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Early life exposure to mercury and relationships with telomere length and mitochondrial DNA content in European children

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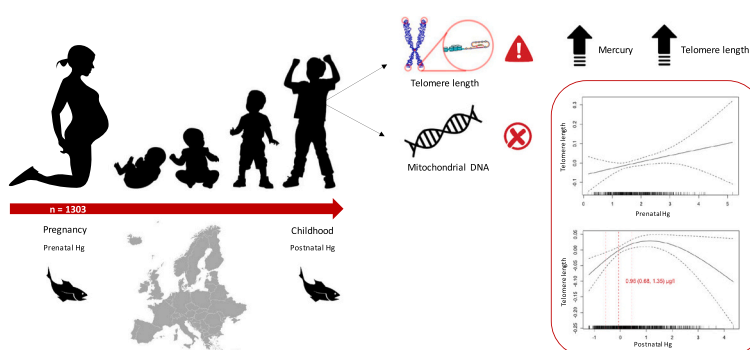
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HIGHLIGHTS

- Higher mercury concentrations were related to longer telomere length in children.
- Mercury exposures were associated with telomere length even at low exposure levels.
- Postnatal mercury and telomere length showed a non-linear relationship.
- Fish consumption did not affect the association between mercury and telomere length.
- No association between mercury exposure and mitochondrial DNA was found.

GRAPHICAL ABSTRACT



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ABSTRACT

Background: Telomere length (TL) and mitochondrial function expressed as mitochondrial DNA copy number (mtDNAcn) are biomarkers of aging and oxidative stress and inflammation, respectively. Methylmercury (MeHg), a common pollutant in fish, induces oxidative stress. We hypothesized that elevated oxidative stress from exposure to MeHg decreases mtDNAcn and shortens TL.

Methods: Study participants are 6–11-year-old children from the HELIX multi-center birth cohort study, comprising six European countries. Prenatal and postnatal total mercury (THg) concentrations were measured in blood samples, TL and mtDNAcn were determined in child DNA. Covariates and confounders were obtained by questionnaires. Robust regression models were run, considering sociodemographic and lifestyle covariates, as well as fish consumption. Sex, ethnicity, and fish consumption interaction models were also run.

Results: We found longer TL with higher pre- and postnatal THg blood concentrations, even at low-level THg exposure according to the RfD proposed by the US EPA. The prenatal association showed a significant linear relationship with a 3.46 % increase in TL for each unit increased THg. The postnatal association followed an inverted U-shaped marginal non-linear relationship with 1.38 % an increase in TL for each unit increased THg until reaching a cut-point at 0.96 µg/L blood THg, from which TL attrition was observed. Higher pre- and postnatal blood THg concentrations were consistently related to longer TL among cohorts and no modification effect of fish consumption nor children's sex was observed. No association between THg exposure and mtDNAcn was found.

Discussion: We found evidence that THg is associated with TL but the associations seem to be time- and concentration-dependent. Further studies are needed to clarify the mechanism behind the telomere changes of THg and related health effects.

1. Introduction

Telomere length (TL) and mitochondrial function, expressed as mitochondrial DNA copy number (mtDNAcn), are biomarkers linked to age-related diseases (Sahin and DePinho, 2012). Both have been considered as cellular sensors for environmental stressors on the basis of their sensitivity to oxidative DNA damage and inflammation (Martens and Nawrot, 2016; Meyer et al., 2013).

Mercury (Hg) is ubiquitously present in the environment. For humans, the diet is usually the main source of exposure, through the consumption of fish that contains methylmercury (MeHg) (United Nations, 2018). MeHg accumulates and biomagnifies through the food chain, reaching the highest concentrations in large, oily, predatory fishes and marine mammals (Hintelmann, 2010). Early life exposure to MeHg has been related to adverse effects on foetal and children's health and development, such as neurotoxicity (Grandjean et al., 2014; Karagas et al., 2012; Sharma et al., 2019; Vejrup et al., 2022; Vejrup et al., 2018), impaired growth (Ballester et al., 2018; Murcia et al., 2016; Vejrup et al., 2014), and cardiovascular insults such as higher blood pressure (Farzan et al., 2021; Ying Chan et al., 2021; Zhang et al., 2021). MeHg from dietary and inhalation exposures is almost completely absorbed (around 90 %) into the bloodstream (Gad, 2024). About 95 % is taken up by red blood cells, and then distributed throughout the maternal body over the next 3 to 4 days. In pregnant women, MeHg readily crosses the placenta and has a high affinity for fetal hemoglobin (Myers and Davidson, 1998). However, the results from the literature on toxicity related to a early exposure to MeHg are inconsistent and several studies have found no adverse effect (Jj et al., 2021; Klus et al., 2023). Biomarkers of intermediate effects may aid in clarifying such inconsistencies. Several intermediary mechanisms of MeHg-related toxicity have been suggested, as a consequence of the MeHg-related increased oxidative stress (Crespo-López et al., 2009), including epigenetic changes (Cardenas et al., 2017; Cediel-Ulloa et al., 2023; Lozano et al., 2022), and effects on mtDNAcn (Dreiem et al., 2005; Smith et al., 2021) and TL (Smith et al., 2021; Vriens et al., 2019).

The mitochondria are the main site of oxidative phosphorylation and the dominant cellular site for the generation of reactive oxidative species (Meyer and Chan, 2017). Mitochondrial DNA lack histones and DNA repair (Yakes and Van Houten, 1997), making mitochondrial DNA more vulnerable to oxidative stress than nuclear DNA, thus, with time mitochondrial DNA accumulates mutations and mtDNAcn is reduced (Kowalski et al., 2020). Telomeres are DNA-protein structures at the

ends of chromosomes. Telomeres (due to their Guanine-rich sequence) are hyper-sensitive to oxidative stress, which lead to telomere shortening with time (Kawanishi and Oikawa, 2004; von Zglinicki, 2002). When the telomere reaches a certain short length, cells go into senescence or apoptosis. In this way, the telomeres preserve chromosome stability and integrity (Blackburn, 1991) and accordingly, TL is a marker of cellular health and aging (Shammas, 2011).

TL at birth predicts TL later in life but there are dynamic changes of TL throughout life (Martens et al., 2021). Multiple environmental factors in adulthood have been found to influence TL, but less is known about the environmental factors influencing TL early in life (Gorenjak et al., 2020). Studies assessing the relationship between the pre- and postnatal exposure to pollutants and TL during childhood could be useful in public health since TL in this period has been associated with chronic diseases in adulthood (Kemp and Ferraro, 2021), such as the metabolic syndrome (Elks and Scott, 2013; Révész et al., 2014; Zhao et al., 2017), cardiovascular (Barracough et al., 2019; Ghoussaini et al., 2022; Haycock et al., 2014) and neurodegenerative diseases (Lee et al., 2020; Rodríguez-Fernández et al., 2022). Similarly, lower mtDNAcn during childhood has been related to an increased risk of cardiovascular (Liu et al., 2021; Sazonova et al., 2021) and neurodegenerative diseases (Burr and Chinnery, 2022; Pillalamarri et al., 2023), non-alcoholic fatty liver disease and high insulin levels (Ganel et al., 2021; Zhang et al., 2022) in adulthood.

There is limited and inconsistent evidence about the impact of early exposure to MeHg on TL or mtDNAcn. Results from the Project Viva from the US showed a marginal negative association between maternal blood MeHg and cord blood TL and a statistically significant non-linear cubic relationship between maternal blood MeHg and mtDNAcn (Smith et al., 2021). Results from the Seychelles Child Development study showed no relation between prenatal MeHg (measured in maternal hair) and child TL (measured at birth and at 5 years of age) (Yeates et al., 2017). In a larger mother child cohort from the Seychelles, MeHg concentrations in cord blood were associated with lower cord blood mtDNAcn (Xu et al., 2019).

Previous research relating TL and mtDNAcn with other metals inducing oxidative stress, (such as arsenic, cadmium, chromium, manganese, nickel, and lead), showed both positive and negative relationships (Alegria-Torres et al., 2020; Ameer et al., 2016; Fillman et al., 2016; Li et al., 2020; Pawlas et al., 2016; Wu et al., 2012). Dose-dependencies and non-linear relationships have been suggested to explain the inconsistencies (Zhang et al., 2003). Telomere lengthening,

as observed in relation to exposure to low-to-moderate levels of arsenic, has been explained by oxidative stress-related upregulation of expression of the telomerase encoding gene *TERT* and upregulation of the telomerase independent pathway (Chatterjee et al., 2015; Fernandes et al., 2021; Ferrario et al., 2009a; Li et al., 2012).

Our primary aim in this study was to assess the relationships, considering potential concentration-dependencies and non-linear associations, between prenatal and postnatal exposure to Hg in relation to TL and mtDNAcn in children from a multi-centre birth cohort study in six European countries. Our secondary aim was to examine the role of fish consumption as an effect modifier of the MeHg effect.

2. Methods

2.1. Subjects

This study used data collected from the European Human Early-Life Exposome (HELIX) project. The characteristics of the HELIX cohorts and the inclusion criteria have been described elsewhere (Maitre et al., 2018; Vrijheid et al., 2014). This study assesses pre- and postnatal exposure to a broad range of chemical and physical exposures in the following cohorts: BiB (Born in Bradford; United Kingdom) (Wright et al., 2013), EDEN (Étude des Déterminants pré et postnataux du développement et la santé de l'Enfant, France) (Heude et al., 2016), INMA (Infancia y Medio Ambiente) (Guxens et al., 2012), KANC (Kaunas Cohort; Lithuania) (Grazuleviciene et al., 2009), MoBa (Norwegian Mother, Father and Child Cohort Study; Norway) (Magnus et al., 2016), and Rhea (the Mother-Child Cohort in Crete, Greece) (Chatzi et al., 2017).

We used data from participants with childhood TL and mtDNAcn measurements ($N = 1303$). To be included in the present study, participants had to have also analytical measurements of pre- and postnatal total blood mercury (THg) (N prenatal = 926 and N postnatal = 1164). The present study used the available THg concentrations in all the HELIX cohorts. THg has been previously used as a biomarker of MeHg intake in several studies (90 % of THg has been considered MeHg (Llop et al., 2017; Wells et al., 2022) and correlated with fish consumption in general human populations (Berglund et al., 2005; Clarkson and Magos, 2006; Jenssen et al., 2012).

Informed consent was obtained from all participants in each phase, and the study was approved by the national committees for medical and health research ethics in each participating region. This study conforms to the ethical principles of research embodied in the Declaration of Helsinki.

2.2. Mercury measurements

THg was measured in blood samples for both the pre- and postnatal (childhood) periods. Maternal blood samples (prenatal exposure) were collected in mid-pregnancy for MoBa (mean = 18.7 (SD = 0.9) weeks) and Rhea (14.1 (3.7) weeks), in late pregnancy for BiB (26.6 (1.4) weeks), KANC (39.4 (1.3) weeks), and EDEN (26.1 (1.2) weeks), while, for the INMA, cord blood samples were collected at delivery. Cord blood concentrations were divided by 1.7 to calculate values equivalent to maternal whole blood concentrations (Stern and Smith, 2003). Children's blood samples in all HELIX cohorts (postnatal exposure) were available and collected between the age of 6 and 11 years (mean [CI 95 %] = 8.2 [6.5, 9.1]). Maternal and child THg concentrations in BiB, EDEN, KANC, MoBa and Rhea cohorts were measured in the same laboratory (ALS Scandinavia, Sweden) and cord blood THg concentrations in the INMA cohort were measured in the Public Health Laboratory in Alava (Spain). Details of the analytical and quality control procedures used for the HELIX project have been described previously (Haug et al., 2018; Llop et al., 2020).

