Preterm Infant Growth Velocity Calculations: A Systematic Review

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abstract

CONTEXT: Clinicians assess the growth of preterm infants and compare growth velocity using a variety of methods.

OBJECTIVE: We determined the numerical methods used to describe weight, length, and head circumference growth velocity in preterm infants; these methods include grams/kilogram/day (g/kg/d), grams/day (g/d), centimeters/week (cm/week), and change in *z* scores.

DATA SOURCES: A search was conducted in April 2015 of the Medline database by using PubMed for studies that measured growth as a main outcome in preterm neonates between birth and hospital discharge and/or 40 weeks' postmenstrual age. English, French, German, and Spanish articles were included. The systematic review was conducted by using Preferred Reporting Items for Systematic Reviews and Meta-analyses methods.

STUDY SELECTION: Of 1543 located studies, 373 (24%) calculated growth velocity.

DATA EXTRACTION: We conducted detailed extraction of the 151 studies that reported g/kg/d weight gain velocity.

RESULTS: A variety of methods were used. The most frequently used method to calculate weight gain velocity reported in the 1543 studies was g/kg/d (40%), followed by g/d (32%); 29% reported change in *z* score relative to an intrauterine or growth chart. In the g/kg/d studies, 39% began g/kg/d calculations at birth/admission, 20% at the start of the study, 10% at full feedings, and 7% after birth weight regained. The kilogram denominator was not reported for 62%. Of the studies that did report the denominators, the majority used an average of the start and end weights as the denominator (36%) followed by exponential methods (23%); less frequently used denominators included birth weight (10%) and an early weight that was not birth weight (16%). Nineteen percent (67 of 355 studies) made conclusions regarding extrauterine growth restriction or postnatal growth failure. Temporal trends in head circumference growth and length gain changed from predominantly cm/wk to predominantly *z* scores.

LIMITATIONS AND CONCLUSIONS The lack of standardization of methods used to calculate preterm infant growth velocity makes comparisons between studies difficult and presents an obstacle to using research results to guide clinical practice.

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During the third trimester of gestation, the human fetus, whose growth rates preterm infants are recommended to mimic,[1,2] grows from ~500 to 3500 g between 22 and 40 weeks of gestation, a 7 times multiple in only 4 months.[3] Such growth velocity is faster than other age groups. Although preterm infants can double or triple their weight during their first 2 to 3 months,[4–7] term infants take 4 to 5 months and teenagers take 9 years to double their weight.[8] Preterm infants without morbidities can replicate these rapid fetal growth rates when nutrition is not limiting.[9,10]

Length gain is also rapid during gestation. Term infants have an average length of ~50 cm after 9 months of gestation, whereas length growth in the first year of life (25 cm in 12 months) is one-half of that amount grown in a longer time period.[8]

Measuring growth velocity in preterm infants is of crucial importance because poor growth is associated with severe long-term outcomes.[11–13] Growth patterns of preterm infants have changed with recent advances in medical[14–16] and nutritional[14,17–19] care. Researchers in several countries have observed that rates of growth failure have declined in the past decade.[14,18,19] Our previous research revealed that compared with infants born between 1994 and 1995, infants born between 2001 and 2009 regained their birth weight sooner after birth and experienced higher rates of weight gain.[17]

Several investigators have identified that researchers use a variety of methods to summarize growth velocity of preterm infants.[20–22] Assessing grams/kilogram/day (g/kg/d) calculation methods for birth until discharge, Patel et al[21,23] and Senterre and Rigo,[20] in separate analyses, found that different calculation methods have been documented to alter results by as much as 73% in g/kg/d estimates.

