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ORIGINAL ARTICLE

Demographic Composition of Participants in Sex Chromosome Aneuploidy Studies Across the Globe: A 20-Year Systematic Review

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ABSTRACT

Sex chromosome aneuploidies (SCAs), including Klinefelter syndrome (47,XXY), Turner syndrome (45,X), XYY syndrome, trisomy X (47,XXX), and rarer tetrasomies and pentasomies, affect approximately 1 in 400 births and are associated with a wide range of developmental, cognitive, and physical health outcomes. While clinical research on SCAs has expanded over the past two decades, it is unclear whether the populations included in these studies reflect the demographic diversity of those affected. Assessing representation is critical to ensuring research findings are generalizable and applicable to diverse patient populations. We conducted a systematic review of global clinical research on SCAs published in English between January 2004 and May 2024. Searches were performed in Ovid MEDLINE ALL, Embase, and Web of Science. Studies were included if they enrolled ≥ 10 participants and excluded if they were case reports, reviews, or meta-analyses. We extracted data from 1474 studies on geographic location, participant karyotypes, and demographic metrics, including race, ethnicity, and socioeconomic status (SES) reported. Trends in demographic reporting were examined over time and by geographic region. For US-based studies reporting race/ethnicity, we compared pooled participant demographics to national census data. SCA research is concentrated within a small number of geographic areas, primarily in Europe (51.4%) and the United States (23.6%). Reporting rates of race or ethnicity for US papers increased over the 20-year observation period, with an average increase of 1.5% ± 0.4% per year ($p = 0.003$), peaking in 2024 with 61.4% of US-based papers presenting demographics. When reported, studies consistently overrepresented White non-Hispanic ($p < 0.001$) and college-educated ($p < 0.001$) participants relative to US census benchmarks. This systematic review reveals persistent gaps in the demographic reporting and representation of participants in SCA research. Even in the United States, where population diversity is high, published studies do not reflect the expected racial, ethnic, and socioeconomic makeup of affected individuals. To ensure that research findings are equitable and clinically relevant, future studies should adopt standardized demographic reporting and prioritize inclusive enrollment strategies to reflect the full spectrum of individuals with SCAs.

1 | Introduction

Sex chromosome aneuploidies (SCAs) are a group of genetic conditions characterized by the presence of an extra or a missing sex chromosome. Together, SCAs affect approximately 1 in 400 live births and include Klinefelter syndrome (47,XXY), Turner syndrome (TS, 45,X), trisomy X (47,XXX), XYY syndrome, 48,XXYY, and other rarer tetrasomies and pentasomies (Gravholt et al. 2024; Stochholm et al. 2010). These conditions affect individuals of any sex and are associated with a range of neurodevelopmental, cognitive, reproductive, and physical health outcomes (Tartaglia et al. 2024; Urbanus et al. 2023). While the volume of research on SCAs has grown, it remains unclear whether the participants included in clinical studies are representative of the broader population affected by these conditions.

Representation in clinical research is critical to ensuring that findings are generalizable, clinical guidance is evidence-based for diverse populations, and existing health disparities are not inadvertently reinforced. Race, ethnicity, and socioeconomic status (SES) have been shown to influence access to care, participation in research, and health outcomes across many conditions (Cheng et al. 2015). The challenges of ensuring representative research samples are magnified in rare disease research, where small study populations limit opportunities to achieve demographic diversity. While some conditions may be enriched in certain populations due to founder effects or environmental exposures, SCAs are believed to occur with equal frequency across all populations (Skuse et al. 2018). However, SCAs are significantly underdiagnosed: an estimated 75% of individuals with 47,XXY and up to 90% with 47,XXX or 47,XYY remain undiagnosed (Davis et al. 2024). Importantly, disparities in access to genetic testing have been well documented, with studies showing that individuals from minoritized racial and ethnic groups are less likely to be offered or accept genetic screening (Canedo et al. 2019). This creates the potential for bias in who is diagnosed and who ultimately participates in research. However, the increasing uptake of prenatal cell-free DNA (cfDNA) provides an opportunity to shift the landscape, enabling earlier and more equitable diagnosis, if care pathways are optimized.

The objective of this systematic review is to evaluate the demographic composition of participants included in original clinical research studies on SCAs. Specifically, we assess reporting of race, ethnicity, SES, and geographic location in peer-reviewed publications over the past two decades. By characterizing demographic trends over time and comparing US study populations to national census benchmarks, we aim to determine whether the current literature accurately reflects the populations affected by SCAs. These results have implications for clinical care and future research priorities.

2 | Methods

This systematic review was conducted in accordance with PRISMA guidelines, and the search strategy was registered with Prospero (ID# CRD42024550312) prior to initiating the literature search (Page et al. 2021). A comprehensive search strategy including both controlled vocabulary and free-text terms related to SCAs was developed in collaboration with a health sciences librarian (ES) and peer reviewed by a second librarian (see Table S1). The search was performed on May 21, 2024, across the following databases: Ovid MEDLINE ALL (1946–May 20, 2024), Embase (Embase.com, 1974–May 21, 2024), and Web of Science. Results were limited to human studies published in English between January 2004 and May 2024, inclusive of observational clinical studies, interventional studies, and registries. Case reports, reviews, meta-analyses, editorials, commentaries, letters, news, and meeting abstracts were excluded. The term "parsonage" was excluded to remove irrelevant records related to Parsonage–Turner Syndrome.

The search retrieved 19,031 citations, which were downloaded into EndNote version 21 and uploaded into Covidence, a systematic review management platform (Covidence, n.d.). A total of 8451 duplicates were identified and removed by EndNote or Covidence. The remaining 10,621 citations were screened with titles and abstracts; 8651 were removed for not meeting inclusion criteria (i.e., human studies on SCAs with at least 10 participants), leaving 1929 for full-text review (Figure 1).

Because this search involves no patient-level data, it is exempt from local institutional review board approval.

2.1 | Article Review and Data Extraction

Title and abstract screening were performed independently by two reviewers (KSS, AZ, AS, SD, KS, AC, LG, KN, KM). Discrepancies were resolved by consensus or adjudicated by KSS. Of the 1929 articles identified for full-text review, a reviewer (AZ, AS, KS) retrieved the full-text manuscripts via open access or InterLibrary Loan. Full texts were independently reviewed by two reviewers to determine inclusion eligibility, with disagreements resolved by KSS. Four hundred fifty-five manuscripts were excluded at the full-text review stage for not meeting inclusion criteria.

The final dataset comprised 1474 manuscripts. Data were extracted using an author-developed template that included publication characteristics (title, year), author information (location, contact), geographic region based on the location of the corresponding author, study design, SCA conditions included, general topic studied, number of participants, and participant race, ethnicity, and any socioeconomic metrics (e.g., education, income, insurance status, Hollingshead index). We used a broad inclusion methodology, considering any mention of culturally relevant race or ethnicity indicators (e.g., "all Nigerian" would be counted as reporting race/ethnicity). Each manuscript extraction was completed by one reviewer (KSS, AZ, AS, SD, KS, AC, LG, KN, KM), with the first 20 extractions for each reviewer verified by KSS. Any questions or discrepancies were resolved through discussion with KSS.

