Systematic Review

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Kidney disease among children in sub-Saharan Africa: systematic review

Neema M. Kayange[1], Luke R. Smart[2,3], Jacob E. Tallman[4], Emily Y. Chu[4], Daniel W. Fitzgerald[3], Kevin J. Pain[5] and Robert N. Peck[2,3]

The global burden of kidney disease is increasing, and several etiologies first begin in childhood. Risk factors for pediatric kidney disease are common in Africa, but data regarding its prevalence are lacking. We completed a systematic review of community-based studies describing the prevalence of proteinuria, hematuria, abnormal imaging, or kidney dysfunction among children in sub-Saharan Africa (SSA). Medline and Embase were searched. Five hundred twenty-three references were reviewed. Thirty-two references from nine countries in SSA were included in the qualitative synthesis. The degree of kidney damage and abnormal imaging varied widely: proteinuria 32.5% (2.2–56.0%), hematuria 31.1% (0.6–67.0%), hydronephrosis 11.3% (0.0–38.0%), hydroureter 7.5% (0.0–26.4%), and major kidney abnormalities 0.1% (0.0–0.8%). Serum creatinine was reported in four studies with insufficient detail to identify the prevalence renal dysfunction. A majority of the studies were performed in *Schistosoma haematobium* endemic areas. A lower prevalence of kidney disease was observed in the few studies from nonendemic areas. Published data on pediatric kidney disease in SSA are highly variable and dependent on *S. haematobium* prevalence. More community-based studies are needed to describe the burden of pediatric kidney disease, particularly in regions where *S. haematobium* infection is nonendemic.

Worldwide, the number of deaths attributable to chronic kidney disease (CKD) has almost doubled in the past 20 years, ranking it among the top 20 causes of death globally (1). Along with other noncommunicable diseases, CKD has begun to gain recognition as an important contributor to the burden of disease not only in high-income countries, but also in low-income countries in regions such as sub-Saharan Africa (SSA). Although high quality epidemiological data from SSA are sparse, available published data suggest the prevalence of CKD is substantial (2).

Pediatric registries in several high-income countries (3–5) have reported that the incidence of pediatric CKD is relatively low in such settings and that congenital anomalies of the kidney and urinary tract cause 50% or more of CKD in children. In studies from the United States, the incidence of CKD is two to three times higher among African American children than among Caucasian children. This is partly due to the higher frequency of primary glomerular diseases such as focal segmental glomerular sclerosis (3). This difference may be related to the *APOL1* gene mutation (6,7), which may also play a role in kidney disease in SSA (8).

Risk factors for CKD are more common among children in SSA. Intrauterine injury to the developing kidney and malnutrition in childhood are more common in low-income populations and contribute to the increased prevalence of CKD (9,10). Parasitic infections such as schistosomiasis, postinfectious glomerulonephritis, HIV-related nephropathy, and sickle disease all cause damage to the kidney in childhood and are more common in SSA (11–14). In addition, acute kidney disease is more common among children in SSA, particularly due to higher rates of diarrhea, and may progress to CKD (15–17).

Despite these risk factors, data regarding pediatric CKD in SSA remain sparse and are mostly limited to health facility–based studies. Therefore, we completed a systematic review of studies investigating kidney disease among community-dwelling children in SSA.

RESULTS

Search Results

See **Figure 1** for a Preferred Reporting Items for Systematic Reviews and Meta-Analyses diagram explaining the search results and exclusion process. We identified 688 references through database searching. An additional 45 references were found through hand searching. After removal of duplicates, 523 unique references remained. Upon review of titles and abstracts, 432 references were excluded, and 91 references remained for full text review. An additional 59 references were excluded upon full-text review, leaving 32 references that met our inclusion and exclusion criteria. After merging duplicate data sets and identifying distinct data sets, a total of 35 data sets were taken from these 32 references (18–49) for qualitative synthesis.

The first two authors contributed equally to this work.
[1]Department of Pediatrics, Weill Bugando School of Medicine, Catholic University of Health and Allied Sciences, Mwanza, Tanzania; [2]Department of Internal Medicine, Weill Bugando School of Medicine, Catholic University of Health and Allied Sciences, Mwanza, Tanzania; [3]Department of Medicine, Center for Global Health, Weill Cornell Medical College, New York, New York; [4]Cornell University, Ithaca, New York; [5]Samuel J. Wood Library/CV Starr Biomedical Information Center, Weill Cornell Medical College, New York, New York. Correspondence: Luke R. Smart (smart.luke@gmail.com)

