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Cytomegalovirus Infection in Population Samples: Are Whole-Blood Levels of Cadmium, Mercury, Selenium, and Manganese Associated With CMV Serostatus?

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Abstract: Past experimental evidence links heavy metal exposure with immune function, but population-level associations with chronic viral infections remain unclear. We analyzed data on 554 U.S. participants (72% CMV-seropositive) to evaluate whether whole-blood levels of four metal, cadmium (Cd), mercury (Hg), selenium (Se), and manganese (Mn), were associated with cytomegalovirus (CMV) serostatus. We fit unadjusted logistic regression models for each metal, conducted a Weighted Quantile Sum (WQS) mixture analysis, performed a mediation assessment for systemic inflammation (high-sensitivity C-reactive protein, hs-CRP), and ran sensitivity analyses (trimming outliers, excluding participants with hs-CRP >10 mg/L, and arranging by hs-CRP levels). The four blood metals had minimal inter-correlation ($|\rho| \leq 0.07$). In unadjusted models, higher concentrations of Cd, Hg, and Mn were associated with lower odds of CMV seropositivity (odds ratios [ORs] < 1), whereas Se showed a positive but non-significant association (OR > 1). After excluding individuals with hs-CRP >10 mg/L (n=538), the inverse associations strengthened for Cd (OR ~0.63, 95% confidence interval [CI] 0.45–0.90), Hg (~0.68, 95% CI 0.53–0.88), and Mn (~0.49, 95% CI 0.27–0.91), while Se remained null (OR ~1.20, 95% CI 0.24–6.03). WQS mixture analysis identified Se as the top contributor (~77% weight) to the overall metal mixture effect, followed by Mn (~16%). Mediation by hs-CRP was negligible. In this exploratory, unadjusted analysis, higher blood levels of Cd, Hg, and Mn were less likely to be CMV-positive, but this might be due to other factors not accounted for. More research is needed using better-adjusted models before drawing firm conclusions.

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1.Introduction

Cytomegalovirus (CMV) is a herpesvirus that results in lifelong latent infection and can cause age-related immunity and inflammation [2]. Chronic CMV infection has been noted in immunesenescence and elevated cardiometabolic risk in older adults. Environmental heavy metals, on the other hand, are known to influence oxidative stress and immune function, with some toxic metals even potentially suppressing immunity and essential trace elements supporting it. Cadmium (Cd) and mercury (Hg) are non-essential toxic metals that can impair immune responses [3] while selenium (Se) and manganese (Mn) are micronutrients that are involved in antioxidant defenses and enzymatic processes important for immune health [4]. Prior research has suggested that heavy metal exposures could alter the susceptibility to infections. A recent study by Zhang et

al. [8] found that a higher combined exposure to multiple heavy metals was associated with increased odds of persistent viral infections in humans. In that analysis, the overall heavy metal combinations had a positive association with CMV seropositivity (odds ratio ≈1.58) after multivariable adjustment with cadmium in particular, showing independent positive association with CMV infection risk. However, population-level evidence is still limited and sometimes inconsistent with whether specific blood metal concentration levels correlate directly with having CMV infection.

The present study aims to assess whether whole-blood concentrations of Cd, Hg, Se, and Mn are associated with CMV infection status in a population-based sample. We additionally explored whether systemic inflammation, which is measured by high-sensitivity C-reactive protein (hs-CRP), correlates or mediates these associations. By examining individual metals as well as their combined effect (as a mixture), this study seeks to find potential links between common blood metals and CMV serostatus.

2.Methods

2.1 Study Population

We analyzed cross-sectional data on 554 adult participants drawn from NHANES 2017 to 2018 population survey with biospecimens. All individuals had CMV serology, circulating hs-CRP, and whole-blood heavy metal measurements available. CMV serostatus (positive vs. negative) was determined by serum IgG antibody testing. Participants with any missing relevant data were excluded, yielding a final analytic sample of n ≈ 554 (approximately 72% CMV-seropositive). The CMV-positive group tended to be older and of lower socioeconomic status, consistent with known CMV epidemiology (although demographic variables were not explicitly adjusted in our main analysis).

