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Estimation of childhood nephrotic syndrome incidence: data from the atlanta metropolitan statistical area and meta-analysis of worldwide cases

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Abstract

Background—Epidemiological data on childhood idiopathic nephrotic syndrome (INS) are limited. We estimated childhood INS incidence in a racially and ethnically diverse U.S. population and performed a meta-analysis of published reports to examine differences by race, ethnicity, and time.

Methods—One hundred seventy-five children aged 1–17 years living in the Atlanta Metropolitan Statistical Area (MSA) between 2013 and 2018 were identified by retrospective chart review. Annual INS incidence was estimated by dividing cases by population data from the Georgia Department of Public Health. We calculated pooled incidence estimates using random-effects regression models in a meta-analysis of the current and prior studies. Subgroup incidence estimates by race, ethnicity, and time were compared and tested for heterogeneity.

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Author contributions Research idea and study design: JL, CW, LG, EA, LP; data acquisition: JL, CW; data analysis/interpretation: JL, CW, CM; statistical analysis: CM, SG; supervision or mentorship: CW, LG, EA, LP. Each author contributed important intellectual content during manuscript drafting or revision, accepts personal accountability for the author's own contributions, and agrees to ensure that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved.

Code availability Not applicable.

Conflicts of interest E.J.A has received personal fees from AbbVie, Pfizer, and Sanofi Pasteur for consulting, and his institution receives funds to conduct clinical research unrelated to this manuscript from MedImmune, Regeneron, PaxVax, Pfizer, GSK, Merck, Novavax, Sanofi Pasteur, and Micron.

Ethics approval Waiver of informed consent for minimal risk obtained from Emory IRB prior to data collection.

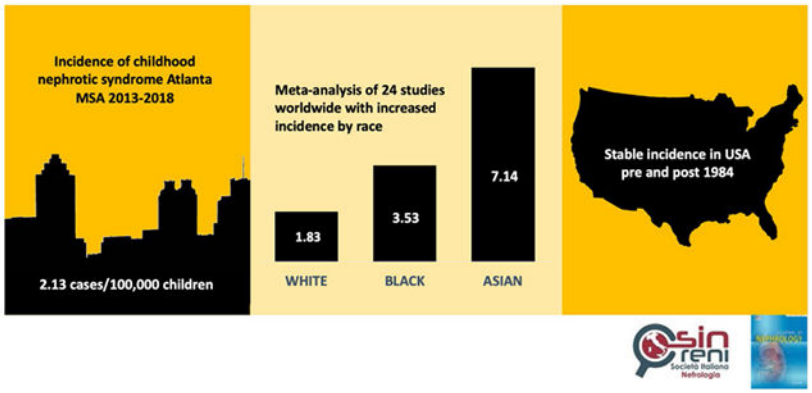
Consent to participate Not applicable.

Consent to publication Not applicable.

Results—One hundred seventy-five children aged 1–17 were diagnosed with INS between 2013 and 2018 in the Atlanta MSA. Average annual incidence was 2.13/100,000 (95% CI, 1.83–2.47). Twenty-four studies were included in meta-analysis. Our study was the only one to report incidence for Hispanic children, 2.13/100,000/y (95% CI, 1.40–3.10). In meta-analysis, incidence was highest in Asian children (7.14/100,000/y; 95% CI, 4.73–9.54), followed by Black (3.53/100,000/y; 95% CI, 2.93–4.12), and Caucasian (1.83/100,000/y; 95% CI, 1.52–2.14). Annual incidence in the U.S. was stable comparing studies performed before and after 1984, 2.05 vs. 2.26/100,000 (p 0.08).

Conclusions—Risk of INS may be higher among Asian and Black children compared to White children. Incidence appears stable over time in the U.S. Future studies should use standardized methodology and assess the contribution of demographic and genetic factors to INS incidence and long-term outcomes.

Graphical Abstract



Keywords

Epidemiology; Incidence; Nephrotic syndrome; Meta-analysis

Introduction

Idiopathic nephrotic syndrome (INS) is one of the most common glomerular diseases in children, yet there are limited epidemiological data to understand the burden of INS. Incidence estimates vary widely, from 1.15 to 16.9 cases per 100,000 children per year worldwide, depending on country of origin and race [1]. In the United States (U.S.), epidemiologic studies of INS are extremely limited. The most frequently referenced U.S. incidence estimates are from two small single-center studies performed in the 1950s and 1960s in New York state[2, 3] and a Kansas City series of 86 patients diagnosed between 1984 and 1995 [4]. The annual incidence of nephrotic syndrome was estimated to be 2.2 cases per 100,000 children in Kansas City, with African-Americans found to have an increased disease incidence of 3.6 cases per 100,000 [4]. Data are limited on disease incidence among Asian and Hispanic children in the U.S. Increasing incidence of INS and the histological subtype of focal segmental glomerulosclerosis (FSGS) have been reported in two adult studies in the U.S, raising the possibility of evolving INS epidemiology

in U.S. children [5, 6]. In this study, we utilized our center's unique position as the only pediatric nephrology provider for the Atlanta Metropolitan Statistical Area (MSA) to provide contemporary childhood INS incidence estimates in a large, racially and ethnically diverse U.S. population. We additionally performed a literature search and meta-analysis of reported pediatric INS incidence estimates worldwide to determine whether the U.S. incidence has evolved over time and how incidence differs by race and ethnicity worldwide as a comparative set to our data.

