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Bibliometric analysis of reviews of outcomes for adults with a complex perinatal history

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OBJECTIVE: To evaluate reviews focused on adult outcomes of patients with complex neonatal history.
STUDY DESIGN: We searched multiple databases in January 2022 and supplemented by hand searching references in included reviews. Two authors assessed reviews for eligibility. Data were extracted by one author, verified by a second. Counts based on neonatal exposure, adult outcome, and journal type for each review were calculated.
RESULTS: Eight-seven reviews were included. Most focused on prematurity. The most common adult outcome assessed was cardiovascular. Papers shifted to publication in pediatric journals over the last decade. Gaps include a lack of reviews focused on those with a history of substance exposure in utero and a lack of reviews on adult autoimmune conditions and gynecologic outcomes.
CONCLUSION: Reviews of adult outcomes of those with complex neonatal history have moved to publication in pediatric journals recently. We identified gaps in both pediatric populations and adult outcomes assessed.

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INTRODUCTION

Survival for neonates with perinatal complications, such as prematurity and congenital infections, has been steadily increasing over the last 30–40 years [1–7] Additionally, our understanding of the short-term risks of prematurity and other neonatal complications, such as being SGA or having intrauterine drug exposure, has grown [1–7].

With an estimated 15 million babies born preterm around the globe every year [8, 9], more people with a history of perinatal health problem reach adolescence and adulthood, which leads to greater interest in the long-term complications of these perinatal issues. Several longitudinal cohorts with perinatal complications, such as prematurity and low birth weight (LBW) are being followed to track in detail their overall health trajectories into adulthood [10–15] In addition, large health system data sets allow for study of the relationship between a history of perinatal risk factors and current health problems [16–21] The fetal origins of adult diseases (FOAD) hypothesis links fetal and neonatal exposures to a variety of adult outcomes [22, 23] The exposures in FOAD are of interest to neonatologists; however, the outcomes are of greatest interest to non-pediatric providers, who will be caring for these previous neonates in adulthood. It is not known if current publication practices related to FOAD meet the needs of clinicians caring for survivors of complex fetal and neonatal exposures.

In this review we sought to synthesize the available reviews published regarding the relationship between perinatal health problems and adult health outcomes to understand what perinatal risk factors have been evaluated, what adult health outcomes have been assessed, and what gaps are still present. We also sought to characterize the journals of publication for these reviews. We believe these are relevant data to report as neonatal and pediatric clinicians may wish to discuss prognosis with parents and adult clinicians need to understand the implications of a complex birth history on an adult patient's current health status.

METHODS

This study followed the standard approach to bibliometric analysis [24, 25] No IRB approval was required as this analysis utilized data in previously published literature.

Inclusion / exclusion criteria

The papers eligible for this bibliometric analysis consisted of systematic reviews that synthesized cohort or case-control studies regarding populations of adults (18 years of age or older) with a history of prematurity, very low or LBW (VLBW, LBW), small for gestational age (SGA), intrauterine growth restriction (IUGR), neonatal abstinence syndrome (NAS), intrauterine drug exposure (IUDE), congenital infection, or neonatal intensive care unit (NICU) admission for another reason. Reviews focused

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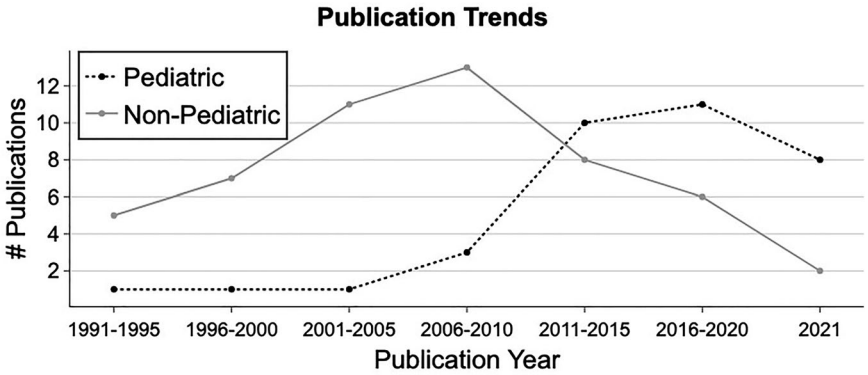

