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ORIGINAL ARTICLE

Kidney injury rates after unilateral nephrectomy in childhood—a systematic review and meta-analysis

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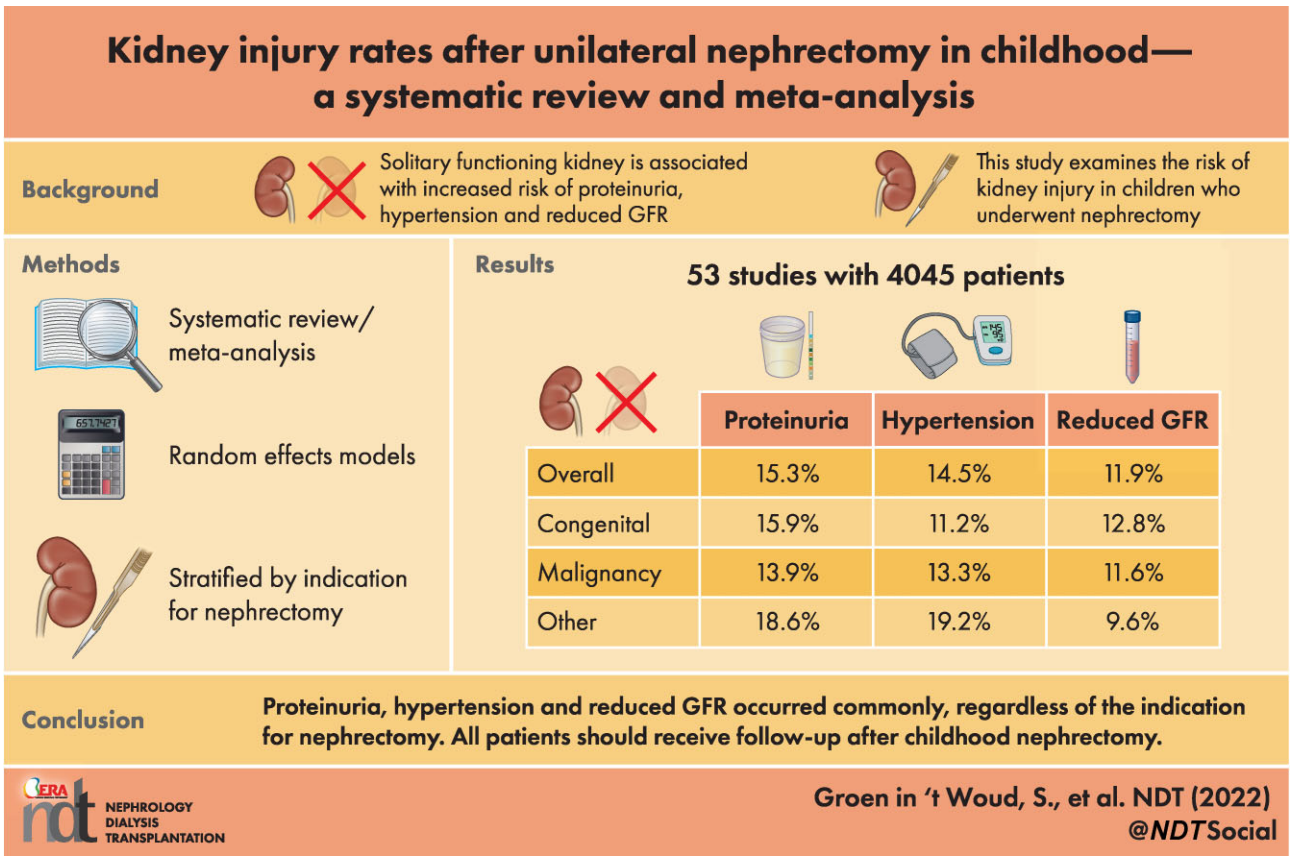
GRAPHICAL ABSTRACT



ABSTRACT

Background. Unilateral nephrectomy is a relatively common procedure in children which results in a solitary functioning kidney (SFK). Living with an SFK predisposes to kidney injury, but it remains unknown which children are most at risk. We aimed to investigate kidney injury rates in patients

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KEY LEARNING POINTS

What is already known about this subject?

- Living with a solitary functioning kidney from childhood predisposes to long-term consequences such as proteinuria, hypertension and a reduction in kidney function.
- Children who undergo nephrectomy may have a different risk for kidney injury than children with a solitary functioning kidney from birth.

What this study adds?

- This systematic review and meta-analysis estimates that proteinuria, hypertension and a reduction in kidney function are present in 15.3, 14.5 and 11.9% of patients who underwent nephrectomy during childhood, respectively.
- The indication for nephrectomy did not influence the proportions of affected patients, indicating that follow-up cannot be tailored based on this factor.

What impact this may have on practice or policy?

- We recommend that all children who undergo nephrectomy should be screened for signs of kidney injury annually, with no differentiation based on the indication for nephrectomy.
- Future studies should report large, unselected cohorts of patients who have undergone nephrectomy during childhood, with high-quality information on kidney injury measures.
- The availability of outcome data on individual-patient level would help to stratify the care for patients with a solitary functioning kidney based on risk categories.

who underwent unilateral nephrectomy in childhood and to investigate differences among nephrectomies performed for a congenital anomaly, malignancy or other condition.

Methods. MEDLINE and EMBASE were searched for studies reporting kidney injury rates [i.e. proteinuria, hypertension and/or a decreased glomerular filtration rate (GFR)] of patients who underwent unilateral nephrectomy during childhood. Studies including five or more patients with at least 12 months of follow-up were eligible. Analyses were performed using random effects models and stratified by indication for nephrectomy. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) and Meta-analysis Of Observational Studies in Epidemiology (MOOSE) guidelines were used for reporting.

Results. Over 5000 unique articles were screened, of which 53 studies reporting on >4000 patients were included in the analyses. Proteinuria, hypertension and a decreased GFR were present in 15.3, 14.5 and 11.9% of patients, respectively. Heterogeneity among the studies was large in several subgroups, impairing quantitative meta-analyses. However, none of our analyses indicated differences in injury rates between a congenital anomaly or malignancy as an indication for nephrectomy.

Conclusions. Unilateral nephrectomy during childhood results in signs of kidney injury in >10% of patients, with no clear difference between the indications for nephrectomy. Therefore, structured follow-up is necessary in all children who underwent nephrectomy, regardless of the indication.

Keywords: CAKUT, chronic kidney disease, nephrectomy, systematic review, Wilms tumour

INTRODUCTION

Each year, over 2000 children undergo a nephrectomy in the US [1]. Approximately 75% of these procedures are performed for benign disease, with indications such as multicystic dysplastic kidney (MCDK) or non-functioning kidney due to vesicoureteral reflux (VUR), duplex kidney or ureteropelvic junction obstruction (UPJO) [1, 2]. A Wilms tumour is by far the most common indication in the remaining 25% with malignancies [1, 2].

After a unilateral nephrectomy, a solitary functioning kidney (SFK) remains. As living with an SFK predisposes to kidney injury due to glomerular hyperfiltration, lifelong follow-up is warranted, although the estimated risk of kidney injury varies greatly [3]. Studies report signs of kidney injury in up to 50% of children with an SFK, with some reporting a higher risk for an acquired SFK (i.e. after nephrectomy) than for an SFK from birth (e.g. after unilateral renal agenesis) [4, 5]. In addition, children undergoing nephrectomy for a malignancy could be at higher risk for kidney injury than children undergoing a nephrectomy for other reasons, especially if they were additionally treated with nephrotoxic chemotherapy or radiotherapy on the remaining kidney.

Although the high rate of kidney injury led to recommendations highlighting the need for follow-up of children with an SFK, the frequency of follow-up is largely opinion-based [3]. Follow-up could be individualized if more information on risk factors for kidney injury were made be available [6]. Therefore, we addressed the following research questions in a systematic review and meta-analysis of the literature: (i) what is the prevalence of kidney injury in children who underwent a unilateral nephrectomy and, (ii) does the indication for nephrectomy influence the rate of kidney injury?

