Motor and cognitive outcomes of neonates with low birth weight in Brazil: a systematic review and meta-analysis

Desfechos motores e cognitivos de recém-nascidos com baixo peso ao nascer no Brasil: uma revisão sistemática e metanálise

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Abstract

Background   Data on the outcomes of preterm newborns in South American countries are scarce. Given the great effect of low birth weight (LBW) and/or prematurity on children's neurodevelopment, it is extremely necessary to conduct studies on these phenomena in greater depth in more heterogeneous populations such as those ones from countries with limited resources.

Methods   We conducted a comprehensive literature search on databases including PubMed, the Cochrane Library, and Web of Science for articles published in Portuguese and English up to March 2021 involving children born and evaluated in Brazil. The analysis of the risk of bias was adapted from the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement and used to evaluate the methodology of the included studies.

Results   From the eligible trials, 25 articles were selected for qualitative synthesis, and 5 of those, for quantitative synthesis (meta-analysis). The meta-analyses showed that children born with LBW presented lower scores on motor development when compared with controls (standardized mean difference: −1.15; 95% confidence interval [95%CI]: −1.56–−0.73]; I^2: 80%) and also scored lower in terms of cognitive development (standardized mean difference: −0.71; 95% CI: −0.99–−0.44; I^2: 67%).

Keywords
► Motor Skills Disorders
► Infant, Premature
► Systematic Review

Conclusion The results of the present study reinforce that impaired motor and cognitive functions can be a significant long-term outcome of LBW. The lower the gestational age at delivery, the higher the risk of impairment in those domains. The study protocol was registered in the International Prospective Register of Systematic Reviews (PROSPERO) database under number CRD42019112403.

Resumo

Antecedentes Dados sobre desfechos de recém-nascidos prematuros em países da América do Sul são escassos. Dado o grande efeito do baixo peso ao nascer (BPN) e/ou da prematuridade no neurodesenvolvimento das crianças, é extremamente necessária a realização de estudos que investiguem esses fenômenos com maior profundidade em populações mais heterogêneas.

Métodos Realizou-se uma busca da literatura em bases de dados, incluindo PubMed, Cochrane Library e Web of Science, por artigos publicados em português e inglês até março de 2021 envolvendo crianças nascidas e avaliadas no Brasil. A análise de risco de viés foi adaptada da declaração de Fortalecimento do Relato de Estudos Observacionais em Epidemiologia (Strengthening the Reporting of Observational Studies in Epidemiology, STROBE), que foi utilizada para avaliar a metodologia dos estudos.

Resultados Dos estudos elegíveis, 25 artigos foram selecionados para síntese qualitativa, e 5 desses 25, para síntese quantitativa (metanálise). As metanálises mostraram que crianças nascidas com BPN apresentaram pontuação menor em desenvolvimento motor quando comparadas aos controles (diferença média padronizada, −1,15; intervalo de confiança de 95% [IC95%]: −1,56−−0,73]; I^2: 80%) e pontuação também menor em termos de desenvolvimento cognitivo (diferença média padronizada, −0,71; IC95%: −0,99^2−0,44; I^2: 67%).

Palavras-chave

► Transtornos das Habilidades Motoras
► Recém-nascido Prematuro
► Revisão Sistemática

Conclusão Os resultados deste estudo reforçam que o comprometimento das funções motoras e cognitivas pode ser um desfecho significativo de longo prazo do BPN. Quanto menor a idade gestacional no momento do parto, maior o risco de prejuízo nesses domínios. O protocolo do estudo foi registrado no banco de dados International Prospective Register of Systematic Reviews (PROSPERO) sob o número CRD42019112403.

INTRODUCTION

The World Health Organization (WHO) defines preterm birth as any birth before 37 weeks of gestation or fewer than 259 days since the first day of the woman's last menstrual period (LMP); it is subdivided based on gestational age: extremely preterm (< 28 weeks), very preterm (between 28 and 31 weeks), and moderate or late preterm (between 32 and 36 weeks of gestation).[1] Birth weight (BW) lower than 2,500 g is considered low BW (LBW); values lower than 1,500 g are considered very LBW (VLBW); and figures lower than 1,000 g are considered extremely LBW (ELBW), and newborns with ELBW are the most vulnerable of all premature survivors.[2]

Prematurity is a growing health problem worldwide, particularly in developing countries, where access to obstetric services and neonatal support are not guaranteed to the entire population.[3] Globally, 965 thousand deaths occur in the neonatal period per year, and 125 thousand deaths occur between 1 and 5 years of age because of prematurity, representing the leading cause of neonatal and infant deaths.[1] The worldwide incidence of deliveries before 37 weeks of gestation is of 11.1%, with large geographical differences, ranging from 5% in developed countries to 18% in countries with less economic power.[4] In South America, the mortality rate of children with VLBW reaches 26%,[4] demonstrating the socioeconomic lability of the countries in that region.

Intrauterine growth restriction (IUGR) is a condition in which the fetus does not reach the expected weight during pregnancy, and "small for gestational age" (SGA) is a term used to describe neonates whose BW is below the 10th percentile for the gestational age (GA). Although sometimes IUGR is used to reflect fetal suffering in the literature,[5,6] SGA only provides a measure of the size, and is not a measure of antenatal growth quality. These conditions are also related to a higher risk of intrauterine fetal death, premature birth, and neonatal death.[7]

Strong evidence shows that prematurely-born or SGA infants have a greater predisposition to deficits and/or delayed neuropsychomotor development, and deficit rates are inversely associated with GA and BW.[8]

Data on the outcomes of preterm newborns in South American countries are scarce, and providing specific follow-up programs in public institutions is challenging. Although Sociedade Brasileira de Pediatria (the Brazilian Pediatrics Society) has specific guidelines for the follow-up of preterm neonates after discharge from a neonatal intensive care unit (NICU), many neonates are left without appropriate attention to long-term follow-up.[9] Given the great effect of LBW and/or prematurity on children's neurodevelopment, it is extremely necessary to conduct studies on these phenomena in greater depth in more heterogeneous populations such as the ones from underprivileged countries.

The aim of the present study was to examine the cognitive and motor outcomes of children with LBW based on studies conducted with the Brazilian population. To our knowledge, the present is the first meta-analysis to combine these specific predictors (motor and cognitive) of neurodevelopment in LBW preterm neonates in a limited-resource country. We hypothesized that being raised in a limited-resource country might have an additional negative effect on the outcomes studied.

