Zinc in psychosis (Review)

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Received November 27, 2024; Accepted April 3, 2025

DOI: 10.3892/mmr.2025.13566

Abstract. Zinc (Zn) may be associated with schizophrenia (SCH), since its altered homeostasis can contribute to abnormal glutamatergic neurotransmission, inflammation, neurodegeneration and autoimmune abnormalities. It has been proposed that a number of patients with SCH could benefit from the use of Zn, either on its own or along with vitamins C, E and B6, and prenatal supplementation of Zn during the gestation period can mitigate the lipopolysaccharide-induced rat model of maternal immune activation. The aim of the present review was to summarize the various effects of Zn dyshomeostasis on patients with psychosis and to clarify in what ways they could benefit from Zn supplementation.

Contents

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Key words: zinc, psychosis, schizophrenia, zinc homeostasis

1. Introduction

Zinc (Zn) is an essential trace element that has a role in prenatal and postnatal growth and development; notably, it is involved in gene expression, DNA and RNA stabilization, neurotransmission and apoptosis (1-3). Zn serves an important role in the activity of several enzymes, including dopamine β-hydroxylase, superoxide dismutase (SOD), thymidylate synthase, DNA and RNA polymerases, matrix metalloproteinases and N-acyl-D-aspartate deacylase (4,5). In addition, Zn is an inhibitor of NMDA receptor (NMDAR) activity, and it interacts with GABA and serotonin receptors (6,7); it is found in high quantities in the hippocampus and limbic system in glutamatergic neurons, and it can cause cognitive and memory impairment (8,9). Sources of Zn include red meat, oysters, crabs, nuts, beans and whole grains (7). Notably, Zn deficiency can result in symptoms of depression, anxiety, growth restriction, loss of appetite, impaired immune function, loss of smell, diarrhea and hair loss as well as in acrodermatitis enteropathica specifically in children (7,10-13). However, increased concentrations of Zn can have a toxic outcome; it has been reported that patients with Parkinson's disease (PD) exhibit increased Zn concentrations in the substantia nigra, and after continuous Zn administration for 12 weeks, rats have demonstrated upregulation of COX-2 mRNA in the substantia nigra (14). The important role of Zn in neurodegenerative disorders, schizophrenia (SCH) and depression has been established in several research studies (8,15-17).

2. Relationship of Zn with psychosis

Researchers have proposed that SCH is a neurodevelopmental disorder (18,19). Notably, Zn is considered a possible diagnostic biomarker associated with SCH, since its altered homeostasis may contribute to irregular glutamatergic neurotransmission, inflammation, neurodegeneration and autoimmune defects (3,5).

It has been suggested that prenatal Zn deficiency, as a result of maternal Zn insufficiency or fetal gene variants, results in decreased brain volume in rodent models (20,21) and increases the incidence of SCH. Other SCH risk genes (including CACNA1G, SOBP, GRIA3, SRRM2, NR3C2, TRIO and RYR2) (22) and Zn deficiency after birth may contribute to the occurrence of SCH. Within this context, a decrease in brain Zn content has been reported in postmortem samples from patients with early onset psychosis compared with that in control samples (15,23). Furthermore, in a post-mortem study of the brains of patients with SCH, ionic Zn staining within the hippocampus was observed; Zn staining in the dentate gyrus was shown to be more intense in female and older donors (24). In another post-mortem study, Zn levels were revealed to be elevated in the hippocampus, and reduced within the amygdala and caudate nucleus; notably, no significant differences were reported in Zn levels between patients with SCH and controls (25).

Dysfunction of Zn transferring molecules, particularly of the SLC39 family responsible for transporting zinc into the cytoplasm, may lead to irregular Zn concentrations and have been implicated in SCH (17). Genome-wide association studies have demonstrated common genetic influences of the SLC39A8 gene for SCH and inflammatory bowel disease (26,27). Variants of this gene have been reported to be associated with metabolic abnormalities (lipid levels, blood pressure and obesity) and SCH-associated inflammatory indicators (a shift in gut microbiome composition and T-cell immunity) (26,28-30).

One missense single nucleotide polymorphism of the SLC39A8 gene, which encodes ZIP8, rs13107325, has been found to be related to brain Zn homeostasis in psychosis (31). Li *et al* (32) demonstrated that cortical dendritic spine density in SLC39A8-p.393T knock-in mice was significantly diminished, and it has been proposed that abnormalities in dendritic spines are associated with the development of SCH. Furthermore, Tseng *et al* (33) reported that the missense variant rs13107325 of gene SLC39A8 resulted in an elevated innate immune response and glutamate receptor hypofunction. Moreover, mRNA expression levels of the SLC39A12 gene, which encodes ZIP12, have been reported to be increased in the dorsolateral prefrontal cortex (PFC) of patients with SCH (34). Perez-Becerril *et al* (35) reported that allelic variants in SLC30A3 were also associated with SCH in female participants. Regarding the ZNF family of genes, ZNF804A has also been demonstrated to be associated with SCH (36).

