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SYSTEMATIC REVIEW: THE EFFECTS OF PREMATURITY ON LONG-TERM RENAL HEALTH

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ABSTRACT:

Objective: To investigate the literature and determine if prematurity has an impact on long-term adverse renal outcomes

Setting: OVID Medline, PubMed, SCOPUS, CINAHL and EMBASE databases were searched for studies relating to the adverse outcomes of prematurity from 1990 – Nov 2020.

Outcome Measures: Prescence and impact of nephrocalcinosis, blood pressure, renal function (glomerular filtration rate) and development of chronic kidney disease

Results: The literature search yielded 25 human studies which investigated the short- and long-term renal outcomes of prematurity. These studies were conducted in 17 different countries. The most common outcomes measured were blood pressure, nephrocalcinosis and renal function. Other common outcomes measured included renal size and mass, urine analysis, chronic kidney disease and physical parameters like height, weight and body mass index.

Conclusion: Prematurity is unlikely to be associated with adverse renal outcomes in childhood but is likely to be associated with impaired renal function from adolescence into adulthood. Preterm birth conferred a twofold increased risk of CKD and extremely preterm birth conferred a threefold increased risk of CKD. Prematurity likely does not affect blood pressure in the ex-preterm population up to 20 years of age.

Keywords: Premature, preterm, renal, kidney, impairment

STRENGTHS AND LIMITATIONS

- This systematic review yielded 25 relevant human studies
- The long-term adverse outcomes of renal function can only be evaluated up to 20 years of age as research into the aging population is lacking

INTRODUCTION:

Prematurity is the leading cause of mortality in children under the age of five.[1] However, with advances in technology and modern medicine, both the incidence of prematurity and the number of ex-preterm babies living into adulthood are increasing, especially in population-dense countries.[1] Approximately 15 million, or just over 1 in 10 babies, are born prematurely every year.[2] The highest number of preterm births are seen in India, China and Nigeria; while the highest rates of preterm births are seen in Malawi, Comoros and Congo.[3] In Australia, 8.6% of babies born in 2014 were born prematurely. Higher rates of prematurity were observed in babies born in remote and regional Australia, babies born to indigenous mothers, babies born in multiple births and babies born to younger (<20 years) or older (<40 years) mothers.[4]

Though preterm birth is becoming more commonplace, it is not without its own challenges. The Barker hypothesis proposes that diseases of adulthood are due to factors pertaining to fetal life. [5-7] This proposition is also commonly known as the Developmental Origins of Health and Disease (DOHaD) hypothesis. This conclusion was first drawn when Barker et al. found that early death secondary to coronary artery disease was inversely related to weight at birth.[8] Thus the DOHaD paradigm was created. It proposed that developmental factors, including nutrition, stressors, and environmental exposures such as drugs and infections, could lead to functional changes in tissues which may predispose to disease in later life.[9]

Despite advancements in neonatal medicine, including the use of continuous positive airway pressure, mechanical ventilation, antenatal steroids and exogenous surfactant, 20-50% of preterm infants will still experience morbidity as a result of their prematurity.[10] In the shorter

term, preterm infants have higher rates of neonatal intensive care admission, severe morbidity in the first weeks of life, prolonged hospital stay and readmission to the hospital within the first year of life.[1] In 2014, 72% of preterm babies required special care or intensive care admission in Australia, compared to only 10% of term babies.[4] Prematurity is associated with both physical and neurological disability.[1, 11-12] Hearing impairment is seen in 5-10% of extremely premature infants.[11] Visual impairment, in the form of blindness, myopia and hypermetropia, affects around 25% of extremely preterm children.[12] Chronic lung disease associated with prematurity, which ranges from reduced exercise tolerance all the way through to requiring home oxygen, is seen in 40% of children born extremely premature.[13] Reduced lung function, greater rates of asthma, high blood pressure (BP) and growth failure have also been associated with prematurity.[1] In the aging population, studies have shown that prematurity confers an increased risk of chronic disease; particularly coronary artery disease, heart failure, obstructive lung disease, glucose intolerance, diabetes, obesity and osteopenia.[5-6, 14] From a neurological perspective, higher rates of learning and cognitive impairment, dyslexia, attention deficit hyperactivity disorder, motor impairment and cerebral palsy have all been noted as prematurity associated morbidities.[1] Higher rates of anxiety and depression are also common in the ex-preterm population.[1]

The impact of prematurity on long-term renal dysfunction or chronic kidney diseases (CKD) is still not fully understood. Impaired nephrogenesis due to poor fetal growth, prematurity, antenatal and post-natal medication and other factors most likely lead to reduced nephron endowment and CKD. [15-16] Nephrogenesis is completed by 37 weeks gestation, and the majority of nephrogenesis occurs in late gestation.[17] Therefore, in preterm neonates, nephrogenesis is terminated early conferring reduced nephron numbers. Nephrons do not

regenerate. The number of functional nephrons over time decreases as part of normal aging.[6] As preterm children are born with reduced nephron numbers, an increased risk of renal dysfunction is postulated. Brenner et al. also proposed that as a compensatory measure for low nephron numbers, nephron surface area increases. This maladaptive response causes systemic hypertension and increased sodium retention, which in turn causes disrupted autoregulation.[19] The resulting nephron sclerosis leads to increased functional nephron decline creating a vicious cycle. [18-19]

As the ex-preterm population is living longer and becoming part of the aging population, understanding the effects of prematurity become imperative in anticipating the likely chronic health outcomes the premature population will face. This review is intended to investigate the literature to determine if a link is present between prematurity and adverse long-term renal health. Identifying a link will be the first step in deciding how best to follow-up and manage ex-preterm children and adults to prevent renal morbidity and premature mortality in the long term.

METHODS

This systematic review was completed in accordance with the PRISMA guidelines. [20] The systematic search was conducted using OVID Medline, PubMed, SCOPUS, CINAHL and EMBASE. The search criteria were developed and refined from January to November 2020. Relevant keywords were identified, and all relevant Medical Subject Headings (MeSH) and non-MeSH synonyms were included. Relevant keywords included prematurity, chronic renal failure, chronic kidney disease, kidney volume and long-term adverse outcomes. An example of the database search can be seen in Appendix A. Only articles published in English between January 1990 and November 2020 have been included. Animal studies were excluded. Finally, articles shortlisted for inclusion were screened for bias and re-evaluated for inclusion if there was significant bias.

Once the literature search was completed, article selection was performed independently and in a non-blinded manner by two reviewers. The articles were initially screened by title and then by the abstract. All remaining articles were reviewed and determined for inclusion based on examination of the full text. Articles which were unclear were re-reviewed by both reviewers, and a unanimous decision was taken as to whether they should be included.

Articles were included if they studied premature and low birth weight infants to determine if they developed adverse renal outcomes as a result of being premature or having a low birth weight. Outcomes that were evaluated included glomerular filtration rate (GFR), nephrocalcinosis, BP, tubular function, kidney length and volume, and urinary protein and electrolytes. It was decided that case series with less than 20 participants, and case studies

would be excluded from this review as they would not provide the level of evidence or relevant information required.

Patient and Public Involvement

Patients were not involved in the development or design of this systematic review.

RESULTS

The collective search from the five databases revealed 967 studies. A total of 927 articles remained after duplicates were omitted. All 927 articles were screened, and 775 were excluded based on title and abstract. For the remaining 152 articles, full texts were assessed for eligibility. 61 articles were excluded due to long term adverse renal outcomes not being investigated. Nine articles were excluded as prematurity or low birth weight were not investigated. Seven were excluded for being animal studies, and 50 were excluded for being case reports or case series with less than 20 participants. Thus, the literature search yielded 25 human studies which investigated the long-term renal outcomes of prematurity. [21-45] These studies were conducted in 17 different countries: Australia, Israel, Japan, Italy, Greece, Poland, France, Egypt, Sweden, Belgium, Mexico, the Netherlands, Scotland, Spain, the USA, Finland and Norway. [21-45] A flow diagram demonstrating the selection process can be seen in Figure 1. The lead author surname, year of publication, sample size, birth weight, gestation, outcome measures, age at which outcome measured and conclusions of the selected studies can be seen in Appendix A Table 1.

Of the included studies, the smallest cohort size was 19, and the largest cohort size was 4186615. [23, 40] The youngest gestational age from the preterm cohorts was 22 weeks, and the most mature gestational age for the preterm cohorts was 36 weeks.[40] The youngest age at which outcomes were measured was at birth, and the oldest age at which outcomes were measured was at 43 years.[40] The most common outcomes measured were BP, nephrocalcinosis and renal function. Other outcomes measured included renal size and mass, urine analysis, chronic kidney disease and physical parameters (height, weight and BMI). Some studies also commented on insulin resistance and serum lipid profile.

Nephrocalcinosis

Seven studies investigated for nephrocalcinosis. [22-23,25, 35, 27-28, 42] Out of the eleven children born preterm and found to have renal calcifications, Jones et al. found that 5 of them still had renal calcifications at age 4-5 years. However, nephrocalcinosis in isolation was not found to be a major predisposing factor to long term renal dysfunction.[22] Porter et al. concluded that nephrocalcinosis is not associated with long-term renal dysfunction.[27] They also found that 75% of nephrocalcinosis cases resolve by 6.75 years of age.[27] Kist-van Holthe et al. concluded that premature infants with nephrocalcinosis had a significantly higher risk of developing chronic renal insufficiency when compared to controls and premature children without nephrocalcinosis.[28] Abitbol et al. found 4 out of their 20 participants had nephrocalcinosis and noted that all these cases resolved with age and discontinuation of diuretic use.[25] Rakow et al. found no significant difference in renal function in extremely premature infants with and without nephrocalcinosis.[42] Giapros et al. concluded that nephrocalcinosis in preterm infants was associated with renal tubular dysfunction and shorter kidney length in the first year of life.[35] Of the seven studies, Giapros et al. had the largest cohort size with 107 participants.[35] Toffolo et al. looked specifically at premature children with bronchopulmonary dysplasia.[23] Their study group consisted of 12 children with nephrocalcinosis. [23] Three of these children passed away. Nephrocalcinosis was found to have resolved in all cases by 12 months of age. [23]

GFR

22 out of the 25 studies investigated GFR as an outcome measure.[22, 24-36, 38-39, 41-43, 44-45] Four studies, comparing premature children and term children, found no significant difference in GFR between groups.[27, 43] Rakow et al. measured their outcomes at 9 years, Kandasmay et

al. measured their outcomes at 0.5, 1 and 2 years, Porter et al. measured outcomes at approximately 5-7 years, and Staub et al. measured GFR at 12 years.[27, 31, 43, 45] Four further studies found no statistically significant difference in GFR between study and control groups.[24, 33, 35, 38] Ojala et al. compared premature infants with and without indomethacin exposure in the neonatal period and measured outcomes at 2-4 years.[24] Raaijmakers et al. compared premature infants with and without ibuprofen exposure in the neonatal period and assessed outcomes at 11 years.[38] Zaffanello compared very low birth weight and extremely low birth weight children at 5-6 years.[33] Finally, Giapros compared preterm infants with and without nephrocalcinosis for the first 2 years of life.[35]

Chan et al. found nil difference in GFR prior to giving participants a protein load. [34] However, they found a significant reduction in renal reserve in the small for gestational age children after protein loading at 13-14 years of age. [34] There was no difference in preterm compared to term children after protein load. [34] Keijer Veen et al. found that GFR was significantly lower in the preterm small for gestational age group compared to term controls at 20 years. [29] This was not the case for the preterm appropriate for gestational age group. [29] When the small for gestational age group had their GFR adjusted for body surface area, there was no significant difference between groups. [29] Yael et al. found that all their 103 study participants that were very low birth weight and preterm all had normal values of GFR. [44]

Eight found significantly diminished GFR between the study groups and controls. [25-26, 28, 30, 32, 37, 39, 42] Four out of these eight found significantly diminished GFR between premature babies and term babies. Outcomes were measured at approximately 7.5 years, eight years, 8.5 years, and 11.5 years for these four studies. [26, 28, 32, 39] Finken et al. noted significantly decreased

GFR in premature infants who received betamethasone in the neonatal period when compared to premature infants who did not.[30] This outcome was measured at 19 years of age.[30] Rakow et al. also found significantly diminished GFR between preterm infants and term infants when reviewed at approximately eight years of age. However, they also noted that this GFR was still within normal limits.[42] Abitolol et al. found ex-preterm children had normal GFRs when aged 5.7 years but children assessed at 9.9 years were found to have diminished GFR.[25] Starzec et al. concluded that GFR was significantly lower in the extremely low birth weight group compared to term controls when assessed at 11 years.[37] Jones et al found that four out of their 11 preterm babies with nephrocalcinosis had an abnormal GFR at 4-5 years of age. Jones et al did not however have a term control group to compare these results too.[22]

Only one study (Carballo-Magdaleno et al.) found an increased GFR in premature infants when compared to term infants. Outcomes were measured at two years of age.[36]

Horie et al. compared two groups of preterm children.[41] Children were separated into control or study groups based on GFR. Of the 168 people followed up 10.7% had low GFR (18 out of 168). GFR at 2 years was found to be significantly and positively correlated with birthweight and gestational age. [41] However, this relationship was no longer significant at 3-4 years of age. [41]

CKD

Crump et al. was the only study that exclusively investigated for CKD. From their large cohort size of 4 186 615, they concluded that preterm birth conferred a twofold increased risk of

CKD and extremely preterm birth conferred a threefold increased risk of CKD.[40] This risk was found to be highest between ages 0-9 years and slightly weakened but still increased from ages 10-19 years.[40]

Blood Pressure

16 out of the 25 studies investigated BP as one of their outcome measures.[24-26, 28-34, 36, 39, 42-45] 12 out of the 25 studies found no significant difference in BP between study and control groups.[24-26, 28, 30-34, 39, 42-43] Seven of these studies found no significant difference in BP between term babies and preterm babies at differing ages.[25-26, 31, 34, 39, 42-43] Four studies compared premature babies with and without different variables including exposure to betamethasone, exposure to indomethacin, presence or absence of nephrocalcinosis, and having extrauterine growth restriction, intrauterine growth restriction or being appropriate for gestational age.[25, 28, 30, 32] All concluded no significant difference in BP between these groups of premature babies at differing ages. Zaffanello et al. found no significant difference in BP between very low birth weight and extremely low birth weight infants at 5-6 years of age. [33] It should be noted that Zaffanello did not compared these blood pressures with normal birth weight or term infants. [33]

Carballo-Magdaleno et al., Keijzer-Veen et al., Yael et al. and Staub et al. found increased BP in premature children compared to controls. [29, 36, 44-45] Carballo-Magdaleno et al. found that 2-year-old infants born prematurely had significantly higher blood pressures than 2-year-old infants born at term.[36] Keijzer-Veen et al. found significantly increased systolic BP in premature children compared to term children when BP was assessed at 20 years.[29] Yael et al. reported a 15.8% prevalence rate of systolic hypertension in their study group of preterm

children with very low birth weight when assessed at 10-13 years. [44] This is compared to the general United States paediatric population which has a 1.6% prevalence rate of systolic hypertension. [44] Finally, Staub et al. found that systolic BP was significantly higher in preterm boys compared to term boys, however they did not find a significant difference in preterm and term girls. [45] They also noted that low birth weight was associated with higher BP in boys. [45]

Bias

In all studies included in this review, bias was minimal. Some bias may be present in single centre studies as these may only provide results from a particular population demographic. [21-26, 29, 31-35,37-38, 41-45] However, as this review correlates the results of numerous single centre studies, this bias is minimised. Randomisation of study subjects was not done in any of the 25 included studies as birth weight and gestational age are not variables that could be influenced. [21-45] Furthermore, 11 studies did not have term born controls. [21-25, 28, 30, 33, 35, 38, 42]] Abitolol et al. did however match their study participants to age-, gender- and height-matched population norms when reviewing outcomes.[25] Yael et al. also did not have a term control group; however, they did compare their results to known population prevalence's.[44]

DISCUSSION

25 studies that assessed long term renal outcomes of premature infants were identified in this review. [21-45] There was a relatively even split between the studies that investigated GFR as to whether there was or was not a significant difference between study and control groups. [22, 24-36, 38-39, 41-43, 44-45] It should be noted that the studies which favoured no significant difference between preterm and term participants investigated GFR in children from 0.5-11 years, while the studies that favoured a significant difference between the two populations measured outcomes at 7.5-20 years. [21-45] Thus, it is likely that in the short term, GFR is not significantly affected by prematurity. However, as the ex-preterm population ages, their renal function becomes diminished considerably compared to the term population. This is likely the case as premature infants start out with reduced nephron numbers. Furthermore, they are at a known increased risk of coronary artery disease, obesity and metabolic disease. [5-6, 14] These chronic conditions will impact and damage kidney functioning, leading to reduced GFR.

From the 16 studies that investigated BP, 12 found that prematurity did not affect BP in the ex-preterm population. [24-26, 28-34, 36, 39, 42-45] This conclusion is only relevant in the ex-preterm population up to 20 years of age as none of the studies investigated BP in ex-preterm adults above the age of 20. It is likely that there is no significant impact on BP before the age of 20 as the decreased nephron number in preterm infants compared to term infants is not large enough for compensatory BP effects at this age. However, as the ex-preterm population ages into late adulthood and their already reduced nephron numbers decline, this deficit is likely to cause a clinically significant increase in BP.

From the seven studies that investigated for nephrocalcinosis, it is difficult to draw a conclusion as to its effect. [22-23, 25, 35, 27-28, 42] The study with the largest cohort size concluded that nephrocalcinosis in preterm infants was associated with renal tubular dysfunction and shorter kidney length in the first year of life.[35] The study with the second largest cohort found that premature children with nephrocalcinosis had an increased risk of developing chronic renal insufficiency when compared to controls and premature children without nephrocalcinosis. [28] Four studies with smaller cohort sizes found no difference between preterm babies with and without nephrocalcinosis, as well as term babies without nephrocalcinosis. [22-23, 27, 42,] Porter et al. Toffolo et al. and Abitolol et al. found the resolution of nephrocalcinosis in 75%, 100% and 100% of their participants respectively. [23, 25, 27] It is thought that the presence of nephrocalcinosis may further impair renal function and in turn, compensatory measures such as blood pressure. Therefore, it would be expected that a greater risk of adverse renal outcomes would be associated with persistent nephrocalcinosis in the preterm neonate. However, further investigation on the effects of nephrocalcinosis are needed before a solid conclusion can be drawn.

The risk of CKD is twofold and threefold greater in preterm and extremely preterm children respectively compared to those born at term as per Crump et al. [40] The risk of CKD over the age of 19 years cannot be commented on as it was not investigated in any of the included articles. The conclusion drawn by Crump et al. is reliable by itself, given their methodology and massive cohort size. The conclusion is logical, given the decreased nephron endowment associated with prematurity. It should be noted that renal function must be significantly impaired (GFR <15) before evidence of renal failure will be present clinically.

There are some limitations to our systematic review. The majority of the included studies were conducted in Caucasian predominant countries. Therefore, they do not reflect the true impact of prematurity of long-term renal dysfunction as they do not encompass population rich countries including India, China and Nigeria where the highest number of preterm births occur each year. This means the conclusions from this review do not apply to all ethnicities and cannot be generalised for non-Caucasian ethnic groups. Additionally, all the studies included in this review analysed renal function through quantifiable measures such as blood tests. Clinically significant renal outcomes, symptomatology, quality of life and renal dysfunction associated mortality were not commented on or investigated in these studies. Finally, the majority of studies did not investigate outcomes over the age of 20 years. One study had participants up to the age of 43; however, the proportion of their study cohort over the age of 20 was minimal. Thus, this systematic review can only draw conclusions on the long-term renal outcomes of premature infants up to the age of 20 years. Finally, only studies conducted after 1990 and written in English were considered for inclusion.

