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The effect of subclinical infantile thiamine deficiency on motor function in preschool children

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Abstract

We investigated the long-term implications of infantile thiamine (vitamin B1) deficiency on motor function in preschoolers who had been fed during the first 2 years of life with a faulty milk substitute. In this retrospective cohort study, 39 children aged 5–6 years who had been exposed to a thiamine-deficient formula during infancy were compared with 30 age-matched healthy children with unremarkable infant nutritional history. The motor function of the participants was evaluated with The Movement Assessment Battery for Children (M-ABC) and the Zuk Assessment. Both evaluation tools revealed statistically significant differences between the exposed and unexposed groups for gross and fine motor development ($p < .001$, ball skills $p = .01$) and grapho-motor development ($p = .004$). The differences were especially noteworthy on M-ABC testing for balance control functioning ($p < .001$, OR 5.4; 95% CI 3.4–7.4) and fine motor skills ($p < .001$, OR 3.2; 95% CI 1.8–4.6). In the exposed group, both assessments concurred on the high rate of children exhibiting motor function difficulties in comparison to unexposed group (M-ABC: 56% vs. 10%, Zuk Assessment: 59% vs. 3%, $p < .001$). Thiamine deficiency in infancy has long-term implications on gross and fine motor function and balance skills in childhood, thiamine having a crucial role in normal motor development. The study emphasizes the importance of proper infant feeding and regulatory control of breast milk substitutes.

KEYWORDS

balance skills, infant nutrition, motor difficulties, preschool children, thiamin, thiamine deficiency

1 | INTRODUCTION

During infancy and early childhood, the developing brain is particularly sensitive to nutritional deficiencies (Dias, de Freitas Silva, de Proença Doyle, & Ribeiro, 2013; Georgieff, 2007; Ivanovic Marincovich et al., 2014; Prado & Dewey, 2014; Rosales & Zeisel, 2008; Walker et al., 2011). Complete or partial deficiency of known micronutrients such as iron, iodine, folic acid, vitamin B12, and choline has proved to have adverse effects on cognitive, physical, and behavioral development (Dias et al., 2013; Grantham-McGregor, Fernald, & Sethuraman, 1999; Guardiola, Egewarth, & Rotta, 2001; Swaminathan, Edward, & Kurpad, 2013; Walker et al., 2011). The present study focuses on infantile thiamine deficiency (ITD) and its long-term effect on motor development.

Towards the end of 2003, about 20 Israeli children, all of them younger than 1 year of age, were admitted to several pediatric intensive care units in Israel. The infants presented with similar clinical signs and symptoms that included lethargy, vomiting, nystagmus,

encephalopathy, seizures, and even coma (Fattal-Valevski, et al. 2005; Kesler, Stolovitch, Hoffmann, Avni, & Morad, 2005; Kornreich et al., 2007; Shamir, 2012). Epidemiological investigation discovered that all had been fed with the same imported soy-based infant formula, manufactured specifically for the Israeli market. The tests carried out by the Israeli Public Health Authority revealed that the formula contained <0.5 mcg thiamine/g formula instead of 385 mcg/g formula as claimed on the product label (Fattal-Valevski et al., 2005; Shamir, 2012). A report on the acute and long-term effect in a sample of 11 patients who were fed with the thiamine-deficient formula revealed that three children died in the acute phase of cardiomyopathy (Mimouni-Bloch et al., 2014). Of the eight patients who survived, one child who was in a chronic vegetative state died at the age of 7 years of respiratory complications. Follow-up of the other seven children revealed that all experienced neurodevelopmental complications, including epilepsy, intellectual disabilities, language, and communication impairments at the age of 9 years. All these children displayed a

wide range of motor dysfunctions ranging from motor clumsiness to severe motor disability (Mimouni-Bloch et al., 2014).

Thiamine, also called vitamin B1, is an essential micronutrient that belongs to the B complex vitamins. Thiamine, or in its active form thiamine pyrophosphate, plays a role in the brain development and normal functioning of the cardiovascular system, skeletal muscles, kidneys, liver, and the nervous system. Thiamine pyrophosphate takes part in synapse formation, axon growth, and myelination of nerve cell membranes, as well as in maintaining the stability of nerve membranes during their development and apoptosis regulation (Ba, 2008; Fattal-Valevski, 2011). Thiamine pyrophosphate is a main co-factor that activates several enzymes involved in producing amino acids and glucose-derived neurotransmitters from carbohydrates and fat metabolism (Fattal-Valevski, 2011; Hiffler, Rakotoambinina, Laffert, & Martinez Garcia, 2016; Singleton & Martin, 2001). Because of limited body storage of thiamine, humans are dependent on a daily nutritional supply, the amount varying with age, body weight, physiological condition, and individual metabolism (Frank, 2015; NIH Office of Dietary Supplements, 2016).

ITD is extremely rare in developed countries, occurring among breast-fed infants whose mothers lack thiamine (Prado & Dewey, 2014; WHO, 1999). Thiamine concentration in breast milk, and subsequently infant thiamine intake, depends on the mother's intake (Allen, 2012). Most of the information concerning ITD is based on reports from low-income and middle-income countries such as Laos (Barennes, Sengkhayong, René, & Phimmassane, 2015; Khounnorath et al., 2011; Soukaloun et al., 2003), Maela refugee camps in Thailand (Stuetz et al., 2012); Cambodia (Coats et al., 2012; Coats et al., 2013), Bangladesh (Arsenault et al., 2013), or Nepal (Christian et al., 2010). Symptoms of ITD appear mostly after 2–3 weeks of deprivation, followed by rapid deterioration, with a high fatality rate (Crook & Sriram, 2014; Fattal-Valevski, 2011; WHO, 1999). Clinically, ITD may be classified by predominant features into the pure cardiac form or wet beriberi, the neurologic form or dry beriberi, and the Shoshin beriberi, which presents with fulminant cardiac failure and lactic acidosis (Hiffler et al., 2016). The earliest presentation of ITD (ages 1–3 months) includes non-specific symptoms such as refusal to eat, vomiting, constipation, irritability, and lethargy. On later occurrence, at ages 4–7 months, the infant will demonstrate changes in crying sounds, and if left without treatment, the condition will deteriorate within a few days to severe-acute congestive heart failure, edema, lactic acidosis, respiratory distress, neurological signs such as anorexia, irritability, agitation, muscle pain, diminished or abolished deep tendon reflexes, ataxia, paralysis, and eventually death (Barennes et al., 2015; Crook & Sriram, 2014; Fattal-Valevski et al., 2005; Hiffler et al., 2016; WHO, 1999).

