IJCRT.ORG ISSN : 2320-2882

INTERNATIONAL JOURNAL OF CREATIVE RESEARCH THOUGHTS (IJCRT)

An International Open Access, Peer-reviewed, Refereed Journal

Nephrotic Syndrome: An Integrative Review Of Epidemiology, Environmental Triggers And Clinical Implications

Gurinder Kaur Walia[1], Lipsa Dehal[2*], Navjot Kaur[3]

Professor[1], Research Scholar[2*], M.Sc. Student[3]

Department of Zoology and Environmental Sciences, Punjabi University, Patiala

Abstract

Peripheral edema, severe proteinuria, and hypoalbuminemia often in combination with hyperlipidemia are the hallmarks of nephrotic syndrome (NS). People typically exhibit fatigue and edema, but no indications of severe liver disease or heart failure. NS can be identified by its distinctive medical symptoms, hypoalbuminemia, and severe proteinuria. Understanding NS outside of the clinic necessitates paying consideration to its epidemiological trends, lifestyle causes, and preventive methods, even though its clinical manifestations and management are well-established. With a growing burden seen in both developed and low-resource nations, this study summarizes global and regional epidemiological patterns, emphasizing differences in prevalence among age groups, gender, and geographic contexts. The importance of lifestyle and environmental factors, such as eating patterns, obesity, sedentary behavior, and exposure to environmental pollutants such pesticides, heavy metals, and air pollution, is highlighted by new research. Disease risk and consequences are further increased by socioeconomic variables, especially poverty, delayed access to healthcare, and urban–rural inequities. Understanding disease heterogeneity also heavily relies on immunological triggers and genetic predispositions. Crucially, there are ways to lower the incidence and course of disease through preventive measures that range from public health initiatives that support a healthy diet and regular exercise to early screening of groups at risk and reducing environmental exposures. This review highlights a comprehensive approach to NS by combining epidemiological findings with lifestyle and prophylactic aspects, thereby bridging the gap between clinical therapy and community-level health promotion.

Keywords: Nephrotic syndrome, epidemiology, lifestyle, environmental risk, prevention, kidney disease.

1. INTRODUCTION

The renal disease known as nephrotic syndrome (NS), which can be primary glomerular disorders or due to systemic problems, is typified by significant proteinuria and hypoalbuminemia. There is a dearth of recent data on the prevalence and mortality of adult nephrotic syndrome. Diabetes and cancer, two diseases linked to secondary nephrotic syndromes, have become more common worldwide in recent decades as the population ages. The prevalence of nephrotic syndrome might have been affected by this. Nephrotic syndrome mortality could have been impacted by a variety of variables throughout that time. On the one hand, the ageing population and the overall worldwide rise in the economic burden of noncommunicable conditions may have altered the demographics of patients with nephrotic syndrome (Chesnaye et al. 2024). On the other hand, novel treatment regimens, such as biologics, have improved the treatment of some types of primary nephrotic syndrome. These, along with better cardiovascular care and prevention, may have reduced the death rate from nephrotic syndrome (Robinson et al. 2025). Prior research on the incidence and mortality of nephrotic syndrome has concentrated on patients who have had kidney biopsies, even though not all people with the condition have one. According to these studies, the overall death rate during the first five years of follow-up following nephrotic syndrome is 6-21%, and the frequency of adult nephrotic syndrome (NS) ranges from 0.58 to 4.2 per 100,000 person years (Bogdanović et al. 2025). Furthermore, a number of research have looked at the mortality rate from nephrotic syndrome in patient subgroups with particular glomerulopathy types.

Based mostly on histology findings, there are many forms of nephrotic syndrome. MCD, the most prevalent kind in children, frequently reacts favorably to corticosteroids. With varying levels of treatment response and progression risk, membranous nephropathy (MN) and focal segmental glomerulosclerosis (FSGS) are more common in adulthood (Gembillo et al. 2025). Systemic diseases including kidney failure due to diabetes, lupus nephritis, hepatitis B or C infections, malaria, or even the use of specific medications like NSAIDs or gold salts might cause secondary nephrotic syndrome. In familial or steroid-resistant cases, especially in early-onset disease, genetic mutations in podocyte-related proteins such NPHS1 (nephrin) or NPHS2 (podocin) have also been found (Roman et al. 2024).

Minimal change disease is the most prevalent glomerular lesion in children with nephrotic syndrome, and the majority of them have either primary or idiopathic nephrotic syndrome. Idiopathic nephrotic syndrome is more frequent in boys and often manifests between the ages of 2 and 6; 95% of cases are steroid responsive. Idiopathic nephrotic syndrome has no known origin, although there is evidence that it is caused by a primary T cell disease that results in glomerular prodocyte malfunction. Sahana (2014). 96% of the 195 instances had it. 69 patients (36%) had onset before the ages of 5 and 14, and 77% of these patients were male (Rahiman, 2015).

From infancy to puberty, children of all ages can be affected by nephrotic syndrome, although school-aged children and adolescents are most frequently affected. Considering an average of 2 to 7 occurrences per 100,000 children, the frequency is roughly 16 instances per 100,000 children worldwide. In children, boys seem to be more impacted than females at a 2:1 ratio; however, this trend does not continue throughout adolescents. Seventy-five percent of the impacted children are under ten years old, and around half are between the ages of one year six months and five. Nephrotic syndrome primarily affects South Asian children, with 95% of cases being primary (idiopathic Nephrotic syndrome) (Banh et al. 2016).

Studies on the clinical characteristics of nephrotic syndrome are scarce in India. Although the prevalence of nephrotic syndrome has not changed, pediatricians are seeing fewer cases than in the past as a result of more accessible healthcare and a dispersed patient population. Therefore, the purpose of this study is to examine the clinical presentation, related problems, investigation profile, and response to treatment in children having nephrotic syndrome.