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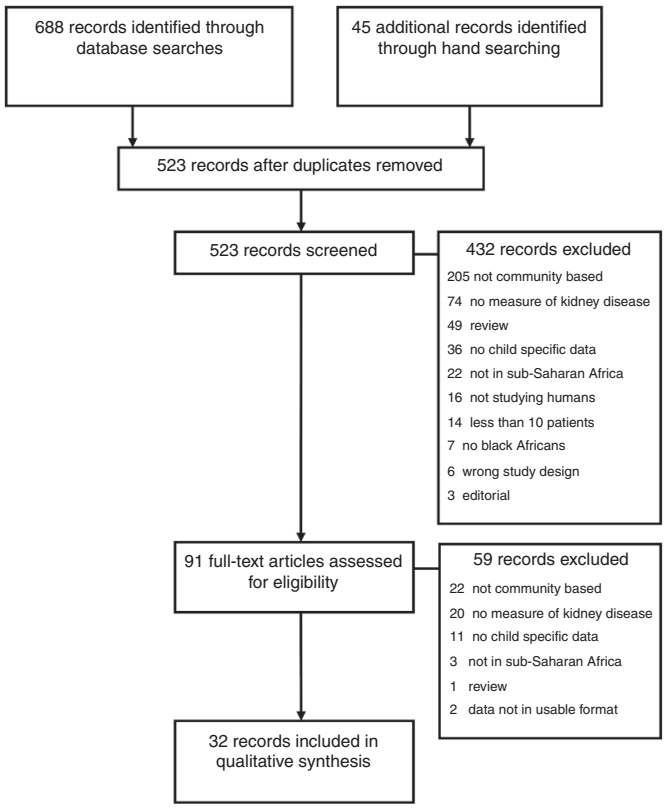

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) diagram of study selection process.

Study Characteristics

See **Table 1** for characteristics of included data sets. The data represented nine countries in SSA (Benin, Cameroon, Kenya, Liberia, Mali, Niger, Nigeria, Tanzania, and Zimbabwe), and was published between 1964 and 2012. The age range of subjects was 0–21 y old (average age 8.7–13.6). Female subjects represented 0–55%. Home-based sampling was done in 12 instances and school-based sampling in 23. Sample size was from 40 to 2,628 subjects. The risk of selection bias score ranged from 1 to 2 (good to moderate). The risk of measurement bias score ranged from 2 to 3 (moderate to poor).

Several of the studies were carried out as part of multi-year projects. Often these studies described the prevalence of *S. haematobium*, or the effects of treatment for schistosomiasis. Examples include the Msambweni project in Kenya from 1984 to 1992 (31–34,36,38), Malumfashi Endemic Research Project and other sites in Nigeria (25,44), and several studies in both Tanzania (20,22,23) and Mali (29,47,48).

Proteinuria

See **Table 2** for the reported prevalence of proteinuria in included data sets. The prevalence of proteinuria was 2.2–56.0% (average 32.5%). In the majority of data sets, the only identified factor associated with proteinuria was the presence and/or intensity of *S. haematobium* infection. Only four studies investigated populations without *S. haematobium* (28,39–42). Two of these did not find any factors associated with proteinuria (39,42). One found that proteinuria was associated with malaria infection ($P < 0.05$) (28). The last found that microalbuminuria was associated with hypertension (odds ratio (OR) = 5.4; 95% CI = 1.8–16.2; $P = 0.001$) (40,41).

The prevalence of proteinuria varied considerably even in these populations unaffected by *S. haematobium*. The two lowest outliers reported proteinuria in 2.2 and 4.7% of urban secondary school students from Nairobi, Kenya (39) and Benin City, Nigeria (42), respectively. In contrast, 49.8% of students in Port Harcourt City, Nigeria had proteinuria (23.7% with macroalbuminuria and 26.1% with microalbuminuria). A fourth study found pathologic proteinuria in 18.2% of rural primary school children in Kenya who had a high prevalence of *S. mansoni* (91.9% infected) (28). The cut off for pathologic proteinuria in this study was 200 mg/l (as opposed to the 30 mg/l that most other studies used), suggesting that the number of students with proteinuria was likely much higher.

Hematuria

See **Table 2** for details of reported prevalence of hematuria in included data sets. The prevalence of hematuria varied widely from 0.6 to 67.0% (average 31.1%). In the majority of data sets, the only identified factor associated with hematuria was the presence and/or intensity of *S. haematobium* infection. Other associated factors were female sex, sickle cell anemia, and glomerulonephritis (18,42). The three studies with lowest prevalence (0.6–3.5%) were conducted in urban populations that were not tested for *S. haematobium* (39–42). None of these identified any factors associated with hematuria. The next lowest prevalence (5.4%) was identified in rural primary school children (18) with a low prevalence of schistosomiasis (5.2%), but 46 of the 48 subjects with hematuria (96%) were infected with *S. haematobium*.

Serum Creatinine

See **Table 3** for details of reported serum creatinine (SCr) in included data sets. No studies calculated an estimated glomerular filtration rate (eGFR). Only one study from Kenya tested SCr in all subjects (28). They reported that all of the children had normal values, but they did not specify a reference range or report a median, mean, or range of creatinine values.

Three other studies reported SCr values for Nigerian children. One stated that children with hematuria or proteinuria had an SCr <115 μmol/l both at enrollment and at follow up 1 y later (42). Another reported a mean SCr of 83.3 μmol/l (range 71–108) in 46 subjects infected with *S. haematobium* (18). The last one found an SCr range of 30–82 μmol/l in 69 male subjects (age 7–17) who had a high intensity schistosomiasis infection (44). None of these studies made any attempt to adjust their range of normal to accommodate the weight, nutritional status, or age of the patient.

