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## Relationship Between Prematurity and Chronic Kidney Disease - What is Known?



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### ABSTRACT

An integrative literature review was conducted with publications from 2016 to 2020, in Portuguese and English, that addressed the relationship between prematurity and the development of kidney disease as well as the mechanisms that explain this association, based on the hypothesis that preterm newborn are more vulnerable to CKD. The search strategy was conducted using the databases Medline/PubMed, Bireme/Lilacs, Cochrane Library. Were included 16 articles. Among the results of the studies included in this review, it was identified that more recent findings point to the direct effect of prematurity in increasing the risk of developing CKD. Some studies identified the influence of preterm birth as the only adverse event on impaired renal function while other results suggest additional factors involved in this relationship or mediating the strength of the association such as low birth weight and intrauterine growth restriction. This relationship between prematurity and kidney disease is justified three main mechanisms, interrupted nephrogenesis; effect of environmental factors in intrauterine life and early life by newborn; effect of prematurity on renal volume. Our results opens space for reflections on the importance of systematizing the follow-up of neonate throughout life, focusing on renal function. There are gaps regarding the institution of clinical protocols from the discharge plan in Neonatal Units to the follow-up in outpatient clinics for preterm infants, to monitor, in addition to blood pressure measurements, renal function.

## **INTRODUCTION:**

Prematurity is a worldwide epidemic[1]. It is estimated that approximately 12% of total births in the Brazilian population are premature [2]. The World Health Organization defines premature birth as births before 37 completed weeks of gestation or less than 259 days from the first date of the last menstrual period [3].

The causes for preterm birth include mother related factors, such as age (pregnancy in adolescence or over 35 years), multiple pregnancies, elective cesarean sections, chronic gestational diseases, infections, and unfavorable socioeconomic and nutritional conditions; and to the fetus, such as genetic disorders. Even in healthy women with low risk pregnancies, a percentage of children may be born preterm, so preterm birth can be considered a risk factor impacting health, well being, and development in adulthood [2].

The advancement and qualification of neonatal care combined with greater investments in the coverage of prenatal, labor, birth services has contributed to the survival of an increasing number of preterm newborn[4,5].

On the other hand, this population may present long-term morbidities [3,6] and different vulnerabilities in adulthood, associated with structural or functional developmental problems of key organs and systems, such as chronic kidney disease (CKD) [7,8]. In this regard, interest in investigating the long term prognosis of organ function among preterm newborns including renal function has been growing [9].

Studies have been demonstrating the influence of prematurity on the development of kidney disease due to different mechanisms that may explain this relationship [7,10-16] but there is still divergence among these findings [17] and different issues may constitute important confounding factors [18].

Furthermore, the various etiological complexities of preterm birth are not entirely clear, making it difficult to establish prevention and treatment of complications [19].

It is verified that the available information is not very systematized, making it difficult to update the health professionals involved in neonatal care, which can compromise the proper establishment of the management of this disease and better development of follow-up actions for these children.

As more preterm newborns survive, research describing the consequences of prematurity is essential to guide actions to ensure adequate support and the organization of early preventive efforts for this high-risk group [7,11]. Thus, it was the aim of this study to gather the most recent scientific publications on the influence of prematurity on the development of CKD to present a synthesis the information available in the literature.

#### **METHODOLOGY:**

An integrative literature review was conducted, following the preparation steps proposed by Mendes, Silveira, Galvão [20]. We considered publications from 2016 to 2020, in Portuguese and English, that addressed the relationship between prematurity and the development of kidney disease as well as the mechanisms that explain this association, based on the hypothesis that preterm newborns are more vulnerable to CKD.

Inclusion criteria were publications on the evaluation of renal function in individuals of any age who had a premature birth (<37 weeks). Studies involving evaluation of renal function in specific populations (indigenous), in groups with acute kidney injury or specific diseases (e.g., IgA nephropathy, congenital anomalies, minimal change nephropathy, and diabetic nephropathy), and animals research were not included. Literature review studies, *guidelines*, consensus, case studies, and editorials were also not included in this study.

