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REVIEW ARTICLE

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Physical activity during pregnancy and offspring neurodevelopment: A systematic review

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Abstract

Background: Maternal physical activity (PA) during pregnancy could affect offspring's neurodevelopment. However, studies in humans in early childhood are scarce and show inconsistent results. We aimed to review the literature on the association between physical activity during pregnancy and offspring neurodevelopment.

Methods: LILACS, MEDLINE and Web of Science were searched for studies published since 1977. Original studies conducted in humans, without language, country, or study type restriction, were eligible. Information on the study methodology like study design, sample size, PA exposure and neurodevelopment assessment, covariates, and the effect measure were extracted from the selected articles.

Results: From 802 non-duplicated titles initially located, 6 articles were selected and included (one randomised clinical trial and 5 cohort studies). The instruments used to measure PA during pregnancy and neurodevelopment varied between the studies. PA was self-reported at different gestational ages and neurodevelopment was assessed prospectively in offspring aged 1-8 years old. Only the randomised clinical trial found no effect of PA over offspring neurodevelopment. Cohort studies found a positive association between PA practice during pregnancy and offspring neurodevelopment.

Conclusions: These findings suggest that leisure-time physical activity practice may have positive association with language offspring's neurodevelopment in the age range of 18 from 60 months.

KEYWORDS
childhood, infancy, neurodevelopment, physical activity, pregnancy

1 | INTRODUCTION

Neurodevelopment is one of the most important human processes in the first 1000 days of life. In this period neurological pathways influencing intelligence, language, motor, and social functions are developed.[1,2] As a continuum process resulting of the interaction between biological and environmental conditions, neurodevelopment occurs sequentially beginning at conception, continuing throughout pregnancy and after birth. A proper neurodevelopment sets the foundation for a child's physical and mental health, affecting not only disease incidence but socio-emotional, language/cognitive development, and lifelong learning capacity.[3,4]

Early stage (prenatal and perinatal) determinants of neurodevelopment include exposure to teratogens and other substances, micronutrients supplementation, maternal morbidity and perinatal complications, gestational age, birthweight,

maternal sociodemographic characteristics and maternal life style. Disturbances during this stage may contribute to a decrease in neurodevelopmental functions that could be expressed ranging from functional abnormalities to neurodisability.[5-10]

In terms of life style during pregnancy, physical activity (PA) practice has shown beneficial maternal and child health effects.[11-13] Current evidence suggests a lower incidence of pregnancy-related complications such as gestational diabetes, preeclampsia, preterm birth and postpartum depression.[14,15] In addition, studies focusing on the neonatal period and child growth have shown a lower incidence of low birthweight, improved child body composition (lower body fat percentage), and a greater ponderal index.[16]

Specifically, for neurodevelopment, research in animal models have shown that PA during pregnancy is associated with improved neurogenesis, proliferation in learning and memory cells and brain plasticity among other neurobiological processes.[17-19] In contrast, studies in humans being exposed to PA during pregnancy are scarce and show inconsistent results. In order to better understand the association between maternal PA during pregnancy and offspring neurodevelopment, we conducted a systematic review.

2 | METHODS

This systematic review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[20]

2.1 | Search strategy

We searched LILACS, MEDLINE and Web of Science for eligible studies published since 1977. The search was conducted in September 2017 and was updated in January 2018. The search terms were: ((prenatal physical activity) OR antenatal physical activity) OR pregnancy physical activity) OR gestational physical activity) OR prenatal exercise) OR antenatal exercise) OR pregnancy exercise) OR gestational exercise) OR prenatal motor activity) OR antenatal motor activity) OR pregnancy motor activity) OR gestational motor activity) OR prenatal sports) OR antenatal sports) OR pregnancy sports) OR gestational sports) OR prenatal walking) OR antenatal walking) OR pregnancy walking) OR gestational walking) OR prenatal fitness) OR antenatal fitness) OR pregnancy fitness) OR gestational fitness) OR prenatal leisure time physical activity) OR antenatal leisure time physical activity) OR pregnancy leisure time physical activity) OR gestational leisure time physical activity)) AND ((child neurodevelopment) OR child motor development) OR child psychomotor development) OR child cognitive development) OR child language development) OR developmental outcomes)).

The terms could be found anywhere in the text and were entered individually and combined on the advanced search field on each database. Two researchers conducted the screening process independently, and disagreements were solved by consensus. The reference list of each of the selected articles was evaluated to determine the availability of studies meeting the inclusion criteria that could be added in this review.

