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Effects of Regular Exercise During Pregnancy on Early Childhood Neurodevelopment: The Physical Activity for Mothers Enrolled in Longitudinal Analysis Randomized Controlled Trial

Otávio Amaral de Andrade Leão, Marlos Rodrigues Domingues, Andréa Dâmaso Bertoldi, Luiza Isnardi Cardoso Ricardo, Werner de Andrade Müller, Luciana Tornquist, Rafaela Costa Martins, Joseph Murray, Mariângela Freitas Silveira, Inácio Crochemore-Silva, Pedro Curi Hallal, and Gregore Iven Mielke

Background: The aim of this study was to investigate the effect of exercise during pregnancy on early childhood neurodevelopment (cognitive, motor, and language domains). **Methods**: A randomized controlled trial nested into the 2015 Pelotas (Brazil) Birth Cohort was conducted. Healthy pregnant women were enrolled between 16 and 20 weeks of gestation; 424 women and their children (intervention [n = 141]; control [n = 283]) were analyzed. An exercise-based intervention 3 times per week was delivered over 16 weeks. Child neurodevelopment and its domains were assessed at 1, 2, and 4 years. Standardized mean differences and 95% confidence intervals are presented. **Results**: No effects of exercise during pregnancy on child neurodevelopment and its domains at age 1 year were observed. Compared with the control group, children from women in the exercise group had higher language score at age 2 years (standardized mean differences = 0.23; 95% confidence intervals, 0.02 to 0.44) and higher cognitive score (standardized mean differences = 0.22; 95% confidence intervals, 0.03 to 0.41) at age 4 years. No effects of exercise during pregnancy were observed in the motor domain at 1, 2, and 4 years. **Conclusions**: No detrimental effects of exercise during pregnancy on child neurodevelopment were observed. In addition, these findings suggest that exercise during pregnancy can result in small benefits for language and cognitive development.

Keywords: child development, gestation, neuroscience

In 2020, the World Health Organization updated the recommendations for physical activity across the lifespan and, for the first time, included specific recommendations for physical activity during pregnancy and postpartum.[1] Based on the best evidence, these guidelines recommend that women should engage in at least 150 minutes per week of moderate-intensity aerobic activity during pregnancy unless in the presence of contraindications.[1] Moreover, guidelines for physical activity during pregnancy from Australia,[2] Brazil,[3] Canada,[4] the United States,[5] and other countries[6] are unanimous in stating that, in the absence of contraindications, physical activity during pregnancy is safe and can be beneficial for the health of both women and children.

These recommendations were based on extensive evidence that showed benefits of exercise during pregnancy in terms of reduced risk for a range of health problems, including gestational weight gain, gestational diabetes, gestational hypertension and preeclampsia, premature delivery, and large-for-gestational age baby, among other positive effects.[7–10] However, women are still resistant to engage in any exercise during this period, possibly due to lack of counseling by health personnel or concerns that it may be harmful for mother–child health.[11–13]

Leão, Bertoldi, Ricardo, Silveira, and Hallal are with the Postgraduate Program in Epidemiology, Federal University of Pelotas, Brazil. Domingues, Müller, Tornquist, and Crochemore-Silva are with the Postgraduate Program in Physical Education, Federal University of Pelotas, Brazil. Martins and Murray are with the Postgraduate Program in Epidemiology and Human Development, and the Violence Research Centre (DOVE), Federal University of Pelotas, Pelotas, Brazil. Mielke is with the School of Public Health, The University of Queensland, Brisbane, QLD, Australia. Leão (otavioaaleao@gmail.com) is corresponding author.

Besides the well-known benefits of exercise during pregnancy on maternal and child health, evidence suggests that exercise during pregnancy may have benefits and affect early child development.[14–16] Systematic reviews show that exercise during pregnancy is not associated with neonatal complications or other adverse childhood outcomes[14] and might lead to improvements in children's cognition, intelligence, and language development.[15,16] Those positive effects may be due to biological mechanisms triggered by physical activity that lead to increases in placental functional capacity and blood flow, which contribute to oxygen and nutrient uptake and, consequently, stimulate fetoplacental growth.[17,18]

Despite the potential benefits of exercise during pregnancy for childhood neurodevelopment, the evidence regarding this relationship is still very low, indicating the necessity of studies with multiple neurodevelopment measures across childhood.[2,16] In addition, most evidence on the effects of gestational physical activity, or exercise, on children's health is based on observational studies, which reinforce the necessity to complement the current evidence with experimental trials.[2,16,19–21]

Thus, the objective of the present study was to investigate the effects of exercise during pregnancy on early child neurodevelopment and its domains (cognitive, motor, and language) at 1, 2, and 4 years.