2.2 | Statistical Analysis

Descriptive statistics are presented as medians with interquartile ranges (IQR) for continuous variables and as *n* (%) for categorical variables. Geographic distributions of included studies are visualized globally and by US states using the usmap R package, version 0.7.1. The proportion of studies reporting race, ethnicity,

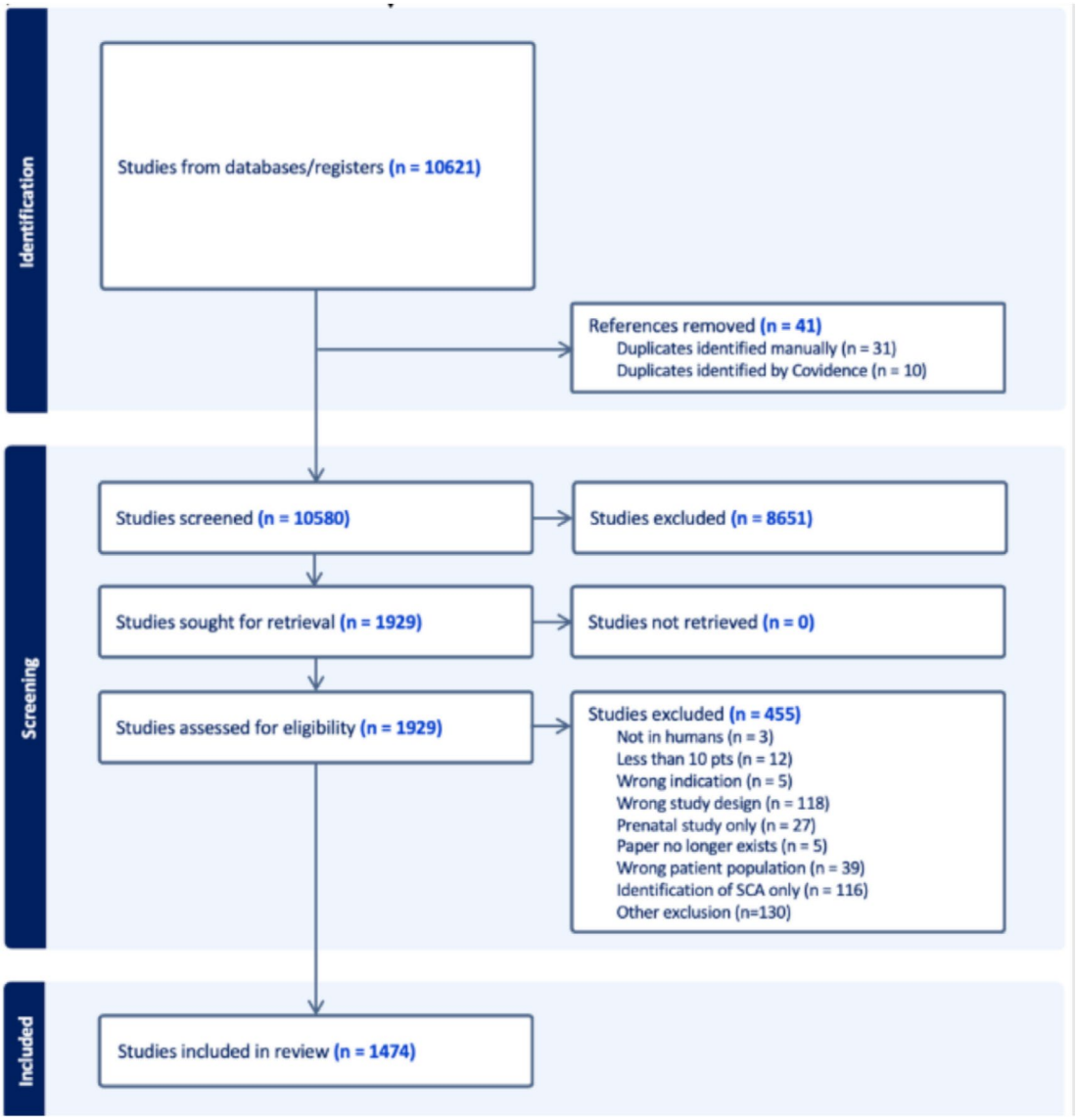

FIGURE 1 | PRISMA flow diagram of included studies.

and/or any SES measure was calculated for all and then stratified by specific SCA groups as well as US/International non-US studies to identify global hubs for SCA research. To contextualize geographic diversity in our analysis, we grouped countries based on both geographic proximity and shared socioeconomic or healthcare system characteristics as determined by the author group. For example, Northern European countries such as Sweden, Denmark, and Norway were grouped together given their similar public health infrastructures, population demographics, and research practices. This approach allowed for a more meaningful interpretation of demographic trends and study generalizability across regions with comparable societal structures. Temporal trends in race/ethnicity and SES reporting are visualized from 2004 to 2024. We evaluated linear regressions to assess if an increase in reporting occurred over time as well as general publication rates for SCA research. In 2013, NIH reporting guidelines mandated race and ethnicity reports be included in the publication of clinical research (National Institutes of Health, n.d.). To assess if there was a difference after the guidelines were released, race/ethnicity reporting rates prior to 2013 are compared to after 2013.

For studies within the United States reporting race and/or ethnicity, we conducted a meta-analysis of proportions to estimate the pooled representation of racial and ethnic groups across included studies. Specifically, for papers between 2014 and 2024, the weighted average of the percent of SCA participants who were White non-Hispanic, Hispanic, Black or African American, and Asian participants was calculated. These racial/ethnic groups were chosen based on frequency of reporting across studies. Weighted averages were calculated separately for each racial/ethnic category as the common effect across studies using the metaprop function in the meta R package, version 7.0-0 (Balduzzi et al. 2019). The inverse variance method was applied to weight the studies proportional to their sample size. I^2 measures are reported as a measure of heterogeneity across studies. Weighted proportions are compared to the US census estimates using one-sample z-tests (U.S. Census Bureau 2020). We conducted a similar analysis for education level for the proportion of parents with a college degree or greater. A type 1 error rate of 0.05 was assumed for all analyses. Analyses were performed in R, version 4.4.1.

TABLE 1 | Description of included studies.

	Number of papers
Karyotype[a]	Overall ($n = 1474$)
Turner syndrome	1006 (68.2%)
47,XXY	434 (29.4%)
47,XYY	83 (5.6%)
47,XXX	81 (5.5%)
48,XXYY	29 (2.0%)
Other tetra and pentasomies	36 (2.4%)
Median *n* of participants per study	55 (26–108)
Turner syndrome	57 (28–113)
47,XXY	44 (23–85)
47,XYY	24 (13.5–45)
47,XXX	27 (15–35)
48,XXYY	19 (10–25)
Other tetra and pentasomies	17 (6–36)
Study design	
Cross-sectional study	550 (37.3%)
Cohort study	313 (21.2%)
Chart review	231 (15.7%)
Case control study	216 (14.7%)
Randomized controlled trial	45 (3.1%)
Non-randomized experimental study	40 (2.7%)
Case series	23 (1.6%)
Basic science	22 (1.5%)
Qualitative research	22 (1.5%)
Other	12 (1.2%)
Topic of study	
Cardiac/cardiometabolic	235 (15.9%)
Neurodevelopment/psych/mental health	232 (15.7%)
Physical phenotype	208 (14.1%)
Other or multiple	194 (13.2%)
Growth treatment	149 (10.2%)
Fertility/fertility treatment	145 (9.9%)
Genetics/epigenetics	112 (7.7%)
Sex steroid hormones/hormone treatment	101 (6.9%)
Quality of life/wellbeing	82 (5.6%)
Basic science	16 (1.1%)
Publication year	
Prior to 2004	1 (0.1%)
2004–2008	261 (17.7%)
2009–2013	324 (22.0%)
2014–2018	348 (23.6%)
2019–2023	509 (34.5%)
2024	31 (2.1%)
Age of participants[a]	
Newborns (< 1)	172 (11.7%)
Toddlers (1–2)	275 (18.7%)
Children (3–11)	771 (52.3%)
Adolescents (12–17)	896 (60.8%)
Young adults (18–29)	944 (64.0%)
Middle adults (30–49)	701 (47.6%)
Older adults (50–74)	271 (18.4%)
Elderly (75+)	64 (4.3%)
Funding source[a]	
No funder listed	645 (43.8%)
Public funding	522 (35.4%)
Institutional funding	213 (14.5%)
Nonprofit funding	226 (14.4%)
Industry funding	130 (8.8%)
Other	16 (1.0%)

Note: Data are presented as *N* (%) or median [IQR].
[a]Categories are not mutually exclusive; therefore percentages do not add up to 100%.

3 | Results

3.1 | Study Characteristics

One thousand four hundred seventy-four manuscripts are included in the analysis. Most papers included TS (45,X/variants) (68.2%), representing a total of 163,816 participants (Table 1). Papers on 47,XXY were the next most frequent (29.4%), while all other SCAs were each represented in 2.0%–5.6% of studies. Studies included a median of 55 participants (IQR 26–108). Almost all papers reported on observational studies. Overall, cardiac/cardiometabolic topics were the most common (15.9%), followed by neurodevelopment/psych/mental health (15.7%), and physical phenotype (14.1%), although there was variability by karyotype (Table S2). The number of SCA papers published annually increased during the study period, averaging 4.7 ± 0.5 more papers published year over year ($p < 0.001$, Figure 1).