2.2 | Inclusion and exclusion criteria

Original articles conducted in humans were included if the association between PA exposure during pregnancy and offspring neurodevelopment was assessed. No language, country, or study type restrictions were applied.

2.3 | Definition of exposure

Studies reporting PA practice during any trimester of pregnancy were included. Any type (aerobic, muscle resistance, or strengthening), frequency, duration, intensity, and/or domain of PA were allowed.

2.4 | Definition of outcomes

Neurodevelopment was defined as a process of neurological pathways development that shapes performance or functioning. Intelligence (verbal and nonverbal), language (expressive and receptive), sensory, motor (fine and gross), executive, and social cognition functions are part of this process. Studies assessing any neurodevelopment function during childhood and adolescence (under 18 years old) were eligible.

2.5 | Data extraction

The 2 independent researchers extracted data from selected studies. Characteristics related to the study (publication year, study site, study design, sample size); participants (eligibility criteria, women's gestational age); PA exposure (number of pregnant women exposed and not exposed to physical activity, definition and measurement methods); neurodevelopment outcome in the offspring (cognitive, language, motor, hearing, vision, and behaviour domains, and measurement methods); covariates; and the effect measure (odds ratio [OR] or beta coefficient with respective 95% confidence intervals [CI] were extracted).

3 | RESULTS

The search strategy resulted in 891 titles to be examined. After removing duplicates, 802 titles were identified for review according to inclusion criteria. Ten articles were selected for abstract review and 6 articles were included for full text review (Figure 1). At the titles reading step 792 articles were excluded: 50 were conducted with non-human subjects, 5 were conference proceedings, and 731 did not assess PA during pregnancy and/or neurodevelopment outcomes in offspring. After reading the abstract of the remaining 10 articles, 4 were excluded: one was a narrative review of the biological

