environments

Review

Review of Correlations Between Telomere Length and Metal Exposure Across Distinct Populations

Zachary Beddingfield [1,2], Chao Ji [3], Gregory M. Zarus [1], Patricia Ruiz [3], Obaid Faroon [1], Henry Abadin [1], Breanna Alman [1], James M. Antonini [4] and Mohammad Shoeb [1,*]

[1] Centers for Disease Control and Prevention (CDC), Office of Innovation and Analytics, Toxicology Section, Agency for Toxic Substances and Disease Registry, Atlanta, GA 30341, USA; zbeddingfield3@gatech.edu (Z.B.); gzarus@cdc.gov (G.M.Z.); oxs0@cdc.gov (O.F.); hga0@cdc.gov (H.A.); pcq6@cdc.gov (B.A.)
[2] Georgia Tech School of Biological Sciences, Atlanta, GA 30332, USA
[3] Simulation Science Section, Agency for Toxic Substances and Disease Registry, Atlanta, GA 30341, USA; ugc8@cdc.gov (C.J.); doz8@cdc.gov (P.R.)
[4] Health Effects Laboratory Division, National Institute for Occupational Safety and Health, Morgantown, WV 26505, USA; jga6@cdc.gov
* Correspondence: ywo7@cdc.gov; Tel.: +1-304-285-6260

Abstract: Telomere length (TL) predicts the onset of replicative senescence, and its shortening is a limiter on the number of divisions individual somatic cells can perform. Metal-induced genotoxic events are discussed in Agency for Toxic Substances and Disease Registry's (ATSDR) toxicological profiles. In vivo and in vitro toxicological studies suggest the correlation between toxic metals and TL. However, the correlation between TL and exposure to toxic metals in human populations is unclear despite decades of observational research. We conducted a literature search within the ATSDR toxicological profiles and PubMed database for peer-reviewed articles as of 04/2023 discussing TL and metal exposure in human populations. Through review of the 272 publications meeting these criteria, we identified 25 observational studies that considered the correlation between TL and exposure to some or all of six metals: cadmium (Cd), arsenic (As), nickel (Ni), selenium (Se), lead (Pb), and cesium (Cs). Because reported effect sizes were often not comparable across studies, we performed a sign test based on the reported significance for each metal–TL correlation. We found that Cd was consistently significantly correlated with shorter telomeres ($p = 0.016$). However, no consistent linear relationship was observed between TL and any of the other metals considered. Exploring this association can enhance our understanding of how metal exposure may influence TL dysfunction. Our findings suggest that Cd exposure contributes to shorter TL, which may affect the DNA damage response (DDR) resulting in numerous chronic health conditions. Further, we highlight inconsistencies in findings on the correlation between metal exposure and TL across different populations and exposure levels. This suggests that correlations between some metals and TL may vary across populations, and that correlations may change at different exposure levels. Also, our findings suggest the need for further research on the potential for nonlinear relationships and non-additive effects of co-exposure to multiple hazardous metals, which could explain the inconsistencies observed across studies. The inconsistent incidences of metal–TL correlations justify additional exploration into the complex interaction between metals and TL.

Keywords: telomere; metals; DNA damage; RNA; end replication

Citation: Beddingfield, Z.; Ji, C.; Zarus, G.M.; Ruiz, P.; Faroon, O.; Abadin, H.; Alman, B.; Antonini, J.M.; Shoeb, M. Review of Correlations Between Telomere Length and Metal Exposure Across Distinct Populations. *Environments* **2024**, *11*, 280. https://doi.org/10.3390/environments11120280

Academic Editors: Gabriele Donzelli and María M. Morales Suárez-Varela

Received: 12 November 2024
Revised: 29 November 2024
Accepted: 2 December 2024
Published: 6 December 2024

1. Introduction

To prevent unwanted chromosomal degradation and activation of the DNA damage response (DDR), nature has provided cap-like structures called telomeres at the ends of chromosomes, which are composed of tandem repeats of hexanucleotides 5′-TTAGGG-3′ DNA sequences [1,2]. Telomeres, which cap the ends of DNA and shorten with each round of replication, decrease in length naturally eventually resulting in an end-replication

problem. This can arise when the DNA polymerase enzyme responsible for replication of the leading strand of DNA (5′ to 3′) is unable to replicate the lagging strand (3′ to 5′) due to the absence of hydroxyl groups required to add another nucleotide. This process of DNA replication can result in an end replication problem since no nucleotide can be added at the end of the lagging strand [3].

The enzyme telomerase partially mitigates the end-replication problem [4]. The enzyme telomerase is a reverse transcriptase ribonucleoprotein complex, and its activity is dependent on the expressions of telomerase reverse transcriptase (TERT) and telomerase RNA component (TERC), which vary largely across cell types. For instance, embryonic stem cells have significant expression of telomerase activity compared to somatic cells [3,5,6]. When telomeres shorten past a critical point, a DDR pathway is activated, which can result in G1 phase arrest and cellular senescence [7,8]. Apart from telomerase involvement in maintaining telomeres, double and single stranded telomere DNA are shielded by a complex of six proteins called shelterin. As described in Shoeb et al., 2021, shelterin complex is composed of six proteins known as telomere repeat factors 1 and 2 (TRF1 and TRF2), Trf1-interacting protein 2 (TIN2), tripeptidyl peptidase 1 (TPP1), protection of telomere 1 (POT1), and repressor/activator protein 1 (RAP1). Alteration in any of the shelterin protein could result in dysfunctional telomeres and activation of DDR [2].

Telomere alteration has been proposed as a biomarker for various age-related pathologies such as fibrosis [9–12], neurodegeneration [13,14], cardiovascular dysfunction [12,15], and cancer [10,12,16]. Mice without the telomerase gene display broad tissue dysfunction after several generations, and mice with hyper-long telomeres have decreased incidence of pathology and increased lifespans [17,18]. Further, based on evidence in human populations, researchers have hypothesized that telomere shortening in pre-cancerous cells can produce a selection event, where one cell with mutations that promote telomere elongation (due to elevated telomerase activity) becomes dominant, resulting in tumor initiation [19].