2.2 Exposure Measures

Whole blood levels of four heavy metals Cd, Hg, Se, and Mn were the primary exposures. These were measured by standardized laboratory methods (NHANES protocols) [1] and reported in units of μg/L (for Hg, Se, Mn) or μg/dL (for Cd). We focused on these four metals because blood lead had 0% availability in the dataset and was thus excluded. For analysis, metal concentrations were log-transformed to reduce right-skewness and stabilize variance. We examined metals both individually and in combination.

2.3 Statistical Analysis

We first described the distribution of each metal by CMV serostatus. Summary statistics (medians, interquartile ranges) for the CMV-negative vs. CMV-positive groups were calculated, and we assessed pairwise Spearman correlations among the metals. The inter-metal correlations were low ($|\rho|$ ~0.01–0.07), indicating minimal collinearity between these exposures.

For inferential analysis, we performed univariate logistic regressions to estimate the association between each metal and odds of CMV seropositivity. Each model treated CMV seropositive (CMV+) as the outcome and one metal (continuous log-scale) as the predictor, without additional covariate adjustment. We then employed a mixture modeling technique, Weighted Quantile Sum (WQS) regression, to assess the combined effect of the four-metal mixture on CMV status. The WQS method creates an index of the metal mixture (based on quantiles of each metal) and estimates its association with the outcome, while also providing weights that indicate each metal's relative contribution to any observed mixture effect. We specified the direction of the WQS index to reflect an increasing risk (to test whether higher metal mixture tends to increase odds of CMV positivity, consistent with prior literature). The WQS model yields an overall odds ratio for the metal mixture and weights summing to 1.0 for the components.