2.3. DNA extraction, mitochondrial DNA copy number, and telomere length

DNA was extracted from children 6–11 years old following a protocol described elsewhere (Maitre et al., 2018). MtDNA and single copy-gene reaction mixture and PCR cycles used can be found in Clemente et al. (Clemente et al., 2016) and Janssen et al. (Janssen et al., 2012). More details and the procedure about the relative mtDNAcn calculation and the quality control can be found in the Supplemental Methods.

Relative TL was measured by a modified quantitative real-time PCR (qPCR) protocol, as described previously (Cawthon, 2009). Telomere and single copy-gene reaction mixture and PCR cycles used are described in Martens et al. (Martens et al., 2016). More details and information about the relative TL calculation and quality control can be found in the Supplemental Methods.

2.4. Covariate information

Detailed information on maternal age at birth, smoking status during pregnancy (smoker, non-smoker), parity (primiparous, >1 birth), maternal ethnicity (European, South Asian, and others), and maternal education as the primary indicator of socioeconomic status (categorized according to the International Standard Classification of Education (ISCED): low (less than primary, primary, and lower secondary education, ISCED 2011 levels 0–2), middle (upper secondary and post-secondary nontertiary education, ISCED 2011 levels 3 and 4), and high (tertiary education, ISCED 2011 levels 5–8)) (Schneider, 2013). Maternal fish consumption from each study participant (servings per week) was obtained by each cohort during pregnancy or at birth by food frequency questionnaires, except for the KANC cohort which had no information on maternal diet. Newborn sex was recorded at birth and offspring fish consumption was determined at the 6–11 years follow-up through interviews and food frequency questionnaires. Fish intake was categorized into tertiles.

2.5. Statistical analysis

The geometric mean (GM) and 95 % confidence intervals (95%CI) were calculated for THg concentrations in maternal and child blood, and for child TL and mtDNAcn for each cohort. For further analysis, the logarithmic form (base 2) of THg, TL and mtDNAcn transformed values were calculated. Kernel density plots were plotted. The ANOVA F-test was applied to compare the geometric mean of prenatal and postnatal THg, TL and mtDNAcn across categories of the study population's characteristics.

Association models between pre- and postnatal exposure to THg with children's TL and mtDNAcn were built. To consider potential concentration-dependencies and non-linear associations, multivariable robust quantile regression models were used (Koenker, 2005) following a two-step procedure. In the first step, a core model was built using mixed regression models since both pre- and postnatal THg measurements (log2 transformed) were available (including a nested participant/cohort random term). We included all the available variables as possible covariates. To do this, bivariate and multivariate models were performed. The multivariate model was built using all the covariates associated with a p -value <0.2 in the bivariate analysis. Following a backward elimination procedure, all covariates associated with the THg at a level of $p < 0.1$ were retained in the model. In the second step, we used linear regression models to build a core model for each log-transformed outcome since we only had TL and mtDNAcn postnatal measurements following the same procedure of variable selection. The log2THg variable was then introduced into the outcome-adjusted models and three robust quantile regression models were run (a prenatal model including the prenatal log2THg, a postnatal model including the postnatal log2THg, and a longitudinal model including both). Additional potential confounders were added to these outcome

models if they changed the magnitude of the main effects by >10 %. All covariates in the mixed multivariate model for the THg concentration were considered to be potential confounders (Soler-Blasco et al., 2019) in this step. The cohort variable was included in all models regardless of its statistical significance. Additionally, to assess differences between exposure concentrations, linear regression models including the THg exposure variable categorized into quartiles were run. Generalized additive models (GAM) were fitted to evaluate non-linear patterns. Natural cubic splines with one or two internal knots were compared through Akaike (AIC) scores, graphical examination, and the Likelihood Ratio test (LRT). Segmented regressions were carried out to estimate potential break-points in the linearity (Muggeo, 2003).

Effect modification by sex of the child and total fish consumption was assessed through the inclusion of an interaction term in the main models. The effect modification was considered statistically significant if the interaction *p*-value <0.05, although marginally significant interactions (*p*-value <0.1) were also considered.

The robustness of the results was validated through a full meta-analysis to verify the possible influence of specific cohorts (by means of I^2 random-effects tests, considering low heterogeneity <25 % (Higgins et al., 2003)), followed by a Leave-One-Out procedure (excluding one cohort at a time and rerunning the models), as well as removing the minor ethnicities to avoid potential genetic or socioeconomic bias.

Since the measurement of TL and mtDNAcn are relative measurements, results are additionally presented calculating the percent changes based on the beta coefficients on the logarithmic scale. This was done using the following formula: $10^{(\beta-1)} \times 100$. Thus, one unit of change in the beta of the exposure (log2THg in this case) is associated with a specific percentage of change in the outcomes (TL and mtDNAcn).

The validity of the regression models was tested by residual analysis. No influential data was identified by graphical representation. Collinearity diagnostics were conducted on the final models.

Both outcome and exposure variables transformed into logarithmic form followed a normal distribution, as can be seen in Kernel density plots of the Supplemental Fig. S1, validating the use of the proposed

statistics. Statistical analysis was carried out using the R statistical package version 4.2.3 (R Core Team, 2017).

3. Results

3.1. Characteristics of the study population

Table 1 shows the characteristics of participants in the study. The 1303 mothers from HELIX cohorts with TL and mtDNAcn measurements had a mean (SD) age of 30.7 (4.9) years and reported a fish intake of 3.8 (4.6) servings/week. >50 % of the mothers were highly educated, 15.1 % actively smoked during pregnancy and women were mainly of European origin (89.4 %). The children were in average 8 (1.5) years, consumed 2.6 (2.3) servings/week of fish, and 55.0 % were male.

The geometric mean and confidence interval (95 %) of children's relative TL and mtDNAcn were 1.01 (1.00, 1.02) and 1.07 (1.06, 1.09), respectively. Longer TL were observed in BIB, INMA, MoBa and Rhea cohorts, which also showed higher maternal fish intake (Table 1). Female children showed longer TL than males (0.987 [0.873, 1.000] and 1.037 [1.021, 1.053] for males and females, respectively). There were no differences in TL with respect to ethnicity; however, we observed higher mtDNAcn and prenatal THg concentrations in the European population (data not shown). Significant correlations were found between longer TL and mtDNAcn with maternal age ($r = 0.295$ and $r = 0.130$, respectively, *p*-value ≤ 0.001) without sex differences (Supplemental Fig. S2).

3.2. Factors associated with telomere length and mitochondrial DNA copy number

Higher maternal age, non-European ethnicity, female sex and mtDNAcn were positively associated with longer TL in the multivariate basal model. Non-primiparous mothers, European ethnicity, and longer TL, were associated with higher mtDNAcn (Supplemental Fig. S3).

Table 1
Characteristics of the study participants.

Cohort	Units	BIB	EDEN	INMA	KANC	MoBa	Rhea
Sample size (n = 1303) ^a		205	198	223	204	272	201
Country		UK	France	Spain	Lithuania	Norway	Greece
Children's relative TL	GM	1.01	0.99	1.01	0.99	1.02	1.05
	(CI95%)	(0.98, 1.03)	(0.96, 1.02)	(0.99, 1.02)	(0.97, 1.02)	(1.00, 1.05)	(1.02, 1.07)
Children's mtDNAcn	GM	0.82	1.07	1.06	1.20	1.31	0.98
	(CI95%)	(0.80, 0.84)	(1.03, 1.12)	(1.04, 1.08)	(1.16, 1.23)	(1.26, 1.36)	(0.95, 1.01)
Maternal THg ^b	GM	2.33	4.22	5.89	1.84	3.28	4.54
	(CI95%)	(2.18, 2.49)	(3.60, 4.83)	(5.31, 6.47)	(1.75, 1.94)	(3.09, 3.46)	(4.01, 5.08)
Children's THg ^b	GM	1.42	2.35	3.11	0.78	1.35	1.72
	(CI95%)	(1.29, 1.55)	(2.13, 2.57)	(2.78, 3.45)	(0.73, 0.83)	(1.27, 1.44)	(1.49, 1.96)
Maternal age	Mean (SD), years	28.6 (5.8)	30.8 (4.9)	31.9 (3.9)	29.1 (5.0)	32.8 (3.7)	30.8 (4.8)
Parity	% nulliparous	47.0	47.6	53.6	44.2	46.9	39.9
Child sex	% male	55.0	57.2	54.2	54.8	54.0	55.5
Maternal education							
Up to primary	%	47.7	7.0	23.9	5.7	0	4.6
Secondary	%	17.4	37.1	41.8	34.7	20.2	56.1
University	%	34.8	55.9	34.3	59.6	79.8	39.3
Smoking during pregnancy	% yes	14.0	21.4	24.5	6.2	4.4	20.8
Maternal fish intake ^c	GM (GSD)	3.3 (1.9)	2.1 (1.5)	4.9 (2.4)	NA	6.0 (7.9)	5.9 (7.9)
Children's fish intake ^c	GM (GSD)	2.6 (2.4)	2.5 (1.6)	3.8 (2.1)	1.3 (1.2)	3.8 (3.2)	1.6 (1.0)
Main ethnicity							
European	%	43.0	100	100	100	95.7	100
South Asian	%	38.5	0	0	0	4.3	0
Other	%	18.5	0	0	0	0	0

GM: geometric mean; GSD: geometric standard deviation; mtDNAcn: mitochondrial DNA copy number; THg: total mercury; TL: telomere length.

All the variables showed statistical differences (ANOVA *p*-value <0.05) regarding the cohort except in the case of parity and children's sex for both studies, as well as children's TL in the INMA study.

^a The largest sample size with TL and mtDNAcn is considered.

^b THg concentrations are showed for blood samples in µg/L.

^c Fish intake was collected in servings/week. All dietary covariates were adjusted for calories intake.

3.3. Factors associated with exposure to total mercury

Participating mothers had a geometric mean (95 % CI) concentration of total blood Hg of 3.05 (2.94, 3.16) $\mu\text{g/L}$, and their children at 6–11 years old had 1.37 (1.31, 1.42) $\mu\text{g/L}$. Supplemental Fig. S4 shows the multivariable basal model for THg. Higher THg concentrations in the mixed model were associated with older mothers, being primiparous, with the highest education level, and higher maternal fish consumption.

3.4. Total mercury exposure, telomere length and mitochondrial DNA copy number

Fig. 1 shows the relationship between pre- and postnatal THg concentrations and TL and mtDNAcn. The complete robust multivariable prenatal, postnatal, and longitudinal models for TL and mtDNAcn are shown in Supplemental Figs. S5 and S6, respectively.