While telomeres shorten naturally with replication, this shortening can be accelerated through mechanisms such as oxidative stress [20,21]. Further, several hazardous exposures have been proposed to be associated with accelerated telomere shortening [2]. Several environmental and occupational exposures may result in binary telomere length. Hazardous exposure-induced telomere shortening may result in expressing increased telomerase activity and dysfunctional shelterin which may lead to uncontrolled proliferation of those specific cell types resulting in the activation of DDR and cancer development. On the other hand, cells with elongated telomeres not only have an increased lifespan but can also occasionally bypass the senescence and apoptosis pathways, potentially resulting in mutations, abnormal proliferation, and increased risk of tumorigenesis [2]. Various cross-sectional and cohort studies have reported associations between metal exposure and telomere length (TL); however, findings are often insignificant, and the direction of the correlation can vary across different populations. Given the close association between TL and age-related pathologies, uncovering the role of metal exposure in influencing TL will enhance our understanding of the mechanisms through which metal exposure contributes to these pathologies.

This short review applies a quantitative approach to evaluate whether we have sufficient evidence for a directional association between TL and exposure to any of six metals commonly studied in this context: cadmium (Cd), lead (Pb), cesium (Cs), nickel (Ni), arsenic (As), and selenium (Se), all of which are included in ATSDR's toxicological profiles [22]. Additionally, we explore the literature to better understand the inconsistencies in correlations between metal exposure and telomere length across studies and highlight the importance of identifying potential nonlinear relationships and non-additive effects of co-exposure to address gaps in the current body of research.

2. Methodology

2.1. Search Strategy

A review protocol and methodology as described is not published elsewhere. This study was summarizing toxicological evidence on selected metals and are published by the

ATSDR. These toxicological profiles (federal documents), serve as the main source for this review article, as they contain direct and indirect evidence of such effects for each metal discussed. ATSDR systematically gathers and reviews all published research available on the health effects associated with the substances. The reviews include gray literature which ATSDR has peer-reviewed, as explained in Appendix B of the toxicological profiles [22].

Relevant studies on the effects of Cd, Pb, Cs, Ni, As, and Se on TL were identified through ATDSR's relevant toxicological profiles and PubMed by searching "[Metal] telomere". The time range considered included all studies published through March 2023, and only studies in English language were considered. Our complete search strategy is available in Supplementary Table S1.

2.2. Study Selection

Studies that directly measured blood TL and metal concentration in all individuals and then directly analyzed the relationship between these factors were considered. Studies that relied on geographical distributions as a proxy for metal levels or TL were excluded, and studies with overlapping datasets were filtered by selecting the studies that considered the greatest number of metals of interest such that each dataset was represented only once.

While this review considers Cd, Pb, Cs, Ni, As, and Se, individual studies included in our analysis may look at only one or a subset of these metals. However, only studies considering the individual effects of these metals, rather than solely correlating the mixed effects of multiple metals to TL, were included. In mother–infant studies, results based on TL from maternal leukocytes were used when available, and results based on TL from cord blood were used otherwise. If studies analyzed two distinct cohorts independently, the findings for each were treated as two separate studies for this review.

Our selection criteria are summarized as a PECOS (Population, Exposure, Comparator, Outcome, and Study) framework in Table 1.

Table 1. Study eligibility criteria (PECOS).

	Inclusion Criteria	**Exclusion Criteria**
Population	• Human populations • Any age, sex	• Animal research • Cell populations
Exposure	• Measured levels for at least one metal of interest	• Relied on proxies such as dietary intake or geographic location for metal exposure or TL
Comparators	• None	• None
Outcomes	• Quantified correlations between telomere length and one or more types of metal exposure	• Did not evaluate significance of a correlation between metal and telomere length • Used non-blood samples for measuring TL
Study design	• Observational studies	• Experimental research

2.3. Data Extraction

For each study included in this review, author, title, population parameters, cell type for TL analysis, study design, and results were extracted including sample size, population age, geographic location, collection period, and any cohorts that participants were drawn from. Collection period was determined based on dates reported in the methodologies of each study. Significant correlations were recorded for any case where a relationship was reported and identified as significant, either explicitly by providing a p-value < 0.05 or implicitly by including a confidence interval which includes the null value. Insignificant correlations were recorded for any case where a paper explicitly notes that no significant relationship was found, or when it implicitly notes this by saying that a correlation was tested but does not say the relationship was significant.

2.4. Evidence Synthesis

To analyze whether there is a consensus on a directional metal–TL correlation for each metal, we utilized vote counting and sign testing using reported significance results [23,24]. Vote counting was performed by assigning a +1 for each significantly positive correlation with TL, a −1 for each significantly negative correlation with TL, and a 0 for no significance. Then, a two-tailed sign test [25] was performed around a median of 0 (code available in Supplementary Table S2) for each metal to evaluate whether a significant directional effect could be observed across studies.

Sign testing was applied for each metal–TL correlation independently. Further breaking down the data, such as applying sign testing for only child or mother-infant pair populations, was not possible since the resulting sample sizes would have been too small. Figures were produced using the TidyVerse package (version 2.0.0) [26] in R-Studio (version 2024.09.1+394) [27] and with Office Suite products.

3. Results

3.1. Summary of Studies

In total, 272 studies discussing the correlation between metals and telomeric alterations were initially identified through PubMed for screening as part of this review. Among them, 239 studies that did not include observational studies of human populations considering the effects of selected metals on telomeres are excluded, leaving 33 studies that tracked the effects of these metals on telomeres. Eight studies were excluded due to the overlapping datasets and inconsistent sample collection with other studies, resulting in 25 studies that met our criteria for analyzing the relationship between Cd, Pb, Cs, Ni, As, and Se and TL (Figure 1).

