

Effect of childhood nutrition counselling on intelligence in adolescence: a 15-year follow-up of a cluster-randomised trial

Tiago N Munhoz^{1,2,*}, Iná S Santos¹, Simone de M. Karam³, Jose Martinez⁴, Gretel Pelto⁵, Raquel Barcelos¹, Helen Gonçalves¹, Neiva CJ Valle¹, Luciana Anselmi¹ and Alicia Matijasevich^{1,6}

¹Postgraduate Program in Epidemiology, Federal University of Pelotas, Pelotas, Brazil; ²Centro de Pesquisas Epidemiológicas, Universidade Federal de Pelotas, Rua Marechal Deodoro, CEP: 96020-220 – Caixa Postal 464, 1160 Pelotas, RS, Brasil; ³Faculty of Medicine, Federal University of Rio Grande, Rio Grande, Brazil; ⁴Centre for Intervention Science in Maternal and Child Health, Centre for International Health, University of Bergen, Bergen, Norway; ⁵Division of Nutritional Sciences, Cornell University, Ithaca, NY, USA; ⁶Department of Preventive Medicine, Faculty of Medicine, University of São Paulo, São Paulo, Brazil

Submitted 30 March 2016: Final revision received 2 February 2017: Accepted 4 April 2017: First published online 23 May 2017

Abstract

Objective: The present study aimed to assess the effects of an early childhood nutrition counselling intervention on intelligence (as measured by the intelligence quotient (IQ)) at age 15–16 years.

Design: A single-blind, cluster-randomised trial.

Setting: In 1998, in Southern Brazil, mothers of children aged 18 months or younger were enrolled in a nutrition counselling intervention (n 424). Counselling included encouragement and promotion of exclusive breast-feeding until 6 months of age and continued breast-feeding supplemented by protein-, lipid- and carbohydrate-rich foods after age 6 months up to age 2 years. The control group received routine feeding advice. In 2013, the fourth round of follow-up of these individuals, at the age of 15–16 years, was undertaken. IQ was assessed using the short form of the Wechsler Adult Intelligence Scale (WAIS-III). Mental disorders (evaluated using the Development and Well-Being Assessment (DAWBA)) and self-reported school failure, smoking and alcohol use were also investigated. Adjusted analyses were conducted using a multilevel model in accordance with the sampling process.

Subjects: Adolescents, mean (SD) age of 15.4 (0.5) years (n 339).

Results: Mean (SD) total IQ score was lower in the intervention group than the control group (93.4 (11.4) and 95.8 (11.2), respectively) but the association did not persist after adjustment. The prevalence of any mental disorders was similar between intervention and control groups (23.1 and 23.5%, respectively). There were no differences between groups regarding school failure, smoking and alcohol use.

Conclusions: Nutrition counselling intervention in early childhood had no effect on intelligence measured during adolescence.

Keywords
Child growth
Adolescence
Nutrition counselling
Cognition
Randomised controlled trial
Intelligence

Adequate nutrition during pregnancy and in the first years of life is essential for appropriate child development. A body of evidence from observational studies shows that maternal dietary supplementation during pregnancy has a protective effect against low birth weight, intra-uterine growth restriction and preterm birth^(1,2). Longitudinal studies have shown that early-life factors such as breast-feeding and adequate nutrition during a child's first years have positive effects on academic performance and human capital⁽³⁾, and are associated with better socio-economic status⁽⁴⁾, higher intelligence quotient (IQ) and higher income in adulthood⁽⁵⁾.

In the 1990s, the WHO and UNICEF developed the Integrated Management of Childhood Illness (IMCI) strategy⁽⁶⁾. This strategy was devised with the objective of reducing child mortality, illness, and disability attributable to health problems that occur during the first 5 years of life, by improving: (i) case management skills of health-care staff; (ii) overall health systems; and (iii) family and community health practices. The IMCI was implemented in several countries and generally achieved its main objective of reducing child mortality^(7,8).

In 1998, a randomised trial was conducted in Southern Brazil to evaluate the efficacy of the nutritional counselling

*Corresponding author: Email tyagomunhoz@hotmail.com

component of the IMCI strategy. The counselling intervention consisted of providing information and negotiating with mothers about improving the child's diet, with a substantial focus on encouragement of breast-feeding and appropriate complementary feeding. Counselling was provided by doctors during routine well-child visits to primary health-care facilities. The results of this trial showed that the intervention improved physician counselling performance, maternal practices, child feeding and child growth^(9,10). The results of the second follow-up (45 d after the counselling visits) suggested that daily intake of fats was higher in the intervention group than in the control group. The results of the fourth follow-up (15 years after the intervention) showed that males in the intervention group were taller and had lower total cholesterol levels than those in the control group. Among females, those in the intervention group had lower TAG and total cholesterol:HDL cholesterol than those in the control group⁽¹¹⁾.

Studies of the effects of dietary interventions during pregnancy and early childhood on the cognitive development of children and adolescents have been conducted in several countries. Nearly all of these interventions included supplementation of fatty acids⁽¹²⁾, Fe⁽¹³⁾ and other micronutrients⁽¹⁴⁾. The long-term effects of the interventions on cognitive development were seldom investigated in these studies and the limited evidence suggests that there was no effect of these interventions on cognition. Larson and Yousafzai, in a meta-analysis, found very little evidence for an effect of postnatal nutritional interventions on mental development for children under 2 years of age⁽¹⁵⁾.