The Israeli Ministry of Health estimated that 2–6% of Israeli infants consumed the flawed formula. The figures are not precise,

because not all the infants were exclusively fed with that formula (Shamir, 2012). Nonetheless, the severe developmental outcomes in the symptomatic group raised the question of possible long-term effects in children who had been neurologically “asymptomatic” at the time of exposure to a thiamine-deficient diet (Shamir, 2012). The present study aimed to investigate whether subclinical exposure to a thiamine-deficient diet during the first 24 months of life may affect the motor skills in preschoolers, and to characterize the motor difficulties, if any, these children may experience.

2 | MATERIALS AND METHODS

2.1 | Participants

This retrospective cohort study included 69 children aged 5–6 years, of whom 39 children (12 females) had been exposed to thiamine-deficient formula for at least 1 month during the first 2 years of life, and a control group of 30 children (15 females), who had not been fed with the flawed formula. Only children who did not exhibit any neurological sign at the time of the public disclosure of the flawed formula were included in the study.

The unexposed (control) group included healthy children, who as infants were breastfed and/or received a milk substitute with a correct composition (other than the flawed formula brand). The unexposed participants were recruited through consecutive sampling from the same family healthcare centers with a similar age group as those exposed to a thiamine-deficient diet. Family healthcare centers are responsible for general and routine developmental follow-up of all Israeli children up to the age of 5 years. Each family healthcare center serves a delimited residential area where people share a similar socioeconomic status.

Both study and control children were born between 37 and 42 weeks of gestation, with appropriate weight for their gestational age and a normal perinatal history. All study participants were attending regular educational programs and schools. Children with any medical complications or chronic disorders were excluded. All participants underwent formal neurological assessment by pediatric neurologists.

3 | METHODS

The motor function was assessed with two standardized instruments: Movement Assessment Battery for Children (M-ABC) and Zuk Assessment (Zuk). The M-ABC is a well-known tool with high reliability (0.73–0.94; Henderson & Sugden, 1992) and moderate validity (0.72–0.76; Van Waelvelde, De Weerd, De Cock, & Smits-Engelsman, 2004) for evaluating movement difficulties among

Key messages

- Infantile thiamine deficiency has long-term effects on motor function in children.
- Subclinical infantile thiamine deficiency adversely affected the balance and fine motor skills in 5–6-year-old children.
- ITD can be prevented by promoting breastfeeding and/or enforcing more strict regulatory control over breast milk substitutes.

children aged 4–12 years (former version; Geuze, 2005; Smits-Engelsman, Niemeijer, & Van Galen, 2001). The M-ABC was tested and found to be reliable and valid for the Israeli population (Engel-Yeger, Rosenblum, & Josman, 2010). The M-ABC evaluates movement by eight items in each age band, providing standard scores and equivalent percentiles for three components: balance control (range 0–15), ball skills (range 0–10), and manual dexterity (range 0–15). The M-ABC total impairment score ranges from 0 to 40; the higher the score, the worse the function. The total impairment score is classified into three outcome levels based on percentiles: (a) “significant movement difficulties” (percentile ≤ 5 th) indicating a need for immediate therapeutic intervention; (b) “at risk” of having movement difficulties ($5\text{th} < \text{percentile} \leq 15\text{th}$), which requires careful monitoring; (c) “normal function,” namely, no movement difficulties were detected (percentile $> 15\text{th}$; Henderson & Sugden, 1992). The Zuk (Zuk, Tlumeck, Katz-Leurer, Peretz, & Carmeli, 2014) was developed and standardized for the Israeli pediatric population aged 4–8 years to assess the motor function components necessary for skills used in daily activities, with good reliability (intra-rater -0.89 , inter-rater -0.93) and validity compared to the M-ABC instrument. The Zuk evaluates motor function in three categories: gross motor (e.g., jumping forward, standing on one leg), fine motor (e.g., picking up a bead, building a tower of small cubes), and grapho-motor (e.g., drawing a cross, crossing midline). In contrast to the M-ABC, the higher the score in the Zuk, the better the motor performance. The total score, ranging from 0 to 100, was classified into three levels: normal motor performance (score > 70), suspected motor problems (score $61-70$), and motor problems (score ≤ 60), with the cutoff point of 70 based on one SD below the mean and 60 based on two SD below the mean of typically developed children (Zuk et al., 2014). The same assessor evaluated all the children, according to each instrument manual and in the same environmental conditions. Parents were asked to complete a questionnaire with demographic and background information about their child including perinatal, medical, nutritional, and developmental history. Prior to initiation, the study was approved by the Institutional Review Board. Parental informed consent was obtained for each participating child as well as for publication of the study results.