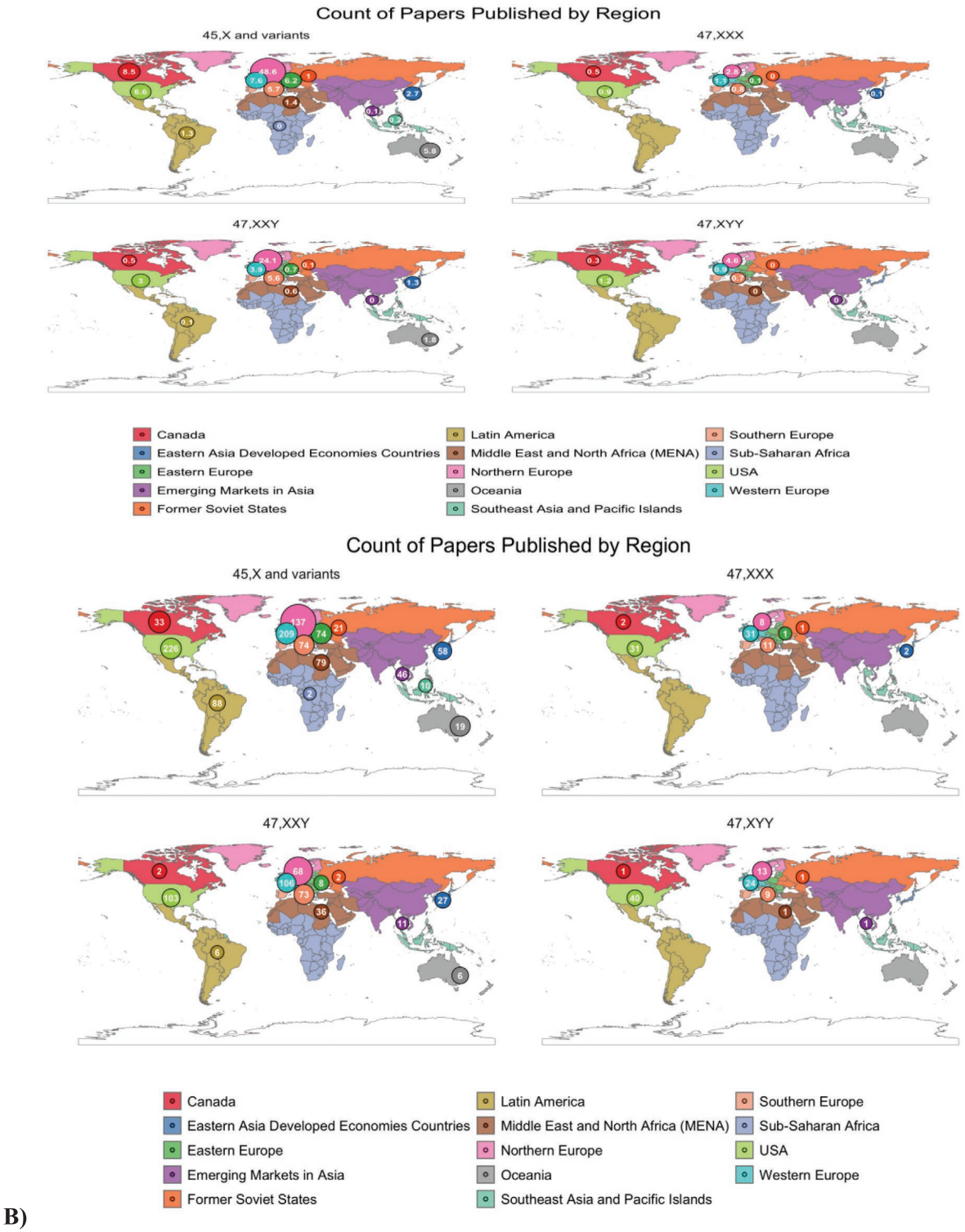

FIGURE 2 | Global distribution of SCA research varies by karyotype, with prominent areas in the United States and Europe. Circled numbers indicate (A) the number of manuscripts per 10 million residents from that region and (B) the total number of manuscripts from that region.

3.2 | Global Distribution of SCA Research

Visualizing the number of papers by global region revealed most research being conducted in Europe (51.4%) followed by the United States (23.6%) (Figure 2). There are almost no publications from Sub-Saharan Africa, and fewer than 22% were conducted in Latin America, Asian, or African countries. In 47,XXX, 47,XYY, tetrasomy, and pentasomy conditions, 85.7% of the studies were conducted in the United States or Western Europe. While 8.9% and 5.8% of all TS papers were from Latin America and Japan, respectively, these regions had no papers including 47,XYY and only two including 47,XXX.

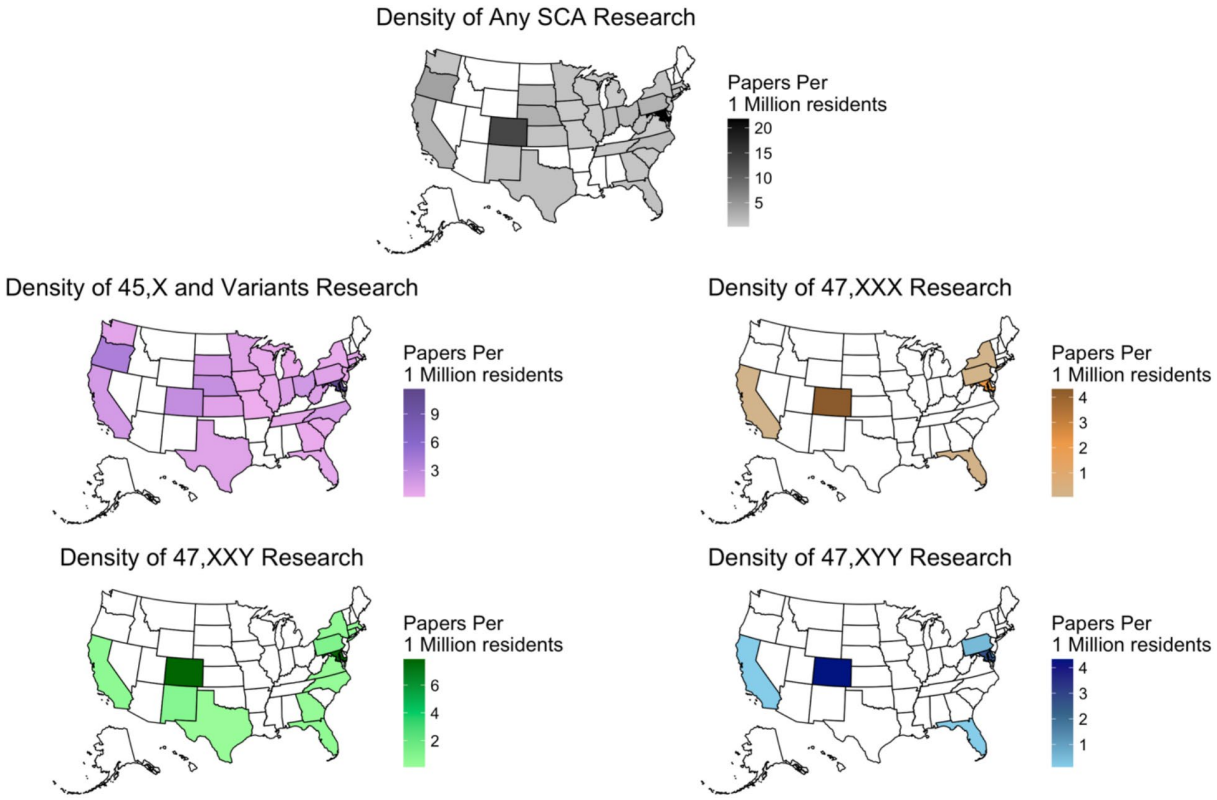

FIGURE 3 | US-based research hubs. US-based distribution of 329 SCA clinical research manuscripts varies by karyotypes, with prominent states including Maryland, California, Colorado, New York, Pennsylvania, and Florida. Legends indicate the number of clinical research manuscripts per 1 million residents by state.

3.3 | United States Regional Distribution

A more granular analysis of research locations within the United States (Figure 3) reveals regional centers for SCA research in Maryland, California, Colorado, New York, Pennsylvania, and Florida. TS research was more geographically dispersed compared to research for all other karyotypes.

