cry-face reactions to the odour matching their prenatal exposure than to the unfamiliar one ($p<0.001$), even though Kale carries a bitter smell children typically dislike; Kale produced more cry-face reactions overall, but this reversed when it matched a child's prenatal exposure. Smile and laughter reactions declined with age regardless of exposure, and maternal stress or depression had no significant effect. The findings suggest flavour memories formed in the womb during late pregnancy can persist for years, potentially nudging early vegetable acceptance.

Source:

RESEARCH PAPER

Reissland N, Einbeck J, Baguckaitė D, Ustun-Elayan B, Schaal B, Blissett J. Do Human Foetuses Form Long-Lasting Chemosensory Memories? Longitudinal Follow-Up from Foetus to Young Child of Facial Responses to Flavour/ Odour Stimuli. Dev Psychobiol. 2026 May;68(3): e70165. doi: 10.1002/dev.70165. PMID: 42120040; PMCID: PMC13167224.





High-Dose Vitamin D3 in Pregnancy Linked to Better Memory in 10-Year-Olds (2026)

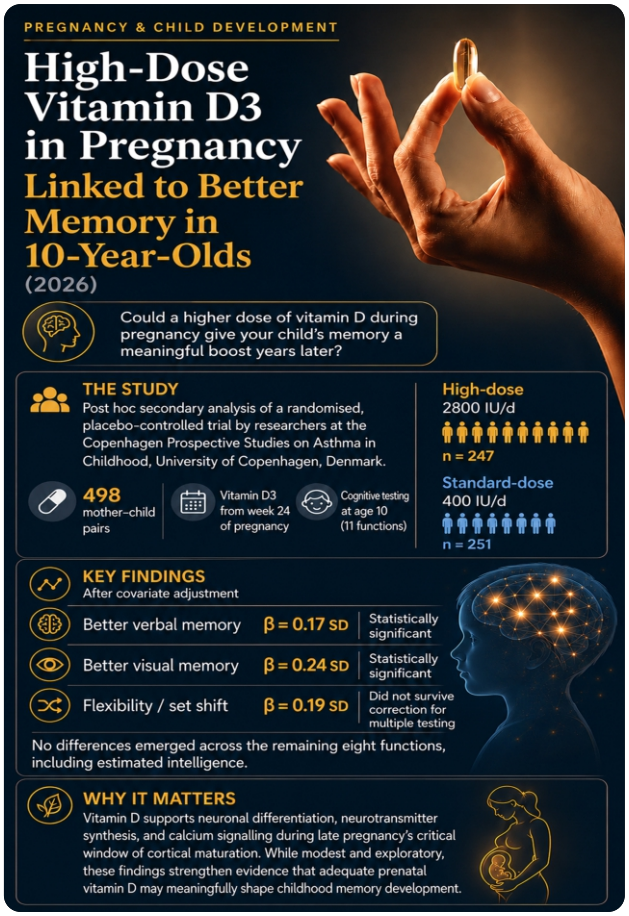
Could a higher dose of vitamin D during pregnancy give your child's memory a meaningful boost years later?

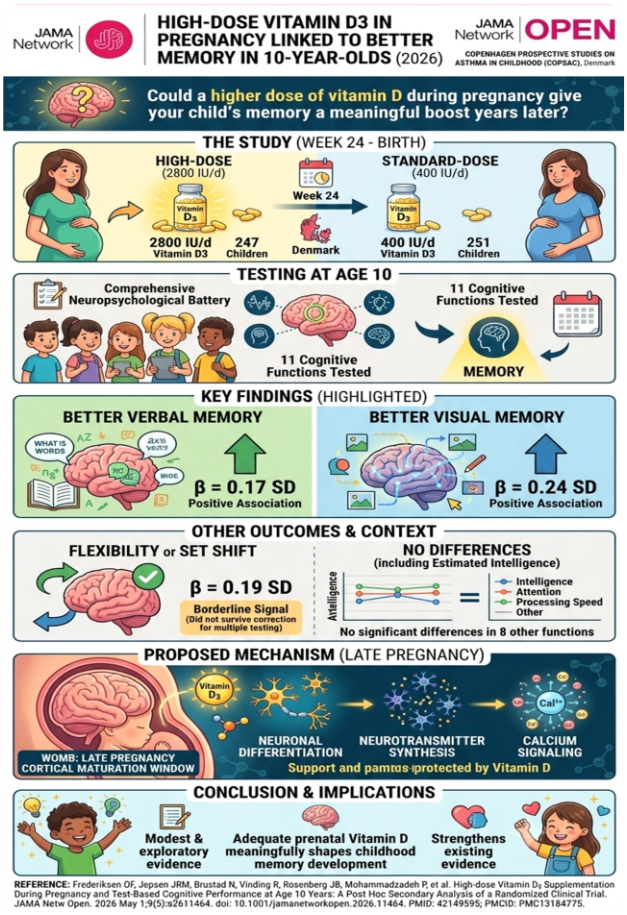
This post hoc secondary analysis of a randomised, placebo-controlled trial, published in JAMA Network Open in 2026, examined whether high-dose vitamin D3 supplementation during pregnancy influences offspring cognition. Conducted by researchers at the Copenhagen Prospective Studies on Asthma in Childhood, University of Copenhagen, Denmark, the study included 498 mother-child pairs, with 247 children prenatally exposed to high-dose (2800 IU/d) and 251 to standard-dose (400 IU/d) vitamin D3 from week 24 of pregnancy. At age 10 years, children underwent a comprehensive neuropsychological battery covering 11 cognitive functions. After covariate adjustment, high-dose supplementation was associated with better verbal memory (β=0.17 SD) and visual memory (β=0.24 SD), with a weaker signal for flexibility or set shift (β=0.19 SD) that did not survive correction for multiple testing. No differences emerged across the remaining eight functions, including estimated intelligence. The authors propose that vitamin D supports neuronal differentiation, neurotransmitter synthesis, and calcium signalling during late pregnancy's critical window of cortical maturation. While modest and exploratory, these findings strengthen evidence that adequate prenatal vitamin D may meaningfully shape childhood memory development.

Source:

SECONDARY ANALYSIS

Frederiksen OF, Jepsen JRM, Brustad N, Vinding R, Rosenberg JB, Mohammadzadeh P, et al. High-dose Vitamin D3 Supplementation During Pregnancy and Test-Based Cognitive Performance at Age 10 Years: A Post Hoc Secondary Analysis of a Randomized Clinical Trial. JAMA Netw Open. 2026 May 1;9(5): e2611464. doi: 10.1001/jamanetworkopen.2026.11464. PMID: 42149595; PMCID: PMC13184775.





Vitamin K Shot Refusal in Newborns: A Growing Threat to Infant Brain Health (2026)

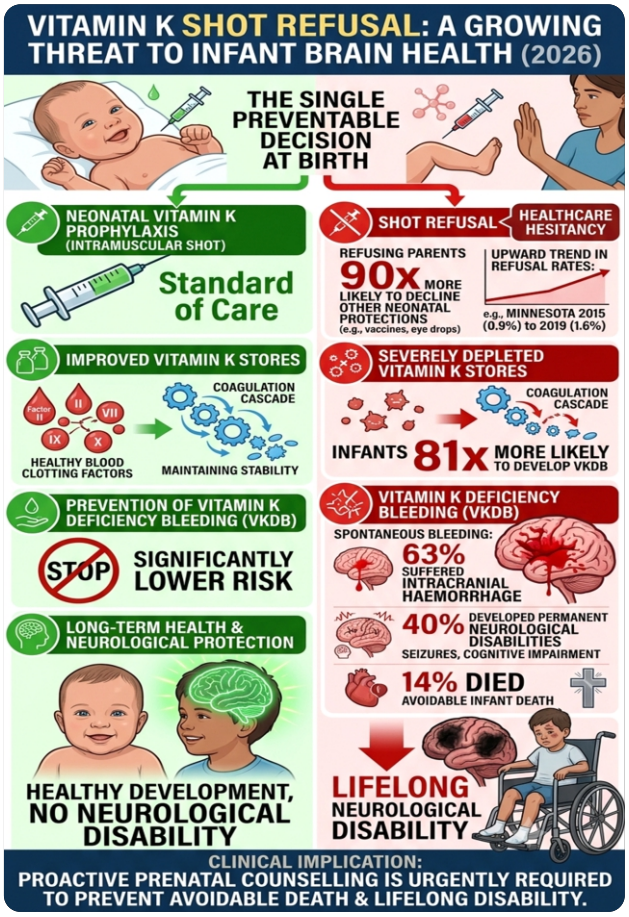
Can a single preventable decision at birth lead to lifelong neurological disability in your newborn?

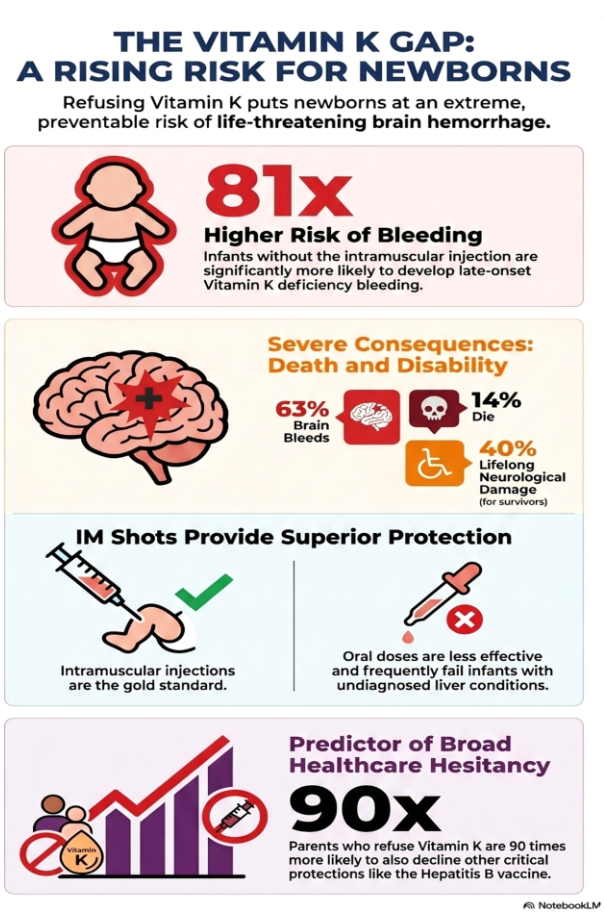
A preliminary systematic review presented at the American Academy of Neurology's 78th Annual Meeting (April 2026, Chicago) by researchers at Florida International University's Herbert Wertheim College of Medicine examined 25 studies spanning two decades of global data on parental refusal of intramuscular Vitamin K prophylaxis in newborns. Lead investigator Dr. Kate Semidey and colleagues found that while refusal rates remain below 1% in most United States hospitals, a concerning upward trend has been documented across multiple states, with Minnesota recording a near-doubling from 0.9% in 2015 to 1.6% in 2019. Critically, infants who do not receive the Vitamin K injection are 81 times more likely to develop Vitamin K deficiency bleeding. Among affected infants, 63% suffered intracranial haemorrhage, 40% developed permanent neurological disabilities including seizures and cognitive impairment, and 14% died. Parental refusal was strongly linked to broader healthcare hesitancy, with refusing parents 90 times more likely to decline other neonatal protections. Investigators emphasise that proactive prenatal counselling is now urgently required to prevent avoidable infant death and lifelong developmental disability.

Source:

RESEARCH PAPER

De Faria Sousa B, Patel NB, Marandi R, Alshammari M, Olaru AM, Sideridis G, et al. Rising parental refusal of newborn vitamin K: Implications for neurology and child development. Neurology. 2026 Jun 10;106(11). doi:10.1212/WNL.0000000000215265.





PCOS Renamed to PMOS: Why Scientists Changed the Name of a Condition Affecting 170 million Women (2026)

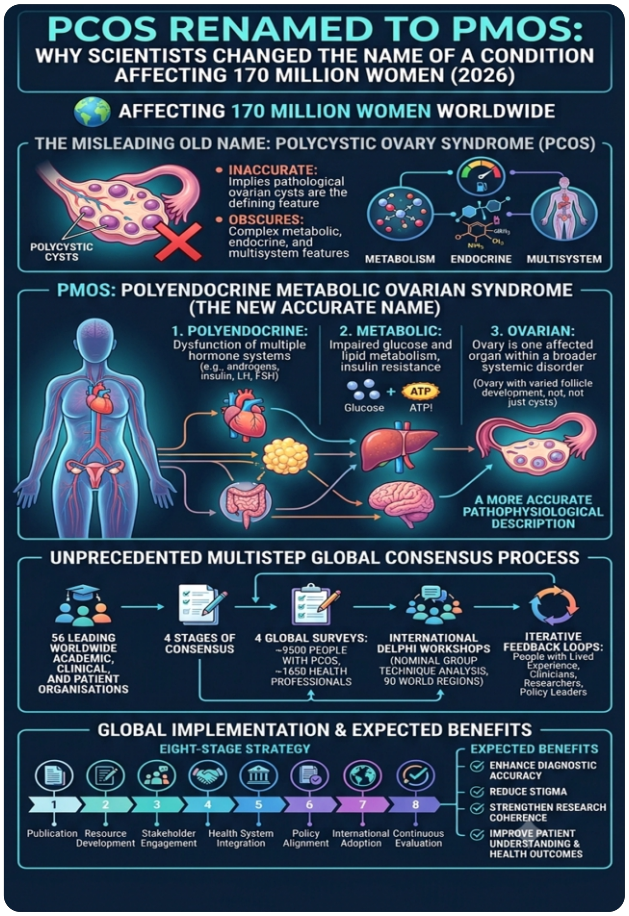
🌍 ***Should a condition affecting 170 million women worldwide have a name that truly describes what it actually is?***

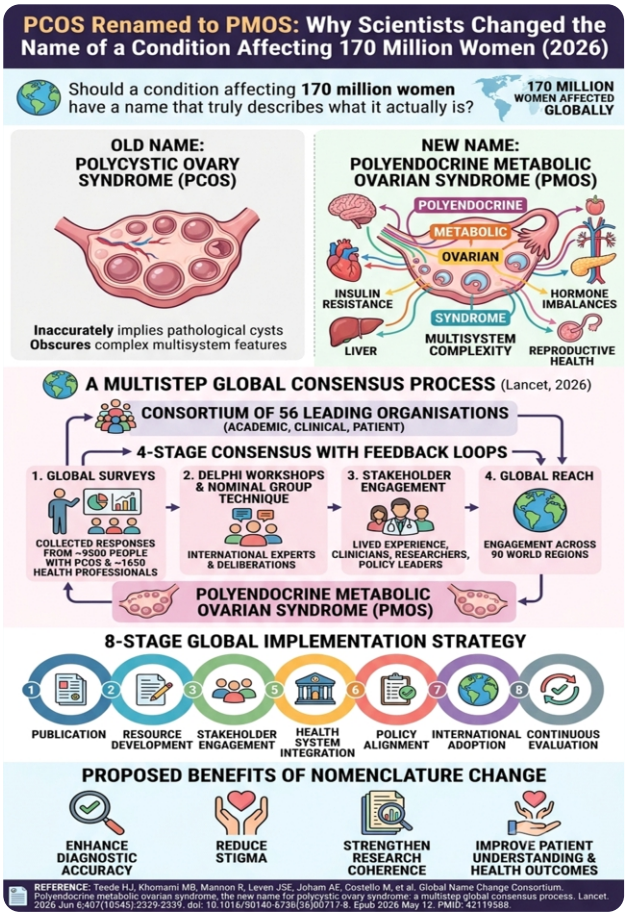
Fifty-six leading academic, clinical, and patient organisations worldwide conducted an unprecedented multistep global consensus process to rename polycystic ovary syndrome (PCOS) to polyendocrine metabolic ovarian syndrome (PMOS). The research team recognised that "polycystic ovary syndrome" inaccurately implies pathological ovarian cysts whilst obscuring the condition's complex metabolic, endocrine, and multisystem features. The four-stage consensus process included four surveys collecting responses from approximately 9500 people with PCOS and 1650 health professionals, international Delphi workshops incorporating nominal group technique analysis, and engagement across 90 world regions. Iterative feedback loops involved people with lived experience, clinicians, researchers, and policy leaders. The consortium identified polyendocrine metabolic ovarian syndrome as the preferred new name, more accurately reflecting the condition's diverse pathophysiology and clinical presentation. An eight-stage global implementation strategy was developed, spanning publication, resource development, stakeholder engagement, health system integration, policy alignment, international adoption, and continuous evaluation. The authors propose that this nomenclature change will enhance diagnostic accuracy, reduce stigma, strengthen research coherence, and improve patient understanding and health outcomes worldwide.

Source:

📄 CONSENSUS PAPER

📌 Teede HJ, Khomami MB, Mannon R, Leven JSE, Joham AE, Costello M, et al. Global Name Change Consortium. Polyendocrine metabolic ovarian syndrome, the new name for polycystic ovary syndrome: a multistep global consensus process. Lancet. 2026 Jun 6;407(10545):2329-2339. doi: 10.1016/S0140-6736(26)00717-8. Epub 2026 May 12. PMID: 42119588.





Women with PCOS Experience Menopause Later and With Fewer Symptoms (2026)

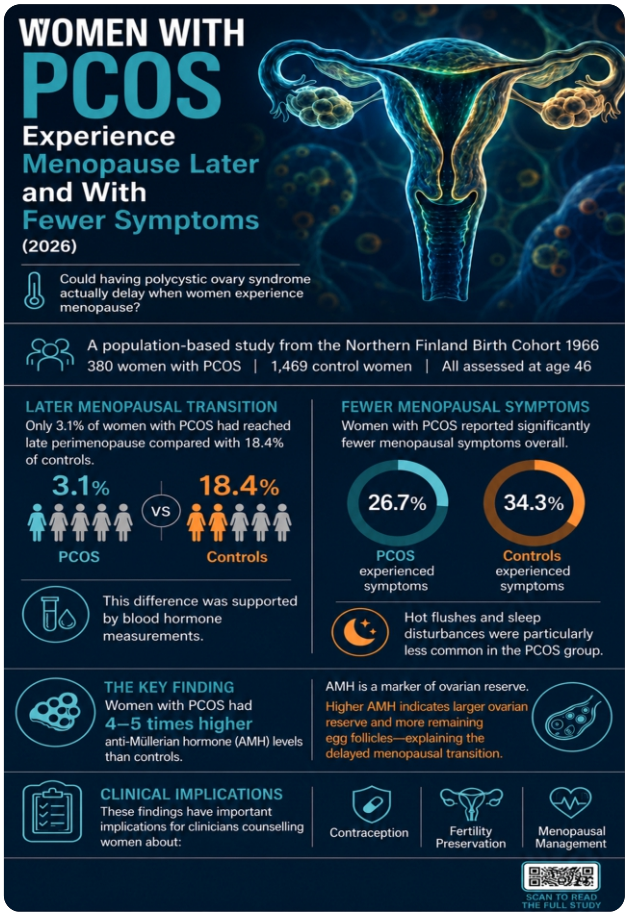
Could having polycystic ovary syndrome actually delay when women experience menopause?

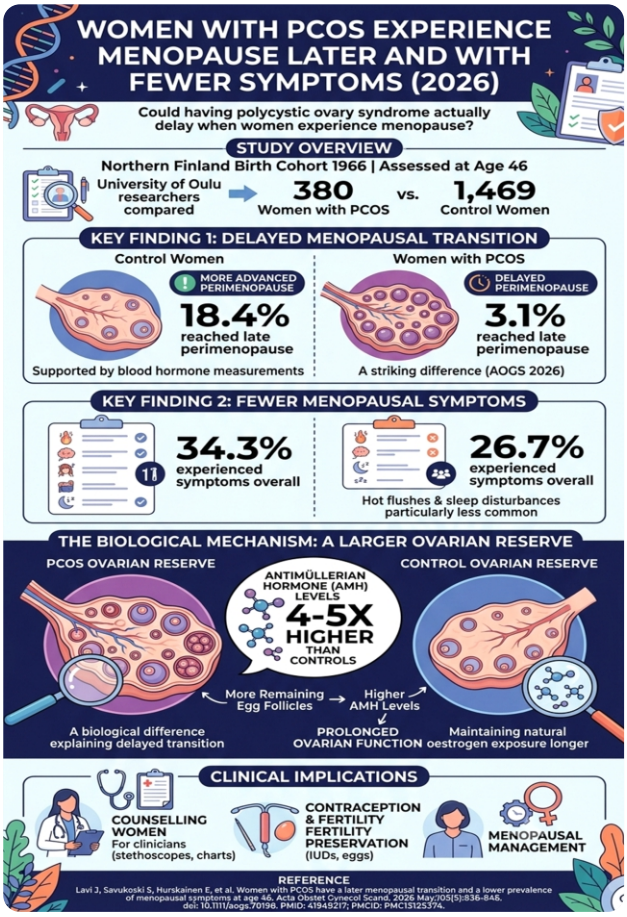
Researchers from the University of Oulu conducted a population-based study comparing women with and without polycystic ovary syndrome (PCOS) from the Northern Finland Birth Cohort 1966. The study included 380 women with PCOS and 1,469 control women, all assessed at age 46. Only 3.1 per cent of women with PCOS had reached late perimenopause compared with 18.4 per cent of controls, a striking difference supported by blood hormone measurements. Women with PCOS reported significantly fewer menopausal symptoms overall: 26.7 per cent experienced symptoms versus 34.3 per cent of control women. Hot flushes and sleep disturbances were particularly less common in the PCOS group. The key finding was that women with PCOS had anti-Müllerian hormone levels four to five times higher than controls, a marker indicating larger ovarian reserve and more remaining egg follicles. This biological difference explains the delayed menopausal transition. The research provides robust evidence that women with PCOS experience prolonged ovarian function, maintaining natural oestrogen exposure longer. These findings have important implications for clinicians counselling women about contraception, fertility preservation, and menopausal management.

Source:

RESEARCH PAPER

Lavi J, Savukoski S, Hurskainen E, Ollila MM, Morin-Papunen L, Niinimäki M, et al. Women with PCOS have a later menopausal transition and a lower prevalence of menopausal symptoms at age 46: A population-based birth cohort study. Acta Obstet Gynecol Scand. 2026 May;105(5):836-846. doi: 10.1111/aogs.70198. Epub 2026 Apr 8. PMID: 41949217; PMCID: PMC13125374.





How Ageing Ovaries Quietly Turn into Sites of Chronic Inflammation (2026)

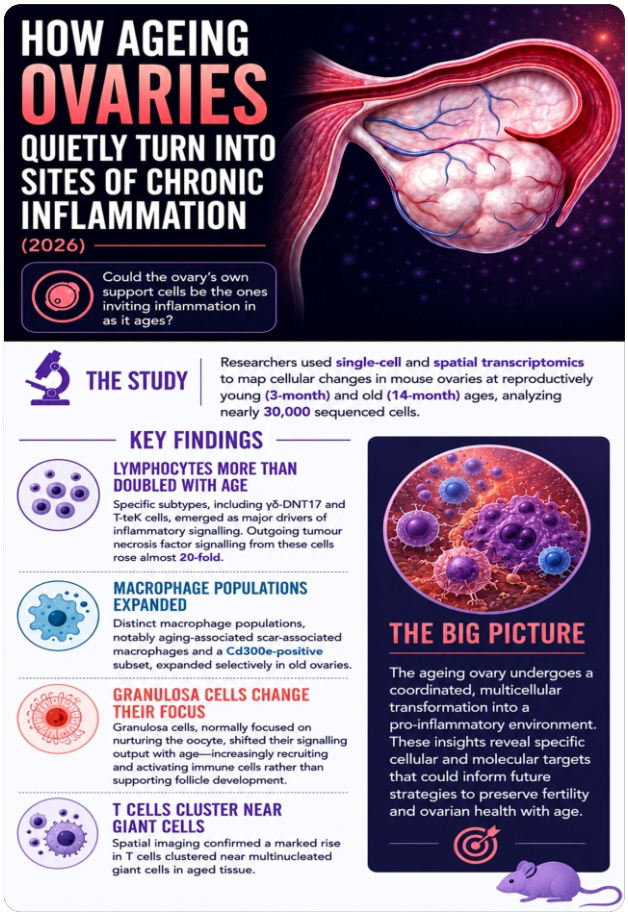
🥚 ***Could the ovary's own support cells be the ones inviting inflammation in as it ages?***

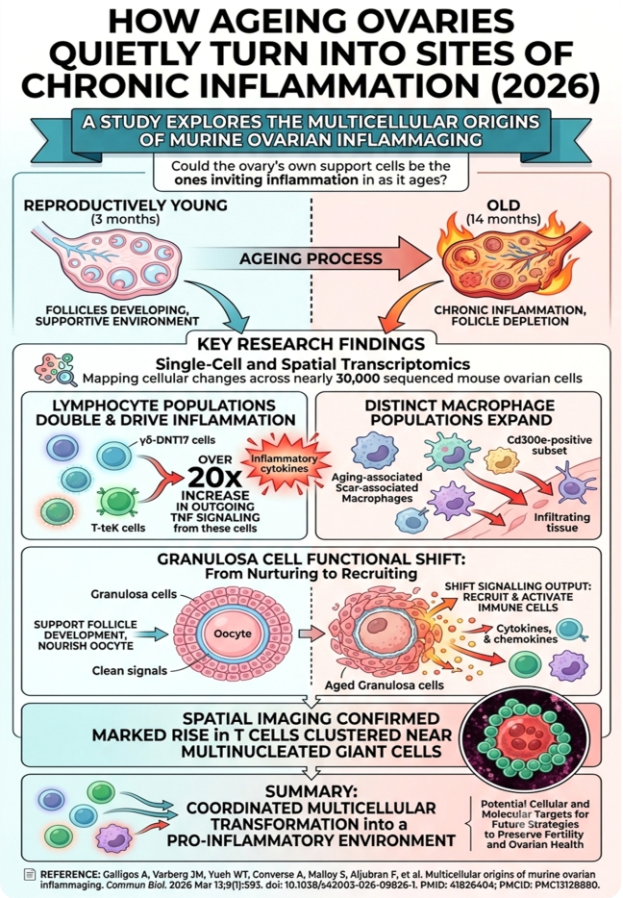
Researchers from the Stowers Institute for Medical Research and Northwestern University's Feinberg School of Medicine combined single-cell and spatial transcriptomics to map cellular changes in mouse ovaries, comparing reproductively young (three-month) and old (fourteen-month) animals across nearly 30,000 sequenced cells. Lymphocytes more than doubled in proportion with age, with specific subtypes, including γδ-DNT17 and T-teK cells, emerging as major drivers of inflammatory signalling; outgoing tumour necrosis factor signalling from these cells rose almost twentyfold. Distinct macrophage populations, notably aging-associated scar-associated macrophages and a Cd300e-positive subset, also expanded selectively in old ovaries. Granulosa cells, normally focused on nurturing the oocyte, were shown to shift their signalling output with age, increasingly recruiting and activating immune cells rather than supporting follicle development. Spatial imaging confirmed a marked rise in T cells clustered near multinucleated giant cells in aged tissue. Together, these findings suggest the ageing ovary undergoes a coordinated, multicellular transformation into a pro-inflammatory environment, offering specific cellular and molecular targets that could inform future strategies to preserve fertility and ovarian health with age.

Source:

📄 RESEARCH PAPER

📌 Galligos A, Varberg JM, Yueh WT, Converse A, Malloy S, Aljubran F, et al. Multicellular origins of murine ovarian inflammaging. Commun Biol. 2026 Mar 13;9(1):593. doi: 10.1038/s42003-026-09826-1. PMID: 41826404; PMCID: PMC13128880.





Genetic Variation in Meiosis Genes Shapes Miscarriage Risk (2026)

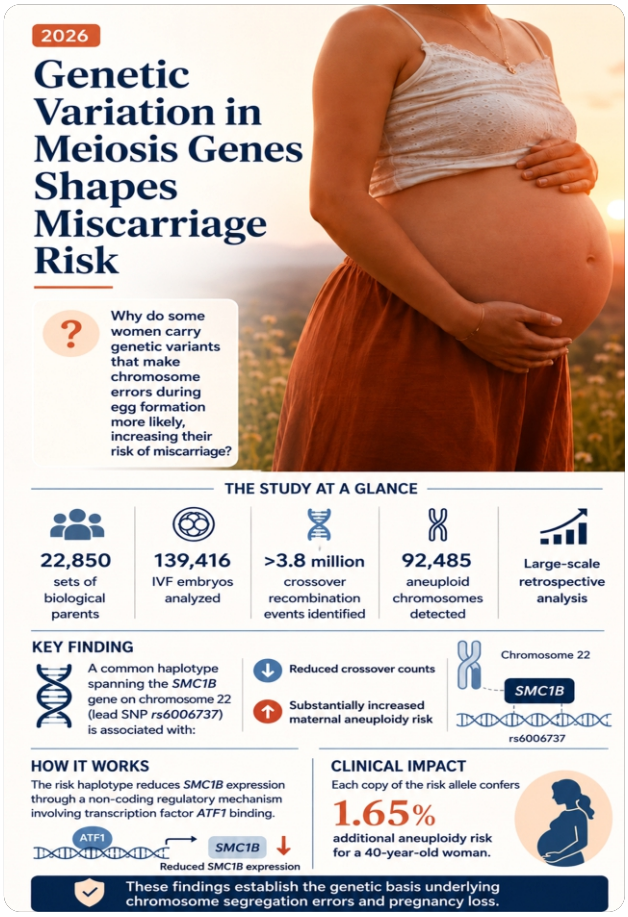
Why do some women carry genetic variants that make chromosome errors during egg formation more likely, increasing their risk of miscarriage?