Materials and methods

Setting and study design

The Atlanta MSA is a 29-county region surrounding the city of Atlanta, Georgia, and is the 9th largest MSA in the U.S. with 5.9 million people. Children make up 23% of the population, at 1.3 million, according to the Georgia Department of Health and Office of Health Indicators for Planning (OHIP). The population is racially and ethnically diverse, with 35% African American, 6% Asian, and 10% Hispanic [7]. The Children's Healthcare of Atlanta Children's Physician Group (CHOA-CPG) is the only pediatric nephrology practice in the Atlanta MSA since 2013 and operates the only children's hospitals in the Atlanta MSA. We retrospectively reviewed all inpatient and outpatient CHOA-CPG records to identify and describe all patients diagnosed with INS between 2013 and 2018 in the Atlanta MSA. The Atlanta MSA population demographic data during the same period was obtained through the Georgia Department of Health's online analytical statistical information system, OASIS. OASIS is an open access database that uses U.S. census data with interim yearly estimates based on OHIP data (https://oasis.state.ga.us/oasis/webquery/qryPopulation.aspx). This study was approved by the CHOA institutional review board.

Study population

Our study population included children > 1 and < 18 years of age living in the Atlanta MSA between 2013 and 2018. The number of children each year between 2013 and 2018 were obtained from OASIS and were used to determine the population at risk for developing INS during a single year (denominator).

Case identification

The annual number of Atlanta MSA children > 1 and < 18 years of age who developed INS between 2013 and 2018 were identified from CHOA-CPG records (numerator). Potential cases were identified using International Classification of Disease–9 and 10 (ICD9/10) codes for glomerular diseases: 580, 581, 582, 583 and N00, N01, N02, N03, N04, N05, N06, N07 in the outpatient and inpatient electronic medical records (Fig. 1). Each patient record identified by the ICD9/10 codes was then reviewed by at least one pediatric nephrologist (JL and/or CW) for inclusion. Cases were included if the patient resided in the Atlanta MSA at time of diagnosis, were diagnosed between 2013 and 2018, and were > 1 and < 18 years of age at time of diagnosis. INS was defined by documented edema, nephrotic range proteinuria [urine protein creatinine ratio (UPCR) > 2 mg/mg or 3 + protein on urine dipstick], and hypoalbuminemia [serum albumin < 2.5 g/dL]) on presentation. Exclusion criteria were secondary nephrotic syndrome (e.g., lupus nephritis)

based on clinical, serologic, or pathologic findings and those with end stage kidney disease (e.g., renal transplant status, chronic renal replacement therapy) at presentation. We tested the sensitivity of the selected ICD9/10 codes to identify INS cases by a manual review of all patients seen by the CHOA-CPG Nephrology Division during two selected time periods, January 2013 (ICD9 codes used) and January 2016 (ICD10 codes used). A total of 879 patients cared for in these two selected periods were reviewed. All 63 patients in January 2013 and 64 patients in January 2016 with nephrotic syndrome were identified by the ICD9/10 codes, giving a sensitivity of 100%. Demographic data at time of diagnosis were collected and included age at presentation, sex, race, and ethnicity.

Literature search

We performed a literature search for studies reporting the incidence of INS in children. With the support of our hospital librarian, Emily Lawson, we devised a search strategy. We searched PubMed and Embase databases from the establishment of each database to August 10, 2019. Specific search strategy results are described in Fig. 2. Search terms were nephrotic syndrome, children, incidence, and epidemiology. Abstracts were screened by JL for inclusion criteria which included: defining incidence (new cases in a population over a specified time) of INS in children 0–17 years in nationwide or a hospital-based population study in either a retrospective or prospective manner. We excluded studies of congenital or infantile nephrotic syndrome or secondary nephrotic syndrome. No restrictions were set for study type, publication type, or language. In those abstracts and manuscripts in other languages, we reviewed translated versions when available. Abstracts without available manuscripts and unpublished studies were excluded. Identified study's manuscripts were reviewed by JL, CW, and CM for inclusion criteria and extraction of data.