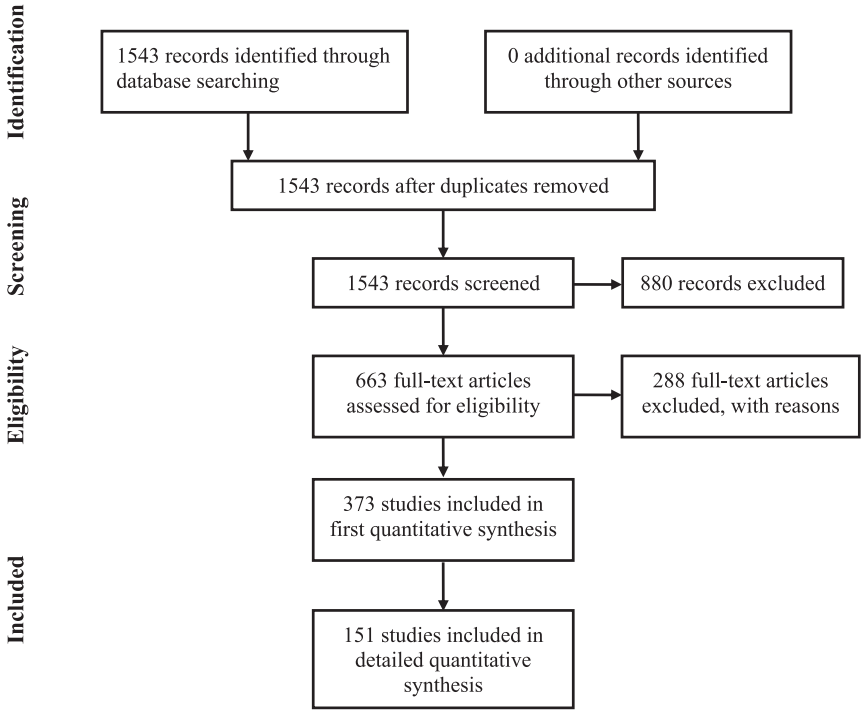

FIGURE 1
Flow diagram of articles identified in the literature search, screened, found eligible, and included in the systematic review.

We believe that research is needed to identify which methods to quantify preterm infant growth are superior and which are inferior. We also see a need to make recommendations to achieve some uniformity of methods used so the neonatal community can achieve the best conclusions about growth and to support comparisons across research studies. This initial article by our group defines the range of growth velocity methods used by the neonatal community; it describes the problem of using many different methods, making comparisons between studies and centers difficult, if not impossible. The additional research is large enough to justify additional articles; we view this article as the first of a series.

We hypothesized that a systematic review to describe the range of numerical summary methods used in the literature to calculate growth velocity of early preterm infants, and to quantify the frequency of each method, would identify a large variety of methods. The purpose of the present study was to determine the frequency of numerical methods used to quantify growth velocity (weight gain as g/kg/d, grams/day [g/d],

TABLE 1 Frequency of Methods Used to Report Weight Gain in the Studies of Preterm Infant Weight Gain Before Term Age, Before and After 2005, in the 1543 Located Studies

Variable	g/d	g/kg/d	*Z* Score
Overall	120 (32%)	151 (40%)	108 (29%)
<2005*	71 (59%)	67 (44%)	21 (19%)
2005–2015*	49 (41%)	84 (56%)	87 (81%)

* $P < .001$.

and change in *z* score [SD score]; head circumference and length as centimeters/week [cm/wk] and *z* scores) in preterm infants (gestational age <37 weeks at birth) who had growth assessed at or before hospital discharge and/or 40 weeks' postmenstrual age in published studies that reported growth as a primary outcome. The primary objective was to examine the variability of the g/kg/d calculations, the time frames, and the denominators. The secondary objective was to document the variability of methods for the calculation of gain in weight, head circumference, and length.

METHODS

A search was conducted of the Medline database in April 2015 for published studies that reported growth as a main outcome in preterm infants between birth and hospital discharge or 40 weeks' postmenstrual age. The systematic review methods recommended by the Preferred Reporting Items for Systematic Reviews and Meta-analyses statement[24] were used. Search terms included the Medical Subject Headings and text words: ("Infant, Premature"[Mesh] OR "Infant, Very Low Birth Weight"[Mesh]) and ("Weight Gain"[Mesh] OR "growth velocity" OR (weight and "rate of growth") OR (("g/kg/day" OR "g/kg/d") and weight) OR ((z-score OR z-scores OR "SD score" OR "SD scores") and change and weight)).

This search was conducted in Medline (PubMed), and it was not limited by date of publication. Intervention and observational studies were included in English, French, Spanish, and German languages. Because our objective was to quantify the methods used in the published literature, authors were not contacted for additional information, and studies were