The only published study that assessed the long-term effect of a system-wide implementation of the WHO's Baby Friendly Hospital Initiative on cognitive development was the Promotion of Breastfeeding Intervention Trial (PROBIT). This randomised clinical trial, which included over 17 000 neonates, evaluated encouragement of breast-feeding and its effects on a variety of outcomes, including cognition. The results of PROBIT were indicative of superior verbal IQ at age 6.5 years in the intervention group⁽¹⁶⁾. There is a significant evidence gap regarding the long-term effects of nutrition counselling interventions on cognition, which hinders assessment of the causality of potential associations⁽¹⁷⁾.

The present study aimed to assess the effects of an early childhood nutrition counselling intervention on intelligence (as measured by IQ) at age 15–16 years.

Participants and methods

Design of the trial

This was a single-blind, cluster-randomised controlled trial. Detailed information on the intervention and methods of the first rounds of follow-up has been published

elsewhere^(9,10,18). In brief, in 1998, a trial was carried out among the twenty-eight primary health-care centres of Pelotas, a mid-sized city in the state of Rio Grande do Sul, Brazil, which were randomly allocated (1:1) across intervention and control groups. The twenty-eight health-care centres were paired according to prevalence of child underweight and socio-economic indicators in their respective neighbourhoods. Then, one centre from each pair was selected for allocation to the intervention group (which received nutrition counselling training) by flipping a coin; the other centre joined the control group (continued to provide usual feeding advice). Because this was an educational intervention, only outcome assessors could be blinded. At centres allocated to the intervention group, doctors were trained to provide nutritional counselling to all mothers of children aged 18 months or younger. All children in the intervention and control group were followed up at 8, 45 and 180 d after the intervention. The fourth round of follow-up took place in 2013, at which time the original participants had a mean age of 15.4 (SD 0.5) years (Fig. 1).

Inclusion and exclusion criteria

The target population of the trial included all children aged 18 months or younger who were treated within the local health-care network in the year 1998. The initial study included the first thirteen children aged 18 months or younger who were seen by doctors at primary health-care centres after the randomisation process. Thirty-three doctors participated in the study: seventeen in the intervention group and sixteen in the control group. All children who presented with congenital defects that might interfere with feeding were ineligible for the trial.

Study setting

Pelotas is a city located in Southern Brazil. According to the 2000 and 2010 censuses, its population was estimated at 323 000 and 328 000, respectively, living predominantly in urban areas. As of 2010, the mean per capita monthly income of permanent dwellers in the urban area was \$US 490 and the median monthly income for the same population was \$US 271. The gross domestic product was \$US 5976, which is considerably below that recorded for the country as a whole (\$US 8161).

Physicians' training for the 1998 intervention

Before fieldwork began, training materials for nutritional counselling were adapted to local conditions as recommended in the IMCI handbook (Adaptation Guide, section D)⁽⁶⁾. Doctors in the intervention group received 20 h of training. Special emphasis was given to the development of communication skills (empathetic listening and asking, praising appropriate behaviour, providing guidance in plain language and checking whether mothers understood the recommendations given). Two training sessions were conducted, one week apart, both to ensure coverage of providers who worked different shifts

(morning and evening) and to reduce the overload of home visits that might have occurred if only one training session had taken place. The performance of all participants was evaluated formally through a written test, which was taken at the end of each course as a means of documenting the effectiveness of training⁽¹⁰⁾. For comparison, doctors in the control group were evaluated using the same instrument.

The 1998 intervention

The study intervention was based on an adaptation of the IMCI feeding guidelines aiming to promote age-appropriate child feeding. Based on this adaptation, the protocol promoted the following practices: (i) for children aged 4 months or younger, exclusive breast-feeding; (ii) for children aged 4 to 6 months, exclusive breast-feeding (if the child failed to gain weight adequately or still appeared hungry after feedings, other foods should be added); (iii) for children aged 6 to 12 months, breast-feeding plus chicken liver, shredded chicken and beef, egg yolks, various fruits and vegetables, addition of one teaspoon of vegetable oil, margarine or butter to the child's plate, crushed beans; and (iv) for children aged 1 to 2 years, breast-feeding and continued introduction of complementary solid foods. Mothers were encouraged to give the child at least five meals per day to ensure appropriate feeding. The key recommendations of these adapted IMCI feeding guidelines were summarized in a leaflet⁽¹⁸⁾ that was discussed with and handed to the mothers during medical appointments.

Follow-up at age 15–16 years (2013)

The participants of the original study were located by means of several strategies: home visits to the addresses registered at last follow-up (180 d after enrolment); a search of school records of the State Department of Education, social networks and Ministry of Health databases; and collaboration with informants in the neighbourhood, at health-care facilities and at schools. Additional information on the methods used for the 2013 round of follow-up has been published elsewhere⁽¹¹⁾.

