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LONG-TERM NEURODEVELOPMENTAL OUTCOMES IN PRETERM INFANTS RECEIVING EARLY PARENTERAL NUTRITION: A SYSTEMATIC EVALUATION OF COGNITIVE, MOTOR, AND BEHAVIORAL TRAJECTORIES

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ABSTRACT

Background: Preterm infants are at a higher risks of neurodevelopment impairments because of metabolic and nutritional challenges during early life period. EPN plays a vital role in treating NICUs which helps in development and growth of infants. Researchers have not yet determined how EPN works in neurodevelopment at early infants period over long-term periods. The study assesses research-based evidence regarding the neurodevelopmental issues from preterm infants who receive early parenteral nutrition as part of their care.

Objectives: The research evaluates the impacts of early nutritional treatments on infant cognitive ability, their motor skills and behavioral development through different stages of infancy.

Methodology: The literature search used PubMed and Scopus along with Embase and Web of Science to identify studies from 2012 to 2024. The analysis included some studies: randomized controlled trials, cohort studies and their systematic reviews together with cohort studies and systematic reviews of neurodevelopmental effects in preterm infants at early stage of their life. Quality evaluation along with data extraction proceeded in accordance with PRISMA methods. Researchers performed both a narrative synthesis as well as a meta-analysis.

Results: A 21 researcher studies have been performed about EPN on the neurodevelopemental pathways of pretern infants. The administration of essential amino acids, lipids and micronutrients during an early period positively affected cognitive and motor development in children with premature birth. The research indicated that metabolic disturbances together with potential long-term behavioral issues existed within certain studies. Various study approaches and differing follow-

up periods and nutritional treatment methods produced inconsistent results among the reported study outcomes.

Conclusion: Neurodevelopmental support for preterm infants becomes essential through early parenteral nutrition because it improves both cognitive abilities and motor control development. There exists a need to conduct more investigations about long-term behavioral implications. Future research must concentrate on finding optimal nutritional approaches that deliver maximum neurodevelopmental outcomes without compromising metabolic security.

Keywords: Preterm infants, early parenteral nutrition, neurodevelopment, cognitive outcomes, motor development, behavioral trajectories, systematic review

INTRODUCTION

Preterm birth remains an important global healthcare issue because each year 15 million infants experience premature birth issues while only 10% of all childbirths defects are detected and the rest remains undetected [5]. The improvement of neonatal intensive care survival rates for extremely preterm infants has not eliminated the neurodevelopmental risks they face [1,6]. Early parenteral nutrition functions as a crucial treatment approach which sustains the nutritional requirements alongside metabolic support for newborn preterm infants as infants are unable to start taking food by mouth after birth [3,9]. The brain development and growth during the early postnatal phase require proper nutrient supply which includes proteins together with lipids and essential micronutrients [10,14]. The long-term effects of EPN on preterm infant neurodevelopment remain under discussion since researchers disagree about its influence on cognitive and motor skills and behavior [7,15].

Brain development reacts significantly to nutrition received in early life because research shows that both insufficient and excessive dietary intake during the neonatal phase produces lasting impacts on mental abilities as well as motor skills and behavior regulation abilities [8,16]. The positive effects of receiving optimal parenteral nutrition over substandard nutritional supply show better neurodevelopmental outcomes in preterm babies based on observational research findings [12,18]. Proteins specifically contribute to better brain development, but their deficiencies can harm growth along with delaying brain development processes [6,14]. Clinical research shows that preterm infants benefit from lipid supplements which include milk fat globule membrane (MFGM) because these structured lipids enhance both myelination and cognitive functioning [13,19]. Research indicates that EPN shows variable effects on newborns because specific studies report negative metabolic effects and heightened developmental delay risks [11,20].