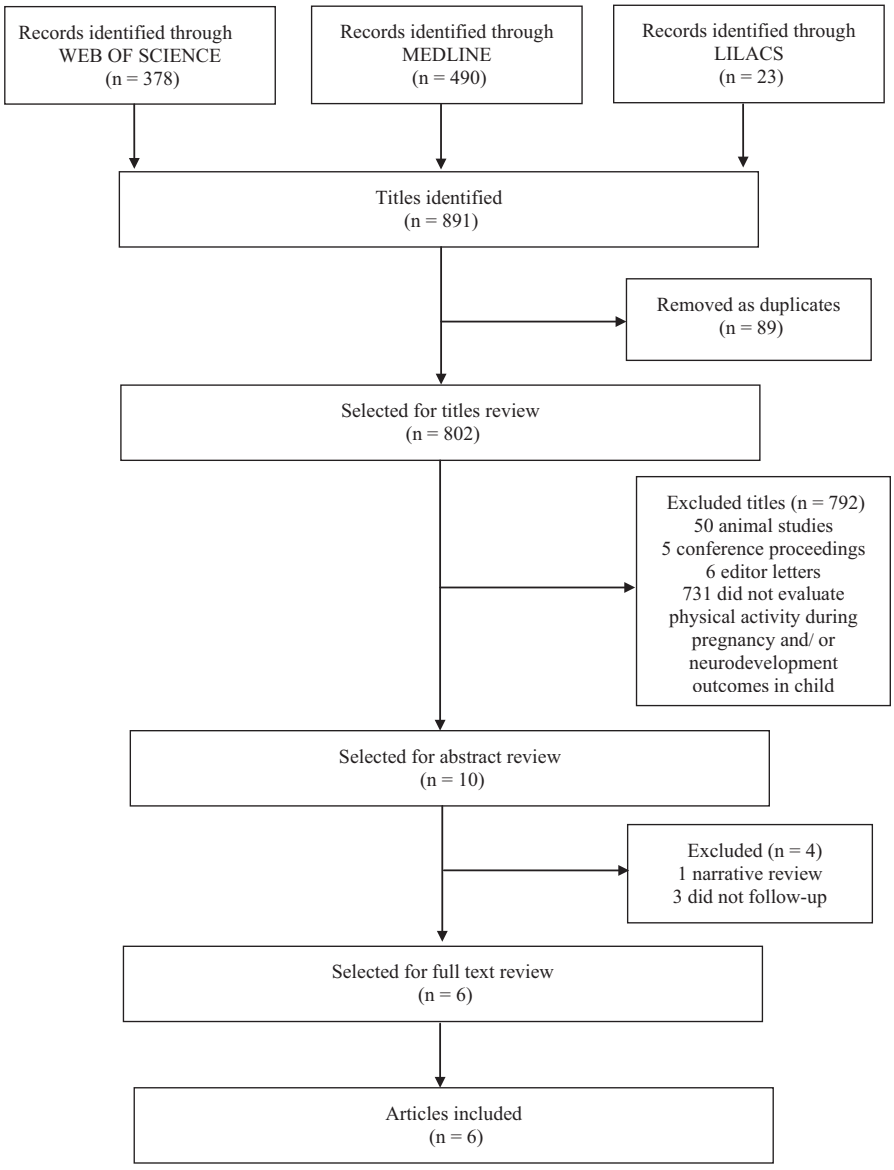

FIGURE 1 Review flow chart

effects of PA in brain development mostly in animals; and, the other 3 had not followed up children.

Of the 6 retained articles, one was a randomised clinical trial[21] and 5 were cohort[22-26] studies. Table 1 contains a summary of the reviewed studies, which were published between 1996 and 2015. According to author's country of affiliation, 2 articles had a lead author in the US, followed by the UK (n = 1); Norway (n = 1); Brazil (n = 1); and Poland (n = 1).

A large variability was found in the number of participants for each study, ranging from 40 (Clapp[22] in 1996) to 7162 (Jukic et al[24] in 2013). Also, the instruments used to assess PA during pregnancy and neurodevelopment were heterogeneous. PA was self-reported in all observational studies using study-specific questionnaires that assessed general or leisure time PA (LTPA) practice during pregnancy, at different gestational ages.

Neurodevelopment assessments ranged from children 1-8 years old, but it was most commonly evaluated in the offspring at the age of 1 year. Trained examiners including physiotherapists and psychologists performed the children assessment. Instruments included: Wechsler Preschool and Primary Scale of Intelligence;[22,24,25] Peabody Picture Vocabulary Test (first edition);[22] Bruininks-Oseretsky Test of Motor Proficiency (first edition);[22] Developmental Test of Visual Motor Integration;[22] Bayley Scales of Infant and Toddler Development (BSID) (second and third editions);[21,23,26] modified MacArthur-Bates Communicative Development Inventories;[24] Ages Stages Questionnaire (second edition);[21] and Battelle's Development Inventory (first edition).[25] The questionnaires assessed intelligence (attention, memory); language (verbal and non-verbal, oral, expressive, receptive, vocabulary use, comprehension); motor skills (fine and gross); intelligence (attention); memory; and, social skills.

Regarding the control for confounding in the cohort studies, 3 of them included data on maternal and child sociodemographic characteristics (age, education, family income, skin colour, occupation) and

TABLE 1 Summary data of studies included in the systematic review

Author year country	Design	Sample size	Eligibility criteria	PA at gestational age /PA definition / PA instrument measurement	Neurodevelopment definition	Neurodevelopment instrument/ domains/ administered by	Child age	Covariates	Main results
Clapp[22] 1996 US	Cohort	Exercise Group (EG): 40 Control Group (CG): 20	Healthy women practice PA like ran/aerobics exercise or skied cross country ≥3/week, for more than 30 min a session, and at an intensity >55% of maximal capacity, before pregnancy	Not reported/ Ran/aerobics exercise or skied cross country ≥3/ week, for more than 30 min a session, and at an intensity >55% of maximal capacity/Not reported	Standard scores general intelligence, oral language skills, academic readiness, motor performance, perceptual-motor and overall score (the results of all the tests were averaged for each individual)	Wechsler Preschool and Primary Scale of Intelligence/general intelligence verbal and nonverbal areas Peabody Picture Vocabulary Test (first edition) /language skills: vocabulary comprehension, word usage, and expressive and receptive skills Bruininks-Oseretsky Test of Motor Proficiency (first edition)/gross and fine motor skills Developmental Test of Visual Motor Integration/ perceptual motor function All instruments were applied by professional trained	5 y old	The 2 groups were matched by Mother characteristics: smoking status, family income, education, marital stability, maternal and paternal body fat and height, parity, maternal work outside the home, preconceptional fitness, type of PA they performed. Children characteristics: gestational age, gender, birth order clinically normal growth, absence of serious illness, type of child care and breast feeding.	Mean (95% CI) General intelligence EG = 125 (124.7, 125.3) CG = 117 (116.1, 117.9) Oral language skill EG = 119 (118.7 119.3) CG = 109 (108.1, 109.9) Overall score EG = 115 (114.7, 115.3) CG = 111 (110.1, 112.0)
Clapp[23] 1998 US	Cohort	104 Exercise Group (EG): 52 Control Group (CG): 52	Women age (25-38 y), weight (45-75 kg), body fat (12% to 28%), health (no chronic illness, tobacco, or drug abuse), fitness (active life style, maximum aerobic capacity >32 mL/kg/min^{1}), and family income >50th percentile	Not reported/Ran/ aerobics exercise or stair climbing machines ≥3/ week, for more than 20 min a session at an intensity >55% of maximal capacity/ Not reported	Raw and percentile scores of mental and psychomotor scales	Bayley Scales of Infant and Toddler Development (second edition) / mental and psychomotor/ Applied by professional trained with presence of the mother or relative	12 mo	The same as the study of 1996	Mean (95% CI) Mental raw score EG = 120 (119.7, 120.3) CG = 118 (117.7, 118.3) Mental percentile EG = 88 (87.7,88.3) CG = 84 (83.4,84.5) Psychomotor raw score EG = 108 (107.7, 108.3) CG = 101 (100.4, 101.5) Psychomotor percentile EG = 69 (68.2,69.8) CG = 53 (51.9,54.1)

