

New Research Strategy for Measuring Pre- and Postnatal Metal Dysregulation in Psychotic Disorders

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While previous studies have found evidence for detrimental effects of metals on neurodevelopment, the long-term effects on mental health remain unclear. The objective was to explore the effect of early metal exposure on risk of psychotic disorder and on symptom severity following illness onset. Through the use of validated tooth-biomarkers, we estimated pre- and postnatal exposure levels of essential elements (copper, magnesium, manganese, and zinc) and elements associated with neurotoxicity (lead, arsenic, lithium, and tin). We found consistently higher levels of lithium in patients compared to controls. Higher levels of magnesium and lower levels of zinc were associated with more severe psychopathology over 20 years after metal exposure. The results show promise for the use of teeth biomarkers in examining early environmental risk for psychosis and underscore the relevance of studying metal exposure during critical neurodevelopmental periods.

Key words: environmental exposure/neurodevelopmental disorders/psychosis/tooth/trace elements

Introduction

The neurodevelopmental model posits that psychotic disorders may be a consequence of interactions between early neurological abnormalities and later maturational events.¹ Metal exposure is of particular interest in this context because low-level exposure is ubiquitous, and unlike other environmental factors studied in schizophrenia (eg, immigration and preterm birth), it is modifiable. Early life low-level exposure to metal toxicants, such as lead, arsenic, and tin, has well-documented adverse effects on neurodevelopment.^{2–4} Even essential nutritive elements (eg,

zinc, copper, manganese) may be detrimental to healthy neurodevelopment in excess as well as deficiency.^{5–7}

For this proof-of-concept study, we investigated whether it was possible to detect effects of early exposure to neurotoxicants and nutritive elements with an established influence on neurotransmitter, neuropsychological, and behavioral processes similar to those found in psychotic disorders.^{2,3,5,6,8–21} For example, an excess of both copper and lithium has been linked with psychotic behavior^{14,22}; Wilson's disease, a genetic disorder that causes excessive copper accumulation, is often initially misdiagnosed as schizophrenia.²² Patients with schizophrenia have been found to have lower levels of zinc than healthy controls,^{9,23} and higher delta-aminolevulinic acid levels (marker of prenatal lead exposure) were associated with increased risk of schizophrenia.¹⁷

Remarkably, despite the strong relationship between early metal exposure and abnormal neurodevelopment, biological plausibility, and importance for the neurodevelopmental model, the impact of early life exposure to metals has not been studied systematically. Metal exposure has been generally measured after disease onset using blood or urine assays that do not uncover historical exposure during fetal and early childhood critical developmental windows. Even when exposure was measured during pregnancy, it tended to be done indirectly (eg, through maternal blood samples) and without accurate measurements of exposure timing or changes in exposure over time.¹⁷

It is now possible to overcome these limitations by objectively reconstructing the timing and dose of early life (pre- and postnatal) environmental metal exposure. Through the use of biomarkers in shed deciduous teeth, we are able to derive detailed temporal profiles of exposure to multiple

metals. In the present study, we were specifically interested in exploring and generating hypotheses about the association between metal exposure and psychotic symptom severity in patients diagnosed with schizophrenia and the differential exposure levels of patients and unaffected siblings (a genetically high-risk control sample).

Methods

To determine the effects of timing and dose of prenatal and early childhood exposure to metals associated with neurotoxicity lead, arsenic, tin, and lithium and essential elements manganese, copper, zinc, and magnesium on the development and severity of psychotic disorders/experiences, we analyzed shed deciduous teeth from 20 individuals with a *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, diagnosis of schizophrenia and 5 unaffected siblings of patients with psychosis, ascertained from the referrals to the Academic Medical Center in Amsterdam from 2014 to 2017. Nine patients took part in an earlier, smaller explorative analysis.²⁴

Deciduous teeth (ie, “baby teeth”), kept by parents and voluntarily provided to researchers, were evaluated using the biomarker method of laser ablation inductively coupled plasma mass spectrometry, generating integrated, longitudinal 1- to 2-week metal exposure estimates in utero and during early childhood. For full description and validation, see articles.^{10,25–30} The time-varying difference between early-life (–4 to 6 months) metal concentrations, as measured in the tooth biomarker, and case/control designation was evaluated using a distributed lag model (DLM).³¹ Severity of positive symptoms, negative symptoms, and general psychopathology were assessed by the Positive and Negative Symptom Scale (PANSS).³² We restrict the data from –120 days before birth to 40 days postnatally due to sparse data at later time points. In the analysis, a critical window is defined as a time point in the DLM model when the 95% confidence band (shaded) does not cross the 0 line of no association. A *P* value below .05 was considered statistically significant. The vertical bars represent Holm-Bonferroni corrections for multiple comparisons, and because the sample size is small, associations are not likely to remain significant after this stringent adjustment. However, we prefer to take a conservative approach and display this limitation clearly in the results. In all analyses, sex and biological age were adjusted for.