3.4 | Trends in Inclusion of Demographic Data

Globally, 14.3% of manuscripts reported race and/or ethnicity of study participants. This was significantly higher for US papers (34.4%) compared to non-US international papers (7.9%) ($p < 0.001$). Reporting rates of race or ethnicity for US papers increased over the 20-year observation period, with an average increase of $1.5\% \pm 0.4\%$ per year ($p = 0.003$, Figure 4). After NIH reporting guidelines were established in 2013 (National Institutes of Health, n.d.), reporting rates of race or ethnicity for US papers significantly increased from a mean of $26\% \pm 12.7\%$ to $40.2\% \pm 14.9\%$ per year. There was not an observed trend over time for international studies.

3.5 | Comparison to US Census Demographics

For the US studies that did report race and/or ethnicity, the pooled proportion of White non-Hispanic was significantly higher than that of the US population (U.S. Census Bureau 2020), while the proportion of Hispanic and Black participants was significantly lower (Table 2). The overall heterogeneity, as measured with I^2, of proportions for race and/or ethnicity and SES across studies was generally high, ranging from 86.2% to 96.4% indicating that between-study variability was substantially higher than within-study variability (Figure 5). While, on average, our included studies differed from the US estimate for White non-Hispanic, Hispanic, and Black participants, the between-study variability is high, indicating that non-included or future studies could still be within range of the census report.

When broken up by SCA, trends stay generally consistent with significantly higher proportions of White non-Hispanic (ranging 68.3%–87%) and lower proportions of Black or African American participants (ranging 4.4%–8.7%) compared to the US census (57.8% and 13.7%, respectively) (Table 3). Significantly lower proportions of Hispanic and Asian participants were seen in 47,XXY and All Other SCT cohorts, but not in 45,X included cohorts. While I^2 dropped as low as 3.1% for the All Other SCT cohorts, this low heterogeneity could be attributable to the smaller number of studies, putting more weight on within-study variance relative to between-study variance.

3.6 | SES Reporting Trends

In the last 20 years, 11.1% of total papers have presented one or more SES metrics for participants, which was significantly

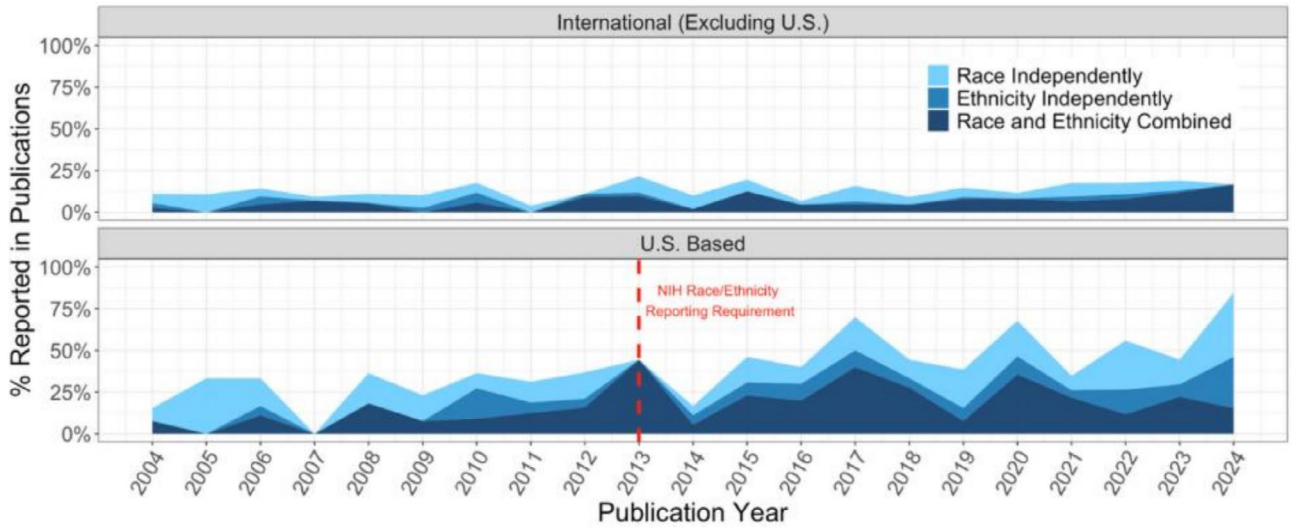

FIGURE 4 | Reporting of race and/or ethnicity over time. Stacked line graphs over time reveal the inclusion of race and/or ethnicity in SCA research is increasing from 2004 to 2024 in the United States, though international studies are stable. The 2013 NIH guidelines on reporting race and ethnicity in research is indicated with the red dashed line.

TABLE 2 | Meta-analysis of race/ethnicity and SES proportions for SCA studies in the United States compared to the 2020 US census (U.S. Census Bureau 2020).

	US estimate (%)	# of studies	Pooled percentage (95% CI)	I^2 value	*p*
Race/ethnicity					
White non-Hispanic	57.8	56	75.1% (71.8%–78.2%)	96.4%	< 0.001
Hispanic	19.5	49	12.5% (10.2%–15.3%)	93.4%	< 0.001
Black or African American	13.7	55	7.4% (6.3%–8.6%)	86.2%	< 0.001
Asian	6.4	21	4.1% (2.6%–6.5%)	93.0%	0.060
College degree or greater	37.0	19	54.6% (42.6%–58.4%)	92.8%	0.002

higher for US compared to non-US papers (25.4% vs. 8.9%, $p < 0.001$). Figure 6 demonstrates that though there is not a statistically significant increase in reporting SES for US-based papers, there is a general upward trend. Results show a < 1% increase (0.65% ± 0.4%, $p = 0.088$) in SES presentation, with a nadir in 2007 and a peak in 2015.

For studies within the United States reporting one or more SES metrics, many used custom categorical or ordinal scales (e.g., income brackets or 0 for primary school to 3 for university education) (Simm and Zacharin 2006). The lack of uniform metrics limited pooled analyses across studies for statistical comparison to national benchmarks. Educational attainment (either for the participant or the parent(s) of a child participant) was the most common SES metric presented (10.5%). Of the 19 papers that presented parental educational attainment, the pooled and weighted mean percentage for college degree or higher was 54.6% (42.6%–58.4%), which is significantly higher than the 2020 US census rates (Samango-Sprouse et al. 2015) of 37.0% for bachelor's degree or higher ($p = 0.002$). A minority of US-based studies utilized standardized indices such as the Hollingshead Four-Factor Index (2.9%) and only one paper presented the Area Deprivation Index. Of the 20 papers which reported the Hollingshead Index, the pooled and weighted mean (95% CI) estimate was 50.1 (46.7, 53.5), which is equivalent to the second highest social strata.

3.7 | Demographics as Analytical Variables

Of the 160 US studies that presented any race/ethnicity or SES variable, 27 included the race/ethnicity or SES metrics in their analyses. Eight papers matched their control populations on race/ethnicity (3), SES (3), or both (2) (Alzahrani 2024; Blunden et al. 2021; Kruszka et al. 2020; Lee et al. 2012; Lee et al. 2011; Lukowski et al. 2020; Udhnani et al. 2018; Wade et al. 2014). Twelve studies incorporated race/ethnicity (4), SES (4), or both (4) as covariates in analytic models but did not report results specific to these variables (Davenport et al. 2020; Ehrhart et al. 2018; Giedd et al. 2007; Hoag et al. 2022; Janusz et al. 2020; Reardon et al. 2016; Sandberg et al. 2019; Tran et al. 2019; Turriff et al. 2011; Turriff et al. 2015; Vijayakanthi et al. 2022; Wooten et al. 2008). Seven studies incorporated race/ethnicity (3), SES (3), or both (1) in their analysis and presented results about the impact of this metric on relevant

outcomes (Table 4) (Davenport et al. 2010; Donate et al. 2023; Hamberis et al. 2020; Kremen et al. 2023; Martin-Giacalone et al. 2023; Reinhartsen et al. 2021; Samango-Sprouse et al. 2018). Among these, two found no impact of the demographic metric(s) while five did find significant impacts (Figure 7).

