Manganese Exposure and Metabolic Syndrome

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Manganese (Mn) is an essential element acting as a co-factor of superoxide dismutase, and it is potentially beneficial for cardiometabolic health by reducing oxidative stress. Metabolic syndrome (MetS) is defined as a cluster of metabolic alterations that contributes to a higher risk of cardiovascular disease (CVD), type 2 diabetes (T2D), and all-cause mortality. Association between Mn exposure from diet and environment, and the risk of MetS are described here.

manganese micronutrient metal exposure metabolic syndrome meta-analysis

1. Introduction

Metabolic syndrome (MetS) is defined as a cluster of metabolic alterations that contributes to a higher risk of cardiovascular disease (CVD), type 2 diabetes (T2D), and all-cause mortality [1][2]. According to data from the 2011–2016 National Health and Nutrition Examination Survey (NHANES), more than a third of adults in the United States (U.S.) have MetS, and the rate can be as high as 48.6% among those aged at least 60 years [3].

In recent years, an increasing number of researchers have been investigating how manganese (Mn) is potentially beneficial for cardiometabolic health. Mn is an essential element that acts as a co-factor of superoxide dismutase, an enzyme responsible for the degradation of reactive oxygen species (ROS) [4]. Evidence from in vitro and animal studies has demonstrated that Mn supplementation could downregulate ROS generation [5], prevent endothelial dysfunction [6], and reduce the levels of serum inflammatory biomarkers [7]. However, excessive exposure to Mn from polluted air and water may lead to impaired cognitive development and Parkinson's disease (PD), especially among workers and general populations residing near factories [4][8]. Although the mechanisms linking Mn overexposure and PD are still under investigation, a combination of mitochondrial dysfunction and oxidative stress, protein misfolding and trafficking, and neuroinflammation, may play major roles in Mn neurotoxicity [9]. Mn can be obtained from water, nuts, grains, fruits, green vegetables, and caffeinated drinks [10]. Mn exposure can also be reflected from its level from blood and urine. The half-life of blood Mn is 10 to 42 days, but that for urinary Mn is less than 30 h, indicating a more recent exposure than blood Mn [11].

2. Dietary Mn and MetS

Three of the included studies examined the association between dietary Mn and the presence of MetS [12][13][14]. Among the 2111 adults that participated in the Chinese National Nutrition and Health Survey 2010–2012 [14], men

with the highest Mn intake (>6.87 mg/day) had a significant lower likelihood for MetS (OR: 0.62, 95% C.I. = 0.42, 0.92), but a positive association (OR: 1.56, 95% C.I. = 1.02, 2.45) was found for women with the highest Mn intake (>5.79 mg/day). There was significant interaction between sex and dietary Mn in affecting the likelihood for MetS. On the other hand, for a case-control study conducted among 550 adults [13], the highest quartile of Mn intake was associated with a lower likelihood of MetS (OR: 0.47, 95% C.I. = 0.29, 0.79), but the result was not stratified by sex. Choi et al. analyzed the data of 5136 adults from the general population of Korea [12], but did not found a significant relationship between the highest quartile of Mn intake and MetS among men (OR: 1.01, 95% C.I. = 0.68, 1.49) nor women (OR: 0.82, 95% C.I. = 0.55, 1.22). When pooling the results from included studies (**Figure 1**), the overall association between the highest level of dietary Mn and MetS was not significant (OR: 0.83, 95% C.I. = 0.57, 1.21, I^2 = 74%), and the heterogeneity across study was substantial (I^2 > 50%). When omitting one analysis at a time, the heterogeneity remained substantial (53% to 81%). The overall association changed to significant (pooled OR: 0.72, 95% C.I. = 0.53, 0.98) only after omitting the analysis on dietary Mn and MetS among participating women in the study of Zhou and colleagues (OR: 1.56, 95% C.I. = 1.02, 2.45) [14].

