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Early life programming of attention capacity in adolescents: The HELENA study

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Abstract
The study aims to examine the individual and combined association of early life factors (birth weight, birth length, and any and exclusive breastfeeding) with attention capacity in adolescents. The study included 421 European adolescents (243 girls), aged 12.5–17.5 years, who participated in the Healthy Lifestyle in Europe by Nutrition in Adolescence Study. Body weight and length at birth of adolescents were collected from parental records. The duration of any and exclusive breastfeeding were self-reported. The d2 Test of Attention was administered to assess attention capacity. The main results showed that birth weight, birth length, breastfeeding, and exclusive breastfeeding were related to attention capacity in boys (β ranging from 0.144 to 0.196; all $p < .05$) after adjustment for age, centre, gestational age, maternal education, family affluence scale, and body mass index. Among boys, differences in attention capacity were found according to tertiles of birth weight and birth length ($p < .05$), as well as borderline significant differences across groups of any and exclusive breastfeeding ($p = 0.055$ and $p = 0.108$, respectively) after adjusting for potential confounders. In addition, boys with 3 early life risk factors (low birth weight, low birth length, and <3 months of breastfeeding) had significantly lower scores in attention capacity compared with boys with 0 risk factors (percentile score − 15.88; $p = 0.009$). In conclusion, early life factors, both separately and combined, may influence attention capacity in male European adolescents. Importantly, the combination of the 3 early life risk factors, low birth weight, low birth length, and <3 months of breastfeeding, even in normal ranges, may provide the highest reduction in attention capacity.

KEYWORDS

adolescent, attention capacity, birth length, birth weight, breastfeeding, early life factors

1 | INTRODUCTION

Early life environment, specifically prenatal and perinatal nutrition, affects fetal growth and long term health of the offspring (Batty & Deary, 2004; Osler et al., 2003; Victora et al., 2008). An increasing number of early life factors (e.g., birth weight, birth length, head circumference or breastfeeding) are known to predict different aspects of executive function in youth (Gordon, 1998). Executive function includes inhibition, working memory, cognitive flexibility and attention (Steenbergen-Hu, Olszewski-Kubilius, & Calvert, 2015). Indeed, a crucial element for comprehension, learning processes, and problem-solving behaviors and actions during adolescence is attention capacity (Petersen & Posner, 2012). It is likely that birth weight and birth length as indicators of prenatal nutrition, or breastfeeding as indicator of perinatal nutrition may influence attention capacity in adolescents.

Previous studies on birth weight and attention capacity have mainly focused on cohorts with low or very low birth weight (Anderson et al., 2011; Elgen, Lundervold, & Sommerfelt, 2004; Elgen, Sommerfelt, & Ellertsen, 2003; Shum, Neulinger, O'Callaghan, & Mohay, 2008; Wilson-Ching et al., 2013). Importantly, low birth weight infants have an increased risk of attention deficit hyperactivity disorder later in life, and this fact can hamper the extent to which early life factors in normal size infants may influence attention capacity (Bohnert & Breslau, 2008). In the normal birth weight range, only one study examined the association between birth weight and attention in children showing a curvilinear association (van Mil et al., 2015), and to our knowledge, no previous studies examined the association between birth length and attention capacity.

Similarly, evidence for a beneficial effect of breastfeeding on cognition in youth has mainly focused on global intelligence measures or academic abilities (Der, Batty, & Deary, 2006; Horta, Loret de Mola, & Victora, 2015; Victora et al., 2016). Only two studies examined the association of breastfeeding with attention capacity during infancy and childhood, and found no beneficial effects (Cai et al., 2015; Veena et al., 2010). Thus, a better understanding of the association between individual early life factors and attention capacity in both low and normal birth size adolescents is required.