Methods

Study Design

This analysis was part of the Physical Activity for Mothers Enrolled in Longitudinal Analysis Study (PAMELA), a randomized controlled trial (RCT) nested within the 2015 Pelotas (Brazil) Birth Cohort,[22,23] which primarily aimed to evaluate the effects of exercise during pregnancy on maternal–child health outcomes, such as prematurity and preeclampsia. The 2015 Pelotas (Brazil) Cohort Study included 98.7% (N = 4275) of all live births that occurred in 2015 in the city of Pelotas, Brazil. The PAMELA study included 424 women of the original cohort who were recruited across multiple health services and invited to participate in the antenatal phase of the study when the randomized trial was conducted. After delivery, children were followed-up when they were 3 months, 1, 2, and 4 years old. Detailed information on recruitment and logistic details of the PAMELA study and the 2015 Pelotas (Brazil) cohort study has been published elsewhere.[22,23] The protocols of both studies were approved by the School of Physical Education Ethics Committee from the Federal University of Pelotas (protocol numbers 649.244 and 522.064, respectively). All participants provided written informed consent. The trial was registered on clinicaltrials.gov (number NCT02148965), and no deviations from the original study protocol were made.

Recruitment and Participants for the PAMELA Trial

All pregnant women living in Pelotas (Brazil) with expected deliveries between January 1, 2015 and December 31, 2015 were eligible for the 2015 Pelotas Birth Cohort Study. All pregnant women who met inclusion criteria were invited to participate in the randomized clinical trial. To be eligible for the PAMELA trial, pregnant women should have been at least 18 years old and between 16 and 20 weeks of gestation. Exclusion criteria were the existence of the following health conditions and behavioral characteristics: hypertension, diabetes, cardiovascular disease, persistent bleeding, history of preterm birth or miscarriage, multiple pregnancy confirmed by ultrasound, body mass index above 35 kg/m^2, smoking more than 20 cigarettes a day, and leisure-time physical activity >150 minutes per week.

For the sample size calculation, 213 women were estimated as necessary in the intervention group and 426 women in the control group (intervention–control ratio 1:2), based on statistical power of 80%, significance level at 5%, and estimated risk reduction of 30% in the primary outcomes (preterm birth and preeclampsia).[22] However, in the present analyses, only women who were participants in the 2015 Birth Cohort were included (N = 424).

Randomization

Pregnant women who agreed to participate in the PAMELA trial were allocated to intervention or control groups using a random sampling software. The randomization process was carried out using blocks of 9 pregnant women. In each block, 3 women were allocated to the intervention group and 6 women to the control group. We used a balance of 1:2 in recruitment to increase precision and statistical power as well as minimize intervention costs and behavior changes in women participating in the cohort study. The group allocation process, data collection, and data analysis were performed blindly by independent staff.

Intervention

The intervention consisted of a 16-week exercise program starting between the 16th and 20th weeks of gestation, 3 times a week, lasting 60 minutes per session. The program was guided by a team of trained physical education professionals who attended up to 3 pregnant women per session at the university gym. With the aim of improving compliance to the protocol, all participants received a training kit (T-shirt, running pants, and running shoes), door-to-door transportation, and reschedule opportunities whenever a participant missed a session. Adherence to intervention sessions was controlled by the instructors who registered the attendance to the exercise sessions. Adherence to the intervention was defined by attending at least 70% of exercise sessions (34 out of 48 sessions) and not missing more than 6 consecutive sessions.