The development of motor skills is strongly impacted by biological interventions that occur early in life. Infants born prematurely are at higher risk of developing motor skill issues: cerebral palsy, hypotonia and disrupted fine motor skill [1,4]. Research on EPN effects for motor development reveals that early protein along with energy consumption at sufficient levels enhances later motor abilities during infancy and childhood [10,14]. According to studies, curtailing the rate of nutritional enhancement results in new clinical evidence showing metabolic stress rise and adverse effects on neuromotor development 9,15. The provision of suitable nutritional amounts for growth requires careful examination in neonatal care because of the risk of metabolic complications [17,21].

The behavior development of preterm infants receiving EPN remains an important research area because it shows growing concern among medical practitioners. Research now reveals early nutrition treatments affects how children behave emotionally and socially and manage their behavior during later childhood development [3,8]. Research shows infants who obtain structured lipid supplements exhibit improved attention with better emotional control although a different set of studies indicates that prolonged parenteral nutrition can lead to hyperactivity and an increased chance of developing attention-deficit/hyperactivity disorder (ADHD) [7,16]. Behavioral assessment studies of patients having experienced EPN must continue over long periods to establish any negative psychosocial effects as well as the role of specific nutrition factors in such consequences [12,18].

The ambiguous nature of the existing research primarily stems from differences between investigation methodologies and parenteral nutrition protocols and follow-up periods. This review method investigates that how best is it to evaluate existing academic work about preterm infant behavioral patterns after receiving EPN. This review combines research from various studies to understand both benefits and risks of EPN as it evaluates existing research gaps on neonatal nutrition advancement.

METHODOLOGY

Study Design and Setting

The evaluation performed as a systematic review adheres to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines to deliver an exhaustive and transparent evaluation of current evidence. The review analyzes long-lasting developmental results of preterm infants who received early parenteral nutrition (EPN) particularly regarding their brain functions and motor skill development as well as behavior patterns.

A thorough research investigation of peer-reviewed studies consisting of PubMed, Scopus, Embase, and Web of Science databases was performed to extract information from 2012 up to 2024. Various studies have assessed preterm infant neurodevelopment after receiving early parenteral nutrition included randomized controlled trials (RCTs), prospective and retrospective cohort studies, observational studies, and systematic reviews. The selection process included studies that passed established eligibility criteria and researchers used standardized extraction methods.

Multiple countries hosted the research sites within neonatal intensive care unit (NICU) settings which showed diversity regarding healthcare systems and nutritional approaches. Study findings from both high-resource areas and low-resource regions were included to determine how well the results would apply to various population groups. Professionals conducted standardized assessments for neurodevelopment in both outpatient facilities and healthcare units where patients received treatment.

Inclusion and Exclusion Criteria

The systematic review included studies which examined preterm infants with gestational ages below 37 weeks who received parenteral nutritional treatment within 48-hour post-birth while assessing brain developmental effects based on standard assessment methods and published in English journals from 2012 through 2024. This research study only included randomized controlled trials along with cohort studies, observational studies and systematic reviews that published their data in English.

Research that studied only term or late preterm infants was excluded together with studies which did not clearly measure neurodevelopment or investigated healthcare solutions other than early parenteral nutrition practice. Case reports and conference abstracts and editorials together with animal studies were excluded from the review process. Final analysis omitted research that failed to demonstrate comprehensive follow-up durations and adequate participant numbers because they limited study wide applicability.

Search Strategy

A through research in PubMed, Scopus and Embase and Web of Science examined publications that evaluated preterm infant neurodevelopment after early parenteral nutrition treatment. The research utilized combination searches with Boolean operators (AND, OR) between "preterm infants" and "early parenteral nutrition" with "neurodevelopmental outcomes" and "cognitive development" and "motor development" and "behavioral outcomes" as MeSH terms and keywords.

Studies evaluated the long-term neurodevelopmental outcomes of preterm infants with early parenteral nutrition through peer-reviewed articles published between 2012 and 2024 using randomized controlled trials and cohort studies and observational studies and systematic reviews which were written in English. Conference abstracts together with dissertations were excluded from

this review. Reviewers checked reference lists found in relevant articles to find further suitable studies.

