

Role of zinc in maternal and child mental health^{1–4}

Ann M DiGirolamo and Manuel Ramirez-Zea

ABSTRACT

Mental health problems in women, children, and adolescents are a significant public health issue. Given current barriers to the effective treatment of these problems, researchers are looking to the field of nutrition for potential alternatives to better understand and address mental health issues. The purpose of this article was to review current evidence on the relation between zinc and mental health disorders with a focus on 2 mental health problems that commonly affect women and children: depression and attention-deficit hyperactivity disorder (ADHD). A literature search of the databases Medline and PsychInfo was conducted with the use of key terms. The review included articles from 1975 to May 2008, but focused on articles published in recent years. Relations between zinc concentrations and behavior in animals; the relation between zinc deficiency, depression, and ADHD in patient and community samples; and the potential biological mechanisms for these relations were explored. The data support a relation between low concentrations of zinc and mental health problems, especially in at-risk populations. Evidence for the potential use of zinc in treating mental health problems comes mainly from patient populations and is strongest when zinc is given in combination with pharmacologic treatment. Less conclusive evidence exists for the effectiveness of zinc alone or in general community samples. Recommendations for further research in this area are provided. *Am J Clin Nutr* 2009;89(suppl):940S–5S.

INTRODUCTION

Mental health problems in women, children, and adolescents are a significant public health issue. Maternal depression is very common globally, the prevalence of which ranges from 15% in the United States to 35% in low-income South African mothers (1–5). Furthermore, the average prevalence of maternal postpartum depression within 6–8 wk after childbirth is 13% in the general population (6). The high prevalence of maternal depression is of concern because of its effects on maternal physical and emotional well-being (7) and because of the link with deficient childcare, negative caregiver/child interactions, child growth impairment, and increased medical problems, accidents, and emotional problems among children (8–10).

One in 10 children and adolescents in the United States have a mental illness severe enough to significantly impair functioning (11, 12), with worldwide prevalence rates for child and adolescent mental disorders of $\approx 20\%$ (13, 14). Examples of common childhood disorders include attention-deficit hyperactivity disorder (ADHD), depression, and anxiety. The World Health Organization suggests that childhood neuropsychiatric disorders will increase worldwide by $>50\%$ by 2020, with these disorders

becoming 1 of 5 of the most common causes of morbidity, mortality, and disability in children (14).

Fewer than 1 in 5 children currently receive the necessary treatment services for these disorders (11), and the situation in developing countries may be worse for both women and children (14). Although there has been significant progress in identifying effective treatments for adults, more information is needed, particularly for women of reproductive age and children. Psychotherapy is costly, requires time and commitment from both children and parents, and often is not available or acceptable, particularly in developing countries. Pharmacotherapy is also costly, is often unavailable, and has potential side effects for children and for women who may be pregnant (15, 16). In addition, problems of awareness, access, lack of resources, and stigma regarding mental health services may prevent women and children from receiving the necessary treatment of mental health problems, especially in developing countries where these problems are more pronounced. Therefore, we need alternative treatments or preventive methods that are readily accessible and acceptable to populations nationally and internationally.

Researchers have begun to look to the field of nutrition for potential alternatives to better understand and address mental health issues. Compelling evidence for the role of micronutrients in mental health has come from studies focusing on the role of zinc in depression and ADHD, disorders that are common among women and children, respectively. Studies in animals and humans have shown relations between low zinc concentrations and symptoms of depression and ADHD and have suggested the potential effectiveness of zinc supplementation for these disorders. This information is important given the large number of populations at risk of zinc deficiency, both nationally and internationally, particularly infants, children, and pregnant and lactating women (17, 18).

The purpose of this article was to review evidence on the relation between zinc deficiency and mental health with a focus

¹ From the Hubert Department of Global Health, Emory University, Atlanta, GA (AMD), and the Institute of Nutrition of Central America and Panama, Guatemala City, Guatemala (MR-Z).

² Presented at the symposium “Maternal and Child Mental Health: Role of Nutrition,” held at Experimental Biology 2008, San Diego, CA, 8 April 2008.

³ Supported by NIH grant R01 MH067981.

⁴ Reprints not available. Address correspondence to AM DiGirolamo, Hubert Department of Global Health, Emory University, 1518 Clifton Road, NE, Atlanta, GA 30307. E-mail: adigiro@sph.emory.edu.

First published online January 28, 2009; doi: 10.3945/ajcn.2008.26692C.

on 2 mental health disorders that commonly affect women and children: depression and ADHD. This article has 3 sections. The first section reviews animal studies of the relation between zinc concentrations and behavior, as an analog to mental health disorders. The second section reviews potential biological mechanisms for the relation between zinc deficiency and depression and ADHD. The final section reviews human studies conducted in patient and community samples experiencing depression or ADHD. The databases Medline and PsychInfo were searched with the use of the following key terms: *zinc*, *zinc deficiency*, *zinc supplementation*, *intervention*, *treatment*, *mental health*, *depression*, *anxiety*, *ADHD*, *stress*, *mood*, and *behavior*. The review included articles from 1975 to May 2008, but the focus was on the more recent articles and on disorders that predominantly affect women and children; however, studies of other populations (eg, men and the elderly) were included in an attempt to shed light on the relation between zinc and these mental health issues.