The intervention protocol was planned following the recommendations of the American College of Gynecologists and Obstetricians.[24] Protocol-specific training was provided involving aerobic activities (treadmill or stationary bike), strength training (dumbbells, machines, or elastic bands), and floor exercises (pregnancy-specific exercises for pelvic and low back), according to the progressive periodization in 3 stages: first (1–4 wk), 15 minutes of aerobic exercise and 35 minutes of strength and floor exercises (3 sets of 12 repetitions); second (5–10 wk), 20 minutes of aerobic exercise and 30 minutes of strength and floor exercises (3 sets of 10 repetitions); and third (11–16 wk), 25 minutes of aerobic exercise and 25 minutes of strength and floor exercises (3 sets of 8 repetitions). All stages contained 5 minutes warm-up and 5 minutes stretching. The exercise intensity was measured by perceived effort according to the Borg scale and ideally ranged from 12 to 14 points. A full description of the exercise session has been published in the study protocol[22] and is provided in the Supplementary Table S1 (available online). The participants of the control group were instructed to continue their usual routines. They received the same baseline and postintervention assessments as the intervention group and continued to be followed by the 2015 Pelotas (Brazil) Birth Cohort Study.

Outcome Measures

The primary outcome of the study was child neurodevelopment and its respective domains, which were assessed at 1, 2, and 4 years of age. At 1 year of age, children were assessed with the Oxford Neurodevelopment Assessment (Ox-NDA). This instrument was developed based on the principles of the INTERGROWTH-21st Neurodevelopment Assessment (INTER-NDA)[25,26] and measures early childhood development between 10 and 14 months of age, using a combination of play-based tasks, caregiver report, and direct observation. Oxford Neurodevelopment Assessment measures cognition, language, motor, behavior, executive function, attention, and social–emotional reactivity and takes around 20 minutes to be administered. The instrument was evaluated against the Bayley Scale for Infant Development third edition in a subsample of the 2015 Pelotas Birth Cohort, presenting excellent interrater and intrarater reliability for the total score, showing an intraclass correlation coefficient of .93 and .96, respectively.[27]

At 2 years, the INTER-NDA was used.[25] The INTER-NDA is an early childhood development assessment, measuring cognition, language, and motor skills (fine and gross) between 22 and 26 months of age. It assesses development through a combination of tasks, caregiver reports, and observation, lasting approximately 15 minutes. For the present analyses, a continuous variable was used, with higher scores indicating more advanced development, based on 13 research items from the cognitive domain, 4 from fine motor, 3 from gross motor, and 12 from language.[26] The INTER-NDA is a validated instrument compared with the Bayley Scale for Infant Development third edition[26] and was applied at the research clinic by a trained interviewer. The instrument retraining sessions were carried out every 3 months during the study.

At 4 years, neurodevelopment was assessed using an adapted version of the Battelle Development Inventory.[28] This adapted version included all 66 items (of the original 96) pertinent to normal development up to age 4–5 years, divided into personal–social, adaptive, fine and gross motor, communication, and cognitive. The adaption was made to maintain comparability with a previous cohort and assess suspected developmental delay at the measurement age.[29] Assessment was performed by trained interviewers, with the supervision of psychologists, and was carried out based on direct observation of the children and interviews with caregivers.[28,29] The instrument presented good and stable correlation to predict later development.[30] In each follow-up measure, children with severe disabilities did not have their neurodevelopment assessed due to incapacity to collect the data.

Covariates

Maternal information was collected with questionnaires administered at the perinatal assessment. The variables used in the current analyses were maternal age (complete years), schooling (complete years of study), family income (quintiles of monthly household income in *Brazilian Reais*), parity (number of previous births), gestational weight gain (classified according to the guidelines of the US Institute of Medicine),[31] pregestational body mass index (calculated by pregestational weight divided by squared height), and gestational age (weeks at delivery). Child sex (male or female) and preterm birth (gestational age <37 wk; yes or no) were assessed during the perinatal visit. Child characteristics, collected at 1-year follow-up, were: center-based childcare (yes or no), play with someone (yes or no), and breastfeeding (yes or no). Maternal physical activity during pregnancy was measured in the perinatal study using a standardized questionnaire. Women were asked about the type, frequency, and duration of physical activities in their leisure time. Further details about the physical activity questionnaire have been previously published.[32]