Kidney or Ureter Imaging

See **Table 4** for details of reported imaging abnormalities in included data sets. The prevalence of any imaging abnormality was 0.5–38.0% (average 14.8%), and except for five studies, all

Table 1. Characteristics of included studies

Study	Year	Age range (average)	Female (%)	Schisto (%)	Sampling method	Sample size	Quality	
							Risk of selection bias	Risk of measure bias
Benin (24)	2000	5–16 (9.4)	48.5	19.7	School	412	2	3
Cameroon (26)	1989	4–15 (N/A)	17.5	71.7	School	212	2	3
Kenya (49)	1979	5–18 (11)	36.0	83.6	School	390	2	3
Kenya (37)	1983	5–19 (N/A)	43.8	66.9	School	121	2	3
Kenya (31,32)	1984	4–21 (N/A)	44.9	69.4	School	2,628	2	3
Kenya (31,32)	1985	4–21 (N/A)	45.6	19.0	School	2,035	2	3
Kenya[a] (33,38)	1986	5–21 (N/A)	N/A[b]	15.2	School	N/A[b]	2	3
Kenya[a] (33,38)	1987	5–21 (N/A)	N/A[b]	17.1	School	N/A[b]	2	3
Kenya[a] (33,38)	1988	5–21 (N/A)	N/A[b]	23.2	School	N/A[b]	2	3
Kenya (30)	1988B	0–15[c] (N/A)	*55.0*[d]	64.8	Home	274	2	3
Kenya[a] (33,38)	1989	5–21 (N/A)	N/A[b]	29.9	School	N/A[b]	2	3
Kenya[a] (33,38)	1990	5–21 (N/A)	N/A[b]	21.2	School	N/A[b]	2	3
Kenya[a] (33,38)	1991	5–21 (N/A)	N/A[b]	17.2	School	N/A[b]	2	3
Kenya (28)	1994	N/A (12.3)	49.3	0[e]	School	418	2	2
Kenya (39)	1997	13–18 (N/A)	49.4	N/A	School	403	2	3
Kenya[a] (34,36)	2004	2–19[c] (N/A)	49.5	59.0	Home	1,589	1	3
Liberia (45)	1983	0–15 (N/A)	N/A	70.8	Home	267	1	3
Mali (29)	1994	2–20[c] (N/A)	N/A	75.0	Home	504	1	3
Mali (47,48)	1997	0–14[c] (N/A)	44.6	52.8–74.2	Home	428	1	3
Niger (27)	1986A	4–15[c] (N/A)	41.9	69.0	Home	129	2	3
Niger (27)	1986B	4–15[c] (N/A)	42.5	0	Home	40	2	3
Niger (35)	1989	0–15[c] (N/A)	41.7	93.8	Home	216	2	3
Niger (46)	2008A	7–11 (8.7)	44.0	75.7	School	1,642	2	3
Niger (46)	2008B	8–12 (9.7)	44.0	38.0	School	1,436	2	3
Nigeria (25)	1965	9–15 (N/A)	53.8	91.0	School	78	2	3
Nigeria (43)	1975	6–15 (N/A)	N/A	59.9	School	314	2	3
Nigeria (44)	1980	7–17 (N/A)	0	100.0	Home	69	2	2
Nigeria[a] (42)	1994	13–20 (N/A)	52.7	N/A	School	2,169	2	2–3
Nigeria (18)	2008	6–14 (9.32)	43.7	5.2	School	894	2	2–3
Nigeria (40,41)	2010	10–19 (13.6)	51.4	N/A	School	820	2	3
Tanzania (22,23)	1964	6.5–17 (N/A)	34.9	87.1	School	358	2	3
Tanzania (21)	1966	0–17[c] (N/A)	35.1	65.0	Home	598	2	3
Tanzania (20)	1969	0–20[c] (N/A)	41.2	60.7	Home	422	2	3
Tanzania (45)	1983	0–15 (N/A)	N/A	29.6	Home	548	1	3
Zimbabwe (19)	2004	9–16 (N/A)	N/A	59.7	School	551	1	3

IVP, intravenous pyelogram; N/A, not available; Schisto, schistosomiasis.
[a]Data extracted from figures in article using ImageJ software (US National Institutes of Health). [b]Follow up study in the Msambweni project. [c]Original study included adults. Data reported in this table are only for pediatric patients <21 y old. [d]Data provided in italics are for the whole study population including adults. These statistics are not provided for the pediatric subpopulation. Total population and female ratio not reported in summary articles. [e]This population was endemic for *S. mansoni* rather than *S. haematobium* with a 91.9% prevalence of *S. mansoni*.

reported a prevalence >10.0%. The prevalence of hydronephrosis was 0–38.0% (average 11.3%), the prevalence of hydroureter was 0–26.4% (average 7.5%), and the prevalence of major kidney abnormalities was 0–0.8% (average 0.1%).