Evidence of how different early life factors separately and in combination are related to later attention might provide new insight for cognitive development. However, no previous study has examined the early life programming of attention capacity in adolescents considering several early life factors together. Adolescence is a critical period for maturation of emotional, social and cognitive abilities (Yurgelun-Todd, 2007); it is important to stress that around 40% of adolescents displayed attentional and inhibitory difficulties that affect academic performance, psycho-social development and emotional independence (Todd et al., 2002). Besides, the fact that cognition was negatively associated with all-cause mortality and had implications on human capital (Batty & Deary, 2004; Osler et al., 2003; Victora et al., 2008), highlights even more the need for further research on this topic. Therefore, the aim of the present study was to examine the individual and combined association of early life factors (birth weight, birth length, and any exclusive breastfeeding) with attention capacity in adolescents.

Key messages

- Poor prenatal nutrition (i.e., low weight and length at birth) may have a negative influence on cognitive potential later in life.
- The combination of the three early life risk factors—low birth-weight, low birth-length, and less than three months of breastfeeding, even in normal ranges, may provide the highest reduction in attention capacity in boys.
- There is a need for targeting early interventions focused on improving obstetric and neonatal care and promotion of breastfeeding to achieve long-term cognitive benefits.

2 | PARTICPANTS AND METHODS

2.1 | Design and participants

The Healthy Lifestyle in Europe by Nutrition in Adolescence study (HELENA) is a randomized multicenter investigation designed to obtain reliable and comparable data on nutrition and other health-related parameters in European adolescents. Detailed information about the study methods is available elsewhere (Moreno, De Henauw, et al., 2008; Moreno, González-Gross, et al., 2008). In brief, a multiple-stage cluster random sample of adolescents, stratified for geographic location, age, and socioeconomic status, was obtained, striving for representativeness on the level of 10 cities from nine European countries. Data collection took place in schools during 2006 and 2007. The total sample in the HELENA study consisted of 3,528 adolescents aged 12.5–17.5 years old; however, attention capacity was assessed only in six convenience cities (n = 652). Thus, the present analyses included 421 adolescents (243 girls; 14.5 $\pm$ 1.3 years old) with complete data on attention capacity and neonatal characteristics.

Adolescents and their parents or guardians were informed about the nature and purpose of the study. Written parental consent and adolescents' assent were obtained. Ethics committees from each country approved the HELENA study protocol and good clinical practices were conducted according to ethical guidelines (Béghin et al., 2008).

2.2 | Anthropometric neonatal data

Body weight and length at birth of adolescents were collected from parental records. Parents were asked to recall this information from the health booklets (Iliescu et al., 2008). Two neonatal body compositions indexes were calculated: (a) BMI at birth was calculated as birth weight in kilograms divided by birth length in meters squared (kg/m^2) and (b) ponderal index (PI) was calculated as birth weight in kilograms divided by birth length in meters cubed (kg/m^3).

2.3 | Infant-feeding data

Parents were asked about the duration of any and exclusive breastfeeding. The duration of exclusive breastfeeding was defined as a feeding pattern exclusively on the basis of breast milk with no complementary foods (neither fluid nor solid). Any and exclusive breastfeeding duration were both coded in four categories as never, <3 months, 3–5 months, and ≥6 months (Toschke et al., 2007).

2.4 | Attention capacity

Attention capacity was assessed through the d2 Test of Attention (d2T). The d2T is a measure of selective attention and response inhibition, key components of executive functioning. It consists on a paper and pencil test that comprising 14 rows, each with 47 randomly interspersed *p* and *d* characters; each character appears with 1 or 2 dashes placed above and/or below it. Participants were instructed to mark any character *d* that appeared with two dashes (i.e., relevant elements) in a maximum of 20 s per raw. The remaining combinations are considered as irrelevant elements. The test lasts 4 min and 40 s and no pauses are permitted (Brickenkamp & Zillmer, 1998). The d2T was administered in a classroom under the supervision of a HELENA fieldworker. The reliability and validity of the d2T have been shown to be high (Bates & Lemay, 2004). The attention capacity index was calculated as number of relevant elements marked minus number of irrelevant elements marked, and then this score was transformed into age-specific percentiles. Higher values indicate greater attention capacity.