CONCLUSION

Prematurity is likely to be linked to increased risk of renal dysfunction from ages 7.5-20 years. Prematurity likely does not affect BP in the ex-preterm population up to 20 years of age. The risk of CKD is twofold and threefold higher in preterm and extremely preterm children compared to those born at term. Sufficient evidence was not available for a conclusion to be drawn on the long-term renal effects of nephrocalcinosis in prematurity.

Further studies need to be conducted to investigate the effects of prematurity on long term renal health in the aging population; reliable information at this time is only available up until

the age of 20 years. Thus, renal outcomes in the ex-preterm population over the age of 20 years cannot be concluded from the current research. Furthermore, more high-quality studies should be conducted on nephrocalcinosis in prematurity in order to determine if it affects long-term renal outcomes. However, enough evidence is present to warrant ongoing monitoring of premature infants as they age in order to optimise and prevent other chronic health conditions associated with prematurity and reduce the risk of developing adverse renal outcomes in the future.

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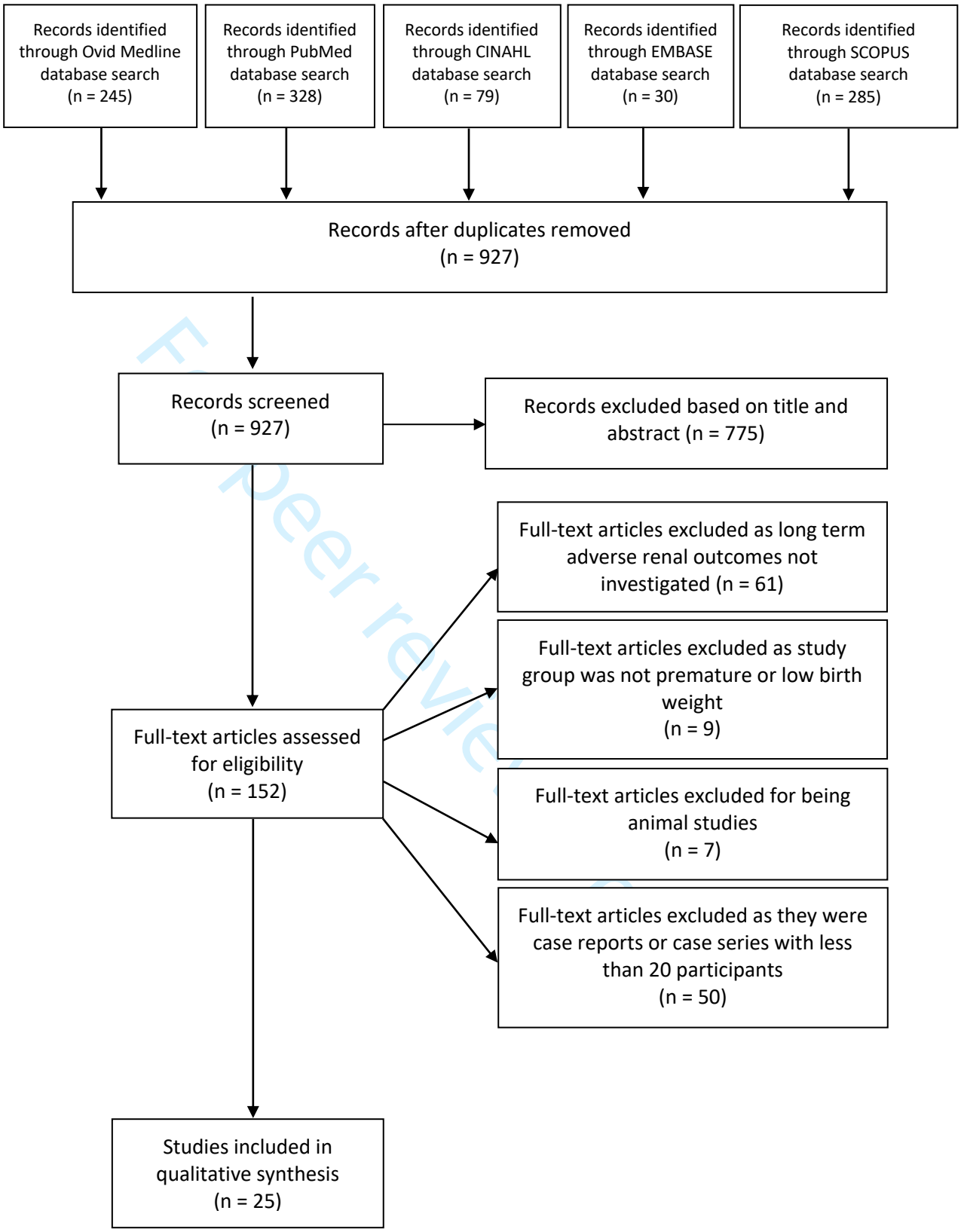

Figure 1: PRISMA Flow diagram

Table 1 – Characteristics of included studies (n = 25)

	Source (Y)	Sample Size	Birth weight (g) (study group)	Gestation (wks.) (study group)	Age at which outcomes measured (years)	Outcome measure (for example eGFR or BP or KV)	Conclusion (briefly)
1	Downing et al (1992) [21]	Control N=7 (no frusemide therapy and no renal calcifications) Group 2 N=10 (frusemide therapy but no renal calcifications) Group 3 N=10 (frusemide therapy and renal calcifications)	Control (743(84)) Group 2 (806(103)) Group 3 (678(95))	Control (25.3(0.6) Group 2 (26.1(0.5)) Group 3 (26.2(0.4))	Control (1.2(0.01)) Group 2 (1.3 (0.1)) Group 3 (1.2 (0.1))	Creatinine clearance Urinary calcium:creatinine ratio Fractional excretion of sodium Lower tubular reabsorption of phosphate Urine-blood difference in carbon dioxide tension after oral acetazolamide load	• No significant difference in renal function between the control group and group 2 • Creatinine clearance in group 3 was significantly lower than in the control group and group 2 • Urinary calcium:creatinine ratios, fractional excretion of sodium and lower tubular re-absorption of phosphate was significantly higher in Group 3 compared to the group 2 and control group • Group 3 had lower urine-blood differences in carbon dioxide tension after oral acetazolamide load when compared to the controls and group 2 • Concluded that frusemide related renal calcifications may be associated with long-term renal function impairment
2	Jones et al (1997) [22]	Control Group (preterm without renal calcifications) N=17 Study Group (preterm with renal calcifications) N=11	Control (982 (710–1760)) Study (850 (580–1856))	Control (28 (25–31)) Study (27 (24–31))	4-5	eGFR Renal calcifications/ nephrocalcinosis	• In the study group the median GFR was 61 ml/min/1.73m2 (range 46-79 ml/min/1.73m2) • Five of the 11 children born preterm and found to have renal calcifications, still had renal calcifications at age 4-5 years. • Nephrocalcinosis in isolation was not found to be a major predisposing factor to long term renal dysfunction • Four out of the 11 preterm babies with nephrocalcinosis had an abnormal GFR at 4-5 years of age

3	Toffolo et al (1997) [23]	Control Group (Premature with bronchopulmonary dysplasia and without renal calcifications (NRC)) N=7 Study Group (Premature with bronchopulmonary dysplasia and with renal calcifications (RC)) N=12	Control (875 (70)) Study (916 (50))	Control (27.7(0.8) Study (28(0.5))	0.083, 0.167, 0.25, 0.5, 0.75, 1	Renal calcifications/ nephrocalcinosis	• Toffolo et al. found the resolution of nephrocalcinosis in 100% of participants
4	Ojala et al (2001) [24]	Control Group N=35 (nil perinatal indomethacin) Study Group N=31 (perinatal indomethacin exposure)	Control Group (1360 (680–2680)) Study Group (1150 (670–2060))	Control Group (31 (24-32)) Study Group (28 (24-32))	2-4	Serum cystatin C and protein Plasma creatinine, sodium and potassium Urine protein, calcium: creatinine ratios and alpha-1 microglobulin GFR BP Renal sonography examination	• The control group showed higher mean serum cystatin concentrations than the study group • No difference was found between the groups for mean serum protein, plasma creatinine and sodium, median plasma potassium concentrations, urine protein:creatinine ratio and urine calcium:creatinine ratio. • No statistical difference was found in GFR or renal structural abnormalities between the two groups • Umbilical artery catheter use, frusemide treatment and assisted ventilation may correlate with long term renal structural and functional abnormalities
5	Abitbol et al (2003) [25]	N=20	686 (133)	25 (2)	3.1-18.3	Proteinuria Kidney function/kidney failure (GFR, sCr) Renal size and mass BP Growth (height, weight and BMI) Nephrocalcinosis	• Significant age difference was found between the normal GFR and low GFR groups, the age of outcome measure was 5.7+/-2.2 and 9.9+/-5.6 years respectively. • Nephrocalcinosis was present in 4/20 patients All nephrocalcinosis resolved or improved with age and discontinuation of diuretic therapy • Concluded that the length of initial hospitalisation, degree of peak elevation of sCr and loss of renal mass were unreliable in predicting disease progression

							• BP was not significantly different between study participants and population norms
6	Rodriguez-Soriano et al (2005) [26]	Control Group N=43 Study Group N=40 (premature and weighing <1000g at birth)	845 (540-1000)	27.6 (23-35)	Control Group (8.5 (1.8)) Study Group (8.6(1.8))	BP Renal length and volume Plasma creatinine Estimated creatinine clearance TmP/GFR TRP Urinary phosphate excretion Urinary calcium excretion GFR	• No significant difference in BP, microalbuminuria, and renal length and volume was found between the study and control groups • Plasma creatinine, urinary calcium excretion and urinary phosphate excretion were significantly higher in the study group than the control group • The study group had significantly lower estimated creatinine clearance and TmP/GFR compared to controls • Concluded that school aged children who were born extremely premature had significantly diminished GFR and tubular phosphate transport
7	Porter et al (2006) [27]	Control Group N=14 Study Group N=14 (very low birth weight, premature and with nephrocalcinosis)	Control Group (1210 (670-1870) Study Group (1180 (565-1880)	Control Group (28.5 (25-31)) Study Group (27.5 (25-31)	Control Group (7.21 (6.38-7.68)) Study Group (6.69 (5.81-7.09))	Early morning urine osmolality Creatinine:albumin ratio Creatinine:phosphate ratio Creatinine:calcium ratio Beta microglobulin UEC GFR TmP/GFR Renal length Nephrocalcinosis	• No significant differences in GFR or urinary concentrating capacity between the groups • 75% of patients who underwent renal ultrasound were found to have resolved nephrocalcinosis by a median age of 6.75 years • There was evidence of hypercalciuria in both the control and study groups suggesting prematurity may be a risk factor • No evidence suggested that nephrocalcinosis is associated with long term renal dysfunction
8	Kist-van Holthe et al (2007) [28]	Control N=32 (ex-preterm infants without Nephrocalcinosis) Study Group N=42 (ex-preterm infants with neonatal Nephrocalcinosis)	Control Group (1353 (337)) Study Group (1148 (394))	Control Group (29.8 (1.6)) Study Group (28.9 (2.3))	Control Group (7.5 (1.0)) Study Group (7.4 (1.0))	BP GFR Tubular function Nephrocalcinosis Kidney length	• There was no difference in the BP between the two groups • Blood pressure in both groups was found to be higher than expected for otherwise healthy children • The study group was found to have significantly more chronic renal insufficiency when compared to healthy children. This was not the case for the control group. • Tubular function, urine albumin, kidney length and GFR was not significantly different between the study and control groups

							• Tubular phosphate reabsorption, plasma bicarbonate, and early-morning urine osmolality were significantly lower in both control and study groups when compared to otherwise healthy children
9	Keijzer-Veen et al (2007) [29]	Control (Term) N=30 Group 1 (Premature SGA) N=23 Group 2 (Premature AGA) N=29	Control (3632 (40.2)) Group 1 (859 (126)) Group 2 ((1489 (257))	Control (40.2 (1.3)) Group 1 (30.6 (1.0)) Group 2 (29.5 (1.4))	20	eGFR Serum urea sCr Serum electrolytes ERPF BP Urine albumin Kidney length and volume	• Height, weight, kidney length and volume, GFR, and ERPF were significantly lower in the SGA group than in controls. After adjustment for body surface area, GFR did not differ significantly among groups. • There was increased BP in premature compared to controls
10	Finken et al (2008) [30]	Control N=328 (premature and did not receive betamethasone) Study Group N=84 (premature and received betamethasone)	Control (1319 (337)) Study Group (1348 (275))	Control (29.7 (1.5)) Study Group (29.8 (1.5))	19	Body composition Insulin resistance Serum lipid profile BP eGFR	• eGFR was found to be lower in 19-year-old born preterm who received antenatal betamethasone • This difference was clinically irrelevant at age 19, however the decreased eGFR may increase the risk of chronic kidney disease long term
11	Rakow et al (2008) [31]	Control (term AGA) N=37 Group 1 (preterm) N=39 Group 2 (term SGA) N=29	Control (3485 (502)) Group 1 (954 (203)) Group 2 (2436 (331))	Control (39.6 (1.0)) Group 1 (26.6 (2.0)) Group 2 (39.3 (1.4))	Control (9.8 (0.2)) Group 1 (9.6 (0.3)) Group 2 (9.8 (0.3))	eGFR Kidney volume sCr Serum Cystatin C Blood pressure Urinary albumin, Immunoglobulin G, alpha-1 microglobulin, N-acetylglucosamine	• Estimated glomerular filtration rate (eGFR) and urinary protein patterns were similar between the groups. • Kidney volume was smaller in the preterm group than in the controls, but the difference was not significant when adjusted for body surface area, gender and age • No significant differences were found in renal function, renal volume or blood pressure between the three groups at school age.

12	Bacchetta et al (2009) [32]	Control N=11 Group 1 (EUGR) N=16 Group 2 (IUGR) N=23	Control (1039 (278)) Group 1 (845(146)) Group 2 (773 (155))	Control (27.1 (1.8)) Group 1 (26.2(1.8)) Group 2 (28.2 (1.8))	Control (6.8 (0.9)) Group 1 (7.9 (1.3)) Group 2 (7.8 (1.3))	BP GFR Microalbuminuria Urine calcium-creatinine ratio Kidney size	• Children in groups 1 and 2 had decreased GFR compared to controls • Nil significant difference in blood pressure was found between the three groups • EUGR was concluded as a risk factor for long term renal impairment in premature children
13	Zaffanello et al (2010) [33]	Group 1 (Very Low Birth Weight) N=43 Group 2 (Extremely Low Birth Weight) N=26	Group 1 (1315 (1248–1352)) Group 2 (850 (775–883))	Group 1 (30.1 (29.9–31.3)) Group 2 (27.0 (26.3–27.7))	Group 1 (5.4 (5.2–6.1)) Group 2 (5.3 (5.2–6.3))	Plasma creatinine concentration Plasma Cystatin C eGFR Plasma renin Urinary alpha 1-microglobulin Total kidney volume BP	• Renal function parameters (i.e. estimated glomerular filtration rate and albuminuria) did not differ between the two groups of children. • Systolic and diastolic blood pressures and did not differ between the two birth- weight categories.
14	Chan et al (2010) [34]	Control (Term AGA) N=25 Group 1 (Premature SGA) N=14 Group 2 (Premature AGA) N=25 Group 3 (Term SGA) N=7	Control (3302 (3105-3690)) Group 1 (980(768-1038)) Group 2 (1635 (991-1850)) Group 3 (2750 (2430-2870))	Control (40 (38.5-41.0)) Group 1 (31(28.8-31.0)) Group 2 (30 (27.5-31.0)) Group 3 (39 (38.0-40.0)	Control (13.6 (12.54-14.78)) Group 1 (13.5 (12.48-13.97)) Group 2 (14.1 (13.66-15.03)) Group 3 (13.6 (12.35-14.83))	BP Augmentation index GFR following protein load Plasma glucose Serum insulin levels	• Nil difference in GFR prior to giving participants a protein load. • SGA had higher SBP and lower GFR following protein load than AGA. There was no effect of prematurity on SBP or GFR

15	Giapros et al (2011) [35]	Control Group (Preterm without nephrocalcinosis) N=44 Study Group (preterm with nephrocalcinosis) N=63	Control (1651 (430)) Study (1615 (480))	Control (31.9 (2.2)) Study (31.8 (3))	0.25, 0.5, 1, 2	sCr eGFR Fractional excretion of sodium, potassium, phosphate, magnesium and uric acid Kidney length	• Serum creatinine and eGFR did not differ between the groups at any time point • The NC group had a shorter KL up to 12 months of life (left kidney) or 24 months (right kidney) • Nephrocalcinosis in preterm infants was associated with renal tubular dysfunction and shorter kidney length in the first year of life
16	Carballo-Magdaleno et al (2011) [36]	Control N=30 Group 1 N=30 (premature and no steroids) Group 2 N=30 (premature with steroids)	Control (3088 (177)) Group 1 (1669 (426)) Group 2 (1501 (410))	Control (38.6 (1.0)) Group 1 (31.9 (2.3)) Group 2 (31.3 (1.7))	Control (2.0 (0.4)) Group 1 (1.8 (0.5)) Group 2 (1.8 (0.4))	Renal volume eGFR Cystatin C BP	• Groups 1 and 2, when compared to the controls had higher BP, cystatin C levels and GFR • No significant difference in these parameters was found between groups 1 and 2 • Concluded that prematurity (independent of antenatal steroids) was associated with higher blood pressure levels, cystatin C levels and glomerular filtration rates in infants aged 12-36 months
17	Starzec et al (2016) [37]	Control (term) N=36 Study Group (extremely low birth weight) N=64	Control (3570 (3395–3880)) Study (875 (750–960))	Control (40 (39–40)) Study (27 (25–28))	7, 11	Serum cystatin C levels sCr BUN eGFR Kidney length and width	• Renal ultrasound examination revealed a significantly smaller renal volume in the 7- and 11-year-old ELBW children compared to the term controls • Serum cystatin C levels were significantly higher in ELBW children than in the controls at 7 years of age, and this difference remained statistically significant at 11 years of age • GFR was significantly lower in the extremely low birth weight group compared to term controls when assessed at 11 years
18	Raaijmakers et al (2018) [38]	Control = 45 (premature and exposed to ibuprofen) Study Group = 48 (premature and not	815 (430-1000)	27 (24-33)	0.75, 2, 11	eGFR-Cystatin C Renal length	• There with no significant differences in renal length or eGFR-Cystatin C in young adolescence who experienced neonatal ibuprofen exposure

		exposed to ibuprofen)					
19	Vollsaeter et al (2018) [39]	Control (Term Born AGA) N=54 Group 1 (Preterm-born AGA) N=37 Group 2 (Preterm-born SGA) N=20	Control (3701 (3582, 3581)) Group 1 (918 (867, 968)) Group 2 (724 (657, 791))	Control = Term born Group 1 (26.1 (25.7, 26.5) Group 2 (28.0 (27.2, 28.7)	Control (11.7 (11.2-12.0)) Group 1 (11.4 (11.1-11.8)) Group 2 (11.3 (11.0-11.8))	Height Weight Abdominal circumference Triceps and subscapular skin fold thickness BP Plasma creatinine Cystatin C GFR SDMA	• SDMA levels were significantly higher Group 1 and 2 when compared to the controls • GFR was significantly lower in Groups 1 and 2 compared to the controls • No significant differences in creatinine or cystatin C between the groups • Systolic BP had a significant relationship with fat mass indices but not renal function • Systolic BP did not significantly differ between the groups • Concluded that children from Groups 1 and 2 (especially Group 2) had impaired renal function by 11 years of age (as shown by GFR and SDMA) • Findings suggest being born preterm or SGA increases risk of developing kidney disease in the future
20	Crump et al (2019) [40]	Extremely Preterm N=8129 Very preterm N=43516 Late preterm N=155626 Early term N=737412 Full term N=2895746	NA	Extremely Preterm (22-27) Very preterm (28-33) Late preterm (34-36) Early term (37-38)	0-43	CKD	• Preterm and extremely preterm birth were associated with twofold and threefold risks of CKD respectively • Preterm birth and CKD were found to have the strongest association at ages 0-9 years (hazard ratio 5.09) and weakened but remained increased at ages >9 years (hazard ratio 1.97 for 10-19 years and 1.34 for 20-43 years)