Studies used either intravenous pyelogram or ultrasound (USS). Intravenous pyelogram was completed in hospitals or clinics. USS was usually completed in the field. Five of the USS data sets stated that a radiologist performed the test. In other studies, the investigators performed the USS. None of the studies described the training of USS technicians or operators. Abnormal findings were reported differently in the various studies, but abnormalities invariably fell into one of three

Table 2. Urine proteinuria and hematuria from included studies

Study	Year	Dipstick proteinuria	Dipstick hematuria	Explanatory factors
Benin (24)	2000	NA/395 (43.0%)	NA/395 (43.0%)	*S. haematobium* infection status (*P* = N/A)
Kenya (49)	1979	123/390 (31.5%)	211/390 (54.1%)	Intensity of *S. haematobium* infection (*P* = N/A)
Kenya (37)	1983	NA/121 (55.0%)	NA/121 (67.0%)	Intensity of *S. haematobium* infection (*P* = N/A)
Kenya (31,32)	1984	NA/2,609 (56.0%)	NA/2,609 (54.0%)	Intensity of *S. haematobium* infection (*P* = N/A)
Kenya (31,32)	1985	NA/2,035 (26.0%)	NA/2,035 (16.0%)	Intensity of *S. haematobium* infection (*P* = N/A)
Kenya (33,38)	1986	NA/NA (18.0%)	NA/NA (22.0%)	*S. haematobium* infection status (*P* = N/A)
Kenya (33,38)	1987	NA/NA (16.2%)	NA/NA (19.0%)	*S. haematobium* infection status (*P* = N/A)
Kenya (33,38)	1988	NA/NA (22.0%)	NA/NA (27.2%)	*S. haematobium* infection status (*P* = N/A)
Kenya (30)	1988B	N/A	NA/274 (53.0%)	Intensity of *S. haematobium* infection (*P* = N/A)
Kenya (33,38)	1989	NA/NA (34.0%)	NA/NA (33.0%)	*S. haematobium* infection status (*P* = N/A)
Kenya (33,38)	1990	NA/NA (28.9%)	NA/NA (29.8%)	*S. haematobium* infection status (*P* = N/A)
Kenya (33,38)	1991	NA/NA (25.3%)	NA/NA (22.0%)	*S. haematobium* infection status (*P* = N/A)
Kenya (28)	1994	76/418 (18.2%)	N/A	Malaria infection (*P* < 0.05)
Kenya (39)	1997	9/403 (2.2%)	14/403 (3.5%)	No positive associations identified
Liberia (45)	1983	118/267 (44.2%)	139/267 (52.1%)	*S. haematobium* infection status and intensity. Proteinuria among 12.8% of uninfected and 57.1% of infected. Hematuria among 12.8% of uninfected and 68.3% of infected
Mali (47,48)	1997	232/428 (54.2%)	182/428 (58.4%)	*S. haematobium* infection status (*P* = N/A)
Niger (46)	2008A	N/A	NA/1,642 (53.3%)	*S. haematobium* infection status and intensity (*P* < 0.03)
Niger (46)	2008B	N/A	NA/1,436 (6.0%)	*S. haematobium* infection status and intensity (*P* < 0.03)
Nigeria (42)	1994	102/2,169 (4.7%)	12/2,169 (0.6%)	Proteinuria: younger age (greatest in 13–14 y old, declined up to 19 y old) (*P* = N/A). Hematuria: female sex (*P* = N/A)
Nigeria (18)	2008	N/A	48/894 (5.4%)	*S. haematobium* infection status (*P* = N/A). Sickle cell anemia (1 subject). Acute glomerulonephritis (1 subject)
Nigeria (40,41)	2010	408/820 (49.8%)	11/820 (1.3%)	Proteinuria: hypertension (OR = 5.4, 95% CI = 1.8–16.2, *P* = 0.001). Older age (higher in 15–17 y old compared to 10–14 y old). Hematuria: none noted
Tanzania (45)	1983	201/548 (36.7%)	181/548 (33.0%)	*S. haematobium* infection status and intensity. Proteinuria among 17.6% of uninfected and 82.1% of infected. Hematuria among 10.9% of uninfected and 85.8% of infected
Zimbabwe (19)	2004	NA/551 (52.0%)	N/A	*S. haematobium* infection status (*P* = N/A)
Pooled prevalence		32.5% (2.2–56.0%)	31.1% (0.6–67%)	*S. haematobium* infection status and intensity, malaria infection, sickle cell anemia, acute glomerulonephritis, hypertension, female sex, and age

CI, confidence interval; N/A, not available; OR, odds ratio.

categories: hydronephrosis, hydroureter, or major kidney abnormality. All imaging studies were completed in populations endemic for *S. haematobium*. In 12 of the data sets, all subjects underwent imaging, whereas only a randomly selected subgroup of study subjects underwent imaging in the other 6 data sets.

Association With *S. haematobium* Infection

See **Table 5** for details of the relationship between *S. haematobium* prevalence and kidney disease. The majority of the studies investigating pediatric kidney disease in SSA were performed in areas with a high prevalence of *S. haematobium* (15.0–93.8%). Two studies had a prevalence of 0–5% (18,27), and three did not record the prevalence of *S. haematobium* (39–42). In Niger, investigators found significantly more hydronephrosis (38.0%) in an area with a high prevalence of *S. haematobium* (69.0%) compared to the amount of hydronephrosis (12.5%) in an area without any *S. haematobium* (27). Other studies documented the decrease in prevalence of kidney disease after treatment for *S. haematobium* (31–33,38,46).

For data sets that reported proteinuria, there was not a clearly defined association between schistosomiasis prevalence and prevalence of proteinuria, but an increasing *S. haematobium endemicity* was generally associated with a higher prevalence of proteinuria as seen in **Table 5**. Two notable outliers from this trend were Okpere who found a 49.8% prevalence of proteinuria in a population that was not endemic for schistosomiasis (40,41) and Warren who found a 31.5% prevalence of proteinuria despite a 83.6% prevalence of *S. haematobium* (49).

