

## Supplementary Material

### Exploring the relationship between metal exposure, BDNF, and behavior in adolescent males

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**Table S1. Limits of detection (LOD) and limits of quantification (LOQ) of metals and Bisulfite-converted primers used for PCR amplification**

Metals	As	Cd	Hg	Pb
LOD ( $\mu\text{g/L}$ )	0.60	0.01	0.05	0.16
LOQ ( $\mu\text{g/L}$ )	1.81	0.04	0.14	0.48
Gene	Forward primer		Reverse primer	
<i>BDNF</i>	GATTGGTAATTAGTGTATTAGA GTGTT		/5Biosg/ATCAACCAAAACTCCATTAA ATCTC	

**Table S2. Correlation between urinary metal concentrations ( $\mu\text{g/L}$ )**

		As	Cd	Hg	Pb
<b>As</b>	Spearman's rho	1	0.22	0.52	0.19
	P		0.01	<0.01	0.03
<b>Cd</b>	Spearman's rho	0.22	1	0.52	0.36
	P	0.01		<0.01	<0.01
<b>Hg</b>	Spearman's rho	0.52	0.52	1	0.10
	P	<0.01	<0.01		0.26
<b>Pb</b>	Spearman's rho	0.19	0.36	0.10	1
	P	0.03	<0.01	0.26	

**Table S3. Distribution of CBCL outcome scores (n=125)**

CBCL scores	Range	Mean <sup>a</sup>	SD	Median	n (%) in borderline or clinical range <sup>b</sup>
<b>Syndrome scores</b>					
Anxious/depressed	50-79	55.1	6.1	54.0	37 (25.7)
Withdrawn	50-89	57.5	7.3	54.0	50 (34.7)
Somatic complaints	50-79	58.1	7.2	58.0	53 (36.8)
Social problems	50-79	55.1	6.4	51.0	33 (22.9)
Thought problems	50-82	54.9	6.0	51.0	23 (15.1)
Attention problems	50-86	56.1	7.0	53.0	31 (20.4)
Rule-breaking behavior	50-89	54.0	6.2	51.0	22 (15.3)
Aggressive behavior	50-81	55.2	6.4	52.0	33 (21.7)
<b>Composite scores</b>					
Internalizing problems	34-79	55.6	9.2	55.0	46 (31.9)
Externalizing problems	34-79	51.0	9.2	51.0	23 (16.0)
Total problems	31-84	54.0	9.2	54.0	38 (26.4)

<sup>a</sup>For all scales, raw scores were transformed to T-scores to compare each subject to a normative sample of adolescents.

<sup>b</sup>Adolescents were grouped in two groups according to the T-score obtained in each scale: clinical or subclinical ( $\geq 60$ ) and normal ( $< 60$ ) T-score.

SD: Standard deviation.

**Table S4. Linear regression for the association between metal exposure and CBCL scores (n=125)**

CBCL scores	Metals			
	As	Cd	Hg	Pb
<b>Syndrome scores</b>	<b><math>\beta</math> (95% CI)</b>	<b><math>\beta</math> (95% CI)</b>	<b><math>\beta</math> (95% CI)</b>	<b><math>\beta</math> (95% CI)</b>
Anxious/depressed	0.02 (-1.10,1.14)	0.44 (-1.88,2.76)	0.04 (-1.48,1.56)	-0.58 (-2.23,1.07)
Withdrawn	0.07 (-1.21,1.34)	0.05 (-2.59,2.70)	-0.82 (-2.55,0.92)	-0.29 (-2.17,1.59)
Somatic complaints	0.79 (-0.63,2.21)	-2.08 (-5.02,0.86)	0.35 (-1.58,2.28)	-0.81 (-2.90,1.28)
Social problems	0.36 (-0.76,1.47)	1.82 (-0.48,4.12)	-1.62 (-3.13,-0.11)*	-0.19 (-1.83,1.45)
Thought problems	0.02 (-1.03,1.06)	1.31 (-0.85,3.47)	0.32 (-1.10,1.74)	-0.58 (-2.12,0.97)
Attention problems	-0.09 (-1.14,0.97)	0.84 (-1.34,3.02)	0.27 (-1.16,1.70)	-0.74 (-2.29,0.81)
Rule-breaking behavior	-0.70 (-1.65,0.25)	-0.57 (-2.54,1.39)	0.04 (-1.25,1.32)	1.11 (-0.29,2.51)
Aggressive behavior	-0.09 (-1.22,1.03)	2.11 (-0.22,4.44)†	-0.74 (-2.27,0.79)	-0.33 (-1.98,1.33)
<b>Composite scores</b>				
Internalizing problems	0.99 (-0.87,2.86)	-0.71 (-4.57,3.16)	-0.25 (-2.78,2.29)	-1.36 (-4.11,1.39)
Externalizing problems	-0.53 (-2.26,1.20)	1.86 (-1.71,5.43)	-0.51 (-2.85,1.83)	-0.35 (-2.89,2.20)
Total problems	0.20 (-1.52,1.93)	0.78 (-2.78,4.35)	-0.53 (-2.87,1.81)	-0.98 (-3.52,1.56)

Model was adjusted for adolescent's age (continuous: months), BMI (continuous: kg/m<sup>2</sup>), and creatinine (mg/dL), maternal schooling (primary/secondary/university) and intelligence, and for all metals simultaneously (continuous: ln-transformed concentrations).

\*For all scales, raw scores were transformed to T-scores to compare each subject to a normative sample of adolescents.

SD: Standard deviation.