MATERIALS AND METHODS

Review methods

Prior to the initiation of the systematic review, a protocol was created with detailed information on the research question, search strategy, inclusion and exclusion criteria and risk

of bias assessment. Furthermore, we defined how to investigate heterogeneity and when meta-analysis would be performed and registered the protocol on the PROSPERO website (registration number CRD42019129501). The PRISMA and MOOSE checklists were used to aid transparent reporting of the review [7, 8].

Search strategy

Our search strategy was formulated with the assistance of a professional librarian and aimed at identifying all relevant articles on paediatric nephrectomy (a complete search strategy is included as Supplementary material). We first searched the MEDLINE and EMBASE libraries in March 2019 and used the snowballing technique to identify relevant studies from the reference list of selected articles. Since no randomized clinical trials on the subject of our review were expected, trial registers and the Cochrane library were not searched. The identified studies were imported into EndNote and duplicates were removed using the methods of Bramer *et al.* [9]. In September 2020, both MEDLINE and EMBASE were searched again to update our database with the most recent articles.

Selection of eligible studies

After deduplication, the articles were imported into Rayyan for title/abstract screening by two independent reviewers (S.G.W. and A.G.) [10]. In case of disagreement, a third reviewer (M.F.S.) was consulted. Articles were considered eligible if they: (i) reported on children (0–18 years) who underwent a unilateral simple or radical nephrectomy, (ii) reported at least one of the outcomes related to kidney injury (defined as proteinuria, hypertension, a decreased eGFR and/or use of antihypertensive or antiproteinuric medication), (iii) measured the outcomes at least 12 months after nephrectomy, (iv) included at least five patients and (v) were available in English. Studies including only children undergoing nephrectomy for hypertension were excluded since it would not be possible to determine whether hypertension during follow-up was pre-existing or a consequence of living with an SFK in these children. To avoid misclassification of tumour-associated hypertension as hypertension caused by living with an SFK, only outcomes measured after at least 1 year of follow-up were taken into account.

Data extraction

Full text screening and data extraction were performed in duplicate by the same two reviewers. We extracted information on study characteristics (e.g. study type, in- and exclusion criteria, duration of follow-up), the indications for nephrectomy and the measurement of the outcomes using a predefined form. We grouped the indications for nephrectomy into congenital anomalies (i.e. MCDK, hydronephrosis, obstructive uropathy, VUR and congenital not otherwise specified), malignancies and mixed/other (e.g. trauma or calculi). If a study included nephrectomies for both congenital anomalies and malignancies, subgroups by indication were created within individual studies. If this was not possible, study outcomes were reported under the mixed/other indication groups. Data on children who did not undergo nephrectomy were not extracted. Authors were contacted to provide more information when ambiguity about the patients who underwent nephrectomy was present. If the available data permitted, kidney injury was defined as the presence of albuminuria or proteinuria (in our article combined and referred to as proteinuria), hypertension, an eGFR <60 mL/min/1.73 m^2, or the use of antihypertensive and/or antiproteinuric medication. Generally, the outcome definitions from the studies were applied. When individual eGFR values were reported, the numbers of patients with an eGFR <60 and an eGFR <90 mL/min/1.73 m^2 were extracted. A selection of items from the Newcastle-Ottawa Scale was used to assess the quality of the studies [11].

Data analysis

For three outcome measures (proteinuria, hypertension and eGFR), sufficient studies were available to perform quantitative analyses. The number of participants with the specific outcome was divided by the number of participants at risk in the particular study to calculate the proportion of affected patients. The proportions of affected patients from the individual studies were combined in meta-analyses using random effect models for all three outcomes separately. Between-study heterogeneity was assessed using the I^2 statistic and we established a maximum heterogeneity of 75% in our protocol to avoid overinterpreting meta-analyses results on incomparable studies leading to spurious conclusions [12, 13]. The Paule–Mandel method was used to calculate the heterogeneity τ^2 and to assign weights to the studies [14]. The method by Hartung, Knapp, Sidik and Jonkman was used to adjust test statistics and confidence intervals since this method reduces type 1 errors in case of substantial heterogeneity and/or a small number of studies [15]. Subgroup analyses were performed to compare the different indication groups (i.e. congenital, malignancy and mixed/other) and to investigate other potential sources of heterogeneity, including follow-up duration (<7.5 years, 7.5–15 years and ≥ 15 years), way of reporting (mean or median), study design (cohort or cross-sectional), size of the study (≤ 10, 11–49 or ≥ 50 participants) and year of publication (before or after 2010). Meta-regression analyses were used to evaluate the effect of these factors on estimated proportions and heterogeneity in multivariate analyses. All analyses were performed using R software (version 3.5.1).

RESULTS

Study selection

Our initial search yielded 7237 results, of which 2087 were duplicates. The title and abstract of 5150 articles were screened for eligibility and 4832 articles were excluded. From the remaining 318 articles, 26 had to be excluded because no full-text article was available (e.g. conference presentations), while 227 were excluded after reading the full text because they did not fulfil the inclusion criteria. At this stage, 65 studies were selected for data extraction, during which four

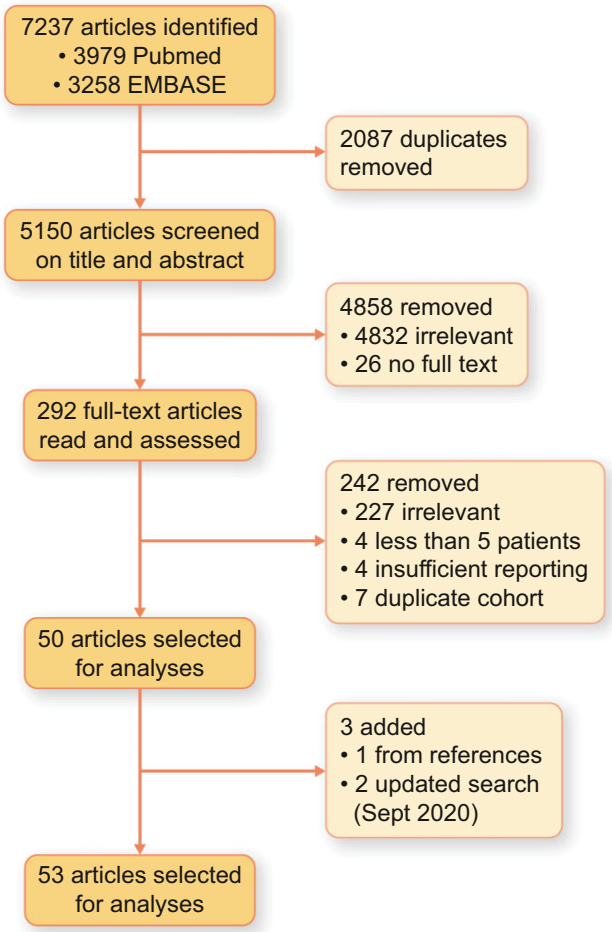

FIGURE 1: Flowchart of article selection.

additional studies [16–19] had to be excluded because of an insufficient number of patients with nephrectomy from whom data were available, four studies [20–23] were excluded because of insufficient reporting of outcomes and seven studies [24–30] were removed because a more recent article about the same cohort was available. This resulted in 50 articles for the initial analyses. Reference searching ($n = 1$) and the updated search in September 2020 ($n = 2$) yielded three more suitable articles, leading to a total of 53 articles included for analyses (Figure 1).

Study characteristics

The selected studies were published between 1969 and 2019 and consisted of cohort ($n = 31$) and cross-sectional ($n = 22$) studies (Table 1). Five studies reported on patients with a congenital indication for nephrectomy only, 34 reported on patients with a malignancy only and 14 on both types of patients or patients with other indications. For seven of the studies reporting on both types of patients, we were able to create subgroups by indication, resulting in a total of 69 studies and subgroups for analyses. In total, 4045 patients were included of whom 648 had congenital anomalies, 3293 had malignancies and 104 had other indications for nephrectomy (Table 2).

