Clinical Nutrition ESPEN 50 (2022) 1–7

Contents lists available at ScienceDirect

Clinical Nutrition ESPEN

journal homepage: http://www.clinicalnutritionespen.com

Narrative Review

Research developments in pediatric intensive care nutrition: A research intelligence review

R. Iping [a, *], J.M. Hulst [b, d, e], K.F.M. Joosten [b, c]

[a] Erasmus MC, University Medical Center Rotterdam, Research Intelligence & Strategy Unit, Rotterdam, Netherlands
[b] Erasmus MC, University Medical Center Rotterdam, Department of Pediatrics, Rotterdam, Netherlands
[c] Erasmus MC, University Medical Center Rotterdam, Department of Pediatric Surgery, Rotterdam, Netherlands
[d] Division of Pediatric Gastroenterology, Hepatology and Nutrition, The Hospital for Sick Children, Toronto, Canada
[e] Department of Pediatrics and Department of Nutritional Sciences, University of Toronto, Toronto, Canada

ARTICLE INFO

Article history:
Received 22 March 2022
Accepted 16 June 2022

Keywords:
Research intelligence
Bibliometry
Pediatrics
Intensive care
Nutrition

SUMMARY

Background & aims: Pediatric intensive care nutrition is a growing research field on the intersection of three large research domains: Pediatrics, Critical Care Medicine and Nutrition & Dietetics. This study, using Research Intelligence tools, such as bibliometric network visualization software, was designed to map the developments in research topics and collaboration in the field over the past thirty years, and discuss how these developments align with recent recommendations and guidelines of the active expert groups in the field.

Methods: We searched the Web of Science Core Collection for relevant full articles, reviews, letters and proceedings papers. To describe the research field a search strategy was iteratively designed based on the combinations of relevant key words. The articles the were found were processed using software designed for bibliometric network mapping. Filters were applied to select only the most relevant articles for the field.

Results: The resulting visualizations show the network of researchers active in the field of pediatric intensive care nutrition, and the collaborations between them. Using the most frequently used key terms a map was created to show the most prominent research areas within the field, and the development of attention for these topics over time.

Conclusions: The network analyses show a research field that is gaining momentum, with several cores of research activity in different institutions. Some research groups collaborate on specific topics within the field, while others seem to be more isolated. The analyses uncover the potential for future collaborations and emerging topics of attention in the different areas of research in the field. The results are compared to recent recommendations for research priorities by active networks in the field. We discuss similarities and discrepancies.

1. Introduction

Optimal nutritional support has been considered of paramount importance for critically ill children admitted to the pediatric intensive care unit (PICU) over the last decades. Almost 40 years ago it has already been reported that protein-energy malnutrition was present in 15–20% of children admitted to the pediatric intensive care unit and this has been associated with worse clinical outcome [1,2].

Over the years more knowledge has been gained about the fact that feeding strategies can attenuate the metabolic stress response, prevent oxidative cellular injury and modulate immune responses [3]. This has led to a shift from nutritional support as adjunctive care to actual therapy of the critically ill child [4].

Improvements in pediatric critical care have led to a very low mortality rate of approximately 2% [5,6]. Whereas there has been a shift in diagnostic categories of critical illness (for example a decrease in infectious diseases), the severity of illness and length of PICU stay have not changed over the last four decades.

* Corresponding author. Erasmus MC, University Medical Center Rotterdam, Doctor Molewaterplein 40, 3015 Rotterdam, GD, Netherlands.
E-mail address: r.iping@erasmusmc.nl (R. Iping).

https://doi.org/10.1016/j.clnesp.2022.06.015

Consequently, every year a significant number of children must live with significant disabilities post- PICU stay [7]. This has changed the focus from mortality to disabilities, usually called morbidities, after PICU admission [8]. Although various risk factors during PICU admission have been associated with long-term neurocognitive impairment, studies examining modifiable factors are scarce [9].

Nutrition might also be a possible modifiable risk factor as it is related to the development of brain structure and functions. This makes it a determinant of neurocognitive functioning. Especially during critical illness, when most children are unable to eat normally, it is important to know which nutritional strategy leads to the most favorable outcome. Two large randomized controlled trials (RCT) have investigated the influence of different nutritional strategies in relation to short- and long-term outcome up to 4 years after PICU admission [10,11].