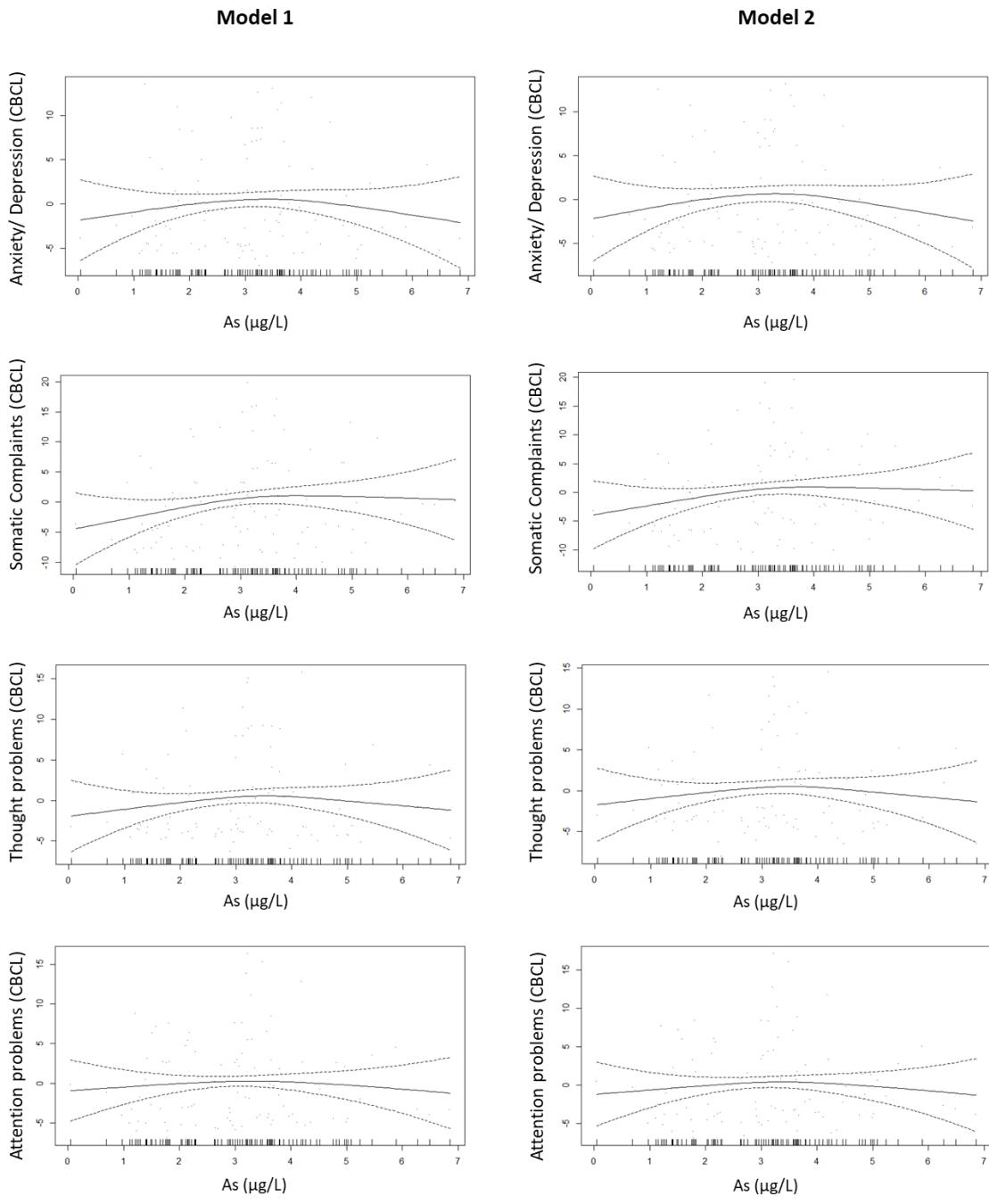
\*p<0.05; †p< 0.1

**Table S5. Linear regression for the association between metal exposure and effect biomarkers (serum BDNF; n=125; BDNF gene DNA methylation, n=113)**

