Volume 3, Issue 10, 2025

Frontier in Medical & Health Research

ISSN: (e) 3007-1607 (p) 3007-1593

BEYOND THE EXTRA CHROMOSOME: A MULTIDISCIPLINARY APPROACH TO UNDERSTANDING THE COMPLEXITIES OF DOWN SYNDROME AND ADVANCING THERAPEUTIC STRATEGIES

Shahid Mahmood[*1], Abeera Maryam[2], Amina Shehzadi[3], Hafsa Khalid[4], Areeba Amjad[5], Rumaisa Cheema[6]

[*1,2,3,4,5,6]*Department of Zoology, University of Gujrat, Gujrat 50700, Pakistan*

[*1]shahid.mahmood@uog.edu.pk

DOI: https://doi.org/10.5281/zenodo.18160590

Keywords

Trisomy 21, Multi-omics approach, Redox imbalance, Brain inflammation, Interferon response, Gut floral imbalance, Immune dysfunction

Article History

Received: 03 November 2025
Accepted: 17 December 2025
Published: 31 December 2025

Copyright @Author

Corresponding Author: *
Shahid Mahmood

Abstract

Down syndrome, most frequently triggered by trisomy 21, remains one of complicated neurodevelopmental disorder, affecting development from the Prenatal stage through adulthood. While its heredity basis has been known for long periods, Down syndrome persists to be under-investigated in multiple physiological and clinical aspects. This review supplies a comprehensive, multi-omics analysis that moves beyond the standard chromosomal perspective awareness of the syndrome. By re-examining the historical trajectory of Down syndrome, from its early medical description to detection of trisomy 21, we emphasize how research progress has defined modern diagnostic and treatment strategies. Upcoming genomic and epigenetic evidence highlights that Down syndrome pathology is not only the result of an additional chromosome 21 but shows wider dosage alterations, disturbed regulatory network, and global epigenetic drift. These modifications impacted mitochondrial performance, immune monitoring, biochemical pathways, and neurodevelopment, leading to the condition's wide phenotypic range. Specific alterations are given to mosaic and segmented trisomy types, which offers distinct possibilities to clarify genotype. Despite progress, significance gaps remain, including limited understanding of cortical formation, immune imbalance, nutritional factors and age associated risks. By gathering insights from genome wide analysis, protein profiling, metabolite analysis and clinical research, this review highlights how holistic biology can reframe the upcoming periods of Down syndrome. Ultimately, we argue for a unified multi-omics framework that can inform targeted diagnostic, early stage strategy and advanced, therapeutic approaches for individuals with Down syndrome.

1. Introduction

Down syndrome, the most common disease caused majorly by Trisomy 21 in humans occurs roughly about one out of every 675 births (Hendrix *et al.*, 2021). Down syndrome is originally a genetic disorder and mainly consist of three main forms helping in recognition of symptom differences in DS patients. First one and most common is Trisomy 21 cause by full or partial copy of chromosome 21, it causes many problems like slow growth and hearing problems (Donovan *et al.*, 2024). Next is mosaic DS in which some cells got extra chromosome 21 others stay normal and last one is translocation Down syndrome which shows binding of extra chromosome 21 piece to another chromosome (Danopoulos *et al.*, 2024). People

Frontier in Medical & Health Research

ISSN: (e) 3007-1607 (p) 3007-1593

having Down syndrome are at greater risk of getting dementia usually at the age of 40 due to Alzheimer's disease caused by pathological changes which leads to cognitive abnormalities (Dekker *et al.*, 2021).

1.1. Symptoms

People with Down syndrome usually shows physical symptoms including short eye opening, shortened neck, flattened face usually short from mid, and long tongue (Olagunju & Masud, 2021). Down syndrome patients also get cardiovascular problems including heart disorders, sleeping issues, obesity, and hypertension (Dimopoulos *et al.*, 2023).

2. Historical Evolution of Down Syndrome

The initial medical depiction of Down syndrome was presented by Esquirol and Gridley in 1838. They linked the disorder with neurological system impairment and attempted to provide care for affected individuals (Alldred *et al.*, 2021). In 1866, Langdon Down explicitly categorized the disorder according to distinctive anatomical features, putting forward the label “Mongolian family" which was subsequently disapproved however, it was essential for preliminary medical classification. (Akhtar & Bokhari, 2023).

Afterward, Fraser and Mitchell studied 62 patients indicating rapid physiological decline, limited life duration and early death, naming this pattern "general decay" although the root cause still remained undiscovered. (Maure-Blesa *et al.*, 2025). In 1959, a significant discovery took place when Lejeune, Gautier and Turpin recognized Trisomy 21 as the underlying genetic reason of Down syndrome confirming it as a chromosomal abnormality which facilitates current genomic research (Bertini & Raimondo, 2024).

2.1. Epidemiological Trends

Down syndrome patients have different type of pathological issues including very low survival rate, heart disorders, late growth, abnormal digestion and high cancer rates on which research is ongoing regionally and globally (Shimada, 2021).

2.2. Global Prevalence

Down syndrome patients show very high death rate in children and teenagers under 20, especially among females in underdeveloped countries (Ye *et al.*, 2025). The main cause of death rate in children is respiratory issues along with low immunity and in older people it is dementia (Chen *et al.*, 2022).

2.3. Regional Prevalence

In Pakistan, babies born with Down syndrome are about 1 out of every 300 and their death rate is too high (Siddiqui *et al.*, 2021). The main reasons of high death rate in Pakistan are under development, financial issues, lack of care, unawareness and social discrimination against infected Individuals (Batool *et al.*, 2024). One major cause is congenital heart disorders leading to 13% death in children and 23% death in adults due to late diagnosis. So, proper and on time treatment is important (Haider *et al.*, 2024). Down syndrome research is still ongoing and it is under reviewed due to lack of financial resources, public unawareness, carelessness, late diagnosis and limited analysis. Overtime, research has recognized death rate and other causes among DS patients but many other aspects still remain under-addressed and require further study as explained in Fig. 01 (Bai *et al.*, 2024).

Volume 3, Issue 10, 2025

Frontier in Medical & Health Research

ISSN: (e) 3007-1607 (p) 3007-1593

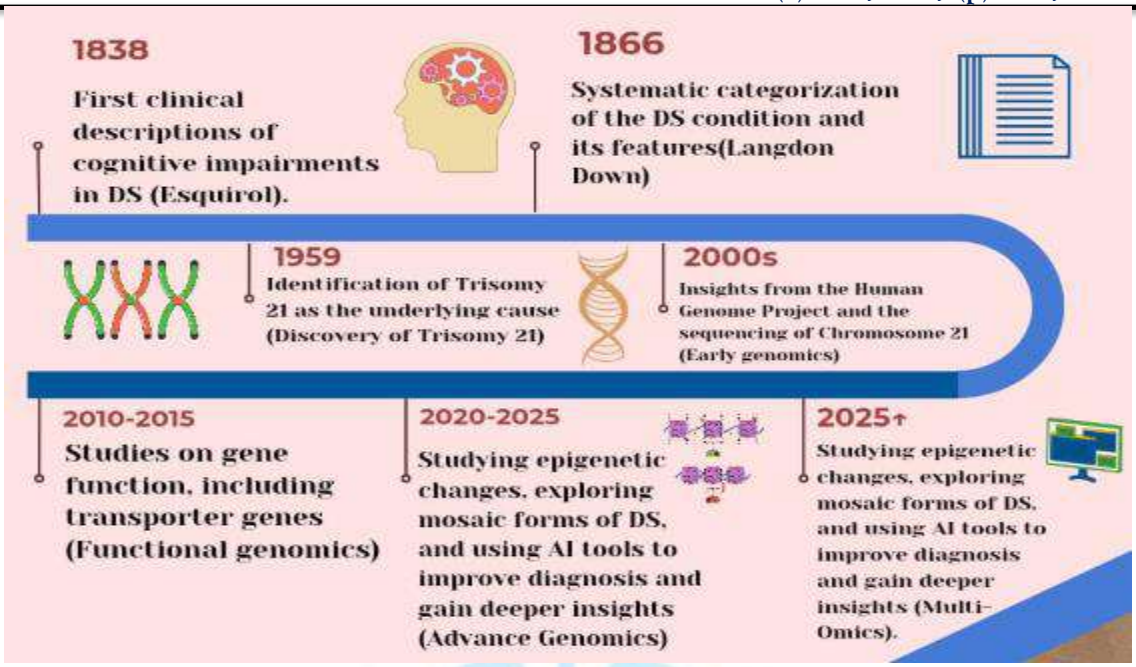


Fig. 01: Historical progression of Down syndrome

3. Major Gaps in DS study

3.1. Biological gaps

Down syndrome has been in-depth studied but many aspects remained poorly understood including limited data access, incomplete mechanism understanding, limited structural and neurological knowledge, cellular composition, lack of trans-locational research and limitation of models that are very important for DS diagnosis (Risgaard *et al.*, 2022).

3.2. Clinical Gaps

There is vast list of clinical gaps in Down syndrome study which should be studied to overcome this disease efficiently. It includes incomplete understanding of cortical development which is important for studying psychiatric behavior in patients as well as understanding sensory development difficulties, sleep problems, proper diet plan and also the feeding strategies (Hielscher *et al.*, 2023).

3.3. Nutritional Gaps in Down syndrome

Individuals with Down syndrome have major biochemical differences in comparison to normal individuals. This includes insufficient work on minerals, limited knowledge of micronutrient levels and dietary supplements in children and adults (Barisic *et al.*, 2023).