(Continued)

TABLE 1 (Continued)

Author year country	Design	Sample size	Eligibility criteria	PA at gestational age /PA definition / PA instrument measurement	Neurodevelopment definition	Neurodevelopment instrument/ domains/ administered by	Child age	Covariates	Main results
Jukic[24] 2013 England	Cohort: Prospective cohort, the Avon Longitudinal Study of Parents and Children (ALSPAC)	15-mo follow-up: 7162 8-year-old follow-up: 4529	Pregnant women residents in Avon who are delivered between, April 1st 1991 and March 31st 1992	18 wk/Quintiles of LTPA Index (11 types of leisure time that women currently practice) and Quintiles of general PA ('Nowadays, at least once a week do you engage in any regular activity like brisk walking, gardening, housework, jogging, cycling etc., long enough to work up a sweat?)/ Self-reported Questionnaire	Percentiles scores of vocabularies acquisition: number of words whose meaning the child understands (Dichotomised at 75th percentile) Verbal IQ raw score	Modified MacArthur-Bates Communicative Development Inventories / language/Report of the mother or relative Wechsler Intelligence Scale for Children (third edition) /Verbal IQ / Applied by trained professional	15 mo 8 y old	Mother: age, race, education, parity, hours worked, any infection, smoking and alcohol use, HOME score, household SES, parenting score, anxiety and depression. Child: age, duration of breast feeding, childcare, consumption of white, oil or shellfish	*Vocabulary acquisition 15 mo* Quintiles LTPA Index OR (95% CI) ≥27.6 = 1.40 (1.13;1.74) General PA (hours per week) OR (95% CI) >10 = 1.26 (1.02;1.55) *Verbal IQ raw score 8 y old* Quintiles LTPA Index OR (95% CI) ≥27.6 = 0.89 (−0.74;2.53) General PA (hours per week) OR (95% CI) >10 = −2.82 (−4.50; −1.14)
Hellenes[21] 2014 Norway	RCT	336 Exercise Group: 188 Control Group: 148	White pregnant women aged 18 y or older with a singleton live fetus	20-36 wk/ Moderate intensity exercise, 1/week between weeks 20 and 36 of pregnancy/Not reported	Mean of composite and raw scores (for Bayley scale) and raw scores by subtest (Ages Stages Questionnaire)	Bayley Scales of Infant and Toddler Development (third edition) /receptive and expressive language, fine and gross motor and cognitive, language and motor composite score/Applied by trained professional Ages Stages Questionnaire (second edition)/ Communication, gross and fine motor, problem-solving and personal-social/ Report of the mother or relative	20 mo	Not applicable	*Bayley III* Mean composite raw score (95% CI) *Exercise group* Cognitive: 105.4 (103.8;106.9) Language: 98.0 (96.4;99.6) Motor: 98.6 (97.3;99.9) *Control group* Cognitive: 107.4 (105.7;109.2) Language: 98.5 (96.7;100.3) Motor: 100.0 (98.6;101;5) *Ages stages questionnaire* Mean subtest raw score (95% CI) *Exercise group* Communication: 46.0 (44.0;48.1) Gross motor: 57.6 (56.6;58.6) Fine motor: 57.3 (56.4;58.2) Problem solving: 48.6 (47.1;50.1) Personal /social: 51.8 (50.6;53.1) *Control group* Communication: 48.0 (45.7;50.4) Gross motor: 57.7 (56.6;58.8) Fine motor: 56.9 (55.9;58.0) Problem solving: 49.8 (48.1;51.4) Personal /social: 53.1 (51.7;54.5)