2.5 | Covariates

Socioeconomic status was defined by the family affluence scale on the basis of 4 items: own bedroom, number of cars in the family, number of PCs in the home, and Internet access. Family affluence scale was classified as low, medium, or high (Currie, Elton, Todd, & Platt, 1997). Maternal education level was reported by mothers as elementary school, middle school, high school, and university (Cleland, Ball, Magnussen, Dwyer, & Venn, 2009). Weight was measured to the nearest 0.1 kg using a balance scale (SECA 861) and height to the nearest 0.1 cm with a stadiometer (SECA 225) with participants barefoot and in underwear (Nagy et al., 2008). BMI was expressed as kg/m^2.

2.6 | Statistical analyses

Descriptive characteristics of the study sample were shown as means (SD) or percentages. Differences between sexes were tested by one-way analysis of variance and chi-squared tests for continuous and nominal variables, respectively. We used regression analysis to test interactions among sex and early life factors and all analyses were performed separately for boys and girls; although interactions term did not quite reach statistical differences (p = .061 – .223), we clearly identified a different trend in boys and girls, consistently with previous studies (Dannemiller, 2004; Esteban-Cornejo et al., 2015; Matte, Bresnahan, Begg, & Susser, 2001; Spinillo et al., 1994).

The associations between early life factors (i.e., birth weight and length, BMI at birth, PI at birth, breastfeeding and exclusive breastfeeding) and attention capacity percentile score was examined by linear regression using three models. Model 1 was unadjusted. Model 2 included age, centre (dummy variables), gestational age, maternal education, and family affluence scale as confounder variables. Model 3 was additionally controlled for current BMI. Each early life factor variable was examined in a different regression model.

We examined differences in attention capacity percentile score among sex- and age-specific tertiles of birth weight and length (low, middle, and high) using one-way analysis of covariance (ANCOVA) adjusted for the previous covariates included in Model 3. We also examined differences in attention capacity among the three groups of any and exclusive breastfeeding (i.e., <3 months, 3–5 months, and ≥6 months) using ANCOVA, including the same confounding variables. Adolescents were classified in groups according to the number of early life risk factors (ranging from 0 to 3). Those participants in groups of low birth weight, low birth length, and <3 months of breastfeeding were considered at risk. Differences in attention capacity percentile score among the number of risk factors were tested by ANCOVA, adjusted for the previous covariates. All statistical analyses were performed using the SPSS version 23.0 for Windows (IBM, Armonk, New York), and the level of significance was set at $p < .05$.

3 | RESULTS

Supplementary table 1 presents the descriptive characteristics of the study sample. The adolescents included in the present analyses did not differ from remaining HELENA participants in regard to average weight, height, body mass index (BMI), anthropometric neonatal data, and breastfeeding data (all $p > .10$). The associations between early life factors and attention capacity are shown in Table 1. As previous studies, we also found a pattern for interactions among sex and early life factors; the interaction terms are included in Table 1: $p_{\text{birth weight}} = .158$, $p_{\text{birth length}} = .058$; $p_{\text{BMI at birth}} = .855$; $p_{\text{PI at birth}} = 0.278$; $p_{\text{any breastfeeding}} = .775$ and $p_{\text{exclusive breastfeeding}} = .932$. Among boys, birth weight, birth length, breastfeeding, and exclusive breastfeeding were related to attention capacity with β ranging from 0.150 (95% CI: 0.009; 0.291) to 0.199 (95% CI: 0.057; 0.341; all $p < .05$) after adjustment for age, centre, gestational age, maternal education, and family affluence scale (model 2). In model 3, these associations remained significant after further adjustment for BMI with β ranging from 0.144 (95% CI: 0.003; 0.284) to 0.196 (95% CI: 0.055; 0.338; all $p < .05$). BMI at birth and PI at birth were not associated with attention capacity. Among girls, there were no significant associations between early life factors and attention capacity (all $p > .2$).