Large differences in the in- and exclusion criteria, outcome assessment and definitions of kidney injury were present among the included studies (Table 1). A total of 21 studies excluded patients with a form of contralateral (i.e. in the SFK) disease and six used some form of kidney injury as exclusion criterion (e.g. patients with GFR <90 mL/min/1.73 m^2 were excluded). Two studies did not report how proteinuria was measured and 13 had missing information on the method of blood pressure measurement used. Of studies that did report their measurement details, some used office blood pressure measurements ($n = 17$) whereas others used ambulatory blood pressure monitoring (ABPM) ($n = 4$). Urinalysis was reported

Table 1. Study design and characteristics

Author	Year	Study type	Cases: inclusion criteria	Cases: exclusion criteria	Outcome assessment		
					Proteinuria	Blood pressure	Kidney function
Abou Jaoude [4]	2011	Cohort	SFK	Contr. structural anomalies	Single	Aavg 3 readings	Inulin Cl
Aperia [31]	1977	Cross sectional	Nx	?	–	?	24 h Cr Cl
Argueso [32]	1992	Cross sectional	Nx at age <15 y	Contr. structural anomalies	24 h	?	24 h Cr Cl
Barrera [33]	1989	Cross sectional	Nx for WT	–	Single	?	Cr
Basto Catalina [34]	2019	Cohort	Nx	Stage 5 CKD	–	–	Cr
Baudoin [35]	1993	Cross sectional	Nx at age <16 y	Contr. structural anomalies	24 h	Avg 4 readings	Polyfr Cl
Bhisitkul [36]	1991	Cross sectional	Nx for WT	RT	Single	?	Cr Cl
Cost [37]	2014	Cohort	Nx for WT	Syndromic WT	–	–	Inulin Cl
Cozzi [38]	2013	Cohort	Nx for WT	Bilateral disease	–	–	Cr
Cuckow [39]	1997	Cohort	VURD	–	–	–	EDTA Cl
Daw [40]	2009	Cohort	Nx for WT at age < 21 y	Life expectancy <6 wks	?	?	24 h Cr Cl
de Graaf [41]	1996	Cohort	Nx for WT	–	–	–	Iothalamaat Cl
de Lucas [42]	2006	Cohort	SFK	–	Single	?	Cr Cl
Dekkers [43]	2013	Cross sectional	Nx for cancer	Bilateral cancer, no Cr available, <18 y at study measurement	Single	Osc	Cr
Donckerwolcke [44]	2001	Cross sectional	Nx for cancer	–	?	?	Inulin Cl
Dursun [45]	2007	Cohort	Nx	Contr. structural anomalies or GFR <90	Single	ABPM	–
Elli [46]	2013	Cohort	Nx for WT at age <16 y	–	–	ABPM	–
Finklestein [47]	1993	Cohort	Nx for WT	Relapse within 5 y, bilateral WT, cardiac disease	–	?	–
Gibson [48]	2017	Cohort	Nx for cancer	<18 y old or <10 y after diagnosis at study measurement	–	Avg 3 readings	–
Godbole [49]	2004	Cohort	Nx for benign disease	Contr. structural anomalies	–	–	EDTA/inulin Cl
Indolfi [50]	2001	Cohort	Nx for WT	–			–
Interiano [51]	2015	Cohort	Nx for WT at age <15 y	RT, bilateral or syndromic WT	Single	Avg 3 readings	Cr
Janeczko [52]	2015	Cohort	WT (incl. 9 with NSS)	–	Single	Osc	Cr
Jereb [53]	1973	Cross sectional	Nx for WT	Bilateral WT, <6 y old at study measurement	–	?	Inulin Cl
Kazama [54]	2018	Cohort	Nx for WT	Bilateral or syndromic WT, genitourinary anomalies	Single	–	Cr
Kern [55]	2014	Cohort	Nx for WT <18 y	Syndromic or metastatic WT, NSS, no GFR	–	–	Cr
Kishore [56]	2014	Cross sectional	Nx for WT at age <12 y, >1 y FU	Bilateral, relapsed or syndromic WT, nephrotoxic drugs	24 h	Avg 3 readings	Cr Cl
Knijnenburg [57]	2012	Cohort	Nx for WT at age <18 y, >5 y FU	–	Single	?	Cr
Kolvek [58]	2014	Cohort	SFK	Nx for malignancy	24 h	Avg 3 ausc readings	Cr

Table 1. Continued

Author	Year	Study type	Cases: inclusion criteria	Cases: exclusion criteria	Outcome assessment		
					Proteinuria	Blood pressure	Kidney function
Kosiak [59]	2018	Cross sectional	Nx for WT	Heminephrectomy, CAKUT, UTI, relapse, sec cancer	Single	Avg 3 osc readings	Cr
Lubrano [60]	2017	Cohort	SFK at age <18 y	Non-traumatic cause for Nx, nephrotoxic drugs, CAKUT, orthostatic proteinuria	24 h	Ausc (<120 cm)/ABPM (>120 cm)	DTPA Cl
Makipernaa [61]	1991	Cross sectional	Nx for WT	Survival <10 y	24 h	?	EDTA Cl
Mavinkurve-Groothuis [62]	2016	Cohort	Nx for WT	Bilateral or syndromic WT	–		Cr
Mitus [63]	1969	Cross sectional	Nx for cancer	–	–	–	Picrate Cl
Mpofu [64]	1992	Cross sectional	Nx for WT	–	–	Ascultatory	Cr Cl
Neu [65]	2017	Cross sectional	Nx for WT	–	–	Oscillometric	24 h Cr Cl
Regazzoni [66]	1998	Cohort	Nx	Neoplastic syndrome	–	–	Cr + In Cl
Robitaille [67]	1985	Cross sectional	Nx	–	24 h	?	24 h Cr Cl
Sanpakit [68]	2013	Cohort	Tumour at age <15 y	–	–	–	Cr
Schell [69]	1995	Cohort	Nx for NB or WT	–	1st	1×	Inulin Cl
Schiavetti [70]	2015	Cross sectional	Nx for WT	Bilateral disease, NSS	24 h	Ascultatory	24 h Cr Cl
Schmidt [71]	1992	Cross sectional	Nx	Contralateral kidney damage	–	–	Cr Cl
Seminara [72]	2019	Cohort	Nx for WT	–	–	–	Cr
Simon [73]	1982	Cohort	Nx	–	–	–	Inulin Cl (4×)
Spira [74]	2009	Cross sectional	SFK at age <1 y	Kidney transplant	–	–	Cr Cl
Spreafico [75]	2014	Cohort	Nx for WT	Nephrotoxicity	24 h	APBM	24 h Cr Cl
Srinivas [76]	1998	Cross sectional	Nx for WT	–	24 h	–	24 h Cr Cl
Stefanowicz [77]	2011	Cohort	SFK	Bilateral disease	–	Ascultatory	Cr Cl
Taranta-Janusz [78]	2012	Cohort	SFK	Other urinary tract abnormalities, HT, MA, cardiovascular or secondary kidney disease	–	–	Cr Cl
Warshaw [79]	1985	Cross sectional	PUV	–	–	–	Cr Cl
Westland[a] [5]	2013	Cohort	SFK	GFR <30, dead by age of 1 y	24 h	Oscillometric	Cr
Wikstad [80]	1986	Cross sectional	Nx	Contralateral abnormalities, RT or chemotherapy	–	1×	24 h polyfr Cl
Zambaiti [81]	2019	Cross sectional	SFK	No antihypertensive medication, systemic disease or contr. kidney pathology	–	Osc, Avg 2 measurements	–

? investigated/measured but not reported; – none/not measured; [a]additional data were provided by the authors.

