Correlation of trace metal and Depression

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The authors made the following contributions. Hao Chen: Conceptualization, Writing - Original Draft Preparation, Writing - Review & Editing.

Abstract

This study explores the link between Major Depressive Disorder (MDD) and essential trace elements, analyzing data from the National Health and Nutrition Examination Survey (NHANES). MDD, affecting an estimated 280 million people worldwide, manifests through diverse symptoms impacting emotional, physical, and cognitive well-being. The focus is on trace elements necessary for metabolic functions, as alterations in these elements are implicated in MDD's development. Utilizing NHANES data, the study examines urine samples from participants aged 3 and above for trace metal analysis, employing mass spectrometry for precise quantification. Depressive symptoms are assessed via the PHQ-9 questionnaire, a recognized depression screening tool. By investigating the relationship between trace metals and MDD symptoms, this research aims to enhance our understanding of MDD's etiology and inform potential treatment approaches.

Keywords: Trace metal, Depression

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Introduction

Major Depressive Disorder (MDD) is a prevalent yet severe mood condition marked by experience of low mood and negative emotions for a long period of time(American Psychiatric Association, 2013). In 2019, approximately 280 million individuals, which includes 5% of the adult population, were estimated to have experienced depression(“GBD Results,” n.d.). According to the statistics from the United States National Institute of Mental Health, around 21.0 million adults in the United States experienced at least one major depressive episode, accounting for 8.3% of all U.S. adults(“Major Depression - National Institute of Mental Health (NIMH),” n.d.). MDD is a multifaceted and intricate condition, which can result in impairment of psychosocial functioning and quality of life(Saragoussi et al., 2018). In addition to depressed feelings, patients with MDD may experience a wide range of physical and cognitive symptoms, including feelings of sadness, irritability, loss of interest or pleasure in activities, changes in appetite or weight, sleep disturbances, fatigue, feelings of worthlessness or guilt, difficulty concentrating, and thoughts of death or suicide(American Psychiatric Association, 2013). Etiology of MDD includes biological, environmental, and personal vulnerabilities(National Research Council (US) and Institute of Medicine (US) Committee on Depression, England, & Sim, 2009). Lately, there has been growing attention towards metallomic research in psychiatry, with a focus on examining the involvement of essential trace elements in both the development and progression of MDD symptoms. An essential trace element refers to a mineral or dietary element necessary in small amounts for an organism’s proper growth, development, and physiology(Bowen, 1966). These elements are vital for conducting essential metabolic activities in organisms. Examples of essential trace metals in human nutrition include Na, K, Mg, Ca, Fe, Mn, Co, Cu, Zn and Mo(Zoroddu et al., 2019). The trace metals play important catalytic and structural roles. These elements facilitate essential biochemical reactions by serving as cofactors for numerous enzymes and as stabilizing agents for the structures of enzymes and proteins(Prashanth, Kattapagari, Chitturi, Baddam, & Prasad, 2015). Alterations in the accumulation or absence of these components can trigger alternative metabolic pathways, potentially contributing to various neurodevelopmental diseases and conditions (Yui, 2016). Baj et al. (2013) conducted an narrative review of the relationship between levels of selected trace elements in the serum of individuals with MDD and the initiation and advancement of this mental health disorder(Baj et al., 2023). Findings of this review reveal that the levels of metal content in the body are related to the outcomes of individuals with MDD in various ways. For example, Li et al. (2020) has demonstrated that elevated levels of copper can disrupt the functioning of NMDA receptors, contributing to cognitive deficits in MDD(Li et al., 2020). Increased copper concentrations can also impair AMPA receptor function, leading to disruptions in glutamatergic transmission, supporting the Glu hypothesis of depression(Gerhard, Wohleb, & Duman, 2016; Peters et al., 2011; Styczeń et al., 2017). Although there relationship between the trace metals in human serum and MDD has been widely studied, there are limited research on the results of trace metal and how they relate to the frequency of MDD symptom. This study aims to reveal the relationship between the two.