ANIMAL STUDIES

Many studies using rats, mice, and monkeys have examined relations between zinc concentrations and behavior as analogs to depression, anxiety, aggression, and attention problems. These studies fall into 2 categories: 1) those that examined behavioral outcomes after zinc deficiency, and 2) those that assessed the antidepressant-like properties of zinc. Several studies have reported that zinc deficiency is associated with low levels of activity, lethargy, apathy, and attention in rats and rhesus monkeys (19–22). For example, studies in prepubertal monkeys with moderate zinc restriction found lower spontaneous motor activity and reduced performance of tasks that require visual attention (21–23). Others have noted more aggressive behavior in isolated zinc-deficient mice than in isolated control mice (24) and anxiety-like behavior (eg, decreased time spent in the open arms of a maze test) in young rats with serum zinc concentrations 50% of those of control rats after a zinc-deficient diet (25, 26). Similarly, studies using animal models of psychological stress have suggested that concentrations of zinc in mice exposed to both acute and chronic stress situations were significantly lower than those in a control group (27), and evidence in rats suggests that zinc deficiency may lower the body's adaptability to stress (28).

Experimental studies in mice and rats have examined reduced locomotor activity or fighting behavior during exposure to stress or the insecticide malathion, as an analog for depression, and found that zinc supplementation induced antidepressant-like effects, reductions in immobility time during forced-swim tests, and increases in fight responses previously inhibited during stress (29–31). Effects were seen for zinc alone, but the effects were augmented when zinc was paired with an antidepressant such as imipramine (30).

POTENTIAL BIOLOGICAL MECHANISMS

Zinc is a trace element essential for brain development and central nervous system function (32). More than 200 enzymes are zinc metalloenzymes, requiring zinc for normal neuronal development (32). In addition, zinc is present in synaptic vesicles in a subgroup of glutamatergic neurons in the brain. This form of zinc may modulate responses at receptors for a number

of different neurotransmitters, both excitatory and inhibitory, including the *N*-methyl-D-aspartate (NMDA) and γ -aminobutyric acid (GABA_A) receptors involved in depression and anxiety (33). Because of the importance of zinc metabolism in the brain, zinc deficiency has been associated with neurological dysfunction and human brain pathology (32, 33).

Several researchers have attempted to identify the mechanisms through which zinc may be involved in mental health disorders such as depression and ADHD. One suggested pathway for depression is through zinc's effects on neurotransmitter responses at the NMDA receptors (29, 33, 34). For example, studies have suggested that NMDA glutamate receptors in depressed patients may be supersensitive, with dysregulation of glutamate often described in depression (35). Glutamate, the major neurotransmitter in excitatory hippocampal pathways, may overstimulate the NMDA pathway in sensitive individuals, leading to aberrant brain biochemical activity or brain cell atrophy and loss associated with depression (36–39). Studies, including double-blind trials, have shown that NMDA receptor antagonists dampen NMDA receptor function and exhibit antidepressant properties (40–42). Zinc is a very potent inhibitor of the NMDA receptor complex, with recent studies suggesting that zinc can induce an antidepressant-like effect in animals and may enhance the effect of other antidepressant medications such as imipramine (29, 30, 43). Others have suggested that zinc may exhibit an antidepressant effect through direct or indirect activation of adenosine A₁ and A_{2A} receptors (44) or a possible up-regulation of neuroprotective effectors (eg, glutathione) (45).

Several mechanisms have been suggested to explain the relation between zinc and ADHD symptoms, possibly through alterations in the neurotransmitters dopamine and serotonin. Zinc is important for the production and modulation of melatonin, which regulates dopamine function (46–48), and for the conversion of dietary pyridoxine to its active form, pyridoxal phosphate, which is necessary for the conversion of tryptophan to serotonin (49). Both the dopamine and serotonin neurotransmitter systems appear to be involved in ADHD (50). Supplementation with zinc may resolve the reduction in melatonin and serotonin synthesis and improve ADHD symptoms, such as impulsivity (46, 49, 51). Zinc may also influence the N2 wave in the frontal and parietal regions of the brain, with effects seen on information processing and possibly on the inhibitory processes of children with ADHD (52).

Dopamine and serotonin neurotransmitter systems may be implicated in both ADHD and depression (50, 53), which suggests that there may be a common pathway whereby zinc is involved in both disorders. More research is needed to delineate the actual mechanisms involved, to better understand the possibility of common pathways between the 2 disorders, and to determine potential treatment implications.

DEPRESSION

Human studies of association

Clinical patient samples

Several studies in clinical patient samples (ie, diagnosed major depression) have shown lower zinc concentrations in patients than in control subjects. Patients with depression have lower plasma or serum zinc concentrations than do nondepressed patients, and

some studies suggest that low serum zinc may be a marker of treatment resistance in depression (54–56). Whether low zinc concentrations are a result of depression, indicating poor appetite, reduced dietary intake, or an immune/inflammatory response that occurs in depression, or actually result in or exacerbate a depressive disorder is still unclear (54, 55).