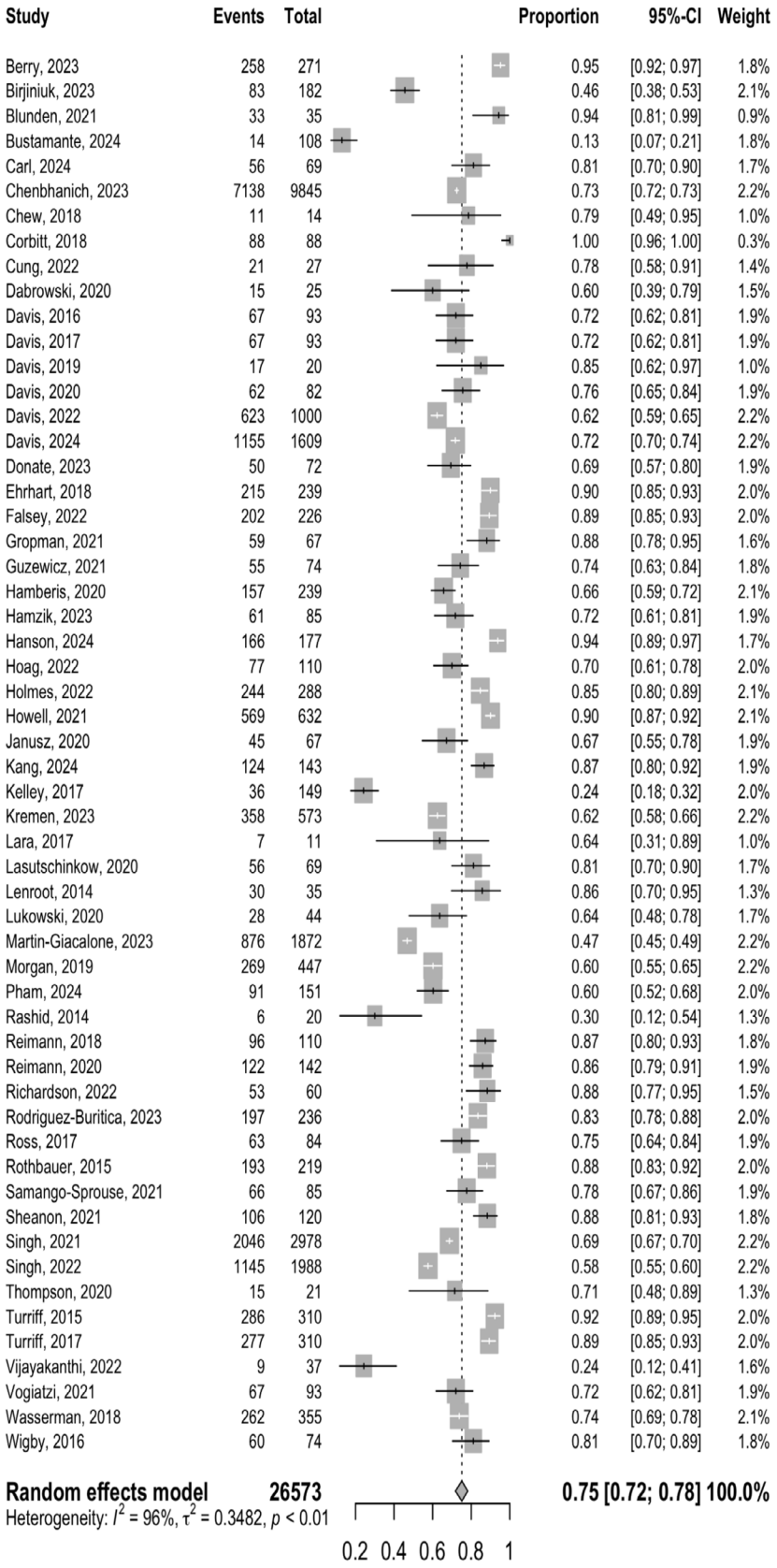

FIGURE 5 | Legend on next page.

FIGURE 5 | Meta-analysis forest plot for White non-Hispanic prevalence across US studies. Forest plot depicting meta-analysis results for all papers, representing all SCAs, which report White non-Hispanic proportions between 2014 and 2024. Events represent the number of White non-Hispanic included in the study. Total represents the total number of people included in the study, factoring out participants whose race/ethnicity were reported as unknown. Weights are calculated as the inverse of the variance such that papers with higher sample sizes and therefore lower variability are given higher weights. Points and error bars represent the proportion and 95% confidence intervals, respectively, of White non-Hispanic participants. The random effects model presents the pooled proportion and 95% confidence interval, 0.75 [0.72–0.78]. Heterogeneity measures the variability of estimates across studies, where an I^2 estimate closer to 100% indicates substantial between-study variability relative to within-study variability.

TABLE 3 | Meta-analysis of race/ethnicity and SES proportions by SCA compared to the 2020 US census.

		45,X			47,XXY			All others		
	US estimate (Covidence, n.d.) (%)	#	I^2	Pooled percentage (95% CI)	#	I^2	Pooled percentage (95% CI)	#	I^2	Pooled percentage (95% CI)
Race/ethnicity										
White non-Hispanic	57.8	32	97.0%	68.3%*** (63.3%–72.8%)	15	92.7%	78.3%*** (72.1%–83.5%)	10	64.7%	87.0%*** (82.5%–90.5%)
Hispanic	19.5	28	93.4%	17.6% (14.0%–21.8%)	12	72.6%	8.9%*** (6.7%–11.7%)	8	3.1%	5.6%*** (3.9%–8.1%)
Black or African American	13.7	34	84.8%	7.3%*** (6.0%–9.0%)	14	83.9%	8.7%*** (6.6%–11.3%)	7	54.8%	4.4%*** (2.3%–8.3%)
Asian	6.4	20	93.3%	4.2% (2.6%–6.7%)	11	63.0%	2.9%*** (2.1%–4.0%)	6	40.4%	3.3%* (1.7%–6.4%)
College degree or higher	37.0	9	85.1%	47.2%** (39.1%–55.4%)	6	96.3%	51.0% (31.0%–70.6%)	4	80.1%	59.8%* (39.6%–77.1%)

Note: p-values represent one-sample z-tests compared to the US census report.
*$p < 0.05$.
**$p < 0.01$.
***$p < 0.001$.

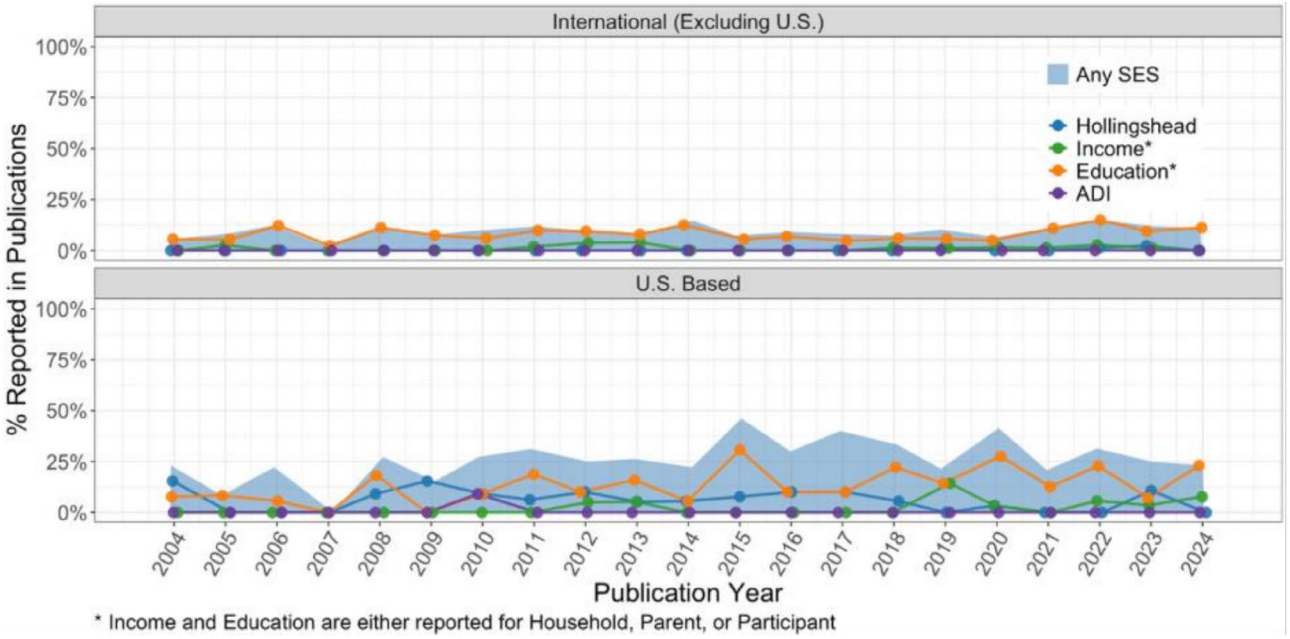

FIGURE 6 | Reporting of SES over time. US-based studies trend toward an increase in SES metrics in SCA research from 2004 to 2024 while international studies remain stable.