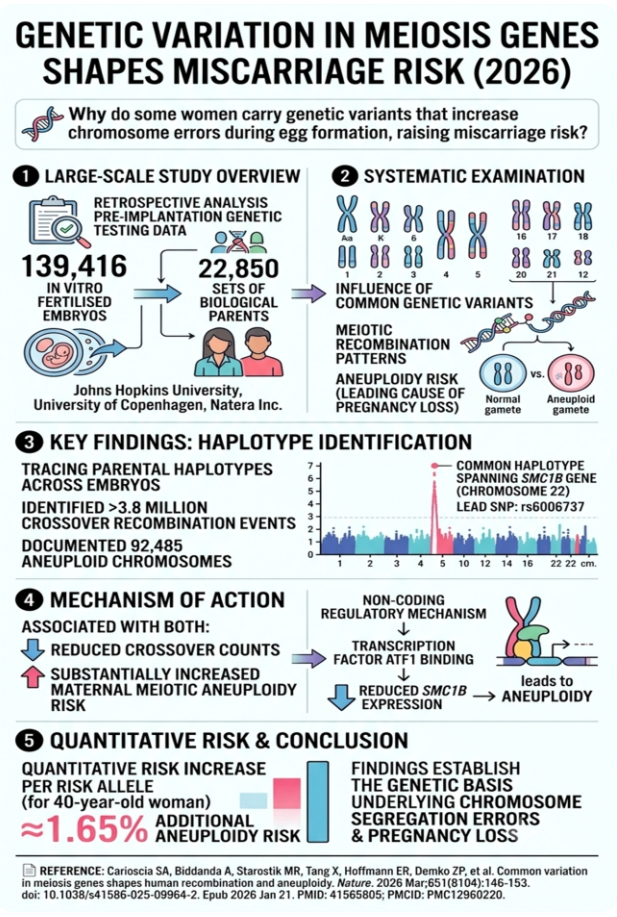
Researchers at Johns Hopkins University, the University of Copenhagen, and Natera Inc. conducted a large-scale retrospective analysis of pre-implantation genetic testing data from 139,416 in vitro fertilised embryos derived from 22,850 sets of biological parents. The study systematically examined how common genetic variants influence meiotic recombination patterns and aneuploidy risk, the leading cause of human pregnancy loss. By tracing transmission of parental haplotypes across embryos, the team identified over 3.8 million crossover recombination events and documented 92,485 aneuploid chromosomes. Genome-wide association studies revealed that a common haplotype spanning the SMC1B gene on chromosome 22 (lead SNP rs6006737) significantly associated with both reduced crossover counts and substantially increased maternal meiotic aneuploidy risk. The effect operates through reduced SMC1B expression via a non-coding regulatory mechanism involving transcription factor ATF1 binding. Each copy of the risk allele confers approximately 1.65 per cent additional aneuploidy risk for a 40-year-old woman. These findings establish the genetic basis underlying chromosome segregation errors and pregnancy loss.

Source:

RESEARCH PAPER

Carioscia SA, Biddanda A, Starostik MR, Tang X, Hoffmann ER, Demko ZP, et al. Common variation in meiosis genes shapes human recombination and aneuploidy. Nature. 2026 Mar;651(8104):146-153. doi: 10.1038/s41586-025-09964-2. Epub 2026 Jan 21. PMID: 41565805; PMCID: PMC12960220.





Why Storing Sperm for Longer May Backfire (2026)

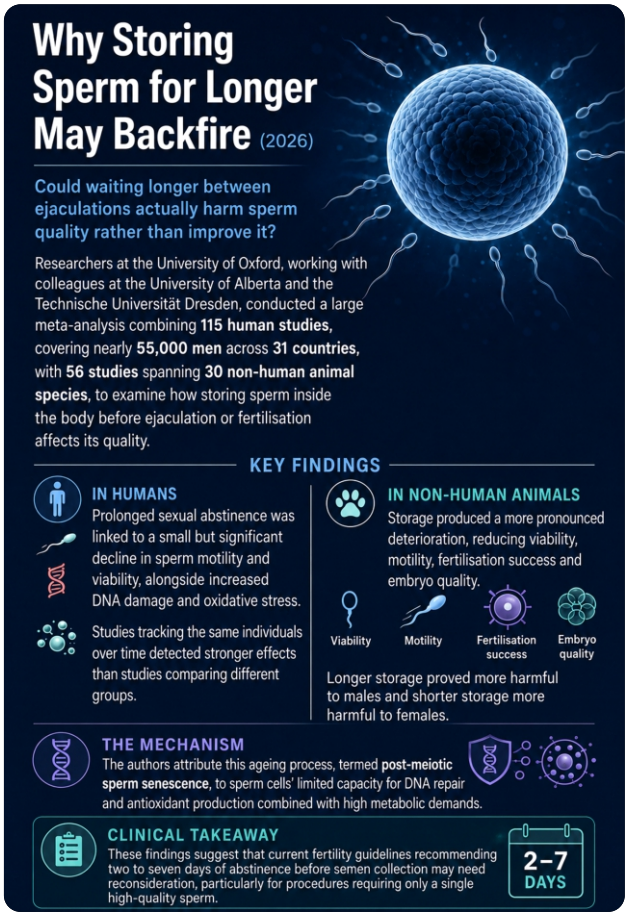
Could waiting longer between ejaculations actually harm sperm quality rather than improve it?

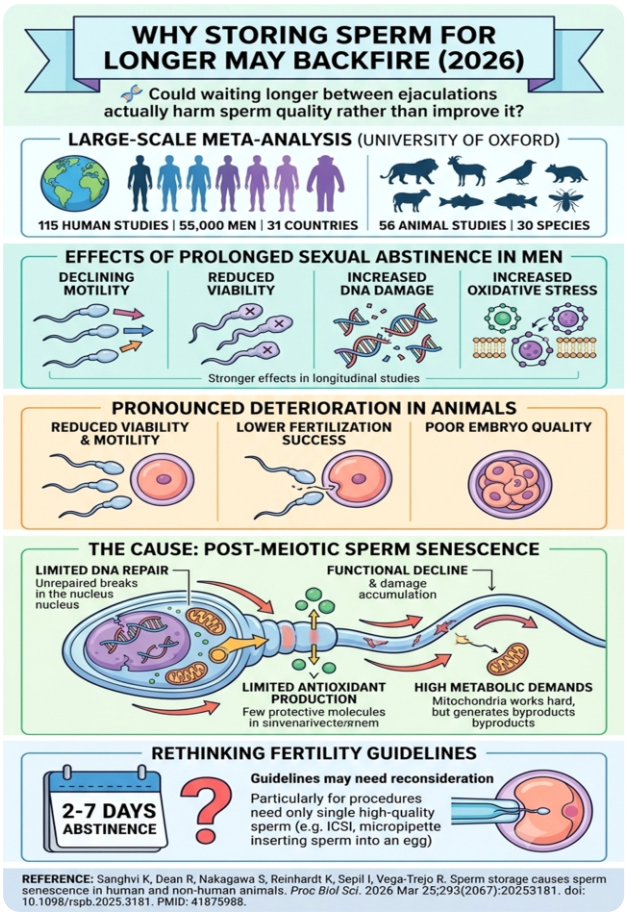
Researchers at the University of Oxford, working with colleagues at the University of Alberta and the Technische Universität Dresden, conducted a large meta-analysis combining 115 human studies, covering nearly 55,000 men across 31 countries, with 56 studies spanning 30 non-human animal species, to examine how storing sperm inside the body before ejaculation or fertilisation affects its quality. In men, prolonged sexual abstinence was linked to a small but significant decline in sperm motility and viability, alongside increased DNA damage and oxidative stress, with studies tracking the same individuals over time detecting stronger effects than those comparing different groups. Across non-human animals, storage produced a more pronounced deterioration, reducing viability, motility, fertilisation success and embryo quality, with longer storage proving more harmful to males and shorter storage more harmful to females. The authors attribute this ageing process, termed post-meiotic sperm senescence, to sperm cells' limited capacity for DNA repair and antioxidant production combined with high metabolic demands. These findings suggest that current fertility guidelines recommending two to seven days of abstinence before semen collection may need reconsideration, particularly for procedures requiring only a single high-quality sperm.

Source:

COHORT STUDY

Sanghvi K, Dean R, Nakagawa S, Reinhardt K, Sepil I, Vega-Trejo R. Sperm storage causes sperm senescence in human and non-human animals. Proc Biol Sci. 2026 Mar 25;293(2067):20253181. doi: 10.1098/rspb.2025.3181. PMID: 41875988.





A Better-Timed Stem Cell Protocol Yields Purer, More Reliable Insulin-Producing Islets (2026)

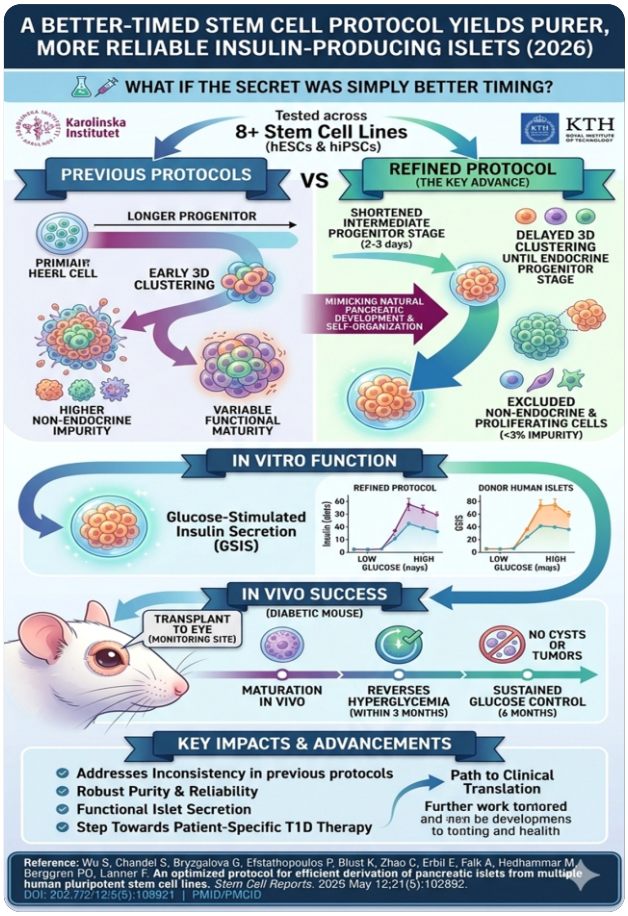
What if the secret to growing better insulin-producing cells from stem cells was simply better timing?

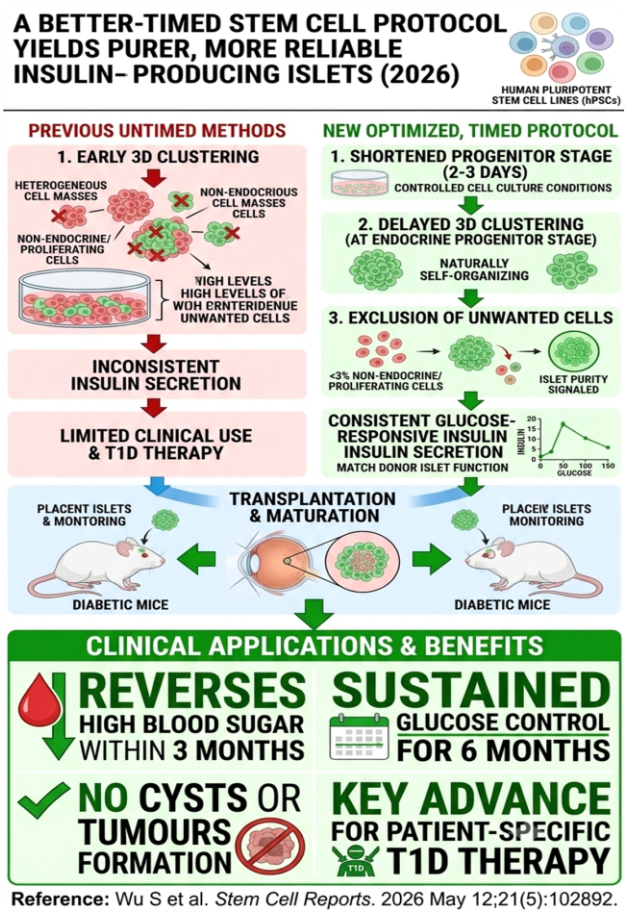
Researchers at Karolinska Institutet and KTH Royal Institute of Technology refined the process for converting human stem cells into pancreatic islet cells, testing it across eight stem cell lines, both embryonic and induced pluripotent. The key advance was shortening an intermediate progenitor stage to two to three days and delaying three-dimensional clustering until cells reached the endocrine progenitor stage, rather than earlier as in previous protocols. This timing let cells self-organise as they do during natural pancreatic development, excluding non-endocrine and proliferating cells, which fell to under 3% of the final population. The resulting islets secreted insulin in response to glucose, matching donor human islet responses. Transplanted into the eyes of diabetic mice, a site enabling monitoring, the cells matured further, reversed high blood sugar within three months, and sustained glucose control for six months without forming cysts or tumours. These findings address the inconsistency that has long limited stem cell-derived islet therapies across cell lines, representing a meaningful step toward patient-specific cell therapy for type 1 diabetes, with further work needed before clinical translation.

Source:

PROTOCOL PAPER

Wu S, Chandel S, Bryzgalova G, Efstathopoulos P, Blust K, Zhao C, Erbil E, Falk A, Hedhammar M, Berggren PO, Lanner F. An optimized protocol for efficient derivation of pancreatic islets from multiple human pluripotent stem cell lines. Stem Cell Reports. 2026 May 12;21(5):102892. doi: 10.1016/j.stemcr.2026.102892. Epub 2026 Apr 16. PMID: 41997152; PMCID: PMC13163220.





Stem Cell Transplant Achieves 15+ Years of Disease-Free Remission in Neuromyelitis Optica (2026)

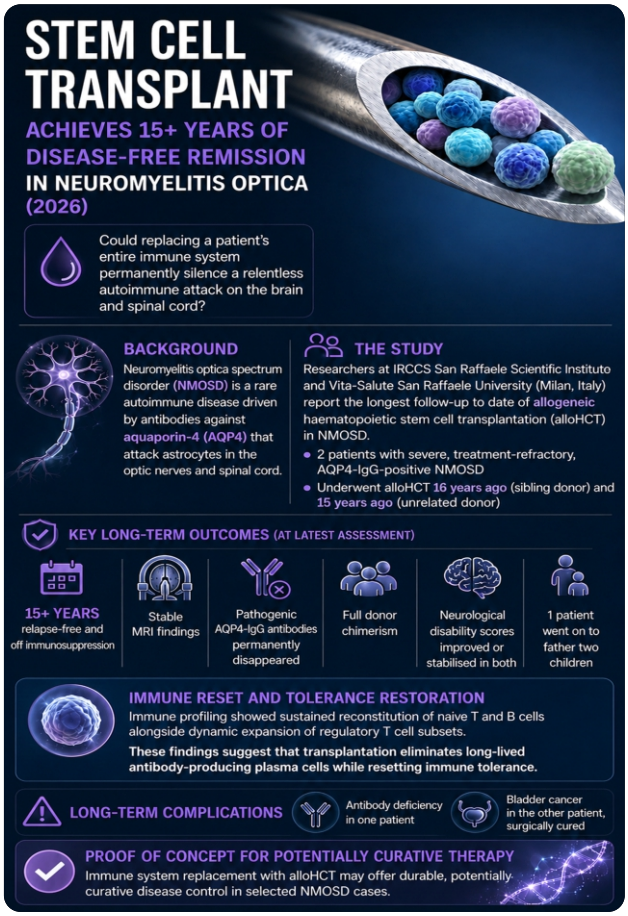
Could replacing a patient's entire immune system permanently silence a relentless autoimmune attack on the brain and spinal cord?

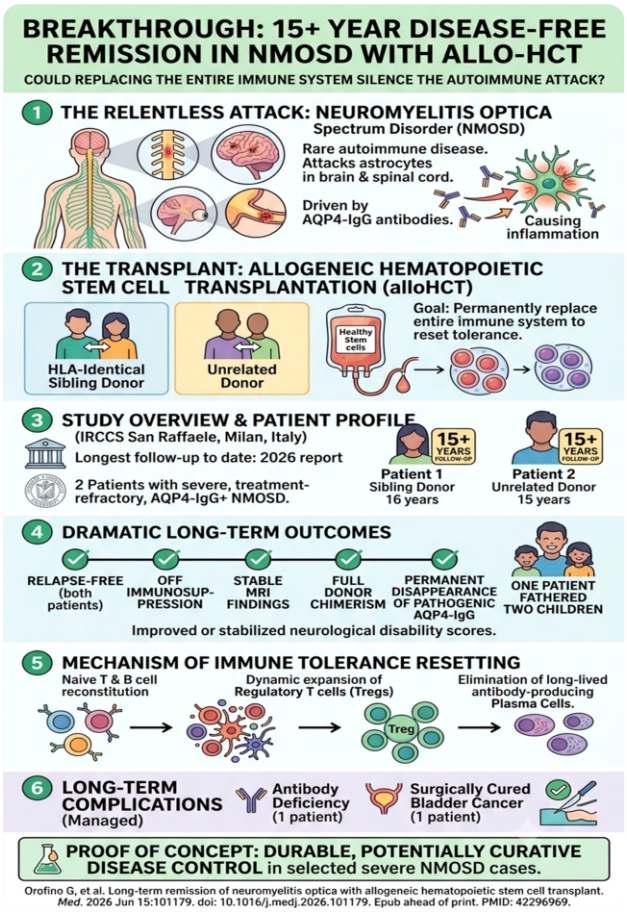
Researchers at the IRCCS San Raffaele Scientific Institute and Vita-Salute San Raffaele University in Milan, Italy, report the longest follow-up to date of allogeneic haematopoietic stem cell transplantation (alloHCT) in neuromyelitis optica spectrum disorder (NMOSD), a rare autoimmune disease driven by antibodies against aquaporin-4 (AQP4) that attack astrocytes in the optic nerves and spinal cord. Two patients with severe, treatment-refractory, AQP4-IgG-positive disease underwent alloHCT 16 and 15 years earlier, one from an HLA-identical sibling and one from an unrelated donor. At the latest assessment, both remained relapse-free and off immunosuppression, with stable MRI findings and full donor chimerism; pathogenic AQP4-IgG antibodies had permanently disappeared, and one patient went on to father two children. Neurological disability scores improved or stabilised in both. Immune profiling showed sustained reconstitution of naive T and B cells alongside dynamic expansion of regulatory T cell subsets, suggesting that transplantation eliminates long-lived antibody-producing plasma cells while resetting immune tolerance. Long-term complications included antibody deficiency in one patient and a surgically cured bladder cancer in the other. These findings offer proof of concept that immune system replacement may provide durable, potentially curative disease control in selected NMOSD cases.

Source:

RESEARCH PAPER

Orofino G, Genchi A, Lupo Stanghellini MT, Doglio M, Noviello M, Mandelli A, et al. Long-term remission of neuromyelitis optica with allogeneic hematopoietic stem cell transplant. Med. 2026 Jun 15:101179. doi: 10.1016/j.medj.2026.101179. Epub ahead of print. PMID: 42296969.





Menstrual Blood Could Hold a Natural Repair Kit for Damaged Joint Cartilage (2026)

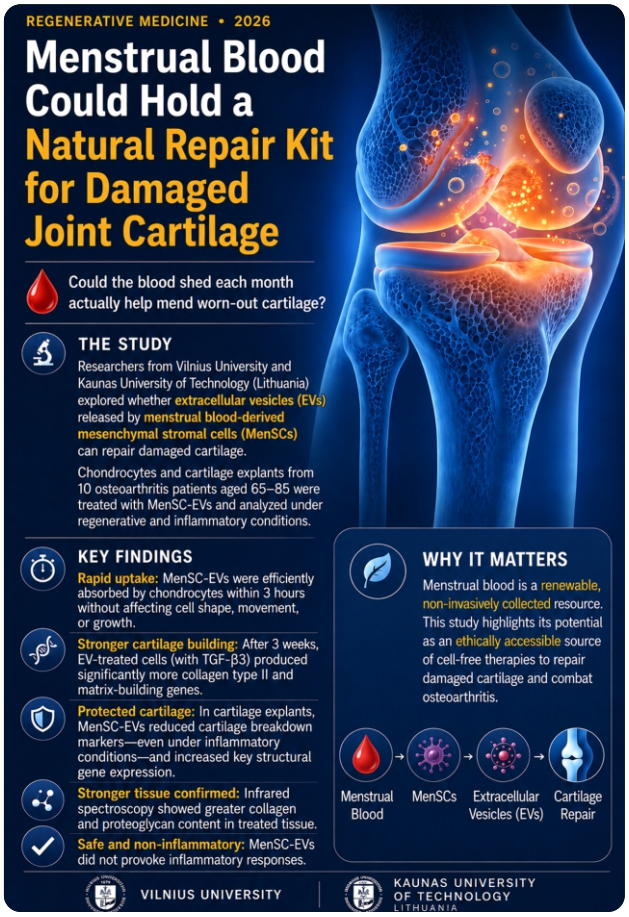
Beyond a biological waste product: Could menstrual blood stem cells hold the key to repairing degenerated cartilage?

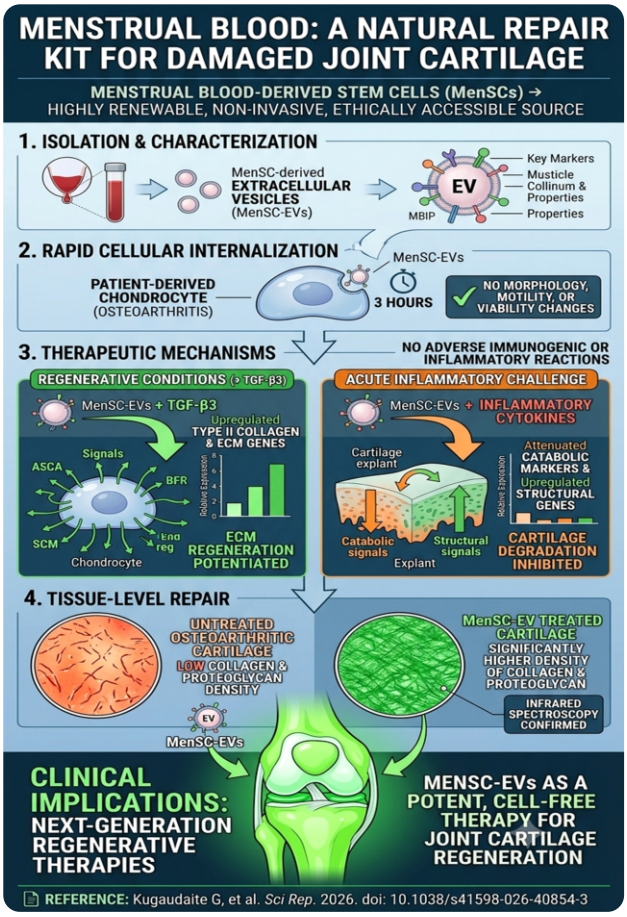
Researchers from Vilnius University and Kaunas University of Technology in Lithuania evaluated whether extracellular vesicles (EVs) isolated from menstrual blood-derived mesenchymal stromal cells (MenSCs) could promote articular cartilage repair. Chondrocytes and cartilage explants obtained from ten osteoarthritis patients aged 65–85 were treated with MenSC-EVs under both regenerative and pro-inflammatory in vitro conditions. The EVs demonstrated rapid endocytosis, being efficiently internalized by chondrocytes within three hours without altering baseline cellular morphology, motility, or overall viability. Following a three-week incubation period, EV-treated chondrocytes exhibited a significantly upregulated expression of type II collagen and extracellular matrix structural genes when co-administered with transforming growth factor-beta 3 (TGF-β3). In patient-derived cartilage explants, MenSC-EVs successfully attenuated the release of catabolic cartilage degradation markers, even under acute inflammatory challenge, while simultaneously upregulating key structural genes. Infrared spectroscopy confirmed a significantly higher density of both collagen and proteoglycan within the treated tissue matrix. Crucially, the EVs elicited no adverse immunogenic or inflammatory reactions. These definitive data position menstrual blood as a highly renewable, non-invasively obtained, and ethically accessible biological source for next-generation, cell-free cartilage regeneration therapies.

Source:

RESEARCH PAPER

Kugaudaite G, Bakutyte I, Bagdonas E, Vaiciuleviciute R, Talaikis M, Miksiunas R, et al. Menstrual blood-derived mesenchymal stromal cell extracellular vesicles stimulate chondrocytes and cartilage extracellular matrix synthesis in vitro. Sci Rep. 2026 Feb 25;16(1):11059. doi: 10.1038/s41598-026-40854-3. PMID: 41741553; PMCID: PMC13043950.





New Hydrogel Could Deliver Biologic Drugs Directly to the Oesophagus, MIT Study Shows (2026)

💊 ***Could a swallowable gel one day replace injections for treating inflamed oesophagus conditions?***

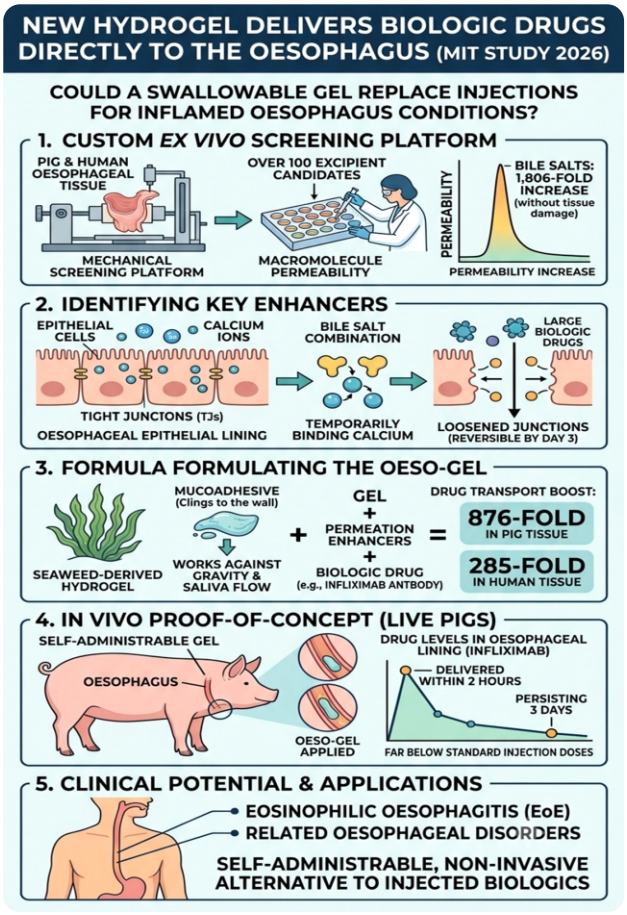
Researchers at MIT and Brigham and Women's Hospital, Harvard Medical School, developed a custom ex vivo screening platform to identify excipients that help large biologic drugs cross the oesophageal lining, an overlooked barrier. After testing over 100 candidate compounds on pig and human oesophageal tissue, they identified a combination of two bile salts that increased the permeability of a model macromolecule up to 1,806-fold without damaging the tissue. They combined these permeation enhancers with a mucoadhesive seaweed-derived hydrogel, called Oeso-gel, that clings to the oesophageal wall against gravity and saliva flow. The formulation boosted drug transport 876-fold in pig tissue and 285-fold in human tissue. In live pigs, Oeso-gel delivered the antibody drug infliximab into the oesophageal lining within two hours, with levels persisting three days, at doses far below standard injections. The bile salts appear to work by temporarily binding calcium and loosening the junctions between epithelial cells, an effect that reversed by day three. The authors propose Oeso-gel as a self-administrable, non-invasive alternative to injected biologics for eosinophilic oesophagitis and related oesophageal disorders.