Outcome of interest

Participant IQ at age 15–16 years (fourth round of follow-up) was evaluated using the Wechsler Adult Intelligence Scale (WAIS-III)⁽¹⁹⁾. A short-form version of the WAIS-III was used, which included four subtests: 'Similarities' and 'Arithmetic' (verbal scales); and 'Picture Completion' and 'Coding' (performance scales). The Picture Completion subtest consists of a series of colour pictures with missing elements. These pictures represent common objects and environments and the test-taker is tasked with finding the missing elements. This measures word knowledge and verbal concept formation. For the Coding subtest, the test-taker is shown a series of symbols that are paired with numbers. Using a key, the test-taker draws each symbol under its corresponding number, within a 120 s time limit;

this measures processing speed, short-term visual memory, psychomotor speed, visual perception, visual-motor coordination, visual scanning ability, attention and concentration. For the Similarities subtest, the examinee is shown two words that represent common objects or concepts and asked to describe how they are similar; this measures verbal concept formation and reasoning. For the Arithmetic subtest, working within a specified time limit, the examinee mentally solves a series of arithmetic problems, which measures mental manipulation, concentration, attention, short- and long-term memory, numerical reasoning ability and mental alertness. These four subtests were considered appropriate to measure IQ in research settings⁽²⁰⁾. Duly trained psychologists who were blind to the group allocation of the adolescent (intervention or control) administered the instrument. Crude scores for each subtest were converted into weighted scores in accordance with the Brazilian standard⁽¹⁹⁾. These weighted scores were then used to generate total IQ scores, as appropriate for the age range of the participants⁽²⁰⁾.

Secondary outcomes

To evaluate mental disorders, we used the Development and Well-Being Assessment (DAWBA) questionnaire⁽²¹⁾. The DAWBA consists of open and closed questions identifying the occurrence of symptoms based on the diagnostic criteria for mental disorders of the *Diagnostic and Statistical Manual of Mental Disorders* and the International Classification of Diseases. It was developed for use in children and adolescents between 5 and 17 years of age. The open questions allow qualitative description of the symptoms, frequency and other characteristics of the disorders assessed. In addition, a clinical evaluator (rater) can evaluate each of the questionnaires individually, integrating the responses to the questions and determining the diagnosis. The DAWBA was validated in Brazil and the agreement between the two clinical raters was 0.93 (SE 0.03) for any disorder, 0.91 (SE 0.05) for internalizing disorders and 1.0 for externalizing disorders⁽²²⁾. Psychologists who had been trained in its standardised administration applied the DAWBA to mothers or caregivers. The training included lectures, role playing, and supervised clinical interviews with paediatric and mental health outpatients at the Federal University of Pelotas, totalling more than 40 h. The DAWBA was applied via computer, allowing direct input of the data into an online system. Details of the questionnaire can be found online, as well as in other studies⁽²³⁾. School failure and unhealthy behaviours (smoking and alcohol use) were evaluated by self-report using a pre-tested and standardised questionnaire. School failure was defined as having ever repeated a grade at school. Smokers were those who reported having smoked at least one cigarette in their life and alcohol use was defined as the consumption of any alcoholic beverage in their life.

Sample size calculation

The intervention study, started in 1998, used primary health-care centres as sampling units. The sample size calculation took into account clustering by primary health-care centre, and was based on a significance level of 5% (one-tailed), fourteen sampling units per group (control and intervention) and a primary outcome of mean weight gain of 6.7 (SD 0.19) kg at 12 months. These parameters yielded 80% statistical power to detect a mean weight gain difference, per sampling unit (health-care centre), of 180 g or more.

At the 2013 round of follow-up, 339 individuals had full information completed (169 in the intervention group and 170 in the control group). Taking into consideration the aforementioned sample size and α and β error rates of 0.05 (two-tailed) and 0.20, respectively, the study was powered to find a difference ≥ 3.4 IQ points between the intervention and control groups ($\alpha = 0.05$, two-tailed).

Statistical analysis

The primary exposure variable was the study intervention. All analyses were based on intention-to-treat principles. Despite randomisation, differences at baseline between the intervention and control groups were noted on maternal education (years of schooling), weight-for-age Z-score, length-for-age Z-score and weight-for-length Z-score⁽¹⁰⁾; hence, these variables were included in the adjusted analysis. Adjusted analyses were conducted using a multilevel model that considered the primary health-care centre (doctor) at the first level and the adolescent at the second level. First, losses and refusals to participate were compared with the individuals allocated at baseline. Absolute and relative frequencies were calculated for categorical variables, and means and standard deviations for continuous or discrete variables. A *P* value of < 0.05 was considered statistically significant. Multilevel analysis was performed using the statistical software package Stata version 12.0.

Missing data

We had eighty-five missing values for IQ. Thus, we analysed the effect of missing outcome data via a sensitivity analysis, estimated by multiple imputation (mi Stata command) by the Bayesian paradigm from a frequentist (randomisation-based) perspective⁽²⁴⁾, using the following variables: intervention indicator (intervention or control group), maternal schooling, weight-for-age Z-score, weight-for-height Z-score and height-for-age Z-score. We used least-squares regression and twenty multiple data sets for the missing values.

Ethics

The study was conducted according to the guidelines laid down in the Declaration of Helsinki and all procedures were approved by the Research Ethics Committee of Universidade Federal de Pelotas (protocol no. OF 25/12), an institutional review board affiliated with the Brazilian National Commission for Research Ethics (CONEP).