4. Beyond Trisomy 21: Integrative perspective

Although broad level researches have been done on different perspectives of Down syndrome but there is not a unified version of these studies. This review aims to provide sequential multi-dimensional approach to understand Down syndrome on clinical, molecular and cellular level (Abukhaled *et al.*, 2024). As vast knowledge of neurological patterns involved in Down syndrome patients has been discovered but some aspects like full impact of mosaicism and immune imbalance remained poorly understood. This article aims to cover those gaps (Hamadelseed *et al.*, 2023). Moreover, a broader study on trisomy 21 has been discovered but detailed sequencing data is still missing. This article aims to study in depth biological mechanism of Down syndrome in an integrated manner (Rastogi *et al.*, 2024).

Frontier in Medical & Health Research

ISSN: (e) 3007-1607 (p) 3007-1593

4.1. Genomic Dosage Imbalance

Down syndrome is caused by an extra Copy of chromosome 21 but it involves more complexity then we think, because chromosome 21 genes alone cannot show different phenotypic expressions rather they need high genetic activity. Gene dosage hypothesis which states that gene copying is directly proportional to gene expression, explains this concept (Hunter *et al.*, 2023). Gene Dosage Imbalance refers to Increase in gene expression due to triplication of chromosome 21 genes that increases gene activity disturbing development pathways (Chapman *et al.*, 2024).

4.2. Effect of gene dosage Imbalance

Gene dosage imbalance not only shows gene expression on chromosome 21 rather it effects thousands of other genes not only by over expression but it also changes expressions of proteins and microRNAs. It also effects isoforms of genes in RNA splicing causing alternations and it is a major cause of cognitive, neurological imbalance and different phenotypic expressions showing differences in psychological behavior in DS patients (Muskens *et al.*, 2021). Gene dosage imbalance also effects cellular activity causing severe changes and alterations in chromatin sequence that disturbs cell mechanism, even it causes DNA damage that leads to serious issues. However, some genes are observed that help to retain normal cellular activity (Liu *et al.*, 2024). DS patients show dis-functioning of cells by causing change in redox and oxidation stages. Specifically, lipid peroxidation helps in signal integration. It also acts in alteration of neuron activity which causes difference in cognitive behavior. Moreover, gene dysregulation also causes behavioral differences in DS individuals (Buczyńska *et al.*, 2023).

4.3. Effect of gene dosage imbalance across different age groups

Gene dosage imbalance leads to vast phenotypic differences in DS patients of different age groups. Infants show feeding difficulties, heart, vision, hearing issues and thyroid problems. Children are associated usually with low immunity, slow learning, vision and hearing issues. Adults are affected mainly with early aging, chronic problems and less social skills development (Bull *et al.*, 2022).

4.4. Mosaicism in Down syndrome

Mosaicism occurs when there is trisomic genetic difference only in one cell. It occurs in individuals less than 1% only, so its genes are individual specific and show different expressions in different individuals. Thus, number of trisomic cells are inversely proportional to cognitive ability of the patient. More the defective cells, lesser will be the IQ level (Moncada Arita *et al.*, 2022). Mosaic Down Syndrome consists of trisomic and disomic cells that help naturally in research of Down syndrome. Trisomic cells are more reactive then disomic cells because they cause chromosomal instability, health and age issues causing early death (Rafferty *et al.*, 2021).

There is variation in tissues of trisomic cells that lead to difference in phenotypic characters like the lymphocytes of trisomic cells shows hearts defects while the mucosa is strongly linked with cognitive effects making it individual specific (Brown *et al.*, 2025). The risk of Alzheimer's disease in mosaic syndrome patients is unique and vary person to person but studies shows that mDS have low chances of getting disease than a trisomic patient of DS. Mosaic Down syndrome (mDS) can be detected by karyotype or single nucleotide polymorphism microarray analyses. There is more need of understanding clinical dimensions to get proper data for DS (Xicota *et al.*, 2024).

4.5. Partial Trisomy in DS

Partial Trisomy occurs when a segment of chromosome 21 is duplicated regardless of copying of full chromosome. It helps in understanding relationship between phenotype and genotype of Down syndrome. Studies shows that person with 3 copies of Partial trisomy can get affected with Down

Frontier in Medical & Health Research

ISSN: (e) 3007-1607 (p) 3007-1593

syndrome while others show mild effects (Pelleri *et al.*, 2022). After many experiments, it is believed that there's specific critical region in chromosome 21 that express the traits of Down syndrome. Partial trisomy has helped a lot in recognizing Down syndrome's critical region which becomes the roadmap for understanding Down syndrome traits. This makes its diagnosis very easy (Murray *et al.*, 2023).

Partial trisomy rarely shows imbalanced translocations by addition or deletion of chromosomes thus altering the phenotypic expressions i.e. by addition of a chromosome part in case of Partial trisomy causes ketotic hypoglycemia. Its research is still ongoing to understand clinical dimensions and phenotypic expressions of Down syndrome. (Drachmann *et al.*, 2021).

4.6. Epigenomic drift

Down syndrome shows complexity but not only due to chromosome 21, it also involves genetic effects. Chromosome 21 contains DNA methyl transferase (DNMT3L) which helps in making new DNA marks when it is over copied, it changes the methylation patterns of other genes giving a wide genomic effect that is called epigenetic drift. It affects according to age and may show hypo-methylation or hyper-methylation (Naumova *et al.*, 2021). Down syndrome shows phenotypic variability because of tissue specific gene dosage effects that means there is difference in gene number on different tissues in random order which makes the path of phenotypic differences in DS individuals The epigenetic changes in methylation also causes clinical variation including immunity and heart problems that vary in newborns, males and females (Mouat *et al.*, 2023)

Aging signs in Down syndrome patients occurs before birth and are detectable using epigenetic clocks to diagnose it but this aspect still needs wide range study to get more efficient work. Down syndrome affects many tissues and organs causing immunity problems, improper physical development, heart, brain, blood diseases and aging following phenotypic variability (Xu *et al.*, 2022). Down syndrome is beyond the triplication of chromosome 21 including epigenetic drifts and genomic mechanisms but its research is still limited as there's need of models and organs like stem cells to understand the clinical, neurological and other vast aspects. A multi-omics integration (Fig. 02) is strictly needed to cover all the gaps for future improvement (Ghosh *et al.*, 2023).

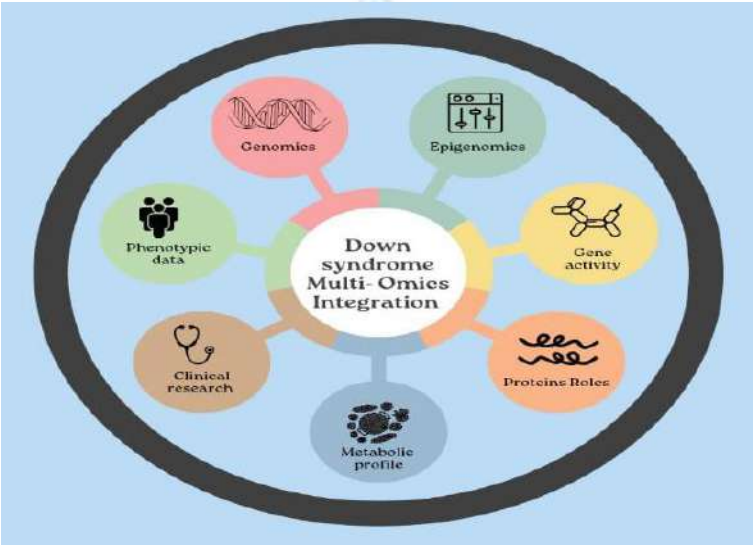


Fig. 02: Down syndrome multi-omics integration

Frontier in Medical & Health Research

ISSN: (e) 3007-1607 (p) 3007-1593

5. Alteration of Cellular and molecular pathway

The pathway activation of interferon in Down syndrome is overexpressed, which leads to constant inflammatory response. Cells with trisomy 21 shows uninterrupted activation of interferon-alpha, interferon-gamma, tumor necrosis factor-alpha, and immune compliment pathways. Mediator cyclic dependent kinase-8 and cyclic dependent kinase can cause excessive activation and if their activity was suppressed by Cortistatin A, it lessens the activity of interferon genes, alters RNA splicing, enhance lipid metabolism and normalizes mitochondrial activity (Cozzolino *et al.*, 2024).

Persons with trisomy 21 have increased level of some inflammatory cytokines (Interleukin-6, Interleukin-16, Interleukin-17C/D, monocyte chemoattractantprotein-1, Interferon gamma induced protein-10) and down regulated level of others (Tumor necrosis factor-beta, Interleukin-12/Interleukin-23p40). There cellular metabolites also alter, some of the amino acids are decreases (like glycine, serine, histidine, tyrosine) and some also increases (like sphingosine, hydroxyeicosatetra enoic acid, kynurenine, bile acids). These modification influence Interferons-γ signaling, heme metabolism and energy production, demonstrating a complicated immune system and metabolic Dysregulation. Blocking mediator kinase may help in normalizing cellular function (Gillenwater *et al.*, 2024).

5.1. Transcriptomic Alterations

Having an additional chromosome 21 may enhance the performance of many genes especially crucial ones like Amyloid precursor protein, Dual-specificity Tyrosine-Y-phosphorylation-regulated kinase 1A, and Regulator of calcineurin1, which influence proper cell functions (De Toma *et al.*, 2021).

Extra APP gene may increase the chance of early Alzheimer's disease, DYRKIA gene also affects brain growth, learning skills, and retention of information, similarly extra RCAN1 gene may cause inflammatory response and chance of cancer. Other genes like High mobility group nucleosome binding protein-1 (HMGN1) and Myxo virus resistance protein-1 (MX1) also alters inflammatory response, mitochondria, calcium regulation, cardiac cells resulting in leukemia, chronic inflammation and heart complications in Down syndrome (Venegas-Zamora *et al.*, 2022). In general, this gene alteration can cause stress, uneven protein levels and disturb cell processes can lead to inflammatory processes and many common Down syndrome features (Krivega *et al.*, 2022).