The search strategy was conducted using the electronic databases United States American National Library of Medicine (Medline/PubMed), Virtual Health Library (Bireme/Lilacs), Cochrane Library, based on the combination of the following terms indexed in the Mesh platform: premature birth; infant, premature; kidney disease; kidney failure, chronic; renal insufficiency. Free terms were also used to make the search more comprehensive and the snowball strategy was used to analyze the references of each publication included.

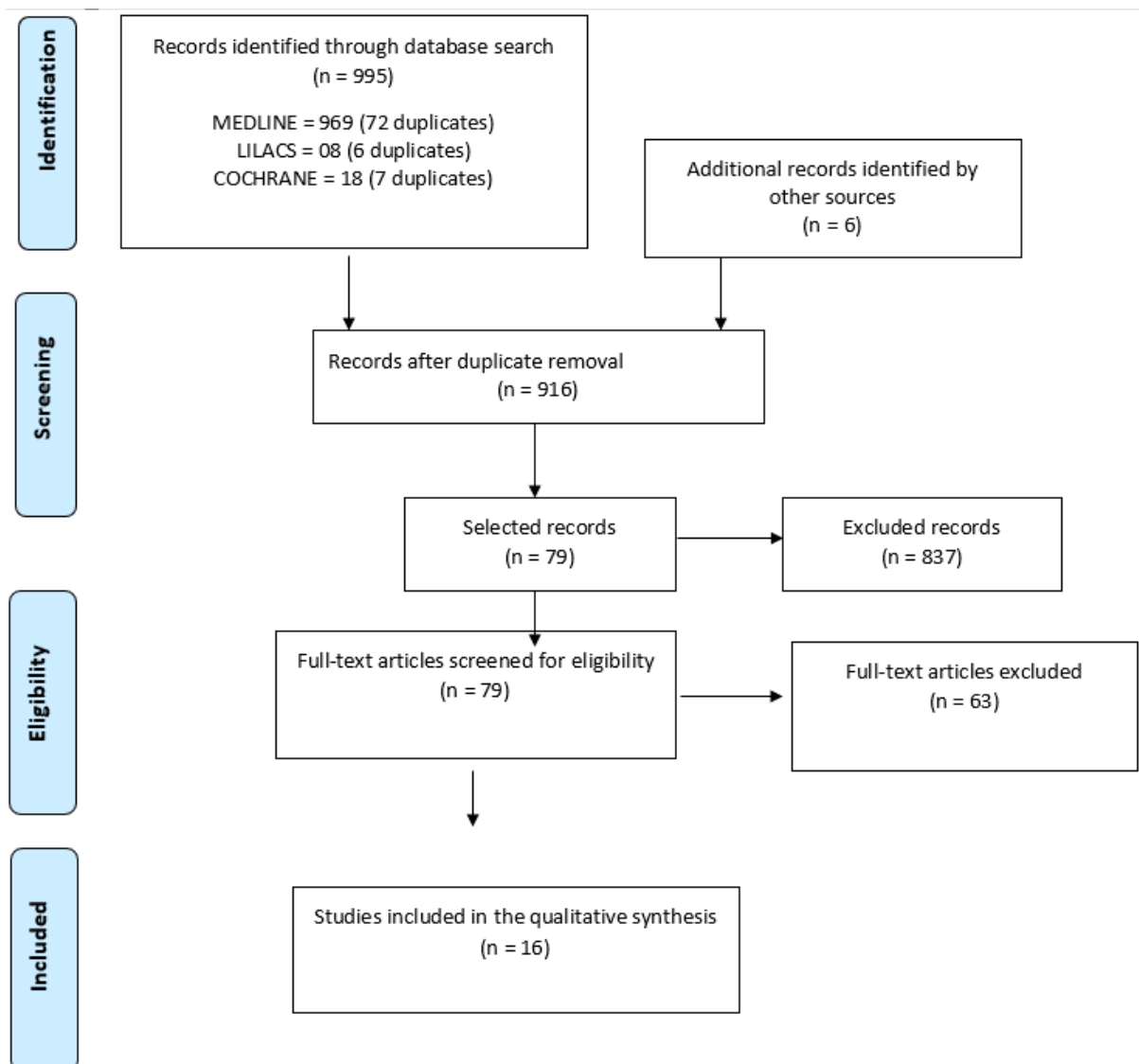
Data collection occurred from March to May 2021, and all identified publications were submitted to the initial selection stage by two independent reviewers, in each article of interest for this study screened from the evaluation of the titles and abstracts. When these were not enlightening, the articles were read in their entirety. Repeated articles were excluded and disagreements between the evaluators were resolved by consensus.

