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LITERATURE REVIEW

Cord-Blood and Neonatal BDNF in Early Neurodevelopment: A Systematic Review and Meta-analysis

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Abstrak

Tujuan: Mengevaluasi hubungan antara kadar brain-derived neurotrophic factor (BDNF) dalam darah tali pusat atau darah neonatal awal dengan luaran perkembangan saraf selama tiga tahun pertama kehidupan. **Metode:** Tinjauan sistematis dan meta-analisis ini mengikuti pedoman PRISMA 2020. Pencarian literatur dilakukan melalui PubMed, ScienceDirect, dan SpringerLink hingga 7 September 2026. Penelitian pada manusia yang mengukur kadar BDNF saat lahir atau dalam tujuh hari pertama setelah kelahiran serta melaporkan luaran perkembangan saraf diikutsertakan. Risiko bias dinilai menggunakan instrumen Quality In Prognosis Studies (QUIPS). Koefisien korelasi yang sebanding ditransformasikan menggunakan metode Fisher's z dan digabungkan melalui model efek acak dengan pembobotan varians terbalik. **Hasil:** Dari 1.421 rekaman yang teridentifikasi, 14 penelitian memenuhi kriteria inklusi dan empat penelitian berkontribusi pada setidaknya satu meta-analisis. Hubungan yang ditemukan tergolong lemah dan tidak signifikan secara statistik untuk perkembangan kognitif (r=0,17; IK 95% −0,00 hingga 0,34; I^2=0%) maupun perkembangan motorik (r=0,13; IK 95% −0,04 hingga 0,30; I^2=0%). Hubungan dengan perkembangan bahasa mendekati nol (r=0,03; IK 95% −0,14 hingga 0,21; I^2=0%). Tujuh penelitian memiliki risiko bias keseluruhan sedang dan tujuh lainnya memiliki risiko bias tinggi. **Kesimpulan:** Kadar BDNF neonatal berpotensi mencerminkan hubungan biologis yang lemah dengan perkembangan kognitif dan motorik. Namun, bukti yang tersedia belum memadai untuk mendukung penggunaannya sebagai penanda prognostik dalam praktik klinis.

Kata kunci: BDNF; darah tali pusat; neonatus; neuroperkembangan; meta-analisis

Abstract

Objective: To evaluate the association between cord-blood or early neonatal brain-derived neurotrophic factor (BDNF) concentrations and neurodevelopmental outcomes during the first three years of life. **Methods:** This systematic review and meta-analysis followed PRISMA 2020. PubMed, ScienceDirect, and SpringerLink were searched through September 7, 2026. Human studies measuring BDNF at birth or within the first seven postnatal days and reporting neurodevelopmental outcomes were eligible. Risk of bias was assessed using the Quality In Prognosis Studies tool. Comparable correlation coefficients were Fisher-z transformed and pooled using random-effects inverse-variance models. **Results:** Of 1,421 records, 14 studies met the inclusion criteria and four contributed to at least one meta-analysis. Associations were small and statistically inconclusive for cognitive development (r=0.17; 95% CI −0.00 to 0.34; I^2=0%) and motor development (r=0.13; 95% CI −0.04 to 0.30; I^2=0%). The language association was near null (r=0.03; 95% CI −0.14 to 0.21; I^2=0%). Seven studies had moderate and seven high overall risk of bias. **Conclusion:** Neonatal BDNF may carry a modest biological signal for cognitive and motor development, but current evidence is insufficient for clinical prognostic use.

Keywords: *BDNF; cord blood; neonate; neurodevelopment; meta-analysis*

INTRODUCTION

Brain development during fetal life and early infancy proceeds through coordinated neuronal proliferation, migration, differentiation, synapse formation, maturation, and activity-dependent refinement of neural circuits. Brain-derived neurotrophic factor (BDNF) is a major neurotrophin involved in neuronal differentiation and growth, synaptic maturation, plasticity, learning, and memory. These biological functions provide a strong rationale for investigating BDNF as an early marker of nervous-system development.[1-4]

Umbilical cord blood and early neonatal blood provide practical biological specimens because they can be obtained before developmental impairment becomes clinically apparent. However, circulating BDNF is not a direct measure of cerebral BDNF activity. Peripheral concentrations may vary according to biological specimen, platelet content, gestational age, sex, mode of delivery, perinatal exposures, sample handling, and clinical condition.[3,5] Consequently, an association between circulating BDNF at birth and subsequent neurodevelopment cannot be inferred from biological plausibility alone.