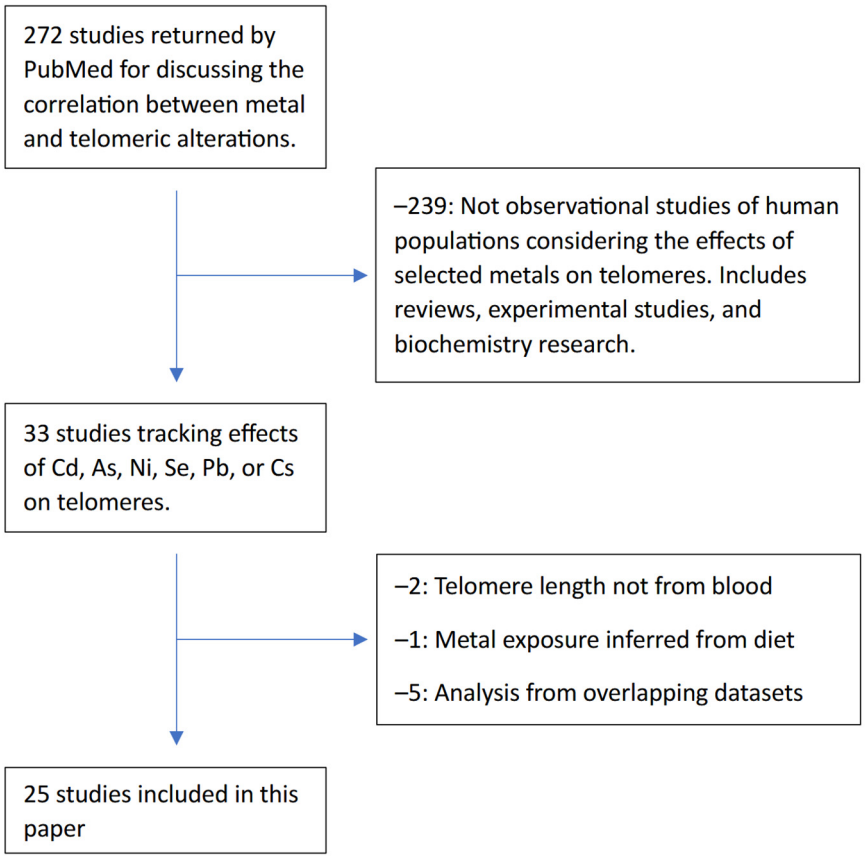

Figure 1. Flow diagram of screening for studies included in this review.

These 25 studies are summarized in Table 2, which includes the study citation, sample size, location, sample group, collection period, and study type (cross-sectional and cohort

studies) [28–51]. Across the 25 studies included in this paper, 55 conclusions were reported regarding the correlations between metals and TL: findings for Cd, Pb, Cs, Ni, As, and Se totaled 15, 9, 3, 3, 12, and 13, respectively (Table 2). We classified each finding as either a significant correlation between the metal and shorter TL (<), the metal and elongated TL (>), or no significant correlation (o) (Figure 2). For Cd, seven studies found a correlation with shorter TL, while eight studies found no correlation. For Pb, four studies found a correlation with shorter TL, while five studies found no correlation. For both Cs and Ni, one study found a correlation with shorter TL, while two studies found no correlation. For As, two studies found a correlation with elongated TL, four studies found a correlation with shorter TL, and six studies found no correlation. For Se, 1 study found a correlation with elongated TL, 1 study found a correlation with shorter TL, and 11 studies found no correlation.

Table 2. Papers meeting the criteria of this study. The symbol > indicates a correlation between metal and longer TL, < indicates a correlation between metal and shorter TL, and o indicates no significant correlation. Grau-Perez et al., 2019 [33] was included as two studies because it completed independent analysis of the SHS and SHFS cohorts.

Paper	Sample Size	Location	Sample Group	Collection Period	Study Type	Cadmium	Arsenic	Nickel	Selenium	Lead	Cesium
O'Callaghan et al., 2014 [28]	89	Australia	Individuals (M and F) between 18–32 and 65–83 yo		Cross–sectional				o		
Gao et al., 2015 [29]	167	Bangladesh	Adults in BEST or HEALS cohorts	2000–2002	Cohort		>				
Milne et al., 2015 [30]	437	Australia	Children 3–9	2009–2011	Cross–sectional				o		
Pawlas et al., 2015 [31]	99	Poland	Children 8yo in PHIME cohort	2007–2010	Cross–sectional	o			o	<	
Pawlas et al., 2016 [32]	394	Poland	Male pb smelters and non–smelters		Cross–sectional	o			o	<	
Grau-Perez et al., 2019 [33]	1702	United States	Adults in SHS cohort	1989–1991	Cohort	<	<				
Grau-Perez et al., 2019 [33]	1793	United States	Adults in SHFS cohort	1998–2004	Cohort	o	o				
Herlin et al., 2019 [34]	169	Argentina	Mother–infant pairs	2012–2013	Cross–sectional	o	o		o	o	o
Mizuno et al., 2019 [35]	73	Japan	Female university students	2017	Cross–sectional	o					
Vriens et al., 2019 [36]	175	Belgium	Adults 50–65 in FLEHS cohort	2014	Cross–sectional	o	o	o			
Zhang et al., 2019 [37]	410	China	Mother–infant pairs	2013–2015	Cross–sectional	<					
Cowell et al., 2020 [38]	100	Boston/NYC	Mother–infant pairs in PRISM cohort	2011–2020	Cross–sectional	<	o	o		<	
Vahter et al., 2020 [39]	99	Argentina	Mother–infant pairs	2012–2013	Cross–sectional				o		
Wai et al., 2020 [40]	408	Myanmar	Mother–infant pairs	2016	Cohort	<	<		o	o	
Farzan et al., 2021 [41]	476	Bangladesh	Children 5–7 in BiRCH cohort	2014–2016	Cross–sectional		<				
Mizuno et al., 2021 [42]	73	Japan	Female university students	2017	Cross–sectional				<		
Smith et al., 2021 [43]	408	United States	Mother–infant pairs in Project Viva cohort	1999–2002	Cohort	o	o		o	o	o
Wang et al., 2021a [44]	757	China	Workers at a lead–acid storage battery plant	2016–2018	Cross–sectional					<	
Wang et al., 2021b [45]	746	China	Mother–infant pairs	2013–2015	Cohort				>		
Chen et al., 2022 [46]	12584	United States	Adults 20+ with osteoarthritis in NHANES cohort	1999–2016	Cross–sectional	<				o	<

Table 2. *Cont.*

Paper	Sample Size	Location	Sample Group	Collection Period	Study Type	Cadmium	Arsenic	Nickel	Selenium	Lead	Cesium
He et al., 2022 [47]	316	China	Ferro–manganese refinery workers in MEWHC cohort	2012–2020	Cohort	o			o	o	
Lai et al., 2022 [48]	4906	China	Retired employees of a motor corporation in DF–TJ cohort	2008–2013	Cross–sectional		<	<	o		
Loma et al., 2022 [49]	193	Bolivian Andes	Indigenous women	2015–2017	Cross–sectional		>				
Zhang et al., 2022 [50]	547	China	Adults 18+		Cross–sectional	<					
Mizuno et al., 2023 [51]	341	Laos	Adults from three villages	2018–2019	Cross–sectional	<	o		o		