24 h, 24 hours; ABPM, ambulatory blood pressure measurement; ausc, auscultatory; Avg, average; CAKUT, congenital anomalies of the kidney and urinary tract; CKD, chronic kidney disease; Cl, clearance; Contr, contralateral; Cr, creatinine; DTPA, diethylenetriaminepentaacetic acid; EDTA, ethylenediaminetetraacetic acid; FU, follow-up; GFR, glomerular filtration rate; HT, hypertension; In, inulin; incl, including; MA, microalbuminuria; NB, nephroblastoma; NSS, nephron sparing surgery; Nx, nephrectomy; Osc, oscillometric; PAH, Para-aminohippurate; Polyfr, polyfructosan; PUV, posterior urethral valves; RT, radiotherapy; SFK, solitary functioning kidney; UTI, urinary tract infection; VURD, posterior urethral valves, unilateral vesicoureteral reflux and renal dysplasia; wks, weeks; WT, Wilms tumour; y, year.

Table 2. Results from included studies

Author	Year	Subgroup	*N*	*N* (%) proteinuria	*N* (%) hypertension	*N* (%) decreased GFR	Follow-up duration (years)	Kidney injury before nephrectomy	Lost during follow-up	Gender (% male)
Abou Jaoude [4]	2011	Total	53	9 (17)	–	–	9.1	No	0%	45
		Congenital	41	–	1 (2)	7 (17)	9.1			
		Malignancy	12	–	0 (0)	0 (0)	2.9			
Aperia [31]	1977	Congenital	6	–	0 (0)	0 (0)	4	–	–	38
		Mixed	2	–	0 (0)	0 (0)	10.6			
Argueso [32]	1992	Total	50[a]	–	5 (10)	–	28	No	–	57
		Congenital	26	7 (27)	–	8 (31)				
		Malignancy	2	1 (50)	–	1 (50)				
		Mixed	2	0 (0)	–	0 (0)				
Barrera [33]	1989	Malignancy	16[a]	2 (14)	6 (38)	0 (0)	17	–	–	50
Basto Catalina [34]	2019	Congenital	32	12 (38)	6 (19)	7 (22)	5.6	Yes, 45	2	45
		Malignancy	6	1 (17)	3 (50)	1 (17)	7.3			
Baudoin [35]	1993	Mixed	111	23 (21)	25 (23)	3 (3)	26	–	23	50
Bhisitkul [36]	1991	Malignancy	12	0 (0)	0 (0)	1 (8)	15	–	69	50
Cost [37]	2014	Malignancy	15	–	–	0 (0)	2.1	–	0	47
Cozzi [38]	2013	Malignancy	60	–	–	32 (53)	38.4	Yes	–	42
Cuckow [39]	1997	Congenital	12	–	–	10 (83)	8.3	–	0	100
Daw [40]	2009	Malignancy	11	2 (18)	–	6 (55)	11.2	No	8	25
de Graaf [41]	1996	Malignancy	41	–	–	7 (17)	13		0	39
de Lucas [42]	2006	Mixed	39	–	1 (3)	3 (8)	9.5	–	0	62
Dekkers [43]	2013	Malignancy	85[a]	15 (25)	22 (31)	7 (8)	24.4	–	–	53
Donckerwolcke [44]	2001	Malignancy	11	0 (0)	0 (0)	0 (0)	5.5	–	–	73
Dursun [45]	2007	Total	22	–	7 (32)	–	4.1	–	0	45
		Congenital	14	0 (0)	–	–				
		Malignancy	6	0 (0)	–	–				
		Mixed	2	0 (0)	–	–				
Elli [46]	2013	Malignancy	15	–	3 (20)	–	9.9	–	40	36
Finklestein [47]	1993	Malignancy	1171	–	83 (7)	–	5	–	48	48
Gibson [48]	2017	Malignancy	226	–	68 (30)	–	32	–	35	52
Godbole [49]	2004	Congenital	44	–	–	0 (0)	1	–	0	52
Indolfi [50]	2001	Malignancy	27	10 (37)	0 (0)	0 (0)	14.5	–	21	33
Interiano [51]	2015	Malignancy	75[a]	5 (7)	5 (7)	0 (0)	19.6	–	0	41
Janeczko [52]	2015	Malignancy	50	2 (4)	4 (8)	12 (24)	2	15/50	0%	44

Table 2. Continued

Author	Year	Subgroup	*N*	*N* (%) proteinuria	*N* (%) hypertension	*N* (%) decreased GFR	Follow-up duration (years)	Kidney injury before nephrectomy	Lost during follow-up	Gender (% male)
Jereb [53]	1973	Malignancy	16	–	0 (0)	1 (6)	6	–	–	–
Kazama [54]	2018	Malignancy	9[a]	1 (13)	–	0 (0)	20	–	–	22
Kern [55]	2014	Malignancy	55	–	–	2 (4)	6.3	–	–	40
Kishore [56]	2014	Malignancy	29	1 (3)	2 (7)	1 (3)	4.8	–	–	66
Knijnenburg [57]	2012	Malignancy	206[a]	33 (18)	43 (22)	23 (11)	9.9	–	Different per measurement	56
Kolvek [58]	2014	Mixed	15	1 (7)	5 (33)	2 (13)	11.6	–	0	55
Kosiak [59]	2018	Malignancy	53	7 (13)	12 (23)	0 (0)	8.5	–	–	49
Lubrano [60]	2017	Mixed	17	–	9 (53)	–	14	2/17	0	73
Makipernaa [61]	1991	Malignancy	30[a]	3 (10)	5 (17)	0 (0)	19.2	–	12	50
Mavinkurve-Groothuis [62]	2016	Malignancy	23	–	6 (26)	1 (4)	9.1	–	0	50
Mitus [63]	1969	Malignancy	108	–	–	54 (50)	6.5	2/85	–	40
Mpofu [64]	1992	Malignancy	71[a]	7 (10)	0 (0)	1 (2)	9	No	–	47
Neu [65]	2017	Malignancy	37[a]	5 (14)	15 (41)	6 (21)	24.8	No	60	43
Regazzoni [66]	1998	Congenital	37	0 (0)	0 (0)	0 (0)	15.2	No	–	62
Robitaille [67]	1985	Total	27	3 (11)	3 (11)	–	23.3	–	–	67
		Congenital	21	–	–	2 (10)				
		Malignancy	4	–	–	0 (0)				
		Mixed	2	–	–	0 (0)				
Sanpakit [68]	2013	Malignancy	29	0 (0)	9 (31)	2 (7)	4.8	Yes	–	63
Schell [69]	1995	Malignancy	40	–	0 (0)	16 (40)	1.9	No	–	–
Schiavetti [70]	2015	Malignancy	35	3 (9)	1 (3)	8 (23)	19	No	14	40
Schmidt [71]	1992	Mixed	34[a]	–	1 (3)	2 (11)	11.9	No	–	34
Seminara [72]	2019	Malignancy	46[a]	8 (23)	–	5 (11)	5	No	–	48
Simon [73]	1982	Malignancy	17	–	–	0 (0)		–	–	–
Spira [74]	2009	Congenital	21	1 (5)	–	1 (5)	1.8	No	–	57
		Malignancy	28	1 (4)	–	1 (4)				
		Mixed	4	0 (0)	–	0 (0)				
Spreafico [75]	2014	Malignancy	15	1 (7)	0 (0)	0 (0)	13.3	No	–	–
Srinivas [76]	1998	Malignancy	25	21 (84)	0 (0)	0 (0)	4.9	No	30	56
Stefanowicz [77]	2011	Malignancy	30	7 (23)	4 (13)	9 (30)	9.4	–	0	50
Taranta-Janusz [78]	2012	Mixed	21	–	–	6 (29)	–	–	–	33
Warshaw [79]	1985	Congenital	6	1 (17)	2 (33)	1 (17)	5.8	Yes	16	100
Westland[b] [5]	2013	Mixed	227	43 (19)	67 (30)	13 (6)	5.8	–	–	64
Wikstad [80]	1986	Congenital	22	0 (0)	–	–	13.2	–	–	50
		Malignancy	15	4 (27)	–	–	17.1	–	–	40
Zambaiti [81]	2019	Congenital	11	–	2 (18)	–	6.7	–	–	64

[a]Not all measurements were performed on the entire cohort.
[b] Additional data were provided by the authors.
– no data were available.