All studies that investigated the association between proteinuria and *S. haematobium* infection found that *S. haematobium* status and/or intensity were associated with proteinuria. For example, in the first year of the Msambweni project in Kenya (31,32), the prevalence of proteinuria was 15.0% among uninfected schoolchildren and 74.0% among infected children. Moreover, when students were treated for schistosomiasis, the prevalence of proteinuria decreased in the overall study

Table 3. Serum creatinine data from included studies

Study	Year	Creatinine (μmol/l)
Kenya (28)	1994	"All values were found to be within normal range"[a]
Nigeria (44)	1980	Range 30–82[b]
Nigeria (42)	1994	All measurements <115[c]
Nigeria (18)	2008	Range 71–108 (mean 83.3)[d]

[a]Direct quote from study manuscript. No median, mean, or range provided in study manuscript. No specification of normal reference range provided. [b]Only tested in 69 boys (7–17 y old) selected for intense schistosomiasis infection. No median or mean provided in study manuscript. Normal reference range was stated as 9–124 μmol/l. [c]Only tested in those with previously identified kidney abnormalities (e.g., hematuria or proteinuria). Serum creatinine was measured both at the beginning of the study and after 1 y of follow up. No median, mean, or range provided in study manuscript. Normal reference range was stated as <115 μmol/l. [d]Only tested in those with schistosomiasis infection. Normal reference range was stated as 50–110 μmol/l.

population the following year (from 56.0% before treatment to 26.0% after treatment) along with the prevalence of schistosomiasis (from 69.4% before treatment to 19.0% after treatment).

For studies of hematuria, a similar association with *S. haematobium* prevalence was observed. All studies that investigated hematuria and *S. haematobium* found an association between the two. Again, the Msambweni project is a case in point (32). The prevalence of hematuria was 6.0% among uninfected subjects and 76.0% among infected subjects. One year after treatment, the population prevalence of hematuria in the overall population decreased (from 54.0% before treatment to 16.0% after treatment) along with the prevalence of schistosomiasis (from 69.4% before treatment to 19.0% after treatment) (31,32). Tohon also observed this phenomenon. One year after treatment for *S. haematobium*, the prevalence of hematuria decreased (from 60.2% before treatment to 6.4% after treatment) along with the *S. haematobium* prevalence (from 75.7% before treatment to 38.0% after treatment) (46).

In imaging studies, the association between *S. haematobium* infection and imaging abnormalities was not as consistent. Some studies showed a high prevalence of *S. haematobium* (19.7, 38.0, 59.0, and 75.7%) but a very low prevalence of abnormal imaging (0.5, 0.6, 0.9, and 4.2%) (24,34,36,46). One study (35) found no association between *S. haematobium* infection and imaging abnormalities at all. This was in contrast to 17 other data sets which identified an association between imaging abnormalities and *S. haematobium* infection. Improvement in imaging abnormalities after treatment was also variable, with some studies demonstrating variable improvement in imaging (20) and others failing to show improvement (31,32).

Only one study examined the relationship between *S. mansoni* infection and kidney disease (28). The population studied had a very high prevalence of *S. mansoni* (91.9%) and no *S. haematobium* (0%). They found pathologic proteinuria (≥200 mg/l) in 18.2% of the children, and a normal SCr in all children. Despite setting their limit for pathologic proteinuria higher than other studies (≥200 mg/l rather than 30 mg/l), they still identified a significant amount of kidney disease. They reported no association between *S. mansoni* infection intensity and kidney function or proteinuria in these subjects. However, the prevalence of *S. mansoni* was so high that the power to detect pathologic differences between children with and without *S. mansoni* infection was very low.

DISCUSSION

Markers of kidney disease are very common among children living in of SSA. In the community-based studies that we reviewed, average proteinuria prevalence was 32.5% (2.2–56.0%), average hematuria prevalence was 31.1% (0.6–67%), and imaging abnormalities were found in 14.8% (0.5–38.0%). This is higher than the degree of damage identified in adults both in the United States (50) and SSA (2). It is much higher than the amount of disease identified in children in the United States (51–53). Data from the US National Health and Nutritional Examination Survey identified microalbuminuria in 9.9% of children between 6 and 19 y old (52). In a larger study of school children in the United States, Dodge *et al.* found that cumulative proteinuria and hematuria amounted to only 6.0% (54).

Proteinuria, in particular, seems to be common among African children. Except for two lower outliers, proteinuria was found in 16.2–56.0% of children. Unfortunately, none of the studies used the gold-standard measurement of albumin-creatinine ratio to diagnose albuminuria. This amount of proteinuria is substantially more than the amount of proteinuria in children (9.9%) and adults (9.2%) from the United States (50,52) and is also higher than adults from SSA (6–24%) (2). Albuminuria in adults is known to increase a patient's risk of cardiovascular disease and mortality (55), but these associations have primarily been observed in high-income countries. The long-term implications of pediatric albuminuria are still unclear in high-income countries, and the significance of such high levels of proteinuria in children from SSA is even more obscure. Specifically, we do not know if community dwelling children in SSA with proteinuria will progress to end stage renal disease or whether it will lead to increased risk of cardiovascular disease and death. Prospective long-term cohort studies are needed to define the outcomes of these patients.