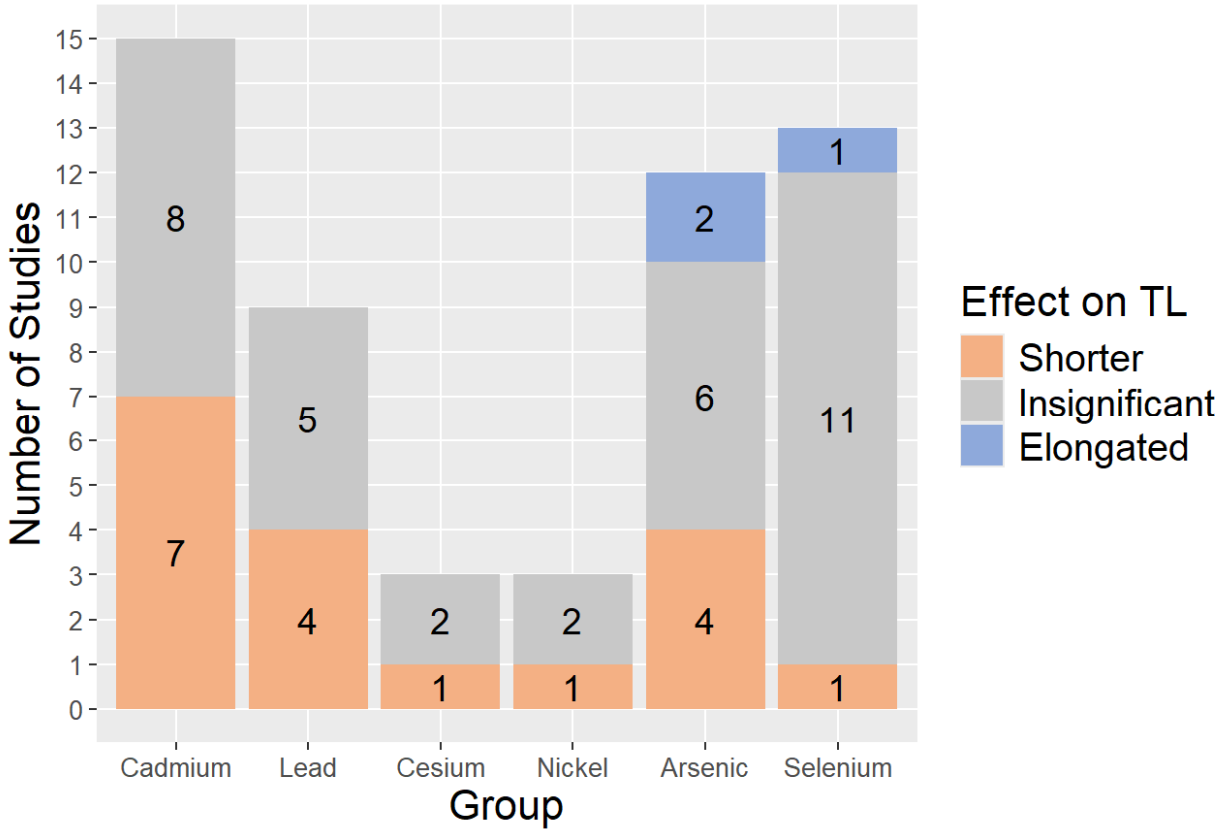

Figure 2. Conclusions of observational studies on the correlation between telomere length and metal. Numbers represent the number of studies that reported a given finding.

3.2. Sign Test Results

We found that, across all studies, there was a significant consensus that Cd was correlated with shorter TL ($p = 0.016$, $n = 15$). No significant consensus for a linear correlation between any other metal and TL was observed. The results of sign testing for each metal are summarized in Table 3.

Table 3. Two-tailed sign test analysis on consensus across studies of a relationship between metal and telomere length. Conclusions of a significant association between metal and shorter TL were assigned a value of −1, conclusions of a significant association between metal and longer TL were assigned a value of +1, and conclusions of no significant association were assigned a value of 0.

	Cadmium	Lead	Cesium	Nickel	Arsenic	Selenium
p	0.0156	0.125	1.00	1.00	0.688	1.00

4. Discussion

4.1. Evidence for Inverse Correlation Between Cadmium and Telomere Length

There is very limited evidence on the toxic effects of metal exposures and TL alterations. As reported in our previous studies [52,53] and ATSDR's toxicological profiles [22], exposure to various hazardous substances including several toxic metals can cause genetic alterations and mutations resulting in numerous pathologies [2,53]. However, the correlation between metal exposure and TL is unclear and inconsistent.

Our findings corroborate the existence of a correlation between Cd and decreased TL ($p = 0.016$, n = 15). No significant consensus was confirmed, however, for a linear correlation between TL and As, Ni, Se, Pb, or Cs. It is possible that any relationship varies across different populations or that a non-additive or nonlinear correlation exists between TL and some of these metals.

The correlation between Cd and decreased TL could be mediated by oxidative stress, which has been correlated with shorter TL [20,21]. Cd exposure has been linked to an increase in reactive oxygen species [54]. However, Pb [55], Cs [56], Ni [57,58], and As [59] have each been linked to increased oxidative stress, and Se has been shown to have an antioxidative effect [60,61]. Therefore, the correlation between Cd and altered TL being observed more consistently than for other metals could lie in the differences in mechanisms driving oxidative stress or in Cd-specific biological responses related to oxidative stress [62]. Future research is needed to define an exact mechanism that explains the stronger correlation between Cd and TL.

4.2. Variation in Correlation Across Groups

The studies included in Table 2 represent a broad range of populations, exposure levels, and age groups, and recent literature suggests that the correlation between metal and TL may not be equivalent across different conditions. Wai et al. [63] reviewed several observational studies on the correlation between TL and As and concluded that age may be a factor in why both positive and negative correlations have been demonstrated between As and TL in different populations. As such, it is possible that some of the correlations that have been observed between metal and TL are influenced by variation in study populations.

4.3. Non-Additive and Nonlinear Interactions

While this paper focuses on linear relationships between metals and TL, it is possible that non-additive (mixture effect) interactions or nonlinear relationships could exist between the metals and TL. Non-additive effects refer to the effects of exposure to a metal that are dependent upon exposure to a secondary metal, while nonlinear effects refer to a nonlinear relationship between a given metal and TL.