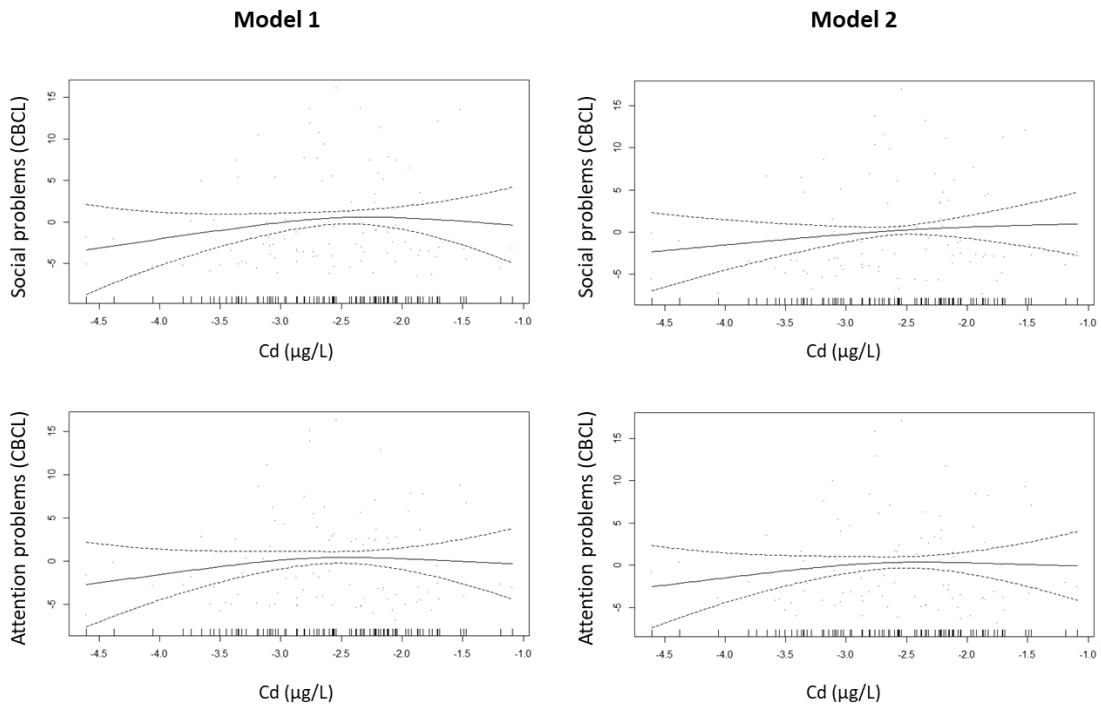
Effect biomarkers	Metals			
	As	Cd	Hg	Pb
<b>Serum BDNF</b>	<b><math>\beta</math> (95% CI)</b>	<b><math>\beta</math> (95% CI)</b>	<b><math>\beta</math> (95% CI)</b>	<b><math>\beta</math> (95% CI)</b>
Serum BDNF	-0.64 (-2.36,1.08)	-2.02 (-2.36,1.55)	-0.44 (-2.80,1.91)	1.65 (-0.84,4.15)
<b>BDNF methylation</b>				
CpG 1	0.02 (-0.15,0.19)	-0.11 (-0.48,0.27)	-0.02 (-0.26,0.22)	0.22 (-0.04,0.48)†
CpG 2	0.08 (-0.02,0.19)	-0.06 (-0.29,0.18)	-0.04 (-0.19,0.11)	-0.02 (-0.17,0.03)
CpG 3	0.08 (-0.04,0.20)	-0.20 (-0.47,0.06)	-0.02 (-0.19,0.14)	0.06 (-0.11,0.24)
CpG 4	0.15 (-0.09,0.39)	-0.17 (-0.73,0.38)	-0.07 (-0.43,0.30)	0.18 (-0.18,0.54)
CpG 5	0.12 (-0.04,0.28)	-0.06 (-0.42,0.31)	-0.04 (-0.27,0.20)	0.03 (-0.21,0.28)
CpG 6	0.16 (-0.09,0.40)	-0.01 (-0.56,0.55)	-0.05 (-0.41,0.31)	0.10 (-0.25,0.46)
CpG total	0.12 (-0.00,0.25)†	-0.11 (-0.39,0.18)	-0.03 (-0.20,0.15)	0.08 (-0.10,0.27)

Model was adjusted for adolescent's age (continuous: months), BMI (continuous: kg/m<sup>2</sup>), and creatinine (mg/dL), maternal schooling (primary/secondary/university) and intelligence, and for all metals simultaneously (continuous: ln-transformed concentrations).

\*p<0.05; †p< 0.1



**Figure S1.** Generalized additive models (GAM) for the relationship between urinary As concentrations (natural log-transformed concentrations) and adolescents' behavior. Model 1: adjusted for adolescents' age (continuous: months), BMI (continuous:  $\text{kg}/\text{m}^2$ ), and urinary creatinine ( $\text{mg}/\text{dL}$ ), maternal education (primary/secondary/university) and maternal intelligence, and for all metals simultaneously (continuous: ln-transformed concentrations); Model 2: additionally adjusted for passive tobacco smoking (yes/no) and total fish consumption (<1 portion/month/>1 portion/month/>1 portion/week).



**Figure S2.** Generalized additive models (GAM) for the relationship between urinary Cd concentrations (natural log-transformed concentrations) and adolescents' behavior. Model 1: adjusted for adolescents' age (continuous: months), BMI (continuous: kg/m<sup>2</sup>), and urinary creatinine (mg/dL), maternal education (primary/secondary/university) and maternal intelligence, and for all metals simultaneously (continuous: ln-transformed concentrations); Model 2: additionally adjusted for passive tobacco smoking (yes/no) and total fish consumption (<1 portion/month/>1 portion/month/>1 portion/week).

**Table S6. Association between serum BDNF protein levels and CBCL outcome scores (n=113).**

CBCL scores	Serum BDNF protein tertiles (ng/mL)			
	1st (16.0-28.0)	2nd (28.3-36.7)	3rd (36.8-56.0)	p-trend
Syndrome scores	Mean (SD)	β (95% CI)	β (95% CI)	
Anxious depressed	55.2 (5.1)	-0.52 (-3.48,2.44)	-0.22 (-3.39,2.95)	0.88
Withdrawn	59.2 (8.0)	-3.77 (-7.00,-0.53)*	-3.49 (-6.95,-0.02)*	0.04
Somatic complaints	59.0 (8.7)	-0.76 (-4.60,3.09)	-1.73 (-5.85,2.39)	0.41
Social problems	55.9 (6.3)	-1.46 (-4.42,1.50)	-2.52 (-5.69,0.65)	0.12
Thought problems	56.0 (6.3)	-1.72 (-4.42,0.98)	-2.88 (-5.78,0.01)†	0.04
Attention problems	55.8 (5.4)	-1.21 (-3.86,1.62)	-0.80 (-3.74,2.14)	0.58
Rule-breaking behavior	54.7 (5.7)	-1.35 (-3.85,1.14)	-1.89 (-4.57,0.78)	0.16
Aggressive behavior	56.2 (6.2)	-1.55 (-4.51,1.41)	-1.50 (-4.67,1.68)	0.34
Composite scores				
Internalizing problems	57.3 (8.8)	-4.13 (-9.01,0.74)†	-2.65 (-7.87,2.58)	0.30
Externalizing problems	53.3 (9.1)	-2.99 (-7.51,1.53)	-2.26 (-7.11,2.58)	0.34
Total problems	55.3 (8.3)	-3.85 (-8.28,0.58)†	-2.87 (-7.62,1.88)	0.22

CI: Confidence Interval; SD: Standard deviation.