Fig. 1 Publication Trends based on type of journal published.

on children or adolescents (less than 18 years of age) were excluded. Reviews that included papers regarding people both over and under the age of 18 were included if they: a) had a mean age ≥ 18 years, b) had > 50% of participants ≥ 18 years, and/or c) had an analysis stratified by age with those 18 and over as at least one of the strata. Case series and case reports were excluded. Gray literature (defined as work published outside of peer-reviewed journals, such as dissertations and pre-prints) was not included, due to the focus on journal of publication for this review.

Search strategy for article identification and selection

The following databases were searched in January of 2022: MEDLINE, CINAHL, PsycINFO, EMBASE, and Cochrane. The MEDLINE search was as follows: ("logistic models"[MeSH Terms] AND "adult"[MeSH Terms] AND (("prematurity"[All Fields] OR "NAS"[MeSH Terms] OR "intrauterine drug exposure"[All Fields] OR "very low birthweight"[All Fields] OR "LBW"[All Fields] OR "SGA"[All Fields] OR "fetal growth retardation"[MeSH Terms] OR "intrauterine growth restriction"[All Fields] OR "syphilis, congenital"[MeSH Terms] OR "infections/congenital"[MeSH Terms] OR "intensive care, neonatal"[MeSH Terms] OR "NICU"[All Fields]) AND "English"[Languages])) AND (alladult[Filter]). Searches for the other databases were done similarly, adapted for the requirements of the specific database.

After completion of the database search, two reviewers independently screened each article's title and abstract to identify articles meeting the pre-determined criteria detailed above. Following this initial screen, the eligible articles were reviewed in full by two authors prior to inclusion. Discrepancies found during the review process were resolved by a third review or group consensus.

The reference lists from the systematic reviews and meta-analyses identified during the literature search were hand-searched for additional eligible articles. The reference lists from any additional relevant reviews, systematic reviews, or meta-analyses identified during the hand-search were also hand-searched for potentially relevant citations. All unique potentially relevant citations from the hand-search process were then reviewed by two authors to determine inclusion or exclusion.

Data extraction

Data extraction from each review was performed by one team member and then verified by a second team member for accuracy. Specifically, we extracted the neonatal risk factor(s) assessed, adult health outcome(s) assessed, and the journal of publication. Journals of publication for each article were classified according to their audience. Any journal with pediatric, neonatal, perinatal, child, adolescent, or developmental (or their derivations) in the title was considered pediatric. All other journals were considered non-pediatric. Additionally, the journal of publication was classified as a "general journal" (or not) to understand how many of these papers were reaching a wide audience. The list of "general journals" was determined using the Google Scholar Top 20 list for "health and medical sciences – general" and "primary care" from June 6, 2022, and included journals, such as the New England Journal of Medicine (NEJM), the Journal of the American Medical Association (JAMA), the Annals of Family Medicine, and the Journal of General Internal Medicine (JGIM). (See Appendix 1 for detailed list).

Adult health outcomes were grouped into the following larger categories to aid in analysis: obesity, function, mental health, growth, renal, mortality, pulmonary, developmental, cardiovascular, general health, bone health, neurological, cancer, diabetes, and liver. Reviews could be listed in multiple categories if they reported on health outcomes that fell into more than one of these groups.

Data analysis

We compared the site of publication (pediatric vs. non-pediatric) across several different dimensions, 1) site of publication over time, 2) site of publication by neonatal risk factor, and 3) site of publication by adult outcome. We also generated a Sankey plot to map neonatal risk factors to the adult outcomes for which we had data. Because these were done with risk factors and outcomes as the unit of analysis, there was the potential for many links per publication. For example, if a paper looked at LBW and prematurity and assessed 3 different adult outcomes, both LBW and prematurity would be mapped to each of the three outcomes for that paper. Analyses were conducted in Python and figures were generated using the python graphics library plotly (Plotly Technologies Inc. Collaborative data science. Montréal, QC, 2015. https://plot.ly).