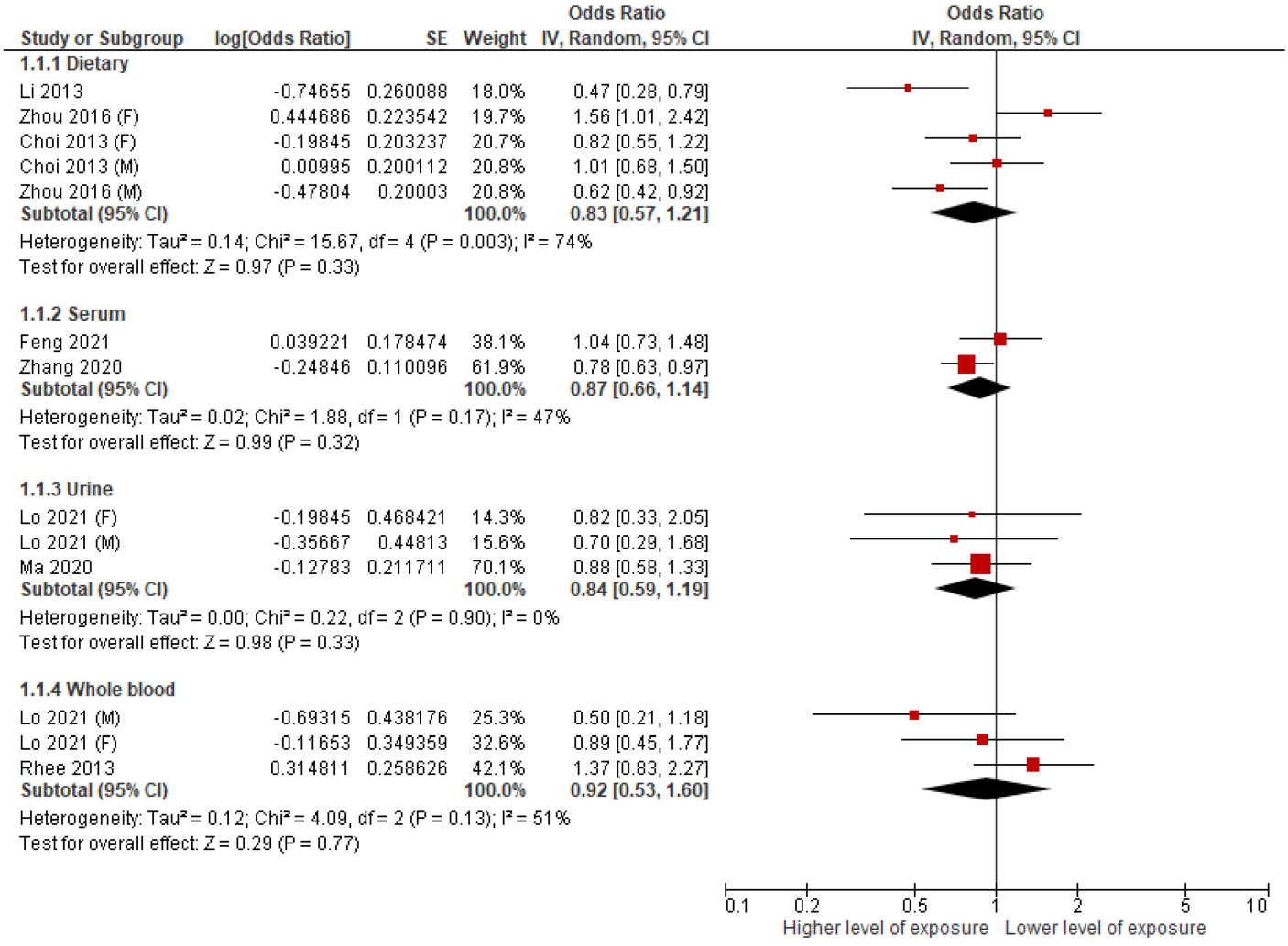

Figure 1. Forest plot for different exposures of manganese and metabolic syndrome. The Figure summarizes the overall association between the highest Mn level from diet, serum, urine, whole blood, and the likelihood of metabolic syndrome. Random effects models using the inversed variance (IV) approach were used to pool the

estimates from individual studies. The effect estimates are presented as odds ratio with 95% confidence intervals (CI).