\*For all scales, raw scores were transformed to T-scores to compare each subject to a normative sample of adolescents. Higher scoring indicated worse behavioral outcomes.

All models were adjusted for adolescent's age and BMI, and maternal education and intelligence.

\*p≤ 0.05; †p< 0.10

## Sensitivity Analyses

**Table S7. Adjusted models for the association between tertiles of urinary metal concentrations and CBCL scores (n=125).**

CBCL scores	Model 1				Model 2							
	As tertiles ( $\mu\text{g/L}$ )			p-trend	1 <sup>st</sup> (LOD-2.29) Mean (SD)	2 <sup>nd</sup> (2.31-3.56) β (95% CI)	3 <sup>rd</sup> (3.57-6.85) β (95% CI)	1 <sup>st</sup> (LOD-2.29) Mean (SD)	2 <sup>nd</sup> (2.31-3.56) β (95% CI)	3 <sup>rd</sup> (3.57-6.85) β (95% CI)	p-trend	
	1 <sup>st</sup> (LOD-2.29) Mean (SD)	2 <sup>nd</sup> (2.31-3.56) β (95% CI)	3 <sup>rd</sup> (3.57-6.85) β (95% CI)									
<b>Syndrome scores</b>												
Anxious/depressed	54.2 (5.1)	1.18 (-1.91,4.28)	0.44 (-2.65,3.52)	0.80	54.5 (5.2)	1.40 (-1.88,4.67)	0.36 (-2.84,3.56)	0.88				
Withdrawn	57.1 (6.0)	-0.62 (-4.17,2.94)	-0.77 (-4.31,2.78)	0.67	57.2 (6.2)	-0.50 (-4.23,3.24)	-0.44 (-4.08,3.21)	0.82				
Somatic complaints	55.7 (6.0)	3.76 (-0.20,7.71)†	258 (-1.36,6.52)	0.22	55.7 (6.1)	3.86 (-0.28,7.99)†	2.68 (-1.35,6.72)	0.24				
Social problems	55.0 (5.7)	-0.06 (-3.22,3.10)	-1.27 (-4.42,1.88)	0.41	54.7 (5.6)	1.26 (-2.01,4.53)	-0.30 (-3.49,2.89)	0.79				
Thought problems	53.3 (4.2)	2.08 (-0.81,4.98)	0.74 (-2.15,3.62)	0.66	53.3 (4.3)	2.08 (-0.98,5.14)	0.79 (-2.20,3.77)	0.68				
Attention problems	54.8 (4.7)	1.91 (-0.97,4.80)	-0.36 (-3.23,2.52)	0.75	54.6 (4.7)	2.67 (-0.37,5.70)†	0.15 (-2.81,3.12)	0.95				
Rule-breaking behavior	54.6 (5.6)	-1.10 (-3.77,1.57)	-1.60 (-4.26,1.06)	0.24	54.8 (5.8)	-0.79 (-3.50,1.92)	-1.39 (-4.03,1.26)	0.30				
Aggressive behavior	55.9 (6.0)	-1.26 (-4.43,1.90)	-0.93 (-4.08,2.22)	0.58	55.9 (6.0)	-0.40 (-3.68,2.88)	-0.40 (-3.61,2.80)	0.81				
<b>Composite scores</b>												
Internalizing problems	52.9 (10.1)	1.76 (-3.42,6.95)	3.15 (-2.02,8.32)	0.23	53.1 (10.5)	2.15 (-3.37,7.67)	3.53 (-1.86,8.92)	0.20				
Externalizing problems	52.8 (9.2)	-2.24 (-7.03,2.56)	-1.01 (-5.79,3.77)	0.70	53.0 (9.1)	-1.16 (-6.06,3.74)	-0.31 (-5.10,4.47)	0.93				
Total problems	52.9 (9.0)	0.15 (-4.63,4.93)	0.42 (-4.35,5.18)	0.86	52.8 (9.2)	1.24 (-3.75,6.23)	1.25 (-3.62,6.12)	0.63				
Cd tertiles ( $\mu\text{g/L}$ )												
CBCL scores	1 <sup>st</sup> (LOD-0.06) Mean (SD)	2 <sup>nd</sup> (0.06-0.10) β (95% CI)	3 <sup>rd</sup> (0.11-0.34) β (95% CI)	p-trend	1 <sup>st</sup> (LOD-0.06) Mean (SD)	2 <sup>nd</sup> (0.06-0.10) β (95% CI)	3 <sup>rd</sup> (0.11-0.34) β (95% CI)	p-trend				