It has been reported that Zn serves an antioxidant protective role in patients with diabetes and patients undergoing hemodialysis, and it decreases inflammation, ameliorates mucociliary clearance, inhibits ventilator-induced lung injury, and regulates antiviral and antibacterial immunity in patients with COVID-19, respiratory syncytial virus, common cold and pneumonia (37-40). Moreover, Zn seems to be implicated in chronic liver disease through Zn-supported metalloproteinase enzymes (41). In addition, it has been reported that an anti-aging telomerase-activating nutraceutical preparation, containing vitamins D3 and C, *Centella asiatica* extract and Zn, can exhibit anti-aging properties on rat brains, by preserving or even enhancing telomere size and action (42,43).

Santa Cruz *et al* (44) suggested that low Zn concentrations may indicate that patients with SCH and bipolar disorder exhibit enduring oxidative stress; among the free radicals produced during oxidative stress, reactive oxygen species and reactive nitrogen species have been associated with the occurrence of SCH and bipolar disorder. Furthermore, it has been suggested that decreased Zn within the hippocampus may activate the hypothalamus-pituitary-adrenal (HPA) axis (45), while at the same time quinolinic acid, an NMDAR agonist, is produced; consequently, there is an elevation in NMDAR activity that results in increased glutamate release and neurotoxicity. Decreased Zn levels in patients with SCH and bipolar disorder who exhibit enduring oxidative stress do not permit effective inhibition of the NMDAR (46). Reactive oxygen species and reactive nitrogen species are the free radicals that are the most associated with SCH and bipolar disorder (47,48). Guo *et al* (49) identified a positive correlation between SOD, which exerts antioxidant enzyme activity against reactive oxygen species, and the copper (Cu)/Zn ratio, and Kunz *et al* (50) detected elevated concentrations of SOD in patients with SCH treated with antipsychotics vs. the controls. Furthermore, Hendouei *et al* (51) observed increased SOD activity in patients treated with clozapine compared with other antipsychotics. Al-Hakeim *et al* (52) reported that subjects with reduced levels of IL-10, magnesium, calcium and Zn exhibited generalized neurocognitive deficits within the context of deficit SCH due to the pathogenic IL-6/IL-23/Th17-axis. In another study by the same group (53), lower Zn levels, elevated lipid peroxidation and reduced antioxidant procedures were reported to predicted methamphetamine-induced psychosis.

3. Materials and methods

An extensive electronic search was conducted using the databases included in the National Library of Medicine (https://www.nlm.nih.gov/; accessed November 7, 2024), as well as PsycInfo (https://www.apa.org/pubs/databases/psycinfo; accessed November 7, 2024) and Google Scholar (https://scholar.google.com/; accessed November 7, 2024), for studies that have investigated Zn levels (including in serum and scalp hair) in patients with psychosis (such as SCH and bipolar disorder). In addition, studies in which the therapeutic effects of Zn in psychosis were demonstrated were searched for. In addition, the Cochrane Library (https://www.cochranelibrary.com/; accessed November 7, 2024) was searched for the references of retrieved articles. The exclusion criteria included studies on other psychiatric conditions, depression, anxiety disorders, other neurological conditions, drug abuse, and severe systematic or malignant conditions. Two authors read the abstracts, and when agreement could not be reached between the two, the senior author resolved the matter. There were no limitations regarding study design, the present narrative review includes meta-analyses, systematic reviews, randomized controlled trials (RCTs) and open-label studies; unpublished studies were not searched for.

4. Trials assessing Zn levels in psychosis

A number of studies have estimated Zn levels in patients with psychosis compared with in controls (Table I). Pfeiffer *et al* was

Table I. Studies assessing Zn levels in psychosis.

First author, year	Country	Subjects	Method	Results	(Refs.)
Srinivasan, 1982	UK	43 patients with SCH; 85 controls	Mean serum Zn levels detected by atomic absorption spectrometry	Mean serum Zn levels in patients with SCH were lower than those in healthy controls	(55)
Potkin, 1982	USA	10 ex-heroin addicts; 14 normal controls; 23 neuroleptic-treated patients with SCH	Mean CSF Zn concentrations detected with atomic absorption spectrometry	No significant differences in mean CSF Zn concentrations between drug-free patients with SCH, patients with SCH treated with neuroleptics and normal controls.	(57)
Vaddadi, 1986	UK	16 patients with SCH; 14 normal controls	Serum Zn levels detected with atomic absorption spectrometry	Serum Zn levels in patients with SCH under treatment with depot neuroleptics were reduced vs. healthy controls	(58)
Craven, 1997	Ireland	31 patients with SCH; 29 healthy controls	Serum Zn levels detected with atomic absorption spectrometry	Serum Zn levels in patients with SCH were reduced, but not significantly, vs. healthy controls	(59)
Herrán, 2000	Spain	62 patients with SCH; 62 healthy controls	Serum Zn levels detected with atomic absorption spectrometry	Serum Zn levels of patients with SCH on depot neuroleptics did not differ from those of healthy controls	(60)
Stanley and Wakwe, 2002	Nigeria	21 patients with depression; 20 patients with manic depression; 20 patients with SCH; 20 healthy controls	Serum Zn levels detected with atomic absorption spectrometry	Patients with mania and SCH were found to have lower serum Zn levels vs. healthy controls	(61)
Tokdemir, 2003	Turkey	44 patients with SCH with no criminal record; 44 patients with SCH with a criminal record	Mean plasma Zn values detected with an atomic absorption flame emission spectrophotometer	Mean plasma Zn values were significantly lower in criminal subjects vs. non-criminal subjects	(62)
Nechifor, 2004	Romania	56 patients with paranoid SCH; 20 healthy controls	Plasma Zn levels detected with a spectrophotometer	Patients with paranoid SCH exhibited lower plasma Zn levels vs. healthy controls; after antipsychotic treatment plasma Zn levels were increased	(63)
Yanik, 2004	Turkey	39 patients with SCH; 34 healthy controls	Plasma Zn levels detected with an atomic absorption spectrometer	Plasma Zn levels did not differ between patients with SCH and healthy controls	(64)
Farzin, 2006	Iran	40 patients with SCH; 50 healthy controls	Zn plasma levels detected with an atomic absorption spectrophotometer	Plasma Zn levels were significantly lower in patients with SCH vs. healthy controls; Cu/Zn ratio in patients with SCH was elevated	(65)
Devi, 2008	India	60 patients with SCH; 60 healthy controls	Mean plasma Zn levels detected with flame atomic absorption spectrometry	Mean plasma Zn levels were significantly lower in patients with SCH vs. healthy controls	(66)