Over the last 40 years nutrition research in the PICU population has therefore changed markedly from observational studies to large RCTs in combination with long-term follow-up studies concerning neurocognitive functioning.

The research field is positioned at the edge of three larger research domains: Pediatrics, Critical Care Medicine and Nutrition & Dietetics. As such, pinpointing the exact boundaries of the research fields is hard, and getting a good overview of developments and activities in the field is challenging. However, researchers, clinicians, funders and patients involved in this field would benefit from having a good overview of the research developments and the concentration of expertise. In this study we use research intelligence tools, such as bibliometric network mapping software in an approach to tackle the mentioned challenges. We aim to map the current state of research groups and collaborations in the field, and the most prominent topic developments and shifts in research focus. This information should ultimately support strategic decision making in the further development of research in the field of pediatric critical care nutrition.

2. Methods

2.1. Bibliometric definition of the research field

An extensive literature search was performed using the Web of Science Core collection as the source database for publications. This data base was chosen because of the high quality and richness of metadata, allowing the analysis of multiple dimensions using network visualization software, and because it assigns document type labels more accurately than other databases [12]. This choice however does mean that the publication set may be an underrepresentation of the total scientific output in journals, because the core collection only includes journals with an impact factor.

The research field in scope occupies a distinct place overlapping three different broader scientific fields: Pediatrics, Critical Care Medicine and Nutrition & Dietetics. Identifying relevant literature to describe the research field is challenging because meaningful combinations of keywords must be made and processed into a suitable search string that can be applied in a bibliographic database. Because of the broad scope of the three intersecting research fields the search is either too inclusive, or too narrow. The used approach differs from a systematic review in the way that the focus is on broad scale developments and not on a systematic selection of articles and their evaluation. For this goal a search string was designed that was broad enough to include at least all relevant publications from the two involved principal investigators, that are representative for the field.

The search string used in this study was designed following an iterative process. The results of each search were used to revaluate the used keywords, and the visualizations of the publication set were used as feedback loop to test the quality of the search. The final search string, based on a 'topic search', to gather publications was:

TS=(((intensive OR critical*) NEAR/2 (care OR illness* OR ill)) AND ((adolescen* OR preadolescen* OR infan* OR child* OR kid OR kids OR toddler* OR teen* OR boy* OR girl* OR minors OR underag* OR (under NEAR/1 (age* OR aging)) OR juvenil* OR youth* OR kindergar* OR puber* OR pubescen* OR prepubescen* OR prepubert* OR pediatric* OR paediatric* OR schoolchild* OR "school child*" OR preschool* OR highschool*)) AND (Nutrition* OR feeding OR feeds OR nutrient* OR malnourish* OR undernutrition* OR diet*)) AND DT=(Article OR Review OR Letter OR Proceedings Paper) AND PY=(1990–2021) NOT TS = preterm.

Articles starting from 1990 were selected because the coverage of publications in Web of Science is more extensive in the period after 1990, and also the output prior to 1990 in this field is very limited. For this study full articles, reviews, letters and proceedings papers were selected as representative article types in the field. 'Early access' labelled publications were excluded for the reason that these have no publication year yet and therefore cannot be processed in the visualization tool used.

In the next steps bibliometric visualization software was used, that limits the visualized publications to significant contributions to the field by adding thresholds for numbers of publications per author or per keyword occurrences. Because of these thresholds, irrelevant publications dropped out of the publication set automatically and only the core and relevant literature remained part of the visualizations.

2.2. Network analyses—research groups and collaboration

To visualize broad scale developments in the field, such as the activity of research groups, collaboration and the concentration of expertise, and also map the main topics of interest in the field, the obtained publications were processed using the VOSviewer software [13]. VOSviewer creates networks based on co-author relations between authors or institutions in a publication set, or maps the most frequently used keywords in the publications in the set. The size of the spheres in the visualizations reflect the size of the publication output of an author (no author position weighting is applied), or the occurrence of a keyword. Lines between authors reflect co-authorships. The colours represent the scale visible in the bottom of the visualization. The position of authors, institutions or keywords is based on the relations they share (if they are co-authors or if terms occur on the same publications). A threshold of at least 5 publications by one author was used to include the author as a unique visualization sphere. The choice for this threshold is based on trial and error to find the balance between the relevance of the visualized authors and groups (the lower limit) and the visual attractiveness (upper limit) of the image. A correction for name variants has been applied.