2. EPIDEMIOLOGICAL TRENDS OF NEPHROTIC SYNDROME (NS)

Genetic, demographic, socioeconomic, and environmental factors all influence the epidemiology of nephrotic syndrome (NS), which exhibits significant variation across populations. Prevalence rates range from 12 to 16 cases per 100,000 children, although the annual incidence of NS in children is estimated to be 2–7 cases per 100,000 worldwide (Eddy & Symons, 2003; Noone et al. 2018). Although the burden is relatively smaller in adults, it is more likely to be linked to more complicated etiologies, higher rates of treatment resistance, and an increased risk of developing end-stage renal disease (ESRD) and chronic kidney disease (CKD). Important epidemiological insights have been obtained from long-term follow-up investigations. While nearly 80% of children with primary NS experienced their initial remission with corticosteroids, relapse was common, and approximately 10% eventually developed compromised renal function, according to Koskimies et al. (1982) observations of outcomes in 114 children over a ten-year period. Additionally, Tarshish et al. (1996) shown that early steroid response was a strong predictor of future outcomes, with children who did not reach remission within 8 weeks having a significantly increased risk of developing end-stage renal disease. Epidemiological studies clearly show the role of hereditary variables. Congenital nephrotic syndrome of the Finnish type (CNF) has one of the highest occurrences in the world, occurring in about 1 in 8,200 live births in Finland. This indicates that NPHS1 gene mutations have a substantial founder impact. With up to 70–90% of cases in pediatric cohorts, minimal change disease (MCD) continues to be the most prevalent subtype in children (Bilinska et al. 2004). However, throughout the past 20 years, focal segmental glomerulosclerosis (FSGS) has gained more recognition in both adults and children, especially in North America, Africa, and South Asia, where it currently accounts for 20–40% of cases. There are worries over the changing natural history of NS because FSGS is commonly linked to steroid resistance and a worse prognosis. According to studies, socioeconomic hurdles, repeated infections, and environmental exposures all play a role in the development and progression of disease. Furthermore, the accuracy of prevalence and incidence estimates is limited in India due to the absence of population-wide renal registries, hence hospital-based data serves as the primary source of statistical information. Notwithstanding these drawbacks, patterns show that although the majority of children have steroid-sensitive disease at presentation, a sizeable minority up to 20–30% develop steroid dependence or relapse frequently, and roughly 10–15% have primary steroid resistance, requiring second-line immunosuppressive treatments (Daetwyler et al. 2024).

Because of improved supportive care, antimicrobial prevention, and accessibility to renal replacement therapy, NS mortality has significantly decreased in high-income nations. However, because of infections, malnutrition, and treatment expenses, NS continues to be linked to high rates of morbidity and mortality in low- and middle-income nations. The burden of NS-related disability-adjusted life years (DALYs) is currently poorly understood but probably underestimated worldwide, especially in children whose quality of life, growth, and education are disrupted by chronic relapses. When combined, the epidemiological profile of NS shows a disorder that presents serious clinical and public health issues despite being comparatively uncommon. Although mortality has decreased and remission rates have increased due to advancements in therapy, regional differences in results still exist.

Table 1. Epidemiological Trends of Nephrotic Syndrome (NS)

Region	Prevalence	Age and gender distribution	Histological patterns	References
Global	Approximately 16 / 100,000; prevalence: 2–7 per 100,000 children annually	prevalence 2–6 years; Male: Female ≈ 2:1	Minimal Change Disease (MCD) most common	Eddy & Symons, 2003; Noone et al. 2018
Global	Approx 3 per 100,000/year	Balanced gender distribution	FSGS (Focal Segmental Glomerulo Sclerosis) and Membranous Nephropathy (MN) dominate	Kitiyakara et al. 2004
South Asia (India, Pakistan, Bangladesh)	90–120/ million population	Frequent in children; boys more affected	MCD; infection-related NS also high	Gulati et al. 2009; Hogg et al. 2007
East Asia (China, Japan, Korea)	4–6/ 100,000/year (children)	Male predominance varies; childhood burden high	IgA nephropathy frequent; MN rising in adults	Hattori et al. 2016
Africa	Sparse data; prevalence under-reported; high secondary NS	All ages affected; secondary forms common	FSGS frequent; HIV, malaria, HBV linked NS	Olowu et al. 2017
Europe and North America	2–5 per 100,000/year (children); prevalence 15–20 per 100,000	Peak in children; slight male excess	MCD in children; MN & FSGS common in adults	McGrogan et al. 2011
Middle East	Increasing incidence, esp. Steroid-Resistant NS (SRNS)	Both children & adults	Genetic NS (NPHS1, NPHS2, WT1 mutations) more common	Banh et al. 2016
Latin America	Limited registries; prevalence underestimated	Mostly pediatric burden	FSGS most common	Vega et al. 2018

The trend of increasingly treatment-resistant histological subgroups, like FSGS, emphasizes the necessity of strong, geographically localized monitoring networks and genetic epidemiology studies to guide customized approaches for early detection, therapy, and prevention..

Congenital/infantile nephrotic syndrome (CNS), steroid-sensitive nephrotic syndrome (SSNS), and steroid-resistant nephrotic syndrome (SRNS) are the three categories into which NS can be classified according to the underlying pathophysiological causes (Boyer et al. 2021). The onset of proteinuria during its initial three months of life is a characteristic of the central nervous system. On the other hand, NS that appears later, that is, within the first year of life, specifically within four and twelve months, is referred to as infantile NS. On the other hand, NS that appears later is known as childhood NS, which can be further classified into SSNS and SRNS according to one's reaction to corticosteroid treatment that is seen four weeks

after therapy (Wang et al. 2019). The way that NS is approached has evolved due to advancements in next-generation sequencing technology.