		Post-term N=346186		Full term (39-41) Post-term (≥42)			
21	Horie et al (2019) [41]	Control Group (Preterm and normal eGFR) N=150 Study Group (Preterm and low eGFR) N=18	<1000g N=73 1000-1500g N=76 >1500g N=19	<28+0 N=63 ≥28+0 N=105	2-15	sCr eGFR Gestational age Body weight and length at birth Sex Apgar score Use of antimicrobial agents, steroids or indomethacin	• eGFR at 2 years of age was significantly correlated with birthweight and gestational age. This relationship was no longer significant at 3-4 years of age. • Approximately 10.7% of the children had low eGFR without clinical symptoms or abnormal urine examination. These children had high sCr on day 7 after birth and delayed recovery of these levels during the first month after birth.
22	Rakow et al (2019) [42]	Control N=19 Group 1 (Extremely preterm and nephrocalcinosis) N=20 Group 2 (extremely preterm and non nephrocalcinosis) N=21	Control (3586 (477)) Group 1 (755 (124)) Group 2 (841 (202))	Control (39.7 (1.6)) Group 1 (25.5 (1.2)) Group 2 (25.9 (1.3))	Control (8.1 (2.2)) Group 1 (7.8 (1.0)) Group 2 (7.4 (1.1))	Kidney volume 24-hour ambulatory BP Cystatin C calculated eGFR Plasma creatinine Urinary protein and electrolytes	• Groups 1 and 2 had significantly smaller kidneys compared to the controls • Cystatin C based GFR was significantly lower (however still normal) in groups 1 and 2 when compared to the control group • Nil significant difference between kidney volume and function between Groups 1 and 2 • The control groups had significantly higher plasma creatinine compared to groups 1 and 2 • Urinary protein and electrolytes were not significantly different between all groups • BP was not significantly different between all groups • Significantly more children from group 1 had a negative evolution of kidney function from the neonatal period to school age • Concluded that being extremely premature affects kidney growth and volume, and nephrocalcinosis is a potential aggravating factor
23	Kandasamy et al (2020) [43]	Control group (term) N=31 Study Group (preterm) N=53	NA	Control = Born at term Study = <28	0.5, 1, 2	TKV eGFR Urine ACR BP	• The study group had significantly reduced TKV compared to the controls • Both groups had a similar eGFR • No significant difference was found in BP and urine ACR between the groups

24	Yael et al (2020) [44]	Control group = known paediatric population prevalence rates Study group (very low birth weight and preterm) N = 103	Study Group (1086 (243))	Study Group (29.4 (24-35))	Study Group (11.6 (10-13.3))	BP PCR ACR eGFR	• The prevalence of systolic hypertension was 15.8% and of systolic pre-hypertension was 6.9%. This is compared to the general United States paediatric population which has a 1.6% prevalence rate of systolic hypertension. • Hypertension was associated with a significantly diminished mean birth weight compared to the remainder of the cohort (939.3 grams vs 1111 grams P=0.024) • 103 study participants that were very low birth weight and preterm all had normal values of GFR
25	Staub et al (2020) [45]	Control Group (term) N=82 Study Group (preterm) N=51	Control (3250 (555)) Study (1360 (532))	Control (39 + 6 (2 + 5)) Study (31 + 0 (2 + 6))	Control (12.1 (1.20)) Study (12.3 (1.87))	BP sCr Cystatin C eGFR Beta-2 Microglobulin Uromodulin Neutrophil gelatinase-associated lipocalin	• Systolic BP was significantly higher in preterm boys compared with term boys, however there was not significant difference in girls • Low birth weight was associated with higher BP in preterm boys • In the preterm group maternal hypertension/preeclampsia and adolescent height were associated with higher systolic BP • Serum creatinine and neutrophil gelatinase-associated lipocalin were significantly higher in the preterm group • There was no significant difference in GFR between groups

Abbreviations: BP (blood pressure), eGFR (estimated glomerular filtration rate), GFR (glomerular filtration rate), BMI (body mass index), TmP (tubular maximum reabsorption of phosphate), sCr (serum creatinine), CKD (chronic kidney disease), ACR (albumin creatinine ratio), PCR (protein creatinine ratio), SDMA (Symmetric dimethylarginine), TKV (total kidney volume), IUGR (intrauterine growth restriction), EUGR (extrauterine growth restriction), SGA (small for gestational age), AGA (appropriate for gestational age), BUN (blood urea nitrogen), ERPF (effective renal plasma flow)

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1/Title page
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	2-6
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	2
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	NA
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	7
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	7
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	7 and Appendix A Figure 1
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	7
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	7
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	7
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	7
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	7
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	NA

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	7
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	NA
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	9
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	9 and Appendix A Table 1
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	14
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	9-14
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	NA
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	14
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	NA
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	15-16
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	16-17
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	17-18
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	NA

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THE EFFECTS OF PREMATURITY ON LONG-TERM RENAL HEALTH: A SYSTEMATIC REVIEW

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ABSTRACT:

Objective: To investigate the literature and determine if prematurity has an impact on long-term adverse kidney outcomes

Design: Systematic review

Data sources: OVID Medline, PubMed, SCOPUS, CINAHL and EMBASE databases were searched for studies relating to the adverse outcomes of prematurity from 1990 – April 2021.

Eligibility criteria for selecting studies: All articles published between January 1990 and April 2021 that investigated whether premature infants developed long term adverse renal outcomes were included in this review. Articles must have been human studies and written in English. Case series with less than 20 participants and case studies were excluded.

Data extraction and synthesis: One reviewer completed the database searches. Article selection was performed independently and in a non-blinded manner by both reviewers. Initial screening was by title and abstract. Full texts of remaining articles were reviewed. Articles for which inclusion was unclear were re-reviewed by both reviewers, and a unanimous decision was taken as to whether they should be included. The Newcastle-Ottawa Scale was used for quality assessment of the included articles.

Results: The literature search yielded 31 human studies which investigated the short- and long-term kidney outcomes of prematurity. These studies were conducted in 17 different countries. The most common outcomes measured were blood pressure, and glomerular

filtration rate. Other common outcomes measured included kidney size and mass, proteinuria, albuminuria, chronic kidney disease and physical parameters like height, weight and body mass index.

Conclusion: Prematurity is likely linked to increased risk of kidney dysfunction and high blood pressure in childhood and into early adulthood. Premature birth conferred a twofold increased risk of CKD and extremely premature birth conferred a threefold increased risk of CKD. However, further larger multi-centre studies are needed to draw definitive conclusions on the long-term kidney outcomes of prematurity.

Keywords: Premature, preterm, renal, kidney, impairment proteinuria, albuminuria, hypertension, high blood pressure, reduced estimated glomerular filtration rate, decreased kidney function

STRENGTHS AND LIMITATIONS

- This systematic review yielded 31 relevant human studies from a wide search of five reputable databases
- We used the Newcastle Ottawa Scale to assess the quality of included studies
- The long-term adverse outcomes of prematurity on kidney function can only be evaluated up to approximately 40 years of age as research into the aging population is still needed
- As current research into the long-term kidney outcomes of prematurity is lacking, the available research is not sufficient to draw definitive conclusions as to the long-term

kidney outcomes of premature children and further larger multicentre studies are still needed.

INTRODUCTION:

Prematurity is the leading cause of mortality in children under the age of five.[1] However, with advances in technology and modern medicine, both the incidence of prematurity and the number of ex-premature babies living into adulthood are increasing, especially in population-dense countries.[1] Approximately 15 million, or just over 1 in 10 babies, are born prematurely every year.[2] The highest number of premature births are seen in India, China and Nigeria; while the highest rates of premature births are seen in Malawi, Comoros and Congo.[3]

Though premature birth is becoming more commonplace, it is not without its own challenges. The Barker hypothesis proposes that diseases of adulthood are due to factors pertaining to fetal life. [4-6] This proposition is also commonly known as the Developmental Origins of Health and Disease (DOHaD) hypothesis. This conclusion was first drawn when Barker et al. found that early death secondary to coronary artery disease was inversely related to weight at birth.[7] Thus the DOHaD paradigm was created. It proposed that developmental factors, including nutrition, stressors, and environmental exposures such as drugs and infections, could lead to functional changes in tissues which may predispose to disease in later life.[8]

The impact of prematurity on long-term kidney dysfunction or chronic kidney diseases (CKD) is still not fully understood. Impaired nephrogenesis due to poor fetal growth, prematurity, antenatal and post-natal medication and other factors most likely lead to reduced nephron endowment and CKD. [9-10] Nephrogenesis is completed by 37 weeks gestation, and the majority of nephrogenesis occurs in late gestation.[11] Therefore, in premature neonates, nephrogenesis is terminated early conferring reduced nephron numbers. Nephrons do not

regenerate. The number of functional nephrons over time decreases as part of normal aging.[5] As premature children are born with reduced nephron numbers, an increased risk of kidney dysfunction is postulated. Brenner et al. also proposed that as a compensatory measure for low nephron numbers, nephron surface area increases. This maladaptive response causes systemic hypertension and increased sodium retention, which in turn causes disrupted autoregulation.[12] The resulting nephron sclerosis leads to increased functional nephron decline creating a vicious cycle. [12-13]

As the ex-premature population is living longer and becoming part of the aging population, understanding the effects of prematurity is imperative in anticipating the likely chronic health outcomes the premature population will face. This review is intended to investigate the literature to determine if a link is present between prematurity and adverse long-term kidney health. Identifying a link will be the first step in deciding how best to follow-up and manage ex-premature children and adults to prevent morbidity and premature mortality in the long term.

METHODS

This systematic review was completed in accordance with the PRISMA guidelines. [14] The systematic search was conducted using OVID Medline, PubMed, SCOPUS, CINAHL and EMBASE. The search criteria were developed and refined from January 2020 to April 2021. Relevant keywords were identified, and all relevant Medical Subject Headings (MeSH) and non-MeSH synonyms were included. Relevant keywords included prematurity, chronic kidney failure, chronic kidney disease, kidney volume, proteinuria, albuminuria, hypertension, high blood pressure, reduced GFR, decreased kidney function and long-term adverse outcomes. The final search was conducted on April 1st, 2021. An example of the database search for OVID Medline can be seen in the supplementary files. Only articles published in English between January 1990 and April 2021 have been included. Animal studies were excluded. Finally, articles shortlisted for inclusion were screened for bias and re-evaluated for inclusion if there was significant bias.

Once the literature search was completed, article selection was performed independently and in a non-blinded manner by two reviewers. The articles were initially screened by title and then by the abstract. All remaining articles were reviewed and determined for inclusion based on examination of the full text. Articles which were unclear were re-reviewed by both reviewers, and a unanimous decision was taken as to whether they should be included.

Articles were included if they studied premature and/or low birth weight infants to determine if they developed adverse kidney outcomes as a result of being premature. Studies that investigated low birth weight infants were only included if their low-birth-weight cohort were also premature. Outcomes that were evaluated included glomerular filtration rate (GFR),

blood pressure (BP), tubular function, kidney length and volume, and urinary protein/albuminuria and electrolytes. It was decided that case series with less than 20 participants, and case studies would be excluded from this review as they would not provide the level of evidence or relevant information required. Included articles and their characteristics can be found in Supplementary Table 1. [15-45] Articles underwent quality assessment using the Newcastle-Ottawa scale. [46] This can be seen in Table 1.

Patient and Public Involvement

Patients were not involved in the development or design of this systematic review.

Table 1: Quality assessment of included observation studies using the Newcastle-Ottawa Scale

Cohort Studies			
Study	**Selection***	**Comparability****	**Outcome*****
Downing et al (1992)	★★★	★	★★★
Jones et al (1997)	★★★	★★	★★★
Ojala et al (2001)	★★★★	★	★★★
Rodriguez-Soriano et al (2005)	★★★	★	★★
Porter et al (2006)	★★★	★★	★★★
Kist-van Holthe et al (2007)	★★★	★	★★
Keijzer-Veen et al (2007)	★★		★★
Finken et al (2008	★★★	★	★★★
Rakow et al (2008)	★★★★	★	★★
Bacchetta et al (2009)	★★★★	★★	★★
Zaffanello et al (2010)	★★★★	★	★★★
Chan et al (2010)	★★	★	★★
Giapros et al (2011)	★★★★	★★	★★★
Carballo-Magdaleno et al (2011)	★★★	★	★★★
Starzec et al (2016)	★★		★★
Bruel et al (2016)	★★★★	★	★★
Harer et al (2017)	★★★		★★
Raaijmakers et al (2017)	★★★	★	★★
Vollsaeter et al (2018)	★★★		★★
South et al (2019)	★★		★★
Crump et al (2019)	★★★★	★★	★★★
Rakow et al (2019)	★★★★	★	★★★
Horie et al (2019)	★★★★	★	★★★
Crump et al (2019)	★★★★	★★	★★★
Kandasamy et al (2020)	★★★	★	★★★
Sanderson et al (2020)	★★	★	★★
Yael et al (2020)	★★★		★★
Staub et al (2020)	★★	★★	★★
Case Series			
Abitolol et al (2003)	★	NA	★★
Case Control			
Study	**Selection***	**Comparability****	**Exposure*****
Masqood et al (2017)	★★★	★	★★★

* Maximum 4 stars

** Maximum 2 stars

*** Maximum 3 stars

RESULTS

The collective search from the five databases revealed 1311 studies. A total of 1263 articles remained after duplicates were omitted. All 1263 articles were screened, and 1101 were excluded based on title and abstract. For the remaining 162 articles, full texts were assessed for eligibility. Sixty-four articles were excluded due to long term adverse kidney outcomes not being investigated. Nine articles were excluded as prematurity or low birth weight were not investigated. Eight were excluded for being animal studies, and 50 were excluded for being case reports or case series with less than 20 participants. Thus, the literature search yielded 31 human studies which investigated the long-term kidney outcomes of prematurity. [15-45] These studies were conducted in 17 different countries: Australia, Israel, Japan, Italy, Greece, Poland, France, Egypt, Sweden, Belgium, Mexico, the Netherlands, Scotland, Spain, the USA, Finland and Norway. [15-45] A flow diagram demonstrating the selection process can be seen in Figure 1. The lead author surname, year of publication, sample size, birth weight, gestation, outcome measures, age at which outcome measured and conclusions of the selected studies can be seen in Supplementary Table 1. A quality assessment of included studies was conducted using the Newcastle Ottawa Scale and can be seen in Table 1.

Of the included studies, the smallest cohort size was 20, and the largest cohort size was 4193069. [18, 40] The youngest gestational age from the premature cohorts was 22 weeks, and the most mature gestational age for the premature cohorts was 36 weeks. [37, 40] The youngest age at which outcomes were measured was at birth, and the oldest age at which outcomes were measured was at 43 years.[37, 40] The most common outcomes measured were BP and kidney function (GFR and proteinuria/microalbuminuria). Other outcomes measured included

kidney size and mass, urine analysis, chronic kidney disease and physical parameters (height, weight and BMI). Some studies also commented on insulin resistance and serum lipid profile.

Glomerular filtration rate

Twenty-seven out of the 31 studies investigated GFR as an outcome measure. [16-36, 38-39, 41, 43-45] Ten of these 27 studies compared premature children and term children. [19, 21-22, 24, 27, 35-36, 38, 41, 44] Four found no significant difference in GFR while 6 did. Of the 4 studies that found no significant difference, Rakow et al. measured their outcomes at 9 years, Kandasmay et al. measured their outcomes at 0.5, 1 and 2 years, Staub et al. measured GFR at 12 years and Chan et al. measured outcomes at approximately 13.5 years. [24, 27, 41, 44] Of the 7 studies that found a significantly decreased GFR in premature children, outcomes were measured at approximately 7.5 years, 8 years, 8.5 years, 11.5, 14 and 20 years respectively for Kist-Van Holthe et al., Rakow et al., Rodriguz-Soriano et al., Vollsaeter et al., South et al. and Keijer Veen et al. [19, 21-22, 35-36, 38] It should be noted that Keijer Veen et al. found that GFR was significantly lower in the premature small for gestational age group compared to term controls at 20 years. [22] This was not the case for the premature appropriate for gestational age group. [22] When the small for gestational age group had their GFR adjusted for body surface area, there was no significant difference between groups. [22] One additional study conducted by Harer et al. investigated cystatin C and found significantly higher levels of cystatin C in premature children at 5 years compared to term children.[33]

Twelve studies investigated GFR in study and control groups with differing characteristics including no term birth comparison. [16-18, 20, 23, 25-26, 28, 30-32, 34] Seven of these studies found no statistically significant difference in GFR between study and control groups.[17, 20, 26, 28, 31-32, 34]

Ojala et al. compared premature infants with and without indomethacin exposure in the neonatal period and measured outcomes at 2-4 years.[17] Raaijmakers et al. compared premature infants with and without ibuprofen exposure in the neonatal period and assessed outcomes at 11 years.[34] Porter et al. compared two groups of very low birth weight children with and without nephrocalcinosis at 5-7 years of age. [20] Zaffanello compared very low birth weight and extremely low birth weight children at 5-6 years.[26] Giapros compared premature infants with and without nephrocalcinosis for the first 2 years of life.[28] Masqood et al. compared three groups of extremely low birth weight children with no AKI, Stage 1 AKI and stage 2 AKI, and found no significant difference in the prevalence of diminished GFR values. [32] Finally, Bruel et al. found nil significant difference between premature children with and without neonatal AKI when assessed at 7 years of age. [31] Bruel et al. did however note that GFR was significantly lower in children with a birth weight less than 1000 grams. [31]

On the other hand, 5 of these studies did find significantly differences in GFR between study and control groups. [16, 18, 23, 25, 30] Finken et al. noted significantly decreased GFR in premature infants who received betamethasone in the neonatal period when compared to premature infants who did not.[23] This outcome was measured at 19 years of age.[23] Abitbol et al. found ex-premature children had normal GFRs when aged 5.7 years but children assessed at 9.9 years were found to have diminished GFR.[18] Starzec et al. concluded that GFR was significantly lower in the extremely low birth weight group compared to term controls when assessed at 11 years.[30] Bacchetta et al. found significantly decreased GFR in premature extra-uterine growth retardation and intrauterine growth retardation when compared to premature normotrophic children at 7-8 years of age. [25] Jones et al found that four out of

their 11 premature babies with nephrocalcinosis had an abnormal GFR at 4-5 years of age. Jones et al did not however have a term control group to compare these results too.[16]

Only one study (Carballo-Magdaleno et al.) found an increased GFR in premature infants when compared to term infants. Outcomes were measured at two years of age.[29]