Community samples

Studies of associations among community samples have been fairly consistent in reporting associations between low zinc concentrations and depression or emotional difficulties. Most studies have involved postpartum women and the elderly. Among women, lower serum zinc concentrations have been associated with the severity of postpartum depressive symptoms (57). Several studies that examined the role of zinc status in the elderly, mainly in Europe through the Zincage Study, have suggested that zinc is important in reducing stress in the elderly. Lower plasma zinc concentrations were related to poorer results for several psychological variables, including measures of cognitive status, mood, and perceived stress, especially in areas with low zinc intakes and a limited variety of foods containing zinc (58, 59). An additional study from Italy noted a relation between the concentration of albumin (as an indicator of zinc status) and depression; 71% of participants with an albumin deficiency had a higher score on a measure of depression than did the 29% of participants with a normal albumin value (60). However, another study in an aging European sample found no association between mood and zinc status; zinc status was within the normal range, which suggests that the potential influence of zinc on mood may be small and undetectable when zinc status is within normal limits (61).

Intervention studies

Clinical patient samples

Intervention studies in clinical samples that examined the role of zinc in depression have focused on patients with major unipolar depression and anorexia nervosa. These studies, although conducted in fairly small sample sizes, provide strong evidence that zinc may play a role in depression and may be helpful in treatment. In a study of male and female patients aged 25–57 y who met the criteria for major unipolar depression, 6 were treated with 25 mg Zn/d for 12 wk and 8 were treated with a placebo; both groups were treated with standard antidepressant therapy (34). Scores on depression inventories were obtained at baseline and 2, 6, and 12 wk after treatment; those in the zinc-supplemented group had significantly lower depression scores after 6 and 12 wk of supplementation than did the placebo group (antidepressant but no zinc). This finding suggests that zinc may enhance the effects of antidepressant treatments on symptoms of depression (34). Recent reviews by Nowak et al (62) and Levenson (63) concluded that zinc has an important role in both the psychopathology and treatment of depression, which suggests that zinc has antidepressant properties.

Randomized controlled trials of zinc supplementation in patients with anorexia nervosa have suggested that zinc therapy enhances the rate of recovery in anorexia by increasing weight gain and improving levels of depression and anxiety (64–66). For example, in a double-blind randomized controlled trial in adolescents with anorexia nervosa, patients were randomly assigned to a zinc supplementation group (50 mg elemental zinc

daily for 6 mo in the form of zinc sulfate) or a placebo group. Both groups received the conventional therapeutic regimen for anorexia of psychotherapy, behavior modification, and nutritional rehabilitation. At the end of 6 mo, significant decreases in symptoms of both depression and anxiety were found in the adolescents supplemented with zinc; similar decreases were not found for the placebo group. There was no change in serum zinc concentrations for either group (65).

Community samples

We found no intervention studies that specifically examined the role of zinc in depression among community samples. Large population-based studies with community samples that examined the effects of zinc supplementation on emotional, psychosocial, and behavioral outcomes in infants and children have produced mixed results. Most studies have been conducted in at-risk populations of children. Several studies examined activity levels and behavior in infants and preschool children. Infants in rural Guatemala supplemented with zinc for 7 mo sat up more frequently, played more, and cried or whined less than did an unsupplemented group (67). A similar zinc supplementation trial among preschool children in India showed significantly greater activity levels among the supplemented children than among control subjects (68). Several studies of zinc supplementation among infants in developing countries have noted positive effects of zinc supplementation on exploratory behavior and behaviors such as responsiveness, emotional tone, activity level, cooperation, and vocalization (69, 70). Other studies found no direct effects of zinc on infant behavior (71–73). This evidence is important to consider when examining the relation between zinc and depression, as sad or irritable affect, psychomotor retardation, and loss of energy are all symptoms related to depression in children and adults.

ADHD

Human studies of association

Clinical patient samples

Lower blood zinc concentrations have been found in children with ADHD than in control subjects in several countries (52, 74–76), with some suggestion that zinc concentrations may be related to the severity of symptoms. For example, Arnold et al (77) found that serum zinc concentrations were negatively correlated ($r = -0.45$) with parent-teacher ratings of inattention in US children with ADHD; however, no relation was found with ratings of hyperactivity-impulsivity. A review by Arnold and DiSilvestro (48) reports numerous controlled studies with cross-sectional evidence of lower zinc tissue concentrations (eg, serum, red blood cells, hair, urine, and nails) in children with ADHD than in normal control subjects and compared with population norms (74–76, 78, 79).

Community samples

Although they did not specifically examine the relation between zinc and ADHD symptoms, several studies in community samples of children have examined the relation between zinc status and behavioral or emotional problems that often coexist in children with ADHD. Zinc intake based on probed oral recall and weighing

of food portions was positively related to social behavior in girls and to activity level in boys in a sample of Egyptian children aged 7–10 y (80), and plasma zinc concentrations were inversely related to teacher ratings of anxiety in 3–5-y-old boys in the Head Start program (81). In the latter study, zinc explained 39% of the variance in anxiety, but was not related to ratings of sociability or aggressive behavior.