Table I. Continued.

First author, year	Country	Subjects	Method	Results	(Refs.)
Rahman, 2009	Bangla-desh	30 patients with SCH; 30 healthy controls	Zn hair concentration detected with flame atomic absorption spectroscopy	Significant decrease in Zn hair concentration in patients with SCH vs. healthy controls	(67)
Ghanem, 2009	Egypt	30 patients with SCH; 20 healthy controls; 30 patients with major depressive disorder	Mean hair Zn levels detected with atomic absorption spectrophotometry	Mean hair Zn level were significantly lower in participants with SCH vs. healthy controls	(68)
Arinola, 2010	Nigeria	35 patients with SCH (20 on antipsychotics 15 drug-free); 30 healthy controls	Serum Zn levels detected with an atomic absorption spectrophotometer	Patients with SCH on anti-psychotics had elevated serum Zn levels vs. newly diagnosed drug-free patients with SCH and healthy controls	(69)
Kaya, 2012	Turkey	32 patients with SCH; 32 healthy controls	Serum Zn levels detected with an atomic spectrophoto-meter	Reduced serum Zn levels in patients with SCH vs. healthy controls	(70)
Cai, 2015	China	111 patients with SCH; 110 healthy controls	Serum Zn levels assessed by coupled plasma-mass spectrometry	Serum Zn levels were reduced in patients with SCH vs. healthy controls	(71)
Olabanji, 2011	Nigeria	60 patients with psychosis; 43 healthy controls	Zn hair concentration	Zn hair concentration did not differ from that of the controls	(72)
Vidović, 2013	Serbia	60 patients with SCH; 60 healthy controls	Plasma Zn levels detected with coupled plasma-mass spectrometry	Plasma Zn levels were not significantly higher in patients with SCH vs. healthy controls	(73)
Sharma, 2013	India	150 patients with SCH; 150 healthy controls	Serum Zn levels detected with an atomic absorption spectrophotometer	Serum Zn levels in patients with SCH were significantly higher vs. healthy controls	(74)
Asare, 2014	Ghana	81 patients with SCH; 25 healthy controls	Serum Zn levels detected with flame atomic absorption spectroscopy	Serum Zn levels were lower in patients with SCH vs. controls	(75)
Nawaz, 2014	Pakistan	35 patients with SCH (23 on antipsychotics and 12 drug free); 20 healthy controls	Serum Zn levels detected with inductive couple plasma optical emission spectroscopy	No statistical difference in serum Zn levels in newly diagnosed patients with SCH vs. controls and chronic patients with SCH	(76)
Liu, 2015	China	114 patients with SCH; 114 healthy controls	Serum Zn levels detected with coupled plasma-mass spectrometry	No significant differences were detected in serum Zn levels between patients with SCH and healthy controls	(77)
Lin, 2017	China	114 patients with SCH; 114 healthy controls	Serum Zn levels detected with coupled plasma-mass spectrometry	No significant differences in serum Zn levels were detected between patients with SCH and healthy controls	(78)

Table I. Continued.