Three studies looked at the prevalence of low GFR in their premature cohorts. [39, 43, 45] Horie et al. found that of their 168 premature children, 10.7% had persistently low GFR at >2 years of age. [39] Yael et al. found that 100% of their 103 study participants with a history of very low birth weight and premature birth had normal GFR values at 10-13 years of age. [43] Ashkenazi et al found that of their 923 extremely premature study participants 16% had a GFR <90mL/min/1.73m2 at 22-26 months of age. [45]

Chronic kidney disease

Crump et al. was the only study that exclusively investigated for CKD. [37] From their large cohort size of 4 186 615, they concluded that premature birth conferred a twofold increased risk of CKD and extremely premature birth conferred a threefold increased risk of CKD.[37] This risk was found to be highest between ages 0-9 years and slightly weakened but still increased from ages 10-19 years.[37]

Blood Pressure

Twenty-three out of the 31 studies investigated BP as one of their outcome measures.[17-19, 21-27, 29, 31-33, 35-36, 38, 40-45] Fifteen found no significant difference in BP between study and control groups.[17-19, 21, 23-27, 31-33, 35, 38, 41] Seven of these studies found no significant difference in BP

between term babies and premature babies at differing ages ranging from 1.5-27.6 years.[19, 24-25, 27, 35, 38, 41] Six studies compared premature babies with and without different variables including exposure to betamethasone, exposure to indomethacin, presence or absence of nephrocalcinosis, having neonatal acute kidney injury, and having extrauterine growth restriction, intrauterine growth restriction or being appropriate for gestational age.[17, 21, 23, 25, 31, 33] All six concluded no significant difference in BP between these groups of premature babies at differing ages ranging from 2-19 years.[17, 21, 23, 25, 31, 33] Zaffanello et al. found no significant difference in BP between very low birth weight and extremely low birth weight infants at 5-6 years of age. [26] Masqood et al. also compared groups of extremely low birth weight children with no or varying severities of neonatal acute kidney injury and found no significant difference in BP at approximately 6-8 years.[32] It should be noted that both Zaffanello and Maqsood did not compared these blood pressures with term infants. [26, 32]

Carballo-Magdaleno et al., Keijzer-Veen et al., Yael et al., South et al., Staub et al. and Crump et al. found increased BP in premature children compared to controls. [22, 29, 36, 40, 43-44] Carballo-Magdaleno et al. found that 2-year-old infants born prematurely had significantly higher blood pressures than 2-year-old infants born at term.[29] Keijzer-Veen et al. found significantly increased systolic BP in premature children compared to term children when BP was assessed at 20 years.[22] Yael et al. reported a 15.8% prevalence rate of systolic hypertension in their study group of premature children with very low birth weight when assessed at 10-13 years. [43] This is compared to the general United States paediatric population which has a 1.6% prevalence rate of systolic hypertension. [43] South et al. found significantly higher BP in premature children compared to term children at 14 years of age. [36] Staub et al. found that systolic BP was significantly higher in premature boys compared to term boys, however they

did not find a significant difference in premature and term girls. [44] They also noted that low birth weight was associated with higher BP in boys. [44] Crump et al. found that prematurity was associated with an increased risk of hypertension in early adulthood.[40] They found that at 18-29 years of age adjusted hazards ratios were 1.28 and 2.45 respectively for premature and extremely premature birth compared to term birth.[40] Furthermore at 30-43 years of age hazards ratios were calculated as 1.25 and 1.68 for premature and extremely premature birth respectively when compared to full term birth. [40]

Sanderson et al found that of their 42 premature participants, 33.3% had elevated blood pressures at 15 years of age. [42] Ashkenazi et al. found that of their 923 extremely low gestational age participants at 22-26 months of age, 23% have a systolic blood pressure >95th percentile for their age and 40% had a diastolic blood pressure >95th percentile. [45]

Proteinuria/Albuminuria

Nineteen studies commented on proteinuria or albuminuria. [15-22, 24-26, 31, 33, 36, 38, 41-43, 45] Of these, 11 studies found no significant difference between study and control groups. [17, 20, 21, 24, 26, 29, 31, 33, 36, 38, 41] Six out of these 11 studies compared term and premature infants at ages ranging from approximately 0.5-14 years. [19, 24, 33, 36, 38, 41] The other 5 studies compared groups of premature children with varying characteristics including neonatal AKI, low or extremely low birth weight, the presence of nephrocalcinosis and indomethacin exposure. For these studies outcomes were measured at 2-7.5 years. [17, 20, 21, 26, 31]

Seven studies commented on prevalence of proteinuria or albuminuria. [15-16, 22, 25, 42-43, 45] Askenazi et al. found that at 22-26 months 35.8% of their 923 participants had a urine

albumin/creatinine ratio greater than 30mg/g. [45] Bacchetta et al. found that 2 out of their 50 participants had moderate microalbuminuria approximately 7 years of age. [25] Jones et al. found that 2 out of their cohort of 28 premature had microalbuminuria at 4-5 years of age. [16] Sanderson et al. found 11.9% of their 42 premature children had microalbuminuria at 15 years of age.[42] Keijer Veen et al. reported microalbuminuria in 2 patients of their premature small for gestational age group. [22] However, none of their participants in the premature appropriate for gestational age group or term group was found to have microalbuminuria. [22] Yael et al. found that the prevalence of microalbuminuria was 14.3% while the prevalence of proteinuria was 7.9% in their low-birth-weight premature cohort of 103 at 11.6 years. [43] Finally, Downing et al. found that 4 out of the 10 participants in their premature cohort with renal calcifications who received frusemide therapy, had trace proteinuria. [15] The other 17 participants from their other 2 study groups did not have any proteinuria. [15]

Abitbol et al. only had data for urine protein/creatinine ratios available for 10 out of 20 of their premature extremely low birth weight participants. [18] Out of these 10, those with low GFR (n=3) had significantly higher urine protein/creatinine ratios compared to the participants with normal GFR (n=7) at follow up. [18] Follow up ranged from 3.1-18.3 years. [18]

Bias

In all studies included in this review, bias was minimal. Some bias may be present in single centre studies as these may only provide results from a particular population demographic. [15-19, 22, 24-28, 30-34, 36, 38-39, 41, 43, 44] However, as this review correlates the results of numerous single centre studies, this bias is minimised. Randomisation of study subjects was only done in one of the 31 included studies with was a randomised control trial where all study

participants were premature. [45] All other studies were observational, and randomisation was not possible as birth weight and gestational age are not variables that can be ethically influenced. [15-44] Furthermore, 17 studies did not have term born controls. [15-18, 20-21, 23, 25-26, 28, 31-32, 34, 39, 42-43, 45] Abitbol et al. did however match their study participants to age-, gender- and height- matched population norms when reviewing outcomes.[18] Yael et al. also did not have a term control group; however, they did compare their results to known population prevalence's.[43]

DISCUSSION

Thirty-one studies that assessed long term kidney outcomes of premature infants were identified in this review. [15-45] There was a relatively even split between the studies that investigated GFR as to whether there was or was not a significant difference between study and control groups. [16-36, 38-39, 41, 43-45] It should be noted that the studies which favoured no significant difference between premature and term participants investigated GFR in children from 0.5-13.5 years, while the studies that favoured a significant difference between the two populations measured outcomes at 7.5-20 years. [19, 21-22, 24, 27, 35-36, 38, 41, 44] Thus, it is possible that in the short term, GFR is not significantly affected by prematurity. However, as the ex-premature population ages, their kidney function may become considerably diminished compared to the term population. This could possibly be due to the fact that premature infants start out with reduced nephron numbers.

From the 23 studies that investigated BP, 12 compared term and premature children. [18-19, 22, 24, 27, 29, 35, 36, 38, 40, 41, 44] Seven found no significant difference between premature children and term children while five did find a significant difference. [18-19, 22, 24, 27, 29, 35, 36, 38, 40, 41, 44] The studies which found no significant difference measured outcomes from approximately 0.5-27.6 years of age while those that did find a significant difference, measured outcomes at 2-43 years of age. [18-19, 22, 24, 27, 29, 35, 36, 38, 40, 41, 44] Crump et al. was the largest included study and also had one of the highest rating on the quality assessment. [40] It demonstrates that from 30-43 years of age premature and extremely premature children are at a 25% and 68% greater risk of developing hypertension compared to controls. [40] As with GFR, this may be because in early childhood the effects of prematurity on blood pressure are not as obvious as the kidneys are able to compensate, or the reduced nephron number is may not yet be significant.

However, it is possible that as the ex-premature population ages, their initially reduced nephron number may no longer be able to compensate for BP.

From the 19 studies that investigated for microalbuminuria or proteinuria, most commented on prevalence as opposed to comparing groups. [15-22, 24-26, 31, 33, 36, 38, 41-43, 45] Only 6 studies, that commented on proteinuria or albuminuria, compared term children and premature children but all 6 of these studies found no significant difference between groups when assessed at 0.5-14 years of age. [19, 24, 33, 36, 38, 41] Albuminuria or proteinuria are signs of kidney damage and progression of kidney disease. As with GFR and BP, it is possible that in childhood the kidneys are able to compensate for the shortened nephrogenesis. However, in the aging population ex-premature adults may be more likely to demonstrate markers of kidney disease or poor kidney function like microalbuminuria or proteinuria sooner than their ex-term counterparts due to further reduction in an already deplete nephron reserve. Further larger studies with longer follow-up are required to assess for microalbuminuria and proteinuria.

The risk of CKD is twofold and threefold greater in premature and extremely premature children respectively compared to those born at term as per Crump et al. [37] The risk of CKD over the age of 43 years cannot be commented on as it was not investigated in any of the included articles. The conclusion drawn by Crump et al. is reliable, given their methodology and massive cohort size despite other included articles not specifically commenting on CKD but GFR instead. The conclusion could be explained due to the decreased nephron endowment associated with prematurity. It should be noted that kidney function must be significantly impaired (GFR <15) before evidence of kidney failure will be present clinically.

There are some limitations to our systematic review. The majority of the included studies were conducted in Caucasian predominant countries. Therefore, they do not reflect the true impact of prematurity of long-term kidney dysfunction as they do not encompass population rich countries including India, China and Nigeria where the highest number of premature births occur each year. This means the conclusions from this review do not apply to all ethnicities and cannot be generalised for non-Caucasian ethnic groups. Additionally, all the studies included in this review analysed kidney function through quantifiable measures such as blood tests. Clinically significant kidney outcomes, symptomatology, quality of life and kidney dysfunction associated mortality were not commented on or investigated in these studies. Finally, the majority of studies did not investigate outcomes over the age of 20 years. Two study had participants up to the age of 43; however, the proportion of their study cohort over the age of 20 was minimal. Thus, this systematic review could only investigate long-term kidney outcomes of prematurity up until adolescence and early adulthood. Finally, only studies conducted after 1990 and written in English were considered for inclusion.

CONCLUSION

Prematurity is likely linked to increased risk of kidney dysfunction and high blood pressure in childhood and into early adulthood. The risk of CKD is twofold and threefold higher in premature and extremely premature children compared to those born at term. Further studies need to be conducted to investigate the effects of prematurity on long term kidney health in the aging population; reliable information at this time is only available up until the age of 43 years. Thus, kidney outcomes in the ex-premature population over the age of 43 years cannot be concluded from the current research. However, enough evidence is present

to warrant ongoing monitoring of kidney function and blood pressure in premature infants as they age in order to optimise and prevent earlier morbidity and mortality.

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Figure 1: PRISMA Flow diagram

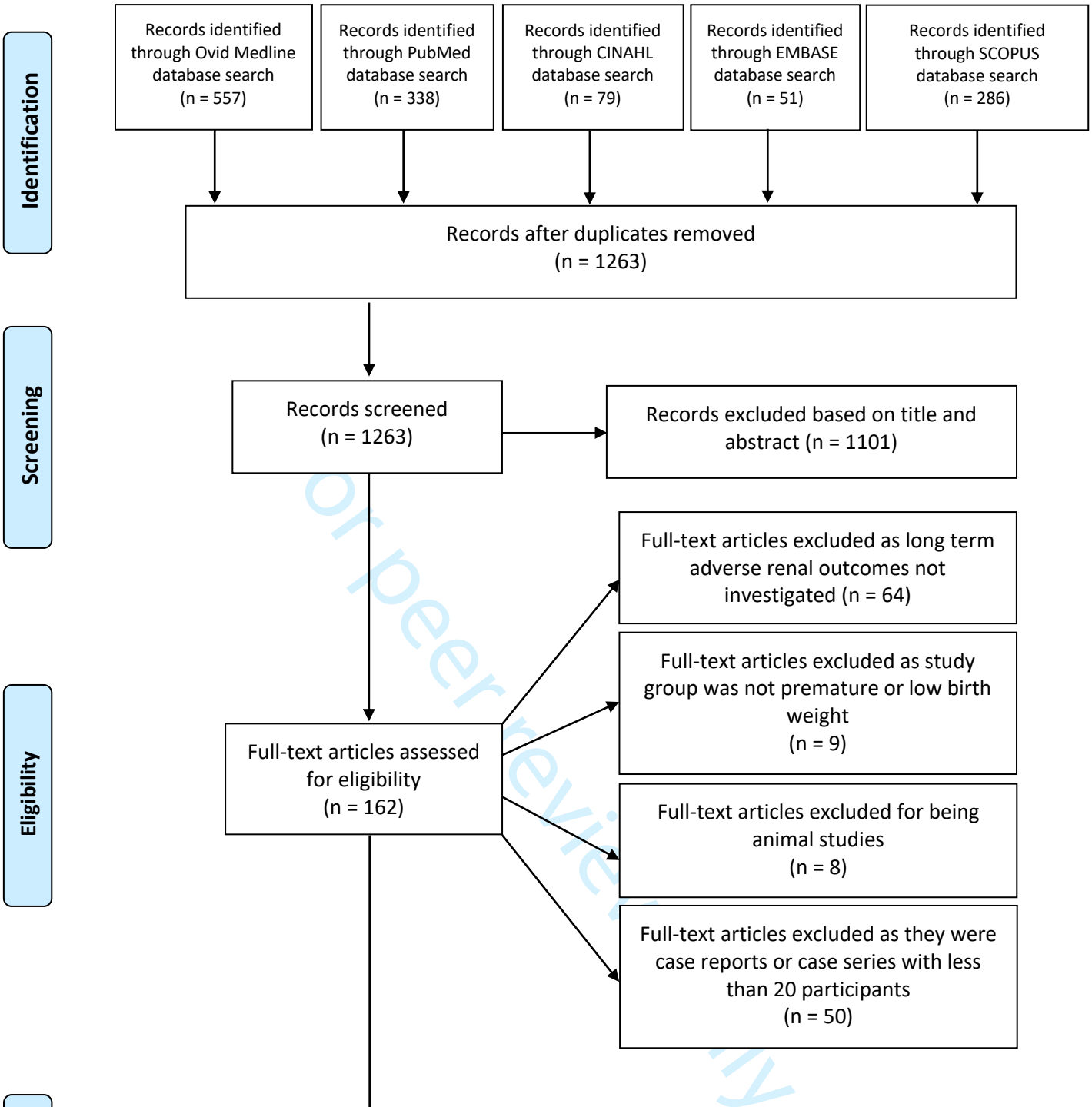

Figure 1: PRISMA Flow diagram

Supplementary Table 1 – Characteristics of included studies (n = 31)

	Source (Y)	Sample Size	Birth weight (g) (study group)	Gestation (wks.) (study group)	Age at which outcomes measured (years)	Outcome measure (for example eGFR or BP or KV)	Conclusion (briefly)
1	Downing et al (1992) [15]	Control N=7 (Premature no frusemide therapy and no renal calcifications) Group 2 N=10 (Premature frusemide therapy but no renal calcifications) Group 3 N=10 (Premature frusemide therapy and renal calcifications)	Control (743(84)) Group 2 (806(103)) Group 3 (678(95))	Control (25.3(0.6) Group 2 (26.1(0.5)) Group 3 (26.2(0.4))	Control (1.2(0.01)) Group 2 (1.3 (0.1)) Group 3 (1.2 (0.1))	Creatinine clearance Urinary calcium:creatinine ratio Fractional excretion of sodium Lower tubular reabsorption of phosphate Urine-blood difference in carbon dioxide tension after oral acetazolamide load Proteinuria	• No significant difference in renal function between the control group and group 2 • In group 3, trace proteinuria was present in 4/10 participants • Creatinine clearance in group 3 was significantly lower than in the control group and group 2 • Urinary calcium:creatinine ratios, fractional excretion of sodium and lower tubular re-absorption of phosphate was significantly higher in Group 3 compared to the group 2 and control group • Group 3 had lower urine-blood differences in carbon dioxide tension after oral acetazolamide load when compared to the controls and group 2
2	Jones et al (1997) [16]	Control Group (premature without renal calcifications) N=17 Study Group (premature with renal calcifications) N=11	Control (982 (710–1760)) Study (850 (580–1856))	Control (28 (25–31)) Study (27 (24–31))	4-5	eGFR Renal calcifications/ nephrocalcinosis	• In the study group the median GFR was 61 ml/min/1.73m2 (range 46-79 ml/min/1.73m2) • Five of the 11 children born premature and found to have renal calcifications, still had renal calcifications at age 4-5 years. • Nephrocalcinosis in isolation was not found to be a major predisposing factor to long term renal dysfunction • Four out of the 11 premature babies with nephrocalcinosis had an abnormal GFR at 4-5 years of age • Two children from the collective premature cohort had microalbuminuria at 4-5 years of age

3	Ojala et al (2001) [17]	Control Group N=35 (premature without perinatal indomethacin) Study Group N=31 (premature with perinatal indomethacin exposure)	Control Group (1360 (680–2680)) Study Group (1150 (670–2060))	Control Group (31 (24-32)) Study Group (28 (24-32))	2-4	Serum cystatin C and protein Plasma creatinine, sodium and potassium Urine PCR Urine alpha-1 microglobulin eGFR BP Renal sonography examination	• The control group showed higher mean serum cystatin concentrations than the study group • No difference was found between the groups for mean serum protein, plasma creatinine and sodium, median plasma potassium concentrations, urine protein:creatinine ratio and urine calcium:creatinine ratio. • No statistical difference was found in GFR or renal structural abnormalities between the two groups • Nil significant difference in urine PCR between groups • Umbilical artery catheter use, frusemide treatment and assisted ventilation may correlate with long term renal structural and functional abnormalities
4	Abitbol et al (2003) [18]	N=20	686 (133)	25 (2)	3.1-18.3	Proteinuria Kidney function/kidney failure (eGFR, sCr) Renal size and mass BP Growth (height, weight and BMI) Nephrocalcinosis	• Significant age difference was found between the normal GFR and low GFR groups, the age of outcome measure was 5.7+/-2.2 and 9.9+/-5.6 years respectively. • BP was not significantly different between study participants and population norms • Urine PCR was available for 10 out of 20 of the participants. Participants with low GFR (n=3) had significantly higher urine protein/creatinine ratios compared to the participants with normal GFR (n=7) at follow up.
5	Rodriguez-Soriano et al (2005) [19]	Control Group N=43 Study Group N=40 (premature and weighing <1000g at birth)	845 (540-1000)	27.6 (23-35)	Control Group (8.5 (1.8)) Study Group (8.6(1.8))	BP Renal length and volume Plasma creatinine Estimated creatinine clearance TmP/GFR TRP Urinary phosphate excretion Urinary calcium excretion eGFR	• No significant difference in BP, microalbuminuria, and renal length and volume was found between the study and control groups • Plasma creatinine, urinary calcium excretion and urinary phosphate excretion were significantly higher in the study group than the control group • The study group had significantly lower estimated creatinine clearance and TmP/GFR compared to controls • No significant differences were observed in microalbuminuria values, but five study subjects (12.5%) presented values above the upper limit of normal.
6	Porter et al (2006) [20]	Control Group N=14 (without nephrocalcinosis – matched for birth weight, gestational age and sex)	Control Group (1210 (670-1870)	Control Group (28.5 (25-31)) Study Group (27.5 (25-31)	Control Group (7.21 (6.38-7.68)) Study Group (6.69 (5.81-7.09))	Early morning urine osmolality Urine ACR and PCR Creatinine:phosphate ratio Creatinine:calcium ratio Beta microglobulin	• No significant differences in GFR or urinary concentrating capacity between the groups • 75% of patients who underwent renal ultrasound were found to have resolved nephrocalcinosis by a median age of 6.75 years • There was evidence of hypercalciuria in both the control and study groups suggesting prematurity may be a risk factor