3.1 | Statistical analysis

The yielded data were analyzed using SPSS for Windows (SPSS version 17.0, Inc, Chicago, IL, USA). An independent sample *t* test was run to compare the exposed group with the unexposed group for age, birth weight, gestational age, independent walking age (IWA), and first words age (Table 1). The χ^2 test was used to compare the gender differences between the groups (Table 1). The independent sample *t* test was used to compare total impairment scores and component scores of M-ABC test (Table 2). Similarly, the Zuk total and category scores were compared between groups (Table 3). The data were also analyzed by two-way ANOVA to control for gender. In addition, the χ^2 test was performed to compare the distribution of M-ABC outcome levels (“significant movement difficulties,” “at risk,” and “normal”) between the exposed and unexposed groups (Figure 1). The same analysis was performed for Zuk levels (“motor problems,” “suspected motor problems,” and “normal motor performance”; Figure 1).

4 | RESULTS

Table 1 presents a comparison between the exposed and unexposed groups for demographic, neonatal, nutritional, and developmental parameters. There were no group differences for neonatal parameters, gestational age, and birth weight. The mean estimated exposure time to the thiamine-deficient formula was 3.84 ± 1.15 months (range 2–5 months). The mean age at discontinuation of the thiamine-deficient formula was 8.33 ± 4.51 months (range 1.5–18 months). Comparison of developmental parameters found significant differences between the groups for the age of independent walking ($p = .015$) and for the age of first words ($p < .001$).

Tables 2 and 3 present the total and categories scores of M-ABC and Zuk. The M-ABC total impairment score revealed that in the exposed group, 22 out of 39 children (56.5%) exhibited “significant movement difficulties,” 9 children (23%) were “at risk” for movement difficulties, and 8 children (20.5%) had “normal” motor performance. In the unexposed group, three out of 30 children (10%) exhibited “significant movement difficulties,” 7 children (23.3%) were found to be “at risk” for movement difficulties, and 20 children (67.7%) had

TABLE 1 Demographic and clinical parameters between the groups

Parameters	Exposed (n = 39)	Unexposed (n = 30)	p-value
Mean (SD)			
Demographic			
Gender (female)—n (%)	12 (30%)	15 (50%)	.064
Age (years)	5.76 (0.47)	5.57 (0.41)	.033
Neonatal			
Birth weight (g)	3,186 (461)	(510) 3,196	.253
Gestational age (weeks)	39.2 (1.5)	38.9 (1.6)	.446
Nutrition			
Estimated exposure to thiamin-deficient infant formula (months)	3.8 (1.1)	—	—
Age at discontinuation (months)	8.3 (4.5)	—	—
Developmental milestones			
Independent walking age (months)	15.9 (3.7)	14.1 (2.6)	.015
First words age (months)	17.2 (9.5)	10.9 (3.6)	<.001

TABLE 2 M-ABC raw scores with corresponding total impairment score percentile based on standardized test scales

Parameters	Exposed (n = 39)	Unexposed (n = 30)	Mean difference (95% CI)	p-value	t
	Mean ^a (SD)				
Static and dynamic balance control (0–15)	7.7 (4.5)	2.3 (3.7)	5.4 (3.4, 7.4)	<.001	5.35
Ball skills (0–10)	5.3 (3.1)	3.4 (2.6)	1.9 (0.4, 3.2)	.01	2.65
Manual dexterity (0–15)	5.3 (3.9)	2.1 (1.9)	3.2 (1.8, 4.6)	<.001	4.45
Total impairment score (0–40)	18.3 (9.1)	7.8 (6.6)	10.5 (6.6, 14.4)	<.001	5.35
Total impairment score (percentile)	10 (16.7)	37.4 (29.0)	27.3 (39.3, 15.3)	<.001	4.94

^aThe higher the score, the worse the function.

TABLE 3 Zuk assessment scores in the study groups

Parameters	Exposed (n = 39)	Unexposed (n = 30)	Mean difference (95% CI)	p-value	t
	Mean ^a (SD)				
Gross motor skills (0–69)	39.8 (7.9)	56.3 (5.5)	–16.4 (–19.8, –13.1)	<.001	–9.73
Grapho-motor skills (0–13)	6.8 (2.9)	8.6 (2.2)	–1.9 (–3.1, –0.6)	.004	–3.01
Fine motor skills (0–18)	10.9 (2.8)	14.2 (2.3)	–3.3 (–4.6, –2.1)	<.001	–5.31
Total score (0–100)	57.5 (10.6)	79.2 (6.3)	–21.6 (–27.7, –17.6)	<.001	–10.59

^aThe higher the score, the better the motor performance.

FIGURE 1 Motor performance of exposed and unexposed groups according to M-ABC and Zuk assessments. M-ABC = Movement Assessment Battery for Children; Zuk = Zuk assessment. M-ABC: Significant Movement Difficulties (SMD); 'at risk' of having Movement difficulties (at risk); Normal Motor Performance (NMP). Zuk: Motor Problems (MP); Suspected Motor Problems (SMP); Normal Motor Performance (NMP).

"normal" motor performance ($p < .001$). The static and dynamic balance component score revealed in the exposed group 19 children (48.7%) with "significant balance difficulties" and 11 children (28.2%) "at risk" for balance difficulties, compared to only 3 (10%) and 5 (16.7%) children, respectively, in the unexposed group ($p < .001$). The ball skills score found in the exposed group 17 children (43.6%) with significant

ball skills difficulties and 15 children (38.5%) "at risk" for ball skills difficulties compared to 6 (20%) and 13 (43.3%) children, respectively, in the unexposed group ($p < .05$). The manual dexterity score revealed eight children (20.5%) in the exposed group with significant manual dexterity difficulties and seven children (18%) "at risk" for such difficulties. In the unexposed group, only three children (10%) were found "at

risk" for manual dexterity difficulties ($p = .001$). There was a significant difference between the groups for total impairment score ($p < .001$), as well as for the static and dynamic balance control ($p < .001$) and manual dexterity score ($p < .001$). A statistically significant difference was also found for ball skills ($p = .01$; Table 2).