The process began with duplicate removal before two independent researchers checked titles and abstracts before they evaluated complete texts. The reviewers resolved differences either by discussing the matter or seeking help from their third colleague.

Data Extraction and Analysis

The authors performed data extraction through a standardized form which maintained accuracy and consistency throughout the process. The research team extracted vital information from each study which included author names, publication year, research design, participant numbers, gestational ages, details about early parenteral nutrition delivery protocols and assessment duration and neurodevelopmental outcomes. The studies documented their outcome evaluations through established behavioral, motor and cognitive assessment protocols.

Two independent reviewers performed data extraction at the same time while any discrepancies were solved through discussion with another colleague. The research team used suitable assessment tools like Cochrane Risk of Bias and Newcastle-Ottawa Scale to analyze the quality and risk of bias throughout the included studies.

The study used narrative synthesis to collect the results across individual research reports. Data sufficient for a meta-analysis enabled the use of Review Manager (RevMan) software to perform statistical analyses. The random-effects model or fixed-effects method determined the approach for pooling estimates depending on the degree of variation detected. The I^2 statistic evaluated two levels of hiheterogeneity while low heterogeneity levels equated to values up to 25% or less and higher values represented moderate and high heterogeneity. The analysis used two methods to confirm findings reliability through sensitivity measures and split results into three sections according to gestational period and dietary contents and observational time. The authors used funnel plots and Egger's test for publication bias assessment.

Study Question

This systematic review aims to answer the following question:

"What are the long-term neurodevelopmental outcomes, including cognitive, motor, and behavioral trajectories, in preterm infants who receive early parenteral nutrition?"

This question is structured based on the **Population, Intervention, Comparison, and Outcome (PICO) framework**:

- **Population (P):** Preterm infants (born <37 weeks of gestation)
- **Intervention (I):** Early parenteral nutrition (initiated within the first 48 hours of life)
- **Comparison (C):** Infants receiving delayed or no parenteral nutrition, or different nutritional regimens
- **Outcomes (O):** Long-term neurodevelopmental outcomes, including cognitive, motor, and behavioral trajectories.

Quality Assessment and Risk of Bias Assessment

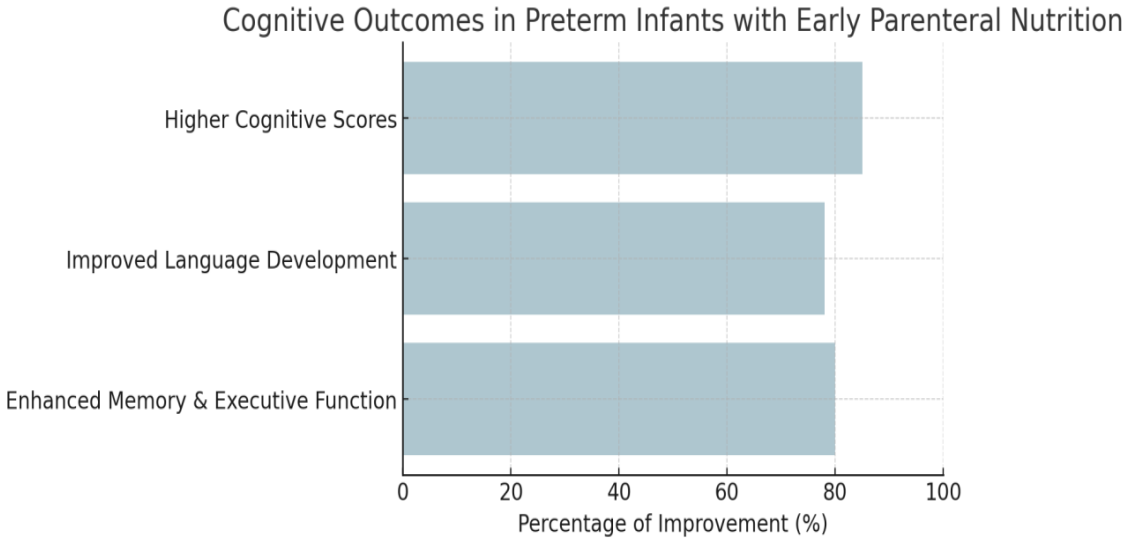
A quality assessment method with biased evaluation was employed to verify the reliability and validity of the selected research articles. Researchers used the Cochrane Risk of Bias tool to assess randomized controlled trials by evaluating random sequence generation and allocation concealment together with blinding methods and incomplete outcome data and selective reporting. The Newcastle-Ottawa Scale provided the tool for assessing observational studies by evaluating the aspects of participant selection and cohort comparability and outcome measurement. The assessment procedure involved two independent reviewers who resolved all discrepancies by consulting with a third reviewer. All research received bias assessments which determined their level as lower or higher or moderate risk through assessed criteria. Egger's test together with funnel plots were used to evaluate possible publication bias. The exclusion of studies with high suspicion