Higher prenatal THg concentrations were related to longer TL (β [CI95%] = 0.049 [0.011, 0.087] (3.46 % of change), p -value = 0.002). There were marginally significant differences between the first and the

fourth quartiles of THg exposure (0.068 [−0.012, 0.147] (4.81 %), 0.095). Postnatal THg exposure was also marginally associated with longer TL (0.020 [−0.001, 0.041] (1.38 %), 0.067) showing the participants with higher THg quartiles significant TL changes (between 4.61 and 4.88 %, p -values < 0.05) with respect to those belonging to the first THg quartile. Neither prenatal THg nor postnatal THg were associated with mtDNAcn (Fig. 1). Longitudinal models were consistent with these results (Supplemental Table S1). Results from the meta-analysis showed a positive relationship between THg and TL across the HELIX cohorts (TL significant mean differences of 0.04 [0.01, 0.07], p -value = 0.011, and 0.02 [0.01, 0.5], p -value = 0.040, for the pre- and postnatal models, respectively) (Fig. 2), except for the prenatal exposure in EDEN. No heterogeneity was detected in either the prenatal nor postnatal models (I^2 = 0 %, p -value = 0.92 and 0.84, respectively).

3.5. Sensitivity analysis

The Leave-One-Out analysis found that the BIB cohort was influencing the postnatal THg associations with TL (β without BIB cohort =

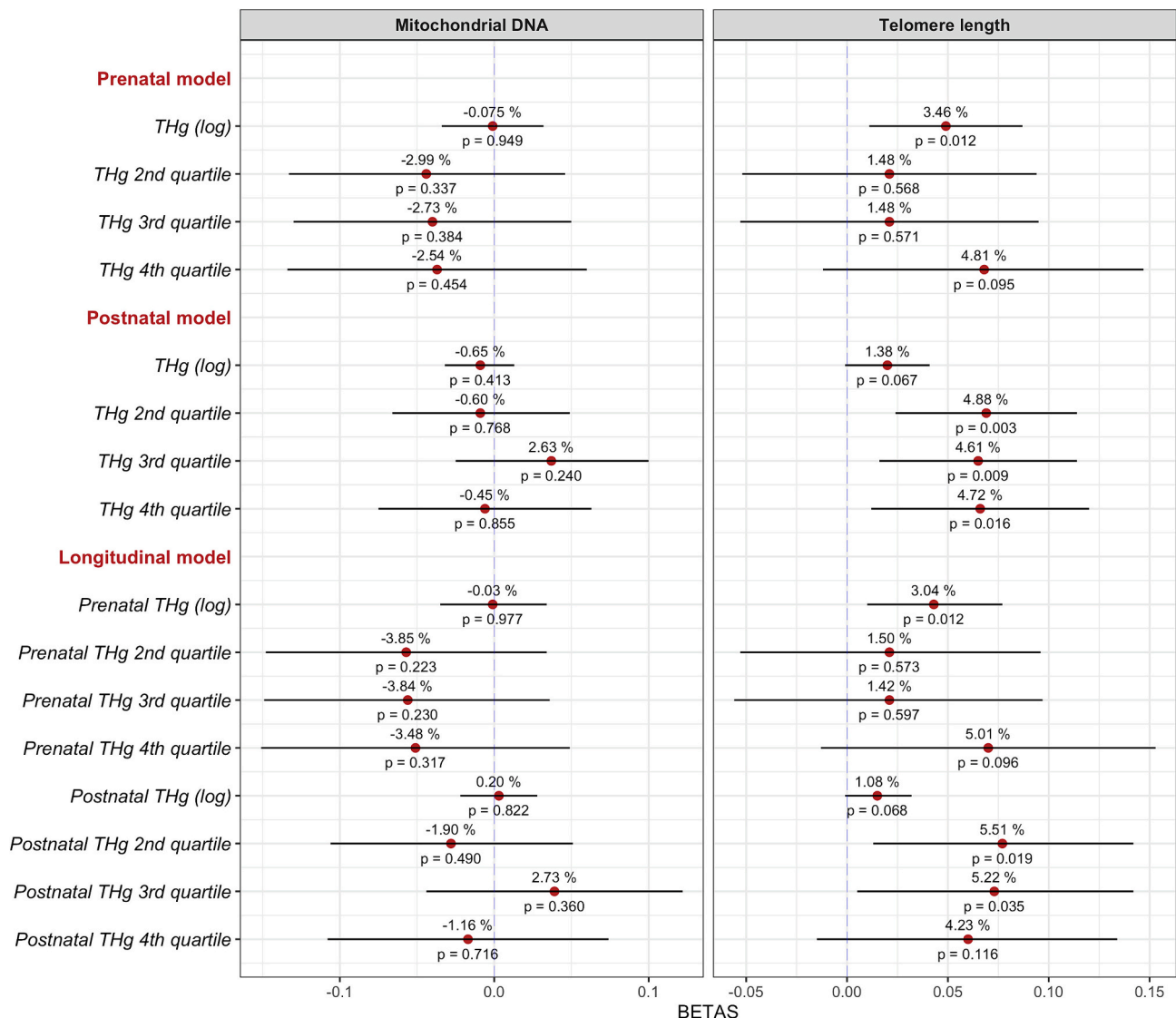


Fig. 1. Total mercury (THg) association models with telomere length and mitochondrial DNA copy number. Betas, p -values and percentage of telomere and mitochondrial DNA change for each unit of increase in logTHg are shown for: 1) THg concentrations in prenatal, postnatal, and longitudinal robust multivariable models; and 2) Quartiles of THg in the linear prenatal, postnatal, and longitudinal models. All models are adjusted for maternal age, parity, ethnicity and education, child's sex, fish consumption, and cohort. Telomere length models are additionally adjusted for mitochondrial DNA copy number as well as mitochondrial DNA copy number models for telomere length.

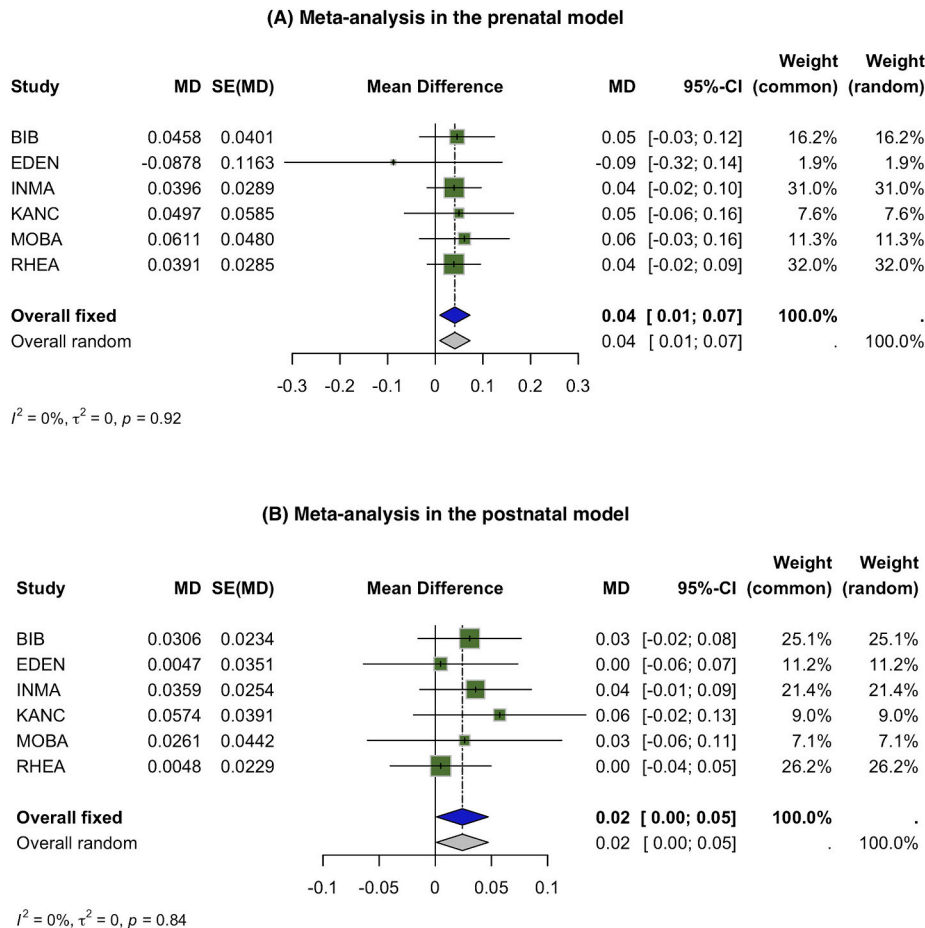


Fig. 2. Forest plots of the telomere length change (MD = mean difference) associated with total mercury exposure in HELIX prenatal (A) and postnatal (B) models. Fish consumption is not included in the KANC prenatal model.

0.016 (−0.010, 0.043), p -value = 0.234). This is consistent with the attenuation of THg significance in the sensitivity postnatal model excluding study participants with non-European origin/ethnicity (β without non-Europeans = 0.016 (−0.007, 0.040), p -value = 0.170), since these participants mainly belonged to BIB (Supplemental Table S1). There were no interactions with sex and fish consumption (interaction term p -values >0.05) and changes in THg coefficients proportional to the fish intake was not observed either (Supplemental Fig. S7). However, it should be noted that the fish coefficients in the multivariate model were negative and proportional to the amount of fish consumed (Supplemental Figs. S5 and S6).

3.6. Linearity assessment

Fig. 3 shows that the prenatal relationship between THg concentrations and TL was linear (linear AIC = 109.16, non-linear AIC = 111.16). However, the postnatal THg and TL association was non-linear, assuming the best fit with an inverted U-shaped relationship considering one internal knot (smooth term p -value = 0.008, linear AIC = 139.24, non-linear AIC = 133.50) with an estimated linearity breakpoint at 0.96 (0.68, 1.35) $\mu\text{g/L}$ of THg in children’s blood.

4. Discussion

This work was carried out in six European countries with a wide range of exposure to THg and to our knowledge, represents the largest-scale cohort study assessing the relation between pre- and postnatal exposure to THg with TL and mtDNAcn in children. Only mothers from

the Spanish cohort INMA presented prenatal THg concentrations above the RfD proposed by the US EPA (5.8 $\mu\text{g/L}$ in blood) (Rice, 2004). Postnatal levels were below these values in all the included cohorts. In contrast to our hypothesis, the results showed that higher THg concentrations were associated with longer TL. Interaction effect by children’s sex or by fish consumption was not observed. The postnatal association displayed an inverted U-shaped relationship between longer TL with increasing THg exposure in maternal blood. No association between THg exposure and mtDNAcn was found.

