

## NEW ACTIONS FOR OLD NUTRIENTS

Carlos Lifschitz✉

Section of Pediatric Gastroenterology, Hepatology and Transplantation, Hospital Italiano  
Gascón 450 (C1181ACH), Buenos Aires, **Argentina**

### ABSTRACT

The purpose of this review is to present information regarding new effects for certain nutrients other than those traditionally known. Zinc has been found to prevent and reduce the duration of common colds. In developing countries, zinc has been shown to reduce the duration and severity of diarrhea and even decrease relapses. Iron supplementation in iron deficient children, has been shown to improve several aspects of brain function. In studies where iron was given to the mother, 3 of 5 randomized, controlled trials showed a beneficial effect of iron supplementation on the Psychomotor Development Index at some time points, whereas 2 did not. The chances for infants supplemented with docosahexaenoic acid in the first year of life of having at least 1 event of allergic manifestation or upper respiratory infection or at least 1 event of wheezing/asthma, wheezing/asthma/atopic dermatitis, any allergy, or an upper respiratory tract infection during the first 3 years of life were significantly lower than in the non supplemented group. Epidemiological studies have established a relationship between low levels of serum vitamin D and reduced lung function in healthy adults and asthma onset and severity in children. There was a trend for an independent association between higher levels of maternal circulating 25(OH)D3 levels in pregnancy and decreased odds of lower respiratory tract infections in offspring.

**Key words:** minerals, zinc, iron, vitamin D, nutrition

Abbreviations: zinc – Zn, iron – Fe, randomized, controlled trials – RCT, intelligence quotient – IQ, docosahexaenoic acid – DHA, therapy resistant asthma – STRA, forced expiratory volume in 1 second – FEV1.

The purpose of this review is to present information regarding new effects for certain nutrients other than those traditionally known. As these topics are the subject of ongoing research, results vary and not all studies support the findings reported here. However, they all come from peer reviewed publications. We will discuss zinc, iron, docosahexaenoic acid and vitamin D.

### ZINC

Zinc (Zn) is a metalloenzyme required for the activity of a multitude of enzymes [Keith et al. 2000].

Zn in proteins can either participate directly in chemical catalysis or be important for maintaining protein structure and stability. Zn is involved in numerous aspects of cellular metabolism as it is required for the catalytic activity of approximately 100 enzymes [Institute of Medicine... 2001] and it plays a role in immune function [Prasad 1995], protein synthesis [Prasad 1995], wound healing [Heyneman 1996], DNA synthesis [Institute of Medicine... 2001], and cell division [Prasad 1995]. Zn also supports normal growth and development during pregnancy, childhood, and adolescence [Simmer and Thompson 1985, Fabris and Mocchegiani 1995] and is required for proper sense of taste and smell [Prasad et al. 1997]. Zn is an essential mineral that is naturally present in some foods, added to others, and available as a dietary supplement.

✉Carlos.Lifschitz@hospitalitaliano.org.ar

Zn deficiency is characterized by growth retardation, loss of appetite, and impaired immune function. In more severe cases, Zn deficiency causes hair loss, diarrhea, delayed sexual maturation, impotence, hypogonadism in males, and eye and skin lesions [Institute of Medicine... 2001, Prasad 2004, Hambidge 1989]. Weight loss, delayed healing of wounds, taste abnormalities, and mental lethargy can also occur [King and Cousins 2005, Nishi 1996]. Zn deficiency can occur as a consequence of insufficient intake, malabsorption, urinary or stool losses.

### **ZINC FOR THE COMMON COLD**

The literature indicates that Zn ions inhibit the replication of diverse viruses *in vitro* by inhibition of viral polypeptide cleavage, including eight of nine rhinoviruses tested known to cause common colds [Butterworth and Korant 1974, Duchateau et al. 1981 a, b]. The first clinical study of the use of Zn to treat the common cold dates from 1983 [Eby et al. 1984]. In that study, Zn was administered as a 25 mg lozenge every 2 h while patients were awake and significantly shortened the durations of symptoms. Since then several studies have looked into the preventive and therapeutic role of Zn for the common cold. The purpose of one study was to determine the effect of Zn gluconate lozenges administered 1 day before rhinovirus inoculation. Al Nakib et al. carried out a double-blind, placebo-controlled prophylactic study and found that total mean clinical score was reduced to 5.7 in the Zn group versus 8.2 for the placebo group [Al-Nakib et al. 1987]. Two additional studies provide support to the prophylactic role of Zn for the common cold [McElroy and Miller 2002, 2003]. Similar conclusions were reached in a pediatric study [Kurugöl et al. 2006, Akilli et al. 2006]. A recent Cochrane review identified 13 therapeutic trials with 966 participants and two preventive prospective trials including 394 participants [Singh and Das 2011]. The authors concluded that Zn administered within 24 hrs. of onset of symptoms reduces the duration and severity of the common cold in healthy people. When supplemented for at least five months, it reduces cold incidence, school absenteeism and prescription of antibiotics in children. There is potential for Zn lozenges, however, to produce side effects. In view of this and the differences in study