TABLE 1 (Continued)

Author year country	Design	Sample size	Eligibility criteria	PA at gestational age /PA definition / PA instrument measurement	Neurodevelopment definition	Neurodevelopment instrument/ domains/ administered by	Child age	Covariates	Main results
Domingues[25] 2014 Brazil	Cohort: The 2004 Pelotas Birth Cohort	4147	All live births from women living in the urban area of Pelotas, from 1 January to 31 December 2004	Throughout pregnancy (All trimesters of gestation)/ Any LTPA during pregnancy, any LTPA in 1st, 2nd, and 3rd trimester, LTPA ≥150 min/wk in 1st, 2nd, and 3rd trimester, tertiles of physical activity/ Self-report Questionnaire	Percentile score and suspected development delay (90th percentile) IQ raw score	Battelle's Development Inventory (first edition)/school readiness, interaction communications skills, attention, motor skills and memory/Applied by trained professional in the presence of the mother or relative Wechsler Preschool and Primary Scale of Intelligence /IQ Applied by trained professional	12, 24 and 48 mo	Family income, schooling, smoking, skin colour, maternal age, number of previous births, maternal occupational characteristics and preterm birth	*12 mo* 90th percentile Battelle PR (95%CI) Any LTPA during pregnancy = 1.51 (1.17;1.94) Any LTPA 1st trimester = 1.33 (1.01;1.77) Any LTPA 2nd trimester = 1.48 (1.17;1.94) Any LTPA 3rd trimester = 1.41 (1.01;1.97) Tertiles PA First tertile = 2.53 (1.83;3.50) Second tertile PA = 0.97 (0.62;1.53) Third tertile = 1.31 (0.86;1.98) *24 mo* 90th percentile Battelle PR (95% CI) Any LTPA during pregnancy = 1.05 (0.79;1.39) Any LTPA 1st trimester = 1.12 (0.84;1.51) Any LTPA 2nd trimester = 1.10 (0.80;1.53) Any LTPA 3rd trimester = 1.03 (0.70;1.50) Tertiles PA First tertile = 1.19 (0.74;1.92) Second tertile PA = 0.77 (0.47;1.27) Third tertile = 1.23 (0.82;1.84) *48 mo* 90th percentile Battelle PR (95% CI) Any LTPA during pregnancy = 0.91 (0.63;1.32) Any LTPA 1st trimester = 0.77 (0.50;1.19) Any LTPA 2nd trimester = 0.83 (0.53;1.32) Any LTPA 3rd trimester = 1.05 (0.65;1.69) Tertiles PA First tertile = 0.99 (0.52;1.90) Second tertile PA = 1.04 (0.61;1.76) Third tertile = 0.709 (0.35;1.39)

(Continued)

TABLE 1 (Continued)

Author year country	Design	Sample size	Eligibility criteria	PA at gestational age /PA definition / PA instrument measurement	Neurodevelopment definition	Neurodevelopment instrument/ domains/ administered by	Child age	Covariates	Main results
Polańska[26] 2015 Poland	Cohort: The Polish Mother and Child Cohort Study (REPRO_PL)	538	Women with single pregnancy up to 12 wk of gestation, no assisted conception, no pregnancy complications and no chronic diseases	8-12 wk/ LTPA Index: type of activity and hours per week spent on the activity during the first trimester of pregnancy/ Self-report Questionnaire LTPA (MET indicator) <3 MET and <2.5 h/week of moderate exercise — reference category	Raw score/ chronologic age of composite score and subtest score	Bayley Scales of Infant and Toddler Development (third edition)/ language, motor, and cognitive memory/Applied by trained professional in the presence of the mother or relative	12 and 24 mo	Examiner, maternal age, maternal education, child gender, marital status and child care attendance	*12 mo* LTPA Index β (95% CI) Language >2.5 h/week and >3 METS = −1.0 (−4.1;2.81) *24 mo* LTPA Index β (95% CI) Language >2.5 h/week and >3 METS = 4.8 (0.8;8.8)

CG, Control Group; CI, Confidence Intervals; EG, Exercise Group; HOME, Home Observation for Measurement of Environment; IQ, Intelligence Quotient; LTPA, Leisure-Time Physical Activity; MET, Metabolic Equivalent Task; OR, Odds Ratio; PA, Physical Activity; PR, Prevalence Ratio; RCT, Randomised Clinical Trial; SES, Socio-economic Status.