Statistical methods

Atlanta MSA INS incidence

Demographic characteristics were summarized using means and standard deviations for continuous variables and frequencies and percentages for discrete characteristics, as appropriate. Annual incidence for each observation year between 2013 and 2018 was calculated by the number of new cases of INS in persons > 1 and < 18 living in the Atlanta MSA (numerator), divided by the number of children > 1 and < 18 years of age in the Atlanta MSA (denominator), and multiplied by 100,000. Average annual incidence was calculated as an average of these yearly incidences over the 6 years of observation (2013–2018) and were accompanied by 95% Fisher's exact confidence intervals. Average annual incidences were calculated overall, by race, ethnicity, and age categories. To examine the possibility that patients living around the border of the Atlanta MSA may have been cared for at other centers, we performed a sensitivity analysis comparing the estimated incidence of INS in the Atlanta MSA versus a smaller 8-county region immediately surrounding CHOA-CPG, Health District 3 (HD3), Atlanta MSA vs. HD3 incidence estimates were compared using an incidence rate ratio. Additionally, incidence rate ratios and 95% Fisher's exact confidence intervals were calculated to compare racial and ethnic sub-groups. Incidences, rate ratios, 95% confidence intervals and p values were derived in OpenEpi v.3.01 (available at: www.OpenEpi.com).

Meta-analysis of INS in reported literature

Other INS incidence estimates were extracted from the literature and further categorized by race (Black, Asian, and Caucasian) and ethnicity (Hispanic versus non-Hispanic). If race information was not provided by the study, cases reported from studies done in Asia were assumed to be Asian (e.g., Taiwan and Japan). Due to the lack of standardization and reporting of confidence intervals around incidence estimates, incidence estimates were converted to number of cases per 100,000 persons or person-years. Pooled estimates of incidence were estimated using random effects regression models. Results were presented as number of cases per 100,000 persons accompanied by 95% confidence intervals. Incidence estimates were compared between different subgroups by computing pooled estimates within each subgroup and testing for significant heterogeneity between subgroup estimates.

U.S. incidence over time using Atlanta MSA data and meta-analysis

We specifically examined reported incidence from studies performed in the U.S., including the current study, in order to evaluate for change in incidence over time in the U.S. We subdivided the studies performed before and after 1984, based on equal numbers of studies published before and after this year. Incidence estimates for the two time periods were compared by computing pooled estimates within each period and testing for significant heterogeneity between subgroup estimates. All incidence estimates were computed using Comprehensive Meta-Analysis v.3.3 (Englewood, NJ) and statistical significance was assessed at the 0.05 level.

Results

Incidence of pediatric INS in the Atlanta MSA

Between January 1, 2013 and December 31, 2018, 175 children aged 1–17 years were diagnosed with INS in the Atlanta MSA. Demographic characteristics of incident patients are described in Table 1. Black (43%) and Asian (13%) children made up higher proportions of diagnosed patients compared to the general pediatric Atlanta MSA population of 37% Black and 6% Asian. The average annual incidence between 2013 and 2018 was 2.13 cases per 100,000 children (95% confidence interval [95% CI], 1.83–2.47). This was similar to the average annual incidence in HD3, which was 2.27 cases per 100,000 (95% CI, 1.90–2.69 $p = 0.615$).

Incidence of childhood INS by race and ethnicity in the Atlanta MSA (Fig. 3)

Disease incidence rate among Hispanic Atlanta MSA children was 2.13 cases per 100,000 children (95% CI, 1.40–3.10), which was not significantly different from non-Hispanic children. Asian children had the highest incidence rate at 5.04 cases per 100,000 (95% CI, 3.20–7.57) followed by Black children at 2.47 cases per 100,000 children (95% CI, 1.94–3.10). Both groups had statistically significant higher incidence compared to Caucasian children in the Atlanta MSA (incidence rate ratios [IRRs], 3.15 [95% CI, 1.88–5.12] and 1.55 [95% CI, 1.10–2.18], respectively).

Incidence of pediatric idiopathic nephrotic syndrome in reported literature

Twenty-three studies were included in the meta-analysis [2–4, 8–27]. Detailed descriptions of each included study and study findings are shown in Table 2. Studies reporting pediatric INS were found as early as 1940 and most recently from 2014. Studies were performed in Australia ($n = 1$), Canada ($n = 1$), France ($n = 2$), Germany ($n = 1$), Japan ($n = 1$), Kuwait ($n = 1$), Libya ($n = 1$), Netherlands ($n = 1$), New Zealand ($n = 1$), Saudi Arabia ($n = 1$), Singapore ($n = 1$), Taiwan ($n = 1$), United Kingdom ($n = 3$) and the United States ($n = 7$). Of note, we failed to find sub-Saharan African studies. There was a wide range of incidence reported in the individual studies: 1.15–11.6 per 100,000 children. Overall average incidence based on all 23 studies exclusive of our findings was 2.21 cases per 100,000 children (95% CI, 2.05–2.36), similar to our findings of 2.13 cases per 100,000 children (95% CI, 1.83–2.47).