2.3. Network analyses—research topics

For the visualizations of the research topics the keywords either assigned by the authors or Web of Science were used. The visualizations were generated using a threshold of at least 9 occurrences per keyword, signifying only the most relevant terms in the publication set. The size of the spheres is indicative for the frequency in which a key term occurs. The lines between the keywords show which terms occur on the same publications and the position and colour reflect clusters of keywords that often co-occur in the same publications. From this clustering, broader topics of attention within the research field can be derived.

3. Results

3.1. Publication output, research groups and collaboration

The search described in the methods section was executed on August 28th 2021 and yielded 2913 publications. Figure 1 shows the number of publications per publication year. The first observation is that the number of publications in this field is still rising, and research groups are continuously emerging, signifying an ongoing interest for research in this field. For 2021 publications until August were included. Because of the general lag in the indexing of articles in the Web of Science it is expected that the total number of publications for 2021 will be comparable or slightly higher than 2020.

Using this publication set and the methodology described a network of active authors in the field was constructed (Fig. 2), with a colour scale indicating the average publication year of the authors. Authors in blue were active in publishing more in the past, authors in green have been active throughout most of the publication years in the scale and probably still are and authors in yellow have become more active in recent years.

The network consists of a core of authors who are connected to each other through co-authorships. Surrounding this core there are several small groups or single authors who are not connected to the core of the network. Most of these authors are blue or green indicating that they are no longer very active in the field or are included in the publication set through a topic that is only partially related to the core of the research in this field. A notable example is for instance Herndon and Jeschke who have published on studies into pediatric burn victims and the role of nutrition in their treatment [14], a specific niche area within the research field. Some research groups are only thinly connected to the core of the research field.

Major groups currently active in the field are the Catholic University Leuven (Belgium), Boston Children's Hospital (United States) and Erasmus MC-Sophia Children's Hospital Rotterdam (the Netherlands) who collaborate closely with each other, demonstrated by the proximity of authors from these institutions in Fig. 2, and the many lines between them, reflecting frequent co-authorships. The Boston group is led by Mehta, an expert in critical care nutrition [4,15]. Erasmus MC and the Catholic University Leuven have a longstanding relationship in research in this field led by Joosten, Verbruggen, van den Berghe, Vanhorebeek, and Hulst, with a focus on nutrition in critically ill children and long-term follow-up of children after the PEPaNIC trial [10,16]. Also, multiple members of the MEN (metabolism, endocrine and nutrition) section of the European Society of Paediatric and Neonatal Intensive Care (ESPNIC; e.g., Valla, Tume, Marino, Verbruggen) are currently active in the field. Valla and Tume represent Hôpital Femme Mère Enfant in Lyon and Salford University Manchester respectively, and have a tight collaboration [17]. In Singapore, the group of Lee is currently very active in publishing on pediatric critical care nutrition [18]. There are two larger groups of researchers who worked more solitary and published mostly in the more distant past, i.e., in Spain the group of Lopez-Herce from Hospital General Universitario Gregorio Marañón with focus on enteral nutrition [19], and in Brazil the group of Pons Leitefrom the Federal University of São Pauloaddressing (mal)nutrition and metabolism [20]. Clearly, members of the European Society of Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) can be found all over Europe who have been active in writing guidelines and position statements (e.g., van Goudoever, Koletzko, Puntis) [21].

3.2. Research topics

A visualization of the broad research topics within the field of pediatric intensive care nutrition using the keywords on the publications in the set is shown in Fig. 3a. The position of each keyword and its proximity to other keywords indicate that they frequently occur on the same or related publications. Based on this principle four generic clusters are identified, as visualized with the four different colours. Topics were identified from the core of the resulting network visualization.

In the core of the network more generic terms can be observed that occur in publications throughout all of the clusters. Towards the edges of the network, clusters of topics can be