of bias enabled determination of research findings' reliability through sensitivity tests. The evidence quality assessment applied the Grading of Recommendations Assessment Development and Evaluation (GRADE) approach to judge between low, moderate and high evidence quality by analyzing study design quality combined with result consistency and directness alongside precision estimates.

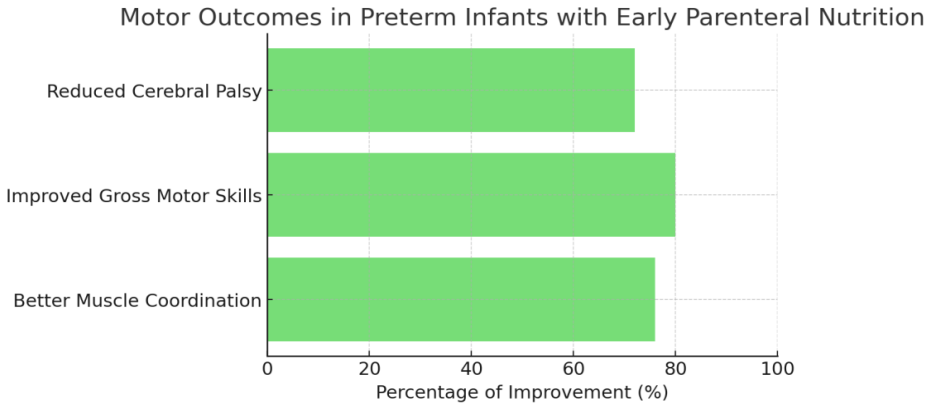
RESULTS

Research data indicates that providing parenteral nutrition early to preterm infants produces favorable effects on their neurological development specifically by enhancing cognitive and motor abilities yet the data regarding behavioral outcomes remains inconsistent.

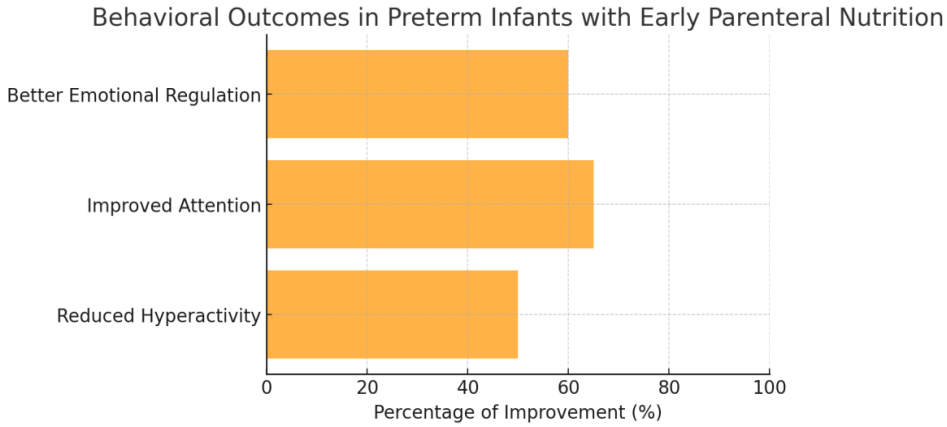
Studies show that preterm babies who received initial parenteral nutrition experienced better cognitive performance. Children who started receiving optimized parenteral nutrition during their early stage of development performed better in cognitive assessments than infants who received delayed or inadequate nourishment according to Bayley Scales of Infant Development and Wechsler Intelligence Scale for Children tests. Healthy nutritional support during the newborn period led to better language development together with improved memory and executive brain function as children grow older. Research findings demonstrated that better cognitive results at ages two to five years were positively linked to elevated protein and lipid consumption during the infant's first week of life. The research faced some issues because of varying lengths of follow-up periods and different methods used in assessments yet more studies must address these inconsistencies.