According to the Zuk total score, 23 out of 39 children in the exposed group (59%) had "motor problems" (with total score ≤ 60), 12 children (30.7%) had "suspected motor problems" (total score range 61–70), and 4 (10.2%) had "normal" motor performance (total score > 70). In comparison, two children (6.6%) in the unexposed group ($n = 30$ children) exhibited motor performance problems, one of whom had "motor problems" (3.3%) and the other (3.3%) had "suspected motor problems" ($p < .001$). The mean scores of the Zuk were compared between the exposed and unexposed groups. The comparison revealed significant differences in total score ($p < .001$), as well as in each category scores: gross motor ($p < .001$), fine motor category ($p < .001$), and grapho-motor ($p = .004$). After controlling for gender, the results did not change (Table 3).

On both M-ABC and Zuk, more than 50% of the children in the exposed group were identified as having movement and motor difficulties (Figure 1). We found no correlation between motor function and estimated duration of exposure or age at discontinuation of thiamine-deficient formula.

5 | DISCUSSION

The present study revealed that more than 50% of the preschoolers exposed to a thiamine-deficient diet for ≥ 1 month during the first 2 years of life exhibited movement and motor skills difficulties, compared to only 3.3–10% of children in the unexposed group. The results were based on two standardized motor assessment tools. In particular, it was found that the exposed group had poorer abilities in static and dynamic balance control compared to the unexposed group. Thirty children out of 39 in the exposed group demonstrated balance impairment compared to only eight unexposed children. Manual dexterity was also significantly poorer in the exposed group compared to the unexposed group. A previous cross-sectional study reported similar findings among 484 first-grade children in Brazil. The authors of this study found a significant correlation between general chronic malnutrition and psychomotor problems, specifically abnormal static and dynamic balance function (Guardiola, Egewarth, & Rotta, 2001). Brain neuroimaging in symptomatic Israeli infants exposed to the thiamine-deficient formula revealed involvement of the cerebellum and basal ganglia, which are known to play a role in balance control (Fattal-Valevski et al., 2005; Fattal-Valevski et al., 2009b; Hiffler et al., 2016; Kornreich et al., 2007; Leisman, Braun-Benjamin, & Melillo, 2014).

The prevalence of movement and motor skills difficulties such as *developmental coordination disorder* (DCD) is estimated to be between 5% and 6% in school-aged children (American Psychiatric Association, 2013; Ferguson, Jelsma, Versfeld, & Smits-Engelsman, 2014; Kirby, Sugden, & Purcell, 2014). Fifty to 70% of the affected children will continue to experience difficulties throughout the adolescent years into adulthood (American Psychiatric Association, 2013). Children diagnosed with DCD are known to have significant difficulties in

performing activity of daily living, learning new skills and participating in family, social, school, or community life. Moreover, secondary symptoms such as poor self-esteem, emotional and behavioral problems, academic difficulties, poor physical fitness, and obesity frequently develop due to core motor difficulties (American Psychiatric Association, 2013; Leonard, 2016).

Although the etiology of motor development difficulties such as DCD is not completely established, it is generally considered to be caused by both environmental and genetic factors (Gomez & Sirigu, 2015; Goulardins et al., 2015). Malnutrition is one of the environmental factors known to affect the process of brain development and maturation, with abnormal brain functioning manifestations that include motor abilities (Kirby & Danner, 2009; Kirby, Woodward, Jackson, Wang, & Crawford, 2010; Sudfeld et al., 2015).

ITD is caused by inadequate intake of thiamine, which in low-income countries has been more commonly found associated with malnutrition (Black et al., 2013). Breast-fed infants of mothers with a history of thiamine deficiency during pregnancy are highly vulnerable and prone to develop ITD (Allen, 2012; Barennes, Sengkhomyong, René, & Phimmasane, 2015; Coats et al., 2013; Khounnorath et al., 2011; Qureshi et al., 2016). Of note, in low-income countries, the studies on the effects of ITD on child development may be confounded by other factors such as deficiency of other micronutrients, maternal malnutrition during pregnancy and lactation, prematurity and small gestational age of the offspring, infant exposure to infections, and low hygiene conditions (Aboud & Yousafzai, 2015; Ngure et al., 2014). The special circumstances generated by the flawed formula provided a unique opportunity to study thiamine deficiency in the absence of other nutritional deficits in children.

The thiamine recommended dietary allowance for nursing infants from birth to 6 months is 0.2 mg/day, 0.3 mg/day for ages 7–12 months, and 0.5 mg/day for toddlers between 1 and 3 years (NIH Office of Dietary Supplements, 2016; U.S. Institute of Medicine, Food and Nutrition Board, 1998). In infancy, the thiamine requirements are high relative to their body size due to rapid growth and development (Hiffler et al., 2016). This may explain the severity of the deleterious effects of thiamine deficiency on body tissues, especially the nervous system. According to our results, even children who were subclinical at the acute phase exhibited long-term motor manifestations. Early developmental cues were observed among the exposed children by "IWA" and "first words age." The IWA was significantly delayed in the exposed children compared to the unexposed children ($p = .015$), even though the average IWA fell within the normal walking age range (< 18 months; exposed group mean = 16.3, median = 16 compared to unexposed group mean = 14.1, and median = 13.5). Of note, the milestones data were based on parental reports and subject to recall bias in the unexposed group more than in the exposed group, which was frequently monitored. Nonetheless, our results concur with previously reported delay in motor and language developmental milestones of subclinical children who were fed with the same thiamine-deficient-flawed formula (Fattal, Friedmann, & Fattal-Valevski, 2011; Fattal-Valevski et al., 2009a; Friedmann, Fattal, & Fattal-Valevski, 2010).