Written consent was witnessed and signed by participants' mothers or guardians, as well as by participants themselves, before the start of data collection. Registration of randomised trials was not required at the time of the baseline study.

Results

In 2013, 401 of the 424 participants of the original study were located, and 363 (85.6%) were assessed (183 from the intervention group and 180 from the control group). Of these, 339 (80.0%) adolescents completed the WAIS-III. The trial flowchart (Fig. 1) shows the number of clusters and doctors allocated in 1998 and the number of adolescents assessed at the fourth follow-up in 2013.

Except for maternal educational level and weight-for-age Z-score at baseline, the characteristics of participants assessed for the 2013 follow-up were similar between the intervention and control groups. In the 2013 pool of subjects, there was a smaller proportion of mothers with high educational attainment (≥ 8 years of schooling) in the intervention group than in the control group (Table 1). The weight-for-age Z-score was also lower in the intervention group than in the control group (0.13 (SD 1.1) *v.* 0.39 (SD 1.1), respectively). Losses to follow-up were higher among adolescents from the control group whose mothers had a lower education level.

Table 2 shows the results of IQ analyses. Crude analyses showed a lower mean total IQ score and a lower mean Similarities subtest score in the intervention group, but the associations did not persist after adjustment. Multiple data imputation for the primary outcome produced an imputed estimate that was similar to the available data (mean total IQ score of 93.2 (SD 11.4) in the intervention group and 95.6 (SD 11.3) in the control group; adjusted *P* value = 0.299). This similarity showed that no analyses were affected by missing data or differential rates of follow-up between trial arms. The prevalence of any mental disorders was similar between intervention and control groups (23.1 and 23.5%, respectively). There were no differences between groups regarding school failure, smoking and alcohol use (Table 2).

Discussion

The focus of the tested intervention was nutritional counselling (consistent with the IMCI strategy) of mothers with children under 18 months of age. The results of initial evaluations demonstrated a positive effect of the intervention on anthropometric parameters during childhood and on adolescent health^(9,10,18). In the present study, a lower mean Similarities subtest score was found in the intervention group, but the association was biased towards the null hypothesis after controlling for baseline unbalanced characteristics. One possible explanation for this finding is

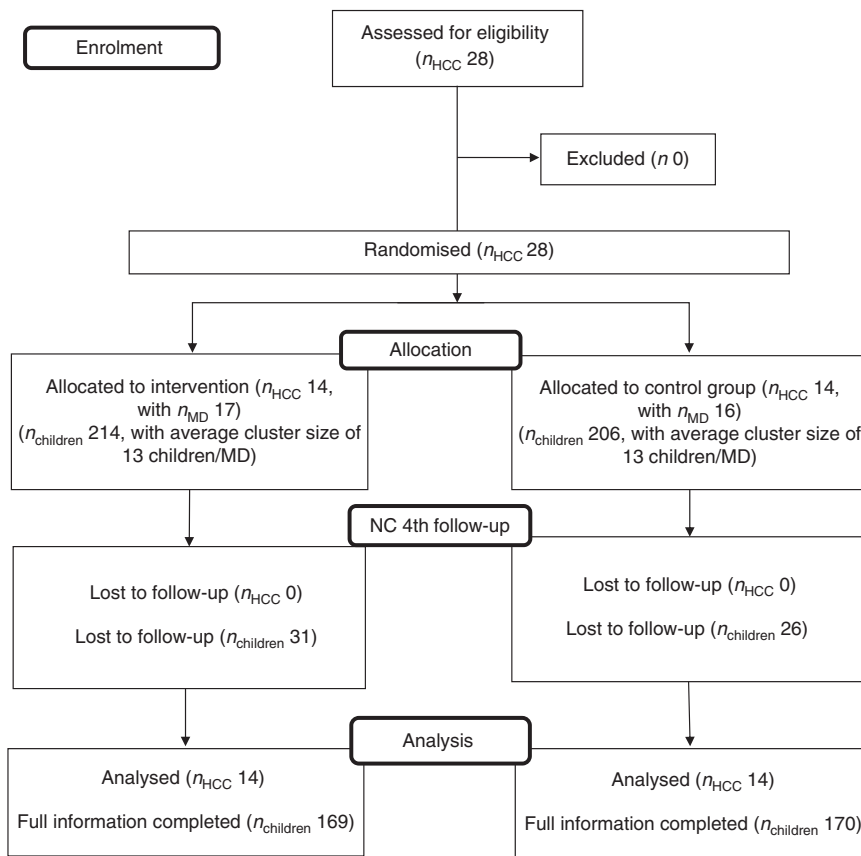


Fig. 1 Trial flowchart from enrolment (in 1998) to fourth follow-up (in 2013), Pelotas, Brazil (HCC, health-care centre; MD, medical doctor; NC, nutrition counselling)