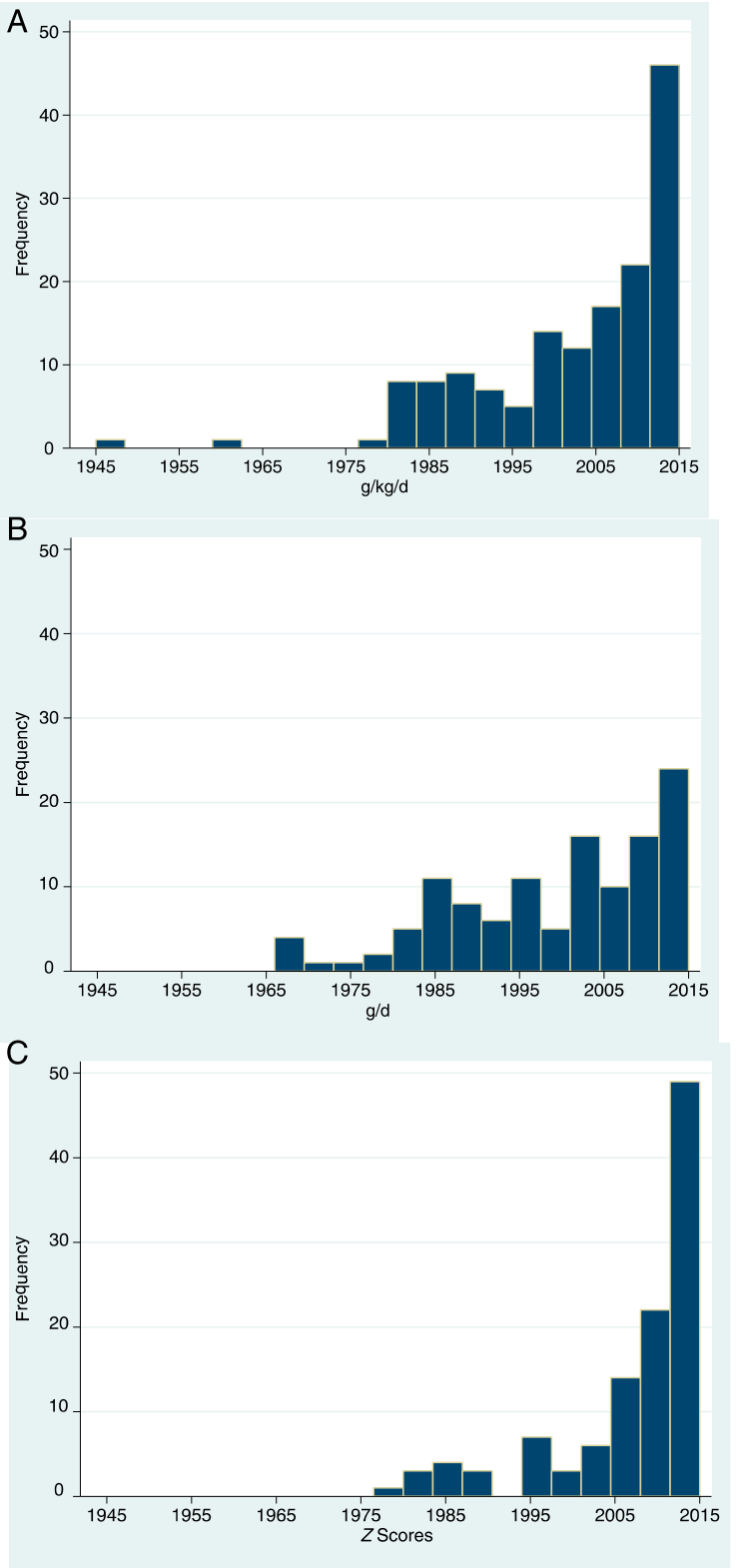

FIGURE 2
Temporal trends of the frequency of reported weight gain calculations for preterm infants before term age: (A) g/kg/d, (B) g/d, and (C) *z* scores.

not assessed for risk of bias. We noted when the method used was not reported. Gray literature was not included because a pilot search located sufficient studies to indicate that the search of the 1 database would be able to provide a description of the range of methods used to report growth of preterm infants.

After reading selected abstracts, further examination of full articles and the inclusion of relevant articles were made based on previously determined inclusion and exclusion criteria. The inclusion criteria for the articles were: (1) growth as a main outcome, measured in terms of weight gain, or growth of head circumference and/or length; and (2) participants of the study were preterm infants (gestational age <37 weeks). The exclusion criteria for the selected articles were as follows: (1) the only growth end point was >40 weeks' postmenstrual age; (2) not all participants of the study were preterm; (3) lack of reported data in the article; and (4) animal studies and review articles. Because the interest in this systematic review was about how growth was calculated, studies when researchers reported size (eg, mean weight or head circumference at discharge) without growth summarized over time were not included.

Two reviewers extracted the data from the English articles; any differences of opinion were resolved in discussion with one of the collaborators. One of the collaborators each extracted the data from the French, Spanish, and German articles, with discussions with the principal investigator about any dilemmas. The data were extracted in a 2-part process. The following information was extracted from all 373 included articles: (1) authors, year of publication, and first title word; (2) PubMed identification number; (3) whether weight gain, growth of head circumference, and/or length was included; (4) how weight gain was summarized (g/day, g/kg/d, z scores, or other); (5) whether weight was assessed for extrauterine growth restriction or postnatal growth failure using size less than the 10th percentile or similar; and (6) if *z* scores or a percentile was used to assess growth at discharge to assess growth failure, and which growth or intrauterine chart was used as the comparison reference.