TABLE 4 | Summary of SCA studies that incorporated demographic variables in analyses.

	Year	SCA	Metric	Findings
1	2010	45,X	Daytime care setting	Abnormal hearing was associated with the child's daytime care setting being outside the home (e.g., daycare) compared to in-home settings (Davenport et al. 2010)
2	2018	XXY	Parental education	Higher parental education was a predictor of higher child IQ (Samango-Sprouse et al. 2018)
3	2020	45,X	Race/ethnicity	Race and ethnicity did not impact changes in pure tone average on audiological exam (Hamberis et al. 2020)
4	2021	45,X	Maternal education	No association was found between maternal education and child language performance (Reinhartsen et al. 2021)
5	2023	45,X	Race/ethnicity	Higher prevalence of 45,X among White non-Hispanic mothers, followed by Hispanic, and non-Hispanic Alaska Native, American Indian, or Pacific Islander, and non-Hispanic Black mothers (Martin-Giacalone et al. 2023)
6	2023	45,X	Race/ethnicity	Hispanic and non-White patients were less likely to be aware of their karyotype compared to White non-Hispanic patients (Donate et al. 2023)
7	2023	45,X	Insurance, race	Neuropsychological concerns were independently associated with Medicaid insurance, but not with race (Kremen et al. 2023)

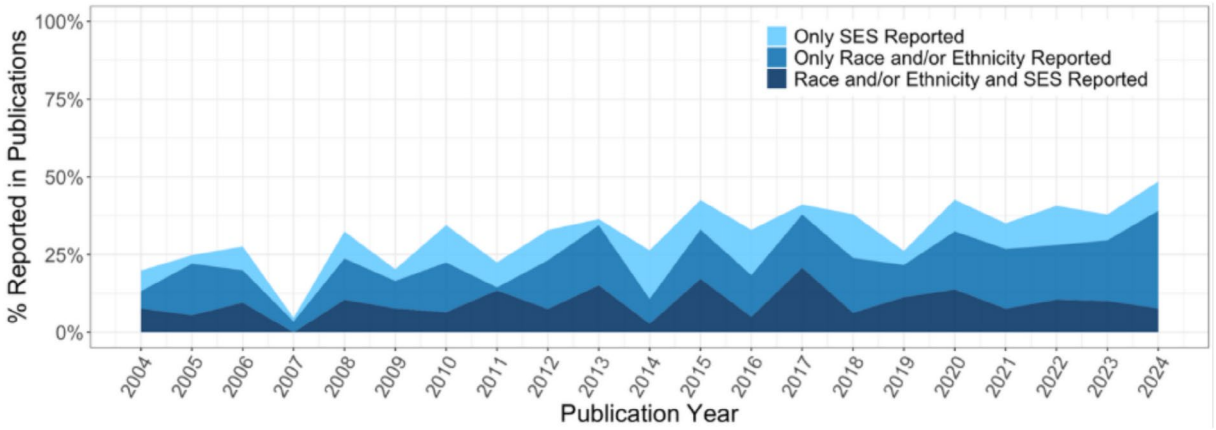

FIGURE 7 | Combined inclusion of race/ethnicity and/or SES variables. US-based studies trend toward an increase in reporting of SES, and race/ethnicity, but not both, in SCA research from 2004 to 2024.

4 | Discussion

This systematic review provides a comprehensive overview of clinical research on SCA conditions across the world, with a focus on participant demographics and geographic representation. Our findings suggest that the existing SCA literature does not accurately reflect the population of individuals living with these conditions. Studies are heavily weighted toward TS, concentrated in the United States and Western Europe, and reflect an imbalanced distribution of (or mostly reflect) White, affluent, educated participants. These gaps have significant implications for the generalizability of findings, the development of evidence-based guidelines, and equity in SCA research.

A major limitation of the current SCA research landscape is the inconsistent reporting of participant demographics. Despite the heterogeneous population within the United States, fewer than half of US-based studies included information on race, ethnicity, or SES. While reporting improved over time, potentially influenced by the 2013 mandate requiring the inclusion of race and ethnicity in NIH-funded studies, there remains substantial room for progress (Gogovor et al. 2021). Comprehensive reporting of demographic variables is essential for understanding how health outcomes may vary across populations and for identifying disparities in diagnosis, access to care, and treatment response (Lee et al. 2023). Without this information, it is impossible to determine whether clinical research is inclusive, study samples reflect the broader population, and observed findings can be generalized to all individuals with SCAs.

Among the US-based studies that did report participant demographics, we observed striking underrepresentation of racially, ethnically, and socioeconomically diverse populations. Compared to US census data, study populations were disproportionately composed of White non-Hispanic participants and individuals from more affluent, highly educated backgrounds. These findings are especially concerning given that SCAs arise from random chromosomal errors during meiosis and, unlike

many genetic or environmentally acquired conditions, should occur with roughly equal frequency across all racial, ethnic, and socioeconomic groups (Skuse et al. 2018). Disparities in study representation likely reflect structural barriers in access to healthcare, inequities in genetic testing, and differences in referral patterns for specialty care and research (Matalon et al. 2023). As prenatal screening becomes more widespread, with increasing diagnoses in infancy and early childhood, it is essential that research infrastructure be prepared to engage a broader and more diverse participant base (Howard-Bath et al. 2018). Ensuring representative research is not only a matter of scientific rigor but a matter of health equity and justice.

Multiple factors may contribute to the demographic skew observed in SCA studies. Families with greater resources, financial, educational, or geographic, are more likely to receive a timely diagnosis, access specialized care, and engage in longitudinal research (Kim et al. 2024; Wang et al. 2015). Meanwhile, underdiagnosis remains a major challenge in SCAs, particularly among the trisomy conditions (47,XXY, 47,XXX, 47,XYY), where rates of identification are estimated at only 10%–25% (Davis et al. 2024). Cultural differences in awareness and acceptance of genetic testing, language barriers, and historical mistrust of the medical system may further reduce research participation among minoritized groups (Canedo et al. 2019). At the same time, participation in clinical research can feel overwhelming for families already navigating a new diagnosis, especially those facing additional socioeconomic or cultural stressors. Without intentional strategies to address these barriers, disparities in SCA research will persist, and may widen, as diagnosis rates increase.

The overrepresentation of 45,X in the literature also warrants mention. While 45,X is a clinically important condition with unique care needs, it has received disproportionate attention relative to the more prevalent trisomy conditions. This imbalance likely reflects a higher diagnosis rate, more established clinical care infrastructure, and research funding and priorities. Future research should aim for greater inclusion across all SCA karyotypes, with attention to the distinct developmental trajectories and healthcare challenges associated with each condition.

In sum, this systematic review highlights a critical need for more equitable and inclusive clinical research practices in the field of SCAs. As the landscape of diagnosis continues to shift, particularly with the rise of cfDNA, clinical research must evolve to capture the diversity of those affected. Improving demographic reporting, reducing barriers to participation, and expanding access to diagnosis and specialty care are essential steps toward that goal.

5 | Limitations

This systematic review has several limitations. First, we restricted our search to studies published in English, which may have excluded relevant non-English literature and limited the geographic diversity of the included studies. Second, our ability to evaluate demographic representation was constrained by inconsistent reporting across studies, particularly regarding SES. Many studies that reported SES used imprecise or proxy measures (e.g., education or income groupings), and only a minority included validated instruments. Third, our analysis was based on unique publications rather than unique cohorts; as a result, some studies may be overrepresented due to multiple papers derived from the same participant sample. Without standardized identifiers for study populations, we were unable to adjust for this potential duplication. In addition, while we aimed to capture original clinical research, our inclusion criteria excluded small case reports and conference abstracts, which may have included data from underrepresented populations. Finally, we were limited to evaluating reported data; we could not assess participant demographics in studies that did not report them, potentially over or underestimating the extent of underrepresentation.

6 | Conclusions

This systematic review reveals gaps in the demographic reporting and representation of participants in SCA research, with overrepresentation of White non-Hispanic and higher SES individuals. The lack of demographic data across much of the literature limits the ability to assess generalizability, and applicability of findings to the broader population of individuals with SCAs. As research advances and diagnostic practices evolve, there is a critical need to ensure demographic and socioeconomic variation that reflects the population affected by SCA is prioritized, reported, and analyzed. Future research should adopt standardized demographic reporting practices, develop intentional recruitment strategies for underrepresented populations, and build infrastructure to support equitable access to clinical research. Closing these gaps is essential to ensuring that research translates into inclusive, evidence-based care for the full spectrum of individuals with SCAs.