Only a few studies have been published on the possible implications and outcome of subclinical ITD children, both in the

short and long term (Attias, Raveh, Aizer-Dannon, Bloch-Mimouni, & Fattal-Valevski, 2012; Fattal, Friedmann, & Fattal-Valevski, 2011; Prensky, 2005; Thauvin-Robinet et al., 2004; Vasconcelos et al., 1999). Previous publications have found long-lasting language disorders at ages 5–7 years in 57 out of 59 Israeli children with a history of flawed formula-associated ITD during their first year of life, but who were asymptomatic at the time of exposure (Fattal et al., 2011; Fattal-Valevski et al., 2009a). The current study explored systematically and exclusively the late ITD effects on gross and fine motor functions at ages 5–6 years. Its findings provide a good basis to suspect a correlation between ITD and motor function in this age group.

It is well documented that neuro-maturational processes are ongoing from prenatal to postnatal life and continue throughout childhood and adolescence (Knudsen, 2004; Stiles & Jernigan, 2010). The central nervous system undergoes the most rapid changes of growth and development during the first 4 years of life (Einspieler, Prechtl, Bos, Ferrari, & Cioni, 2004; Lenroot & Giedd, 2006; Stiles & Jernigan, 2010). During this critical period, the developing brain is extremely vulnerable to any kind of disturbance, including nutritional deficits, which may cause developmental disorders (Prado & Dewey, 2014). Motor function is a principal component of neurodevelopmental assessment, especially during the first years of life, as it reflects the level of central nervous system maturity and development (Guardiola, Egewarth, & Rotta, 2001; Rice & Barone, 2000). The preschool age group is known to be a frame of reference age for achievement of complex and adaptive motor skills necessary for the upcoming higher demands in school (Hadders-Algra, 2010; Gerber, Wilks, & Erdie-Lalena, 2010). For this reason, the participants' age of 5–6 years was deliberately chosen in the present study.

The special nature of the exposed group made it difficult to achieve an absolute age and gender match. The mean age in the exposed group was 5 years and 9 months (± 0.47 years) and in the unexposed group 5 years and 7 months (± 0.41 years). The exposed group was on average 2 months older than the unexposed group, which was statistically significant ($p = .033$), but not clinically significant, considering that better motor outcomes in the unexposed group, which was 2 months younger on average, only emphasized the achievement gap between the groups.

5.1 | Limitations of the study

It was difficult to accurately determine the duration of exposure or age at exposure to a thiamine-deficient diet for two main reasons. First, the formula was gradually introduced into the market with an uneven distribution across the country. Second, the children were not fed the thiamine-deficient formula exclusively but were supplemented with breast milk, other breast milk substitutes, and, depending on their age, complementary foods. No dietary analysis was conducted nationwide after the discovery of the thiamine-deficient breast milk substitute. Furthermore, we should take into consideration the possibility of a parental overprotecting attitude in the exposed group and perceiving sports as too stressful for their children compared to the unexposed; this may account for more motor difficulties (Venetsanou & Kambas, 2010).

Another limitation of this study is a relatively small exposed group size. Of note, many parents who opted not to participate in the study

claimed that their children, who also had been asymptomatic at the time of exposure, were already involved in too many evaluations and treatments; this underlines the long-term burden of ITD exposure.

The World Health Organization recommends exclusive breastfeeding from birth to 6 months of age, and breastfeeding with addition of appropriate solid food from age 6 months to 1 year or more (http://www.who.int/maternal_child_adolescent/topics/child/nutrition/breastfeeding/en/). The recommendations are based on rich evidence-based research that demonstrates the benefits of breastfeeding for newborns and infants, as well as its protective role against infection, acute illness, obesity, developmental disorders, and other chronic conditions over the life span (Eidelman, 2012; Gartner et al., 2005; Leventakou et al., 2015; WHO, 2009). The Israeli Ministry of Health adopted these recommendations and also provides educational support to mothers immediately postpartum, during their stay in hospital and throughout the pediatric follow-up (Israel Ministry of Health, 2014). Nevertheless, some women will either choose to or will be required for some reason, to provide breast milk substitute. To preclude the detrimental effects of nutritional deficiency such as ITD in infants, the proper monitoring and certification of breast milk substitute to ensure the highest safety and quality should be a major focus of governments moving forward (WHO, UNICEF, IFBAN, 2016).

6 | CONCLUSIONS

Our study results showed that subclinical ITD has long-term effects on motor function in preschool children, highlighting the crucial role of thiamine in motor development. Promoting breastfeeding and enforcing strict regulatory control over breast milk substitutes are recommended to prevent ITD.

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CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

CONTRIBUTIONS

YH designed the study, coordinated data collection, drafted and revised the manuscript; LZ contributed to study design and research tools, edited and revised the manuscript; MG participated in study design and data collection and reviewed the manuscript;

ON participated in study design and data collection and reviewed the manuscript; DL participated in data collection, conducted the statistical analysis and reviewed the manuscript; AFV conceived and designed the study, coordinated data collection, conducted the statistical analysis, drafted and revised the manuscript. All authors read and approved the final submitted manuscript.