Previous studies relating Hg in any chemical form with TL or mtDNA are scarce. The Supplemental Table S2 shows three studies in humans and two in seabirds using telomere data. Human studies are inconclusive. The US Project Viva of 893 pregnant women did not find associations between low prenatal total blood Hg exposure (0.0025 $\mu\text{g/g}$) and maternal TL or mtDNAcn (Smith et al., 2021). The Seychelles study of 229 mothers and children measured hair THg in maternal and 5-year-old children and found that at high exposure levels (5.70 and 12.83 $\mu\text{g/g}$, respectively), children’s TL showed a shortening tendency with increasing prenatal THg concentrations but a lengthening with postnatal levels, however, none of these observations were statistically significant (Yeates et al., 2017). Animal studies have shown non-linear relationships between increasing THg concentrations and shorter TL at high environmental exposures and fish-only diets, but this relationship was only significant in male seabirds (Bauch et al., 2022; Eckbo et al., 2019). A study in snails exposed to mercury chloride via the soil at toxic doses did not find any association and proposed a strong ability of snails to maintain their TL under increased oxidative stress. Authors suggested that this resilience may be linked to telomerase activity and alternative

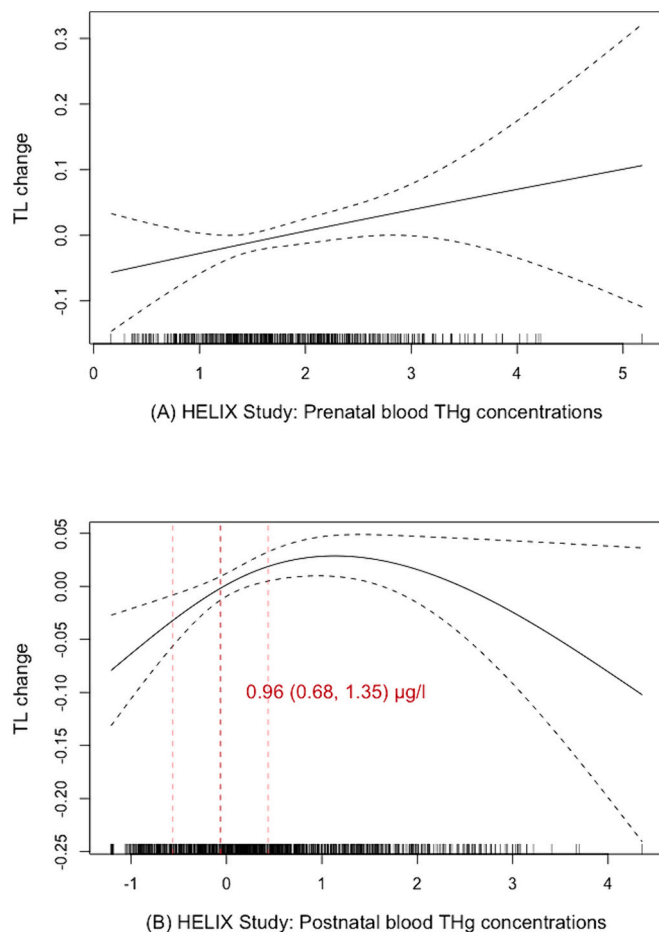


Fig. 3. Generalized additive models of the log-transformed THg prenatal (A) and postnatal (B) concentrations and the log-transformed telomere length (TL) in the HELIX Study. Models are adjusted for the same variables as in Fig. 1. Vertical line in red color represents the linearity break-point transformed into THg concentrations and its 95 % confident interval.

lengthening of TL, or the induction of other mechanisms to protect and repair telomeres, such as efficient DNA repair (Louzon et al., 2020).

Negative and proportional relationship between fish consumption and TL showed in the present study contradicts most previous research relating fish intake with TL (Valera-Gran et al., 2022). A US study including adult 2494 males found significant positive associations between males who consumed more canned tuna and TL (Seo et al., 2022), and higher oily fish consumption was related to longer TL in a large cohort study based in UK (Bountziouka et al., 2022). This positive relationship has also been shown among children (aged 5 to 7) (Meshkani et al., 2021). Other studies did not find significant associations in adults nor children (Bethancourt et al., 2017; Yeates et al., 2017). To our knowledge, there are no studies reporting negative associations between fish consumption and TL. Some studies have attributed telomere lengthening to the role of the n-3 polyunsaturated fatty acids (PUFA) and attributed shortening to greater n-6/n-3 ratios (Ali et al., 2022; Chang et al., 2020). Further studies evaluating different beneficial compounds in fish and fish contaminants are needed in order to clarify if the MeHg-related positive association with TL is a true effect or reflects other nutrients or compounds in fish.

These results can be interpreted in the light of findings for other metals, metalloids and trace elements that also have been linked to oxidative stress. Supplemental Table S3 shows recent articles carried out in humans relating different elements to TL, and the results are not consistent. Most elements have shown telomere shortening with both pre- (cadmium, lead and thallium) and postnatal (cadmium, copper,

nickel, lead and vanadium) exposure (Fillman et al., 2016; He et al., 2022; Pawlas et al., 2016; Wai et al., 2020; Wai et al., 2018; Wu et al., 2021; Wu et al., 2021; Zhang et al., 2019; Zota et al., 2015). Arsenic on the other hand have shown telomere lengthening. Moderate prenatal arsenic was related to longer TL in the placenta and maternal moderate urinary arsenic concentrations were associated with longer TL in Argentinian and Bolivian adults, respectively (Ameer et al., 2016; De Loma et al., 2022; Herlin et al., 2019). The inconsistent results concerning TL and metals involved in oxidative stress may be explained by alterations in the expression of the telomerase reverse transcriptase (TERT) (Ferrario et al., 2009b; Li et al., 2012; Mo et al., 2009) caused by a dose-dependency modulation of the TERT expression induced by oxidative stress (Ferrario et al., 2009b; Wai et al., 2023; Zhang et al., 2003). It is hypothesized that low to moderate exposure to arsenic stimulates TERT expression, which in turn results in telomere lengthening as well as stimulation of mitochondrial DNA production. This hypothesis has been supported by both in vitro and in vivo studies (Ameer et al., 2016; Ferrario et al., 2009a). This dose-dependent effect via differential regulation on TERT may also be the mechanism for the observed positive association between THg and TL in the present study.

Previous studies evaluating relationships between metals and mtDNA are scarce and inconclusive. To date, it has been proposed that after an acute chemical exposure and oxidative stress, mtDNA increases as a compensatory mechanism in response to decreased energy production. Under conditions of reduced antioxidant capacity, such as those resulting from chronic environmental exposure, oxidative stress may overwhelm the mitochondria and decrease mtDNA (Kupsco et al., 2019). As far as we know, only the Seychelles study assessed the relationship between THg and mtDNA, including the role of fish consumption. In this birth cohort study, increasing fetal cord blood THg was associated with lower fetal cord mtDNA (Xu et al., 2019). Among other metals, higher cord blood lead concentrations were related to higher mtDNA in maternal blood from mothers participating in the US VIVA Project and the Mexican PROGRESS cohort (Sanchez-Guerra et al., 2019; Smith et al., 2021), and urinary thallium has been associated with lower mtDNA in newborns (Wu et al., 2019). In adults, urinary arsenic and cadmium concentrations have been related to higher mtDNA in blood, and urinary lead with lower mtDNA in blood (Ameer et al., 2016; De Loma et al., 2022; Vriens et al., 2019).

This study has several strengths. The inclusion of six mother-child European cohorts with different THg exposure levels allowed us to obtain robust associations, including dose-dependent associations, between THg, TL and mtDNA. Another advantage of this study is its prospective design, which made it possible to obtain detailed information concerning maternal and child characteristics. This study also has limitations. The longitudinal analyses had less power in the follow-up due to loss of study participants. However, this is an inherent characteristic of most longitudinal studies and usually related to socioeconomic status. This situation could bias the observed associations; however, it has been observed that even when more than half of the cohort is lost to follow-up, qualitative conclusions about the direction and approximate magnitude of inequalities do not change dramatically (Howe et al., 2013). Other study limitations were: (1) effect modifications were not examined for genetic factors such as genetic variation in TERT and those associated with THg accumulation (Engström et al., 2016); (2) the fish consumption in HELIX was measured as total fish without differentiating between types of fish and seafood either; (3) the lack of information on PUFA content in the HELIX study prohibited us to assess the role of PUFA in TL alterations; (4) batch effects and blood cell types for the blood samples were not available for this study and models could not be adjusted for these potential confounders; and (5) we used THg instead of MeHg measurements since we were not able to ensure the interindividual variability in the THg/MeHg ratio in our specific sample.

In conclusion, our study found evidence that low-to-moderate exposure to THg was associated with longer TL, but not with mtDNA. The non-linear relationship with postnatal exposure supports

previous suggestions about concentration-dependencies and non-linear associations, estimating 0.96 µg/L as a blood THg concentration from which TL attrition is observed. Neither fish consumption nor children's sex showed relevant modification effects. Further studies are needed to clarify the mechanism behind the observed telomere lengthening of THg and the related health effects.

CRediT authorship contribution statement

Manuel Lozano: Writing – original draft, Investigation, Formal analysis. **Rosemary R.C. McEachan:** Writing – review & editing, Investigation. **John Wright:** Writing – review & editing, Investigation. **Tiffany C. Yang:** Writing – review & editing, Validation. **Courtney Dow:** Writing – review & editing, Investigation. **Manik Kadawathagedara:** Writing – review & editing, Investigation. **Johanna Lepeule:** Writing – review & editing, Validation. **Mariona Bustamante:** Writing – review & editing, Funding acquisition, Data curation. **Lea Maitre:** Writing – review & editing, Investigation. **Martine Vrijheid:** Writing – review & editing, Project administration. **Anne Lise Brantsæter:** Writing – review & editing, Investigation. **Helle Margrete Meltzer:** Writing – review & editing, Investigation. **Vasiliki Bempi:** Writing – review & editing, Investigation. **Theano Roumeliotaki:** Writing – review & editing, Investigation. **Cathrine Thomsen:** Writing – review & editing, Data curation. **Tim Nawrot:** Writing – review & editing, Data curation. **Karin Broberg:** Writing – review & editing, Supervision, Investigation, Conceptualization. **Sabrina Llop:** Writing – review & editing, Supervision, Investigation, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

The authors do not have permission to share data.