RESULTS

Characteristics of included reviews

A total of 87 narrative and systematic reviews met inclusion criteria [23 26–111]. Details regarding included reviews can be found in Appendix 2.

Bibliometric data

The number of reviews published in non-pediatric journals increased from the early 1990s to 2010 after which the rate declined (Fig. 1). The rate of publications in pediatric journals remained low during this time and then has increased rapidly since 2010. The number of reviews in non-pediatric journals since 2010 has remained low.

Most reviews (59/87) focused on one neonatal risk factor, with 26 focusing on two risk factors, and two reviews focusing on three risk factors. Almost all reviews considered the long-term effect of prematurity and/or LBW (86/87) (Fig. 2). Few reviews reported on SGA and/or Intrauterine Growth Restriction ($n = 5$) [26, 30, 55, 94, 102] or NICU stay for another reason ($n = 2$) [53, 69]. The reviews for NICU stay for another reason were focused on bronchopulmonary dysplasia specifically, which is the result of prematurity, but represents a distinct population among those born prematurely. None of the reviews focused on those with a history of substance exposure in utero or neonatal infection.

The most common adult outcome of interest was cardiovascular (33/87; Fig. 3), followed by mental health [19], diabetes [18], developmental outcomes [17], and functional outcomes [14]. We did not identify any reviews examining the adult outcomes of autoimmune conditions, endocrine disorders other than diabetes and bone health, and gynecologic outcomes (including abnormal uterine bleeding and dysmenorrhea).

As Fig. 4 shows, reviews have evaluated the relationship between prematurity and adult outcomes across a wide variety

of domains. The relationship between LBW / very LBW and adult outcomes also spans a wide variety of domains. While there were fewer reviews focused on SGA/IUGR, those papers assessed the relationship to adult outcomes across many of the domains as well. The papers focused on NICU admission for another reason mostly focused on adult pulmonary outcomes.

DISCUSSION

This study sought to analyze systematic and narrative reviews reporting on adult health outcomes in patients with complex neonatal history and understand the gaps in the neonatal exposures studied, gaps in reported adult outcomes, and examine secular trends in publications. We found that while reviews on considering the adult health outcomes of those with a complex neonatal history were predominately published in non-pediatric journals initially, over the past decade, there has been a trend toward publication in pediatric journals. We also found that most reviews examined the effect of LBW (including Very LBW and LBW) and prematurity on adult outcomes with significantly fewer reviews reporting on SGA and Intrauterine Growth Restriction and NICU admissions for other reasons. No reviews identified in this search examined the long-term effects of substance exposure in utero. There was a paucity of reviews reporting on gynecologic outcomes (despite females being more likely to survive than males across all degrees of prematurity), endocrine disorders beyond diabetes and bone health, liver health, and autoimmune disorders in adults.

As survival beyond the neonatal period has become more common for infants with prematurity and other perinatal complications, there is a growing importance of examining the FOAD. We recognize that several audiences may be interested in this data. For example, neonatologists and pediatricians can use this data to discuss long-term outcomes with families; adult specialists and sub-specialists can use this data to understand the specific needs for their patients; non-physician clinicians, such as nurses, psychologists, or social workers, may also use this data to guide their counseling and care practices. However, an important group that may be overlooked is primary care clinicians with whom adults often interact the most. Thus, it may be important for studies to continue publishing articles related to adult outcomes in non-pediatric, specifically primary care, journals so that primary care clinicians can be aware of diagnoses that may affect their adult patients who were previously neonates. This may be of growing importance for diagnoses, such as substance exposure in utero, though we did not find any reviews focused on the adult outcomes for those with this history.