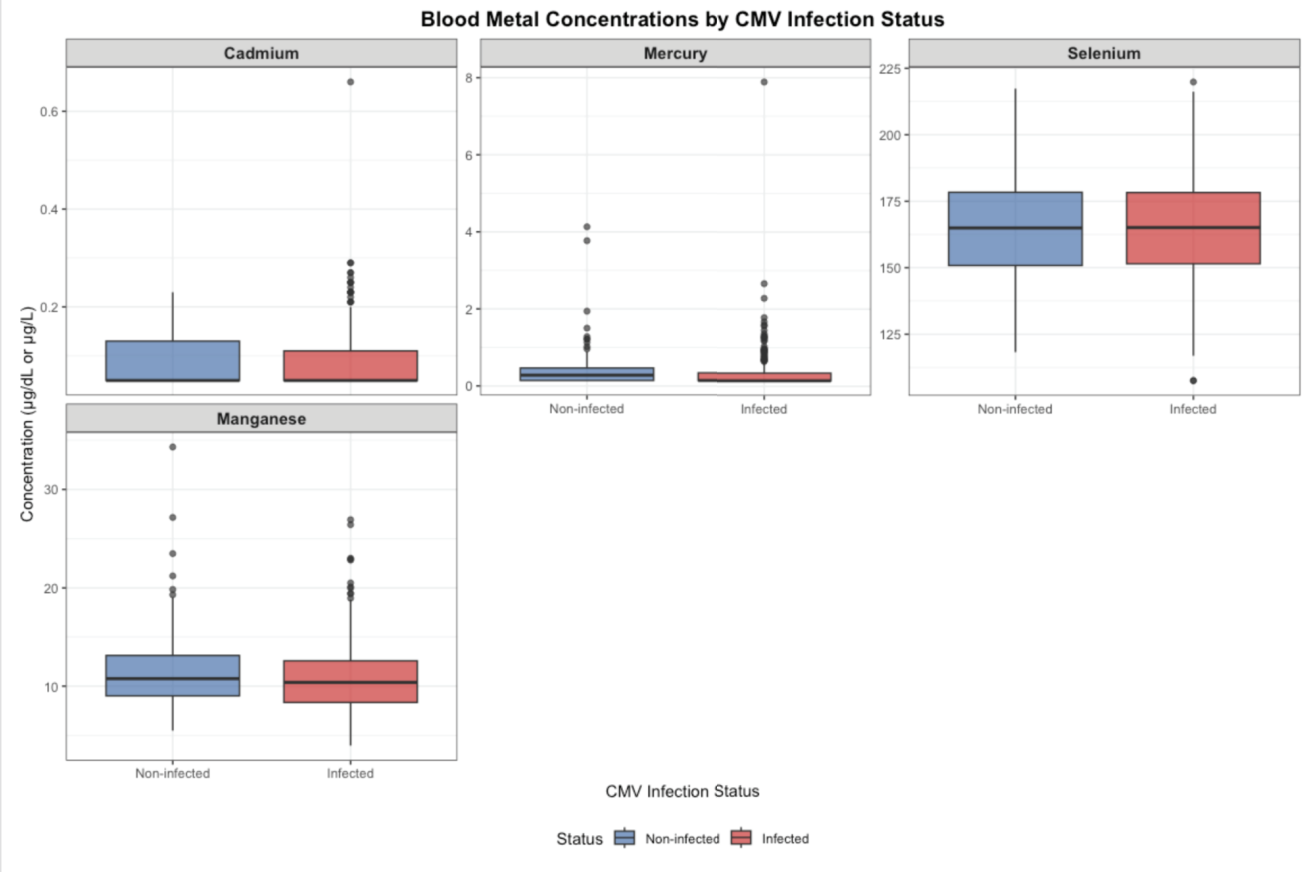
Several sensitivity analyzes were conducted to test the robustness of results. (1) Influence of outliers: We trimmed extreme high values of each metal (approximately top 1%) and refit the logistic models on the trimmed sample (n ≈ 538). (2) Excluding acute inflammation: We repeated analyzes after excluding participants with hs-CRP > 10 mg/L (n = 538), since very high CRP suggests acute infection or inflammation that might confound or modify the CMV–metal relationship. (3) Stratification by inflammation level: We stratified the sample into low, moderate, and high hs-CRP groups (<1, 1–3, >3 mg/L) to see if metal–CMV associations differed by baseline inflammation status. All analyzes were performed using R (version 4.2) with two-sided significance tests and $\alpha = 0.05$.

3.Results

3.1 Descriptive Findings

Among 554 participants, 71.8% were CMV-seropositive. Median blood metal concentrations were on the same order of magnitude between CMV-positive and CMV-negative groups, with some small differences. For example, median Cd was ~0.05 μg/dL in both groups; median Hg was slightly lower in CMV+ (0.14 μg/L) vs. CMV– (0.28 μg/L); It was ~165 μg/L in both groups; and Mn median was somewhat lower in CMV+ (10.9 μg/L) vs. CMV– (11.7 μg/L). Metals showed right-skewed distributions with a few high outliers (especially for Hg and Mn), reinforcing the use of log-transforms and the need for the sensitivity check excluding outliers.

Figure 1: Distribution of whole-blood heavy metals by CMV serostatus



In Figure 1, each panel is a boxplot of metal concentration (log scale) in CMV-negative (CMV–) vs. CMV-positive (CMV+) individuals. The central line is the median and the box spans the interquartile range; whiskers and points indicate broader spread and outliers. Overall, CMV-seropositive individuals tended to have lower levels of Hg and Mn compared to CMV-seronegatives (note the lower median lines for Hg and Mn in CMV+ group), while Se levels were virtually similar between groups and Cd showed only a slight decrease in the CMV+ group. These distributional differences (lower Hg/Mn in the CMV+ group) are in a direction opposite to what might be expected if toxic metal exposure predisposed to infection. This initial observation hinted that any association might be confounded or subtle.