Source:

📄 RESEARCH PAPER

📌 Karavasili C, Young T, Chan A, Lal N, Chang CJ, Neufeld L, et al. Oesophageal tissue screening system for assessing the retention and mucosal absorption of biologics. Nat Biomed Eng. 2026 Jun 12. doi: 10.1038/s41551-026-01685-9. Online ahead of print.





Semaglutide Slows Biological Ageing in Adults with HIV-Associated Fat Gain (2026)

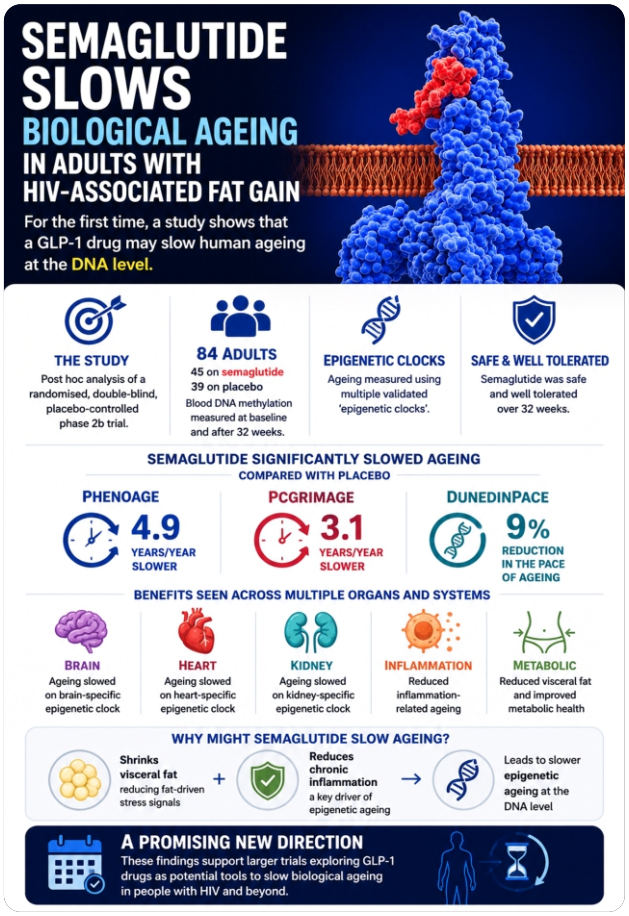
Could a once-weekly diabetes and weight-loss jab also slow the body's ageing clock in people living with HIV?

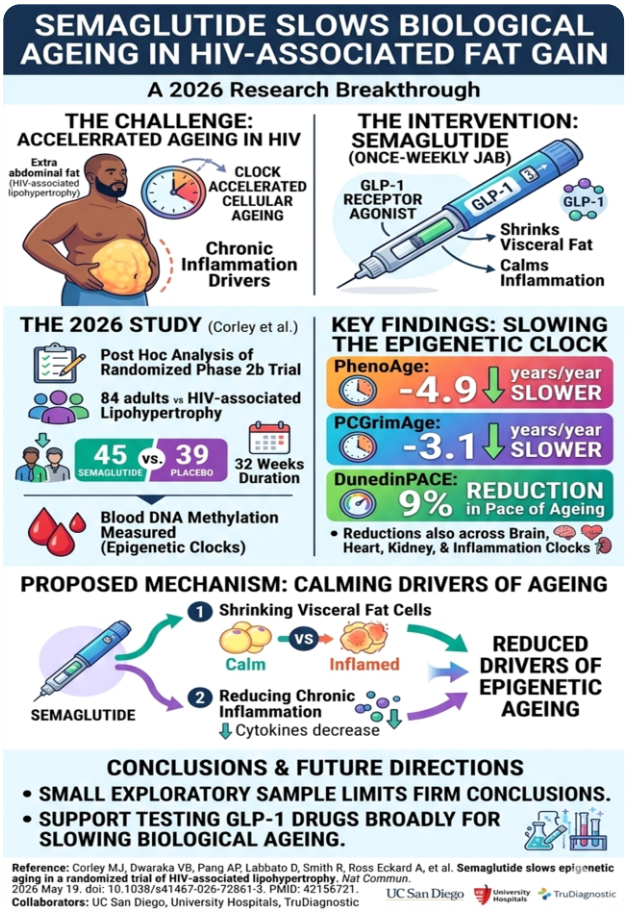
This post hoc analysis of a randomised, double-blind, placebo-controlled phase 2b trial, led by researchers at the University of California San Diego and University Hospitals Cleveland Medical Centre in collaboration with TruDiagnostic, examined whether the GLP-1 receptor agonist semaglutide could slow biological ageing in people living with HIV-associated lipohypertrophy, a condition marked by excess abdominal fat and accelerated cellular ageing. Eighty-four adults (45 on semaglutide, 39 on placebo) had blood DNA methylation measured at baseline and after 32 weeks using several validated 'epigenetic clocks'. Compared with placebo, semaglutide significantly slowed ageing on multiple clocks, including PhenoAge (4.9 years/year slower), PCGrimAge (3.1 years/year) and DunedinPACE, which showed a 9% reduction in the pace of ageing. Reductions were also seen across brain, heart, kidney and inflammation specific clocks. The researchers suggest these effects may stem from semaglutide's ability to shrink visceral fat and calm chronic inflammation, both known drivers of epigenetic ageing. While the small, exploratory sample limits firm conclusions, the findings support further trials testing GLP-1 drugs as potential tools for slowing biological ageing more broadly.

Source:

RESEARCH PAPER

Corley MJ, Dwaraka VB, Pang AP, Labbato D, Smith R, Ross Eckard A, et al. Semaglutide slows epigenetic aging in a randomized trial of HIV-associated lipohypertrophy. Nat Commun. 2026 May 19. doi: 10.1038/s41467-026-72861-3. Epub ahead of print. PMID: 42156721.





Arts and Cultural Engagement Linked to Slower Biological Ageing, Comparable to Exercise (2026)

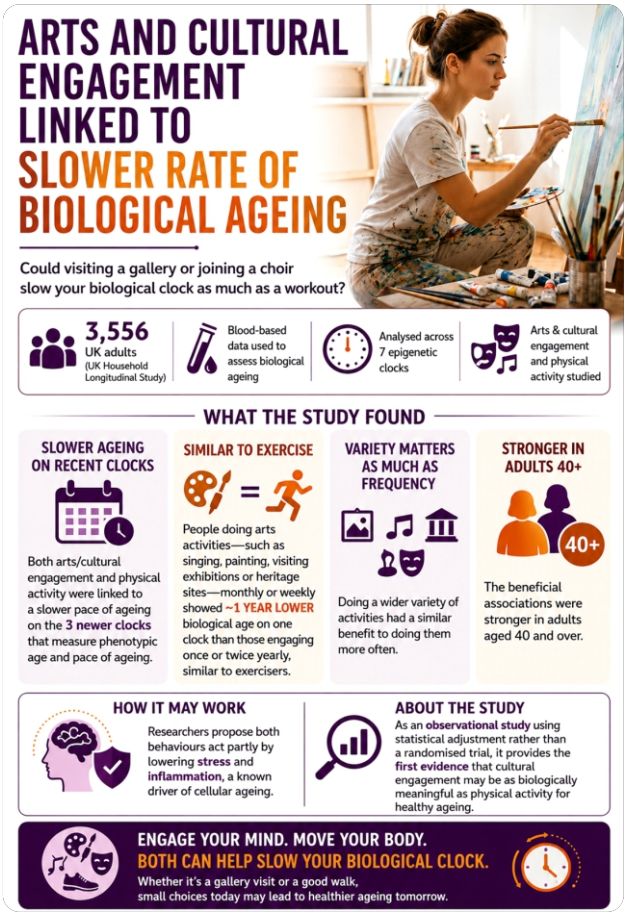
🎨 ***Could visiting a gallery or joining a choir slow your biological clock as much as a workout?***

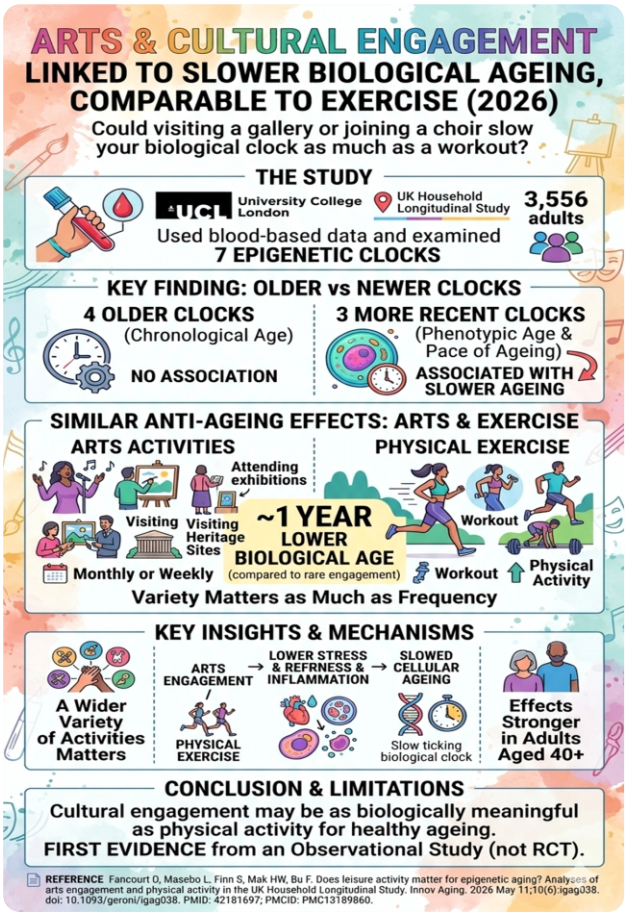
This study, led by researchers at University College London, used blood-based data from 3,556 adults in the UK Household Longitudinal Study to examine whether arts and cultural engagement and physical activity relate to slower biological ageing across seven epigenetic clocks. Both behaviours were linked to a slower pace of ageing on the three more recent clocks tracking phenotypic age and pace of ageing, though no association appeared on the four older clocks based on chronological age. People doing arts activities, such as singing, painting, attending exhibitions or visiting heritage sites, monthly or weekly showed roughly a year lower biological age on one clock than those engaging once or twice yearly, with similar effects for exercisers. Doing a wider variety of activities mattered as much as frequency. The researchers propose both behaviours act partly by lowering stress and inflammation, a known driver of cellular ageing. Effects were stronger in adults aged 40 and over. As an observational study using statistical adjustment rather than a randomised trial, it offers the first evidence that cultural engagement may be as biologically meaningful as physical activity for healthy ageing.

Source:

📄 RESEARCH PAPER

📌 Fancourt D, Masebo L, Finn S, Mak HW, Bu F. Does leisure activity matter for epigenetic aging? Analyses of arts engagement and physical activity in the UK Household Longitudinal Study. Innov Aging. 2026 May 11;10(6): igag038. doi: 10.1093/geroni/igag038. PMID: 42181697; PMCID: PMC13189860.





Steadier Daily Activity and Rest Patterns Linked to Slower Biological Ageing in Older Adults (2026)

🕐 ***Could how consistently you move and rest each day be quietly shaping how fast your body ages?***

This cross-sectional study, led by researchers at the Johns Hopkins Bloomberg School of Public Health, examined 207 community-dwelling adults in Baltimore (mean age 68) who wore wrist actigraphy devices continuously for seven days, alongside blood samples analysed using four established epigenetic clocks that estimate biological age from DNA methylation patterns. People with stronger, steadier daily rhythms, distinct periods of activity and rest, showed lower biological age acceleration on two of the four clocks, GrimAge and PhenoAge, both of which incorporate clinical and mortality-related markers and appear more sensitive to lifestyle influences than older, chronological clocks. Conversely, those with more fragmented activity and greater night-to-night variability in sleep timing showed faster biological ageing on these same measures. The researchers propose that stable rhythms support metabolic and mitochondrial function, limiting oxidative stress and DNA damage, while disrupted rhythms may trigger low-grade inflammation. Associations were stronger in women and in White participants than in other groups. As this study only captured a single snapshot in time, it cannot establish whether irregular rhythms cause faster ageing or simply accompany it, but the findings support wearable-based monitoring as a potential early marker of biological ageing.

Source:

RESEARCH PAPER

Liu C, Sosnowski DW, Nyhuis CC, Rabinowitz JA, Eaton WW, Callow DD, et al. Twenty-Four-Hour Rest-Activity Rhythms and Epigenetic Age Acceleration in Middle-Aged and Older Adults. JAMA Netw Open. 2026 May 1;9(5): e2611474. doi: 10.1001/jamanetworkopen.2026.11474. PMID: 42096199; PMCID: PMC13153996.





Moderate Long-Term Strength Training Linked to Lower Risk of Death from All Causes (2026)

🏋️ ***Could lifting weights for around two hours a week over many years meaningfully lower your risk of dying from heart disease, neurological illness, or any cause at all?***

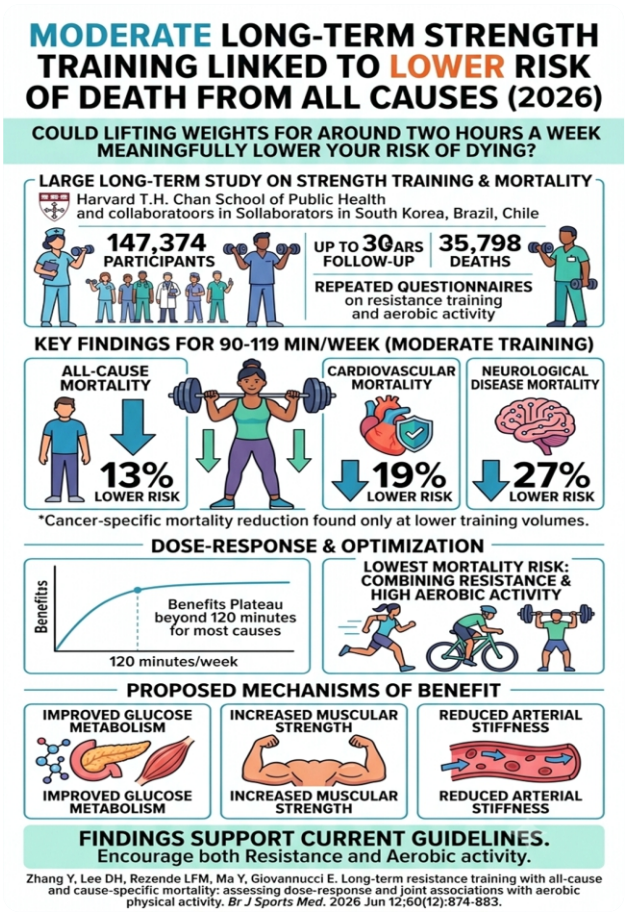
Researchers from the Harvard T.H. Chan School of Public Health and collaborating institutions in South Korea, Brazil, and Chile analysed data from three long-running US cohorts, the Health Professionals Follow-up Study and the two Nurses' Health Studies, following 147,374 participants for up to 30 years, during which 35,798 deaths occurred. Using repeated questionnaire measures of resistance training and aerobic activity, they found that 90 to 119 minutes of resistance training weekly was associated with a 13% lower risk of all-cause mortality, a 19% lower risk of cardiovascular mortality, and a 27% lower risk of neurological disease mortality, after accounting for aerobic activity. Benefits plateaued beyond 120 minutes weekly, while reduced cancer mortality appeared only at lower training volumes. Combining resistance training with high aerobic activity produced the lowest mortality risk overall. The proposed mechanisms include improved glucose metabolism, muscular strength, and, with long-term training, reduced arterial stiffness. These findings support current guidelines encouraging both resistance and aerobic activity, while suggesting that different amounts of resistance training may optimise different health outcomes.

Source:

📄 COHORT STUDY

📌 Zhang Y, Lee DH, Rezende LFM, Ma Y, Giovannucci E. Long-term resistance training with all-cause and cause-specific mortality: assessing dose-response and joint associations with aerobic physical activity. Br J Sports Med. 2026 Jun 12;60(12):874-883. doi: 10.1136/bjsports-2025-110503. PMID: 42230125.





Retinal Biological Age Could Signal Weakening Bones and Fracture Risk (2026)

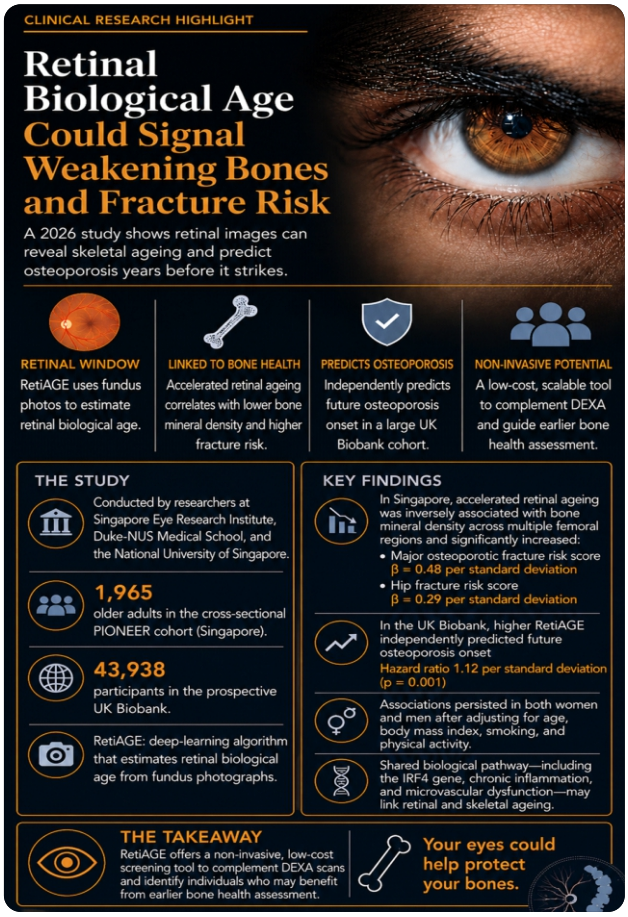
Can the retina act as a window into your skeletal health and predict osteoporosis years before it strikes?

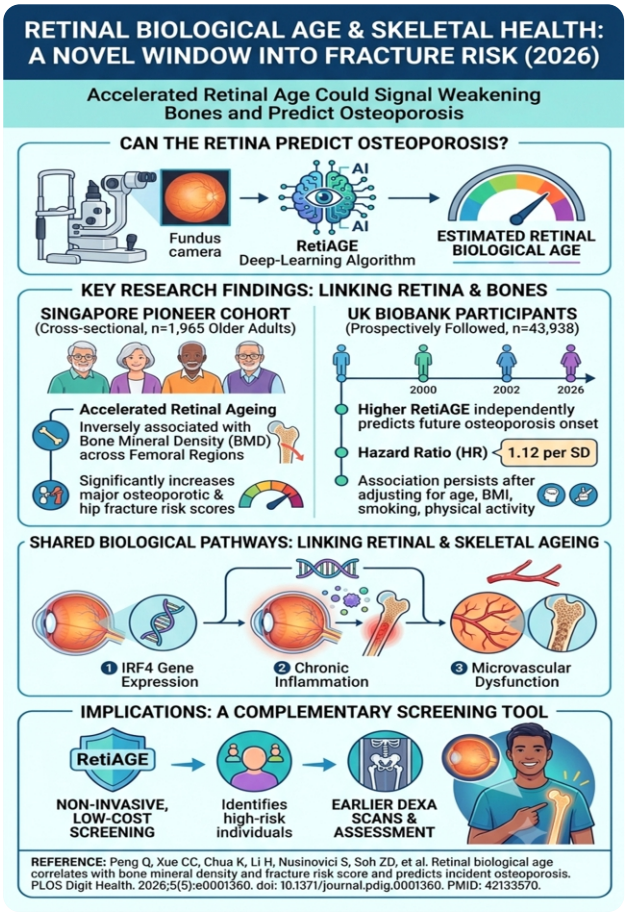
Researchers at Singapore Eye Research Institute, Duke-NUS Medical School, and the National University of Singapore investigated whether retinal photographs could identify individuals at risk of bone loss. Using RetiAGE, a deep-learning algorithm that estimates retinal biological age from fundus images, they studied 1,965 older adults in the cross-sectional PIONEER cohort and 43,938 prospectively followed UK Biobank participants. In Singapore, accelerated retinal ageing was inversely associated with bone mineral density across multiple femoral regions and significantly increased major osteoporotic and hip fracture risk scores (β=0.48 and 0.29 per standard deviation, respectively). In the UK Biobank, higher RetiAGE independently predicted future osteoporosis onset (hazard ratio 1.12 per standard deviation, p=0.001), with associations persisting in women and men after adjusting for age, body mass index, smoking, and physical activity. Shared biological pathways including the IRF4 gene, chronic inflammation, and microvascular dysfunction appear to link retinal and skeletal ageing. The authors propose RetiAGE as a non-invasive, low-cost screening tool to complement DEXA scans and identify patients warranting earlier bone assessment.

Source:

RESEARCH PAPER

Peng Q, Xue CC, Chua K, Li H, Nusinovici S, Soh ZD, et al. Retinal biological age correlates with bone mineral density and fracture risk score and predicts incident osteoporosis. PLOS Digit Health. 2026;5(5): e0001360. doi: 10.1371/journal.pdig.0001360. PMID: 42133570.





Scientists Pinpoint the 'Goldilocks Zone' of Sleep for Slower Body-Wide Ageing (2026)

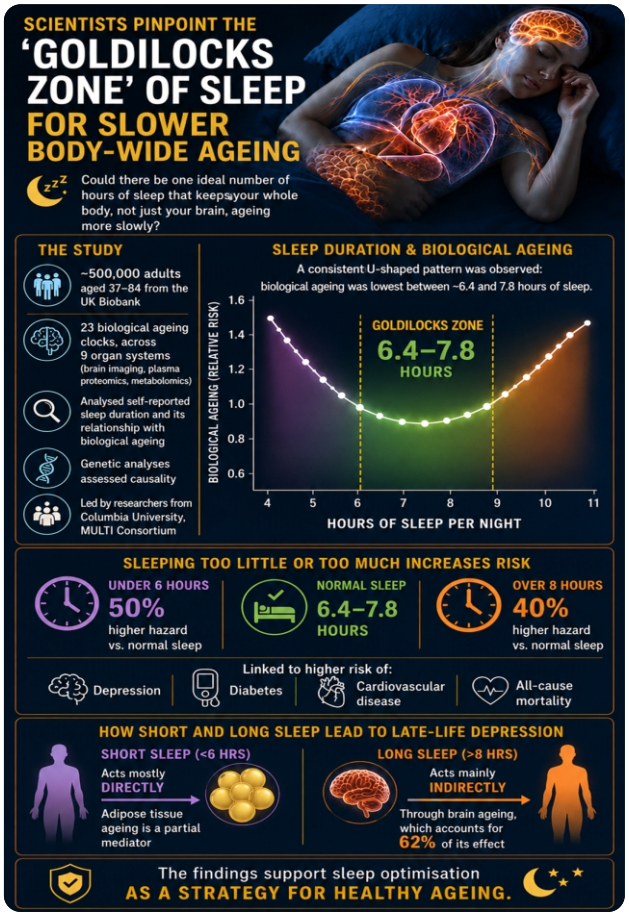
😴 ***Could there be one ideal number of hours of sleep that keeps your whole body, not just your brain, ageing more slowly?***

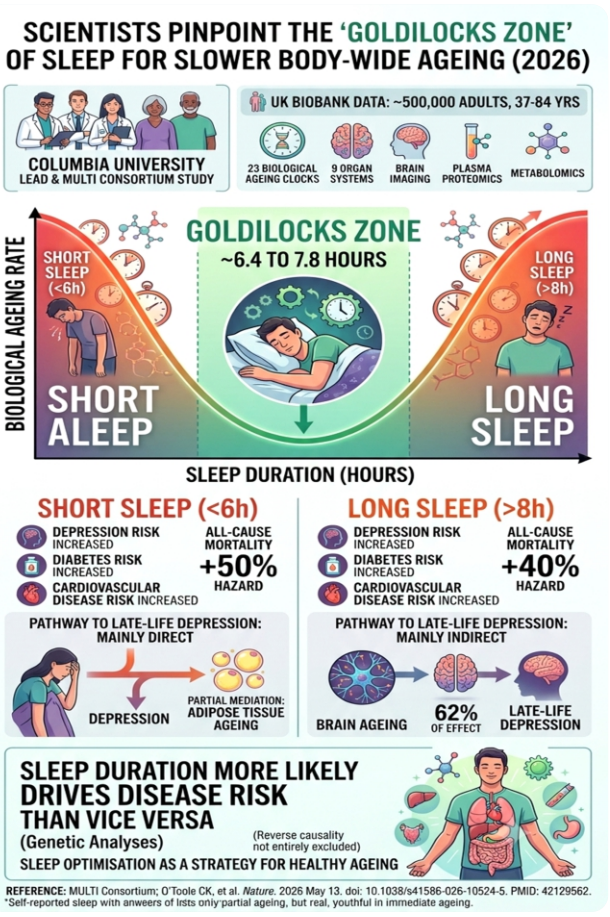
Researchers from Columbia University, leading the MULTI Consortium, analysed UK Biobank data from around 500,000 adults aged 37 to 84 to study how self-reported sleep duration relates to 23 biological ageing clocks built from brain imaging, plasma proteomics, and metabolomics across nine organ systems. They found a consistent U-shaped pattern: biological ageing was lowest between roughly 6.4 and 7.8 hours of sleep, varying by organ and sex. Sleeping under 6 hours or over 8 hours raised the risk of conditions including depression, diabetes, and cardiovascular disease, and increased all-cause mortality, with short sleep raising the hazard by 50 percent and long sleep by 40 percent versus normal sleep. The pathways to late-life depression differed: short sleep acted mostly directly, with adipose tissue ageing as a partial mediator, while long sleep worked mainly indirectly through brain ageing, accounting for 62 percent of its effect. Genetic analyses suggested sleep duration more likely drives disease risk than the reverse, though reverse causality could not be entirely excluded. The findings support sleep optimisation as a strategy for healthy ageing.

Source:

📄 COHORT STUDY

📌 MULTI Consortium; O'Toole CK, Song Z, Anagnostakis F, Yang Z, Tian YE, et al. Sleep chart of biological ageing clocks in middle and late life. Nature. 2026 May 13. doi: 10.1038/s41586-026-10524-5. Epub ahead of print. PMID: 42129562.





Two Days of Intensive Oats Cut Cholesterol via Gut Bacteria (2026)

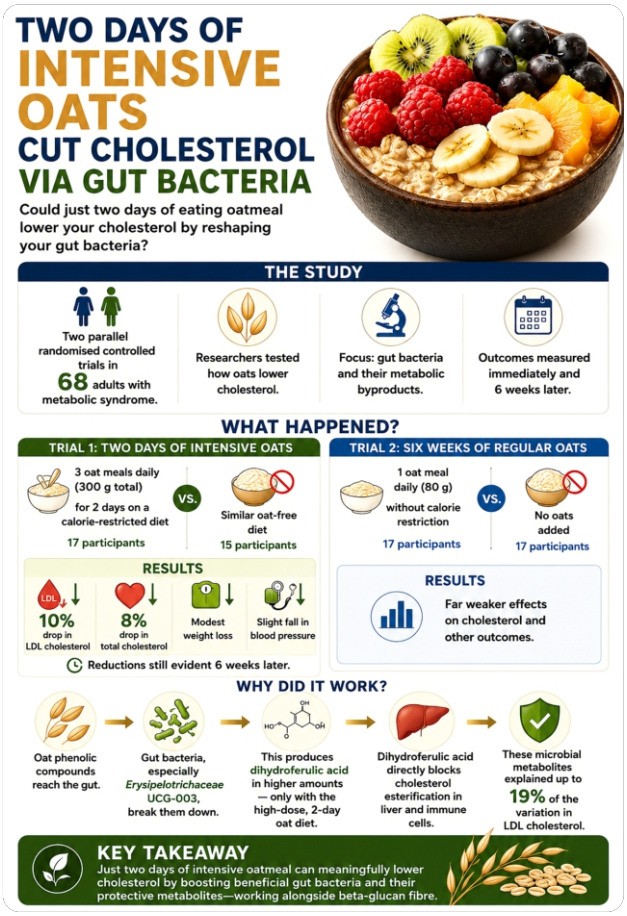
Could just two days of eating oatmeal l0ower your cholesterol by reshaping your gut bacteria?