Author Contributions

Dr. Karli S. Swenson led the organization of the project, formal analysis, and manuscript drafting and editing. Ms. Anastasia Zhivotov, Ms. Amanda Sieverts, Ms. Shalika Devireddy, Ms. Kira Shuff, Ms. Alexandra Carl, Ms. Lidia Grzybacz, Ms. Kayla Nocon, and Ms. Kayla Molison reviewed manuscripts for inclusion and reviewed and edited the manuscript. Ms. Samantha Bothwell performed all statistical analyses and reviewed and edited the manuscript. Ms. Brisa Avila performed the initial study design and reviewed and edited the manuscript. Ms. Ellie Svoboda designed and performed the literature search and reviewed and edited the manuscript. Dr. Chijioke Ikomi and Dr. Lilian Cohen contributed to study design, reviewed, and edited the manuscript. Dr. Shanlee Davis was responsible for the design, oversight, funding, and reviewing and editing the manuscript. All authors approve the version of the manuscript for publication.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

References

Alzahrani, T. 2024. "Cardiovascular Disease and Inpatient Complications in Turner Syndrome: A Propensity Score Analysis." *Texas Heart Institute Journal* 51, no. 1: e238245. https://doi.org/10.14503/THIJ-23-8245.

Balduzzi, S., G. Rücker, and G. Schwarzer. 2019. https://cran.r-project.org/web/packages/meta/vignettes/meta-tutorial.pdf. "How to Perform a Meta-Analysis With R: A Practical Tutorial." *Evidence-Based Mental Health* 22: 153–160.

Blunden, C. E., E. M. Urbina, S. A. Lawson, et al. 2021. "Progression of Vasculopathy in Young Individuals With Turner Syndrome." *Pediatric Cardiology* 42, no. 3: 481–491. https://doi.org/10.1007/s00246-020-02505-w.

Canedo, J. R., S. T. Miller, H. F. Myers, and M. Sanderson. 2019. "Racial and Ethnic Differences in Knowledge and Attitudes About Genetic Testing in the US: Systematic Review." *Journal of Genetic Counseling* 28, no. 3: 587–601. https://doi.org/10.1002/jgc4.1078.

Cheng, T. L., E. Goodman, and Committee on Pediatric Research. 2015. "Race, Ethnicity, and Socioeconomic Status in Research on Child Health." *Pediatrics* 135, no. 1: e225–e237. https://doi.org/10.1542/peds.2014-3109.

Covidence. n.d. Covidence Systematic Review Software. Veritas Health Innovation, Melbourne, Australia. www.covidence.org.

Davenport, M. L., E. Cornea, K. Xia, et al. 2020. "Altered Brain Structure in Infants With Turner Syndrome." *Cerebral Cortex* 30, no. 2: 587–596. https://doi.org/10.1093/cercor/bhz109.

Davenport, M. L., J. Roush, C. Liu, et al. 2010. "Growth Hormone Treatment Does Not Affect Incidences of Middle Ear Disease or Hearing Loss in Infants and Toddlers With Turner Syndrome." *Hormone Research in Paediatrics* 74, no. 1: 23–32. https://doi.org/10.1159/000313964.

Davis, S. M., C. Teerlink, J. A. Lynch, et al. 2024. "Prevalence, Morbidity, and Mortality of Men With Sex Chromosome Aneuploidy in the Million Veteran Program Cohort." *JAMA Network Open* 7, no. 3: e244113. https://doi.org/10.1001/jamanetworkopen.2024.4113.

Donate, P., M. Rivera-Davila, and S. K. Prakash. 2023. "Health Disparities in Turner Syndrome: UTHealth Turner Syndrome Research Registry." *Rare Disease and Orphan Drugs Journal* 2, no. 1: 4. https://doi.org/10.20517/rdodj.2023.02.

Ehrhart, M. D., I. R. Guthrie, F. Qeadan, and M. R. Burge. 2018. "Metabolic Effects of Androgen-Associated Body Mass in Klinefelter Syndrome." *Archivos de Medicina (Oviedo)* 10, no. 1: 8. https://doi.org/10.21767/1989-5216.1000257.

Giedd, J. N., L. S. Clasen, G. L. Wallace, et al. 2007. "XXY (Klinefelter Syndrome): A Pediatric Quantitative Brain Magnetic Resonance Imaging Case-Control Study." *Pediatrics* 119, no. 1: e232–e240. https://doi.org/10.1542/peds.2005-2969.

Gogovor, A., H. T. V. Zomahoun, G. Ekanmian, et al. 2021. "Sex and Gender Considerations in Reporting Guidelines for Health Research: A Systematic Review." *Biology of Sex Differences* 12, no. 1: 62. https://doi.org/10.1186/s13293-021-00404-0.

Gravholt, C. H., N. H. Andersen, S. Christin-Maitre, et al. 2024. "Clinical Practice Guidelines for the Care of Girls and Women With Turner Syndrome." *European Journal of Endocrinology* 190, no. 6: G53–G151. https://doi.org/10.1093/ejendo/lvae050.

Hamberis, A. O., C. H. Mehta, J. R. Dornhoffer, and T. A. Meyer. 2020. "Characteristics and Progression of Hearing Loss in Children With Turner's Syndrome." *Laryngoscope* 130, no. 6: 1540–1546. https://doi.org/10.1002/lary.28264.

Hoag, B. D., S. L. Tsai, D. D. Williams, and J. T. Cernich. 2022. "International Guideline Adherence in Girls With Turner Syndrome: Multiple Subspecialty Clinics Versus Coordinated Multidisciplinary Clinic." *Endocrine Practice* 28, no. 12: 1203–1209. https://doi.org/10.1016/j.eprac.2022.08.011.

Howard-Bath, A., A. Poulton, J. Halliday, and L. Hui. 2018. "Population-Based Trends in the Prenatal Diagnosis of Sex Chromosome Aneuploidy Before and After Non-Invasive Prenatal Testing." *Prenatal Diagnosis* 38, no. 13: 1062–1068. https://doi.org/10.1002/pd.5363.

Janusz, J., C. Harrison, C. Boada, et al. 2020. "Executive Function in XXY: Comparison of Performance-Based Measures and Rating Scales." *American Journal of Medical Genetics. Part C, Seminars in Medical Genetics* 184, no. 2: 469–481. https://doi.org/10.1002/ajmg.c.31804.

Kim, J. Y., M. Florez, and E. Botto. 2024. "The Influence of Socioeconomic Status on Individual Attitudes and Experience With Clinical Trials." *Communications Medicine* 4: 172. https://doi.org/10.1038/s43856-024-00586-9.

Kremen, J., S. M. Davis, L. Nahata, et al. 2023. "Neuropsychological and Mental Health Concerns in a Multicenter Clinical Sample of Youth With Turner Syndrome." *American Journal of Medical Genetics. Part A* 191, no. 4: 962–976. https://doi.org/10.1002/ajmg.a.63103.

Kruszka, P., Y. A. Addissie, C. Tekendo-Ngongang, et al. 2020. "Turner Syndrome in Diverse Populations." *American Journal of Medical Genetics. Part A* 182, no. 2: 303–313. https://doi.org/10.1002/ajmg.a.61461.

Lee, L. K., C. Narang, C. A. Rees, et al. 2023. "Reporting and Representation of Participant Race and Ethnicity in National Institutes of Health-Funded Pediatric Clinical Trials." *JAMA Network Open* 6, no. 8: e2331316. https://doi.org/10.1001/jamanetworkopen.2023.31316.

Lee, N. R., G. L. Wallace, E. I. Adeyemi, et al. 2012. "Dosage Effects of X and Y Chromosomes on Language and Social Functioning in Children With Supernumerary Sex Chromosome Aneuploidies: Implications for Idiopathic Language Impairment and Autism Spectrum Disorders." *Journal of Child Psychology and Psychiatry* 53, no. 10: 1072–1081. https://doi.org/10.1111/j.1469-7610.2012.02573.x.

Lee, N. R., G. L. Wallace, L. S. Clasen, et al. 2011. "Executive Function in Young Males With Klinefelter (XXY) Syndrome With and Without Comorbid Attention-Deficit/Hyperactivity Disorder." *Journal of the International Neuropsychological Society* 17, no. 3: 522–530. https://doi.org/10.1017/S1355617711000312.