Table 1 Participant characteristics at enrolment (in 1998) among the overall study population and among those assessed in 2013, Pelotas, Brazil

| Variable | 1998 (n 424) | | 2013 (n 339) | | P value | | | | |
|--|--------------------------|-------------------------------|--------------------------|-------------------------------|---------|------|-------|------|-------|
| | Control group (n 206) | Intervention group (n 214) | Control group (n 170) | Intervention group (n 169) | | | | | |
| Sociodemographic characteristics* | | | | | | | | | |
| Female gender, n and % | 89 | 43.2 | 104 | 47.7 | 76 | 44.7 | 83 | 49.1 | 0.416 |
| Maternal schooling (years), n and % | | | | | | | | | 0.002 |
| 0–3 | 37 | 18.0 | 57 | 26.4 | 23 | 13.5 | 43 | 25.6 | |
| 4–7 | 101 | 49.0 | 111 | 51.4 | 86 | 50.6 | 90 | 53.0 | |
| ≥8 | 68 | 33.0 | 48 | 22.2 | 61 | 35.9 | 36 | 21.4 | |
| Age (months), mean and SD | 7.5 | 5.3 | 7.8 | 5.4 | 7.4 | 5.4 | 7.9 | 5.4 | 0.394 |
| Weight (kg), mean and SD | 10.1 | 1.9 | 10.0 | 1.9 | 10.1 | 1.9 | 10.0 | 2.0 | 0.692 |
| Length (cm), mean and SD | 75.3 | 6.5 | 75.1 | 7.0 | 75.3 | 6.4 | 75.1 | 7.1 | 0.877 |
| Weight-for-age Z-score, mean and SD | 0.32 | 1.1 | 0.07 | 1.1 | 0.39 | 1.1 | 0.13 | 1.1 | 0.035 |
| Weight-for-height Z-score, mean and SD | 0.41 | 1.0 | 0.28 | 0.9 | 0.46 | 0.98 | 0.31 | 0.93 | 0.148 |
| Height-for-age Z-score, mean and SD | −0.05 | 1.0 | −0.23 | 1.1 | −0.00 | 1.1 | −0.17 | 1.1 | 0.164 |
| Breast-feeding (yes) | | | | | | | | | |
| At enrolment, n and %† | 84 | 40.8 | 90 | 41.7 | 74 | 43.5 | 74 | 44.1 | 0.924 |
| At second follow-up, n and %‡ | 70 | 34.8 | 68 | 32.2 | 61 | 36.1 | 57 | 34.6 | 0.767 |
| At third follow-up, n and %§ | 50 | 25.6 | 45 | 21.5 | 45 | 27.1 | 38 | 23.3 | 0.428 |

*Baseline (assessed in 1998).

†Sample size at enrolment: control group, n 206; intervention group, n 214.

‡Sample size at second follow-up: control group, n 201; intervention group, n 211.

§Sample size at third follow-up: control group, n 195; intervention group, n 209.

Table 2 Effects of the nutrition counselling intervention on total intelligence quotient (IQ), IQ subtests, mental disorders, school failure, smoking and alcohol use in the intervention and control groups (*n* 339). Pelotas, Brazil, 2013

| Variable | Control group (<i>n</i> 170) | | Intervention group (<i>n</i> 169) | | Crude <i>P</i> value | Adjusted <i>P</i> value* |
|-----------------------------------|----------------------------------|---------|---------------------------------------|---------|----------------------|--------------------------|
| | Mean or <i>n</i> | SD or % | Mean or <i>n</i> | SD or % | | |
| IQ (total), mean and SD | 95.8 | 11.2 | 93.4 | 11.4 | 0.047 | 0.362 |
| IQ subtests†, mean and SD | | | | | | |
| Picture Completion | 9.2 | 2.8 | 8.7 | 2.7 | 0.135 | 0.331 |
| Coding | 10.1 | 2.3 | 10.0 | 2.1 | 0.446 | 0.654 |
| Similarities | 9.2 | 2.3 | 8.5 | 2.2 | 0.006 | 0.054 |
| Arithmetic | 9.1 | 1.9 | 9.0 | 2.2 | 0.655 | 0.816 |
| Mental disorders‡, <i>n</i> and % | | | | | | |
| Any mental disorders | 40 | 23.5 | 40 | 23.1 | 0.929 | 0.927 |
| Any internalizing disorder | 33 | 19.4 | 35 | 20.2 | 0.849 | 0.897 |
| Any externalizing disorder | 5 | 2.9 | 11 | 6.4 | 0.153 | 0.090 |
| School failure, <i>n</i> and % | 123 | 72.4 | 114 | 67.5 | 0.326 | 0.216 |
| Smoking, <i>n</i> and % | 13 | 7.7 | 16 | 9.5 | 0.549 | 0.477 |
| Alcohol use, <i>n</i> and % | 118 | 69.4 | 129 | 76.3 | 0.152 | 0.131 |

*Adjusted for the baseline variables: maternal schooling in years and child weight-for-age Z-score, height-for-age Z-score and weight-for-height Z-score.

†Assessed using the short form of the Wechsler Adult Intelligence Scale (WAIS-III)⁽¹⁹⁾.

‡Evaluated using the Development and Well-Being Assessment (DAWBA) questionnaire⁽²¹⁾.

that, despite paired randomisation, children from the intervention group had lower family income, social class and maternal schooling⁽¹⁰⁾. The main reasons for the failure of an intervention include the inadequacy of its contents to the needs of the target population, the non-adherence of the participants and failures in the delivery of the intervention. Considering that the intervention content was based on previous studies carried out with the infant population at the same city, that the acceptability, feasibility and affordability of the intervention were previously tested in household trials⁽²⁵⁾, and that the delivery of the intervention was formally evaluated through observation of thirteen consultations of the physicians in both groups, we have no reasons to suspect that the intervention had not been consistently administered^(9,10). Additionally, the lack of effect of the intervention on the adolescent mental health, school failure and unhealthy behaviours gives consistence to the finding of no effect on IQ.