Intervention studies

Clinical patient samples

Several studies have examined the potential treatment effects of zinc on ADHD symptoms in children (49, 82), with some suggestion that, as in depression, zinc may enhance the treatment effects of traditional treatments for ADHD, such as methylphenidate (also known as ritalin). Zinc supplementation in a small group of Iranian children with ADHD aged 5–11 y enhanced the effects of methylphenidate; children in the zinc supplementation plus methylphenidate group showed a significantly greater improvement in parent- and teacher-rated ADHD symptoms than did the placebo group who received methylphenidate alone (82). Similarly, Arnold et al (79, 83) noted that the response of boys aged 6–12 y with ADHD to amphetamine treatment was related to zinc concentration; stronger effects were observed in the children with adequate zinc status. The one controlled study in Turkey that examined the potential treatment effects of zinc alone on ADHD noted significant decreases in some ADHD symptoms (eg, hyperactivity and impulsivity) in children supplemented with 150 mg Zn as zinc sulfate for 12 wk as compared with the placebo group (49); however, this study had a high dropout rate, used rather high doses of zinc, and the outcome variables may not have been comparable with those in other ADHD trials because the measures were locally developed or adapted from English (48). More controlled trials are needed before the use of zinc supplementation for the treatment of ADHD can be recommended.

Community samples

As for depression, we found no intervention studies that specifically examined the role of zinc in addressing ADHD symptoms among community samples. However, in community studies of older children and adolescents, zinc supplementation did not appear to produce significant and consistent improvements in psychosocial or behavioral functioning (84, 85). In a sample of first-grade Mexican children exposed to lead, there were no effects of zinc supplementation on mean changes in scores from behavioral rating scales over time (ie, 6 mo), but children who received zinc had a higher likelihood of no longer receiving clinically significant teacher ratings of oppositional behaviors (84). Similarly, in a 10-wk fruit juice zinc fortification program among US adolescents, psychosocial functioning was unrelated to zinc treatment, except that conduct problems increased by 10% in girls who received placebo; no change was observed in the zinc-treated girls (85).

Given the large prevalence of zinc deficiency in many of these at-risk populations and the evidence suggesting a relation between zinc, depression, and ADHD, more controlled community-based studies of zinc supplementation are needed to address the potential of zinc to enhance psychological functioning and im-

prove or prevent mental health problems. The authors are currently conducting a community-based randomized controlled trial of zinc supplementation in 722 school-age children in Guatemala, an area at risk of zinc deficiency, to assess the effects of zinc supplementation for 6 mo compared with placebo on the mental health and school performance of children.

CONCLUSIONS

Support exists from both animal and human studies for a relation between low concentrations of zinc and certain mental health problems (eg, depression and ADHD), especially in at-risk populations; some support exists for the improvement of these mental health problems with zinc treatment. Evidence for the treatment potential of zinc comes mainly from patient populations and is strongest when zinc is given in combination with pharmacologic treatments. There is less conclusive evidence of the effectiveness of zinc alone or of the effectiveness of zinc on mental health and behavior among general community samples, in whom fewer studies have been conducted.

More research is needed to understand whether low zinc status is a cause or an effect of mental health problems, with more controlled studies examining the treatment potential and preventive effects of zinc supplementation, especially in women and children. We need to better understand the neurological mechanisms underlying the role of zinc in depression and ADHD and to examine whether there are common pathways for the role of zinc in these and other mental health disorders.

Children of depressed mothers are at risk of emotional and behavioral problems, although the pathways underlying this relation have not been clearly defined (8, 86). For example, in the face of depressed mothers, children may have difficulty adapting to their environment or may develop a cognitive vulnerability to mental health problems through exposure to highly critical, hostile, and inconsistent maternal behavior. Alternatively, children may be vulnerable to developing depression and other disorders because of a biological predisposition or a hyperreactive physiologic response to stress (86–89). Zinc deficiency may play a role in mental disorders in both parents and children through its possible effects on neurotransmitters and the developing brain. Prospective studies are needed to evaluate the role of zinc deficiency in the development of ADHD, depression, and other childhood disorders in children of mothers who are depressed.

Several of the studies reviewed in this article used age- and sex-matched control subjects (54, 56, 65) or controlled for potential confounding variables such as sex, age, and income (67, 77); however, this has not been done consistently. Very few studies have focused on women of childbearing age to examine the potential treatment or preventive effects of zinc for depression, especially postpartum depression. Childbearing women are especially vulnerable to the adverse effects of poor nutrition on mood because pregnancy and lactation are major nutritional stressors (90). More studies are needed in older children and adolescents to better determine the effects of zinc on the mental health and behavior in this group, especially among children at risk of mental health problems and zinc deficiency. In addition, evidence suggests that zinc deficiency may affect cognitive development in children by decreasing activity, increasing emotional behavior, and impairing memory and the capacity to learn (91). Finally, given the cost and potential risks associated with many psychiatric

medications, especially in children and pregnant or lactating women, further exploration of zinc's role in augmenting the effects of certain medications is recommended, which may result in lower doses of medication being needed. Because mental health problems continue to be a significant public health issue, future research is needed to explore the potential role of zinc and other micronutrients in mental health and to consider whether promoting a balanced diet rich in micronutrients, such as zinc, is an effective way to improve mental health and reduce the burden of neuropsychiatric disorders. (Other articles in this supplement to the Journal include references 92–97.)