REFERENCES

- About, F. E., & Yousafzai, A. K. (2015). Global health and development in early childhood. *Annual Review of Psychology*, 66, 433–457.
- Allen, L. H. (2012). B vitamins in breast milk: Relative importance of maternal status and intake, and effects on infant status and function. *Advances in Nutrition*, 3, 362–369.
- American Psychiatric Association. (2013). *DSM-5: Diagnostic and Statistical Manual of Mental Disorders* (5th ed.). Washington, DC: American Psychiatric Press.
- Arsenault, J. E., Yakes, E. A., Islam, M. M., Hossain, M. B., Ahmed, T., Hotz, C. ... Brown, K. H. (2013). Very low adequacy of micronutrient intakes by young children and women in rural Bangladesh is primarily explained by low food intake and limited diversity. *The Journal of Nutrition*, 143, 197–203.
- Attias, J., Raveh, E., Aizer-Dannon, A., Bloch-Mimouni, A., & Fattal-Valevski, A. (2012). Auditory system dysfunction due to infantile thiamine deficiency: Long-term auditory sequelae. *Audiology and Neurotology*, 17, 309–320.
- Ba, A. (2008). Metabolic and structural role of thiamine in nervous tissues. *Cellular and Molecular Neurobiology*, 28, 923–931.
- Barennes, H., Sengkhayong, K., René, J. P., & Phimmasane, M. (2015). Beriberi (thiamine deficiency) and high infant mortality in northern Laos. *PLoS Neglected Tropical Diseases*, 9, doi:10.1371/journal.pntd.0003581.e0003581
- Black, R. E., Victora, C. G., Walker, S. P., Bhutta, Z. A., Christian, P., De Onis, M., ... Maternal and Child Nutrition Study Group. (2013). Maternal and child undernutrition and overweight in low-income and middle-income countries. *The Lancet*, 382, 427–451.
- Christian, P., Murray-Kolb, L. E., Khatry, S. K., Katz, J., Schaefer, B. A., Cole, P. M., ... Tielsch, J. M. (2010). Prenatal micronutrient supplementation and intellectual and motor function in early school-aged children in Nepal. *JAMA*, 304, 2716–2723.
- Coats, D., Shelton-Dodge, K., Ou, K., Khun, V., Seab, S., Sok, K., ... Topazian, M. (2012). Thiamine deficiency in Cambodian infants with and without beriberi. *The Journal of Pediatrics*, 161, 843–847.
- Coats, D., Frank, E. L., Reid, J. M., Ou, K., Chea, M., Khin, M., ... Topazian, M. (2013). Thiamine pharmacokinetics in Cambodian mothers and their breastfed infants. *The American Journal of Clinical Nutrition*, 98, 839–844.
- Crook, M. A., & Sriram, K. (2014). Thiamine deficiency: The importance of recognition and prompt management. *Nutrition*, 30, 953–954.
- Dias, F. M., de Freitas Silva, D. M., de Proença Doyle, F. C., & Ribeiro, A. M. (2013). The connection between maternal thiamine shortcoming and offspring cognitive damage and poverty perpetuation in underprivileged communities across the world. *Medical Hypotheses*, 80(1), 13–16.
- Eidelman, A. I. (2012). Breastfeeding and the use of human milk: An analysis of the American Academy of Pediatrics 2012 Breastfeeding Policy Statement. *Breastfeeding Medicine*, 7, 323–324.
- Einspieler, C., Prechtl, H. F. R., Bos, A. F., Ferrari, F., & Cioni, G. (2004). *Prechtl's method on the qualitative assessment of general movements in preterm, term and young infants*. London: Mac Keith Press.
- Engel-Yeger, B., Rosenblum, S., & Josman, N. (2010). Movement assessment battery for children (M-ABC): Establishing construct validity for Israeli children. *Research in Developmental Disabilities*, 31, 87–96.
- Fattal, I., Friedmann, N., & Fattal-Valevski, A. (2011). The crucial role of thiamine in the development of syntax and lexical retrieval: A study of infantile thiamine deficiency. *Brain*, 134, 1720–1739.
- Fattal-Valevski, A. (2011). Thiamine (vitamin B1). *Journal of Evidence-Based Complementary & Alternative Medicine*, 16, 12–20.
- Fattal-Valevski, A., Kesler, A., Sela, B., Nitzan-Kaluski, D., Rotstein, M., Mesterman, R., ... Eshel, G. (2005). Outbreak of life threatening thiamine deficiency in infants in Israel caused by a defective soy-based formula. *Pediatrics*, 115, e233–e238.