In the second extraction step, the 151 articles (Supplemental References) that reported growth velocity in g/kg/d were examined in more detail for: (1) which denominator and whether an exponential transformational term was used for the g/kg/d calculation;

TABLE 2 Growth Charts Used to Assign *Z* Scores for Weight Gain ≥2 Times to Either Assign *Z* Scores or Postnatal Growth Failure Identified in the 2015 Literature Search

Intrauterine or Preterm Growth Chart	Frequency for *Z* Scores	Frequency for Postnatal Growth Failure
Alexander et al 1996[33]	4 (6%)	4 (10%)
Babson 1970[32]	5 (7%)	1 (3%)
Cole et al 1998[31]	5 (7%)	1 (3%)
Fenton 2003[28]	18 (25%)	11 (27%)
Fenton et al 2013[17]	6 (8%)	4 (10%)
Kramer et al 2001[34]	2 (3%)	2 (5%)
Kitchen et al 1983[35]	1 (1%)	2 (5%)
Lubchenco et al 1966[36]	3 (4%)	2 (5%)
Niklasson et al 1991[37]	4 (5%)	1 (3%)
Olsen et al 2010[30]	5 (7%)	2 (5%)
Pihkala et al 1989[38]	2 (3%)	2 (5%)
Roberts and Lancaster 1999[39]	2 (3%)	1 (3%)
Skjaerven et al 2000[40]	3 (4%)	2 (5%)
Usher and McClean 1969[29]	9 (12%)	4 (10%)
Voigt et al 2010[41]	2 (3%)	0
Yudkin et al 1987[42]	2 (3%)	2 (5%)

Charts that were used by only 1 study for either to assign *z* scores or growth failure were not included in this table.

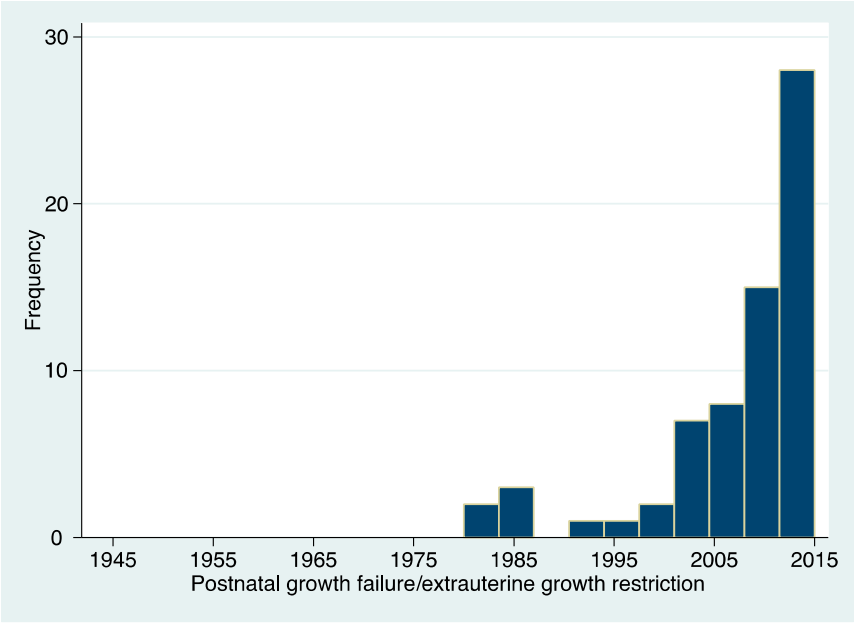

FIGURE 3
Temporal trends of the frequency of reported postnatal growth failure or extrauterine growth restriction.

TABLE 3 Time Reported for the Beginning and End of Calculations in the 151 Studies of Preterm Infant g/kg/d Weight Gain Before Term Age

Start Times	*n*	%	End Times	*n*	%
Birth/day 1/admission	59	39	Discharge	45	30
Study start/randomization	30	20	Day of life 7 to 56	50	33
Full feeds	15	10	Study end	21	14
Day of life 3 to 13	14	9	34–40 wk gestational age	15	10
Regain birth weight	11	7	Weight 1.7–2 kg	10	7
Feeding initiation	2	1	Other	3	2
Weight nadir	2	1	Not specified	8	5
Other	11	7			
Not specified	8	5			

(2) the time frame for which growth was measured; and (3) how growth in head circumference and/or length was summarized (cm/wk, change in *z* scores, or other).