We especially thank Maureen Black and Usha Ramakrishnan, Chairs of the symposium, for their review of the manuscript and excellent feedback.

The authors' responsibilities were as follows—AMD: participated in the data collection, the review of the literature, and the writing and reviewing of the manuscript; and MR-Z: participated in the data collection and the review of the literature, critically reviewed the manuscript, and provided feedback. No conflicts of interest existed for either AMD or MR-Z.

REFERENCES

- Walker SP, Wachs TD, Gardner JM, et al. Child development: risk factors for adverse outcomes in developing countries. *Lancet* 2007;369:145–57.
- Dietz PM, Williams SB, Callaghan WM, Bachman DJ, Whitlock EP, Hornbrk MC. Clinically identified maternal depression before, during, and after pregnancies ending in live births. *Am J Psychiatry* 2007;164:1515–20.
- Patel V, Rodrigues M, DeSouza N. Gender, poverty, and postnatal depression: a study of mothers in Goa, India. *Am J Psychiatry* 2002;159:43–7.
- Rahman A, Iqbal Z, Bunn J, Lovel H, Harrington R. Impact of maternal depression on infant nutritional status and illness. *Arch Gen Psychiatry* 2004;61:946–52.
- Cooper PJ, Tomlinson M, Swartz L, Woolgar M, Murray L, Molteno C. Post-partum depression and the mother-infant relationship in a South African peri-urban settlement. *Br J Psychiatry* 1999;175:554–8.
- O'Hara MW, Swain AM. Rates and risk of postpartum depression—a meta-analysis. *Int Rev Psychiatry* 1996;8:37–54.
- Blehar MC, Keita GP. Women and depression: a millennial perspective. *J Affect Disord* 2003;74:1–4.
- Hammen C. Children of depressed parents: the stress context. In: Wolchik SA, Sandler IN, eds. *Handbook of children's coping: linking theory and intervention*. New York, NY: Plenum Press, 1997:131–57.
- Rutter M. Psycho-social resilience and protective mechanisms. In: Rolf J, Masten AS, Cicchetti D, Nuechterlein KH, Weintraub S, eds. *Risk and protective factors in the development of psychopathology*. Cambridge, United Kingdom: Cambridge University Press, 1990:181–214.
- Stewart RC. Maternal depression and infant growth—a review of recent evidence. *Matern Child Nutr* 2007;3:94–107.
- US Department of Health and Human Services. Report of the Surgeon General's Conference on Children's Mental Health: a National Action Agenda. Rockville, MD: US Department of Health and Human Services, 2001.
- The National Advisory Mental Health Council Workgroup on Child and Adolescent Mental Health Intervention Development and Deployment. *Blueprint for change: research on child and adolescent mental health*. Washington, DC: National Institute of Mental Health, 2001.
- Belfer ML, Saxena S. WHO Child Atlas Project. *Lancet* 2006;367:551–2.
- World Health Organization. *The World Health Report 2001: Mental Health: New Understanding*. New Hope. Geneva, Switzerland: World Health Organization, 2001.
- Birmaher B, Brent DA, Benson RS. Summary of practice parameters for the assessment and treatment of children and adolescents with depressive disorders. *J Am Acad Child Adolesc Psychiatry* 1998;37:1234–8.
- Ward RK, Zamorski MA. Benefits and risks of psychiatric medications during pregnancy. *Am Fam Physician* 2002;66:629–36.
- Briefel RR, Bialostosky K, Kennedy-Stephenson J, McDowell MA, Ervin RB, Wright JD. Zinc intake of the U.S. population: findings from the third National Health Nutrition Examination Survey, 1988–1994. *J Nutr* 2000;130:1367S–73S.
- Black RE. Preface: zinc for child health. *Am J Clin Nutr* 1998;68(suppl):409S.
- Halas ES, Sandstead HH. Some effects of prenatal zinc deficiency on behavior of the adult rat. *Pediatr Res* 1975;9:94–7.
- Hesse GW, Hesse KAF, Catalanotto F. Behavioural characteristics of rat experiencing chronic zinc deficiency. *Physiol Behav* 1979;22:211–5.
- Golub MS, Gershwin ME, Hurley LS, Hendrickx AG, Saito WY. Studies of marginal zinc deprivation in rhesus monkeys: infant behavior. *Am J Clin Nutr* 1985;42:1229–39.