5.2. Proteomic and Metabolomics Signatures

In Down syndrome extra copy of chromosome 21 is associated with mitochondrial inefficiency, body's inflammatory response and oxidative damage (Slivšek *et al.*, 2025). Mitochondria in Down syndrome cells produces less ATP, lower energy production, disturbed membrane activity and abnormal structures which increase reactive oxygen and harmful nitrogen molecule that can destroy proteins, lipids, DNA, and RNA (Ganguly & Kadam, 2023). Antioxidant defenses including catalase, glutathione peroxidase, vitamin C and vitamin E and glutathione are often inadequate to reduce this stress (Ma *et al.*, 2024).

6. Immune Landscape

Individual with Down syndrome have altered immune system, they usually have increased level of cytokines, overactive T-lymphocytes, unusual B-lymphocytes responses and autoantibodies. These changers are different in everyone. Some shows higher cytokines level, some shows few and some shows normal level of cytokines. More T cells turn into memory-type and B cells decreases, while plasma blasts and unusual B cells communicates to self-attacking antibodies increase (Bordon, 2023).

6.1. Hypo- and Hyperactive Immunity Paradox

People with DS, have a different immune system that is both less active and hyperactive. They are

Frontier in Medical & Health Research

ISSN: (e) 3007-1607 (p) 3007-1593

more probably to get infections and develop self-attacking immune disease like thyroid problems, type1 diabetes gut disease and hair loss (Malle *et al.*, 2023). Their immune system shows multiple alteration, fewer naive B cells and memory B cells, weaker regulatory T cells, overactive Cluster of differentiation 4 positive (CD4+) T cells, and more plasma blasts that can damage the body's own cells (Szczawińska-Popłonyk *et al.*, 2024). Blood tests show higher amount of molecules that cause inflammation like interferons which triggers long-term inflammation and self-attacking immune response (Rachubinski *et al.*, 2024).

6.2. Autoimmune Risk & Early Immune Aging

People with Down syndrome have a different immune system that makes them more prone to get infection immune system disorders like thyroid issues, type1 diabetes and gluten intolerance (Lambert *et al.*, 2022). Their T cells regularly switch from naive to memory types and some become hyperactive. B cells also influenced, most are declined but some unusual types like plasma blasts and Cluster of differentiation 11c positive (CD11c+) B cells, boost and make self-attacking antibodies. These alterations along with the symptoms of early aging, cause a mix of less active and overactive immunity. Gluten intolerance, high cytokine level and disturbed B and T cell function describes why individuals with Down syndrome face both infection risk and self-attacking immune issue (Ramba & Bogunovic, 2024).

6.3. Interferon Hyper activation and Immune Signaling Dysregulation

Individuals with Down syndrome have a different immune system because they have extra copies of some genes that make interferon's-detecting proteins on chromosome 21 Interferon alpha receptor subunit 1 (IFNAR1), Interferon alpha receptor subunits 2 (IFNAR2), Interferon gamma receptor subunit 2 (IFNGR2), Interleukin-10 receptor subunit beta (IL-10RB) (Chung *et al.*, 2021).

They make their body defense cells like T cells, B cells, monocytes, and fibroblasts and easily affected by interferons. Their cells are often in slightly activated state, with increased activity in the Janus Kinase-signal transducer and activator of transcription (JAK-STAT) pathway and interferon's responsive genes. This can help initially fight infection but also creates problems, their cell generates proteins Ubiquitin specific peptidase 18 (USP18) that stops interferon's response later making it difficult to fight against viral infection that just has started. Because of this individual with Down syndrome can get more intense viral infection and are also more likely have body-attacking immune problem or inflammatory problems (Notarangelo & Bosticardo, 2022).

7. Neurodevelopmental impacts

7.1. Prevalence of co-occurring neurodevelopmental disorders

Babies with DS have autism, only about 1 in 10 affected. Mostly boys have both conditions and tend to have tummy problems like constipation, feeding issues and also have a higher ratio of scoliosis. They mostly have fewer heart disorders rather than the infants with only Down syndrome. Thyroid issues, celiac disease and cognitive disorders are about the same in both. Infants with both DS and autism have unique medical profile, so they benefit from more modified health monitoring (Spinazzi *et al.*, 2023).

7.2. Cognitive and behavioral phenotype

Magnetic resonance imaging (MRI) studies show that the people with Down syndrome have distinguished difference in the size and the shape of brain. These shapes and sizes are totally different from the individuals not having trisomy 21. These distinct pattern of brain development can be seen on regular MRI scans (Levman *et al.*, 2024).

Frontier in Medical & Health Research

ISSN: (e) 3007-1607 (p) 3007-1593

7.3. Dissociative Seizures with Unusual Features

Dissociative seizures (DS) may look like epileptic seizures with eyes rolling upward, which may cause misdiagnosis. Video-EEG (Electroencephalography) helps the doctors to distinguish DS from epilepsy, and it is very crucial for checking mood and emotional problems of patients (Bao *et al.*, 2025).

7.4. Early Detection of growth delay

Research studies shows that countries with low and middle income found few tools to check the development delay in infants under five. Some tools worked well but here more research is needed to adapt and test of these tools for different cultures, so that delay can be found and treated early (Faruk *et al.*, 2020).

8. Systemic Impacts

8.1. Cardiovascular: congenital heart defects, developmental biology

In Down Syndrome, about 50% of the individuals develop congenital heart defects (CHD), which is caused by an extra copy of chromosome 21 and environmental factors like maternal folic acid intake (Asim & Agarwal, 2021).

Early research indicates that congenital heart disease (CHD) comes from the combined effects of several genes, not only a gene on chromosome 21 but also occur a gene on other chromosomes, such as regulatory RNAs like mRNAs. CHD is due to upregulation of some chromosome 21 genes, including Run-related transcriptional factor 1 (RUNX1), which falsify extracellular matrix proteins, united with effects from other genes and regulatory RNAs, interrupting heart development (Mollo *et al.*, 2023).

Recent stem cell and mouse model studies recognize High mobility group nucleosome binding protein (HMGN1), which is an epigenetic control factor in trisomy 21, serve as key contributor. HMGN1 in Down syndrome interrupt the normal developmental identity of atrioventricular canal cardiomyocytes, promoting septal defects which can be saved by decreasing its dosage (Ranade *et al.*, 2025).

8.2. Endocrine: thyroid dysfunction, obesity, metabolic regulation

Down syndrome, caused by trisomy 21, is identified not only by its neurological features but also by its metabolic complications like obesity, thyroid dysfunction, and diabetes. Upcoming research point out interaction among Inflammation and changed food intake may provide these disorders, focusing potential targets to better health and quality of life (Moreau *et al.*, 2021).

Infants with DS show greater metabolic rates with changed thyroid hormone levels and sensitivity closely linked to glucose and lipid abnormalities, pointing as a vital role of thyroid regulation in their metabolic disturbance. Immune defects contribute to Type 1 diabetes, while inflammation and gene like Regulator of calcineurin 1 (RCAN1) and Dual-specificity tyrosine-phosphorylation regulated kinase 1A (DYRK1A) increase vulnerability to Type 2 diabetes (Calcaterra *et al.*, 2023).

8.3. Gastrointestinal: celiac disease, Hirschsprung disease, gut microbiome role

8.3.1. Feeding and Gastrointestinal Disorders in Down Syndrome

Patients with Down syndrome (DS) often face feeding difficulties and gastrointestinal (GI) problems. Research studies show these problems including Anatomical anomalies (duodenal atresia, Hirschsprung's disease), liver and immune infection (cholestasis, celiac disease), and functional issues (reflux, constipation, obesity) which influence the quality of life badly. Advance detection, nutritional support, observing for deficiencies and infections and also patients care improves quality of life (Ravel *et al.*, 2020).

8.3.2. Disrupted Gut-Brain Communication in DS

DS is linked to coexisting condition, like congenital heart disease and gastrointestinal (GI) issues. About

Frontier in Medical & Health Research

ISSN: (e) 3007-1607 (p) 3007-1593

50% of individual with Down syndrome have a disorder of gut brain interaction, especially functional constipation is common, often linked to hypotonia, hirschsprung's disease and celiac issues that influence the quality of life. Better management of Gastrointestinal (GI) issues is needed (Park, 2023).

8.3.3. Celiac disease

Celiac disease modifies about 1% of the individuals but is sometimes missed because symptoms differ greatly. Individuals with autoimmune diseases, Irritable bowel syndrome (IBS)-like symptoms, certain genetic syndromes, or Immunoglobulin A (IgA)-related condition should undergo serology as the first step, followed by biopsies during endoscopy when these at risk patients are evaluated (Hom *et al.*, 2024).

8.3.4. Hirschsprung disease

Individuals with Hirschsprung disease also with the presence of Down syndrome (DS) are often detected later, prolonged hospitalization, deal with difficulties, and have higher risk of death, emphasize the importance of early care and close monitoring (Saberi *et al.*, 2022)

8.4. Transient myeloproliferative disorder

Infants with severe anemia, high white blood cells, enlarged liver and spleen, but with no physical signs of Down syndrome. Genetic test results showed trisomy 21 in the blood cells and also have GATA binding protein 1 mutation which shows (TMD) transient myeloproliferative disorder (Zacny et *al.*, 2025).

Some infants often show red bumps and blisters on the face. Most of the cases get better with their own with gentle care. So, care is very important to cure it (Zhang & Zhao, 2024).

8.5. Leukemia Risk in Down Syndrome

Acute lymphoblastic leukemia is the major cause of cancer in infants with DS. Recent studies show it has unique gene changes, sometimes influencing FMS-like tyrosine kinase (FLT3) genes (Li et *al.*, 2023).

This review focuses attention on current knowledge, clinical challenges, and key questions for future research (Baruchel *et al.*, 2023).