The methods reported in the included studies were described by using frequencies and percentages: g/d, g/kg/d, cm/wk, change in *z* scores, percentile, or other. For g/kg/d, the denominator used and whether an exponential method was used were documented. Frequencies of the methods used over time were illustrated graphically. The statistical comparison of the frequencies of velocity calculations before and after 2005 was made by using Fisher's exact test.

RESULTS

Description of Studies

Among the 1543 studies located in the search, 373 (24%) reported growth velocity of the infants studied and were included in the systematic review (Fig 1). Studies were excluded at the abstract stage if growth was not a primary outcome (*n* = 670 [43%]), the article was a review article (*n* = 157 [10%]), growth was only calculated with an end point after term age (*n* = 108 [7%]), language was other than 1 of the 4 included languages (*n* = 69 [4%]), they were animal studies (*n* = 13 [1%]), preterm and term infants were grouped together (*n* = 10, 1%), and it was a duplicate publication (*n* = 2 [0.1%]). Studies were excluded at the article stage if no growth data (*n* = 81 [5%]) or if size (and not growth) was reported (*n* = 58 [4%]).

Weight Gain, or Growth of Head Circumference, and/or Length Inclusion

Among the 373 included studies, weight gain was assessed in 95% (*n* = 355), head circumference growth in 51% (*n* = 191), and length gain in 48% (*n* = 180).

Methods Used to Calculate Weight Gain Velocity

The most frequently used method to calculate weight gain velocity reported in the 1543 studies was g/kg/d (40%), followed by g/d (32%); 29% reported change in *z* score relative to an intrauterine or growth chart (Table 1). Some studies used >1 method; thus, the sum of these methods totals >100%. Of the studies that reported weight gain, 17% (*n* = 59) reported using 2 methods, and 2.2% (*n* = 8) reported all 3 methods (g/kg/d, g/d, and change in *z* score). The methods used to calculate weight gain velocity varied significantly over time (Table 1, Fig 2). The most frequently reported method before 2005 was g/d; the change in *z* scores was the most frequently used method between 2005 and 2015.

The first reports using each weight gain calculation method were published in 1947 for g/kg/d,[25] 1966 for g/d,[26] and 1979 for *z* scores.[27]

Calculation of *Z* Scores

The calculation of *z* scores requires a growth reference from which to calculate how many SDs a measurement is from the median/mean of either an intrauterine or preterm growth chart. Of the 108 studies that reported using *z* scores to calculate growth of preterm infants, most (*n* = 104 [96%]) reported which chart they used for comparison. The most frequently reported reference charts for the calculation of *z* scores in this 2015 literature search were those published by Fenton[28] in 2003 (25%), Usher and McLean[29] in 1969 (12%), Fenton and Kim[3] in 2013 (8%), Olsen et al[30] in 2010 (7%), Cole et al[31] in 1998 (7%), and Babson[32] in 1976 (7%) (Table 2).

Assessment of Extrauterine Growth Restriction or Postnatal Growth Failure

Almost one-fifth of the studies (19% [67 of the 355 weight studies]) evaluated the weight gain of preterm

TABLE 4 Frequencies of Methods Used to Report Head Circumference and Length Growth in the 151 Studies That Reported Weight Gain as g/kg/d for Preterm Infants

Variable	Head Circumference (*n* = 74 [49%])		Length (*n* = 74 [49%])	
	cm/wk	Change in *Z* Scores	cm/wk	Change in *Z* Scores
Overall	46 (61%)	20 (27%)	44 (59%)	18 (24%)
<2005*	28 (61%)	1 (5%)	27 (61%)	1 (6%)
2005–2015*	18 (39%)	19 (95%)	17 (39%)	17 (94%)

* $P < .001$ for changes over time for both head circumference and length.