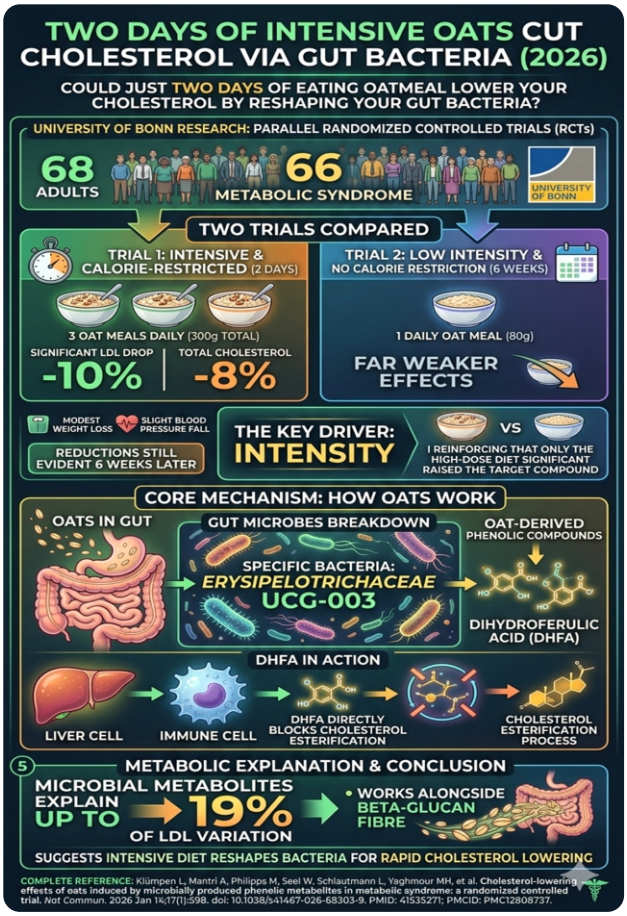
Researchers at the University of Bonn ran two parallel randomised controlled trials in 68 adults with metabolic syndrome to identify how oats lower cholesterol. In the first trial, 17 participants ate three oat meals daily (300 grams total) for two days on a calorie-restricted diet, versus 15 controls on a similar oat-free diet. The oat group showed a significant 10% drop in LDL cholesterol and 8% drop in total cholesterol, alongside modest weight loss and a slight fall in blood pressure, with reductions still evident six weeks later. A separate six-week trial, where 17 participants added one daily 80-gram oat meal without calorie restriction, produced far weaker effects. The key driver was intensity: only the high-dose diet significantly raised dihydroferulic acid, a compound produced when gut bacteria, particularly Erysipelotrichaceae UCG-003, break down oat-derived phenolic compounds. Subsequent laboratory tests notably confirmed dihydroferulic acid directly blocks cholesterol esterification in liver and immune cells. These microbial metabolites explained up to 19% of the variation in LDL cholesterol, suggesting they work alongside oats' well-known beta-glucan fibre to lower cholesterol.

Source:

RESEARCH PAPER

Klümpen L, Mantri A, Philipps M, Seel W, Schlautmann L, Yaghmour MH, et al. Cholesterol-lowering effects of oats induced by microbially produced phenolic metabolites in metabolic syndrome: a randomized controlled trial. Nat Commun. 2026 Jan 14;17(1):598. doi: 10.1038/s41467-026-68303-9. PMID: 41535271; PMCID: PMC12808737.





Coffee Reshapes Gut Bacteria and Mood, Not Just via Caffeine (2026)

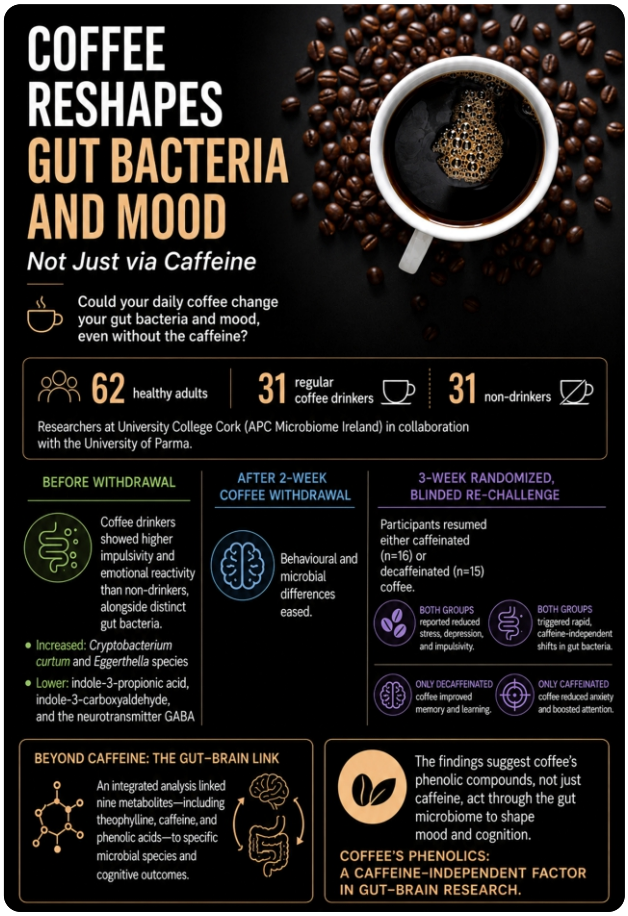
☕ ***Could your daily coffee change your gut bacteria and mood, even without the caffeine?***

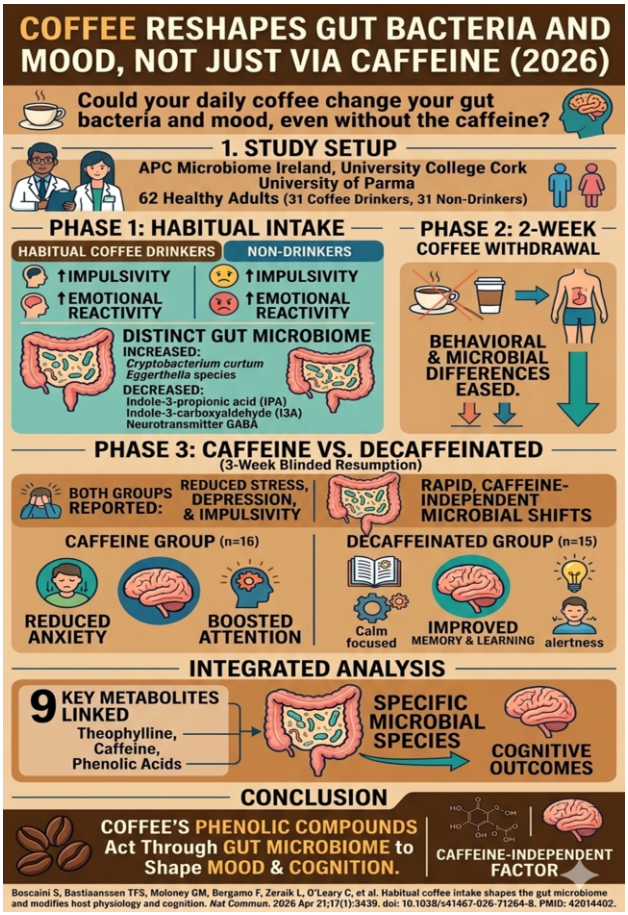
Researchers at University College Cork's APC Microbiome Ireland, working with the University of Parma, recruited 62 healthy adults, 31 regular coffee drinkers and 31 non-drinkers, to explore how coffee shapes the gut-brain axis. Coffee drinkers showed higher impulsivity and emotional reactivity than non-drinkers, alongside distinct gut bacteria, including increased Cryptobacterium curtum and Eggerthella species, and lower levels of indole-3-propionic acid, indole-3-carboxyaldehyde, and the neurotransmitter GABA. After a two-week coffee withdrawal, these behavioural and microbial differences eased. Participants then resumed either caffeinated (n=16) or decaffeinated (n=15) coffee for three weeks under blinded conditions. Both groups reported reduced stress, depression, and impulsivity, and both triggered rapid, caffeine-independent shifts in gut bacteria, while only decaffeinated coffee improved memory and learning, and only caffeinated coffee reduced anxiety and boosted attention. An integrated analysis linked nine metabolites, including theophylline, caffeine, and phenolic acids, to specific microbial species and cognitive outcomes. The findings suggest coffee's phenolic compounds, not just caffeine, act through the gut microbiome to shape mood and cognition. This positions coffee's phenolic compounds as a caffeine-independent factor in gut-brain research.

Source:

📄 RESEARCH PAPER

📌 Boscaini S, Bastiaanssen TFS, Moloney GM, Bergamo F, Zeraik L, O'Leary C, et al. Habitual coffee intake shapes the gut microbiome and modifies host physiology and cognition. Nat Commun. 2026 Apr 21;17(1):3439. doi: 10.1038/s41467-026-71264-8. PMID: 42014402.





Phytic Acid in Beans, Rice, and Nuts Acts as a Cellular Switch, Not Just a Nutrient, to Seal the Gut Barrier (2026)

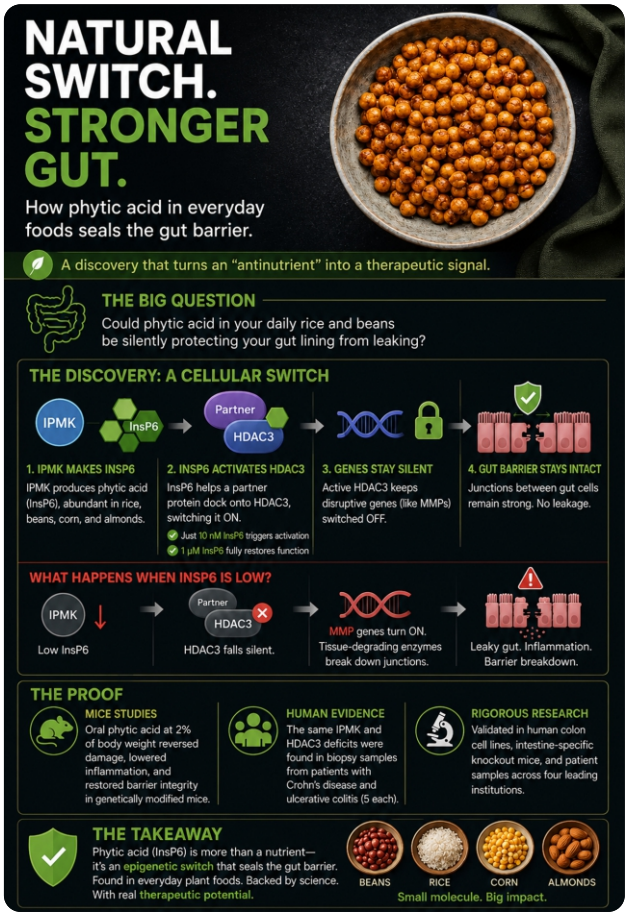
Could the phytic acid in your daily rice and beans be silently protecting your gut lining from leaking?

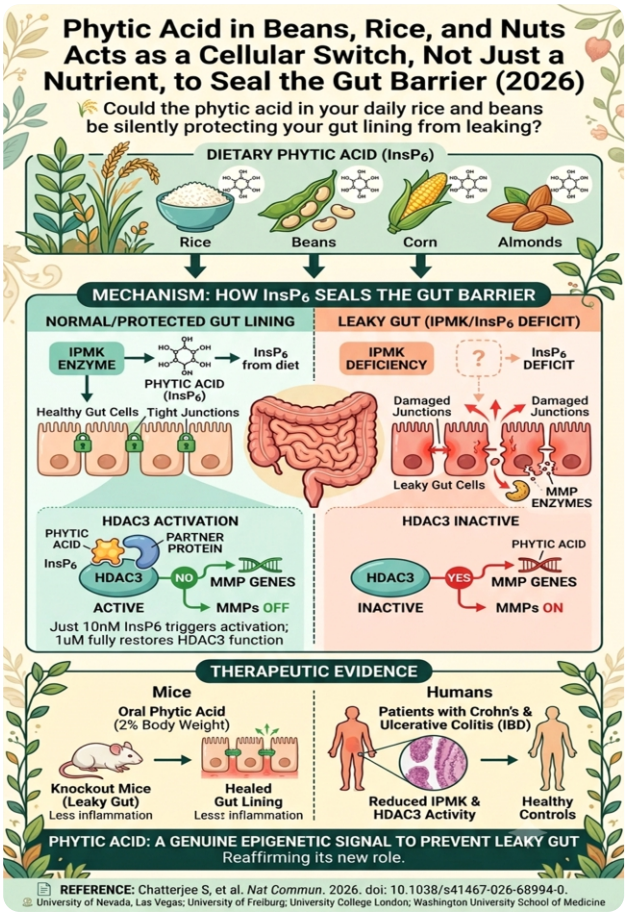
Researchers at the University of Nevada, Las Vegas, with collaborators at the University of Freiburg, University College London, and Washington University School of Medicine in St Louis, used human colon cell lines, intestine-specific knockout mice, and biopsy samples from patients with Crohn's disease and ulcerative colitis (five each) to study how the enzyme IPMK protects the gut lining. IPMK produces phytic acid (InsP6), abundant in rice, beans, corn, and almonds, which activates HDAC3, an enzyme that normally keeps disruptive genes switched off, by helping its partner protein dock onto it; just 10 nanomolar InsP6 triggered activation, and 1 micromolar fully restored HDAC3 function in IPMK-deficient cells. Without enough InsP6, HDAC3 falls silent, letting genes for tissue-degrading enzymes called MMPs switch on and break down the junctions between gut cells, producing a leaky gut. Oral phytic acid at 2% of body weight reversed this damage in mice, lowering inflammation and restoring barrier integrity, and the same IPMK and HDAC3 deficits appeared in patients with inflammatory bowel disease. The findings position phytic acid, long dismissed as an "antinutrient," as a genuine epigenetic signal with therapeutic potential for leaky gut.

Source:

RESEARCH PAPER

Chatterjee S, Sin Z, Tran N, Vierra L, Shukla A, Tran T, et al. Phytic acid (InsP6) activates HDAC3 epigenetic axis to maintain intestinal barrier function. Nat Commun. 2026 Feb 9;17(1):4770. doi: 10.1038/s41467-026-68994-0. PMID: 41663400; PMCID: PMC13219500





Does Wanting to Change Your Diet Affect Your Gut Bacteria and Memory (2026)

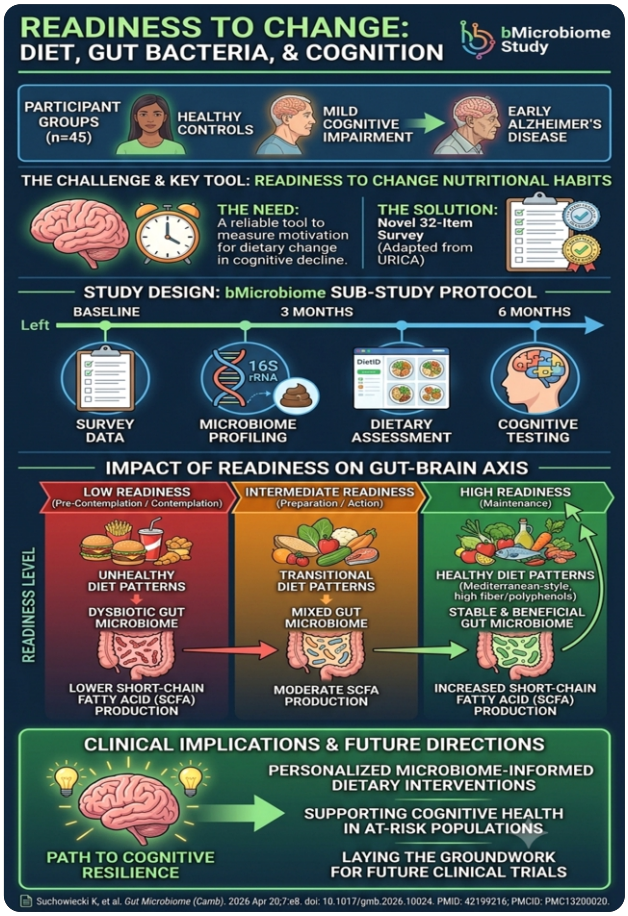
Could someone's readiness to change their eating habits shape how their gut microbiome affects their brain?

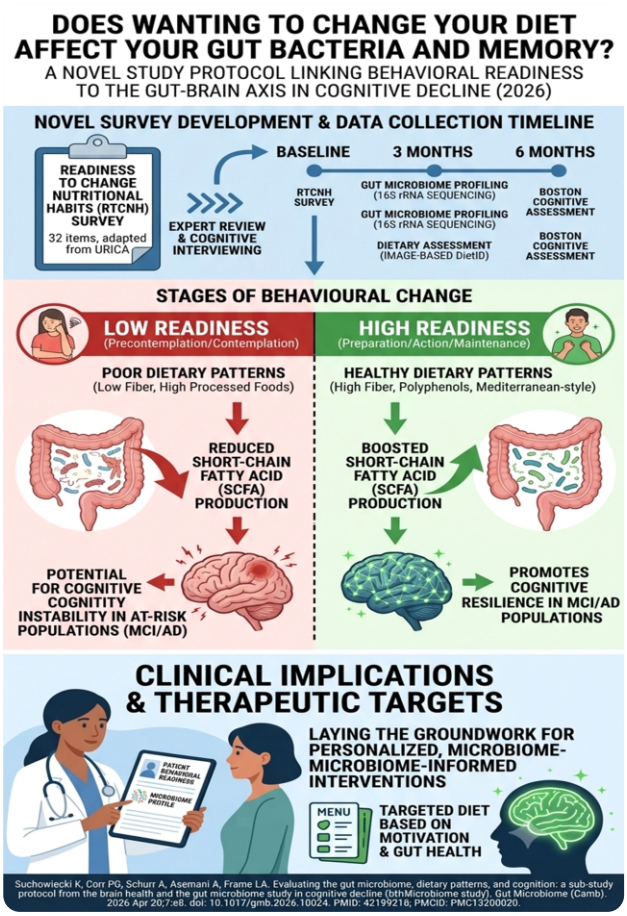
This methods paper, developed by researchers in the Department of Clinical Research and Leadership at The George Washington University alongside the Department of Medicine at the University of Connecticut Health Center, describes a sub-study protocol embedded within the bMicrobiome study, a proof-of-concept observational trial mapping gut microbiome composition in 45 participants split evenly across healthy controls, mild cognitive impairment, and early Alzheimer's disease dementia. Since no validated tool existed to measure readiness to change nutritional habits, the authors developed a novel 32-item Readiness to Change Nutritional Habits survey, adapted from the well-established University of Rhode Island Change Assessment, refined through expert review and cognitive interviewing with participants resembling the study population. At baseline, three months, and six months, participants complete this survey alongside gut microbiome profiling via 16S rRNA sequencing, dietary assessment using the image-based DietID platform, and the Boston Cognitive Assessment. The authors hypothesise that participants further along in the stages of behavioural change will show healthier dietary patterns and less dysbiotic microbiomes, given that fibre, polyphenols, and Mediterranean-style diet components are known to boost beneficial short-chain fatty acid production. By pairing behavioural readiness data with objective microbiome and cognitive measures, this protocol lays groundwork for personalised, microbiome-informed dietary interventions that could eventually support cognitive resilience in populations at risk of decline.

Source:

METHODS PAPER

Suchowiecki K, Corr PG, Schurr A, Asemani A, Frame LA. Evaluating the gut microbiome, dietary patterns, and cognition: a sub-study protocol from the brain health and the gut microbiome study in cognitive decline (bMicrobiome study). Gut Microbiome (Camb). 2026 Apr 20;7: e8. doi: 10.1017/gmb.2026.10024. PMID: 42199216; PMCID: PMC13200020.





Ultra-processed Food Consumption Linked to Worse Health and Earlier Death (2026)

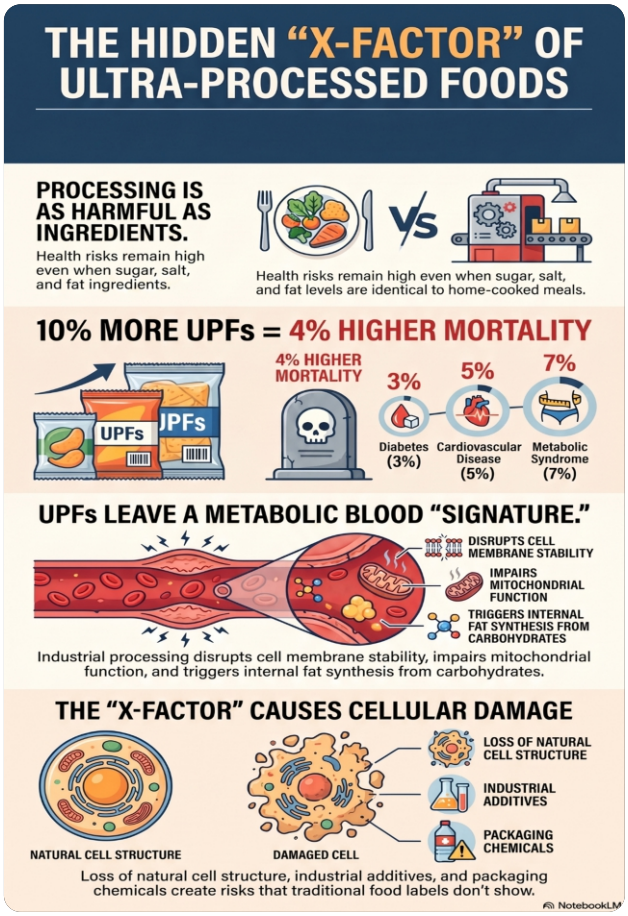
Does the amount of ultra-processed food you eat predict your risk of heart disease and premature death?

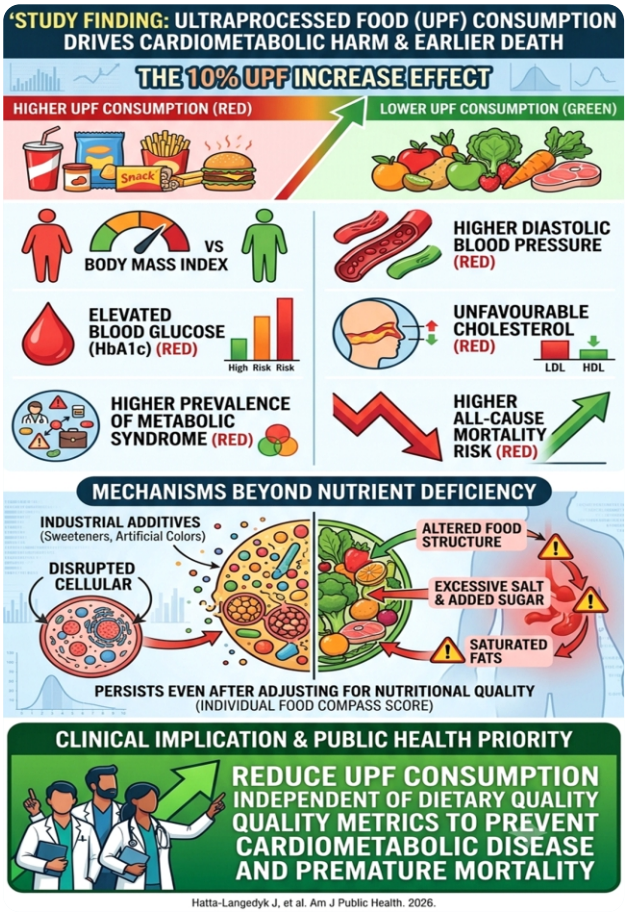
Researchers at Tufts University, Boston, Massachusetts, analysed 20 years of data from 47,999 US adults in the National Health and Nutrition Examination Survey (NHANES, 1999-2018) to examine associations between ultra-processed food (UPF) consumption, cardiometabolic risk factors, and mortality. For every 10% of daily energy intake from UPFs, participants showed significantly higher body mass index, blood glucose (HbA1c), diastolic blood pressure, and unfavourable cholesterol profiles, alongside greater prevalence of metabolic syndrome and higher all-cause mortality risk. Notably, these associations persisted even after adjusting for overall nutritional quality using the Individual Food Compass Score, suggesting that UPF harms operate through mechanisms beyond simple nutrient deficiency. The authors attribute this to industrial additives (sweeteners, artificial colours), excessive salt and added sugar, saturated fats, and alterations to food structure during manufacturing. Findings remained consistent across demographic subgroups. The research demonstrates that reducing UPF consumption, independent of dietary quality metrics, represents a distinct public health priority for preventing cardiometabolic disease and premature mortality.

Source:

COHORT STUDY

Hatta-Langedyk J, Wang L, Fan B, Shi P, Mozaffarian D. Ultra-processed food versus diet quality in relation to cardiometabolic health and all-cause mortality: NHANES 1999-2018. Am J Public Health. 2026 Jul;116(7):1015-1024. doi: 10.2105/AJPH.2026.308499. Epub 2026 Jun 3. PMID: 42233198; PMCID: PMC13277460.





Do Shoppers Know Which Foods Count as "Ultra-Processed" (2026)

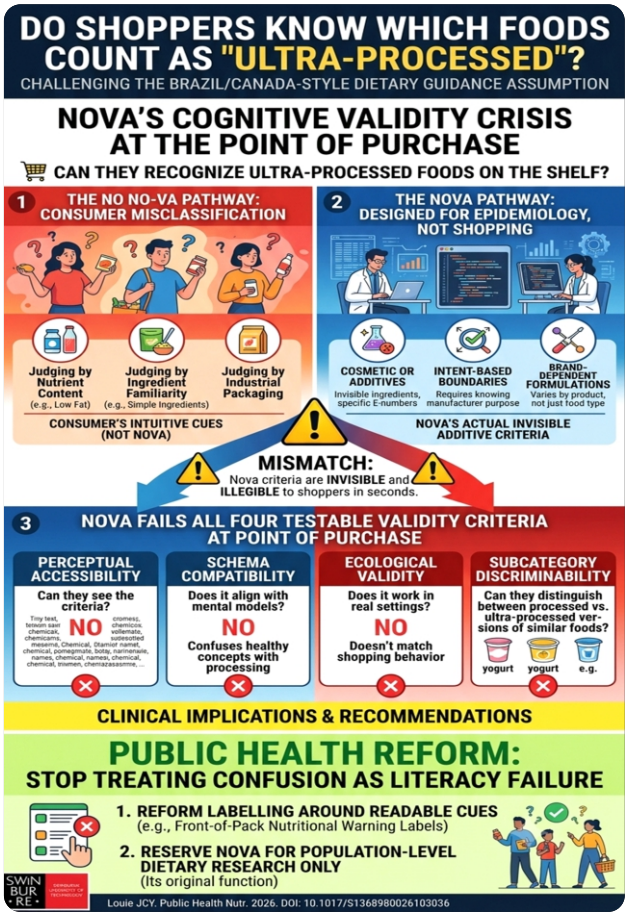
🛒 ***We tell people to avoid ultra-processed foods, but can they actually recognise one when they see it on a supermarket shelf?***

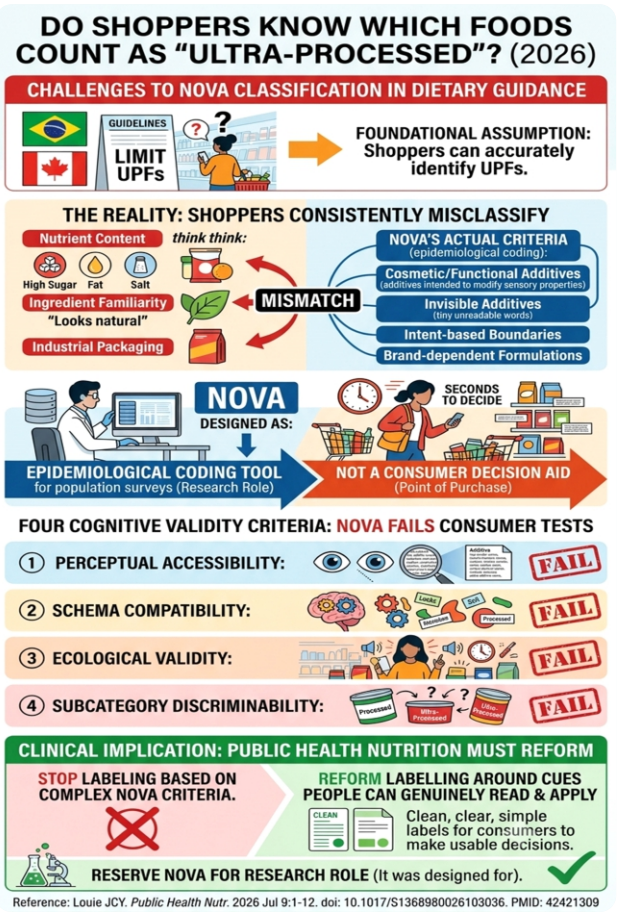
This commentary from the Discipline of Dietetics at Swinburne University of Technology in Australia challenges a foundational assumption behind dietary guidance in Brazil, Canada, and other jurisdictions that increasingly advise limiting ultra-processed foods based on the Nova classification. Drawing on published consumer research, the author shows that shoppers consistently misclassify foods, judging processing by nutrient content, ingredient familiarity, or industrial packaging rather than Nova's actual criterion of cosmetic or functional additive purpose. This mismatch arises because Nova was designed as an epidemiological coding tool for population-level dietary surveys, not a consumer decision aid, so its defining features, invisible additives, intent-based boundaries, and brand-dependent formulations, are illegible within the few seconds shoppers spend reading a label. The author proposes four testable validity criteria, perceptual accessibility, schema compatibility, ecological validity, and subcategory discriminability, arguing Nova fails all four when applied at the point of purchase. The commentary concludes that public health nutrition should reform labelling around cues people can genuinely read and apply, reserving Nova for the research role it was designed to serve, rather than treating consumer confusion as a literacy failure.