METHODS

The present systematic review followed the criteria of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[10] The protocol of this systematic review was registered in the International Prospective Register of Systematic Reviews (PROSPERO) under number CRD42019112403.

Eligibility criteria
The inclusion criteria were: original articles investigating the association among GA, BW, and neurodevelopment in Brazilian children; and studies published in Portuguese and English until March 2021 with cohort, case-control, longitudinal, cross-sectional, descriptive analytical, or retrospective designs. The dependent variables were those obtained as the result of tests (cognitive and motor outcomes). The independent variables were GA, BW, gender, and age at the time of the evaluation. The present study included preterm neonates as defined by the WHO:[1] LBW ($< 2,500\,g$), VLBW ($< 1,500\,g$), and ELBW ($< 1,000\,g$). For the meta-analysis, we only included studies with a control group, defined as the group of term newborns (GA $\geq$ 37 weeks).

Research strategies
A systematic review was performed using the PubMed, LILACS, and SciELO databases, using combinations of the following keywords and terms: *preterm birth* OR *prematurity* OR *premature infants* OR *premature children* AND *low birth weight children* OR *very low birth weight children* AND *neurodevelopment* OR *cognitive development* OR *motor development* OR *follow-up* AND *humans*.

Data synthesis
The Endnote software (Clarivate, London, United Kingdom), version X9 was used for data extraction. The databases were searched, and duplicate entries were removed. Abstracts that did not provide sufficient information on the inclusion and exclusion criteria were selected for full-text evaluation. In the second stage, the same reviewers independently evaluated the full text of these articles and made their selection according to the eligibility criteria. Two reviewers (MRT and FTB) performed the literature search and study selection independently. Disagreements were solved by consensus or by a third reviewer.

Risk of bias in individual studies
Two authors (MRT and FTB) reviewed the methodological quality and risks of bias according to the scale adapted from the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement[11] considering only those studies that fit the inclusion criteria. A third author (GR) evaluated and settled any disagreements. The STROBE Statement aims to evaluate studies not related to randomized clinical trials; it comprises 22 applicable questions/items to assess the quality and biases of articles. These criteria are used to assess the quality of data, the internal validity (biases and confounding factors), the external validity, and the ability of the study to detect a significant effect. To assess the risk of bias using the STROBE criteria, the articles in the present systematic review were divided into three different categories, each with a specific score: articles involving prevalence-type cross-sectional studies, with a maximum score of 12; articles with a cross-sectional and cohort methodological design, with a maximum score of 22; and articles involving case-control studies, with intervention and a maximum score of 22. To guarantee the proportion of results among the categories, the score obtained from each article was divided by the maximum possible score for each of the three established categories.

Statistical analysis
Statistical analysis of the data was performed using R software (R Foundation for Statistical Computing, Vienna, Austria), version 4.0.3, for the meta-analysis. He statistical heterogeneity of the treatment effects among the studies was assessed using the Cochran Q test, and the inconsistency, using the I-squared test.[12] In addition, we performed the primary measurement of prognosis (Hedges g, random-effects model) using the standardized mean difference (SMD).

For the continuous outcomes, if the unit of measurement was consistent throughout the trials, the results were presented as the weighted mean difference with 95% confidence intervals (95%CIs). Calculations were performed using the random-effects model, and the statistical method used was inverse variance. Values of $p < 0.05$ were considered statistically significant.

For the descriptive results, we performed the random effects calculation of weighted estimated averages in each article (►Table 1). A *t*-test was performed to confirm the statistical differences between the two groups (LBW versus control group) using the information on BW and GA, to find statistically significant statistical differences ($p < 0.05$) and to confirm the reliability of the study.

Table 1 Characteristics of the studies included in this systematic review

Author	Year of publication	N	Birth weight (grams)	Birth weight of the control group (grams)	Gestational age (weeks)	Age at thr assessment (months)	Proportion of girls	Developmental outcomes
Mello et al.[29]	1998	70	1,185	-	32.2	21	0.6	Cognitive and motor
Grantham-McGregor et al.[21]	1998	262	2,338	3,210	37	6 to 12	0.6	Cognitive and motor
Mello et al.[30]	1999	83	1,176	-	32	12 to 30	-	Cognitive and motor
Eickman et al.[15]	2002	152	2,332	3,255	37	24	0.6	Cognitive and motor
Méio et al.[27]	2003	94	1,903	-	32.04	48 to 60	0.6	Cognitive and motor
Meio et al.[28]	2004	129	1,220	-	32	0 to 36	0.6	Cognitive and motor
Emond et al.[16]	2006	164	2,346	3,212	39	96	-	Cognitive and motor
Schirmer et al.[35]	2006	69	1,552	-	32.06	36	0.5	Only motor
Carvalho et al.[14]	2008	36	1,058	-	30.44	12	0.5	Cognitive and motor
Manacero and Nunes[26]	2008	88	1,753	-	32.8	4 to 8	0.3	Cognitive and motor
Espírito Santo et al.[17]	2009	80	1,788	-	32.3	48 to 60	0.5	Only motor
Mello et al.[31]	2009	100	1,126	-	29.6	12	0.5	Cognitive and motor
Bühler et al.[13]	2009	32	1,073	3,291	29.4	24	0.4	Only motor
Magalhães et al.[25]	2009	70	1,171	3,215	30.23	84	0.6	Only motor
Procianoy et al.[33]	2009	131	1,190	-	30.5	24	0.5	Only motor
Silva et al.[36]	2011	69	1,236	-	31	24	0.4	Only cognitive
Oliveira et al.[32]	2011	46	1,201	3,273	30	60 to 72	0.6	Only cognitive
Guimarães et al.[23]	2011	92	1,424	3,158	28	36	0.5	Cognitive and motor
Reis et al.[34]	2012	109	1,122	-	29	24	0.5	Cognitive and motor
Fernandes et al.[19]	2012	58	1,172	-	30	18 to 2	0.5	Cognitive and motor
Lemos et al.[24]	2012	98	1,439	-	31	2 to 7	0.5	Cognitive and motor
Fan et al.[18]	2013	97	1,890	-	33,6	6 to 7	0.5	Cognitive and motor
Guerra et al.[22]	2014	100	1,744	-	33.2	18 to 24	0.5	Cognitive and motor
Saccani et al.[37]	2017	42	1,886	2,878	36	0 to 12	-	Only motor
Fuentefria et al.[20]	2018	135	1,098	3,348	29.1	8 to 18	0.5	Cognitive and motor
Mean (±standard deviation)			1,497 (±427)	3,204 (±134)	32.73 (±3.5)			
$p < 0.0001$								

Notes: *Gestational age at delivery is presented as mean ± standard deviation values; $p < 0.001$ (significant); birthweight in grams of also in weeks.