Table 1

Racial Demographics

Var1	Freq
Mexican American	263
Non-Hispanic Asian	262
Non-Hispanic Black	430
Non-Hispanic White	636
Other	104
Other Hispanic	164

Methods

Dataset

This research employs a cross-sectional methodology, leveraging data from the National Health and Nutrition Examination Survey (NHANES) conducted by the US National Center for Health Statistics. Objectives of the survey encompass evaluating the health and nutritional conditions of individuals across the United States, as well as identifying the prevalence of significant diseases and their risk contributors. The NHANES database includes a wide array of information, such as demographic specifics, nutritional insights, results from physical exams, laboratory test results, participant questionnaire answers, and confidential data.

Participants

Participants aged 3 to 5 years, along with a one-third subset of those aged 6 and above, were considered eligible for this study. Due to privacy concerns, access to urine lead data for the 3 to 5 age group and urine strontium and uranium data for those aged 3 and above is restricted to the NCHS Research Data Center. However, the dataset does include urine lead data for participants aged 6 and older, as well as urine barium, cadmium, cesium, cobalt, manganese, molybdenum, antimony, thallium, tin, and tungsten for all eligible participants aged 3 and above. For further details on accessing urine lead, strontium, and uranium data, refer to the Analytic Notes.

Description of Laboratory Methodology for Trace Metal

This technique accurately quantifies various metals in urine samples by utilizing mass spectrometry, preceded by a straightforward dilution preparation of the samples. The process begins with the introduction of liquid specimens into the mass spectrometer via an inductively coupled plasma (ICP) ionization source. Here, a nebulizer converts the sample into fine droplets within an argon gas stream. These droplets then proceed into the ICP, where they are ionized. The ions navigate through a focusing area, enter the dynamic reaction cell (DRC), pass through the quadrupole mass filter, and ultimately, the detector sequentially counts them in rapid succession. This method enables the precise identification of individual isotopes for each element analyzed.

Detection Limits for Trace Metal

The detection limits remained uniform across all analytes within the dataset. For each analyte, two specific variables are furnished. A variable name ending with "LC" (for example, URDUBALC) signifies if the measurement fell below the detection limits : a "0" value indicates the measurement was at or above this limits, whereas a "1" denotes it was below. Conversely, the variable starting with URX (for example, URXUBA) reports the actual measurement for the analyte. When the measurement for an analyte is below the detection limit (for instance, URDUBALC=1), a predetermined substitute value is used in its place. This substitute value is calculated as the detection limit divided by the square root of 2.

Depression Assessment

The assessment of participants' depressive symptoms was conducted using the Patient Health Questionnaire-9 (PHQ-9), a nine-item instrument designed for depression screening. The PHQ-9 is recognized as a reliable and validated method for detecting common depression and related disorders, especially in primary care environments(Kim, Choi, Lim, & Hong, 2016). This questionnaire includes nine prompts, with responses scored based on the Diagnostic and Statistical Manual of Mental Disorders (DSM) criteria as follows: 0 ("Never"), 1 ("A few days"), 2 ("More than a week"), and 3 ("Almost every day"), leading to a total possible score between 0 and 27. A score within the 0-9 range is considered indicative of a non-depressive state, whereas a score of 10 or higher suggests the presence of depression. The PHQ-9 has demonstrated high sensitivity (0.88) and specificity (0.85) for identifying depression at a threshold score of 10 or above(Levis, Benedetti, & Thombs, 2019).

Data analysis

We used R (Version 4.3.2; R Core Team, 2023) and the R-packages *dplyr* (Version 1.1.4; Wickham, François, Henry, Müller, & Vaughan, 2023), *ggplot2* (Version 3.5.0; Wickham, 2016), *kableExtra* (Version 1.4.0; Zhu, 2024), *knitr* (Version 1.45; Xie, 2015), *papaja* (Version 0.1.2; Aust & Barth, 2023), *readr* (Version 2.1.5; Wickham, Hester, & Bryan, 2024), *shiny* (Version 1.8.0; Chang et al., 2023), and *tinylabels* (Version 0.2.4; Barth, 2023) for all our analyses.