Our finding is in line with the results of a randomised controlled trial conducted with undernourished children in Jamaica^(17,26,27) to evaluate the effect of nutrition supplementation and psychosocial stimulation on mental development. At age 17–18 years, there were long-standing benefits of childhood psychosocial stimulation on cognition⁽²⁷⁾, educational achievement⁽²⁷⁾ and psychological functioning⁽²⁸⁾. Nevertheless, no effect of nutritional intervention on mental development was found⁽²⁷⁾. Additionally, six out of nine systematic reviews and meta-analysis that evaluated the effects of fatty acids^(12,29,30), Fe^(13,31,32) or Zn^(33–35) supplementation during childhood reported small positive effects on cognition. In sum, the positive effects on cognition were detected among those children with nutritional deficits^(13,31,32) or under 5 years of age^(12,30), suggesting no long-term effects of nutritional interventions on cognition.

The association between adequate nutrition during the early formative years and child development has been

shown in previous studies^(36,37), but the causal pathway between child development and cognition is not completely understood⁽³⁸⁾. Randomised controlled trials have been conducted in several countries to assess the effects of micronutrient and macronutrient supplementation on cognition and mental health throughout the life cycle. Three meta-analyses and two systematic reviews on this subject have been published^(12,13,29,30,39). Jiao *et al.* investigated the effect of *n*-3 PUFA supplementation on cognition in children and adults. The results suggested a positive effect of supplementation in children under 2 years of age, although the estimated effect size was small and no effect of the intervention was seen in older children⁽¹²⁾. Two other meta-analyses with the same purpose did not find any evidence for an effect of fatty acid supplementation on cognitive development in children up to 12 years old^(29,30). Heroso *et al.*⁽¹³⁾ conducted a systematic review of fourteen studies to assess the effects of Fe on cognitive development in children and adolescents aged 6 months to 18 years, which suggested a small positive effect of Fe supplementation on cognition in anaemic infants. In a meta-analysis of seven randomised trials that evaluated Fe supplementation in pregnant women or children (aged 0–9 months) and its effects on cognition in childhood, Szajewska *et al.*⁽³⁹⁾ failed to yield any evidence of the intervention on mental development. There are considerable limitations in the studies that comprised those systematic reviews and meta-analyses, including the small sample size of most trials⁽³⁰⁾, poor methodological quality^(29,30), failure to account properly for dropouts and failure to describe adequate safeguards to ensure allocation concealment and blinding^(12,29,30), and high attrition rate (up to 86%)⁽³⁰⁾; moreover, few trials conducted intention-to-treat analyses and many of the trials carried out multiple comparisons on small samples, increasing the odds of type I error⁽³⁰⁾. Although the data included in these systematic reviews and meta-analyses

cannot be seen with a high degree of confidence, those trials classified as having low risk of bias did not find evidence of effect on cognition^(13,29,30).

A systematic review conducted by Leung *et al.* included eighteen trials which evaluated the effects of multiple-micronutrient supplementation during pregnancy on cognitive, psychomotor, visual, auditory and behavioural development in children (aged 2–9 months) and adolescents⁽¹⁴⁾. That review did not find any conclusive evidence that micronutrient supplementation during pregnancy improves child development during childhood and adolescence. Eilander *et al.* conducted a systematic review of twenty studies, with a total sample size of 4303 children and adolescents, designed to assess the effects of multiple-micronutrient dietary interventions on cognitive development between the ages of 5 and 16 years⁽⁴⁰⁾. No differences in cognitive development were found between the intervention and control groups.

The advantages of the current study include the use of a randomised controlled design, which was appropriate to evaluate the efficacy of the intervention, and the low percentage of losses and refusals (20%), especially considering the long follow-up period, thus reducing the chance of differential bias in the sample. The instrument used to assess intelligence in the study is widely recognised and used internationally⁽¹⁹⁾. Trained investigators, who were supervised at every step of the trial, carried out all follow-up procedures.

Limitations of the present study include the fact that, despite randomisation, between-group differences were observed at baseline. However, these differences were taken into account in the present analysis. As the study was underpowered to detect differences between groups, we cannot rule out type II error (false negative), i.e. whether a true difference between groups exists. Pelotas is a medium-sized city in Brazil with several unique economic and cultural characteristics compared with other Brazilian cities and other countries. Thus, our findings may not be generalisable to different socio-economic backgrounds or settings where anaemia is common among children. In these scenarios the intervention could have had a positive impact on child cognition and development as shown in previous studies^(13,26). Also, although we used one of the best intelligence and mental health questionnaires available, we did not measure other developmental outcomes, nor did we employ other intelligence tests that might have been able to detect differences between groups. Finally, considering the long time gap between the first and the final follow-up, it is not possible to know if the differences in changed dietary habits between those who did and did not receive the intervention remained at the same level; consequently, our results may not specifically reflect the lack of relationship between nutrition and intelligence but instead may reflect the failure of the intervention to change long-term dietary habits.