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Appendix A. Supplementary data

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References

- Alegria-Torres, J.A., Pérez-Rodríguez, R.Y., García-Torres, L., Costilla-Salazar, R., Rocha-Amador, D., 2020. Exposure to arsenic and lead in children from Salamanca México, effects on telomeric lengthening and mitochondrial DNA. *Environ. Sci. Pollut. Res.* 27, 6420–6428. <https://doi.org/10.1007/s11356-019-07108-4>.
- Ali, S., Scapagnini, G., Davinelli, S., 2022. Effect of omega-3 fatty acids on the telomere length: a mini meta-analysis of clinical trials. *Biomol. Concepts* 13, 25–33. <https://doi.org/10.1515/bmc-2021-0024>.
- Ameer, S.S., Xu, Y., Engström, K., Li, H., Tallving, P., Nermell, B., Boemo, A., Parada, L.A., Peñaloza, L.G., Concha, G., Harari, F., Vahter, M., Broberg, K., 2016. Exposure to inorganic arsenic is associated with increased mitochondrial DNA copy number and longer telomere length in peripheral blood. *Front. Cell Dev. Biol.* 4, 87. <https://doi.org/10.3389/fcell.2016.00087>.
- Ballester, F., Iñiguez, C., Murcia, M., Guxens, M., Basterretxea, M., Rebagliato, M., Vioque, J., Lertxundi, A., Fernandez-Somoano, A., Tardon, A., Sunyer, J., Llop, S., 2018. Prenatal exposure to mercury and longitudinally assessed fetal growth: relation and effect modifiers. *Environ. Res.* 160, 97–106. <https://doi.org/10.1016/j.envres.2017.09.018>.
- Barracough, J.Y., Skilton, M.R., Garden, F.L., Toelle, B.G., Marks, G.B., Celemajer, D.S., 2019. Early and late childhood telomere length predict subclinical atherosclerosis at age 14 yrs. – the CardioCAPS study. *Int. J. Cardiol.* 278, 250–253. <https://doi.org/10.1016/j.ijcard.2018.12.065>.
- Bauch, C., Gatt, M.C., Verhulst, S., Granadeiro, J.P., Catry, P., 2022. Higher mercury contamination is associated with shorter telomeres in a long-lived seabird - a direct effect or a consequence of among-individual variation in phenotypic quality? *Sci. Total Environ.* 839, 156359. <https://doi.org/10.1016/j.scitotenv.2022.156359>.
- Berglund, M., Lind, B., Björnberg, K.A., Palm, B., Einarsson, O., Vahter, M., 2005. Inter-individual variations of human mercury exposure biomarkers: a cross-sectional assessment. *Environ. Health Glob. Access Sci. Source* 4, 20. <https://doi.org/10.1186/1476-069X-4-20>.
- Bethancourt, H.J., Kratz, M., Beresford, S.A.A., Hayes, M.G., Kuzawa, C.W., Duazo, P.L., Borja, J.B., Eisenberg, D.T.A., 2017. No association between blood telomere length and longitudinally assessed diet or adiposity in a young adult Filipino population. *Eur. J. Nutr.* 56, 295–308. <https://doi.org/10.1007/s00394-015-1080-1>.
- Blackburn, E.H., 1991. Structure and function of telomeres. *Nature* 350, 569–573. <https://doi.org/10.1038/350569a0>.
- Bountziouka, V., Musicha, C., Allara, E., Kaptoge, S., Wang, Q., Angelantonio, E.D., Butterworth, A.S., Thompson, J.R., Danesh, J.N., Wood, A.M., Nelson, C.P., Codd, V., Samani, N.J., 2022. Modifiable traits, healthy behaviours, and leukocyte telomere length: a population-based study in UK biobank. *Lancet Healthy Longev.* 3, e321–e331. [https://doi.org/10.1016/S2666-7568\(22\)00072-1](https://doi.org/10.1016/S2666-7568(22)00072-1).
- Burr, S.P., Chinnery, P.F., 2022. Measuring single-cell mitochondrial DNA copy number and Heteroplasmy using digital droplet polymerase chain reaction. *J. Vis. Exp.* 2022. <https://doi.org/10.3791/63870>.
- Cardenas, A., Rifas-Shiman, S.L., Agha, G., Hivert, M.-F., Litonjua, A.A., DeMeo, D.L., Lin, X., Amarasiwardena, C.J., Oken, E., Gillman, M.W., Baccarelli, A.A., 2017. Persistent DNA methylation changes associated with prenatal mercury exposure and cognitive performance during childhood. *Sci. Rep.* 7. <https://doi.org/10.1038/s41598-017-00384-5>.
- Cawthon, R.M., 2009. Telomere length measurement by a novel monochrome multiplex quantitative PCR method. *Nucleic Acids Res.* 37. <https://doi.org/10.1093/nar/gkn1027>.
- Cediel-Ulloa, A., Lindner, S., Ruegg, J., Broberg, K., 2023. Epigenetics of methylmercury. *NeuroToxicology* 97, 34–46. <https://doi.org/10.1016/j.neuro.2023.05.004>.
- Chang, X., Dorajoo, R., Sun, Y., Wang, L., Ong, C.N., Liu, J., Khor, C.C., Yuan, J.-M., Koh, W.P., Friedlander, Y., Heng, C.-K., 2020. Effect of plasma polyunsaturated fatty acid levels on leukocyte telomere lengths in the Singaporean Chinese population. *Nutr. J.* 19, 119. <https://doi.org/10.1186/s12937-020-00626-9>.
- Chatterjee, D., Bhattacharjee, P., Sau, T.J., Das, J.K., Sarma, N., Bandyopadhyay, A.K., Roy, S.S., Giri, A.K., 2015. Arsenic exposure through drinking water leads to senescence and alteration of telomere length in humans: a case-control study in West Bengal, India. *Mol. Carcinog.* 54, 800–809. <https://doi.org/10.1002/mc.22150>.
- Chatzi, L., Leventakou, V., Vafeiadi, M., Koutra, K., Roumeliotaki, T., Chalkiadaki, G., Karachaliou, M., Daraki, V., Kyriklaki, A., Kampouri, M., Fthenou, E., Sarri, K., Vassilaki, M., Fasoulaki, M., Bitsios, P., Koutis, A., Stephanou, E.G., Kogevinas, M., 2017. Cohort profile: the mother-child cohort in Crete, Greece (Rhea study). *Int. J. Epidemiol.* 46, 1392–1393k. <https://doi.org/10.1093/ije/dyx084>.
- Clarkson, T.W., Magos, L., 2006. The toxicology of mercury and its chemical compounds. *Crit. Rev. Toxicol.* 36, 609–662. <https://doi.org/10.1080/10408440600845619>.