Source:

📄 COMMENTARY

📌 Louie JCY. Before we tell people to avoid ultra-processed foods, can they identify them? The case for cognitive validity criteria in food classification. Public Health Nutr. 2026 Jul 9:1-12. doi: 10.1017/S1368980026103036. Epub ahead of print. PMID: 42421309.





Common Food Preservatives Linked to Higher Risk of High Blood Pressure and Heart Disease (2026)

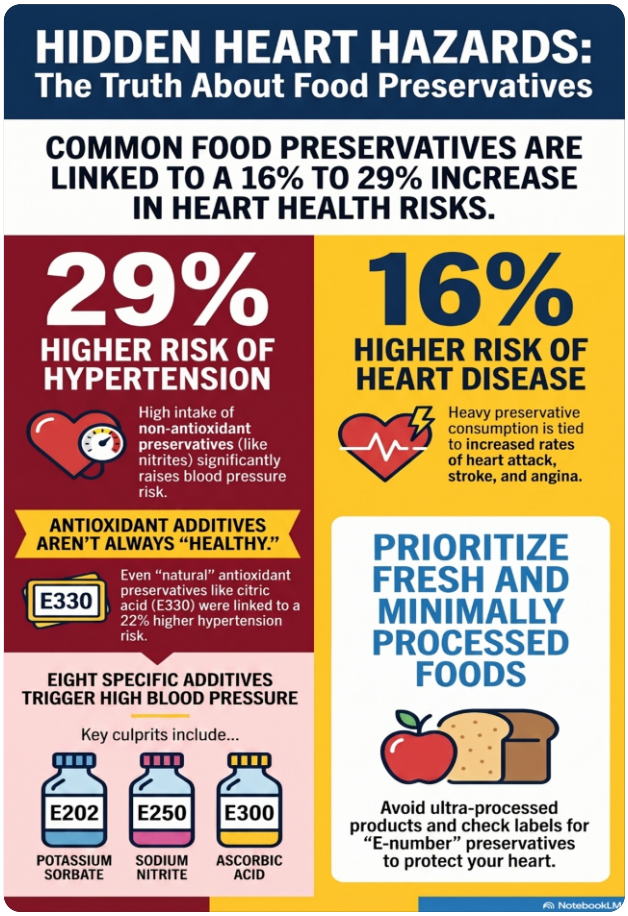
🧂❤️ ***Could the preservatives keeping your food fresh also be quietly raising your blood pressure?***

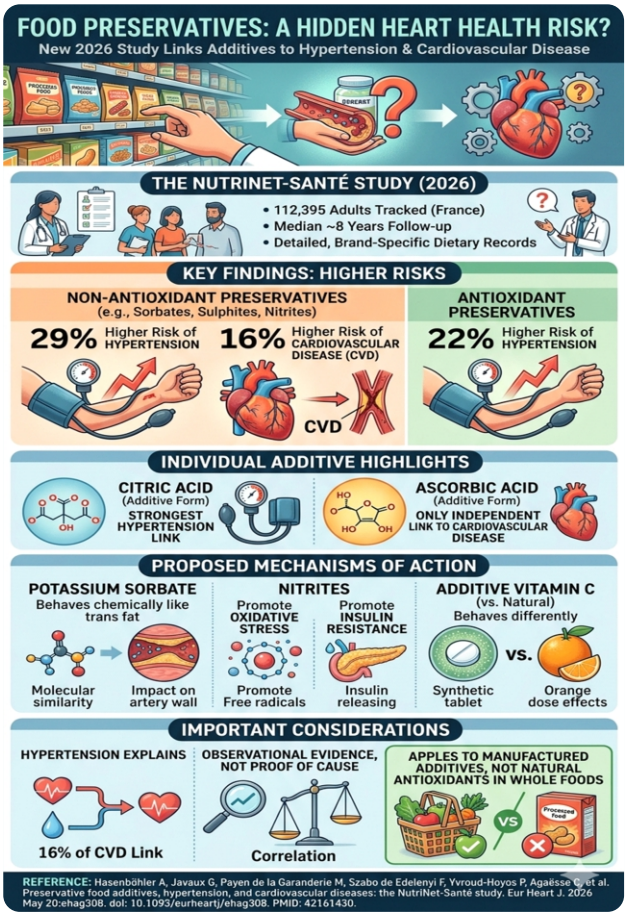
Researchers from INSERM and Université Paris Cité in France tracked 112,395 adults in the NutriNet-Santé cohort for a median of nearly eight years, using detailed, brand-specific dietary records to estimate preservative additive intake. Non-antioxidant preservatives, including sorbates, sulphites and nitrites, were linked to a 29% higher risk of hypertension and a 16% higher risk of cardiovascular disease, while antioxidant preservatives carried a 22% higher hypertension risk. Among individual additives, citric acid showed the strongest hypertension link, while ascorbic acid was the only substance independently associated with cardiovascular disease. Proposed mechanisms vary by compound: potassium sorbate behaves chemically like a trans-fat, with known vascular effects, nitrites are thought to promote oxidative stress and insulin resistance, and additive forms of vitamin C may behave differently from the same molecule occurring naturally in fruit, depending on dose and food matrix. 16% of the cardiovascular disease link was explained by hypertension itself. The authors stress this is observational evidence, not proof of cause, and that the findings apply to manufactured additives, not antioxidants naturally occurring in whole foods.

Source:

📄 RESEARCH PAPER

📌 Hasenböhler A, Javaux G, Payen de la Garanderie M, Szabo de Edelenyi F, Yvroud-Hoyos P, Agaësse C, et al. Preservative food additives, hypertension, and cardiovascular diseases: the NutriNet-Santé study. Eur Heart J. 2026 May 20: ehag308. doi: 10.1093/eurheartj/ehag308. Epub ahead of print. PMID: 42161430.





Alcohol Intake and Mortality: Even Moderate Weekly Drinking Raises Risk of Death, US Study Finds (2026)

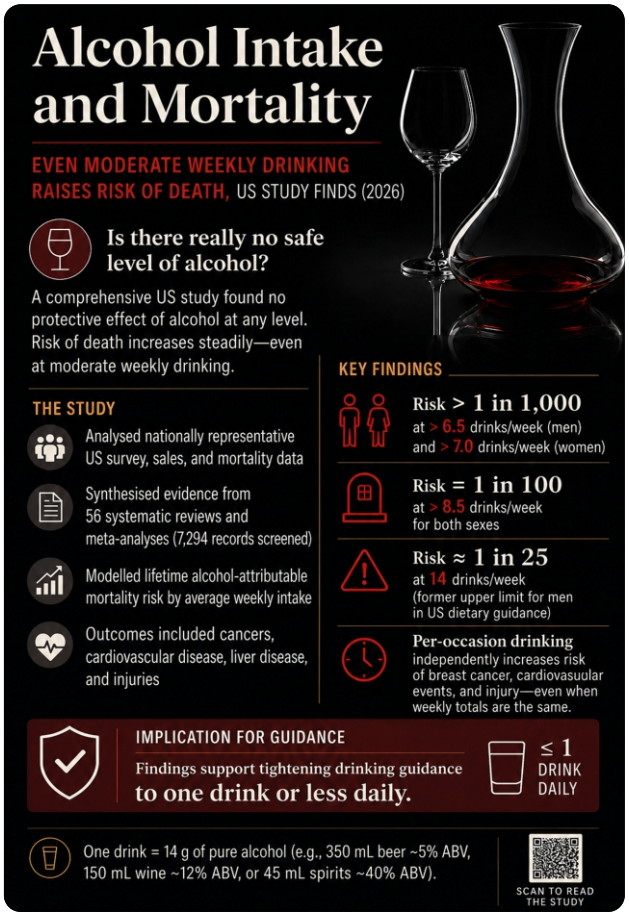
Is there really no safe level of alcohol consumption?

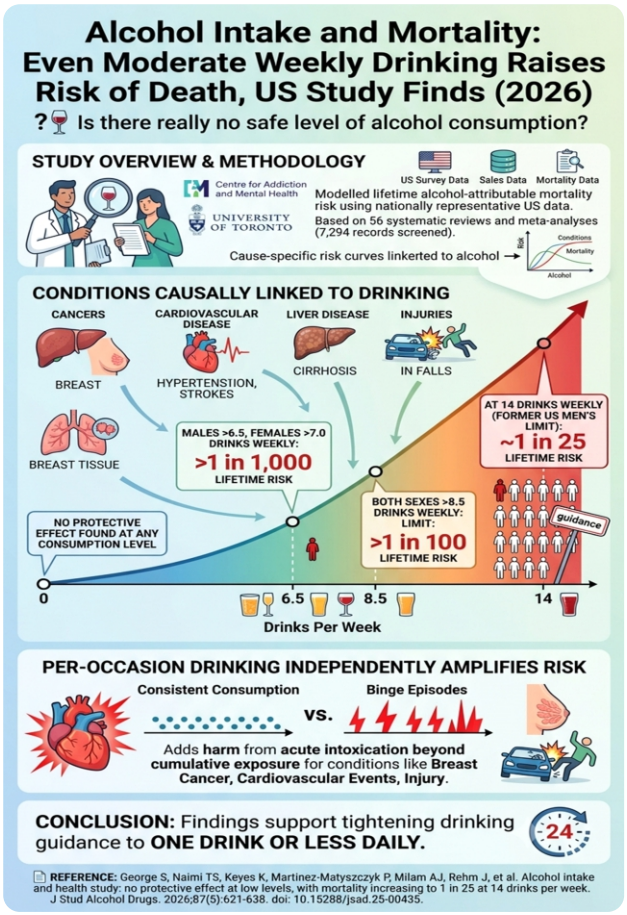
Published in the Journal of Studies on Alcohol and Drugs, this study led by researchers at the Centre for Addiction and Mental Health and the University of Toronto modelled lifetime alcohol-attributable mortality risk using nationally representative United States survey, sales, and mortality data. Drawing on 56 systematic reviews and meta-analyses identified after screening 7,294 records, the authors-built cause-specific risk curves linking average weekly alcohol intake to death from conditions with established causal links to drinking, including cancers, cardiovascular disease, liver disease and injuries. No protective effect was observed at any consumption level. Males exceeding 6.5 drinks weekly and females exceeding 7.0 drinks weekly reached a lifetime risk greater than 1 in 1,000, rising to 1 in 100 above 8.5 drinks weekly for both sexes. At 14 drinks weekly, the former upper limit for men in US dietary guidance, the risk of an alcohol-caused death reached approximately 1 in 25. Per-occasion drinking independently amplified risks for breast cancer, cardiovascular events and injury, even when weekly totals remained constant, reflecting added harm from acute intoxication beyond cumulative exposure. The findings support tightening drinking guidance to one drink or less daily.

Source:

COHORT STUDY

George S, Naimi TS, Keyes K, Martinez-Matyszczyk P, Milam AJ, Rehm J, et al. Alcohol intake and health study: no protective effect at low levels, with mortality increasing to 1 in 25 at 14 drinks per week. J Stud Alcohol Drugs. 2026;87(5):621-638. doi: 10.15288/jsad.25-00435.





Trans Fats Naturally Found in Dairy Foods Do Not Raise Heart Disease or Diabetes Risk (2026)

🧀 ***Could the natural trans fats in butter and cheese actually be harmless, contrary to decades of caution around trans fats generally?***

Researchers from the Centre National Interprofessionnel de l'Economie Laitière (France), the National Dairy Council (USA), and the University of Reading (UK) conducted a systematic review and meta-analysis combining ten randomised controlled trials and twelve prospective cohort studies to assess the cardiometabolic effects of ruminant trans fatty acids, mainly vaccenic acid and rumenic acid, found naturally in dairy foods. Across the trials, which tested TFA intakes ranging from 1.3 to 13.2 grams daily, there were no significant differences in total cholesterol, LDL cholesterol, triacylglycerols, or apolipoproteins, aside from a small reduction in HDL cholesterol. In the cohort studies, circulating concentrations of these fatty acids were not linked to a higher risk of cardiovascular disease, cardiovascular mortality, or Type 2 Diabetes. Unlike industrially produced trans fats, ruminant TFA occur within a natural dairy food matrix alongside beneficial nutrients, which may explain the lack of adverse metabolic effect. These findings suggest that dairy foods enhanced with or naturally containing ruminant trans fats need not be restricted on cardiometabolic grounds, offering reassurance as global policies increasingly target industrial trans fats specifically.

Source:

REVIEW

Gayet-Boyer C, Tenenhaus-Aziza F, Torres-Gonzalez M, Givens DI, Schweitzer C. Trans fatty acids from dairy foods do not affect risk of cardiometabolic diseases: systematic review and meta-analysis of evidence from randomized controlled trials and systematic review of prospective cohort studies. Nutr Res. 2026 Jun; 150:33-48. doi: 10.1016/j.nutres.2026.03.009. Epub 2026 Mar 27. PMID: 42034918.





One Avocado a Day May Meaningfully Lower Blood Sugar Impact of the Diet (2026)

🥑 Could adding just one avocado a day to your usual meals actually blunt how much your diet spikes blood sugar?

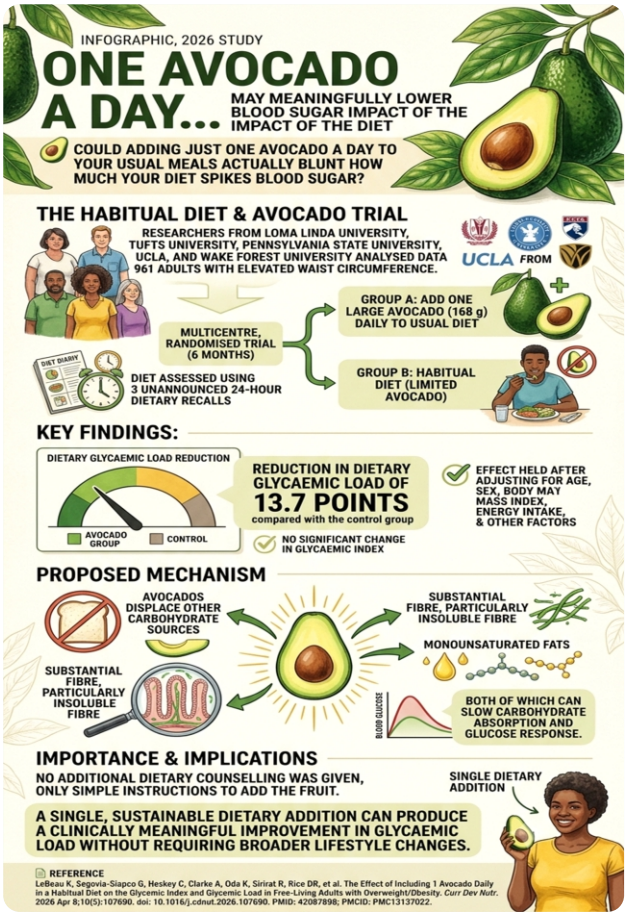
Researchers from Loma Linda University, Tufts University, Pennsylvania State University, UCLA, and Wake Forest University analysed data from 961 adults with elevated waist circumference enrolled in the multicentre, randomised Habitual Diet and Avocado Trial. Participants either added one large avocado (168 g) daily to their usual diet for six months or continued their habitual diet while limiting avocado intake. Diet was assessed using three unannounced 24-hour dietary recalls. The avocado group showed a reduction in dietary glycaemic load of 13.7 points compared with the control group, with no significant change in glycaemic index. This effect held even after adjusting for age, sex, body mass index, energy intake, and other factors. The likely mechanism involves avocados displacing other carbohydrate sources while contributing substantial fibre, particularly insoluble fibre, along with monounsaturated fats, both of which can slow carbohydrate absorption and glucose response. Importantly, no additional dietary counselling was given, only simple instructions to add the fruit. The findings suggest that a single, sustainable dietary addition can produce a clinically meaningful improvement in glycaemic load without requiring broader lifestyle changes.

Source:

RESEARCH PAPER

LeBeau K, Segovia-Siapco G, Heskey C, Clarke A, Oda K, Sirirat R, Rice DR, et al. The Effect of Including 1 Avocado Daily in a Habitual Diet on the Glycaemic Index and Glycaemic Load in Free-Living Adults with Overweight/ Obesity. Curr Dev Nutr. 2026 Apr 8;10(5):107690. doi: 10.1016/j.cdnut.2026.107690. PMID: 42087898; PMCID: PMC13137022.





Following Standard "Five-a-Day" Advice May Not Give You Enough Heart-Protective Plant Compounds Called Flavanols (2026)

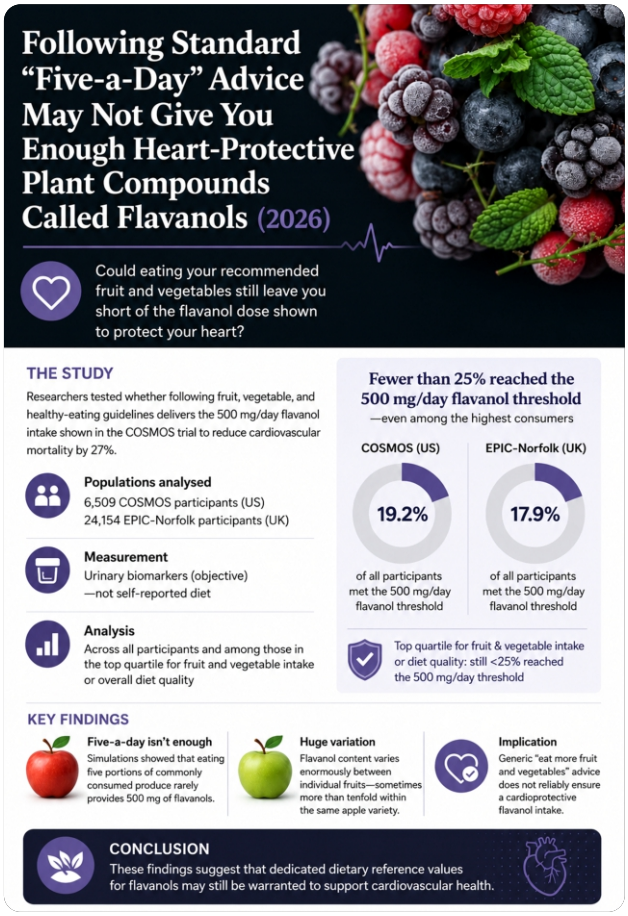
Could eating your recommended fruit and vegetables still leave you short of the flavanol dose shown to protect your heart?

Researchers from Mars Incorporated, the University of Illinois at Urbana-Champaign, the University of California Davis, Harvard Medical School and Harvard T.H. Chan School of Public Health, and the University of Reading, UK, tested whether following fruit, vegetable, and healthy-eating guidelines delivers the 500 mg/day flavanol intake shown in the COSMOS trial to reduce cardiovascular mortality by 27%. Using urinary biomarkers rather than self-reported diet, the team analysed 6,509 COSMOS participants (US) and 24,154 EPIC-Norfolk participants (UK). Even among those in the top quartile for fruit and vegetable intake or overall diet quality, fewer than 25% reached the 500 mg/day threshold, closely mirroring the 19.2% and 17.9% meeting it across the full COSMOS and EPIC-Norfolk cohorts, respectively. Simulations confirmed that eating five portions of commonly consumed produce rarely supplies this amount, largely because flavanol content varies enormously between individual fruits, sometimes more than tenfold within the same apple variety. The authors conclude that generic "eat more fruit and vegetables" advice does not reliably ensure a cardioprotective flavanol intake, and that dedicated dietary reference values for flavanols may still be warranted.

Source:

RESEARCH PAPER

Ottaviani JI, Erdman JW Jr, Steinberg FM, Manson JE, Sesso HD, Schroeter H, Kuhnle GGC. Adhering to dietary guidelines does not yield flavanol intake levels associated with beneficial cardiovascular effects. Food Funct. 2026 Jun 22;17(12):5715-5725. doi: 10.1039/d6fo00867d. PMID: 42300445; PMCID: PMC13244133.





The Vitamin D Paradox: Why Pills Don't Seem to Help the Lungs (2026)

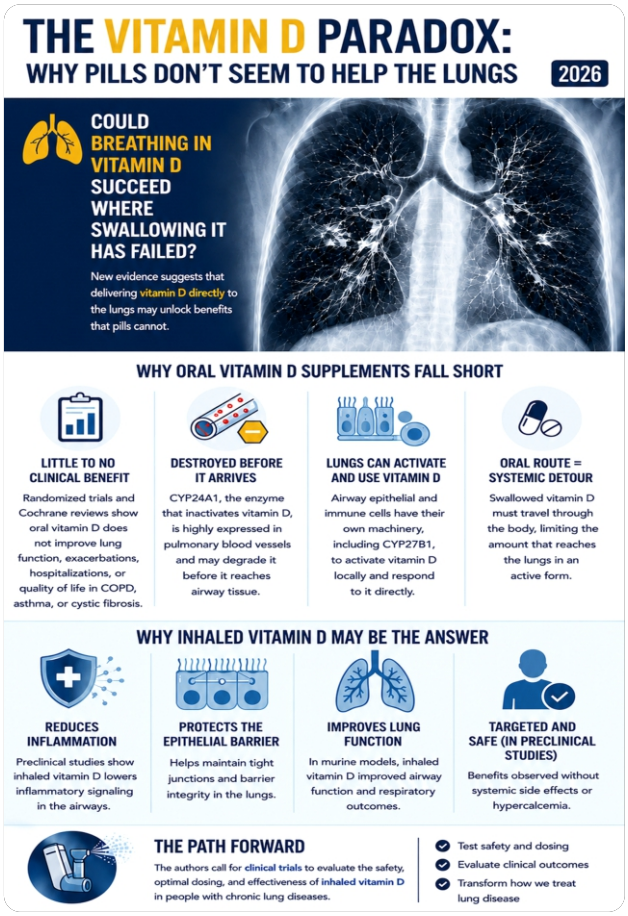
Could breathing in Vitamin D succeed where swallowing it has failed?

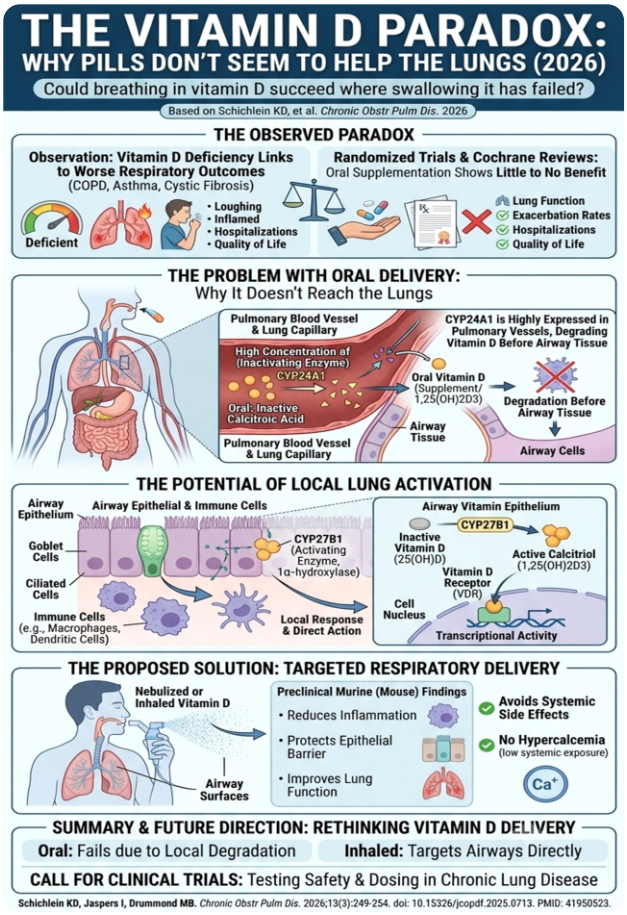
Researchers at the University of North Carolina at Chapel Hill's Marsico Lung Institute propose that oral Vitamin D supplementation has failed patients with chronic obstructive pulmonary disease (COPD), asthma, and cystic fibrosis not because Vitamin D lacks therapeutic value, but because oral dosing cannot reach the lungs effectively. Despite observational links between Vitamin D deficiency and worse respiratory outcomes, randomized trials and Cochrane reviews have consistently shown little to no benefit from oral supplementation on lung function, exacerbation rates, hospitalizations, or quality of life. The authors highlight that CYP24A1, the enzyme that inactivates Vitamin D, is highly expressed in pulmonary blood vessels, potentially degrading it before it reaches airway tissue. Airway epithelial and immune cells possess their own machinery, including CYP27B1, to locally activate Vitamin D and respond to it directly. Preclinical studies in murine models show nebulized or inhaled Vitamin D reduces inflammation, protects the epithelial barrier, and improves lung function without systemic side effects or hypercalcemia. The authors call for clinical trials testing inhaled Vitamin D's safety and dosing in chronic lung disease.

Source:

RESEARCH PAPER

Schichlein KD, Jaspers I, Drummond MB. Reconsidering vitamin D supplementation in pulmonary disease: the case for targeted respiratory delivery. Chronic Obstr Pulm Dis. 2026;13(3):249-254. doi: 10.15326/jcopdf.2025.0713. PMID: 41950523.





Higher Vitamin C Levels Linked to Healthier Brain Structure in Older Adults (2026)

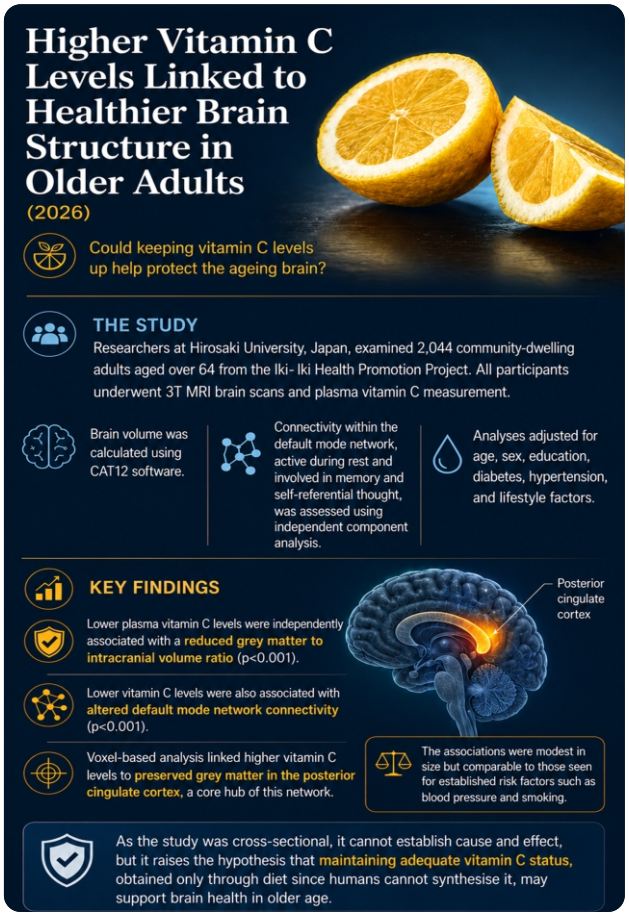
🍊 ***Could keeping Vitamin C levels up help protect the ageing brain?***

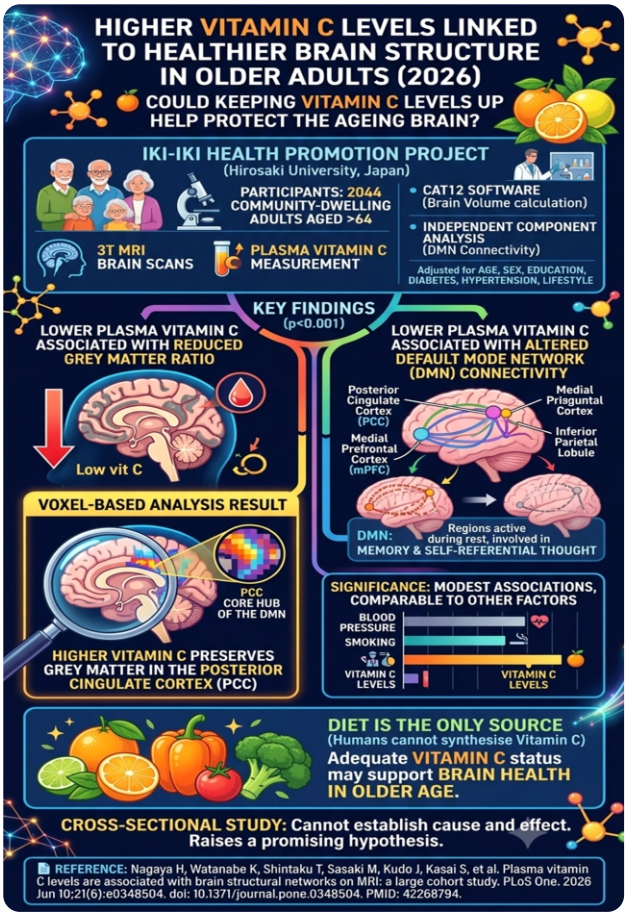
Vitamin C is a key antioxidant in the brain, and dietary intake has previously been linked to a lower risk of cognitive decline, but whether blood levels of the vitamin directly relate to brain structure remained unclear. Researchers at Hirosaki University in Japan examined 2044 community-dwelling adults aged over 64 from the Iki-Iki Health Promotion Project, all of whom underwent 3T MRI brain scans and plasma Vitamin C measurement. Brain volume was calculated using CAT12 software, while connectivity within the default mode network, a set of brain regions active during rest and involved in memory and self-referential thought, was assessed using independent component analysis. After adjusting for age, sex, education, diabetes, hypertension, and lifestyle factors, lower plasma Vitamin C levels were independently associated with a reduced grey matter to intracranial volume ratio and with altered default mode network connectivity (both $p<0.001$). Voxel-based analysis further linked higher Vitamin C levels to preserved grey matter in the posterior cingulate cortex, a core hub of this network. The associations were modest in size but comparable to those seen for established risk factors such as blood pressure and smoking. As the study was cross-sectional, it cannot establish cause and effect, but it raises the hypothesis that maintaining adequate Vitamin C status, obtained only through diet since humans cannot synthesise it, may support brain health in older age.