The information of interest for this study was inseried in an Excel spreadsheet, as follows: type of study, objective, sample size, main results, and the mechanisms presented to explain

this relationship. Next, qualitative analysis of the studies was used to synthesize and interpret the results.

**RESULTS:**

We located 1000 articles (Medline/PubMed=969; Bireme/Lilacs=08; Cochrane=18; other sources=6) from the cross-references of the descriptors of this study and the use of the snowball strategy. This step was followed by the exclusion of duplicates (n=85) that 79 publications were submitted to the initial selection step by two researchers. After analyzing the eligibility criteria, 16 articles were included in this study. Figure 1 details the selection process for these articles.



**Figure No. 1:** Detail of the process of selecting publications from 2015 to 2020 on the relationship between prematurity and development of chronic kidney disease.

Among the results of the studies included in this review, it was identified that more recent findings point to the direct effect of prematurity in increasing the risk of developing CKD [21-25]. The study by Vieux et al.[17] did not show this relationship.

Some studies identified the influence of preterm birth as the only adverse event on impaired renal function[7,10,14,26,27] while other results suggest additional factors involved in this relationship or mediating the strength of the association such as low birth weight and intrauterine growth restriction[28-32].

This relationship between prematurity and kidney disease is explained from three main mechanisms, interrupted nephrogenesis[7,10,25-29,31-33]; effect of environmental factors in intrauterine life and early life in newborns[17,23,24]; effect of prematurity on renal volume[14,21,22,27].



**Table No. 1:** Publications from 2016 to 2020 on the relationship between prematurity and Chronic Kidney Disease.

Title	Goal	Relationship between prematurity and CKD	Mechanism
Albuminuria, Hypertension, and Reduced Kidney Volumes in Adolescents Born Extremely Prematurely.	To characterize the prevalence and predictors of microalbuminuria, high blood pressure, and/or abnormal renal volume in adolescent preterm newborns with extremely low gestational age at birth.	Half of the adolescents evaluated had at least one risk factor for kidney disease (reduced kidney volume, microalbuminuria, and/or high blood pressure) at age 15.	Renal disease resulting from interrupted nephrogenesis in preterm newborns.
Intrauterine growth restriction, preterm birth and risk of end-stage renal disease during the first 50 years of life.	To assess whether low birth weight is associated with an increased risk of end-stage CKD.	The low birth weight was associated with a 70% increased risk and small for gestational age with a 50% increased risk for developing CKD during the first 50 years of life, supporting Brenner's hypothesis that impaired nephron endowment with a less glomerulos number and compensatory larger glomeruli leads to an increased risk of progression into kidney disease.	Renal disease resulting from interrupted nephrogenesis in preterm newborns.

<p>Kidney volume, kidney function, and ambulatory blood pressure in children born extremely preterm with and without nephrocalcinosis.</p>	<p>To investigate whether extreme prematurity affects renal volume, function, and blood pressure in school-age children and whether nephrocalcinosis developed during the neonatal period had additional effects</p>	<p>Children aged 6 to 10 years who were born prematurely had significantly smaller kidneys, lower cystatin C-based glomerular filtration rate, but normal, compared to children born at term. Renal volume and function were not different between the groups with and without nephrocalcinosis. Change in renal volume relative to body surface area from neonatal to school age showed significantly more preterm children with neonatal nephrocalcinosis and negative evolution of renal volume. Blood pressure was normal among the three groups; 50% of the preemies had less than 10% in the 24-h ambulatory blood pressure decline.</p>	<p>Renal disease resulting from interrupted nephrogenesis in preterm newborns.</p>
<p>The impact of prematurity on postnatal growth of different renal</p>	<p>To evaluate the relative growth of renal compartments in preterm newborns compared to</p>	<p>This study shows that prematurity affects postnatal growth and remodeling of the renal</p>	<p>CKD and prematurity, according to renal volume.</p>