We also think the timing of these publications is noteworthy. For example, the majority of the papers focused on the relationship between neonatal risk factors and adult cardiovascular

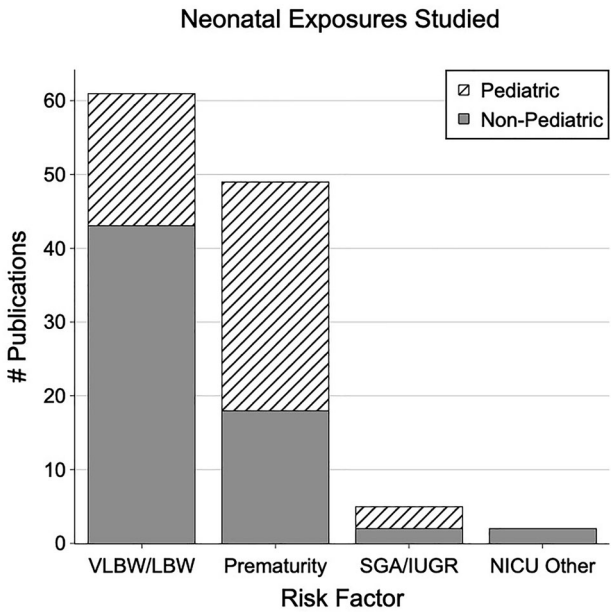

Fig. 2 Neonatal Risk Factors Represented in Publications.

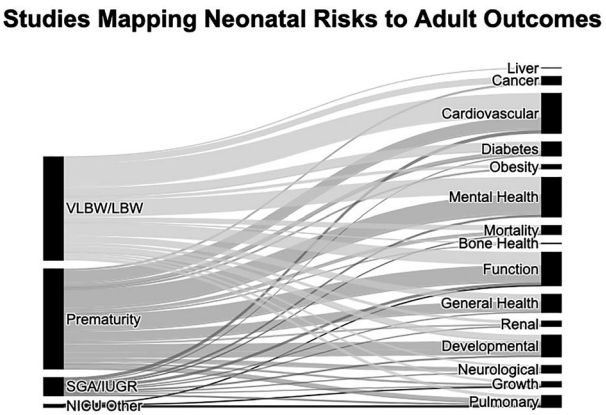

Fig. 4 Sanky Diagram connecting Neonatal Diagnoses to Adult Outcomes.

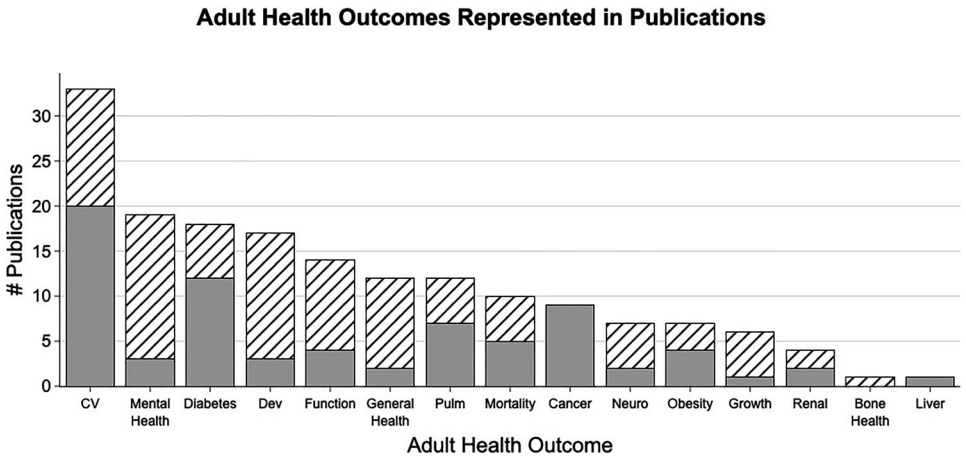

Fig. 3 Adult Health Outcomes Represented in Publications.