	1 <sup>st</sup> (LOD-0.06) Mean (SD)	2 <sup>nd</sup> (0.06-0.10) β (95% CI)	3 <sup>rd</sup> (0.11-0.34) β (95% CI)		1 <sup>st</sup> (LOD-0.06) Mean (SD)	2 <sup>nd</sup> (0.06-0.10) β (95% CI)	3 <sup>rd</sup> (0.11-0.34) β (95% CI)					
	1 <sup>st</sup> (LOD-0.06) Mean (SD)	2 <sup>nd</sup> (0.06-0.10) β (95% CI)	3 <sup>rd</sup> (0.11-0.34) β (95% CI)	p-trend	1 <sup>st</sup> (LOD-0.06) Mean (SD)	2 <sup>nd</sup> (0.06-0.10) β (95% CI)	3 <sup>rd</sup> (0.11-0.34) β (95% CI)	p-trend				
<b>Syndrome scores</b>												
Anxious/depressed	54.3 (5.1)	0.33 (-2.65,3.30)	1.15 (-2.27,4.58)	0.51	54.3 (5.1)	0.64 (-2.41,3.70)	1.52 (-1.98,5.02)	0.39				
Withdrawn	56.3 (5.4)	1.47 (-1.92,4.87)	0.26 (-3.66,4.18)	0.83	56.3 (5.4)	1.15 (-2.33,4.63)	0.40 (-3.58,4.38)	0.79				
Somatic complaints	58.7 (7.5)	-1.78 (-5.57,2.01)	-4.35 (-8.72,0.0)†	0.06	58.7 (7.5)	-1.74 (-5.60,2.11)	-4.34 (-8.74,0.07)	0.06				
Social problems	53.1 (4.0)	3.88 (0.94,6.81)**	2.28 (-1.11,5.66)	0.14	53.1 (4.0)	3.77 (0.81,6.72)*	1.98 (-1.41,5.36)	0.18				
Thought problems	52.9 (3.9)	1.81 (-0.95,4.56)	2.91 (-0.27,6.08)†	0.06	52.9 (3.9)	1.92 (-0.91,4.75)	2.90 (-0.34,6.13)†	0.07				
Attention problems	54.1 (4.5)	3.13 (0.40,5.86)*	0.75 (-2.39,3.90)	0.50	54.1 (4.5)	3.23 (0.43,6.03)*	0.58 (-2.62,3.78)	0.56				
Rule-breaking behavior	53.7 (4.9)	0.43 (-2.15,3.01)	-0.01 (-2.99,2.97)	0.98	53.7 (4.9)	0.55 (-2.00,3.09)	0.13 (-2.78,3.04)	0.90				
Aggressive behavior	53.9 (4.8)	2.85 (-0.13,5.83)†	2.79 (-0.65,6.22)	0.09	53.9 (4.8)	3.19 (0.22,6.17)*	2.71 (-0.69,6.11)	0.09				
<b>Composite scores</b>												
Internalizing problems	54.4 (10.2)	0.25 (-4.76,5.27)	-0.78 (-6.56,5.0)	0.81	54.4 (10.2)	0.19 (-5.01,5.39)	-0.47 (-6.42,5.48)	0.89				
Externalizing problems	50.5 (8.6)	2.64 (-1.94,7.22)	3.09 (-2.19,8.37)	0.23	50.5 (8.6)	3.09 (-1.42,7.61)	3.17 (-2.00,8.34)	0.20				
Total problems	52.0 (8.2)	2.81 (-1.74,7.36)	1.11 (-4.13,6.36)	0.60	52.0 (8.2)	2.96 (-1.66,7.58)	1.07 (-4.21,6.35)	0.60				
Hg tertiles ( $\mu\text{g/L}$ )												
CBCL scores	1 <sup>st</sup> (LOD-0.40) Mean (SD)	2 <sup>nd</sup> (0.41-0.86) β (95% CI)	3 <sup>rd</sup> (0.86-4.57) β (95% CI)	p-	1 <sup>st</sup> (LOD-0.40) Mean (SD)	2 <sup>nd</sup> (0.41-0.86) β (95% CI)	3 <sup>rd</sup> (0.86-4.57) β (95% CI)	p-				
	1 <sup>st</sup> (LOD-0.40) Mean (SD)	2 <sup>nd</sup> (0.41-0.86) β (95% CI)	3 <sup>rd</sup> (0.86-4.57) β (95% CI)		1 <sup>st</sup> (LOD-0.40) Mean (SD)	2 <sup>nd</sup> (0.41-0.86) β (95% CI)	3 <sup>rd</sup> (0.86-4.57) β (95% CI)					