Figure 1 presents differences in attention capacity percentile score according to tertiles of birth weight and birth length, after adjusting for potential confounders. Among boys, significant differences in attention capacity were found across tertiles ($p < .05$). Boys in the lowest tertile of birth weight had significantly lower scores in attention capacity compared with adolescents in the middle tertile (score = −11.27, 95% CI: −10.59; −11.95, p = .027) and lower scores compared with those in the highest tertile (score = −6.58, 95% CI: -5.45; −7.71, p = .095). For birth length, boys in the lowest tertile had significantly lower scores in attention capacity compared with adolescents in the highest tertile (score = −11.42, 95% CI: −9.00; −13.84, p = .013). Among girls, there were not significant differences in attention capacity (all $p > .2$).

TABLE 1 Association between early life factors and attention capacity in European adolescents

	Attention capacity percentile score						
	Model 1		Model 2		Model 3		
	β (95% Ci)	p	β (95% Ci)	p	β (95% Ci)	p	p for sex interaction
All (*n* = 421) [a]							
Birth weight (kg)	0.055 (−0.081;0.106)	0.261	0.061 (−0.041;0.151)	0.211	0.068 (−0.027;0.164)	0.158	0.153
Birth length (cm)	0.104 (0.009;0.200)	**0.033**	0.089 (−0.005;0.183)	0.062	0.090 (−0.003;0.183)	0.058	0.223
BMI at birth (kg/m^2)	−0.030 (−0.125;0.065)	0.534	−0.017 (−0.109;0.075)	0.723	−0.008 (−0.100;0.083)	0.855	0.336
PI at birth (kg/m^3)	−0.076 (−0.171;0.020)	0.122	−0.056 (−0.145;0.034)	0.224	−0.049 (−0.139;0.040)	0.278	0.322
Any breastfeeding (1–4)[b]	0.072 (−0.125;0.065)	0.141	0.024 (−0.070;0.118)	0.612	0.014 (−0.080;0.107)	0.775	0.168
Exclusive breastfeeding (1–4)[b]	0.054 (−0.042;0.150)	0.272	0.013 (−0.079;0.106)	0.774	0.004 (−0.088;0.096)	0.932	0.061
Boys (*n* = 178)							
Birth weight (kg)	0.093 (−0.055;0.241)	0.219	0.153 (0.004;0.302)	**0.045**	0.164 (0.015;0.313)	**0.031**	–
Birth length (cm)	0.157 (0.010;0.304)	**0.037**	0.199 (0.057;0.341)	**0.006**	0.196 (0.055;0.338)	**0.007**	–
BMI at birth (kg/m^2)	−0.037 (−0.185;0.112)	0.626	−0.007 (−0.150;0.136)	0.923	0.008 (−0.136;0.152)	0.915	–
PI at birth (kg/m^3)	−0.113 (−0.261;0.034)	0.132	−0.095 (−0.232;0.043)	0.176	−0.084 (−0.222;0.054)	0.231	–
Any breastfeeding (1–4)[b]	0.124 (−0.023;0.272)	0.098	0.169 (−0.027;0.311)	**0.020**	0.161 (0.019;0.303)	**0.027**	–
Exclusive breastfeeding (1–4)[b]	0.094 (−0.054;0.242)	0.212	0.150 (0.009;0.291)	**0.037**	0.144 (0.003;0.284)	**0.045**	–
Girls (*n* = 243)							
Birth weight (kg)	0.029 (−0.098;0.156)	0.650	0.026 (−0.101;0.152)	0.687	0.030 (−0.096;0.156)	0.642	–
Birth length (cm)	0.070 (−0.057;0.197)	0.277	0.022 (−0.104;0.148)	0.731	0.027 (−0.098;0.153)	0.670	–
BMI at birth (kg/m^2)	−0.031 (−0.158;0.096)	0.632	−0.004 (−0.126;0.117)	0.943	−0.003 (−0.124;0.118)	0.960	–
PI at birth (kg/m^3)	−0.059 (−0.186;0.068)	0.360	−0.019 (−0.139;0.100)	0.751	−0.019 (−0.138;0.099)	0.748	–
Any breastfeeding (1–4)[b]	0.042 (−0.085;0.169)	0.513	−0.067 (−0.192;0.058)	0.291	−0.077 (−0.202;0.047)	0.223	–
Exclusive breastfeeding (1–4)[b]	0.030 (−0.097;0.157)	0.640	−0.067 (−0.189;0.055)	0.282	−0.077 (−0.199;0.046)	0.218	–