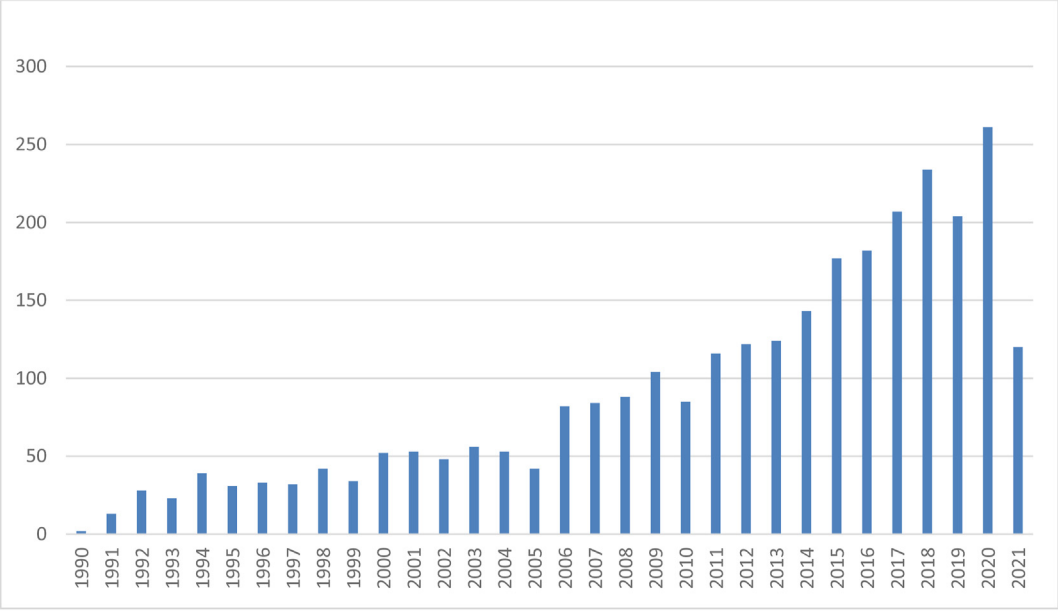

Fig. 1. Number of publications from our search in web of science in the field of nutrition in pediatric critical illness per year since 1990 (total n = 2913).