	Mean (SD)	$\beta$ (95% CI)	$\beta$ (95% CI)	trend	Mean (SD)	$\beta$ (95% CI)	$\beta$ (95% CI)	trend
<b>Syndrome scores</b>								
Anxious/depressed	55.4 (5.9)	-1.28 (-4.27,1.72)	-0.52 (-3.69,2.64)	0.71	55.8 (5.9)	-1.50 (-4.61,1.61)	-0.55 (-3.89,2.80)	0.72
Withdrawn	57.4 (6.1)	-0.67 (-4.11,2.76)	-1.61 (-5.24,2.02)	0.38	57.5 (6.3)	-0.52 (-4.06,3.01)	-1.76 (-5.56,2.05)	0.36
Somatic complaints	58.1 (7.6)	-0.92 (-4.82,2.99)	-0.15 (-4.28,3.97)	0.92	58.2 (7.8)	-1.73 (-5.72,2.26)	-1.28 (-5.58,3.02)	0.54
Social problems	56.3 (6.7)	-2.46 (-5.46,0.54)	-3.24 (-6.41,-0.07)*	0.04	56.0 (6.9)	-1.91 (-4.99,1.16)	-2.55 (-5.86,0.76)	0.12
Thought problems	53.7 (4.6)	0.14 (-2.69,2.97)	1.11 (-1.88,4.10)	0.47	53.8 (4.7)	-0.29 (-3.22,2.65)	0.50 (-2.66,3.66)	0.76
Attention problems	55.4 (5.2)	0.50 (-2.34,3.34)	-0.39 (-3.39,2.60)	0.82	55.2 (5.3)	0.56 (-2.39,3.50)	-0.31 (-3.48,2.86)	0.86
Rule-breaking behavior	54.3 (5.4)	-1.58 (-4.17,1.01)	-0.30 (-3.03,2.43)	0.77	54.5 (5.5)	-1.98 (-4.53,0.58)	-0.77 (-3.52,1.98)	0.54
Aggressive behavior	55.4 (5.5)	-0.06 (-3.13,3.02)	-0.37 (-3.62,2.88)	0.82	55.4 (5.5)	0.04 (-3.08,3.16)	-0.04 (-3.40,3.32)	0.98
<b>Composite scores</b>								
Internalizing problems	55.1 (10.9)	-1.29 (-6.35,3.76)	0.27 (-5.07,5.61)	0.95	55.3 (11.2)	-1.46 (-6.74,3.82)	-0.03 (-5.72,5.66)	0.97
Externalizing problems	52.1 (9.1)	-1.01 (-5.67,3.65)	0.53 (-4.40,5.45)	0.86	52.3 (9.1)	-1.12 (-5.76,3.53)	0.65 (-4.35,5.66)	0.82
Total problems	53.7 (9.0)	-1.58 (-6.21,3.04)	-0.58 (-5.46,4.30)	0.79	53.8 (9.2)	-1.65 (-6.39,3.08)	-0.63 (-5.73,4.47)	0.79
<b>Pb tertiles (<math>\mu\text{g/L}</math>)</b>								
CBCL scores	1 <sup>st</sup> (LOD-0.34) Mean (SD)	2 <sup>nd</sup> (0.34-0.58) $\beta$ (95% CI)	3 <sup>rd</sup> (0.59-4.45) $\beta$ (95% CI)	p-trend	1 <sup>st</sup> (LOD-0.34) Mean (SD)	2 <sup>nd</sup> (0.34-0.58) $\beta$ (95% CI)	3 <sup>rd</sup> (0.59-4.45) $\beta$ (95% CI)	p-trend
<b>Syndrome scores</b>								
Anxious/depressed	53.7 (9.0)	0.74 (-2.25,3.74)	-1.61 (4.73,1.51)	0.29	55.1 (6.0)	0.58 (-2.58,3.74)	-1.55 (-4.87,1.77)	0.33
Withdrawn	57.0 (5.2)	0.57 (-2.90,4.04)	-0.88 (-4.49,2.74)	0.61	57.0 (5.3)	0.67 (-2.95,4.28)	-0.96 (-4.76,2.83)	0.59
Somatic complaints	59.2 (7.1)	-2.73 (-6.61,1.16)	-3.19 (-7.24,0.86)	0.13	59.3 (7.2)	-2.14 (-6.18,1.91)	-3.36 (-7.60,0.89)	0.12
Social problems	54.4 (5.4)	1.52 (-1.56,4.61)	0.15 (-3.07,3.36)	0.96	54.2 (5.4)	2.06 (-1.11,5.22)	0.67 (-2.65,3.99)	0.73
Thought problems	54.2 (4.7)	0.31 (-2.56,3.17)	-0.24 (-3.22,2.75)	0.87	54.2 (4.8)	1.02 (-1.97,4.02)	0.12 (-3.02,3.27)	0.97
Attention problems	55.6 (5.6)	-0.50 (-3.35,2.36)	-1.51 (-4.48,1.47)	0.31	55.5 (5.7)	0.02 (-2.98,3.02)	-1.27 (-4.42,1.89)	0.41
Rule-breaking behavior	53.8 (4.5)	-0.54 (-3.16,2.08)	0.75 (-1.98,3.48)	0.57	53.8 (4.6)	0.30 (-2.33,2.93)	1.52 (-1.23,4.28)	0.26
Aggressive behavior	55.1 (5.5)	0.45 (-2.65,3.56)	0.07 (-3.16,3.30)	0.98	54.9 (5.5)	1.32 (-1.86,4.49)	1.31 (-2.02,4.64)	0.45
<b>Composite scores</b>								
Internalizing problems	56.3 (8.7)	-2.50 (-7.56,2.56)	-3.63 (-8.90,1.64)	0.18	56.4 (8.9)	-2.46 (-7.82,2.90)	-3.75 (-9.37,1.88)	0.19
Externalizing problems	52.7 (7.2)	-1.75 (-6.45,2.95)	-1.40 (-6.30,3.49)	0.58	52.5 (7.2)	-0.49 (-5.25,4.28)	0.38 (-4.62,5.37)	0.87
Total problems	54.4 (7.3)	-1.73 (-6.38,2.91)	-2.69 (-7.53,2.14)	0.27	54.3 (7.4)	-0.72 (-5.56,4.12)	-1.74 (-6.83,3.34)	0.49