Table 3. Proportions of affected patients and estimated heterogeneity

Outcome	Subgroup	Number of studies	Total number of patients	Number of patients with outcome	Calculated affected proportion (%)	Estimated affected proportion* (%)	95% Confidence interval (%)	I^2
Proteinuria	Overall	42	1537	248	16.1	15.3	(11.6–20.0)	59%
	Congenital	7	151	25	16.6	15.9	(5.3–39.0)	57%
	Malignancy	26	906	136	15.0	13.9	(9.1–20.6)	69%
	Mixed	9	480	87	18.1	18.6	(16.2–21.3)	0%
Hypertension	Overall	43	3039	427	14.1	14.5	(10.5–19.8)	83%
	Congenital	6	133	11	8.3	11.2	(3.1–33.4)	46%
	Malignancy	27	2362	293	12.5	13.3	(8.6–20.2)	86%
	Mixed	10	544	123	22.6	19.2	(9.6–34.8)	70%
GFR	Overall	55	1983	262	13.2	11.9	(8.6–16.2)	80%
	Congenital	10	217	29	13.4	12.8	(3.9–34.7)	72%
	Malignancy	35	1324	204	15.4	11.6	(7.6–17.4)	81%
	Mixed	10	442	29	6.6	9.3	(5.3–16.1)	47%

*Estimated using random-effect meta-analyses. The I^2 statistic was used to quantify between study heterogeneity [12].
GFR, glomerular filtration rate

for a single random sample ($n = 11$) and for 24 h urine collection ($n = 11$). To estimate or measure GFR, some studies used creatinine based GFR estimations ($n = 15$) while others used clearances based on GFR measurements ($n = 33$). Only five studies reported on antihypertensive medication use.

Outcomes

All outcomes were reported in more than 10% of the included patients: proteinuria was reported in 16.1% (248 of 1537 patients, 42 studies), hypertension in 14.1% (427 of 3039 patients, 43 studies) and a decreased eGFR in 13.2% (262 of 1983 patients, 55 studies) (Table 3). Antihypertensive or antiproteinuric medication use was reported for 13.7% of patients (60 of 437), but in only five studies. Therefore, this outcome was not considered for further separate analyses.

Meta-analyses confirmed that signs of kidney injury were present in a considerable proportion of patients. The estimated proportions of patients with proteinuria, hypertension and a decreased eGFR were 15.3, 14.5 and 11.9%, respectively (Table 3, Figures 2–4). Because the heterogeneity was larger than 75% in 2 out of the 9 indication subgroups, results of our meta-analyses should be interpreted with care. Nevertheless, no differences in kidney injury rates across indication subgroups were visible and confidence intervals were largely overlapping.

Differences in follow-up duration, way of reporting (i.e. mean or median), study design, size of the study and year of publication were all regarded as potential confounding factors and contributors to the large heterogeneity. However, sensitivity analyses in which subgroups were made for these variables did not substantially change point estimates for the affected proportions or decrease heterogeneity in most subgroups (Supplementary data, Tables S1–S3). The only statistically significant difference was seen between the proportions of patients with hypertension in studies published before or after 2010, which were 10 and 20%, respectively ($P = 0.02$, Supplementary data, Table S2). Meta-regression including all potential confounders explained 0–21% of the heterogeneity and did not result in statistically significant differences between patients with congenital or malignant indications for nephrectomy for any outcome (Supplementary data, Tables S1–S3). As can be expected, the cut-off used to define an abnormal GFR was strongly associated with the affected proportion of patients in both univariate analyses and meta-regression (Supplementary data, Table S3).

We hypothesized that the effect of follow-up duration on kidney injury rates could be substantial and was not sufficiently corrected for by creating tertiles of follow-up duration. Therefore, we plotted the proportion of patients affected with the different outcomes against the median (or mean, if the median was not available) duration of follow-up for each study, as well as the proportion of patients with any outcome (Figure 5). No specific trends were visible in these scatterplots and separating studies reporting mean or median follow-up duration did not change these results.

DISCUSSION

In this systematic review, we found that many studies were performed on the prevalence of signs of kidney injury in patients who have undergone a nephrectomy during childhood. The estimated proportions of patients with proteinuria, high blood pressure and a decreased eGFR were 15.3, 14.5 and 11.9% of patients, respectively, which clearly indicates that children undergoing a nephrectomy need long-term follow-up. Our results indicated no differences between children with a congenital anomaly or malignancy as an indication for their nephrectomy. However, these results cannot be used to rule out the possibility of subgroups and should be interpreted with care due to the large heterogeneity among the studies included.

Heterogeneity is a common problem in meta-analyses of observational studies and is an issue that requires careful examination [12]. In our study, several underlying reasons could be identified, including the study in- and exclusion criteria,

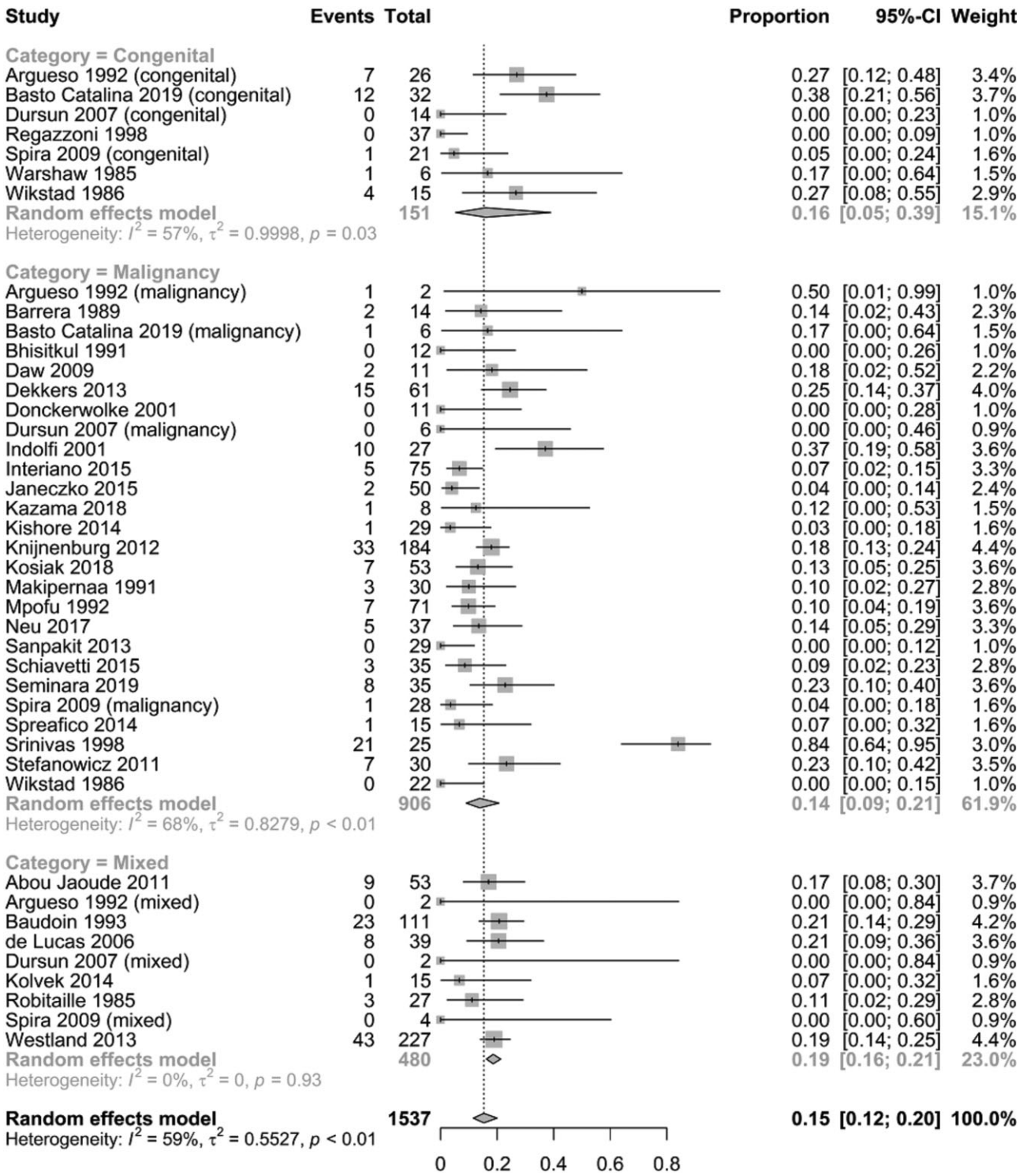

FIGURE 2: Forest plot with proportions of patients with proteinuria for different indications for nephrectomy.

methods of outcome assessment, criteria used to determine the presence of kidney injury and duration of follow-up.