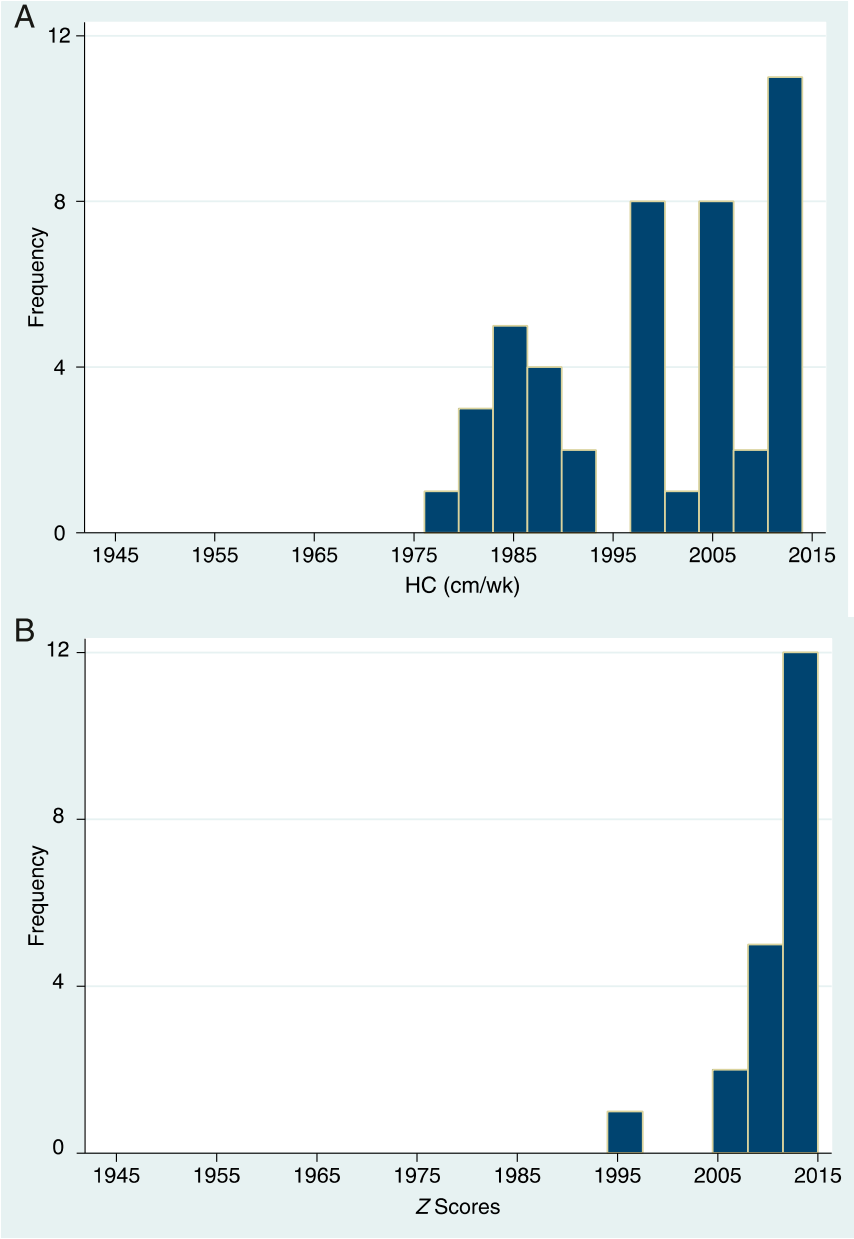

FIGURE 4

Temporal trends of the frequency of reported head circumference (HC) calculations for preterm infants before term age, among the 151 papers that reported g/kg/d weight gain calculations: (A) cm/week, (B) z-scores.

infants at discharge or at a point after the early postnatal weight loss and made conclusions about extrauterine growth restriction or postnatal growth failure. This evaluation of postnatal growth has become more frequent in recent years (11% of the pre-2005 studies [16 of 152] and 25% [51 of 203] of the 2005–2015 studies, among the 355 studies that evaluated weight) (Fig 3). The most frequently reported reference charts for the calculation of postnatal growth failure in this 2015 literature search were those published by Fenton[28] in 2003, Alexander et al[33] in 1996, Fenton and Kim[3] in 2013, and Usher and MacLean[29] in 1969 (Table 2).

Calculation Methods Using g/kg/d

The time frames and denominators used for the 151 studies that reported g/kg/d varied among the studies, and some calculated the growth velocity over subdivisions of time within the studies (Table 3).

The most frequently reported time of the start of the g/kg/d calculations was on the day of birth, day 1, or NICU admission (39%), followed by the start of a study (20%) or at the achievement of full feeds (10%) (Table 3). Less frequent g/kg/d calculation starting times were when birth weight was regained (7%), the weight nadir (1%), and at the time of feeding initiation (1%). The most frequent end time of the g/kg/d calculations was at the time of discharge (30%). Many of the studies used a specific day-of-life to end their g/kg/d calculations, and these ranged from day 7 to day 56, with a mode of 28 days (n = 21 [42%]). Several studies (7%) used a specific weight for the end of the g/kg/d calculation; the most frequently used weight was equal to 2 kg.