In the past, genetic types of NS were regarded as uncommon conditions. However, recent studies have revealed that up to 30% of SRNS cases with onset below the age of 25 are caused by an underlying monogenic abnormality and that at least 66% of cases occur around the first year of life (Boyer et al. 2021). This percentage rises to 57% to 100% in familial NS and childhood-onset NS, compared to 10% to 20% in random childhood-onset instances. Significant questions still surround the pathophysiology of SSNS and SRNS of unknown genetic origin, despite advancements in genetics (Morello, 2020). The fact those glucocorticoids and other immunosuppressive medications work well in some SRNS instances and in every SSNS case suggests that the immune system plays a major role in the pathophysiology of both disorders. Recent studies, however, indicate that immunosuppressive treatments might affect podocytes directly as an additional to their immunosuppressive effects. There are 1.15 to 2.1 new cases of NS for every 100,000 children each year (Bogdanović et al. 2025). Boys are known to experience it more frequently than girls, but as people age, this disparity vanishes.

Articles demonstrating that up to 80% of children in Nigeria with NS have a type that responds extremely well to corticosteroid therapy a condition that is very similar in pediatric populations in Asia and Europe supports this (Hattori et al. 2016). Studies carried out in France also documented a seasonal increase in the incidence of this particular clinical condition that was ascribed to infections as potential triggers. These findings lend credence to the idea that both hereditary and environmental variables impact the disease. This is comparable to the findings of a study carried out in the United States that discovered a connection between the prevalence of NS and asthma and allergies (Vega et al. 2018). It is crucial to note that there are notable differences between the diagnosis of NS in adults and children. In particular, a kidney biopsy and subsequent histological classification are typically the first steps in the diagnostic procedure when NS symptoms are observed in the adult population. However, in the diagnostic process for the pediatric population, physicians initially track the response to the administered corticosteroid therapy for a number of weeks. NS is categorized according to the clinically documented response to corticosteroids after a specific amount of time. Accordingly, it is said that eight weeks after beginning corticosteroid medication, 80% of children with NS experienced remission (Chirico et al. 2025).

According to histopathological results, MCD is the cause of NS in roughly 93% of children with NS who react well to corticosteroid therapy, while another glomerular pathology is present in roughly 7% of instances. Regretfully, 20% of children fail to respond to corticosteroid medication, in addition to the cases that have a positive response to the treatment. Histopathological analysis of kidney tissue samples in children with NS resistant to corticosteroids reveals FSGS, an illness that indicates permanent damage to podocytes. While MCD and FSGS are frequently referred to as related conditions, some cases designated as MCD may eventually develop into FSGS; it is unclear whether these are distinct diseases or just different stages of the same issue (Morello, 2020).

3. GENETICS OF NEPHROTIC SYNDROME

Nephrotic syndrome (NS) comprises a complex etiology, but accumulating evidence underscores the major role of genetic abnormalities in its pathogenesis. The structural integrity of the glomerular filtration filter depends on about 50 genes, particularly those involved in podocyte formation and signaling. Steroid-resistant nephrotic syndrome (SRNS), familial focal segmental glomerulosclerosis (FSGS), and neonatal nephrotic syndrome are all closely linked to mutations in genes including NPHS1, NPHS2, WT1, and LAMB2 (Rheault and Gbadegesin, 2016). The significance of genetic testing for diagnostic and treatment decision-making is highlighted by the fact that these monogenic variants frequently manifest early in childhood and usually respond poorly to traditional immunosuppressive medication. Beyond the kidney, some mutations also result in syndromic traits; for instance, WT1 variations are associated with gonadal dysgenesis and an elevated risk of Wilms' tumor (Ha, 2016) (Figure 1).

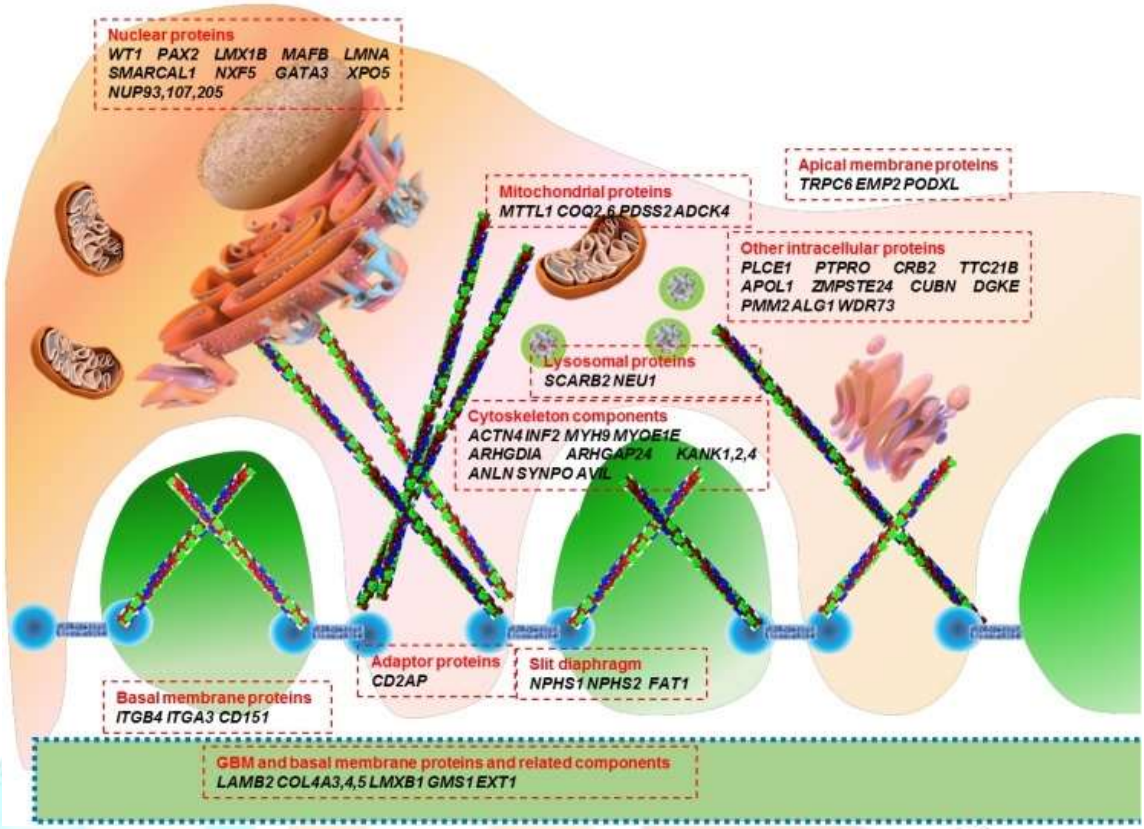

Figure 1: Podocyte gene mutations associated with nephrotic syndrome (Ha, 2016)