populations, dosages, formulations and duration of treatment, it is difficult to make firm recommendations about the dose, formulation and duration that should be used. Zn is not completely nontoxic, even in the therapeutic dose range on a long-term basis. Frequently, doses of Zn in excess of 50 mg cause gastrointestinal side effects, including nausea.

### **ZINC AND CHILDHOOD DIARRHEA**

Several hospital and community-based randomized trials in developing countries, consistently showed that Zn is an effective treatment for acute or persistent diarrhea in children younger than 5 years [Berni Canani and Ruotdo 2006]. Benefits include reduction of diarrhea duration and its severity, and these effects have been obtained in both mild and severe gastroenteritis associated with severe dehydration requiring hospitalization [Bhutta et al. 2000]. The incidence and duration of acute and persistent diarrhea were significantly lower in Zn supplemented children versus placebo-treated counterparts [Sachdev et al. 1988, Strand et al. 2002]. Moreover, in children younger than 5, Zn treatment during acute diarrhea illness resulted in fewer subsequent diarrhea episodes and in a concomitant reduction in the use of antibiotics [Roy et al. 1997, Baqui et al. 2002]. The preventive and therapeutic effects of Zn in reducing diarrhea morbidity have relevant economic implications in terms of hospitalization and antibiotic use [Patel et al. 2003]. The only negative data from developing countries come from a trial in 1 to 6 months old Bangladeshi infants in which different doses of Zn (5 or 20 mg/d given for the duration of the illness) did not affect the duration or severity of diarrhea [Brooks et al. 2005].

### **IRON**

Iron (Fe) deficiency is the most common single cause of anemia worldwide, accounting for about half of all anemia cases. It is more common in women than men. In areas of the world where parasitic infection with hookworms, whipworms, and roundworms is prevalent, Fe deficiency could be secondary to undetected intestinal bleeding, caused by the worms. Estimates of occurrence of Fe deficiency in industrialized countries are usually derived from nationally

representative samples with specific indicators of Fe status [CDC 2002]. Fe deficiency is also common in women and young children in industrialized countries. In 2002 in the UK, 21% of female teenagers between 11 and 18 years, and 18% of women between 16 and 64 years were Fe deficient [Heath and Fairweather-Tait 2002]. In the USA, 9-11% of non pregnant women aged between 16 and 49 years were found to be Fe deficient, and 2-5% had Fe deficiency anemia, with more than twofold higher frequency in poorer, less educated, and minority populations [Scholl 2005]. In pregnant women of low-income areas in the USA, the frequency of Fe deficiency anemia in the first, second, and third trimesters is 2%, 8%, and 27%, respectively [Scholl 2005]. In France, Fe deficiency and Fe deficiency anemia affect 29% and 4% of children younger than 2 years [Herberg et al. 2001]. In the USA, 2% of children between 1 and 2 years have Fe deficiency anemia [CDC 2002].

## **IRON AND COGNITION**

The behavioural and developmental sequelae of Fe deficiency in young children have received much interest recently. However, data on the consequences of Fe deficiency in women of reproductive age are just beginning to emerge [Murray-Kolb 2011]. Interest in this area has increased as a result of the findings that brain Fe is much more fluid than previously thought and Fe-deficient animals experience nondevelopment-dependent brain alterations. Additional consideration should be given to the fact that detriments to cognition and behaviour in a woman of reproductive age may have negative implications beyond the woman's health; specifically, they may negatively influence her children. Infants who experience Fe deficiency during the first 6-12 months of life are likely to experience persistent effects of the deficiency that alter functioning in adulthood. A lack of sufficient Fe intake may significantly delay the development of the central nervous systems a result of alterations in morphology, neurochemistry, and bioenergetics [Beard 2008].