- Clemente, D.B.P., Casas, M., Vilahur, N., Begiristain, H., Bustamante, M., Carsin, A.-E., Fernández, M.F., Fierens, F., Gyselaers, W., Iñiguez, C., Janssen, B.G., Lefebvre, W., Llop, S., Olea, N., Pedersen, M., Pieters, N., Santa Marina, L., Souto, A., Tardón, A., Vanpoucke, C., Vrijheid, M., Sunyer, J., Nawrot, T.S., 2016. Prenatal ambient air pollution, placental mitochondrial DNA content, and birth weight in the INMA (Spain) and ENVIRONAGE (Belgium) birth cohorts. *Environ. Health Perspect.* 124, 659–665. <https://doi.org/10.1289/ehp.1408981>.
- Crespo-López, M.E., Macêdo, G.L., Pereira, S.I.D., Arriano, G.P.F., Picanço-Diniz, D.L.W., Nascimento, J.L.M.D., Herculano, A.M., 2009. Mercury and human genotoxicity: critical considerations and possible molecular mechanisms. *Pharmacol. Res.* 60, 212–220. <https://doi.org/10.1016/j.phrs.2009.02.011>.
- De Loma, J., Kraus, A.M., Lindh, C.H., Mamani, J., Tirado, N., Gardon, J., Broberg, K., 2022. Arsenic exposure and biomarkers for oxidative stress and telomere length in indigenous populations in Bolivia. *Ecotoxicol. Environ. Saf.* 231, 113194 <https://doi.org/10.1016/j.ecoenv.2022.113194>.
- Dreim, A., Gertz, C.C., Seegal, R.F., 2005. The effects of methylmercury on mitochondrial function and reactive oxygen species formation in rat striatal synaptosomes are age-dependent. *Toxicol. Sci.* 87, 156–162. <https://doi.org/10.1093/toxsci/kfi224>.
- Eckbo, N., Le Bohec, C., Planas-Bielsa, V., Warner, N.A., Schull, Q., Herzke, D., Zahn, S., Haarr, A., Gabrielsen, G.W., Borgå, K., 2019. Individual variability in contaminants and physiological status in a resident Arctic seabird species. *Environ. Pollut.* 249, 191–199. <https://doi.org/10.1016/j.envpol.2019.01.025>.
- Elks, C.E., Scott, R.A., 2013. The long and short of telomere length and diabetes. *Diabetes* 63, 65–67. <https://doi.org/10.1016/j.2013.07.013>.
- Engström, K., Love, T.M., Watson, G.E., Zareba, G., Yeates, A., Wahlberg, K., Alhamdow, A., Thurston, S.W., Mulhern, M., McSorley, E.M., Strain, J.J., Davidson, P.W., Shamlaye, C.F., Myers, G.J., Rand, M.D., van Wijngaarden, E., Broberg, K., 2016. Polymorphisms in ATP-binding cassette transporters associated with maternal methylmercury disposition and infant neurodevelopment in mother-infant pairs in the Seychelles child development study. *Environ. Int.* 94, 224–229. <https://doi.org/10.1016/j.envint.2016.05.027>.
- Farzan, S.F., Howe, C.G., Chen, Y., Gilbert-Diamond, D., Korrick, S., Jackson, B.P., Weinstein, A.R., Karagas, M.R., 2021. Prenatal and postnatal mercury exposure and blood pressure in childhood. *Environ. Int.* 146 <https://doi.org/10.1016/j.envint.2020.106201>.
- Fernandes, S.G., Dsouza, R., Khattar, E., 2021. External environmental agents influence telomere length and telomerase activity by modulating internal cellular processes: implications in human aging. *Environ. Toxicol. Pharmacol.* 85, 103633 <https://doi.org/10.1016/j.etap.2021.103633>.
- Ferrario, D., Collotta, A., Carfi, M., Bowe, G., Vahter, M., Hartung, T., Gribaldo, L., 2009a. Arsenic induces telomerase expression and maintains telomere length in human cord blood cells. *Toxicology* 260, 132–141. <https://doi.org/10.1016/j.tox.2009.03.019>.
- Ferrario, Daniele, Collotta, A., Carfi, M., Bowe, G., Vahter, M., Hartung, T., Gribaldo, L., 2009b. Arsenic induces telomerase expression and maintains telomere length in human cord blood cells. *Toxicology* 260, 132–141. <https://doi.org/10.1016/j.tox.2009.03.019>.
- Fillman, T., Shimizu-Furusawa, H., Ng, C.F.S., Parajuli, R.P., Watanabe, C., 2016. Association of cadmium and arsenic exposure with salivary telomere length in adolescents in Terai. *Nepal. Environ. Res.* 149, 8–14. <https://doi.org/10.1016/j.envres.2016.04.037>.
- Gad, S.C., 2024. *Encyclopedia of Toxicology (Fourth Edition)*. Academic Press.
- Ganel, L., Chen, L., Christ, R., Vangipurapu, J., Young, E., Das, I., Kanchi, K., Larson, D., Regier, A., Abel, H., Kang, C.J., Scott, A., Havulinna, A., Chiang, C.W.K., Service, S., Freimer, N., Palotie, A., Ripatti, S., Kuusisto, J., Boehnke, M., Laakso, M., Locke, A., Stitzel, N.O., Hall, I.M., 2021. Mitochondrial genome copy number measured by DNA sequencing in human blood is strongly associated with metabolic traits via cell-type composition differences. *Hum. Genomics* 15. <https://doi.org/10.1186/s40246-021-00335-2>.
- Ghoussaini, R., Tamim, H., Elbejjani, M., Makki, M., Nasreddine, L., Ismael, H., Nasrallah, M.P., Zgheib, N.K., 2022. C-peptide is a predictor of telomere shortening: a five-year longitudinal study. *Front. Endocrinol.* 13 <https://doi.org/10.3389/fendo.2022.978747>.
- Gorenjak, V., Petrelis, A.M., Stathopoulou, M.G., Visvikis-Siest, S., 2020. Telomere length determinants in childhood. *Clin. Chem. Lab. Med. CCLM* 58, 162–177. <https://doi.org/10.1515/cclm-2019-0235>.
- Grandjean, P., Weihe, P., Debes, F., Choi, A.L., Budtz-Jørgensen, E., 2014. Neurotoxicity from prenatal and postnatal exposure to methylmercury. *Neurotoxicol. Teratol.* 43, 39–44. <https://doi.org/10.1016/j.ntt.2014.03.004>.
- Grazuleviciene, R., Danileviciute, A., Nadisauskienė, R., Vencloviene, J., 2009. Maternal smoking, GSTM1 and GSTT1 polymorphism and susceptibility to adverse pregnancy outcomes. *Int. J. Environ. Res. Public Health* 6, 1282–1297. <https://doi.org/10.3390/ijerph6031282>.
- Guxens, M., Ballester, F., Espada, M., Fernández, M.F., Grimalt, J.O., Ibarluzea, J., Olea, N., Rebighiato, M., Tardón, A., Torrent, M., Vioque, J., Vrijheid, M., Sunyer, J., 2012. Cohort profile: the INMA—Infancia y Medio Ambiente—(environment and childhood) project. *Int. J. Epidemiol.* 41, 930–940. <https://doi.org/10.1093/ije/dyr054>.
- Haug, L.S., Sakhi, A.K., Cequier, E., Casas, M., Maitre, L., Basagana, X., Andrusaityte, S., Chalkiadaki, G., Chatzi, L., Coen, M., de Bont, J., Dedele, A., Ferrand, J., Grazuleviciene, R., Gonzalez, J.R., Gutzkow, K.B., Keun, H., McEachan, R., Meltzer, H.M., Petravičienė, I., Robinson, O., Saulnier, P.-J., Slama, R., Sunyer, J., Urquiza, J., Vafeiadi, M., Wright, J., Vrijheid, M., Thomsen, C., 2018. In-utero and childhood chemical exposome in six European mother-child cohorts. *Environ. Int.* 121, 751–763. <https://doi.org/10.1016/j.envint.2018.09.056>.
- Haycock, P.C., Heydon, E.E., Kaptoge, S., Butterworth, A.S., Thompson, A., Willeit, P., 2014. Leucocyte telomere length and risk of cardiovascular disease: systematic review and meta-analysis. *BMJ* 349, g4227. <https://doi.org/10.1136/bmj.g4227>.
- He, J., Ge, X., Cheng, H., Bao, Y., Feng, X., Zan, G., Wang, F., Zou, Y., Yang, X., 2022. Sex-specific associations of exposure to metal mixtures with telomere length change: results from an 8-year longitudinal study. *Sci. Total Environ.* 811 <https://doi.org/10.1016/j.scitotenv.2021.151327>.
- Herlin, M., Broberg, K., Igra, A.M., Li, H., Harari, F., Vahter, M., 2019. Exploring telomere length in mother-newborn pairs in relation to exposure to multiple toxic metals and potential modifying effects by nutritional factors. *BMC Med.* 17 <https://doi.org/10.1186/s12916-019-1309-6>.
- Heude, B., Forhan, A., Slama, R., Douhaud, L., Bedel, S., Saurel-Cubizolles, M.-J., Hankard, R., Thiebaugeorges, O., De Agostini, M., Annesi-Maesano, I., Kaminski, M., Charles, M.-A., Annesi-Maesano, I., Bernard, J.Y., Botton, J., Charles, M.-A., Dargent-Molina, P., de Lauzon-Guillain, B., Ducimetière, P., de Agostini, M., Foliguet, B., Forhan, A., Fritel, X., Germa, A., Goua, V., Hankard, R., Heude, B., Kaminski, M., Larroque, B., Lelong, N., Lepeule, J., Magnin, G., Marchand, L., Nabet, C., Pierre, F., Slama, R., Saurel-Cubizolles, M.J., Schweitzer, M., Thiebaugeorges, O., EDEN, mother-child cohort study group, 2016. Cohort profile: the EDEN mother-child cohort on the prenatal and early postnatal determinants of child health and development. *Int. J. Epidemiol.* 45, 353–363. <https://doi.org/10.1093/ije/dyv151>.
- Higgins, J.P.T., Thompson, S.G., Deeks, J.J., Altman, D.G., 2003. Measuring inconsistency in meta-analyses. *BMJ* 327, 557–560. <https://doi.org/10.1136/bmj.327.7414.557>.
- Hintelmann, H., 2010. Organomercurials. Their formation and pathways in the environment. *Met. Ions Life Sci.* 7, 365–401.
- Howe, L.D., Tilling, K., Galobardes, B., Lawlor, D.A., 2013. Loss to follow-up in cohort studies: bias in estimates of socioeconomic inequalities. *Epidemiol. Camb. Mass* 24, 1–9. <https://doi.org/10.1097/EDE.0b013e3182762b31>.
- Janssen, B.G., Munters, E., Pieters, N., Smeets, K., Cox, B., Cuypers, A., Fierens, F., Penders, J., Vangronsveld, J., Gyselaers, W., Nawrot, T.S., 2012. Placental mitochondrial DNA content and particulate air pollution during in utero life. *Environ. Health Perspect.* 120, 1346–1352. <https://doi.org/10.1289/ehp.1104458>.
- Jenssen, M.T.S., Brantsæter, A.L., Haugen, M., Meltzer, H.M., Larssen, T., Kvale, H.E., Birgisdottir, B.E., Thomassen, Y., Ellingsen, D., Alexander, J., Knutsen, H.K., 2012. Dietary mercury exposure in a population with a wide range of fish consumption — self-capture of fish and regional differences are important determinants of mercury in blood. *Sci. Total Environ.* 439, 220–229. <https://doi.org/10.1016/j.scitotenv.2012.09.024>.
- Jj, S., Tm, L., Aj, Y., D, W., Ms, M., Em, M., Sw, T., Ge, W., D, M., K, B., Md, R., J, H., Cf, S., Gj, M., Pw, D., van E, W., 2021. Associations of prenatal methylmercury exposure and maternal polyunsaturated fatty acid status with neurodevelopmental outcomes at 7 years of age: results from the Seychelles child development study nutrition cohort 2. *Am. J. Clin. Nutr.* 113 <https://doi.org/10.1093/ajcn/nqaa338>.
- Karagas, M.R., Choi, A.L., Oken, E., Horvat, M., Schoeny, R., Kamai, E., Cowell, W., Grandjean, P., Korrick, S., 2012. Evidence on the human health effects of low-level methylmercury exposure. *Environ. Health Perspect.* 120, 799–806. <https://doi.org/10.1289/ehp.1104494>.
- Kawanishi, S., Oikawa, S., 2004. Mechanism of telomere shortening by oxidative stress. *Ann. N.Y. Acad. Sci.* 1019, 278–284. <https://doi.org/10.1196/annals.1297.047>.
- Kemp, B.R., Ferraro, K.F., 2021. Are biological consequences of childhood exposures detectable in telomere length decades later? *J. Gerontol. - Ser. Biol. Sci. Med. Sci.* 76, 7–14. <https://doi.org/10.1093/GERON/GGLAA019>.
- Klus, J.K., Thurston, S.W., Myers, G.J., Watson, G.E., Rand, M.D., Love, T.M., Yeates, A., J., Mulhern, M.S., McSorley, E.M., Strain, J.J., Shamlaye, C.F., van Wijngaarden, E., 2023. Postnatal methylmercury exposure and neurodevelopmental outcomes at 7 years of age in the Seychelles child development study nutrition cohort 2. *Neurotoxicology* 99, 115–119. <https://doi.org/10.1016/j.neuro.2023.10.004>.
- Koenker, R., 2005. Quantile regression. *Quantile Regression*. <https://doi.org/10.1017/CBO9780511754098>.
- Kowalski, S., Wyrzykowski, D., Inkielewska-Stepniak, I., 2020. Molecular and cellular mechanisms of cytotoxic activity of vanadium compounds against cancer cells. *Molecules* 25. <https://doi.org/10.3390/molecules25071757>.
- Kupsco, A., Sanchez-Guerra, M., Amarasiwardena, C., Brennan, K.J.M., Estrada-Gutierrez, G., Svensson, K., Schnaas, L., Pantic, I., Téllez-Rojo, M.M., Baccarelli, A., Wright, R.O., 2019. Prenatal manganese and cord blood mitochondrial DNA copy number: effect modification by maternal anemic status. *Environ. Int.* 126, 484–493. <https://doi.org/10.1016/j.envint.2019.02.029>.
- Lee, E.-H., Han, M.-H., Ha, J., Park, H.-H., Koh, S.-H., Hye Choi, S., Lee, J.-H., 2020. Relationship between telomere shortening and age in Korean individuals with mild cognitive impairment and Alzheimer's disease compared to that in healthy controls. *Aging* 13, 2089–2100. <https://doi.org/10.18632/aging.202206>.
- Li, H., Engström, K., Vahter, M., Broberg, K., 2012. Arsenic exposure through drinking water is associated with longer telomeres in peripheral blood. *Chem. Res. Toxicol.* 25, 2333–2339. <https://doi.org/10.1021/bx300222t>.
- Li, Z., Liu, H., Qian, Y., Li, X., Guo, C., Wang, Z., Wei, Y., 2020. Influence of metals from e-waste dismantling on telomere length and mitochondrial DNA copy number in people living near recycling sites. *Environ. Int.* 140, 105769 <https://doi.org/10.1016/j.envint.2020.105769>.
- Liu, X., Longchamps, R.J., Wiggins, K.L., Raffield, L.M., Bielak, L.F., Zhao, W., Pitsillides, A., Blackwell, T.W., Yao, J., Guo, X., Kurniansyah, N., Thyagarajan, B., Pankratz, N., Rich, S.S., Taylor, K.D., Peyser, P.A., Heckbert, S.R., Seshadri, S., Cupples, L.A., Boerwinkle, E., Grove, M.L., Larson, N.B., Smith, J.A., Vasan, R.S., Sofer, T., Fitzpatrick, A.L., Fornage, M., Ding, J., Correa, A., Abecasis, G., Psaty, B. M., Wilson, J.G., Levy, D., Rotter, J.I., Bis, J.C., Satizabal, C.L., Arking, D.E., Liu, C., TOPMed, mtDNA W.G. in N.T.-O. for P.M. (TOPMed) C, 2021. Association of