Statistical Analysis

Intention-to-treat analyses were conducted to assess the effects of the intervention on domains of child neurodevelopment at ages 1, 2, and 4 years. In addition, per protocol analyses including only those participants who adhered to the protocol (minimum participation in 34 out of 48 sessions; not missing more than 6 consecutive sessions) were conducted. For the intention-to-treat analysis, only complete cases were considered. Descriptive analyses were performed, and nonpaired *t* tests and chi-squared tests were used to compare maternal and child characteristics between the intervention and control group. The same procedure was performed to compare women included in the trial with those in the entire 2015 Birth Cohort population (Supplementary Table S2 [available online]). Differences in child neurodevelopment scores between the intervention and control group at ages 1, 2, and 4 years were converted into SD units. Thus, standardized mean differences between groups and respective 95% confidence intervals were presented. All statistical procedures were conducted using Stata (version 16.0; StataCorp, College Station, TX).

Results

Of the 2902 mothers assessed for eligibility, 963 declined to participate and 1341 did not meet the inclusion criteria (Figure 1). Of the 639 randomized women, 213 were allocated to the intervention group and 426 to the control group. Finally, deriving from the 424 included in the cohort, the number of women/children included in the analyses varied by outcome, as seen in Figure 1.

Mothers from the intervention group presented higher schooling and family income and gained more weight during pregnancy than mothers in the control group. Characteristics of intervention and control groups of the PAMELA trial were very similar with mean age of 27.7 years, about 12 years of schooling, similar mean family income (about BRL 3650), had on average <2 children, gained around 13 kg during pregnancy, with a pregestational body mass index of 25 kg/m^2, and final gestational age of 38 weeks (Table 1). Maternal physical activity was higher in the intervention than in the control group in all trimesters of gestation (Table 1). No differences were observed between the intervention and control group regarding alcohol consumption and smoking during pregnancy (Table 1). Some differences between mothers included in the PAMELA study and mothers included in the 2015 Birth Cohort were observed. The PAMELA study sample included women who were older, with higher education and mean family income, fewer children, higher gestational weight gain, and higher gestational age than the original cohort (Supplementary Table S2 [available online]).

Table 2 presents child characteristics at 12 months. There was no significant difference between sex, center-based childcare, having someone to play with, and preterm birth in the intervention and control groups. In both groups, about 20% of children attended center-based childcare, 90% of children had someone to play with, 6% were born preterm, and 41% to 53% were still breastfeeding.

Results from Table 3 indicate that, at 1 year, no effects of the intervention were observed for cognitive, motor, and language domains. At 2 years, children from mothers in the intervention group presented higher language scores than the control group (standardized mean differences = 0.23, 95% confidence intervals, 0.02 to 0.44). For the other domains, null effects were observed. At 4 years, positive effects were observed in the cognitive domain—children with mothers in the intervention group presented higher scores than the control group (standardized mean differences = 0.22, 95% confidence intervals, 0.03 to 0.41).

Only 81 women (57.4% out of the 141 included in the intention-to-treat analyses) were included in the per protocol analyses (70% of the sessions in the intervention group). In this sample, null effects were observed at 1, 2, and 4 years in every domain of neurodevelopment (Supplementary Table S3 [available online]).

Discussion

To the best of our knowledge, this study is the first RCT in a middle-income country evaluating the effect of a supervised exercise program during pregnancy on child neurodevelopment up to age 4 years. The results indicate benefits of a small size magnitude of the exercise program on child language and cognitive development. In addition, it is important to highlight that no significant effects in the opposite direction were observed, showing that exercise during pregnancy did not harm child cognitive, motor, or language neurodevelopment.