Values are standardized regression coefficients (β). Model 1: Unadjusted model. Model 2: Analyses were adjusted by centre, age (years), gestational age (<37 wk/ 37–40 wk/>40 wk), maternal education (university level or below university level) and family affluence scale (low or medium or high). Model 3: Adjustment for model 2 plus body mass index (kg/m^2).

[a]Sex included in models 2 and 3.

[b]Any or exclusive breastfeeding coded in four categories as never, <3 months, 3–5 months, and ≥6 months.

Abbreviations: CI = confidence intervals; BMI = body mass index; PI = ponderal index.

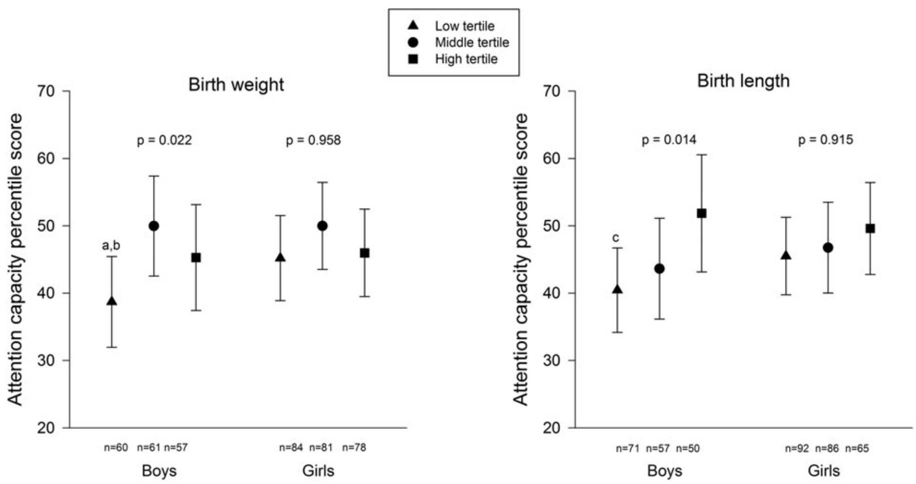

FIGURE 1 Differences in attention capacity according to tertiles of birth weight and birth length in European adolescents. Error bars represent mean and 95% confidence interval. Analyses were adjusted by centre, age (years), gestational age (<37 wk/37–40 wk/>40 wk), maternal education (university level or below university level), family affluence scale (low or medium or high) and body mass index (kg/m^2). *Note*: a = differences between low and middle tertile of birth weight (*p* = .027);b = differences between low and high tertile of birth weight (*p* = .095); c = differences between low and high tertile of birth length (*p* = .013)

Figure 2 shows differences in attention capacity percentile score according to duration of breastfeeding. Among boys, nonsignificant differences in attention capacity were found across groups of any and exclusive breastfeeding (*p* = .055 and *p* = .108, respectively) after adjusting for potential confounders. Boys who were breastfed for <3 months as infants had lower scores in attention capacity compared