RESULTS

Study selection

The initial database search yielded 2,440 articles. After removing the duplicates, 2,310 articles were filtered according to our inclusion criteria, 2,248 of which were excluded after the analysis of their titles and abstracts, and 62 articles remained for a full-text evaluation. From the remaining articles, 25 studies[13–37] were selected for the qualitative synthesis and 6 of those,[15,16,21,23,25,28,32] for the quantitative synthesis (meta-analysis). The flowchart is shown in ►Figure 1.

Study characteristics

The 25 studies[13–37] included were published between 1998 and 2017, and all of the participants were children who had been born preterm. The average sample size was of 96 (standard deviation [SD]: ±49; range: 32–262) participants. Approximately 52.8% (SD: ±7.8%) of the participants were female. The mean BW of the premature participants was of 1.497 Kg (SD: ±0.427; range: 1.058–2.346 Kg). The mean GA at delivery was of 32.73±3.5 weeks (range: 29.2–36.2 weeks). Motor and cognitive assessments were performed at 29.2±24.5 (range: 0–96) months of age. A total of 9 of the 25 articles included a control group composed of newborns. The mean BW of the controls was of 3.204 Kg (SD: ±0.134 Kg; range: 2.878–3.348 Kg). The details of the individual studies are shown in ►Table 1.

Cognitive and motor outcomes of development in preterm/low birth weight/very low birth weight children

Of the included articles, 12 (48%) were cohort studies,[13,14,16,20,21,27–31,33,34] 12 (48%) were cross-sectional studies,[15–19,22–26,35–37] and 1 (4%) was a case-control study.[32] Among the cohort studies, 5 (42%) had a control group,[13,16,20,21,33] and 7 (58%) did not.[14,27–31,34] as for the cross-sectional studies, only 4 (33.3%) included a control group,[15,23,25,37] and 8 (66.7%) did not.[17–19,22,24,26,35,36] Most studies (17; 68%) evaluated cognitive and motor outcomes,[13–19,21,22,24,29–35] 5 (20%) only assessed motor outcomes,[20,23,25,26,37] and 3 (12%), only cognitive outcomes.[27,28,36]

The instruments most commonly used were the Bayley Scales of Infant Development, in 13 (54.1%) studies,[14–19,21,22,30,31,33–35] and the Home Observation for Measurement of the Environment[15,16,21,32] and the Denver Developmental Screening Test,[17,18,26,35] each used in 4 studies (16.6%). An overview of the predictors of development in preterm/LBW/VLBW children in the studies is demonstrated in ►Table 2.

Risk of bias assessment in studies

The assessment of the methodological quality and risk of bias are shown in ►Table 3. Of the 25 articles[13–37] evaluated, a mean score of 93.16 (±3.9) was obtained, with a maximum
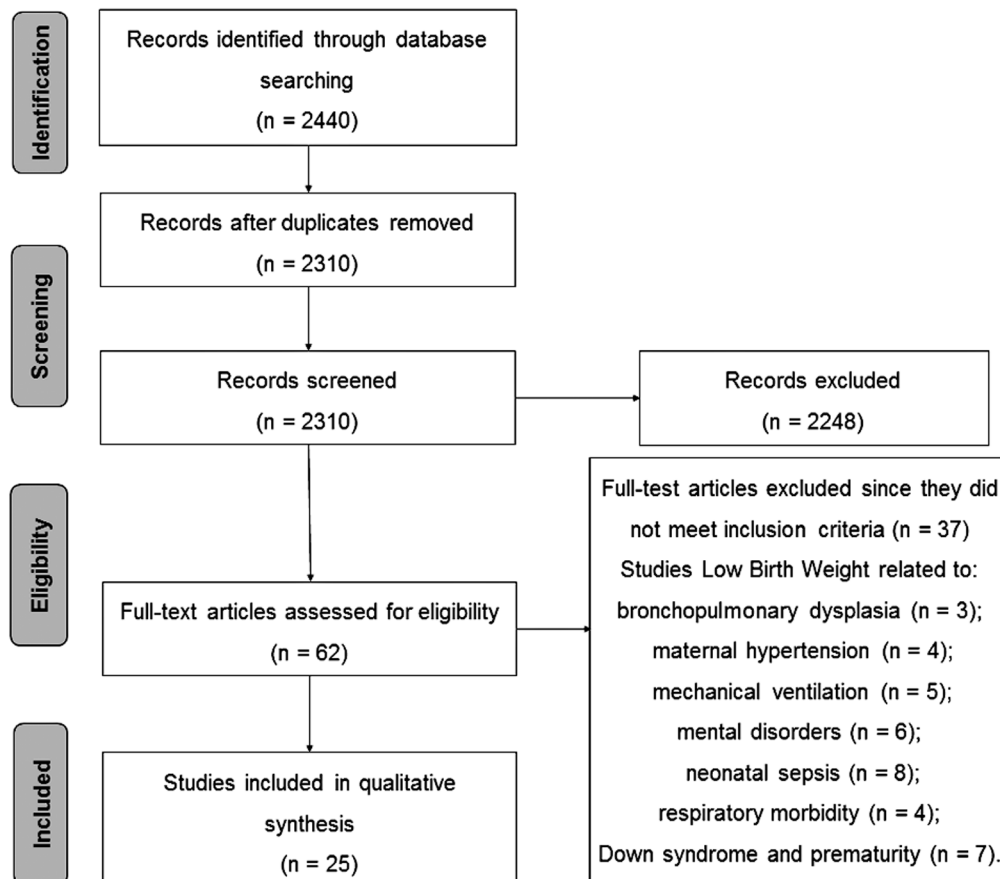

Figure 1 Summary of the search for and selection of studies.