<p>compartments.</p>	<p>full-term infants of the same age, and to explore the impact of preterm birth on postnatal renal maturation, remodeling, and possible long term implications.</p>	<p>medulla with potentially negative functional consequences and may contribute to a higher burden of CKD among preterm newborns.</p>	
<p>Preterm birth and risk of chronic kidney disease from childhood into mid-adulthood: national cohort study.</p>	<p>To investigate the relationship between preterm birth (gestational age &lt;37 weeks) and the risk of CKD from infancy to middle age.</p>	<p>Preterm birth, especially extreme preterm birth (&lt;28 weeks) were associated with almost two- and threefold increased risks of CKD, respectively, from birth to middle adulthood. The association between preterm birth and CKD was strongest at ages 0-9 years and, although weakening, remained high at ages 10-19 years. Thus, preterm birth and extreme preterm birth are strong risk factors for the development of CKD from infancy through middle age.</p>	<p>Renal disease resulting from interrupted nephrogenesis in preterm newborns.</p>



<p>Renal function and blood pressure are altered in adolescents born preterm.</p>	<p>Assessing the impact of preterm birth on the kidney</p>	<p>Prematurity was associated with higher blood pressure and reduced kidney function among adolescents born prematurely, compared to adolescents born at term, who had more adjusted systolic blood pressure and diastolic blood pressure, lower estimated glomerular filtration rate, and higher albumin-creatinine ratio. This study also identified that obesity and sex may modify the strength of these relationships, i.e., being obese modified the term <i>versus</i> preterm difference in diastolic blood pressure and albumin-creatinine ratio, and females had higher albumin-creatinine ratio than males.</p>	<p>Renal disease resulting from interrupted nephrogenesis in preterm newborns.</p>
<p>Long term renal follow-up of preterm neonates born before 35 weeks of gestation.</p>	<p>To understand the renal function of premature neonates born before 35 weeks gestation and to identify potential risk factors for renal</p>	<p>Premature gestational age and low weight directly affect renal function in young children and high seric creatinine on day 7 after birth is a risk factor</p>	<p>Relationship between CKD and environmental factors in intrauterine life and early life in preterm newborns.</p>

	dysfunction in Japanese children older than 2 years.	for CKD in children.	
Extrauterine development of preterm kidneys.	To determine the impact of prematurity on renal development considering primary endpoints: nephrinuria and albuminuria; and secondary endpoints: renal volume and estimated glomerular filtration rate.	Despite having a smaller renal volume and fewer nephrons, extremely preterm infants achieved similar estimated glomerular filtration rate as term neonates, probably due to single nephron hyperfiltration. Extremely premature neonates also show evidence of glomerular injury.	Renal disease resulting from interrupted nephrogenesis in preterm newborns.
Prenatal Growth and CKD in Older Adults: Longitudinal Findings From the Helsinki Birth Cohort Study, 1924-1944.	Explore prenatal programming for CKD, taking into consideration age, socioeconomic factors, and neonatal characteristics.	Being born small for gestational age was a risk factor for developing CKD in men and prematurity was predictive of increased risk for CKD in women.	Relationship between CKD and environmental factors in intrauterine life and early life in preterm newborns.
Kidney size, renal function, ang (angiotensin) peptides, and blood pressure in Young adults born preterm - The HAPI Study.	To evaluate the renal size and function of adults born preterm versus full term and examine their relationship with blood pressure and circulating renin-angiotensin system peptides.	Young adults born prematurely had smaller kidneys, higher urine albumin-creatinine ratio, higher blood pressure, higher levels of circulating Angiotensin I compared to term controls, but similar estimated glomerular	Renal disease resulting from interrupted nephrogenesis in preterm newborns.