**Model 1:** adjusted for adolescent's age (continuous: months), BMI (continuous:  $\text{kg}/\text{m}^2$ ), and creatinine (mg/dL), and maternal schooling (primary/secondary/university) and intelligence.

**Model 2:** additionally adjusted for passive tobacco smoking (yes/no) and total fish intake of adolescents (<1 portion/month/>1 portion/month/>1 portion/week).

For all subscales, higher score indicates more behavioral problems.

\*\*p<0.0; \*p<0.05; †p<0.10

**Table S8. Adjusted models for the association of tertiles of urinary metal concentration with serum BDNF (n=125) and BDNF gene methylation (n=113).**

Model 1				Model 2					
As tertiles ( $\mu\text{g/L}$ )									
	1 <sup>st</sup> (LOD-2.29)	2 <sup>nd</sup> (2.31-3.56)	3 <sup>rd</sup> (3.57-6.85)	p-trend	1 <sup>st</sup> (LOD-2.29)	2 <sup>nd</sup> (2.31-3.56)	3 <sup>rd</sup> (3.57-6.85)	p-trend	
sBDNF metBDNF	Mean (SD)	$\beta$ (95% CI)	$\beta$ (95% CI)		Mean (SD)	$\beta$ (95% CI)	$\beta$ (95% CI)		
	35.8 (10.3)	-2.22 (-7.02,2.58)	-3.57 (-8.38,1.24)	0.14	35.7 (10.6)	-1.60 (-6.75,3.54)	-3.21 (-8.26,1.83)	0.21	
	CpG 1	4.6 (0.8)	-0.13 (-0.60,0.34)	0.09 (-0.38,0.57)	0.67	4.6 (0.9)	-0.03 (-0.55,0.43)	0.14 (-0.34,0.63)	0.53
	CpG 2	3.1 (0.5)	0.17 (-0.12,0.46)	0.19 (-0.10,0.49)	0.20	3.09 (0.5)	0.15 (-0.15,0.46)	0.19 (-0.11,0.49)	0.23
	CpG 3	3.2 (0.5)	0.10 (-0.23,0.43)	0.16 (-0.17,0.50)	0.33	3.2 (0.5)	0.05 (-0.28,0.39)	0.12 (-0.21,0.45)	0.46
	CpG 4	5.8 (0.9)	0.24 (-0.44,0.91)	0.45 (-0.24,1.14)	0.20	5.8 (0.9)	0.18 (-0.52,0.87)	0.42 (-0.28,1.12)	0.23
	CpG 5	3.1 (0.7)	0.29 (-0.17,0.75)	0.37 (-0.09,0.84)	0.12	3.1 (0.7)	0.22 (-0.23,0.67)	0.33 (-0.13,0.78)	0.16
	CpG 6	2.5 (0.9)	0.36 (-0.31,1.04)	0.46 (-0.25,1.16)	0.20	2.5 (0.8)	0.28 (-0.37,0.93)	0.38 (-0.29,1.06)	0.26
	CpG t	3.7 (0.5)	0.21 (-0.13,0.55)	0.34 (0.00,0.68)*	0.05	3.7 (0.5)	0.16 (-0.18,0.50)	0.30 (-0.04,0.64)†	0.08
Cd tertiles ( $\mu\text{g/L}$ )									
	1 <sup>st</sup> (LOD-0.06)	2 <sup>nd</sup> (0.06-0.10)	3 <sup>rd</sup> (0.11-0.34)	p-trend	1 <sup>st</sup> (LOD-0.06)	2 <sup>nd</sup> (0.06-0.10)	3 <sup>rd</sup> (0.11-0.34)	p-trend	
sBDNF metBDNF	Mean (SD)	$\beta$ (95% CI)	$\beta$ (95% CI)		Mean (SD)	$\beta$ (95% CI)	$\beta$ (95% CI)		
	37.3 (10.1)	-5.65 (-10.21,-1.09)*	-4.36 (-9.59,0.87)	0.08	37.3 (10.1)	-5.80 (-10.51,-1.08)*	-4.86 (-10.23,0.50)†	0.06	
	CpG 1	4.6 (1.0)	-0.10 (-0.56,0.36)	-0.01 (-0.55,0.52)	0.93	4.6 (1.0)	-0.12 (-0.59,0.35)	-0.01 (-0.55,0.53)	0.93
	CpG 2	3.3 (0.5)	-0.07 (-0.36,0.21)	-0.24 (-0.57,0.09)	0.16	3.3 (0.5)	-0.09 (-0.38,0.20)	-0.25 (-0.59,0.08)	0.14
	CpG 3	3.4 (0.6)	-0.26 (-0.57,0.05)†	-0.37 (-0.73,-0.00)*	0.04	3.4 (0.6)	-0.27 (-0.58,0.03)†	-0.38 (-0.73,-0.02)*	0.03
	CpG 4	6.0 (1.1)	0.01 (-0.65,0.68)	-0.01 (-0.81,0.79)	0.98	6.0 (1.1)	0.01 (-0.66,0.69)	-0.04 (-0.84,0.77)	0.94
	CpG 5	3.3 (0.8)	-0.06 (-0.51,0.40)	-0.11 (-0.64,0.41)	0.67	3.3 (0.8)	-0.05 (-0.49,0.39)	-0.12 (-0.62,0.39)	0.64
	CpG 6	2.7 (1.1)	0.10 (-0.58,0.78)	-0.04 (-0.82,0.73)	0.93	2.7 (1.1)	0.14 (-0.52,0.79)	-0.05 (-0.78,0.68)	0.92
	CpG t	3.9 (0.6)	-0.07 (-0.41,0.27)	-0.14 (-0.55,0.27)	0.49	3.9 (0.6)	-0.09 (-0.42,0.24)	-0.19 (-0.59,0.21)	0.34
Hg tertiles ( $\mu\text{g/L}$ )									
	1 <sup>st</sup> (LOD-0.40)	2 <sup>nd</sup> (0.41-0.86)	3 <sup>rd</sup> (0.86-4.57)	p-trend	1 <sup>st</sup> (LOD-0.40)	2 <sup>nd</sup> (0.41-0.86)	3 <sup>rd</sup> (0.86-4.57)	p-trend	
sBDNF metBDNF	Mean (SD)	$\beta$ (95% CI)	$\beta$ (95% CI)		Mean (SD)	$\beta$ (95% CI)	$\beta$ (95% CI)		
	35.2 (9.9)	-1.60 (-6.34,3.15)	-2.85 (-7.72,2.02)	0.25	35.1 (10.2)	-1.17 (-6.14,3.80)	-2.17 (-7.36,3.02)	0.41	
	CpG 1	4.6 (0.9)	-0.33 (-0.76,0.11)	0.32 (-0.14,0.78)	0.25	4.6 (1.0)	-0.25 (-0.70,0.19)	0.41 (-0.07,0.89)†	0.13
	CpG 2	3.2 (0.5)	0.10 (-0.19,0.38)	-0.03 (-0.33,0.27)	0.88	3.2 (0.5)	0.07 (-0.22,0.36)	-0.07 (-0.39,0.24)	0.69
	CpG 3	3.3 (0.6)	-0.05 (-0.36,0.27)	-0.22 (-0.55,0.11)	0.20	3.3 (0.6)	-0.06 (-0.37,0.26)	-0.21 (-0.55,0.13)	0.23
	CpG 4	5.9 (1.1)	0.38 (-0.25,1.00)	-0.23 (-0.94,0.48)	0.66	5.9 (1.1)	0.35 (-0.30,0.99)	-0.26 (-1.01,0.49)	0.59