8.6. Reproductive & Musculoskeletal: fertility patterns, bone mineral deficits

8.6.1. Fertility in the Down syndrome

Individuals with Down syndrome are long-lived, so fertility has become an essential issue. Research shows that men have sperm issues while women tend to early menopause. Pregnancy is at higher risks in women with DS, so counselling and close monitoring is very important for it. More research is still required for this issue (Marqui & Borges, 2024).

8.6.2. Sensory Neuron Development and Skeletal Deficits in Down Syndrome

Individuals with trisomy 21 have low bone density and skeletal abnormalities caused by impaired communication between bone and sensory neuron. Research on mouse shows that mechanical loading on bone strengthen them but response is limited. More studies are required to find best method to support bone health in DS (Thomas, 2025).

9. Unveiling Underlying Mechanisms and Therapeutic Opportunities

People with Down syndrome have different alternations in their body system like in their eyes, brain and skin (Alasmari *et al.*, 2025). As people with Down syndrome in the latter half of the twentieth century start living longer and get Alzheimer disease earlier and in large amounts then other people (Bhattacharyya *et al.*, 2025). Immune system problems in Down syndrome, involving interferon related gene and due to aging, which can make them get more infections and may affect how severe COVID-19 is (Chen *et al.*, 2021).

Frontier in Medical & Health Research

ISSN: (e) 3007-1607 (p) 3007-1593

9.1. Neuroimmune Axis in Down Syndrome

The human gut has a diverse microbial community of approximately 100 trillion microorganisms in them, like archaea, fungi, bacteria and viruses. Metabolic and genetic abilities are strong of these microbes so they affect every aspect of human health like development, immunity, aging and disease (Zhuang *et al.*, 2024).

It explores the link between gut microbes and systematic health and makes spotlight how it helps to maintain the microbial balance for restore through non- digestible fibre, beneficial bacteria, nutritional interventions and lifestyle modifications (Oter-Quintana *et al.*, 2025).

9.2. Alterations in Down Syndrome

Research shows that people with Down syndrome have unusual diet plans. They usually eat too little fruits, vegetables, whole grain cereals and dairy products and take more sweets and meat. It's necessary to refine eating habits and eat healthy food not unhealthy ones (Gruszka & Włodarek, 2024). Youth with Down syndrome have high overweight and obesity risk. Normal weight rules are not perfect for controlling their weight so specialists give guidance to families and doctors (Ptomey *et al.*, 2023).

9.3. Microglial Activation and Brain Inflammation

Mitochondrial problems and extra Human chromosome 21 (HSA21) gene effects in Down syndrome are increased cellular damage which triggers microglial activation and brain inflammation.

These inflammations help to decline cognitive and brain damage like Alzheimer's disease (Zuo, 2025). Research shows that dementia and vaccine in cognitive problems are focus comes on innate immunity and brain inflammation and the same process in Down syndrome increases early neurodegeneration (Wang *et al.*, 2025).

9.4. Blood brain barrier dysfunction

Alzheimer disease and Human immuno-deficiency virus (HIV) the crucial element in both diseases involves the aggregation of protein and neuroinflammation seems to breakdown the blood brain barrier. It shows Blood Brain Barrier (BBB) dysfunction in both conditions is important which increases cognitive decline (Zhang *et al.*, 2025).

In multiple sclerosis, harmful substances in blood increase due to imbalance of gut bacteria and active brain cells which affect blood brain barrier. On other side, nanoparticles are designed to cross blood brain barriers more efficiently, where size, shape and surface helping them reach the brain (Nájera-Maldonado, 2025).

10. Gut brain microbiome interaction

Gut flora connect orally taken traditional medicines and metabolites may affect mental health and cognitive consequences (Hao *et al.*, 2025). Chronic stress affects the gut brain axis but beneficial bacteria and stool transplant like procedure restore the balance of gut microbiota, improve barrier honesty and reduce brain inflammation (Neves *et al.*, 2025).

Gut microbiota play specific role in health by affecting metabolism, immunity, stress response and behavior making gut brain axis. Healthy gut microbiome and its collaboration with bulk and other byproduct help balance brain function and reduce stress impact (Feng *et al.*, 2025).

10.1. Diversity and functional role of gut microbes

A healthy gut microbe is very important and when it gets disturbed, may impact the process linked to Down syndrome development (Ternák *et al.*, 2023). Gut microbiome and mRNA regulate each other and this interaction affects immunity, chemical processes and inflammation (Zur *et al.*, 2025). Gut and oral microbiota become imbalance in Down syndrome which affect immunity, digestion and inflammation and increase the risk of oral problems (Botero *et al.*, 2024).

Frontier in Medical & Health Research

ISSN: (e) 3007-1607 (p) 3007-1593

10.2. Pathways linking the gut and brain

Gut and brain are linked two ways communication process via the neurological, hormonal, immunological pathways. Probiotic, prebiotics and symbiotic are modify gut microbiota which impact the communication network. Through this modulation cognitive function and mood regulation becomes better and get protection from neurodegenerative disorders. This mediation supports the immune balance and improves long term digestive issues (Kezer *et al.*, 2025).

Gut microbiota works as functional organ and metabolizes substance to change their activity. Traditional Chinese medicine improves gut balance by promoting beneficial bacteria and bile acids metabolites are regulated. These gut changes influence mental health and physiological functions. Additionally, Omega-3 fatty acids help regulate mood by reducing inflammation and modulate neurochemical pathway like kynurenine (Ładno *et al.*, 2025).

10.3. Impact of gut microbiota

Changes in gut microflora can contribute to stress, despair, dysbiosis and other neurological disorders (Gupt *et al.*, 2024). Gut bacteria produce various metabolites which impact directly on brain function and behavior. These metabolites regulate neural signaling, neuroinflammation and changes in them linked to stress, depression and neurodegenerative disease (Srivastava & Gupta, 2025).

When a child faces stress in early life, it can disturb gut microbes changing its overall functioning. From this disruption alter synthesis of microbial metabolite, neurotransmitter and key metabolites pathway. Research suggests that early life stress and gut microbiome association can impact on stress, anxiety and post-traumatic disorders (Borrego-Ruiz & Borrego, 2025).

10.4. Nutritional and Microbial interventions

The goal of clinical interventions should promote swallowing safety and feeding abilities. Children with low weight or who have feeding problems to improve their nutritional status for deep analysis of fundamental factors are necessary (Nordstrøm *et al.*, 2020).

In Down syndrome patient periodontal disease risk is higher due to local and systematic factors. Early monitoring of oral health is necessary which help to plan nutritional and microbial interventions. Nutrition and immune status in systematic factors influencing patient sensitivity and disease advancement (Si *et al.*, 2025).

11. New treatment and future ideas

Correction of eating habits are necessary. Individuals with trisomy 21 should take a healthy diet including specific nutrients that supports mental and health issues related with DS. (Gruszka & Włodarek, 2024). For future early diagnosis, proper counseling and comprehensive long term care support provide to Down syndrome individual for improving their health and quality of life (Tu *et al.*, 2025).

11.1. Gene and chromosome therapy

In future, there is a potential of Clustered regularly interspaced short palindromic repeats (CRISPR-Cas) gene- editing technology in treatment of Down syndrome including silence chromosome 21 or correcting Down syndrome associated gene (Gondek *et al.*, 2025). Emerging therapies and genetic studies provide better healthcare and targeted interventions for Down syndrome in future. International developments like CRISPR and neurodevelopmental imaging use in development countries improve care for Down syndrome patient (Ahmed & Tamim, 2025). On chromosome 21, the App gene become overactive which produce Alzheimer problems. Therefore, specific targeting genes are important for the future treatment. All of this shows that gene- editing and chromosome level treatment become an important part for the next-generation therapies of Down syndrome (Hamadelseed & Skutella, 2025).

Frontier in Medical & Health Research

ISSN: (e) 3007-1607 (p) 3007-1593

11.2. Treatment

Researchers for Down syndrome works on precision medicine, aiming by using biomarkers make personalized treatment for each patient to improve their health care and well-being across lifespan (Waugh *et al.*, 2025). At the International summit on food defense (ISFDS) summit, scientist came together to discuss latest research and therapies to improve physical fitness for Down syndrome and create practical guidelines for their future uses (Oreskovic *et al.*, 2025).

Study highlights that better counseling and support is compulsory for parents when they do screening and diagnosis in Down syndrome, especially in parental care (de Graaf & Skotko, 2025). Investing in treatment for Down syndrome related Alzheimer helps people live longer, decline unhealthy years and lower the need for support which shows the benefit of medicine for Down syndrome patients (Weden *et al.*, 2025).

11.3. Stem cells

Mesenchymal stem cell therapy (MSC) must be beneficial for the patient of Down syndrome in improving mental, behavioral and body related problems. After 6 month of mesenchymal stem cell therapy on two children improved language, attention, social skills and reduce inflammation. Therapy was safe and has no side effect. MSC therapy may be helpful for regulating the immune system and can become a useful treatment for Down syndrome. Large scale trials are needed to verify these results and recognized course of therapy (Vinski *et al.*, 2025).

12. Clinical Management and personalized medicine

Patients with Down syndrome have exclusive health problems but still there is lack of proper guideline for such patients (Tsou *et al.*, 2020). Acute leukemia associated with Down syndrome can be overcome with particular DNA/RNA testing followed by meticulous personalized therapeutic support, preventing the risk of death and increasing chances of survival. Due to lack of suitable standard treatment, there is dire need of personalized medicine (Verma *et al.*, 2023).

12.1. Phenotypic variability and Individualized care

Diverse phenotypes have been observed in persons with Down syndrome. Keeping in view the fact, initiatives have been taken to maximize person's basic strengths with this disorder. For monitoring and management of associated health issues and specific problems, proper guidelines and care directions have been provided (Bull, 2020).