Results

Sample characteristics

The shed deciduous teeth of 20 patients with a psychotic disorder and 5 controls (whose siblings had schizophrenia) were analyzed. The patient group was comprised of 18 (90%) males and 2 (10%) females (mean age = 24.35, SD = 3.78). The control group was comprised of one

(20%) male and four (80%) females (mean age = 28, SD = 8.40). Ninety-one percent of the sample was never married/never lived together with a partner. IQ measures were available for 11 patients (mean IQ = 99.1; SD = 11.3; range = 75–112) and 5 controls (mean IQ = 114; SD = 19.2; range 87–132). Twenty-one out of 23 participants reported being Dutch (data were missing on two individuals).

The patient group mean had mean PANSS positive subscale = 15.06(SD = 8.90), mean PANSS negative subscale = 15.53(SD = 6.99), mean PANSS general psychopathology subscale score = 31.82(SD = 11.51), and mean PANSS total score = 62.41(SD = 25.07).

Early metal dysregulation and psychosis

Patients had consistently higher lithium levels than controls, a trend that reached statistical significance from about –12 to 4 weeks before birth and the first month after birth (figure 1a). Patients had consistently higher concentrations of magnesium and lower concentrations of zinc compared to controls, although these results were not statistically significant.

Early metal exposure and psychotic symptom severity

To examine whether early life metal exposure also has a long-term effect on clinical severity in individuals diagnosed with a psychotic disorder, we subsequently correlated the tooth-matrix biomarkers with the severity of positive, negative, and general symptom scores of the PANSS in the patient sample (all assessed within the first 10 years of the illness).³² Higher magnesium levels in the first postnatal month were significantly associated with higher levels of general ($r = 0.18$), positive ($r = 0.20$), and negative ($r = 0.15$) PANSS scores. (figure 1e, 1h, 1k). As seen in figure 1g and 1j, elevated lithium levels at the beginning of the third trimester were associated with positive ($r = 0.22$) symptoms and significantly with negative ($r = 0.28$) symptoms. Lower zinc concentrations in the final prenatal weeks were associated with higher positive ($r = -0.28$) and general ($r = -0.25$) PANSS scores (figure 1i and 1f). None of the other metals showed significant associations with general symptom severity in this exploratory analysis. All distributions of metal exposure in the sample are summarized in table 1.

Discussion

Among the body of literature investigating environmental factors that may increase the risk for psychotic disorders, few, if any, studies have examined early metal exposure in relation to the expression and severity of psychotic symptoms decades later. The proof-of-concept findings point to pre- and postnatal case-control differences for three metals (lithium, zinc, and magnesium). Taken together