Table 2 Cognitive and motor outcomes of development in preterm/low birth weight/very low birth weight children

Study	Design	Age N Sex	BW(g), GA	Domains	Measures	Data analysis	Results
Bühler et al.[13]	Cohort (incl control group)	2 years N = 32 n₁ = 12 PT n₂ = 20 FT Sex 18 boys 14 girls	≤1500 Mean BW: 1073 GA: 29.4 Vs ≥2500 BW:3291 GA: 39.1	Motor and cognitive	PELCDO	Analysis of variance, (Mann-Whitney test), Kruskal-Wallis test Spearman correlations tests	VLBW preterm infants displayed poorer cognitive development scores than term infants starting at 6 months of age. Expressive language among VLBW preterm infants was also delayed.
Carvalho et al.[14]	Cohort (no control group)	N = 36 Mothers and their children	GA < 37 BW < 2500	Motor and cognitive	Bayley-II Scale	The data from the instruments was analyzed according to their respective standards	The majority of the infants exhibited normal development on Bayley-II at 12 months CCA; however, 25% of the infants displayed cognitive problems and 40% motor problems.
Eickman et al.[15]	Cross-sectional (incl control group)	2 years N = 152 64 boys 88 girls n₁ = 76 LBW n₂ = 76 ABW	1500–2499 BW: 2332 ± 160 Vs. 3000–3499 BW: 2332 ± 160	Motor and cognitive	Bayley Scale HOME	Chi-squared, Analysis of variance (T-test), Multiple linear regression.	LBW term infants showed poorer motor development (95.1 ± 19.2, p <.001) than ABW term infants (105.3 ± 13.6) after controlling for SES factors. Mental development followed the same pattern (89.8 ± 15.8 for LBW; 98.9 ± 14.8, p <.001). BW was a risk factor for impaired motor and mental development (p = .010; p = .005). Socio-economic level and home stimulation were predictors of both motor and cognitive development (p <.01).
Emond et al.[16]	Cohort (incl control group)	8 years N = 164 n₁ = 83 LBW-T n₂ = 81 ABW-T Sex unknown	1500–2499. BW: 2346 ± 148 GA: 39 ± 1.4; Vs. 3000–3499 BW: 3212 ± 147 GA:40 ± 1.3 All GA > 37	Motor and cognitive	WISC III WISC TEAch Bayley Scale M-ABC Strengths and Difficulties questionnaires Educational assessments HOME	Comparison of means, Chi-squared, Analysis of variance (T-test, Mann-Whitney test), Spearman correlations tests, Multiple linear regression.	LBW term infants were more vulnerable to have motor and cognitive impairments. Home factors (e.g. stimulation) as significant predictors on motor and cognitive scores. Low developmental levels among children with least-educated mothers. Growth in head size was strongly associated with IQ as a better predictor of cognitive outcomes than BW.
Espírito Santo et al.[17]	Cross-sectional (no control group)	4–5 years N = 80 40 boys 40 girls	≤2500 + Born preterm Mean BW: 1788 ± 502 GA: 32.3 ± 3 Subdivision <1000 vs. <1500 vs. 1500–2500	Motor and cognitive	WPPSI, CPRS-R Denver Test Bayley Scale Neurological examination	Chi-square Analysis of variance	Significant positive correlations between Bayley cognitive scale (p <.05) the Denver test (p <.01), and ADHD symptoms. Lower IQ was associated with the Bayley cognitive scale (p <.001) the Denver test (p <.001), and neurobiological examination (p<.01).

(Continued)

Table 2 (*Continued*)

Study	Design	Age N Sex	BW(g), GA	Domains	Measures	Data analysis	Results
Fan et al.[18]	Cross-sectional (no control group)	6–7 years N = 97 49 girls 48 boys	GA < 37 BW < 1500	Motor and cognitive	WISC-II Bayley-II Scale Denver-II Test	Z-test to compare the mean values obtained in the sample with the WISC-III reference.	The results of the Denver and Bayley tests were associated with the cognitive performance (p.0.001).
Fernandes et al.[19]	Cross-sectional (no control group)	18–24 months N = 58 30 girls 28 boys	GA < 37 VLBW (<1500)	Motor and cognitive	Bayley-III Scale	Numerical variables were compared by Mann-Whitney or Student t test and categorical variables by chi-square or Fisher's exact test. Factors associated with developmental scores were analyzed by linear regression, and statistical significance level was established at p < 0.05.	Out of the 58 children included, four presented cognitive delay, four motor, 17 language, 16 social-emotional and 22 adaptive-behavior delay. The female sex was associated with higher motor, language and social-emotional developmental scores.
Fuentefria et al.[20]	Cohort (incl control group)	N = 135 Preterm infants (N = 83) Control group (N = 52)	Preterm infants GA: 29.1 BW:1098 Control group GA: 39.1 BW: 3348	Motor	AIMS BLS	SPSS, version 21.0. To compare the means between the groups, the Student's t-test was applied. For the control of confounding factors, the analysis of covariance (logistic regression) was utilized. In the comparison of proportions, Pearson's chi-square test was used. The associations between numerical variables in each group were evaluated by Pearson's correlation coefficient.	At 8 months corrected age, preterm infants scored significantly lower in total AIMS score (p 1/4 0.001). At 18 months, they scored significantly lower on the stand subscale from AIMS (p 1/4 0.040) and exhibited poor psychomotor development in the BLS (p 1/4 0.006). The nutritional status showed significant differences between the groups, in both age groups (p < 0.001). There were positive correlations between nutritional status and AIMS (r 1/4 0.420; p < 0.001) and BLS (r 1/4 0.456; p < 0.001) at 8 months, and between head circumference and BLS (r 1/4 0.235; p < 0.05) at 8 months and AIMS (r 1/4 0.258; p < 0.05) at 18 months. Conclusion Very low BW preterm infants at 8 and 18 months corrected age showed significant differences in the neurodevelopment and growth pattern when compared with their full-term peers.
Grantham-McGregor et al.[21]	Cohort (incl control group)	6 and 12 months N = 262 Sex 157 girls 105 boys n₁ = 131 LBW n₂ = 131 ABW	<2500 Mean BW: 2338 ± 152 vs. ≥2500 Mean BW: 3210 ± 142	Motor and cognitive	Bayley Scale HOME	Chi-squared, Analysis of variance (T-test), Multiple linear regression	LBW term infants showed poorer motor and cognitive development than term infants. LBW term infants with literate mothers had higher scores than those with illiterate mothers (p =.003). Home factors as significant predictors on motor and cognitive scores.