		Study Group N=14 (very low birth weight, premature and with nephrocalcinosis)	Study Group (1180 (565-1880)			UEC eGFR TmP/GFR Renal length Nephrocalcinosis	• No evidence suggested that nephrocalcinosis is associated with long term renal dysfunction • Nil significant difference in urine ACR and PCR in controls and patients
7	Kist-van Holthe et al (2007) [21]	Control N=32 (Premature without Nephrocalcinosis) Study Group N=42 (Premature with neonatal Nephrocalcinosis)	Control Group (1353 (337)) Study Group (1148 (394))	Control Group (29.8 (1.6)) Study Group (28.9 (2.3))	Control Group (7.5 (1.0)) Study Group (7.4 (1.0))	BP eGFR Tubular function Nephrocalcinosis Kidney length	• There was no difference in the BP between the two groups • Blood pressure in both groups was found to be higher than expected for otherwise healthy children • The study group was found to have significantly more chronic renal insufficiency when compared to healthy children. This was not the case for the control group. • Tubular function, urine albumin, kidney length and GFR was not significantly different between the study and control groups • Tubular phosphate reabsorption, plasma bicarbonate, and early-morning urine osmolality were significantly lower in both control and study groups when compared to otherwise healthy children
8	Keijzer-Veen et al (2007) [22]	Control (Term) N=30 Group 1 (Premature SGA) N=23 Group 2 (Premature AGA) N=29	Control (3632 (40.2)) Group 1 (859 (126)) Group 2 ((1489 (257))	Control (40.2 (1.3)) Group 1 (30.6 (1.0)) Group 2 (29.5 (1.4))	20	eGFR Serum urea sCr Serum electrolytes ERPF BP Albuminuria Kidney length and volume	• Height, weight, kidney length and volume, GFR, and ERPF were significantly lower in the SGA group than in controls. After adjustment for body surface area, GFR did not differ significantly among groups. • There was increased BP in premature compared to controls • Two participants from group 1 had microalbuminuria
9	Finken et al (2008) [23]	Control N=328 (premature and did not receive betamethasone) Study Group N=84	Control (1319 (337)) Study Group (1348 (275))	Control (29.7 (1.5)) Study Group (29.8 (1.5))	19	Body composition Insulin resistance Serum lipid profile BP eGFR	• eGFR was found to be lower in 19-year-old born premature who received antenatal betamethasone • This difference was clinically irrelevant at age 19, however the decreased eGFR may increase the risk of chronic kidney disease long term

		(premature and received betamethasone)					
10	Rakow et al (2008) [24]	Control (term AGA) N=37 Group 1 (premature) N=39 Group 2 (term SGA) N=29	Control (3485 (502)) Group 1 (954 (203)) Group 2 (2436 (331))	Control (39.6 (1.0)) Group 1 (26.6 (2.0)) Group 2 (39.3 (1.4))	Control (9.8 (0.2)) Group 1 (9.6 (0.3)) Group 2 (9.8 (0.3))	eGFR Kidney volume sCr Serum Cystatin C BP Urinary ACR, Immunoglobulin G, alpha-1 microglobulin, N-acetylglucosamine	• Estimated glomerular filtration rate (eGFR) and urinary protein patterns were similar between the groups. • Kidney volume was smaller in the premature group than in the controls, but the difference was not significant when adjusted for body surface area, gender and age • No significant differences were found in renal function, urine ACR, renal volume or blood pressure between the three groups at school age.
11	Bacchetta et al (2009) [25]	Control (Premature normotrophic children) N=11 Group 1 (Premature EUGR) N=16 Group 2 (Premature IUGR) N=23	Control (1039 (278)) Group 1 (845(146)) Group 2 (773 (155))	Control (27.1 (1.8)) Group 1 (26.2(1.8)) Group 2 (28.2 (1.8))	Control (6.8 (0.9)) Group 1 (7.9 (1.3)) Group 2 (7.8 (1.3))	BP eGFR Microalbuminuria Urine calcium-creatinine ratio Kidney size	• Children in groups 1 and 2 had decreased GFR compared to controls • Nil significant difference in blood pressure was found between the three groups • EUGR was concluded as a risk factor for long term renal impairment in premature children • Two children out of the entire cohort had moderate microalbuminuria
12	Zaffanello et al (2010) [26]	Group 1 (VLBW) N=43 Group 2 (ELBW) N=26	Group 1 (1315 (1248–1352)) Group 2 (850 (775–883))	Group 1 (30.1 (29.9–31.3)) Group 2 (27.0 (26.3–27.7))	Group 1 (5.4 (5.2–6.1)) Group 2 (5.3 (5.2–6.3))	Plasma creatinine concentration Plasma Cystatin C eGFR Plasma renin Urinary alpha 1-microglobulin Albuminuria Total kidney volume BP	• Renal function parameters (i.e., estimated glomerular filtration rate and albuminuria) did not differ between the two groups of children. • Systolic and diastolic blood pressures and did not differ between the two birth- weight categories.

13	Chan et al (2010) [27]	Control (Term AGA) N=25 Group 1 (Premature SGA) N=14 Group 2 (Premature AGA) N=25 Group 3 (Term SGA) N=7	Control (3302 (3105-3690)) Group 1 (980(768-1038)) Group 2 (1635 (991-1850)) Group 3 (2750 (2430-2870))	Control (40 (38.5-41.0)) Group 1 (31(28.8-31.0)) Group 2 (30 (27.5-31.0)) Group 3 (39 (38.0-40.0)	Control (13.6 (12.54-14.78)) Group 1 (13.5 (12.48-13.97)) Group 2 (14.1 (13.66-15.03)) Group 3 (13.6 (12.35-14.83))	BP Augmentation index eGFR following protein load Plasma glucose Serum insulin levels	• Nil difference in GFR prior to giving participants a protein load. • SGA had higher SBP and lower GFR following protein load than AGA. There was no effect of prematurity on SBP or GFR
14	Giapros et al (2011) [28]	Control Group (Premature without nephrocalcinosis) N=44 Study Group (premature with nephrocalcinosis) N=63	Control (1651 (430)) Study (1615 (480))	Control (31.9 (2.2)) Study (31.8 (3))	0.25, 0.5, 1, 2	sCr eGFR Fractional excretion of sodium, potassium, phosphate, magnesium and uric acid Kidney length	• sCr and eGFR did not differ between the groups at any time point • The NC group had a shorter KL up to 12 months of life (left kidney) or 24 months (right kidney) • Nephrocalcinosis in premature infants was associated with renal tubular dysfunction and shorter kidney length in the first year of life
15	Carballo-Magdaleno et al (2011) [29]	Control N=30 Group 1 N=30 (premature and no steroids) Group 2 N=30 (premature with steroids)	Control (3088 (177)) Group 1 (1669 (426)) Group 2 (1501 (410))	Control (38.6 (1.0)) Group 1 (31.9 (2.3)) Group 2 (31.3 (1.7))	Control (2.0 (0.4)) Group 1 (1.8 (0.5)) Group 2 (1.8 (0.4))	Renal volume eGFR Cystatin C BP	• Groups 1 and 2, when compared to the controls had higher BP, cystatin C levels and GFR • No significant difference in these parameters was found between groups 1 and 2 • Concluded that prematurity (independent of antenatal steroids) was associated with higher blood pressure levels, cystatin C levels and glomerular filtration rates in infants aged 12-36 months

16	Starzec et al (2016) [30]	Control (term) N=36 Study Group (ELBW) N=64	Control (3570 (3395–3880)) Study (875 (750–960))	Control (40 (39–40)) Study (27 (25–28))	7, 11	Serum cystatin C levels sCr BUN eGFR Kidney length and width	• Renal ultrasound examination revealed a significantly smaller renal volume in the 7- and 11-year-old ELBW children compared to the term controls • Serum cystatin C levels were significantly higher in ELBW children than in the controls at 7 years of age, and this difference remained statistically significant at 11 years of age • GFR was significantly lower in the extremely low birth weight group compared to term controls when assessed at 11 years
17	Bruel et al (2016) [31]	Control (premature without AKI) N=25 Study Group (premature with AKI) N=49	Control (1034 (853-1348)) Study (815(708-1110))	Control (28(27-30)) Study (28 (26-29.2))	Control (7 (5-8)) Study (7 (5-8))	eGFR BP ACR Albuminuria Microalbuminuria Renal volume	• There was no difference in microalbuminuria or eGFR at the time of follow up • No significant difference in eGFR between groups. • Renal volume was significantly lower in the study group • In the collective premature cohort, 10.8% had microalbuminuria and 23% had diminished eGFR • eGFR was noted to be significantly lower in children with VLBW <1000g • Blood pressure was not significantly difference between both groups
18	Masqood et al (2017) [32]	Control (ELBW with no AKI) N=112 Group 1 (ELBW with AKI stage 1) N=87 Group 2 (ELBW with AKI Stages 2 and 3) N=23	Control (813 (127)) Group 1 (725(140)) Group 2 (664(172))	Control (26.8(2.3)) Group 1 (25.5(2.0)) Group 2 (25.3(1.9))	Control (6.6(2.5)) Group 1 (6.9(2.9)) Group 2 (8.3(3.3))	BP BMI Creatinine BUN eGFR	• No significant difference in the prevalence of CKD between groups, however ELBW was noted to increase the risk of CKD independent of neonatal AKI • There was no difference in growth parameters or prevalence of hypertension or prehypertension among the three groups at their latest follow up (age of outcome measure)
19	Harer et al (2017) [33]	Control (term) Group 1 (premature VLBW with AKI) N=20	Control Group 1 (790(730-1018)) Group 2 (1040(855-1443))	Control Group 1 (25(24-26)) Group 2 (29(27-29))	Control Group 1 (5(4-5)) Group 2 (5(4-6))	eGFR Urine PCR BP Cystatin C Kidney size	• There was a significant difference in the cystatin C values when the premature infants were compared with the term infants. The premature groups combined had higher mean cystatin C values that the term cohort • 65% of premature children with AKI had kidney dysfunction at a median 5 years of age and 14% of premature children with no history of AKI has kidney dysfunction at a median 5 years. • Nil significant difference in Urine PCR between groups

		Group 2 (premature VLBW without AKI) N=14					
20	Raaijmakers et al (2017) [34]	Control = 45 (premature and exposed to ibuprofen) Study Group = 48 (premature and not exposed to ibuprofen)	815 (430-1000)	27 (24-33)	0.75, 2, 11	eGFR-Cystatin C Renal length	• There with no significant differences in renal length or eGFR-Cystatin C in young adolescence who experienced neonatal ibuprofen exposure
21	Vollsaeter et al (2018) [35]	Control (Term Born AGA) N=54 Group 1 (Premature-born AGA) N=37 Group 2 (Premature-born SGA) N=20	Control (3701 (3582, 3581)) Group 1 (918 (867, 968)) Group 2 (724 (657, 791))	Control = Term born Group 1 (26.1 (25.7, 26.5) Group 2 (28.0 (27.2, 28.7)	Control (11.7 (11.2-12.0)) Group 1 (11.4 (11.1-11.8)) Group 2 (11.3 (11.0-11.8))	Height Weight Abdominal circumference Triceps and subscapular skin fold thickness BP Plasma creatinine Cystatin C eGFR SDMA	• SDMA levels were significantly higher Group 1 and 2 when compared to the controls • GFR was significantly lower in Groups 1 and 2 compared to the controls • No significant differences in creatinine or cystatin C between the groups • Systolic BP had a significant relationship with fat mass indices but not renal function • Systolic BP did not significantly differ between the groups • Concluded that children from Groups 1 and 2 (especially Group 2) had impaired renal function by 11 years of age (as shown by GFR and SDMA) • Findings suggest being born premature or SGA increases risk of developing kidney disease in the future
22	South et al (2019) [36]	Control (term) N=43 Study group (premature with VLBW) N=96	Control (3458 (451)) Study (1048 (276))	Control (39.7 (1.1)) Study (27.8 (2.6))	Control (14) Study (14)	BP ACR eGFR BMI BUN	• Premature children had significantly higher BP and significantly lower eGFR compared to the term children at 14 years of age • Albuminuria, ACR, creatinine and BUN were not significantly different

23	Crump et al (2019) [37]	Extremely Premature N=8129 Very premature N=43516 Late premature N=155626 Early term N=737412 Full term N=2895746 Post-term N=346186	NA	Extremely Premature (22-27) Very premature (28-33) Late premature (34-36) Early term (37-38) Full term (39-41) Post-term (≥42)	0-43	CKD	• Premature and extremely premature birth were associated with twofold and threefold risks of CKD respectively • Premature birth and CKD were found to have the strongest association at ages 0-9 years (hazard ratio 5.09) and weakened but remained increased at ages >9 years (hazard ratio 1.97 for 10-19 years and 1.34 for 20-43 years)
24	Rakow et al (2019) [38]	Control N=19 Group 1 (Extremely premature and nephrocalcinosis) N=20 Group 2 (extremely premature and no nephrocalcinosis) N=21	Control (3586 (477)) Group 1 (755 (124)) Group 2 (841 (202))	Control (39.7 (1.6)) Group 1 (25.5 (1.2)) Group 2 (25.9 (1.3))	Control (8.1 (2.2)) Group 1 (7.8 (1.0)) Group 2 (7.4 (1.1))	Kidney volume 24-hour ambulatory BP Cystatin C calculated eGFR Plasma creatinine Urinary PCR Urine electrolytes	• Groups 1 and 2 had significantly smaller kidneys compared to the controls • Cystatin C based GFR was significantly lower (however still normal) in groups 1 and 2 when compared to the control group • Nil significant difference between kidney volume and function between Groups 1 and 2 • The control groups had significantly higher plasma creatinine compared to groups 1 and 2 • Urinary PCR and electrolytes were not significantly different between all groups • BP was not significantly different between all groups • Significantly more children from group 1 had a negative evolution of kidney function from the neonatal period to school age

25	Horie et al (2019) [39]	Control Group (Premature and normal eGFR) N=150 Study Group (Premature and low eGFR) N=18	<1000g N=73 1000-1500g N=76 >1500g N=19	<28+0 N=63 ≥28+0 N=105	2-15	sCr eGFR Gestational age Body weight and length at birth Sex Apgar score Use of antimicrobial agents, steroids or indomethacin	• eGFR at 2 years of age was significantly correlated with birthweight and gestational age. This relationship was no longer significant at 3-4 years of age. • Approximately 10.7% of the children had low eGFR without clinical symptoms or abnormal urine examination. These children had high sCr on day 7 after birth and delayed recovery of these levels during the first month after birth.
26	Crump et al (2019) [40]	Extremely Premature N=8324 Very premature N=44373 Late premature N=157342 Early term N=740391 Full term N=2896444 Post-term N=346195	NA	Extremely Premature (22-27) Very premature (28-33) Late premature (34-36) Early term (37-38) Full term (39-41) Post-term (≥42)	0-43	BP	• In this study, premature birth was associated with increased risk of hypertension in early adulthood • Adjusted hazards ratios for new-onset hypertension at 18-29 years of age associated with premature (<37 weeks) and extremely premature (22-27 weeks) were 1.28 and 2.45 respectively when compared to full term birth. At ages 30-43 years the adjusted hazards ratios were 1.25 and 1.68 respectfully for premature and extremely premature birth when compared to full term birth.
27	Kandasamy et al (2020) [41]	Control group (term) N=31 Study Group (premature) N=53	NA	Control = Born at term Study = <28	0.5, 1, 2	TKV eGFR Urine ACR BP	• The study group had a significantly reduced TKV compared to the controls • Both groups had a similar eGFR • No significant difference was found in BP and urine ACR between the groups

28	Sanderson et al (2020) [42]	N=42 (premature)	770 (173.1)	25.7 (1.1)	15 (15, 15.3).	Albuminuria BP Kidney volume	• 33.3% of participants had an elevated BP at 15 years of age • 11.9% of the cohort had microalbuminuria • 14% had a kidney volume below the 10th percentile of normative data • 50% of the sample had at least one kidney abnormality (microalbuminuria, elevate BP and/or kidney hypoplasia
29	Yael et al (2020) [43]	Control group = known paediatric population prevalence rates Study group (VLBW and premature) N = 103	Study Group (1086 (243))	Study Group (29.4 (24-35))	Study Group (11.6 (10-13.3))	BP Urine PCR Urine ACR eGFR	• The prevalence of systolic hypertension was 15.8% and of systolic pre-hypertension was 6.9%. This is compared to the general United States paediatric population which has a 1.6% prevalence rate of systolic hypertension. • Hypertension was associated with a significantly diminished mean birth weight compared to the remainder of the cohort (939.3 grams vs 1111 grams P=0.024) • 103 study participants that were very low birth weight and premature all had normal values of GFR • Prevalence of microalbuminuria was 14.3% while the prevalence of proteinuria was 7.9% at 11.6 years.
30	Staub et al (2020) [44]	Control Group (term) N=82 Study Group (premature) N=51	Control (3250 (555)) Study (1360 (532))	Control (39 + 6 (2 + 5)) Study (31 + 0 (2 + 6))	Control (12.1 (1.20)) Study (12.3 (1.87))	BP sCr Cystatin C eGFR Beta-2 Microglobulin Uromodulin Neutrophil gelatinase-associated lipocalin	• Systolic BP was significantly higher in premature boys compared with term boys, however there was not significant difference in girls • Low birth weight was associated with higher BP in premature boys • In the premature group, maternal hypertension/preeclampsia and adolescent height were associated with higher systolic BP • sCr and neutrophil gelatinase-associated lipocalin were significantly higher in the premature group • There was no significant difference in GFR between groups
31	Askenazi et al (2021) [45]	N=923 (extremely low gestational age)	801.1 (187.9)	24-27	1.83-2.17	eGFR Urine ACR BP	• The prevalence of Stage 2 or 3 AKI was 18.2% • At 22-26 months 16% had an eGFR <90mL/min/1.73m^2, 35.8% had elevated urine ACR, 23% had aSBP > 95th percentile for their age and 40% had a DBP >95th percentile for age

Abbreviations: BP (blood pressure), SBP (systolic blood pressure), DBP (diastolic blood pressure) eGFR (estimated glomerular filtration rate), BMI (body mass index), TmP (tubular maximum reabsorption of phosphate), sCr (serum creatinine), CKD (chronic kidney disease), ACR (albumin creatinine ratio), PCR (protein creatinine ratio), SDMA (Symmetric dimethylarginine), TKV (total kidney volume), IUGR (intrauterine growth retardation), EUGR (extrauterine growth retardation), SGA (small for gestational age), AGA (appropriate for gestational age), BUN (blood urea nitrogen), ERPF (effective renal plasma flow), AKI (acute kidney injury), VLBW (very low birth weight), ELBW (extremely low birth weight)

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1 renal insufficiency.mp. or exp Renal Insufficiency/ (188865)
2 chronic kidney disease.mp. or exp Renal Insufficiency, Chronic/ (136800)
3 exp Acute Kidney Injury/ or exp Renal Insufficiency, Chronic/ or kidney function.mp. or exp Glomerular Filtration Rate/ (221756)
4 kidney failure.mp. (100456)
5 blood pressure.mp. or exp Blood Pressure/ (438835)
6 proteinuria.mp. or exp Proteinuria/ (60170)
7 albuminuria.mp. or exp Albuminuria/ (19579)
8 exp Hypertension/ (293215)
9 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 (867063)
10 exp Premature Birth/ or exp Infant, Premature/ or exp Infant, Extremely Premature/ or premature.mp. or exp Infant, Premature, Diseases/ (198355)
11 preterm birth.mp. (15605)
12 10 or 11 (202175)
13 term.mp. or exp Term Birth/ (1043152)
14 long term.mp. (735729)
15 long term adverse outcomes.mp. (286)
16 long term outcome.mp. (24999)
17 14 or 15 or 16 (735729)
18 9 and 12 and 13 and 17 (685)
19 limit 18 to (yr="1990 -Current" and english) (553)

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PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1/Title page
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	5-6
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	2
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	NA
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	7
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	7
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Supplementary File
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	7
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	7
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	7
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	7-8
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	7
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	NA

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	7-8
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	NA
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	10
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	10 and Appendix A Table 1
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	16
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	10-16
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	NA
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	16
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	NA
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	18-19
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	20
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	18-20
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	21

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

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THE EFFECTS OF PREMATURITY ON LONG-TERM RENAL HEALTH: A SYSTEMATIC REVIEW

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THE EFFECTS OF PREMATURITY ON LONG-TERM RENAL HEALTH: A SYSTEMATIC REVIEW

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ABSTRACT:

Objective: To investigate the literature and determine if prematurity has an impact on long-term adverse kidney outcomes

Design: Systematic review

Data sources: OVID Medline, PubMed, SCOPUS, CINAHL and EMBASE databases were searched for studies relating to the adverse outcomes of prematurity from 1990 – April 2021.