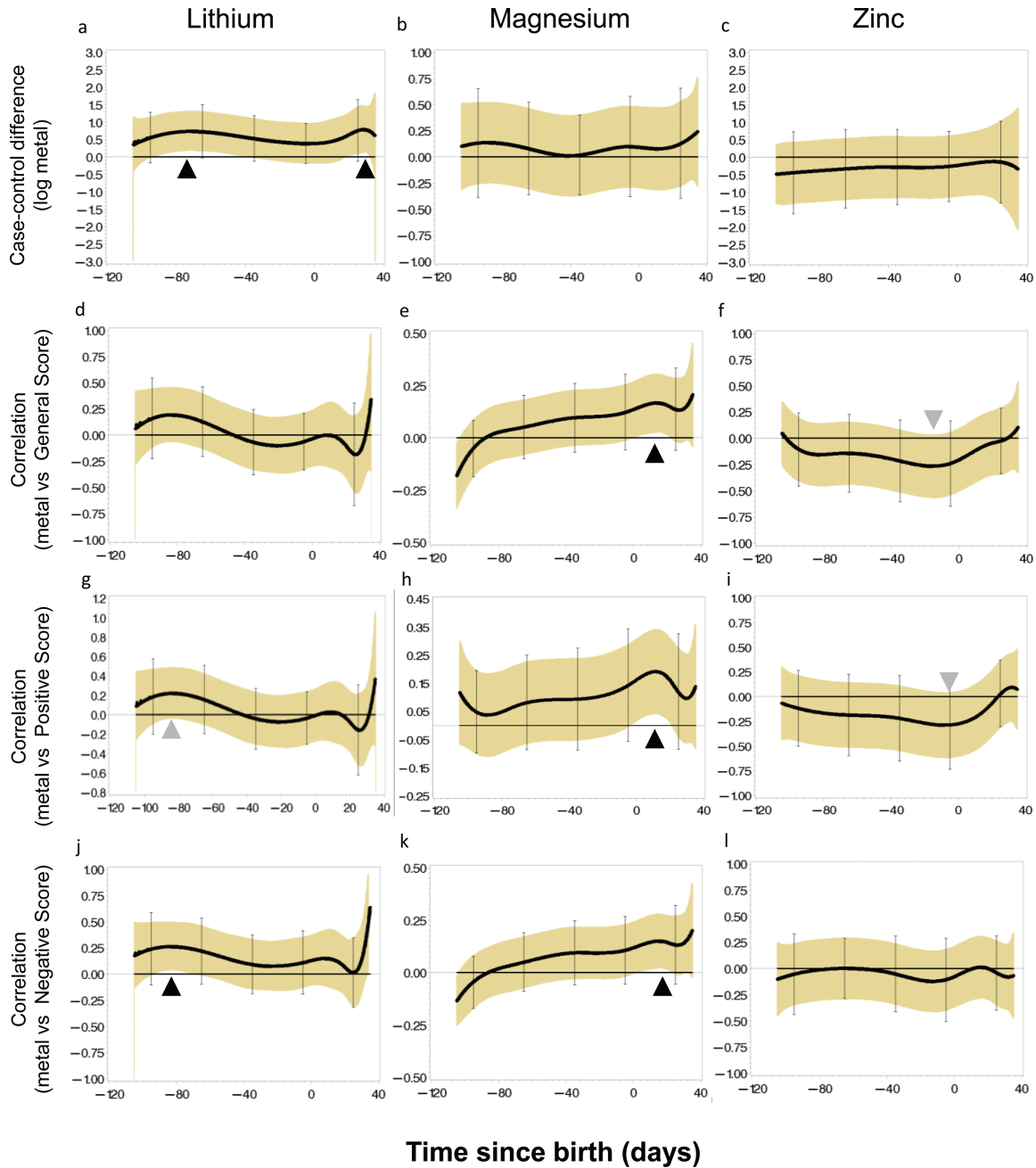


Fig. 1. Association of lithium, magnesium and zinc uptake with schizophrenia diagnosis and severity measures. Lithium and magnesium uptake were consistently higher in cases (A) and associated with increased severity (B–D) but only at distinct developmental periods (black arrowheads). Zinc was generally lower in cases and inversely associated with severity, approaching significance at specific time points (gray arrowheads).

with results from a previous explorative study showing lower pre- and postnatal levels of manganese and copper in patients diagnosed with schizophrenia,²⁴ these results suggest that early life metal dysregulation is a potential important contributor of risk to psychotic disorder.

Interestingly, levels of lithium were elevated in the patient group during two critical neurodevelopmental windows, and higher levels of lithium were consistently associated with higher symptom severity over 20 years later. There are several possible explanations for this

finding. First, although we did not have data on parental medication use, it is possible that maternal medication may have contributed to elevated lithium concentrations in the patient group—especially because the effects of lithium levels on symptom severity were significant only during the prenatal period. However, lithium uptake does not necessarily indicate medication because lithium presents in other sources such as water and food.¹⁴ Medication use could instead be a proxy of increased genetic risk, and lithium levels alone may not have a direct causal effect

Table 1. Distribution of Element Exposure

Variable	Minimum	Maximum	5th Pctl	Median	95th Pctl
Zn	0.0186311	0.1184584	0.0263683	0.0494432	0.0825733
Cu	0.000099816	0.0761735	0.0006245	0.0027339	0.0132552
Li	3.59E-06	0.001	2.426E-05	0.0001687	0.0004843
Mg	0.6369624	2.2494252	0.8319266	1.4670307	1.8343537
Mn	0.000069174	0.0571423	0.0016282	0.0047491	0.0092598
Pb	0.000049718	0.00626	0.0001787	0.000903	0.0029021
Sr	0.1855598	1.1205665	0.251711	0.4454806	0.7570979
Sn	6.97E-06	0.0016906	2.368E-05	0.0001714	0.0005196

Zn, zinc; Cu, copper; Li, lithium; Mg, magnesium; Mn, manganese; Pb, lead; Sr, strontium; Sn, tin.

on psychosis. However, we did find significant differences between lithium levels in patients and a genetically high-risk control group, potentially discounting this explanation. These elevated levels of lithium may also partly explain the association between magnesium and increased symptom levels, because lithium has been found to increase magnesium levels in the blood.³³

A potential mechanism for metal dysregulation during fetal development is placental dysregulation. Recent evidence from human and animal studies suggests that under stress, placental transfer of nutrients to the fetus is disrupted, and factors such as prenatal stress and placental inflammation increase hyperactivity in offspring.^{34,35} In the case of monozygotic twins sharing a placenta, external stressors that affect only one twin may induce epigenetic modification; notably, in one study, fetal zinc deficiency induced epigenetic alterations in the gene coding for the metal transporter, metallothionein-2, which also regulates other metals.³⁶

We urge caution in interpreting these findings due to the small sample size, and the diversity of the sample under study. Despite the small sample size, with few controls compared to patients, we were able to uncover significant associations between pre- and early postnatal metal concentrations and the presentation and severity of psychotic disorders two decades later, generating interesting hypotheses that could be further explored in future studies. The neurodevelopmental model posits that early life events may affect the risk of developing a psychotic illness, and the tentative results of this study point to a class of preventable public health relevant exposures that have not been investigated in reference to psychosis. Future larger studies are needed to extend the preliminary findings we report here. In these studies, it will be important to explore the impact that other environmental factors, such as low socioeconomic status, upbringing in rural vs urban neighborhoods (potentially associated with increased exposure to certain toxins), and (physical) health of the mother during pregnancy may have on the observed differences.

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