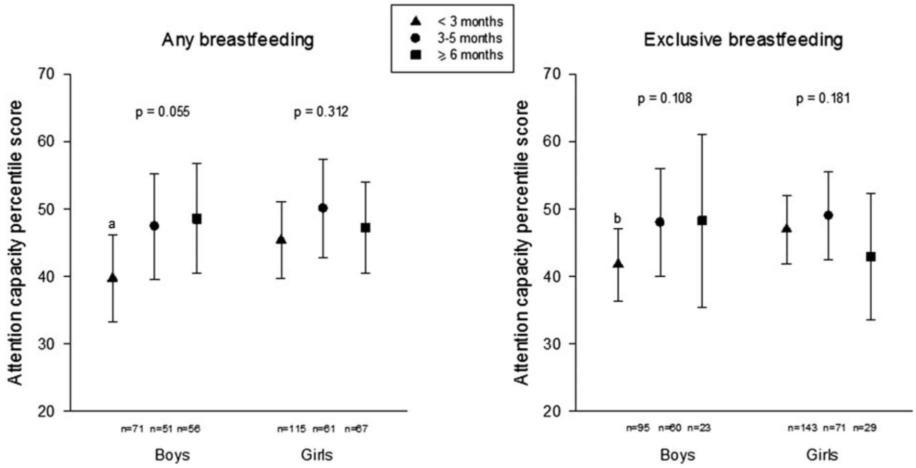

FIGURE 2 Differences in attention capacity according to duration of breastfeeding in European adolescents. Error bars represent mean and 95% confidence interval. Analyses were adjusted by centre, age (years), gestational age (<37 wk/37–40 wk/>40 wk), maternal education (university level or below university level), family affluence scale (low/medium/high) and body mass index (kg/m^2). *Note.* a = differences between <3 months and ≥6 months of any breastfeeding (p = .078). [b] differences between <3 months and 3–5 months of exclusive breastfeeding (p = .117)

with those who were breastfed for ≥6 months (score = −8.84, 95% CI: −7.06; −10.62, p = 0.078). Boys who had <3 months of exclusive breastfeeding had borderline nonsignificantly lower scores in attention capacity compared with those who had 3–5 months of exclusive breastfeeding (score = −6.21, 95% CI: -3.55; −8.88, p = .117). Among girls, there were not significant differences in attention capacity.

Figure 3 shows differences in attention capacity percentile score according to combination of early life risk factors. Boys with three early life risk factors had significantly lower scores in attention capacity compared with boys with zero risk factors (score = −15.88, 95% CI: −20.04; −11.72, p = .009). Among girls, there were no significant differences in attention capacity. For the combined analyses, we included exclusive breastfeeding instead of any breastfeeding and results were similar (data not shown). Additionally, all the analyses were repeated excluding those adolescents with birth weight < 2.5 kg and gestation age < 37 weeks or including physical activity and tanner stage pubertal development as covariates, and results were virtually the same.

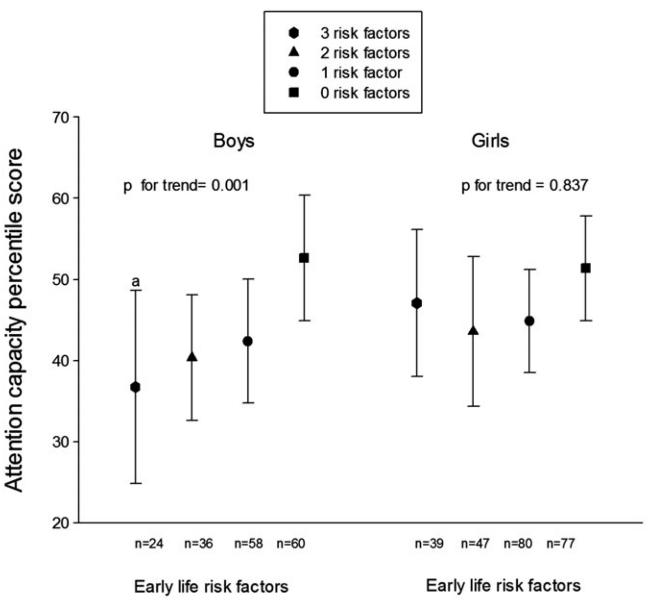

FIGURE 3 Differences in attention capacity according to combination of early life risk factors in European adolescents. Error bars represent mean and 95% confidence interval. Analyses were adjusted by Centre, age (years), gestational age (<37 wk/37–40 wk/>40 wk), maternal education (university level or below university level), family affluence scale (low or medium or high), and body mass index (kg/m^2). Early life risk factors included low tertile of birth weight, low tertile of birth length, and <3 months of breastfeeding. *Note.* a = differences between three risk factors group and zero risk factors group (p = .009)