The field of NS genetics has significantly grown since the introduction of next-generation sequencing (NGS), which enables more accurate genotype–phenotype correlations. In addition to assisting physicians in avoiding needless and potentially hazardous immunosuppressive treatments, genetic insights also enhance genetic counseling for impacted families and offer prognostic advice (Watanabe et al. 2019). Crucially, knowledge of the molecular processes behind podocyte dysfunction paves the way for precision medicine techniques and focused treatments. A significant improvement in the treatment of individuals with nephrotic syndrome can be seen in the transition from a "one-size-fits-all" to a tailored management paradigm.

4. IMMUNOLOGICAL TRIGGERS

Immunological triggers emphasize the importance of rigorous infection control in situations with limited resources and early screening in individuals with autoimmune diseases. A complex pathophysiology of nephrotic syndrome is highlighted by the interaction of infections, immunological dysregulation, and genetic vulnerability.

The pathophysiology of idiopathic nephrotic syndrome, especially minimally modified nephrotic syndrome (MCNS), is significantly influenced by the immune system. Clinical links between NS and allergic events such pollen allergic reactions, food allergies, insect stings, and immunizations confirm Shalhoub's early theories that suggested a lymphocyte-mediated permeability factor as the origin of proteinuria. Although defining atopy varies and the high background frequency of allergies makes it difficult to show causality, greater incidences of atopy (17–40%) have been recorded in NS patients when compared to controls (Al-Aubodah et al. 2025). Due to the variability of the disease and the response to treatment, some research indicates that dietary changes or anti-allergic medications may aid in remission; however, results are not always constant. Although there is conflicting information about glomerular IgE deposition, elevated serum IgE is commonly seen in NS patients, supporting the association between allergy and illness.

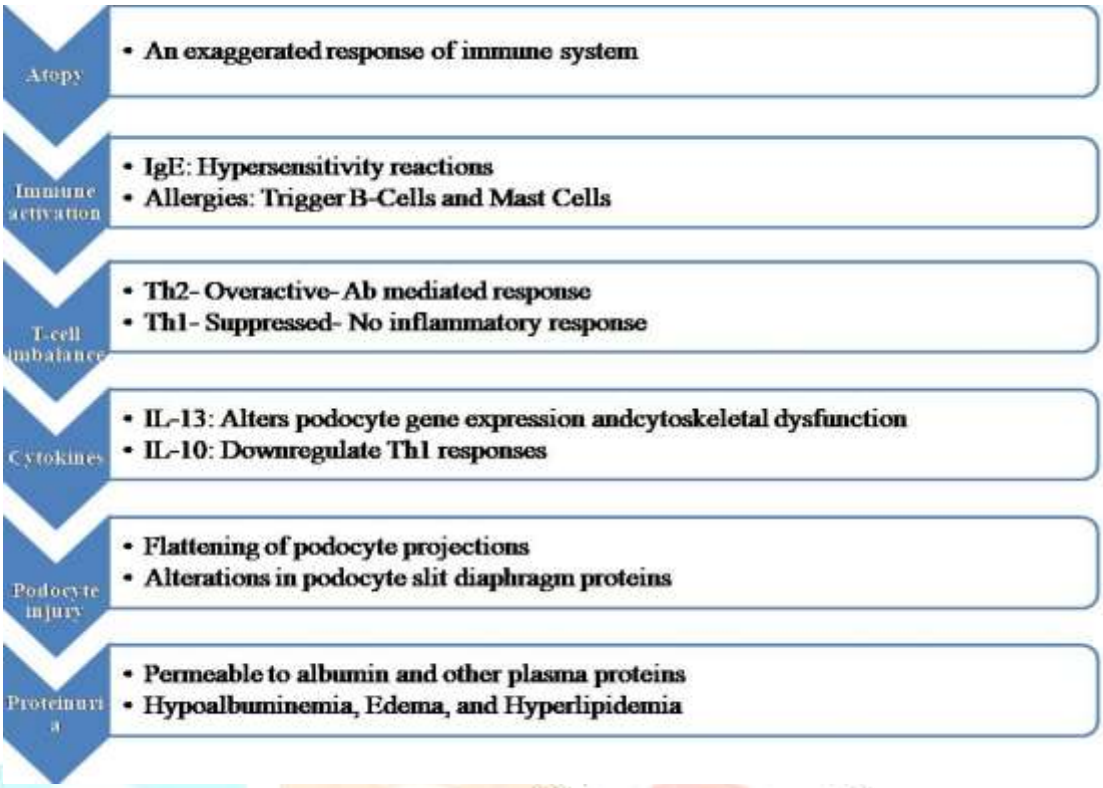

Figure 2. Domains in the Pathogenesis of Nephrotic Syndrome

More research shows that T-cells and cytokines play a key role in the pathophysiology of NS. T-cell activation, especially Th2-skewed immune responses, results in an elevated level of cytokines like IL-4, IL-10, and IL-13. In contrast, Th1 cytokines like IFN-γ and TNF-α are frequently decreased, which supports the theory of Th2 dominance (Campbell and Thurman, 2022). However, variations in research designs, therapy status, and patient heterogeneity make interpretations more difficult, and hyperlipidemia in the nephrotic condition itself can change immune function, which can skew results (Figure 2). The immune system serves a well-established function in nephrotic syndrome, especially in focal segmental glomerulosclerosis (FSGS) and minimal change disease (MCD), where aberrant immune activation is a major contributing factor (Al-Aubodah et al. 2025).