- Golub MS, Takeuchi PT, Keen CL, Hendrickx AG, Gershwin ME. Activity and attention in zinc-deprived adolescent monkeys. *Am J Clin Nutr* 1996;64:908–15.
- Golub MS, Takeuchi PT, Keen CL, Gershwin ME, Hendrickx AG, Lonnerdal B. Modulation of behavioral performance of prepubertal monkeys by moderate dietary zinc deprivation. *Am J Clin Nutr* 1994;60:238–43.
- Takeda A, Tamano H, Kan F, Hanajima T, Yamada K, Oku N. Enhancement of social isolation-induced aggressive behavior of young mice by zinc deficiency. *Life Sci* 2008;82:909–14.
- Takeda A, Itoh H, Yamada K, Tamano H, Oku N. Enhancement of hippocampal mossy fiber activity in zinc deficiency and its influence on behavior. *Biomaterials* 2008;21:545–52.
- Takeda A, Tamano H, Kan F, Itoh H, Oku N. Anxiety-like behavior of young rats after 2-week zinc deprivation. *Behav Brain Res* 2007;177:1–6.
- Teng WF, Sun WM, Shi LF, Hou DD, Liu H. Effects of restraint stress on iron, zinc, calcium, and magnesium whole blood levels in mice. *Biol Trace Elem Res* 2008;121:243–8.
- Chen WQ, Cheng YY, Zhao XL, Li ST, Hou Y, Hong Y. Effects of zinc on the induction of metallothionein isoforms in hippocampus in stress rats. *Exp Biol Med (Maywood)* 2006;231:1564–8.
- Krocicka B, Branski P, Palucha A, Pilc A, Nowak G. Antidepressant-like properties of zinc in rodent forced swim test. *Brain Res Bull* 2001;55:297–300.
- Cieslik K, Klenk-Majewska B, Danilczuk Z, Wrobel A, Lupina T, Ossowska G. Influence of zinc supplementation on imipramine effect in a chronic unpredictable stress (CUS) model in rats. *Pharmacol Rep* 2007;59:46–52.
- Brocardo PS, Assini F, Franco JL, et al. Zinc attenuates malathion-induced depressant-like behavior and confers neuroprotection in the rat brain. *Toxicol Sci* 2007;97:140–8.
- Wallwork JC. Zinc and the central nervous system. *Prog Food Nutr Sci* 1987;11:203–47.
- Cuajungco MP, Lees GJ. Zinc metabolism in the brain: relevance to human neurodegenerative disorders. *Neurobiol Dis* 1997;4:137–69.
- Nowak G, Siwek M, Dudek D, Zieba A, Pilc A. Effect of zinc supplementation on antidepressant therapy in unipolar depression: a preliminary placebo-controlled study. *Pol J Pharmacol* 2003;55:1143–7.
- Berk M, Plein H, Ferreira D. Platelet glutamate receptor supersensitivity in major depressive disorder. *Clin Neuropharmacol* 2001;24:129–32.
- Dingledine R, Conn PJ. Peripheral glutamate receptors: molecular biology and role in taste sensation. *J Nutr* 2000;130:1039S–42S.
- Storm-Mathisen J, Ottersen OP. Immunocytochemistry of glutamate at the synaptic level. *J Histochem Cytochem* 1990;38:1733–43.
- Michael-Titus AT, Bains S, Jeetle J, Whelpton R. Imipramine and phenelzine decrease glutamate overflow in the prefrontal cortex—a possible mechanism of neuroprotection in major depression? *Neuroscience* 2000;100:681–4.
- Sheline YI. Hippocampal atrophy in major depression: a result of depression-induced neurotoxicity? *Mol Psychiatry* 1996;1:298–9.
- Berman RM, Cappiello A, Anand A, et al. Antidepressant effects of ketamine in depressed patients. *Biol Psychiatry* 2000;47:351–4.
- Skolnick P, Layer RT, Popik P, Nowak G, Paul IA, Trullas R. Adaptation of N-methyl-D-aspartate (NMDA) receptors following antidepressant treatment: implications for the pharmacotherapy of depression. *Pharmacopsychiatry* 1996;29:23–6.
- Skolnick P. Antidepressants for the new millennium. *Eur J Pharmacol* 1999;375:31–40.
- Nowak G, Kubera M, Maes M. Neuroimmunological aspects of alterations on zinc homeostasis in the pathophysiology and treatment of depression. *Acta Neuropsychiatr* 2000;12:51–3.
- Lobato KR, Binfare RW, Budni J, Rosa AO, Santos AR, Rodrigues AL. Involvement of the adenosine A₁ and A_{2A} receptors in the antidepressant-like effect of zinc in the forced swimming test. *Prog Neuropsychopharmacol Biol Psychiatry* 2008;32:994–9.
- Franco JL, Posser T, Brocardo PS, et al. Involvement of glutathione, ERK1/2 phosphorylation and BDNF expression in the antidepressant-like effect of zinc in rats. *Behav Brain Res* 2008;188:316–23.