CpG 5	3.3 (0.8)	0.08 (-0.37,0.52)	-0.20 (-0.68,0.28)	0.44	3.2 (0.8)	0.06 (-0.37,0.50)	-0.20 (-0.68,0.28)	0.44
CpG 6	2.7 (1.0)	0.09 (-0.56,0.74)	-0.30 (-1.03,0.42)	0.45	2.7 (1.1)	0.09 (-0.54,0.73)	-0.22 (-0.93,0.49)	0.58
CpG t	3.8 (0.6)	0.11 (-0.23,0.45)	-0.03 (-0.39,0.33)	0.94	3.8 (0.6)	0.09 (-0.24,0.43)	-0.05 (-0.41,0.32)	0.84
<b>Pb tertiles (µg/L)</b>								
	<b>1<sup>st</sup> (LOD-0.34) Mean (SD)</b>	<b>2<sup>nd</sup> (0.34-0.58) β (95% CI)</b>	<b>3<sup>rd</sup> (0.59-4.45) β (95% CI)</b>	<b>p-trend</b>	<b>1<sup>st</sup> (LOD-0.34) Mean (SD)</b>	<b>2<sup>nd</sup> (0.34-0.58) β (95% CI)</b>	<b>3<sup>rd</sup> (0.59-4.45) β (95% CI)</b>	<b>p-trend</b>
<b>sBDNF</b>	34.2 (9.7)	-0.34 (-5.19,4.51)	1.37 (-3.59,6.32)	0.56	34.0 (9.8)	-0.17 (-5.28,4.95)	2.01 (-3.26,7.27)	0.42
<b>metBDNF</b>								
CpG 1	4.5 (1.0)	0.05 (-0.42,0.53)	0.06 (-0.43,0.55)	0.81	4.5 (1.0)	0.02 (-0.47,0.52)	0.06 (-0.44,0.56)	0.81
CpG 2	3.2 (0.5)	0.05 (-0.25,0.35)	-0.05 (-0.35,0.25)	0.68	3.19 (0.5)	0.08 (-0.22,0.39)	-0.08 (-0.39,0.23)	0.55
CpG 3	3.2 (0.5)	0.10 (-0.24,0.43)	-0.00 (-0.34,0.34)	0.94	3.2 (0.5))	0.07 (-0.27,0.41)	-0.07 (-0.41,0.26)	0.61
CpG 4	5.8 (1.1)	0.36 (-0.32,1.04)	0.35 (-0.34,1.03)	0.35	5.8 (1.1)	0.41 (-0.28,1.11)	0.29 (-0.41,0.99)	0.44
CpG 5	3.0 (0.7)	0.13 (-0.33,0.60)	0.03 (-0.43,0.49)	0.93	3.2 (0.7)	0.14 (-0.31,0.59)	-0.07 (-0.52,0.38)	0.69
CpG 6	2.6 (0.9)	0.27 (-0.41,0.95)	0.25 (-0.43,0.93)	0.49	2.6 (0.9)	0.24 (-0.44,0.91)	0.10 (-0.56,0.75)	0.82
CpG t	3.8 (0.5)	0.17 (-0.19,0.52)	0.07 (-0.29,0.43)	0.75	3.8 (0.5)	0.17 (-0.18,0.53)	0.01 (-0.34,0.36)	0.96

**Model 1:** adjusted for adolescent's age ([continuous: months](#)), BMI ([continuous: kg/m<sup>2</sup>](#)), and creatinine (mg/dL), and maternal schooling ([primary/secondary/university](#)) and intelligence.

**Model 2:** additionally adjusted for passive tobacco smoking ([yes/no](#)) and total fish intake of adolescents ([<1 portion/month](#)/[>1 portion/month](#)/[>1 portion/week](#)).

For all subscales, a higher score indicates more behavioral problems.

sBDNF: serum BDNF; metBDNF: BDNF gene methylation.

\*p<0.05; †p<0.10