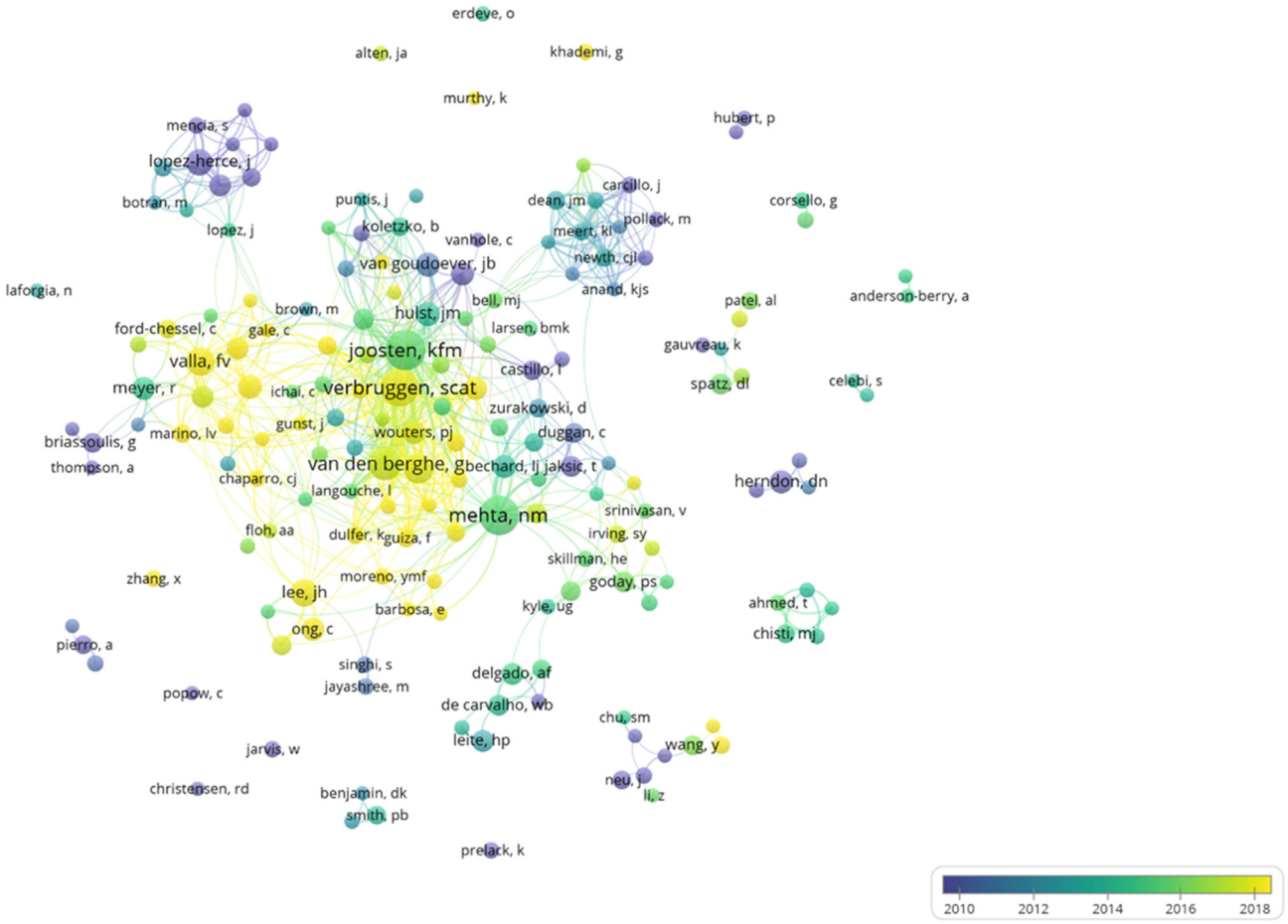

Fig. 2. Network of researchers active in the field of pediatric intensive care nutrition since 1990. The size of the spheres reflects the relative size of the output of an author in this field. Lines reflect co-authorships, and the colour shows the average publication year of an author with the yellow colour indicating more recent years.

identified, such as the terms in green that cluster around parenteral nutrition (PN), glucose, protein and metabolism-catabolism in pediatric critical illness. The terms in the yellow cluster contain research into enteral nutrition and malnutrition, energy expenditure and indirect calorimetry, nitrogen balance and nutrition support for critically ill children. The terms in the red cluster contain research on complications, outcome, nutritional management and specific diseases like gastroschisis and omphalocele. The terms in the blue cluster indicate research on nutrition and feeding in neonatal intensive care, infections and sepsis.

Figure 3b shows the same key terms as in Fig. 3 but with an overlay showing the average publication year of each term. Research using terms in the red and yellow clusters from Fig. 3 have more recent average publication years indicating a shift in focus of research towards these clusters. Specifically, more recent research is focused on (early) enteral nutrition, specific diets and protein intake in the setting of larger clinical multicentre studies. There is also more focus on short and long-term outcome studies in critically ill children. Both the Boston and the Rotterdam/Leuven group have focused on feeding strategies during admission in relation with PICU outcomes and neurocognitive outcome years after PICU admission [11,15,22–24]. Also, in recent years several guidelines on parenteral and enteral nutrition (by ESPGHAN, ESPEN, ESPR and/or CSPEN, ESPNIC) [25,26] were published with the most up-to-date practices based on the current state of research in the field of pediatric intensive care nutrition.

4. Conclusions and discussion

This study used novel methodology to map the state of research groups, collaborations and topics studied in the field of pediatric intensive care nutrition over time. The analyses uncovered not only clusters of topics in which most research has been performed but also international network connections. The map of these connections shows a core network, and several groups surrounding this core, sometimes connected by co-publications. We believe there is an opportunity to further integrate the collaboration between the active groups in the field to accelerate research progress, knowledge sharing and dissemination, and for joint grant acquisition. Furthermore, four larger clusters of research within the field could be identified using the network visualization of keywords from the publications in the set. Concerning these clusters of topics, both pediatric intensive care and neonatal intensive care are plotted and have an overlap. This is due to the fact that in many intensive care units pediatric and neonatal care are combined in one unit. Interestingly different topics are related to the pediatric and neonatal care.

When comparing the most recently published research topics from our analysis with the proposed future research agenda published by two professional scientific bodies (ESPGHAN/ESPNE/ESPEN/CSPEN [27]) on PN and ESPNIC on pediatric critical care nutrition [22], shown in Table 1, both similarities and discrepancies can be found. In 2018 the societies of ESPGHAN/ESPEN/ESPR/CSPEN published the pediatric PN guidelines [28] and the first authors of