46. Sandyk R. Zinc deficiency in attention-deficit/hyperactivity disorder. *Int J Neurosci* 1990;52:239-41.
47. Chen MD, Lin PY, Sheu WH. Zinc coadministration attenuates melatonin's effect on nitric oxide production in mice. *Biol Trace Elem Res* 1999;69:261-8.
48. Arnold LE, DiSilvestro RA. Zinc in attention-deficit/hyperactivity disorder. *J Child Adolesc Psychopharmacol* 2005;15:619-27.
49. Bilici M, Yildirim F, Kandil S, et al. Double-blind, placebo-controlled study of zinc sulfate in the treatment of attention deficit hyperactivity disorder. *Prog Neuropsychopharmacol Biol Psychiatry* 2004;28:181-90.
50. Quist JR, Kennedy JL. Genetics of childhood disorders: XXIII. ADHD, Part 7: the serotonin system. *J Am Acad Child Adolesc Psychiatry* 2001;40:253-6.
51. Arnold LE. Treatment alternatives for attention-deficit/hyperactivity disorder (ADHD). *J Atten Disord* 1999;3:30-48.
52. Yorbik O, Ozdag MR, Olgun A, Senol MG, Bek S, Akman S. Potential effects of zinc on information processing in boys with attention deficit hyperactivity disorder. *Prog Neuropsychopharmacol Biol Psychiatry* 2008;32:662-7.
53. Delgado PL. Depression: the case for a monoamine deficiency. *J Clin Psychiatry* 2000;61:7-11.
54. McLoughlin IJ, Hodge JS. Zinc in depressive disorder. *Acta Psychiatr Scand* 1990;82:451-3.
55. Maes M, Vandoolaeghe E, Neels H, et al. Lower serum zinc in major depression is a sensitive marker of treatment resistance and of the immune/inflammatory response in that illness. *Biol Psychiatry* 1997;42:349-58.
56. Maes M, de Vos N, Demedts P, Wauters A, Neels H. Lower serum zinc in major depression in relation to changes in serum acute phase proteins. *J Affect Disord* 1999;56:189-94.
57. Wojcik J, Dudek D, Schlegel-Zawadzka M, et al. Antepartum/postpartum depressive symptoms and serum zinc and magnesium levels. *Pharmacol Rep* 2006;58:571-6.
58. Marcellini F, Giuli C, Papa R, et al. Zinc status, psychological and nutritional assessment in old people recruited from five European countries: Zincage study. *Biogerontology* 2006;7:339-45.
59. Marcellini F, Giuli C, Papa R, et al. Zinc in elderly people: effects of zinc supplementation on psychological dimensions in dependence of IL-6-174 polymorphism: a Zincage study. *Rejuvenation Res* 2008;11:479-83.
60. Marcellini F, Giuli C, Papa R, Malavolta M, Mocchegiani E. Psychosocial aspects and zinc status: is there a relationship with successful aging? *Rejuvenation Res* 2006;9:333-7.
61. McConville C, Simpson EEA, Rae G, et al. Positive and negative mood in the elderly: the ZENITH study. *Eur J Clin Nutr* 2005;59:S22-5.
62. Nowak G, Szewczyk B, Pilc A. Zinc and depression: an update. *Pharmacol Rep* 2005;57:713-8.
63. Levenson CW. Zinc: the new antidepressant? *Nutr Rev* 2006;64:39-42.
64. Su JC, Birmingham CL. Zinc supplementation in the treatment of anorexia nervosa. *Eat Weight Disord* 2002;7:20-2.
65. Katz RL, Keen CL, Litt IF, Hurley LS, Kellams-Harrison KM, Glader LJ. Zinc deficiency in anorexia nervosa. *J Adolesc Health Care* 1987;8:400-6.
66. Birmingham CL, Gritzner S. How does zinc supplementation benefit anorexia nervosa? *Eat Weight Disord* 2006;11:e109-11.
67. Bentley ME, Caulfield LE, Ram M, et al. Zinc supplementation affects the activity patterns of rural Guatemalan infants. *J Nutr* 1997;127:1333-8.
68. Sazawal S, Bentley M, Black RE, Dhingra P, George S, Bhan MK. Effect of zinc supplementation on observed activity in low socioeconomic Indian preschool children. *Pediatrics* 1996;98:1132-7.
69. Black MM, Baqui AH, Zaman K, et al. Iron and zinc supplementation promote motor development and exploratory behavior among Bangladeshi infants. *Am J Clin Nutr* 2004;80:903-10.
70. Ashworth A, Morris SS, Lira PIC, Grantham-McGregor SM. Zinc supplementation, mental development and behaviour in low birth weight term infants in northeast Brazil. *Eur J Clin Nutr* 1998;52:223-7.
71. Hamadani JD, Fuchs GJ, Osendarp SJM, Huda SN, Grantham-McGregor SM. Zinc supplementation during pregnancy and effects on mental development and behaviour of infants: a follow-up study. *Lancet* 2002;360:290-4.
72. Black MM, Sazawal S, Black RE, Khosla S, Kumar J, Menon V. Cognitive and motor development among small-for-gestational-age infants: impact of zinc supplementation, birth weight, and caregiving practices. *Pediatrics* 2004;113:1297-305.