Many earlier human infancy studies used the Bayley Scales of Infant Development as the primary dependent variable and only half of them were case-controlled intervention trials. Some studies showed

significant developmental delays that were irreversible with Fe therapy. Three studies showed developmental delays that were mostly reversed with Fe therapy, and only a few of the trials evaluated both cognitive and emotional or behavioural measures. Thus, there is a mixed historical perspective [Grantham-McGregor and Ani 2003].

An important new step forward, however, was the increased utilization of electrophysiology to begin looking into biological systems [Walker et al. 2007]. Both visual and auditory evoked potential approaches are being utilized and reveal some very powerful information [Roncagliolo et al. 1998]. Auditory brainstem responses (noninvasive) were tested at 6, 12, and 18 months, and Fe therapy was started at 6 months in infants known to have Fe deficiency anemia. Response to the intervention was tested in 85% of infants at 12 months of age and in 71% of infants at 18 months of age. The AEP studies showed slowed nerve conduction velocity in Fe-deficient infants that did not improve even after several years of Fe treatment [Algarin et al. 2003]. These are important data in that they strongly suggest hypomyelination and/or alterations in neurotransmitters as a result of Fe deficiency in the first year of life. These children were growing normally, so it is unlikely other nutrient deficiencies may have been present and undetected.

## **IRON AND BRAIN FUNCTION**

Multiple studies have looked into the effect of Fe supplementation on several brain functions. In one of them the purpose was to examine the effects of Fe supplementation on vigilance, attention and conceptual learning in preschool children in Greece [Metallinos-Katsaras et al. 2004]. The intervention consisted of a 2-month supplementation of 15 mg Fe (and multivitamins vs. placebo (multivitamins alone) which resulted in the anemic subjects making significantly fewer errors of commission, exhibiting 8% higher accuracy ( $P < 0.05$ ) and significantly more efficiency (mean difference = 1.09,  $P < 0.05$ ) than those given placebo. These effects of Fe were not found among preschoolers with good Fe status.

A review by Sachdev et al. indicated that Fe supplementation improves mental development score modestly [Sachdev et al. 2005]. This effect is particularly

apparent for intelligence tests above 7 years of age and in initially anemic or Fe-deficient anemic subjects.

Two recent reviews support the role of Fe in psychomotor development. In one of them, the effects of Fe supplementation in nonanemic pregnant women and in nonanemic healthy children aged < 3 yrs on mental performance and psychomotor development of children were assessed [Szajewska et al. 2010]. Three of 5 randomized, controlled trials (RCT) identified showed a beneficial effect of Fe supplementation on the Psychomotor Development Index at some time points, whereas 2 did not. Meta-analysis of 3 RCT that included 561 children showed significant improvement on the Psychomotor Development Index at approximately 12 months of age in the Fe-supplemented group compared with the control group. Two RCT showed no effect of Fe supplementation on behaviour. Neither of the 2 RCT that addressed the influence of prenatal Fe supplementation showed an effect of Fe on either the intelligence quotient or behavioural status of the children. However, none of 5 RCT individually showed a beneficial effect of Fe supplementation during early life on the Mental Developmental Index of the Bayley Scales of Infant Development at different ages throughout the first 18 months of life. The authors of this review concluded that limited available evidence suggests that Fe supplementation in infants may positively influence children's psychomotor development, whereas it does not seem to alter their mental development or behaviour.

The aim of the other review was to assess whether Fe supplementation improved cognitive domains such as concentration, intelligence, memory, psychomotor skills and scholastic achievement [Falkingham et al. 2010]. The authors identified fourteen RCT of children aged 6 yrs and older, adolescents and women but no RCT in men or older people. Fe supplementation improved attention and concentration irrespective of baseline Fe status without heterogeneity. In anemic groups supplementation improved intelligence quotient (IQ) by 2.5 points, but had no effect on non-anemic participants, or on memory, psychomotor skills or scholastic achievement. However, the funnel plot suggested modest publication bias. The limited number of included studies was generally small, short and methodologically weak. In conclusion, there was some evidence that Fe supplementation improved

attention, concentration and IQ, but this requires confirmation with well-powered, blinded, independently funded RCT of at least one year duration in different age groups including children, adolescents, adults and older people, and across all levels of baseline Fe status.