Available clinical evidence is inconsistent. Studies conducted in population birth cohorts, environmental-exposure cohorts, preterm infants, neonatal encephalopathy, maternal metabolic disease, and maternal endocrine disorders have reported associations ranging from favorable cognitive, motor, social, or neurobehavioral findings to essentially null, subgroup-specific, sex-specific, or nonlinear relationships.[6-19] Previous systematic reviews have addressed related but distinct questions, including neurotrophic-factor concentrations in preterm infants, biomarkers of neuropsychomotor development in prematurity, neonatal BDNF in relation to autism spectrum disorder, and broad inflammatory or neurotrophic biomarkers of motor development.[20-22] None specifically synthesized cord-blood or very early neonatal BDNF in relation to multidomain neurodevelopment throughout the first three years of life.

Early identification of infants at increased developmental risk could facilitate closer surveillance and timely developmental intervention. Nevertheless, a prognostic biomarker would be clinically useful only if its relationship with meaningful developmental outcomes were reproducible and added information beyond established perinatal predictors. Previous biomarker reviews and the available BDNF studies show substantial variation in clinical populations, specimen type, laboratory assay, exposure scaling, neurodevelopmental instruments, follow-up age, and covariate adjustment.[5,6]

Meta-analysis in this field is therefore challenging. Neurodevelopment has been assessed using the Bayley Scales of Infant and Toddler Development, Gesell Developmental Schedules or Inventory, Ages and Stages Questionnaire, Alberta Infant Motor Scale, Warner Initial Developmental Evaluation, Laboratory Temperament Assessment Battery, and

Neonatal Behavioral Neurological Assessment.[6-19] Primary studies also report different effect measures, including correlations, regression coefficients, odds ratios, categorical comparisons, and descriptive proportions. This systematic review and meta-analysis therefore aimed to evaluate the association between cord-blood or early neonatal BDNF concentrations and cognitive, motor, language, and other neurodevelopmental outcomes during the first three years of life.

METHODS

This study was a systematic review and meta-analysis reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement.[23] The final search was conducted on September 7, 2026, in PubMed, ScienceDirect, and SpringerLink. Search terms combined concepts for "brain-derived neurotrophic factor" or BDNF, cord or neonatal blood, and neurodevelopmental outcomes. The complete database-specific search strategy is provided in the supplementary file.

The population included term or preterm neonates and infants. Eligible exposure was circulating BDNF protein measured in umbilical cord blood, neonatal serum or plasma, whole blood, or dried blood spots obtained at birth or within the first seven postnatal days. Primary outcomes were cognitive, motor, and language or communication development. Additional outcomes included global, social-emotional, adaptive, neurobehavioral, and developmental-impairment outcomes assessed from the neonatal period through 36 months of age. Prospective and retrospective cohorts, birth cohorts, longitudinal observational studies, prognostic biomarker studies, and observational analyses nested within trials were eligible when the BDNF-development association could be evaluated independently.

Studies were excluded if they evaluated maternal BDNF only, placental tissue without an eligible neonatal blood measure, BDNF polymorphism or methylation without circulating protein concentration, animal models, BDNF first measured beyond the prespecified neonatal window, or no relevant neurodevelopmental outcome. Studies focusing exclusively on autism spectrum disorder diagnosis without an eligible early developmental assessment were outside the primary scope.

All records were managed and screened using Rayyan. A total of 1,421 records were identified: 951 from PubMed, 243 from ScienceDirect, and 227 from SpringerLink. Before screening, 221 duplicates were removed, leaving 1,200 records for title and abstract screening. Of these, 1,139 were excluded and 61 reports were sought for retrieval. One report could not be retrieved, leaving 60 reports for full-text eligibility assessment. Forty-six full-text reports were excluded because of wrong exposure or timing (n=14), no eligible neurodevelopmental outcome (n=12), wrong population (n=8), wrong publication type (n=7), or non-human/duplicate report (n=5). Fourteen studies were included in the systematic review; four contributed to

at least one primary or sensitivity meta-analysis and ten were synthesized without pooling. The selection process is shown in Figure 1.

Data extraction was conducted by four reviewers, comprising one lead reviewer and three senior reviewers, using a structured form. Extracted data included author, year, country, study design, population, sample size, gestational age, BDNF specimen and collection timing, assay method, developmental instrument, follow-up age, effect estimate, uncertainty measure, and adjustment variables. Disagreements were resolved through discussion and consensus. Potentially overlapping cohorts were examined by cohort name, setting, recruitment period, participating centers, and authorship to reduce the risk of double counting.

Risk of bias was assessed using the Quality In Prognosis Studies (QUIPS) tool, covering study participation, study attrition, prognostic factor measurement, outcome measurement, study confounding, and statistical analysis and reporting.[24] Each domain was rated as low, moderate, or high risk of bias, and an overall judgment was assigned based on the pattern and importance of domain-level concerns rather than a numerical score.