4 | DISCUSSION

The main finding of the present study was that early life factors, both separately and combined, were associated with attention capacity in male European adolescents. Birth weight, birth length, and the duration of any and exclusive breastfeeding were positively related to attention capacity. Indeed, boys who had low birth weight, low birth length, or <3 months of any or exclusive breastfeeding had lower attention capacity. Collectively, those who had three early life risk factors (low birth weight, low birth length, and <3 months of breastfeeding) had the lowest attention capacity with a linear dose–response association. Our results support the idea of early life programming of attention capacity and emphasize that even small variation in birth weight, birth length, and breastfeeding duration may impact attention capacity during adolescence.

Previous studies on birth weight and attention capacity have been focused on cohorts with low or very low birth weight youth rather than across the normal range (Anderson et al., 2011; Elgen et al., 2003; Elgen et al., 2004; Shum et al., 2008; Wilson-Ching et al., 2013). There is only one study conducted in the full range of birth size, which found that a high birth weight (up to 3.6 kg) was related to attention but from a birth weight of about 3.6 kg, a high birth weight did not further reduce the risk of attention problems (van Mil et al., 2015). Our findings in a sample of European adolescents showed that birth weight was related to attention capacity in boys independently of potential confounders including current body composition. Interestingly, we also found a similar reverse J-shape association; from a birth weight of >3.6 kg (those in the upper tertile), the benefit of birth weight on attention capacity, although not disappeared, was reduced around 40% compared to those in the middle tertile (i.e., birth weight between 3.2–3.6 kg). More important, previous studies found that higher birth weight may be influenced by maternal obesity and gestational diabetes (Wang et al., 2017), which in turn, has been shown to affect offspring brain function in early years (Li et al., 2016) as well as may have long-term adverse effects on attention capacity (Ornoy, 2005). Therefore, although we lacked information on maternal obesity, present results may reflect that the greatest benefit on attention capacity is for those boys whose weight at birth was between 3.2 and 3.6 kg (those in the middle tertile).

The neuroscientific basis for the beneficial effects of birth weight on attention capacity is hypothesized to be based on changes in the volume and shape of the striatum. The striatum is one of the principal components of the basal ganglia. It is divided into dorsal and ventral sections; the dorsal striatum contains the caudate and putamen, while the ventral striatum contains the nucleus accumbens. A study focused on normal size birth boys showed that birth weight was associated with brain striatal volumes, specifically with smaller caudate volumes reflected by shape contraction in the middle body (Qiu et al., 2012). More important, the striatum has a known role in attention capacity and executive function along with its established vulnerability to low birth weight, what might be a reasonable explanation for our findings (Qiu et al., 2012; Raz & Buhle, 2006). However, further research examining potential pathways of the long-term effect of birth weight on attention capacity in both boys and girls within the normal birth size range is needed.

Another early life factor that has received less attention in the prediction of cognition is birth length, and particularly, in relation to attention capacity (Broekman et al., 2009). We found that birth length was positively associated with attention capacity in boys. This association showed a different pattern than the aforementioned with birth weight; in this case, there was a linear dose–response trend, that is, higher birth length was related to higher attention capacity with greatest benefits for those in the upper tertile. However, the extent of these benefits on attention capacity was similar in relation to birth length (+11.4 score) and to birth weight (+11.3 score). Although maternal obesity and gestational diabetes may have a higher negative influence on birth weight than on birth length, and affect offspring cognition (Gordon, 1998; Wang et al., 2017), previous studies on fetal growth retardation showed that intrauterine undernutrition may also have a similar influence on stunting and wasting (Andersen & Osler, 2004; Victora et al., 2015) which in turn, might affect cognition later in life (Gordon, 1998).Thus, present finding suggests that birth length as well as birth weight, may similarly reflect the phases of fetal growth related to later attention capacity.