4.1 Infections: Secondary nephrotic syndrome is closely linked to bacterial (streptococcal infections), transmissible viruses (HIV, hepatitis B and C, SARS-CoV-2), and parasitic (malaria, schistosomiasis) infections, particularly in endemic areas. Immune-mediated podocyte damage brought on by infections can result in elevated glomerular permeability.

4.2 Autoimmune diseases: The most prevalent autoimmune disorders associated with nephrotic syndrome include systemic lupus erythematosus (SLE), IgA nephropathy, and membranous nephropathy. Pathogenic autoantibodies and cytokines are produced as a result of dysregulated B- and T-cell responses, and these substances target glomerular components.

4.3 Immune Dysregulation: Podocyte effacement is caused by aberrant T-cell subsets, especially Th2 cells, and raised levels of circulating cytokines, such as IL-13, TNF-α, and IFN-γ. Recent data indicates that hyperactive B-cell pathways and regulatory T-cell deficiencies worsen the course of the disease (Hazim et al. 2025).

5. ENVIRONMENTAL- LIFESTYLE INTERACTIONS AND PREVENTIVE APPROACH

Several modifiable factors can delay the progression of the disease, minimize complications, and lower the likelihood of emergence in secondary types of nephrotic syndrome (NS), despite the fact that NS is frequently idiopathic or genetically driven. Lifestyle interventions, medication assistance, prevention of

infections, comorbidity control, and ecological changes are the basic categories into which preventive measures can be divided as summarized in Table 2.

5.1 Patterns of Diet

The onset and progression associated with nephrotic syndrome (NS) are significantly influenced by dietary choices. Consuming too much salt, processed food, and refined carbs has been associated with metabolic dysfunction, obesity, and hypertension, all of which exacerbate glomerular damage and proteinuria. A typical metabolic characteristic of NS, hyperlipidemia, is made worse by diets heavy in saturated fats (Hagström et al. 2025). Blood pressure and edema can be controlled with a low-sodium diet. It is recommended that patients consume no more than 2,300 mg of sodium daily. Avoiding packaged foods, canned meals, and salty snacks is part of this. Patients might be empowered to choose healthier diets by learning how to read food labels and select fresh, complete foods. Eating more foods high in potassium can assist balance electrolytes and promote cardiovascular health in addition to lowering sodium intake (Younis Bakheet et al. 2025).

On the other hand, malnutrition and protein-energy deficiency have been identified as significant problems in low-resource environments, particularly in pediatric NS, which can result in growth retardation and ongoing infection. To improve results, nutritional interventions that emphasize appropriate protein, plant-based foods high in antioxidants, and restricted sodium intake are recommended (Mititelu et al. 2024). It is advised to consume 0.8 to 1.0 grams of protein per kg of body weight every day. Prioritize high-quality protein sources including fish, eggs, and lean meats. To offer a varied nutrient profile, plant-based proteins like beans and lentils can also be incorporated into the diet (Masago et al. 2025). One typical symptom of nephrotic syndrome is hyperlipidemia. Lipid levels can be controlled with a heart-healthy diet reduced in cholesterol and saturated fats. It can also be helpful to include meals high in omega-3 fatty acids, like flaxseeds and fatty salmon (Chandra et al. 2024).

5.2 Obesity and Physical Activity

Sedentary living exacerbates hypertension and obesity, two conditions that hasten chronic kidney disease. Lack of exercise is known to increase the risk of developing CKD and proteinuria. Due to elevated glomerular filtration load and adipokine-mediated inflammation, obesity in particular is closely linked to secondary focal segmental glomerulosclerosis (FSGS) (Chintam and Chang, 2021). According to studies conducted on children, the prevalence among NS and steroid-resistant infections is rising in tandem with the growth in childhood obesity. On the other hand, consistent exercise lowers the risk of CKD and NS by preserving body weight, enhancing insulin sensitivity, and lowering renal stress (Fan et al. 2024).

5.3 Exposures to the surroundings

In NS epidemiology, environmental toxicants are becoming being well acknowledged. Proteinuria and glomerular damage have been associated with exposure to heavy metals such lead, cadmium, and arsenic through tainted food and water (Järup & Åkesson, 2009). Studies have shown a connection between glomerular injury and exposure to pesticides, heavy metals (such as lead and cadmium), and tainted water (Wu et al. 2025). Occupational safety, pesticide regulation, and clean drinking water are all examples of preventive measures. Chronic exposure to pesticides is thought to play a role in kidney disease in rural areas; findings from India, show that excessive usage of pesticides and kidney-related morbidity coincide. Nephrotoxic effects are also observed in groundwater contaminated with fluoride and nitrate. More recently, epidemiological studies have linked increased exposure to air pollution to lower estimated GFR, and PM2.5 has been linked to systemic inflammation and renal impairment (Bowe et al. 2020).

According to research, long-term exposure to air pollutants may cause renal endothelial damage and systemic inflammation, which may exacerbate CKD and NS. Renal protection is indirectly aided by public health initiatives to enhance air quality (Chintam and Chang, 2021).