This is a plot showing the correlation of LCsum and DPQsum. As shown in the plot 1, we see…

The Spearman test result for the type of trace metal exceed detection limits and the frequency of depression symptom shows a correlation coefficient (rho) of 0.18 with a p-value of 0.04.

```
##    Min. 1st Qu.  Median    Mean 3rd Qu.    Max.
##   7.000  10.000  10.000   9.961  11.000  11.000
```

```
##    Min. 1st Qu.  Median    Mean 3rd Qu.    Max.
##   11.00   12.00   14.00   15.09   18.00   27.00
```

Means of LCsum is 9.96, which means participants have an average of 10 types of trace metal above detection limits. For the same people group, their average score for frequency of depression symptom is 15.09.

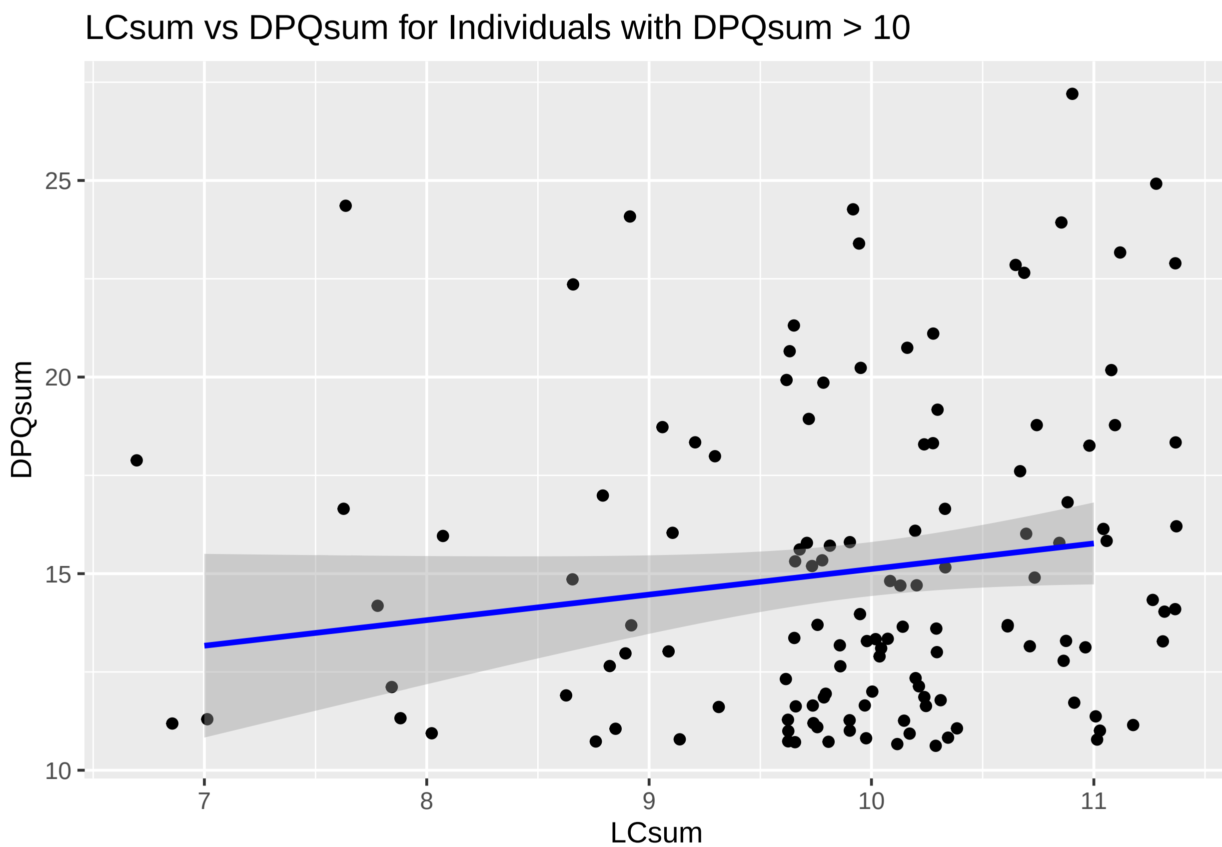

Figure 1. LCsum vs DPQsum for Individuals with DPQsum > 10

Results

Discussion

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