12.2. Biomarkers for early detection of comorbidities

Treatment of dementia in patients with DS is hard as they already face slow deterioration of thinking capacity and everyday skills along with neurological and psychiatric signs (Montoliu-Gaya *et al.*, 2021).

12.3. Nutritional, Occupational and Neurocognitive management strategies

Children that have Down syndrome require balanced, varied and specific diet according to their needs. It's crucial to pay close attention to the consumption of specific nutrients due to their metabolic dysfunction and health problems (Zur *et al.*, 2025).

Rehabilitation therapists often focus on deterioration in daily tasks for people that are suffering from both Down syndrome and cognitive impairment. It is crucial that care options are provided in a cooperative way to assist active involvement in significant daily tasks for these individuals and supports the requirements of their nonprofessional caregiver (Raj *et al.*, 2020).

13. Psychosocial and Educational dimensions

The active contribution of individuals suffering from Down syndrome is significantly jammed by physiological or cognitive elements, the assistance and perceptions of guardians and the lack of availability of customized programs (Souto *et al.*, 2024). Findings show the absence of transparency

Frontier in Medical & Health Research

ISSN: (e) 3007-1607 (p) 3007-1593

and uniformity regarding the duties and obligations of instructors and therapeutic assistants that are helping learners with Down syndrome (Boundy *et al.*, 2023).

14. Future Directions

Areas for future research should emphasize on raising understanding and engagement among the health-based and general population tackling health disparities and setting up reliable research models to further specify the distinct disease processes and affecting multiple system features of Down syndrome (Maure-Blesa *et al.*, 2025). It has increasingly been recognized by researchers that study of Down syndrome at gene level is not enough rather than epigenetic study in multi-omics is needed to understand underlying mechanism to develop precise treatments (Waugh *et al.*, 2025).

15. Conclusion:

Down syndrome is a multifaceted disorder that outreaches trisomy 21 encompassing inherited, epigenetic, immunological and metabolic dysfunctions that clarify its wider phenotypic diversity. These genetic changes lead to core medical problems such as inborn heart defects, thyroid dysfunction, metabolic impairments, gastrointestinal abnormalities, aberrant immune pathway, probability of leukemia and early manifestation of Alzheimer's disease. Regardless of ongoing scientific development key limitations remain in preliminary detection, treatment and local medical resources. To pursue further progress, the field must implement multi-omics strategy, refine cell-based and growth related models and review diversity in greater depth.

REFERENCES

Abukhaled, Y., Hatab, K., Awadhalla, M., & Hamdan, H. (2024). Understanding the genetic mechanisms and cognitive impairments in Down syndrome: towards a holistic approach. Journal of neurology, 271(1), 87–104. https://doi.org/10.1007/s00415-023-11890-0

Ahmed, R., & Tamim, M. T. R. (2025). Understanding Down Syndrome: Global Perspectives, Advances, and Challenges in the Context of Bangladesh. THRIVE Health Science Journal, 2(1), 16-28.

Akhtar, F., & Bokhari, S. R. A. (2023). Down Syndrome. In StatPearls. StatPearls Publishing.

Alasmari, F., Ahmad, A., Alsanea, S., Hammad, A. M., & Al-Qerem, W. (2025). Current insights and prospects for the pathogenesis and treatment of clinical manifestations associated with Down syndrome through neurotransmitter, inflammatory, and oxidative stress pathways. Frontiers in Pharmacology, 16, 1592277.

Alldred, M. J., Martini, A. C., Patterson, D., Hendrix, J., & Granholm, A. C. (2021). Aging with Down syndrome—where are we now and where are we going? Journal of clinical medicine, 10(20), 4687.

Asim, A., & Agarwal, S. (2021). Congenital heart defects among Down's syndrome cases: An updated review from basic research to an emerging diagnostics technology and genetic counselling. Journal of Genetics, 100(2), 45.

Frontier in Medical & Health Research

ISSN: (e) 3007-1607 (p) 3007-1593

Bai, Z., Han, J., An, J., Wang, H., Du, X., Yang, Z., & Mo, X. (2024). The global, regional, and national patterns of change in the burden of congenital birth defects, 1990–2021: an analysis of the global burden of disease study 2021 and forecast to 2040. EClinicalMedicine, 77.

Bao, S., Egbuta, C.O. & Li, J. Dissociative seizures mimicking epileptic seizures: diagnostic challenges in a case with atypical eye movements. Acta Epileptologica 7, 15 (2025). https://doi.org/10.1186/s42494-025-00210-w

Barišić, A., Ravančić, M. E., Majstorivić, D., & Vraneković, J. (2023). Micronutrient status in children and adolescents with Down syndrome: systematic review and meta-analysis. Journal of intellectual disability research: JIDR, 67(8), 701–719. https://doi.org/10.1111/jir.13042

Baruchel A, Bourquin JP, Crispino J, Cuartero S, Hasle H, Hitzler J, Klusmann JH, Izraeli S, Lane AA, Malinge S, Rabin KR, Roberts I, Ryeom S, Tasian SK, Wagenblast E. Down syndrome and leukemia: from basic mechanisms to clinical advances. Haematologica. 2023 Oct 1; 108(10):2570-2581. doi: 10.3324/haematol.2023.283225. PMID: 37439336; PMCID: PMC10542835.

Batool, A., Aftab, M. J., Bibi, I., Shafiq, M., Irshad, S., & Laghari, M. S. N. (2024). Addressing the issues faced by children with Down syndrome in community settings: Insights from psychologists and parents. Migration Letters, 21(S8), 397-407.

Bertini, I., & Raimondi, C. (2024). Jérôme Lejeune (1926-1994): A Pioneer in Uncovering the Connection between Congenital Conditions and Chromosomal Anomalies. Cureus, 16(12).

Bhattacharyya, A., de la Torre-Ubieta, L., Zhu, Y., Head, E., Swarup, V., & Sousa, A. M. (2025). Development of Molecular Neuropathology in Down Syndrome across the Lifespan. Journal of Neuroscience, 45(46).

Bordon Y. (2023). Immune dysregulation in Down syndrome. Nature reviews. Immunology, 23(4), 201. https://doi.org/10.1038/s41577-023-00855-z

Borrego-Ruiz, A., & Borrego, J. J. (2025). Early Life Stress and Gut Microbiome Dysbiosis: A Narrative Review. Stresses, 5(2), 38.

Botero, J. E., Rodríguez-Medina, C., Amaya-Sanchez, S., Salazar, C. L., & Contreras, A. (2024). A comprehensive review of the relationship between oral health and Down syndrome. Current Oral Health Reports, 11(1), 15-22.

Boundy, L., Hargreaves, S., Baxter, R., Holton, S., & Burgoyne, K. (2023). Views of educators working with pupils with Down syndrome on their roles and responsibilities and factors related to successful inclusion. Research in developmental disabilities, 142, 104617. https://doi.org/10.1016/j.ridd.2023.104617

Brown, R. C., D'Aguilar, A., Hurshman, Q., NailorZee, R., York, T. P., Capone, G., Amstadter, A. B., & Jackson-Cook, C. (2025). Internalizing Psychiatric Symptoms in People with Mosaicism for Trisomy 21. American journal of medical genetics. Part B, Neuropsychiatric genetics: the official publication of the International Society of Psychiatric Genetics, 198(5), e33022. https://doi.org/10.1002/ajmg.b.33022

Frontier in Medical & Health Research

ISSN: (e) 3007-1607 (p) 3007-1593

Buczyńska, A., Sidorkiewicz, I., Krętowski, A. J., & Zbucka-Krętowska, M. (2023). The role of oxidative stress in trisomy 21 phenotype. Cellular and Molecular Neurobiology, 43(8), 3943-3963.

Bull, M. J. (2020). Down syndrome. New England Journal of Medicine, 382(24), 2344-2352.

Bull, M. J., Trotter, T., Santoro, S. L., Christensen, C., Grout, R. W., & Council on Genetics. (2022). Health supervision for children and adolescents with Down syndrome. Pediatrics, 149(5), e2022057010.

Calcaterra, V., Gazzarri, A., De Silvestri, A., Madia, C., Baldassarre, P., Rossi, V., ... & Zuccotti, G. (2023). Thyroid function, sensitivity to thyroid hormones, and metabolic syndrome in euthyroid children and adolescents with Down syndrome. Journal of Endocrinological Investigation, 46(11), 2319-2325.

Chapman, L. R., Ramnarine, I. V., Zemke, D., Majid, A., & Bell, S. M. (2024). Gene expression studies in Down syndrome: what do they tell us about disease phenotypes? International journal of molecular sciences, 25(5), 2968.

Chen, L., Wang, L., Wang, Y., Hu, H., Zhan, Y., Zeng, Z., & Liu, L. (2022). Global, regional, and national burden and trends of Down syndrome from 1990 to 2019. Frontiers in Genetics, 13, 908482.

Chen, X. Q., Xing, Z., Chen, Q. D., Salvi, R. J., Zhang, X., Tycko, B., ... & Yu, Y. E. (2021). Mechanistic analysis of age-related clinical manifestations in Down syndrome. Frontiers in Aging Neuroscience, 13, 700280.

Chung, H., Green, P. H. R., Wang, T. C., & Kong, X. F. (2021). Interferon-Driven Immune Dysregulation in Down Syndrome: A Review of the Evidence. Journal of inflammation research, 14, 5187–5200. https://doi.org/10.2147/JIR.S280953

Cozzolino, K., Sanford, L., Hunter, S., Molison, K., Erickson, B., Courvan, M. C. S., Jones, T., Ajit, D., Galbraith, M. D., Espinosa, J. M., Bentley, D. L., Allen, M. A., Dowell, R. D., & Taatjes, D. J. (2024). Mediator kinase inhibition suppresses hyperactive interferon signaling in Down syndrome. bioRxiv: the preprint server for biology, 2023.07.05.547813. https://doi.org/10.1101/2023.07.05.547813

Danopoulos, S., Deutsch, G. H., Dumortier, C., Mariani, T. J., & Al Alam, D. (2021). Lung disease manifestations in Down syndrome. American journal of physiology. Lung cellular and molecular physiology, 321(5), L892–L899.