5.4 Aspects of Socioeconomic Status

The frequency and consequences of NS are strongly influenced by socioeconomic conditions. Poor illness outcomes are a result of poverty, malnutrition, and prolonged access to healthcare in low-income communities (Hogg et al. 2007). Conversely, sedentary lifestyles, poor eating habits, and environmental contaminants pose greater hazards in urbanized and affluent areas Urban–rural differences are notable: rural people often have increased pesticide and hazardous drinking consumption, while urban populations suffer increased physiological and lifestyle-associated risks (WHO, 2015). Prevention requires public health initiatives that emphasize early management, screening, and lowering socioeconomic disparities. The burden of disease is increased in low-resource settings by delayed diagnosis and limited access to nephrology care. Community-driven screening and education initiatives must be incorporated into preventive efforts.

Table 2: Summery of preventive measures for NS

S.No.	Aspects	Preventive Measures	Impact on Patients	References
1.	Dietary Management	Low-Sodium Diet, Proteinuria and Hyperlipidemia (omega-3 rich diet) Management.	↓ Edema, ↓ Proteinuria, ↓ CKD risk	Younis Bakheet et al. 2025; Masago et al. 2025
2.	Pharmacological and Clinical Supportive Measures	ACE inhibitors, diuretics, Statins, Vitamin D Supplementation.	↓ Proteinuria, ↓ Hyperlipidemia, ↓ CKD progression	Bouillon et al. 2022; Frățilă et al. 2024
3.	Physical Activity and Thrombosis Prevention	Avoid bed rest, moderate exercise daily	↓ Obesity, ↓ Thrombosis risk	Chintam and Chang, 2021
4.	Immunological protection and infection prevention	Vaccination against immunosuppressants, Preventive Antibiotics, IVIG therapy.	↓ Infection risk, ↓ Relapses	Robert and Fishman, 2021; Ahmed et al. 2025
5.	Comporbidity Control	Diabetes, hypertension Hyperlipidemia management, anticoagulation when needed.	↓ CKD, ↓ Cardiovascular risk	Frățilă et al. 2024; Cubilier et al. 2025
6.	Socioeconomic and Environmental Factors	Occupational safety, pesticide regulation, and clean drinking water, enhance air quality, Community-driven screening.	Delayed treatment avoided, ↓ Morbidity	Wu et al. 2025

5.5 Pharmacological and Clinical Supportive Measures

- Even in cases when blood pressure is normal, proteinuria can be decreased and kidney function preserved by using renin-angiotensin system (RAS) medications such as ACE inhibitors and ARBs.
- Loop diuretics, either by themselves or in conjunction with thiazides, are useful in treating NS-related edema. Diuretics used to treat edema, but careful observation is necessary to avoid electrolyte imbalances and hypovolemia.
- Statins aid in the management of dyslipidemia in NS, though it is unknown how they will affect long-term results. Although primarily used to manage hyperlipidemia, statins also have pleiotropic effects, such as endothelium stability and anti-inflammatory properties, which may lower cardiovascular morbidity in NS (Frățilă et al. 2024).

- Vitamin D Supplementation: Individuals with NS are at risk for vitamin D deficiency and bone damage because their urine contains less of the protein that binds vitamin D. It is possible to avoid osteodystrophy by taking supplements early (Bouillon et al. 2022).

5.6 Immunological protection and infection prevention

- Vaccinations: Infections, particularly when receiving immunosuppressive treatment, are an important factor of morbidity in NS. Vaccinations against influenza and pneumococcal disease are highly advised. Prior to beginning immunosuppressants, hepatitis B immunization should also be taken into consideration (Robert and Fishman, 2021).
- Preventive Antibiotics: It is recommended that individuals receiving prolonged use of steroids or calcineurin inhibitors take precautions against *Pneumocystis jirovecii* pneumonia (Zhou and Aitken, 2023).
- Immunoglobulin Replacement: IVIG therapy might lessen an individual's vulnerability to infections in cases of chronic hypogammaglobulinemia (Ahmed et al. 2025).

5.7 Comporbidity Control

- Two of the main warning signs for secondary NS are diabetes and hypertension. tight blood pressure control (<130/80 mmHg) and tight glycemic control (HbA1c < 7%) slow the course of CKD and proteinuria (Chintam and Chang, 2021).
- Hyperlipidemia: Cardiovascular disease and atherosclerosis are accelerated by persistent dyslipidemia. Preventive measures include dietary changes and early statin intervention (Frățilă et al. 2024).
- Cardiovascular Risk Reduction: Patients associated severe hypoalbuminemia (<2 g/dL) or a history of thrombotic events may benefit from preventative anticoagulation because NS is associated with thromboembolism (Cubilier et al. 2025).

5.8 Patient Education and Long-Term Monitoring

- Patients should receive counseling on how to spot early indicators of relapse, such as frothy urine and periorbital edema (Collins and Collins, 2012).
- Frequent follow-ups with renal function monitoring and urine protein testing help identify progression early.
- One of the most important preventive measures is education about avoiding over-the-counter nephrotoxic medications (NSAIDs, certain antibiotics).

6. CONCLUSION

Environmental exposures, immunological triggers, and genetic predispositions all contribute to the multifactorial nature of nephrotic syndrome (NS). With higher levels of incidence and prevalence in Asia and India than in Europe and North America, epidemiological evidence shows significant global variance that reflects both genetic heterogeneity and inequalities in healthcare access. The immunological-mediated damage to podocytes that underlies proteinuria is highlighted by immunological findings, especially the function of T-cell imbalance and Th2 cytokines (e.g., IL-13, IL-10). The limitations of existing therapeutic approaches are highlighted by the persistence of issues including steroid resistance, long-term consequences, and frequent relapses despite advancements in treatment.

Future perspectives necessitate a multifaceted strategy. To improve epidemiological patterns particular to a certain location, find modifiable risk factors, and evaluate environmental issues like pollution and pesticide exposure, large-scale population-based research are required. Precision medicine approaches may be made possible by early detection of high-risk individuals using genetic and immunological profiling. Disease development and recurrence may be decreased by preventive measures such as immunization, infection control, nutrition optimization, and lowering environmental pollutants. Furthermore, new immunomodulatory treatments that focus on podocyte defense and T-cell pathways could aid in overcoming the drawbacks of traditional steroids. Reducing the burden of NS and enhancing long-term results, especially in places with limited resources, would require combining medical treatment with epidemiological surveillance and innovative research.