Meta-analysis was performed when at least two independent studies reported sufficiently comparable developmental domains and effect measures. Correlation coefficients were transformed to Fisher's z using $z=0.5 \ln[(1+r)/(1-r)]$ with standard error $1/\sqrt{(n-3)}$, pooled using generic inverse-variance random-effects models, and back-transformed to correlation coefficients for interpretation. Heterogeneity was reported using τ^2, Cochran's Q, and I^2. Because each primary analysis contained only two studies, $I^2=0\%$ was interpreted as no statistical heterogeneity detected rather than evidence of true homogeneity. Analyses were performed using Review Manager 5.4.1 and RStudio. Funnel plots and formal small-study-effect tests were not performed because each meta-analysis contained far fewer than 10 studies.

RESULTS AND DISCUSSION

Fourteen studies published between 2014 and 2025 met the inclusion criteria.[6-19] Study populations included general birth cohorts, environmental-exposure cohorts, premature infants, neonatal encephalopathy cohorts, infants of mothers with gestational diabetes, and infants born to women with subclinical hypothyroidism. Sample sizes ranged from 24 infants in Su et al. to 2,637 neonates with available BDNF measurements in Ghassabian et al.[10-15]

BDNF was assessed using cord serum or plasma, neonatal serum, newborn dried blood spots, or serial neonatal plasma samples. Developmental outcomes were evaluated with the Gesell Developmental Schedules or Inventory, Bayley Scales, Ages and Stages Questionnaire, Alberta Infant Motor Scale, Warner Initial Developmental Evaluation, Laboratory Temperament Assessment Battery, and Neonatal Behavioral Neurological Assessment.[6-19] Complete study characteristics are presented in Table 1.

Risk of bias

The QUIPS assessment demonstrated an overall moderate-to-high study-level risk of bias. Seven of 14 studies (50.0%) were judged to have moderate overall risk of bias and seven (50.0%) high overall risk; none was classified as overall low risk. Outcome measurement was the strongest domain, with 71.4% of studies classified as low risk, whereas study attrition, residual confounding, and statistical analysis/reporting were the principal methodological concerns.[6-19,24]

These findings are clinically relevant because BDNF concentrations and developmental performance may both be influenced by gestational age, birth weight, sex, delivery mode, prenatal exposures, maternal metabolic or endocrine conditions, severity of neonatal illness, therapeutic interventions, and socioeconomic circumstances.[6-19] The complete risk-of-bias assessment is presented in Table 3 and Figure 3.

Cognitive development

Two studies involving a total of 131 infants provided sufficiently comparable correlation estimates for the primary cognitive-development meta-analysis. Simpson et al. reported a correlation of r=0.20, whereas Dietrick et al. reported r=0.16.[13,14]

The pooled random-effects estimate was: r=0.17 (95% CI -0.00 to 0.34). No statistical heterogeneity was detected (τ^2=0.000; I^2=0%; Q=0.04; df=1; p=0.834). The confidence interval reached the null, indicating that the evidence for a positive association was statistically inconclusive. The magnitude of the pooled correlation was also small and does not support neonatal BDNF as a stand-alone predictor of later cognitive development.[13,14]

Motor development

Simpson et al. and Dietrick et al. also contributed to the primary motor-development analysis, with a combined sample of 131 participants. Both studies reported r=0.13.[13,14]

The pooled estimate was: r=0.13 (95% CI -0.04 to 0.30). No statistical heterogeneity was detected (τ^2=0.000; I^2=0%; Q=0.00; df=1; p=1.000). The direction of association was positive but small, and the confidence interval crossed the null.

A sensitivity analysis incorporating the day-5 BDNF estimate from Massaro et al. increased the pooled motor correlation to r=0.16 (95% CI 0.02 to 0.31).[12-14] However, the Massaro analytic denominator of 47 participants was inferred from day-5 sample availability rather than explicitly stated as the outcome-specific denominator. This estimate was therefore retained as sensitivity evidence rather than incorporated into the primary analysis.

Language development

Two studies involving 128 participants were pooled for language development. Simpson et al. reported r=0.04 and Dietrick et al. r=0.03.[13,14]

The pooled correlation was: r=0.03 (95% CI -0.14 to 0.21). No statistical heterogeneity was detected (τ^2=0.000; I^2=0%; Q=0.00; df=1; p=0.960). The pooled

association was close to the null and provided no statistically conclusive evidence that early neonatal BDNF was associated with subsequent language development.[13,14]

The contrast between the cognitive, motor, and language analyses suggests that any developmental information carried by circulating neonatal BDNF may not be uniform across neurodevelopmental domains.