Table 2 (Continued)

Study	Design	Age N Sex	BW(g), GA	Domains	Measures	Data analysis	Results
Guerra et al.[22]	Cross-sectional (no control group)	With delay (N = 55) Without delay (N = 45)	With delay GA: 33.2 BW: 1727 Without delay GA: 33.3 BW: 1762	Motor and cognitive	Bayley-III Scale	The numerical variables were compared by the Mann–Whitney-U test or t-test and the categorical variables by the chi-square or Fisher's exact-test.	The percentages and 95% confidence intervals of those children with developmental delays were as follows: cognitive (2.0%; 0.6–7.0%), language (5.0%;2.2–11.2%), motor (3.0%; 1.0–8.5%), socio-emotional (13.0%; 7.8–20.1%), general adaptive (26.0%; 18.4–35.4%), conceptual (17.0%; 10.9–25.6%), social (46.0%; 36.6–55.7%) and practical (21.0%; 14.2–30.0%). Factors associated with delay in at least one developmental domain were as follows: caesarean delivery, low per capita income and peri-intraventricular haemorrhage. Factors associated with a reduction in developmental scores were as follows: non-white ethnicity, lower social class, caesarean delivery, male gender, peri-intraventricular haemorrhage, mechanical ventilation and length of hospitalisation.
Guimarães et al.[23]	Cross-sectional (incl control group)	3 years N = 92 n₁ = 46 PT n₂ = 46 FT Sex: 46 girls 46 boys	PT GA:28–33 31.1 ± 1.5 BW:1424 ± 321.1 Vs. FT GA:38–40 38.6 ± 0.5 BW:3158 ± 565.4	Motor	TIMP	Homogeneity of variance between groups, Analysis of variance (T-test, Mann-Whitney), Spearman and Pearson correlations, F-test.	PT infants showed poorer motor development (58 ± 7.9; p < .001) than FT infants (67.9 ± 5.3) after controlling for SES factors. 100% of PT were showed atypical motor development (p < .001) whereas 100% of FT infants showed normal scores. Prematurity was associated with impaired motor development.
Lemos et al.[24]	Cross-sectional (no control group)	Preschool (2–7 years) N = 98	GA < 37 BW < 2500	Motor and cognitive	PEDI	Chi-square and the variance analysis.	There was found a delay of 10,2%, 12,2% and 14,3% in the functional abilities in the areas of self-care, mobility and social function, respectively, and of 11,2%, 19,4% and 15,3% in the assistance level received from the caregivers (independence), in the same areas. It was not found statistically significant differences or associations between groups of different degrees of prematurity or birth weight and the PEDI performance.
Magalhães et al.[25]	Cross-sectional (incl control group)	7 years	1.GA </= 34 BW </= 1500 2. GA > 37	Motor	M-ABC test	Wilcoxon's test	Significant difference between the two groups in terms of the overall score (Z = −4,866, p < 0,001) and the score for specific sub-sections of the M-ABC, the preterm group performing less well than the term group.

(Continued)

Table 2 (*Continued*)

Study	Design	Age N Sex	BW(g), GA	Domains	Measures	Data analysis	Results
Manacero and Nunes[26]	Cross-sectional (no control group)	<1 year N=44 21 boys 23 girls n_1 = 14 <1750 n_2 = 30 ≥1750	≤2500 Subdivision <1750 BW: 1417±292 GA:32.4±0.7 vs. ≥1750 BW: 2090±278 GA:33.2±0.8	Motor Motor	AIMS Neurological examination Denver Test	Analysis of variance (ANOVA)	Despite BW differences, motor ability acquisition exhibited a normal progress at 40 weeks, 4 months, and 8 months according to mean percentile of normality on the AIMS (43.2% to 45.7%).
Meio et al.[27]	Cohort (no control group)	N=94 (64,6% girls)	GA < 37 BW < 1500	Cognitive	WPPSI-R	T-student Chi-squared with Yates correction	Seventy-nine children aged 4 and 5 years were studied. The mean full WIPPSI-R score was 75.6 (±11.9). The incidence of abnormal 1 and 2 SD full score was 77.2% and 32.9%, respectively. After adjusting for the method of delivery, small for gestational age (OR = 6.19, 95% CI 1.60-23.86), abnormal cerebral ultrasound exam (OR = 5.90, 95% CI 1.04-9.83) and male sex (OR = 3.20, 95% CI 1.32-26.35) were predictors of full score <70.
Meio et al.[28]	Cohort (no control group)	N= 79/129 Age pre-school	GA < 37 BW < 1500	Cognitive	WPPSI-R	Epi-Info 6.0 SPSS 6.1 Chi-square T-student Fischer's test	No significant statistical difference was found between the groups (study and loss). Children who entered this study showed to have a borderline intellectual functioning at the moment of the evaluation. Results indicate they may face learning difficulties at school, thus requiring adequate stimuli that should be provided by the family and the school.
Mello et al.[29]	Cohort (no control group)	N=70; Mean GA:32.2 weeks	GA < 37 BW < 1500	Motor and cognitive	Dubowitz & Dubowitz method and brain US	Analysis of variance through the F-test; the differences between the proportions were tested by chi-square. The statistical significance, prevalence, sensitivity, specificities, predictive values and confidence intervals were calculated.	25.7% of the children had neuromotor impairment, and 20.3% had cognitive impairment. Neonatal neurological examination was more sensitive than neuromotor change (sensitivity: 77.7%, specificity: 57.6%), and cognitive (sensitivity: 78.5%, specificity: 56.4%). Low predictive value for neuromotor change (38.9%) and cognitive (31.4%). Ultrasonography was discharged specificity for neuromotor (92.3%) and cognitive development (89.1%). The predictive value of ultrasonography was high for neuromotor abnormalities (69.2%) and low for changes cognitive (50.0%).