Eligibility criteria for selecting studies: All articles published between January 1990 and April 2021 that investigated whether premature infants developed long term adverse renal outcomes were included in this review. Articles must have been human studies and written in English. Case series with less than 20 participants and case studies were excluded.

Data extraction and synthesis: One reviewer completed the database searches. Article selection was performed independently and in a non-blinded manner by both reviewers. Initial screening was by title and abstract. Full texts of remaining articles were reviewed. Articles for which inclusion was unclear were re-reviewed by both reviewers, and a unanimous decision was taken as to whether they should be included. The Newcastle-Ottawa Scale was used for quality assessment of the included articles.

Results: The literature search yielded 31 human studies which investigated the short- and long-term kidney outcomes of prematurity. These studies were conducted in 17 different countries. The most common outcomes measured were blood pressure, and glomerular

filtration rate. Other common outcomes measured included kidney size and mass, proteinuria, albuminuria, chronic kidney disease and physical parameters like height, weight and body mass index.

Conclusion: Prematurity is likely linked to increased risk of kidney dysfunction and high blood pressure in childhood and into early adulthood. Premature birth conferred a twofold increased risk of CKD and extremely premature birth conferred a threefold increased risk of CKD. However, further larger multi-centre studies are needed to draw definitive conclusions on the long-term kidney outcomes of prematurity.

Keywords: Premature, preterm, renal, kidney, impairment proteinuria, albuminuria, hypertension, high blood pressure, reduced estimated glomerular filtration rate, decreased kidney function

STRENGTHS AND LIMITATIONS

- This systematic review yielded 31 relevant human studies from a wide search of five reputable databases
- We used the Newcastle Ottawa Scale to assess the quality of included studies
- The long-term adverse outcomes of prematurity on kidney function can only be evaluated up to approximately 40 years of age as research into the aging population is still needed
- As current research into the long-term kidney outcomes of prematurity is lacking, the available research is not sufficient to draw definitive conclusions as to the long-term

kidney outcomes of premature children and further larger multicentre studies are still needed.

INTRODUCTION:

Prematurity is the leading cause of mortality in children under the age of five.[1] However, with advances in technology and modern medicine, both the incidence of prematurity and the number of ex-premature babies living into adulthood are increasing, especially in population-dense countries.[1] Approximately 15 million, or just over 1 in 10 babies, are born prematurely every year.[2] The highest number of premature births are seen in India, China and Nigeria; while the highest rates of premature births are seen in Malawi, Comoros and Congo.[3]

Though premature birth is becoming more commonplace, it is not without its own challenges. The Barker hypothesis proposes that diseases of adulthood are due to factors pertaining to fetal life. [4-6] This proposition is also commonly known as the Developmental Origins of Health and Disease (DOHaD) hypothesis. This conclusion was first drawn when Barker et al. found that early death secondary to coronary artery disease was inversely related to weight at birth.[7] Thus the DOHaD paradigm was created. It proposed that developmental factors, including nutrition, stressors, and environmental exposures such as drugs and infections, could lead to functional changes in tissues which may predispose to disease in later life.[8]

The impact of prematurity on long-term kidney dysfunction or chronic kidney diseases (CKD) is still not fully understood. Impaired nephrogenesis due to poor fetal growth, prematurity, antenatal and post-natal medication and other factors most likely lead to reduced nephron endowment and CKD. [9-10] Nephrogenesis is completed by 37 weeks gestation, and the majority of nephrogenesis occurs in late gestation.[11] Therefore, in premature neonates, nephrogenesis is terminated early conferring reduced nephron numbers. Nephrons do not

regenerate. The number of functional nephrons over time decreases as part of normal aging.[5] As premature children are born with reduced nephron numbers, an increased risk of kidney dysfunction is postulated. Brenner et al. also proposed that as a compensatory measure for low nephron numbers, nephron surface area increases. This maladaptive response causes systemic hypertension and increased sodium retention, which in turn causes disrupted autoregulation.[12] The resulting nephron sclerosis leads to increased functional nephron decline creating a vicious cycle. [12-13]

As the ex-premature population is living longer and becoming part of the aging population, understanding the effects of prematurity is imperative in anticipating the likely chronic health outcomes the premature population will face. This review is intended to investigate the literature to determine if a link is present between prematurity and adverse long-term kidney health. Identifying a link will be the first step in deciding how best to follow-up and manage ex-premature children and adults to prevent morbidity and premature mortality in the long term.

METHODS

This systematic review was completed in accordance with the PRISMA guidelines. [14] The systematic search was conducted using OVID Medline, PubMed, SCOPUS, CINAHL and EMBASE. The search criteria were developed and refined from January 2020 to April 2021. Relevant keywords were identified, and all relevant Medical Subject Headings (MeSH) and non-MeSH synonyms were included. Relevant keywords included prematurity, chronic kidney failure, chronic kidney disease, kidney volume, proteinuria, albuminuria, hypertension, high blood pressure, reduced GFR, decreased kidney function and long-term adverse outcomes. The final search was conducted on April 1st, 2021. An example of the database search for OVID Medline can be seen in the supplementary files. Only articles published in English between January 1990 and April 2021 have been included. Animal studies were excluded. Finally, articles shortlisted for inclusion were screened for bias and re-evaluated for inclusion if there was significant bias.

Once the literature search was completed, article selection was performed independently and in a non-blinded manner by two reviewers. The articles were initially screened by title and then by the abstract. All remaining articles were reviewed and determined for inclusion based on examination of the full text. Articles which were unclear were re-reviewed by both reviewers, and a unanimous decision was taken as to whether they should be included.

Articles were included if they studied premature and/or low birth weight infants to determine if they developed adverse kidney outcomes as a result of being premature. Studies that investigated low birth weight infants were only included if their low-birth-weight cohort were also premature. Outcomes that were evaluated included glomerular filtration rate (GFR),

blood pressure (BP), tubular function, kidney length and volume, and urinary protein/albuminuria and electrolytes. It was decided that case series with less than 20 participants, and case studies would be excluded from this review as they would not provide the level of evidence or relevant information required. Included articles and their characteristics can be found in Supplementary Table 1. [15-45] Articles underwent quality assessment using the Newcastle-Ottawa scale. [46] This can be seen in Table 1.

Patient and Public Involvement

Patients were not involved in the development or design of this systematic review.

Table 1: Quality assessment of included observation studies using the Newcastle-Ottawa Scale

Cohort Studies			
Study	**Selection***	**Comparability****	**Outcome*****
Downing et al (1992)	★★★	★	★★★
Jones et al (1997)	★★★	★★	★★★
Ojala et al (2001)	★★★★	★	★★★
Rodriguez-Soriano et al (2005)	★★★	★	★★
Porter et al (2006)	★★★	★★	★★★
Kist-van Holthe et al (2007)	★★★	★	★★
Keijzer-Veen et al (2007)	★★		★★
Finken et al (2008	★★★	★	★★★
Rakow et al (2008)	★★★★	★	★★
Bacchetta et al (2009)	★★★★	★★	★★
Zaffanello et al (2010)	★★★★	★	★★★
Chan et al (2010)	★★	★	★★
Giapros et al (2011)	★★★★	★★	★★★
Carballo-Magdaleno et al (2011)	★★★	★	★★★
Starzec et al (2016)	★★		★★
Bruel et al (2016)	★★★★	★	★★
Harer et al (2017)	★★★		★★
Raaijmakers et al (2017)	★★★	★	★★
Vollsaeter et al (2018)	★★★		★★
South et al (2019)	★★		★★
Crump et al (2019)	★★★★	★★	★★★
Rakow et al (2019)	★★★★	★	★★★
Horie et al (2019)	★★★★	★	★★★
Crump et al (2019)	★★★★	★★	★★★
Kandasamy et al (2020)	★★★	★	★★★
Sanderson et al (2020)	★★	★	★★
Yael et al (2020)	★★★		★★
Staub et al (2020)	★★	★★	★★
Case Series			
Abitolol et al (2003)	★	NA	★★
Case Control			
Study	**Selection***	**Comparability****	**Exposure*****
Masqood et al (2017)	★★★	★	★★★

* Maximum 4 stars

** Maximum 2 stars

*** Maximum 3 stars

RESULTS

The collective search from the five databases revealed 1311 studies. A total of 1263 articles remained after duplicates were omitted. All 1263 articles were screened, and 1101 were excluded based on title and abstract. For the remaining 162 articles, full texts were assessed for eligibility. Sixty-four articles were excluded due to long term adverse kidney outcomes not being investigated. Nine articles were excluded as prematurity or low birth weight were not investigated. Eight were excluded for being animal studies, and 50 were excluded for being case reports or case series with less than 20 participants. Thus, the literature search yielded 31 human studies which investigated the long-term kidney outcomes of prematurity. [15-45] These studies were conducted in 17 different countries: Australia, Israel, Japan, Italy, Greece, Poland, France, Egypt, Sweden, Belgium, Mexico, the Netherlands, Scotland, Spain, the USA, Finland and Norway. [15-45] A flow diagram demonstrating the selection process can be seen in Figure 1. The lead author surname, year of publication, sample size, birth weight, gestation, outcome measures, age at which outcome measured and conclusions of the selected studies can be seen in Supplementary Table 1. A quality assessment of included studies was conducted using the Newcastle Ottawa Scale and can be seen in Table 1.

Of the included studies, the smallest cohort size was 20, and the largest cohort size was 4193069. [18, 40] The youngest gestational age from the premature cohorts was 22 weeks, and the most mature gestational age for the premature cohorts was 36 weeks. [37, 40] The youngest age at which outcomes were measured was at birth, and the oldest age at which outcomes were measured was at 43 years. [37, 40] The most common outcomes measured were BP and kidney function (GFR and proteinuria/microalbuminuria). Other outcomes measured included

kidney size and mass, urine analysis, chronic kidney disease and physical parameters (height, weight and BMI). Some studies also commented on insulin resistance and serum lipid profile.

Glomerular filtration rate

Twenty-seven out of the 31 studies investigated GFR as an outcome measure. [16-36, 38-39, 41, 43-45] Ten of these 27 studies compared premature children and term children. [19, 21-22, 24, 27, 35-36, 38, 41, 44] Four found no significant difference in GFR while 6 did. Of the 4 studies that found no significant difference, Rakow et al. measured their outcomes at 9 years, Kandasamy et al. measured their outcomes at 0.5, 1 and 2 years, Staub et al. measured GFR at 12 years and Chan et al. measured outcomes at approximately 13.5 years. [24, 27, 41, 44] Of the 6 studies that found a significantly decreased GFR in premature children, outcomes were measured at approximately 7.5 years, 8 years, 8.5 years, 11.5, 14 and 20 years respectively for Kist-Van Holthe et al., Rakow et al., Rodriguz-Soriano et al., Vollsaeter et al., South et al. and Keijer Veen et al. [19, 21-22, 35-36, 38] It should be noted that Keijer Veen et al. found that GFR was significantly lower in the premature small for gestational age group compared to term controls at 20 years. [22] This was not the case for the premature appropriate for gestational age group. [22] When the small for gestational age group had their GFR adjusted for body surface area, there was no significant difference between groups. [22]

Twelve studies investigated GFR in study and control groups with differing characteristics including no term birth comparison. [16-18, 20, 23, 25-26, 28, 30-32, 34] Seven of these studies found no statistically significant difference in GFR between study and control groups.[17, 20, 26, 28, 31-32, 34] Ojala et al. compared premature infants with and without indomethacin exposure in the neonatal period and measured outcomes at 2-4 years.[17] Raaijmakers et al. compared

premature infants with and without ibuprofen exposure in the neonatal period and assessed outcomes at 11 years.[34] Porter et al. compared two groups of very low birth weight children with and without nephrocalcinosis at 5-7 years of age. [20] Zaffanello compared very low birth weight and extremely low birth weight children at 5-6 years.[26] Giapros compared premature infants with and without nephrocalcinosis for the first 2 years of life.[28] Masqood et al. compared three groups of extremely low birth weight children with no AKI, Stage 1 AKI and stage 2 AKI, and found no significant difference in the prevalence of diminished GFR values. [32] Finally, Bruel et al. found nil significant difference between premature children with and without neonatal AKI when assessed at 7 years of age. [31] Bruel et al. did however note that GFR was significantly lower in children with a birth weight less than 1000 grams. [31]

On the other hand, 5 of these studies did find significantly differences in GFR between study and control groups. [16, 18, 23, 25, 30] Finken et al. noted significantly decreased GFR in premature infants who received betamethasone in the neonatal period when compared to premature infants who did not.[23] This outcome was measured at 19 years of age.[23] Abitbol et al. found ex-premature children had normal GFRs when aged 5.7 years but children assessed at 9.9 years were found to have diminished GFR.[18] Starzec et al. concluded that GFR was significantly lower in the extremely low birth weight group compared to term controls when assessed at 11 years.[30] Bacchetta et al. found significantly decreased GFR in premature extra-uterine growth retardation and intrauterine growth retardation when compared to premature normotrophic children at 7-8 years of age. [25] Jones et al found that four out of their 11 premature babies with nephrocalcinosis had an abnormal GFR at 4-5 years of age. Jones et al did not however have a term control group to compare these results too.[16]

Only one study (Carballo-Magdaleno et al.) found an increased GFR in premature infants when compared to term infants. Outcomes were measured at two years of age.[29] Table 2 shows all the studies that investigated GFR and whether or not they found a significant difference between groups.

Table 2: A comparison of the studies that did and did not report a significant difference in GFR (listed in descending order of cohort size).

Studies that found a significant difference in GFR between groups	Studies that did not find a significant difference in GFR between groups
Askenazi et al (2021)	Masqood et al (2017)
Finken et al (2008)	Staub et al (2020)
Horie et al (2019)	Giapros et al (2011)
South et al (2019)	Rakow et al (2008)
Vollsaeter et al (2018)	Yael et al (2020)
Starzec et al (2016)	Raajimakers et al (2017)
Carballo-Magdaleno et al (2011)	Kandasamy et al (2020)
Rodriguz-Soriano et al (2005)	Bruel et al (2016)
Keijer Veen et al (2007)	Chan et al (2020)
Kist-Van Holthe et al (2007)	Zaffanello et al (2010)
Rakow et al (2019)	Ojala et al (2001)
Bacchetta et al (2009)	Porter et al (2006)
Harer et al (2017)	
Jones et al (1997)	
Abitbol et al (2003)	

Four studies looked at the prevalence of low GFR in their premature cohorts. [33, 39, 43, 45] Harer et al. found that 26% of their 34 premature very low birth weight participants had an abnormally low eGFR using cystatin C at 5 years of age. [33] Horie et al. found that of their 168 premature children, 10.7% had persistently low GFR at >2 years of age. [39] Yael et al. found that 100% of their 103 study participants with a history of very low birth weight and premature birth had normal GFR values at 10-13 years of age. [43] Askenazi et al found that of

their 923 extremely premature study participants 16% had a GFR <90mL/min/1.73m2 at 22-26 months of age. [45]

Chronic kidney disease

Crump et al. was the only study that exclusively investigated for CKD. [37] From their large cohort size of 4 186 615, they concluded that premature birth conferred a twofold increased risk of CKD and extremely premature birth conferred a threefold increased risk of CKD.[37] This risk was found to be highest between ages 0-9 years and slightly weakened but still increased from ages 10-19 years.[37]

Blood Pressure

Twenty-three out of the 31 studies investigated BP as one of their outcome measures.[17-19, 21-27, 29, 31-33, 35-36, 38, 40-45] Fifteen found no significant difference in BP between study and control groups.[17-19, 21, 23-27, 31-33, 35, 38, 41] Seven of these studies found no significant difference in BP between term babies and premature babies at differing ages ranging from 1.5-27.6 years.[19, 24-25, 27, 35, 38, 41] Six studies compared premature babies with and without different variables including exposure to betamethasone, exposure to indomethacin, presence or absence of nephrocalcinosis, having neonatal acute kidney injury, and having extrauterine growth restriction, intrauterine growth restriction or being appropriate for gestational age.[17, 21, 23, 25, 31, 33] All six concluded no significant difference in BP between these groups of premature babies at differing ages ranging from 2-19 years.[17, 21, 23, 25, 31, 33] Zaffanello et al. found no significant difference in BP between very low birth weight and extremely low birth weight infants at 5-6 years of age. [26] Masqood et al. also compared groups of extremely low birth weight children with no or varying severities of neonatal acute kidney injury and found no

significant difference in BP at approximately 6-8 years.[32] It should be noted that both Zaffanello and Maqsood did not compared these blood pressures with term infants. [26, 32]

Carballo-Magdaleno et al., Keijzer-Veen et al., Yael et al., South et al., Staub et al. and Crump et al. found increased BP in premature children compared to controls. [22, 29, 36, 40, 43-44] Carballo-Magdaleno et al. found that 2-year-old infants born prematurely had significantly higher blood pressures than 2-year-old infants born at term.[29] Keijzer-Veen et al. found significantly increased systolic BP in premature children compared to term children when BP was assessed at 20 years.[22] Yael et al. reported a 15.8% prevalence rate of systolic hypertension in their study group of premature children with very low birth weight when assessed at 10-13 years. [43] This is compared to the general United States paediatric population which has a 1.6% prevalence rate of systolic hypertension. [43] South et al. found significantly higher BP in premature children compared to term children at 14 years of age. [36] Staub et al. found that systolic BP was significantly higher in premature boys compared to term boys, however they did not find a significant difference in premature and term girls. [44] They also noted that low birth weight was associated with higher BP in boys. [44] Crump et al. found that prematurity was associated with an increased risk of hypertension in early adulthood.[40] They found that at 18-29 years of age adjusted hazards ratios were 1.28 and 2.45 respectively for premature and extremely premature birth compared to term birth.[40] Furthermore at 30-43 years of age hazards ratios were calculated as 1.25 and 1.68 for premature and extremely premature birth respectively when compared to full term birth. [40] Table 3 shows all the studies that investigated BP and whether or not they found a significant difference between groups.