To the best of our knowledge, our group is the first to explore the association between inhalation of welding fumes, a complex mixture of different metals (e.g., Cr, Ni, Mn, and Fe), and its possible correlation with telomere length, epigenetic alterations [16], and markers of neurodegeneration [13] using an in vivo approach that mimics an occupational setting [52]. We demonstrated that mixed exposure to the metals in these fumes increases oxidative stress and affects TL, but further investigation is needed into whether these interactions are nonlinear or non-additive [16].

Smith et al. [43], which found no evidence for a linear relationship between TL and Cd, As, Se, Pb, or Cs in an observational study, explored evidence for a nonlinear relationship using Bayesian kernel machine regression (BKRM) [64] in combination with a generalized additive model and considered non-additive interactions using BKRM in combination with multivariate linear regression with multiplicative terms. These approaches yielded no evidence for a nonlinear relationship between TL and Cd, As, Se, Pb, or Cs nor for the existence of non-additive effects, although they did identify a nonlinear relationship between barium and TL that was not seen with a linear approach. Lai et al. [48] successfully used BKRM to validate significant linear relationships observed between shorter TL and both As and Ni. He et al. [47], which found no evidence for a linear relationship between

TL and Cd, Se, or Pb, used BKRM to observe a significant non-additive mixed interaction between 10 metals and TL in men but not in women.

While early research has not conclusively demonstrated a non-additive or nonlinear relationship between TL and the metals reviewed, we still recommend that future researchers test for non-additive and nonlinear interactions using novel techniques such as BKRM as a possible explanation for the inconsistency across reported findings of linear correlations.

4.4. Limitations of Employing Sign Testing

It should be acknowledged that the sign test used in this paper has limited power to detect significant trends in a TL–metal correlation across papers, especially for lower sample sizes in the cases of Ni and Cs. It is therefore possible that a true linear correlation exists between TL and As, Ni, Se, Pb, or Cs but is not sufficiently supported by evidence to be detected by our methods.

One solution for generating additional power is to use effect sizes, but this was not possible in our case because effect sizes could not be compared across studies due to different statistical approaches and transformations applied to predictor and response variables. Further, methods for standardizing beta coefficients across linear regressions with different transformations [65,66] failed because of data gaps and variation in the quantitative values reported by different studies. To account for this, we urge future researchers studying urinary metal concentrations using regression modeling to use creatine-adjusted values in ug/g creatinine [67], report the base used in any data transformations, report the mean, GM, and median for all predictor and response variables, and report exact *p*-values and effect sizes for both significant and insignificant variables.

5. Conclusions

Studies across different populations and exposure levels consistently report an inverse correlation between Cd and TL. As shorter telomeres have been shown to be a biomarker for age-related pathologies [2,10], our findings suggest that higher Cd levels could increase the risk of age-related pathologies.

We did not find evidence that correlations are consistently observed between TL and As, Ni, Se, Pb, or Cs, despite initial evidence for each correlation in at least one of the studies we reviewed. The inconsistency of observational findings could be explained by differences in populations and exposure levels. Further, we hypothesize that nonlinear or non-additive 'mixed' effects of co-exposure could explain why correlations are not consistently observed. Further research is needed to address significant differences in correlations existing across populations and exposure levels, and emphasis should be made on employing methods such as BKRM [64] to investigate nonlinear and non-additive effects.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/environments11120280/s1, Table S1: Search strategy used in our review; Table S2: Code used to calculate sign test values.

Author Contributions: Study design and conception: M.S. and Z.B. data collection, interpretation, and analysis: Z.B., C.J. and M.S. manuscript preparation and composition: Z.B., C.J., P.R., J.M.A., H.A., G.M.Z., B.A., O.F. and M.S. All authors have read and agreed to the published version of the manuscript.

Funding: This study was supported by funding from CDC-ATSDR.

Data Availability Statement: No new data were created or analyzed in this study.

Conflicts of Interest: The authors declare no conflicts of interest.