Table 2 (Continued)

Study	Design	Age N Sex	BW(g), GA	Domains	Measures	Data analysis	Results
Mello et al.[30]	Cohort (no control group)	12–30 months N = 83	GA < 37 BW < 1500	Motor and cognitive	Bayley Scale	Comparison of means (Chi-squared, F-test.)	Cerebral ultrasonography (US) was normal in 68 babies (81.9%) and abnormal in 15 (18.8%). With a mean age of 21 months, 63 children (75.9%) had normal motor development and 20 (24.0%) had motor abnormalities. The cognitive development was normal in 68 children (81.9%). The negative predictive value of the cerebral US for motor development was 85.3%, and for cognitive development, 86.8%. The positive predictive value of the cerebral US for motor development was 66.7% and for cognitive development, 42.9%. The probability for children with normal neonatal ultrasonography to have normal motor and cognitive development is greater than 85%.
Mello et al.[31]	Cohort (no control group)	N = 100	BW: 1126 GA: 29.6	Motor and cognitive	Bayley Scale	A multivariate logistic regression model was constructed. Neonatal variables and neuromotor abnormalities up to 6 months of corrected age were selected by bivariate analysis.	Mean birth weight was 1126g (SD: 240). Abnormal neuromotor development was presented in 60 children at 12 months corrected age.
Oliveira et al.[32]	Case-control (incl control group)	5–6 years N = 46 n₁ = 23 ≤1500 9 boys 14 girls n₂ = 23 ≥2500 Sex unknown	≤1500 Mean BW: 1201 ± 177 GA: 30 ± 2 Vs. ≥2500 BW:3273 ± 348 GA: 39 ± 0.4	Motor and cognitive	M-ABC WISC DCDQ HOME	Comparison of means (Mann-Whitney test), Spearman correlations tests	LBW children were more vulnerable to have motor and cognitive impairments. Home factors as significant predictors on motor and cognitive scores.
Procianoy et al.[33]	Cohort (incl control grup)	2 years N = 96 49 boys 47 girls n₁ = 55 SGA n₂ = 41 AGE	SGA <1500 GA: 31.7 ± 2 BW:1130 ± 250 vs. AGE <1500 GA: 29.3 ± 1.6 BW:1250 ± 218	Motor and cognitive	Bayley Scale	Comparison of means (Chi-squared, F-test.), ANOVA, ANCOVA	Mental and motor development were similar between both groups of term infants at 8,12, 18, and 24 months corrected age. Both groups had similar neurodevelopment outcome.
Reis et al.[34]	Cohort (no control group)	N = 109 <2 years (6 m, 12 m, 18–24 m)	GA < 37 BW < 1500	Motor and cognitive	Bayley-II Scale MDI	The stability of the scores between assessments was verified by the analysis of variance for repeated measures. The association of the major social and neonatal characteristics with mental development was confirmed using multivariate analysis by linear regression,	The association of the major social and neonatal characteristics with mental development was confirmed using multivariate analysis by linear regression, considering the following outcomes: mental development indices at 6 months, 12 months and between 18–24 months of corrected age. The cognitive development index did not show stability during the first two years, except for children with neonatal pneumonia.

(Continued)

Table 2 (*Continued*)

Study	Design	Age N Sex	BW(g), GA	Domains	Measures	Data analysis	Results
Schirmer et al.[35]	Cross-sectional (no control group)	3 years N = 69 n₁ = 30 <1500 n₂ = 39 1500–2500 Sex unknown	≤2500 Subdivision <1500 vs. 1500–2500 All GA > 37	Motor and cognitive	Denver-II Test Bayley-II Scale Language Assessment	Chi-squared, Analysis of variance (T-test), multivariate regression, Risks estimates (OR, Wald)	GA correlates with language development; GA predicts language acquisition. Gestational age < 32 weeks increases 3 times the risk for delay in language acquisition.
Silva et al.[36]	Cross-sectional (no control group)	4–24 months N = 69	GA < 37 BW < 1500	Cognitive Hand-eye coordination Language Posture Sociability	Brunet Scale Lèzine's Scale	Data were analyzed using descriptive and inferential statistics.	85% of scores within the normal range in the third assessment. The specific areas of hand-eye coordination and language had the worst initial results, while posture had the best scores. Correlation was found between birth weight and posture, language and social areas at the first assessment and between birth weight and social and hand-eye coordination at the third assessment.
Saccani et al.[37]	Cross-sectional (incl control group)	0–12 months N = 42 n1 = 21 n2 = 21	<2500 Mean BW: 1886 ± 402 GA: 36 Vs ≥2500 BW:2878 ± 348 GA: 36	Motor	Alberta Infant Motor Scale	The independent t-test, the chi-square test of Pearson and the Eta2 test (strong association> 0.60).	Fifteen (71.42%) children with low birth weight were classified as small for gestational age. The mean motor development score percentile was 17.90 ± 17.74 for the LBW group and 34.57 ± 25.80 for the ABW group, indicating a better motor development of the second group (p = 0.02). There was a greater number of children with developmental delay in the LBW group (52.4%), whereas in the ABW group most were within the normal range (47.6%).

Abbreviations: GA, Gestational age; BW, birth weight; LBW, low-birthweight; ABW, adequate birth weight; VLBW, very low birth weight; SGA, small for gestational age; AGE, appropriate for gestational age; PT, Preterm infants; FT, Full term newborns; HOME, Home Observation for Measurement of the Environment; WPPSI-R, Wechsler Preschool and Primary Intelligence Scales; WISC III, Weschsler Intelligence Test for Children-III; WISC, Weschsler Intelligence Test for Children; TEAch, Test of Everyday Attention for Children; STAI, State-Trait Anxiety Inventory; BDI, Beck Depression Inventory; CCA, chronological corrected age; AIMS, Alberta Infant Motor Scale; ADHD, attention deficit/hyperactivity disorder; PELCDO, Protocol for Expressive Language and Cognition Development Observation; M-ABC test, Movement Assessment Battery for Children; DCDQ, Developmental Coordination Disorder Questionnaire; SNAP IV, Swanson, Nolan and Pelham IV Scale; TIMP, Test of Infant Motor Performance; PEDI, Pediatric Evaluation Disability Inventory; CBCL, Child Behavior Checklist; BLS, Brunet–Lèzini scale; CPRS-R, Conners' Parent Rating Scale-Revised; IQ, Intelligence quotient; US, Ultrasonography; p, Spearman's Rank-Order Correlation; r, Pearson's correlation coefficient; z, standard score; OR, odds ratio; CI, confidence interval; SD, standard deviation; ANOVA, analysis of variance; ANCOVA, analysis of covariance; SPSS, Statistical Package for Social Sciences.