De Toma, I., Sierra, C., & Dierssen, M. (2021). Meta-analysis of transcriptomic data reveals clusters of consistently deregulated gene and disease ontologies in Down syndrome. PLoS computational biology, 17(9), e1009317. https://doi.org/10.1371/journal.pcbi.1009317

Dekker, A. D., Ulgiati, A. M., Groen, H., Boxelaar, V. A., Sacco, S., Falquero, S., ... & De Deyn, P. P. (2021). The behavioral and psychological symptoms of dementia in Down syndrome scale (BPSD-DS II): Optimization and further validation. Journal of Alzheimer's Disease, 81(4), 1505-1527.

Frontier in Medical & Health Research

ISSN: (e) 3007-1607 (p) 3007-1593

Dimopoulos, K., Constantine, A., Clift, P., Condliffe, R., Moledina, S., Jansen, K., Inuzuka, R., Veldtman, G. R., Cua, C. L., Tay, E. L. W., Opotowsky, A. R., Giannakoulas, G., Alonso-Gonzalez, R., Cordina, R., Capone, G., Namuyonga, J., Scott, C. H., D'Alto, M., Gamero, F. J., Chicoine, B., ... for Down Syndrome International (DSi). (2023). Cardiovascular Complications of Down Syndrome: Scoping Review and Expert Consensus. Circulation, 147(5), 425–441.

Donovan, M. G., Eduthan, N. P., Smith, K. P., Britton, E. C., Lyford, H. R., Araya, P., Granrath, R. E., Waugh, K. A., Enriquez Estrada, B., Rachubinski, A. L., Sullivan, K. D., Galbraith, M. D., & Espinosa, J. M. (2024). Variegated overexpression of chromosome 21 genes reveals molecular and immune subtypes of Down syndrome. Nature communications, 15(1), 5473.

Drachmann, D., Carrigg, A., Weinstein, D. A., Petersen, J. S., & Christesen, H. T. (2021). Ketotic hypoglycemia in patients with Down syndrome. JIMD reports, 62(1), 70-73.

Faruk T, King C, Muhit M, Islam MK, Jahan I, Baset KU, Badawi N, Khandaker G. Screening tools for early identification of children with developmental delay in low- and middle-income countries: a systematic review. BMJ Open. 2020 Nov 23; 10(11): e038182. doi: 10.1136/bmjopen-2020-038182. Erratum in: BMJ Open. 2021 Nov 16; 11(11): e038182corr1. doi: 10.1136/bmjopen-2020-038182corr1. PMID: 33234622; PMCID: PMC7684835.

Feng, Y., Jin, Q., Liu, X., Lin, T., Johnson, A., & Huang, H. (2025). Advances in understanding dietary fiber: Classification, structural characterization, modification, and gut microbiome interactions. Comprehensive Reviews in Food Science and Food Safety, 24(1), e70092.

G. de Graaf, G., & Skotko, B. G. (2025). Parents' Experiences of Diagnosis and Screening for Down Syndrome in The Netherlands. American Journal of Medical Genetics Part A, e64250.

Ganguly, B. B., & Kadam, N. N. (2023). Therapeutics for mitochondrial dysfunction-linked diseases in Down syndrome. Mitochondrion, 68, 25–43. https://doi.org/10.1016/j.mito.2022.11.003

Ghosh, S., Jackson-Cook, C., Singhal, N., & Hui, S. P. (2023). Down syndrome: Genetic and epigenetic influences on this multi-faceted condition. Frontiers in Genetics, 14, 1163133.

Gillenwater, L. A., Galbraith, M. D., Rachubinski, A. L., Eduthan, N. P., Sullivan, K. D., Espinosa, J. M., & Costello, J. C. (2024). Integrated analysis of immunometabolic interactions in Down syndrome. Science advances, 10(50), eadq3073. https://doi.org/10.1126/sciadv.adq3073

Gondek, K., Wojcieszek, M., Czarnota, M., Gacka, D., Fidelis, M., Żołnierek, A., & Tanç, Z. (2025). Gene Therapy and Down Syndrome: Can the future of Medicine bring a breakthrough? Journal of Education, Health and Sport, 82, 60525-60525.

Gruszka, J., & Włodarek, D. (2024). General Dietary Recommendations for People with Down Syndrome. Nutrients, 16(16), 2656.

Gupt, A., Naudiyal, S., Rani, A., & Kumar, S. (2024). Mental health and the microbiome: a review of psychological impacts of gut microflora. Current Pharmacology Reports, 10(4), 223-236.

Frontier in Medical & Health Research

ISSN: (e) 3007-1607 (p) 3007-1593

Haider, A., Khan, S., Tafweez, R., & Yaqoob, M. (2024). Gender and its association with cardiac defects in Down syndrome population at Children Hospital & Institute of Child Health, Lahore, Pakistan. Pakistan journal of medical sciences, 40(3Part-II), 371–375. https://doi.org/10.12669/pjms.40.3.7346

Hamadelseed, O., & Skutella, T. (2025). Stem cell-based therapeutic strategies for Down syndrome and Alzheimer's disease. Stem Cell Research & Therapy, 16(1), 420.

Hamadelseed, O., Chan, M. K. S., Wong, M. B. F., & Skutella, T. (2023). Distinct neuroanatomical and neuropsychological features of Down syndrome compared to related neurodevelopmental disorders: a systematic review. Frontiers in neuroscience, 17, 1225228. https://doi.org/10.3389/fnins.2023.1225228

Hao, X., Zhang, J., Ma, R., Yao, B., & Yang, W. (2025). Traditional Chinese medicine and gut microbiota: biotransformation, interaction, and implications for chronic disease treatment. Drug Metabolism Reviews, 57(4), 338-361.

Hendrix, J. A., Amon, A., Abbeduto, L., Agiovlasitis, S., Alsaied, T., Anderson, H. A., ... & Yi, J. S. (2021). Opportunities, barriers, and recommendations in Down syndrome research. Translational science of rare diseases, 5(3-4), 99-129.

Hielscher, L., Irvine, K., Ludlow, A. K., Rogers, S., & Mengoni, S. E. (2023). A Scoping Review of the Complementary Feeding Practices and Early Eating Experiences of Children with Down Syndrome. Journal of pediatric psychology, 48(11), 914–930. https://doi.org/10.1093/jpepsy/jsad060

Hom B, Boyd NK, Vogel BN, Nishimori N, Khoshnood MM, Jafarpour S, Nagesh D, Santoro JD. Down Syndrome and Autoimmune Disease. Clin Rev Allergy Immunol. 2024 Jun;66(3):261-273. doi: 10.1007/s12016-024-08996-2. Epub 2024 Jun 24. PMID: 38913142; PMCID: PMC11422465.

Hunter, S., Hendrix, J., Freeman, J., Dowell, R. D., & Allen, M. A. (2023). Transcription dosage compensation does not occur in Down syndrome. BMC biology, 21(1), 228. https://doi.org/10.1186/s12915-023-01700-4

Kezer, G., Paramithiotis, S., Khwaldia, K., Harahap, I. A., Čagalj, M., Šimat, V., ... & Esatbeyoglu, T. (2025). A comprehensive overview of the effects of probiotics, prebiotics and synbiotics on the gut-brain axis. Frontiers in Microbiology, 16, 1651965.

Krivega, M., Stiefel, C. M., & Storchova, Z. (2022). Consequences of chromosome gain: A new view on trisomy syndromes. American journal of human genetics, 109(12), 2126–2140. https://doi.org/10.1016/j.ajhg.2022.10.014

Ładno, D., Nowak, B., Palka, A., Strzelecki, D., & Gawlik-Kotelnicka, O. (2025). Selected Lipidome Components and Their Association with Perinatal Depression. Nutrients, 17(22), 3590.

Lambert, K., Moo, K. G., Arnett, A., Goel, G., Hu, A., Flynn, K. J., Speake, C., Wiedeman, A. E., Gersuk, V. H., Linsley, P. S., Greenbaum, C. J., Long, S. A., Partridge, R., Buckner, J. H., & Khor, B. (2022). Deep immune phenotyping reveals similarities between aging, Down syndrome, and autoimmunity. Science translational medicine, 14(627), eabi4888. https://doi.org/10.1126/scitranslmed.abi4888

Frontier in Medical & Health Research

ISSN: (e) 3007-1607 (p) 3007-1593

Levman, J., McCann, B., Baumer, N., Lam, M. Y., Shiohama, T., Cogger, L., MacDonald, A., & Takahashi, E. (2024). Structural Magnetic Resonance Imaging-Based Surface Morphometry Analysis of Pediatric Down Syndrome. Biology, 13(8), 575. https://doi.org/10.3390/biology13080575

Li Z, Chang TC, Junco JJ, Devidas M, Li Y, Yang W, Huang X, Hedges DJ, Cheng Z, Shago M, Carroll AJ, Heerema NA, Gastier-Foster J, Wood BL, Borowitz MJ, Sanclemente L, Raetz EA, Hunger SP, Feingold E, Rosser TC, Sherman SL, Loh ML, Mullighan CG, Yu J, Wu G, Lupo PJ, Rabin KR, Yang JJ. Genomic landscape of Down syndrome-associated acute lymphoblastic leukemia. Blood. 2023 Jul 13; 142(2):172-184. doi: 10.1182/blood.2023019765. PMID: 37001051; PMCID: PMC10352600.