First author, year	Country	Subjects	Method	Results	(Refs.)
Velthorst, 2017	Netherlands	20 individuals with SCH; 5 unaffected siblings of patients with psychosis	Zn deciduous teeth samples assessed via laser ablation inductively coupled plasma-mass spectrometry	Zn concentrations in teeth were not significantly reduced vs. controls during the perinatal period of subjects who later developed SCH	(79)
Modabbernia, 2016	Netherlands	9 individuals with SCH; 5 healthy controls	Zn deciduous teeth samples assessed via laser ablation inductively coupled plasma-mass spectrometry	Zn concentrations in teeth during the perinatal period did not differ between controls and subjects who later developed SCH	(80)
Chen, 2018	China	165 patients with SCH; 614 healthy controls	Serum Zn levels detected via colorimetric method	Lower serum Zn levels were detected in patients with SCH vs. healthy controls; risperidone treatment reduced Zn concentrations, with the effect being stronger in female participants	(81)
Li, 2018	China	158 patients with SCH; 669 healthy controls	Serum Zn levels detected with coupled plasma-mass spectrometry	No significant differences in serum Zn levels were detected between patients with SCH and healthy controls	(82)
Cao, 2019	China	105 patients with SCH; 106 healthy controls	Serum Zn levels detected with coupled plasma-mass spectrometry	No significant differences in serum Zn levels were detected between patients with SCH and healthy controls	(83)
Ma, 2020	China	99 patients with SCH; 99 healthy controls	Serum Zn levels detected with coupled plasma-mass spectrometry	Serum Zn levels were reduced in Chinese patients vs. healthy controls	(84)
de Souza Pessôa, 2020	Brazil	19 patients with SCH; 13 healthy controls; 19 patients with bipolar disorder	Zn serum levels detected with a mass spectrometer	No statistical difference in serum Zn levels was detected between patients with SCH and healthy controls; reduced serum Zn levels were observed in patients with bipolar disorder vs. healthy controls	(85)
Santa Cruz, 2020	Brazil	11 patients with SCH; 11 healthy controls; 18 patients with bipolar disorder	Serum Zn concentrations detected with coupled plasma-mass spectrometry	Serum Zn concentrations were significantly reduced in patients with SCH and bipolar disorder vs. healthy controls; a significantly higher Cu/Zn ratio was observed in patients with SCH vs. healthy controls	(44)
Uddin, 2021	Bangladesh	63 patients with SCH; 63 healthy controls	Serum Zn levels detected with flame atomic absorption spectrometry	Patients with SCH exhibited lower serum Zn levels vs. healthy controls	(86)
Awais, 2022	Pakistan	35 patients with SCH; 80 healthy controls	Serum Zn levels detected with atomic absorption spectrophotometry	Reduced serum Zn levels were detected in patients with SCH vs. healthy controls	(87)

Table I. Continued.

First author, year	Country	Subjects	Method	Results	(Refs.)
Lotan, 2023	Australia	86 SCH cases; 85 controls	Post-mortem prefrontal cortex specimens assessed via coupled plasma-mass spectrometry and western blotting	In post-mortem prefrontal cortex specimens no difference in Zn distribution was observed between patients with SCH and controls	(88)
Dos Santos, 2019	Brazil	22 patients with PD; 33 healthy controls	Zn hair samples	Higher levels of Zn in hair samples were associated with hallucinations, illusion and paranoid ideation in patients with PD vs. controls and patients with PD with no psychotic symptoms	(89)
Tabata, 2022	Japan	252 community-dwelling 14-year-old drug-naïve adolescents	Zn hair samples assessed via coupled plasma-mass spectrometry	Hair zinc levels were negatively associated with the Thought Problems Scale from the Child Behavior Checklist	(90)

Cu, copper; PD, Parkinson's disease; SCH, schizophrenia; Zn, zinc.

the first to report on reduced Zn serum level in patients with SCH (4,54). Subsequently, Srinivasan *et al* (55) reported that mean serum Zn levels in patients with SCH were lower than those in the control group, as assessed by atomic absorption spectrometry. However, Gillin *et al* (56) reported that patients with acute and chronic SCH, on or off treatment with various major tranquillizers, did not exhibit significant deviation from normal regarding concentrations of Zn in serum, urine, gastric fluid or hair. Potkin *et al* (57) observed that cerebrospinal fluid Zn concentrations did not differ significantly between drug-free patients with SCH, patients with SCH on antipsychotics and controls. By contrast, Vaddadi *et al* (58) reported that Zn serum levels in patients with SCH under treatment with depot neuroleptics were reduced compared with in controls, as assessed by atomic absorption spectrometry.

Craven *et al* (59) demonstrated that Zn serum levels in patients with SCH were not significantly reduced compared with in controls, as assessed using an atomic absorption spectrophotometer. In addition, Herrán *et al* (60) revealed that the Zn serum levels of patients with SCH on depot neuroleptics did not differ from those in the control group, as assessed with an atomic absorption spectrophotometry. In Stanley and Wakwe (61), Nigerian patients with mania and SCH were found to have lower serum Zn levels vs. controls, as assessed using an atomic absorption spectrophotometer. Tokdemir *et al* (62) revealed that mean plasma Zn values were significantly lower in criminal subjects with SCH when compared with noncriminal subjects with SCH, as assessed using an atomic absorption flame emission spectrophotometer. Nechifor *et al* (63) observed that patients with paranoid SCH exhibited lower Zn plasma levels compared with those in controls, and after treatment with haloperidol or risperidone there was an increase in Zn plasma levels as assessed by spectrophotometry. Notably, Yanik *et al* (64) reported that Zn plasma levels did not differ between Turkish patients with SCH and controls, as assessed by atomic absorption spectrometry. However, Farzin *et al* (65) revealed that mean Zn plasma levels were significantly lower in Iranian patients with SCH vs. controls, as assessed using an atomic absorption spectrophotometer; furthermore, the Cu/Zn ratio was elevated in the patients with SCH. Devi *et al* (66) demonstrated that the mean Zn plasma levels were significantly lower in Indian patients with SCH compared with in the controls, as assessed by flame atomic absorption spectrometry; furthermore, there was no significant difference among patients with SCH and with various symptomatology. In addition, Rahman *et al* (67) detected a significant decrease in Zn hair concentration in Bangladeshi patients with SCH vs. controls, as assessed by flame atomic absorption spectroscopy. Ghanem *et al* (68) also observed that the mean hair Zn level was significantly lower in participants with SCH vs. controls.