health behaviour to adjust the models estimating the association of interest.[24-26]

Specific study characteristics are worth mentioning. Clapp[23] conducted the first peer-reviewed publication in the field in the United States in 1996. It was a cohort study including 40 women at any age that were physically active before pregnancy. Half of the group voluntarily discontinued physical activity practice during the entire pregnancy (control group) and the other half were encouraged to continue their regular levels (exercise group). Offspring's neurodevelopment was assessed at 5 years old, finding a higher mean score in the general intelligence (mean 125, 95% CI 124.7, 125.3) and oral language skills (mean 119, 95% CI 118.7, 119.3) in children from mothers that remained active during pregnancy compared with control group (general intelligence mean: 117, 95% CI 116.1, 117.9); and oral language skills mean: 109, 95% CI 108.1, 109.9.[22]

The same author conducted another study in 1998, including 104 pregnant women aged 25-38 years with no co-morbidities, normal weight, healthy and active life style and a family income above the 50% percentile of the US population at the time. Similar to the previous study, half of the group discontinued physical activity practice during pregnancy. Offspring's was assessed at 12 months old, finding a higher mean in the psychomotor score (mean 108, 95% CI 107.7, 108.3) children from mothers that remained active during pregnancy compared with children of control group (mean: 101, 95% 100.4, 101.5).[23]

After a decade without publications in the field, Jukic et al[24] in 2013 published a birth cohort study including 7162 pregnant women in England. PA practice was assessed on the 18th week of gestation as LTPA index. Offspring's language skills were assessed at 15 months and 8 years old. Results from adjusted analyses showed that 15- month-old children, whose mothers were in the highest LTPA quintile and highest general PA category during pregnancy, had an increased probability of obtaining a higher score in language (OR 1.40, 95% CI 1.13, 1.74) compared to their counterparts (OR 0.97, 95% CI 0.78, 1.21). At 8 years old, highest quintiles of LTPA were not associated with modified MacArthur-Bates Communicative Development Inventories raw score (OR 0.89, 95% CI 0.74, 2.53).

The only randomised controlled trial in the field was published in 2014 in Norway.[21] Participants included 336 white women aged 18 years or more. Supervised weekly moderate PA from week 20 to 36 was the assigned intervention for 188 pregnant women. The control group did not receive any intervention or counselling. Offspring's language, motor, cognitive, and social skills were assessed at 20 months. Parents were asked to report on development milestones.

Adherence to the intervention was defined by the authors as the attendance to 3 or more sessions of moderate PA each week during training period. Of the originally intervention and control groups, 56.9% and 44.6%, respectively, were included in the analysis. Except the mean cognitive composite score (intervention group: 105, 95% CI 103.8, 106.9; and control group: 107, 95% CI 105.7, 109.2), all other mean BSID composite and raw scores were higher in intervention than in control group.

The only study in Latin America was published in Brazil[25] in 2014. It was a birth cohort study including 4147 children. Information related to leisure time physical activity during all pregnancy trimesters was collected retrospectively. Offspring's language, motor, cognitive and social skills were assessed at 12, 24 and 48 months. Intelligence quotient was assessed at 48 months. In the adjusted analyses, a positive association was found between LTPA practice at any trimester and offspring neurodevelopment at 12 months (Prevalence Ratio (PR) 1.51, 95% CI 1.17, 1.94). However, at 24 and 48 months this association disappeared (PR 1.05, 95% CI 0.79, 1.39 and PR 0.91, 95% CI 0.63, 1.32, respectively), when comparing children from active and inactive mothers.

In 2015, a birth cohort study in Poland[26] was published including the children of 538 healthy pregnant women. Information related to LTPA was collected as LTPA index and the PA practice data was self-reported at 8-12 weeks of pregnancy. Offspring's language, motor, cognitive, and social skills were assessed at 12 and 24 months. Maternal practice of 2.5 hours per week of LTPA was not associated with higher offspring language development at 12 (β −1.0, 95% CI −4.1, 2.81) or 24 months (β 4.8, 95% CI 0.80, 8.88).

4 | COMMENT

4.1 | Principal findings

This study suggests that LTPA practice is positively associated with total neurodevelopment and specific language neurodevelopment in the first 18 months of life, independent of the instrument of evaluation. No associations were found between LTPA and motor, cognitive, and social skills.