Lukowski, S. L., E. R. Padrutt, K. Sarafoglou, et al. 2020. "Variation in Early Number Skills and Mathematics Achievement: Implications From Cognitive Profiles of Children With or Without Turner Syndrome." *PLoS One* 15, no. 10: e0239224. https://doi.org/10.1371/journal.pone.0239224. Erratum in: PLoS One. 2021 Apr 13;16(4):e0250388.

Martin-Giacalone, B. A., A. E. Lin, S. A. Rasmussen, et al. 2023. "Prevalence and Descriptive Epidemiology of Turner Syndrome in the United States, 2000–2017: A Report From the National Birth Defects Prevention Network." *American Journal of Medical Genetics. Part A* 191, no. 5: 1339–1349. https://doi.org/10.1002/ajmg.a.63181.

Matalon, D. R., C. J. Zepeda-Mendoza, M. Aarabi, et al. 2023. "Clinical, Technical, and Environmental Biases Influencing Equitable Access to Clinical Genetics/Genomics Testing: A Points to Consider Statement of the American College of Medical Genetics and Genomics (ACMG)." *Genetics in Medicine* 25, no. 6: 100812. https://doi.org/10.1016/j.gim.2023.100812.

National Institutes of Health. n.d. "Discontinuation of Form Using the 1977 Office of Management and Budget (OMB) Racial Standards." National Institutes of Health. NOT-OD-13-058. April 16, 2013. https://grants.nih.gov/grants/guide/notice-files/not-od-14-085.html#:~:text=The%20previous%20system%20(known%20as,deploy%20the%20Inclusion%20Management%20System.&text=Awards%20with%20start%20dates%20BEFORE,previous%20inclusion%20enrollment%20reporting%20format.

Page, M. J., J. E. McKenzie, P. M. Bossuyt, et al. 2021. "The PRISMA 2020 Statement: An Updated Guideline for Reporting Systematic Reviews." *BMJ (Clinical Research Ed.)* 372: n71. https://doi.org/10.1136/bmj.n71.

Reardon, P. K., L. Clasen, J. N. Giedd, et al. 2016. "An Allometric Analysis of Sex and Sex Chromosome Dosage Effects on Subcortical Anatomy in Humans." *Journal of Neuroscience* 36, no. 8: 2438–2448. https://doi.org/10.1523/JNEUROSCI.3195-15.2016. Erratum in: J Neurosci. 2016 May 4;36(18):5181–5182.

Reinhartsen, D. B., E. Cornea, M. DeRamus, et al. 2021. "Turner Syndrome: Language Profile of Young Girls at 12 and 24 Months of Age." *Journal of Neurodevelopmental Disorders* 13, no. 1: 52. https://doi.org/10.1186/s11689-021-09401-1.

Samango-Sprouse, C., E. Stapleton, S. Chea, et al. 2018. "International Investigation of Neurocognitive and Behavioral Phenotype in 47,XXY (Klinefelter Syndrome): Predicting Individual Differences." *American Journal of Medical Genetics. Part A* 176, no. 4: 877–885. https://doi.org/10.1002/ajmg.a.38621.

Samango-Sprouse, C., E. J. Stapleton, P. Lawson, et al. 2015. "Positive Effects of Early Androgen Therapy on the Behavioral Phenotype of Boys With 47,XXY." *American Journal of Medical Genetics. Part C, Seminars in Medical Genetics* 169, no. 2: 150–157. https://doi.org/10.1002/ajmg.c.31437.

Sandberg, D. E., D. Singer, B. Bugajski, et al. 2019. "Research Priorities of People Living With Turner Syndrome." *American Journal of Medical Genetics. Part C, Seminars in Medical Genetics* 181, no. 1: 43–51. https://doi.org/10.1002/ajmg.c.31676.

Simm, P. J., and M. R. Zacharin. 2006. "The Psychosocial Impact of Klinefelter Syndrome—A 10 Year Review." *Journal of Pediatric Endocrinology and Metabolism* 19, no. 4: 499–505.

Skuse, D., F. Printzlau, and J. Wolstencroft. 2018. "Sex Chromosome Aneuploidies." *Handbook of Clinical Neurology* 147: 355–376. https://doi.org/10.1016/B978-0-444-63233-3.00024-5.

Stochholm, K., S. Juul, and C. H. Gravholt. 2010. "Diagnosis and Mortality in 47,XYY Persons: A Registry Study." *Orphanet Journal of Rare Diseases* 5: 15. https://doi.org/10.1186/1750-1172-5-15.

Tartaglia, N., S. Davis, S. Howell, et al. 2024. "Medical Findings in Infants Prenatally Identified With Sex Chromosome Trisomy in Year One of Life." Preprint, MedRxiv. https://doi.org/10.1101/2024.07.10.24310206.

Tran, S. L., C. A. Samango-Sprouse, T. Sadeghin, S. Powell, and A. L. Gropman. 2019. "Hormonal Replacement Therapy and Its Potential Influence on Working Memory and Competency/Adaptive Functioning in 47,XXY (Klinefelter Syndrome)." *American Journal of Medical Genetics. Part A* 179, no. 12: 2374–2381. https://doi.org/10.1002/ajmg.a.61360.

Turriff, A., H. P. Levy, and B. Biesecker. 2011. "Prevalence and Psychosocial Correlates of Depressive Symptoms Among Adolescents and Adults With Klinefelter Syndrome." *Genetics in Medicine* 13, no. 11: 966–972. https://doi.org/10.1097/GIM.0b013e3182227576.

Turriff, A., H. P. Levy, and B. Biesecker. 2015. "Factors Associated With Adaptation to Klinefelter Syndrome: The Experience of Adolescents and Adults." *Patient Education and Counseling* 98, no. 1: 90–95. https://doi.org/10.1016/j.pec.2014.08.012.

Udhnani, M., M. Maiman, J. D. Blumenthal, et al. 2018. "Phonemic and Semantic Verbal Fluency in Sex Chromosome Aneuploidy: Contrasting the Effects of Supernumerary X Versus Y Chromosomes on Performance." *Journal of the International Neuropsychological Society* 24, no. 9: 917–927. https://doi.org/10.1017/S1355617718000723.

Urbanus, E., H. Swaab, N. Tartaglia, C. Stumpel, and S. van Rijn. 2023. "Structural and Pragmatic Language in Young Children With Sex Chromosome Trisomy (XXX, XXY, XYY): Predictive Value for Neurobehavioral Problems One Year Later." *Clinical Neuropsychologist* 37, no. 3: 650–675. https://doi.org/10.1080/13854046.2022.2067078.

U.S. Census Bureau. 2020. "U.S. Census Bureau QuickFacts: United States". https://www.census.gov/quickfacts/fact/table/US/PST045224.

Vijayakanthi, N., D. J. Marcus, S. P. Fritz, Y. Xiang, and D. Fadoju. 2022. "Body Image, Self-Perception, and Satisfaction Among Girls With Turner Syndrome: A Prospective Cross-Sectional Study." *Journal of Clinical Endocrinology and Metabolism* 107, no. 4: e1382–e1389. https://doi.org/10.1210/clinem/dgab889.

Wade, B. S., S. H. Joshi, M. Reuter, et al. 2014. "Effects of Sex Chromosome Dosage on Corpus Callosum Morphology in Supernumerary Sex Chromosome Aneuploidies." *Biology of Sex Differences* 5: 16. https://doi.org/10.1186/s13293-014-0016-4.

Wang, N., F. Cao, F. Liu, et al. 2015. "The Effect of Socioeconomic Status on Health-Care Delay and Treatment of Esophageal Cancer." *Journal of Translational Medicine* 13: 241. https://doi.org/10.1186/s12967-015-0579-9.

Wooten, N., V. K. Bakalov, S. Hill, and C. A. Bondy. 2008. "Reduced Abdominal Adiposity and Improved Glucose Tolerance in Growth Hormone-Treated Girls With Turner Syndrome." *Journal of Clinical Endocrinology and Metabolism* 93, no. 6: 2109–2114. https://doi.org/10.1210/jc.2007-2266.

Supporting Information

Additional supporting information can be found online in the Supporting Information section. **Table S1:** ajmga64285-sup-0001-Tables.docx. **Table S2:** Topic of research by karyotype.