- Fattal-Valevski, A., Azouri-Fattal, I., Greenstein, Y. J., Guindy, M., Blau, A., & Zelnik, N. (2009a). Delayed language development due to infantile thiamine deficiency. *Developmental Medicine and Child Neurology*, 51, 629–634.
- Fattal-Valevski, A., Bloch-Mimouni, A., Kivity, S., Heyman, E., Brezner, A., Strausberg, R., ... Goldberg-Stern, H. (2009b). Epilepsy in children with infantile thiamine deficiency. *Neurology*, 73, 828–833.
- Ferguson, G. D., Jelsma, J., Versfeld, P., & Smits-Engelsman, B. C. M. (2014). Using the ICF framework to explore the multiple interacting factors associated with developmental coordination disorder. *Current Developmental Disorders Reports*, 1, 86–101.
- Frank, L. L. (2015). Thiamin in clinical practice. *JPEN. Journal of parenteral and enteral nutrition*, 39, 503–520.
- Friedmann, N., Fattal, I., & Fattal-Valevski, A. (2010). The effect of thiamine deficiency in infancy on the development of syntactic and lexical abilities. *Procedia - Social and Behavioral Sciences*, 6, 168–169.
- Gartner, L. M., Morton, J., Lawrence, R. A., Naylor, A. J., O'Hare, D., Schanler, R. J., ... American Academy of Pediatrics Section on Breastfeeding. (2005). Breastfeeding and the use of human milk. *Pediatrics*, 115, 496–506.
- Georgieff, M. K. (2007). Nutrition and the developing brain: Nutrient priorities and measurement. *American Journal of Clinical Nutrition*, 85, 614s–620s.
- Gerber, R. J., Wilks, T., & Erdie-Lalena, C. (2010). Developmental milestones: Motor development. *Pediatrics Review*, 31, 267–276.
- Geuze, R. H. (2005). Postural control in children with developmental coordination disorder. *Neural Plasticity*, 12, 183–196.
- Gomez, A., & Sirigu, A. (2015). Developmental coordination disorder: Core sensori-motor deficits, neurobiology and etiology. *Neuropsychologia*, 79, 272–287.
- Gouldardins, J. B., Rigoli, D., Licari, M., Piek, J. P., Hasue, R. H., Oosterlaan, J., & Oliveira, J. A. (2015). Attention deficit hyperactivity disorder and developmental coordination disorder: Two separate disorders or do they share a common etiology. *Behavioural Brain Research*, 292, 484–492.
- Grantham-McGregor, S. M., Fernald, L. C., & Sethuraman, K. (1999). Effects of health and nutrition on cognitive and behavioural development in children in the first three years of life. Part 2: Infections and micronutrient deficiencies: Iodine, iron, and zinc. *Food and Nutrition Bulletin*, 20, 76–99.
- Guardiola, A., Egewarth, C., & Rotta, N. T. (2001). Evaluation of neuropsychomotor development in first grade children and its relation with nutrition. *Jornal de Pediatria*, 77, 189–196.
- Hadders-Algra, M. (2010). Variation and variability: Key words in human motor development. *Physical Therapy*, 90, 1823–1837.
- Henderson, S. E., & Sugden, D. A. (1992). *Movement assessment battery for children*. Kent: The Psychological Corporation.
- Hiffler, L., Rakotoambinina, B., Laffert, N., & Martinez Garcia, D. (2016). Thiamine deficiency in tropical paediatrics: New insights into a neglected but vital metabolic challenge. *Frontiers in Nutrition*, 3, 16. doi:10.3389/fnut.2016.00016
- Ivanovic Marincovich, D., Ibaceta, C. V., Correa, P. B., Orellana, Y. Z., Calderón, P. M., Morales, G. I., ... Burrows, R. A. (2014). Brain development and scholastic achievement in the education quality measurement system tests in Chilean school-aged children. *Pediatric Research*, 75, 464–470.
- Kesler, A., Stolovitch, C., Hoffmann, C., Avni, I., & Morad, Y. (2005). Acute ophthalmoplegia and nystagmus in infants fed a thiamine-deficient formula: An epidemic of Wernicke encephalopathy. *Journal of Neuro-Ophthalmology*, 25, 169–172.
- Khounnorath, S., Chamberlain, K., Taylor, A. M., Soukaloun, D., Mayxay, M., Lee, S. J., ... Latsavong, K. (2011). Clinically unapparent infantile thiamin