The detailed in- and exclusion criteria of most studies likely resulted in a selected study population: whereas data from a US registry showed that 74% of paediatric nephrectomies was for a benign indication, >80% of the patients in our systematic review had a malignant indication [1]. Since studies often excluded patients with contralateral anomalies or bilateral disease, the included patients likely represent a relatively healthy subset. We do not expect that this was a result of a narrow search strategy since we identified over 5000 unique articles and reference searching identified only one additional article.

The assessment of the study outcomes is also an important factor in explaining heterogeneity. Three main indicators of kidney injury were selected for this study. Proteinuria is an

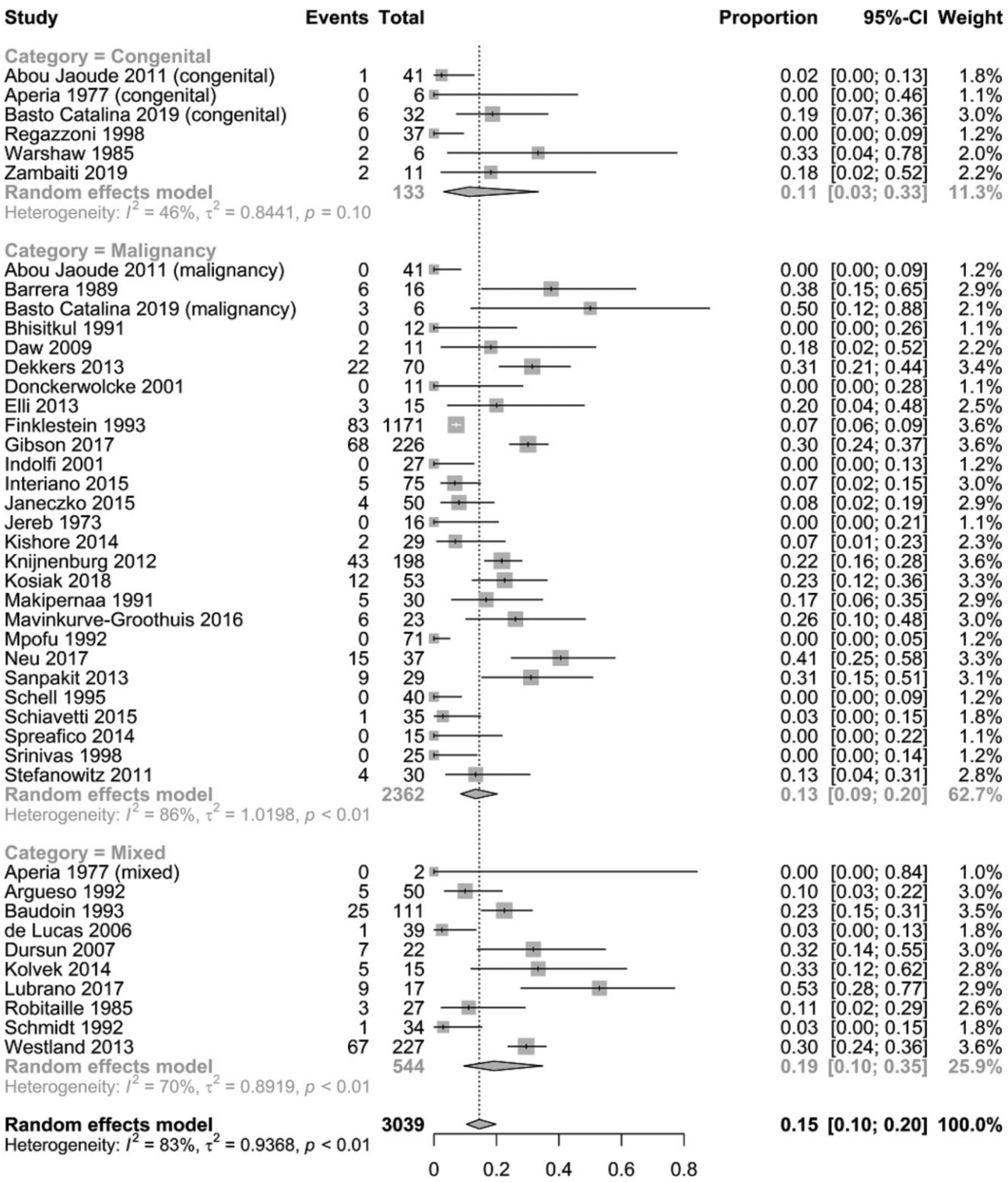

FIGURE 3: Forest plot with proportions of patients with hypertension for different indications for nephrectomy.

early marker of kidney damage and can be measured using 24-h urine collection, which is considered to be the most reliable method, or spot urines, which is more convenient and has been shown to yield reliable results as well [82]. Hypertension is a key component of glomerular hyperfiltration and the consequence of kidney injury. Although blood pressure measurement using ambulatory blood pressure monitoring is more accurate than office blood pressure [83, 84], it was used in four studies only [45, 46, 60, 75]. This may have led to measurement errors in the studies included in this systematic review. The probability of a measurement error is probably even larger when determining GFR, for which many different measurement techniques and estimations were used [85]. Furthermore, different cut-offs for GFR were used, with a much lower proportion of affected patients in studies using a cut-off of 60 mL/min/1.73 m^2 than in studies using