Conclusions

In this sample, a nutrition counselling intervention in early childhood had no effect on intelligence as measured during adolescence.

Acknowledgements

Acknowledgements: The authors are extremely grateful to Professor Cesar G. Victora for his unique contribution to this research. *Financial support:* The study was supported by the Brazilian National Research Council (grant number 477438/2012-1); the Research Support Foundation of the State of Rio Grande do Sul (grant number 12/2006-9); and Children's Pastorate. The WHO Department of Child and Adolescent Health supported the original trial. I.S.S., H.G. and A.M. are supported by the CNPq (Conselho Nacional de Desenvolvimento Científico e Tecnológico). T.N.M. is supported by a doctoral scholarship from CAPES (Coordenação de Aperfeiçoamento de Pessoal de Nível Superior). The funders had no role in the design, analysis or writing of this article. *Conflict of interest:* The authors declare that they have no conflict of interest. *Authorship:* I.S.S. conceived and designed the research. T.N.M. analysed the data. All authors interpreted the data and collaborated with the interpretation/writing of the paper. All authors have critically reviewed its content and have approved the final version submitted for publication. *Ethics of human subject participation:* This study was conducted according to the guidelines laid down in the Declaration of Helsinki and all procedures involving human subjects/patients were approved by the Research Ethics Committee of Universidade Federal de Pelotas (protocol no. OF 25/12). Written informed consent was obtained from all participants' mothers or guardians, as well as from participants themselves, before the start of data collection. Registration of randomised trials was not required at the time of the baseline study.

References

1. Ramakrishnan U, Grant F, Goldenberg T *et al.* (2012) Effect of women's nutrition before and during early pregnancy on maternal and infant outcomes: a systematic review. *Paediatr Perinat Epidemiol* **26**, Suppl. 1, 285–301.
2. Imhoff-Kunsch B, Briggs V, Goldenberg T *et al.* (2012) Effect of *n*-3 long-chain polyunsaturated fatty acid intake during pregnancy on maternal, infant, and child health outcomes: a systematic review. *Paediatr Perinat Epidemiol* **26**, Suppl. 1, 91–107.
3. Victora CG, Barros FC, Horta BL *et al.* (2005) Breastfeeding and school achievement in Brazilian adolescents. *Acta Paediatr* **94**, 1656–1660.
4. Hoddinott J, Maluccio JA, Behrman JR *et al.* (2008) Effect of a nutrition intervention during early childhood on economic productivity in Guatemalan adults. *Lancet* **371**, 411–416.
5. Victora CG, Horta BL, de Mola CL *et al.* (2015) Association between breastfeeding and intelligence, educational attainment,