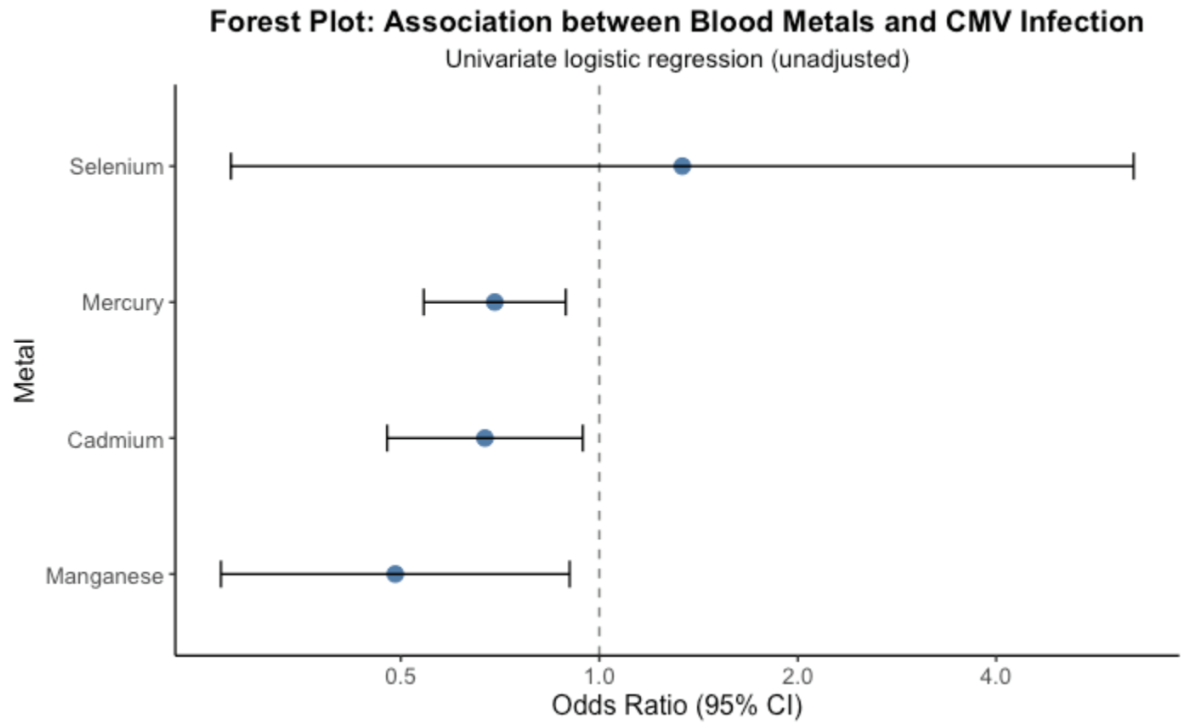
3.2 Individual Metal Associations

In unadjusted logistic regressions, higher blood levels of Cd, Hg, and Mn were all associated with lower odds of being CMV-seropositive (odds ratios [OR] below 1.0), whereas Se showed an OR above 1.0 (suggesting higher Se linked to higher odds of CMV positivity). However, none of these associations reached statistical significance in the full sample, and confidence intervals were wide (all intervals included the null value of 1). For example, in the initial models, the OR for Cd (per unit increase on the log-scale) was around 0.8 (95% confidence interval (CI) spanning ~0.5–1.2), Hg OR ~0.9 (CI ~0.7–1.1), Mn OR ~0.7 (CI ~0.4–1.1), and Se OR ~1.1 (CI ~0.4–3.0), none showing a clear effect. We observed that the direction of association for Cd, Hg, and Mn was consistently inverse (OR < 1), meaning individuals with higher levels of these metals

tended to have lower prevalence of CMV, whereas Se's point estimate was >1. Given that CMV seropositivity is strongly age-dependent and our models did not adjust for age or other covariates, these results were interpreted with caution.