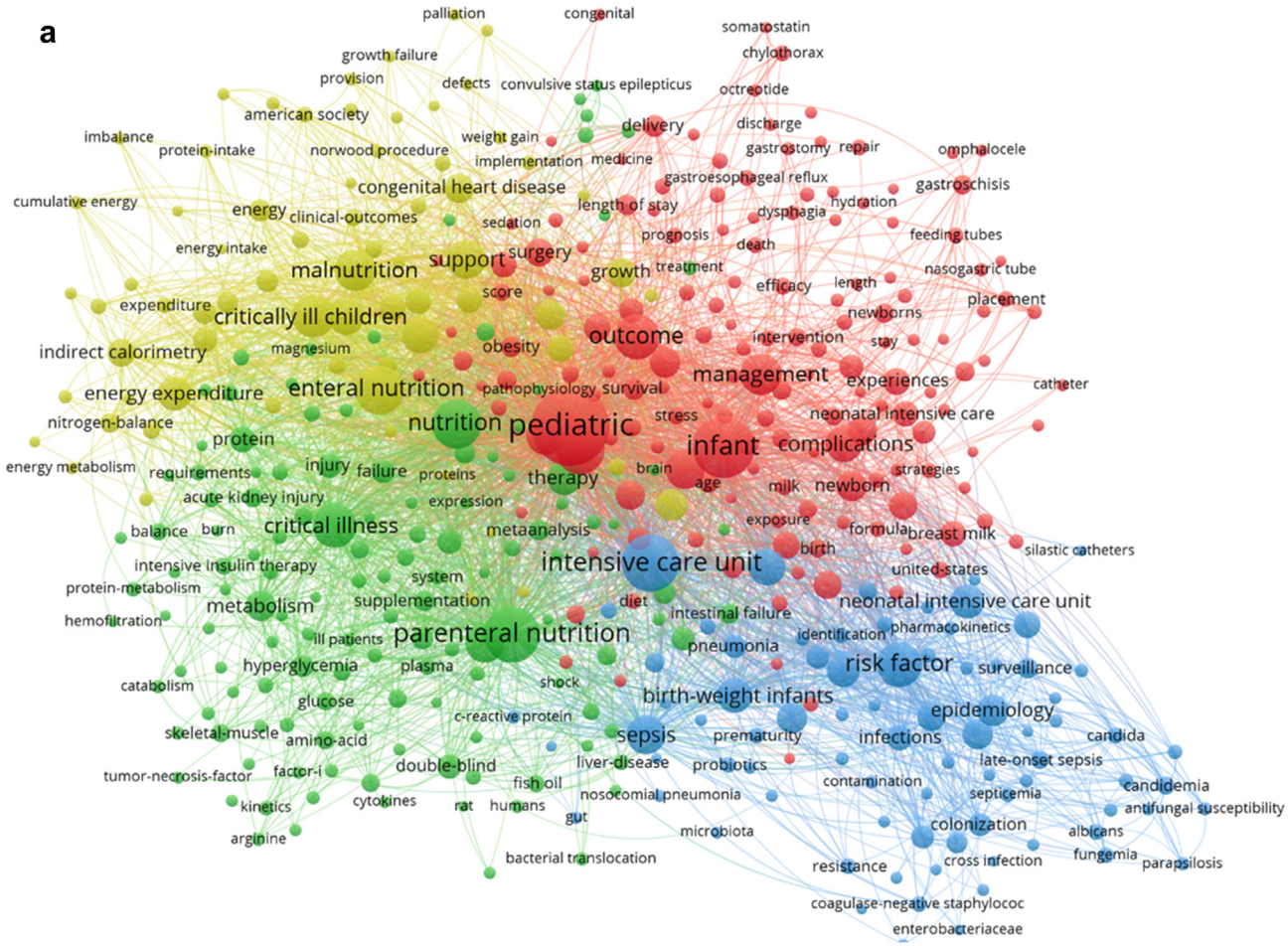

Fig. 3. a: Visualization of most frequently used keywords in publications on pediatric intensive care nutrition since 1991. The size of the spheres indicates the frequency a keyword occurs in the publication set. The lines show which keywords occur on the same publications. The colours are clusters of keywords that often occur on the same or related publications. b: Visualization of keywords in publications on pediatric intensive care nutrition since 1991 in relation to publication date. The size of the spheres indicates the number of times a keyword occurs in the publication set. The lines show which keywords occur on the same publications. The colours indicate the average publication year of each term.

the different topics identified research priorities to help future research in pediatric PN [26]. The first and second priority out of the top 5 address relationships between energy intake, rapid catch-up growth and later neurocognitive function and energy intake in relation with different phases of illness. Our study shows that in recent years more research is conducted concerning outcome but not really on energy intake and catch-up growth. The other 3 priorities of this top 5 addressed preterm infants which is beyond the interest of this study.