Finally, a study addressed the issue whether daily Fe supplementation of Fe-replete children could impair their growth [Aguayo 2000]. For that purpose, 73 Bolivian non-anemic school-age children were randomly assigned either to the treatment group (n = 37; receiving supplements containing FeSO<sub>4</sub> during 18 wk) or the control group (n = 36; receiving a placebo during the same period). Hemoglobin concentration and anthropometric measures were determined for each child at the beginning (T0) and the end (T18) of the study. Results showed that the treatment group did not show any significant variation in hemoglobin concentration between T0 and T18 whereas the control group showed a significant decrease in hemoglobin concentration ( $-4.6 \pm 10.9$  g/L; P = 0.03). The authors concluded that week Fe supplementation of non-anemic school-age children had no negative effect on their growth while having a positive effect in preventing significant decreases in hemoglobin concentration.

## DOCOSAHEXAENOIC ACID

Docosahexaenoic acid (DHA) is a long chain polyunsaturated fatty acid (LCPUFA) of the n-3 family. There are multiple studies investigating the effects of DHA supplementation in humans on different functions and ages. In some areas of investigation, the literature is so convincing that the European Food Safety Authority (EFSA) has recognized its merits as is the case of DHA as supportive of visual acuity, particularly in preterm infants [SanGiovanni et al. 2000]. The 2008 Cochrane Database publication identified twenty randomized studies in term infants [Simmer et al. 2008]. Eleven studies were included and those were of good quality. Three studies reported beneficial effect of LCPUFA supplementation on visual acuity. Neurodevelopmental outcome was measured at different ages throughout the first two years by eleven studies. One study reported better novelty preference measured by Fagan Infant test at nine months in supplemented infants compared with controls. Another study reported better problem solving at 10 months

with supplementation. Pooled meta-analysis of the data also did not show a statistically significant benefit of LCPUFA supplementation on either mental or psychomotor developmental index of BSID. The problem with analysing all studies together is that populations, doses and sources of DHA, duration of supplementation and outcome are not always comparable.

### **LCPUFA SUPPLEMENTATION IN HIGH RISK PREGNANCIES**

A possible imbalance between n-3 and n-6 fatty acids may be associated with disturbances in the production of prostaglandins responsible for placental blood flow that participate in the initiation of labour. It has been shown that supplementation with LCPUFA decreases the risk of certain pregnancy complications, particularly pre-eclampsia, pregnancy-induced hypertension, intra-uterine growth retardation and preterm delivery [Bulstra-Ramakers et al. 1995, Moodley and Norman 1989, Onwude et al. 1995, Olsen et al. 2000]. The meta-analysis by Szajewska et al. showed that n-3 LCPUFA supplementation even in low-risk pregnancy may enhance the duration of pregnancy and head circumference [Szajewska et al. 2006]. Findings indicate an overall risk reduction of 31%. Results for risk reduction were even more impressive in a meta-analysis of high risk pregnancies where the risk was reduced by 61% [Horvath et al. 2007]. Compared with controls, supplementation with DHA was associated with a significantly lower rate of early preterm delivery (< 34 weeks of gestation). There was no significant difference in infant birth weight, rate of low birth weight (< 2500 g or < 10th percentile) and recurrence of intra-uterine growth retardation.

### **EFFECTS OF LCPUFA ON IMMUNITY**

LCPUFA play a role in maintaining membrane fluidity and regulating cell signalling, gene expression and cellular function [Calder et al. 2010] and can influence the functioning of immune cells [Calder 2006, 2008]. In a study by Field et al. addition of DHA (plus arachidonic acid (ARA)) to a preterm infant formula resulted in lymphocyte populations, phospholipid composition, cytokine production, and antigen maturity that are more consistent with those in