Sensitivity analyses and non-pooled evidence

When the Kyslova et al. subgroup estimate was added to the cognitive analysis, the pooled association increased to r=0.19 (95% CI 0.02 to 0.35). The complete motor sensitivity analysis combining Simpson, Dietrick, Massaro, and Kyslova yielded r=0.19 (95% CI 0.04 to 0.33).[11-14]

Although the confidence intervals in these analyses no longer crossed zero, the Kyslova estimate was derived from a very small disability subgroup (n=8), and the study had high overall risk of bias.[11] The shift from an inconclusive primary analysis to a statistically positive sensitivity estimate should therefore not be regarded as confirmation of a robust association.

The broader non-pooled evidence was likewise inconsistent. Tang et al. and Perera et al. reported positive relationships between cord-blood BDNF and selected developmental outcomes.[6,7] Wang et al. and Yu et al. identified domain-specific associations within related Laizhou Wan birth-cohort reports.[8,9] By contrast, Ghassabian et al., Dingsdale et al., and Zhang et al. found largely null overall developmental relationships, although subgroup, sex-specific, or nonlinear findings were observed.[10,17,18] These heterogeneous results do not support a simple monotonic relationship in which progressively higher BDNF concentrations consistently correspond to better neurodevelopment.

Biological and methodological interpretation

A relationship between neonatal BDNF and subsequent neurodevelopment is biologically plausible. BDNF-TrkB signaling participates in neuronal differentiation and growth, synaptic formation and maturation, activity-dependent plasticity, and processes related to learning and memory.[1-4] Nevertheless, peripheral BDNF cannot be assumed to represent central nervous system BDNF directly.[3,5]

Serum, plasma, whole blood, and dried blood spots also should not be treated as interchangeable biological matrices. Peripheral BDNF is influenced by platelet content, specimen processing, collection timing, storage, assay platform, and clinical status.[3,5] These methodological differences are important because included studies variously analyzed raw BDNF concentrations, logarithmically transformed BDNF, standardized values, and categorical concentrations.[6-19] For this reason, incompatible regression coefficients were not combined merely to increase the number of studies in the meta-analysis.

Confounding and clinical heterogeneity

The observational nature of the evidence creates substantial potential for residual confounding. Gestational age, birth weight, sex, delivery mode, maternal metabolic or thyroid disease, prenatal psychological distress, environmental toxicants, socioeconomic circumstances, severity of neonatal encephalopathy, and neonatal interventions may affect BDNF concentrations, developmental outcomes, or both.[6-19,24]

Although several studies used adjusted regression models, the choice and measurement of confounders differed substantially between studies. Consequently, the observed associations cannot establish that neonatal BDNF itself causally determines later neurodevelopment.

Clinical heterogeneity also remained relevant despite I^2=0% in all primary analyses. With only two studies contributing to each pooled estimate, the statistical power of Cochran's Q and I^2 to identify between-study heterogeneity is limited. Therefore, the absence of detected statistical heterogeneity should not be interpreted as demonstrating equivalence of populations, BDNF measurements, or developmental assessments.

Comparison with previous reviews

The present findings complement rather than duplicate previous systematic reviews. Krey et al. primarily evaluated neurotrophic-factor concentrations in preterm compared with term infants.[5] Magalhães et al. examined inflammatory molecules and neurotrophic factors as biomarkers of neuropsychomotor development specifically among preterm neonates.[20] Liu et al. evaluated neonatal BDNF in relation to subsequent autism spectrum disorder diagnosis rather than multidomain developmental performance.[21] Gabriel et al. assessed a broader panel of inflammatory and neurotrophic biomarkers in relation to motor development among preterm infants.[22]

The present review differs by focusing specifically on circulating cord-blood or early neonatal BDNF and by separating cognitive, motor, and language developmental outcomes. This distinction is important because a biomarker associated with prematurity or a later categorical neuropsychiatric diagnosis does not necessarily have the same prognostic meaning for multidomain developmental performance.

Clinical implications

Current evidence does not justify using neonatal BDNF testing as a substitute for developmental surveillance, serial neurological assessment, or validated developmental instruments. Even the statistically positive sensitivity estimates represented only small correlations of approximately r=0.16-0.19.[10-19]

A clinically useful prognostic biomarker would require reproducible laboratory methodology, defined reference ranges, independent external validation, and evidence of incremental predictive value beyond readily available perinatal and clinical predictors. At present,

circulating neonatal BDNF should therefore be regarded as a candidate biological marker for research, rather than a clinically validated prognostic test.