Table 3 Risk of bias assessment adapted from the STROBE[11] statement

No.	Author	Obtained score/ maximum score	Relative frequency (%)
01	Bühler et al.[13]	19/22[b]	86
02	Carvalho et al.[14]	21/22[b]	95
03	Eickman et al.[15]	21/22[a]	95
04	Emond et al.[16]	22/22[b]	100
05	Espírito Santo et al.[17]	21/22[a]	95
06	Fan et al.[18]	20/22[a]	91
07	Fernandes et al.[19]	20/22[a]	91
08	Fuentefria et al.[20]	20/22[b]	91
09	Grantham-McGregor et al.[21]	19/22[b]	86
10	Guerra et al.[22]	20/22[a]	91
11	Guimarães et al.[23]	21/22[a]	95
12	Lemos et al.[24]	20/22[a]	91
13	Magalhães et al.[25]	20/22[a]	91
14	Manacero and Nunes[26]	21/22[a]	95
15	Méio et al.[27]	20/22[b]	91
16	Meio et al.[28]	20/22[b]	91
17	Mello et al.[29]	22/22[b]	100
18	Mello et al.[30]	21/22[b]	95
19	Mello et al.[31]	20/22[b]	91
20	Oliveira et al.[32]	22/22[c]	100
21	Procianoy et al.[33]	22/22[b]	95
22	Reis et al.[34]	22/22[b]	100
23	Schirmer et al.[35]	20/22[a]	91
24	Silva et al.[36]	20/22[a]	91
25	Saccani et al.[37]	20/22[a]	91

Abbreviation: STROBE, Strengthening the Reporting of Observational Studies in Epidemiology.
Notes: [a]Cross-sectional prevalence study; [b]cohort study; [c]case-control study.

score of 100.0% and a minimum score of 86%. In total, 14 articles[13,18–22,24,25,27,28,31,35–37] showed values below the mean score; therefore, they were considered of lower methodological quality.

Assessment of motor development
To evaluate motor development, we included five studies[15,21,23,25,32] that had control groups to compare their scores with those of premature/LBW children. The studies were grouped according to the tests used, and an average of the SMD is shown in ►**Figure 2**. In the study by Meio et al.,[28] which was included in this meta-analysis, the LBW group consisted of 79 children, but the authors only assessed the motor outcomes of 75 participants, as shown in ►**Figure 2**. The random-effects model showed an SMD of −1.15 (95%CI: −1.56−−0.73; I^2: 80%). Thus, an inferior score on motor development in LBW children was observed when compared with the control population. The results on motor development in the cross-sectional studies without a control group are described in ►**Table 2**, but it was not possible to calculate

the scores because of the high heterogeneity among the studies.

Assessment of cognitive development
To compare the results on cognitive development between the case and the control populations, 5 studies were included[15,16,21,28,32]; the random-effects model showed an SMD of −0.71 (95%CI: −0.99−−0.44; I^2 67%) (►**Figure 3**). Therefore, the studies indicated that premature LBW children have slower cognitive development than term children with normal birth weight. The results on cognitive development from the cross-sectional studies without a control group are described in ►**Table 2**, but it was not possible to calculate the scores because of the high heterogeneity among the studies.

DISCUSSION

The present study reinforces that LBW associated with prematurity represented risks to cognitive and motor
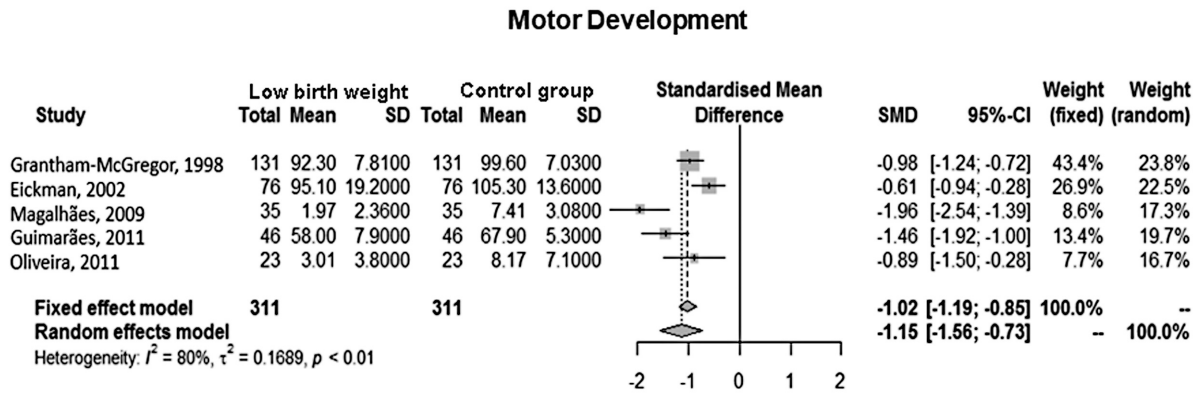
Motor Development

Study	Low birth weight Total	Mean	SD	Control group Total	Mean	SD	Standardised Mean Difference	SMD	95%-CI	Weight (fixed)	Weight (random)
Grantham-McGregor, 1998	131	92.30	7.8100	131	99.60	7.0300		-0.98	[-1.24; -0.72]	43.4%	23.8%
Eickman, 2002	76	95.10	19.2000	76	105.30	13.6000		-0.61	[-0.94; -0.28]	26.9%	22.5%
Magalhães, 2009	35	1.97	2.3600	35	7.41	3.0800		-1.96	[-2.54; -1.39]	8.6%	17.3%
Guimarães, 2011	46	58.00	7.9000	46	67.90	5.3000		-1.46	[-1.92; -1.00]	13.4%	19.7%
Oliveira, 2011	23	3.01	3.8000	23	8.17	7.1000		-0.89	[-1.50; -0.28]	7.7%	16.7%
Fixed effect model	311			311				-1.02	[-1.19; -0.85]	100.0%	--
Random effects model								-1.15	[-1.56; -0.73]	--	100.0%

Heterogeneity: $I^2 = 80\%$, $\tau^2 = 0.1689$, $p < 0.01$

Figure 2 Forest plots showing motor development in children.