Table 3: A comparison of the studies that did and did not report a significant difference in BP (listed in descending order of cohort size).

Studies that found a significant difference in BP between groups	Studies that did not find a significant difference in BP between groups
Crump et al (2019)	Finken et al (2008)
Askenazi et al (2021)	Masqood et al (2017)
South et al (2019)	Vollsaeter et al (2018)
Staub et al (2020)	Rakow et al (2008)
Yael et al (2020)	Kandasamy et al (2020)
Carballo-Magdaleno et al (2011)	Rodriguz-Soriano et al (2005)
Keijer Veen et al (2007)	Kist-Van Holthe et al (2007)
Sanderson et al (2020)	Bruel et al (2016)
	Chan et al (2020)
	Zaffanello et al (2010)
	Ojala et al (2001)
	Rakow et al (2019)
	Bacchetta et al (2009)
	Harer et al (2017)
	Abitbol et al (2003)

Sanderson et al found that of their 42 premature participants, 33.3% had elevated blood pressures at 15 years of age. [42] Askenazi et al. found that of their 923 extremely low gestational age participants at 22-26 months of age, 23% have a systolic blood pressure >95th percentile for their age and 40% had a diastolic blood pressure >95th percentile. [45]

Proteinuria/Albuminuria

Nineteen studies commented on proteinuria or albuminuria. [15-22, 24-26, 31, 33, 36, 38, 41-43, 45] Of these, 11 studies found no significant difference between study and control groups. [17, 20, 21, 24, 26, 29, 31, 33, 36, 38, 41] Six out of these 11 studies compared term and premature infants at ages ranging from approximately 0.5-14 years. [19, 24, 33, 36, 38, 41] The other 5 studies compared groups of premature children with varying characteristics including neonatal AKI, low or extremely low birth weight, the presence of nephrocalcinosis and indomethacin exposure. For these studies outcomes were measured at 2-7.5 years. [17, 20, 21, 26, 31]

Seven studies commented on prevalence of proteinuria or albuminuria. [15-16, 22, 25, 42-43, 45] Askenazi et al. found that at 22-26 months 35.8% of their 923 participants had a urine albumin/creatinine ratio greater than 30mg/g. [45] Bacchetta et al. found that 2 out of their 50 participants had moderate microalbuminuria approximately 7 years of age. [25] Jones et al. found that 2 out of their cohort of 28 premature had microalbuminuria at 4-5 years of age. 16] Sanderson et al. found 11.9% of their 42 premature children had microalbuminuria at 15 years of age.[42] Keijer Veen et al. reported microalbuminuria in 2 patients of their premature small for gestational age group. [22] However, none of their participants in the premature appropriate for gestational age group or term group was found to have microalbuminuria. [22] Yael et al. found that the prevalence of microalbuminuria was 14.3% while the prevalence of proteinuria was 7.9% in their low-birth-weight premature cohort of 103 at 11.6 years. [43] Finally, Downing et al. found that 4 out of the 10 participants in their premature cohort with renal calcifications who received frusemide therapy, had trace proteinuria. [15] The other 17 participants from their other 2 study groups did not have any proteinuria. [15]

Abitbol et al. only had data for urine protein/creatinine ratios available for 10 out of 20 of their premature extremely low birth weight participants. [18] Out of these 10, those with low GFR (n=3) had significantly higher urine protein/creatinine ratios compared to the participants with normal GFR (n=7) at follow up. [18] Follow up ranged from 3.1-18.3 years. [18]

Bias

In all studies included in this review, bias was minimal. Some bias may be present in single centre studies as these may only provide results from a particular population demographic.

[15-19, 22, 24-28, 30-34, 36, 38-39, 41, 43, 44] However, as this review correlates the results of numerous single centre studies, this bias is minimised. Randomisation of study subjects was only done in one of the 31 included studies with was a randomised control trial where all study participants were premature. [45] All other studies were observational, and randomisation was not possible as birth weight and gestational age are not variables that can be ethically influenced. [15-44] Furthermore, 17 studies did not have term born controls. [15-18, 20-21, 23, 25-26, 28, 31-32, 34, 39, 42-43, 45] Abitbol et al. did however match their study participants to age-, gender- and height- matched population norms when reviewing outcomes.[18] Yael et al. also did not have a term control group; however, they did compare their results to known population prevalence's.[43]

DISCUSSION

Thirty-one studies that assessed long term kidney outcomes of premature infants were identified in this review. [15-45] There was a relatively even split between the studies that investigated GFR as to whether there was or was not a significant difference between study and control groups. [16-36, 38-39, 41, 43-45] It should be noted that the studies which favoured no significant difference between premature and term participants investigated GFR in children from 0.5-13.5 years, while the studies that favoured a significant difference between the two populations measured outcomes at 7.5-20 years. [19, 21-22, 24, 27, 35-36, 38, 41, 44] Thus, it is possible that in the short term, GFR is not significantly affected by prematurity. However, as the ex-premature population ages, their kidney function may become considerably diminished compared to the term population. This could possibly be due to the fact that premature infants start out with reduced nephron numbers.

From the 23 studies that investigated BP, 12 compared term and premature children. [18-19, 22, 24, 27, 29, 35, 36, 38, 40, 41, 44] Seven found no significant difference between premature children and term children while five did find a significant difference. [18-19, 22, 24, 27, 29, 35, 36, 38, 40, 41, 44] The studies which found no significant difference measured outcomes from approximately 0.5-27.6 years of age while those that did find a significant difference, measured outcomes at 2-43 years of age. [18-19, 22, 24, 27, 29, 35, 36, 38, 40, 41, 44] Crump et al. was the largest included study and also had one of the highest rating on the quality assessment. [40] It demonstrates that from 30-43 years of age premature and extremely premature children are at a 25% and 68% greater risk of developing hypertension compared to controls. [40] As with GFR, this may be because in early childhood the effects of prematurity on blood pressure are not as obvious as the kidneys are able to compensate, or the reduced nephron number is may not yet be significant.

However, it is possible that as the ex-premature population ages, their initially reduced nephron number may no longer be able to compensate for BP.

From the 19 studies that investigated for microalbuminuria or proteinuria, most commented on prevalence as opposed to comparing groups. [15-22, 24-26, 31, 33, 36, 38, 41-43, 45] Only 6 studies, that commented on proteinuria or albuminuria, compared term children and premature children but all 6 of these studies found no significant difference between groups when assessed at 0.5-14 years of age. [19, 24, 33, 36, 38, 41] Albuminuria or proteinuria are signs of kidney damage and progression of kidney disease. As with GFR and BP, it is possible that in childhood the kidneys are able to compensate for the shortened nephrogenesis. However, in the aging population ex-premature adults may be more likely to demonstrate markers of kidney disease or poor kidney function like microalbuminuria or proteinuria sooner than their ex-term counterparts due to further reduction in an already deplete nephron reserve. Further larger studies with longer follow-up are required to assess for microalbuminuria and proteinuria.

The risk of CKD is twofold and threefold greater in premature and extremely premature children respectively compared to those born at term as per Crump et al. [37] The risk of CKD over the age of 43 years cannot be commented on as it was not investigated in any of the included articles. The conclusion drawn by Crump et al. is reliable, given their methodology and massive cohort size despite other included articles not specifically commenting on CKD but GFR instead. The conclusion could be explained due to the decreased nephron endowment associated with prematurity. It should be noted that kidney function must be significantly impaired (GFR <15) before evidence of kidney failure will be present clinically.

There are some limitations to our systematic review. The majority of the included studies were conducted in Caucasian predominant countries. Therefore, they do not reflect the true impact of prematurity of long-term kidney dysfunction as they do not encompass population rich countries including India, China and Nigeria where the highest number of premature births occur each year. This means the conclusions from this review do not apply to all ethnicities and cannot be generalised for non-Caucasian ethnic groups. Additionally, all the studies included in this review analysed kidney function through quantifiable measures such as blood tests. Clinically significant kidney outcomes, symptomatology, quality of life and kidney dysfunction associated mortality were not commented on or investigated in these studies. Finally, the majority of studies did not investigate outcomes over the age of 20 years. Two study had participants up to the age of 43; however, the proportion of their study cohort over the age of 20 was minimal. Thus, this systematic review could only investigate long-term kidney outcomes of prematurity up until adolescence and early adulthood. Finally, only studies conducted after 1990 and written in English were considered for inclusion.

CONCLUSION

Prematurity is likely linked to increased risk of kidney dysfunction and high blood pressure in childhood and into early adulthood. The risk of CKD is twofold and threefold higher in premature and extremely premature children compared to those born at term. Further studies need to be conducted to investigate the effects of prematurity on long term kidney health in the aging population; reliable information at this time is only available up until the age of 43 years. Thus, kidney outcomes in the ex-premature population over the age of 43 years cannot be concluded from the current research. However, enough evidence is present

to warrant ongoing monitoring of kidney function and blood pressure in premature infants as they age in order to optimise and prevent earlier morbidity and mortality.

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Figure 1: PRISMA Flow diagram

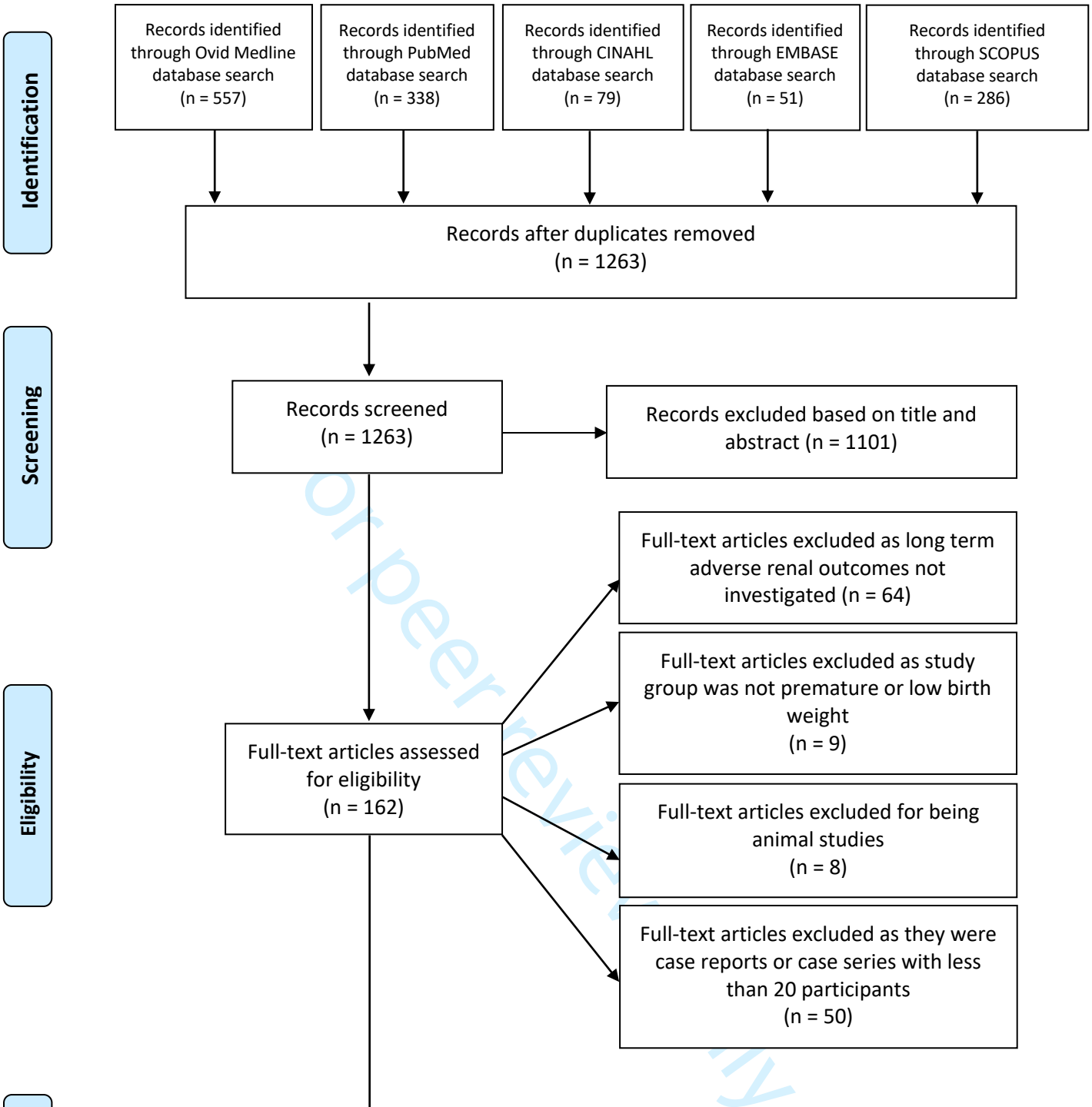

Figure 1: PRISMA Flow diagram

Supplementary Table 1 – Characteristics of included studies (n = 31)

	Source (Y)	Sample Size	Birth weight (g) (study group)	Gestation (wks.) (study group)	Age at which outcomes measured (years)	Outcome measure (for example eGFR or BP or KV)	Conclusion (briefly)
1	Downing et al (1992) [15]	Control N=7 (Premature no frusemide therapy and no renal calcifications) Group 2 N=10 (Premature frusemide therapy but no renal calcifications) Group 3 N=10 (Premature frusemide therapy and renal calcifications)	Control (743(84)) Group 2 (806(103)) Group 3 (678(95))	Control (25.3(0.6) Group 2 (26.1(0.5)) Group 3 (26.2(0.4))	Control (1.2(0.01)) Group 2 (1.3 (0.1)) Group 3 (1.2 (0.1))	Creatinine clearance Urinary calcium:creatinine ratio Fractional excretion of sodium Lower tubular reabsorption of phosphate Urine-blood difference in carbon dioxide tension after oral acetazolamide load Proteinuria	• No significant difference in renal function between the control group and group 2 • In group 3, trace proteinuria was present in 4/10 participants • Creatinine clearance in group 3 was significantly lower than in the control group and group 2 • Urinary calcium:creatinine ratios, fractional excretion of sodium and lower tubular re-absorption of phosphate was significantly higher in Group 3 compared to the group 2 and control group • Group 3 had lower urine-blood differences in carbon dioxide tension after oral acetazolamide load when compared to the controls and group 2
2	Jones et al (1997) [16]	Control Group (premature without renal calcifications) N=17 Study Group (premature with renal calcifications) N=11	Control (982 (710–1760)) Study (850 (580–1856))	Control (28 (25–31)) Study (27 (24–31))	4-5	eGFR Renal calcifications/ nephrocalcinosis	• In the study group the median GFR was 61 ml/min/1.73m2 (range 46-79 ml/min/1.73m2) • Five of the 11 children born premature and found to have renal calcifications, still had renal calcifications at age 4-5 years. • Nephrocalcinosis in isolation was not found to be a major predisposing factor to long term renal dysfunction • Four out of the 11 premature babies with nephrocalcinosis had an abnormal GFR at 4-5 years of age • Two children from the collective premature cohort had microalbuminuria at 4-5 years of age

3	Ojala et al (2001) [17]	Control Group N=35 (premature without perinatal indomethacin) Study Group N=31 (premature with perinatal indomethacin exposure)	Control Group (1360 (680–2680)) Study Group (1150 (670–2060))	Control Group (31 (24-32)) Study Group (28 (24-32))	2-4	Serum cystatin C and protein Plasma creatinine, sodium and potassium Urine PCR Urine alpha-1 microglobulin eGFR BP Renal sonography examination	• The control group showed higher mean serum cystatin concentrations than the study group • No difference was found between the groups for mean serum protein, plasma creatinine and sodium, median plasma potassium concentrations, urine protein:creatinine ratio and urine calcium:creatinine ratio. • No statistical difference was found in GFR or renal structural abnormalities between the two groups • Nil significant difference in urine PCR between groups • Umbilical artery catheter use, frusemide treatment and assisted ventilation may correlate with long term renal structural and functional abnormalities
4	Abitbol et al (2003) [18]	N=20	686 (133)	25 (2)	3.1-18.3	Proteinuria Kidney function/kidney failure (eGFR, sCr) Renal size and mass BP Growth (height, weight and BMI) Nephrocalcinosis	• Significant age difference was found between the normal GFR and low GFR groups, the age of outcome measure was 5.7+/-2.2 and 9.9+/-5.6 years respectively. • BP was not significantly different between study participants and population norms • Urine PCR was available for 10 out of 20 of the participants. Participants with low GFR (n=3) had significantly higher urine protein/creatinine ratios compared to the participants with normal GFR (n=7) at follow up.
5	Rodriguez-Soriano et al (2005) [19]	Control Group N=43 Study Group N=40 (premature and weighing <1000g at birth)	845 (540-1000)	27.6 (23-35)	Control Group (8.5 (1.8)) Study Group (8.6(1.8))	BP Renal length and volume Plasma creatinine Estimated creatinine clearance TmP/GFR TRP Urinary phosphate excretion Urinary calcium excretion eGFR	• No significant difference in BP, microalbuminuria, and renal length and volume was found between the study and control groups • Plasma creatinine, urinary calcium excretion and urinary phosphate excretion were significantly higher in the study group than the control group • The study group had significantly lower estimated creatinine clearance and TmP/GFR compared to controls • No significant differences were observed in microalbuminuria values, but five study subjects (12.5%) presented values above the upper limit of normal.
6	Porter et al (2006) [20]	Control Group N=14 (without nephrocalcinosis – matched for birth weight, gestational age and sex)	Control Group (1210 (670-1870)	Control Group (28.5 (25-31)) Study Group (27.5 (25-31)	Control Group (7.21 (6.38-7.68)) Study Group (6.69 (5.81-7.09))	Early morning urine osmolality Urine ACR and PCR Creatinine:phosphate ratio Creatinine:calcium ratio Beta microglobulin	• No significant differences in GFR or urinary concentrating capacity between the groups • 75% of patients who underwent renal ultrasound were found to have resolved nephrocalcinosis by a median age of 6.75 years • There was evidence of hypercalciuria in both the control and study groups suggesting prematurity may be a risk factor