Source:

RESEARCH PAPER

Nagaya H, Watanabe K, Shintaku T, Sasaki M, Kudo J, Kasai S, et al. Plasma vitamin C levels are associated with brain structural networks on MRI: a large cohort study. PLoS One. 2026 Jun 10;21(6): e0348504. doi: 10.1371/journal.pone.0348504. PMID: 42268794.





Vegetarian Diets and Cancer: A Mixed Picture from 1.8 million People Worldwide (2026)

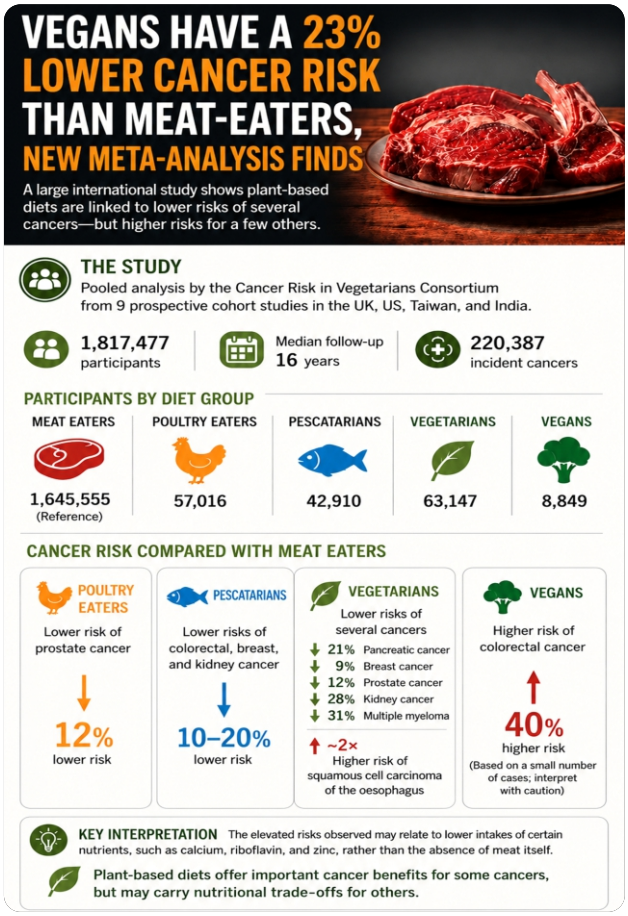
Does giving up meat actually lower your overall cancer risk, or is the answer more complicated than that?

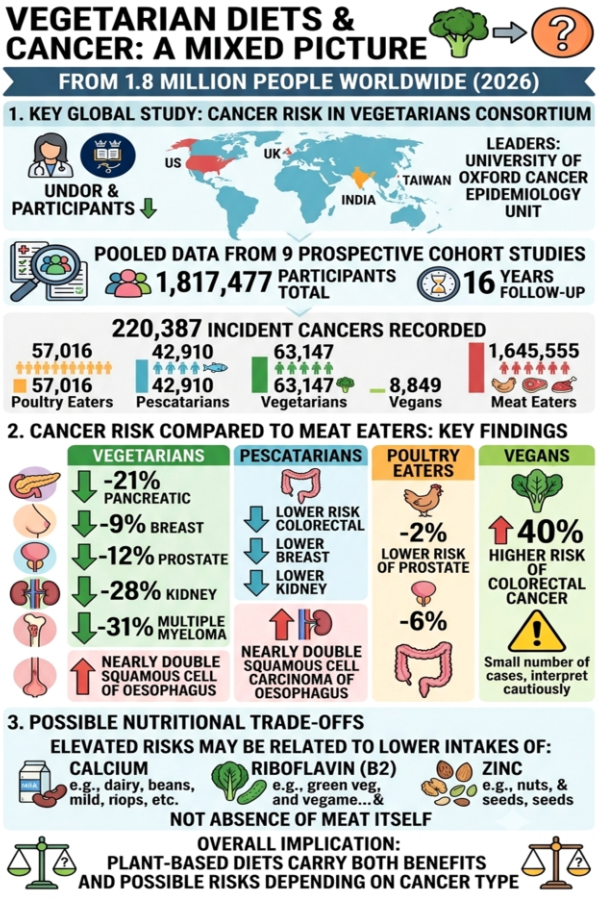
Researchers from the University of Oxford's Cancer Epidemiology Unit led the Cancer Risk in Vegetarians Consortium, pooling data from 1,817,477 participants across nine prospective cohort studies in the UK, US, Taiwan, and India. Over a median follow-up of 16 years, 220,387 incident cancers were recorded among 1,645,555 meat eaters, 57,016 poultry eaters, 42,910 pescatarians, 63,147 vegetarians, and 8,849 vegans. Compared with meat eaters, vegetarians had lower risks of pancreatic (21 per cent), breast (9 per cent), prostate (12 per cent), and kidney cancer (28 per cent), as well as multiple myeloma (31 per cent), but nearly double the risk of squamous cell carcinoma of the oesophagus. Pescatarians showed lower risks of colorectal, breast, and kidney cancer, while poultry eaters had a lower risk of prostate cancer. Vegans showed a 40 per cent higher risk of colorectal cancer, though this was based on a small number of cases and should be interpreted cautiously. The authors suggest the elevated risks observed may relate to lower intakes of certain nutrients, such as calcium, riboflavin, and zinc, rather than the absence of meat itself. These findings highlight that plant-based diets carry both benefits and possible nutritional trade-offs depending on cancer type.

Source:

COHORT STUDY

Dunneram Y, Lee JY, Watling CZ, Lawson I, Parsaeian M, Fraser GE, et al. Vegetarian diets and cancer risk: pooled analysis of 1.8 million women and men in nine prospective studies on three continents. Br J Cancer. 2026 Apr;134(8):1218-1229. doi: 10.1038/s41416-025-03327-4. Epub 2026 Feb 27. PMID: 41748939; PMCID: PMC13035945.





Grape Consumption Alters Skin Gene Activity Linked to UV Defence (2026)

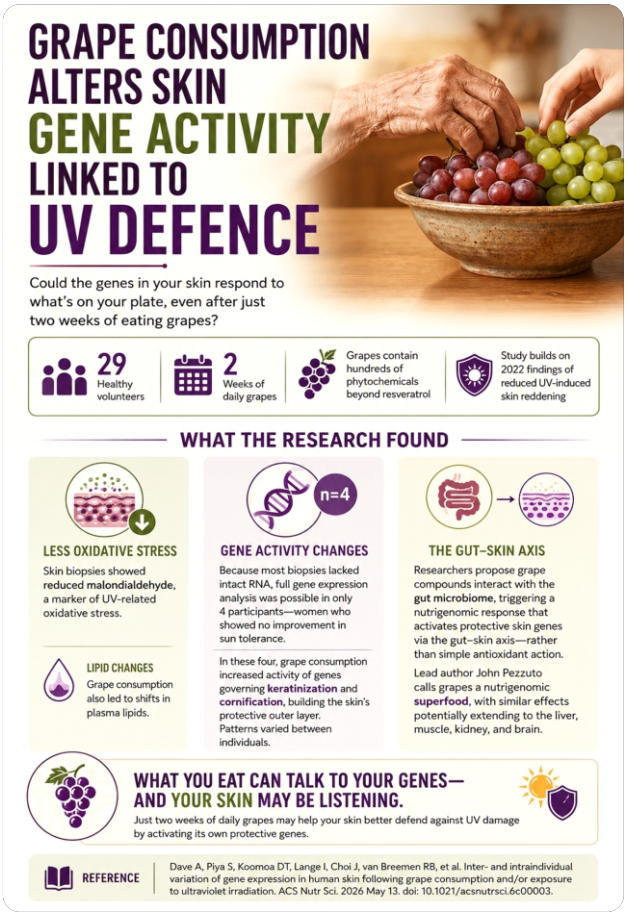
Could the genes in your skin respond to what's on your plate, even after just two weeks of eating grapes?

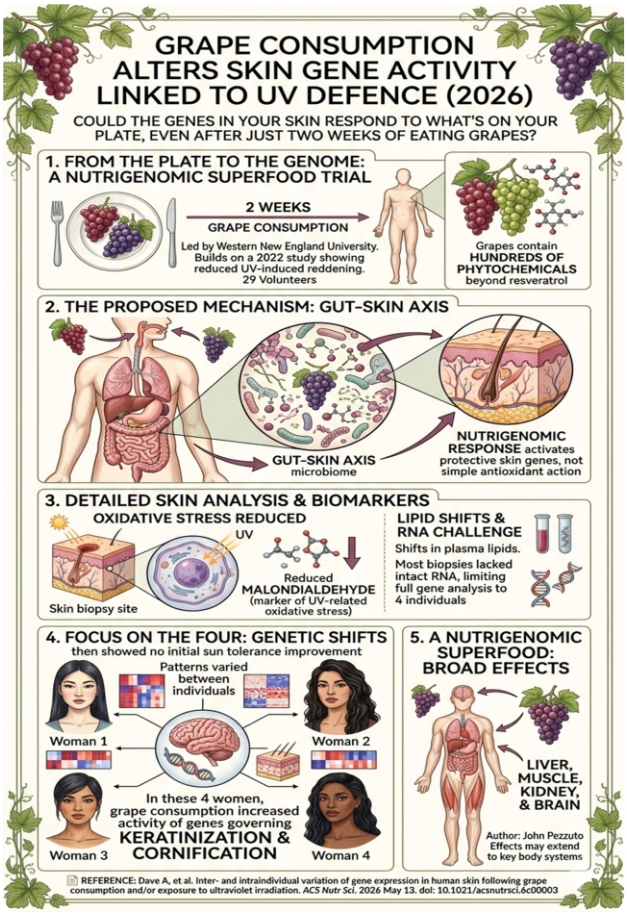
This trial, led by researchers at Western New England University, builds on a 2022 study by some of the same authors that first showed short-term grape consumption reduced UV-induced skin reddening in the same 29 volunteers, and examined whether grape consumption could also alter skin biology at the genetic level. Grapes contain hundreds of phytochemicals beyond the antioxidant resveratrol, present in only minuscule amounts and unlikely to act alone. The researchers propose that grape compounds interact with the gut microbiome, triggering a nutrigenomic response that activates protective skin genes via the gut-skin axis, rather than simple antioxidant action. Skin biopsies showed reduced malondialdehyde, a marker of UV-related oxidative stress, alongside shifts in plasma lipids. Because most biopsies lacked intact RNA, full gene expression analysis was possible in only four participants, women who had shown no improvement in sun tolerance on standard testing. In these four, grape consumption increased activity of genes governing keratinization and cornification, the processes building the skin's protective outer layer, though patterns varied between individuals. Lead author John Pezzuto has since called grapes a 'nutrigenomic superfood', suggesting similar effects extend to the liver, muscle, kidney, and brain.

Source:

RESEARCH PAPER

Dave A, Piya S, Koomoa DT, Lange I, Choi J, van Breemen RB, et al. Inter- and intraindividual variation of gene expression in human skin following grape consumption and/or exposure to ultraviolet irradiation. ACS Nutr Sci. 2026 May 13. doi: 10.1021/acsnutrsci.6c00003.





CDC's 24-Year Nutrition Biomarker Database Now Covers 131 Indicators (2026)

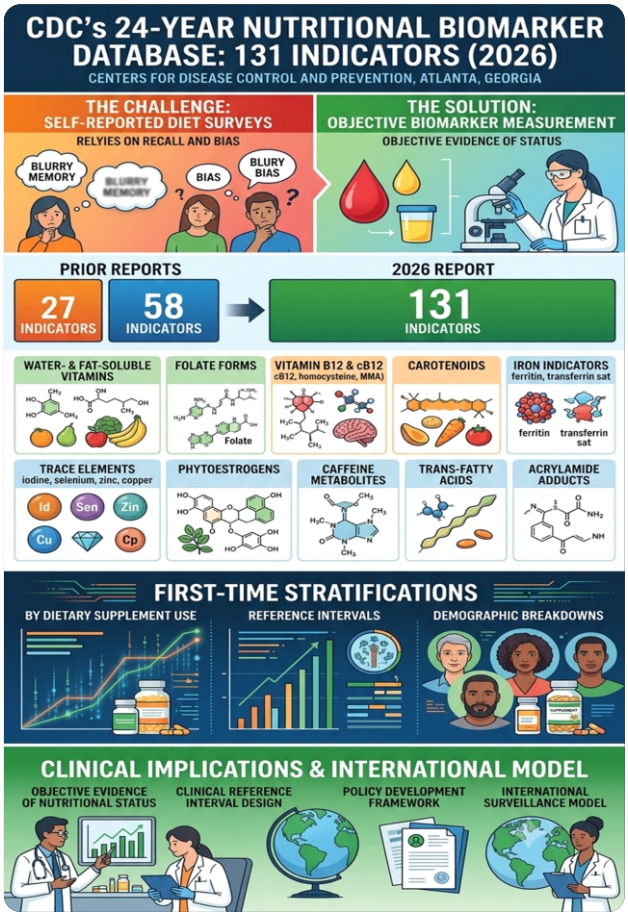
How healthy is the average American's diet, according to two decades of actual blood and urine testing rather than self-reported surveys?

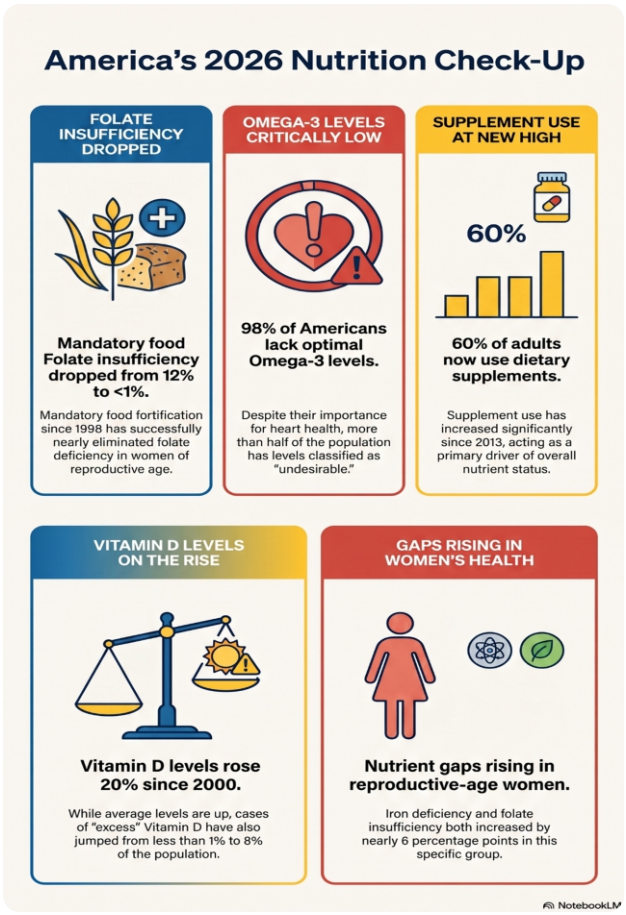
Researchers at the Centres for Disease Control and Prevention, Atlanta, Georgia, alongside collaborators from the Food and Drug Administration and National Institutes of Health, released an overview of the 2026 CDC Nutrition Report, drawing on data from the National Health and Nutrition Examination Survey (NHANES) collected between 1999 and August 2023 from a representative population aged one year and older. The report compiles laboratory-measured concentrations of 131 nutritional biomarkers, spanning water- and fat-soluble vitamins, folate forms, vitamin B12 and its combined indicator cB12, homocysteine, methylmalonic acid, carotenoids, iron indicators including ferritin and transferrin saturation, trace elements such as iodine, selenium, zinc and copper, phytoestrogens, caffeine metabolites, trans-fatty acids, and acrylamide adducts. This is a substantial expansion from earlier reports, which covered only 27 and 58 biomarkers respectively. For the first time, concentrations are stratified by dietary supplement use, alongside reference intervals and demographic breakdowns. Unlike dietary recall surveys, which rely on self-reported intake, biomarker measurement provides objective evidence of nutritional status, offering a model framework that nutrition surveillance systems in other countries can draw upon for policy development and clinical reference interval design.

Source:

OVERVIEW OF NUTRITION REPORT

Pfeiffer CM, Sternberg MR, Powers CD, Ogden CL, Jefferds MED, Crider KS, Juan W, Gahche JJ, Rybak ME, Fazili Z, Zhang M, Mineva EM, Vesper HW, Archibold E, Jarrett JM. Centres for Disease Control and Prevention's 2026 Nutrition Report presents data for 131 biomarkers from the cross-sectional National Health and Nutrition Examination Survey (NHANES 1999-August 2023). Curr Dev Nutr. 2026 Apr 8;10(5):107688. doi: 10.1016/j.cdnut.2026.107688. PMID: 42163864; PMCID: PMC13185974.





AI Foundation Model Turns One Night's Sleep Study into a Disease Risk Forecast (2026)

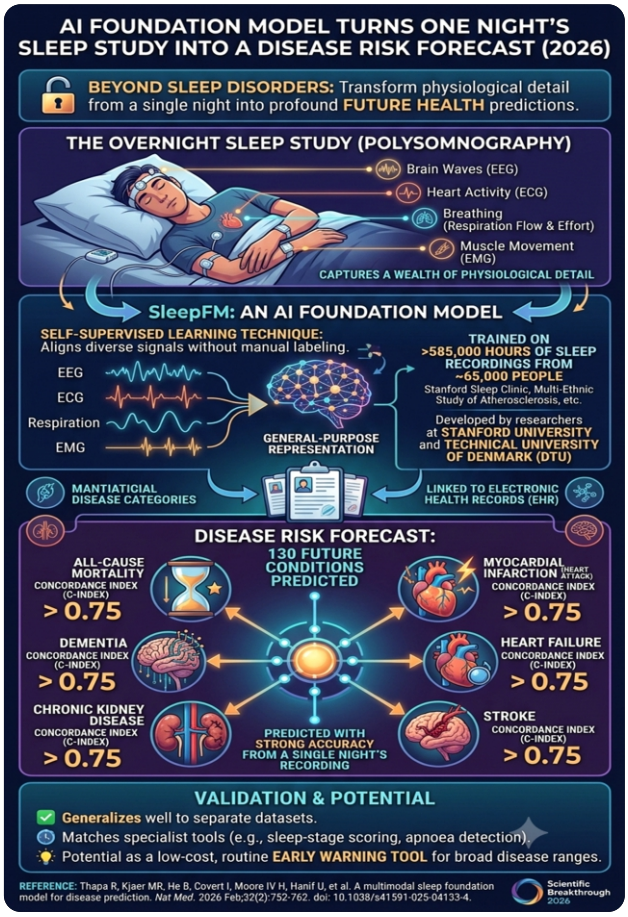
Could a single night of sleep monitoring flag your risk of dementia, heart failure, or stroke years in advance?

Polysomnography, the overnight sleep study that records brain waves, heart activity, breathing, and muscle movement, captures a wealth of physiological detail that is rarely used beyond diagnosing sleep disorders. Researchers at Stanford University and the Technical University of Denmark developed SleepFM (Sleep Foundation Model), an artificial intelligence foundation model trained on more than 585,000 hours of sleep recordings from around 65,000 people across four cohorts, including the Stanford Sleep Clinic and the Multi-Ethnic Study of Atherosclerosis. Using a self-supervised learning technique that aligns information across the different signal types, the model builds a general-purpose representation of a person's sleep without needing manually labelled data. When linked to electronic health records covering 1,041 disease categories, SleepFM predicted 130 future conditions with strong accuracy from a single night's recording, including all-cause mortality, dementia, myocardial infarction, heart failure, chronic kidney disease, and stroke, with concordance indices of 0.75 or higher. The model also generalised well to an entirely separate dataset excluded from its training, and matched specialist tools for standard tasks like sleep-stage scoring and apnoea detection. The authors note their sample was drawn from patients already referred for sleep studies, so results may not generalise to the wider population, but the findings suggest routine sleep recordings could become a low-cost early warning tool for a broad range of diseases.

Source:

RESEARCH PAPER

Thapa R, Kjaer MR, He B, Covert I, Moore IV H, Hanif U, et al. A multimodal sleep foundation model for disease prediction. Nat Med. 2026 Feb;32(2):752-762. doi: 10.1038/s41591-025-04133-4. Epub 2026 Jan 6. PMID: 41495409; PMCID: PMC12920147.



How Cells Keep Their Mitochondrial DNA Evenly Spaced (2026)

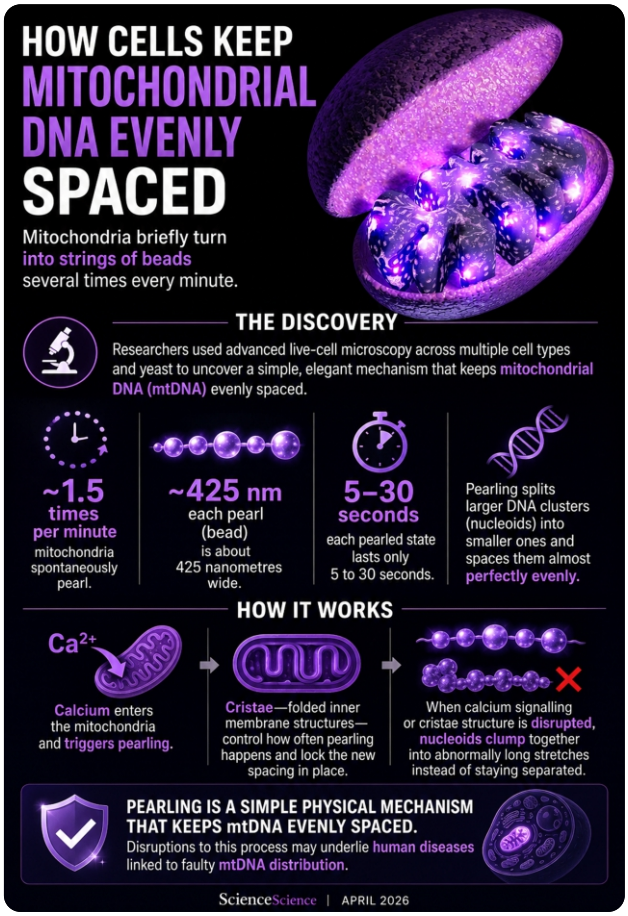
Why do your mitochondria briefly turn into strings of beads several times every minute?

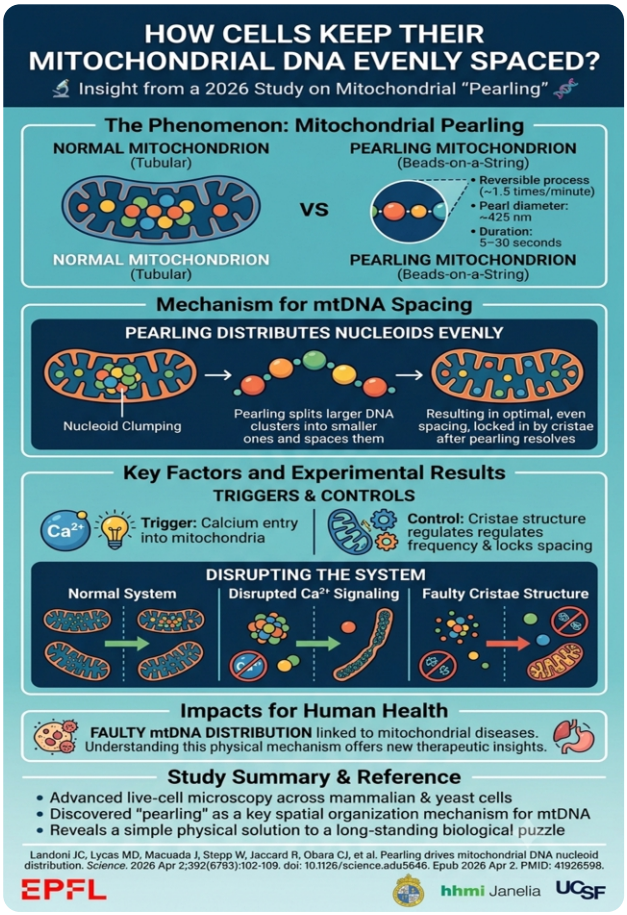
Researchers at EPFL in Switzerland, together with collaborators from Pontificia Universidad Católica de Chile, the Howard Hughes Medical Institute's Janelia Research Campus, and the University of California, San Francisco, used advanced live-cell microscopy across several mammalian cell types and yeast to study how mitochondrial DNA (mtDNA) stays evenly spaced inside mitochondria. They found that mitochondria spontaneously and reversibly "pearl," forming beads-on-a-string shapes roughly 1.5 times per minute, each pearl about 425 nanometres wide and lasting only 5 to 30 seconds. This pearling splits larger DNA clusters, called nucleoids, into smaller ones and spaces them almost perfectly evenly, matching the natural spacing seen between pearls themselves. Calcium entering the mitochondria triggers pearling, while folded inner membrane structures called cristae control how often it happens and lock the new spacing in place afterwards. When either calcium signalling or cristae structure was disrupted, nucleoids clumped together into abnormally long stretches instead of staying separated. The findings reveal a simple physical mechanism behind a long-standing puzzle in mitochondrial biology, with implications for human diseases linked to faulty mtDNA distribution.

Source:

RESEARCH PAPER

Landoni JC, Lycas MD, Macuada J, Stepp W, Jaccard R, Obara CJ, et al. Pearling drives mitochondrial DNA nucleoid distribution. Science. 2026 Apr 2;392(6793):102-109. doi: 10.1126/science.adu5646. Epub 2026 Apr 2. PMID: 41926598.