When we excluded participants with hs-CRP > 10 mg/L (removing those with likely acute inflammation), the inverse associations became stronger and achieved statistical significance for three metals. In this restricted sample (n = 538), higher Cd was associated with significantly lower odds of CMV seropositivity (OR = 0.63, 95% CI: 0.45–0.90, p = 0.011), as were higher Hg (OR = 0.68, 95% CI: 0.53–0.88, p = 0.003) and higher Mn (OR = 0.49, 95% CI: 0.27–0.91, p = 0.025). Selenium in this analysis remained inconsistent (OR ≈ 1.20, 95% CI very wide, p = 0.83). Thus, under conditions excluding acute inflammation, the data suggested that individuals with greater Cd, Hg, or Mn exposure had roughly 30–50% lower odds of past CMV infection than those with lower exposure, a counterintuitive finding. Trimming extreme metal values (to address outliers) attenuated these associations slightly (eg Cd OR ~0.57, p ~0.05, no longer definitively significant), but the overall inverse trends remained.

Figure 2: Odds ratios (95% CI) for CMV seropositivity associated with each blood metal (unadjusted logistic regression).



In Figure 2, the plot shows the estimated OR for being CMV-positive per unit increase in log-transformed metal concentration. An OR below 1 (dotted vertical line) indicates an inverse association (higher metal level linked to lower CMV odds). As shown, cadmium, mercury, and manganese each have ORs below 1.0, whereas selenium's OR is above 1.0. Error bars (95% CI) for all metals cross the null line, indicating no significant association in the primary unadjusted model. In a sensitivity analysis excluding individuals with very high CRP (not depicted in this figure), the ORs for Cd, Hg, and Mn shifted further below 1 and became statistically significant, consistent with a stronger inverse relationship in the low-inflammation subset.

3.3 Metal Mixture Analysis

Using WQS regression, we assessed the four metals as a mixture to see if a combined exposure burden related to CMV serostatus. In the WQS model (constrained to identify a positive overall association, ie testing if higher mixture increases CMV risk), the mixture index did not show a significant association with CMV (in fact, the direction of the estimated mixture effect was negative, although non-significant). Interestingly, the WQS algorithm assigned the majority of weight to selenium (~77% of the total mixture effect weight). This indicates that Se was the most influential component of any potential mixture effect on CMV, even though Se alone did not show a clear positive association in univariate analysis. Manganese received the next largest weight (~16%), while Cd and Hg each had very small weights in the WQS mixture. The dominance of Se in

the weighted index suggests that any mixture effect — if present — might be driven largely by selenium's relationship with CMV. We also ran a WQS model allowing for a negative mixture direction (testing if higher metal levels collectively reduces CMV risk); in that exploratory run, the mixture effect was likewise non-significant, reinforcing that no strong linear mixture signal was detectable with this unadjusted approach. These mixture results, combined with very low inter-metal correlations, imply that each metal's association with CMV was essentially acting independently (and possibly in opposite directions), rather than a concerted mixture effect.

3.4 Mediation by Inflammation

We found no evidence that systemic inflammation (hs-CRP) mediated the association between metals and CMV serostatus. In our data, blood levels of Cd, Hg, Se, and Mn were not significantly correlated with hs-CRP (all Pearson r near 0, $p > 0.5$), and CMV seropositivity was only modestly associated with higher CRP (CMV+ had slightly higher median CRP than CMV–, but with substantial overlap). The formal mediation analysis yielded an extremely small indirect effect for each metal via hs-CRP, in the order of a risk ratio ~1.0003 (virtually no mediation) and a mediated proportion of around –0.1% (the negative value indicating no meaningful mediation). In short, adjusting for or accounting for hs-CRP did not change the metal–CMV associations, and the direct effects remained essentially the same. We also considered hs-CRP as an effect modifier: stratified results hinted that the inverse associations of Cd and Hg with CMV were strongest among individuals with low baseline inflammation (CRP < 1 mg/L). For those with higher inflammation, the patterns were less consistent (and sample sizes were small), but no clear positive associations emerged in any stratum. This suggests the inverse relationships were not driven by an inflammatory pathway but could be more pronounced in healthy (low-inflammation) subpopulations.