Cognitive Development

Study	Low birth weight Total	Mean	SD	Control group Total	Mean	SD	Standardised Mean Difference	SMD	95%-CI	Weight (fixed)	Weight (random)
Grantham-McGregor, 1998	131	90.50	6.2900	131	94.70	4.1600		-0.79	[-1.04; -0.53]	35.5%	25.0%
Eickman, 2002	76	89.80	15.8000	76	98.90	14.8000		-0.59	[-0.92; -0.27]	21.2%	21.9%
Méio, 2004	75	75.61	11.9100	41	85.10	13.2500		-0.76	[-1.15; -0.37]	14.5%	19.2%
Emond, 2006	83	73.00	15.4000	81	78.10	16.0000		-0.32	[-0.63; -0.02]	23.6%	22.6%
Oliveira, 2011	23	9.61	2.6200	23	13.48	2.4500		-1.50	[-2.16; -0.84]	5.1%	11.3%
Fixed effect model	388			352				-0.67	[-0.82; -0.52]	100.0%	--
Random effects model								-0.71	[-0.99; -0.44]	--	100.0%

Heterogeneity: $I^2 = 67\%$, $\tau^2 = 0.0635$, $p = 0.02$
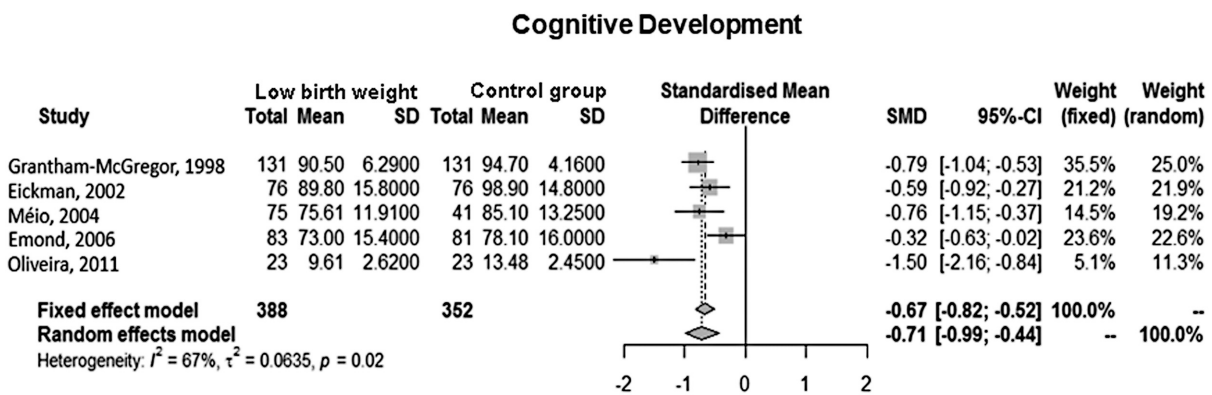
Figure 3 Forest plots showing cognitive development in children.

development. The lower the gestational age, the higher the risk of impairment in those domains. All children with IUGR included in the present study were premature, although IUGR is not synonymous with prematurity.

The risk of unfavorable neurodevelopmental outcomes in the first years of life and at school age after intrauterine malnutrition and extreme prematurity has been previously reported by several authors reporting data from developed countries.[4–6,38–41] In the present study, we gathered all data published on the Brazilian population and studied if the low-resource setting might influence neurodevelopmental outcomes.

Although the Brazilian Ministry of Health has published guidelines for neonatal care[42], the approach is only related to the management of different pathologies during hospitalization. After discharge, there are no official governmental guidelines related to the follow-up of high-risk neonates; there is only a set of recommendations by an expert panel from the Brazilian Pediatrics Society published in 2012. This means that each hospital that has a NICU, if interested, can design its own follow-up program.

In three previous studies[39–41] from different countries in Europe that have followed VLBW preterm neonates until 5 to 6 years of age, the prevalence of cerebral palsy varied from 3.9% to 12%. In the French study,[39] special health care

resources were necessary for 31% to 42% of the sample, and a mental evaluation showed a rate of 32% of moderately and of 12% of severely lower scores. In the English[40] study, severe disability was reported in 22%, moderate, in 24%, and mild, in 34% of the sample, and cognitive impairment reached a rate of 21%. However, longitudinal studies developed in a single center demonstrated that the percentage of significant cognitive impairment decreased by 9.4% from 1980 to 2015, except for infants with BW < 750 g.

Most studies developed in Brazil included patients assisted on neonatal units of university hospitals that belong to our national public health system (Sistema Único de Saúde, SUS, in Portuguese), and most of its users are from lower socioeconomic classes. In the present review, the mean age of the children when the follow-up ended was of approximately 30 months of life, and only 5 studies[9,16,17,27,32] had longer follow-ups (of up to 8 years of age). In four studies,[15,21,22,32] socioeconomic-educational variables (environmental aspects, literacy of the mothers, and/or income) and poorer outcomes on the motor and cognitive measurements were significantly associated with an unfavorable home environment, illiteracy, and low income. Seven out of nine studies with a control population (term neonates from the same unit) showed a significant unfavorable outcome for cognitive and motor issues among the LBW neonates.[13,15,16,20,21,25,32] One study[33]

compared LBW neonates with and without IUGR; both groups had similar neurodevelopment up to 24 months, and all children with IUGR included were premature, although IUGR is not synonymous with prematurity. However, half of the patients had abnormal scores on the Bayley Scales of Infant Development.

There were a few limitations to the present study. Firstly, Most Brazilian follow-up studies were old and seemed to lack homogeneity. Secondly, the number of target studies was as small as 5, and the heterogeneity was also high, of 80%. Thirdly, although 25 Brazilian studies[13–37] were selected, only 7[15,16,21,23,25,28,32] were eligible for meta-analysis. Fourthly, we compared studies that employed different developmental assessment tools, which offered a variable delay detection power. However, when compared with the most recent scientific literature, the compiled data mostly reiterate the association of prematurity with a delayed neurological outcome, regardless of the scales used for analysis.[40,41]

In conclusion, LBW associated with prematurity represented risks to cognitive and motor development, particularly in the early years of life. From the perspective of public health, it is essential that pediatricians/primary care physicians be aware of those risks so that these children may be referred to a follow-up in adequate facilities for proper treatment and prevention.

Authors' Contributions

GR: conception, design, and interpretation of data; drafting the article; and final approval of the version to be published; ELC: analysis and interpretation of data; and final approval of the version to be published; FKN: article draft; and final approval of the version to be published; MRGT, FTKB: acquisition of data; and final approval of the version to be published; FM: interpretation of data; and final approval of the version to be published; LB: analysis of data; and final approval of the version to be published; and MLN: article draft and critical review for important intellectual content; and final approval of the version to be published.

Conflict of Interest
The authors have no conflict of interests to declare.

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