The association between exercise during pregnancy and child language development found in our study is reinforced by findings from longitudinal studies conducted in high-income countries, which demonstrate a positive relationship between physical activity during pregnancy and language development at 15 months and

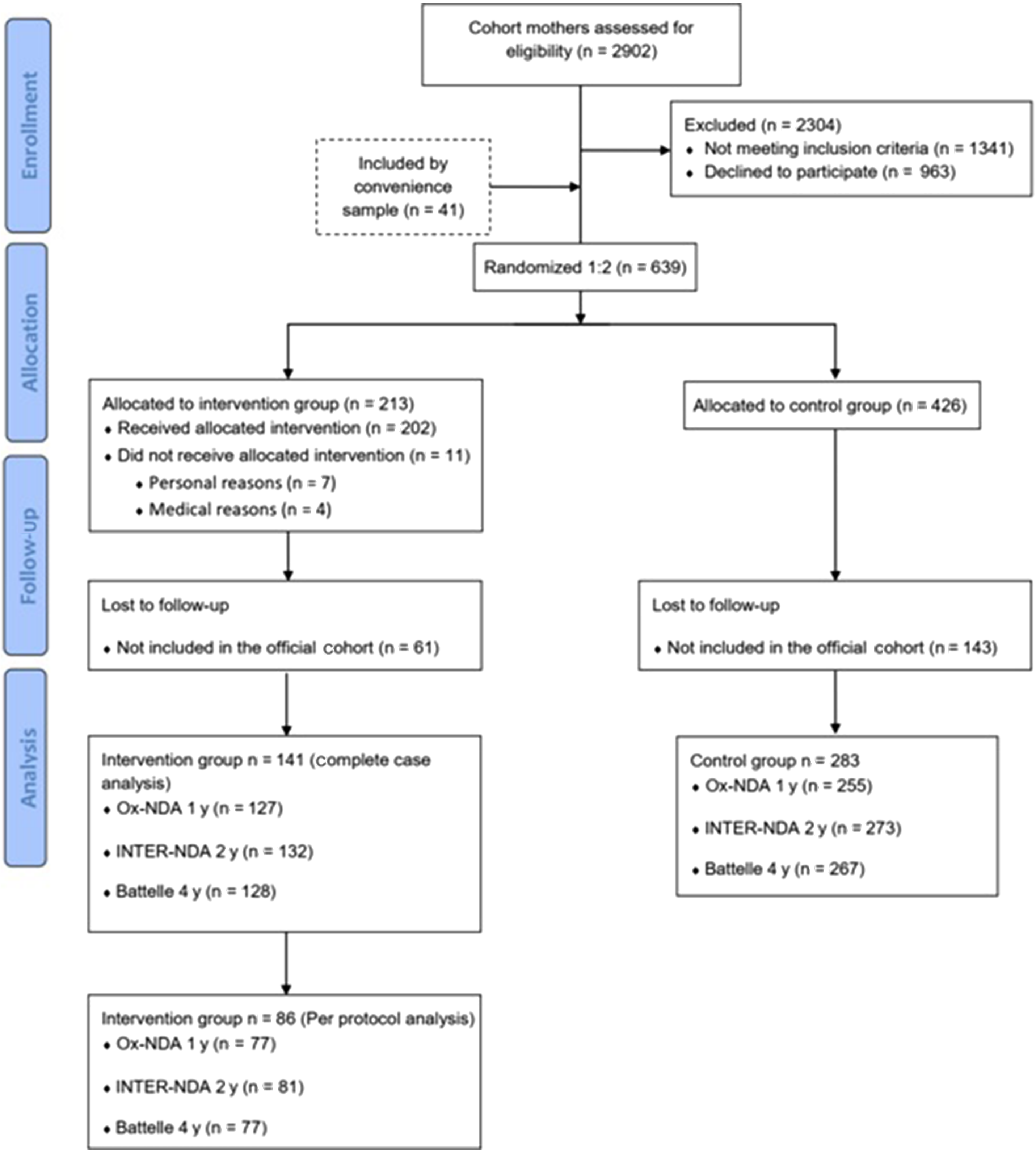

Figure 1 — Flow diagram of the PAMELA study following the CONSORT guidelines. Per protocol analysis (70% of sessions). CONSORT indicates consolidated standards of reporting trials; INTER-NDA, INTERGROWTH-21st Neurodevelopment Assessment; Ox-NDA, Oxford Neurodevelopment Assessment; PAMELA, Physical Activity for Mothers Enrolled in Longitudinal Analysis Study.