Arinola *et al* (69) reported that patients with SCH on antipsychotic medication exhibited elevated Zn serum levels compared with those in newly diagnosed drug-free patients with SCH and controls, as assessed with an atomic absorption spectrophotometer. Kaya *et al* (70) observed reduced serum Zn levels in patients with SCH compared with in controls, as assessed with an atomic spectrophotometer. Cai *et al* (71) assessed serum Zn levels with coupled plasma-mass spectrometry and revealed that they were reduced in Chinese patients with SCH vs. controls. By contrast, Olabanji *et al* (72) investigated patients with psychosis (most of them with SCH), and reported that Zn concentration in the hair of patients did not differ from that in controls. Vidović *et al* (73) also demonstrated that Zn plasma levels were not significantly higher in Serbian patients with SCH vs. controls, as assessed by coupled plasma-mass

spectrometry. However, Sharma *et al* (74) observed that serum Zn levels in patients with SCH were significantly higher than those in controls, as assessed using an atomic absorption spectrophotometer. Asare *et al* (75) found that serum Zn levels were lower in patients with SCH than in controls, as assessed with flame atomic absorption spectroscopy. Nawaz *et al* (76) did not identify a statistical difference in serum Zn levels between newly diagnosed Pakistani patients with SCH compared with in controls and chronic patients with SCH. Liu *et al* (77) also did not identify significant differences serum in Zn levels between Chinese patients with SCH and controls, as assessed by coupled plasma-mass spectrometry. In a study by Lin *et al* (78), serum Zn levels between Chinese patients with SCH and controls were not significantly different, as assessed by coupled plasma-mass spectrometry. Furthermore, Velthorst *et al* (79) reported that Zn concentrations in teeth were reduced, but not significantly, during the perinatal period of subjects who later developed SCH vs. controls; however, in a previous study, Zn concentrations in teeth during the perinatal period did not differ between controls and subjects who later developed SCH (80). Chen *et al* (81) detected lower serum Zn levels in patients with SCH compared with those in the control group, as assessed u the colorimetric method. Zn has been shown to be significantly decreased, particularly in mixed type SCH, acute SCH and SCH with schizotypal characteristics, following antipsychotic treatment.

Li *et al* (82) revealed no difference in serum Zn levels between Chinese patients with SCH and controls, as assessed by coupled plasma-mass spectrometry. In addition, Cao *et al* (83) revealed no statistical difference in serum Zn levels between Chinese patients and controls, as assessed with coupled plasma-mass spectrometry. By contrast, Ma *et al* (84) reported that there were reduced serum Zn levels in Chinese patients with SCH vs. controls, as assessed by coupled plasma-mass spectrometry. de Souza Pessôa *et al* (85) demonstrated that there was no statistical difference in serum Zn levels between patients with SCH and controls, whereas serum Zn levels were reduced in patients with bipolar disorder vs. controls, as assessed with a mass spectrometer. Santa Cruz *et al* (44) observed that serum Zn concentrations were significantly reduced in patients with SCH and bipolar disorder vs. controls, as assessed by coupled plasma-mass spectrometry; furthermore, a significantly higher Cu/Zn ratio was observed in patients with SCH than in the control group. In a study by Uddin *et al* (86), Bangladeshi patients with SCH exhibited lower serum Zn levels than controls, as assessed by flame atomic absorption spectrometry. In addition, Awais *et al* (87) observed reduced serum Zn levels in Pakistani patients with SCH than in controls. By contrast, Lotan *et al* (88) found no differences in Zn distribution between patients with SCH and controls in post-mortem PFC specimens. Dos Santos *et al* (89) reported that significantly higher levels of Zn in hair samples were associated with the presence of hallucinations, illusions and paranoid ideation in patients with PD vs. controls and in patients with PD who did not present these symptoms, as assessed with flame atomic absorption spectrometry. Furthermore, Tabata *et al* (90) reported that hair Zn levels (measured with coupled plasma-mass spectrometry) of drug-naïve adolescents were negatively associated with psychosis risk, as assessed by the Thought Problems Scale from the Child Behavior Checklist.

Two reviews have found similar results to the present review (91,92). Most of the studies assessed reported reduced Zn concentrations in patients with psychosis (such as SCH and bipolar disorder) vs. controls (4,44,54,55,59,61,63, 65-68,70,71,75,81,84,86,87). Notably, in three studies reduced Zn levels were found to be associated with increased Positive and Negative Syndrome Scale (PANSS) scores (68,79,84). In a number of studies there was no difference observed in serum, whole blood and plasma levels between patients with psychosis and controls (56,57,60,64,72,73,76-78,82,83,85,88). Just a few studies detected elevated Zn levels in patients with psychosis vs. controls (69,74,89); one of which found elevated levels in medicated patients, but not in newly diagnosed, non-medicated patients (69). Regarding treatment, serum Zn levels in patients with SCH under treatment with depot neuroleptics were found to be reduced vs. controls in one study (58), whereas there was no difference found in another study (60). Nechifor *et al* (63) observed that patients with paranoid SCH after treatment with haloperidol or risperidone exhibited an increase in plasma Zn levels; however, Chen *et al* (81) revealed that risperidone treatment reduced Zn concentrations, with the effect being stronger in female participants, whereas no association was observed when olanzapine treatment was administered. Finally, it is worth noting that valproate has been reported to stabilize decreased Zn and potassium concentrations when synchrotron radiation X-ray microfluorescence spectroscopy was used to compare trace element levels in neural progenitor cells derived from two clones of induced pluripotent stem cell lines from a patient with clozapine-resistant SCH and two controls (93).