The majority of studies that reported g/kg/d calculations did not report what they used for the weight as denominator (n = 94 [62%]). Of the studies that reported the denominators for the g/kg/d calculations, the majority used an average of the start and end weights as the denominator (36%) followed by exponential methods (23%). Less frequently used denominators included birth weight (10%) and an early weight that was not birth weight (16%). Seven of the studies (11%) reported performing a daily g/kg/d calculation; 4 of these reported that they used the weight on the previous day for the denominator, 2 studies used the average weight, and the remaining study reported using the later weight.

Several studies reported using subdivisions of time to calculate

the g/kg/d velocity. The most commonly used subdivision was calculation of g/kg/d weekly (n = 15), whereas 3 studies calculated it daily. Six studies reported g/kg/d growth velocity over 2 time periods, such as birth to regain birth weight, followed by regained birth weight to the end of the study. Nine studies calculated the g/kg/d velocity over a unique set of time subdivisions, including days 1 to 7, days 1 to 35, days 8 to 35, and days 1 to 70.[43]

Head Circumference and Length Growth Velocity Calculations

Almost one-half of the 152 studies that reported g/kg/d growth velocity calculations reported that they calculated head circumference and length (n = 74 [49% for both]) growth (Table 4). The most common methods used for calculating head and length growth velocity were as cm/wk. We included calculations that were simple mathematic variations (eg, millimeters/day and centimeters/4 weeks) in the counts for cm/week, followed by z scores. The first reports of head circumference and length growth velocity calculations were reported as growth in cm/wk in 1979.[44] The first reports of z scores for both head and length growth was in a study by Simmer et al,[45] published in 1997, in which they used the 1983 intrauterine growth chart by Kitchen et al[35] as the growth reference.

Similar to weight gain, there were temporal trends in the use of head circumference and length velocity calculations over time. The most frequently reported methods before 2005 used cm/wk, whereas the change in z scores was the most frequently used method between 2005 and 2015 (Table 4, Figs 4 and 5).