Incidence of pediatric idiopathic nephrotic syndrome by race in meta-analysis

Including the current study, 13 of 24 studies (54%) included descriptive information on race. Our study is the only report that included incidence information on Hispanic ethnicity. Because our study is the only work reporting the incidence of Hispanic ethnicity, no meta-analysis could be performed on ethnicity. Ten of twenty-four studies (42%), including 3/7 (43%) from Europe, one from Canada (100%), and 6/8 (75%) from the U.S. estimated incidence rates by race. Two studies (one from Japan and one from Taiwan) did not sub-divide incidence by race, but all patients in those studies were assumed to be of Asian descent. In total, 12 studies with 7052 cases were used to generate childhood INS incidence estimates by race. Table 3 describes the incidence of childhood INS by race based on meta-analysis of 13 studies and 26 subgroups (including our study) [2–4, 9, 10, 16, 19–24]. Incidence rates by race are consistent with our Atlanta MSA data and show Asian children with the highest incidence (7.14 cases per 100,000 children; 95% CI, 4.73–9.54), followed by Black children (3.53 cases per 100,000 children; 95% CI, 2.93–4.12), and Caucasian children (1.83 cases per 100,000 children; 95% CI, 1.52–2.14).

Incidence of pediatric idiopathic nephrotic syndrome over time in the U.S. by meta-analysis

Incidence of INS in the U.S. from studies performed before 1984 and after 1984 are shown in Table 4. Incidence prior to 1984 was 2.05 cases per 100,000 children (95% CI, 1.85–2.25), compared to 2.26 cases per 100,000 (95% CI, 2.14–2.37) children after 1984; results were not different statistically ($p = 0.08$).

Discussion

We provided contemporary childhood INS incidence data of a large geographic region in the U.S., including incidence estimates by race and the first-known incidence estimate for Hispanic ethnicity, 2.13 cases per 100,000 children per year (95% CI, 1.40–3.10). We determined that the overall incidence estimates of INS in the Atlanta MSA from 2013 to 2018 were similar to aggregated estimate identified by meta-analysis of prior studies. In the U.S., incidence of childhood INS appears to be stable based on studies before and after 1984. In our dataset and in our meta-analysis, incidence varied significantly by race, with

Asian children having the highest incidence rates, followed by Black children, and finally Caucasian children.

Differences in childhood INS disease incidence among racial groups have been reported since the initial U.S. study in the 1940s, with higher incidence observed in non-white children compared to white children [2]. Since that time, variations in childhood INS incidence by geographical location and ethnicity have been documented, with increased incidence in South Asian children and African American children compared to Caucasian children, presumed to be due to a combination of environmental and genetic factors [4, 9, 16]. Rapidly advancing technology has identified genetic variants associated with INS, from monogenic gene mutations to single nucleotide polymorphisms in the major histocompatibility complex and risk alleles of the APOL1 gene [28]. Certain genetic variants are more prevalent in specific regions and racial groups (e.g., APOL1 risk alleles in those of African descent) [28, 29]. However, they explain only a small fraction of INS cases, primarily steroid-resistant type, and may not completely explain the differences in disease incidence between racial groups [28–30]. Polymorphisms in the major histocompatibility complex are associated with increased risk for steroid-sensitive nephrotic syndrome across racial and geographic populations [28, 31–34]. Genetic information is thus important to capture in epidemiologic studies going forward to gain a more complete understanding of possible genetic contributions to INS development.

The increase in disease risk for Black and Asian children compared to White children is important to recognize not only because it offers signals to possible genetic contributions to disease pathogenesis, but also because these minority groups have additional vulnerabilities. In the U.S., minority groups are disproportionally affected by health disparities which have been linked to poor outcomes [35]. To fully understand the morbidity and disease burden of INS, it is important to capture demographic and genetic information with long-term follow-up to examine how genetic and environmental/societal factors affect the outcomes of vulnerable populations. We plan to address these questions in follow-up studies in the Atlanta MSA.

We did not find a higher disease incidence of pediatric INS in the U.S. comparing studies performed before and after 1984. However, it is important to note that the U.S. studies included in this analysis were single-center studies and included a relatively small number of cases compared to modern studies in other countries. No national registry or database are available in the U.S., unlike Germany, Japan, The Netherlands, New Zealand and Taiwan [10, 13, 17, 19, 25]. Furthermore, in many of the studies, case and at-risk population identification methods were incompletely described. The degree of confidence around incidence estimates were not provided in any of the U.S. studies except the current study. These issues limit the validity of our analyses. To address these deficiencies, the U.S. needs a robust INS disease registry from which future studies can be drawn.