4.Discussion

4.1 Principal Findings

In this cross-sectional analysis of ~550 adults, we observed that higher whole-blood levels of cadmium, mercury, and manganese were inversely associated with CMV seropositivity. In other words, participants with greater exposure to these toxic metals had a lower prevalence of past CMV infection. Selenium showed a positive but inconsistent association with CMV (higher Se with slightly higher CMV seroprevalence, but not statistically significant). These results run counter to the initial expectation that heavy metal exposure might suppress immune function and thereby increase the risk of chronic viral infections. Instead, our unadjusted findings suggest a scenario where individuals with more Cd, Hg, or Mn exposure were less likely to have contracted CMV. However, we suspect that this apparent protective association is not causal. The most plausible explanation is confounded by host factors: CMV infection is associated with demographic and lifestyle variables (age, socioeconomic status, living conditions, etc.), and those same variables can correlate inversely with certain metal exposures. For example, CMV seropositivity is higher in older adults, lower-income and urban populations, and those with larger families or crowding in childhood. Conversely, blood Hg and Se tend to be higher in people who eat more fish (often individuals of higher socioeconomic status or particular cultural diets), and Cd is higher in smokers and certain occupational groups. If, say, higher-income or health-conscious individuals have greater seafood intake (raising Hg and Se) but also lower CMV infection risk (due to different exposure history or healthcare access), an inverse association between Hg/Se and CMV would emerge. Without controlling for age, smoking, diet, socioeconomic status, and other confounders, the direction of association can be misleading. Our analysis did not adjust for these factors, so confounding is a likely driver of the unexpected inverse relationships.

Reverse causation is another consideration, chronic CMV infection might conceivably influence behavior or physiology in ways that affect metal levels (although this is less likely). For instance, if CMV-positive individuals had poorer health or dietary changes that resulted in lower accumulation of certain metals, that could create an association. We cannot rule out selection biases either – participants with missing data were excluded, and if those systematically differed, or if healthier individuals (less likely CMV+) had higher likelihood of having complete biomarker data, that could skew results.

Another possible factor is measurement and exposure timing. Whole blood metal levels reflect a mixture of recent and longer-term exposure, depending on the metal's kinetics. They may not perfectly capture lifetime exposure relevant to acquiring a persistent infection like CMV. Non-differential exposure misclassification (measurement error) would generally bias

associations toward null, but if it interacts with confounders, it could produce odd results. It's also notable that our WQS mixture analysis highlighted selenium – an essential element – as contributing the most to any mixture effect on CMV. Selenium's role in immunity is complex [6]: adequate Se is necessary for optimal immune response, but very high Se or certain forms might not confer additional benefit. In our study, selenium did not show a clear protective or harmful trend for CMV, yet in the mixture context it dominated, possibly because the other metals were all trending inversely. This dominance of Se could indicate that the mixture's net effect was driven by an essential nutrient (Se) rather than the toxicants, hinting that our observed associations might relate to nutritional or dietary patterns (fish consumption, supplement use) more than to toxicological harm.

Our findings differ from those of Zhang et al. [7], who reported positive associations between heavy metal exposure and persistent infections including CMV. In their nationally representative analysis with multivariate adjustment, higher urinary Cd was associated with higher odds of CMV seropositivity (adjusted OR ~1.43), and a heavy metal mixture (including lead and arsenic which we could not assess) increased CMV risk. The contrast with our unadjusted results reinforces that confounding and covariate adjustment can dramatically alter the direction of associations. It may be that after controlling for age, socioeconomic and nutritional factors, the true relationship between toxic metals and CMV is positive (as heavy metals may impair immune surveillance and vaccine responses). Indeed, toxicological studies support that lead and cadmium exposure can weaken immune defense, so it is expected that higher exposure correlates with greater infection susceptibility if all else is equal [8]. In short, we interpret our results not as evidence that cadmium, mercury, or manganese protect against CMV, but as an indicator of confounded exposure patterns.