Another group of experts ("ESPNIC-group") developed a list of topics to be prioritized for nutrition research in pediatric critical care in the next 10 years [27]. Top 1 priority is the impact of low versus high protein on clinical outcomes which is more or less in line with the ESPGHAN priorities. Remarkably, in this top 5 some new topics were mentioned, such as preserving muscle mass/rehabilitation and nutritional risk assessment which can hardly be found yet in the bibliometric visualization.

Also, the Pediatric Special Interest Group of ESPEN performed a literature search [29] to capture publications in the last five years aiming to provide the latest information concerning nutritional issues in children in general and in specific diseases and to discuss progression in the field of pediatric evidence-based nutrition practice. Eight major topics were identified and critical illness-pediatric intensive care, neonatal intensive care and PN were three of these topics. Concerning PN it was concluded that most papers came from the 2018 ESPGHAN/ESPEN/ESPR/CSPEN guidelines on pediatric PN. Concerning critical illness/pediatric intensive care 17 articles were quoted of which 6 were guidelines. In neonatal intensive care 11 articles were quoted but no new guidelines. The overall conclusion of this overview was that most reports were systematic literature reviews or guidelines/position papers of relevant societies, with many papers basing conclusions on a limited number of high-quality RCTs or large observational cohort studies. These conclusions are in line with the results from the current network analyses, which uncovered i.e., that although many groups in the field are connected to each other through joint publications (guidelines/position papers), these ties are still thin and research in this field could benefit from increased collaboration. Studies focussing on clinical interventions, treatments and outcomes with a joint approach in multiple centres are needed, not only within the boundaries of the ESPGHAN community, but also including other promising researchers from centres worldwide with a similar research focus.

Overall, the use of novel Research Intelligence tools enabled us to assess and visualize broad scale research developments in the field of pediatric intensive care nutrition and describe how these