		Study Group N=14 (very low birth weight, premature and with nephrocalcinosis)	Study Group (1180 (565-1880)			UEC eGFR TmP/GFR Renal length Nephrocalcinosis	• No evidence suggested that nephrocalcinosis is associated with long term renal dysfunction • Nil significant difference in urine ACR and PCR in controls and patients
7	Kist-van Holthe et al (2007) [21]	Control N=32 (Premature without Nephrocalcinosis) Study Group N=42 (Premature with neonatal Nephrocalcinosis)	Control Group (1353 (337)) Study Group (1148 (394))	Control Group (29.8 (1.6)) Study Group (28.9 (2.3))	Control Group (7.5 (1.0)) Study Group (7.4 (1.0))	BP eGFR Tubular function Nephrocalcinosis Kidney length	• There was no difference in the BP between the two groups • Blood pressure in both groups was found to be higher than expected for otherwise healthy children • The study group was found to have significantly more chronic renal insufficiency when compared to healthy children. This was not the case for the control group. • Tubular function, urine albumin, kidney length and GFR was not significantly different between the study and control groups • Tubular phosphate reabsorption, plasma bicarbonate, and early-morning urine osmolality were significantly lower in both control and study groups when compared to otherwise healthy children
8	Keijzer-Veen et al (2007) [22]	Control (Term) N=30 Group 1 (Premature SGA) N=23 Group 2 (Premature AGA) N=29	Control (3632 (40.2)) Group 1 (859 (126)) Group 2 ((1489 (257))	Control (40.2 (1.3)) Group 1 (30.6 (1.0)) Group 2 (29.5 (1.4))	20	eGFR Serum urea sCr Serum electrolytes ERPF BP Albuminuria Kidney length and volume	• Height, weight, kidney length and volume, GFR, and ERPF were significantly lower in the SGA group than in controls. After adjustment for body surface area, GFR did not differ significantly among groups. • There was increased BP in premature compared to controls • Two participants from group 1 had microalbuminuria
9	Finken et al (2008) [23]	Control N=328 (premature and did not receive betamethasone) Study Group N=84	Control (1319 (337)) Study Group (1348 (275))	Control (29.7 (1.5)) Study Group (29.8 (1.5))	19	Body composition Insulin resistance Serum lipid profile BP eGFR	• eGFR was found to be lower in 19-year-old born premature who received antenatal betamethasone • This difference was clinically irrelevant at age 19, however the decreased eGFR may increase the risk of chronic kidney disease long term

		(premature and received betamethasone)					
10	Rakow et al (2008) [24]	Control (term AGA) N=37 Group 1 (premature) N=39 Group 2 (term SGA) N=29	Control (3485 (502)) Group 1 (954 (203)) Group 2 (2436 (331))	Control (39.6 (1.0)) Group 1 (26.6 (2.0)) Group 2 (39.3 (1.4))	Control (9.8 (0.2)) Group 1 (9.6 (0.3)) Group 2 (9.8 (0.3))	eGFR Kidney volume sCr Serum Cystatin C BP Urinary ACR, Immunoglobulin G, alpha-1 microglobulin, N-acetylglucosamine	• Estimated glomerular filtration rate (eGFR) and urinary protein patterns were similar between the groups. • Kidney volume was smaller in the premature group than in the controls, but the difference was not significant when adjusted for body surface area, gender and age • No significant differences were found in renal function, urine ACR, renal volume or blood pressure between the three groups at school age.
11	Bacchetta et al (2009) [25]	Control (Premature normotrophic children) N=11 Group 1 (Premature EUGR) N=16 Group 2 (Premature IUGR) N=23	Control (1039 (278)) Group 1 (845(146)) Group 2 (773 (155))	Control (27.1 (1.8)) Group 1 (26.2(1.8)) Group 2 (28.2 (1.8))	Control (6.8 (0.9)) Group 1 (7.9 (1.3)) Group 2 (7.8 (1.3))	BP eGFR Microalbuminuria Urine calcium-creatinine ratio Kidney size	• Children in groups 1 and 2 had decreased GFR compared to controls • Nil significant difference in blood pressure was found between the three groups • EUGR was concluded as a risk factor for long term renal impairment in premature children • Two children out of the entire cohort had moderate microalbuminuria
12	Zaffanello et al (2010) [26]	Group 1 (VLBW) N=43 Group 2 (ELBW) N=26	Group 1 (1315 (1248–1352)) Group 2 (850 (775–883))	Group 1 (30.1 (29.9–31.3)) Group 2 (27.0 (26.3–27.7))	Group 1 (5.4 (5.2–6.1)) Group 2 (5.3 (5.2–6.3))	Plasma creatinine concentration Plasma Cystatin C eGFR Plasma renin Urinary alpha 1-microglobulin Albuminuria Total kidney volume BP	• Renal function parameters (i.e., estimated glomerular filtration rate and albuminuria) did not differ between the two groups of children. • Systolic and diastolic blood pressures and did not differ between the two birth- weight categories.

13	Chan et al (2010) [27]	Control (Term AGA) N=25 Group 1 (Premature SGA) N=14 Group 2 (Premature AGA) N=25 Group 3 (Term SGA) N=7	Control (3302 (3105-3690)) Group 1 (980(768-1038)) Group 2 (1635 (991-1850)) Group 3 (2750 (2430-2870))	Control (40 (38.5-41.0)) Group 1 (31(28.8-31.0)) Group 2 (30 (27.5-31.0)) Group 3 (39 (38.0-40.0)	Control (13.6 (12.54-14.78)) Group 1 (13.5 (12.48-13.97)) Group 2 (14.1 (13.66-15.03)) Group 3 (13.6 (12.35-14.83))	BP Augmentation index eGFR following protein load Plasma glucose Serum insulin levels	• Nil difference in GFR prior to giving participants a protein load. • SGA had higher SBP and lower GFR following protein load than AGA. There was no effect of prematurity on SBP or GFR
14	Giapros et al (2011) [28]	Control Group (Premature without nephrocalcinosis) N=44 Study Group (premature with nephrocalcinosis) N=63	Control (1651 (430)) Study (1615 (480))	Control (31.9 (2.2)) Study (31.8 (3))	0.25, 0.5, 1, 2	sCr eGFR Fractional excretion of sodium, potassium, phosphate, magnesium and uric acid Kidney length	• sCr and eGFR did not differ between the groups at any time point • The NC group had a shorter KL up to 12 months of life (left kidney) or 24 months (right kidney) • Nephrocalcinosis in premature infants was associated with renal tubular dysfunction and shorter kidney length in the first year of life
15	Carballo-Magdaleno et al (2011) [29]	Control N=30 Group 1 N=30 (premature and no steroids) Group 2 N=30 (premature with steroids)	Control (3088 (177)) Group 1 (1669 (426)) Group 2 (1501 (410))	Control (38.6 (1.0)) Group 1 (31.9 (2.3)) Group 2 (31.3 (1.7))	Control (2.0 (0.4)) Group 1 (1.8 (0.5)) Group 2 (1.8 (0.4))	Renal volume eGFR Cystatin C BP	• Groups 1 and 2, when compared to the controls had higher BP, cystatin C levels and GFR • No significant difference in these parameters was found between groups 1 and 2 • Concluded that prematurity (independent of antenatal steroids) was associated with higher blood pressure levels, cystatin C levels and glomerular filtration rates in infants aged 12-36 months

16	Starzec et al (2016) [30]	Control (term) N=36 Study Group (ELBW) N=64	Control (3570 (3395–3880)) Study (875 (750–960))	Control (40 (39–40)) Study (27 (25–28))	7, 11	Serum cystatin C levels sCr BUN eGFR Kidney length and width	• Renal ultrasound examination revealed a significantly smaller renal volume in the 7- and 11-year-old ELBW children compared to the term controls • Serum cystatin C levels were significantly higher in ELBW children than in the controls at 7 years of age, and this difference remained statistically significant at 11 years of age • GFR was significantly lower in the extremely low birth weight group compared to term controls when assessed at 11 years
17	Bruel et al (2016) [31]	Control (premature without AKI) N=25 Study Group (premature with AKI) N=49	Control (1034 (853-1348)) Study (815(708-1110))	Control (28(27-30)) Study (28 (26-29.2))	Control (7 (5-8)) Study (7 (5-8))	eGFR BP ACR Albuminuria Microalbuminuria Renal volume	• There was no difference in microalbuminuria or eGFR at the time of follow up • No significant difference in eGFR between groups. • Renal volume was significantly lower in the study group • In the collective premature cohort, 10.8% had microalbuminuria and 23% had diminished eGFR • eGFR was noted to be significantly lower in children with VLBW <1000g • Blood pressure was not significantly difference between both groups
18	Masqood et al (2017) [32]	Control (ELBW with no AKI) N=112 Group 1 (ELBW with AKI stage 1) N=87 Group 2 (ELBW with AKI Stages 2 and 3) N=23	Control (813 (127)) Group 1 (725(140)) Group 2 (664(172))	Control (26.8(2.3)) Group 1 (25.5(2.0)) Group 2 (25.3(1.9))	Control (6.6(2.5)) Group 1 (6.9(2.9)) Group 2 (8.3(3.3))	BP BMI Creatinine BUN eGFR	• No significant difference in the prevalence of CKD between groups, however ELBW was noted to increase the risk of CKD independent of neonatal AKI • There was no difference in growth parameters or prevalence of hypertension or prehypertension among the three groups at their latest follow up (age of outcome measure)
19	Harer et al (2017) [33]	Control (term) Group 1 (premature VLBW with AKI) N=20	Control Group 1 (790(730-1018)) Group 2 (1040(855-1443))	Control Group 1 (25(24-26)) Group 2 (29(27-29))	Control Group 1 (5(4-5)) Group 2 (5(4-6))	eGFR Urine PCR BP Cystatin C Kidney size	• There was a significant difference in the cystatin C values when the premature infants were compared with the term infants. The premature groups combined had higher mean cystatin C values that the term cohort • 65% of premature children with AKI had kidney dysfunction at a median 5 years of age and 14% of premature children with no history of AKI has kidney dysfunction at 5 years. • Nil significant difference in Urine PCR between groups

		Group 2 (premature VLBW without AKI) N=14					
20	Raaijmakers et al (2017) [34]	Control = 45 (premature and exposed to ibuprofen) Study Group = 48 (premature and not exposed to ibuprofen)	815 (430-1000)	27 (24-33)	0.75, 2, 11	eGFR-Cystatin C Renal length	• There with no significant differences in renal length or eGFR-Cystatin C in young adolescence who experienced neonatal ibuprofen exposure
21	Vollsaeter et al (2018) [35]	Control (Term Born AGA) N=54 Group 1 (Premature-born AGA) N=37 Group 2 (Premature-born SGA) N=20	Control (3701 (3582, 3581)) Group 1 (918 (867, 968)) Group 2 (724 (657, 791))	Control = Term born Group 1 (26.1 (25.7, 26.5) Group 2 (28.0 (27.2, 28.7)	Control (11.7 (11.2-12.0)) Group 1 (11.4 (11.1-11.8)) Group 2 (11.3 (11.0-11.8))	Height Weight Abdominal circumference Triceps and subscapular skin fold thickness BP Plasma creatinine Cystatin C eGFR SDMA	• SDMA levels were significantly higher Group 1 and 2 when compared to the controls • GFR was significantly lower in Groups 1 and 2 compared to the controls • No significant differences in creatinine or cystatin C between the groups • Systolic BP had a significant relationship with fat mass indices but not renal function • Systolic BP did not significantly differ between the groups • Concluded that children from Groups 1 and 2 (especially Group 2) had impaired renal function by 11 years of age (as shown by GFR and SDMA) • Findings suggest being born premature or SGA increases risk of developing kidney disease in the future
22	South et al (2019) [36]	Control (term) N=43 Study group (premature with VLBW) N=96	Control (3458 (451)) Study (1048 (276))	Control (39.7 (1.1)) Study (27.8 (2.6))	Control (14) Study (14)	BP ACR eGFR BMI BUN	• Premature children had significantly higher BP and significantly lower eGFR compared to the term children at 14 years of age • Albuminuria, ACR, creatinine and BUN were not significantly different

23	Crump et al (2019) [37]	Extremely Premature N=8129 Very premature N=43516 Late premature N=155626 Early term N=737412 Full term N=2895746 Post-term N=346186	NA	Extremely Premature (22-27) Very premature (28-33) Late premature (34-36) Early term (37-38) Full term (39-41) Post-term (≥42)	0-43	CKD	• Premature and extremely premature birth were associated with twofold and threefold risks of CKD respectively • Premature birth and CKD were found to have the strongest association at ages 0-9 years (hazard ratio 5.09) and weakened but remained increased at ages >9 years (hazard ratio 1.97 for 10-19 years and 1.34 for 20-43 years)
24	Rakow et al (2019) [38]	Control N=19 Group 1 (Extremely premature and nephrocalcinosis) N=20 Group 2 (extremely premature and no nephrocalcinosis) N=21	Control (3586 (477)) Group 1 (755 (124)) Group 2 (841 (202))	Control (39.7 (1.6)) Group 1 (25.5 (1.2)) Group 2 (25.9 (1.3))	Control (8.1 (2.2)) Group 1 (7.8 (1.0)) Group 2 (7.4 (1.1))	Kidney volume 24-hour ambulatory BP Cystatin C calculated eGFR Plasma creatinine Urinary PCR Urine electrolytes	• Groups 1 and 2 had significantly smaller kidneys compared to the controls • Cystatin C based GFR was significantly lower (however still normal) in groups 1 and 2 when compared to the control group • Nil significant difference between kidney volume and function between Groups 1 and 2 • The control groups had significantly higher plasma creatinine compared to groups 1 and 2 • Urinary PCR and electrolytes were not significantly different between all groups • BP was not significantly different between all groups • Significantly more children from group 1 had a negative evolution of kidney function from the neonatal period to school age

25	Horie et al (2019) [39]	Control Group (Premature and normal eGFR) N=150 Study Group (Premature and low eGFR) N=18	<1000g N=73 1000-1500g N=76 >1500g N=19	<28+0 N=63 ≥28+0 N=105	2-15	sCr eGFR Gestational age Body weight and length at birth Sex Apgar score Use of antimicrobial agents, steroids or indomethacin	• eGFR at 2 years of age was significantly correlated with birthweight and gestational age. This relationship was no longer significant at 3-4 years of age. • Approximately 10.7% of the children had low eGFR without clinical symptoms or abnormal urine examination. These children had high sCr on day 7 after birth and delayed recovery of these levels during the first month after birth.
26	Crump et al (2019) [40]	Extremely Premature N=8324 Very premature N=44373 Late premature N=157342 Early term N=740391 Full term N=2896444 Post-term N=346195	NA	Extremely Premature (22-27) Very premature (28-33) Late premature (34-36) Early term (37-38) Full term (39-41) Post-term (≥42)	0-43	BP	• In this study, premature birth was associated with increased risk of hypertension in early adulthood • Adjusted hazards ratios for new-onset hypertension at 18-29 years of age associated with premature (<37 weeks) and extremely premature (22-27 weeks) were 1.28 and 2.45 respectively when compared to full term birth. At ages 30-43 years the adjusted hazards ratios were 1.25 and 1.68 respectfully for premature and extremely premature birth when compared to full term birth.
27	Kandasamy et al (2020) [41]	Control group (term) N=31 Study Group (premature) N=53	NA	Control = Born at term Study = <28	0.5, 1, 2	TKV eGFR Urine ACR BP	• The study group had a significantly reduced TKV compared to the controls • Both groups had a similar eGFR • No significant difference was found in BP and urine ACR between the groups

28	Sanderson et al (2020) [42]	N=42 (premature)	770 (173.1)	25.7 (1.1)	15 (15, 15.3).	Albuminuria BP Kidney volume	• 33.3% of participants had an elevated BP at 15 years of age • 11.9% of the cohort had microalbuminuria • 14% had a kidney volume below the 10th percentile of normative data • 50% of the sample had at least one kidney abnormality (microalbuminuria, elevate BP and/or kidney hypoplasia
29	Yael et al (2020) [43]	Control group = known paediatric population prevalence rates Study group (VLBW and premature) N = 103	Study Group (1086 (243))	Study Group (29.4 (24-35))	Study Group (11.6 (10-13.3))	BP Urine PCR Urine ACR eGFR	• The prevalence of systolic hypertension was 15.8% and of systolic pre-hypertension was 6.9%. This is compared to the general United States paediatric population which has a 1.6% prevalence rate of systolic hypertension. • Hypertension was associated with a significantly diminished mean birth weight compared to the remainder of the cohort (939.3 grams vs 1111 grams P=0.024) • 103 study participants that were very low birth weight and premature all had normal values of GFR • Prevalence of microalbuminuria was 14.3% while the prevalence of proteinuria was 7.9% at 11.6 years.
30	Staub et al (2020) [44]	Control Group (term) N=82 Study Group (premature) N=51	Control (3250 (555)) Study (1360 (532))	Control (39 + 6 (2 + 5)) Study (31 + 0 (2 + 6))	Control (12.1 (1.20)) Study (12.3 (1.87))	BP sCr Cystatin C eGFR Beta-2 Microglobulin Uromodulin Neutrophil gelatinase-associated lipocalin	• Systolic BP was significantly higher in premature boys compared with term boys, however there was not significant difference in girls • Low birth weight was associated with higher BP in premature boys • In the premature group, maternal hypertension/preeclampsia and adolescent height were associated with higher systolic BP • sCr and neutrophil gelatinase-associated lipocalin were significantly higher in the premature group • There was no significant difference in GFR between groups
31	Askenazi et al (2021) [45]	N=923 (extremely low gestational age)	801.1 (187.9)	24-27	1.83-2.17	eGFR Urine ACR BP	• The prevalence of Stage 2 or 3 AKI was 18.2% • At 22-26 months 16% had an eGFR <90mL/min/1.73m^2, 35.8% had elevated urine ACR, 23% had aSBP > 95th percentile for their age and 40% had a DBP >95th percentile for age

Abbreviations: BP (blood pressure), SBP (systolic blood pressure), DBP (diastolic blood pressure) eGFR (estimated glomerular filtration rate), BMI (body mass index), TmP (tubular maximum reabsorption of phosphate), sCr (serum creatinine), CKD (chronic kidney disease), ACR (albumin creatinine ratio), PCR (protein creatinine ratio), SDMA (Symmetric dimethylarginine), TKV (total kidney volume), IUGR (intrauterine growth retardation), EUGR (extrauterine growth retardation), SGA (small for gestational age), AGA (appropriate for gestational age), BUN (blood urea nitrogen), ERPF (effective renal plasma flow), AKI (acute kidney injury), VLBW (very low birth weight), ELBW (extremely low birth weight)

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1 renal insufficiency.mp. or exp Renal Insufficiency/ (188865)
2 chronic kidney disease.mp. or exp Renal Insufficiency, Chronic/ (136800)
3 exp Acute Kidney Injury/ or exp Renal Insufficiency, Chronic/ or kidney function.mp. or exp Glomerular Filtration Rate/ (221756)
4 kidney failure.mp. (100456)
5 blood pressure.mp. or exp Blood Pressure/ (438835)
6 proteinuria.mp. or exp Proteinuria/ (60170)
7 albuminuria.mp. or exp Albuminuria/ (19579)
8 exp Hypertension/ (293215)
9 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 (867063)
10 exp Premature Birth/ or exp Infant, Premature/ or exp Infant, Extremely Premature/ or premature.mp. or exp Infant, Premature, Diseases/ (198355)
11 preterm birth.mp. (15605)
12 10 or 11 (202175)
13 term.mp. or exp Term Birth/ (1043152)
14 long term.mp. (735729)
15 long term adverse outcomes.mp. (286)
16 long term outcome.mp. (24999)
17 14 or 15 or 16 (735729)
18 9 and 12 and 13 and 17 (685)
19 limit 18 to (yr="1990 -Current" and english) (553)

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PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1/Title page
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	5-6
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	2
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	NA
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	7
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	7
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Supplementary File
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	7
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	7
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	7
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	7-8
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	7
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	NA

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	7-8
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	NA
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	10
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	10 and Appendix A Table 1
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	16
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	10-16
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	NA
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	16
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	NA
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	18-19
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	20
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	18-20
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	21

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