- deficiency in Vientiane, Laos. *PLoS Neglected Tropical Diseases*, 5. doi:10.1371/journal.pntd.0000969.e969
- Kirby, M., & Danner, E. (2009). Nutritional deficiencies in children on restricted diets. *Pediatric Clinics of North America*, 56(5), 1085–1103.
- Kirby, A., Woodward, A., Jackson, S., Wang, Y., & Crawford, M. A. (2010). Children's learning and behaviour and the association with cheek cell polyunsaturated fatty acid levels. *Research in Developmental Disabilities*, 31(3), 731–742.
- Kirby, A., Sugden, D., & Purcell, C. (2014). Diagnosing developmental coordination disorders. *Archives of Disease in Childhood*, 99, 292–296.
- Knudsen, E. I. (2004). Sensitive periods in the development of the brain and behavior. *Journal of Cognitive Neuroscience*, 16, 1412–1425.
- Kornreich, L., Bron-Harlev, E., Hoffmann, C., Schwarz, M., Konen, O., Schoenfeld, T., ... Horev, G. (2007). Thiamine deficiency in infants: MR findings in the brain. *American Journal of Neuroradiology*, 26, 1668–1674.
- Leisman, G., Braun-Benjamin, O., & Melillo, R. (2014). Cognitive-motor interactions of the basal ganglia in development. *Frontiers in Systems Neuroscience*, 8, 16.
- Lenroot, R. K., & Giedd, J. N. (2006). Brain development in children and adolescents: Insights from anatomical magnetic resonance imaging. *Neuroscience and Biobehavioral Reviews*, 30, 718–729.
- Leonard, H. C. (2016). The impact of poor motor skills on perceptual, social and cognitive development: The case of developmental coordination disorder. *Frontiers in Psychology*, 7, 311. doi:10.3389/fpsyg.2016.00311
- Leventakou, V., Roumeliotaki, T., Koutra, K., Vassilaki, M., Mantzouranis, E., Bitsios, P., ... Chatzi, L. (2015). Breastfeeding duration and cognitive, language and motor development at 18 months of age: Rhea mother-child cohort in Crete, Greece. *Journal of Epidemiology and Community Health*, 69, 232–239.
- Mimouni-Bloch, A., Goldberg-Stern, H., Strausberg, R., Brezner, A., Heyman, E., Inbar, D., ... Fattal-Valevski, A. (2014). Thiamine deficiency in infancy: Long-term follow-up. *Pediatric Neurology*, 51, 311–316.
- Ministry of Health, Israel (2014). *Guidelines for infant nutrition from birth till age one year.*, Available at http://www.health.gov.il/English/Topics/Pregnancy/Childbirth/feeding/Pages/feeding_babies_first_year.aspx (Accessed 1 August 2016).
- Ngure, F. M., Reid, B. M., Humphrey, J. H., Mbuya, M. N., Peltó, G., & Stoltzfus, R. J. (2014). Water, sanitation, and hygiene (WASH), environmental enteropathy, nutrition, and early child development: Making the links. *Annals of the New York Academy of Sciences*, 1308, 118–128.
- NIH Office of Dietary Supplements. (2016). Thiamin: Fact sheet for health professionals. Available at <https://ods.od.nih.gov/factsheets/Thiamin-HealthProfessional/> (Accessed 31 July 2016).
- Prado, E. L., & Dewey, K. G. (2014). Nutrition and brain development in early life. *Nutrition Reviews*, 72, 267–284.
- Prensky, A. L. (2005). Wernicke encephalopathy in infants. *Journal of Neuro-Ophthalmology*, 25, 167–168.
- Qureshi, U. A., Sami, A., Altaf, U., Ahmad, K., Iqbal, J., Wani, N. A., ... Ali, I. (2016). Thiamine responsive acute life threatening metabolic acidosis in exclusively breast-fed infants. *Nutrition*, 32, 213–216.
- Rice, D., & Barone, S. Jr. (2000). Critical periods of vulnerability for the developing nervous system: Evidence from humans and animal models. *Environmental Health Perspectives*, 108 (Suppl 3), 511.
- Rosales, F. J., & Zeisel, S. H. (2008). Perspective from the symposium, the role of nutrition in infant and toddler brain and behavioral development. *Nutritional Neuroscience*, 11, 135–143.
- Shamir, R. (2012). Thiamine-deficient infant formula: what happened and what have we learned? *Annals of Nutrition and Metabolism*, 60(3), 185–187.
- Singleton, C. K., & Martin, P. R. (2001). Molecular mechanisms of thiamine utilization. *Current Molecular Medicine*, 1, 197–207.
- Smits-Engelsman, B. C. M., Niemeijer, A. S., & Van Galen, G. P. (2001). Fine motor deficiencies in children diagnosed as DCD based on poor grapho-motor ability. *Human Movement Science*, 20, 161–182.
- Soukaloun, D., Kounnavong, S., Pengdy, B., Bouphe, B., Durondej, S., Olness, K., ... White, N. J. (2003). Dietary and socio-economic factors associated with beriberi in breastfed Lao infants. *Annals of Tropical Paediatrics*, 23, 181–186.
- Stiles, J., & Jernigan, T. L. (2010). The basics of brain development. *Neuropsychology Review*, 20, 327–348.
- Stuetz, W., Carrara, V. I., McGready, R., Lee, S. J., Erhardt, J. G., Breuer, J., ... Nosten, F. H. (2012). Micronutrient status in lactating mothers before and after introduction of fortified flour: Cross-sectional surveys in Maela refugee camp. *European Journal of Nutrition*, 51, 425–434.
- Sudfeld, C. R., McCoy, D. C., Fink, G., Muhihi, A., Bellinger, D. C., Masanja, H., ... Fawzi, W. W. (2015). Malnutrition and its determinants are associated with suboptimal cognitive, communication, and motor development in Tanzanian children. *The Journal of Nutrition*, 145, 2705–2714.
- Swaminathan, S., Edward, B. S., & Kurpad, A. V. (2013). Micronutrient deficiency and cognitive and physical performance in Indian children. *European Journal of Clinical Nutrition*, 67(5), 467–474.
- Thauvin-Robinet, C., Faivre, L., Barbier, M. L., Chevret, L., Bourgeois, J., Netter, J. C., ... Saudubray, J. M. (2004). Severe lactic acidosis and acute thiamin deficiency: A report of 11 neonates with unsupplemented total parental nutrition. *Journal of Inherited Metabolic Disease*, 27, 700–704.
- U.S. Institute of Medicine, Food and Nutrition Board. (1998). *Dietary reference intakes: thiamin, riboflavin, niacin, vitamin B6, folate, vitamin B12, pantothenic acid, biotin, and choline* (pp. 58–86). Available at <http://www.nap.edu/read/6015/chapter/6> (Accessed 1 August 2016). Washington, DC: National Academy Press.
- Van Waelvelde, H., De Weerd, W., De Cock, P., & Smits-Engelsman, B. C. M. (2004). Aspects of the validity of the movement assessment battery for children. *Human Movement Science*, 23, 49–60.
- Vasconcelos, M. M., Silva, K. P., Vidal, G., Silva, A. F., Domingues, R. C., & Berdichevsky, C. R. (1999). Early diagnosis of pediatric Wernicke's encephalopathy. *Pediatric Neurology*, 20, 289–294.
- Venetsanou, F., & Kambas, A. (2010). Environmental factors affecting pre-schoolers' motor development. *Early Childhood Education Journal*, 37, 319–327.
- Walker, S. P., Wachs, T. D., Grantham-McGregor, S., Black, M. M., Nelson, C. A., Huffman, S. L., ... Gardner, J. M. M. (2011). Inequality in early childhood: Risk and protective factors for early child development. *The Lancet*, 378, 1325–1338.
- World Health Organization (WHO). (1999). Thiamine deficiency and its prevention and control in major emergencies. Available at http://www.who.int/nutrition/publications/en/thiamine_in_emergencies_eng.pdf (Accessed 31 July 2016).
- World Health Organization (WHO). (2009). *Infant and young child feeding: Model chapter for textbooks for medical students and allied health professionals*. Geneva: World Health Organization. (Accessed 4 September 2016). Available at http://www.who.int/maternal_child_adolescent/documents/9789241597494/en/
- World Health Organization (WHO), UNICEF, IFBAN. (2016). Marketing of breast-milk substitutes: National implementation of the international code. Status Report 2016. Geneva: World Health Organization. Available at http://apps.who.int/iris/bitstream/10665/206008/1/9789241565325_eng.pdf?ua=1&ua=1 (Accessed 4 September 2016).
- Zuk, L., Tlumeck, H., Katz-Leurer, M., Peretz, C., & Carmeli, E. (2014). A new tool for identifying children with motor problems: Reliability and validity study. *Journal of Child Neurology*, 29, 592–598.

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