The Pathway to Genome Doubling Shapes the Cell Fate (2026)

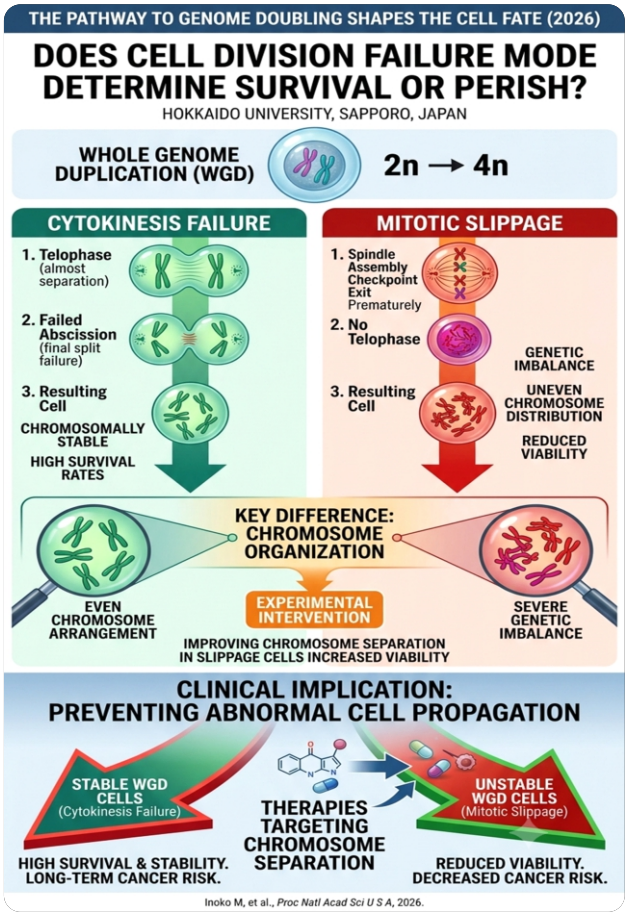
Does the way a cell fails to divide determine whether it will survive or perish?

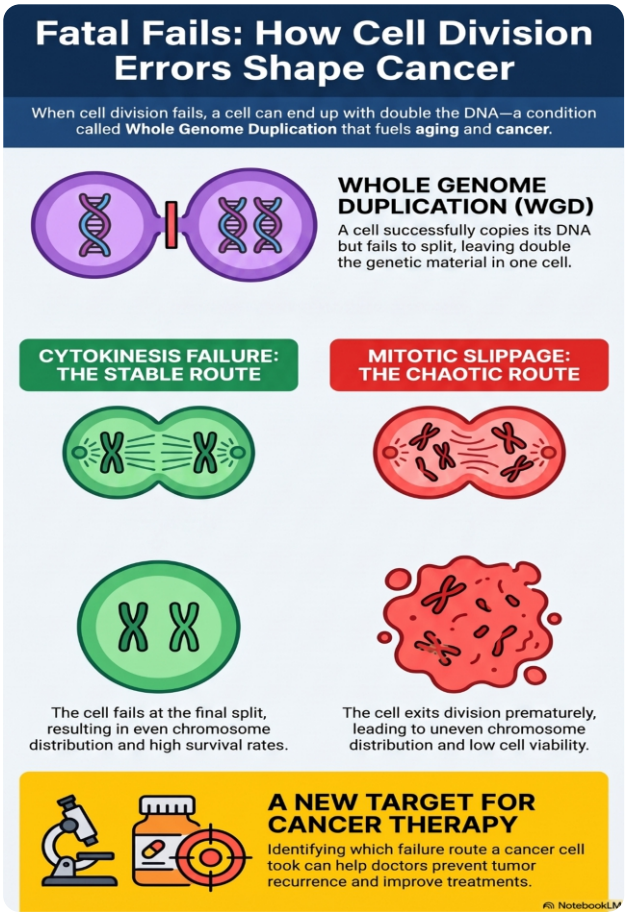
Researchers at Hokkaido University, Sapporo, Japan, investigated whole genome duplication (WGD), a condition in which cells successfully copy their DNA but fail to split into two, leaving them with twice the normal genetic material. The team compared two mechanisms by which this occurs: cytokinesis failure, where the cell completes division but fails at the final physical split, and mitotic slippage, where division begins but exits prematurely before chromosomes fully separate. Using live cell imaging and chromosome-specific labelling, they tracked cell behaviour following each type of failure. Cells produced through cytokinesis failure showed significantly higher survival rates and remained chromosomally stable, whilst those from mitotic slippage exhibited uneven chromosome distribution and reduced viability. Chromosome organisation emerged as the critical factor: mitotic slippage created severe genetic imbalance through unequal chromosome division, whereas cytokinesis failure maintained more balanced distribution. Experimentally improving chromosome separation in mitotic slippage cells substantially increased their viability. These findings suggest that the route to genome duplication influences long-term cell fate and carry implications for cancer prevention, as therapies targeting chromosome separation processes may prevent abnormal cells from surviving and propagating.

Source:

RESEARCH PAPER

Inoko M, Yang G, Tsukada Y, Uehara R. Sister chromatid separation determines the proliferative properties upon whole-genome duplication via homologous chromosome arrangement. Proc Natl Acad Sci U S A. 2026 Apr 21;123(16): e2524135123. doi: 10.1073/pnas.2524135123. Epub 2026 Apr 15. PMID: 41984834; PMCID: PMC13099657.





Tendons, Cartilage and Bone Renew Far More Slowly Than Muscle, and Two Weeks of Extra Protein Doesn't Speed This Up (2026)

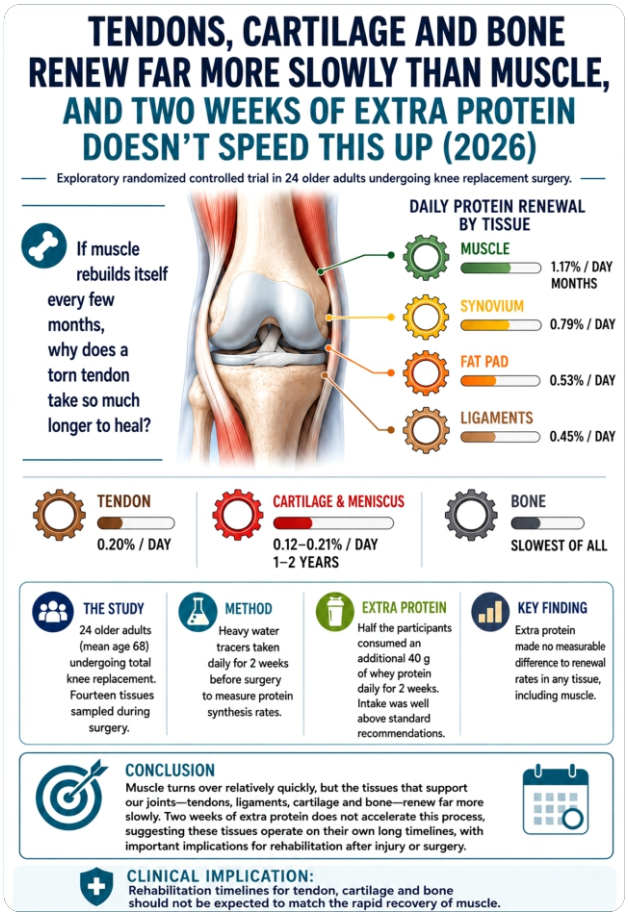
🦴 ***If muscle rebuilds itself every few months, why does a torn tendon take so much longer to heal?***

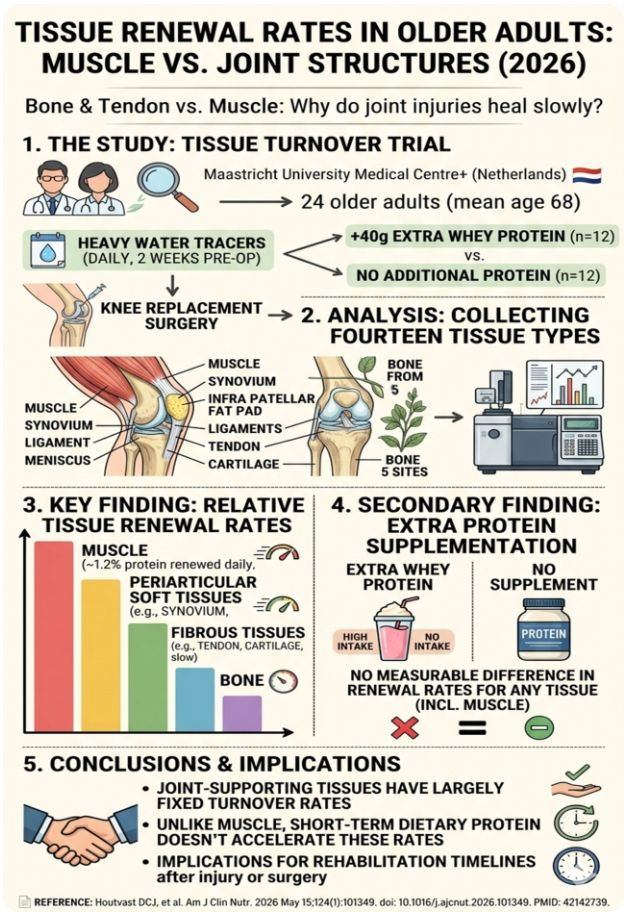
This trial, led by researchers at Maastricht University Medical Centre+ in the Netherlands, measured how quickly different tissues around the knee rebuild themselves in 24 older adults (mean age 68) scheduled for total knee replacement surgery. Using heavy water tracers taken daily for two weeks before surgery, the team tracked protein synthesis rates across fourteen tissue types collected during the operation, including muscle, synovium, ligaments, tendon, meniscus, cartilage and bone from five different sites. Muscle rebuilt fastest, at just over one percent of its protein renewed daily, followed by periarticular soft tissues such as synovium and the infrapatellar fat pad, then fibrous tissues including ligaments, tendon, meniscus and cartilage, with bone renewing slowest of all. Half the participants also drank an additional 40 grams of whey protein daily for the same two weeks, raising their protein intake well above standard recommendations. Despite this, supplementation made no measurable difference to renewal rates in any tissue, including muscle itself. The findings suggest that, unlike muscle, the turnover of joint-supporting tissues is largely fixed and not readily accelerated by short-term dietary protein, with implications for rehabilitation timelines after joint injury or surgery.

Source:

📄 RESEARCH PAPER

📌 Houtvast DCJ, Hendriks FK, Weijzen MEG, Zorenc AH, Smeets JSJ, Emans PJ, et al. Assessing the responsiveness of musculoskeletal tissues to protein supplementation in vivo in older adults: an exploratory randomized controlled trial. Am J Clin Nutr. 2026 May 15;124(1):101349. doi: 10.1016/j.ajcnut.2026.101349. Epub ahead of print. PMID: 42142739.





Wild Orangutans Pair Up Medicinal Plants in Their Diet (2026)

Could wild orangutans be choosing specific plant combinations on purpose, the way people reach for herbal remedies?

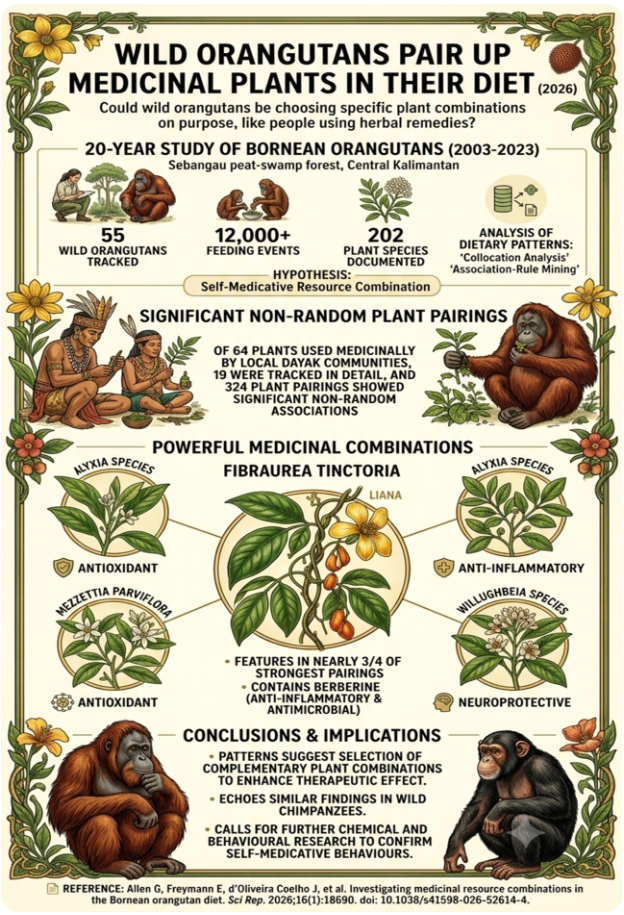
Researchers from the University of Exeter and the Borneo Nature Foundation, working with the University of Palangka Raya, analysed twenty years of feeding data (2003 to 2023) from 55 wild Bornean orangutans in the Sebangau peat-swamp forest, Central Kalimantan, comprising over 12,000 feeding events across 202 plant species. Using statistical techniques called collocation analysis and association-rule mining, the team tested whether orangutans combine specific plants with known medicinal properties more often than chance would predict, a concept known as the self-medicative resource combination hypothesis. Of 64 plants used medicinally by local Dayak communities, 19 were tracked in detail, and 324 plant pairings showed significant non-random associations. The species Fibraurea tinctoria, a liana containing the anti-inflammatory and antimicrobial compound berberine, featured in nearly three-quarters of the strongest pairings, often alongside Mezzettia parviflora, Alyxia species and Willughbeia species, each independently linked to antioxidant, anti-inflammatory or neuroprotective effects. Rather than proving conscious self-treatment, these patterns suggest orangutans may select complementary plant combinations that enhance therapeutic effect, echoing similar findings in wild chimpanzees. The authors call for further chemical and behavioural research to confirm these candidate self-medicative behaviours.

Source:

COHORT STUDY

Allen G, Freymann E, d'Oliveira Coelho J, Shagara H, Shinyo I, Panda A, Jaya A, Hockings KJ, Morrogh-Bernard HC. Investigating medicinal resource combinations in the Bornean orangutan diet. Sci Rep. 2026;16(1):18690. doi: 10.1038/s41598-026-52614-4.





When Modern Living Clashes with Ancient Biology: An Evolutionary Lens on Disease (2026)

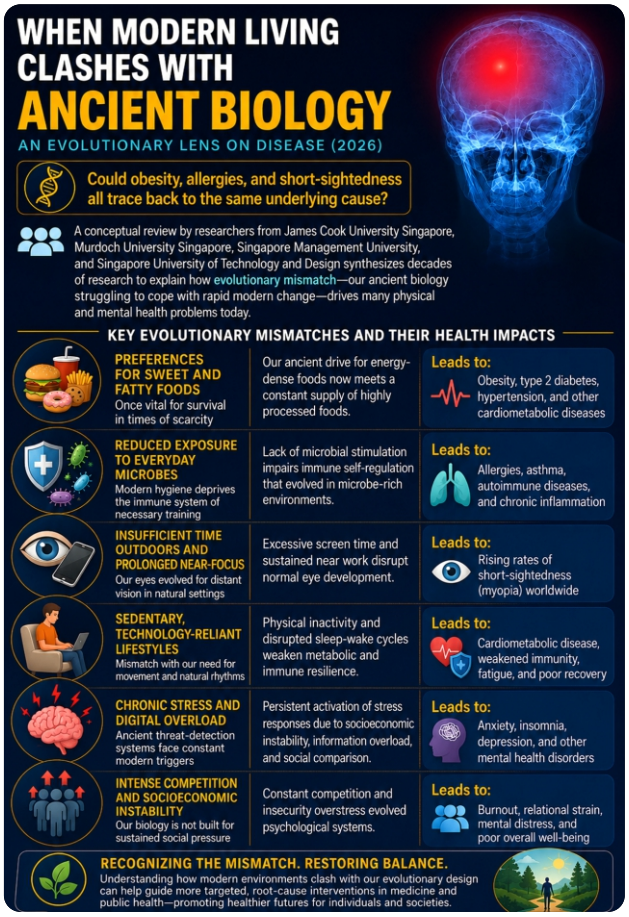
Could obesity, allergies, and short-sightedness all trace back to the same underlying cause?

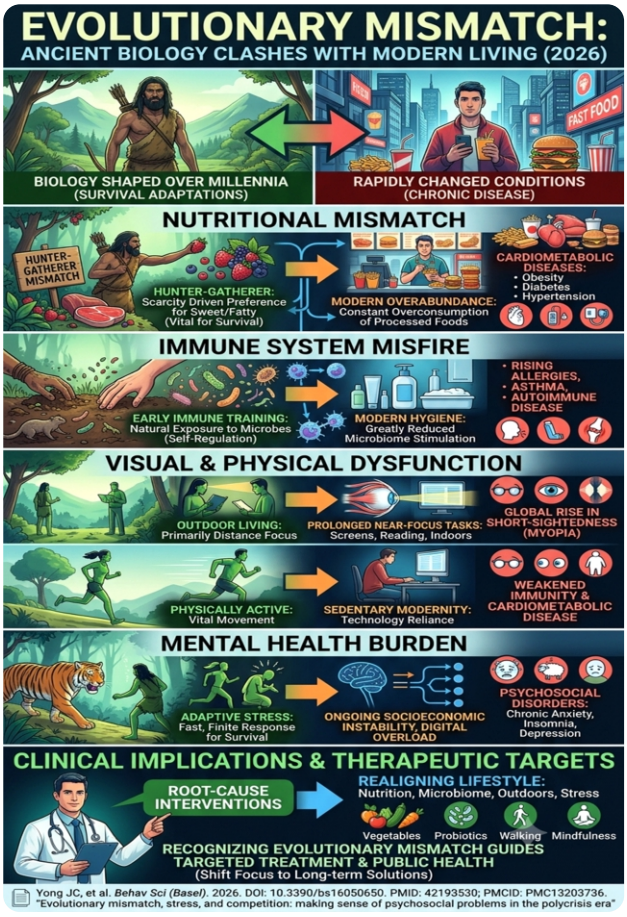
Researchers from James Cook University Singapore, Murdoch University Singapore, Singapore Management University, and the Singapore University of Technology and Design have proposed that many contemporary physical and mental health problems stem from evolutionary mismatch. Here, biology shaped over millennia of hunter-gatherer life struggles to cope with rapidly changed modern conditions. Their conceptual review synthesises decades of published research. It argues that the human preference for sweet and fatty tastes was once vital for survival amid scarcity. Now it drives overconsumption of processed foods. This contributes to obesity, diabetes, and hypertension when constantly satisfied. Greatly reduced exposure to everyday microbes, a consequence of modern hygiene practices, similarly deprives the immune system of stimulation it needs for proper self-regulation. This mechanism is implicated in rising rates of allergies, asthma, and autoimmune disease. The authors also link insufficient time outdoors and prolonged near-focus tasks, such as reading and screen use, to global increases in short-sightedness. They connect sedentary, technology-reliant lifestyles to cardiometabolic disease and weakened immune function. Beyond physical illness, the review associates chronic anxiety, insomnia, and depression with evolved stress and threat-detection systems being persistently activated by ongoing socioeconomic instability and digital overload. Recognising these mismatches, they argue, can guide more targeted, root-cause interventions in medicine and public health.

Source:

REVIEW

Yong JC, Lim AJ, Tan E, Chan SHM. Evolutionary mismatch, stress, and competition: making sense of psychosocial problems in the polycrisis era. Behav Sci (Basel). 2026 Apr 26;16(5):650. doi: 10.3390/bs16050650. PMID: 42193530; PMCID: PMC13203736.





How Leucine Keeps Mitochondria Running Strong (2025)

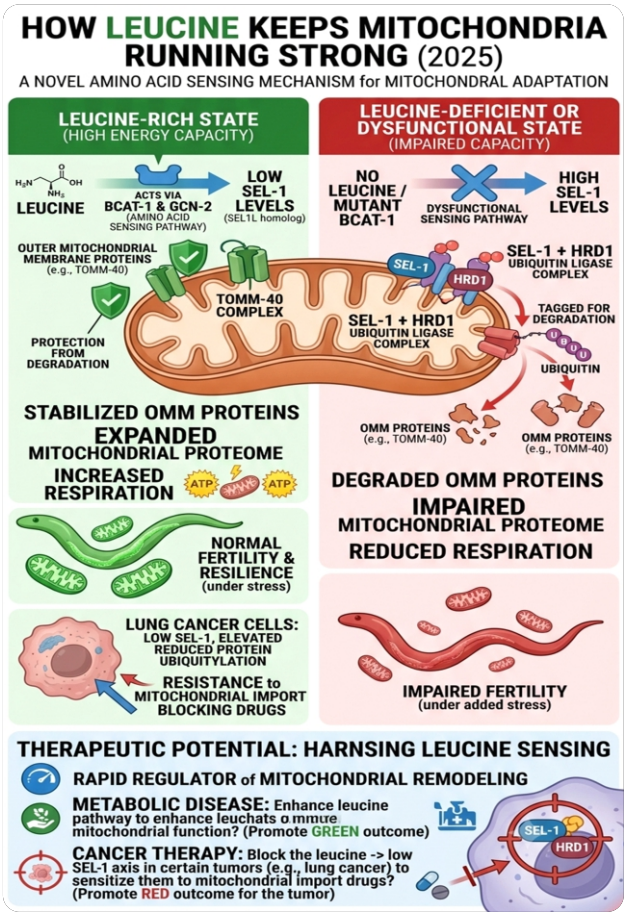
Could a single amino acid decide how much energy your mitochondria can produce?

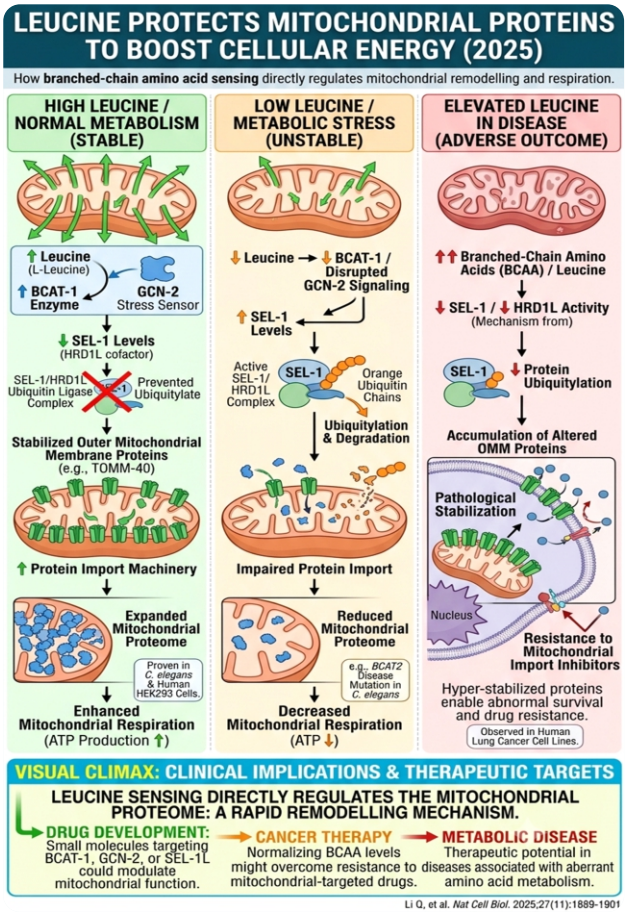
Researchers at the University of Cologne have discovered that leucine, one of the branched-chain amino acids, protects key proteins on the outer surface of mitochondria from being broken down, thereby boosting the cell's energy-generating capacity. Using a newly developed fluorescent reporter system in Caenorhabditis elegans, the team screened 135 amino acid metabolism genes and found that leucine acts through the enzyme BCAT-1 and the stress sensor GCN-2 to reduce degradation of outer mitochondrial membrane proteins. Mechanistically, high leucine levels lower mitochondrial levels of SEL-1 (the worm equivalent of human SEL1L), a cofactor of the HRD1 ubiquitin ligase complex, which normally tags these proteins for destruction. This stabilises components of the mitochondrial protein import machinery, such as TOMM-40, expanding the mitochondrial proteome and increasing respiration in both worms and human HEK293 cells. The effect proved biologically consequential: worms carrying a disease-associated BCAT2 mutation showed impaired fertility under added stress, while human lung cancer cell lines with naturally elevated branched-chain amino acid levels displayed reduced protein ubiquitylation and resistance to drugs blocking mitochondrial protein import. These findings position amino acid sensing as a direct, rapid regulator of mitochondrial remodelling, with potential relevance to metabolic disease and cancer therapy.

Source:

RESEARCH PAPER

Li Q, Weiss K, Niwa F, Riemer J, Hoppe T. Leucine inhibits degradation of outer mitochondrial membrane proteins to adapt mitochondrial respiration. Nat Cell Biol. 2025 Nov;27(11):1889-1901. doi: 10.1038/s41556-025-01799-3. Epub 2025 Oct 31. PMID: 41174002; PMCID: PMC12611767.





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The key aims of the journal are to provide authoritative interpretations of emerging developments in medical knowledge by trusted experts in their respective fields, and to assist practitioners in incorporating not only evidence-based findings but also new conceptual frameworks and ways of thinking into their clinical practice.

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All manuscripts submitted to PJMHS are initially subjected to in-house screening for scope, format, relevance, novelty, and originality. Manuscripts that fall beyond the scope of the journal, those not addressing a relatively novel research question, and those with gross methodological errors will be rejected without initiating the peer-review process; authors will be notified within 48 to 72 hours. Manuscripts with significant textual similarity are also rejected at this stage.

Manuscripts that pass the initial screening are subjected to a double-blind peer-review process. These are typically sent to two or three technical reviewers and one statistical expert, based on the nature of the study. Manuscripts are evaluated on the basis of originality, relevance, methodological rigour, scientific merit, ethical standards, and soundness of conclusions. Following peer review, accepted manuscripts will be edited for language and style in accordance with PJMHS guidelines.

Where an Editorial Board Member is listed as an author or has any competing interest regarding a specific manuscript, another member of the Editorial Board will be assigned to oversee that submission. All such manuscripts undergo the same review process as any other submission, irrespective of institutional affiliations.

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PJMHS publishes manuscripts based on quantitative, qualitative, or mixed-method investigation approaches in the following categories:

#	Manuscript Type	Word Limit*	Abstract	Notes
1	**Original Research Article**	Up to 3,000	Structured, 250 words	4-point structured abstract; IMRAD format
2	**Research Brief**	1,500 to 2,000	Structured, 150 words	Limited methodology/sample size; published as Original Article
3	**Review Article**	Up to 3,000	Unstructured, 250 words	Includes rapid, mapping, and scoping reviews; max. 100 references
4	**Systematic Review / Meta-analysis**	Up to 3,000	Structured, 250 words	IMRAD format; structured abstract with 5 sections
5	**Case Report**	Up to 2,000	Unstructured, 150 words	Must include patient consent; clear clinical learning points
6	**Health Technology Innovation**	1,500 to 2,000	Structured, 200-250 words	Rapid revision within 7 days; published online within 6 weeks
7	**Perspectives / Viewpoint / Commentary**	Up to 1,500	Unstructured, 150 words	Opinion pieces by experienced clinicians or public health experts

* *Word limits exclude Abstract and References.*

Specific Details for Each Manuscript Type

1. Original Research Articles

Original research articles should be up to 3,000 words (excluding Abstract and References) and include a structured abstract of no more than 250 words under four subheadings: (i) Background and Objectives, (ii) Methods, (iii) Results, and (iv) Interpretation and Conclusions, followed by 4 to 6 keywords arranged alphabetically. The main article must include sections in the following order: Introduction, Methods, Results, Discussion, Acknowledgements (if any), References, Tables, Legends to Figures, and Figures.

Ethical clearance from an Institutional Ethics Committee or Institutional Review Board (IRB) is mandatory for all studies involving human participants or animals, and must be mentioned in the Methods section. Registration of clinical trials is mandatory; the registration number or CTRI number must be stated.

2. Research Briefs

Original research manuscripts with a well-defined study design and sample size, or submissions with preliminary investigative data with limited methodology but important clinical implications, may be submitted as Research Briefs. These should be between 1,500 and 2,000 words and contain a 4-point structured abstract of no more than 150 words, consistent with the format for Original Articles. A Research Brief may include one or two Tables or Figures. Research Briefs will be published under the category of Original Articles.

3. Review Articles

Various types of review articles are published in PJMHS, including but not limited to rapid, mapping, and scoping reviews. Review articles written by scientists or experts who have published quality original research in the relevant area will be considered. The article should be up to 3,000 words (excluding Abstract and References), with no more than 100 recent and relevant references, a clear description of the search strategy employed, and an unstructured abstract of approximately 250 words. Tables and Figures may be included as required. Copyright permission must be obtained from the copyright holder in advance if a published Table or Figure is reproduced in part or in whole.

4. Systematic Reviews (Including Meta-analysis)

Systematic reviews and meta-analyses should be critical appraisals of studies on important topics of clinical or public health significance, aimed at obtaining an unbiased quantitative estimate of the overall effect of an intervention or variable for a defined outcome. These should be written in the IMRAD format, with a maximum of 3,000 words and a minimum number of Tables and Figures. A structured abstract of 250 words is required, including the following sections: Context (clinical question and its significance), Objective, Evidence Acquisition (data sources, search strategies, years searched), Results (major findings with emphasis on the highest quality evidence), and Conclusions.