References

1. Shoeb, M.; Joseph, P.; Kodali, V.; Mustafa, G.; Farris, B.Y.; Umbright, C.; Roberts, J.R.; Erdely, A.; Antonini, J.M. Silica inhalation altered telomere length and gene expression of telomere regulatory proteins in lung tissue of rats. *Sci. Rep.* **2017**, *7*, 17284. [CrossRef] [PubMed]
2. Shoeb, M.; Meier, H.C.; Antonini, J.M. Telomeres in toxicology: Occupational health. *Pharmacol. Ther.* **2021**, *220*, 107742. [CrossRef] [PubMed]
3. Shay, J.W.; Wright, W.E. Telomeres and telomerase: Three decades of progress. *Nat. Rev. Genet.* **2019**, *20*, 299–309. [CrossRef] [PubMed]
4. Greider, C.W.; Blackburn, E.H. A telomeric sequence in the RNA of Tetrahymena telomerase required for telomere repeat synthesis. *Nature* **1989**, *337*, 331–337. [CrossRef]
5. Roake, C.M.; Artandi, S.E. Regulation of human telomerase in homeostasis and disease. *Nat. Rev. Mol. Cell Biol.* **2020**, *21*, 384–397. [CrossRef]
6. Londoño-Vallejo, J.A.; Wellinger, R.J. Telomeres and telomerase dance to the rhythm of the cell cycle. *Trends Biochem. Sci.* **2012**, *37*, 391–399. [CrossRef]
7. d'Adda di Fagagna, F.; Reaper, P.M.; Clay-Farrace, L.; Fiegler, H.; Carr, P.; von Zglinicki, T.; Saretzki, G.; Carter, N.P.; Jackson, S.P. A DNA Damage Checkpoint Response in Telomere-Initiated Senescence. *Nature* **2003**, *426*, 194–198. [CrossRef]
8. Herbig, U.; Jobling, W.A.; Chen, B.P.; Chen, D.J.; Sedivy, J.M. Telomere Shortening Triggers Senescence of Human Cells through a Pathway Involving ATM, p53, and p21(CIP1), but Not p16(INK4a). *Mol. Cell* **2004**, *14*, 501–513. [CrossRef]
9. Shoeb, M.; Mustafa, G.M.; Joseph, P.; Umbright, C.; Kodali, V.; Roach, K.A.; Meighan, T.; Roberts, J.R.; Erdely, A.; Antonini, J.M. Initiation of Pulmonary Fibrosis after Silica Inhalation in Rats is linked with Dysfunctional Shelterin Complex and DNA Damage Response. *Sci. Rep.* **2019**, *9*, 471. [CrossRef]
10. Fasching, C.L. Telomere length measurement as a clinical biomarker of aging and disease. *Crit. Rev. Clin. Lab. Sci.* **2018**, *55*, 443–465. [CrossRef]
11. Courtwright, A.M.; El-Chemaly, S. Telomeres in Interstitial Lung Disease: The Short and the Long of It. *Ann. Am. Thorac. Soc.* **2019**, *16*, 175–181. [CrossRef] [PubMed]
12. Armanios, M.; Blackburn, E.H. The telomere syndromes. *Nat. Rev. Genet.* **2012**, *13*, 693–704. [CrossRef] [PubMed]
13. Shoeb, M.; Mustafa, G.M.; Kodali, V.K.; Smith, K.; Roach, K.A.; Boyce, G.; Meighan, T.; Roberts, J.R.; Erdely, A.; Antonini, J.M. A possible relationship between telomere length and markers of neurodegeneration in rat brain after welding fume inhalation exposure. *Environ. Res.* **2019**, *180*, 108900. [CrossRef]
14. Yu, H.-J.; Koh, S.-H. Is Telomere Length Shortening a Risk Factor for Neurodegenerative Disorders? *Dement. Neurocognitive Disord.* **2022**, *21*, 83–92. [CrossRef]
15. Serrano, A.L.; Andrés, V. Telomeres and cardiovascular disease: Does size matter? *Circ. Res.* **2004**, *94*, 575–584. [CrossRef]
16. Shoeb, M.; Kodali, V.K.; Farris, B.Y.; Bishop, L.M.; Meighan, T.G.; Salmen, R.; Eye, T.; Friend, S.; Schwegler-Berry, D.; Roberts, J.R.; et al. Oxidative stress, DNA methylation, and telomere length changes in peripheral blood mononuclear cells after pulmonary exposure to metal-rich welding nanoparticles. *NanoImpact* **2017**, *5*, 61–69. [CrossRef]
17. Muñoz-Lorente, M.A.; Cano-Martin, A.C.; Blasco, M.A. Mice with hyper-long telomeres show less metabolic aging and longer lifespans. *Nat. Commun.* **2019**, *10*, 4723. [CrossRef]
18. Strong, M.A.; Vidal-Cardenas, S.L.; Karim, B.; Yu, H.; Guo, N.; Greider, C.W. Phenotypes in $mTERT^{+/-}$ and $mTERT^{-/-}$ Mice Are Due to Short Telomeres, Not Telomere-Independent Functions of Telomerase Reverse Transcriptase. *Mol. Cell. Biol.* **2011**, *31*, 2369–2379. [CrossRef]
19. Wu, X.; Amos, C.I.; Zhu, Y.; Zhao, H.; Grossman, B.H.; Shay, J.W.; Luo, S.; Hong, W.K.; Spitz, M.R. Telomere Dysfunction: A Potential Cancer Predisposition Factor. *JNCI J. Natl. Cancer Inst.* **2003**, *95*, 1211–1218. [CrossRef]
20. Von Zglinicki, T. Oxidative stress shortens telomeres. *Trends Biochem. Sci.* **2002**, *27*, 339–344. [CrossRef]
21. Barnes, R.P.; Fouquerel, E.; Opresko, P.L. The impact of oxidative DNA damage and stress on telomere homeostasis. *Mech. Ageing Dev.* **2019**, *177*, 37–45. [CrossRef] [PubMed]
22. Agency for Toxic Substances and Disease Registry, "Toxicological Profiles". Available online: https://www.atsdr.cdc.gov/toxprofiledocs/index.html (accessed on 1 December 2024).
23. Ho, S.H.; Soh, S.X.H.; Wang, M.X.; Ong, J.; Seah, A.; Wong, Y.; Fang, Z.; Sim, S.; Lim, J.T. Perfluoroalkyl substances and lipid concentrations in the blood: A systematic review of epidemiological studies. *Sci. Total. Environ.* **2022**, *850*, 158036. [CrossRef] [PubMed]
24. Chen, J.C.; Baumert, B.O.; Li, Y.; Li, Y.; Pan, S.; Robinson, S.; Rubbo, B.; Costello, E.; He, J.; Hampson, H.; et al. Associations of per- and polyfluoroalkyl substances, polychlorinated biphenyls, organochlorine pesticides, and polybrominated diphenyl ethers with oxidative stress markers: A systematic review and meta-analysis. *Environ. Res.* **2023**, *239*, 117308. [CrossRef]
25. Seabold, S.; Perktold, J. Statsmodels: Econometric and Statistical Modeling with Python. In Proceedings of the 9th Python in Science Conference, Austin, TX, USA, 28 June–3 July 2010; pp. 92–96. [CrossRef]
26. Wickham, H.; Averick, M.; Bryan, J.; Chang, W.; McGowan, L.D.A.; François, R.; Grolemund, G.; Hayes, A.; Henry, L.; Hester, J.; et al. Welcome to the Tidyverse. *J. Open Source Softw.* **2019**, *4*, 1686. [CrossRef]
27. RStudio Team. *RStudio: Integrated Development Environment for R*; RStudio Team: Boston, MA, USA, 2020; Available online: http://www.rstudio.com/ (accessed on 2 September 2024).