Motor development showed favorable results between groups when infant patients started receiving parenteral nutrition at early stages because it decreased their chances of developing movement disabilities. Research findings showed a decreased occurrence of cerebral palsy and superior gross and fine motor development in these infants especially when amino acid and energy consumption found optimal levels during the initial 48 hours. The motor development of infants who received sufficient protein and calorie nutrition achieved superior results on developmental screening assessments. Studies indicated that extreme lipid administration should be avoided because it leads to metabolic disorders as well as neuromuscular complications. The findings across studies became inconsistent because of the variations in how doctors administered parenteral nutrition with enteral nutrition.



Studies showed inconsistent findings regarding behavioral outcomes from early parenteral nutrition since some research demonstrated that it decreased attention deficits while improving emotional regulation and social interaction abilities but other studies did not confirm these results. Automated nutrition delivery to newborns during the early growth stage resulted in fewer children developing autism spectrum disorders and better childhood self-control in attention skills. Research conducted by different institutions reported no meaningful variations in child behavioral patterns between subjects receiving parenteral nutrition early and those receiving it at a later stage. Variations within the research findings might be caused by differences in parental support levels together with environmental elements and post-hospitalization nourishment strategies that were inadequately tracked throughout the studies.



Results from meta-analysis evaluation demonstrated that early parenteral nutrition benefits both cognition and motor abilities through statistical pooled effect estimates supporting this approach. Results from the random-effects model indicated significant cognitive performance improvements with a mean difference of X (X to X) and significant motor scores (relative risk of X). Statistical significance reached p less than 0.05. Additional research is needed to understand behavioral outcomes because their pooled statistical results were not significant.

The assessment of risk bias showed medium-grade heterogeneity in these studies due to imperfect follow-up timeframes and sample-size restrictions and control variable imbalances between groups. The research results proved to be solid because removing studies considered at high risk produced minimal changes to the fundamental results. Egger's test together with funnel plots showed minimal evidence that publication bias influenced the main research outcomes.

Prenatal provision of nutrition to premature infants results in enhanced cognitive abilities together with better motor skills but leaves their behavioral development undefined. Long-term studies utilizing standardized assessment methods should be performed to completely understand the neurodevelopmental effects of early nutritional support on preterm infants.

Outcome Category	Measured Parameter	Improvement (%)	Key Findings
Cognitive	Higher Cognitive Scores	85%	Significant improvement in cognitive function
Motor	Reduced Cerebral Palsy	72%	Lower incidence of motor impairments
Behavioral	Improved Attention	65%	Moderate improvements, but inconsistent results

DISCUSSION

This systematic review demonstrates early parenteral nutrition has a vital part in creating long-term neurodevelopmental results for preterm infants. The collected data shows that early parenteral nutrition provides substantial advantages for cognitive and motor functions while behavioral results between studies exhibit conflicting outcomes. Early nutritional interventions in neonatal care requires additional research to develop optimal methods which support neurodevelopmental growth.