Genitourinary imaging abnormalities were common among included studies. All but five studies had imaging abnormalities that were greater than 10%. The degree of hydronephrosis and hydroureter in particular were very high in some studies. Some of these abnormalities were reversible after treatment for schistosomiasis, but many were not. While the number of major abnormalities (nonfunctioning or missing kidney) was very low (<1%), a high prevalence of hydronephrosis is worrisome. The effects of obstructive uropathy in high-income countries are more often observed in young children from anatomic congenital disease of the urinary tract or elderly males from prostatic hypertrophy, but chronic partial obstruction of the ureter from any cause will result in deterioration of renal function (56,57). The ongoing damage caused to the kidney by the obstruction involves a complex interplay of physics and molecular inflammatory signaling that can lead to progressive kidney disease, especially when the damage has been acquired in childhood (58). Screening renal USS and regular follow up of renal function and obstructive pathology in SSA, especially

Table 4. Imaging data from included studies

Study	Year	Test	Abnormal (%)	Specific findings	Explanatory factors
Benin[a] (24)	2000	USS	2/389 (0.5%)[b]	Hydronephrosis: 2/389 (0.5%) Hydroureter: 2/389 (0.5%)	*S. haematobium* ($P = 0.005$). Male sex ($P < 0.001$)
Cameroon[a] (26)	1989	USS	51/212 (24.1%)[c]	Grade 1 hydro: 31/212 (14.6%) Grade 2 hydro: 44/212 (20.8%) Grade 3 hydro: 1/212 (0.5%) NB: 25/212 had bilateral disease Hydronephrosis: 3/212 (1.4%)	*S. haematobium* infection and intensity (P = N/A). Kidney lesions in 5% of uninfected and 48% of infected
Kenya[d] (37)	1983	IVP	3/20 (15.0%)[c]	Hydronephrosis: 2/20 (10.0%) Hydroureter: 2/20 (10.0%)	Intensity of *S. haematobium* infection (P = N/A)
Kenya[d] (31,32)	1984	USS	NA/363 (14.0%)	Hydronephrosis: NA/363 (14.0%)	*S. haematobium* infection and intensity ($P < 0.03$)
Kenya[d] (31,32)	1985	USS	NA/363 (16.0%)	Hydronephrosis: NA/363 (16.0%)	*S. haematobium* infection and intensity ($P < 0.03$)
Kenya[a] (34,36)	2004	USS	14/1,589 (0.9%)	Hydronephrosis: 14/1,589 (0.9%) Ectopic/missing kidney: 5/1,589 (0.3%)	*S. haematobium* infection and intensity (P = N/A)
Mali[a] (29)	1994	USS	104/504 (21.0%)[b]	Hydronephrosis: 65/504 (13.0%) Hydroureter: 104/504 (21.0%)	*S. haematobium* ($P < 0.03$)
Mali[a] (47,48)	1997	USS	107/428 (25.0%)[b]	Hydronephrosis: 63/428 (14.7%) Hydroureter: 107/428 (25.0%)	*S. haematobium* ($P < 0.0001$). Adolescent age >10 y ($P < 0.001$)
Niger[a] (27)	1986A	USS	49/129 (38.0%)[c]	Mild hydro: 54/129 (41%) Moderate hydro: 15/129 (12%) NB: 20/129 had bilateral disease	*S. haematobium* ($P < 0.001$). Moderate hydronephrosis more common in boys ($P < 0.01$).
Niger[a] (27)	1986B	USS	5/40 (12.5%)[c]	Mild hydro: 7/40 (17%) Moderate hydro: 0/40 (0%) NB: 2/40 had bilateral disease	*S. haematobium* ($P < 0.001$)
Niger[d] (35)	1989	USS	20/130 (15.4%)[c]	Mild hydro: 29/130 (22.3%) Mod hydro: 15/130 (11.6%) Major hydro: 3/130 (2.3%) NB: 27/130 had bilateral disease	None noted
Niger[a] (46)	2008A	USS	NA/NA (4.2%)[b]	Hydronephrosis: NA/NA (4.2%) Hydroureter: NA/NA (4.1%)	*S. haematobium* infection and intensity ($P < 0.03$). Older age ($P < 0.03$)
Niger[a] (46)	2008B	USS	NA/NA (0.6%)[b]	Hydronephrosis: NA/NA (0.6%) Hydroureter: NA/NA (0.3%)	*S. haematobium* infection and intensity ($P < 0.03$). Older age ($P < 0.03$)
Nigeria[a] (25)	1965	IVP	14/78 (17.9%)	Hydroureter: 14/78 (17.9%)	More common in boys (63.9% of boys, 35.7% of girls). Intensity of *S. haematobium* infection (P = N/A)
Nigeria[a] (43)	1975	IVP	26/314 (8.3%)[b]	Hydronephrosis: 20/314 (6.4%) Hydroureter: 26/314 (8.3%) Ectopic/horseshoe kidney: 2/314 (0.6%)	Intensity of *S. haematobium* infection (P = N/A)
Tanzania[a] (22,23)	1964	IVP	41/405 (10.1%)[b]	Hydronephrosis: 33/405 (8.1%) Hydroureter: 41/405 (10.1%) Nonfunctioning kidney: 1/405 (0.2%)	*S. haematobium* (P = N/A)
Tanzania[d] (21)	1966	IVP	14/88 (15.9%)[e]	Hydronephrosis: 5/88 (5.7%) Hydroureter: 9/88 (10.2%)	*S. haematobium* (P = N/A)
Tanzania[d] (20)	1969	IVP	64/242 (26.4%)	Hydronephrosis: 45/242 (18.6%)[f] Hydroureter: 64/242 (26.4%)[f] Nonfunctioning kidney: 2/242 (0.8%)	*S. haematobium* (P = N/A)
Pooled prevalence			14.8% (0.5–38.0%)	Hydronephrosis: 11.3% (0–38.0%) Hydroureter: 7.5% (0–26.4%) Major abnormality: 0.1% (0–0.8%)	*S. haematobium* infection status and intensity, male sex, and increasing age