human milk-fed infants than what seen in infants fed formula not containing LCPUFA [Field et al. 2000]. Birch et al. reviewed data for respiratory health for the first 3 years of life from a study that included 2 cohorts of term infants who had received formula containing DHA (+ ARA) from < 5 days of age until 12 months of age or no supplementation at all [Birch et al. 2010]. Chances of having at least 1 event of allergic manifestation or upper respiratory infection or at least 1 event of wheezing/asthma, wheezing/asthma/atopic dermatitis, any allergy, or an upper respiratory tract infection during the first 3 years of life were significantly lower in the DHA group. The hazards ratio for the time to first diagnosis of each of these 4 outcomes was also significantly lower in the DHA group, meaning that it was less likely that infants in the DHA group would get the diagnosis before infants in the control group. Finally, the number of doctor visits for 3 of the outcomes was significantly fewer in the DHA group and doctor visits for other outcomes and overall tended to be fewer in this group. In another study, 3 year old children were randomly assigned in a blinded fashion to receive a toddler formula containing either 0, 43 mg, or 130 mg of DHA per 1 glass daily serving for 60 days [Minns et al. 2010]. Supplementation with 130 mg/d of DHA for 60 days resulted in a 62% reduction of the chances of having at least one episode of respiratory illness compared to controls. During the study, at least one respiratory event was recorded for 46% of the participants in the no supplementation group in contrast to 17% in the group provided 130 mg of DHA per day. Another study was aimed at determining whether n-3 polyunsaturated fatty acids affected illness and selected plasma cytokines in school children. Thai schoolchildren aged 9 to 12 years consumed milk containing placebo (soybean) oil (n = 86) or fish oil (n = 94) on 5 days per week for 6 months; the latter provided 200 mg eicosapentaenoic acid plus 1 g DHA daily [Thienprasert et al. 2009]. The fish oil group showed fewer episodes (P = 0.014) and shorter duration (P = 0.024) of illness (mainly upper respiratory tract) than the placebo group. Plasma IL-2 receptor, IL-10, and IL-6 were not affected by either treatment. Plasma TGF-beta1 increased in both groups, but the increase was smaller in the fish oil group, and at the end of supplementation TGF-beta1 concentration was lower in the fish oil group (P < 0.001). The effect of prenatal DHA



supplementation on infant morbidity was investigated in Mexico in a double-blind randomized controlled trial conducted in which more than 800 pregnant women received daily supplementation with 400 mg of DHA of algal origin or placebo from 18 to 22 weeks' gestation through delivery [Imhoff-Kunsch et al. 2011]. At the age of 1, 3, and 6 months, caregivers reported the occurrence of common illness symptoms in the preceding 15 days. Results showed that the occurrence of a combined measure of cold symptoms was lower in the DHA group at 1 month at which time the DHA group experienced 26%, 15%, and 30% shorter duration of cough, phlegm, and wheezing, respectively, but 22% longer duration of rash (all  $P \leq 0.01$ ). At 3 months, infants in the DHA group spent 14% less time ill ( $P < 0.0001$ ). At 6 months, infants in the DHA group experienced 20%, 13%, 54%, 23%, and 25% shorter duration of fever, nasal secretion, difficulty breathing, rash, and "other illness," respectively, but 74% longer duration of vomiting (all  $P < 0.05$ ). The authors concluded that DHA supplementation during pregnancy decreased the occurrence of colds in children at 1 month and influenced illness symptom duration at 1, 3, and 6 months.

#### **LCPUFA AND LUNG FUNCTION IN PREMATURE INFANTS**

In a multicenter, randomized controlled trial 657 preterm infants were assigned to receive either a high-DHA diet or a standard diet and were followed until they were 18-months old [Manley et al. 2011]. There was a significant reduction in bronchopulmonary dysplasia in boys and in all infants with a birth weight of  $< 1250$  g. There was no effect, however, on duration of respiratory support, admission length, or home oxygen requirement. There was a reduction in reported hay fever in all infants in the high-DHA group at either 12 or 18 months.

#### **VITAMIN D**

Traditionally, Vitamin D is associated to calcium and bone metabolism. Vitamin D<sub>3</sub> is made in the skin when 7-dehydrocholesterol reacts with ultraviolet light [Hume et al. 1927]. Overt Vitamin D deficiency is rare in healthy individuals consuming a regular diet

and with at least moderate exposure to sunlight. National Hospital Discharge Survey data revealed that nine per million children in the United States were hospitalized with rickets between 1990 and 1998. The codes used on the NHDS do not distinguish nutritional deficiencies from other causes of rickets. However, rickets was a common childhood disease in the United States until vitamin D was added to milk.