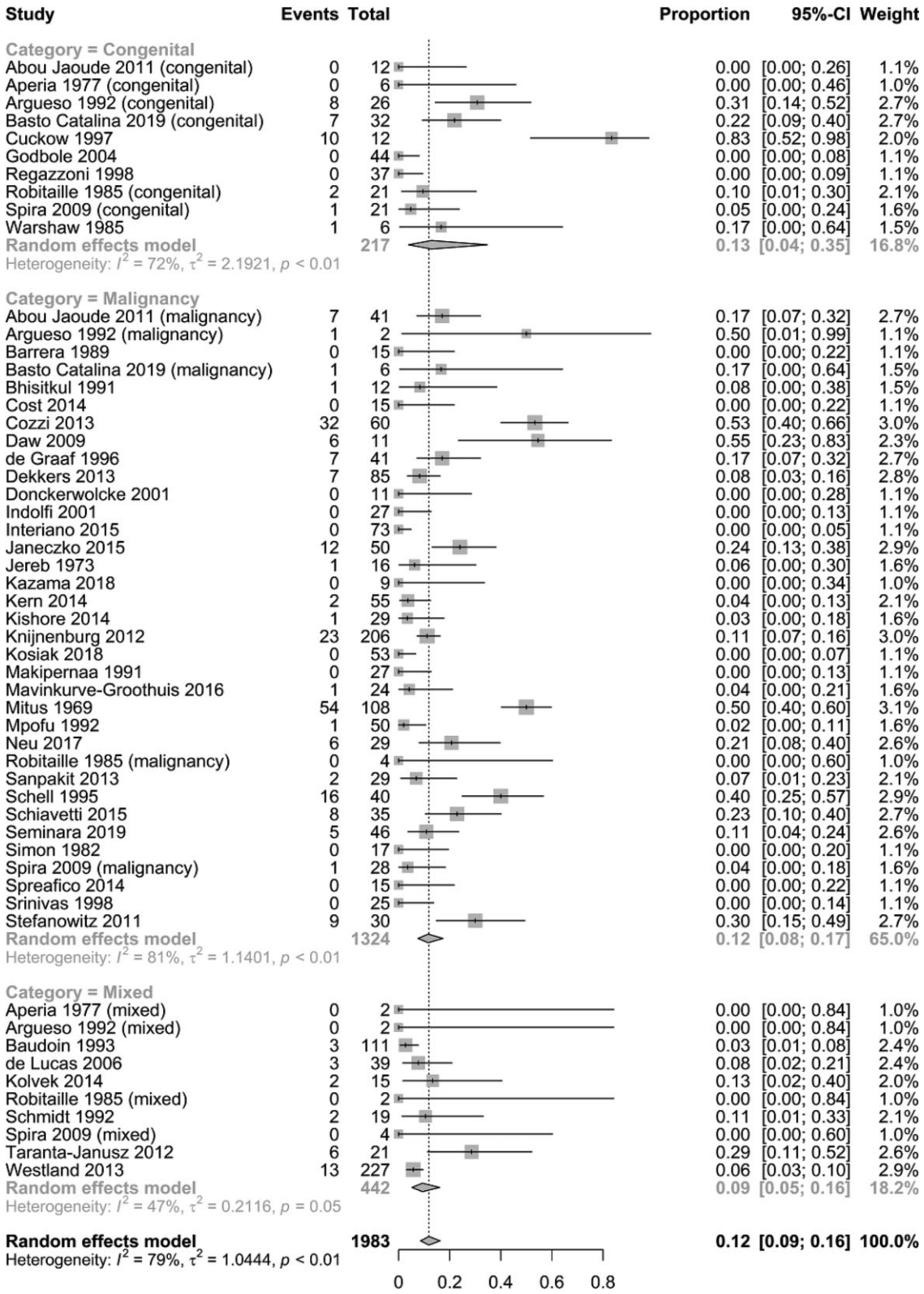

FIGURE 4: Forest plot with proportions of patients with a decreased estimated glomerular filtration rate (eGFR) for different indications for nephrectomy.

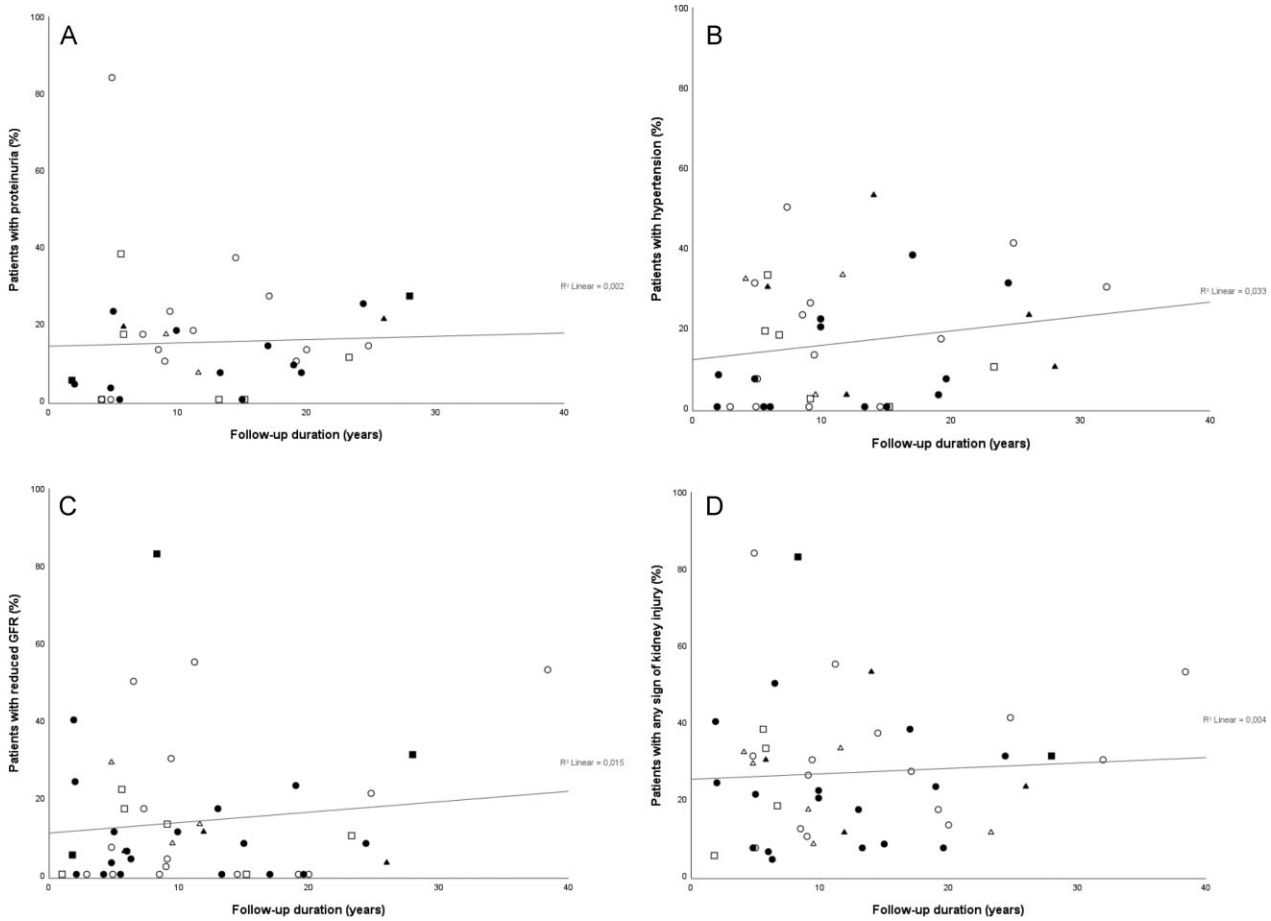

FIGURE 5: Scatterplots of study follow-up duration and percentage of affected individuals for the main outcomes [(**A**) proteinuria, (**B**) hypertension, (**C**) decreased estimated glomerular filtration rate, (**D**) any sign of kidney injury (studies with at least one affected participant only)], separated by indication for nephrectomy. Squares represent studies with congenital indication for nephrectomy only, circles represent studies with malignant indications, triangles represent studies with mixed indications. Filled symbols represent studies reporting median follow-up duration, empty symbols represent mean follow-up duration.

90 mL/min/1.73 m^2 (6.0 and 26.6%, respectively). Given these issues, it is not surprising that heterogeneity was larger for hypertension (83%) and a decreased GFR (80%) than for proteinuria (59%).

We attempted to correct for follow-up duration and several additional sources of variation by creating subgroups and performing meta-regression analyses. We expected that the follow-up duration would be a main determinant of the number of patients with kidney injury, since hyperfiltration is considered to be the main mechanism behind kidney injury in patients who are living with an SFK. However, creating subgroups based on follow-up duration did not substantially reduce heterogeneity, follow-up duration was not statistically significantly associated with estimated proportions in meta-regression analyses and no clear associations between follow-up duration and the proportion of affected patients was visible in our scatterplots including all studies (Figure 5). Since this was an unexpected finding, we investigated whether an effect of follow-up was visible when focussing on only the larger studies with over 50 included patients. The variance explained by follow-up duration was much larger, especially when focussing only on patients with a tumour as an indication for nephrectomy (Figure 6). As such, the effect of follow-up duration in our overall analyses is probably diluted and confounded by the many small studies with widely varying results that were given equal weight as the larger studies. An additional factor could be the definition of follow-up, which we defined as age at outcome assessment minus age at nephrectomy. Children with congenital indications for nephrectomy may have lived with a unilateral malfunctioning or non-functioning kidney before nephrectomy, however, and might be prone to kidney injury at an earlier age as a result.