5. Treatment of psychosis with Zn

Several studies have demonstrated the therapeutic effects of Zn on psychosis. In a 6-week double blind placebo-controlled study, Mortazavi *et al* (94) reported that patients with SCH exhibited marked reductions in the PANSS subscale scores, aggression risk subscale and PANSS total score when they received risperidone treatment combined with Zn sulfate compared with those receiving risperidone treatment plus a placebo.

Pfeiffer and Sohler (95) proposed that adequate doses of B6 (up to 3.0 g/day) and Zn relieved the psychotic symptoms in patients who excreted kryptopyrrole; however, discontinuation of B6-Zn resulted in a rapid return of serious psychotic symptoms within 48 h. Notably, it has been observed that the rate of intestinal Zn absorption is augmented when B6 and Zn are supplied simultaneously (96). Rohde *et al* (97) described the case of a male patient with psychosis, Pica syndrome and hippocampal sclerosis, who was treated successfully after combined treatment with carbamazepine, clozapine, diazepam and Zn. In a study by Russo and de Vito (98), the use of Zn in combination with vitamins C, E and B6 in patients with SCH resulted in a reduction in anxiety, but not depression or overall psychopathology. In another study, Russo (99) reported an improvement in overall bipolar symptomatology following Zn and antioxidant therapy.

Czerniak and Haim (100) reported that three phenothiazine compounds (chlorpromazine, thioridazine and perphenazine) increased the total brain Zn uptake in rats and mice (more so in rats) that were injected with Zn

chloride Zn 65. Alizadeh *et al* (101) demonstrated that Zn supplementation during pregnancy mitigated lipopolysaccharide (LPS)-induced abnormalities in working memory, as well as GAD67 mRNA levels, in male rats. Furthermore, Mousaviyan *et al* (102) revealed that prenatal supplementation of Zn alleviated the LPS-induced rat model of maternal immune activation; consequently, prenatal LPS exposure could be mitigated by Zn supplementation during pregnancy. Moreover, Savareh *et al* (103) used an animal model of SCH and showed the beneficial effect of Zn supplementation during pregnancy to protect against LPS-induced inflammation in the hippocampus of adult rats. Similarly, Coyle *et al* (104) reported that, in mice, maternal dietary supplementation with Zn mitigated LPS-induced abnormalities in object recognition. Onaolapo *et al* (105) observed that Zn, being administered on its own or together with antipsychotics, was associated with reversal of ketamine impact. In addition, Joshi *et al* (106) revealed that the administration of Zn in rats resulted in decreased stereotypic movements, mean velocity, distance travelled and increase in rest time in comparison with the control group. Moreover, Zn combined with amphetamine resulted in antipsychotic qualities (a reduction in locomotor activity and decreased stereotypic movements).

6. Models explaining the link between altered Zn homeostasis and psychosis

It has been proposed that genetic susceptibility and prenatal/perinatal risk issues (viral infection, LPS-induced inflammation, malnutrition, hypoxia and maternal stress) may result in the individual being more susceptible to environmental stressors (childhood trauma, migration, substance abuse and urbanicity) (107-112). Therefore, following trauma (108,109), gene-environment interplay (108) and epigenetic mechanisms (110,111) may alter the expression of genes implicated in neurodevelopment, the stress reaction and synaptic transmission, and could increase the incidence of psychosis through their influence on neurotransmitters, the immune response and subsequent oxidative stress (112). Within this context, elevated glucocorticoid signaling has been found to induce acceleration of DNA methylation age, leading to hippocampal atrophy (110). Both DNA hypermethylation and hypomethylation, non-coding of microRNAs and long-chain non-coding RNAs, and histone modification are among the types of epigenetic mechanisms that have been reported to be associated with SCH (111). In addition, Zn deficiency may result in oxidative stress and abnormal immune response, which leads to cell apoptosis (113).

Notably, it has been indicated that early adversity may alter the HPA axis, leading to an abnormal stress reaction (114), and amplified sensitivity to potential stressors in adolescence and adulthood (115-117), thus stimulating the incidence of SCH symptoms through dopaminergic hyperactivity (118). In addition, extended contact with stress and glucocorticoids may ensue a decrease in hippocampal volume (119) and decreased brain-derived neurotrophic factor levels, as detected in SCH (120-125).