CI, confidence interval; IVP, intravenous pyelogram; N/A, not available; NB, nota bene; OR, odds ratio; USS, ultrasound.
[a]Imaging performed on whole study population. [b]No explicit mention of whether lesions cooccur, therefore the greatest number of single lesions was taken as a conservative estimate of the prevalence of abnormal imaging to avoid overestimation. [c]Total prevalence of imaging abnormalities lower than cumulative number of individual abnormalities because of children with bilateral abnormalities. [d]Imaging performed on random sample of study population. [e]Lack of cooccurrence clearly stated. [f]Bilateral lesions in the same patient counted separately resulting in overestimate of prevalence.

Table 5. Relationship between *S. haematobium* and markers of renal disease

Study	Year	Schistosomiasis prevalence (%)	Hematuria (%)	Proteinuria (%)	Abnormal imaging (%)
Niger (27)	1986B	0	N/A	N/A	12.5
Nigeria (18)	2008	5.2	5.4	N/A	N/A
Kenya (33,38)	1986	15.2	22.0	18.0	N/A
Kenya (33,38)	1987	17.1	19.0	16.2	N/A
Kenya (33,38)	1991	17.2	22.0	25.3	N/A
Kenya (31,32)	1985	19.0	16.0	26.0	16.0
Benin (24)	2000	19.7	43.0	43.0	0.5
Kenya (33,38)	1990	21.2	29.8	28.9	N/A
Kenya (33,38)	1988	23.2	27.2	22.0	N/A
Tanzania (45)	1983	29.6	33.0	36.7	N/A
Kenya (33,38)	1989	29.9	33.0	34.0	N/A
Niger (46)	2008B	38.0	6.4	N/A	0.6
Kenya (34,36)	2004	59.0	N/A	N/A	0.9
Zimbabwe (19)	2004	59.7	N/A	52.0	N/A[b]
Nigeria (43)	1975	59.9	N/A	N/A	8.3
Tanzania (20)	1969	60.7	N/A	N/A	26.4
Kenya (30)	1988B	64.8	53.0	N/A	N/A[b]
Tanzania (21)	1966	65.0	N/A	N/A	15.9
Kenya (37)	1983	66.9	55.0	67.0	15.0
Niger (27)	1986A	69.0	N/A	N/A	38.0
Kenya (31,32)	1984	69.4	54.0	56	14.0
Liberia (45)	1983	70.8	52.1	44.2	N/A
Cameroon (26)	1989	71.7	N/A	N/A	24.1
Mali (29)	1994	75.0	N/A	N/A	21.0
Niger (46)	2008A	75.7	60.2	N/A	4.2
Kenya (49)	1979	83.6	54.1	31.5	N/A[b]
Tanzania (22,23)	1964	87.1	N/A	N/A	10.1
Nigeria (25)	1965	91.0	N/A	N/A	17.9
Niger (35)	1989	93.8	N/A	N/A	15.4[a]
Mali (47,48)	1997	52.8–74.2	58.4	54.2	25.0

Studies have been arranged in ascending order of schistosomiasis prevalence.
N/A, not available.
[a]This study did not find a positive association between schistosomiasis and ultrasound findings. [b]These studies reported imaging results, but only in a nonrandom subpopulation and therefore their results are excluded from analysis.

in communities where *S. haematobium* is common, might allow for early identification and treatment of underlying causative factors. This could prevent further damage and progression to more advanced CKD. Such a preventive measure is all the more important in a location with little to no access to renal replacement therapy.

Markers of kidney disease in children in SSA appear to be strongly associated with schistosomiasis. All studies found *S. haematobium* to be associated with hematuria and proteinuria if investigators tested for both *S. haematobium* and urine abnormalities. When tests were repeated at the same location in consecutive years after treatment for *S. haematobium*, a lower prevalence of proteinuria and hematuria was consistently discovered (30,31,33,38,46). The association between *S. haematobium* and urine abnormalities has been known for some time, and the presence of hematuria on dipstick has been proposed as a fairly reliable and cheap method for diagnosing *S. haematobium* (59). It is also known that *S. haematobium* can lead to proteinuria and obstructive uropathy, although the long-term progression of urinary schistosomiasis is still debated (60). Even if the hematuria, proteinuria, and obstructive uropathy from urinary schistosomiasis are reversible (after treatment for schistosomiasis), the question remains whether pediatric patients have sustained baseline kidney injury, leaving them more vulnerable to later damage from other noncommunicable diseases that are highly prevalent in low-income countries. Regular treatment of schistosomiasis in school

children and eradication campaigns must remain a priority in areas where *S. haematobium* is highly prevalent.