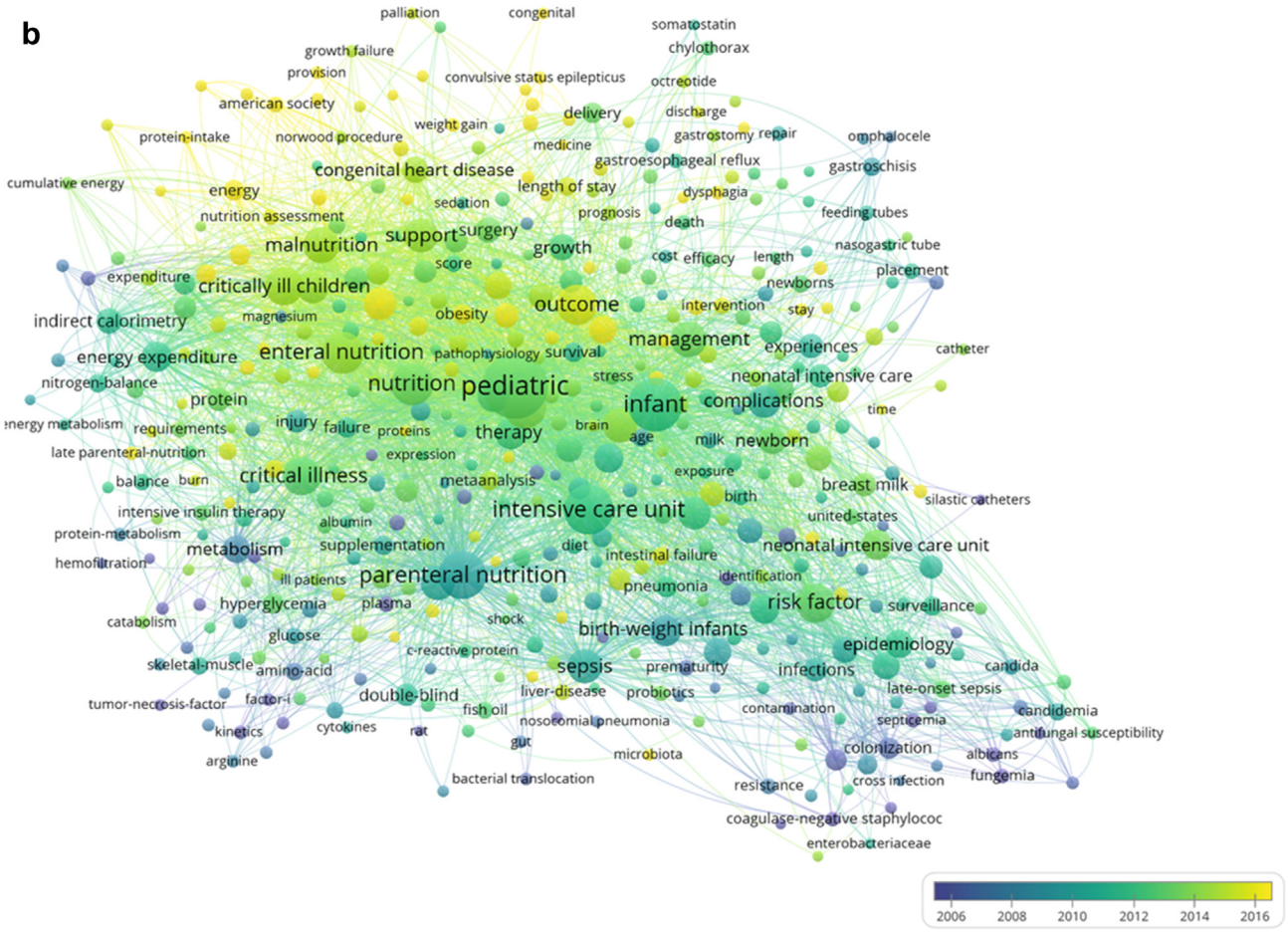

Fig. 3. (*continued*).

Table 1
Top research priorities in pediatric critically ill nutrition as proposed by 2 professional organisations.

Research priorities	ESPGHAN [25]	ESPNIC [26]
1	Understanding of the relationship between total energy intake, the potential adverse effects of rapid catch-up growth on later metabolic function and potential neurocognitive benefit.	To determine the impact of low versus high protein intake on clinical outcomes
2	Defining the optimal energy intake in the different phases of illness (acute, stable and recovery) in critically ill children, including the optimal route and doses of macro- and micronutrients	To determine whether early protein provision in the first 48 h preserves muscle mass
3	Establishing how should hyperglycemia be defined in the preterm population, and whether is it best managed with a reduction in carbohydrate or higher carbohydrate in combination with insulin	To understand the role of combined mobilisation and protein supplementation on preserving muscle mass and function
4	Assessing the initial, optimal and/or maximal dose of lipid infusion and the ideal fatty acid (FA) composition needed to achieve the best long-term effects on morbidity, growth, and neurodevelopment in preterm infants	To determine the impact of an early combined mobilisation/ rehabilitation and targeted nutritional strategy on preserving muscle mass and function
5	Defining the optimal energy:protein ratio for preterm infants	To develop a valid nutritional risk assessment score that identifies children at risk of nutritional deterioration, and those who might benefit from timely interventions

results align with recent guidelines and recommendations. The snapshots of the research field can be used to monitor trends and developments in the network over the coming years. The results can help to further structure the future research agenda in pediatric intensive care nutrition. Another dimension that is generally of interest in bibliometry is citations. These could potentially be used to identify topics of specific interest within the dataset. However, in our data we found that the average number of citations per topic was too skewed towards older topics which have had more time to get cited. The average normalized number of citations showed a scattered image of isolated terms that were on average more highly cited, but no clusters within the topic map that were generally more highly cited. Because this information was of no added value to the other analyses, we therefore chose not to include the citations dimension in this paper.

Based on the analyses it can be recommended to set up more collaborative large scale interventional research projects (observational studies and randomized controlled trials), focussing on the topics that are gaining momentum shown in the maps. It is imminent that the research groups active in the field (both established and emerging) collaborate more in setting up international databases and combine patient cohorts to advance and generalize research outcomes. From a research intelligence perspective, it can be recommended to further analyse developments in the larger research fields (Nutrition, Intensive Care and Pediatrics) to establish the position of pediatric intensive care nutrition within these fields, find interesting links and developments for cross-over research opportunities.

Author contributions

Rik Iping: Conceptualization, Methodology, Formal Analysis, Data Curation, Visualization, Writing- Original draft preparation.

Koen Joosten: Conceptualization, Validation, Writing- Original draft preparation, Supervision.

Jessie Hulst: Conceptualization, Validation, Writing- Reviewing and Editing.

Funding statement

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Declaration of competing interest

The authors declare that there are no conflicts of interest.

Acknowledgements

No acknowledgements.

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