Individuals who experience metal dysregulation during early placental nutrition are more susceptible to memory disorders and psychotic symptomatology (79,80,126). Velthorst *et al* (79) reported that lower Zn levels (as assessed with tooth biomarkers) in the final prenatal weeks were associated with significantly elevated positive and general PANSS scores. Notably, contact with inflammation throughout gestation may have perpetuating behavioral and neuronal outcomes in children (127). Placental inflammation during fetal development has been suggested to account for nutritional disruption and metal dyshomeostasis of the fetus (128,129); in a previous study, fetal Zn deficiency has been reported to induce epigenetic alterations in the gene coding for the metal transporter, metallothionein-2, which also regulates other metals (130). In addition, Tellez-Merlo *et al* (131) revealed that LPS-treated rats developed behavioral abnormalities along with elevations in Zn and nitric oxide brain concentrations; furthermore, post-pubertal neuronal hypertrophy was detected in the PFC and basolateral amygdala, and decreased spine density in the nucleus accumbens. In a study by Camacho-Abrego *et al* (132), an increase in nitric oxide, Zn and metallothionein levels was found in pre-pubertal rats with neonatal ventral hippocampus lesions (an animal model of SCH), particularly in the lesion. Post puberty, the observed changes were considered to be the final result of the excitotoxic neonatal ventral hippocampus lesions, resulting in lower levels of the neuroprotective molecule metallothionein in the PFC, and an increase in the levels of nitric oxide and Zn in the PFC, both of which have an excitotoxic effect at high levels. In another study by Savareh *et al* (103), an animal model of SCH was used to demonstrate the beneficial effect of Zn supplementation during pregnancy to protect against LPS-induced inflammation in the hippocampus of adult rats. It has been proposed that decreased Zn levels within the hippocampus may result in the activation of the HPA axis (45), and the concurrent production of the NMDAR agonist quinolinic acid; consequently, there is an elevation in NMDAR activity, which results in increased glutamate release and neurotoxicity. Decreased Zn levels in patients with SCH and bipolar disorder who exhibit enduring oxidative stress do not permit effective inhibition of the NMDAR (46). There are two ways that the inhibitory effects of Zn on NMDARs unfold (Fig. 1). First, allosteric inhibition is caused by Zn binding to the GluN2A subunit of the NMDAR, which diminishes the possibility of the channel opening. Second, low-affinity binding to pore-lining residues of NMDAR blocks the channel.

The hypothesis of NMDAR hypofunction in SCH originated from the observation that a sub-class of non-competitive NMDAR antagonists, phencyclidine (PCP) and ketamine, induces behaviors suggestive of all three symptoms of schizophrenia in human subjects (positive, negative, and cognitive) (33,133,134) (Fig. 1). Functional NMDAR blockade appears to occur in cortical GABAergic interneurons in both PCP/ketamine drug abuse and anti-NMDAR encephalitis.

7. Conclusions, clinical implications and future perspectives

Zn is considered a possible diagnostic biomarker associated with SCH since its altered homeostasis can contribute to abnormal glutamatergic neurotransmission, inflammation, neurodegeneration and autoimmune abnormalities. It has been proposed by researchers that a number of patients with SCH could benefit from the use of Zn alone (94), or in combination with vitamins