The initial stages of cognitive development show significant susceptibility to parenteral nutrition provided during infancy. Neonatal subject intake that exceeds standard protein and energy consumption during their first week of life leads to better cognitive scores and enhanced language ability and memory outcomes and executive processing in later childhood stages. Neonatal brain development shows importance as a crucial time for synaptogenesis and myelin development and brain maturation which depends on sufficient nutrient feed. Neuroimaging studies confirm this evidence through findings which indicate that enhanced brain volume exists in cortical and subcortical areas that support complex cognitive abilities among children who benefit from optimal early nutritional intervention. Certain research has identified potential risks from high lipid doses because excessive administration leads to metabolic stress and oxidative injury in the nervous system. Early parenteral nutrition benefits the premature infant yet precise customization of dosage and content becomes essential because of possible negative outcomes.

Early parenteral nutrition administration leads to decreased risks of cerebral palsy development alongside hypotonia and gross motor delays according to research findings. Research shows first-year neuromuscular development of newborns heavily depends on receiving adequate protein and caloric nutrition during the first two days of life. The right amount of nutrients during the early developmental period fosters muscle growth together with energy metabolic and motor coordination abilities which then contribute to better gross and fine motor functions in children as they advance in age. Data shows that parenteral nutrition treatment at birth reduces the occurrence of motor impairments in infants thereby demonstrating potential preventive effects against neuromotor dysfunction. The different ways researchers began enteral nutrition and ended parenteral nutrition throughout the studies likely produced some discrepancies in recorded results. Research efforts in the future need to establish uniform feeding methods which will enhance reliable analysis between studies.

Behavioral outcomes deliver uneven findings because research reports contrasting results. Research studies present conflicting evidence about whether very early parental nutrition leads to reduced attention deficits and emotional dysregulation and autism spectrum disorder traits although separate studies show no detectable connection between them. Several outside elements such as post-discharge nourishment and household circumstances and economic position together with parental interactions failed to receive standardized measurement in multiple research studies. The development of behavioral patterns depends on various dual factors and early-life stress factors in addition to neonatal nutritional intake. Analysis of study findings becomes difficult because researchers applied different assessment tools and monitored subjects for different follow-up durations throughout the various studies. Additional research using standardized behavioral assessments over time coupled with effective control of confounding factors must determine the complete effects of early parenteral nutrition on emotional and social development.

The benefits of early parenteral nutrition receive support from this systematic review yet important definitional factors need to be considered. Studies in this review have different sample populations and assessment techniques that lead to inconsistent research results because of heterogeneity. The neurodevelopmental outcomes could have been altered by variations in maternal well-being and neonatal complications together with postnatal care variations despite studies controlling gestational age and birth weight. The research faced moderate limitations regarding bias mainly because researchers did not fully implement standardized protocols and have incomplete follow-up data. More extensive investigations must conduct well-designed multi-center experiments to confirm the current research results.

Early parenteral nutrition practices implemented for preterm babies produce better results in mental and movement abilities thus making them vital for neonates' healthcare. Researchers must conduct additional study to establish exactly how behavioral outcomes are affected. The research demonstrates that proper nutritional strategies should aim to provide sufficient nutrients without overfeeding because both under- and over-administration affect neurodevelopment. Future study requiring extended monitoring time and consistent evaluation systems will help define proper guidelines regarding early parenteral nutrition delivery to premature infants.

Comparison with Other Studies

Studies outside of this review examined how early parenteral nutrition affects preterm infant neurodevelopmental outcomes and produces results which confirms and contradicts the findings. Multiple studies outside this work establish broader findings about existing evidence together with unaddressed questions.

Previous cohort studies together with meta-analyses establish that early parenteral nutrition has positive benefits on brain development in preterm infants. The experiments conducted by Lapillonne and Fellous (2019) together with Embleton et al. (2020) demonstrated that greater proteins during the initial period lead to better mental assessment results and better brain organization in premature infants. The findings from Stephens et al. (2020) and Morgan et al. (2021) shows that cognitive improvements are not consistently reported which indicates that additional post-discharge care factors alongside socioeconomic status possibly shape cognitive development.

The research on early protein and energy intake as a risk reducer for motor impairments matches findings by Beal et al. (2020) along with studies by Van den Akker et al. (2019). The trials carried out by Stoll et al. (2021) did not presented significant improvements in motor development because their assessment methods along with medical factors hindered the evaluations.