Our study has additional limitations. First, we were unable to confirm that our center was involved in the diagnosis of every pediatric case of INS within the Atlanta MSA between 2013 and 2018. Despite being the only pediatric nephrology practice in the Atlanta MSA, with the next closest practices crossing state lines (Chattanooga, Tennessee

[approximately 121 miles away] and Birmingham, Alabama [approximately 153 miles away]), it is conceivable that some patients may have been diagnosed and cared for by surrounding pediatric or adult practices. However, our sensitivity analyses estimating the incidence within the smaller eight-county region, HD3, for comparison, showed similar results, suggesting that we were successful in capturing nearly all Atlanta MSA cases. It is conceivable that we did not identify every INS case within our center, though this is unlikely: we performed a sensitivity testing of our case identification methods using broad and detailed ICD9/10 codes, which resulted in sensitivity of 100% (ICD 9 and 10). Our literature search was not a registered systematic literature review. While we did attempt to do a comprehensive review of the available literature, we did not perform the rigor of an official systematic review due to time and personnel constraints. In our meta-analysis, studies had variable inclusion criteria and reporting of incidence measures, case demographics, and population sizes (denominator data). The lack of standardization among the studies with high heterogeneity limited the validity of our findings. Future studies that include transparent population measurements, ethnic and racial patient breakdowns, and statistical analysis of incidence rates to include confidence estimates will hopefully improve our understanding of INS epidemiology in the US and Worldwide.

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Availability of data and materials

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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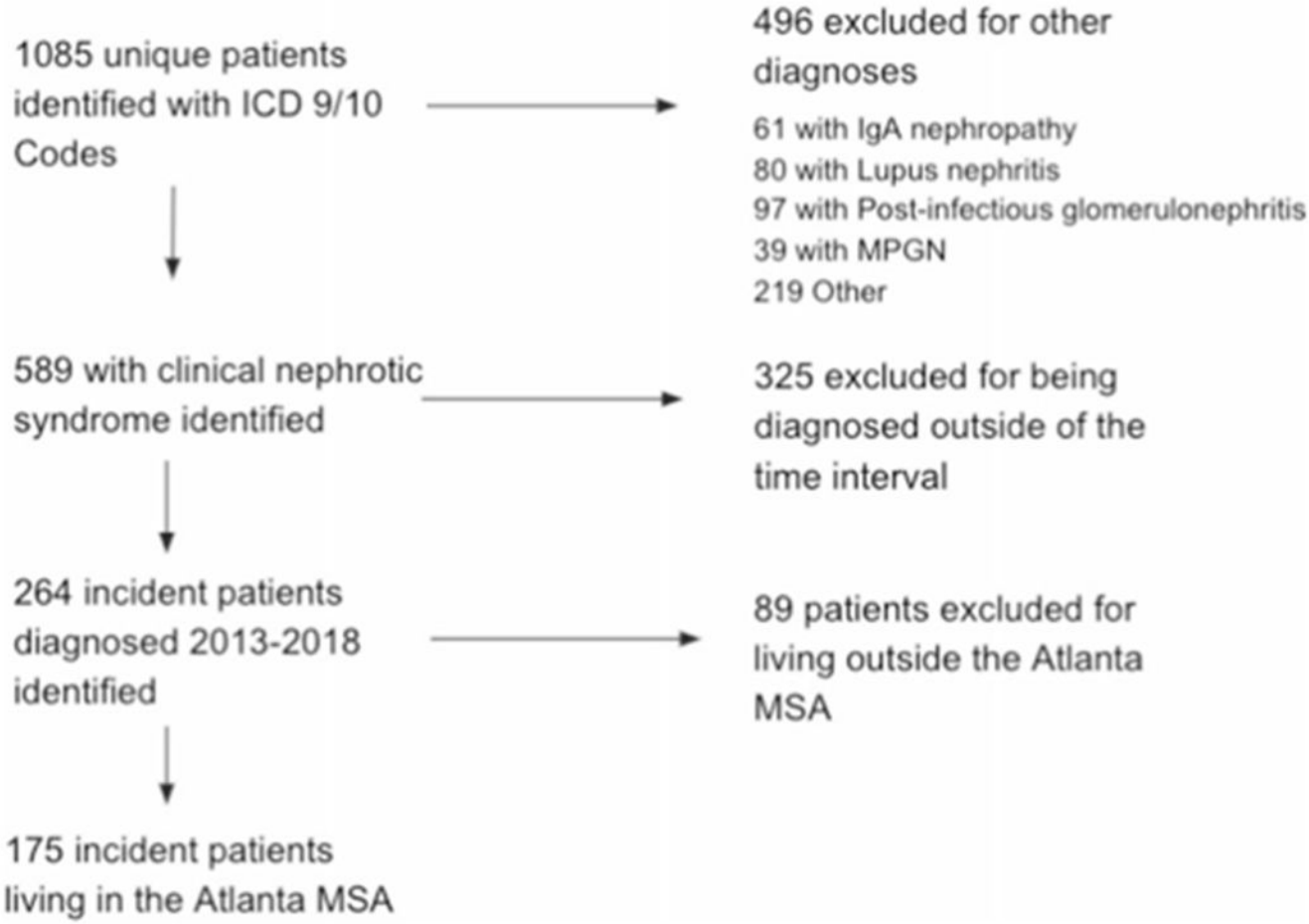

Fig. 1.