		filtration rate.	
Renal function and blood pressure in 11-year-old children born extremely preterm or small for gestational age.	To test the hypothesis that extreme preterm birth and intrauterine growth restriction are associated with decreased kidney function in mid-childhood.	preterm newborns and extreme low birth weight, particularly those born small for gestational age, had impaired renal function at 11 years of age in a cohort that compared preterm newborns <28 weeks gestational age or with extreme low birth weight (<1000 grams) with matched controls of full-term newborn, assessing blood pressure, plasma levels of creatinine, cystatin C, and symmetric dimethylarginine.	Renal disease resulting from interrupted nephrogenesis in preterm newborns.
Ultrasound Imaging of the Renal Parenchyma of Premature Neonates for the Assessment of Renal Growth and Glomerulomegaly.	We hypothesize the use of ultrasound imaging to measure and monitor renal parenchymal growth in premature neonates.	Prematurity may cause the remaining nephrons to undergo compensatory glomerulomegaly causing the size differences when comparing renal parenchyma growth between preterm newborns and full-term infants. When comparing 91 preterm newborns (cases) and 56 full-term infants (controls),	CKD and prematurity, according to renal volume.

		<p>submitted for ultrasound evaluation at 32 weeks and 37 weeks postmenstrual age. At 37 weeks, preterm newborns had a significantly smaller total renal volume compared to full-term infants.</p>	
<p>Kidneys in 5-year-old preterm-born children: a longitudinal cohort monitoring of renal function.</p>	<p>To longitudinally describe systolic blood pressure and renal function in children born prematurely to determine when a change can be diagnosed and to determine what factors in the perinatal period or infancy were associated with altered renal function at 5 years of age in children born prematurely.</p>	<p>In children born at 27-31 weeks gestation and examined at 3, 4, and 5 years of age to assess renal function, including blood pressure, estimated glomerular filtration rate, and albuminuria, overall, 25% of children had systolic blood pressure <math>\geq</math> 90th percentile at 3 and 4 years of age and 11% at 5 years, although most children born prematurely are not yet hypertensive. The glomerular filtration rate at 5 years was significantly decreased, specifically in cases of hyaline membrane disease or necrotizing enterocolitis. No child had renal failure.</p>	<p>Relationship between CKD and environmental factors in intrauterine life and early life in preterm newborns.</p>

<p>Biochemical parameters of renal impairment/injury and surrogate markers of nephron number in intrauterine growth-restricted and preterm neonates at 30-40 days of postnatal corrected age.</p>	<p>To determine the possible early onset of renal damage in infants with intrauterine growth restriction and preterm birth, at 30-40 days postnatal corrected age by measuring urinary indicators of glomerular and tubular impairment/injury.</p>	<p>At this postnatal age, the lower number of nephrons in preterm newborns with low birth weight was associated with tubular injury that could be concomitant with dysfunction of glomerular permeability and that urinary cathepsin B activity may be a marker for early prediction of renal susceptibility to damage in neonates with low birth weight. At 30-40 days of corrected age, the kidneys of preterm newborns and newborns with intrauterine growth restriction were characterized by low nephron numbers, which is associated with tubular damage and higher urinary albumin levels, possibly in combination with increased glomerular permeability.</p>	<p>Renal disease resulting from interrupted nephrogenesis in preterm newborns.</p>
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<p>Longitudinal assessment of renal size and function in extremely low birth weight children at 7 and 11 years of age.</p>	<p>To evaluate kidney size and renal function in school-aged extreme low birth weight children compared to their peers and their evolution within a 4-year observation period.</p>	<p>Renal ultrasound examination revealed significantly smaller renal volume in extreme low birth weight children at 11 years of age compared to term controls. Renal function in the children with extreme low birth weight was also affected and serum cystatin C levels were significantly higher in extreme low birth weight children than in controls at 7 years of age, and this difference remained statistically significant at 11 years of age. Six children with low birth weight also had elevated cystatin C levels at 11 years of age. Blood urea nitrogen levels were higher in extreme low birth weight children at age 11 years.</p>	<p>CKD and prematurity, according to renal volume.</p>
<p>The role of very low birth weight and prematurity on cardiovascular disease risk and kidney development</p>	<p>To evaluate the influence of low birth weight in determining long-term cardiovascular disease and kidney disease in adulthood.</p>	<p>The longitudinal diameters of both kidneys were reduced in cases compared to controls. The finding of smaller kidneys in premature</p>	<p>Renal disease resulting from interrupted nephrogenesis in preterm newborns.</p>