Table 1 Maternal Characteristics According to Intervention Group, PAMELA Study (N = 424)

	Intervention Mean (SD)	Control Mean (SD)
Age, y	27.7 (5.6)	27.7 (5.7)
Schooling (full years)	12.2 (3.6)	12.0 (3.2)
Family income (BRL)	3702.2 (3957.5)	3625.8 (4363.7)
Parity	1.4 (0.6)	1.5 (0.7)
Gestational weight gain, kg	12.5 (5.9)	13.3 (6.5)
Pregestational BMI	25.1 (3.7)	25.4 (4.3)
Gestational age, wk	38.5 (2.0)	38.7 (1.5)
Physical activity first trimester, min/wk	74.01 (112.26)	20.69 (60.76)
Physical activity second trimester, min/wk	138.62 (106.63)	13.74 (49.97)
Physical activity third trimester, min/wk	81.03 (106.52)	9.52 (41.38)
Smoking during pregnancy, n (%)	13 (9.22)	20 (7.07)
Alcohol consumption during pregnancy, n (%)	6 (4.26)	13 (4.59)

Abbreviations: PAMELA, Physical Activity for Mothers Enrolled in Longitudinal Analysis; BMI, body mass index; BRL, Brazilian currency.

Table 2 Child Characteristics at 12 Months, According to Maternal Intervention Group, PAMELA Study

	Intervention n (%)	Control n (%)
Sex		
Female	72 (51.1)	134 (47.3)
Male	69 (48.9)	149 (52.7)
Center-based childcare		
Yes	28 (20.4)	57 (20.6)
No	109 (79.6)	220 (79.4)
Play with someone		
Yes	131 (95.6)	249 (89.9)
No	6 (4.4)	28 (10.1)
Preterm birth		
Yes	9 (6.4)	16 (5.6)
No	132 (93.6)	267 (94.4)
Breastfeeding		
Yes	57 (41.6)	147 (53.1)
No	80 (58.4)	130 (46.9)

Abbreviation: PAMELA, Physical Activity for Mothers Enrolled in Longitudinal Analysis.

2 years of the offspring.[21,33] Similar to our results when children were aged 2 years, a recent review found no evidence of association between maternal leisure-time physical activity and child motor and cognitive skills but indicated a positive association with total neurodevelopment and specific language scores in the first 18 months of life.[16]

The protocol used in our study, which is consistent with the current recommendations for physical activity during pregnancy,[1] provides high-quality evidence for understanding the efficacy of exercise on childhood neurodevelopment. However, the comparability of our findings with other studies might be limited by the wide variation in the intervention protocols used in previous studies. For example, previous studies included exercise protocols with 1 to 7 sessions per week, including light- to vigorous-intensity types of exercise, and with duration of 10 to 90 minutes per session.[14] Similar to our findings, Hellenes et al[34] found null effects of exercise during pregnancy on neurodevelopment in a 16-week intervention, which delivered a moderate-intensity exercise session once a week for pregnant women.

Evidence on the effects of gestational exercise on child neurodevelopment is inconclusive. Although some studies indicate that women participating in exercise programs had children with greater motor skills scores[35] and born with increased brain maturation,[36] other studies indicate no effects of regular exercise during pregnancy on neurodevelopment of offspring at 18 months and 7 years[20,34] and no relationship between levels of physical activity and offspring motor development at 4 months.[37] These differential effects have even been observed in the same setting—data from the 2004 Pelotas Birth Cohort showed positive associations between PA during pregnancy and neurodevelopment at 12 months of the child; however, at 24 and 48 months, no association was observed.[19]

Although our results indicate benefits of the exercise program during pregnancy only for the language and cognitive scores of the offspring, detrimental effects on children's development have not been previously demonstrated. Similarly, another study, conducted with data from this RCT, demonstrated that there was no adverse impact of the exercise program on maternal and child health.[38] This is in line with the growing body of evidence that suggests that physical activity during pregnancy is safe, has health benefits for the woman and her child, and may reduce the risks of some pregnancy-related complications.[5,14,39,40]