4.2 | Interpretation

From the neurobiological perspective, the neurogenesis process may be facilitated by internal stimuli derived from the PA practice, which triggers changes in both the structure and the function of the nervous system. The increase in the precursor of the proliferation of the hippocampal formation cells (area associated with learning) and the increase in the density of dentate gyrus neurons (cells specific for language) are worth mentioning because the PA practice induces a neurometabolic programming in the offspring. This is known to positively regulate the cerebral growth involving the mitochondrial metabolism, leading not only to their proliferation, but also to their differentiation.[17-19]

Although the development of the brain begins in the foetal period, it continues in the postnatal stage as a result of the interaction of biological and environmental conditions. These factors are known to be determinants for learning and maintenance of the skills acquired throughout the life course, thus affecting or modifying the influence of intrauterine exposure to PA during pregnancy in the neurodevelopment after the first 18 months of life. Evidence from animal studies suggests that the action mechanism of PA on the offspring's hippocampus is temporary, continuing just a few weeks after birth. Additionally, other environmental factors may be more strongly

related to acquisition of language skills rather than the PA during pregnancy, explaining the disappearance of the association after 18 months of life.[18,24,27]

From the public health perspective, following important declines in child morbidity and mortality during the twentieth century, there is a need to increase the amount of knowledge generated about child development and the lifelong burden of disease on children, their families and their communities resulting of an impairment in this process.[28]

The prevalence of impairments in neurodevelopment among children varies worldwide but is scarce mainly in low and middle-income countries. Available data from low-income countries, show rates of mild or severe neurodisability ranging from 2.0 to 24.3 per 1000 children.[29] Considering that children is a large segment of the population in low and middle-income countries, a decline in cognitive functioning and intellectual disabilities, delay in language, motor, and social skills may represent the main public health problem and cause of morbidity and loss of lifelong opportunities in this population. Therefore, it is important to identify the association with physical activity and if there are opportunities to promote physical activity in this field.[30]

4.3 | Strengths of the systematic review

Characteristics that make this study unique are the inclusion of the first peer reviewed publication in the field ever and offspring characteristics beyond the perinatal period.

Strengths of the studies included in this review are the neurodevelopment assessment by trained personnel with the presence of the mother or relative child on 3 studies (Clapp et al,[23] Domingues et al[25] for the Battelle′s Development Inventory and Polańska et al[26]); inclusion of representative samples in the cities where the studies were conducted (Jukik et al,[24] Domingues et al,[25] Polańska et al[26]); and, the prospective assessment of neurodevelopment in more than one point of children's lives (Jukik et al,[24] Domingues et al,[25] Polańska et al[26]).

Three cohort studies included in the revision (England,[24] Brazil,[25] and Poland[26]) examined the association of PA and offspring's neurodevelopment using adjusted analysis that took maternal (age, level of education, skin colour, parity, smoking and alcohol use during pregnancy, depressive symptoms, and family monthly income) and child characteristics (gender, age, breast-feeding duration, childcare, and age at birth) as potential confounders, thus adequately controlling the relationship between PA and offspring's neurodevelopment.

The one only randomised clinical trial included in this review (Hellenes et al[21]) had followed the guidelines for monitoring adherence to the PA practice in the intervention group and the BSID-III was administered by trained examiners who were blinded to the group allocation; however, the intention-to-treat analysis was not performed. This leads to a loss of the exchangeability principle achieved with randomisation, potentially biasing the results.

A common characteristic of the included studies was also the neurodevelopment evaluation performed in environments unknown to children (laboratories, clinics) allowing the development of an evaluation that adheres to the application protocol for each of the tests. However, based on the theoretical assumptions that explain a child's development, the environment in which the evaluation of these functions is carried out, determines the level of efficiency with which the child performs the activities, be it language, cognitive, and motor domains among others, thus affecting subtests and overall scores leading to possible classification bias. The literature recommends that neurodevelopmental assessment is conducted not only by direct observation in a controlled environment (following the standardised protocol), but also taking into account parental report of current skills complementing the information about the child's neurodevelopment when observed in a habitual everyday environment.[29,31,32]