REFRENCES

1. Ahmed, J., Choi, Y., Ko, T., Lim, J., and Hajjar, J. (2025). Use of Immunoglobulin Replacement Therapy in Clinical Practice: A Review. *Journal of Immunotherapy and Precision Oncology*, *8*(1), 34-46.
2. Al-Aubodah, T. A., Piccirillo, C. A., Trachtman, H., and Takano, T. (2025). The autoimmune architecture of childhood idiopathic nephrotic syndrome. *Kidney International*, *107*(2), 271-279.
3. Banh, T. H., Hussain-Shamsy, N., Patel, V., Vasilevska-Ristovska, J., Borges, K., Sibbald, C., ... and Parekh, R. S. (2016). Ethnic differences in incidence and outcomes of childhood nephrotic syndrome. *Clinical Journal of the American Society of Nephrology*, *11*(10), 1760-1768.
4. Bilinska, W., Rogowska-Kalisz, A., and Nowicki, M. (2004). Congenital nephrotic syndrome. *Focus on Kidney Cancer Research*, *14*, 173.
5. Bogdanović, L., Babić, I., Prvanović, M., Mijač, D., Mladenović-Marković, A., Popović, D., and Bogdanović, J. (2025). Uncommon Factors Leading to Nephrotic Syndrome. *Biomedicines*, *13*(8), 1907.
6. Bouillon, R., Manousaki, D., Rosen, C., Trajanoska, K., Rivadeneira, F., and Richards, J. B. (2022). The health effects of vitamin D supplementation: evidence from human studies. *Nature Reviews Endocrinology*, *18*(2), 96-110.
7. Bowe, B., Artimovich, E., Xie, Y., Yan, Y., Cai, M., and Al-Aly, Z. (2020). The global and national burden of chronic kidney disease attributable to ambient fine particulate matter air pollution: a modelling study. *BMJ Global Health*, *5*(3), e002063.
8. Boyer, O., Gbadegesin, R., and Waters, A. (2021). Clinical aspects of genetic forms of nephrotic syndrome. In *Pediatric Nephrology* (pp. 1-25). Springer, Berlin, Heidelberg.
9. Campbell, R. E., and Thurman, J. M. (2022). The immune system and idiopathic nephrotic syndrome. *Clinical Journal of the American Society of Nephrology*, *17*(12), 1823-1834.
10. Chandra, R., Katiyar, P., and Kushwaha, K. (2024). Recent Advances in the Understanding and Management of Hyperlipidemia: A Comprehensive Review. *Cuestiones de Fisioterapia*, *53*(03), 5095-5132.
11. Chesnaye, N. C., Ortiz, A., Zoccali, C., Stel, V. S., and Jager, K. J. (2024). The impact of population ageing on the burden of chronic kidney disease. *Nature Reviews Nephrology*, *20*(9), 569-585.
12. Chintam, K., and Chang, A. R. (2021). Strategies to treat obesity in patients with CKD. *American Journal of Kidney Diseases*, *77*(3), 427-439.
13. Chirico, V., Tripodi, F., Conti, G., Silipigni, L., Lacquaniti, A., Monardo, P., and Chimenz, R. (2025). Management of Nephrotic Syndrome in Pediatric Patients Treated by Different Steroid Regimens. *Medicina*, *61*(7), 1257.
14. Collins, D. R., and Collins, R. D. (2012). *Algorithmic Diagnosis of Symptoms and Signs: a cost-effective approach*. Lippincott Williams and Wilkins.
15. Cubilier, E., Chergui, Y., Garrouste, C., Ramos, I., Philipponnet, C., Atenza, A., ... and Heng, A. E. (2025). Nephrotic Syndrome Thromboprophylaxis With Direct Oral Anticoagulants or Vitamin K Antagonists. *Kidney International Reports*.
16. Daetwyler, E., Wallrabenstein, T., König, D., Cappelli, L. C., Naidoo, J., Zippelius, A., and Läubli, H. (2024). Corticosteroid-resistant immune-related adverse events: a systematic review. *Journal for immunotherapy of cancer*, *12*(1), e007409.
17. Eddy, A. A. and Symons, J. M. (2003). Nephrotic syndrome in childhood. *The Lancet*, 362(9384): 629-639.
18. Fan, R., Kong, J., Zhang, J., and Zhu, L. (2024). Exercise as a therapeutic approach to alleviate diabetic kidney disease: mechanisms, clinical evidence and potential exercise prescriptions. *Frontiers in Medicine*, *11*, 1471642.
19. Frățilă, V. G., Lupușoru, G., Sorohan, B. M., Obrișcă, B., Mocanu, V., Lupușoru, M., and Ismail, G. (2024). Nephrotic syndrome: from pathophysiology to novel therapeutic approaches. *Biomedicines*, *12*(3), 569.