In view of the benefits and the absence of harm to the health of the mother or offspring, it is emphasized that women with uncomplicated pregnancies should be encouraged to engage in aerobic and strength conditioning exercises during pregnancy. The choice of physical activity type, duration, intensity, and frequency of sessions should be determined considering the woman's previous physical activity history.[41] This incentive is especially important considering the evidence that pregnancy is associated with reduced physical activity practice[42,43] with a low prevalence of pregnant women achieving current recommendations,[44–46] and low levels of activity are also observed in the postpartum period.[47,48]

This study has some limitations. First, despite many strategies adopted to maintain adherence to the program, there was a relatively large number of dropouts, and a low adherence to the protocol was observed in the intervention group. Another point is that our eligibility criteria may have been very strict, resulting in a population of extremely healthy pregnant women. The main limitation of the study was the lack of control regarding the possible exposure of the control group to exercise during pregnancy, which may have attenuated the observed differences. However, based on data collected at the perinatal assessment, the control group had lower levels of physical activity than intervention group in all trimesters of pregnancy. Given that gestational age may impact on neurodevelopment, additional analyses excluding preterm babies were conducted; however, the results were similar to those observed in the entire sample. Finally, the use of different neurodevelopment measures through early childhood limited the interpretation of the findings. As an attempt to attenuate this problem,

Table 3 Neurodevelopment of 2015 Cohort Children at 12, 24, and 48 Months in the Intervention and Control Group, PAMELA Study

Intention-to-treat	Intervention n	Intervention Mean SD (95% CI)	Control n	Control Mean SD (95% CI)	Mean difference (95% CI)
Ox-NDA (1 y)					
Cognitive	127	–0.10 (–0.29 to 0.10)	255	0.02 (–0.11 to 0.15)	–0.12 (–0.35 to 0.11)
Motor	127	–0.08 (–0.28 to 0.12)	255	0.03 (–0.09 to 0.15)	–0.11 (–0.33 to 0.11)
Language	127	–0.12 (–0.32 to 0.09)	255	0.02 (–0.10 to 0.14)	–0.13 (–0.35 to 0.08)
INTER-NDA (2 y)					
Cognitive	132	0.11 (–0.05 to 0.28)	273	0.14 (0.01 to 0.26)	–0.02 (–0.24 to 0.19)
Fine motor	132	–0.02 (–0.18 to 0.14)	273	–0.01 (–0.14 to 0.11)	–0.004 (–0.21 to 0.20)
Gross motor	132	–0.02 (–0.17 to 0.13)	273	0.01 (–0.09 to 0.12)	–0.03 (–0.22 to 0.15)
Language	132	0.28 (0.11 to 0.45)	273	0.04 (–0.08 to 0.16)	0.23 (0.02 to 0.44)
Battelle (4 y)					
Cognitive	128	0.36 (0.22 to 0.49)	263	0.14 (0.02 to 0.25)	0.22 (0.03 to 0.41)
Motor	123	0.11 (–0.07 to 0.29)	267	–0.01 (–0.13 to 0.10)	0.12 (–0.09 to 0.33)

Abbreviations: CI, confidence interval; INTER-NDA, INTERGROWTH-21st Neurodevelopment Assessment; Ox-NDA, Oxford Neurodevelopment Assessment; PAMELA, Physical Activity for Mothers Enrolled in Longitudinal Analysis.

the scores of each neurodevelopment domain were analyzed based on their SDs, allowing comparison across measures.

It is important to highlight the strengths of this study. Although the protocol used in this study, which was conducted in a supervised environment where the participants' adherence to the exercise protocol could be monitored, may be challenging to replicate in "real-world" settings, this is one of the largest RCTs designed to investigate the efficacy of exercise during pregnancy for improving maternal and child health outcomes. In addition, this is a pioneering study in middle-income countries and one of the few RCTs that investigated the effect of a supervised exercise program on child neurodevelopment. Finally, the use of 3 measures of neurodevelopment in different points of early childhood improves the knowledge on this association.

Conclusions

Our findings indicate that exercise during pregnancy results in a relatively small, but positive, effect on language development at 2 years and cognitive development at 4 years. Despite the lack of effect on other domains of neurodevelopment, exercise during pregnancy did not cause any harm or have any negative effects on child neurodevelopment. Therefore, due to the benefits for maternal and child health, interventions to increase participation in physical activity and exercise during pregnancy should be recommended.

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