Very few studies attempted to investigate the kidney function of pediatric patients, and none of these studies determined an eGFR. Among the four studies in which kidney function was assessed, SCr was the only method used. Only one study with 418 subjects tested SCr in all participants. The other three confined SCr testing to a small subgroup at higher risk for kidney dysfunction (high intensity *S. haematobium* infection, or concurrent proteinuria/hematuria). All of the studies reported creatinine as normal range for participating children, but they used a generous assessment for their range of normal and did not adjust their results for age, weight, or malnutrition status. Some of these values may represent a low eGFR, particularly if children were malnourished. SCr alone is a poor marker of renal function in children, especially in populations that are frequently undernourished with lower muscle mass (61). At a minimum, future studies ought to check SCr in all children and calculate an eGFR to correct for the height, age, and sex of the child. Ideally, eGFR equations should be validated in a cohort of children living in SSA rather than depending on formulae that were derived and validated using children from high-income countries.

Other well known risk factors for kidney disease are likely common among children in SSA (HIV, streptococcus, sickle cell disease, diabetes, and hypertension). None of these were systematically investigated in these studies. None of the studies, for example, intentionally included children with HIV who can have a prevalence of kidney disease as high as 31.6% (62,63). More studies are needed to investigate the relative contribution of these other risk factors to the overall burden of kidney disease in children.

The quality of the studies that we identified in this systematic review was generally moderate to poor. Less than half were completed in the past 20 years. Only four measured SCr, and none calculated a eGFR or other measure of kidney function. Studies that investigated proteinuria overwhelmingly used urine dipsticks to detect urine protein concentration rather than the gold-standard albumin creatinine ratio (61). For pediatric imaging, a number of different scales were used for grading, and reporting was not consistent across studies. The time between kidney injury and kidney damage or dysfunction could not be estimated because the majority of the studies were cross-sectional. These all point to the need for a large scale, intensive prospective cohort study in SSA to examine the degree of kidney disease in the pediatric population, provide a measure of the incidence and natural history of kidney disease at a population level, and clearly identify the contribution of different risk factors towards the overall burden of kidney disease.

In conclusion, this systematic review identified a substantial burden of kidney disease in community dwelling pediatric patients living in SSA. Proteinuria ranged from 2.2 to 56.0% (32.5%), and imaging abnormalities ranged from 0.5 to 38.0% (14.8%). Schistosomiasis was the primary risk factor identified. Screening and mass treatment for schistosomiasis ought to remain a public health priority in order to prevent cumulative renal injury in children. USS screening should be used to identify obstructive lesions. In addition, there is an urgent need for large, high quality, prospective data examining the prevalence and progression of kidney disease among children in SSA, and factors other than schistosomiasis which might be important and preventable risk factors.

METHODS

We completed a systematic review of the literature between March and June 2013 to better understand the prevalence of kidney disease in children living in SSA. An information specialist created a detailed search algorithm with input from two board certified pediatricians that combined the following search concepts: "pediatric" AND "kidney diseases" AND "sub-Saharan Africa" AND "epidemiology." We used Ovid to search both Medline and Embase, selecting controlled vocabulary appropriate to each database. We did not limit the search by study design, date of publication, or language. The search strategies for Medline and Embase are provided in **Supplementary Appendix S1** online. We identified further studies by looking at the reference lists of both review articles and articles that we selected for inclusion in the final analysis. We also looked in Scopus and Web of Science for references which cited the articles that we selected for analysis. Articles in languages other than English were translated by research personnel fluent in that language.

Studies were included if they enrolled a community-dwelling population (rather than a health facility–based population), if they enrolled pediatric patients (<21 y old), if they were performed among black Africans living in SSA, and if they reported an objective measure of kidney function or damage. Acceptable measures of kidney function or damage were SCr, eGFR, urine protein or urine red blood cells (either qualitative or quantitative), USS or intravenous pyelogram of the kidney and ureter, or kidney biopsy. Studies were excluded if they enrolled a combined population (e.g., adults and children, black Africans and other ethnic groups) and did not report outcomes separately for the patients of interest.

References were evaluated by two investigators independently for inclusion in analysis. First references were excluded based on title and abstract. Those which remained were reviewed in full text. Data were extracted from included articles using a standardized questionnaire. For four references (33,34,38,42), data were only available in figures. For these, ImageJ64 (free share software, United States National Institutes of Health, Bethesda, MD) was used to change data into tabular format. If the same data set was reported in two publications, these were combined. If a publication reported data from distinct geographic areas or separate study years, the data sets were reported separately in the results tables.

Differences between investigators were resolved through discussion with a third investigator. Data were entered from the questionnaires into a Microsoft Excel spreadsheet. Assessment of potential selection bias was completed using a three point scale with 1 being a perfectly designed, randomly selected, representative sample of the population, 2 being an imperfectly designed, nonrandom sample of the population, and 3 being a hospital-based, highly biased sample. Measurement bias was graded on a similar three point scale with a score of 1 equivalent to an extremely accurate test of kidney function (clearance of inulin or nuclear clearance scan), 2 being a quantitative test for kidney damage or function, and 3 being a qualitative test of kidney function or damage.

SUPPLEMENTARY MATERIAL

Supplementary material is linked to the online version of the paper at http://www.nature.com/pr

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