5. Case Reports

Case reports should present clinically significant or unusual cases with clear educational value. Manuscripts should be up to 2,000 words with an unstructured abstract of no more than 150 words. Written informed consent from the patient (or guardian) must be obtained and confirmed in the manuscript. Patient identifiers must not appear anywhere in the text or illustrative material.

6. Health Technology Innovations

Articles under this category should present research evaluating innovative, indigenous, low-cost health technologies with clinical validation that are seeking regulatory approval or are being recommended for adoption by national health programmes. Manuscripts found suitable by the Editors will undergo peer review and rapid revision by the authors within seven days. Accepted manuscripts will be published online within six weeks of submission.

These manuscripts should be between 1,500 and 2,000 words (excluding Title, Abstract, and References) and contain a 4-point structured abstract of 200 to 250 words, a combined Results and Discussion section not exceeding 500 words, a maximum of 25 references, and one Figure or one to two Tables. Preference will be given to work completed within six months of manuscript submission.

7. Perspectives / Viewpoint / Commentary

Articles under this category should address current, controversial, and challenging topics in healthcare, including intersections between medicine and society. These are primarily opinion pieces written by senior scientists, public health experts, or policymakers with substantial credible experience on the subject. Such papers will generally be authored by a single contributor, should not exceed 1,500 words, and must include an unstructured abstract of approximately 150 words. All submissions under this category are subject to peer review. Views must be supported by evidence and references.

Preparation of Manuscript

Submitted manuscripts must represent original work that has not been previously published and is not under consideration for publication elsewhere in any form, including as an abstract or as part of another article. All source material must be fully acknowledged and appropriately referenced.

As part of its commitment to research integrity, PJMHS screens all accepted manuscripts for plagiarism using Turnitin software. Plagiarism, including duplicate publication of the author's own work in whole or in part without proper citation, will not be accepted under any circumstances.

General Formatting

Manuscripts must be typed in portrait layout, with 1.5 line spacing, 2.5 cm (approximately 1 inch) margins on all sides, 12-point Times New Roman font, and justified alignment. Pages must be numbered at the bottom centre. British (UK) English must be used throughout.

All abbreviations used in the text must be expanded upon first use, with the acronym in parentheses, in the title, abstract, and main text separately, unless the abbreviation is a standard unit of measurement. The use of acronyms and abbreviations should be kept to a minimum.

Non-proprietary names of drugs, devices, and other products should be used. Where proprietary names are provided, only the first letter should be capitalised, followed by the name of the manufacturer in parentheses. Superscript symbols such as ©, TM, or ® should not be used.

Manuscript Order

Authors must prepare their manuscripts in the following order:

Cover Page / First Page File

The cover page must be submitted as a separate file and should include a covering letter, the title page, and the authors' contributions statement.

The covering letter should explain why the manuscript is appropriate for publication in PJMHS. One author should be identified as the corresponding author, who will be responsible for the contents of the paper and for all communication with the Editorial Office. The covering letter must include a declaration that the article has not been published previously and is not under consideration elsewhere, in part or in whole.

Title Page

The title page must include the following:

- Full title of the article: concise and informative; the study type may be added after a colon
- Running title of no more than 40 characters
- Full names (first name and surname), highest academic degrees, and designations of all authors at the time of the work
- Mobile numbers, email addresses, and ORCID numbers (if available) of all authors
- Department(s) and institution(s) to which the work should be attributed, reflecting affiliation at the time of the study
- Full name, postal address, telephone number, and email address of the corresponding author
- Contributors' credits (specifying each author's role)
- Declaration of competing interests

- Funding: all sources of financial or material support, including grant numbers and funding agencies
- Ethical clearance status, including the name of the Ethics Committee, date, and reference number of clearance
- Clinical trial registration number (for clinical trials)
- Data sharing statement (for all original research)
- Declaration of Artificial Intelligence (AI) tool use in scientific writing
- Word count (excluding Abstract, Tables, Figures, Acknowledgements, and References)
- Number of Tables and number of Figures
- Disclaimers, if any

Competing Interests: Authors must disclose any ties that could influence their judgement, including financial relationships with industry such as employment, consultancies, stock ownership, honoraria, grants, or expert testimony, whether directly or through immediate family members. If an Editorial Board Member has a conflict of interest with any manuscript, this must be communicated to the Editor so that the manuscript can be handled appropriately.

Funding: Authors must disclose all sources of financial and material support for the research, including grant numbers and funding agencies.

Structured Abstract

Since abstracts are often the only substantive portion of an article indexed in electronic databases, authors must ensure that the abstract accurately reflects the content of the manuscript. All Original Research Articles and Research Briefs must have a 4-point structured abstract as specified above. The abstract should be brief, indicate the scope and significant results of the study, and highlight only the principal findings and conclusions. Conclusions and recommendations not found in the main text must not be inserted in the Abstract.

Keywords

A set of 4 to 6 keywords should be provided in alphabetical order below the abstract to facilitate indexing. Terms from the Medical Subject Headings (MeSH) list of the National Library of Medicine should preferably be used. Keywords must not repeat words already included in the title.

Introduction

The Introduction should be brief and include: what is known; what is not yet known (the gap in knowledge); and what is proposed to be done (the aim or objectives). The review of literature should be restricted to reasons for undertaking the present study and provide only the most essential background. The objective of the study must be stated clearly with adequate justification at the end of this section.

Methods

The Methods section should describe the study's design, execution, and data analysis in a logical sequence. It should include, where applicable: study setting, study duration, study population, study design, participant selection (including eligibility and exclusion criteria), outcome variables, sample size calculation, intervention and follow-up, statistical analysis, and ethical considerations.

For standard methods, a reference suffices unless modifications have been made, in which case these must be described in full. Complete details must be provided for any new methods or apparatus. Clinical trials must include a CONSORT flow diagram showing patient progress throughout the trial.

Statistical Analysis: The statistical methods and the significance of findings should be clearly stated. P values should be expressed to three decimal places. Standard and routine statistical methods require only authentic references; detailed descriptions are needed only when new or uncommon methods are employed.

Ethics: For studies involving human participants, the procedures must conform to the ethical standards of the relevant national bodies. For research conducted in India on human participants, the ICMR Ethical Guidelines for Biomedical and Health Research on Human Participants (2017) must be adhered to. For experiments on laboratory animals, the applicable guidelines include ICMR's Use of Animals in Scientific Research (2006), INSA's Guidelines for Care and Use of Animals in Scientific Research (2000), and the guidelines of the Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA). All research must also comply with the Helsinki Declaration of 1964, as revised in 2013. All research studies must have written ethical clearance from an Institutional Ethics Committee, stated in the manuscript with the committee's name, date, and reference number on the title page, and a statement of ethical clearance in the Methods section.

Obtain written informed consent from all human participants. For children over six years of age in clinical studies, assent must also be obtained. Patient names, initials, or hospital numbers must not appear in the manuscript or illustrative material.

Results

Only data essential for understanding the discussion and main conclusions should be included. Data should be arranged in a unified and coherent sequence. Data presented in Tables and Figures must not be repeated in the text. The same data must not be presented in both tabular and graphic form. Interpretation of data must be reserved for the Discussion section.

Numeric results should be reported not only as derivatives (such as percentages) but also as the absolute numbers from which they are derived. Units of measurement: Length, height, weight, and volume should be reported in metric units. Laboratory values should be reported using the International System of Units (SI). Blood pressure should be reported in millimetres of mercury (mmHg); temperatures in degrees Celsius.

Discussion

The Discussion should interpret the results without repeating information already presented in the Results section. It should relate new findings to existing knowledge and include logical deductions. This section should generally not exceed one-quarter of the manuscript's total length, and should include the following elements in order: (i) a summary of the major findings; (ii) an evaluation of the study's limitations and strengths; (iii) a comparison with similar published studies; and (iv) the generalisability of the findings and their implications for practice, policy, or future research. This section should end with a clear concluding remark.

Declaration of AI Tool Use

In accordance with the updated ICMJE guidelines (2023), authors are required to declare any use of artificial intelligence (AI) or AI-assisted writing tools in the preparation of their manuscript. This declaration must appear in either the Methods section or the Acknowledgements section and must clearly specify the tool used and the nature of its application. AI tools may not be listed as authors or co-authors. Where no AI tools have been used, authors must include a statement to this effect.

Acknowledgements

Authors may acknowledge funding sources, institutional support, and contributions of individuals who do not qualify for authorship.

References

Authors should provide direct references to original research sources wherever possible. References should be made to published articles rather than abstracts. Authors should avoid citing articles published in predatory or pseudo-journals. Information from manuscripts submitted but not yet accepted should be cited in text as 'unpublished observations' with written permission from the source. A 'personal communication' may be cited only when it provides information not publicly available, in which case the name of the person and the date of communication should be noted in parentheses in the text, with written permission and confirmation of accuracy from the source.

References must be listed in numerical sequence according to their order of appearance in the text. References should be identified in the text, tables, and figure captions by Arabic numerals as superscripts. Abstracts should not be used as references. The journal follows Vancouver referencing style. If a paper has more than six authors, list the first three followed by 'et al.' Use abbreviated journal titles as listed in Index Medicus. All hyperlinks must be removed from references.

Examples:

Journals:

Candis JH. Artificial joint materials. J Biomed Eng. 1994;45:54-78.

Pail KN, Smith ADF, Manners M, et al. Coagulation mechanisms. J Cell Biol. 1993;430:200-30.

Books:

Acorn AD. Management of rheumatoid arthritis. In: Brown CC, Davies GH, editors. Inflammatory diseases. 3rd ed. London: Apple; 1992. p. 203-30.

Dunlop E, David BC, Winston WDC, editors. Diabetes update. New York: Pullworth; 1983.

Electronic Source (Website or Online Journal Article):

Public Health Laboratory Service. Antimicrobial resistance in 2000: England and Wales [Internet]. [cited 2004 Jan 7]. Available from: http://www.hpa.org.uk/infections/topics_az/antimicrobial_resistance/amr.pdf

Abbreviations and Units

Only standard abbreviations should be used. SI (International System of Units) units must be used for laboratory values throughout the manuscript. For clinical measurements, conventional metric units are preferred. Length, area, mass, and volume should be expressed in metric units. Abbreviations should follow SI conventions throughout the text, tables, and figures.

Year, month, week, day, hour, minute, and second should be abbreviated as y, mo, wk, d, h, min, and s respectively in tables and figures, but should be written out in full in the body text.

Tables

Tables must be included in the main manuscript file in Microsoft Word format and numbered consecutively with Arabic numerals (Table 1, Table 2, etc.). A descriptive heading must be placed above each table. Each column must be given a short heading; units of measurement should be abbreviated and

placed below the column heading. Tables should ideally have between three and five columns and between four and sixteen rows.

All non-standard abbreviations used within a table must be explained in footnotes. Statistical measures of variation such as SD and SE must be identified. Use footnote symbols (*, †, ‡, §) where needed. In the text, tables should be referenced as Table 1, Table 2, and so on, and must not be referred to as 'above table' or 'below table'. Each table must be cited in the text.

Figures and Illustrations

The use of figures is strongly encouraged where they assist reader comprehension and can replace lengthy textual descriptions. Figures must be numbered consecutively in Arabic numerals (1, 2, 3) according to the order in which they are first cited in the text. Where figures are related, they should be numbered 1(a), 1(b), 1(c), and so on.

All images must be submitted in JPEG or TIFF format with a maximum file size of 20 MB. Labels, numbers, and symbols should be clear and of uniform size, legible after reduction to the width of a printed column. Titles and detailed explanations belong in the figure legends, not on the figure itself. Photographs must be of sufficiently high resolution with respect to detail, contrast, and grain, and must be trimmed to remove all unwanted areas.

If photographs of individuals are used, written permission to use the photograph must be provided and the eyes must be covered. Patient names and medical record numbers must be removed. If a figure has been published elsewhere, the original source must be acknowledged and written permission from the copyright holder submitted to reproduce the material. Electronic manipulation of images that materially alters the medical information must be identified and the nature of the alterations described.

Figures should be sent as separate files. For charts and graphs, authors should prepare these in Microsoft Word and not paste from programmes such as PowerPoint or SPSS. Editable files of figures should be provided as supplementary material. Authors' names and affiliations must not appear anywhere on image files.

Figure Captions

Captions should provide a brief description of each figure or illustration. For example: Fig. 1. The diagram shows the distribution of... Where relevant, captions must include definitions for all symbols used.

Photographs

Photographs submitted must be of sufficiently high resolution and quality with respect to detail, contrast, and grain. Use portrait format for photos intended to fit a single column. Patient identifiers must be removed from all photographic material.

Formatting Guidelines

All manuscripts must conform to the following formatting specifications:

File Format	Microsoft Word (.doc or .docx)
Font	Times New Roman
Font Size	Title: 16pt, Bold. Section Headings: 14pt, Bold. Body Text: 12pt.
Line Spacing	1.5
Margins	2.5 cm (approximately 1 inch) on all sides
Layout	Portrait, single column, justified alignment
Language	British (UK) English
Page Numbering	Arabic numerals, bottom-centre alignment
Title Page	Separate file. Must contain: title, author names (with degrees and ORCID if available), designations, institutional affiliation, email address, phone number, and postal address. Authors must not include their name or affiliation anywhere in the main manuscript.
Abstract	Structured (4-point) for Original Articles and Research Briefs; unstructured for Reviews and Commentaries. Maximum as specified per manuscript type.
Keywords	4 to 6, in alphabetical order, from MeSH list where possible
Full Length Paper	Up to 3,000 words for Original Articles, Reviews, and Systematic Reviews (excluding Abstract and References); as specified for other types
Tables and Figures	Each must have its own heading and source. Cited in text as Table 1, Table 2, etc.
References Style	Vancouver (numbered, superscript); abbreviated journal titles per Index Medicus

Submission of Manuscript

Manuscripts must be submitted in Microsoft Word format by email to:

info@medicaladvances.ac.in

All submissions must be accompanied by a cover letter stating the full names of the authors, correspondence address, email address, and contact numbers. As the journal follows a double-blind peer-review process, the identity of the authors must not appear anywhere within the main manuscript document. The editorial team will remove author details before sending the manuscript to referees.

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Pacific Journal of Medical and Health Sciences does not levy any charges on authors. There are no submission fees, article processing charges, editorial processing charges, language editing fees, colour charges, page charges, membership fees, or any other supplementary charges. Publication in this journal is entirely free of cost for authors.

Editorial Independence and Endogeny Policy

Pacific Journal of Medical and Health Sciences is committed to maintaining editorial independence and a broad, diverse authorship base. Manuscripts submitted by authors affiliated with Pacific Medical University are subject to the same rigorous double-blind peer-review process as all other submissions and receive no preferential treatment. The proportion of articles authored by individuals affiliated with the journal or its publisher shall not exceed 20% of the total articles published in any single issue.

Plagiarism Policy

All accepted manuscripts are screened for plagiarism using Turnitin software. Only manuscripts with an acceptable similarity index will be considered for publication. Plagiarism in any form, including self-plagiarism and duplicate submission, will result in immediate rejection.

Pacific Journal of Medical and Health Sciences

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Chief Editor: Dr. S.K. Verma, Professor Emeritus (General Medicine) | Editor: Ravindra Bangar

Peer-Review Policy

Pacific Journal of Medical and Health Sciences

ISSN: 2456-7450 (Print) | ISSN: 3139-6895 (Online) | Quarterly | International | Peer-Reviewed

Overview

Peer review is the primary mechanism by which Pacific Journal of Medical and Health Sciences assesses the quality, originality and scientific rigour of submitted manuscripts prior to publication. In this process, independent researchers with relevant expertise evaluate submitted manuscripts and provide informed assessments to assist the editorial team in making publication decisions.

The journal operates a double-blind peer-review system, in which the identities of both the authors and the reviewers remain confidential throughout the review process. This approach ensures objectivity, impartiality and integrity at every stage of manuscript evaluation.

All peer reviewers are independent of and external to the journal. Reviewers are selected exclusively from outside the Editorial Board and the institution of Pacific Medical University, unless no suitably qualified external reviewer is available, in which case any exception will be clearly documented.

Purpose of Peer Review

Pacific Journal of Medical and Health Sciences regards peer review as the cornerstone of its commitment to publishing research of the highest scientific merit. Given the journal's focus on medical and health sciences, where the quality and accuracy of published findings may directly influence clinical practice and patient outcomes, the integrity of the review process is of paramount importance. Peer review serves the following specific purposes in the context of this journal:

- Quality Assurance: The peer-review process enables the editorial team of Pacific Journal of Medical and Health Sciences to ensure that only scientifically sound, methodologically rigorous and clinically relevant research is accepted for publication. This safeguards the journal's reputation and the trust of its international readership.
- Editorial Independence and Objectivity: All manuscripts submitted to the journal are evaluated by independent reviewers who have no affiliation with the authors or their institutions. This independence ensures that publication decisions are based solely on scientific merit, free from institutional, personal or commercial influence.
- Strengthening Research Quality: Constructive reviewer feedback helps authors refine their methodology, sharpen their conclusions and improve the overall presentation of their work. This collaborative process raises the standard of research disseminated through the journal and ultimately contributes to the advancement of medical knowledge.

Initial Editorial Assessment

All manuscripts submitted to Pacific Journal of Medical and Health Sciences are first assessed by the editorial team. During this initial review, the manuscript is evaluated on the following criteria:

- Relevance to the aims and scope of the journal
- Scientific quality and methodological soundness
- Originality and contribution to the relevant field of knowledge
- Adherence to the journal's formatting and submission guidelines

Manuscripts that do not meet these criteria may be returned to the authors with recommendations for revision or may be rejected without being sent for external peer review. Only manuscripts that pass this initial assessment are forwarded to independent expert reviewers.

External Peer Review

Manuscripts that successfully pass the initial editorial assessment are sent to a minimum of two independent expert reviewers in the relevant subject area. Reviewers are selected on the basis of their expertise, academic standing and absence of conflict of interest with the authors or their institution.

Reviewers are requested to evaluate the manuscript in a prescribed format and to provide a structured assessment that includes:

- An evaluation of the scientific quality and validity of the work
- An assessment of the originality and significance of the findings
- Identification of any weaknesses, inconsistencies or areas requiring clarification
- Specific suggestions for improvement
- A clear recommendation regarding publication

Reviewer recommendations typically fall into one of the following categories: Accept as submitted; Accept with minor revisions; Major revision required; Reject. The editorial team reviews these recommendations in the context of the journal's scope and standards before arriving at a final editorial decision.

Role of the Editor

The role of the reviewers is advisory in nature. The editor is not formally bound to accept the opinions of the reviewers and retains the authority to make the final publication decision. In all cases, the editor's decision is guided by the best interests of scientific integrity and the standards of the journal.

Reviewers do not communicate with one another, do not function as a group, and are not made aware of each other's identities or comments at any stage of the review process. This ensures the independence and confidentiality of each reviewer's assessment.

Handling Divergent Reviewer Opinions

In cases where two reviewers offer substantially divergent assessments of the same manuscript, the editor may adopt one or more of the following approaches:

- Invite one or more additional reviewers to provide an independent assessment
- Exercise editorial judgement on the basis of the available reviewer comments and the journal's scope and standards
- Consult members of the Editorial Board for guidance

In all instances, the editor's decision will be communicated to the authors in a clear, reasoned and timely manner.

Editorial Board Involvement

In circumstances where the editorial team is unable to identify a sufficient number of qualified external peer reviewers within a reasonable timeframe, members of the Editorial Board may be invited to serve as reviewers. This measure is adopted solely to prevent undue delays in the review process and to maintain the quality and timeliness of manuscript assessments.

Review Timeframe

In the interest of transparency and timely communication with authors, the following review timeframe applies:

- Authors will receive an acknowledgement of receipt of their manuscript within 5 working days of submission.
- The peer-review process, from assignment of reviewers to communication of the editorial decision, is completed within 30 to 45 days of submission.
- Authors will be notified of the editorial decision along with reviewer comments within this timeframe.
- In exceptional circumstances where additional time is required, authors will be informed of the delay and provided with a revised estimated timeline.

The journal is committed to maintaining this timeframe as a standard of service to authors and to the wider research community.

Confidentiality

All submitted manuscripts are treated as confidential documents throughout the review process. Reviewers are required to maintain strict confidentiality and must not share, discuss or disclose any aspect of a manuscript under review without the explicit permission of the editor. Any reviewer who suspects a conflict of interest is required to notify the editorial office and decline the review assignment.

Pacific Journal of Medical and Health Sciences

Pacific Medical University, Bhilo Ka Bedla, NH-27, Pratappura, Amberi, Udaipur 313 011, Rajasthan, India
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Chief Editor: Dr. S.K. Verma, Professor Emeritus (General Medicine) | Editor: Ravindra Bangar

Reviewers' Guidelines

Pacific Journal of Medical and Health Sciences

ISSN: 2456-7450 (Print) | ISSN: 3139-6895 (Online) | Quarterly | International | Peer-Reviewed

Overview

Pacific Journal of Medical and Health Sciences values the essential contribution that peer reviewers make to the integrity and quality of academic publishing. Reviewers are invited on the basis of their subject expertise, academic standing and freedom from conflicts of interest. The journal is committed to ensuring that the peer-review process is rigorous, fair, timely and conducted in accordance with the highest ethical standards.

These guidelines are intended to assist reviewers in understanding their responsibilities and in producing reviewer reports that are constructive, objective and beneficial to authors and the editorial process alike.

Type of Peer Review

Pacific Journal of Medical and Health Sciences operates a double-blind peer-review system. Under this system, the identities of both the authors and the reviewers remain confidential throughout the entire review process. Reviewers must not attempt to identify the authors of a manuscript and must notify the editorial office immediately if they become aware of the authors' identity during the review.

All peer reviewers are independent of and external to the journal. Reviewers are selected exclusively from outside the Editorial Board and the institution of Pacific Medical University, unless no suitably qualified external reviewer is available, in which case any exception will be clearly documented. This ensures that the review process is conducted with full objectivity and freedom from institutional bias.

Ethics and Responsibility

Pacific Journal of Medical and Health Sciences is firmly committed to upholding the integrity of published research. Issues of copyright infringement, plagiarism, duplicate submission and other breaches of publication ethics are treated with the utmost seriousness. All submitted manuscripts are screened using plagiarism detection software.

Where a manuscript is found to contain plagiarised content, unauthorised use of third-party copyright material, or where the authorship of the work is contested, the journal reserves the right to take appropriate action. Such action may include, but is not limited to:

- Publishing a correction (erratum or corrigendum)
- Retracting the published article
- Notifying the author's Head of Department, Dean or relevant academic bodies
- Banning the author from future submission to the journal
- Pursuing appropriate legal remedies

Reviewers who identify or suspect any of the following concerns during the course of their review are strongly advised to contact the editor without delay. All such matters must be treated with strict confidentiality and must not be discussed with colleagues other than the editor:

1. The manuscript appears to have been previously published or simultaneously submitted to another journal.
2. The manuscript appears to duplicate the work of others without appropriate acknowledgement.
3. There are concerns regarding the ethical conduct of the research described in the manuscript.
4. There is reason to suspect an undeclared conflict of interest associated with the manuscript. Editors may have access to additional information relevant to such concerns and reviewers are encouraged to consult them.

Conflict of Interest

Reviewers are requested to carefully consider any potential conflicts of interest before agreeing to undertake a review. A conflict of interest may arise where a reviewer has a personal, professional, financial or intellectual relationship with the authors, the institution, or the subject matter of the manuscript that could compromise the objectivity of the review.

Reviewers must inform the editorial office of any such conflict as promptly and discreetly as possible, and decline the review assignment where a conflict is identified. Reviewer assessments must at all times be based solely on the scientific merit, clarity and quality of the manuscript, and must not be influenced by personal, financial, intellectual or other biases.

Accepting or Declining a Review Invitation

Reviewers are invited to assess manuscripts by the editorial team via email. In order to avoid unnecessary delays in the review process, reviewers are requested to respond to invitations as promptly as possible, regardless of whether they are able to accept or must decline. If a reviewer is unable to complete a review within the requested timeframe, the editorial office should be notified at the earliest opportunity.

Suggestions for alternative reviewers who may be suitably qualified to assess the manuscript are always welcome and greatly appreciated.

Review Timeframe for Reviewers

Pacific Journal of Medical and Health Sciences is committed to a transparent and timely review process. The following timeframe applies specifically to reviewers:

- Reviewers are requested to respond to a review invitation within 5 working days of receipt, confirming whether they are able to accept or must decline the assignment.
- Upon accepting the invitation, reviewers are requested to submit their completed review report within 21 days.
- If a reviewer requires additional time to complete the review, the editorial office must be notified before the 21-day deadline so that an extension may be considered without causing undue delay to the author.
- Where a reviewer is unable to complete an accepted review within an agreed extended timeframe, the editorial office reserves the right to reassign the manuscript to an alternative reviewer in the interest of timely communication with the author.

The journal sincerely values the time and expertise that reviewers contribute to the peer-review process. Adherence to these timeframes is greatly appreciated and directly supports the journal's commitment to authors of completing the full review process within 30 to 45 days of submission.

How to Conduct a Review

Reviewers are requested to approach each manuscript systematically and to produce a structured, well-reasoned report. The following guidance is provided to assist reviewers in conducting an effective and thorough assessment.

Reviewers who are undertaking a peer review for the first time, or who are uncertain about any aspect of the review process or the journal's specific requirements, are warmly encouraged to contact the editorial office for guidance. The editorial team is always available to discuss expectations, clarify the scope of the review and offer support to reviewers at all stages of their career.

A. Preliminary Assessment

- Read the manuscript carefully in its entirety before beginning the formal evaluation.
- Consider whether the manuscript falls within the aims and scope of the journal.
- Assess the overall significance and originality of the research within the relevant field.
- Evaluate whether the work makes a meaningful contribution to existing knowledge.
- Consider whether the author has previously published a substantially similar paper elsewhere. If so, please refer to the journal's Publication Ethics policy.

B. Scientific and Methodological Evaluation

- Assess the technical accuracy and scientific validity of the content.
- Evaluate the appropriateness and rigour of the research methodology employed.
- Consider whether the conclusions presented are adequately supported by the results or evidence provided.
- Verify the accuracy and completeness of the references cited.

C. Structure and Presentation

- Assess the overall structure of the manuscript, the clarity of the argument and the logical flow of the content.
- Evaluate the quality of written English and the clarity of expression.
- Consider whether the title accurately and effectively reflects the content of the manuscript.
- Assess whether the abstract provides a clear and accurate summary of the work.
- Evaluate the effectiveness of the introduction in contextualising the research.
- Consider whether the manuscript is accessible to a broad international readership.
- Assess the internal consistency of the manuscript throughout.
- Verify that the manuscript type is consistent with the article types accepted by the journal.

Providing Feedback and Suggestions for Revision

Reviewer reports should be objective, specific, constructive and respectful in tone. The following guidance should be observed when preparing feedback:

- Provide comments that are as objective and impartial as possible. Avoid making negative remarks about other work cited in the manuscript.
- Be specific and constructive in identifying areas that require revision. Clearly indicate what needs to be added, clarified or corrected.

- Where appropriate, suggest additional literature that may enrich the author's argument or strengthen the manuscript.
- Clearly distinguish between comments intended for the authors and those intended solely for the editor's consideration, so as to avoid confusion.
- While reviewers may comment on the quality of written language and suggest improvements to the structure or argument, it is not the role of the reviewer to rewrite sections of the manuscript or to prescribe detailed changes in wording.

Making a Recommendation

Upon completing the review, the reviewer must provide a clear recommendation regarding the disposition of the manuscript. Recommendations should fall within one of the following categories:

- Accept as submitted
- Accept with minor revisions
- Major revision required
- Reject

The recommendation should be consistent with the content of the reviewer report and should be accompanied by sufficient reasoning to assist the editor in making the final publication decision.

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Reviewers must treat all manuscripts under review as strictly confidential documents. The content of the manuscript, the reviewer's assessment, and all correspondence relating to the review must not be shared, disclosed or discussed with any third party without the explicit permission of the editor. This obligation of confidentiality continues after the review process has been completed.

A Sample Reviewer Report form is available for download from the journal website at: www.medicaladvances.ac.in

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Publication Ethics and Publication Malpractice Statement

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Pacific Journal of Medical and Health Sciences is committed to maintaining the highest standards of publication ethics across all stages of the editorial and publishing process. This statement sets out the ethical obligations of editors, reviewers and authors, and is based on the Code of Conduct and Best Practice Guidelines for Journal Editors published by the Committee on Publication Ethics (COPE), and the updated guidelines of the International Committee of Medical Journal Editors (ICMJE, 2023).

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Pacific Journal of Medical and Health Sciences

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