outcomes were published prior to 2010 and utilized data from birth cohorts going back to the 1930s. While this data continues to be important, consideration must be given to reassessing these relationships periodically because of changes in neonatal critical care provision, changing thresholds of viability and/or changes in risk in "healthy term" comparator groups that may influence the relationships between the neonatal risk factors and adult outcomes. Another population that may be of interest are those who were born at term but exposed to antibiotics at the time of birth due to maternal fever, chorioamnionitis or other infections. Studies have shown that this antibiotic exposure can have later effects in childhood [112–115]. We found one review that planned to include any papers looking at the relationship between early antibiotics and eczema in adulthood [116], but only identified one study with any adults, a case-control study looking at people ages 7 to 22 [115]. Given the clearer relationship between early antibiotic exposure and childhood consequences, we believe additional studies to assess adult consequences is warranted.

We noted gaps with respect to certain potentially relevant adult outcomes, such as liver disease, development of autoimmune conditions, gynecologic conditions, and endocrine disorders beyond diabetes. Isolated studies suggest that prematurity and other peri-natal complications can have impacts on these adult outcomes [117–121] but we did not identify any reviews on these topics. Since we did not identify reviews specifically on these topics with our search, but did identify individual studies, this suggests reviews to synthesize the available literature on these topics may be warranted.

There are several limitations to our study. First, we only looked at what was published. It's possible the authors tried submitting to general medicine journals and didn't get accepted, and then subsequently published in a pediatric journal. It is also notable that identifying papers targeted on this topic is challenging because there is also significant interest in the perinatal outcomes of pregnant persons with chronic conditions and differentiating those studies from the studies for this paper using search terms is a challenge.

We recognize that the search is a bit outdated. In post-hoc targeted searches of the literature for new studies, we did identify a few papers that make reference to a neonatal risk factor as a risk factor for later adult disease [38 122–125]. None of the identified papers considered the adult outcomes of those with a history of in utero substance exposure. Two of the reviews were not specifically focused on neonatal risk factors but rather on many early life risk factors for adult disease. [122 124], Another did not provide explicit data but hypothesized the prematurity, by virtue of its disruption of the hypothalamic-pituitary-adrenal axis, might contribute to risk of polycystic ovary syndrome [125]. Two of the five identified papers were published in pediatric journals, [38, 125] two were published in journals focused on reviews, [123, 124] one was published in an adult care journal that was not on the general journal list [122]. Based on this targeted scan, we believe that the identified gaps are still relevant.

CONCLUSIONS

This bibliometric analysis of the published reviews assessing adult outcomes of those with a complex neonatal history identified several gaps, including a preference for publication in the pediatric literature in recent years, a lack of data on those with a history of substance exposure in utero, and a lack of data in certain adult outcomes. Future work in this area should consider addressing these gaps, with a particular focus on examining the adult health outcomes for those who have had an in-utero exposure to substances.

SUMMAY

What's known on this subject:

- A growing body of science is identifying the adult-age outcomes of those with a complex neonatal history and providing further support of the fetal origins of adult disease hypothesis.

What this study adds:

- This study identified gaps in the work describing these outcomes, including a lack of reviews focused on those with a history of in utero substance exposure and lack of reviews looking at autoimmune and gynecologic outcomes.

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AUTHOR CONTRIBUTIONS

Hart participated in conceptualizing the study, assisted with developing the analysis plan, wrote the first draft, and revised the manuscript critically for important content. Khalsa participated in data interpretation and revised the manuscript for critically

important content. Antoniou conducted the analysis and revised the manuscript for critically important content. Bitler, Lure, and Rogers participated in data collection and data analysis and revised the manuscript for critically important content. Gehred participated in conceptualizing the study and conducted the literature search as well as revising the manuscript for critically important content. Chaudhari participated in conceptualizing the study, data collection, and data analysis as well as revising the manuscript for critically important content. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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ETHICS STATEMENTS

This analysis is based on published studies. Analysis documents available upon request to the corresponding author.

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