<p>in children: a pilot study.</p>		<p>children with very low birth weight could explain their increased susceptibility to developing kidney disease in adulthood.</p>	
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CKD - chronic kidney disease.

**DISCUSSION:**

Recent evidence points to the direct effect of prematurity on the risk of developing CKD [22,25]. This relationship was not pointed out in the study by Vieux et al.[17]. Another part of the studies identified changes in renal function parameters due to preterm birth, but despite the increased values, they remained within normal standards indicating a potential causal relationship between these variables [7,10,14,26,27]. In addition, low birth weight and intrauterine growth restriction have been noted in the literature influencing the strength of this association[28-32].

Part of the scholars argue that preterm newborns have a higher risk of developing CKD due to the decreased number of nephrons[7,10,12,14,25-29,31-33] however the pathogenesis of CKD in preterm newborns is still partially understood[7]. It is understood that although nephron formation in humans ceases before birth, the remodeling and functional maturation process does not reach completion until 18 months of age[34].

According to Fanos et al.[35], the two main findings that play importance in clinical practice is that physiologically human nephrogenesis is completed between 36 and 38 weeks of gestation and represent the lifelong burden; the second is that preterm newborns born before 36 weeks of gestational age, may have renal maturation capacity for 2 to 4 weeks, and may generate new nephrons, but will always remain with a deficit, depending on gestational age, becoming oligonephric for life.

In this sense, premature birth leads to adaptation to an extrauterine environment, as an effect of renal function maturation, through glomerular hyperfiltration, when some glomeruli capture more blood flow as a form of compensation[36]. Hyperfiltration in premature kidneys

with lower volume, given the morphological changes of the nephrons, may repercussion in increasing the vulnerability of the preterm newborns to develop CKD[27].

Few studies relating renal structure to function have been identified, but they assume that prematurity, in addition to translating to smaller numbers of nephrons and renal volume, may affect postnatal growth, with important renal functional changes[14,21,22,27]. In addition, the results of the study by Brennan et al.[22] reveal that preterm newborns showed significantly smaller renal parenchyma thickness compared to full term newborns, and prematurity may cause the remaining nephrons to undergo compensatory glomerulomegaly.

Li et al.[27] were the only authors who, to assess the impact of preterm birth on postnatal renal maturation, remodeling, and possible long term implications, investigated the relative growth of the renal cortex and medulla to overall kidney growths and preterm newborns by comparing cortical thickness and medulla thickness over total kidney length in term born preterm newborns and controls of the same age. This study showed evidence of differential growth of separate renal compartments in which, after birth, the renal cortical region underwent a accelerated growth, while renal medulla growth did not follow the same growth rate, finding that prematurity affects postnatal growth and the remodeling process of the renal medulla can functional impairment and lead to CKD in these preterm newborns.

Abnormal renal development caused by an adverse intrauterine environment has also been accumulating evidence in the literature[11,16,17,23,24]. The known factors that may lead to the risk of reduced nephron formation during intrauterine life are discussed and involve besides maternal nutrition (malnutrition and obesity), other factors such as smoking and alcohol, use of other drugs, especially corticosteroids, maternal renal dysfunction, prematurity[16].

Studies on the impact of the intrauterine environment on the development of diseases were first conducted by Barker[37], who showed that low-birth-weight infants had a higher risk of developing diseases in adulthood[38], subsidizing a field of knowledge called Developmental Origins of Health and Disease, which followed on from other studies such as that of Brenner and Chertow[39].