#### **VITAMIN D AND RESPIRATORY HEALTH**

Epidemiological studies have established a relationship between low levels of serum vitamin D and reduced lung function in healthy adults and asthma onset and severity in children. Little is known about vitamin D status and its effect on asthma pathophysiology in children with severe, therapy resistant asthma (STRA). Relationships between serum vitamin 25 hydroxy calciferol (25[OH]D<sub>3</sub>), lung function, and pathology were investigated in pediatric STRA by Gupta et al. [2011]. Results indicated that 25[OH]D<sub>3</sub> levels were significantly lower in STRA than moderate asthmatics and controls. There was a positive relationship between 25[OH]D<sub>3</sub> levels and percentage predicted forced expired volume (FEV) and forced vital capacity (FVC) in all subjects. The link between vitamin D, airway structure and function suggests vitamin D supplementation may be useful in pediatric STRA.

In another study, the relationship between 25[OH]D<sub>3</sub> concentrations and baseline FVC, FEV<sub>1</sub> in 1 second and change in FEV<sub>1</sub> after a standardized exercise challenge in 45 children with intermittent asthma was examined [Chinellato et al. 2011]. Only 11% of the children had desirable serum vitamin D levels. A positive correlation was found between serum 25[OH]D<sub>3</sub> and both FVC and FEV<sub>1</sub>. Subjects with a positive response to the exercise challenge presented lower serum levels of 25[OH]D<sub>3</sub> than children with a negative challenge. The authors' conclusion was that hypovitaminosis D is frequent in asthmatic children who live in a Mediterranean country. In those children, lower levels of vitamin D are associated with reduced lung function and increased reactivity to exercise.

The association between 25[OH]D<sub>3</sub> levels in pregnant women and risk of lower respiratory tract infections, wheezing, and asthma in the offspring was investigated using the data obtained from 1,724 children

of a population-based birth cohort study [Morales et al. 2011]. After multivariable adjustment, there was a trend for an independent association between higher levels of maternal circulating 25(OH)D3 levels in pregnancy and decreased odds of lower respiratory tract infections in offspring but no association was found between 25(OH)D3 levels in pregnancy and risk of wheezing at the age of 1 or 4, or asthma at the age of 4-6.

## CONCLUSION

Although the fundamental role of nutrients, the effects of their deficiencies and the way to correct such deficiencies have been known for decades, newer associations are being described bringing hope to patients with relatively simple and affordable solutions.

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## **NOWE DZIAŁANIA STARYCH SKŁADNIKÓW POKARMOWYCH**

### **STRESZCZENIE**

Celem niniejszej pracy pogładowej jest przedstawienie informacji o nowych, innych niż tradycyjnie uznane, działaniach wybranych składników odżywczych. Stwierdzono, że cynk może zapobiegać i skracać czas trwania przeziębienia. W krajach rozwijających się udokumentowano, iż jego podaż zmniejsza czas trwania i nasilenie biegunki, a nawet wpływa na zmniejszenie częstości jej nawrotów. Podawanie żelaza dzieciom z jego niedoborem poprawiało wiele funkcji mózgowia. W trzech spośród pięciu kontrolowanych badań suplementacyjnych, w których matce podawano żelazo, wykazano jego pozytywny wpływ na wskaźnik rozwoju psychoruchowego niemowląt w niektórych punktach oceny. W dwóch pozostałych badaniach nie odnotowano takiego efektu. U dziecka suplementowanego w pierwszym roku życia kwasem dokozaheksanowym znacząco mniejsze, niż w grupie niesuplementowanej, było ryzyko wystąpienia przynajmniej jednej manifestacji alergicznej, infekcji układu oddechowego, epizodu świszczącego oddechu – astmy, atopowego zapalenia skóry czy jakiegokolwiek alergii lub infekcji górnych dróg oddechowych w pierwszych trzech latach życia. W badaniach epidemiologicznych wykazano zależność pomiędzy małymi stężeniami witaminy D w surowicy a gorszą pracą płuc u zdrowych dorosłych osób oraz momentem wystąpienia i nasileniem astmy u dzieci. Stwierdzono występowanie trendu w kierunku niezależnego związku pomiędzy większymi stężeniami matczynej stężeń 25-OH witaminy D3 w ciąży a zmniejszonym ryzykiem infekcji dolnych dróg oddechowych u potomstwa.

**Słowa kluczowe:** składniki mineralne, cynk, żelazo, witamina D, żywienie

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