- mitochondrial DNA copy number with cardiometabolic diseases. *Cell Genomics* 1. <https://doi.org/10.1016/j.xgen.2021.100006>.
- Llop, S., Ballester, F., Murcia, M., Fornis, J., Tardon, A., Andriarena, A., Vioque, J., Ibarluzea, J., Fernández-Somoano, A., Sunyer, J., Julvez, J., Rebagliato, M., Lopez-Espinosa, M.-J., 2017. Prenatal exposure to mercury and neuropsychological development in young children: the role of fish consumption. *Int. J. Epidemiol.* 46, 827–838. <https://doi.org/10.1093/ije/dyw259>.
- Llop, S., Murcia, M., Amorós, R., Julvez, J., Santa-Marina, L., Soler-Blasco, R., Rebagliato, M., Iniguez, C., Aguinagalde, X., Iriarte, G., Lopez-Espinosa, M.-J., Andriarena, A., Gonzalez, L., Vioque, J., Sunyer, J., Ballester, F., 2020. Postnatal exposure to mercury and neuropsychological development among preschool children. *Eur. J. Epidemiol.* 35, 259–271. <https://doi.org/10.1007/s10654-020-00620-9>.
- Louzon, M., Zahn, S., Capelli, N., Massemin, S., Coeurdassier, M., Pauget, B., Gimbert, F., de Vaulleury, A., 2020. Impact of ageing and soil contaminants on telomere length in the land snail. *Ecotoxicol. Environ. Saf.* 201, 110766 <https://doi.org/10.1016/j.ecoenv.2020.110766>.
- Lozano, M., Yousefi, P., Broberg, K., Soler-Blasco, R., Miyashita, C., Pesce, G., Kim, W.J., Rahman, M., Bakulski, K.M., Haug, L.S., Ikeda-Araki, A., Huel, G., Park, J., Relton, C., Vrijheid, M., Rifas-Shiman, S., Oken, E., Dou, J.F., Kishi, R., Gutzkow, K. B., Annesi-Maesano, I., Won, S., Hivert, M.-F., Fallin, M.D., Vafeiadi, M., Ballester, F., Bustamante, M., Llop, S., 2022. DNA methylation changes associated with prenatal mercury exposure: a meta-analysis of prospective cohort studies from PACE consortium. *Environ. Res.* 204 <https://doi.org/10.1016/j.envres.2021.112093>.
- Magnus, P., Birke, C., Vejrup, K., Haugan, A., Alsaker, E., Daltveit, A.K., Handal, M., Haugen, M., Høiseth, G., Knudsen, G.P., Paltiel, L., Schreuder, P., Tambs, K., Vold, L., Stoltenberg, C., 2016. Cohort profile update: the Norwegian mother and child cohort study (MoBa). *Int. J. Epidemiol.* 45, 382–388. <https://doi.org/10.1093/ije/dyw029>.
- Maitre, L., de Bont, J., Casas, M., Robinson, O., Aasvang, G.M., Agier, L., Andrusaityte, S., Ballester, F., Basagaña, X., Borrás, E., Brochet, C., Bustamante, M., Carracedo, A., de Castro, M., Dedele, A., Donaire-Gonzalez, D., Estivill, X., Evandt, J., Fossati, S., Giorgis-Allemand, L., Gonzalez, J.R., Granum, B., Grazuleviciene, R., Gutzkow, K.B., Haug, L.S., Hernandez-Ferrer, C., Heude, B., Ibarluzea, J., Julvez, J., Karachaliou, M., Keun, H.C., Krog, N.H., Lau, C.-H.E., Leventakou, V., Lyon-Caen, S., Manzana, C., Mason, D., McEachan, R., Meltzer, H.M., Petravičienė, I., Quentin, J., Roumeliotaki, T., Sabido, E., Saulnier, P.-J., Siskos, A.P., Siroux, V., Sunyer, J., Tamayo, I., Urquiza, J., Vafeiadi, M., van Gent, D., Vives-Usano, M., Waiblinger, D., Warembourg, C., Chatzi, L., Coen, M., van den Hazel, P., Nieuwenhuijsen, M.J., Slama, R., Thomsen, C., Wright, J., Vrijheid, M., 2018. Human early life exposome (HELIX) study: a European population-based exposome cohort. *BMJ Open* 8, e021311. <https://doi.org/10.1136/bmjopen-2017-021311>.
- Martens, D.S., Nawrot, T.S., 2016. Air pollution stress and the aging phenotype: the telomere connection. *Curr. Environ. Health Rep.* 3, 258–269. <https://doi.org/10.1007/s40572-016-0098-8>.
- Martens, D.S., Plusquin, M., Gyselaers, W., De Vivo, I., Nawrot, T.S., 2016. Maternal pregnancy body mass index and newborn telomere length. *BMC Med.* 14 <https://doi.org/10.1186/s12916-016-0689-0>.
- Martens, D.S., Van Der Stukken, C., Derom, C., Thiery, E., Bijns, E.M., Nawrot, T.S., 2021. Newborn telomere length predicts later life telomere length: tracking telomere length from birth to child- and adulthood. *EBioMedicine* 63, 103164. <https://doi.org/10.1016/j.ebiom.2020.103164>.
- Meshkani, S.E., Kooshki, A., Alahabadi, A., Lari Najafi, M., Rad, A., Riahi-Manesh, F., Miri, M., 2021. Dietary pattern and telomere length in preschool children in a middle-income country. *Matern. Child Nutr.* 17, e13146 <https://doi.org/10.1111/mcn.13146>.
- Meyer, J.N., Chan, S.S.L., 2017. Sources, mechanisms, and consequences of chemical-induced mitochondrial toxicity. *Toxicology* 391, 2–4. <https://doi.org/10.1016/j.tox.2017.06.002>.
- Meyer, J.N., Leung, M.C.K., Rooney, J.P., Sendoe, A., Hengartner, M.O., Kisby, G.E., Bess, A.S., 2013. Mitochondria as a target of environmental toxicants. *Toxicol. Sci.* Off. J. Soc. Toxicol. 134, 1–17. <https://doi.org/10.1093/toxsci/kft102>.
- Mo, J., Xia, Y., Ning, Z., Wade, T.J., Mumford, J.L., 2009. Elevated human telomerase reverse transcriptase gene expression in blood cells associated with chronic arsenic exposure in Inner Mongolia, China. *Environ. Health Perspect.* 117, 354–360. <https://doi.org/10.1289/ehp.11532>.
- Muggeo, V.M.R., 2003. Estimating regression models with unknown break-points. *Stat. Med.* 22, 3055–3071. <https://doi.org/10.1002/sim.1545>.
- Murcia, M., Ballester, F., Enning, A.M., Iniguez, C., Valvi, D., Basterrechea, M., Rebagliato, M., Vioque, J., Maruri, M., Tardon, A., Riaño-Galán, I., Vrijheid, M., Llop, S., 2016. Prenatal mercury exposure and birth outcomes. *Environ. Res.* 151, 11–20. <https://doi.org/10.1016/j.envres.2016.07.003>.
- Myers, G.J., Davidson, P.W., 1998. Prenatal methylmercury exposure and children: neurologic, developmental, and behavioral research. *Environ. Health Perspect.* 106 (Suppl. 3), 841–847. <https://doi.org/10.1289/ehp.98106841>.
- Pawlas, N., Plachetka, A., Kozłowska, A., Mikołajczyk, A., Kasprczyk, A., Dobrakowski, M., Kasprczyk, S., 2016. Telomere length, telomerase expression, and oxidative stress in lead smelters. *Toxicol. Ind. Health* 32, 1961–1970. <https://doi.org/10.1177/0748233715601758>.
- Pillalamarri, V., Shi, W., Say, C., Yang, S., Lane, J., Guallar, E., Pankratz, N., Arking, D.E., 2023. Whole-exome sequencing in 415,422 individuals identifies rare variants associated with mitochondrial DNA copy number. *Hum. Genet. Genomics Adv.* 4 <https://doi.org/10.1016/j.xhgg.2022.100147>.
- R Core Team, 2017. *R: A Language and Environment for Statistical Computing*. R Foundation for Statistical Computing, Vienna.
- Révész, D., Milaneschi, Y., Verhoeven, J.E., Penninx, B.W.J.H., 2014. Telomere length as a marker of cellular aging is associated with prevalence and progression of metabolic syndrome. *J. Clin. Endocrinol. Metab.* 99, 4607–4615. <https://doi.org/10.1210/jc.2014-1851>.
- Rice, D.C., 2004. The US EPA reference dose for methylmercury: sources of uncertainty. *Environ. Res.* 95, 406–413. <https://doi.org/10.1016/j.envres.2003.08.013>.
- Rodríguez-Fernández, B., Gispert, J.D., Guigo, R., Navarro, A., Vilor-Tejedor, N., Crous-Bou, M., 2022. Genetically predicted telomere length and its relationship with neurodegenerative diseases and life expectancy. *Comput. Struct. Biotechnol. J.* 20, 4251–4256. <https://doi.org/10.1016/j.csbj.2022.08.006>.
- Sahin, E., DePinho, R.A., 2012. Axis of ageing: telomeres, p53 and mitochondria. *Nat. Rev. Mol. Cell Biol.* 13, 397–404. <https://doi.org/10.1038/nrm3352>.
- Sanchez-Guerra, M., Peng, C., Trevisi, L., Cardenas, A., Wilson, A., Osorio-Yáñez, C., Niedzwiecki, M.M., Zhong, J., Svensson, K., Acevedo, M.T., Solano-Gonzalez, M., Amarasiwardena, C.J., Estrada-Gutierrez, G., Brennan, K.J.M., Schnaas, L., Just, A. C., Laue, H.E., Wright, R.J., Téllez-Rojo, M.M., Wright, R.O., Baccarelli, A.A., 2019. Altered cord blood mitochondrial DNA content and pregnancy lead exposure in the PROGRESS cohort. *Environ. Int.* 125, 437–444. <https://doi.org/10.1016/j.envint.2019.01.077>.
- Sazonova, M.A., Ryzhkova, A.I., Sinyov, V.V., Sazonova, M.D., Kirichenko, T.V., Doroshuk, N.A., Karagodin, V.P., Orekhov, A.N., Sobenin, I.A., 2021. Mutations of mtDNA in some vascular and metabolic diseases. *Curr. Pharm. Des.* 27, 177–184. <https://doi.org/10.2174/1381612826999200820162154>.
- Schneider, S.L., 2013. The international standard classification of education 2011. In: Elisabeth Birkelund, G. (Ed.), *Class and Stratification Analysis, Comparative Social Research*. Emerald Group Publishing Limited, pp. 365–379. [https://doi.org/10.1108/S0195-6310\(2013\)0000030017](https://doi.org/10.1108/S0195-6310(2013)0000030017).
- Seo, B., Yang, K., Kahe, K., Qureshi, A.A., Chan, A.T., De Vivo, I., Cho, E., Giovannucci, E. L., Nan, H., 2022. Association of omega-3 and omega-6 fatty acid intake with leukocyte telomere length in US males. *Am. J. Clin. Nutr.* 116, 1759–1766. <https://doi.org/10.1093/ajcn/nqac263>.
- Shammas, M.A., 2011. Telomeres, lifestyle, cancer, and aging. *Curr. Opin. Clin. Nutr. Metab. Care* 14, 28–34. <https://doi.org/10.1097/MCO.0b013e32834212b1>.
- Sharma, B.M., Sānka, O., Kalina, J., Scheringer, M., 2019. An overview of worldwide and regional time trends in total mercury levels in human blood and breast milk from 1966 to 2015 and their associations with health effects. *Environ. Int.* 125, 300–319. <https://doi.org/10.1016/j.envint.2018.12.016>.
- Smith, A.R., Lin, P.-I.D., Rifas-Shiman, S.L., Rahman, M.L., Gold, D.R., Baccarelli, A.A., Claus Henn, B., Amarasiwardena, C., Wright, R.O., Coull, B., Hivert, M.-F., Oken, E., Cardenas, A., 2021. Prospective associations of early pregnancy metal mixtures with mitochondrial DNA copy number and telomere length in maternal and cord blood. *Environ. Health Perspect.* 129, 117007 <https://doi.org/10.1289/EHP9294>.
- Soler-Blasco, R., Murcia, M., Lozano, M., Aguinagalde, X., Iriarte, G., Lopez-Espinosa, M.-J., Vioque, J., Iniguez, C., Ballester, F., Llop, S., 2019. Exposure to mercury among 9-year-old Spanish children: associated factors and trend throughout childhood. *Environ. Int.* 130, 104835 <https://doi.org/10.1016/j.envint.2019.05.029>.
- Stern, A.H., Smith, A.E., 2003. An assessment of the cord blood:maternal blood methylmercury ratio: implications for risk assessment. *Environ. Health Perspect.* 111, 1465–1470.
- United Nations, 2018. *Global Mercury Assessment [WWW Document]*. URL <https://sdg.iisd.org/443/news/unep-publishes-2018-global-mercury-assessment/> (accessed 3.4.21).
- Valera-Gran, D., Prieto-Botella, D., Hurtado-Pomares, M., Baladia, E., Petermann-Rocha, F., Sánchez-Pérez, A., Navarrete-Muñoz, E.-M., 2022. The impact of foods, nutrients, or dietary patterns on telomere length in childhood and adolescence: a systematic review. *Nutrients* 14, 3885. <https://doi.org/10.3390/nu14193885>.
- Vejrup, K., Brantsæter, A.L., Knutsen, H.K., Magnus, P., Alexander, J., Kvale, H.E., Meltzer, H.M., Haugen, M., 2014. Prenatal mercury exposure and infant birth weight in the Norwegian mother and child cohort study. *Public Health Nutr.* 17, 2071–2080. <https://doi.org/10.1017/S1368980013002619>.
- Vejrup, K., Brandlistuen, R.E., Brantsæter, A.L., Knutsen, H.K., Caspersen, I.H., Alexander, J., Lundh, T., Meltzer, H.M., Magnus, P., Haugen, M., 2018. Prenatal mercury exposure, maternal seafood consumption and associations with child language at five years. *Environ. Int.* 110, 71–79. <https://doi.org/10.1016/j.envint.2017.10.008>.
- Vejrup, K., Brantsæter, A.-L., Meltzer, H.M., Mohebbi, M., Knutsen, H.K., Alexander, J., Haugen, M., Jacka, F., 2022. Prenatal mercury exposure, fish intake and child emotional behavioural regulation in the Norwegian mother, father and child cohort study. *BMJ Nutr. Prev. Health* 5, 313–320. <https://doi.org/10.1136/bmjnp-2021-000412>.
- von Zglinicki, T., 2002. Oxidative stress shortens telomeres. *Trends Biochem. Sci.* 27, 339–344. [https://doi.org/10.1016/S0968-0004\(02\)02110-2](https://doi.org/10.1016/S0968-0004(02)02110-2).
- 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., Nelen, V., Schettgen, T., Schoeters, G., Martens, D.S., Plusquin, M., 2019. Exposure to environmental pollutants and their association with biomarkers of aging: a multipollutant approach. *Environ. Sci. Technol.* 53, 5966–5976. <https://doi.org/10.1021/acs.est.8b07141>.
- Vrijheid, M., Slama, R., Robinson, O., Chatzi, L., Coen, M., van den Hazel, P., Thomsen, C., Wright, J., Athersuch, T.J., Avellana, N., Basagaña, X., Brochet, C., Buccchini, L., Bustamante, M., Carracedo, A., Casas, M., Estivill, X., Fairley, L., van Gent, D., Gonzalez, J.R., Granum, B., Grazuleviciene, R., Gutzkow, K.B., Julvez, J., Keun, H.C., Kogevinas, M., McEachan, R.R.C., Meltzer, H.M., Sabido, E., Schwarze, P.E., Siroux, V., Sunyer, J., Want, E.J., Zeman, F., Nieuwenhuijsen, M.J., 2014. The human early-life exposome (HELIX): project rationale and design. *Environ. Health Perspect.* 122, 535–544. <https://doi.org/10.1289/ehp.1307204>.