Liu, J., Chen, S., Huang, G., Wen, P., Zhou, X., & Wu, Y. (2024). Trisomy 21-driven metabolite alterations are linked to cellular injuries in Down syndrome. Cellular and Molecular Life Sciences, 81(1), 112.

Ma, X., Li, W., Ma, J., Han, Z., Deng, S., & Wang, S. (2024). Autophagy is a promising process for linking inflammation and redox homeostasis in Down syndrome. Frontiers in pharmacology, 15, 1491563. https://doi.org/10.3389/fphar.2024.1491563

Malle, L., Patel, R. S., Martin-Fernandez, M., Stewart, O. J., Philippot, Q., Buta, S., Richardson, A., Barcessat, V., Taft, J., Bastard, P., Samuels, J., Mircher, C., Rebillat, A. S., Maillebouis, L., Vilaire-Meunier, M., Tuballes, K., Rosenberg, B. R., Trachtman, R., Casanova, J. L., Notarangelo, L. D., ... Bogunovic, D. (2023). Autoimmunity in Down's syndrome via cytokines, CD4 T cells and CD11c+ B cells. Nature, 615(7951), 305–314. https://doi.org/10.1038/s41586-023-05736-y

Marqui, A. B. T. D., & Borges, M. D. F. (2024). (In) Fertility in the Down syndrome. Revista da Associação Médica Brasileira, 70(9), e20240537.

Maure-Blesa, L., Carmona-Iragui, M., Lott, I., Head, E., Wisniewski, T., Rafii, M. S., & Fortea, J. (2025). The history of Down syndrome–associated Alzheimer's disease; past, present, and future. Alzheimer's & Dementia, 21(6), e70158.

Maure-Blesa, L., Carmona-Iragui, M., Lott, I., Head, E., Wisniewski, T., Rafii, M. S., & Fortea, J. (2025). The history of Down syndrome–associated Alzheimer's disease; past, present, and future. Alzheimer's & Dementia, 21(6), e70158.

Mollo, N., Scognamiglio, R., Conti, A., Paladino, S., Nitsch, L., & Izzo, A. (2023). Genetics and molecular basis of congenital heart defects in Down syndrome: role of extracellular matrix regulation. International journal of molecular sciences, 24(3), 2918.

Moncada Arita, W. A., Perdomo Domínguez, E. S., Rivera Caballero, A. Y., Espinoza-Moreno, N. A., Zavala Galeano, M. E., DuPont, B. R., & Ramos-Zaldívar, H. M. (2022). Multi-tissue cytogenetic analysis for the diagnosis of mosaic Down syndrome: a case report. Clinical Case Reports, 10(4), e05604.

Frontier in Medical & Health Research

ISSN: (e) 3007-1607 (p) 3007-1593

Montoliu-Gaya, L., Strydom, A., Blennow, K., Zetterberg, H., & Ashton, N. J. (2021). Blood biomarkers for Alzheimer's disease in Down syndrome. Journal of Clinical Medicine, 10(16), 3639.

Moreau M, Benhaddou S, Dard R, Tolu S, Hamzé R, Vialard F, Movassat J, Janel N. Metabolic Diseases and Down Syndrome: How Are They Linked Together? Biomedicines. 2021 Feb 22;9(2):221. doi: 10.3390/biomedicines9020221. PMID: 33671490; PMCID: PMC7926648.

Mouat, J. S., Li, S., Myint, S. S., Laufer, B. I., Lupo, P. J., Schraw, J. M., & LaSalle, J. M. (2023). Epigenomic signature of major congenital heart defects in newborns with Down syndrome. Human genomics, 17(1), 92.

Murray, A., Gough, G., Cindrić, A., Vučković, F., Koschut, D., Borelli, V., & Nižetić, D. (2023). Dose imbalance of DYRK1A kinase causes systemic progeroid status in Down syndrome by increasing the un-repaired DNA damage and reducing LaminB1 levels. EBioMedicine, 94.

Muskens, I. S., Li, S., Jackson, T., Elliot, N., Hansen, H. M., Myint, S. S., Pandey, P., Schraw, J. M., Roy, R., Anguiano, J., Goudevenou, K., Siegmund, K. D., Lupo, P. J., de Bruijn, M. F. T. R., Walsh, K. M., Vyas, P., Ma, X., Roy, A., Roberts, I., Wiemels, J. L., ... de Smith, A. J. (2021). The genome-wide impact of trisomy 21 on DNA methylation and its implications for hematopoiesis. Nature communications, 12(1), 821. https://doi.org/10.1038/s41467-021-21064-z

Nájera-Maldonado, L., Parra-González, M., Peralta-Cuevas, E., Gutierrez-Onofre, A. J., Garcia-Atutxa, I., & Villanueva-Flores, F. (2025). Cracking the Blood–Brain Barrier Code: Rational Nanomaterial Design for Next-Generation Neurological Therapies. Pharmaceutics, 17(9), 1169.

Naumova, O. Y., Lipschutz, R., Rychkov, S. Y., Zhukova, O. V., & Grigorenko, E. L. (2021). DNA Methylation Alterations in Blood Cells of Toddlers with Down Syndrome. Genes, 12(8), 1115. https://doi.org/10.3390/genes12081115

Neves, L. B. M., Baldessarini, B. L., Machado, R. C. D. M., Martins, G., Labatut, G., & Magalhães Muniz Filho, J. (2025). The Gut-Brain Axis and Stress: The Inflammatory Frontier–Integrating Barriers, Microbial Metabolites, Therapeutic Interventions, and Sex/Gender Differences.

Nordstrøm, M., Retterstøl, K., Hope, S., & Kolset, S. O. (2020). Nutritional challenges in children and adolescents with Down syndrome. The Lancet Child & Adolescent Health, 4(6), 455-464

Notarangelo, L. D., & Bosticardo, M. (2022). Interferons in Down syndrome: When more is less. Immunity, 55(11), 1967–1969. https://doi.org/10.1016/j.immuni.2022.10.011

Olagunju, A. A., & Masud, M. A. (2021). From the Genesis of Down Syndrome: What we know and what we still need to know. Clin Psychiatry, 7(1), 1-5.

Oreskovic, N. M., Austin, G., Aylward, B., Boer, P., Bricout, V. A., Cheema, N., ... & Skotko, B. G. (2025). The International Summit on Health Benefits of Physical Fitness for People with Down Syndrome: Current Science, Gaps, Priorities, and Research Opportunities.

Oter-Quintana, C., Alameda-Cuesta, A., Brito-Brito, P. R., Parro-Moreno, A. I., Alcolea-Cosín, M. T., González-Gil, T., ... & Esteban-Hernández, J. (2025). Psychosocial Nursing Diagnoses of Individuals with Myalgic Encephalomyelitis-Chronic Fatigue Syndrome: A Descriptive Study. Nursing Open, 12(5), e70212.

Frontier in Medical & Health Research

ISSN: (e) 3007-1607 (p) 3007-1593

Park, J. S. (2023). Disorders of Gut-Brain Interaction in Children with Down Syndrome. Journal of Neurogastroenterology and Motility, 29(1), 3.

Pelleri, M. C., Locatelli, C., Mattina, T., Bonaglia, M. C., Piazza, F., Magini, P., ... & Caracausi, M. (2022). Partial trisomy 21 with or without highly restricted Down syndrome critical region (HR-DSCR): report of two new cases and reanalysis of the genotype–phenotype association. BMC medical genomics, 15(1), 266.

Ptomey, L. T., Oreskovic, N. M., Hendrix, J. A., Nichols, D., & Agiovlasitis, S. (2023). Weight management recommendations for youth with Down syndrome: Expert recommendations. Frontiers in pediatrics, 10, 1064108.

Rachubinski, A. L., Wallace, E., Gurnee, E., Enriquez-Estrada, B. A., Worek, K. R., Smith, K. P., Araya, P., Waugh, K. A., Granrath, R. E., Britton, E., Lyford, H. R., Donovan, M. G., Eduthan, N. P., Hill, A. A., Martin, B., Sullivan, K. D., Patel, L., Fidler, D. J., Galbraith, M. D., Dunnick, C. A., ... Espinosa, J. M. (2024). JAK inhibition decreases the autoimmune burden in Down syndrome. eLife, 13, RP99323. https://doi.org/10.7554/eLife.99323

Rafferty, K., Archer, K. J., Turner, K., Brown, R., & Jackson-Cook, C. (2021). Trisomy 21-associated increases in chromosomal instability are unmasked by comparing isogenic trisomic/disomic leukocytes from people with mosaic Down syndrome. PLoS One, 16(7), e0254806.

Raj, S., Stanley, M., Mackintosh, S., & Fryer, C. (2020). Scope of occupational therapy practice for adults with both Down syndrome and dementia: A cross-sectional survey. Australian Occupational Therapy Journal, 67(3), 218-228.

Ramba, M., & Bogunovic, D. (2024). The immune system in Down Syndrome: Autoimmunity and severe infections. Immunological reviews, 322(1), 300–310. https://doi.org/10.1111/imr.13296

Ranade SS, Li F, Whalen S, Pelonero A, Ye L, Huang Y, Brand A, Nishino T, Mital R, Boileau RM, Koback F, Padmanabhan A, Yu V, Cimarosti B, Presas-Ramos D, Merriman AF, Wallace LG, Nguyen A, Poulis N, Costa MW, Gifford CA, Pollard KS, Srivastava D. Myocardial reprogramming by HMGN1 underlies heart defects in trisomy 21. Nature. 2025 Nov;647(8091):979-987. doi: 10.1038/s41586-025-09593-9. Epub 2025 Oct 22. PMID: 41125893; PMCID: PMC12657217.

Rastogi, M., Bartolucci, M., Nanni, M., Aloisio, M., Vozzi, D., Petretto, A., & Cancedda, L. (2024). Integrative multi-omic analysis reveals conserved cell-projection deficits in human Down syndrome brains. Neuron, 112(15), 2503-2523.