3. Serum Mn and MetS

Two included studies conducted in China examined the association between Mn from serum and the likelihood of MetS [15][16]. Feng et al. analyzed the association of 11 serum metals with MetS among 4303 men who participated in the Fang Chenggang Area Male Health and Examination Survey cohort [15]. As one of the selected serum metals, Mn was only inversely associated with MetS in the second tertile (OR: 0.65, 95% C.I. = 0.43, 0.98), not the highest tertile (OR: 1.06, 95% C.I. = 0.95, 1.18) [15]. Similarly, the case-control study of 4134 adults conducted by Zhang et al. analyzed 15 serum metals and their association with MetS by putting them in the same logistic regression model [16]. Serum Mn was associated with a lower likelihood of MetS (OR: 0.78, 95% C.I.: 0.63, 0.97) only at the highest quartile (>1.69 μg/L) [16]. When pooling the results from included studies (**Figure 1**), the overall association between serum Mn and MetS was not significant (OR: 0.87, 95% C.I. = 0.66, 1.14, I^2 = 47%), and the heterogeneity across studies was not substantial (I^2 < 50%). Given the limited number of studies, researchers did not omit one analysis at a time for this part.

4. Urinary Mn and MetS

Four included studies examined the association between urinary Mn and the presence of MetS [17][18][19][20], and two of them provided adequate data for meta-analysis (**Figure 1**) [18][19], but the overall association between the highest level of Mn from urine and MetS was not significant (OR: 0.84, 95% C.I. = 0.59, 1.19, I^2 = 0%), and the heterogeneity across studies was not substantial (I^2 < 50%). When omitting one analysis at the time, the I^2 value remained as 0% and the overall association remained insignificant. However, nonlinear relationship between urinary Mn and MetS was observed from some of the included studies. By analyzing the data from U.S. NHANES 2011–2016, Lo et al. observed that urinary Mn at the third quartile associated with a lower odd of MetS among overall participants (OR = 0.55, 95% C.I. = 0.32, 0.97) and men (OR = 0.40, 95% C.I. = 0.16, 0.99) [18]. From the restricted cubic spline analysis, the U-shaped dose-response relationship between urinary Mn and MetS was observed among all participants [18]. As demonstrated by posterior inclusion probabilities (PIP), urinary Mn played a less important role in development of MetS (PIP = 0.49 for Mn versus 0.54 to 0.91 for other metals) [18]. For two case-control studies (conducted in Iran and China, respectively) that were not included in the meta-analysis, per unit increment of urinary Mn did not associate with MetS [17][20].

5. Whole Blood Mn and MetS

Four of the included studies examined the association between Mn from whole blood and the presence of MetS [21][18][22][23]. For the three studies that analyzed data from U.S. NHANES, different approaches were adapted in each included study. Bulka et al. put each metal exposure separately into the logistic regression model [21], and found that blood Mn did not associate with MetS across the quartiles (OR at quartile 4: 1.04, 95% C.I. = 0.88, 1.24).

Moreover, Lo et al. observed a null association between blood Mn and MetS for both male and female participants in the multi-metal model (including all whole blood metals into the regression model) [18]. They have further evaluated the relative importance of blood Mn and other metals in the association with MetS by the Bayesian kernel machine regression (BKMR) model. As measured by PIP, they found that blood Mn has the least relative importance in the presence of MetS compared with other blood metals (cadmium, mercury, lead, and selenium) [18]. Zhou et al. demonstrated that the association between blood Mn and MetS per log increment was not significant (OR: 1.22, 95% C.I. = 0.96, 1.56), which was consistent across age groups and sex [23]. In addition, they demonstrated a M-shaped association between blood Mn and MetS using restricted cubic spline analysis [23]. Rhee et al. analyzed data from the Korea NHANES 2008, and they did not find a significant association between blood Mn and MetS across the quartiles (OR at the highest quartile: 1.22, 95% C.I. = 0.76, 1.97) [22]. To perform meta-analysis, the data from Lo et al. were selected out of three studies that analyzed U.S. NHANES, because it covered a larger data set than Bulka et al., while Zhou et al. did not provide the effect estimate across quartiles. When pooling the results from the included studies (**Figure 1**), the overall association between whole blood Mn and MetS was not significant (OR: 0.92, 95% C.I. = 0.53, 1.60, I^2 = 51%), and the heterogeneity across the studies was substantial (I^2 > 50%). When omitting one analysis at the time, the overall association remained insignificant, but the heterogeneity was not substantial after excluding the analysis from the male participants of Lo's study (I^2 = 0%) [18], and the data from Rhee et al. (I^2 = 6%) [22].

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