- Wai, K.M., Umezaki, M., Kosaka, S., Mar, O., Umemura, M., Fillman, T., Watanabe, C., 2018. Impact of prenatal heavy metal exposure on newborn leucocyte telomere length: a birth-cohort study. *Environ. Pollut. Barking Essex 1987* (243), 1414–1421. <https://doi.org/10.1016/j.envpol.2018.09.090>.
- Wai, K.M., Umezaki, M., Umemura, M., Mar, O., Watanabe, C., 2020. Protective role of selenium in the shortening of telomere length in newborns induced by in utero heavy metal exposure. *Environ. Res.* 183 <https://doi.org/10.1016/j.envres.2020.109202>.
- Wai, K.M., Swe, T., Myar, M.T., Aisyah, C.R., Hninn, T.S.S., 2023. Telomeres susceptibility to environmental arsenic exposure: shortening or lengthening? *Front. Public Health* 10.
- Wells, E.M., Kopylev, L., Nachman, R., Radke, E.G., Congleton, J., Segal, D., 2022. Total blood mercury predicts methylmercury exposure in fish and shellfish consumers. *Biol. Trace Elem. Res.* 200, 3867–3875. <https://doi.org/10.1007/s12011-021-02968-9>.
- Wright, J., Small, N., Raynor, P., Tuffnell, D., Bhopal, R., Cameron, N., Fairley, L., Lawlor, D.A., Parslow, R., Petherick, E.S., Pickett, K.E., Waiblinger, D., West, J., on behalf of the Born in Bradford Scientific Collaborators Group, 2013. Cohort profile: the born in Bradford multi-ethnic family cohort study. *Int. J. Epidemiol.* 42, 978–991. <https://doi.org/10.1093/ije/dys112>.
- Wu, Y., Liu, Y., Ni, N., Bao, B., Zhang, C., Lu, L., 2012. High lead exposure is associated with telomere length shortening in Chinese battery manufacturing plant workers. *Occup. Environ. Med.* 69, 557–563. <https://doi.org/10.1136/oemed-2011-100478>.
- Wu, M., Shu, Y., Song, L., Liu, B., Zhang, L., Wang, L., Liu, Y., Bi, J., Xiong, C., Cao, Z., Xu, S., Xia, W., Li, Y., Wang, Y., 2019. Prenatal exposure to thallium is associated with decreased mitochondrial DNA copy number in newborns: evidence from a birth cohort study. *Environ. Int.* 129, 470–477. <https://doi.org/10.1016/j.envint.2019.05.053>.
- Wu, M., Wang, L., Song, L., Liu, B., Liu, Y., Bi, J., Liu, Q., Chen, K., Li, Y., Xia, W., Xu, S., Cao, Z., Zhou, A., Tian, Y., Wang, Y., 2021. The association between prenatal exposure to thallium and shortened telomere length of newborns. *Chemosphere* 265, 129025. <https://doi.org/10.1016/j.chemosphere.2020.129025>.
- Xu, Y., Wahlberg, K., Love, T.M., Watson, G.E., Yeates, A.J., Mulhern, M.S., McSorley, E. M., Strain, J.J., Davidson, P.W., Shamlaye, C.F., Rand, M.D., Myers, G.J., van Wijngaarden, E., Broberg, K., 2019. Associations of blood mercury and fatty acid concentrations with blood mitochondrial DNA copy number in the Seychelles child development nutrition study. *Environ. Int.* 124, 278–283. <https://doi.org/10.1016/j.envint.2019.01.019>.
- Yakes, F.M., Van Houten, B., 1997. Mitochondrial DNA damage is more extensive and persists longer than nuclear DNA damage in human cells following oxidative stress. *Proc. Natl. Acad. Sci. U. S. A.* 94, 514–519. <https://doi.org/10.1073/pnas.94.2.514>.
- Yeates, A.J., Thurston, S.W., Li, H., Mulhern, M.S., McSorley, E.M., Watson, G.E., Shamlaye, C.F., Strain, J.J., Myers, G.J., Davidson, P.W., van Wijngaarden, E., Broberg, K., 2017. PUFA status and methylmercury exposure are not associated with leukocyte telomere length in mothers or their children in the Seychelles child development study. *J. Nutr.* 147, 2018–2024. <https://doi.org/10.3945/jn.117.253021>.
- Ying Chan, P.H., Kwok, K.M., Ming Chan, M.H., Li, A.M., Shuen Chan, I.H., Fok, T.F., Lam, H.S., 2021. Prenatal methylmercury exposure is associated with decrease heart rate variability in children. *Environ. Res.* 111744 <https://doi.org/10.1016/j.envres.2021.111744>.
- Zhang, T.-C., Schmitt, M.T., Mumford, J.L., 2003. Effects of arsenic on telomerase and telomeres in relation to cell proliferation and apoptosis in human keratinocytes and leukemia cells in vitro. *Carcinogenesis* 24, 1811–1817. <https://doi.org/10.1093/carcin/bgg141>.
- Zhang, L., Song, L., Liu, B., Wu, M., Wang, L., Zhang, B., Xiong, C., Xia, W., Li, Y., Cao, Z., Wang, Y., Xu, S., 2019. Prenatal cadmium exposure is associated with shorter leukocyte telomere length in Chinese newborns. *BMC Med.* 17 <https://doi.org/10.1186/s12916-019-1262-4>.
- Zhang, M., Liu, T., Wang, G., Buckley, J.P., Guallar, E., Hong, X., Wang, M.-C., Wills-Karp, M., Wang, X., Mueller, N.T., 2021. In utero exposure to heavy metals and trace elements and childhood blood pressure in a U.S. urban, low-income, minority birth cohort. *Environ. Health Perspect.* 129, 67005 <https://doi.org/10.1289/EHP8325>.
- Zhang, Z., Yang, D., Zhou, B., Luan, Y., Yao, Q., Liu, Y., Yang, S., Jia, J., Xu, Y., Bie, X., Wang, Y., Li, Z., Li, A., Zheng, H., He, Y., 2022. Decrease of MtDNA copy number affects mitochondrial function and involves in the pathological consequences of ischaemic stroke. *J. Cell. Mol. Med.* 26, 4157–4168. <https://doi.org/10.1111/jcmm.17262>.
- Zhao, H., Han, L., Chang, D., Ye, Y., Shen, J., Daniel, C.R., Gu, J., Chow, W.-H., Wu, X., 2017. Social-demographics, health behaviors, and telomere length in the Mexican American Mano a Mano cohort. *Oncotarget* 8, 96553–96567. <https://doi.org/10.18632/oncotarget.19903>.
- Zota, A.R., Needham, B.L., Blackburn, E.H., Lin, J., Park, S.K., Rehkopf, D.H., Epel, E.S., 2015. Associations of cadmium and lead exposure with leukocyte telomere length: Findings from National Health and Nutrition Examination Survey, 1999–2002. *Am. J. Epidemiol.* 181, 127–136. <https://doi.org/10.1093/aje/kwu293>.