20. Gembillo, G., Sessa, C., and Santoro, D. (2025). Advances in the pathophysiology and treatment of focal segmental glomerulosclerosis: The importance of a timely and tailored approach. *World Journal of Nephrology*, *14*(2), 103039.
21. Gulati, S., Sharma, A. P., Sharma, R. K., and Gupta, A. (1999). Changing trends of histopathology in childhood nephrotic syndrome. *American Journal of Kidney Diseases*, 34(4): 646-650.
22. Ha TS. Genetics of hereditary nephrotic syndrome: a clinical review. Korean J Pediatr. 2017 Mar;60(3):55-63. doi: 10.3345/kjp.2017.60.3.55. Epub 2017 Mar 27. PMID: 28392820; PMCID: PMC5383633.
23. Hagström, H., Hagfors, L. N., Hedelin, R., Brunström, M., and Lindmark, K. (2025). Low carbohydrate high fat-diet in real life; A descriptive analysis of cardiovascular risk factors. *International Journal of Cardiology Cardiovascular Risk and Prevention*, *25*, 200384.
24. Hattori, M., Iwano, M., Sako, M., Honda, M., Okada, H., Akioka, Y., ... and Mastuo, S. (2016). Transition of adolescent and young adult patients with childhood-onset chronic kidney disease from pediatric to adult renal services: a nationwide survey in Japan. *Clinical and experimental nephrology*, *20*(6), 918-925.
25. Hazim, H., Horn, R., Varikara, A. K., Mesure, J., and Chacko, B. (2025). Nephrotic Syndrome: Beyond Common Causes. *Nephrology*, *30*(4), e70035.
26. Hogg, R., Middleton, J., and Vehaskari, V. M. (2007). Focal segmental glomerulosclerosis–epidemiology aspects in children and adults. *Pediatric nephrology*, *22*(2), 183-186.
27. Kitiyakara, C., Eggers, P., and Kopp, J. B. (2004). Twenty-one-year trend in ESRD due to focal segmental glomerulosclerosis in the United States. *American Journal of Kidney Diseases*, *44*(5), 815-825.
28. Koskimies, O., Vilska, J., Rapola, J. and Hallman, N. (1982). Long-term outcome of primary nephrotic syndrome. *Archives of Disease in Childhood*, 57(7): 544-548.
29. Masago, S., Yamaoka, K., Uchida, M., Uesawa, Y., Yorifuji, K., and Shimizu, T. (2025). Comprehensive Analysis of Proteinuria and Nephrotic Syndrome Using the Japanese Adverse Drug Event Reporting Database. *In Vivo*, *39*(4), 2073-2084.
30. McGrogan, A., Franssen, C. F., and de Vries, C. S. (2011). The incidence of primary glomerulonephritis worldwide: a systematic review of the literature. *Nephrology Dialysis Transplantation*, *26*(2), 414-430.
31. Mititelu, M., Lupuliasa, D., Neacșu, S. M., Olteanu, G., Busnatu, Ș. S., Mihai, A., ... and Scafa-Udriște, A. (2024). Polyunsaturated fatty acids and human health: a key to modern nutritional balance in association with polyphenolic compounds from food sources. *Foods*, *14*(1), 46.
32. Morello, W. (2020). Underlying mechanisms of Idiopathic Nephrotic Syndrome in children: evidence of a circulating permeability factor.
33. Noone , D. G., Iijima, K. and Parekh, R. (2018). Idiopathic nephrotic syndrome in children. *The Lancet*, 392(10141): 61-74.
34. Olowu, W. A., Ademola, A., Ajite, A. B., and Saad, Y. M. (2017). Childhood nephrotic syndrome in tropical Africa: then and now. *Paediatrics and international child health*, *37*(4), 259-268.
35. Rahiman, F. A. (2015). *A Study of Various Renal Manifestations in HIV Infected Children* (Doctoral dissertation, Rajiv Gandhi University of Health Sciences (India)).
36. Rheault, M. N., and Gbadegesin, R. A. (2016). The genetics of nephrotic syndrome. *Journal of pediatric genetics*, *5*(01), 015-024.
37. Roberts, M. B., and Fishman, J. A. (2021). Immunosuppressive agents and infectious risk in transplantation: managing the "net state of immunosuppression". *Clinical Infectious Diseases*, *73*(7), e1302-e1317.
38. Robinson, C. H., Aman, N., Banh, T., Brooke, J., Chanchlani, R., Cuthbertson, B. H., ... and Parekh, R. S. (2025). Comparative Efficacy of Nonsteroid Immunosuppressive Medications in Childhood Nephrotic Syndrome. *JAMA pediatrics*, *179*(3), 321-331.
39. Roman, M., and Nowicki, M. (2024). Detailed pathophysiology of minimal change disease: insights into podocyte dysfunction, immune dysregulation, and genetic susceptibility. *International Journal of Molecular Sciences*, *25*(22), 12174.

40. Tarshish, P. E. N. I. N. A., Tobin, J. N., Bernstein, J. and Edelmann Jr, C. M. (1997). Prognostic significance of the early course of minimal change nephrotic syndrome: report of the International Study of Kidney Disease in Children. *Journal of the American Society of Nephrology*, 8(5): 769-776
41. Vega, C. M., Orellana, J. D., Oliveira, M. W., Hacon, S. S., and Basta, P. C. (2018). Human mercury exposure in Yanomami indigenous villages from the Brazilian Amazon. *International Journal of Environmental Research and Public Health*, *15*(6), 1051.
42. Wang, Y., Allen, K. J., Suaini, N. H., McWilliam, V., Peters, R. L., and Koplin, J. J. (2019). The global incidence and prevalence of anaphylaxis in children in the general population: a systematic review. *Allergy*, *74*(6), 1063-1080.
43. Watanabe, A., Feltran, L. S., and Sampson, M. G. (2019). Genetics of nephrotic syndrome presenting in childhood: Core Curriculum 2019. *American Journal of Kidney Diseases*, *74*(4), 549-557.
44. Wu, K., Chen, Y., and Huang, W. (2025). Combined molecular toxicity mechanism of heavy metals mixtures. *Toxicological assessment of combined chemicals in the environment*, 125-172.
45. Younis Bakheet, S. A. E., Fawzy, A. M., and Mohammed, M. D. (2025). Effect of Nutritional Education Program Based on Social Cognitive Theory on Sodium Intake among Housewives. *Minia Scientific Nursing Journal*, *18*(1), 2-14.
46. Zhou, S., and Aitken, S. L. (2023). Prophylaxis against Pneumocystis jirovecii pneumonia in adults. *Jama*, *330*(2), 182-183.