73. Hamadani JD, Fuchs GJ, Osendarp SJM, Khatun F, Huda SN, Grantham-McGregor SM. Randomized controlled trial of the effect of zinc supplementation on the mental development of Bangladeshi infants. *Am J Clin Nutr* 2001;74:381-6.
74. Koziolec T, Starobrat-Hermelin B, Kotkowiak L. Deficiency of certain trace elements in children with hyperactivity (Polish). *Psychiatr Pol* 1994;28:345-53.
75. Bekaroglu M, Yakup A, Yusof G, et al. Relationships between serum-free fatty acids and zinc and ADHD. *J Child Psychol Psychiatry* 1996;37:225-7.
76. Toren P, Sofia E, Sela BA, et al. Zinc deficiency in ADHD. *Biol Psychiatry* 1996;40:1308-10.
77. Arnold LE, Bozzolo H, Hollway J, et al. Serum zinc correlates with parent- and teacher-rated inattention in children with attention-deficit/hyperactivity disorder. *J Child Adolesc Psychopharmacol* 2005;15:628-36.
78. Starobrat-Hermelin B. The effect of deficiency of selected bioelements on hyperactivity in children with certain specified mental disorders. *Ann Acad Med Stetin* 1998;44:297-314.
79. Arnold LE, Votolato NA, Kleykamp D, Baker GB, Bornstein RA. Does hair zinc predict amphetamine improvement of ADHD/hyperactivity? *Int J Neurosci* 1990;50:103-7.
80. Wachs TD, Bishry Z, Moussa W, et al. Nutritional intake and context as predictors of cognition and adaptive behaviour of Egyptian school-age children. *Int J Behav Dev* 1995;18:425-50.
81. Hubbs-Tait L, Kennedy TS, Droke EA, Belanger DM, Parker JR. Zinc, iron, and lead: relations to Head Start children's cognitive scores and teachers' ratings of behavior. *J Am Diet Assoc* 2007;107:128-33.
82. Akhondzadeh S, Mohammadi MR, Khademi M. Zinc sulfate as an adjunct to methylphenidate for the treatment of attention deficit hyperactivity disorder in children: a double blind and randomized trial. *BMC Psychiatry* 2004;4:9.
83. Arnold LE, Pinkham SM, Votolato N. Does zinc moderate essential fatty acid and amphetamine treatment of attention-deficit/hyperactivity disorder? *J Child Adolesc Psychopharmacol* 2000;10:111-7.
84. Kordas K, Stoltzfus RJ, Lopez P, Alatorre J, Rosado JL. Iron and zinc supplementation does not improve parent or teacher ratings of behavior in first grade Mexican children exposed to lead. *J Pediatr* 2005;147:632-9.
85. Penland JG, Lukaski HC, Gray JS. Zinc affects cognition and psychosocial function of middle school children. *FASEB J* 2005;19:A973. (Abstr.)
86. Goodman SH, Gotlib IH. Risk for psychopathology in the children of depressed mothers: a developmental model for understanding mechanisms of transmission. *Psychol Rev* 1999;106:458-90.
87. Murray L, Woolgar M, Cooper P, Hipwell A. Cognitive vulnerability to depression in 5-year-old children of depressed mothers. *J Child Psychol Psychiatry* 2001;42:891-9.
88. Coyne JC, Downey G, Boergers J. Depression in families: a systems perspective. In: Cicchetti D, Toth SL, eds. *Developmental perspectives on depression. Rochester symposium on developmental psychopathology. Vol 4.* Ann Arbor, MI: University of Michigan Institute for Social Research, 1992:211-49.
89. Cicchetti D, Rogosch FA, Toth SL. A developmental psychopathology perspective on depression in children and adolescents. In: Reynolds WM, Johnston HF, eds. *Handbook of depression in children and adolescents.* New York, NY: Plenum Press, 1994:123-41.
90. Bodnar LM, Wisner KL. Nutrition and depression: implications for improving mental health among childbearing-aged women. *Biol Psychiatry* 2005;58:679-85.
91. Bhatnagar S, Taneja S. Zinc and cognitive development. *Br J Nutr* 2001;85:S139-45.
92. Black MM, Ramakrishnan U. Introduction. *Am J Clin Nutr* 2009;89(suppl):933S-4S.
93. Wachs TD. Models linking nutritional deficiencies to maternal and child mental health. *Am J Clin Nutr* 2009;89(suppl):935S-9S.
94. Murray-Kolb LE, Beard JL. Iron deficiency and child and maternal health. *Am J Clin Nutr* 2009;89(suppl):946S-50S.
95. Black MM, Baqui AH, Zaman K, El Arifeen S, Black RE. Maternal depressive symptoms and infant growth in rural Bangladesh. *Am J Clin Nutr* 2009;89(suppl):951S-7S.
96. Ramakrishnan U, Imhoff-Kunsch B, DiGirolamo AM. Role of docosahexaenoic acid in maternal and child mental health. *Am J Clin Nutr* 2009;89(suppl):958S-62S.
97. Engle PL. Maternal mental health: program and policy implications. *Am J Clin Nutr* 2009;89(suppl):963S-6S.