Identification of incident patients with childhood idiopathic nephrotic syndrome between 2013 and 2018 in the Atlanta MSA. *GN*glomerulonephritis, *MPGN* Membranoproliferative Glomerulonephritis

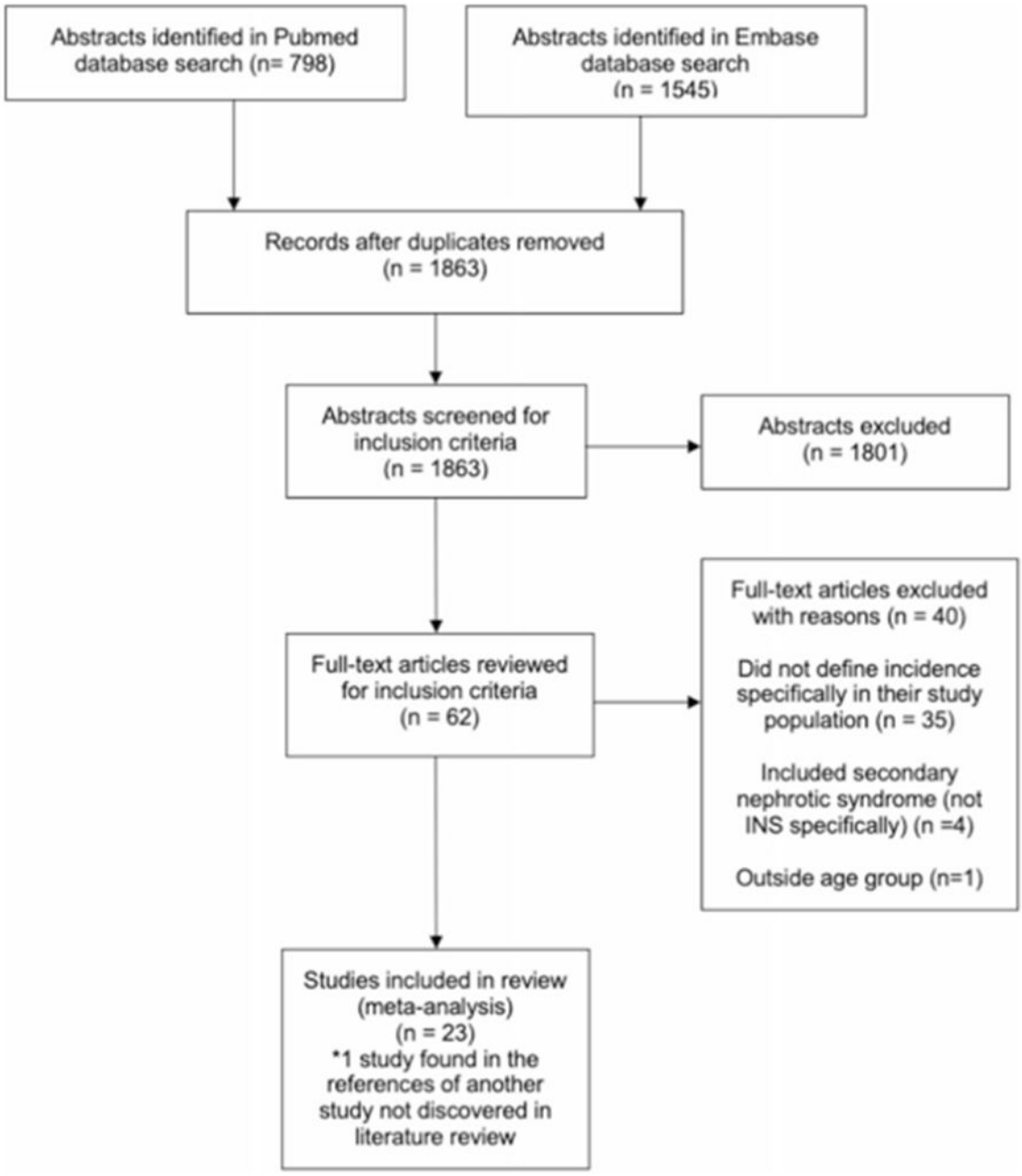

Fig. 2.