- and income at 30 years of age: a prospective birth cohort study from Brazil. *Lancet Glob Health* **3**, e199–e205.
6. World Health Organization (2005) *Handbook: IMCI Integrated Management of Childhood Illness*. Geneva: WHO.
 7. Bryce J, Victora CG, Habicht JP *et al.* (2005) Programmatic pathways to child survival: results of a multi-country evaluation of Integrated Management of Childhood Illness. *Health Policy Plan* **20**, Suppl. 1, i5–i17.
 8. Bryce J, Victora CG, Habicht JP *et al.* (2004) The multi-country evaluation of the integrated management of childhood illness strategy: lessons for the evaluation of public health interventions. *Am J Public Health* **94**, 406–415.
 9. Pelto GH, Santos I, Goncalves H *et al.* (2004) Nutrition counseling training changes physician behavior and improves caregiver knowledge acquisition. *J Nutr* **134**, 357–362.
 10. Santos I, Victora CG, Martines J *et al.* (2001) Nutrition counseling increases weight gain among Brazilian children. *J Nutr* **131**, 2866–2873.
 11. Santos IS, Matijasevich A, Assuncao MC *et al.* (2015) Promotion of weight gain in early childhood does not increase metabolic risk in adolescents: a 15-year follow-up of a cluster-randomized controlled trial. *J Nutr* **145**, 2749–2755.
 12. Jiao J, Li Q, Chu J *et al.* (2014) Effect of *n-3* PUFA supplementation on cognitive function throughout the life span from infancy to old age: a systematic review and meta-analysis of randomized controlled trials. *Am J Clin Nutr* **100**, 1422–1436.
 13. Hermoso M, Vucic V, Vollhardt C *et al.* (2011) The effect of iron on cognitive development and function in infants, children and adolescents: a systematic review. *Ann Nutr Metab* **59**, 154–165.
 14. Leung B, Wiens K & Kaplan B (2011) Does prenatal micronutrient supplementation improve children's mental development? A systematic review. *BMC Pregnancy Childbirth* **11**, 12.
 15. Larson LM & Yousafzai AK (2017) A meta-analysis of nutrition interventions on mental development of children under-two in low- and middle-income countries. *Matern Child Nutr* **13**, e12229.
 16. Kramer MS, Aboud F, Mironova E *et al.* (2008) Breastfeeding and child cognitive development: new evidence from a large randomized trial. *Arch Gen Psychiatry* **65**, 578–584.
 17. Grantham-McGregor SM, Fernald LC, Kagawa RM *et al.* (2014) Effects of integrated child development and nutrition interventions on child development and nutritional status. *Ann N Y Acad Sci* **1308**, 11–32.
 18. Santos IS, Victora CG, Martines J *et al.* (2002) Avaliação da eficácia do aconselhamento nutricional dentro da estratégia do AIDPI (OMS/UNICEF). *Rev Bras Epidemiol* **5**, 15–29.
 19. Wechsler D & MCdVM Silva (2004) *WAIS-III: Escala de Inteligência Wechsler para Adultos: Manual Técnico*. São Paulo: Casa do Psicólogo.
 20. Jeyakumar SL, Warriner EM, Raval VV *et al.* (2004) Balancing the need for reliability and time efficiency: short forms of the Wechsler Adult Intelligence Scale-III. *Educ Psychol Meas* **64**, 71–87.
 21. Goodman R, Ford T, Richards H *et al.* (2000) The Development and Well-Being Assessment: description and initial validation of an integrated assessment of child and adolescent psychopathology. *J Child Psychol Psychiatry* **41**, 645–655.
 22. Fleitlich-Bilyk B & Goodman R (2004) Prevalence of child and adolescent psychiatric disorders in southeast Brazil. *J Am Acad Child Adolesc Psychiatry* **43**, 727–734.
 23. Petresco S, Anselmi L, Santos IS *et al.* (2014) Prevalence and comorbidity of psychiatric disorders among 6-year-old children: 2004 Pelotas Birth Cohort. *Soc Psychiatry Psychiatr Epidemiol* **49**, 975–983.
 24. Rubin DB (1987) *Multiple Imputation for Nonresponse in Surveys*. New York/Chichester: Wiley.
 25. Valle NJ, Santos I, Gigante DP *et al.* (2003) Household trials with very small samples predict responses to nutrition counseling intervention. *Food Nutr Bull* **24**, 343–349.
 26. Grantham-McGregor SM, Powell CA, Walker SP *et al.* (1991) Nutritional supplementation, psychosocial stimulation, and mental development of stunted children: the Jamaican Study. *Lancet* **338**, 1–5.
 27. Walker SP, Chang SM, Powell CA *et al.* (2005) Effects of early childhood psychosocial stimulation and nutritional supplementation on cognition and education in growth-stunted Jamaican children: prospective cohort study. *Lancet* **366**, 1804–1807.
 28. Walker SP, Chang SM, Powell CA *et al.* (2006) Effects of psychosocial stimulation and dietary supplementation in early childhood on psychosocial functioning in late adolescence: follow-up of randomised controlled trial. *BMJ* **333**, 472.
 29. Qawasmi A, Landeros-Weisenberger A, Leckman JF *et al.* (2012) Meta-analysis of long-chain polyunsaturated fatty acid supplementation of formula and infant cognition. *Pediatrics* **129**, 1141–1149.
 30. Gould JF, Smithers LG & Makrides M (2013) The effect of maternal omega-3 (*n-3*) LCPUFA supplementation during pregnancy on early childhood cognitive and visual development: a systematic review and meta-analysis of randomized controlled trials. *Am J Clin Nutr* **97**, 531–544.
 31. Thompson J, Biggs BA & Pasricha SR (2013) Effects of daily iron supplementation in 2- to 5-year-old children: systematic review and meta-analysis. *Pediatrics* **131**, 739–753.
 32. Low M, Farrell A, Biggs BA *et al.* (2013) Effects of daily iron supplementation in primary-school-aged children: systematic review and meta-analysis of randomized controlled trials. *CMAJ* **185**, E791–E802.
 33. Gogia S & Sachdev HS (2012) Zinc supplementation for mental and motor development in children. *Cochrane Database Syst Rev* **12**, CD007991.
 34. Warthon-Medina M, Moran VH, Stammers AL *et al.* (2015) Zinc intake, status and indices of cognitive function in adults and children: a systematic review and meta-analysis. *Eur J Clin Nutr* **69**, 649–661.
 35. Nissensohn M, Sanchez-Villegas A, Fuentes Lugo D *et al.* (2013) Effect of zinc intake on mental and motor development in infants: a meta-analysis. *Int J Vitam Nutr Res* **83**, 203–215.
 36. Christian P, Mullany LC, Hurley KM *et al.* (2015) Nutrition and maternal, neonatal, and child health. *Semin Perinatol* **39**, 361–372.
 37. Daelmans B, Black MM, Lombardi J *et al.* (2015) Effective interventions and strategies for improving early child development. *BMJ* **351**, h4029.
 38. Donders J & Hunter SJ (2010) *Principles and Practice of Lifespan Developmental Neuropsychology*. Cambridge/New York: Cambridge University Press.
 39. Szajewska H, Rusczyński M & Chmielewska A (2010) Effects of iron supplementation in nonanemic pregnant women, infants, and young children on the mental performance and psychomotor development of children: a systematic review of randomized controlled trials. *Am J Clin Nutr* **91**, 1684–1690.
 40. Eilander A, Gera T, Sachdev HS *et al.* (2010) Multiple micronutrient supplementation for improving cognitive performance in children: systematic review of randomized controlled trials. *Am J Clin Nutr* **91**, 115–130.