28. O'Callaghan, N.J.; Bull, C.; Fenech, M. Elevated plasma magnesium and calcium may be associated with shorter telomeres in older South Australian women. *J. Nutr. Heal. Aging* **2014**, *18*, 131–136. [CrossRef]
29. Gao, J.; Roy, S.; Tong, L.; Argos, M.; Jasmine, F.; Rahaman, R.; Rakibuz-Zaman, M.; Parvez, F.; Ahmed, A.; Hore, S.K.; et al. Arsenic exposure, telomere length, and expression of telomere-related genes among Bangladeshi individuals. *Environ. Res.* **2014**, *136*, 462–469. [CrossRef]
30. Milne, E.; O'callaghan, N.; Ramankutty, P.; de Klerk, N.H.; Greenop, K.R.; Armstrong, B.K.; Miller, M.; Fenech, M. Plasma micronutrient levels and telomere length in children. *Nutrition* **2015**, *31*, 331–336. [CrossRef]
31. Pawlas, N.; Płachetka, A.; Kozłowska, A.; Broberg, K.; Kasperczyk, S. Telomere length in children environmentally exposed to low-to-moderate levels of lead. *Toxicol. Appl. Pharmacol.* **2015**, *287*, 111–118. [CrossRef]
32. Pawlas, N.; Płachetka, A.; Kozłowska, A.; Mikołajczyk, A.; Kasperczyk, A.; Dobrakowski, M.; Kasperczyk, S. Telomere length, telomerase expression, and oxidative stress in lead smelters. *Toxicol. Ind. Heal.* **2016**, *32*, 1961–1970. [CrossRef]
33. Grau-Perez, M.; Zhao, J.; Pierce, B.; Francesconi, K.A.; Goessler, W.; Zhu, Y.; An, Q.; Umans, J.; Best, L.; Cole, S.A.; et al. Urinary metals and leukocyte telomere length in American Indian communities: The Strong Heart and the Strong Heart Family Study. *Environ. Pollut.* **2018**, *246*, 311–318. [CrossRef]
34. Herlin, M.; Broberg, K.; Igra, A.M.; Li, H.; Harari, F.; Vahter, M. Exploring telomere length in mother–newborn pairs in relation to exposure to multiple toxic metals and potential modifying effects by nutritional factors. *BMC Med.* **2019**, *17*, 77. [CrossRef] [PubMed]
35. Mizuno, Y.; Konishi, S.; Imai, H.; Fujimori, E.; Kojima, N.; Yoshinaga, J. Cadmium Exposure and Blood Telomere Length in Female University Students in Japan. *Biol. Trace Element Res.* **2019**, *192*, 98–105. [CrossRef] [PubMed]
36. Vriens, A.; Nawrot, T.S.; Janssen, B.G.; Baeyens, W.; Bruckers, L.; Covaci, A.; De Craemer, S.; De Henauw, S.; Den Hond, E.; Loots, I.; et al. Exposure to Environmental Pollutants and Their Association with Biomarkers of Aging: A Multipol-lutant Approach. *Environ. Sci. Technol.* **2019**, *53*, 5966–5976. [CrossRef] [PubMed]
37. Zhang, L.; Song, L.; Liu, B.; Wu, M.; Wang, L.; Zhang, B.; Xiong, C.; Xia, W.; Li, Y.; Cao, Z.; et al. Prenatal cadmium exposure is associated with shorter leukocyte telomere length in Chinese newborns. *BMC Med.* **2019**, *17*, 27. [CrossRef]
38. Cowell, W.; Colicino, E.; Tanner, E.; Amarasiriwardena, C.; Andra, S.S.; Bollati, V.; Kannan, S.; Ganguri, H.; Gennings, C.; Wright, R.O.; et al. Prenatal toxic metal mixture exposure and newborn telomere length: Modification by maternal antioxidant intake. *Environ. Res.* **2020**, *190*, 110009. [CrossRef]
39. Vahter, M.; Broberg, K.; Harari, F. Placental and Cord Blood Telomere Length in Relation to Maternal Nutritional Status. *J. Nutr.* **2020**, *150*, 2646–2655. [CrossRef]
40. Wai, K.M.; Umezaki, M.; Umemura, M.; Mar, O.; Watanabe, C. Protective role of selenium in the shortening of telomere length in newborns induced by in utero heavy metal exposure. *Environ. Res.* **2020**, *183*, 109202. [CrossRef]
41. Farzan, S.F.; Shahriar, M.; Kibriya, M.G.; Jasmine, F.; Sarwar, G.; Slavkovic, V.; Graziano, J.H.; Ahsan, H.; Argos, M. Urinary arsenic and relative telomere length in 5–7 year old children in Bangladesh. *Environ. Int.* **2021**, *156*, 106765. [CrossRef]
42. Mizuno, Y.; Konishi, S.; Imai, H.; Fujimori, E.; Kojima, N.; Kajiwara, C.; Yoshinaga, J. Telomere length and urinary 8-hydroxy-2′-deoxyguanosine and essential trace element concentrations in female Japanese university students. *J. Environ. Sci. Heal. Part A* **2021**, *56*, 1328–1334. [CrossRef]
43. Smith, A.R.; Lin, P.-I.D.; Rifas-Shiman, S.L.; Rahman, M.L.; Gold, D.R.; Baccarelli, A.A.; Henn, B.C.; Amarasiriwardena, C.; Wright, R.O.; Coull, B.; et al. Prospective Associations of Early Pregnancy Metal Mixtures with Mitochondria DNA Copy Number and Telomere Length in Maternal and Cord Blood. *Environ. Heal. Perspect.* **2021**, *129*, 117007. [CrossRef]
44. Wang, T.; Tu, Y.; Wang, K.; Gong, S.; Zhang, G.; Zhang, Y.; Meng, Y.; Wang, T.; Li, A.; Cui, J.; et al. Associations of blood lead levels with multiple genotoxic biomarkers among workers in China: A population-based study. *Environ. Pollut.* **2020**, *273*, 116181. [CrossRef] [PubMed]
45. Wang, L.; Song, L.; Liu, B.; Zhang, L.; Wu, M.; Liu, Y.; Bi, J.; Yang, S.; Cao, Z.; Xia, W.; et al. Association between maternal urinary selenium during pregnancy and newborn telomere length: Results from a birth cohort study. *Eur. J. Clin. Nutr.* **2021**, *76*, 716–721. [CrossRef] [PubMed]
46. Chen, L.; Zhao, Y.; Liu, F.; Chen, H.; Tan, T.; Yao, P.; Tang, Y. Biological aging mediates the associations between urinary metals and osteoarthritis among U.S. adults. *BMC Med.* **2022**, *20*, 207. [CrossRef] [PubMed]
47. He, J.; Ge, X.; Cheng, H.; Bao, Y.; Feng, X.; Zan, G.; Wang, F.; Zou, Y.; Yang, X. Sex-specific associations of exposure to metal mixtures with telomere length change: Results from an 8-year longitudinal study. *Sci. Total. Environ.* **2021**, *811*, 151327. [CrossRef]
48. Lai, X.; Yuan, Y.; Liu, M.; Xiao, Y.; Ma, L.; Guo, W.; Fang, Q.; Yang, H.; Hou, J.; Yang, L.; et al. Individual and joint associations of co-exposure to multiple plasma metals with telomere length among middle-aged and older Chinese in the Dongfeng-Tongji cohort. *Environ. Res.* **2022**, *214*, 114031. [CrossRef]
49. De Loma, J.; Krais, A.M.; Lindh, C.H.; Mamani, J.; Tirado, N.; Gardon, J.; Broberg, K. Arsenic exposure and biomarkers for oxidative stress and telomere length in indigenous populations in Bolivia. *Ecotoxicol. Environ. Saf.* **2022**, *231*, 113194. [CrossRef]
50. Zhang, J.-C.; Li, S.-J.; Guo, J.-Y.; Zhang, G.-Y.; Kang, H.; Shi, X.-J.; Zhou, H.; Liang, Y.-F.; Shen, W.-T.; Lei, L.-J. Urinary cadmium and peripheral blood telomere length predict the risk of renal function impairment: A study of 547 community residents of Shanxi, China. *Environ. Sci. Pollut. Res.* **2022**, *29*, 71427–71438. [CrossRef]