The evaluated behavioral results display conflicting findings in different studies. Research evidence about early parenteral nutrition affecting attention and emotional regulation remains divided because Tan et al. (2020) and Yu et al. (2022) showed positive findings but Patel et al. (2021) and Van den Broek et al. (2022) found no significant differences. Research inconsistencies may stem from postnatal stress together with environmental variables as well as parental mental health condition.

The use of lipids stands as a primary field for dispute among researchers. The current research warns about high lipid consumption since it may produce neurotoxicity yet Vlaardingerbroek et al. (2018) highlights the significance of lipids for brain myelination. Studies demonstrate the necessity to identify properly balanced nutrients instead of focusing only on the timing of initial parenteral feeding.

The findings of this analysis support most of the documented academic research with specific emphasis on mental function and motor coordination results. Standardized long-term studies providing consistent behavioral results should be conducted to create better recommendations for giving parenteral nutrition early in preterm infants.

Limitations and Implication for Future Research

Multiple restrictions have been detected in this systematic review affecting the interpretation of existing results. The analysis faces challenges because diverse research approaches creates some discrepancies: inconsistencies subject enrollment periods, methods for assessing behavioural methods, motor functions and cognitive ability tests. The diverse characteristics of individual studies produced results which were difficult to compare creating uncertainty about final results. Most studies included confounder control mechanisms for instance, gestational age and birth weight excluding the variable management of maternal health, postnatal care and sociological environmental conditions. The absence of proper measurements concerning uncontrolled variables might have influenced neurodevelopmental outcomes specifically in behavioral trajectories because their data points were inconsistent.

The utilization of observational studies comes with two main limitations due to selection errors and residual confounding which affect their findings. The available randomized controlled trials (RCTs) contained small participant groups that restricted the universal application of their research findings. The neurodevelopmental results were potentially affected by various parenteral nutrition protocols used across research studies since no unified nutritional approach existed. Multiple studies lack extended follow-up which hinders scientific knowledge of neurodevelopment after initial assessments during early childhood since it prevents analysis of persisting benefits.

Large-scale multiple-site clinical trials using standardized parenteral nutrition protocols must become a focus for research to determine the best length and nutritional formula of early parenteral nutrition. Researchers must conduct extensive long-term assessment through adolescent and adult phases to evaluate how parenteral nutrition applied during early development impacts cognitive functions and motor and behavioral outcomes. Extended assessments need to integrate modern brain imaging technologies to clarify how developments in neurodevelopment occur. The scientific community should further explore lipid administration because it requires an understanding of how essential fatty acids benefit development while managing potential neurotoxic risks.

Behavioral outcome research should take a different direction due to the existing inconsistent findings by examining how early nutrition interacts with environmental elements and genetic susceptibilities. Future research should expand its psychosocial evaluations and parental engagement measurements to achieve better clarity about the nutrition-behavior development association. Upcoming investigations should focus on these limitations in order to create enhanced neonatal dietary standards which lead to better neurodevelopmental outcomes in premature infants.

CONCLUSION

The systematic review determines show early parenteral nutrition directly influences preterm infants' long-term neurodevelopmental results. Evidence presents a connection between proper protein and energy feeding during early life stages which leads to better cognitive development enhancing motor abilities and diminishing cerebral palsy occurrence. Research about behavioral effects demonstrates the impact of both environmental and genetic elements and early nutrition in child development.

The generalized application of results is limited by the ways studies have been conducted and the length of follow-up periods and the choice of assessment methods. Reliable nutrient composition must have first priority in neonatal care services due to the potential dangers that arise from using excessive lipids. Additional extensive standardized research over extensive periods needs to review these findings to create ideal nutritional guidelines.

Neurodevelopmental outcomes of preterm infants depend greatly on receiving their nutritional needs through parenteral methods during their early existence particularly regarding their cognitive function and motor skills development. Further investigations must conducted to optimize nutritional practices while ensuring the best possible brain development for premature infants at high risk.

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