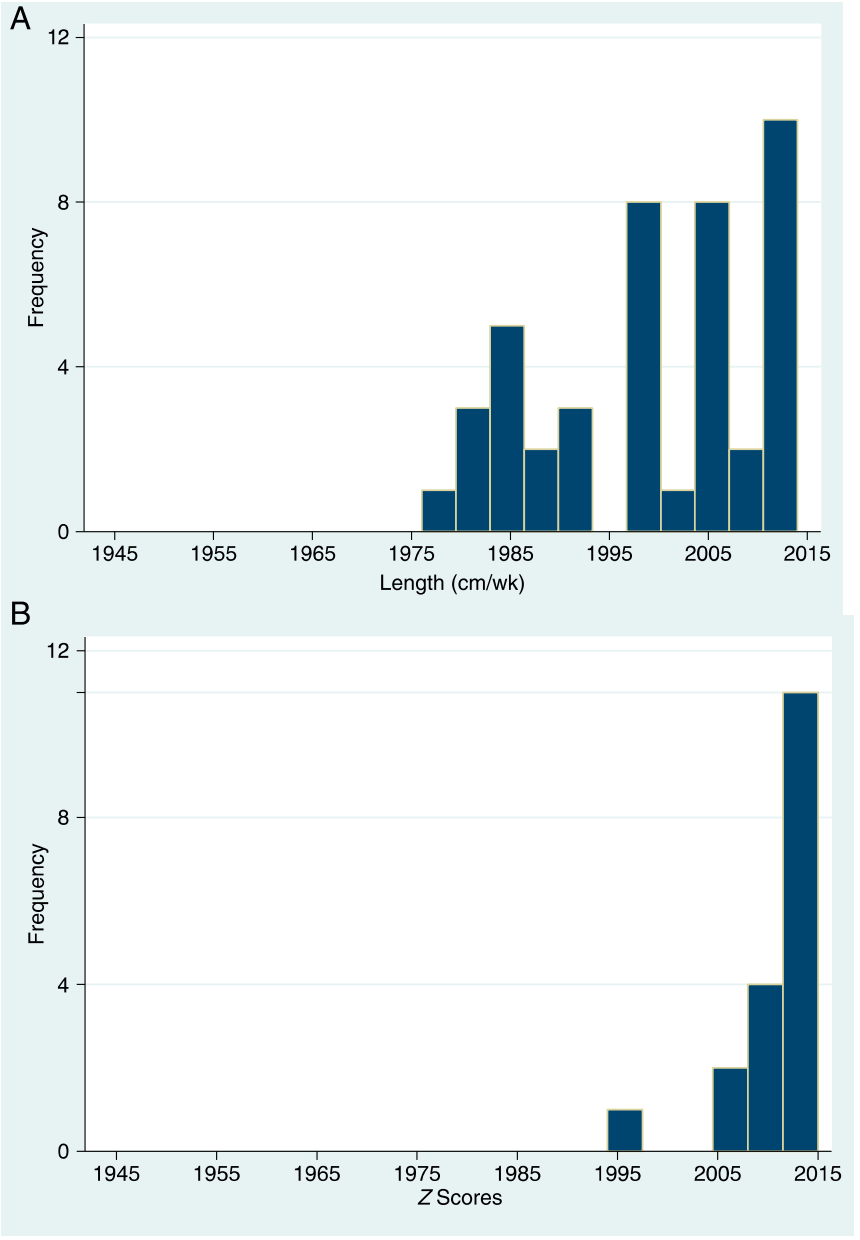

FIGURE 5
Temporal trends of the frequency of reported length calculations for preterm infants before term age, among the 151 papers that reported g/kg/d weight gain calculations: (A) cm/week, (B) z-scores.

DISCUSSION

This first article by our group describes the range of growth velocity methods (a wide variety of measurements and time frames) that have been used by the neonatal community to report growth of preterm infants. Every aspect of growth velocity calculations varied considerably. Weight gain was calculated more frequently than head circumference and length gain, with the latter measures more prevalent in the more recent studies. The many different methods used make comparisons between studies and centers difficult, if not impossible. Additional research is needed to provide guidance for clinicians and researchers; we see this article as the first in a series of articles.

One-quarter of the recent studies of preterm infant weight gain made conclusions about extrauterine growth restriction or growth

failure. A large proportion of healthy preterm infants have weights below the 10th percentile on growth charts after the postnatal extracellular water loss early in postnatal life.[46] Thus, the frequent consideration of weights less than the 10th percentile as extrauterine growth restriction and postnatal growth failure may not be appropriate. We endorse the Pre-B Working Groups' recommendation that assigning extrauterine growth restriction or postnatal growth failure at the time of discharge is not appropriate.[47] They recommend that it is appropriate to use the growth rate of the fetus beginning after the physiologic extracellular volume loss as the growth goal for preterm infants. It is likely more appropriate to evaluate the discharge weight, length and head circumference, and *z* score/percentiles relative to the postphysiologic weight nadir at 2 to 3 weeks of age rather than birth size.[48] Other investigators proposed using day 3 as the start point, considering that it is the postnatal age when weight nadir ideally occurs (when early postnatal nutrition is optimized).[19]

We believe that research is needed to identify which methods are superior and which are inferior in terms of quantifying preterm infant growth. Research is also needed to identify which preterm infants actually have growth failure and how these infants can be identified by using tools readily available to clinicians.

The most prevalent growth velocity measurements have been g/kg/d for weight gain and cm/wk for head circumference and length. There have been some temporal changes in the growth velocity calculations used for preterm infants, with g/d and cm/wk being more prevalent in the earlier studies, and *z* scores becoming popular more recently for weight, head circumference, and length (Figs 2–4). The most frequently used period for preterm infant weight gain velocity calculations was from birth to discharge, which was used by 30% of the reviewed studies.

A substantial proportion of the studies used an exponential calculation of weight gain velocity (23%). Whether an exponential model is relevant is questionable because the rapid early growth rates of infants does not persist or continue in an exponential fashion but rather decreases rapidly after early infancy.[49]

The present study was limited by its observational nature and the frequently incomplete reporting of the methods used in the reviewed studies. An additional limitation was that we only quantified head circumference and length measurements in the 152 studies that reported g/kg/d calculations; thus, we did not capture all of these data in the other 221 studies that calculated growth velocity of preterm infants.

The lack of consistency of methods used to quantify preterm infant growth illustrates that there is a need to develop clinical practice recommendations to standardize preterm infant growth calculations to allow for comparisons between studies.

CONCLUSIONS

The lack of standardization of methods used to calculate preterm infant growth velocity makes comparisons between studies difficult and presents an obstacle for the use of research results to guide clinical practice. It is important for researchers to identify which growth charts were used to calculate *z* scores. At the very least, reports need to describe the methods used for calculation of growth velocity.

Dr Fenton led the design of the study, independently extracted and verified raw data from publications, conducted the initial analysis, and drafted the initial manuscript; and Dr Fenton, Mr Chan, Ms Madhu, Ms Carlson, and Drs Griffin, Groh-Wargo, Hoyos, Senterre, and Ziegler independently extracted and verified raw data from publications. All authors helped design the study, assisted in the preparation of the manuscript, approved the final manuscript as submitted, and agree to be accountable for all aspects of the work.

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