These scholars postulated fewer nephrons among low birth weight infants predispose to glomerular hypertrophy and CKD, through an adaptive response of the fewer existing nephrons that will increase their surface area and favor glomerular hyperfiltration, with



subsequent sodium retention, hypertension, nephron loss, and CKD caused by focal segmental glomerulosclerosis.

In addition, the human fetus may have renal development affected by the adverse extrauterine environment, such as contexts of greater social vulnerability[23,24] or intensive care unit settings, in which there is greater exposure to risks, such as hypotension, hypoxia, and use of nephrotoxic medications in the postnatal period[33,40]. The preterm newborns are at high risk for neonatal acute kidney injury, which can further compromise the number of nephrons and potentiate progression to CKD[12].

Studies included in this review, endorsed the hypothesis that environmental factors during fetal and infant life are risk factors for CKD in adulthood[23,24]. One study, however, did not show this relationship when assessing renal function including low weight, estimated glomerular filtration rate, and albuminuria in children born at 27-31 weeks gestation, and examined at 3, 4, and 5 years of age. Although the findings indicated that the glomerular filtration rate decreased significantly at 5 years, specifically in cases of hyaline membrane disease or necrotizing enterocolitis, no children developed renal failure[17].

Different studies, based on the hypothesis that interrupted nephrogenesis occurring in prematurity is the mechanism that justifies the development of CKD in preterm newborns, suggest factors related to the intrauterine environment as mediators of the strength of this association [28-32]. Aisa et al.[30] report that both prematurity and growth restriction can modulating nephrogenesis and renal function, and when concomitant, their effects tend to be cumulative. In this context, low birth weight is also considered one of the predictors of lower nephron endowment and risk of developing kidney disease in adulthood[32,41].

It is important to consider the variety of methods used for the detection of renal function impairment among the articles included in this review, as well as the divergences regarding the moments in which these alterations may be found, besides the limitations of each study pointed out by the authors themselves, may have jointly influenced the results found.

The age at which impaired renal function becomes apparent is also an important aspect to consider. Authors reinforce the importance of knowing when early morphological changes lead to clinical findings in prematurely born children[7,11]. Some believe that as prematurely born individuals reach young adulthood, differences in renal function are likely to become more apparent[21,42].

However, there is wide variation as to the ages at which assessment of renal function was performed on those born prematurely, with studies detecting impaired renal function during childhood[25]and others showing no differences even in early adulthood despite finding increased values of the parameters assessed they did not identify a statistical association between these variables[7,10].

This study allowed us to gather the most recent evidence available on the relationship between prematurity and CKD. It was not possible to present factors that decrease or increase the confidence of the evidence found, but the quality assessment of primary studies is not common in integrative review studies.

### **CONCLUSION:**

Studies of the association between prematurity and increased susceptibility to CKD are important establish protection for the kidneys, focusing on normal number and functionality, to play its role in the excretion of metabolites, regulation of electrolytes and blood pressure, production of hormones, and thus avoid the harmful consequences of loss of kidney function, including dialysis, transplantation, or loss of life.

Our results opens space for reflections on the importance of systematizing the follow-up of neonate throughout life, focusing on renal function. There are gaps regarding the institution of clinical protocols from the discharge plan in Neonatal Units to the follow-up in outpatient clinics for preterm infants, to monitor, in addition to blood pressure measurements, renal function. It becomes essential that these protocols are also inserted in the competence development plans of health care students, both at the undergraduate and graduate levels.

In this context, it is understood that the coordinated effort by neonatologists, nephrologists, primary care professionals involved in the care of preterm newborns is necessary for the identification of early signs of CKD and to adopt in clinical practice, interventions associated with nephroprotective measures and changes in modifiable risk factors.

There is still a need to generate more robust evidence on the impact of prematurity on the development of CKD and thus guide formal follow-up guidelines for children born from premature birth, from infancy through adulthood.

### **Declarations**

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