4.4 | Limitations of the systematic review

This study has a few limitations. First, the literature identified and selected for the review included mostly observational studies and only one randomised clinical trial with heterogeneous effect measures, limiting the ability to conduct further statistical analyses (i.e. meta-analysis) to explore the association between PA during pregnancy and offspring neurodevelopment.[33] Second, the instruments used to measure maternal PA practice and child neurodevelopment were heterogeneous, therefore results comparability and estimation of effect measures was a challenge. The instruments used assessed different PA domains, at different gestational ages and explored different neurodevelopment functions, which could have influenced the strength and significance of the associations. Third, self-report of total and LTPA practice was the method employed by all studies to estimate PA. Evidence has shown that independent of the questionnaire chosen, self-reported data can be overestimated and may have limited reliability and validity when compared to a laboratory/objective measure of physical activity. In addition, due to the use of different cut-off points and categories there is the potential for misclassification.[34] Fourth, except the modified MacArthur-Bates Communicative Development Inventories used in the Avon Longitudinal Study of Parents and Children, all other studies reported the use of validated tests. However, measures of interrater agreement, reliability or reproducibility were only described in the study conducted by Clapp et al[23] (intraclass correlation coefficient 0.90). The remaining studies did not report the psychometric properties of the employed tests, therefore the variation that is not due to measurement error is unknown.[35] Fifth, very early developmental assessment is not predictive of long term outcomes. This should be mentioned as a weakness of studies that only assessed infants, for instance. Three studies assessed neurodevelopment only once, which may not be the best predictor of long term outcomes. Evidence has shown that it is important to assess children serially to be able to determine normal developmental trajectories and patterns. Studies reporting the ability of abnormal early development assessments to predict abnormal cognitive outcomes consistently show a pattern of low sensitivity and high specificity.[36] Sixth, regarding neurodevelopment assessment, tools have most often been used in the clinical setting to establish the presence of developmental delay by

applying existing clear diagnostic cut-off points. Including multiple functions, specific domain and age tests have been created leading to the existence of innumerous tools.[32] The opposite is true when neurodevelopment tools are used for screening in population-based studies, when the objective is to identify infants and children at increased risk of neurodevelopment delay. As a dynamic and hard to measure process, neurodevelopment milestones could be reached by children at different points in time depending on the specific environment where the child is growing.[36,37] Therefore, its application as a screening tool ideally requires multiple measurements over time. In this systematic review, only Domingues et al[25] conducted continuous monitoring of neurodevelopment. Also, when used for screening, neurodevelopment tests have to be examined for validity, reliability, and accuracy, as well as to be standardised using children and families representing cultural, linguistic, and economic diversity of the population to be studied.

Seventh, it is worth mentioning that there are multiple PA recommendations for pregnant women and that there is no consensus related to intensity and frequency of this practice to obtain maternal and health benefits.[38] Most guidelines were launched <20 years ago, therefore Clapp studies[22,23] were conducted without clarity of the amount and intensity of PA required to obtain health benefits during pregnancy. The American Congress of Obstetricians and Gynaecologists (ACOG) guidelines are among the most acknowledged guidelines internationally, however, they are specific for the US population. Only few countries have national PA guidelines specific to their populations. Currently recommendations from the ACOG include aerobic exercise using large muscle groups in a continuous rhythmic manner; absolute and relative contraindications to aerobic exercise; and, how to write exercise prescriptions during pregnancy and postpartum period.[39] Eighth, another aspect relates to confounding. In the research carried out by Clapp in 1996[22] and 1998,[23] pregnant women were matched by sociodemographic and anthropometric characteristics in addition to the type of PA they performed. Also, the children of these pregnant women were matched individually by perinatal characteristics (gestational age, gender, birth order) and postnatal events (clinically normal growth, absence of serious illness, type of child care and breast feeding). Restriction and matching are suitable strategies to control for confounding at the selection phase of the study participants. Although these variables could confound the possible association between gestational PA and neurodevelopment, matching both pregnant women and children limits the observation of the effect that these characteristics could have on the association under study, thus restricting the statistical analysis.

5 | CONCLUSION

LTPA practice during pregnancy may have a positive impact on specific neurodevelopment functions (expressive and receptive language) of the offspring's neurodevelopment. New studies to determine the strength of this association are warranted and should (i) Evaluate PA during all stages of pregnancy including information about frequency, type of activity, and intensity of PA in all domains; (ii) Conduct multiple neurodevelopment measurements over time that include direct observation and parental report of child functions and skills; (iii) Assess maternal and child sociodemographic characteristics that could potentially confound the association between PA during pregnancy and offspring neurodevelopment; and (iv) Assess the positive effect of PA in neurodevelopment in children aged 3 or more years.

Developmental delay is a relevant global public health problem and cause of morbidity and loss of lifelong opportunities in children. Research to identify opportunities for early intervention during prenatal, ante-natal, postnatal, infancy, and early childhood periods and, to understand the requirement in multidisciplinary services to address special education, health care, social inclusion, and rehabilitation needs in this population is warranted.

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