Another interesting finding was that the duration of any and exclusive breastfeeding were positively related to attention capacity in adolescent boys. The World Health Organization recommended exclusive breastfeeding for the first 6 months to achieve health benefits (World Health Organization, 2001); we found that, for cognitive outcome, even boys who had at least 3 months of any or exclusive breastfeeding had higher attention capacity. Therefore, it is important to highlight that the benefits for attention capacity were similar to those who were mixed breastfed and those exclusively breastfed. This beneficial effect of breastfeeding could be due to the presence of long-chain polyunsaturated fatty acids, such as arachidonic acid and docosahexaenoic acid in breast milk. Breastfed infants have higher concentrations of these fatty acids that are positively associated with brain development, and in turn, with attention capacity (Farquharson, Cockburn, Patrick, Jamieson, & Logan, 1992; Isaacs et al., 2010). However, two previous studies in Asian population conducted during infancy and childhood found not beneficial effects of breastfeeding on attention capacity (Cai et al., 2015; Veena et al., 2010). It is likely that different measures of attention capacity between studies or specific characteristic of the samples (i.e., Asian vs. European population) may account for discrepancies between studies.

Although combination of different early life factors may provide a better measure of prenatal growth and cognitive development, no previous studies examined how multiple early life factors may influence attention capacity. When combining the three early life risk factors (low birth weight, low birth length, and <3 months of breastfeeding), we observed that boys who had the three early life risk factors had lower attention capacity than those who had 0 risk factors. Future studies should take into account multiple early life factors when examining its impact on cognitive outcomes later in life.

The reasons explaining why early life factors might influence attention capacity only in boys remain to be determined. A possible explanation could be that boys in general are more susceptible to adverse prenatal circumstances than girls (Spinillo et al., 1994) with prenatal exposure related to general intelligence and visual attention (Dannemiller, 2004; Matte et al., 2001). Additionally, brain morphological deviations in the striatum in attention deficit hyperactivity disorder are more pronounced in boys than girls (Qiu et al., 2009); it is reasonable to suppose that it might be similar in relation to attention capacity. Lastly, another possible reason might be that that the sex of the offspring may produce different responses to variations in maternal nutrition (Matte et al., 2001). However, further research should replicate and clarify the mechanisms that induce the sex effect found in our study.

Limitations of the present study include its observational design, which precludes drawing conclusions about causality. A second limitation is that attention capacity was only assessed in 6 of the 10 cities included in the HELENA study; however this subsample did not differ from the rest of HELENA sample in key variables tested. Third, another limitation was the use of parental recall for early life factors. Last, the lack of more sophisticated measures of attention capacity beyond performance on the d2T represents another limitation. Future research using electroencephalogram and functional magnetic resonance imaging may provide more robust insights. The present study has several strengths such as the use of standardized procedures across different centres, the inclusion of several relevant confounders (i.e., family affluence scale, maternal education, current BMI), and the combination of several early life factors to predict attention capacity.

In conclusion, our results support the idea of early life programming of attention capacity and highlight that, poor prenatal nutrition, reflected by small variations in birth weight and birth length in normal size infants, may have adverse consequences potential later in life. Importantly, the combination of the 3 early life risk factors, low birth weight, low birth, length and <3 months of breastfeeding, even in normalranges, may provide the highest reduction in attention capacity in boys. Hence, it reveals the need for targeting early interventions focused on improving obstetric and neonatal care and promotion of breastfeeding to achieve long-term cognitive benefits.

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CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

CONTRIBUTIONS

IEC had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: LM, FBO, and IEC. Acquisition of data: JV, MF,FG,JRR, FBO, MK, and KW. Analysis and interpretation of data: IEC, FBO, PH, CCS, and JRR. Drafting of the manuscript: IEC. Critical revision of the manuscript for important intellectual content: all authors. Final approval of the version to be published: all authors.

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