Literature search results for meta-analysis of epidemiologic studies of childhood idiopathic nephrotic syndrome

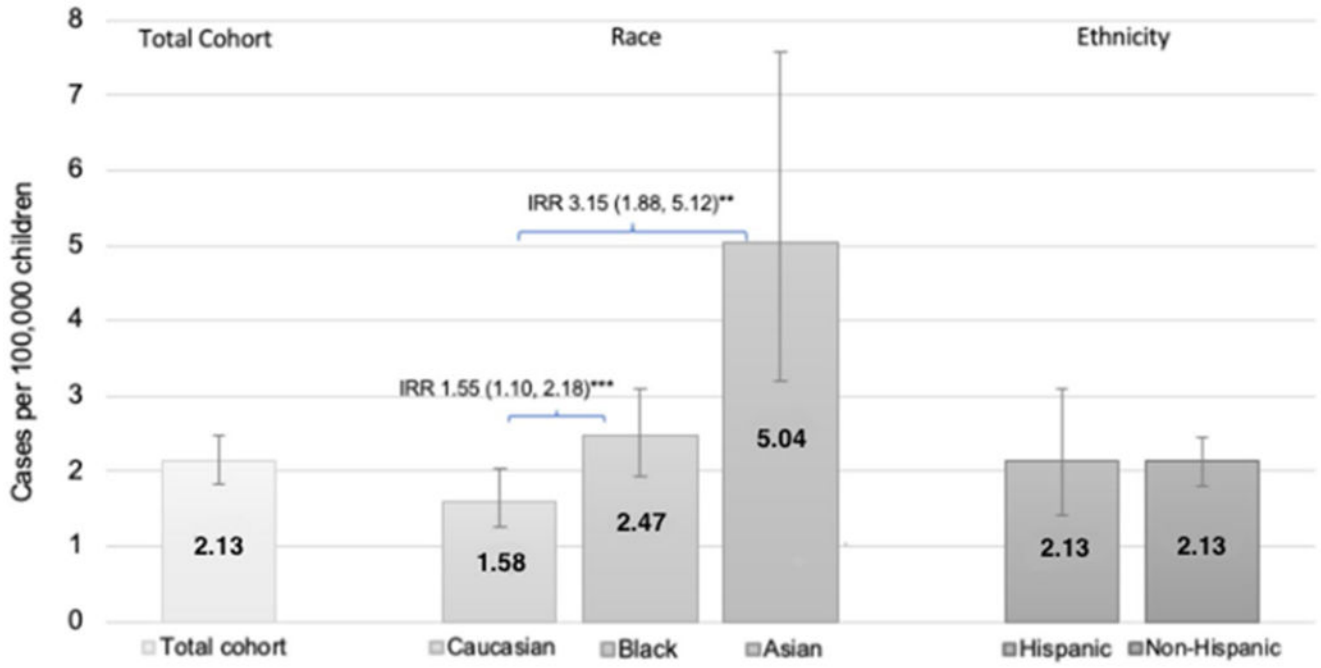

Fig. 3.

Average annual incidence of childhood nephrotic syndrome, overall and by demographic characteristics in the Atlanta MSA*. *Comparisons between subgroups are unadjusted incidence rate ratios with 95% confidence intervals. ** for $p < 0.001$ and *** for $p < 0.05$. *IRR* incidence rate ratio; *MSA* metropolitan statistical area

Table 1

Demographics of incident patients with childhood idiopathic nephrotic syndrome in the Atlanta MSA between 2013 and 2018

Demographics	**INS Cases *N* = 175**
Age of onset (years), Mean ± SD	6.9 ± 4.8
Age of onset	
1 year	9 (5%)
2–10 years	123 (70%)
11–17 years	43 (25%)
Sex	
Female	62 (35%)
Male	113 (65%)
Race *N* (%)	
Caucasian	69 (39%)
Black	75 (43%)
Asian	23 (13%)
Other	8 (5%)
Ethnicity *N* (%)	
Hispanic	27 (15%)
Non-Hispanic	148 (85%)

INS Idiopathic Nephrotic Syndrome; *MSA* metropolitan statistical area; *SD* standard deviation

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Table 2

Results of the literature search on incidence of nephrotic syndrome in children worldwide