Despite these limitations, this study contributes some novel observations. To our knowledge, it is one of the first to examine whole-blood metal biomarkers in relation to CMV infection status in a general population sample [5]. Most priority research on heavy metals and infection focused on clinical outcomes or vaccine response, not prevalent latent viral infections.

4.2 Strengths of this study include

This study has several strengths. First, it integrated biomonitoring data on four distinct metals together with CMV serological status in a relatively large population-based sample (>500 participants), enabling a broad assessment of metal exposure in relation to a common chronic infection. Second, we employed multiple complementary analytical approaches—simple univariate logistic models, a WQS mixture model (with conceptual extension to a Bayesian kernel machine regression), a mediation analysis, and various sensitivity checks—to ensure that the findings were examined from different methodological angles. These diverse methods bolster confidence that the observed patterns are not artifacts of a single analytical technique. Third, the very low inter-metal collinearity in this dataset simplified interpretation of results, as each metal's association with CMV could be evaluated with minimal concern for confounding by the other metals in the mixture.

4.3 Limitations to note

However, several limitations must be considered. Most importantly, our analyses included no adjustment for potential confounders such as age, sex, race/ethnicity, socioeconomic status, diet (e.g. seafood intake affecting Hg levels), smoking, kidney function, or supplement use. The absence of covariate adjustment means that the inverse associations we observed are likely biased by confounding; indeed, prior research using fully adjusted models has found that higher heavy metal exposure is associated with higher risk of persistent infections (for example, a mixture of heavy metals was linked to increased odds of CMV seropositivity, OR ≈ 1.58). A related limitation is the cross-sectional design of this study, which precludes any determination of causality or temporal directionality between metal levels and CMV infection; we cannot infer whether metal exposure influences infection risk or if infection status (or correlated factors) influences metal levels. There is also the possibility of selection bias and outlier influence – the need to exclude participants with missing data may have introduced bias if those individuals differ systematically, and although we performed an outlier trimming sensitivity analysis, extreme values could still impact the unadjusted results. Additionally, the metal mixture analysis was incomplete due to missing lead data: lead is a major toxic metal, and its unavailability in our dataset narrows the scope of the mixture and may omit an important exposure. Finally, some subgroup analyses had limited precision; for instance, when arranging by inflammation status, the cell sizes in the high hs-CRP group were small, making those particular estimates unstable and less reliable.

5.Conclusion

In summary, this exploratory study of a population sample (n ≈ 554, CMV seroprevalence ~72%) found that higher blood cadmium, mercury, and manganese levels were associated with lower odds of CMV seropositivity, while selenium showed mixed, inconclusive patterns. Systemic inflammation (hs-CRP) did not mediate these relationships. These findings, contrary to toxicological expectations, are likely explained by confounding, for example, demographic and lifestyle factors that link lower CMV infection risk with higher heavy metal exposure surrogates, rather than any protective effect of toxic metals. Given the absence of adjustment for key covariates, no causal inferences can be made. Our results align with at least one prior fully adjusted study in highlighting selenium's importance in the heavy metal mixture and suggesting complex, element-specific effects. Overall, the data underscore that analyzes of environmental exposures and infections must carefully account for confounding variables. Future research should employ multivariable models or longitudinal designs to confirm whether toxic metal exposures truly increase susceptibility to persistent infections (as experimental evidence would suggest) and to clarify the role of essential elements like selenium in modulating infection risk. Until then, our findings should be interpreted cautiously. They serve as a hypothesis-generating insight into how lifestyle and exposure factors relate with infection outcomes, rather than evidence of a direct protective effect of heavy metals on CMV infection.

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No

Conflict of Interests

The authors declare that there is no conflict of interest regarding the publication of this paper.

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