Developmental-impairment outcomes

Developmental impairment proportions were available in only a small number of studies and were therefore summarized descriptively rather than pooled. In Kyslova et al., cognitive delay was reported in 11 of 30 infants and motor delay in 9 of 30.[11] In the Dietrick et al. BDNF subset, adverse cognitive outcome occurred in 24 of 92 infants and adverse motor outcome in 28 of 92.[14]

Although some proportions appeared numerically similar, the contributing populations represented different clinical contexts and used non-identical definitions of impairment. Pooling these proportions could therefore generate an apparently precise but clinically ambiguous summary prevalence.

Limitations

The principal limitation was the small number of studies that reported a common estimand. Only Simpson et al. and Dietrick et al. contributed to each primary cognitive, motor, and language analysis.[13,14] Consequently, pooled effect estimates and heterogeneity statistics remain imprecise, and meaningful meta-regression or formal subgroup analysis could not be undertaken.

The evidence base was also methodologically heterogeneous. Biological specimen, sampling time, assay methods, participant characteristics, developmental instruments, follow-up age, and adjustment strategies varied substantially across studies.[6-19] Half of the included studies were judged to have high overall risk of bias, and no study achieved an overall low-risk judgment.

The search was limited to PubMed, ScienceDirect, and SpringerLink. Although these searches identified 1,421 records, ScienceDirect and SpringerLink are publisher platforms rather than comprehensive bibliographic indexing databases. The absence of databases such as Embase, Scopus, Web of Science, PsycINFO, or CINAHL may have reduced retrieval sensitivity. The search limitation should therefore be considered when interpreting the completeness of the evidence base.

One potentially relevant report could not be retrieved in full. Furthermore, potential participant overlap between Wang et al. and Yu et al., and between components of Dietrick et al. and McGowan et al., required caution to prevent double counting.[8,9,14,16] Aggregate published data also limited harmonization of BDNF scaling and covariate-adjustment strategies.

The Massaro sensitivity analysis used a denominator inferred from day-5 sample availability, while Kyslova contributed correlations from a small disability subgroup.[11,12] These estimates therefore should not be assigned the same evidential weight as the primary pooled analyses. Formal assessment of publication bias was not appropriate because every quantitative analysis included far fewer than ten independent studies. A formal GRADE certainty-of-evidence assessment was also

not undertaken.

Strengths

This review has several methodological strengths. It addressed a focused prognostic-factor question, restricted the exposure to cord-blood or very early neonatal BDNF, separated cognitive, motor, and language outcomes rather than creating an artificial composite outcome, and retained null studies alongside positive findings. Correlation coefficients were transformed using Fisher's z before pooling, whereas incompatible regression estimates were preserved in the systematic review rather than forced into a common effect measure.

Risk of bias was assessed using QUIPS, a tool designed specifically for prognostic-factor research.[24] Primary and sensitivity analyses were also clearly separated, allowing the influence of the inferred Massaro denominator and the small Kyslova subgroup to be evaluated transparently.[11-14]

Future research

Future investigations should prioritize large prospective multicenter birth or neonatal cohorts with prespecified BDNF sampling windows, standardized serum or plasma processing, transparent laboratory quality-control procedures, and harmonized reporting of BDNF units and transformations. Existing longitudinal studies suggest that population characteristics and clinical context may meaningfully influence observed associations.[10-19]

Neurodevelopmental outcomes should ideally be evaluated repeatedly using validated examiner-administered instruments at standardized chronological or corrected ages. Analytic models should prespecify major potential confounders including gestational age, sex, birth weight, delivery mode, maternal medical conditions, prenatal environmental exposures, neonatal illness severity, and socioeconomic factors. Effect modification by prematurity, sex, and neurological injury should also be evaluated prospectively rather than exclusively through post hoc subgroup analysis.[10-19]

Individual-participant-data meta-analysis may ultimately provide a useful approach for harmonizing exposure scaling, developmental definitions, follow-up timing, and adjustment variables across cohorts.

CONCLUSION

Cord-blood and early neonatal BDNF concentrations showed small positive trends with cognitive and motor development, whereas the association with language development was close to the null. Primary evidence remained inconclusive because only two studies could be pooled within each developmental domain and the overall evidence base had moderate-to-high risk of bias. At present, BDNF is better regarded as a candidate neurodevelopmental biomarker than as a clinically ready prognostic marker. Larger prospective multicenter studies with standardized sampling time, specimen type, assays, covariate adjustment, and repeated neurodevelopmental assessment are needed to establish its true prognostic value.

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CONFLICT OF INTEREST

The authors declare no conflict of interest related to this study or its publication.

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