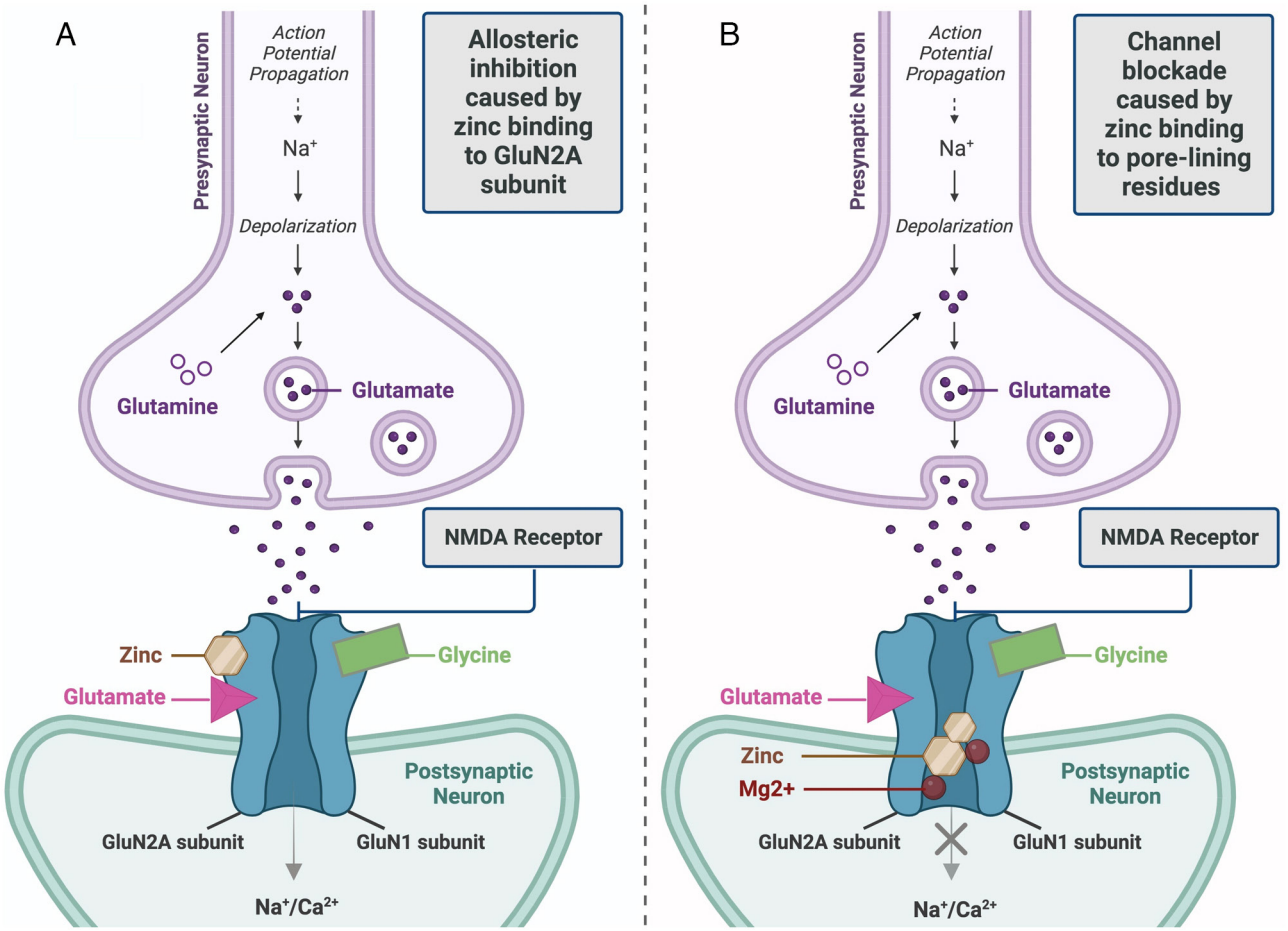

Figure 1. Schematic representation of the inhibitory effects of Zn on NMDARs. (A) High-affinity binding of Zn to the GluN2A subunit of NMDAR causes allosteric inhibition and attenuates channel opening. (B) Low-affinity binding of Zn to pore-lining residues of the NMDAR blocks the channel. Zn deficiency and disrupted Zn transport dynamics (e.g., in the presence of SLC39 gene mutations) could account for abnormal NMDAR function and altered glutamatergic neurotransmission in schizophrenia. The model of NMDAR hypofunction and the consequent inability to downregulate prefrontal glutamatergic neurons is widely accepted by researchers and clinicians, especially since the induction of schizophrenia-like symptoms has been detected following the administration of ketamine and phencyclidine in healthy subjects. Created in BioRender. Stefanou, M. (2025) https://BioRender.com/mcf93wr. NMDAR, NMDA receptor; Zn, zinc.

C, E and B6 (96,98,99). Furthermore, studies have suggested that prenatal supplementation of Zn during the gestation period may mitigate LPS-induced rat models of maternal immune activation (101-104). Notably, in a number of animal studies, Zn has been shown to exert an antipsychotic therapeutic effect on rats and mice (100,105,106), and when supplemented in rats during pregnancy it may mitigate LPS-induced abnormalities in working memory, GAD67 mRNA levels, object recognition and inflammation in the hippocampus (101-103). More studies are required to determine whether Zn can also mitigate LPS-induced abnormalities in humans.

Notably, there are just a few human RCTs exploring the effect of Zn treatment on patients with psychosis. Mortazavi *et al* (94) demonstrated an increased antipsychotic efficacy (positive results regarding PANSS subscale scores and aggression) of a combination of Zn and risperidone in patients with psychosis vs. controls. Similar results to those of Mortazavi *et al* (94) were reported by Tokdemir *et al* (62); this previous study reported that mean plasma Zn values were significantly lower in criminal subjects with SCH vs. noncriminal subjects with SCH. Furthermore, Walsh *et al* (135) reported that serum Cu/plasma Zn concentration in young men with violent behavior was 1.40 compared with 1.02 in noncriminal controls. Estimating Zn and Cu plasma concentrations in patients with psychosis exhibiting aggression, and treatment of these patients with Zn may prove helpful in the mitigation of this symptom. However, there were limitations in the study by Mortazavi *et al* (94): The sample size was small, side effects were not noted in detail, there was a short follow-up period, and plasma Zn concentrations were not available. In the study by Russo and de Vito (98) an improvement only in anxiety was observed in patients with SCH following administration of Zn in combination with vitamins C, E, and B6. Future studies that include an increased number of patients from various countries, with a longer follow-up period than that used in the previous study (94) could provide more information regarding the therapeutic use of Zn in psychosis. Furthermore, a specific treatment target for these studies could be aggression in patients with psychosis, as it was demonstrated in Mortazavi *et al* (94) and Tokdemir *et al* (62). In conclusion, Zn may help a number of patients with psychosis by alleviating psychotic symptoms; consequently, patients may demonstrate better adherence to treatment (17), while the quantity of psychotic drugs needed could be reduced leading to fewer adverse effects.

Acknowledgements

Not applicable.

Funding

No funding was received.

Availability of data and materials

Not applicable.

Authors' contributions

CT and ER contributed to the conception and design of the review, and the acquisition, analysis or interpretation of data that were included. CT and ER were also involved in the drafting of the manuscript, and in revising it critically for important intellectual content. MD, MIS, EA, MM, VZ, MP, NS and DAS contributed to the design of the review. Data authentication is not applicable. All authors read and approved the final version of the manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

DAS is the Editor-in-Chief for the journal, but had no personal involvement in the reviewing process, or any influence in terms of adjudicating on the final decision, for this article. The other authors declare that they have no competing interests.

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