Differences in study type could also have affected our results. Some studies reported on a cohort of patients that had systematically been followed after nephrectomy, whereas others called back individuals for a one-time assessment of kidney injury. However, limiting our analyses to cohort studies did not change our results substantially. Also, several smaller studies were included, in which greater variation due to chance can be expected. Nonetheless, the study size was not statistically associated with the affected proportion of patients in meta-regression analyses. Lastly, the studies included were published between 1969 and 2019 and contain patients undergoing nephrectomy from 1936 onwards. Since

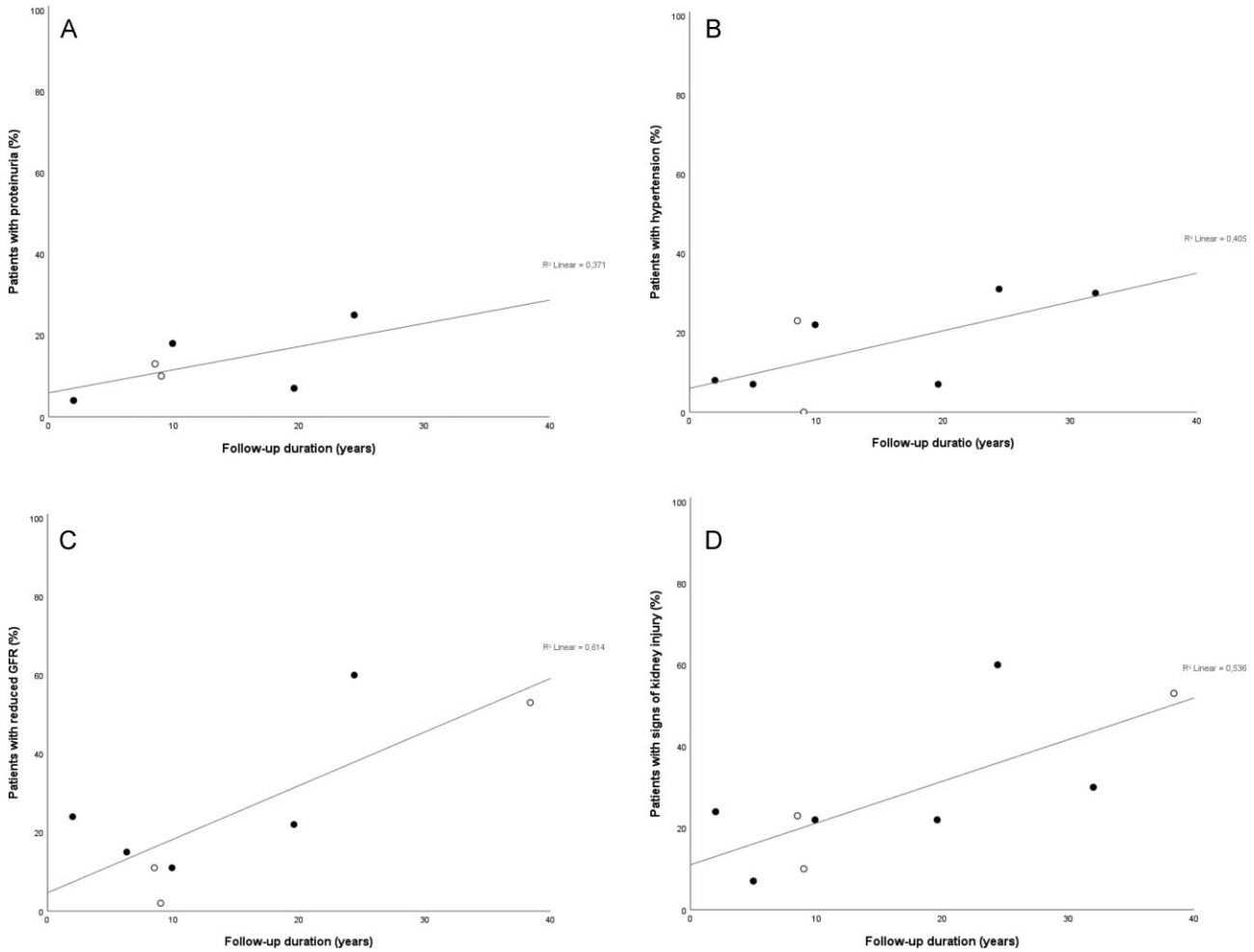

FIGURE 6: Scatterplots of study follow-up duration and percentage of affected individuals for the main outcomes [(**A**) proteinuria, (**B**) hypertension, (**C**) estimated glomerular filtration rate <90 mL/min/1.73 m^2, (**D**) any sign of kidney injury)] in studies with at least 50 participants and malignancy as indication for nephrectomy. Filled symbols represent studies reporting median follow-up duration, empty symbols represent mean follow-up duration.

major advances in surgical techniques and diagnostic possibilities were made during this time period, the long timespan undoubtedly influenced our results. In sensitivity analyses with studies published after 2010 only, however, the estimated proportion of patients with hypertension increased (from 9.7 to 19.6%). Although rather speculative, the stricter application of guidelines on how blood pressure should be measured adequately could have played a role in this difference.

A common approach to deal with heterogeneity in meta-analyses of observational studies is to create subgroups [12]. Although we planned several subgroup analyses *a priori*, these did not decrease heterogeneity substantially in most cases. Another possible approach is to perform meta-regression analyses, in which several possible mediators can be taken into account. Despite the inclusion of six potential contributors to heterogeneity, only a minor part (0–21%) of heterogeneity could be explained. Lastly, individual patient data meta-analyses could be a solution, but we refrained from this option because of the large number of cohorts that were published >10 years ago. Despite the limitations in interpretation of the meta-analyses that come with the large between-study heterogeneity, this systematic review benefits from its large number of included studies and considerable sample size. We showed that more than 10% of patients exhibit some form of kidney injury after undergoing a nephrectomy in childhood, which stresses the importance of a standardized follow-up protocol for these patients and high-quality research into the topic.

Our results show that no indication subgroup remains sufficiently free from kidney injury to justify discharge from follow-up. Although not all patients will develop kidney injury after nephrectomy, stratification is not yet possible, which is similar to patients living with a congenital SFK [6]. Therefore, we recommend to perform screening for kidney injury in line with that performed in patients with congenital SFK, consisting of a yearly measurement of blood pressure and proteinuria and 5-yearly estimation of the GFR [86]. More frequent GFR estimation may be needed in circumstances that increase the demand on the kidney, such as during rapid pubertal growth or pregnancy and in individuals with

obesity. Local practice patterns can guide whether follow-up is performed by a paediatric urologist or nephrologist, or a general care physician.

For future studies, we highly recommend reporting outcomes according to existing guidelines for the measurement and classification of hypertension and kidney function to overcome the limitations we encountered while summarizing the available evidence [84, 87]. Furthermore, structured follow-up of all patients undergoing unilateral nephrectomy in childhood as recommended above will likely lead to more available data on a less selected population. Ideally, these data should be registered in a centralized facility such as the registries of the European Reference Networks (ERNs) (e.g. ERKReg or the ERN eUROGEN registry) and made available for research, since the availability of these data would bring tailored follow-up based on individual risk factors a step closer to clinical practice.

In conclusion, this systematic review and meta-analysis showed that signs of kidney injury were common in a large and heterogeneous population of patients that underwent nephrectomy in childhood. No difference was observed between nephrectomy for benign or malignant conditions. These results indicate that standardized follow-up is needed in all patients who underwent nephrectomy during childhood. More widespread and uniform reporting of data is needed to facilitate the estimation of the risk of kidney injury in specific subpopulations and tailor clinical care accordingly.

SUPPLEMENTARY DATA

Supplementary data are available at *ndt* online.

DATA AVAILABILITY STATEMENT

The data underlying this article are available in the article and in its online supplementary material.

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AUTHORS' CONTRIBUTIONS

S.G.W., L.vd.Z. and M.F.S. conceived the idea of this systematic review. S.G.W. and A.G. extracted the data, carried out the statistical analyses and prepared the draft manuscript. N.R. provided statistical advice. N.R., L.vd.H., W.F., L.vd.Z. and M.F.S. critically revised the manuscript. All authors approved the final manuscript.

CONFLICT OF INTEREST STATEMENT

L.vd.Z. received a VENI (916.180.36) from the Dutch Research Council (NWO). W.F.J.F. serves as ERN eUROGEN Coordinator. No other potential conflicts of interest were reported. The results presented in this paper have not been published previously in whole or part.

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