51. Mizuno, Y.; Inaba, Y.; Masuoka, H.; Kibe, M.; Kosaka, S.; Natsuhara, K.; Hirayama, K.; Inthavong, N.; Kounnavong, S.; Tomita, S.; et al. Determinants of oxidative stress among indigenous populations in Northern Laos: Trace element exposures and dietary patterns. *Sci. Total. Environ.* **2023**, *868*, 161516. [CrossRef]
52. Shoeb, M.; Meighan, T.; Kodali, V.K.; Abadin, H.; Faroon, O.; Zarus, G.M.; Erdely, A.; Antonini, J.M. TERT-independent telomere elongation and shelterin dysregulation after pulmonary exposure to stainless-steel welding fume in-vivo. *Environ. Res.* **2024**, *250*, 118515. [CrossRef]
53. Shoeb, M.; Zarus, G.M.; Abadin, H.E. Profiling Metal-Induced Genotoxic Endpoints. *J. Environ. Health* **2023**, *86*, 30–35. Available online: https://pubmed.ncbi.nlm.nih.gov/39239121/ (accessed on 1 December 2024).
54. Liu, J.; Qu, W.; Kadiiska, M.B. Role of oxidative stress in cadmium toxicity and carcinogenesis. *Toxicol. Appl. Pharmacol.* **2009**, *238*, 209–214. [CrossRef] [PubMed]
55. Lopes, A.C.B.A.; Peixe, T.S.; Mesas, A.E.; Paoliello, M.M.B. Lead Exposure and Oxidative Stress: A Sys-tematic Review. *Rev. Environ. Contam. Toxicol.* **2016**, *236*, 193–238. [CrossRef] [PubMed]
56. Tang, M.-M.; Hou, X.-F.; Sun, J.; Cheng, J.-Y.; Deng, Y.-P.; Li, M.-D.; Liu, L.; Hua, D.-X.; Yang, J.; Jiang, Y.-L.; et al. Cesium exposure and pulmonary function decline: Potential mediating role of oxidative stress in chronic obstructive pulmonary disease patients. *Atmospheric Pollut. Res.* **2023**, *14*, 101719. [CrossRef]
57. Zhang, Z.-N.; Liu, H.; Liu, M.-M.; Yang, D.-L.; Bi, J.; Chen, Q.-Q.; Chen, W.; Xiang, P. Effects of Nickel at Environmentally Relevant Concentrations on Human Corneal Epithelial Cells: Oxidative Damage and Cellular Apoptosis. *Biomolecules* **2022**, *12*, 1283. [CrossRef] [PubMed]
58. Das, S.; Reddy, R.C.; Chadchan, K.S.; Patil, A.J.; Biradar, M.S.; Das, K.K. Nickel and Oxidative Stress: Cell Signaling Mechanism and Protective Role of Vitamin C. *Endocrine, Metab. Immune Disord. Drug Targets* **2020**, *20*, 1024–1031. [CrossRef]
59. Flora, S.J. Arsenic-induced oxidative stress and its reversibility. *Free. Radic. Biol. Med.* **2011**, *51*, 257–281. [CrossRef]
60. Tinggi, U. Selenium: Its role as antioxidant in human health. *Environ. Health Prev. Med.* **2008**, *13*, 102–108. [CrossRef]
61. Zakeri, N.; Kelishadi, M.R.; Asbaghi, O.; Naeini, F.; Afsharfar, M.; Mirzadeh, E.; Naserizadeh, S.K. Selenium supplementation and oxidative stress: A review. *PharmaNutrition* **2021**, *17*, 100263. [CrossRef]
62. Patra, R.C.; Rautray, A.K.; Swarup, D. Oxidative Stress in Lead and Cadmium Toxicity and Its Amelioration. *Vet. Med. Int.* **2011**, *2011*, 457327. [CrossRef]
63. Wai, K.M.; Swe, T.; Myar, M.T.; Aisyah, C.R.; Hninn, T.S.S. Telomeres susceptibility to environmental arsenic exposure: Shortening or lengthening? *Front. Public Heal.* **2023**, *10*, 1059248. [CrossRef]
64. Bobb, J.F.; Valeri, L.; Henn, B.C.; Christiani, D.C.; Wright, R.O.; Mazumdar, M.; Godleski, J.J.; Coull, B.A. Bayesian kernel machine regression for estimating the health effects of multi-pollutant mixtures. *Biostatistics* **2014**, *16*, 493–508. [CrossRef] [PubMed]
65. Rodríguez-Barranco, M.; Tobías, A.; Redondo, D.; Molina-Portillo, E.; Sánchez, M.J. Standardizing effect size from linear regression models with log-transformed variables for meta-analysis. *BMC Med Res. Methodol.* **2017**, *17*, 44. [CrossRef]
66. Linakis, M.W.; Van Landingham, C.; Gasparini, A.; Longnecker, M.P. Re-expressing coefficients from regression models for inclusion in a meta-analysis. *BMC Med Res. Methodol.* **2024**, *24*, 6. [CrossRef] [PubMed]
67. Barr, D.B.; Wilder, L.C.; Caudill, S.P.; Gonzalez, A.J.; Needham, L.L.; Pirkle, J.L. Urinary Creatinine Concentrations in the U.S. Population: Implications for Urinary Biologic Monitoring Measurements. *Environ. Heal. Perspect.* **2005**, *113*, 192–200. [CrossRef]