Source	Study period	Country (area)	Number of patients	Male:Female	Age	Incidence (cases per 100,000 children per year)
Stickler et al. [24]	1940–1956	Buffalo, NY, USA	72	1.9:1	0–9 years	2.1
Schlesinger et al. [2]	1946–1962	Erie County, USA	86	3:1	0–16 years	2
Rothenberg et al. [3]	1949–1953	Ohio, USA	172	1:1	0–9 years	2.3
Chuan et al. [11]	1969–1973	Singapore		3.8:1	0–18 years	3.2
Wyatt et al. [26]	1970–1979	Kentucky, USA	34	2.1:1	1–10 years	1.8
Feehally et al. [16]	1973–1982	Leicestershire United Kingdom	43	Asian 2.0:1 Non-Asian 1.4:1	0–14 years	2.3
Sharples et al. [22]	1979–1983	Birmingham, United Kingdom	44	1.8:1	0–16 years	5.3
Elzouki et al. [14]	1980–1982	Benghazi, Libya	19	1.3:1	0–14 years	11.6
Zaki et al. [27]	1981–1985	Kuwait	55	1.8:1	0–12 years	6
Srivastava et al. [4]	1984–1995	Kansas City MSA, USA	86	1.5:1	0–16 years	2.2
McKinney et al. [21]	1987–1998	United Kingdom	194	1.6:1	0–15 years	2.3
Ernould et al. [15]	Jan 1992-June 2008	Gironde County, France	99	2:1	0–15 years	2.1
Banh et al. [9]	1993–2014	Toronto, Ontario, Canada	105	1.7:1	1–18 years	2.98
Kim et al. [20]	1994–2003	New Orleans, USA	210	1.1:1	1–17 years	2.3
Spencer et al. [23]	1996–2006	Shelby County, TN USA	28	3.8:1	0–9 years	2.4
Chang et al. [10]	1996–2008	Taiwan	4083	1.9:1	6 month-18 years	5.66
Hodson et al. [18]	Jul 1998-Dec 2000	Australia	135	1.2:1	3 months-15 years	1.15
Wong et al. [25]	2001–2004	New Zealand	49	2.5:1	3 month-15 years	1.9
El Bakkali et al. [13]	2003–2006	The Netherlands	231	2:1	0–18 years	1.52
Franke et al. [17]	2005–2006	Germany	347	1.8:1	0–18 years	1.2
Alhassan et al. [8]	2005–2010	Aljouf Region, Saudi Arabia	25	2:1	2–12 years	2 to 6
Dossier et al. [12]	2007–2010	Paris, France	180	1.8:1	6 month-15 years	3.35
Kikunaga et al. [19]	2010–2012	Japan	2099	1.9:1	6 month-15 years	6.49
Londeree et al. (this study)	2013–2018	Atlanta MSA, USA	175	1.8:1	1 year-17 years	2.13

Table 3

Childhood idiopathic nephrotic syndrome incidence estimates by race, meta-analysis of studies completed from 1946 to 2018 [2–4, 9, 10, 16, 19–24]

Race	Number of studies*	Incidence (cases /100,000/ year)	95% CI
Black**	6	3.53	2.93–4.12
Asian***	9	7.14	4.73–9.54
Caucasian****	11	1.83	1.52–2.14
Overall	26	2.26	1.99–2.54
Test for Heterogeneity			
Overall	$Q = 40.54$, df = 2, $p < 0.001$		
CAU vs. AD	$Q = 24.57$, df = 1, $p < 0.001$		
CAU vs. AS	$Q = 18.37$, df = 1, $p < 0.001$		

95% CI confidence interval; *CAU* Caucasian, *AD* African Descent, *AS* Asian Descent, *Q* Cochran's *Q* test for heterogeneity, *df* degrees of freedom

* Number of studies exceeds the total number of studies included because each study can contribute to more than one subgroup

** Includes Afro-Caribbean and African American Children

*** Includes East-Asian children in the UK, Japanese children, Taiwanese children, and children identified as Asian in the United Kingdom, the Netherlands, and Canada

**** Includes Caucasian/White children from the US, Caucasian or European children from Canada and the United Kingdom

Table 4

Childhood idiopathic nephrotic syndrome incidence estimates in the U.S. comparing reports before and after 1984

Study	Year	Incidence (cases/100,000/year)	95% CI
Before 1984		2.05	1.85–2.25
Stickler et al. [24]	1940–1956	2.10	2.09–2.11
Schlesinger et al. [2]	1946–1962	2.00	1.99–2.01
Rothenberg et al. [3]	1949–1953	2.30	2.29–2.31
Wyatt et al. [26]	1970–1979	1.80	1.79–1.81
After 1984		2.26	2.14–2.37
Srivastava et al. [4]	1984–1995	2.20	2.19–2.21
Kim et al. [20]	1994–2003	2.30	2.29–2.31
Spencer et al. [23]	1996–2006	2.40	2.39–2.41
*Londeree et al	2013–2018	2.13	1.83–2.47
Test for Heterogeneity	$Q = 3.02$, df = 1, $\boldsymbol{p} = 0.08$		

95% CI confidence interval; *US* United States; *Q* Cochran's *Q* test for heterogeneity, *df* degrees of freedom

*Current study