Ravel, A., Mircher, C., Rebillat, A. S., Cieuta-Walti, C., & Megarbane, A. (2020). Feeding problems and gastrointestinal diseases in Down syndrome. Archives de Pédiatrie, 27(1), 53-60.

Risgaard, K. A., Sorci, I. A., Mohan, S., & Bhattacharyya, A. (2022). Meta-Analysis of Down Syndrome Cortical Development Reveals Underdeveloped State of the Science. Frontiers in cellular neuroscience, 16, 915272. https://doi.org/10.3389/fncel.2022.915272

Saberi, R. A., Gilna, G. P., Slavin, B. V., Huerta, C. T., Ramsey, W. A., O'Neil Jr, C. F., ... & Thorson, C. M. (2022). Hirschsprung disease in Down syndrome: an opportunity for improvement. Journal of pediatric surgery, 57(6), 1040-1044.

Frontier in Medical & Health Research

ISSN: (e) 3007-1607 (p) 3007-1593

Shimada, A. (2021). Profile of Down syndrome–associated malignancies: Epidemiology, clinical features and therapeutic aspects. Pediatric hematology oncology journal, 6(2), 63-72.

Si, L., Tian, L., Tian, X., & Zhang, S. (2025). Etiological considerations for the heightened incidence and intensity of periodontal disease in Down syndrome: a narrative review. Journal of Clinical Pediatric Dentistry, 49(2).

Siddiqui, A., Ladak, L. A., Kazi, A. M., Kaleem, S., Akbar, F., & Kirmani, S. (2021). Assessing health-related quality of life, morbidity, and survival status for individuals with Down syndrome in Pakistan (DS-Pak): protocol for a web-based collaborative registry. JMIR Research Protocols, 10(6), e24901.

Slivšek, G., Mijač, S., Dolanc, I., Fabijanec, M., Petković, S., Mautner, R., Lončarek, K., Kranjčić, J., Blagaić, A. B., Marinović, M., Vitale, K., Verbanac, D., Čoklo, M., & Vraneković, J. (2025). Oxidative Stress and Down Syndrome: A Systematic Review. Antioxidants (Basel, Switzerland), 14(7), 816. https://doi.org/10.3390/antiox14070816

Souto, D. O., de Sousa, M. O., Ferreira, R. G., Brandão, A. C., Carrera, P. B., & Leite, H. R. (2024). What are the barriers and facilitators to participation of people with Down syndrome? A scoping review. Developmental medicine and child neurology, 66(8), 1013–1030. https://doi.org/10.1111/dmcn.15857

Spinazzi NA, Santoro JD, Pawlowski K, Anzueto G, Howe YJ, Patel LR, Baumer NT. Co-occurring conditions in children with Down syndrome and autism: a retrospective study. J Neurodev Disord. 2023 Mar 2; 15(1):9. doi: 10.1186/s11689-023-09478-w. PMID: 36864370; PMCID: PMC9979529.

Srivastava, R., & Gupta, M. K. (2025). Gut bacteria-derived metabolites and their implications in mental health and neurological diseases. World Journal of Microbiology and Biotechnology, 41(11), 423.

Szczawińska-Popłonyk, A., Popłonyk, N., & Awdi, K. (2024). Down Syndrome in Children: A Primary Immunodeficiency with Immune Dysregulation. Children (Basel, Switzerland), 11(10), 1251. https://doi.org/10.3390/children11101251

Ternák, G., Márovics, G., Sümegi, K., Bánfai, Z., Büki, G., Magyari, L., & Melegh, B. (2023). Down-syndrome-related maternal dysbiosis might be triggered by certain classes of antibiotics: a new insight into the possible pathomechanisms. Antibiotics, 12(6), 1029.

Thomas, J. R. (2025). Sensory Neuron Development and Skeletal Deficits in Down Syndrome (Doctoral dissertation).

Tsou, A. Y., Bulova, P., Capone, G., Chicoine, B., Gelaro, B., Harville, T. O., Martin, B. A., McGuire, D. E., McKelvey, K. D., Peterson, M., Tyler, C., Wells, M., Whitten, M. S., & Global Down Syndrome Foundation Medical Care Guidelines for Adults with Down Syndrome Workgroup (2020). Medical Care of Adults with Down Syndrome: A Clinical Guideline. JAMA, 324(15), 1543–1556. https://doi.org/10.1001/jama.2020.17024

Frontier in Medical & Health Research

ISSN: (e) 3007-1607 (p) 3007-1593

Tu, X., Zhang, F., Chen, J., & Tang, M. (2025). Down syndrome burden in China and globally: a comparative analysis of 1990-2021 trends and future projections based on GBD 2021 database. Frontiers in Public Health, 13, 1632250.

Venegas-Zamora, L., Bravo-Acuña, F., Sigcho, F., Gomez, W., Bustamante-Salazar, J., Pedrozo, Z., & Parra, V. (2022). New Molecular and Organelle Alterations Linked to Down Syndrome Heart Disease. Frontiers in genetics, 12, 792231. https://doi.org/10.3389/fgene.2021.792231

Verma, A., Lupo, P. J., Shah, N. N., Hitzler, J., & Rabin, K. R. (2023). Management of Down Syndrome–Associated Leukemias: A Review. JAMA oncology, 9(9), 1283-1290

Vinski, D. S. P. V. P., Nugroho, A. K., Vinski, N. C., Dollar, D., & Gunawan, D. (2025). Exploring the Role of Stem Cell Therapy in Improving Cognitive and Physical Outcomes for Down Syndrome Patients. Journal of World Science, 4(1), 142-151.

Wang, Z., Xue, X., Zhang, H., Liu, J., Dai, S., Duan, H., & Li, S. (2025). Vaccine research in cognitive impairment and dementia: a bibliometric analysis and future outlook (2000–2025). Frontiers in Neurology, 16, 1662314.

Waugh, K. A., Wilkins, H. M., Smith, K. P., & Ptomey, L. T. (2025). Charting the future: current and future directions in translational research for individuals with Down syndrome. Journal of Neurodevelopmental Disorders, 17(1), 38.

Weden, M. M., Frank, L., Dick, A. W., Wang, Z., Peschin, S., Bovenkamp, D. E., & Fisher, R. A. (2025). Investment in Alzheimer's disease research for the next generation of adults with Down syndrome will yield health benefits for future generations. Alzheimer's & Dementia, 21(9), e70348.

Xicota, L., Dang, L. T., Lee, A., Krinsky-McHale, S., Pang, D., Melilli, L., O'Bryant, S., Henson, R. L., Laymon, C., Lai, F., Rosas, H. D., Ances, B., Lott, I., Hom, C., Christian, B., Hartley, S., Zaman, S., Head, E., Mapstone, M., Jin, Z., ... Alzheimer's Biomarker Consortium – Down Syndrome (ABC-DS) (2024). The effects of mosaicism on biological and clinical markers of Alzheimer's disease in adults with Down syndrome. EBioMedicine, 110, 105433. https://doi.org/10.1016/j.ebiom.2024.105433

Xu, K., Li, S., Muskens, I. S., Elliott, N., Myint, S. S., Pandey, P., Hansen, H. M., Morimoto, L. M., Kang, A. Y., Ma, X., Metayer, C., Mueller, B. A., Roberts, I., Walsh, K. M., Horvath, S., Wiemels, J. L., & de Smith, A. J. (2022). Accelerated epigenetic aging in newborns with Down syndrome. Aging cell, 21(7), e13652. https://doi.org/10.1111/acel.13652

Ye, E., Wu, E., & Han, R. (2025). Global, regional, and national impact of Down syndrome on child and adolescent mortality from 1980 to 2021, with projections to 2050: a cross-sectional study. Frontiers in public health, 13, 1554589. https://doi.org/10.3389/fpubh.2025.1554589

Zacny, A., Saniewska, B., Orzeł, M., Borek-Dzięcioł, B., & Kociszewska-Najman, B. (2025). Case Report: Transient myeloproliferative disorder with trisomy 21 in blast cells. Frontiers in Pediatrics, 13, 1604803.

Zhang, H., Yuan, S., Bao, H., Chen, W., Cai, B., Sun, J., ... & Lu, W. (2025). Mapping the intersection of HIV and Alzheimer's disease: a bibliometric analysis of emerging research trends. Frontiers in Neurology, 16, 1568022.

Frontier in Medical & Health Research

ISSN: (e) 3007-1607 (p) 3007-1593

Zhang, X., & Zhao, W. A Case Report of Neonatal Death due to Transient Myeloproliferative Disorder with Hepatic Fibrosis in Trisomy 21. Clin Case Rep Int. 2024; 8, 1704.

Zhou, Y., Sheehan, R., Guo, L., & Strydom, A. (2025). Blood-based biomarkers for Alzheimer's disease in Down syndrome: A systematic review and meta-analysis. Alzheimer's & dementia: the journal of the Alzheimer's Association, 21(4), e70135. https://doi.org/10.1002/alz.70135

Zhuang, M., Zhang, X., & Cai, J. (2024). Microbiota–gut–brain axis: interplay between microbiota, barrier function and lymphatic system. Gut microbes, 16(1), 2387800.

Zuo, X. (2025). Mitochondrial imbalance in Down syndrome: A driver of accelerated brain aging? Aging and Disease, 16(5), 2674.

Zur, S., Sokal, A., Staśkiewicz-Bartecka, W., Kiciak, A., Grajek, M., Krupa-Kotara, K., & Białek-Dratwa, A. (2025, January). Nutrition for Children with Down Syndrome Current Knowledge, Challenges, and Clinical Recommendations—A Narrative Review. In Healthcare (Vol. 13, No. 17, p. 2222). Multidisciplinary Digital Publishing Institute.